Investigating the implementation and impact of "Better Care Better Value" prescribing policy for Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers for treating hypertension in the UK primary care setting

Submitted by

Amanj Baker, M.Sc.

Thesis submitted to the University of Nottingham for the degree of Doctor of Philosophy

July 2016

Dedication

“In the name of Allah, the most merciful, the most compassionate”

This thesis is dedicated to:

My kind parents,

My dearest wife, Hero

My beloved sons, Ahmed and Barzy

And

My lovely sisters and brothers

Abstract

Background

In April 2009, the NHS Institute for Innovation and Improvement released four Better Care Better Value (BCBV) prescribing indicators. One indicator targeted renin–angiotensin–aldosterone system (RAAS) drugs, i.e., angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), to improve their prescribing efficiency. The indicator affects the proportion of items written for ACEIs as a percentage of the total number of prescriptions for RAAS drugs. A proportion of 80% ACEIs has been proposed and considered as an achievable target based on the small proportion (2–10%) of patients who cannot tolerate the ACEIs-related side effects, mostly dry cough. However, neither the impact of the BCBV indicator on the utilisation of ACEIs/ARBs nor its cost-saving implication is yet known.

The BCBV indicator involves switching established ARBs users to ACEIs, where appropriate. However, no previous studies have specifically investigated the clinical and economic impact of the switch of ARBs and hence it is unclear whether the switch from ARBs to ACEIs, promoted by the BCBV indicator, would be associated with any clinical or economic issues.

Without any financial incentives or legislation enforcement, uptake of the BCBV policy is predicted to be low, especially as evidence suggests that single measures are ineffective in altering GPs' prescribing behaviour. However, the uptake and implementation of the BCBV indicator has not yet been explored.

Aims

This thesis aimed to evaluate the impact of the BCBV indicator for ACEIs/ARBs on the utilisation of ACEIs/ARBs in treating hypertension (HT) and any associated cost savings. The effects of switching patients from ARBs to ACEIs on clinical outcomes (adherence, blood pressure [BP] level and HT-related complications), healthcare resources and costs were also investigated. Prior to this, patients' adherence and persistence patterns (discontinuation and switching), and potential associated factors were studied. Finally, the uptake and implementation of the BCBV indicator in real practice was explored.

Methods

This research used an explanatory sequential mixed-method approach. Firstly, an interrupted time series analysis was used on data extracted from the Clinical Practice Research Datalink (CPRD), from April 2006 to March 2012, to examine the impact of the BCBV indicator on the repeated cross-sectional monthly ACEIs/ARBs prescriptions and costs in patients with primary hypertension, which was validated using national dispensing datasets.

Secondly, a retrospective cohort study was conducted using prescription records extracted from CPRD for patients with primary hypertension who were prescribed antihypertensive drugs from April 2006 to March 2013. Patients' adherence and persistence patterns (including switching) to antihypertensive drug classes were quantified and their association with patients' characteristics tested, using Generalised Linear Models and survival analysis.

Thirdly, a retrospective cohort study was conducted on patients who switched their index drug class from ARBs to ACEIs to evaluate the clinical outcomes and resources used associated with ARBs switching, using data from CPRD in linkage with Hospital Episode Statistics, and applying multilevel regression for data analysis.

Finally, semi-structured interviews were conducted with 16 general practitioners, to explore their views about ACEIs/ARBs prescribing and the BCBV policy to understand the reasons underpinning the effectiveness/ineffectiveness of the BCBV indicator. The interviews were recorded, transcribed verbatim and analysed using a thematic approach.

Results

Impact of the BCBV indicator on ACEIs/ARBs utilisation and cost saving

The ACEIs prescription proportion declined from 71.2% in April 2006 to 70.7% in March 2012. The policy initially resulted in a sudden reduction of 0.3% (95%CI: –0.44, –0.16) in the level of ACEIs prescription proportion; however, it was thereafter associated with a sustained, significant increase of 0.013% (95%CI: 0.0007, 0.02). The failure to achieve the 80% target by the end of the study period resulted in missing a potential cost saving of 23.9% of the total ACEIs/ARBs cost. In June 2014, a potential cost saving of ~£1 million was predicted, had the 80% target been achieved; this substantial saving was several years after the availability of several low-cost generic ARBs.

Adherence and persistence to antihypertensive drug classes

Among the 176,835 patients with primary hypertension included in this analysis, 38.4% and 20% were non-adherent (proportion of days covered [PDC]<80%) to their antihypertensive drug class and therapy, respectively. The discontinuation rate of antihypertensive drug class (56.1%) and therapy (35.5%) was relatively high by the end of six-year follow-up period. Using ARBs as the index drug class, prevalent hypertensive patients, prevalent antihypertensive drug users and increasing age were associated with higher PDC to antihypertensive drug class and therapy but a lower risk of drug discontinuation; whereas a higher deprivation level, comorbidity score and switching of antihypertensive drug class were associated with lower PDC to antihypertensive drug therapy but a higher risk of discontinuation.

Overall, 26% of the included patients switched their antihypertensive drug class. Using ARBs, higher deprivation, higher comorbidity and prevalent antihypertensive drug users were protective factors against switching; whereas female gender, prevalent hypertensive patients, higher BP level and increasing age were associated with a higher risk of switching.

Clinical and economic implications of switching patients from ARBs to ACEIs

Of the 46,193 patients who switched their antihypertensive drug therapy, only 470 patients switched from ARBs to ACEIs – they were included in this study. Based on whether the patient combined ACEIs with other antihypertensive drug classes in the post-switching period, 369 patients were classified into ACEIs-combined group and 101 patients into ACEIs-monotherapy group. Compared

with the pre-switching period, the proportion of non-adherent patients (PDC<80%) in the post-switching period increased significantly (17% vs. 27%); however, this significant increase was observed only in the ACEIs-combined group (17.3% vs. 29%).

The switching of ARBs was associated with a significant reduction in both systolic and diastolic BP (144.2 vs. 141.9 mmHg, p<0.001) and (84.6 vs. 82.6 mmHg, p<0.001), respectively; however, this effect was found only in the ACEIs-combined group. The incidence of all HT-related complications was comparable in both pre- and post-switching periods, except for the incidence of MI, which reduced significantly only in the ACEIs-combined group (OR=0.1, 95%CI: 0.04, 0.6). Importantly, the switching of ARBs to ACEIs was associated with a significant reduction in the total medical costs (mean cost difference: –£329.2, 95%CI: –534.6, –205.7).

Uptake and implementation of the BCBV indicator

Potential barriers suggested for the poor uptake of the BCBV policy, included a lack of GP awareness of the policy, GPs' negative attitudes toward the policy and a lack of financial incentives. Among other reasons, the current high proportion of ARBs users appeared to be related to an over-switching of ACEIs to ARBs in anticipation of an ACEIs-related dry cough.

Suggested measures for increasing the policy uptake included effective dissemination strategies, linking the policy to financial incentives and providing guidance on performing the switching. Furthermore, strategies to address the

over-switching of ACEIs to ARBs were considered essential for the BCBV policy to achieve its 80% ACEIs target.

Conclusions

The BCBV indicator was ineffective and failed to achieve the 80% ACEIs target. The association of achieving the 80% target with a remarkable cost-saving opportunity and the lack of any negative clinical consequences following the switching of ARBs to ACEIs indicate the ongoing necessity to reconsider and reinforce this policy through multiple initiatives to increase its future effectiveness, building on the study's identified barriers and suggested solutions.

This thesis represents a case study of a failed and an ineffective prescribing policy, attributed primarily to inappropriate policy implementation. It provides key lessons for policy makers and healthcare authorities on the importance of effective implementation strategies as an integral component to any successful policy.

List of publications

Peer review journals

Amanj Baker, Li-Chia Chen, Brian Godman, Rachel Elliott, Brian Godman. The impact of the 'Better Care Better Value' prescribing policy on the utilisation of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for treating hypertension in the UK primary care setting: longitudinal quasi-experimental design. ***BMC Health Services Research***, 2015;15:367-382 (DOI: 10.1186/s12913-015-1013-y)

Conference presentations

Amanj Baker, Li-Chia Chen, Brian Godman, Rachel Elliott. Impact of the "Better Care Better Value" prescribing policy on the utilisation of renin-angiotensin system drugs in primary care in England. ***International Journal of Pharmacy Practice***, 2013;21:115-116. (**Poster presentation**, RPS Annual Conference 2013, 8 September 2013 at the Birmingham International Conference Centre, Birmingham, UK)

Amanj Baker, Li-Chia Chen, Rachel Elliott. Factors associated with patients' adherence to antihypertensive drug classes in the UK. ***Pharmacoepidemiology and Drug Safety***, 2014;23 (Issue S1):320. (**Podium presentation**, The 30th Anniversary International Conference on Pharmacoepidemiology and Therapeutic Risk Management, 27 October 2014 at Taipei International Convention Centre, Taipei, Taiwan)

Amanj Baker, Li-Chia Chen, Rachel Elliott. Incidence and Determinants of Antihypertensive Drug Switching in Patients with Primary Hypertension in the

Primary Care Setting in the UK. **Poster Presentation**, EuroDURG 2014 Scientific Meeting, 27-29 August 2014 at University Medical Center Groningen, Groningen, Netherlands.

Amanj Baker, Li-Chia Chen, Rachel Elliott. Determinants of antihypertensive drug discontinuation among patients with primary hypertension in the UK. **Poster Presentation**, EuroDURG 2014 Scientific Meeting, 27-29 August 2014 at University Medical centre Groningen, Groningen, Netherlands.

Amanj Baker, Li-Chia Chen, Rachel Elliott. Lessons on the failure of the "Better Care Better Value" prescribing indicator for renin-angiotensin system drugs in treating hypertension: a qualitative study from general practitioners' perspectives (Abstract number: 319). **Elevator pitch oral presentation**, the 44th Annual Scientific Meeting of the Society for Academic Primary Care (SAPC), 8-10 July 2015, University of Oxford, Oxford, UK

Amanj Baker, Li-Chia Chen, Rachel Elliott. The impact of switching patients with primary hypertension from Angiotensin Receptor Blockers (ARBs) to Angiotensin-Converting Enzyme Inhibitors (ACEIs) on medication adherence and blood pressure control: a retrospective cohort study. The annual Health Services Research and Pharmacy Practice Conference (HSRPP), 7-8 April 2016, University of Reading, Henley Conference Centre, Reading, UK (Submitted abstract)

Acknowledgements

I would like to acknowledge a number of people without whom this research would not have been possible. I would like first to express my sincere thanks to my sponsor, The Higher Committee for Education Development in Iraq (HCED), for offering me this PhD scholarship to conduct this research programme.

I am forever indebted to my academic supervisors, Assist. Prof. Li-Chia Chen and Prof. Rachel Elliott, for their generous time of intensive supervision, continuous, support, sharing their expertise with me, and guidance in developing and executing this research programme. You both will remain an inspiration source for me and you have made my experience of conducting this PhD a very enjoyable journey. I would like also to thank my co-adviser, Prof. Brian Godman (Strathclyde Institute of Pharmacy and Biomedical Sciences, Strathclyde University, Glasgow), for his astute contribution to the development of the research question for part of this PhD as well as his comments and feedback in revising the paper manuscript published in BMC Health Services Research.

I would like to express my appreciation to all the GPs who participated in the qualitative study of this thesis for their generous time and thoughts; without their participation, this study would not have been possible. I would like to especially thank Dr Khalid El-Namasy for his assistance in revising the interview schedule for GPs as well as his great help in recruiting GP participants.

I wish also to express my sincere appreciation to all my fellow PhD students, academic and administrative staff at the Division of Social Research in Medicines and Health for being a great source of support and encouragement throughout

my years of study. Finally, I would like to say a heartfelt thanks to my family, especially my beloved wife, Hero, for her support, love, and looking after our lovely sons, Ahmed and Barzy, which gave me the time and energy to accomplish this work.

Table of contents

List of tables

List of figures

List of appendices

List of abbreviations

95% CI	95% Confidence Interval
A&E	Accident and emergency
ACEIs	Angiotensin-converting enzyme inhibitors
ARBs	Angiotensin receptor blockers
ATC	Anatomical Therapeutic Chemical
BBs	β-blockers
BCBV	Better Care Better Value
BMI	Body Mass Index
BP	Blood Pressure
CCBs	Calcium-channel blockers
CCGs	Clinical Commissioning Groups
CCI	Charlson Comorbidity Index
CHD	Coronary heart disease
CPRD	Clinical Practice Research Datalink
CRF	Chronic renal failure
CVDs	Cardiovascular diseases
DBP	Diastolic blood pressure
DDD	Defined daily dose
DM	Diabetes Mellitus
ESC	European Society of Cardiology
ESH	European Society of Hypertension
FDC	Fixed-dose combinations
GLM	Generalised Linear model
GPs	General practitioners
HES	Hospital Episode statistics
HF	Heart failure
HRGs	Healthcare Resource Groups
HSCIC	Health and Social Care Information Centre
HT	Hypertension
ICD-10	International Classification of Diseases-tenth revision
IMS	Intercontinental Medical Statistics
INN	International Non-proprietary Name
JNC	Joint National Committee
MCAR	Missing completely at random
MI	Myocardial infarction
MPR	Medication possession ratio
NAO	National Audit Office
NDD	Numeric daily dose
NHS	National Health Service
NICE	National Institute for Health and Care Excellence

NPC	National Prescribing Centre
OFT	Office of Fair Trading
OPCS-4	Office of Population Censuses and Surveys Classification-fourth revision
OSOP	One sheet of paper
PCA	Prescription Cost Analysis
PCTs	Primary Care Trusts
PDC	Proportion of days covered
PH	Proportional hazard
PPIs	Proton pump inhibitors
PSSRU	Personal Social Services Research Unit
QIPP	Quality, Innovation, Productivity and Prevention
QoF	Quality and Outcome Framework
R&D	Research & Development
RAAS	Renin-angiotensin-aldosterone system
SBP	Systolic blood pressure
SES	Socioeconomic status
WHO	World health organisation

Chapter 1. Introduction

The continuous increase in the use of medicines and the associated expenditure is a worldwide trend, which has contributed to the increasing cost and pressure on healthcare resources. Spending on medicines is expected to continue to rise due to factors such as an increasingly aging population and stricter clinical targets. Therefore, many healthcare authorities nationwide have initiated multiple intensive measures aiming to improve prescribing quality and efficiency to either reverse or at least control the growth in pharmaceutical expenditure while maintaining or improving the quality of health care.

Globally, over recent years, there has been a dramatic increase in the use of drugs affecting the renin–angiotensin–aldosterone system (RAAS), including angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), and their utilisation is expected to keep increasing in the future. RAAS drugs are widely used; ACEIs are cheaper as they are largely available in both branded and generic forms compared with ARBs. However, there is no supporting evidence differentiating the clinical superiority of ARBs over ACEIs in treating hypertension. Across Europe, including the UK, stakeholders responsible for healthcare budgets have initiated multiple initiatives to improve the efficient prescribing of RAAS drugs and thus alleviate some of the pressure on pharmaceutical expenditure. Therefore, there is an opportunity for potential cost saving in pharmaceutical expenditure via improving the prescribing efficiency of RAAS drugs without compromising quality of care.

The National Health Service (NHS) in the UK is under intense financial pressure, with expectations of further difficulties in the future. In order for the NHS to be

able to provide the same level of quality of care, it is, therefore, crucial for it to become more efficient, especially in terms of pharmaceutical expenditure as spending on medicines is the second largest area of spending in the NHS. Consequently, the NHS initiated a wide range of measures to improve both the quality of delivered healthcare and efficiency in use of healthcare resources, through improving the value for money in three main areas – clinical productivity, workforce, and prescribing – within the NHS[1].

In April 2009, four Better Care Better Value (BCBV) prescribing indicators were released targeting the prescribing of three drug categories, including one indicator that targeted drugs affecting the RAAS (ACEIs, ARBs). The policy aimed at improving the prescribing efficiency of RAAS drugs by proposing a target of ACEIs comprising 80% of RAAS prescribing, assisting NHS organisation and prescribers in reviewing their prescribing appropriateness, and comparing the prescribing pattern among NHS organisations to ensure the appropriate use of lower cost drugs among these three drug categories, including RAAS.

According to the estimated cost-saving figures in 2009 by the National Prescribing Centre of England, the BCBV indicator for ACEIs/ARBs was expected to incur substantial cost saving to the NHS of £68 million, if the 80% ACEIs proposed target was achieved. However, the impact of the BCBV indicator on the utilisation patterns of ACEIs/ARBs, its cost-saving implication, and its effect on patients' clinical outcomes is not yet clearly known, especially given the relative loss of cost differential between ACEIs and ARBs driven by the availability of low-cost generic ARBs recently.

To achieve the goal of the BCBV indicator, general practitioners (GPs) are required to start new patients on ACEIs as first-line treatment whenever RAAS drugs are indicated, and to switch existing ARBs users to ACEIs, where appropriate. Switching of antihypertensive drugs has been shown to be associated with some clinical and economic issues, including deterioration in clinical outcomes and incurring additional cost[2, 3]. However, the impact of switching from ARBs to ACEIs has not been studied previously. There are also concerns around the policy's uptake and implementation as there was no central strategy in place to promote its uptake, such as a financial incentive or legislation enforcement. This could result in low policy uptake and may lead to the policy being ineffective and thus missing the potential cost-saving opportunity.

This thesis describes a PhD research of policy evaluation, which aimed to assess the impact of the BCBV indicator on ACEIs/ARBs utilisation and cost saving, investigate the clinical and wider economic impact of ARBs switching promoted by the BCBV indicator, and explore the degree of success of the implementation of the BCBV indicator in clinical practice to assist in explaining the policy's observed impact. This thesis is divided into seven chapters.

To understand the theory of policy implementation and measures for managing drug utilisation, a comprehensive literature review (Chapter 2) was conducted to outline the rationale and the impact of the multiple intensive measures that have been initiated across Europe to improve the efficiency and quality of prescribing. A brief summary of the clinical pharmacology of ACEIs/ARBs, the policy background of the BCBV indicator, and the potential clinical and economic issues

that may be associated with ARBs switching were also depicted in order to identify the research questions and support the research rationale.

Four different approaches were taken in this PhD research. An interrupted time series analysis using data obtained from the UK largest data set, the Clinical Practice Research Datalink (CPRD) database, was conducted to evaluate the impact of the BCBV indicator on the utilisation of ACEIs/ARBs, and potential cost saving (Chapter 3). Furthermore, the up-to-date national dispensing data of England was also used to estimate the potential cost-saving implication of achieving the 80% policy target several years after the availability of generic ARBs. The results were validated and compared with results obtained from the analysis of national dispensing data of England. The BCBV indicator was found to be ineffective in altering ACEIs/ARBs prescribing and failed to achieve the proposed 80% target, and thus led to a potential cost-saving opportunity being missed. However, even several years after the introduction of generic ARBs, achieving the 80% target could still be associated with substantial cost-saving opportunity, which in turn indicates the ongoing necessity for reinforcing the policy.

Although the BCBV indicator failed to achieve the target on an aggregated level data, it was unclear whether the policy promoted switching of patients from ARBs to ACEIs was associated with any negative consequences. Therefore, a retrospective cohort study was conducted (Chapter 4) to understand the utilisation patterns of antihypertensive drug classes and to identify the associated determinant factors. Patients' adherence and persistence patterns, including switching, were measured and the potential associated factors were identified,

including demographic and clinical factors (Chapter 4). This chapter also reports how data were prepared for the analyses described in Chapter 5 in terms of data cleaning, management and identifying the method for measuring adherence. Furthermore, work carried out in Chapter 4 also assisted in determining the prevalence of patients' switching from one class to another and consequently, patients who switched their antihypertensive drug classes were identified as the study cohort for further outcome research (Chapter 5).

A retrospective cohort study was conducted to evaluate the impact of ARBs switching on patients' clinical outcomes and overall resource use (Chapter 5) using data from a primary care dataset (CPRD) in linkage with a secondary care data (Hospital Episode Statistics, [HES]). The study outcomes (blood pressure [BP] level, hypertension [HT]-related complications and overall healthcare resources) were compared before and after ARBs switching using multilevel regression modelling. Furthermore, the impact of ARBs switching in those patients who switched before the BCBV indicator was compared with those who switched after the policy. The policy-prompted switching from ARBs to ACEIs was not associated with worsening clinical outcome but rather resulted in an overall net saving in total resource use and cost. Furthermore, the impact of the switching was comparable between patients who switched before and after the BCBV policy.

Knowing the potential cost saving for an effective BCBV policy, a qualitative study was needed to explore the reasons underpinning the effectiveness/ineffectiveness of the BCBV policy (Chapter 6). Semi-structured, face-to-face interviews were conducted with GPs to explore the

effectiveness/ineffectiveness of the BCBV policy. The interview data showed that poor policy implementation was the key factor that underpinned the ineffectiveness of the policy.

Finally, the key findings of this PhD research, implications of the results to practice and policy makers, and recommendations for future research in this field are presented in the final chapter (Chapter 7). The integration of the qualitative and quantitative results in a mixed-method design formed an explanatory sequential argument in this thesis.

Overall, this thesis represented a case study of an ineffective policy that was attributed primarily to inappropriate policy implementation. It provides key learning lessons to policy makers on the importance of effective implementing strategies as an integral component to the uptake and effectiveness of any policy and that failure of a policy to demonstrate benefits may be related to the lack of implementation strategies rather than the policy itself. The finding that the policy promoted switching of ARBs to ACEIs was not linked to any negative clinical or economic consequences should reassure policy makers that implementation of the BCBV indicator would not be associated with inadvertent clinical effects.

Chapter 2. Literature review

This chapter aims to summarise literature about healthcare interventions and policies to optimise and ensure efficient utilisation of medicines with emphasis on the BCBV prescribing indicators for ACEIs/ARBs in the UK and then identify the research gap for assessing this policy. Firstly, a briefing of the rationale of optimising drug use, and types of policies for optimising drug utilisation are described. Secondly, ACEIs/ARBs are described in terms of mechanism of action, therapeutic roles in treating HT, clinical and safety profiles, utilisation patterns, and examples of the policies that targeted ACEIs/ARBs in Europe. The UK BCBV indicator for ACEIs/ARBs is then described in detail, including its potential cost-saving impact and potential issues that may be associated with its implementation. Finally, this chapter presents the rationale and research questions for this PhD thesis, and highlights the aims and objectives of this PhD study.

2.1. Optimal use of medicines

Pharmacotherapy is the key component for treating the majority of medical conditions[4]. The optimal use of medicines is crucial as it ensures safe and effective use of medicine, which in turn assures that patients get the best possible outcomes from their medicines[5]. This concept is of great importance considering that ~30–50% of prescribed medicines for long-term conditions are not taken as intended[6], in particular given the increasing prevalence of people with long-term conditions and multimorbidity[7].

Substantial increase in the growth of drug utilisation has become a worldwide trend. The Intercontinental Medical Statistics (IMS) Institute for Healthcare

Informatics estimated a 3–4% increase of drug utilisation globally in 2012 and forecasted further increase of 5–7% in 2016[8]. Multiple factors may have contributed to the rapid growth in pharmaceutical utilisation including the rise in the aging population and life expectancy, and an increase in prevalence of chronic conditions[9]. Furthermore, the IMS Institute for Healthcare Informatics reported a 2.6% increase in global spending on medicines in 2012 and expected further increase of 2–3% over the next five years, which will bring total spending on medicines in 2014 to $1 trillion, with the total spending on medicines expected to reach $1.2 trillion for the first time in 2017, which represents an increase of $205–235 billion from 2012[10].

Drug therapy can act as a 'double-edged sword'; therefore, the substantial growth in drug utilisation could improve health outcomes, quality of life and prolong patients' lives[11, 12], but could also carry risks of introducing unwanted effects through underuse, overuse and/or inappropriate use of drugs[11,6]. It has been reported that ~5–23% of drug-related hospitalisation is linked to inappropriate prescribing, errors in transcriptions, and/or failure of drug therapy monitoring[13]. One of the major consequences of this inappropriate use of drugs is an increase in healthcare resource utilisation and costs[6, 14], which, in combination with the unsustainable drug utilisation growth, have led to a substantial increase in pharmaceutical expenditure[15] and thus an increase in healthcare costs.

In the recent years, there has been an increased demand for healthcare resources and services worldwide, with the focus on pharmaceutical expenditure, as the latter constitutes an essential component of healthcare resource costs[16]. In the UK, for instance, pharmacotherapy represents the largest non-salary costs of

the total NHS expenditure[4]. In Europe, pharmaceutical expenditure rose by >50% in real terms between 2000 and 2009 among the Organisation for Economic Co-operation and Development countries, reaching 17.5% of total healthcare expenditure in 2009[17]. This was lower than the 60% of total healthcare expenditure in some other developing and middle-income countries[18].

The increasing rate of pharmaceutical expenditure was found to be 4–13% per annum[19], which is typically faster than that of other healthcare components[20], resulting in pharmaceutical expenditure becoming the largest or equalling the greatest cost component of healthcare expenditure in ambulatory care[21]. Therefore, pharmaceutical expenditure has been scrutinised continually, as it will continue to increase, driven by well-known factors, unless it is addressed. These factors include an increasingly aging population, rising patient expectations, stricter clinical targets, and the continual launch of new expensive drugs[22]. The last factor was recognised as the major cost driver in a recent systematic review of 25 studies aimed at identifying the main contributing factors to the increase in pharmaceutical expenditure[16].

As a result, the healthcare authorities and health insurance companies across Europe have initiated multiple reforms and measures to slow down or reverse the unsustainable growth in pharmaceutical expenditure, with the aim of maintaining the same ideals of equitable and comprehensive healthcare services without prohibitive enhancement in either health insurance premium or taxes[23, 24].

2.2. Types of strategies to optimise drug utilisation

The various initiatives and measures to improve and optimise the quality and efficiency of prescribing in primary care can be classified into those for new, premium priced drugs and those for established drugs[25]. Initiatives for optimising and improving the efficiency of prescribing new drugs include robust pricing and reimbursement processes[26, 27], as new drugs are considered the major challenge for funding across European countries.

On the other hand, initiatives for reducing costs and optimising the use of established drugs include “supply-side” measures and “demand-side" measures[22, 24, 28]. The former aims to reduce the price of generics and originators and includes compulsory price cuts, measures to reduce the price of generics, reference pricing in a class and delisting of products from the reimbursement list[29-31]. The latter aims to influence prescribing by increasing the prescribing and dispensing of low-cost generics in favour of originators or patented products in a class or related class where all products have similar efficacy in all patients[25, 32].

The “demand-side” measures can be categorised under the “4**E**s” approach (**E**ducation, **E**ngineering, **E**conomics and **E**nforcement), which has been used in other areas to classify the various measures that affect behaviour, and is now adapted to healthcare systems as well[28]. Across Europe and the USA, stakeholders have used various measures to influence physicians’ and patients’ behaviour, which again can be classified under the “4**E**s” approach[28]. In general, Education and Engineering measures are mostly used by researchers and professional institutions, such as drug and therapeutic committees; whereas

Economics and Enforcement measures are mainly applied by authorities and stakeholders[33].

2.2.1. Education measures

This includes measures that influence prescribing via educational activities and dissemination of educational materials and can be both physician and patient directed. The measures range from simple distribution of printed materials and treatment guidelines to more intensive measures such as academic detailing by health authorities and/or insurance company's personnel on a one-to-one or group basis, prescribing monitoring against agreed guidelines coupled with educational feedback, educational visits by trained facilitators, and prescribing benchmarking against colleagues[28, 34].

Examples of the applications of education measures can be found in various countries and include the “Wise List” in Sweden, which contains about 200 drugs covering the majority of conditions encountered in primary care, combined with monitoring of doctors’ prescribing against agreed guidelines[35]. In the UK, education of medical school trainee GPs to prescribe by international non-proprietary name (INN)[36]. In France, addressing patients’ fears about the effectiveness and safety of generics through public education and campaigns[30], and in the UK and Sweden, developing a list of therapeutically substitutable generic products as well as potentially non-substitutable products by physicians and pharmacists[35, 36].

In general, education measures have only a moderate influential effect on prescribing, and improving quality and efficacy of prescribing, unless combined

with other measures[28]. Furthermore, simple dissemination of educational materials and meetings has been found to influence physicians' awareness or knowledge, but they rarely alter their prescribing behaviour[37-39].

2.2.2. Engineering measures

Engineering measures are those that influence prescribing through managerial or organisational interventions that apply various limitations on prescribing[25, 33]. These includes disease management programmes to overcome under or over use of drugs, as in Germany and the USA[40, 41]; measures to optimise medication use; agreement on generic substitution rates in community pharmacies, as in France[30]; provision of supplementary prescribing tasks to pharmacists and nurses; limitation of pharmaceutical company contacts with prescribing doctors; and implementation of prescribing targets to improve quality and/or efficiency of prescribing[25, 28]. The last includes setting targets for generics against originators or patent products in a class or related class such as percentage of proton pump inhibitors (PPIs) prescriptions as generic omeprazole, percentage of statin prescriptions as generic simvastatin, and percentage of ACEIs of all renin-angiotensin drugs (RADs) as in France[30], Spain[22, 31], Sweden[35] and the UK[32, 42].

Engineering measures could be effective in overcoming barriers to change prescribing as it is well known that the effectiveness of measures that improve prescribing quality is influenced by organisational context; however, poor leadership and poor processes may render them ineffective[43].

2.2.3. Economics measures

These are measures that influence prescribing through financial interventions for physicians, pharmacists and patients, including both incentives and penalties[28, 44]. The measure incorporates budgets for physicians coupled with financial incentives and penalties for staying or overspending an agreed drug budget as in Germany[45], Sweden[35] and the UK[21]; patients co-paying for drugs with a higher acquisition cost than the reference price drug in a class as in Finland[46], France[30] and Sweden[35]; and financial incentives and penalties for physicians for achieving or exceeding agreed efficiency or quality targets as in in the Quality and Outcome Framework in the UK[25, 28, 47].

Economics measures have been shown to be effective in moderating the annual rise in pharmaceutical expenditure or even reducing it; however, its long-term impact on pharmaceutical expenditure and quality of provided care has been studied to a lesser extent[48, 49]. Concerns have been reported around potential negative consequences of financial incentives. A systematic review of studies conducted between 1993 and 2000 suggested a potential reduction in the quality of care, after adopting financial incentives for prescribing, through limiting continuity of care, reducing offered preventive services and increasing the use of emergency services inappropriately[50].

Recently, another review also demonstrated negative impact of financial incentives on clinical priorities and utilisation of valued technologies[51]. However, despite all these concerns, other studies have shown the effectiveness of financial incentives in improving the quality and efficiency of prescribing[48, 49, 52, 53]. Furthermore, many European countries and the USA have applied incentives

schemes and drug budgets to control and address pharmaceutical expenditure through improving the quality and efficiency of prescribing[54, 55], even though the effects can be short lived[43, 52].

2.2.4. Enforcement measures

This refers to regulations and rules that restrict the prescribing of certain medications, including those enforced by law. It includes compulsory INN prescribing, as in Abu Dhabi[56] and Lithuania[57]; compulsory generic substitution at pharmacies; prescribing restrictions, which may involve authorisation from chief medical officers; and prior authorisation[25, 28], as for patented statins in Austria[58], Finland[59], Norway[59] and Sweden[60], for patented PPIs in Norway[59], and angiotensin receptor blockers in Austria[61], Croatia[62] and Sweden[63], and prior authorisation in the some regions in the USA[64], even though some of these measures were local initiatives rather than national regulations.

Compared with the other measures, this type of measure should be easier to implement and may be operated at lower cost; therefore, it seems to be a suitable method in policy making[28]. Studies have indicated that these measures are effective in the regulation of the availability and prescribing of drugs; however, they may not be of similar effectiveness in the regulation of human behaviour as it has been reported that physicians and patients may use alternative ways to bypass these measures, which in turn would minimise their impact[35, 58, 65, 66]. Enforcement measures have been effective in improving prescribing efficiency in many countries, including Croatia, Austria, Spain and Sweden[21, 61, 63].

2.3. Single or multiple supply- and demand-side measures

In general, it has been shown that "supply-side" measures are usually effective even when applied as a single measure because they are ideally implemented through new laws[31]. However, for "demand-side" measures there is ample evidence to show that multiple measures are required to influence prescribing decisions given the complex nature of the prescribing process[25, 32, 59, 67].

The prescribing process is made complex by many factors including the various sources from which physicians sift information, and a wide range of social, logistical and personal influences – including habitual behaviours, and pharmaceutical and medical considerations[68, 69]. These are reflected by the high spending of pharmaceutical companies on marketing activity in recent years to influence GPs' prescribing; for instance, more than £850 million/year has been spent by pharmaceutical companies in the last decade in the UK on marketing activities to influence prescribing, with comparable spending rates in other countries[70, 71].

Many studies have confirmed the necessity of multiple "demand-side" measures to influence prescribing effectively, with their effects being additive[22, 25, 32, 42, 59]. This necessity can be clearly observed in the considerable improvement in the efficiency of prescribing PPIs and statins in Scotland following the initiation of multiple "demand-side" measures in comparison with the limited "demand-side" measures in France, Ireland and Portugal between 2001 and 2007 (Table 2.1).

In Scotland, there was a 52% reduction and only a 16% increase in PPIs and statin expenditure, respectively, in spite of 2.4- and 4.9-fold increases in PPIs and

statins utilisation, respectively; whereas PPIs and statin expenditure increased by 38.0% and 19.0%, respectively, in France given the 2.1-fold and 72.0% increase in their utilisation. However, in Ireland, PPIs and statin expenditure increased by 2.6- and 4.9-fold with 2.4- and 7.1-fold increases in their respective utilisation; while in Portugal, their expenditures increased by 1.9- and 2.3-fold with 3.1- and 4.3-fold increase in PPIs and statin utilisation, respectively[32]. In Sweden, the combination of education, engineering and economic measures (Table 2.1) has resulted in appreciable improvement in PPIs and statin prescribing efficiency, comparable to that observed in Scotland, such that PPI and statin expenditure decreased by 48.0% and 51.0%, respectively, in spite of 42.0% and 2.5-fold increases in their utilisation[24].

Studies have also suggested an additive effect of various demand-side measures. The introduction of a prescribing restriction for atorvastatin in Austria, in addition to the other multiple demand-side measures (Table 2.1), further accelerated the prescribing efficiency of statins via additional enhancement in generic simvastatin prescribing[72]. Likewise, in Sweden, the initiation of a prescribing restriction of ARBs, in addition to the previously introduced prescribing targets, financial incentives and educational activities, has resulted in further enhancement in the prescribing efficiency of RADs[73]. This additive nature of demand-side measures has been confirmed in previous studies where multiple measures were more successful in altering prescribing behaviour than single measures[74, 75].

Table 2.1 General and specific demand-side measures to enhance prescribing efficiency in general and of ACEIs/ARBs in particular, across Europe, with the percentage changes in total RAAS utilisation and expenditure between 2001 and 2007

Countries	Demand-side measures		% change in RAAS utilisation, 2001–2007	% change in RAAS expenditure, 2001–2007
Austria[61]	Education	• Simple measures such as benchmarking of prescribing habits, in addition to prescribing guidance	69%	23%
	Economics	• Financial incentives for GPs to improve efficient prescribing such as prescribing the cheapest generic in the class. GPs are faced with financial sanction in case of continuous high-cost prescribing		
	Enforcement	• Prescribing restrictions for ARBs as second line treatment to patients who cannot tolerate ACEIs as first-line treatment		
Croatia[76]	Education	• Prescribing guidance, through the provision of national formulary, in combination with benchmarking and monitoring visits to GPs in case of concerns about high-cost prescribing	87%	–35%
	Engineering	• Limiting the contact of pharmaceutical companies with GPs, coupled with restricting the activities of pharmaceutical companies such as reporting of all promotional expenses.		
	Economics	• Higher patient co-payment for more expensive drug than the reference drug. Financial penalties for GPs, range of 10–30% of monthly income, in case of continuous prescribing of drugs with a high acquisition cost such as ARBs without justification		
	Enforcement	• Prescribing restrictions for ARBs as second-line treatment to patients who cannot tolerate ACEIs as first-line treatment		
Portugal[63]	Education	• Non-mandatory treatment guidelines as well as educational programmes for pharmacists • No financial incentives or sanctions for GPs to promote the prescribing of generics, with limited monitoring of GP prescribing behaviour	72%	41%
	Economics	• Patient co-payment for the more expensive drug than the current reference price drug		
	Enforcement	• Compulsory INN prescribing by GPs for drugs with an approved generic, yet GPs can bypass substitution when they are concerned • Allowance for generic substitution by pharmacist when a drug is prescribed by INN name; however, no financial incentives by law to pharmacist to promote generic dispensing		
UK (England, Scotland)[23, 24, 29, 32, 63, 77]	Education	• Promotion of INN prescribing by GPs through their training in medical schools with follow-up in community combined with computerised supporting system and monitoring of GP prescribing • National and local treatment and prescribing guideline such as NICE • Academic detaining and benchmarking GPs against agreed prescribing standards	159%	20%
	Engineering	• Prescribing indicators to enhance the efficiency of prescribing such as BCBV indicators for statins, PPIs and RAAS drugs		
	Economics	• Quality and Outcomes Framework scheme which incentivises GPs for achieving certain quality indicators across many chronic conditions such as hypertension, DM and stroke • Financial incentive schemes based at a practice level		

(Continued) **Table 2.1 General and specific demand-side measures to enhance prescribing efficiency in general and of ACEIs/ARBs in particular, across Europe, with the percentage changes in total RAAS utilisation and expenditure between 2001 and 2007**

Countries	Demand-side measures			% change in RAAS utilisation, 2001–2007	% change in RAAS expenditure, 2001–2007
Spain[31]	Education	•	Education courses for GPs, combined with prescribing guidance and benchmarking	30%	11.5%
	Engineering	•	Prescribing targets for ACEIs expressed as percentage of RAAS drug items written as ACEIs		
	Economics	•	Financial incentives for GPs for achieving their prescribing targets		
Sweden[35, 73]	Education	•	Treatment guidelines by national health authorities	92%	20%
		•	Benchmarking of GPs prescribing behaviour with continuous feedback		
		•	Computerised prescribing tools to increase quality and efficiency of prescribing		
	Engineering	•	Prescribing indicators and targets to promote generic prescribing against patented drug such as generic omeprazole vs. all PPIs, and percentage of ACEIs vs. ARBs		
	Economics	•	Financial incentives to GPs for the achievement of agreed prescribing targets.		
		•	Drug budgets for primary healthcare centres with opportunities for potential saving		
		•	Patient co-payments for brand or originators with a price more expensive than the reference-priced		
	Enforcement	•	National prescribing restriction of drugs with concerns about their value such as atorvastatin and rosuvastatin		
		•	Mandatory generic substitution in community pharmacists with the cheapest drug in a class		
		•	Restriction of prescribing ARBs as first line treatment		
France[23, 30, 77, 78]	Education	•	Guidelines from national health authorities	Data not available	
		•	Benchmarking GPs on their rates of generic prescribing with the provision of continuous feedback		
		•	Increasing the acceptance of generics and INN prescribing through promotional campaigns		
		•	Academic detailing		
	Engineering	•	Targets for generic substitution rates for community pharmacists		
		•	Efficiency targets for enhancing generic prescribing against patent's drugs in a class or therapeutic area. For example, generic PPIs vs. all PPIs, generic statins vs. all statins		
	Economics	•	Financial incentives for GPs for their INN prescribing against a target of 25% of all prescriptions		
		•	Financial incentives for GPs for their efficient generic prescribing against patented drugs		
		•	Patient co-payment for drugs with a higher price than the current reference-priced drug		
	Enforcement	•	Generic substitution by pharmacists when the generic drug is cheaper than the originator		
Republic of Ireland[24, 32, 77, 79]	Education	•	Published guideline by national health authorities, though not enforced	Data not available	

Furthermore, it has been found that enforcement measures, especially prescribing restrictions, have the most appreciable influence on prescribing efficiency with an impact similar to the combination of intensive educational, engineering and economic measures[22, 25]. For instance, the intensive educational, engineering and economic demand-side measures in Scotland for RADs resulted in reducing ARBs utilisation in a way similar to the ARBs utilisation pattern seen in Austria where a prescribing restriction of ARBs was implemented[63]. Importantly, the impact of demand-side measures, especially prescribing restriction, has been found to be influenced greatly by their intensity of follow-up and time of their introduction[25, 59]. In Croatia, for example, the prescribing restrictions for ARBs resulted in greater limitation of ARBs utilisation in comparison with ARBs prescribing restrictions in Austria, given the greater follow-up of physicians, which included auditing physicians' prescribing of ARBs with possible financial penalties for continually abusing the restrictions[23, 59, 63].

The importance of the timing of introducing a measure should be carefully considered as not to limit its impact[59]; this was the case in Sweden where the recent restrictions of a patented statin to second-line treatment had limited impact on further improving the efficiency of statin prescribing[60]. This was contradictory to the finding in Austria[72]. The study's authors have suggested that the timing of introducing the prescribing restrictions in Sweden may be the cause for the limited impact of the measure as the restriction was introduced some six years after the initiation of multiple measures to increase the prescribing and utilisation of generic statins against patented ones[60].

Although, as described earlier, many studies have shown that multiple demand-side measures are necessary to influence prescribing and are collectively more effective than single measures, these findings need to be interpreted with caution given the limitations of the studies. Firstly, it was impossible to ensure that the observed changes in utilisation patterns were attributed to the initiated demand-side measure, as the studies did not include any reference, comparison or intervention-free groups. Secondly, the observed alterations in utilisation patterns were the net, combined effects of the multiple demand-side measures as it was not possible to separate the impact of individual demand-side measures because the introduction times for the measures overlapped; therefore, it was not clear to what extent each demand-side measure affected the utilisation pattern.

2.4. Drug classes that are targets for supply- and demand-side measures

The existing measures and reforms are largely general and often designed to influence almost all drug classes, especially the supply-side measures and those which aimed to increase INN prescribing. However, several measures have targeted and focused on renin–angiotensin–aldosterone system drugs (RAAS: ACEIs and ARBs) as well as PPIs and statins.

RAAS drugs have been the target for many reforms and initiatives across Europe, that aimed to improve their prescribing efficiency, due to three main factors, including their high prescribing volume and expenditures in primary care, cost differential between ACEIs and ARBs due to their availability as single-source, originators and generic products[25, 31], and having similar pharmacological activities[116, 124, 132, 133]. Collectively, these factors together offer a great opportunity for potential cost saving through improvement in their prescribing efficiency.

2.5. ACEIs and ARBs

2.5.1. Mechanism of action of ACEIs and ARBs

The RAAS plays an important role in the development of hypertension and therefore, drugs affecting the RAAS are considered an effective treatment strategy[80]. ACEIs act on angiotensin-converting enzyme (ACE) that produces angiotensin-II (a potent vasoconstrictor); whereas ARBs directly inhibit the action of angiotensin-II through the blockage of angiotensin-II receptor subtype-1 (AT1)[80]. By preventing the formation of the potent vasoconstrictor angiotensin-II or blocking its action, ACEIs and ARBs, respectively, exert many beneficial pharmacological effects.

Firstly, hemodynamic effects whereby they effectively reduce blood pressure through vasodilatation and subsequent reduction in total peripheral resistance[81]. Secondly, antiproliferative effects whereby they decrease cardiac enlargement, improve diastolic function in case of cardiomegaly, i.e., hypertrophied heart[82], and decrease ventricular remodelling post myocardial infarction (MI), and in heart failure by decreasing ventricular preload/ afterload, inhibiting the proliferative effects of angiotensin-II and sympathetic outflow, and preventing aldosterone-induced ventricular hypertrophy[83]. Finally, renal protection effects whereby they effectively minimise the progression of microalbuminuria to proteinuria and preserve renal function and thus delay the progression of nephropathy in both diabetic and non-diabetic patients[84].

2.5.2. Hypertension prevalence and cardiovascular diseases

Hypertension (defined as systolic blood pressure [SBP] of ≥140 mmHg and/or diastolic blood pressure [DBP] of ≥ 90 mmHg), is one of the most prevalent

chronic conditions[85]. Hypertension is a common problem worldwide, including developed countries. In 2008, approximately one billion (40%) of the adult world population had been diagnosed with hypertension, with a prevalence of 40% and 35% in developed and developing countries, respectively[86].

Kearney and colleagues (2005)[87] expected a continuous rise in hypertension prevalence. They estimate that, by year 2025, the number of hypertensive patients will rise to about 1.56 billion, a 60% increase from 2000, with 24% and 80% increment in developed and developing countries, respectively[87]. However, a study conducted by Karen *et al* (2008)[88] pointed out that hypertension prevalence is steadily increasing, and it would likely far exceed the estimated prevalence of Kearney and colleagues (2005) by 2025. Therefore, public health interventions are urgently required to prevent and manage HT and its complications[88].

Likewise, in Europe, the overall HT prevalence was found to be ~30–45% of the general population, with a sharp increase with aging[89]. In the UK, the 2011 Health Survey for England[90] reported an HT prevalence of 31% in men and 28% in women. Indeed, in 2011, the National Institute for Health and Care Excellence (NICE) reported that at least one-quarter of adults in the UK had primary hypertension[91].

Hypertension is one of the major risk factors for cardiovascular diseases (CVDs) such as cerebrovascular accidents, ischaemic coronary disease, heart failure, myocardial infarction and arterial aneurysm, and is the leading cause for chronic kidney diseases[91]. Epidemiological data indicated a direct relationship between

blood pressure (BP) values and risk of CVD[92, 93]. CVDs are the primary source for morbidity and mortality and are considered the leading cause of death worldwide[94]. According to the Heart Disease and Stroke Statistics in 2011, CVDs account for 33.6% of all deaths recorded in 2007[95]. Furthermore, according to the World Health Organization (WHO), in 2008 about 17 million people died from CVDs, which represents 30% of all deaths globally[86], of which more than half of them (9.4 million deaths) was due to complications of hypertension[96], with high blood pressure accounting for 45% and 51% of deaths due to heart diseases and stroke, respectively[97]. It has been estimated that by year 2030, the number of CVDs deaths will increase to about 23.3 million[96].

Being the major risk factor for CVDs, hypertension puts a great burden on healthcare resources. It has been estimated that the direct and indirect healthcare cost of CVDs was $286 billion in 2007 in the USA; while in the Europe, it accounted for more than €169 billion in 2006[98]; however, in the UK, it accounted for more than $48 billion in 2006[99] and it is considered the most costly among all other diagnostic diseases.

Recently, the Centre for Economic and Business Research[100] has reported that the total cost of CVDs, including direct and indirect costs, is estimated to be €102.1 billion by the end of 2014 in six major European countries (France, Germany, Spain, Italy, Sweden and the UK), and this cost is expected to rise to €122.6 billion by 2020. In the UK, CVDs accounted for €18.9 billion costs in 2014 (1.4% of the UK's GDP), and is expected to reach €23.1 billion in 2020, which is the largest proportion in comparison with the other European nations. Additionally, hypertensive medications alone cost the UK healthcare system

about £1 billion in 2006. Therefore, the economic burden of CVD will become ever more substantial unless measures are taken to address this issue, such as, for instance, effective and efficient management of hypertension.

2.5.3. Therapeutic role of RAAS drugs in the treatment of hypertension

In addition to lifestyle modifications, pharmacotherapy is the key strategy for treating hypertension through the use of antihypertensive drugs to lower BP value to the recommended target of <140/90 mmHg in the non-elderly general population and to <130/90 mmHg in some patient groups, such as patients with chronic kidney diseases and proteinuria[89, 101]. The primary benefits of antihypertensive treatment are attributed to the reduction in BP per se and are mostly independent of the drug class used[89].

Antihypertensive drugs are classified into five major classes, ACEIs, ARBs, calcium-channel blockers (CCBs), diuretics and β-blockers (BBs). Occasional superiority of one class over another for some outcomes is claimed by some meta-analyses[102], but this was largely attributed to selection bias of the included trials[122]. However, the largest available meta-analyses failed to demonstrate any clinically relevant differences among the various drug classes in terms of BP-lowering effect[103, 104]. Therefore, all five antihypertensive drug classes are considered suitable for initiation and maintenance of antihypertensive treatment, either as monotherapy or in combination[107, 122]. Nevertheless, they have significantly different tolerability profile with diuretics, BBs and CCBs having dose-dependent side effects, not observed with ACEIs, and with the best tolerability profile for ARBs among all antihypertensive drug classes[105].

Although the principle of monotherapy for treating hyptertension is phasing out, most hypertension management guidelines recommend the use of RAAS or CCBs drugs as the initial therapy in most conditions as recommended, for instance, by the NICE guidelines in the UK[91], and the most recent European Society of Hypertension (ESH) and European Society of Cardiology (ESC) guidelines[89]. As the presence or absence of comorbidities often determines the choice of first-line therapy, RAAS drugs are considered the preferred first-line drug class in most hypertensive patients because they can be used with all comorbidities except for coronary heart disease, as was clear from the most recent European guidelines.

Drugs affecting the RAAS, particularly ACEIs and ARBs, are the cornerstone for BP control and considered one of the key therapeutic components of the modern comprehensive management of CVD[89]. The RAAS system plays an essential role in the regulation of BP, cardiovascular and renal functions and therefore, is a crucial regulator for the body's hemodynamic stability[106]. RAAS drugs are the most widely prescribed antihypertensive drug class for the treatment of hypertension, as it is recommended by most guidelines[89, 107]. The current NICE/British Hypertension Society guidelines[91] recommend ACEIs or ARBs as first-line treatment in white patients aged <55 years with no compelling indications. However, even in older patients, the efficacy of ACEIs and ARBs has been confirmed by a recent meta-analysis, which found that diuretics followed by ACEIs and ARBs were the most effective antihypertensive drugs in preventing heart failure in elderly patients[108]. Accordingly, the NICE guidelines recommend ACEIs or ARBs in combination with CCBs for people of any age as step-two treatment to achieve the target BP value.

The Joint National Committee (JNC), in its eighth report recommended two-drug therapy for all stage two hypertension (SBP ≥160 mmHg or DBP ≥100 mmHg) of which one should be ACEIs/ARBs[101]. Furthermore, the ESH/ESC[89] and the WHO International Society of Hypertension[109] has suggested ACEIs and ARBs as the drug of first choice in hypertension with most comorbidities including diabetic nephropathy, left ventricular dysfunction, metabolic syndrome and diabetes, history of myocardial infarction and proteinuria. Although ACEIs/ARBs are recommended for the treatment of hypertension, they are also recommended in the treatment of wide range of other medical conditions such as heart failure[110], post myocardial infarction[111], diabetes mellitus[112, 113] and chronic renal diseases[114].

2.5.4. Clinical efficacy of ACEIs and ARBs

Although both ACEIs and ARBs act on the RAAS, they act at a different level of the RAAS, and experimental data suggest that such difference in action could be translated into differences in clinical efficacy[115, 116]. For instance, the increase in bradykinin level associated with ACEIs administration, but not with ARBs, may have specific cardio-protective effects[117]. Furthermore, the selective, long-term blockage of AT1 by ARBs is associated with an increased level of angiotensin-II that overstimulates AT2, which might trigger apoptosis, inhibition of angiogenesis, and reduction of fibrotic tissue synthesis[118]; potentially, these effects could depress the growth of collateral vessels in the event of ischaemia as well as reduce collagen content and thus cause thinner capillaries and a greater possibility of atheroma rupture[119].

On the other hand, unopposed AT2 overstimulation could exert protective effects on the cerebrovascular system via enhancement of collateral vessels recruitment and increasing neuronal resistance to anoxia[120, 121]. Therefore, ACEIs and ARBs may not be considered as interchangeable[122]. However, clinical studies have demonstrated the effectiveness of ARBs in reducing BP similarly to ACEIs, as well as their efficacy in reducing proteinuria and slowing the progression of renal diseases[123].

Since the introduction of ACEIs in the 1980s, and ARBs in 1990s, many clinical trials and studies with these drugs classes have been conducted. In general, there is robust evidence for the efficacy of ACEIs in reducing cardiovascular morbidity and mortality in hypertension over placebo; while the evidence for ARBs on reducing total and cardiovascular mortality over placebo is less clear[124].

Several meta-analyses have been conducted to compare the clinical benefits of ACEIs and ARBs, and they generated some debate about the potential superiority of ACEIs over ARBs in decreasing total and cardiovascular mortality. Strauss and Hall (2006)[125] performed a meta-analysis of 11 clinical trials (55,050 patients) that compared ARBs with either placebo or active comparator and found that ARBs did not reduce total mortality but only stroke, with an 8% increase in MI risk, compared with comparators. However, in a parallel analysis for ACEIs, the same authors found significant reduction in total mortality, cardiovascular death and MI with ACEIs therapy by 9%, 12% and 14%, respectively.

Although ACEIs and ARBs have a similar BP-lowering effect[123], it has been suggested that ACEIs, but not ARBs, have beneficial effects independent of

lowering BP. In a meta-regression analysis of data from 26 clinical trials involving either ACEIs or ARBs, the BP-dependent and independent effects of ACEIs and ARBs on major CV events in patients with hypertension, DM, history of coronary heart disease (CHD) or cerebrovascular diseases were assessed[126]. The authors reported the same BP-dependent effects of ACEIs and ARBs for the risk of CHD, stroke and heart failure (HF); however, in terms of BP-independent effect, only ACEIs were associated with a significant additional reduction in risk of major coronary disease events.

Furthermore, a meta-analysis of 147 trials suggested a significant risk reduction of stroke and CHD with ACEIs therapy compared with placebo; but ARBs therapy versus placebo was not associated with a significant risk reduction of CHD, with no studies of ARBs versus placebo in stroke[103]. However, there was no significant difference in the risk reduction of CHD and stroke when either ACEIs or ARBs were compared with other drug classes.

A recent meta-analysis, which included all the 137 clinical trials that compared ARBs with controls (placebo or active comparators) with >147,000 patients, reported that, overall, ARBs, in comparison with controls, were not associated with a reduction in the risk of MI[127]. Likewise, there was no reduction in risk of MI, all-cause or cardiovascular death with ARBs in comparison with either placebo or active treatment. However, the comparison of ARBs with active treatment was complicated by differences in the examined patient populations and the variety of active treatment used. The active treatment comparator was ACEIs in eight trials; whereas the active comparators in the other 14 trials were diuretics, CCBs and atenolol.

A more recent meta-analysis conducted by Van-Vark *et al* (2012)[107], which included 20 randomised trials of ACEIs or ARBs compared with either placebo or active treatment, and nearly 160,000 patients, assessed the impact of RAAS drugs, as well as ACEIs and ARBs separately, on all-cause mortality in patients with hypertension[107]. The authors found significant reduction in all-cause and cardiovascular mortality with RAAS drugs in comparison with controls; however, subgroup analysis on ACEIs users or ARBs users showed that the reduction in all-cause mortality was completely due to ACEIs, and ARBs were associated with an insignificant reduction in mortality. Therefore, ACEIs were shown to be superior to ARBs in reducing the risk of death in hypertensive patients with uncertainty about the role of ARBs.

Nevertheless, the conclusion from the study by Van-Vark *et al*[107] needs careful scrutiny due to certain limitations. Firstly, the possibility of potential bias resulted from the use of pooled or network meta-analysis, which is based on an indirect comparison of trials with different populations, different designs and different drugs. Secondly, there was marked imbalance between ACEIs and ARBs studies in terms of the absence of active treatment (43% in ACEIs studies vs. 15% in ARBs studies); thus, it might be expected that the ACEIs studies would have better outcomes. Finally, although ARBs were the first-line therapy in all ARBs studies, in about 50% of ACEIs studies, other drugs were used as the first-line therapy and ACEIs were used in combination with other drugs such as thiazide diuretics or CCBs, especially in those studies which generated a more favourable mortality outcome for ACEIs, such as HYVET[128], ASCOT[129] and ADVANCE[130]. Therefore, the influence of ACEIs is unclear as it is not clear what has driven the beneficial effect.

Even more recently, Savarese *et al* (2013)[131] conducted a meta-analysis of 26 randomised trials, which compared ACEIs or ARBs to placebo, with >105,000 patients, to assess their effects in patients at high CV risk without HF. The analysis indicated a significant reduction in the risk of the composite outcome of CV death, MI and stroke with both ACEIs and ARBs. Furthermore, ACEIs were also associated with a significant risk reduction of all-cause mortality, new-onset HF and DM; however, ARBs failed to demonstrate any significant risk reduction of all-cause mortality, MI or new-onset HF. Therefore, the authors concluded that ARBs are considered a valuable alternative to ACEIs in patients who cannot tolerate ACEIs. Nevertheless, the study's conclusion should not be interpreted without considering its limitations. Firstly, the possibility of potential bias resulted from the indirect comparison of ACEIs and ARBs and the variations in population characteristics between ACEIs and ARBs trials since the majority of ACEIs trials included patients with coronary or other atherosclerotic disease; whereas ARBs trials were mostly in patients with DM or impaired glucose intolerance.

In contrast to the conflicting results about the superiority of ACEIs over ARBs from the previous cross-trial comparison meta-analyses, which need careful interpretation because they are hazardous due to the risk of potential biases, several meta-analyses[116, 124, 132, 133] of randomised trials that involved direct, head-to-head comparison of ACEIs and ARBs showed no significant difference between ACEIs and ARBs for all-cause death, cardiovascular mortality, stroke or MI in people with hypertension. In a meta-analysis of six head-to-head comparison trials of ACEIs and ARBs, the authors concluded that ACEIs and ARBs have an equivalent protective effect against total mortality, cardiovascular

mortality and risk of MI; however; ARBs were found to have greater protection against stroke, albeit small[116].

Likewise, Matchar *et al* (2008)[132] conducted a meta-analysis of 61 trials that directly compared ACEIs to ARBs in patients with hypertension, and no differential effects were found between ACEIs and ARBs in terms of lowering BP, death or major cardiovascular events; however, the evidence for the clinical outcomes was low to moderate due to the low number of occurring events since follow-up time exceeding six months in only one-third of the trials.

In 2011, Sanders *et al* (2011)[133] updated Matchar *et al*'s[132] meta-analysis with the inclusion of 97 trials that directly compared ACEIs with ARBs in patients with hypertension, which added 36 new trials since the 2008 study. The authors found that strong evidence remained for the equivalence of ACEIs and ARBs regarding BP lowering; while the evidence remained low to moderate for the equivalence of ACEIs and ARBs for all-cause mortality and cardiovascular mortality, despite the inclusion of the new trials in the analysis[133]. Recently, the Cochrane Hypertension Group conducted a meta-analysis of nine trials that involved head-to-head comparison of ACEIs and ARBs with at least one-year follow-up time in patients with hypertension[124]. The authors reported no differential effects between ACEIs and ARBs for total mortality, and total cardiovascular events or mortality; however, the evidence for total mortality was considered of moderate quality while that of total cardiovascular events was of low quality.

When comparing the equivalency of ACEIs and ARBs in treating hypertension, the most important study to cite is the Ongoing Telmesartan Alone and in

combination with Ramipril Global Endpoint trial (ONTARGET)[134] as it is the most powerful and largest study evaluating the equivalency of ACEIs and ARBs. It included >25,000 patients at high cardiovascular risk with a large proportion of them (69%) being hypertensive, with a long median follow-up time of 56 months. The study found no difference between ACEIs and ARBs in respect to total or cardiovascular mortality, risk of MI, stroke or HF hospitalisation[134].

In summary, there is strong evidence from several meta-analyses of head-to-head trials for equivalence of ARBs and ACEIs in treating patients with hypertension; importantly, the only single large trial comparing the two drug classes failed to demonstrate any relevant differences in their protection against total and cardiovascular mortality. However, the conflicting results from the cross-trial comparisons' meta-analyses might be due to the potential biases resulted from the pooled, indirect comparison of trials with different populations and designs. Additionally, the law of cumulative benefits[135], which means that statistical benefits can become increasingly hard to demonstrate with the addition of each preventive drug, could partly explain the failure of ARBs to show the beneficial effect in their trials in comparison with ACEIs trials; this is because ARBs trials were generally conducted more recently than ACEIs trials, which raises the possibility of greater use of other preventive drugs in ARBs trials such as statins and anti-platelets.

In fact, the guideline development group for the updated NICE guidelines for the management of hypertension[91] indicated that they value the results from head-to-head trials of ACEIs versus ARBs over those obtained from systematic reviews of trials in incomparable groups and considers this the most robust approach to

evaluate the equivalency of ACEIs and ARBs[136]. Therefore, ACEIs and ARBs are considered equivalent by NICE, and ACEIs and low-cost ARBs are offered as first-line drugs for non-black people <55 years old in the updated NICE recommendation[91].

2.5.5. Safety and tolerability profiles of ACEIs and ARBs

ACEIs are well tolerated by the majority of patients[137] and generally they are considered safe, which is the primary explanation for their popularity[138]. However, they are associated with a dry cough, which is proposed to be caused by the accumulation of irritant chemicals, namely bradykinin, substance P or prostaglandin, that irritate the airways resulting in bronchial hyperactivity and hence a dry cough[92]. This cough is not life threatening; however, it might disturb patients and possibly necessities discontinuation of treatment. Although it is difficult to quantify the exact incidence of the ACEIs-induced cough, evidence has suggested that the cough is not common, as most healthcare professionals perceive[139].

A systematic review of trials that directly compared ACEIs and ARBs in treating hypertension reported an incidence rate about 10% from RCTs studies and only 2% from observational studies[132]. Nevertheless, not all ACEIs-induced coughs required discontinuation of treatment since it has been confirmed that only 2–3% of patients left clinical trials due to cough per se[140, 141]. The second rare but potentially life-threatening side effect of ACEIs is angioedema, which has an incidence rate of 0.1–0.5%[142]. Although its exact mechanism is unknown, it is assumed to be linked to hypersensitivity to the accumulated bradykinin[143].

Unlike ACEIs, ARBs have a better tolerability profile with a safety profile similar to placebo[144]. Furthermore, ARBs are not associated with any class-specific side effects[145]. Since ARBs do not affect the metabolism of bradykinin, theoretically they would not cause cough and angioedema. With regard to the cough, some studies indicated a lower incidence of the cough in patients receiving ARBs[132, 146]; however, in a review on the safety of ARBs, Siragy (2011)[144] reported that ARBs therapy is not associated with a cough. In fact, there is strong, high-quality evidence on the superiority of ARBs over ACEIs in terms of the associated cough. In two recent meta-analyses[124, 133] of head-to-head trials of ACEIs and ARBs, which included more than 100 clinical trials, the authors found high-quality evidence for the superiority of ARBs over ACEIs for short-term adverse effects, primarily due to the cough.

Furthermore, this superiority has been confirmed by the only large-scale trial ONTARGET[134] in which 4.2% of patients in the ACEIs group stopped the drug due to cough compared with 1.1% in the ARBs group, which represents an absolute difference of 3.1%, i.e., if 100 participants are treated with ARBs rather than ACEIs for 4.5 years, only three of them will avoid drug discontinuation due to ACEIs-induced cough, but still one of them will stop treatment due to ARBs-induced cough[134].

Likewise, evidence indicated lower incidence of angioedema in patients treated with ARBs (0.1%) compared with those on ACEIs (0.3%) in the ONTARGET trial[134]. Furthermore, a recent meta-analysis of 40 trials conducted in 2012[147] concluded that the incidence of angioedema with ARBs is less than half of ACEIs and not significantly different from placebo.

Therefore, it can be concluded that the major advantage of ARBs over ACEIs is their lower rate of side effects, mainly the cough, which has made ARBs a very attractive alternative to ACEIs especially in patients intolerant of the ACEIs-induced cough. Accordingly, in all NICE guidelines for heart failure[110], post myocardial infarction[111], diabetes mellitus[112, 113] and chronic renal diseases[114, 148], ACEIs are the first-line RAAS drugs of choice given the most robust evidence base for ACEIs, which ARBs lack[139]. The updated NICE guidelines for hypertension state that, ACEIs and low-cost ARBs should be offered as a first-line drug for non-black people <55 years, and that treatment should start with ACEIs as first-line choice and only use low-cost ARBs as an alternative to ACEIs in patients who are intolerant of ACEIs[91].

2.5.6. Utilisation of ACEIs and ARBs

There is clear evidence that suggests a remarkable global increase in the utilisation of ACEIs and ARBs over the past decade. According to the IMS report in 2011, ACEIs were the fifth most commonly prescribed drugs in the USA, accounting for 164 million prescriptions, 4.07% of all US prescriptions; while ARBs were the 16th with 86 million prescriptions (2.1%)[149]. Likewise, Bian *et al* (2010) found a significant increase in ACEIs/ARBs utilisation by 45% between 1991 and 2008 in the USA, with the US Medicaid program spending about $310 million on both ACEIs and ARBs in 2008, which constituted ~1.5% of total USA drug expenditure, with ACEIs accounting for $108 million and ARBs for $202 million[150].

In Europe, a remarkable increase in ACEIs/ARBs utilisation was also observed. In an observational study, Voncina *et al* (2011) had compared the utilisation

trends of ACEIs/ARBs among six European countries (Austria, Croatia, Portugal, Scotland, Spain and Sweden) over a six-year period from 2001 to 2007[62]. The authors found an appreciable increase in ACEIs/ARBs utilisation in all the studied countries during the study period. The increasing rates were similar in all countries, except for Scotland, which showed a greater increasing rate. Between 2001 and 2007, ACEIs/ARBs increased by 69% in Austria, 87% in Croatia, 72% in Portugal, 92% in Sweden, 29.9% in Spain (between 2003 and 2007) and 159% in Scotland[62].

Furthermore, another study found a 1.8-fold increase in ACEIs/ARBs utilisation in the Republic of Serbia between 2005 and 2011[151]. Recently, a study describing self-reported hypertension treatment among primary care physicians in central and eastern European countries concluded that >90% of physicians in all the countries prescribed ACEIs as the drug of first choice in the treatment of hypertension[152].

Similarly, a substantial increase in ACEIs/ARBs utilisation was observed in the UK. In a study conducted by Serumaga *et al* (2010)[153] to evaluate the impact of QoF and updated NICE guidelines on the management of hypertension in the UK primary care setting, a significant increase of ~34% in the utilisation of ACEIs/ARBs between 2000 and 2007 was found, especially after the implementation of QoF in 2004 and NICE guidelines in 2006[153].

Furthermore, the NHS Business Services Authority reported a 66% increase in the prescriptions for ACEIs/ARBs to 13.4 million items in primary care in England, over a five-year period from June/2004 to June/2009[154], with 9.5 million items for

ACEIs and 3.6 million items for ARBs. In contrast to the observed increase in utilisation, the report indicated a 27% reduction in ACEIs/ARBs cost over the same period to £93 million[154]. Although the number of ACEIs items was about 2.5 times that of ARBs in the quarter to June 2009, the ACEIs cost was approximately only a third of the ARBs cost (£24.26 million versus £68.31 million). Overall, the NHS of England spent approximately £277 million on ARBs in 2009 making these drugs the fourth highest costly drugs[155]. Whereas in Scotland, about £26.27 million was spent on ARBs, making them the seventh most expensive drug class[156].

Moreover, the Health and Social Care Information Centre of the UK in its Prescription Cost Analysis of the England-2011 report indicated ACEIs/ARBs as being the second most commonly prescribed drug class in English primary care, accounting for 6% of all prescribed drugs[157]. Recently, a longitudinal study investigating the association between acute kidney injury hospital admission and increase in ACEIs/ARBs utilisation, using data from NHS Prescription Services Prescribing Database from April 2007 to March 2011, found a significant 16% increase in the utilisation of ACEIs/ARBs[158].

This global increase in the utilisation of ACEIs/ARBs may be related, at least partly, to the many evidence-base indications for the effectiveness of this class of drug and their recommendations by several guidelines for the treatment of various long-term conditions, including hypertension, HF, DM, chronic kidney disease and post MI. Furthermore, the utilisation of ACEIs and ARBs was expected to continue to increase in the future[61], driven by many factors, including their clinical efficacy in the management of various medical conditions, their

satisfactory safety profile[137, 138], continuous increase in the prevalence of cardiovascular diseases and diabetes, expanding the indications of these medications, and decrease in cardiovascular mortality, which leads to longer use of these drugs[61, 150].

2.6. Selection of ACEIs versus ARBs

When drugs affecting RAAS are selected, the decision of whether to prescribe ACEIs or ARBs as the first-line drug should be guided by efficacy, safety, patient factors and cost as is the case in any other therapeutic area[159]. In terms of efficacy and safety, as shown earlier, there is no evidence to suggest the superiority of ARBs over ACEIs in these two criteria. Whereas, for patient factors, ARBs are found to cause slightly lower incidence of cough, with only 3.1% difference in the incidence of cough compared with ACEIs in the ONTARGET trial[134]; however, with no relevant differences in dosing regimens or monitoring requirements[139, 160].

In terms of cost, ACEIs are considerably cheaper than ARBs as they are available widely as generics. The cost differential between ACEIs and ARBs, however, has been decreased recently due to the availability of certain ARBs as generics (losartan, candesartan, irbesartan, valsartan), although it may take some years before several ARBs become available at similar costs to the current generic ACEIs costs[139].

Indeed, this can be clearly observed if comparing the monthly cost of the equivalent maintenance dose of the most commonly prescribed ACEI, ramipril, to that of generic ARBs[161] (Table 2.2). Even more than four years after its launch as

generic in July 2010, the cost of 28-day treatment of losartan is still about 14% higher than that of ramipril. Nevertheless, the cost of 28-day candesartan, which came off patent in April 2012, is about 75.9% higher in comparison with ramipril, despite more than two years since its availability as generic. Likewise, irbesartan has a 28-day cost 99.1% higher than that of ramipril despite its availability as a generic in 2013. Notably, the cost of 28-day treatment of valsartan is considerably more expensive than ramipril despite it came off patent in 2011.

Table 2.2 The cost of 28-day treatment of the equivalent maintenance dose of ramipril in comparison with that of available generic ARBs

Drug class	Drug name	Equivalent maintenance dose (mg)[161]	Cost of 28-day treatment (£)[160]	% Cost difference
ACEIs	Ramipril	5	1.12	Not applicable
ARBs	Losartan	100	1.27	13.7
ARBs	Candesartan	16	1.97	75.9
ARBs	Irbesartan	300	2.23	99.1
ARBs	Valsartan	160	18.41	15-fold

2.7. Policies to enhance ACEIs/ARBs prescribing efficiency in Europe

Health authorities and insurance companies across Europe have targeted the prescribing of ARBs to ensure efficient ACEIs/ARBs prescribing through the initiation of multiple "supply-side" and "demand-side" measures[42, 156] (Table 2.1, page 17). The initiatives have ranged from simple measures such as educational activities, including prescribing guidance, academic detailing, and prescribing targets for ACEIs and ARBs alone or in combination with financial incentives[61, 73, 162], to more intensive measures such as prescribing restrictions[59, 61, 73, 162, 163], which limit ARBs only to patients intolerant of ACEIs.

The initiated measures have had various impacts on the utilisation and expenditure of ACEIs and ARBs in these European countries. The implemented measures have limited the utilisation of ARBs to various extents in the different European countries, with the utilisation of ARBs in 2007, as percentage of all RAAS drugs, being ~13% in Croatia, 17.5% in Scotland, 25% in Austria, 38% in Sweden and Spain, and 44% in Portugal[63]. Furthermore, Sweden has also initiated a prescribing restriction for ARBs in 2008, which further improved the prescribing efficacy of ACEIs/ARBs, with the proportion of patients initiated on ARBs as first-line treatment reduced by a relative percentage of 24%, compared with the previous year, just four months after the implementation of the restriction[73].

This limited utilisation of ARBs in these European countries resulted in a substantial improvement in ACEIs/ARBs prescribing efficiency such that despite a remarkable increase in ACEIs/ARBs utilisation between 2001 and 2007, their expenditure increased at a much lower rate, although lowering of the price of generic ACEIs likely played a role as well (Table 2.1, page 17).

For instance, despite an increase in ACEIs/ARBs utilisation of 69% in Austria, and 159% in Scotland, the total ACEIs/ARBs expenditure increased only by 23% and 11.5%, respectively[63]. In contrast, the limited initiated measures in Portugal, in comparison with the other countries, had a lower impact on ACEIs/ARBs efficient prescribing such that total ACEIs/ARBs expenditure increased by 41% between 2001 and 2007 despite a 72% increase in utilisation[63]. In Croatia, the implementation of multiple measures resulted in a 35% reduction in total

ACEIs/ARBs expenditure between 2001 and 2007 despite an 87% increase in utilisation[63].

The differences in ARBs utilisation patterns in Scotland, Spain and Sweden compared with that in Portugal illustrate and further confirm the fact that multiple intensive demand-side measures are typically required to change prescribing behaviour and improve prescribing efficiency as described previously (section 2.3). Likewise, the greater impact of prescribing restriction on limiting ARBs utilisation in Croatia versus Austria may also support the idea that the nature of prescribing restrictions, including intensity of their follow-up, does affect subsequent prescribing patterns[59]. This can be demonstrated in Croatia by further visiting of GPs with subsequent financial penalties on those suspected of abusing the ARBs prescribing restriction, by physicians from the Croatian Institute for Health Insurance[59].

2.8. Policies to enhance ACEIs/ARBs prescribing efficiency in the UK

2.8.1. Drug cost and NHS budget

Prior to describing the prescribing policies in the UK, it is essential to briefly describe the current financial situation of the NHS, which necessities such prescribing initiatives. Spending on drugs is the second largest area of spending in the NHS in the UK[164]. In 2006, about 752 million prescriptions were dispensed in England, which represents a 55% increase in comparison with the 485 million prescriptions dispensed in 1996. Data have shown that drug costs in primary care increased by 60% from £4.0 billion in 1996 to £8.2 billion in 2006, which represents about £22 million every day[70].

Furthermore, the National Audit Office in the UK expects further growth in spending on drugs in future driven mainly by the launch and uptake of new expensive treatment in the NHS, and the increase in prescription volume due to new opportunities for improving health via drugs promoted primarily by the new treatment guidelines[70]. In a recent analysis of NHS expenditure between 2010 and 2014[164], total spending on drugs in the NHS was found to have increased by 9% from £3.68 billion in 2011/12 to £4.02 billion in 2012/13, with a higher proportion of total operating cost being spent on drugs in 2012/13 compared with 2011/12.

Currently, the NHS is under intense fiscal and economic pressure and constraints, facing unprecedented financial challenges[164]. The recent analysis of NHS expenditure conducted by the Nuffield Trust[164] highlighted important key points about the current and future economic position of the NHS. The analysis suggested that the NHS lived within its means since 2010 with its financial status going through a period of comparative stability; however, 2013/14 data suggest that this status has not been sustained, and it will be increasingly hard for the system to manage this prolonged period of austerity given the almost constant budget of the NHS. Furthermore, the 2013/14 data indicated an overall financial deficit of more than £100 million with 66 NHS trusts being currently in deficit, which represents a 50% increase compared with 2012/13, in spite of national financial support of over £360 million from the Department of Health.

Additionally, further reduction in NHS finance is expected in 2014/15 and 2015/16[164]. NHS funding is expected to suffer a shortfall of about £30 billion by 2021[165], given the saving level in the NHS of 2% a year being well below the

NHS's target saving level of 4% a year, which is required to fill the financial gap. Equally important, NHS funding was found to grow at only 0.4% in real terms in 2014/15 and 2015/16[166]. In fact, it is this disparity in cost pressure and funding growth that contributes to NHS finance deterioration[167].

Therefore, in order for the NHS to continue providing the same high quality of care, it is crucial for it to become more productive using a wide range of opportunities, including efficient prescribing of medicines. In an analysis by Monitor[168] (a sector regulator for health services in England), it has been estimated that by 2021 a total recurrent productivity gain of £10.6–18.0 billion could be achieved, thereby reducing the £30 billion funding gap in NHS by 35–60%.

2.9. BCBV prescribing indicators

In response to the intense financial pressure in the NHS, the NHS Institute for Innovation and Improvement in the UK has established BCBV indicators to assist local NHS organisations to improve the quality of delivered healthcare and to efficiently use healthcare resources, through identifying potential areas for efficiency improvement[1]. Several indicators have been developed under this policy – clinical productivity, workforce and prescribing.

In April 2009, the NHS Institute for Innovation and Improvement released four BCBV prescribing indicators covering three therapeutic drug classes, including one related to drugs affecting RAAS (ACEIs and ARBs)[169]. The BCBV prescribing indicator for RAAS drugs was defined as the proportion of items written for ACEIs as a percentage of the total number of prescriptions for drugs affecting RAAS,

with the aim of ensuring prescribing efficiency of RAAS drugs through increased prescribing of low-cost RAAS drugs[169]. These indicators were voluntary and not linked to any financial incentives or enforcement.

The importance of the efficient prescribing of RAAS drugs in saving NHS money has been further emphasised by the Quality, Innovation, Productivity and Prevention (QIPP) programme, established in 2010[170]. QIPP is a national transformational programme for the NHS that aims to enhance the value of NHS money while maintaining or improving quality of provided care through the optimisation of medicines use[170]. The emphasis was demonstrated by identifying and including RAAS drugs as one of the key topic areas in the recent QIPP key therapeutic topics where maintaining or improving quality while improving value for money is a potential opportunity[171].

The BCBV prescribing indicators aim to assist NHS organisations and prescribers in reviewing their current prescribing appropriateness, revise prescribing when needed, and compare the prescribing pattern among NHS organisations to ensure the appropriate utilisation of lower cost drugs within each drug class.

2.9.1. The proposed target

Although the BCBV prescribing indicator for RAAS has not specified a particular percentage or proportion of ACEIs as a target, a proportion of at least 80% ACEIs has been suggested by NICE based on expert opinion[91]. This target of 80% is considered an achievable target[172] given the highest reported percentage of patients intolerant of ACEIs-induced dry cough in randomised trials is only 10%[132]. While the 80% target looks reasonable as it would preserve physicians'

and patients' choice and autonomy, the Office of Fair Trading (OFT) in the UK[173] suggested a target of 95% ACEIs. This was based on the fact that only 2–3% of patients in clinical trials actually stopped ACEIs due to a dry cough[140, 141] and OFT panel opinion that only ~5% of patients would stop ACEIs therapy due to the dry cough.

The BCBV prescribing indicator for RAAS could be a useful tool to compare the prescribing patterns of ACEIs and ARBs and highlight variations across NHS organisations throughout the UK[172]. Indeed, the prescribing pattern of ACEIs and ARBs has been shown to vary greatly across NHS organisations. The National Prescribing Centre (NPC) reported wide variations in the percentage of ACEIs items out of RAAS drugs across Primary Care Trusts (PCT), currently known as Clinical Commissioning Groups (CCGs), in 2009, with the best-performing PCTs having an ACEIs percentage of 79%, and the worst ~60%, which represents ~19% variation[172].

Furthermore, individual practice data shows even greater variations. In 2009, most of the practices had an ACEIs percentage level ranging between 65% and 80%, with only 11.5% of practices having a level >80%, 9% with a level <60%, and some ≤25%, which represents ~70% difference between the best- (90%) and worst- (25%) performing practices in terms of ACEIs prescribing[172].

However, even approximately three years after the establishment of the BCBV indicator, the variations continued to exist. By December 2011, the NHS Business Services Authority reported similar variations in prescribing patterns of ACEIs and ARBs across NHS organisations with the highest ACEIs percentage

value of 72.8% in North East PCTs and the lowest value of 67.7% in South East Coast PCTs, which represents an inter-regional gap of 5.1%[174]. Likewise, recent CCG data for the quarter April–June 2014 indicated 1.3-fold variations in the level of ACEIs percentage across CCGs from 61.3% to 77.3%, with an increase of 1.6% in the variation between CCGs as measured by the inter-decile range (the difference between the highest and lowest ACEIs percentage levels after the removal of the highest and lowest 10%)[175].

2.9.2. Potential cost savings

The efficient prescribing of RAAS drugs, promoted by the implementation of the BCBV prescribing indicator, is expected to incur potential cost saving to the NHS. In fact, the essence of the BCBV prescribing indicator was the reported saving figures from the National Audit Office (NAO) report about the cost of primary care in the UK in 2007[70]. The report estimated a potential cost saving of more than £200 million a year, without compromising quality of care, through efficient prescribing of four therapeutic drug classes (statins, proton pump inhibitors, RAAS drugs and clopidogrel) via prescribing of lower cost drugs with equivalent effectiveness among these four drug classes. The report estimated a saving of £67 million a year just from efficient prescribing of RAAS drugs.

Furthermore, the NAO reported a saving of £443 million in 2009 compared with 2005 through efficient prescribing of the four drug classes. Moreover, Moon *et al* (2010)[155] had suggested yet greater saving of >£1 billion from the most cost-effective use of the top ten most expensive drug classes in the NHS in 2009, including RAAS drugs. Furthermore, the NPC of England estimated a potential annual future saving in RAAS drugs ranging from £68 million to £149 million if the

ACEIs prescription proportion increased from 70% in 2009 to 80% and 90%, respectively[172]. However, neither the potential cost saving of the BCBV indicator for ACEIs/ARBs nor its impact on ACEIs/ARBs utilisation has been fully examined.

2.9.3. Influence of generic ARBs on the BCBV prescribing indicator's incurred saving

Since the issue of the BCBV prescribing indicator for ACEIs/ARBs in April 2009, several ARBs (losartan, candesartan, irbesartan, valsartan) came out of patent in the UK and subsequently, low-cost generic versions of them became available. Generic losartan became available in July 2010; generic valsartan and irbesartan became available after March 2012[176, 177]; whereas candesartan became available as generic after March 2014[160]. Accordingly, the cost of these ARBs decreased dramatically and the cost differential between ACEIs and ARBs started to diminish; although, as described in section 2.6, the cost of ACEIs is still much lower than that of generically available ARBs (Table 2.2, page 39).

Therefore, arguably, it might be reasonable to assume the BCBV prescribing indicator is not necessary, given the reduction in the cost differential between ACEIs and ARBs. However, the impact of the availability of generic ARBs on the potential cost saving of achieving the 80% ACEIs target of the BCBV indicator is not yet known and needs to be determined prior to any assumptions being made.

On the basis of losing the cost differential of ACEIs over ARBs, McInnes (2013)[178] has argued that ARBs should replace ACEIs as the first-line therapy for hypertension treatment, which may indirectly suggest no further requirement for

the BCBV indicator. However, this theoretical argument may not be translated into action in real life with NICE continuing to advocate both ACEIs and low-cost ARBs as a first-line medical treatment for hypertension[91].

Furthermore, re-emphasis on the efficient prescribing of ACEIs/ARBs with ACEIs as first-line treatment is continued by the Medicines and Prescribing Centre at NICE in their recently published Key Therapeutic Topics[179], whereby they continue to consider prescribing RAAS drugs as a potential area for achieving the best value for money for the NHS while maintaining or improving quality of care. This re-emphasis is despite the availability of several generic ARBs, which suggests the continued importance of considering the efficient prescribing of ACEIs/ARBs.

2.9.4. Potential issues with implementation of the BCBV prescribing indicator for RAAS

For the BCBV prescribing indicator for RAAS to achieve efficiency saving and improve the value for money, GPs need to change their prescribing behaviour. In practice, this would entail starting new patients on ACEIs and switching existing patients from ARBs to ACEIs, where appropriate. However, introducing changes to prescribing in this area would not be straightforward[4]. For new patients, it may be easy to start with ACEIs. However, switching patients already on ARBs, whose condition is managed and stabilised by ARBs, is more difficult – it may not be appropriate for all patients and should be tested against the principle of patient-centred care ("no decision about me, without me")[180]. Therefore, one of the possible issues with implementing the BCBV indicator would be around patients switching from ARBs to ACEIs for economic reasons.

Two medicinal products are considered therapeutic equivalents only if they are pharmaceutical equivalent and are expected to demonstrate same clinical and safety profile when administered to patients with the conditions specified in the labelling[181]. Switching of ARBs to ACEIs is a type of therapeutic switching between classes, which encompasses switching between two classes with different active chemical entities and mechanism of actions, but that are assumed to be therapeutically equivalent[2, 3]. The switching process is considered to be valid and successful only if certain key assumptions are achieved, including true therapeutic equivalence between the two classes regarding overall patient outcomes, and active involvement of patients and prescribers[2].

However, switching of ARBs to ACEIs in well-controlled and stabilised patients for a cost-containment purpose is often challenging because factors such as patients' choice and lack of proven therapeutic equivalence play an essential role in the treatment effectiveness and thus overall patient management. In fact, the efficacy and safety of practicing therapeutic switching for economic reasons in the absence of side effects have never been investigated thoroughly in large clinical trials[3].

There are several issues that may arise from the switching process, which could negatively affect the switching success and hence patients' clinical outcomes. These issues are common to all kinds of therapeutic switching and include clinical issues and issues related to the impact of the switching on overall resource use and cost.

2.9.4.1. Clinical issues associated with therapeutic switching

One of the arguable concerns about therapeutic switching is whether the clinical effectiveness and safety would be maintained or not after the switching[3]. Many factors have been reported to potentially affect the maintenance of clinical effectiveness and safety, including lack of guidance for implementing the switching, lack of clinical equivalence and impedance of patients' adherence[2, 3, 182].

2.9.4.1.1. Lack of guidance on implementing switching

Currently, there is poor guidance for GPs and pharmacists on switching antihypertensive drugs, including switching ARBs to ACEIs[3], with the absence of officially published guidance[183] in terms of dose equivalence to ensure the maintenance of BP control after the switching. However, healthcare authorities may provide some guidance in terms of dose equivalence and product selection[161, 184]. For instance, the Leicestershire Medicines Strategy Group[184] issued a protocol guidance for ACEIs/ARBs choices for primary care, including the review of ARBs prescribing and recommended switching patients using ARBs for hypertension, but not for heart failure, diabetes or renal protection, with the provision of guidance on dose equivalence, product selection and monitoring schedule.

Given the substantial variations in individual patient responses to antihypertensive medications and the absence of evidence-based switching guidance, it is likely that the new switched drug would often be started at low doses and titrated upwards. This in turn thus may result in delay of regaining BP control, which could negatively affect patients' clinical outcomes, in particular, in

patients at high cardiovascular risk[3]. It has been demonstrated that loss of BP control even for few weeks or months was associated with a greater risk of stroke by 15%, MI by 19% and death by 4% compared with those who had adequately controlled BP[185].

Furthermore, a randomised study reported that using a stepwise add-on approach for treating hypertension resulted in a better BP control in the first three months of antihypertensive drug therapy when compared with an approach that allowed for drug switching[186]. This suggests that switching of antihypertensive drugs may delay achieving BP control[3]; thus switching often has inherent risks of losing BP control in otherwise well-controlled patients, which in turn could significantly enhance their cardiovascular risks[187].

2.9.4.1.2. Lack of evidence on clinical equivalence

Another factor to consider in therapeutic switching, including ARBs switching to ACEIs, is the level of available evidence for the equivalence in the safety and effectiveness of the switched medications, because different drug classes may have different licensed indications, in particular, for patients with comorbidities and cardiovascular risk factors[3]. While antihypertensive drugs may have similar effects on surrogate markers such as BP, similar effects on patients' clinical outcomes should not be assumed, unless evidence supports such similarities[2].

Regarding the clinical equivalence of ARBs and ACEIs, as described in section 2.5.4 (page 26), there is good-quality evidence for the equal efficacy of ACEIs and ARBs in reducing BP and clinical outcomes in patients with hypertension, which is in accordance with NICE guideline recommendations for treating

hypertension[91]. However, such level of evidence of the equivalence of ACEIs and ARBs on clinical outcomes may not be available when indicated for conditions other than hypertension, including heart failure[188] and diabetes[189], which favour the superiority of ACEIs over ARBs. This has been emphasised in NICE guideline recommendations for treating heart failure[110] and diabetes[112, 113], which recommended ACEIs as first-line treatment while preserving ARBs for patients intolerant of ACEIs. Accordingly, since in all conditions, ACEIs have either similar or better efficacy than ARBs, the notion of clinical equivalence in switching ARBs to ACEIs may not be an issue. However, patients' clinical condition, comorbidities and drugs' licensed indications should all be considered before deciding on the therapeutic switching of ARBs to ACEIs.

2.9.4.1.3. Impedance of patients' adherence

Non-adherence to prescribed medications is another potential source for variations in clinical effectiveness associated with therapeutic switching[2, 182]. Suboptimal adherence to medication is frequently the primary contributing obstacle to the overall effectiveness of pharmacotherapy and variations in medication response[190], including antihypertensive medications. Research evidence has strongly illustrated the association of adherence to antihypertensive medications with BP control[191], reduction of cardiovascular risks[192, 193] and reduction in medical costs[194, 195]. Suboptimal adherence and persistence with antihypertensive medications have been shown to be associated with poor BP control, increased risk of cardiovascular events and medical costs[191, 196-198].

In general, adherence to and persistence with antihypertensive medications were found to be reduced following therapeutic switching of antihypertensive

medications[199-202], although none of the studies evaluated the switching of ARBs to ACEIs. Many potential factors associated with therapeutic switching may contribute to the demonstrated reduction in patients' adherence and persistence following the switching. Those factors include switching to a drug class with a lower adherence and persistence profile[2, 203], patients' confusion and fear associated with alterations in drugs' packaging, taste and/or appearance[204] and, and nocebo effect (negative outcomes as a result of patients' negative expectations toward switching)[205, 206].

Research has demonstrated significant variations in adherence and/or persistence patterns across the various antihypertensive drug classes, with the majority of the studies describing a higher adherence and persistence profile with ARBs followed by ACEIs[204, 207-214]. These findings have been primarily attributed to the better tolerability profile of ARBs and ACEIs in comparison with the other antihypertensive drug classes[204, 209, 210, 212, 215].

Findings from individual observational studies are often difficult to compare due to differences in patient populations, drug class comparisons, and lack of standard methods for defining and measuring adherence and persistence; therefore, the clinical relevance of any observed variations is unclear[203]. Furthermore, it has been argued that the better adherence and persistence profile of ARBs over the other antihypertensive drug classes, in particular, ACEIs, could be possibly due to unmeasured potential confounders[203, 216] or methodological issues related to defining and measuring adherence and persistence[217].

In a meta-analysis of 17 observational studies investigating the adherence across various antihypertensive drug classes, Kronish *et al* (2011)[203] quantified the association between adherence and antihypertensive drug classes and found significantly higher adherence rate with ARBs use compared with other drug classes, followed by ACEIs. However, after accounting for publication bias, adherence was not significantly different between ARBs and ACEIs (HR: 1.10, 95%CI: 0.94, 1.30).

More recently, in a retrospective study of over 36,000 new user hypertensive patients, Evans *et al* (2013)[216] found significant difference in adherence rate (≥80%) among antihypertensive drug classes, ranging from 67.3% for ARBs to 23.4% for diuretics. However, after restricting the analysis to medications that launched relatively at the same time, adherence to neither ACEIs (ramipril) nor CCBs (amlodipine) was significantly different from ARBs (losartan). Accordingly, the authors attributed the reported superiority in adherence of ARBs over ACEIs in the previous observational studies to failure of accounting for medications' market life as a major confounding factor, and pointed out that such better adherence could not be explained solely by the better tolerability profile of ARBs.

Likewise, in another retrospective study of about 51,000 incident users of ACEIs and ARBs with hypertension, Vegter *et al* (2011)[217] found similar adherence and persistence patterns between ARBs and ACEIs. The authors attributed their findings to censoring patients at the time of switching, an important methodological issue which the other observational studies failed to account for in their definition and measurement of adherence and persistence.

Although patients' adherence may not be impeded by switching to a drug class of lower adherence profile, assuming a similar tolerability profile between ARBs and ACEIs, adherence still could be negatively affected by alterations in product packaging, appearance and/or taste or due to nocebo effect[218]. Many studies illustrated an increase in the reporting of side effects or negative experiences by patients following therapeutic switching of their medication[219, 220], which could negatively affect patients' adherence to the new switched-to medicine.

Patients' confusion and anxiety has been reported to result from changes in product packaging and tablet appearance, especially in the elderly, due to a switch of their medications, which may negatively affect patients' medication-taking behaviour and thus may expose them to higher cardiovascular risk[3, 204, 221]. Similar to therapeutic switching of atorvastatin to simvastatin[222], switching of ARBs to ACEIs would be likely to involve generic switching in addition to therapeutic switching, which complicates the process even more, given some patients' beliefs and attitudes of inferiority of generic drugs compared with brand products[205], and not being as powerful as branded drugs[223].

In a survey of 804 patients, one-third of them were concerned about the efficacy and safety of generics and viewed them to be inferior to branded drugs[205]. Surveys of public and patients' views suggest variable opinions on therapeutic and generic switching. A survey of 194 patients (65% response rate) about their satisfaction with their generic switching indicated 83% agreement rate with the switching[224]. However, another survey of 240 patients (48.6% response rate) about their experiences and views on switching from atorvastatin to simvastatin

demonstrated that about a quarter of the participants were unhappy with the switching[222].

Therapeutic switching is considered to be more contentious than generic switching[182], as the former involves not only changing a drug's active ingredient but also the drug's appearance and packaging, while the latter only involves the last element. However, education and communication with patients have been reported to improve patients' acceptance and perceptions of the switching process; thus enhancing the opportunity of successful switching[202, 220]. In a systematic review on customers' views on generic drugs, communication with healthcare professionals to increase patients' understanding of generic drugs had a major positive effect on patients' views on the efficacy and safety of generics[225].

Shared decision making (i.e., involving patients in decisions about their treatment and care) is a crucial component of evidence-base medicine, whereby the best available evidence is used to guide decisions about individual patient's care, accounting for their preference, needs and values[226]. The principle of shared decision making is not a new concept in the UK[5]. Giving patients more choice is a priority in the NHS[227], prompted mainly by research evidence, which has shown better treatment effectiveness by enabling patients to choose, understand and control their care[182]. The NICE guidelines about medication adherence[228] highlight the importance of involving patients in decisions about prescribed medicine through the adoption of a patient-centred approach that encourages informed adherence.

Furthermore, the guidelines advised prescribers to find the most effective communication method with each individual patient to give them the opportunity to be involved in prescribing decisions and to understand their knowledge, beliefs and concerns about their condition and prescribed medicine, which would help to identify and overcome any barriers for their non-adherence to medication. The concepts of shared decision making and involving patients fully in their own care have been emphasised in the Department of Health's white paper Equality and excellence: liberating the NHS[180]. This concept of considering patients' choice and preference in GPs' clinical decisions, including prescribing decision, has been further stressed by the King's Fund report[229], which introduced the concept of "no decision about me, without me".

A patient's involvement in prescribing decisions also depends on their relationship with their GP. In the Department of Health's guidelines[230] for PCTs and CCGs on strategies to achieve cost-effective prescribing, including therapeutic switching, informing and involving patients in the switching process was considered one of the essential principles for any local strategy, and that patients should be given the opportunity to discuss the switching decision. Moreover, involving patients in prescribing decisions has been also emphasised by the General Medical Council[231], which stressed the necessity of considering patients' needs, wishes and preferences as good practice in prescribing medicines.

In summary, given the lack of research about the direct impact of switching ARBs to ACEIs on patients' adherence and persistence, the conflicting results about the better adherence profile of ARBs over ACEIs, and the potential involvement of

patients in the switching decision, it is hard to predict whether the reported reduction in patients' adherence following switching of antihypertensive drugs is applicable to ARBs switching to ACEIs. Further studies, therefore, are required to assess whether switching ARBs to ACEIs affects patients' adherence in the UK setting.

2.9.4.2. Impact of therapeutic switching on overall costs and resource utilisation

Medication switching can be considered a cost-containment approach only if the potential cost saving from switching outweighs the costs of required healthcare resources to implement the switching[3]. While drug acquisition costs are undoubtedly lowered by switching to a medication with a lower acquisition cost, it has been argued that the generated cost saving from switching could be potentially offset by spending in other areas[2].

Potential sources of offsetting costs include costs incurred either in the switching process or as a consequence of switching, which includes costs required for implementing the switching and managing its consequences, costs resulting from the negative impact of switching on patients' satisfaction and adherence to switched-to medication, and costs incurred from lower safety and efficacy profile of the switched-to medication compared with the original choice. For instance, costs could be incurred from administration work, additional visits to GP practice for dose titration or follow-up, extra laboratory tests, and hospitalisation possibly as a result of inadequate control of a patient's condition by the switched-to drug. This action of saving money in one area, but with a subsequent increase in

spending elsewhere, known as "squeezing the balloon"[232], could distort the overall economic benefits of switching, unless all potential costs are included.

Association of switching antihypertensive drugs with additional resource utilisation has been investigated by many studies[200, 233-237], and switching was shown to incur additional direct medical costs. A retrospective study evaluated the economic impact of switching patients from patent ARB (valsartan) to other generic ARBs, and found a significant increase in medication discontinuation, healthcare resource utilisation (outpatient visits and hospitalisations) and medical costs in the switched group compared with the maintainer group[233]. Likewise, Thayer and Dastani (2009)[200] found that patients who switched between ARBs incurred significantly greater all-cause medical costs in comparison with non-switchers.

Furthermore, additional patient visits to GP practices were also found to be associated with switching antihypertensive drugs. In a study evaluating the short-term costs associated with therapeutic switching within ACEIs class (from enalapril to lisinopril)[235], one additional follow-up visit, at least, was needed, with 24% of patients needing a second visit. In addition, other sources of extra costs were also identified and included laboratory tests, staff time and telephone contact with patients. Accordingly, the authors concluded that the additional costs associated with the switching would need up to 17 months to counterbalance the cost saving obtained from reduction in the drug acquisition costs. Therapeutic switching often requires dose titration, as demonstrated by a study[238], which reported that ~44% of patients who switched their CCBs to CCBs/diuretic combination required one dose titration, while 16% required two.

Regarding the long-term impact of antihypertensive drug switching, additional healthcare resources could be utilised such as hospitalisation and emergency visits, possibly because of inadequate BP control after switching. Murawski and Abdelgawad (2005)[239] evaluated the impact of switching, as a result of implementing a preferred drug list policy, on hospitalisation and costs incurred a year following the switching. The authors noticed significant increase in the number of patient visits to the GP, hospital and outpatient clinics in those who switched compared with non-switchers, to address either failure of the treatment or side effects following the switching. Accordingly, the authors estimated that an additional cost of $219–242 per patient would be incurred in those patients who switched.

Therefore, given all the possible clinical issues and sources of incurring additional costs, in practice, the potential benefits and costs of therapeutic switching should be assessed carefully. Subsequently, therapeutic switching should be implemented only after careful consideration of the switched-to drug's clinical equivalence and suitability for individual patients, having accounted for the patient's comorbidities and previous medication history. The effect of possible drug therapy interruptions because of the need for dose titration or adherence impedance, due to the patient's dissatisfaction with the switching or intolerability, should also be considered.

Finally, careful analysis of potential costs incurred due to switching is also required, since switching would be likely to incur additional costs in other sectors of the healthcare system which may offset the cost saving from switching to a drug with a lower drug acquisition cost. Despite these issues, it has been

reported that cost-effectiveness analyses of therapeutic switching rarely consider costs other than drug acquisition costs and presume equivalent efficacy without side effects, but without supporting evidence[240-242].

It is important to mention that all the previous studies were for therapeutic switching within a class and none of them, in fact, evaluated therapeutic switching of ARBs to ACEIs. Accordingly, the full clinical and economic consequences of therapeutic switching of ARBs and ACEIs have yet not been fully evaluated, with the current evidence of the overall clinical and economic implications being rather poor and scant.

However, one prospective cohort study investigated the clinical impact of switching patients from ARBs to ACEIs[183]. The study consisted of a pharmacy-led clinic in four GP practices within a PCT in England, in which ARBs constituted about 50% of the total RAAS drug prescription. Initially, patients taking ARBs were identified and those without a previous use of ACEIs were targeted for the switching. Eligible patients were sent a letter inviting them to attend the clinic for a medication consultation and BP control. Of the 499 patients who attended the clinic, 359 of them switched – mostly from candesartan or irbesartan to either ramipril or lisinopril – and the remaining patients either stayed on ARBs (n=116), or changed to another antihypertensive drug (n=24).

The switched patients were checked again after 8 weeks and one year to check their BP, renal function and adherence. During the follow-up time, 40 patients were intolerant to ACEIs and switched back to ARBs; hence, only 319 patients stayed on ACEIs at the end of the one-year follow-up. The results indicated a

significant reduction in both systolic and diastolic BP in those patients who switched to ACEIs compared with those who stayed on ARBs, which the author attributed partly to higher patient adherence and addition of further antihypertensive drugs. There was no incidence of any major cardiovascular events or death during follow-up period. Furthermore, the author reported a reduction of ~£39,000 in ARBs expenditure after accounting for the cost of implementing the switching, and demonstrated no clinical difference between ACEIs and ARBs on patients' outcomes and considered this kind of switching strategy an effective approach to alleviate the financial tension on the NHS.

However, a number of major limitations need to be considered, and thus the findings need to be interpreted with caution. Firstly, data on patients' characteristics are lacking and the author did not account for any confounders in the analyses, which would likely bias the study results and dispute their validity and credibility. Furthermore, the effect of adding antihypertensive drugs on BP control was not accounted for in the analysis, which could also bias the study results. Despite these flaws, the patients were followed for only one year; hence, the long-term effect of the switching on BP control and hypertension-related complications, which often take a long period of time to develop, was unknown.

Additionally, the study included only drug acquisition costs and cost of the staff implementing the switching, without considering other sources of incurring cost such as additional clinic visits, extra laboratory tests and possibly hospitalisations. Therefore, the study failed to demonstrate a complete picture of the full clinical and economic implications of switching ARBs to ACEIs for non-medical reasons. As a result, further research in this field is required to explore

the clinical and economic consequences of switching patients from ARBs to ACEIs, especially in the absence of any medical reasons for the switching.

2.10. Research questions

Although the BCBV prescribing indicator for ACEIs/ARBs was expected to have a substantial cost-saving impact through improving prescribing efficiency of ACEIs/ARBs, neither its impact on ACEIs/ARBs utilisation patterns nor its implementation and thus its cost-saving implications are yet completely known. Importantly, evidence suggests that single prescribing measures are often ineffective in changing GPs' prescribing behaviour. Furthermore, it is unclear whether patients' switching from ARBs to ACEIs would negatively affect patients' clinical outcomes and whether the resulting cost saving from drug acquisition cost would be offset by incurring additional costs elsewhere.

Therefore, this research outcome focused on the policy measure of the BCBV on ACEI/ARB utilisation and the subsequent effects on overall medical expenditure and quality of care in hypertensive patients, including blood pressure control and incidence of hypertension-related complications. In addition, policy implementation in real practice was evaluated to identify the most important motivators or barriers to the policy implementation.

The research questions were categorised into four areas:

(1) Current utilisation trend of ACEIs and ARBs:

What is the utilisation trend (number of prescriptions, defined daily dose and drug cost) of ACEIs and ARBs?

(2) Impact of the implementation of the BCBV indicator for ACEIs and ARBs (on aggregate level):

What was the impact of the implementation of the BCBV indicator on the utilisation and cost saving of ACEIs/ARBs drugs among hypertensive patients?

What is the potential impact of the availability of low-cost generic ARBs on the BCBV-mediated cost saving?

(3) Impact of the implementation of the BCBV indicator for ACEIs and ARBs (at patient level):

What is the utilisation pattern of ACEIs and ARBs for individual patients (adherence, persistence and switching)?

What are the factors associated with patients' adherence, persistence and switching of ACEIs/ARBs?

What is the impact of patients' switching from ARBs to ACEIs on blood pressure control and incidence of hypertension-related complications?

Is the generated cost saving from the switching of ARBs to cheaper ACEIs translated into an overall cost saving in medical expenditure?

(4) Implementation of the BCBV indicator

How has the BCBV prescribing indicator for ACEIs/ARBs been implemented in primary care?

2.11. Aims and objectives

This PhD study aimed to evaluate the implementation and impact of BCBV prescribing policy for ACEIs/ARBs on drug utilisation, prescribing patterns, medical expenditure and clinical outcomes in the UK, with emphasis on ACEIs

and ARBs in treating hypertension in a primary care setting. The objectives of this study are:

(1) To assess the impact of the BCBV on the current utilisation trend of ACEIs and ARBs

(2) To evaluate the drug utilisation patterns of ACEIs/ARBs at an individual patient level

(3) To assess the impact of patients' switching from ARBs to ACEIs on clinical outcomes and overall medical expenditure among patients with hypertension

(4) To explore the extent of BCBV policy implementation in clinical practice by understanding the attitudes and perceptions of GPs, in order to support and explain the quantitative findings obtained from the analyses of secondary datasets

2.12. Rationale for the mixed-method approach used in this thesis

In order to appropriately answer the research questions and achieve the aims and objectives, a mixed-method approach was adapted and used in this thesis. The rationale for conducting the mixed-method approach is to utilise the advantages and strengths of both quantitative and qualitative approaches to study complex social and health issues, because a single approach may not provide insights into the complete picture[243]. There are six mixed-method designs depending on the following four key characteristics of mixed quantitative and qualitative studies: i) the level of interaction between the studies, ii) the relative priority of the two studies, iii) the time of conducting the both studies and iv) the procedure for mixing the two studies[244].

In this thesis, both quantitative and qualitative methods were used because explanations of the results were required. Accordingly, although the quantitative studies determined the impact of the BCBV indicator on prescribing efficiency of ACEIs/ARBs, the comprehensive and detailed understanding of how the policy was implemented and why the policy had worked/not worked would be lacking. Therefore, it was necessary to conduct a qualitative study to explain why the policy worked/did not work by identifying the potential facilitators/barriers for the policy's effectiveness/ineffectiveness through deep and thorough understanding of the policy implementation in real clinical practice.

This design in mixed-methods research is known as explanatory sequential design[244]. The procedures of conducting this kind of design included four steps. Firstly, designing and conducting the quantitative study that included data collection and analysis. Then, the specific quantitative results that require further explanation were identified, and these results helped in developing and refining the qualitative method, including qualitative research questions, participant selection and sampling procedures, and data collection and analysis protocol, i.e., the qualitative method was based on and built upon the quantitative results. This was followed by conducting the qualitative phase in terms of data collection and analysis. Finally, the extents and ways in which the qualitative results explained and added insights into the quantitative results are discussed and interpreted.

Chapter 3. Impact of the BCBV policy on the utilisation of ACEIs/ARBs

3.1. Introduction

The NHS in the UK is under intense financial pressure that necessitates substantial improvements in productivity across all sectors, including prescribing. In April 2009, the NHS released four new BCBV prescribing indicators, one of which targeted the prescribing of RAAS drugs with the emphasis on improving efficiency by promoting the prescribing of cheaper ACEIs instead of ARBs (Chapter 2).

The BCBV prescribing indicator aimed to assist NHS organisations and prescribers to review, compare and appropriately revise their prescribing patterns of RAAS drugs to ensure their efficient prescribing. Prescribing data showed a wide variation in the prescribing patterns of RAAS drugs across the individual NHS organisations at regional, PCT and GP practice levels, even years after the establishment of the BCBV indicator (Chapter 2, section 2.9.1, page 44). The existence of such variations across NHS organisations at all levels two years following the release of the BCBV indicator could indicate differences in implementation strategies adopted by various regions to promote the uptake of the BCBV indicator, as the policy was not linked originally to any central incentives or enforcements. For instance, some PCTs included the BCBV prescribing indicator for ACEIs prescription proportion in their prescribing incentive scheme[245-247].

When comparing the ACEIs prescription proportion data before the release of the BCBV indicator (March 2009) with that after the policy implementation (December 2011), there is a small reduction in the inter-region variations. However, it is not clear whether this reduction was related to the BCBV

indicator nor if there is variation in the effect of the policy across different regions. There has been no study, to date, that systematically evaluated the impact of this policy implementation on either the national or regional proportion of ACEIs prescribed.

Additionally, the BCBV indicator was estimated to produce a substantial cost saving to the NHS[70, 172]. However, the actual saving impact of the BCBV indicator remains unknown. Importantly, this cost-saving estimation was made prior to the availability of generic ARBs; therefore, it could be argued that those estimation figures would have been minimised due to the loss of the cost differential between ACEIs and ARBs, driven by the availability of low-cost generic ARBs. However, the cost of generic ACEIs is still much lower than generically available ARBs (section 2.6, Table 2.2, page 39), which would suggest the continued opportunity for potential cost saving from improving the efficiency of RAAS prescribing. Therefore, it is crucial to know the actual cost-saving impact of implementing the BCBV indicator, especially in the presence of low-cost generic ARBs.

3.2. Methods to evaluate the impact of healthcare policies

The types of study designs used to evaluate the impact of health interventions can be broadly grouped into randomised control trials (RCTs) and quasi-experimental designs (QE) (controlled before and after [CBA] design and interrupted time series analysis [ITS]).

RCTs are widely considered the gold standard design for measuring the impact of interventions and assessing the causality. However, they are seldom used in the field of health system and policy evaluation usually owing to logistic or ethical considerations, practical difficulties in randomising

interventions and small sample size issues[248]. Furthermore, the external validity and generalisability of findings from RCTs may be limited by certain factors such as the setting of the study, selected participants and the protocol used to implement the experiment[249]. Additionally, despite the wide scope of research questions that can be addressed by RCTs, limitation of resources often constrains the number of RCTs that can be conducted[250].

Therefore, other alternative study deigns are often used to evaluate policy interventions such as QE designs. QE studies refer to those studies that use exogenous variation in the exposure of interests without direct control by the researchers[250]. Similar to RCTs, QE studies aim to demonstrate causal relationship between an intervention and an outcome. The major weakness of QE studies in establishing causality is lack of random assignment; however, QE studies still fulfil two other important criteria for causality – identifying associations between an intervention and an outcome, and demonstrating significant statistical variation of the outcome with the intervention[248].

Furthermore, QE studies can provide evidence of causal relationships with better external validity than RCTs in many settings because, unlike RCTs, the investigated interventions are not controlled by researchers but rather are the results of policies or natural processes. Therefore, issues with external validity that are commonly found with RCTs are not so relevant to QE studies. In contrast to RCTs, the scope of research questions in QE studies is limited by natural processes that introduce exogenous variation in the exposure of interest as well as by availability of both exposure and outcome data. However, in many instances, QE studies use secondary administrative data, which limits the cost and increases the feasibility of the study[250].

QE studies include two main types of designs, CBA and ITS. In the simplest CBA design (also known as pre-post design), an outcome is measured at a single point or at multiple points but averaged to one measure before and after the intervention to identify whether a change occurred only in the group that received the intervention or in both the intervention and control groups[251]. However, the observed changes may be caused by factors other than the intervention – secular trend for instance – and in fact, deriving a valid causal inference from CBA studies requires the parallel trends assumption to be valid, which implies parallel trends of the outcome in both intervention and control groups in case of absence of the intervention. However, this assumption is often violated since unobserved confounders can still bias effect size estimates. Therefore, CBA studies are considered to have a weak quasi-experimental design[250].

ITS is being widely recommended and used in the biomedical sciences and public health for impact evaluation of an intervention or policy change and has been recognised as the strongest QE design alternative to RCTs when the latter are not feasible[252]. A time series is a set of multiple observations measured on an individual or a phenomenon at regularly spaced intervals over time. In a time series, segments are defined when the sequence of observations is split into two or more parts at change points. Change points are specific time points where the value of the time series may demonstrate a change from the previous baseline patterns due to an identifiable real-world event, or a policy change.

Interrupted time series is a term used to indicate a time series in which there is an identifiable event that may or may not cause a change in the secular trend of the values measured in a time series. Segmented regression analysis

is a method of modelling the interrupted time series data statistically to derive more formal conclusions regarding the impact of an intervention on the outcome of interest immediately after its implementation or over time[253]. In a reanalysis of data from eight cluster randomised trials, Fretheim *et al* (2015)[254] have shown that the interrupted time series design is considered a valuable alternative approach in evaluating health interventions when RCTs are not feasible as it provides estimates that are comparable with those obtained from cluster randomised trials. The strength and quality of evidence from QE studies depends on the study design[252]. Studies that include concurrent, non-equivalent control groups, and/or have several observations prior to the intervention, provide stronger evidence about the impact of an intervention than those without a control group and/or with fewer or no pre-intervention observations, respectively.

ITS is particularly convenient to analyse the impact of BCBV in the UK settings. Firstly, the intervention was evaluated retrospectively and implemented nationally because randomisation of subsets of the population to different policy options was not feasible. Therefore, observation designs such as ITS must be relied upon. ITS, unlike the CBA design, accounts for any underlying trends or seasonal patterns prior to the policy introduction and then quantifies accurately the impact of the BCBV indicator on the subsequent levels and trends of the outcome of interest. It has been pointed out that compared with CBA, having multiple measurements of an outcome before and after the introduction of an intervention provides a more sensitive tool for evaluating the potentially confounding effects of other factors over time[253]. Therefore, ITS is used in this chapter to evaluate the impact of the BCBV indicator of the utilisation and cost of ACEIs/ARBs.

3.3. Data source used for ITS

ITS requires data that are collected regularly over time and organised at equally spaced time intervals. Data about medication use, costs or other healthcare records that are collected and maintained routinely are the most commonly used source of time series data, such as pharmacy and medical databases. Although these data are not collected for research purposes, they often offer a reliable measure of outcome variable for time series studies of drug use. Outcome measures in time-series studies may include medication use and clinical outcomes, and can be expressed as averages, proportions or rates. Accordingly, the UK CPRD database was used this study as the main data source.

3.4. The CPRD database

The CPRD is a primary care database and contains anonymised longitudinal data collected from GP daily records in primary care including data on patients' demographics, medical history, clinical events, referrals to hospital and outpatient clinics, test results and prescriptions[255]. It is the largest primary care database in the UK that covers approximately 6.9% of the UK population[256]. In March 2015, it contained clinical records of more than 13.7 million acceptable patients and approximately 5.4 million active patients from 685 primary care practices across the UK[257]. A more detailed description of the CPRD in terms of data collection and quality, structure, applications, and strengths and weaknesses is provided in Appendix 1.

The representative feature of the CPRD population, and the well-documented prescription and clinical data with the ability of linking individual patient's clinical and medical information, as well as its linkage ability to secondary datasets, have made the CPRD optimal for analysing drug use data in relation

to patient characteristics and disease condition. Therefore, the CPRD dataset was selected and used to extract ACEIs/ARBs prescription utilisation data at regular intervals among patients with primary hypertension to produce time-series data to evaluate the impact of the BCBV indicator in this chapter.

3.5. Aims and objectives

This study aimed to evaluate the impact of implementing BCBV prescribing policy on the utilisation of ACEIs/ARBs as well as its cost-saving effects in adults with primary hypertension in UK primary care settings. The objectives were:

- To quantify the prescribing patterns of the six classes of antihypertensive drugs in adults with primary hypertension over time
- To evaluate the impact of BCBV policy on the prescribing of ACEIs/ARBs and the other antihypertensive drug classes and explore any regional variations
- To investigate the potential cost-saving impact of implementing the BCBV indicator and assess the impact of availability of low-cost generic ARBs on the policy's cost-saving consequences
- To validate the observed prescribing trends of all antihypertensive drug classes, by benchmarking with a national dispensing dataset

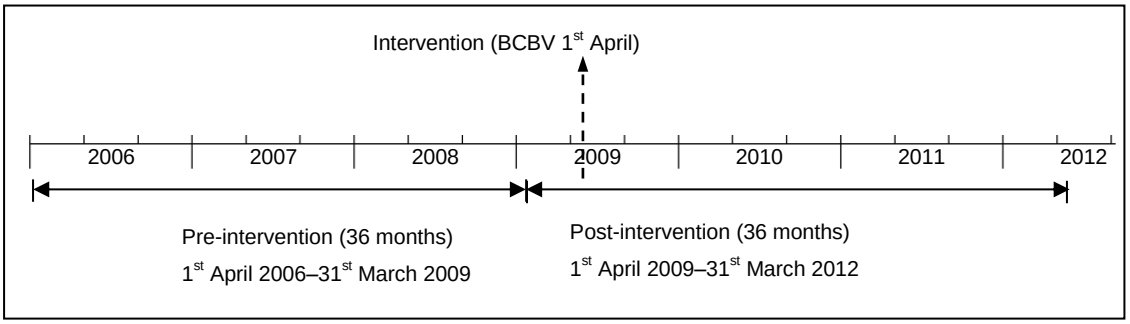
3.6. Method

3.6.1. Study design and data source

This cross-sectional study adopted a natural quasi-experimental design, an interrupted time-series study, to examine the impact of the BCBV prescribing indicator, using the UK CPRD database from April 2006 to March 2012. The time series in this study is a sequence of monthly measured variables for the prescribing and expenditure of ACEIs/ARBs and other antihypertensive drug

classes. The intervention (implementation of BCBV in April 2009) divides the time series into two equal segments of 36 months for the pre- and post-intervention periods (Figure 3.1). Both periods include sufficient data points for the time series analysis, and support the justification for seasonal variation.

Figure 3.1 Timeframe for the interrupted time-series study



3.7. Study subjects and data management

All antihypertensive prescriptions issued for adult (≥18 years old) patients with primary hypertension within the study period were included in the study. Patients with primary hypertension were identified from the clinical, referral and consultation files in CPRD using a list of diagnostic Read codes related to primary hypertension generated by using the inbuilt medical browser of CPRD (Appendix 2). Antihypertensive prescriptions issued during the study period were identified from the therapeutic file in CPRD using a list of British National Formulary (BNF) codes and drug substance codes generated by using the inbuilt product dictionary of the CPRD searching tool (Appendix 3).

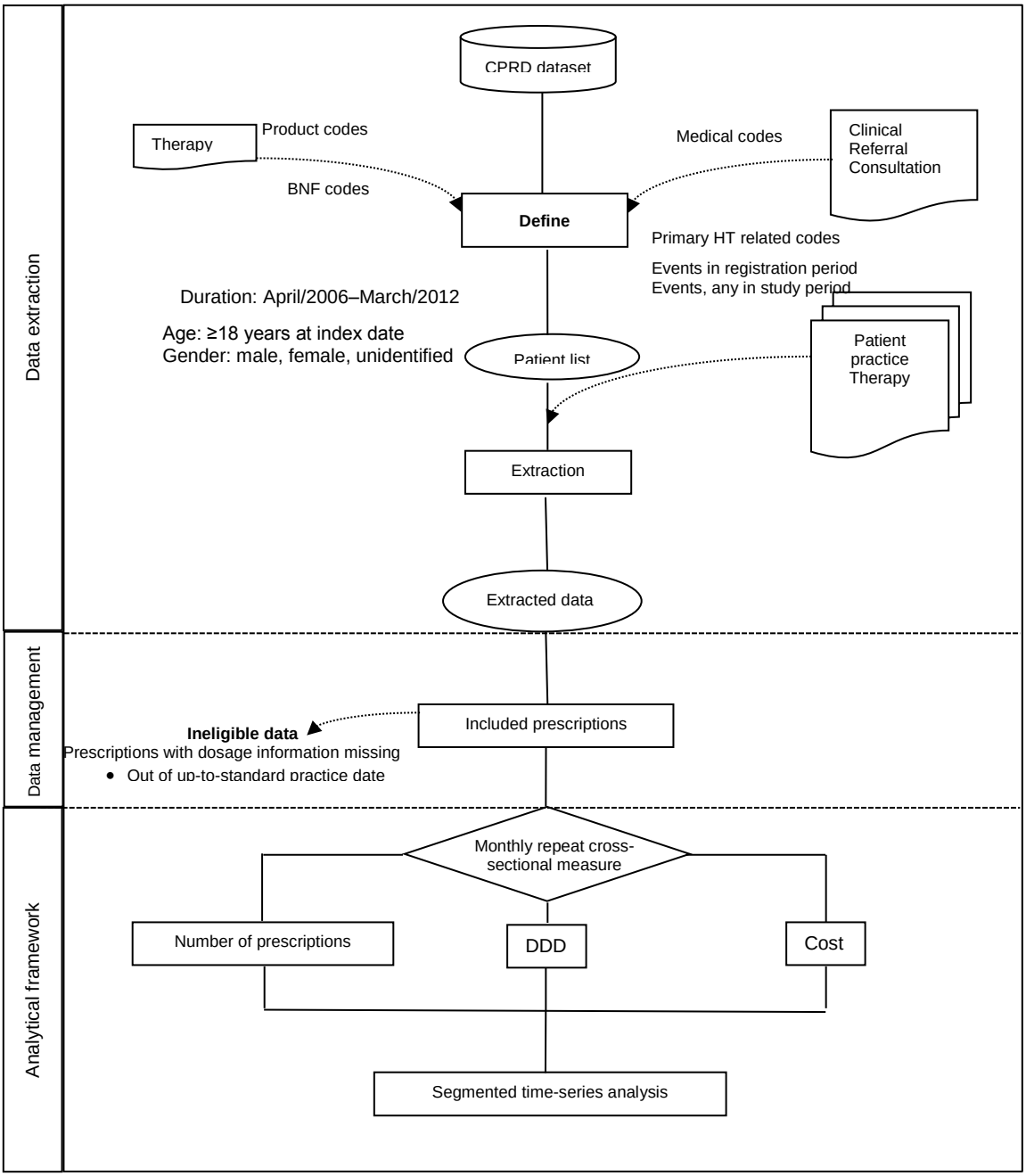
The antihypertensive drugs were first grouped into eight major classes according to the BNF, March 2012[176], including diuretics, beta-blockers (BB), centrally acting drugs, alpha-adrenoceptor blockers, ACEIs, calcium-channel blockers (CCB), ARBs and vasodilators. Thiazide, loop and potassium-

sparing diuretic drugs were collectively grouped as diuretics; whereas the less frequently used drugs (vasodilators, centrally acting drugs and alpha-adrenoceptor blockers) were grouped as “Others” in this study, thus giving a total of six classes. Drugs that are not indicated for the treatment of primary hypertension (e.g. sildenafil, ambrisentan and bosentan, which are vasodilators indicated for erectile dysfunction and pulmonary hypertension) were excluded in this study.

A list of patients with primary hypertension, who were prescribed at least one antihypertensive drug during the study period, was generated by combining both the prescription and patient identification criteria using the “define tool” in CPRD. Additional inclusion criteria, such as the study period (April 2006 to March 2012), age (≥18 years at the index date), gender (male, female or unidentified), events occurring in the registration period, and patients should experience the events such that the first event occurs during the study period, were also specified in the CPRD “define tool”.

Patient records were extracted from the patient, practice and therapy files by using the “extraction tool” in CPRD based on the patient identifier contained in the patient list generated from the “define tool” in the CPRD GOLD online data. All events prior to the up-to-standard practice date, i.e., the date before the practice proved to be of good quality for research purposes based on CPRD's data quality control criteria, were excluded due to poor data quality (Figure 3.2).

Figure 3.2 Data extraction and analytical framework for the cross-sectional study



The extracted data contained information on prescriptions, including prescription date, drug name, strength, quantity, numeric daily dose (NDD), and patient identifier that was used to analyse the use of antihypertensive drugs. NDD is the CPRD inbuilt numerical daily dose information derived from a CPRD algorithm on common dosage text instructions.

3.7.1. Study outcomes

3.7.1.1. Utilisation measures

Numbers of ACEIs and ARBs prescriptions were extracted monthly and then the monthly proportion of ACEIs prescriptions of all ACEIs/ARBs prescriptions (the target of the BCBV indicator) was calculated as the primary study outcome and stratified by the 13 regions in the UK. The total number of patients with primary hypertension and total number of antihypertensive prescriptions were also calculated and stratified by the 13 UK regions.

The prescribing of ACEIs/ARBs was measured using both numbers of prescriptions and number of defined daily dose (DDD)[258] repeatedly for each month. DDD is a standard measurement metric for drug utilisation and defined as the proposed average daily maintenance dose of drug used for its primary indication in adults based on the review of the available drug dose information from different countries[258]. DDD offers a constant unit of measurement regardless of cost, strength and package size.

During the study period, there were 11 ACEIs and seven ARBs available in the UK. Both single-strength ACEIs/ARBs and fixed-dose combinations (FDCs) of ACEIs/ARBs with other antihypertensive drugs were included in the analysis. Previous UK studies have shown that FDCs only accounted for <2% of total RAAS drugs[63, 156]. Number of prescriptions was used as the utilisation measure for ACEIs/ARBs because it is the key utilisation metric of primary care organisations in the UK[42] and has been used in the UK to calculate the BCBV indicators[1].

To ensure that any observed alterations in the trend of the number of prescriptions were real and not an artefact of changes in the number of

patients registered in CPRD, number of prescriptions was transformed and analysed as adjusted monthly number of prescriptions, which was calculated by dividing the number of prescriptions by hypertension prevalence in the same month. Monthly hypertension prevalence was in turn calculated by dividing the number of hypertensive patients by the number of active patients registered in CPRD in the same month.

Utilisation of ACEIs/ARBs was also measured using the number of prescribed DDDs as it is considered the international standard for the assessment of utilisation patterns within and between countries[259]. Prescription dose was calculated by multiplying the strength of the drug item by prescribed quantity. Number of DDDs was derived from dividing the prescription dose by the standard DDD for each drug item as determined by the World Health Organization Collaborating Centre for Drug Statistics and Methodology, based on the Anatomical Therapeutic Chemical classification system[260] (Table 3.1), in line with international guidelines[259, 261, 262], with the use of the WHO methodology for calculation of the DDDs for FDCs, which is based on counting FDCs as one dose[259]. Monthly DDD was then calculated by summing up the DDD for each prescription in a calendar month.

Table 3.1 Defined daily dose for the available ACEI/ARB drug items in the UK

ACEIs		ARBs	
Drug	**DDD (mg)[260]**	**Drug**	**DDD (mg)[260]**
Captopril	50	Candesartan	8
Cilazapril	2.5	Eprosartan	600
Enalapril	10	Losartan	50
Ramipril	10	Olmesartan	20
Quinapril	15	Telmisartan	40
Fosinopril	15	Valsartan	80
Lisinopril	10	Irbesartan	150
Imidapril	10		
Moexipril	15		
Trandolapril	2		
Perindopril	4		

3.7.1.2. ACEIs/ARBs expenditure

Prescription costs were calculated by multiplying prescribed quantities of ACEIs and ARBs by unit price obtained from the BNF, March 2012[176]. The 2012 unit price was used rather than historical annual prices to estimate the actual change in drug expenditure from the NHS perspective using the latest cost figures[263]. Any missing product price in the BNF was taken directly from the Drug Tariff (August 2012) and the Chemist and Druggist (February 2012). Any prescription with missing or outlier quantity (defined as more than twice the 99th percentile) was excluded (0.04%).

Additionally, the monthly proportion of ACEIs cost (defined as the proportion of ACEIs cost to total ACEIs/ARBs cost) was also calculated. For branded ACEIs/ARBs items (losartan, perindopril), which lost patency during the study period, patent unit price was applied to all those prescriptions that were issued prior to the off patent date (July 2010 for losartan, and October 2007 for perindopril).

3.7.1.3. Prediction of the potential cost saving of the BCBV policy

The estimation of potential cost saving had the 80% ACEIs BCBV target been achieved by the end of the study period in March 2012 (point calculation in March 2012) was also calculated. Firstly, total number of ACEIs/ARBs prescriptions in March 2012 was multiplied by 80% to calculate the predicted number of ACEIs prescriptions in March 2012, and then this was subtracted from total ACEIs/ARBs prescriptions to calculate the predicted number of ARBs prescriptions. Secondly, the predicted cost of ACEIs and ARBs prescriptions was calculated by multiplying the predicted number of ACEIs and ARBs prescriptions by the mean cost of ACEIs and ARBs per prescription in March 2012, respectively, which were then summed to calculate predicted total ACEIs/ARBs cost. The mean costs of single ACEIs and ARBs prescriptions were estimated by dividing the total cost of ACEIs and ARBs by their number of prescriptions in March 2012, respectively. Finally, the potential cost saving was calculated by subtracting total actual ACEIs/ARBs cost in March 2012 from the total predicted ACEIs/ARBs cost.

To estimate the impact of the availability of low-cost generic ARBs on the national potential cost saving of BCBV policy if the 80% target had been achieved in June 2014 (point calculation in June 2014), data from Prescription Cost Analysis (PCA) of England in June 2014 (dispensing dataset)[264] (the most up-to-date available data at the time of the study, which contains the number of antihypertensive drug prescriptions and their costs) were also analysed The potential cost saving was estimated using the same procedures described above.

3.8. Data analysis

3.8.1. Segmented time series analysis

Segmented regression (Appendix 4)[253] was used to analyse the time-series of monthly utilisation measures, including ACEIs prescription proportion, number of ACEIs and ARBs prescriptions, number of ACEIs and ARBs DDDs, and the cost of ACEIs and ARBs from April 2006 to March 2012. The analysis of ACEIs prescription proportion was stratified by the 13 UK regions.

The time before and after implementation of the BCBV policy in April 2009 was divided into two equal segments, 36 months pre- and post-intervention. The trends of utilisation (β_1) in the pre-intervention period, and any changes in the levels (β_2) and trends of utilisation (β_3) following the intervention were assessed and presented (Appendix 4)[253]. β_3 represents the change in the monthly outcome trend after the intervention, in comparison with the monthly trend before the intervention, and the sum of β_1 and β_3 gives the final slope of the post-intervention line. To control for potential confounders[265], the fitted models for all utilisation measures included the launch and time after the launch of generic perindopril in October 2007 and the launch and time after the launch of generic losartan in July 2010 in the final fitted model.

As time is a predictor (explanatory) variable in segmented regression, error terms of adjacent observations are often correlated (auto-correlated)[253]. Therefore, to obtain unbiased estimates for the intervention effect, the final fitted models were checked for autocorrelation in the residuals using an autocorrelation function graph[253] and the Portmanteau test[266], and any autocorrelation was adjusted for using Prais–Winsten regression and/or an auto-regressive integrated moving-average model[265]. The regression coefficients with 95% confidence intervals were presented for the most

parsimonious segmented regression model by excluding non-significant trend and level variables (p>0.05) using the stepwise backward elimination method[253], which involves fitting the model with all the possible variables, and then excluding non-significant trend and level variables (p>0.05) one at each time, and refitting the model until the most fitted model is achieved with all the significant terms in it.

Prior to the implementation of BCBV policy, the ACEIs prescription proportion was varied across the regions[267, 268]; therefore, the results of ACEIs prescription proportion's analysis for the 13 UK regions were grouped into high (>74%), intermediate (65–74%) and low (<65%) groups, based on the ACEIs prescription proportion in April 2006.

3.8.2. Estimating the potential impact of the BCBV indicator

Ideally, for the separation of the effect of BCBV policy from the effects of other policies that might have initiated at the same time, and thus obtaining the true BCBV effect, the impact of BCBV policy on ACEIs/ARBs prescribing should be compared into those in a “reference group” (i.e., a BCBV policy-free group). However, as the BCBV policy was implemented nationally it was not possible to identify a BCBV policy-free group. Instead, the prescribing of the other four major antihypertensive drug classes, i.e., diuretics, CCBs, beta-blockers (BBs) and “Others” (including vasodilators, centrally acting drugs, alpha-blockers), that should not be affected by the policy were used separately as reference (policy-free) groups[253, 265].

The results from the segmented regression analyses are presented in tables; whereas prescribing patterns over the study period are presented in figures to visualise the trends and policy impacts. For the figures, the first vertical line at

the 18th month of the study period indicates the time point when generic perindopril became available in October 2007; the second line at the 37th month indicates the time point when the BCBV policy was implemented in April 2009; the third line at the 51st month represents the time point when generic losartan became available in July 2010. The utilisation measures for the six antihypertensive drug classes are presented first, and then followed by more detailed ACEIs/ARBs-related outcome measures.

3.8.3. Validation of the study results

As the preliminary results of the study indicated an unusual reduction of the six antihypertensive drug classes after the implementation of BCBV policy in April 2009, three types of national datasets in the UK were used to validate the study results; this was to ensure that the observed results were correct and not due to mistakes in data management and/or analysis, and that they were reflective of national figures (Table 3.2).

The three national datasets were the monthly dispensing data of all GP practices in England downloaded from the Health and Social Care Information Centre (HSCIC) website[269], quarterly dispensing data for all antihypertensive drugs for all GP practices obtained directly by personal contact with the HSCIC team, and annual dispensing data obtained from the PCA report[267]. These datasets contain the number of prescriptions of antihypertensive drugs dispensed in the community in England; however, the annual dataset also contained information on the dispensed quantity for each item with strength, and thus allowed calculating numbers of DDD in addition to the number of prescriptions. Antihypertensive drug prescriptions were identified using the related BNF code for each drug category.

Table 3.2 Comparison of CPRD and the other external data sources

Characteristics	CPRD	PCA		
	Monthly level	**Monthly level**	**Quarterly level**	**Annual level**
Source	CPRD Gold online	HSCIC website	HSCIC website	NHS Business Services Authority
Settings	Primary care	Primary care	Primary care	Primary care
Duration	April/2006–March/2012	August/2010–March/2012	April/2006–March/2012	2007–2011
Prescription Covered	Prescribed prescriptions	Dispensed prescriptions	Dispensed prescriptions	Dispensed prescriptions
Population	6.9% of England population	Whole England population	Whole England population	Whole England population
Conditions	Primary hypertension	All conditions	All conditions	All conditions
Drugs	All antihypertensive drugs	All antihypertensive drugs	All antihypertensive drugs	All antihypertensive drugs
Utilisation measure	• Number of prescriptions • DDD • Spending	Number of prescriptions	Number of prescriptions	• Number of prescriptions • DDD
Conducting segmented regression?	Yes	No	Yes	No

(Note) **CPRD**: Clinical Practice Research Datalink; **DDD**: defined daily dose; **HSCIC**: Health and Social Care Information Centre **PCA**: Prescription cost analysis dataset.

For the validation procedure, segmented linear regression was conducted only on the quarter level data due to insufficient pre-, and post-intervention data points in the monthly and annual level data; in order to run a segmented linear regression, at least ten data points are required for each parameter in the model, as suggested by Kutner *et al* (2004)[270] and Eliopoulos *et al* (2007)[265].

3.9. Results

The impact of the BCBV prescribing indicator on the utilisation measures of the six antihypertensive drug classes is presented first, followed by impact of the policy on the prescribing and expenditure of ACEIs/ARBs. Finally, results from the validation analyses are presented.

3.9.1. Utilisation of the six antihypertensive drug classes

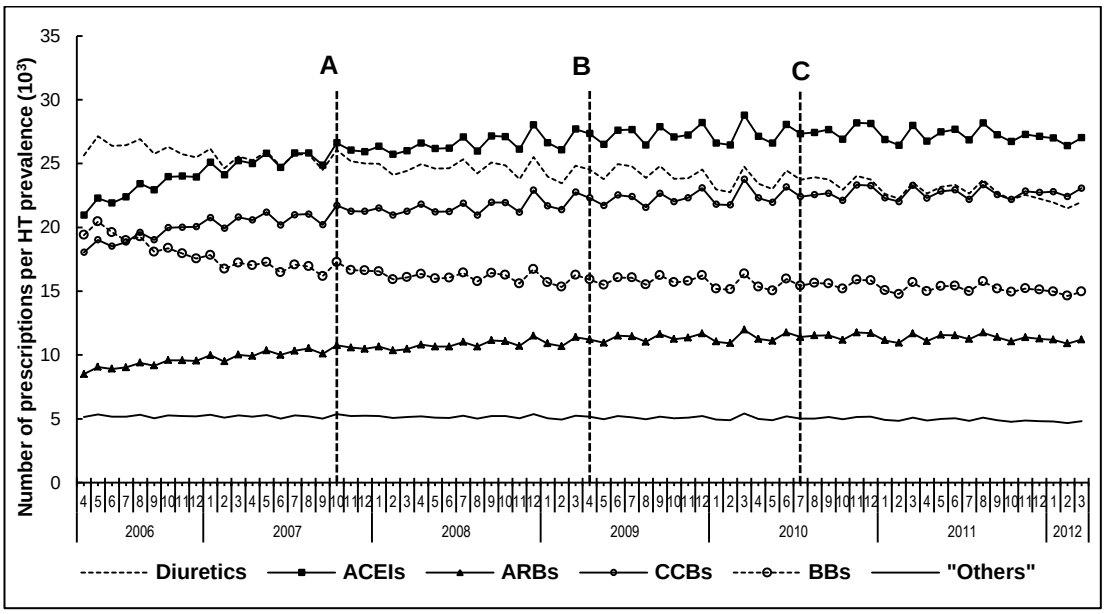
Impact of the policy on the number of prescriptions and DDD of the six antihypertensive drug classes is presented under this subheading.

3.9.1.1. Adjusted monthly number of prescriptions

A total of 44,371,726 prescriptions of the six classes of antihypertensive drugs were issued to 617,334 patients with primary hypertension during the study period. ACEIs were the most frequently prescribed antihypertensive drug class with 11,222,597 (25.3%) prescriptions, followed by diuretics (n=10,297,565, 23.3%), CCBs (n=9,245,498, 20.8%), BBs (n=6,873,068, 15.5%), ARBs (n=4,610,122, 10.4%) and “Others” (n=2,160,081, 4.9%).

In April 2006, diuretics were the most frequently prescribed antihypertensive drug class; however, by the end of the study period, ACEIs became the leading prescribed antihypertensive drug class (Figure 3.3). The adjusted number of prescriptions of ACEIs, ARBs and CCBs was increasing in the pre- and post-intervention segments, although the increase was less steep compared with the pre-intervention segment, but those of BBs remained fairly constant over time. By the end of the study period, adjusted number of prescriptions of ACEIs, ARBs and CCBs increased significantly by 28.9%, 31.9% and 27.8%, respectively.

Figure 3.3 Adjusted monthly number of prescriptions for the six classes of antihypertensive drugs from April 2006 to March 2012



(Note) A: time point when generic perindopril became available (October 2007); **B**: time point when BCBV policy was implemented April 2009); **C**: time point when generic losartan launched (July 2010); **ACEIs**: Angiotensin converting enzyme inhibitors; **ARBs**: Angiotensin receptor blockers; **CCBs**: Calcium channel blockers; **BBs**: Beta-blockers.

In the period prior to the BCBV implementation, the baseline trends (β_1) for the adjusted number of prescriptions of ACEIs (β_1: 135.7, 95%CI: 117.8, 153.6), ARBs (β_1: 65.9, 95%CI: 58.7, 72.0) and CCBs (β_1: 90.4, 95%CI: 77.0, 103.9) increased significantly (Table 3.3), but those of diuretics (β_1: –55.4, 95%CI: –61.9, –48.9), BBs (β_1: –102.7, 95%CI: –119.0, –86.5) and "Others" (β_1: –3.0, 95%CI: –4.9, –1.0) decreased significantly. The implementation of BCBV policy had no significant effect on the level of adjusted number of prescriptions (β_2) for all drug classes; but there was a significant reduction in the trends of adjusted number of prescriptions (β_3) for all drug classes thereafter, except for diuretics (Table 3.3).

Table 3.3 Parsimonious segmented linear regression analysis on the monthly adjusted number of prescriptions of the six antihypertensive drug classes from April 2006 to March 2012

	β_1 [(a)]	β_2 [(b)]	β_3 [(c)]	β_4 [(d)]	β_5 [(e)]	β_6 [(f)]	β_7 [(g)]
ACEIs	135.7 (117.8, 153.6)		–149.9 (–181.4, –118.4)	---	---	---	---
ARBs	65.9 (58.7, 72.0)	---	–67.2 (–79.8, –54.6)	---	---	---	---
Diuretics	–55.4 (–61.9, –48.9)	---	---	---	---	---	---
CCBs	90.4 (77.0, 103.9)	---	–77.4 (–101.1, –53.8)	---	---	---	---
BBs	–102.7 (–119.0, –86.5)	---	–75.3 (–98.3, –52.4)	---	---	---	---
"Others"	–3.0 (–4.9, –1.0)	---	–15.6 (–21.1, –10.1)	---	---	---	---

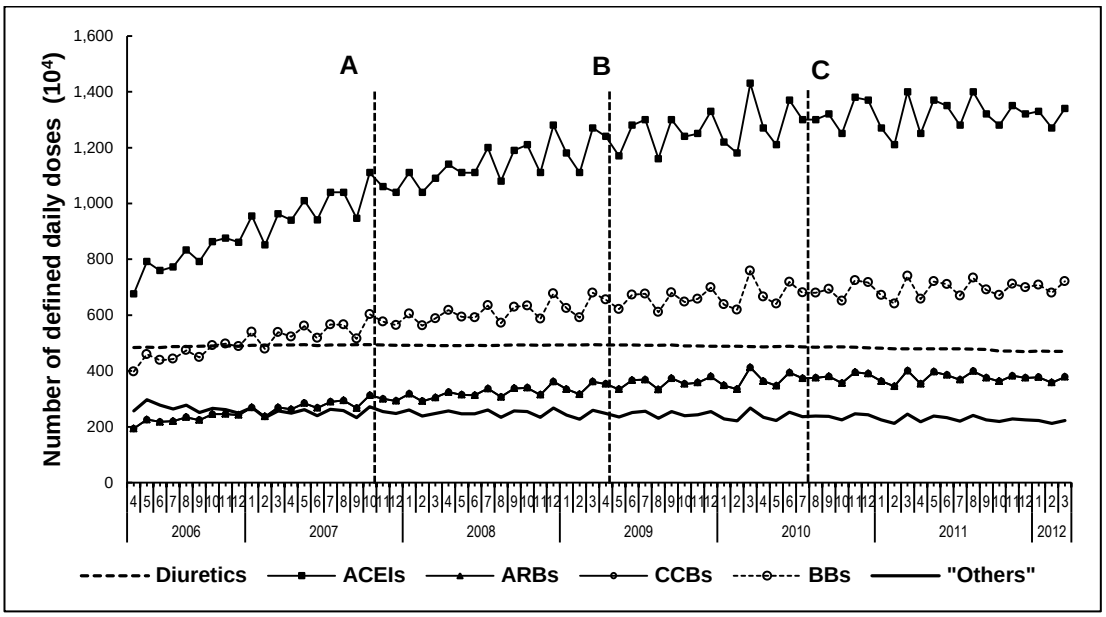
(Note) Regression coefficients (95% confidence intervals) for the final model (the most parsimonious models); [(a)] baseline trend; [(b)] level change following BCBV policy; [(c)] trend change following BCBV policy; [(d)] level change following generic losartan availability; [(e)] trend change following generic losartan availability; [(f)] level change following generic perindopril availability; [(g)] trend change following generic perindopril availability ---: indicates insignificant estimates at 0.05 level, after stepwise backward elimination; **ACEIs**: Angiotensin-converting enzyme inhibitors; **ARBs**: Angiotensin receptor blockers; **CCBs**: Calcium-channel blockers; **BBs**: Beta-blocker.

3.9.1.2. Defined daily dose

Overall, the 44,371,726 antihypertensive prescriptions accounted for 2,176,123,299 DDDs. ACEIs accounted for the highest DDDs of the six antihypertensive drug classes (38.1%, n=829,607,195), followed by CCBs (20.4%, n=443,968,693), diuretics (18.0%, n=390,642,531), ARBs (10.8%, n=235,848,025), BBs (8.1%, n=176,201,245) and “Others” (4.6%, n=99,855,610) (Figure 3.4). During the study period, there was a significant increase in the trends of the number of DDDs for ACEIs, ARBs, CCBs, “Others" and diuretics by an absolute increase of 98.1%, 95.4%, 81.4%, 26.4% and 9.0%, respectively; whereas that of BBs declined by 13.2%.

The results from the segmented regression analyses indicated a significant increase in the trends of number of DDDs (β_1) of all antihypertensive drug classes, except for BBs, which decreased significantly prior to the implementation of the BCBV policy (Table 3.4). Implementation of the BCBV policy had no instant effect on the levels (β_2) of number of DDDs of all antihypertensive drug classes. However, there was a significant reduction in the trends of number of DDDs (β_3) of all antihypertensive drug classes, except for BBs, thereafter in the post-policy period.

Figure 3.4 Monthly number of defined daily dose of the six antihypertensive drug classes from April 2006 to March 2012



(Note) A: time point when generic perindopril became available (October 2007); **B**: time point when BCBV policy was implemented April 2009); **C**: time point when generic losartan launched (July 2010); **ACEIs**: Angiotensin converting enzyme inhibitors; **ARBs**: Angiotensin receptor blockers; **CCBs**: Calcium channel blockers; **BBs**: Beta-blockers.

Table 3.4 Parsimonious segmented linear regression analysis on the monthly number of defined daily dose of the six antihypertensive drug classes from April 2006 to March 2012

	β_1 [a]	β_2 [b]	β_3 [c]	β_4 [d]	β_5 [e]	β_6 [f]	β_7 [g]
ACEIs	137,566 (123,143, 151,990)	---	–132,677 (–167,432, –97,921)	740,751 (701,33, 141,1369)	---	---	---
ARBs	39,947.9 (35,803.2, 44,092.5)	---	–40,369 (–50,356, –30,382)	253,481 (60,777.2, 446,184.9)	---	---	---
Diuretics	14,335.3 (7,632.8, 21,037.8)	---	–28,670 (–40,463, –16,877)	---	---	---	---
CCBs	59,139.6 (51,415.5, 66,683.7)	---	–44,203 (–57,793, –30,613)	---	---	---	---
BBs	–5,931.6 (–7,300.8, –4,562.2)	---	---	---	---	---	---
"Others"	7,344.6 (5,675.5, 9,013.6)	---	–12,752(–16,773, –8,730.4)	---	---	---	---

(Note) Regression coefficients (95% confidence intervals) for the final model (the most parsimonious models); [a] baseline trend; [b] level change following BCBV policy; [c] trend change following BCBV policy; [d] level change following generic losartan availability; [e] trend change following generic losartan availability; [f] level change following generic perindopril availability; [g] trend change following generic perindopril availability ---: indicates insignificant estimates at 0.05 level, after stepwise backward elimination; **ACEIs**: Angiotensin-converting enzyme inhibitors; **ARBs**: Angiotensin receptor blockers; **CCBs**: Calcium-channel blockers; **BBs**: Beta-blocker

3.9.2. Utilisation of ACEIs and ARBs

This section presents the impact of the BCBV prescribing indicator on two outcomes measures – ACEIs prescription proportion (stratified by the UK regions), and prescription expenditure of ACEIs and ARBs.

3.9.2.1. ACEIs prescription proportion

The ACEIs prescription proportion of all ACEIs/ARBs prescriptions was 71.2% in April 2006, but decreased to 70.7% in March 2012. Prior to the implementation of BCBV policy, there was a significant reduction of 0.02% (β_1: –0.02, 95%CI: –0.2, –0.01, p<0.001) in the trend of monthly ACEIs prescription proportion. Implementation of the BCBV policy was associated with a significant initial reduction in the level of ACEIs prescription proportion (β_2: –0.3, 95%CI: –0.44, –0.16, p<0.001), but the trend of the ACEIs prescription proportion significantly increased by 0.013% per month thereafter (β_3: 0.013, 95%CI: 0.0007, 0.02, p<0.001).

The baseline ACEIs prescription proportion in seven of the 13 UK regions ranged from 65% to 74%, and in four and two regions the proportions were >74% and <65%, respectively (Table 3.5). The regional difference between the highest (80.8% in North East) and lowest (60.3% in Northern Ireland) ACEIs prescription proportion was 20.5%, though there were a similar number of patients in the two regions. However, the marginal difference between the highest and the lowest ACEIs prescription proportion declined over time from 20.5% in April 2006 to 12% in March 2012 when the highest ACEIs prescription proportion was 75.8% in East Midlands, and the lowest was 63.8% in South East Coast.

Table 3.5 Total number of hypertensive patients, antihypertensive drug prescriptions and baseline ACEIs prescription proportion in the 13 UK regions

Regions	Baseline ACEIs prescription proportion (%)	Total number of prescriptions	Total number of patients
High baseline ACEIs prescription proportion (>74%)			
North East	80.8	1,143,760	13,319
South East	74.7	3,865,373	53,299
Wales	74.4	6,185,924	63,467
East Midlands	74.3	1,364,324	22,370
Intermediate baseline ACEIs prescription proportion (65-74%)			
Yorkshire and the Humber	73.5	1,554,143	20,968
East of England	72.5	3,505,910	52,733
Scotland	72.2	3,760,187	62,610
South Central	71.7	5,030,800	69,175
West Midlands	69.5	3,764,019	52,920
North West	69.2	6,279,440	80,575
London	69.1	3,401,591	57,108
Low baseline ACEIs prescription proportion (<65%)			
South East Coast	63.6	3,698,109	52,221
Northern Ireland	60.3	801,164	15,256

(Note) **ACEIs**: Angiotensin converting enzyme inhibitors

The results from the regression parsimonious models indicated a wide variation in the policy impact on the ACEIs prescription proportion across various regions, which ranged from a significant increase in the level and trend of ACEIs prescription proportion in some regions to no impact or a significant reduction in other regions (Table 3.6). Although there was no clear pattern of the policy impact, the policy generally seemed to have no influence in regions of either high or low baseline ACEIs prescription proportions.

Table 3.6 Parsimonious segmented linear regression analysis on the monthly ACEIs prescription proportion in the 13 UK regions from April 2006 to March 2012

	β_1 [(a)]	β_2 [(b)]	β_3 [(c)]	β_4 [(d)]	β_5 [(e)]	β_6 [(f)]	β_7 [(g)]
High baseline ACEIs prescription proportion (>74%)							
North East	–0.12 (–0.13, –0.11)	---	---	---	0.04 (0.02, 0.06)	---	---
South East	–0.06 (–0.70, –0.05)	–0.31 (–0.70, –0.07)	0.02 (0.01, 0.04)	---	---	---	---
Wales	---	---	---	---	---	---	---
East Midlands	–0.03 (–0.04, –0.16)	---	---	–0.64 (–1.10, –0.20)	0.16 (0.13, 0.19)	---	---
Intermediate baseline ACEIs prescription proportion (65–74%)							
Yorkshire and the Humber	–0.08 (–0.09, –0.06)	---	0.20 (0.14, 0.24)	–1.80 (–0.26, –0.90)	---	---	---
East of England	–0.08 (–0.70, –0.05)	–0.40 (–0.70, –0.05)	0.02 (0.04, 0.03)	---	---	---	---
Scotland	---	---	0.06 (0.04, 0.08)	–0.49 (–0.80, –0.10)	---	---	---
South Central	–0.01 (–0.20, –0.002)	–0.60 (–0.90, –0.40)	---	–0.47 (–0.70, –0.20)	---	---	---
West Midlands	---	---	–0.03 (–0.04, –0.02)	---	---	---	---
North West	0.001 (0.002, 0.018)	–0.57 (–0.80, –0.33)	0.04 (0.03, 0.05)	---	---	---	---
London	---	0.40 (0.20, 0.60)	---	---	0.04 (0.03, 0.05)	---	---
Low baseline ACEIs prescription proportion (<65%)							
South East Coast	0.013 (0.004, 0.02)	–0.42 (–0.70, –0.20)	–0.02 (–0.03, –0.002)	---	---	---	---
Northern Ireland	0.06 (0.05, 0.08)	---	---	---	0.06 (0.02, 0.09)	---	---

(Note) Regression coefficients (95% confidence intervals) for the final model (the most parsimonious models); [(a)] baseline trend; [(b)] level change following BCBV policy; [(c)] trend change following BCBV policy; [(d)] level change following generic losartan availability; [(e)] trend change following generic losartan availability; [(f)] level change following generic perindopril availability; [(g)] trend change following generic perindopril availability **---**: indicates insignificant estimates at 0.05 level, after stepwise backward elimination; **ACEIs**: Angiotensin-converting enzyme inhibitors

3.9.2.2. ACEIs/ARBs expenditure

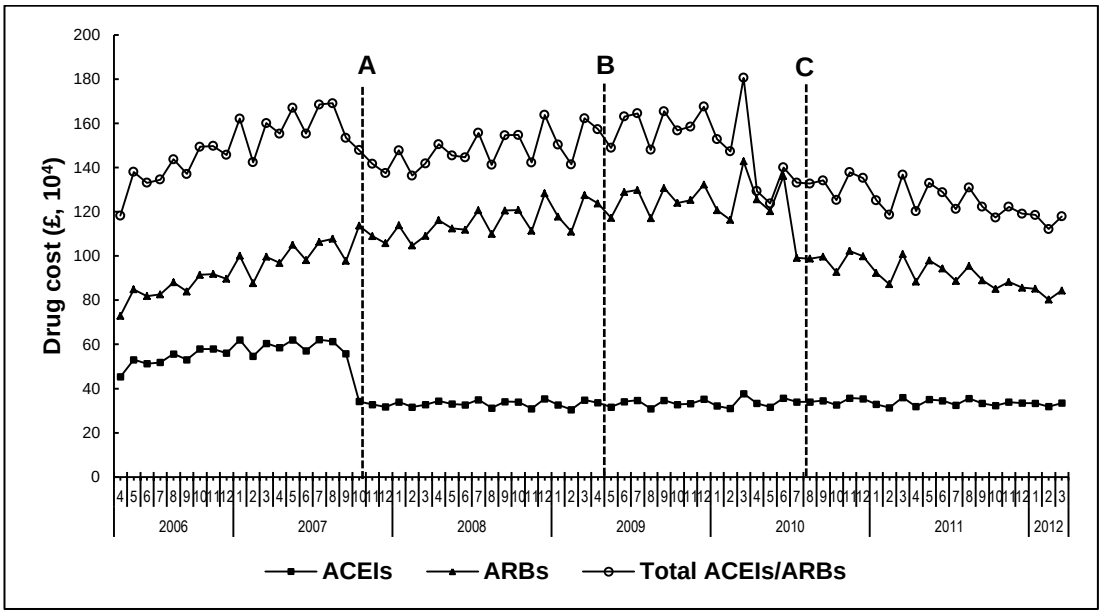
This section presents the impact of BCBV policy on ACEIs/ARBs expenditure and the cost-saving consequences if the 80% policy target would have been achieved by end of study period in March 2012 as well as years after the availability of generic ARBs.

3.9.2.2.1. Monthly ACEIs and ARBs cost

Overall, the cost of total ACEIs/ARBs was decreased by 0.3% during the study period from £1,182,656 in April 2006 to £1,178,674 in March 2012. However, the monthly ACEIs cost reduced by 26.1% from £453,303 in April 2006 to £334,934 in March 2012; whereas the monthly ARBs cost increased by 15.7% from £729,353 to £843,740 (Figure 3.5).

Prior to the BCBV implementation, there was a significantly increased trend (β_1) in monthly costs of total ACEIs/ARBs, ACEIs and ARBs (Table 3.7). The BCBV policy neither affected the level (β_2) nor the trend (β_3) of the costs of total ACEIs/ARBs, ACEIs or ARBs following its implementation in April 2009.

Figure 3.5 Monthly cost of ACEIs/ARBs, ACEIs and ARBs from April 2006 to March 2012



(Note) A: time point when generic perindopril became available (October 2007); **B**: time point when BCBV policy was implemented April 2009); **C**: time point when generic losartan launched (July 2010).

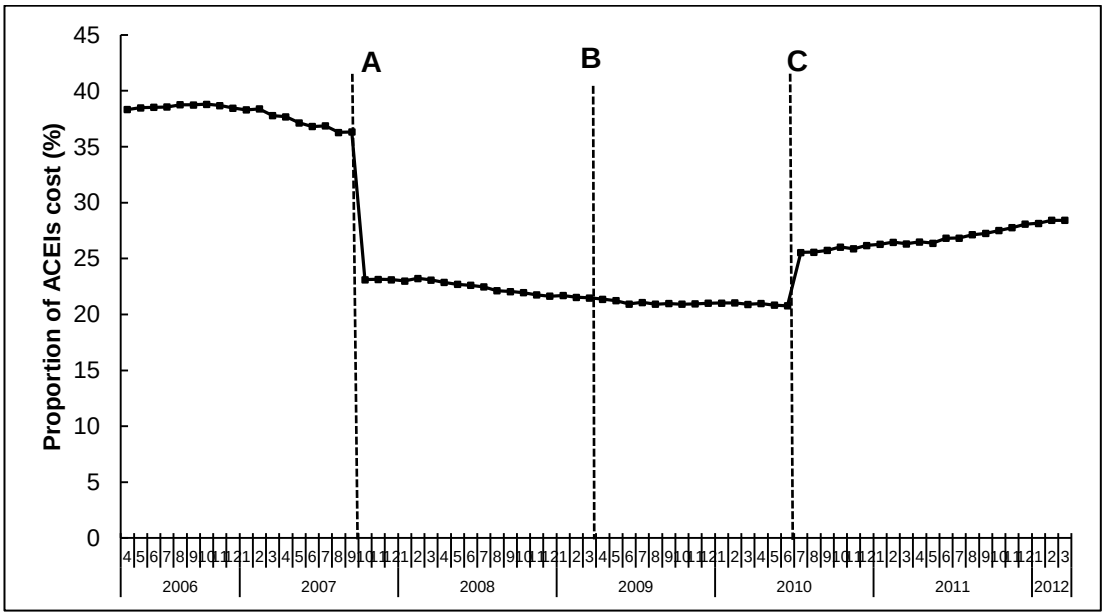
Similar to the trend of ACEIs prescription proportion, ACEIs accounted for 38.0% of the total ACEIs/ARBs cost in April 2006, which decreased to 28.5% by the end of the study period (Figure 3.6). Prior to BCBV implementation, the proportion of ACEIs cost significantly decreased by 0.13% per month (β_1: –0.13, 95%CI: –0.16, –0.01) (Table 3.7). The BCBV policy had no effect on the proportion of ACEIs cost (β_2) instantly at its implementation; however, thereafter the trend of the proportion of ACEIs cost significantly increased by 0.09% per month (β_3: 0.09, 95%CI: 0.05, 0.18).

Table 3.7 Parsimonious segmented linear regression analysis on monthly cost of ACEIs/ARBs, ACEIs and ARBs from April 2006 to March 2012

	β_1 [(a)]	β_2 [(b)]	β_3 [(c)]	β_4 [(d)]	β_5 [(e)]	β_6 [(f)]	β_7 [(g)]
ACEIs and ARBs	22,072 (15,546, 28,599)	---	---	–287,538 (–368,885, –206,192)	–15,970 (–21,775, –10,164)	–266,656 (–349,379, –183,932)	–15,019 (–22,054, –7,983)
ACEIs	6,228.8 (4,372, 8,086)	---	---	---	---	–286,941 (–308,447, –265,435)	–6,094 (–7,971, –4,217)
ARBs	17,030 (13,449, 20,611)	---	---	–298,044 (–357,163, –238,924)	–15,548 (–19,712, –11,384)	---	–9,839 (–14,560, –5,118)
Proportion of ACEIs cost	–0.13 (–0.16, –0.01)	---	0.09 (0.05, 0.18)	3.4 (2.7, 4.1)	0.2 (0.13, 0.28)	–13.2 (–14, –12.5)	---

(Note) Regression coefficients (95% confidence intervals) for the final model (the most parsimonious models); [(a)] baseline trend; [(b)] level change following BCBV policy; [(c)] trend change following BCBV policy; [(d)] level change following generic losartan availability; [(e)] trend change following generic losartan availability; [(f)] level change following generic perindopril availability; [(g)] trend change following generic perindopril availability ---: indicates insignificant estimates at 0.05 level, after stepwise backward elimination

Figure 3.6 Monthly proportion of ACEIs cost of total ACEIs/ARBs cost from April 2006 to March 2012



(Note) A: time point when generic perindopril became available (October 2007); **B**: time point when BCBV policy was implemented April 2009); **C**: time point when generic losartan launched (July 2010).

3.9.2.2.2. Prediction of the potential cost saving of the BCBV policy

In March 2012, the total, national cost of ACEIs/ARBs prescriptions was £1,178,674, and the number of ACEIs and ARBs prescriptions was 174,153 and 72,240, respectively. Accordingly, if the BCBV indicator target of 80% ACEIs had been achieved in March 2012, instead of the current proportion of 70.7%, a potential cost saving of £227,593 would have been made in March 2012, which represents 23.9% of the total ACEIs/ARBs cost.

To estimate the potential cost saving of achieving the 80% BCBV target while accounting for the availability of generic ARBs, the latest June 2014 PCA data of England were analysed. The analysis indicated that, even years after the availability of generic ARBs, a potential, national cost saving of £926,885 (8.7%) of total ACEIs/ARBs cost (£10.6 million) would have been made in June 2014 if the 80% target had been achieved, instead of the current June 2014 value of 70.3%.

3.9.3. Validation of the study findings

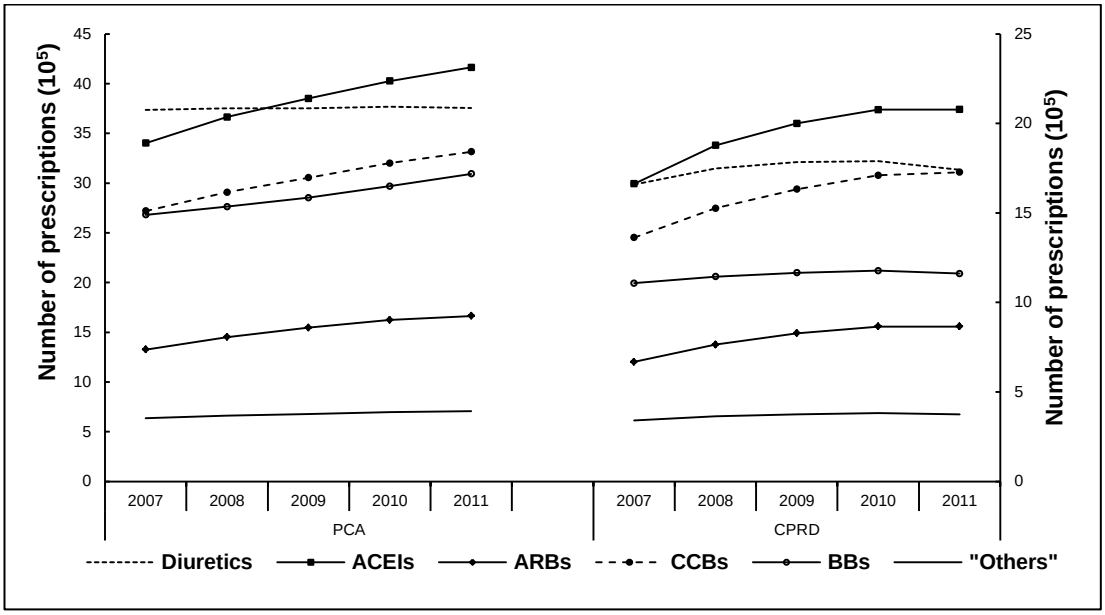
This section presents the validation of results obtained from analysing three national datasets at annual, quarterly and monthly levels that were compared with those obtained from the CPRD dataset.

3.9.3.1. Annual numbers of prescriptions and DDDs of the six antihypertensive drug classes comparing PCA and CPRD datasets

Overall, the annual prescribing trend for all the antihypertensive drug classes increased in both PCA and CPRD datasets, except for diuretics, which remained constant in the PCA dataset (Figure 3.7). In 2007, diuretics were the most frequently prescribed antihypertensive class in the results obtained from the PCA dataset in contrast to the results derived from CPRD, in which ACEIs were the most frequently prescribed drug class. The trend of diuretics remained stable in PCA but declined in the CPRD dataset (Figure 3.7).

In both PCA and CPRD datasets, the number of ACEIs prescriptions presented an increasing trend by about 0.2% during the study period and became the most frequently prescribed antihypertensive drug in 2011, and ARBs accounted for the highest increasing trend (0.3%). In the PCA dataset, there was a significant increase of BBs (102,824 prescriptions per year, $p<0.001$), in contrast to a non-significant increase in the results derived from the CPRD dataset (14,017 prescriptions per a year, $p=0.09$).

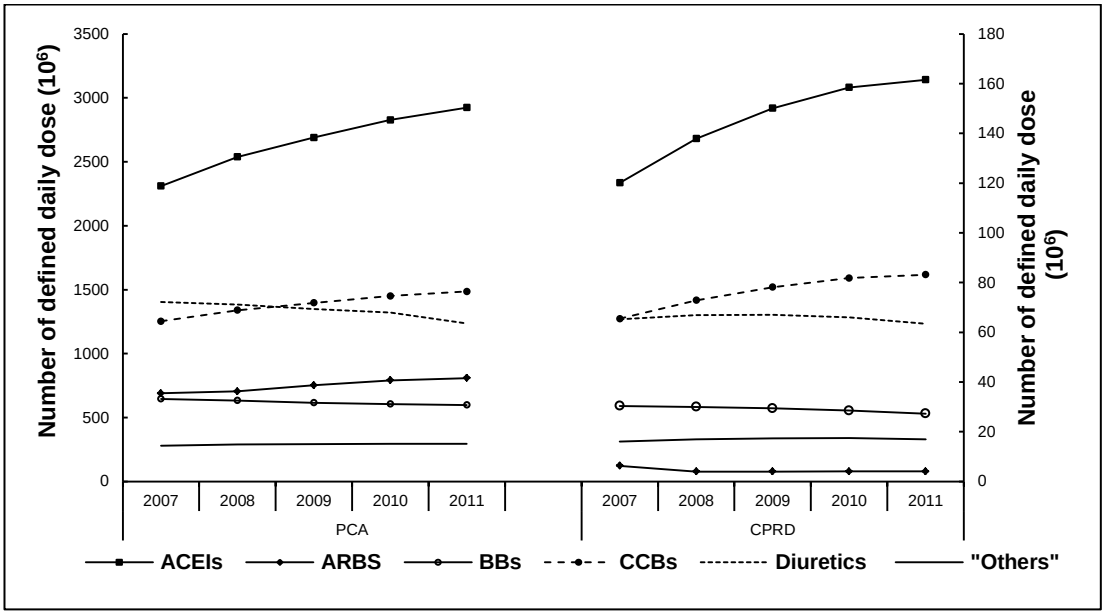
Figure 3.7 Annual numbers of prescriptions of the six antihypertensive drug classes comparing PCA and CPRD datasets from January 2007 to December 2011



(Note) **PCA**: Prescription cost analysis dataset, which contains whole dispensing data for all indications in England; **CPRD**: Clinical Practice Research Datalink, which contains prescription data for essential hypertension patients who registered in the practices included in CPRD.

In both datasets, most antihypertensive drug classes showed a comparable trend of the number of DDD over time (Figure 3.8). Annual numbers of DDD for ACEIs and CCBs presented an increased trend over time (0.3% and 0.2% overall increase in PCA data, and 0.4% and 0.3% in CPRD dataset, respectively). On the other hand, the annual numbers of DDD for BBs declined by 0.07% in the PCA dataset compared with a 0.1% reduction in the CPRD. There was an overall 0.2% increase in the numbers of DDDs for ARBs in the PCA dataset, in comparison with a 0.4% overall reduction in CPRD.

Figure 3.8 Annual number of defined daily doses of antihypertensive drugs comparing the HSCIC and CPRD datasets from January 2007 to December 2011

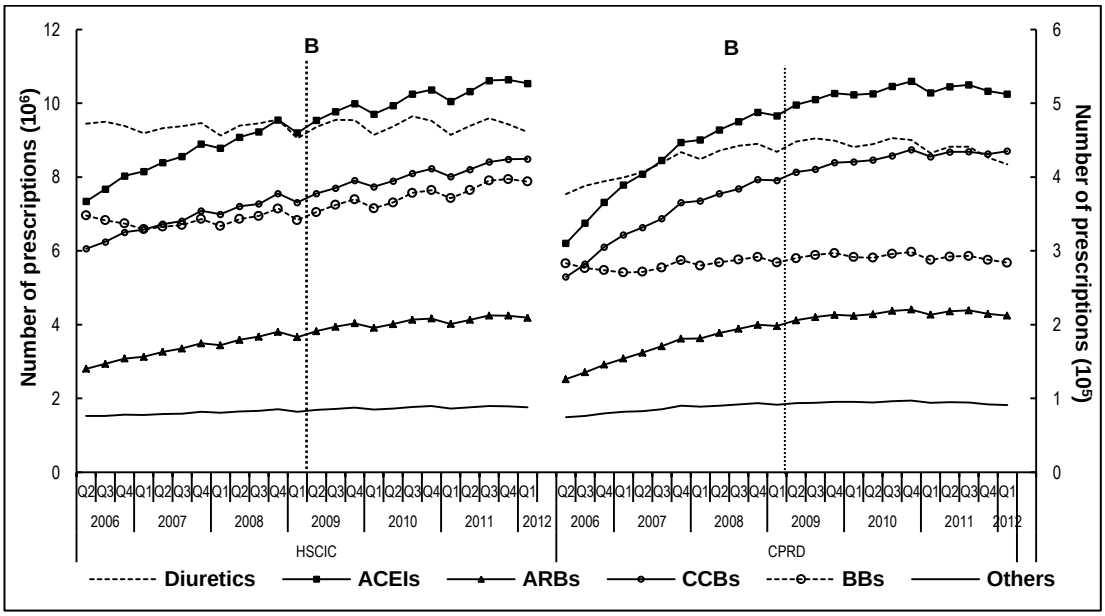


(Note) **PCA**: Prescription cost analysis dataset, which contains whole dispensing data for all indications in England; **CPRD**: Clinical Practice Research Datalink, which contains prescription data for essential hypertension patients who registered in the practices included in CPRD.

3.9.3.2. Quarterly numbers of prescriptions of the six antihypertensive drug classes comparing HSCIC and CPRD datasets

The quarterly number of antihypertensive prescriptions extracted from HSCIC and CPRD datasets suggested a comparable prescribing trend, except for diuretics and BBs (Figure 3.9). In both datasets, diuretics were the major prescribed drug class at the start of the study period, but were then replaced by ACEIs at the end of the study period.

Figure 3.9 Quarterly number of antihypertensive prescriptions comparing HSCIC and CPRD datasets from April 2006 to March 2012



(Note) **B**: time point when BCBV policy was implemented (April 2009); **HSCIC**: Health and Social Care Information Centre dataset, which contains whole dispensing data for all indications in England; **CPRD**: Clinical Practice Research Datalink, which contains prescription data for essential hypertension patients who registered in the practices included in CPRD.

Analyses of HSCIC quarterly dispensing data (Table 3.8) showed a significantly declining trend of ACEIs prescription proportion prior to the BCBV policy implementation (β_1: –0.09, p<0.001) (Table 3.8). Although the policy had no instant impact on the level (β_2) of ACEIs prescriptions proportion, there was a significantly increased trend thereafter (β_3: 0.1, p<0.001). Analyses of quarterly national dispensing data demonstrated a consistent pattern with that obtained from the CPRD dataset (Table 3.8), which showed a significantly decreased trend of ACEIs prescriptions proportion prior to the policy implementation (β_1: –0.04, p<0.001), and no instant policy impact (β_2), but a significantly increased post-policy trend (β_3: 0.04, p<0.001).

Table 3.8 Parsimonious segmented linear regression analysis on the quarterly number of antihypertensive prescriptions and ACEIs prescription proportion comparing HSCIC and CPRD datasets from April 2006 to March 2012

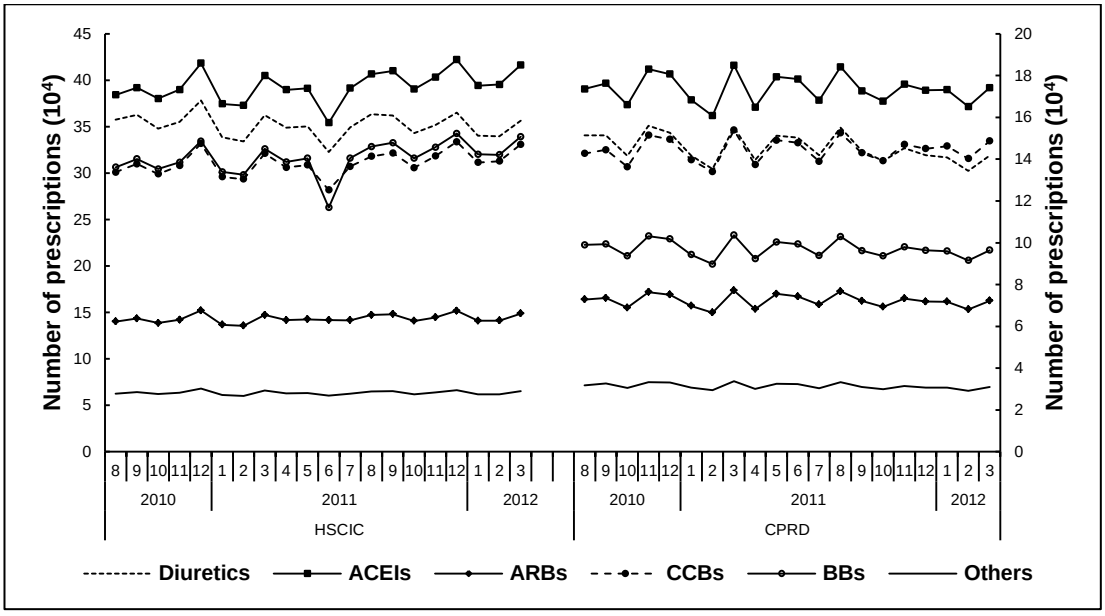
	β_1 [(a)]	β_2 [(b)]	β_3 [(c)]
Health and Social Care Information Centre (HSCIC) data			
ACEIs prescription proportion (%)	–0.09 (–0.10, –0.70)	---	0.10 (0.09, 0.13)
ACEIs	179,422.8 (155,964.2, 202,881.5)	---	–88,326.8 (–12,8278.1, –48,375.6)
ARBs	87,446.1 (77,192.5, 97,699.7)	---	–52,359.4 (–69,821.8, –34,897.1)
Diuretics	---	---	---
CCBs	121,943.8 (106,805.8, 137,081.8)	---	–40,240.7 (–66,021.5, 14,459.9)
BBs	22,331.1 (2,253.2, 42,409.0)	---	61,787.6 (27,593.9, 95,983.2)
"Others"	15,605.9 (12,056.8, 19,154.0)	---	–7,041.9 (–13,085.4, 998.4)
Clinical Practice Research Datalink (CPRD) data			
ACEIs prescription proportion (%)	–0.04 (–0.6, -0.02)	---	0.04 (0.01, 0.07)
ACEIs	15,862.3 (14,300.5, 17,427.0)	---	–14,529.7 (–17,189.5, –11,869.9)
ARBs	6,993.5 (6,377.5, 7,609.4)	---	–6,167.7 (–7,216.6, –5,118.6)
Diuretics	6,414.9 (5,325.2, 7,504.5)	---	–8,312.0 (–10167.6, –6456.2)
CCBs	11,960.5 (10,917.0, 13,003.9)	---	–9576.0 (–11353.1, –7798.9)
BBs	1,681.0 (948.6, 2,413.4)	---	–1689.5 (–2936.7, –442.2)
"Others"	1,765.0 (1,572.7, 2,002.3)	---	–1924.8 (–2328.9, –1520.6)

(Note) Regression coefficients (95% confidence intervals) for the final model (the most parsimonious models); [(a):] baseline trend; [(b):] level change following BCBV policy; [(c):] trend change following BCBV policy; **---** : Indicates insignificant estimates at 0.05 level, after stepwise backward elimination.

3.9.3.3. Monthly numbers of prescriptions of the six antihypertensive drug classes comparing HSCIC and CPRD datasets

Overall, the monthly utilisation of antihypertensive drugs was very similar between HSCIC and CPRD data, except for BBs (Figure 3.10). Results from both datasets indicated that ACEIs were the most frequently prescribed antihypertensive drug class in August 2010, and its trend remained stable over time to March 2012. Diuretics were the second most frequently prescribed drug class in August 2010 in both PCA and CPRD datasets. However, they were replaced by CCBs by the end of the study period in the CPRD data only, as their prescribing trend decreased over time at a higher rate compared with their trend in the HSCIC data. ARBs presented a comparable stable trend in both datasets. However, BBs were the only drug class with dissimilar patterns, with a slightly increased trend over time in the HSCIC dataset compared with an almost stable trend in the CPRD dataset. Drugs classed as “Others” were the least frequently prescribed drugs in both datasets, with an almost constant trend over time.

Figure 3.10 Number of prescriptions of all antihypertensive drug classes



(Note): **HSCIC**: Health and Social Care Information Centre dataset, which contains whole dispensing data for all indications in England; **CPRD**: Clinical Practice Research Datalink (whole prescribed prescriptions for essential HT patients in the UK

3.10. Discussion

3.10.1. Main findings

The study results indicated an overall decline in ACEIs prescription proportion trend during the study period; however, the extent of this declining trend was counterbalanced by the implementation of the BCBV policy as it resulted in a small, but sustained increase in the trend of monthly ACEIs prescription proportion after its implementation in April 2009, and this was not associated with any beneficial cost consequences.

By the end of the study period, the BCBV policy failed to achieve the expected BCBV target of 80% ACEIs as the ACEIs prescription proportion was 70.7%. The impact of the BCBV policy on ACEIs prescription proportion varied across the 13 UK regions. In comparison with the pre-policy trend, the observed post-policy reduction in the trend of the adjusted number of prescriptions and numbers of DDDs for ACEIs/ARBs and the other antihypertensive classes (reference groups), implies that factors other than the BCBV policy could have contributed to the reduction in the number of prescriptions.

The BCBV policy had neither an instant nor sustained effect on the cost of total ACEIs/ARBs, or of ACEIs or ARBs individually. The failure to achieve the proposed BCBV target of 80% in March 2012 led to a missed potential cost-saving opportunity of £227,593 (23.9%) of total ACEIs/ARBs cost. Applying this 23.9% predicted costing-saving figure to the national total ACEIs/ARBs cost in March 2012 (£22,205,484) obtained from the PCA data[271], yielded a potential monthly cost saving of £5,307,111 in March 2012.

Importantly, although the potential cost saving in March 2012 was possibly moderated by the availability of generic ARBs, the analysis of PCA data in June

2014[264] indicated that, even four years after the availability of generic ARBs, the failure of achieving the BCBV target of 80% ACEIs had led to missing a potential national cost-saving opportunity of approximately £ 1 million in June 2014.

3.10.2. Impact of the BCBV policy on ACEIs prescription proportion

The study results showed a contradictory, unexpected decline in the level of ACEIs prescription proportion instantly following its implementation in April 2009. This could be due to a lag in the policy effect and/or delayed implementation of the policy after its announcement. Research has shown that prescribing-related policies may need some time before their effects start to appear, usually after two to three months[272]. Additionally, implementation of the policy could have been delayed in some individual PCTs, which could result in a delay of the policy effect. For instance, Newcastle and North Tyneside PCTs[245] implemented the policy three months after its release. It was important to find similar and comparable findings, regarding the trend of ACEIs prescription proportion and policy impact, between CPRD and the validation datasets, which likely indicates the robustness of data management and analyses.

3.10.3. Ineffectiveness of the BCBV policy in achieving the 80% target

Despite the initial declining effect of the policy on the level of ACEIs prescription proportion, this was followed by a statistically significant post-policy increase in the trend of ACEIs prescription proportion; however, it was extremely small and thus failed to achieve the proposed BCBV target of 80% ACEIs by the end of the study period.

This policy failure could be due to two common causes underpinning the failure of any policy, either inappropriate policy measures and/or inadequate policy implementation[273]. Since the BCBV measure of 80% ACEIs prescription proportion

was considered an achievable target[91], the lack of full and appropriate policy implementation could be the main cause of ineffectiveness of the BCBV policy. In particular, the BCBV policy was not linked to any financial incentives or legislation enforcements; consequently, GPs may be indifferent about, or reluctant to respond to the policy; however, this needs further investigation.

A combination of implementation measures has been shown to be more effective than a single measure. It has been demonstrated in other European countries (Croatia, Austria, Serbia, Sweden, Spain) that multiple intensive measures, e.g. combination of prescribing guidance, prescribing targets, financial incentives and prescribing restrictions, are usually required to improve prescribing efficiency, including limiting the prescribing of patented ARBs vs. generic ACEIs[28, 35, 63, 151], and that limited measures in prescribing policy implementation have failed to address the appreciable increase in ARBs prescribing, as observed in Portugal[32, 63].

Overall, failure of linking BCBV policy with any financial incentive or enforcement, as in Quality and Outcomes Framework (QoF) targets, could be the main contributor to the ineffectiveness of BCBV policy. The observed regional variation of the policy's impact on ACEIs prescription proportion could reflect the possible geographical variation of implementing the BCBV policy by individual PCTs.

It is interesting to note that the observed wide variation in the ACEIs prescription proportion across various regions in this study is consistent with the NPC report[172], which illustrated variations among individual PCTs in England, with only 11.5% of the practices having an ACEIs prescription proportion of >80%, while 9% have a value of <60%. The variation in the BCBV policy impact among the regions could likely indicate the fact that different regions had implemented the policy to different

extents, possibly due to the fact that the policy, unlike QoF, was not linked to any financial incentives or legislation enforcement.

Despite the postulated inappropriateness of implementing the BCBV policy, other potential factors for the failure or ineffectiveness of the policy cannot be ruled out. It could be argued that the observed policy ineffectiveness may merely reflect the fact that the encouragement of prescribing low-cost generic ACEIs against patented ARBs was the focus of health authorities (HAs) in the UK some time before the launch of this BCBV policy[245, 274, 275]. This was seen in Scotland[42], where multiple measures were implemented between 2001 and 2007, including prescribing targets and financial incentives.

Consequently, by the time this BCBV was launched in 2009, GPs and pharmaceutical advisers had turned their attention to other areas, hence, the limited impact of the BCBV policy. A similar scenario was observed in Sweden where the recent implementation of prescribing restrictions for patented statins had limited impact because these were introduced some six to seven years after pharmaceutical advisers had been promoting the use of generic statins[60].

It might be true that previous HAs activities played an important role in slowing down the increased utilisation trend of ARBs that had resulted from intolerance to ACEIs and the continued promotion of ARBs from pharmaceutical companies. However, the decreasing trend of ACEIs prescription proportion in the pre-policy period combined with its value being far below the proposed target of 80% should theoretically enhance rather than impede the effectiveness of BCBV policy, as there were opportunities for further improving the proportion of ACEIs prescriptions. Therefore, the activities of HAs in the UK in the years before implementing the policy are unlikely to fully explain the ineffectiveness of this BCBV. Furthermore,

other factors such as GPs' prescribing preferences and clinical issues related to switching from ARBs to ACEIs, and the patient's choice, could not be ruled out as possible reasons for policy ineffectiveness.

3.10.4. Impact of the BCBV policy on the number of prescriptions and DDDs

The trend of the number of DDDs for all antihypertensive drug classes was comparable with the trend of the adjusted monthly number of prescriptions; therefore, all the discussion points about the latter apply to the former. However, it is worth mentioning that the pre-policy monthly trend of number of DDDs of diuretics and "Others" were increasing despite a reduction in the adjusted monthly number of prescriptions. This could be due to the prescribing of higher strength and/or quantities of these drug classes, in particular when they are used for treating conditions other than HT such as heart failure.

Overall, it is not a surprise for the policy to have had no impact on the level of adjusted monthly number of prescriptions immediately after its implementation; however, there was an unexpected post-policy reduction in the trend of the adjusted monthly number of prescriptions of ACEIs/ARBs that seems to be consistent with the validation results obtained from the three national datasets. Importantly, the study results also showed a similar policy impact on the prescribing trend of the other antihypertensive drug classes (reference group). Therefore, it is reasonable to hypothesise that the observed change in the utilisation of ACEIs and ARBs cannot necessarily be attributed to BCBV policy. Alternatively, other systematic factors or policy measurement changes that influenced antihypertensive drug utilisation in the primary care setting in the UK in general may have confounded the effect of BCBV policy on ACEIs and ARBs utilisation. This hypothesis is plausible since the BCBV prescribing policy was not designed to affect the utilisation of ACEIs or ARBs, nor the utilisation of other antihypertensive classes; instead, it focuses on the

percentage of items written for ACEIs in proportion to all items affecting RAAS drugs[1]. In other words, it did not advise GPs to select a particular antihypertensive drug class, but encouraged GPs to prescribe cheaper, generic ACEIs, instead of expensive, branded ARBs when prescribing a drug that affects the RAAS.

Although it is difficult to explain the exact cause for the observed unexpected impact of the policy on the prescribing of ACEIs/ARBs using CPRD data, some possible explanations could be speculated. One possible explanation could be an increase in hypertension diagnosis and registration after the introduction of QoF in April 2004, which incentivised GPs to produce a hypertension register[276], and hence, hypertension prevalence and antihypertensive drug prescriptions started rising until they plateaued approximately five years after the introduction of the QoF.

The QoF-associated increase in hypertension registration was reflected clearly on the annual increase of hypertension prevalence in the UK by ~2.8% on average, from 12% in 2005 to 13.4% in 2009, in contrast to ~0.75% increase, on average, from 13.4% in 2009 to 13.6% in 2011[277]. Likewise, a similar change in the trend of recording chronic kidney diseases was found after the introduction of QoF as found by Serumaga (2010)[153].

3.10.5. Impact of the BCBV policy on ACEIs/ARBs expenditure

Despite a 29.0% increase in the adjusted total number of ACEIs/ARBs prescriptions, there was a 0.3% reduction in total ACEIs/ARBs cost during the study period. Likewise, for ACEIs, its expenditure declined by 28.1% despite a 28.9% increase in the adjusted number of prescriptions. However, the expenditure of ARBs increased by 15.7% despite a 31.9% increase in the adjusted number of prescriptions.

The BCBV policy had no effect on either total ACEIs/ARBs cost, ACEIs or ARBs cost, which suggests that the small post-policy increase in the trend of ACEIs prescription proportion had no beneficial cost implication. In fact, the availability of generic perindopril and losartan in October 2007 and July 2010, respectively, accounted largely for the observed changes in the cost of ACEIs/ARBs. Furthermore, the continual decline in the cost of other generic ACEIs and losartan over time, prompted by the introduction of the 'M' (Manufacturer) and 'W' (Wholesaler) scheme in April 2005,[173] would likely have contributed to the reduction in ACEIs/ARBs cost.

3.10.6. Impact of the availability of generic ARBs on the cost-saving implication of achieving the proposed 80% target of the BCBV indicator

The results from this study indicated that failure of achieving the 80% target of the BCBV policy in March 2012 would have led to a missed substantial cost-saving opportunity, even in the presence of generic ARBs. It could be argued that due to the loss of cost advantage of ACEIs over ARBs, and the reduction in the cost differential between them, driven by the availability of more low-cost generic ARBs, further consideration of the BCBV indicator would not be required as it would not result in appreciable cost saving. This is especially relevant when considering suggestions to replace ACEIs with low-cost ARBs as the first-line of therapy for hypertension treatment[178], assuming that GPs would prescribe those ARB items that are available generically.

However, analysis of the latest available dispensing PCA data of England at the time of the study (June 2014)[264] contradicted this argument, as the opportunity for a potential saving of £92,688,486 (8.7%) of total ACEIs/ARBs cost was still achievable, if the ACEIs prescription proportion increased from the current June 2014 proportion of 70.3% to 80%, in spite of the availability of four generic ARBs

(losartan, candisartan, irbesartan, valsartan) by June 2014. Furthermore, analysing the March 2012[271] and June 2014[264] PCA data of England (a 26-month time period) illustrated only a small increase of 8.9% in losartan utilisation from 36.8% of all ARB items in March 2012 to 45.7% in June 2014, despite its launch as the firsrt generic ARB in July 2010. This disputes the assumption that GPs would tend to start prescribing generic ARBs once they became available, and thus further supports the necessity to continue considering the BCBV indicator.

This slow increase in the utilisation of losartan, following 39 months of its availability as generic in July 2010, is not surprising given the lack of national initiatives in the UK to improve ARBs prescribing efficiency once generic forms become available. This was observed in Scotland[177] and NHS Bury in England[42], where there was no appreciable change in the utilisation of losartan following its availability as generic in July 2010. However, after the initiation of a set of local multiple measures in March 2011 in the NHS Bury in England[42], the utilisation of losartan increased from 26% of total ARBs items in February 2011 to 65% in October 2011, and thus, this case study concluded that multiple initiatives were required to change GPs' prescribing behaviour in order to improve ARBs prescribing efficency.

Accordingly, due to the current lack of national multiple initiatives in the UK to improve prescribing efficiency of ARBs, it is unlikely that losartan utilisation and ARBs prescribing efficency would be improved further. Therefore, achieving the proposed 80% target of the BCBV indicator would likely continue achieving potential cost savings despite the presence of low-cost generic ARBs, which inturn suggests the necessity to continue considering and reinforcing the BCBV indicator; however, this should be balanced with cost-saving opportunities in other areas.

3.10.7. Difference between the national dispensing data and the CPRD prescribing data

In spite of the general consistency between the results from the national dispensing datasets and CPRD prescribing dataset, in terms of prescribing patterns of antihypertensive drug classes and ACEIs prescription proportion, some discrepancy was found in the observed impact of the BCBV indicator on the prescribing pattern of diuretics and BBs. This inconsistency could be explained by a number of factors.

Firstly, the data in the national datasets is for all patients in the whole of England whereas the CPRD dataset was from some GP practices in England and was limited to patients with primary hypertension. Furthermore, as diuretics and BBs are clinically recommended as first-line treatment in other chronic conditions, such as heart failure[110] and post myocardial infarction[111], their prescribing, therefore, was increasing in the national datasets; whereas in the CPRD dataset, their prescribing was decreasing, possibly as a result of the new NICE guidelines on the management of hypertension[278], which has recommended BBs as the fourth-line of treatment and preferred CCBs over diuretics.

In fact, the observed utilisation pattern of antihypertensive drug classes in this study is consistent with results of another study[153], which found an increase in the utilisation of ACEIs, ARBs and CCBs, but a reduction in the utilisation of BBs and diuretics in patients with primary hypertension.

3.10.8. Strengths and limitations

To my knowledge, this is the first study to quantify and evaluate the impact of the BCBV prescribing indicator on the utilisation of ACEIs/ARBs, using a quasi-experimental design on a large, representative, high-quality CPRD dataset. The use of interrupted segmented regression analysis has adjusted and controlled for existing, pre-intervention trend[253] and therefore, it has ensured that the observed

post-intervention changes were not solely a continuation of the long-term secular trend. Furthermore, the consistency of this study's findings with those obtained from the analysis of the other national datasets indicates the validity of study design and methodology, with the results being reflective of the national figures in general, but with some differences.

Interrupted time-series is recommended widely for evaluating the impact of health policy changes and has been described as the strongest quasi-experimental alternative randomised designs whenever it is not feasible to conduct the latter[252]. However, there were some limitations, which were mostly inherent in secondary database analysis. It was not possible to ensure that the prescribed antihypertensive drugs were solely prescribed for treating hypertension and not for other indications such as heart failure, which may have overestimated the observed antihypertensive drug utilisation quantity. However, the use of both hypertension diagnosis and drug codes in the identification of the study cohort would have likely increased the possibility that the drugs were, at least, prescribed for hypertension treatment.

The identification of an area free of BCBV policy to be used as a reference group to separate the true policy impact from other policies was impossible in this study as the policy was implemented nationally. However, adopting the alternative approach of using other antihypertensive drug classes as reference groups and considering the impact for the potential confounders (launch of generic losartan and generic perindopril), would possibly have allowed the estimation of the true intervention effect to a large extent.

3.10.9. Conclusions

The BCBV indicator did not change the overall ACEIs/ARBs utilisation in patients with primary hypertension. The small, significant policy-induced increase in ACEIs prescription proportion was not associated with any beneficial cost consequence. A considerable potential cost saving could still be achieved by further improving the efficient prescribing of ACEIs/ARBs, highlighting the necessity for reinforcing the BCBV policy, but this must be balanced against other priority areas for improving prescribing quality and efficiency in primary care settings. Further research is needed to evaluate the clinical and economic impact of BCBV-promoted switching from ARBs to ACEIs and to assess whether this switching is a cost-saving strategy. Furthermore, it is necessary to explore the potential factors underpinning the policy ineffectiveness, and determine the most effective measures to improve policy effectiveness in the future.

Chapter 4. Factors associated with antihypertensive drug adherence and persistence patterns

4.1. Introduction

Implementing the BCBV indicator involves switching established ARBs users to ACEIs to improve the value for money without compromising quality of care. However, prior to investigating whether this policy's promoted switching is associated with any clinical or economic issues, it is crucial to understand patients' adherence and persistence patterns (continuation, discontinuation, combination and switching) to antihypertensive drugs and to identify the potential associated factors. Subsequently, the obtained knowledge about factors associated with medication adherence and persistence would play an important role in identifying the potential confounders that need to be considered while evaluating the impact of ARBs switching on patients' adherence and clinical outcomes.

Different terminologies, such as adherence, compliance and concordance, have been used, although inconsistently, to reflect the medication-taking behaviours of patients and their relationship with healthcare professionals. The WHO defined adherence as "the extent to which a person's behaviour-taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider"[279]. Whereas the National Coordinating Centre for NHS Service Delivery and Organisation[280] defined it as "the extent to which the patient's behaviour matches the prescriber's recommendations".

Recently, European research groups in the field of adherence to medications[190] have developed a new taxonomy for describing and defining medication adherence and defined adherence as "the process by which patients take their medications as

prescribed". Accordingly, adherence is considered to consist of three components (initiation, implementation and discontinuation). The process of taking medication starts with taking the first prescribed dose of the medication (initiation), followed by the extent to which actual dosing taken by the patient matches the prescribed dosing regimen (implementation), and ends by omitting the next proposed dose to be taken, with no further doses to be taken thereafter (discontinuation). Persistence represents the time period between initiation and the last dose immediately prior to discontinuation.

The new taxonomy also describes methods for quantifying and analysing adherence, but no single measure is available to cover all three components. Initiation and discontinuation were described as discontinuous actions and thus considered as time-to-event variables that should be analysed using survival analysis; whereas, implementation is considered as a continuous variable and various summary statistics were identified to quantify it such as the proportion of prescribed dose taken[190].

Poor adherence to antihypertensive medications leads to compromised health benefits and substantial negative economic consequences. Several studies have clearly illustrated the significant association between poor adherence and increased risk of cardiovascular events and hospitalisations[192, 198, 281, 282], which has a huge impact on the utilisation of healthcare resources and costs. Adherence and persistence to medications are complex processes and multifactorial in nature[182]. The WHO identified five factors that affect adherence, including factors related to patients, conditions, medications and healthcare systems[182].

Although many studies have evaluated patients' adherence and persistence to antihypertensive medications, the majority of them were limited to either new

hypertensive patients, short follow-up time, conducted in countries with different healthcare systems to the UK – largely the USA, and/or measured and analysed adherence as a binary outcome. In a recent meta-analysis of 17 studies that measured adherence to antihypertensive medication[203], most of the included studies (n=15) were for new patients; 14 studies had follow-up time of <1 year; eight were conducted in the USA, and none of the adherence studies analysed adherence measure as a continuous variable. Therefore, this chapter measured adherence and persistence to antihypertensive drugs while overcoming most of the limitations encountered in the previous adherence studies.

This study assisted in preparing the data for the analysis described in Chapter 5 in terms of data cleaning and management. Additionally, analysis carried out in this chapter helped in identifying the prevalence of antihypertensive drug switching among patients with primary hypertension and subsequently, patients who switched their antihypertensive drug classes were considered as the basis for the study cohort in Chapter 5.

4.2. Aims and objectives

This study aimed to assess and identify factors associated with adherence and persistence patterns of antihypertensive drug classes, among adults with primary hypertension in the UK.

The objectives of this study were to:

1. Identify, describe and quantify antihypertensive drug classes' adherence and persistence patterns, including continuation, discontinuation, combination and switching.

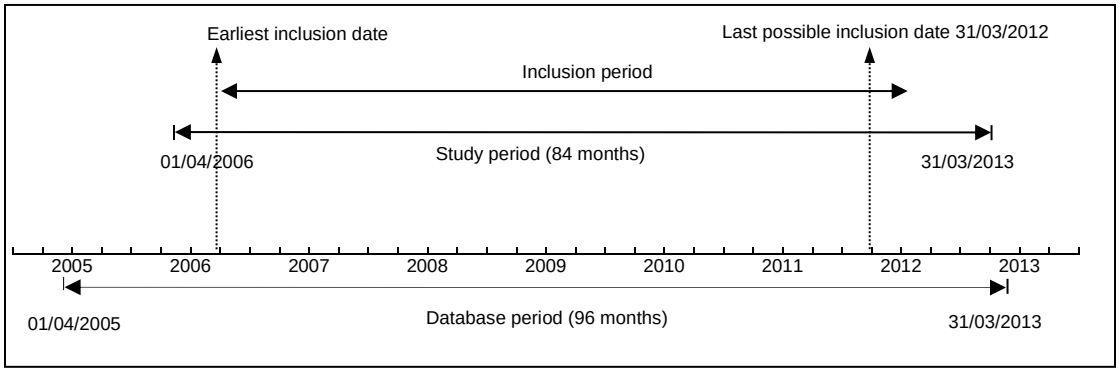
2. Assess the association between patient characteristics and antihypertensive drug classes' adherence and persistence patterns.

4.3. Methods

4.3.1. Study design

This study was a retrospective cohort study of adults with primary hypertension prescribed antihypertensive drugs, using the CPRD database from April 2006 to March 2013 (Figure 4.1). The date of first antihypertensive drug prescription is defined as the index date for each patient.

Figure 4.1 Time framework of the study



4.3.2. Cohort identification and selection

4.3.2.1. Inclusion criteria

The study cohort included people who were aged ≥18 years at the index date, had the diagnosis of primary hypertension and were prescribed at least two antihypertensive drug prescriptions during the study period (April 2006 to March 2013). Included patients were also required to have their first antihypertensive drug prescribed on or after the diagnosis date of hypertension to ensure that hypertension was at least one of the potential indications for the prescribed antihypertensive drug (since some of the

antihypertensive drugs may be used for other indications such as heart failure). Patients were also required to have at least one year of registration within CPRD prior to the index date and at least one-year follow-up time after the index date to retrieve patients' baseline characteristics and to ensure enough follow-up time to assess adherence and persistence patterns, respectively[283].

4.3.2.2. Exclusion criteria

Patients with previous history of hypertension-related CVDs diagnosis (myocardial infarction [MI], stroke, heart failure [HF] and chronic renal failure) are found to have different medication-taking behaviour – they usually have a higher adherence and are more willing to follow medical instructions – characteristics which are attributed partly to their higher awareness of being at greater risk[284, 285]. Therefore, patients with history of CVDs at or prior to the index date were excluded. Furthermore, the existence of CVDs may affect the selection of a particular antihypertensive drug class[89, 283], which in turn may confound the patient's behaviour toward that particular antihypertensive drug class. This criterion also ensured that antihypertensive drugs were purely prescribed for treating hypertension, rather than other CVDs.

Patients who were prescribed more than one antihypertensive drug class on their index date, either as one-pill combination therapy or as multiple combination therapies, were also excluded[211, 215, 286], because this would interfere with the study aim of measuring adherence and persistence to a specific antihypertensive drug class. Furthermore, these patients may have different medication-taking behaviour[89], and be high-risk patients, who were selectively prescribed this combination therapy[215]. Table 4.1 illustrates the inclusion criteria specified in the define tool, provided by the CPRD for cohort identification.

Table 4.1 Cohort identification and inclusion criteria

Criteria	Study definition	Operational definition	
		Inclusion	Exclusion
Prescription	Antihypertensive prescription during the study period	Antihypertensive drug codes to identify prescription	
HT diagnosis	Primary HT diagnosis	Read codes for primary HT to identify cases	
Study period	1/4/2006- 31/3/2013	Define tool	
Age	≥ 18 to 107 year at the index date	Define tool	
gender	Male, female	Define tool	If unidentifiable
Prior registration	At least 12-month registration prior to index date	Define tool	
Follow-up time	At least 12 months of follow-up after the index date	Define tool	

Patients with primary hypertension were identified from the clinical, referral and consultation files in the CPRD using the related diagnostic Read codes (Appendix 2). Antihypertensive prescriptions were identified from the therapeutic files in CPRD using corresponding product codes built in the product dictionary (Appendix 3). A patient list for the study cohort was generated using the same procedure described in Chapter 3 (section 3.7, page 74).

The generated patient list was then used for extracting patients' data from CPRD, and records related to the identified patients were extracted from the following files: patient, practice, clinical, test and therapy files. Any record before practice up-to-standard date (the date at which the practice data is deemed to be of good quality for research) or before patient registration date was excluded (only the record[s] was excluded but not the patient). The extracted data contain patients' demographics (such as age, sex),

medical history, clinical investigation results and drug prescriptions. Prescription data extracted from the therapy file contains information on prescribing date, quantity, strength and daily dose.

4.3.3. Data management

All extracted variable data were checked for any missing data. It was found that about 5.7% of the prescription records (n=623,934) were missing for data of numeric daily dose (NDD). A test suggested by Little in 1988[287] was used to determine the likelihood of NDD being missing completely at random (MCAR), in which the probability of NDD being missed does not depend on any of the observed or unobserved measurements. In this test, a binary variable was created taking the value of one if NDD was missing and zero otherwise, then a chi-squared test was performed to examine whether there was any significant association between this new created variable and an exposure variable (index drug class, for example) in the dataset, which has no missing data.

The highest missing proportion in NDD was for the "Other" drug class (6.5%) and the lowest was for the ARB drug class (5.0%), however, the p-value from a chi-squared test revealed that these differences were not statistically significant at the 5% level (p=0.06) (Table 4.2); therefore, there was no evidence that NDD was not MCAR with regards to the index drug class variable.

Table 4.2 Chi-squared test for missing of NDD completely at random

NDD Variable	ACEI (%)	CCB (%)	Diuretics (%)	BB (%)	ARB (%)	"Others" (%)
Missing	196,815 (5.6)	134,496 (5.4)	135,018 (5.9)	97,630 (6.2)	42,403 (5.0)	17,572 (6.5)
Non-missing	3,334,121 (94.4)	2,353,210 (94.6)	2,141,186 (94.1)	1,482,831 (93.8)	804,182 (95.0)	254,235 (93.5)

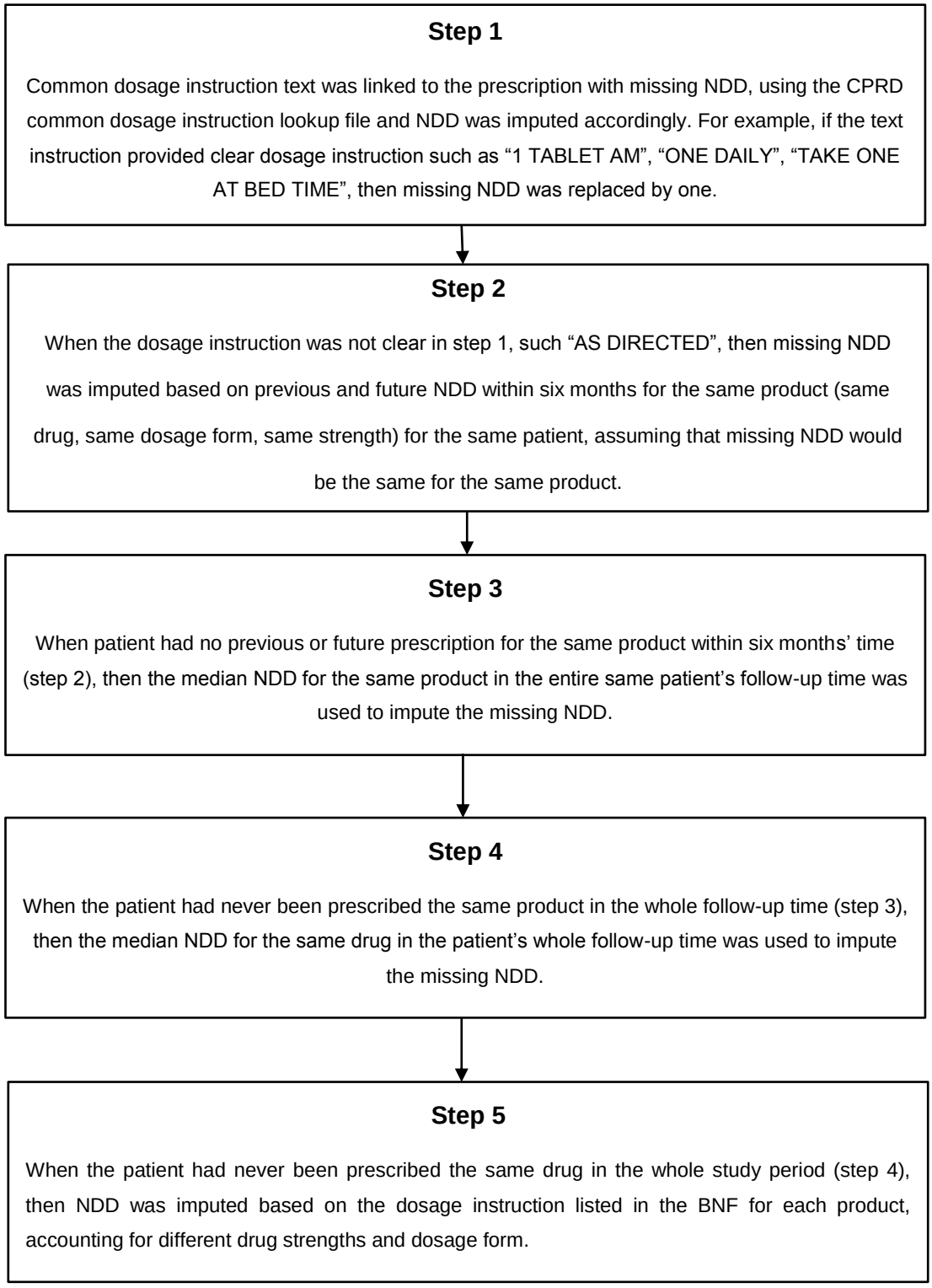
(Note) p=0.06, obtained from chi-squared test

4.3.4. Strategies for imputing missing NDD

Although the statistical test showed that NDD was MCAR with respect to antihypertensive drug classes, it is hard to determine whether the missing data were missing at random or due to another variable[288]. Therefore, two general approaches were applied to impute the missing NDD. The first approach was based on using individual patient data to impute the missing value as previous or future NDD for the same product or the same drug for the same patient. The second approach was to replace missing NDD by the recommended daily dose in BNF[176] for each product, accounting for different strengths and dosage forms.

The first approach was performed through five steps (Figure 4.2) following a sequential hierarchical order to make the best use of available recorded data within CPRD, which can provide the most explicit and accurate daily dose information. For example, the first step was based on dosage instructions for the prescription missing NDD, which certainly provides more accurate information than the second step, which based on the NDD for a future or previous prescription of the same product for the same patient; thus provides more accurate information than step three, which was based on the median NDD for the same product during the whole patient follow-up time, and so on.

Figure 4.2 Strategies for imputing missing NDD based on individual patient data



The baseline mean and median NDD prior to imputation was 1.006 and 1.0, respectively (Table 4.3). Of the five strategies in the first approach, strategy two and five resulted in the highest NDD imputation by 38.4% and 35.7%, respectively, with no change in median NDD, but a slight increase in mean NDD. Consistently, both imputation approaches revealed almost the same mean and median NDD, implying the reliability of the assumptions made; therefore, the first approach was adopted as it was based on patients' data.

Table 4.3 Results of NDD imputation using both patient and BNF based approaches

	Number of prescriptions	Number of Rx with missing NDD (%)	Number of imputed NDD (%)	Mean NDD (SD) after imputation	Median NDD (IQR) after imputation
Raw data	11,825,350	623,934 (5.7)	0	1.006 (1.99)	1.0 (1.0,1.0)
First approach (patients' data-based approach)					
Step 1	11,825,350	617,629 (5.6)	6,305 (1.0)	1.006 (1.99)	1.0 (1.0,1.0)
Step 2	11,825,350	377,874 (3.4)	239,755 (38)	1.03 (2.0)	1.0 (1.0,1.0)
Step 3	11,825,350	335,351 (3.1)	42,523 (6.8)	1.03 (2.0)	1.0 (1.0,1.0)
Step 4	11,825,350	222,988 (2.0)	112,363 (18)	1.04 (2.0)	1.0 (1.0,1.0)
Step 5	11,825,350	0	222,988 (35)	1.07 (2.0)	1.0 (1.0,1.0)
Second approach (BNF based approach)					
Step 1	11,825,350	623,934 (5.7)	623,934 (100)	1.06 (2.0)	1.0 (1.0,1.0)

(Note) BNF: British National Formulary; **IQR**: Inter quartile range; **NDD**: Numeric Daily Dose; **SD**: Standard deviation

4.3.5. Study outcomes

The primary outcome measures of this study were antihypertensive drugs' adherence and persistence patterns, including continuation, discontinuation, combination and switching of index drug.

4.3.5.1. Adherence to antihypertensive drug classes and therapy

The proportion of days covered (PDC) was used as a proxy to measure patients' adherence to antihypertensive drugs. The PDC was calculated as the number of days covered by antihypertensive drug (numerator) divided by the number of days in the measurement period (denominator, i.e. from the index date to end of follow-up date), and then multiplied by 100 to convert it to a percentage, then capped at 100%. The numerator was not solely the summation of day's prescription supplies during the measurement period; rather days' supply of a prescription was treated in such a way that it avoided over-counting covered days by adjusting for overlapping periods.

PDC and medication possession ratio (MPR) are the two most commonly used metrics to measure medication adherence using electronic databases[289]. Both metrics measure adherence by estimating the proportion of day's supply during a determined observation period. In general, the primary difference between PDC and MPR is that any medication oversupply is capped and truncated in PDC; while with MPR adherence, values greater than 100% are allowed[289], with MPR being measured solely using dispensing datasets. Consequently, PDC provides a more conservative estimate of adherence than MPR, especially when patients switch medication or concurrently use more than one drug at the same time[290, 291]. Accordingly, PDC was used as the metric to measure adherence to antihypertensive drug classes, particularly as it is considered the preferred method of medication adherence measurement[18].

In this study, adherence to both specific antihypertensive drug class (class adherence) and any antihypertensive drug therapy (therapy adherence) were measured. For measuring class adherence, patients were followed up from the prescription date of first-ever prescription of a specific antihypertensive drug class.

Prescribing episodes of the six specific antihypertensive drug classes were identified (diuretics, BBs, CCBs, ACEIs, ARBs and "Others"). For measuring therapy adherence, patients were followed up from the date of the patient's first-ever antihypertensive drug prescription (index date). For both class and therapy adherence, follow-up time ended with whichever was the earliest of: the end of the study period (31/03/2013), patient transferred out of the dataset or patient's death.

In measuring class adherence, a patient is considered non-adherent to a drug class if that class is switched to another drug class. The switching would imply that the patient fails to take the drug class as recommended, which, in fact, may not be the case since the patient may follow the prescriber's recommendation for switching the drug class. Therefore, adherence to any antihypertensive drug therapy (therapy adherence) was also measured to avoid misunderstanding of patients' medication-taking behaviours toward a particular antihypertensive drug class.

4.3.5.2. Calculating the numerator for PDC and managing prescription overlapping

The numerator for PDC calculation (the number of days supplied for each drug prescription) was derived from dividing the prescribed quantity by the NDD.

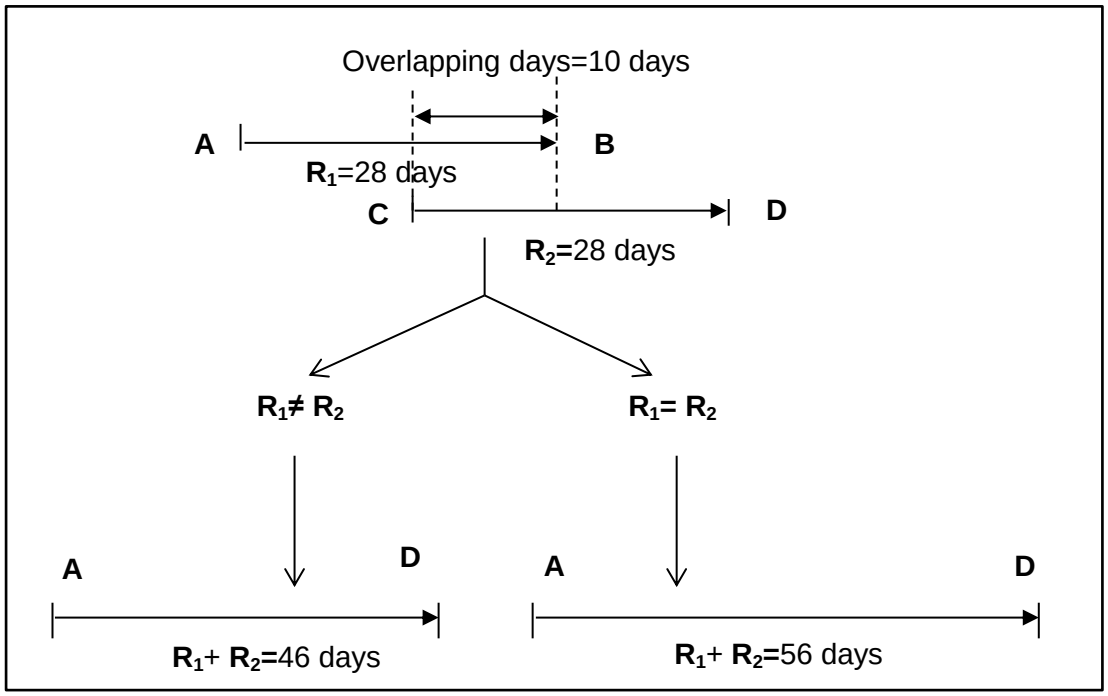
Individual patients' PDCs for both antihypertensive drug class and therapy share the same denominator (observation period) (index date to end of follow-up time), but a different numerator. For calculating class PDC, the numerator equals the number of days covered by the drug class during the observation period; while for calculating therapy PDC, it equals the number of days covered by at least one antihypertensive drug class throughout the observation period.

To avoid overestimation of PDC to antihypertensive drug class by double counting of overlapped supply days of prescriptions, two approaches were used to calculate PDC numerator. In the case of class adherence, where all prescriptions were of the same drug class, any overlapped supply days of prescriptions, resulting from early refills, were treated by shifting the prescribing date of the second overlapped prescription forward to the day after the supply of the previous prescription finished, assuming that the previous supply was consumed completely before the next prescription was initiated (Figure 4.3).

For therapy adherence, overlapped supply days of prescriptions may or may not be from the same class. The same above principle was applied when the overlapped supply days of prescriptions came from the same drug class; however, when the overlapped supply days of prescriptions were not of the same class, the overlapped days were eliminated assuming that any excess drug from the previous prescription was discarded to start the new prescribed drug class (Figure 4.3).

The approach of shifting the prescribing date of the overlapped prescription in case of a similar drug class overlapping, while eliminating the overlapped days in case of overlapping of two different drug classes, has been suggested by several other studies, such as the study by Yen *et al* (2012)[292]. Moreover, Choudhry *et al* (2011)[293] also adopted a similar approach in dealing with overlapping supply days of prescriptions, when evaluating the implications of therapeutic complexity on adherence to cardiovascular medications. Furthermore, Wang *et al* (2013)[294] in their paper at the SAS Global Forum 2013 clearly described the above approach for dealing with the issue of prescription overlapping during PDC calculation. Those studies suggested that there is enough evidence to support the use of these approaches in dealing with prescription overlapping.

Figure 4.3 Management of overlapping prescriptions



A PDC of 100% indicates full patient adherence and that the patient's follow-up duration was completely covered by the drug. PDC can be >100% if the number of days covered is greater than the number of days in the measurement period, which may either, reflect patients' early prescription refilling before the end of medication supply or stocking up medication for later use. However, based on literature, it is unlikely that hypertensive patients will actually use antihypertensive drugs at greater than the prescribed frequency[283]; hence PDC is usually truncated at 100%[283]. Truncation of PDC at 100% has been suggested in the PDC definition proposed by Hess *et al* (2006)[295], which was then used subsequently in many other adherence measurement studies[213, 292, 296, 297].

4.3.5.3. Persistence patterns of antihypertensive drugs

Based on the first-ever (index) antihypertensive drug class and sequential antihypertensive drug classes utilisation patterns, patients were classified into one

of the following four persistence patterns: continuers, combiners, switchers or discontinuers. The proportion of patients who continued, combined, switched or discontinued their index drug class was calculated.

Continuers were defined as patients whose index drug class was continually prescribed until the end of their follow-up time, without prescribing other antihypertensive drug classes. Combiners were patients who were prescribed an additional antihypertensive drug class with their index drug class, and the combination date was defined as the date of adding the prescription of the other antihypertensive drug class. Switchers were patients whose initial index drug classes were stopped, and prescribed another new antihypertensive drug class within 30 days; the switching date was defined as the date when another antihypertensive drug class was prescribed. Discontinuers were defined as patients whose index drug class was stopped, but no additional antihypertensive drug class was prescribed in the follow-up duration.

According to literature[221, 226, 307], a minimum period of discontinuation (gap) of ≥60 days between the end of one prescription day supply and any subsequent prescription of the same drug class is defined as a drug discontinuation episode with discontinuation date defined as the end date of supply for the last prescription. Drug discontinuation is used as a proxy for drug persistence[221, 307, 322].

Time to the first combination date was measured and defined as the first combination episode. Likewise, the time to first switching date (prescribing date of the first additional antihypertensive drug class after stopping index drug class within 30 days) was calculated and defined as the first switching episode. Switching was defined as discontinuation of one medication with the start of new medication at the same approximate time[283]. This approximate time window is recommended to be

about 30 days or equal to the duration of one medication supply[283]; in addition to the fact that medication is usually supplied for one month in the UK, 30 days was therefore chosen in this study.

Time to the first discontinuation episode was defined as the number of days from the index date to the discontinuation date. Time to discontinuing index drug class (class persistence) or discontinuing antihypertensive drug therapy (therapy persistence) was also measured. For the persistence of specific antihypertensive drug class (class persistence), patients were followed up from the prescription date of first-ever prescription of a specific antihypertensive drug class. Discontinuation episodes of the six specific antihypertensive drug classes (diuretics, BBs, CCBs, ACEIs, ARBs, and "Others") were identified. However, for persistence to antihypertensive drug therapy (therapy persistence), patients were followed up from the date of the patient's first-ever antihypertensive drug prescription (index date). For both class and therapy persistence, patients were censored, i.e. follow-up time ended without having the outcome of interest (discontinuation), at the final recorded data (patient leaves the practice), death, or end of the study period, whichever happened first and also when the patient switched their index drug (for class persistence only).

4.3.6. Study covariates

Adherence and persistence to drugs, including antihypertensive drugs, are often affected by many factors such as those related to patients' demographics and clinical status, and the health care system[298]. The WHO has identified five potential categories of factors that may affect adherence to antihypertensive drugs (Table 4.4)[279], in addition to patient demographics such as age and educational level[279].

Table 4.4 Categories of factors influencing adherence and/or persistence to antihypertensive drugs

Factor category	Positive impact	Negative impact
Patient-related	• Understanding of health risk associated with high BP • Contribution to the monitoring and management of high BP	• Lack of understanding the benefits of treating high BP • No belief in drug efficacy
Condition related		• Asymptomatic nature of HT • Life-long nature of HT
Therapy related	• Simple drug regimen (less dose frequency, monotherapy, less frequent changes in drug therapy) • Using newer drug classes (ACEIs, ARBs, CCs)	• Complex drug regimen • Drug adverse effects with drugs of low tolerability profile
Healthcare team and system related	• Good patient and physician relationship	• Failure to involve patient in treatment decision • Lack of physicians' knowledge in treating hypertension • No incentives and feedback on physicians' performance • No adequate follow-up
Socioeconomic related	• Social support[299]	• Low income status • Unemployment

Factors that were included in this study as potential determinants for adherence and persistence to antihypertensive drug classes were based on evidence of their importance in affecting medication-taking behaviour of antihypertensive drugs (Table 4.5). The included factors were related to either patients' demographics, such as age, gender and socioeconomic status, or patients' disease status, such as comorbidity, hypertension status and BP level, or patients' drug status, such as antihypertensive drug class, antihypertensive drug use status and switching of antihypertensive drug class. Although there are conflicting reports about the effect of gender[283], in general, women tend to exhibit more non-adherence and non-persistence than men[300, 301]. New and existing hypertensive patients or drug users have been reported to have different medication-taking behaviour[283], with existing patients being more adherent and persistent[302]. This difference in medication-taking behaviour could be related to differences in their understanding, perceptions and

awareness of the health risk associated with high BP[303] and the benefits of treating high BP[304], and these variations in beliefs and understanding have been identified as an important factor for adherence to antihypertensive drug therapy by the WHO[279].

Presence of comorbid conditions, measured with the Charlson comorbidity index (CCI), has been considered a key factor for non-adherence[305], since it may affect drug adherence either directly, or indirectly, through its effect on the selection of proper antihypertensive drug therapy as it affects the control and the target BP level[283]. Additionally, given the importance of BP level as an indicator of treatment failure and/or treatment inefficacy, it may play an essential role in either combining or switching initially started antihypertensive drug class; therefore, BP level was also included as a potential factor for combining and switching the index drug class.

Table 4.5 Potential factors available in CPRD associated with antihypertensive drug adherence and persistence patterns

Factor	Definition	Hypothesis
Age	Age was calculated at the index date. Its use as a continuous or categorical covariate was tested in each model. Age was categorised into five categories by decades	Older patients have been reported to have higher adherence and persistence rate compared with younger people[191, 209, 213, 302, 306, 307]
Gender	Defined as male or female	Whenever differences found, females seem to have lower adherence and persistence than males [191, 209], although findings are not consistent[204]
Drug class	Defined as six drug classes, Diuretics, ACEIs, CCBs, BBs, ARBs and "Others"	Higher adherence and persistence rates associated with ARBs and ACEIs compared with other drug classes [203, 209, 308, 309]
Comorbidity	Defined into three categories based on the Charlson comorbidity index score	Higher comorbidity index associated with lower adherence and persistence[209, 213, 283, 310]
Hypertension and drug use status	Defined as incident or new HT patient or users and prevalent or old HT patient or users.	Prevalent hypertensive patients and drug users were found to be more adherent and persistent than new patients and drug users [283, 302]
Follow-up time	Defined as the time from the index date to end of study time or follow-up time. Its inclusion as continuous or categorical covariate was tested and categorised into five categories when necessary	Adherence and persistence have shown to be decreased with time [308, 311]
Switching index drug	Defined as stopping index drug and taking new drug class	Switching is associated with lower adherence and persistence rate [3, 233, 292, 312]
Socioeconomic status	Defined based on Townsend deprivation index as a proxy for socioeconomic status	Low income patients tend to have lower adherence and persistence rate[209, 213, 279]
BP level	Defined into four categories according to the new European classification of HT, based on the SBP and DBP values	High BP level may be associated with combining and/or switching index drug class

Study covariates were identified and extracted from the relevant variables within the CPRD files such as gender, year and month of birth variables in patient files at or prior to index date. Age was calculated on the index date, and was analysed both as a continuous and categorical covariate of five categories by categorising it by decades (<50 years, 50–59 years, 60–69 years, 70–79 years, ≥80 years)[212, 278]. Comorbidity was measured by CCI[313] and categorised into three categories (0, 1, 2+).

SBP and DBP were measured at the index date. In case of multiple measurements of SBP or DBP on the index date, the mean of the readings was used. The SBP and DBP values were then used to categorise BP level into four stages according to the 2013 European Society of Hypertension (ESH) and European Society of Cardiology (ESC) classification of hypertension[89]. The stages were high normal (SBP 120–129 and/or DBP 80–84), Grade 1 (SBP 130–139 and/or DBP 85–89), Grade 2 (SBP 140–159 and/or DBP 90–99) and Grade 3 (SBP 160–179 and/or DBP 100–109).

Patients' hypertension status was categorised into either existing (prevalent) or new (incident) based on whether they had any hypertension-related codes in the year prior to index date or not[314], respectively. Likewise, patients' drug use status was categorised into either new (incident) and existing (prevalent) depending on whether they had any prescription of that drug class in the year prior to index date or not, respectively. Based on the antihypertensive drug class at index date (first-ever antihypertensive drug date), index drugs were stratified into six classes, i.e., diuretics, BBs, CCBs, ACEIs, ARBs and "Others".

The socioeconomic status (SES) was measured using Townsend deprivation score quintile-2001 census[315]. The CPRD provided a linkage Townsend score file from which the study patients were linked to their score using the patient identifier. This

score is a measure of deprivation based on areas linked through patients' postcodes, using four domains[315]:

- Unemployment: percentage of unemployment among economically active population over 16 years old
- Car ownership: percentage of households in which no residents own a car
- Home ownership: percentage of households not owning their own home
- Household overcrowding: percentage of private households with ≥1 resident per room

The scores for all four domains are then summed to calculate the overall score. As such the index is the ranking of areas, rather than the actual score itself and was grouped into five quintiles with 1 being the least deprived and 5 being the most deprived.

4.4. Data analysis

4.4.1. Descriptive statistics

The study variables were stratified by the type of index drug class, and were compared among the strata using descriptive analysis. Normally distributed continuous variables, such as age and BP values, were presented as means±SD and compared using one-way analysis of variance. Non-normally distributed continuous variables, such as follow-up time, were presented as medians±IQR and compared using the non-parametric Kruskal–Wallis test. Categorical variables were presented as a proportion of patients and were compared across the six index drug classes using chi-squared and MnNemer tests.

The distribution of PDC (median, IQR) before and after management of overlapping prescriptions and PDC truncation at 100% was examined to evaluate the impact of each of these two procedures on PDC distribution. In this study, PDC was analysed both as a continuous variable and a dichotomous variable. This dichotomisation

makes these results easier to compare with those from other adherence studies as almost all of adherence studies analysed PDC as a dichotomous variable. It is recommended that adherence is measured both in continuous and dichotomous formats[283]. The most common argument for the widespread use of PDC dichotomisation in adherence studies seems to be simplicity, as it is perceived to simplify statistical analysis and lead to easy presentation and interpretation of results[316]. Furthermore, it has been argued that dichotomisation of PDC is generally more informative, in terms of interpretation and its association with clinical outcomes[317]. However, it is well known that dichotomisation of a continuous variable is associated with loss of information from the original data[318], which potentially leads to loss of estimation efficiency and loss of power in hypothesis testing[316, 319, 320] due to decrease in the number of degrees of freedom[321]. Furthermore, it has been recommended by International Society for Pharmaceutical and Outcomes Research (ISPOR) checklist not to convert continuous adherence data into categorical data, unless empirical evidence exists for such a cut-off point for dichotomisation[321]. Therefore, analysing PDC as a continuous variable would provide more accurate insights into patients' medication-taking behaviour.

For dichotomisation of PDC, a cut-off point of 80% was used such that patients with a PDC value of ≥80% were classified as adherent; while those with a PDC value of <80% were classified as non-adherent. Proportions of adherent (PDC≥80%) and non-adherent (PDC<80%) patients were calculated overall and by each study covariate. Proportion of non-adherent patients across the different levels of study covariates was compared using the chi-squared test.

Empirical evidence provided by Karve *et al* (2008)[296] suggested that a cut-off point of ≥ 80% is reasonable for identifying adherent and non-adherent patients, depending on subsequent hospitalisation predication across five highly prevalent

chronic diseases, including hypertension. Furthermore, this 80% cut-off point is also derived empirically by Steiner *et al* (2000)[322], who found that consumption of at least 80% of antihypertensive drugs was associated with adequate BP control. Moreover, it has been reported frequently in previous studies that an adherence rate of 80% was related to less healthcare utilisation and cost[322-325]. Consequently, the majority of adherence studies often dichotomise the adherence measure using a cut-off point of ≥80%[283] as has been supported by the ISPOR[326].

For instance, in a systematic review of 139 studies to assess the significance of compliance and persistence in the management of hypertension, diabetes and dyslipidaemia[327], more than 50% of studies, which presented compliance as a continuous measure, used at least one cut-off point, mostly 80%. Similarly, a recent meta-analysis of 44 studies[305] to assess the adherence to cardiovascular therapy and its clinical consequences indicated that the majority of the included studies categorised adherence using 80% as a cut-off point.

Finally, the proportion of patients with the various persistence patterns (continuation, discontinuations, combination and switching) was estimated and stratified by the six antihypertensive drug classes.

4.4.2. Strategies to assess the association between study covariates and study outcomes

In order to assess the association between the study variables and study outcomes (adherence, persistence patterns), a two-step procedure was followed. Firstly, univariate analyses were performed of all the study variables with the outcome of interest (adherence, persistence patterns) to determine which covariate was significantly associated with outcome. Univariate regression type was selected according to the nature of the study outcome (continuous or categorical). Secondly,

an initial multivariate model was build including all the variables that appeared to be significantly associated with the outcome in the univariate analysis. Only the results from the multivariate models are presented.

In all the regression models for class PDC, the standard errors were estimated using the robust standard error estimate to account for within-patient correlation as some patients may appear more than once in the analysis depending on the number of antihypertensive drug classes being prescribed.

4.4.3. Investigating the association between study covariates and PDC as a continuous variable

The distribution of PDC was checked using a histogram, and it appeared to have a skewed distribution, which violated normality assumption. Therefore, non-parametric tests were used to assess the association between individual study variables and PDC. Three non-parametric tests including spearman's rank correlation, Wilcoxon rank sum (Mann–Whitney) and Kruskal–Wallis tests were used depending on the nature of the studied variable, i.e. whether it is continuous (age, follow-up time), binary (gender, drug use status, hypertension status, switching) or multilevel categorical variable (drug class, CCI).

The multivariate analysis was used to assess the potential association between a single factor and adherence having accounted for other potential influencing factors. All the factors that appeared to be significantly associated with adherence in the univariate analyses were included in the multivariate model. As the underlying linear regression assumption of normally distributed residuals was violated, the Generalised Linear Model (GLM) approach was used as an alternative to normal multivariate linear regression.

In general, multivariate regression analysis of a skewed continuous dependent variable, such as PDC in this study, is conducted either by retaining the normal distribution of the variable, for example via log transformation, or by using an alternative regression model without any distribution assumptions. In this study, log transformation of PDC failed to achieve normality to satisfy the linear regression assumption. As a result, a GLM model with gamma family and log link function was used instead. The latter approach has been used widely to model skewed continuous data with values greater than or equal to zero.

A number of diagnostic tests were used to inform and assess the selection of the appropriate link and variance function, and to check the GLM models' goodness of fit (Appendix 5).

4.4.4. Investigating the association between study covariates and PDC as a binary categorical variable

The association between individual covariates and proportion of patients with PDC<80% was assessed using univariate logistic regression, with proportion of non-adherent patients as the dependent variable. Unadjusted odds ratio (OR) was then calculated and covariates that were significantly associated with patient non-adherence identified.

Covariates that significantly associated with patient non-adherence in the univariate logistic regression were then included in a multivariate logistic regression model to determine the adjusted OR for each single variable having accounted for the other potential influencing variables.

Age and follow-up time were included in the multivariate logistic regression model as categorical rather than continuous variables, as these two variables failed to

satisfy the logistic regression model assumption of a linear relationship between the continuous explanatory variable (age, follow-up time) and log odds of the outcome (proportion of non-adherent patients). This assumption was tested by a two-step procedure. Firstly, age and follow-up time, one at a time, were included in the multivariate logistic regression model as a categorical variable, then the fit of this model was compared with that of another model in which the variable was included as a linear trend across the categories, using likelihood ratio test (LRT). Secondly, if the fit of the first model was significantly better than the fit of the second model (p-value from LRT <0.05), a more complex, non-linear trend relationship between the variable and the outcome is indicated, and it would be better to include the continuous variable as a categorical variable in the model. If, however, there was no difference in the fit between the two models, the variable could be fitted as a continuous variable.

4.4.5. Cox regression of covariates associated with non-persistence and time to non-persistence

The time to first discontinuing specific antihypertensive drug class and antihypertensive drug therapy as well as time to first combining and switching of index drug class were analysed with Cox proportional hazard (PH) models. The main analysis was to find the association between drug discontinuation (as proxy for persistence), combination and switching with the study covariates.

The association between each covariate with the persistence patterns (time to first discontinuation, combining and switching episode) was tested with different univariate Cox PH models and those found to be significantly associated with the persistence patterns were identified.

All the study covariates that significantly associated with persistence patterns in the univariate Cox PH analyses were included in a multivariate Cox PH regression to obtain the proportional hazard ratio for each covariate adjusted for other study covariates. Testing of whether fitting continuous covariates, for example, age, as a continuous or categorical variable was checked in the same way as described earlier for logistic regression (section 4.4.4).

The proportional hazard (PH) assumption of Cox regression was checked statistically using Schoenfeld residuals. Both details about this test and the results from it are presented in Appendix 6.

4.5. Results

4.5.1. Baseline characteristics of the study cohort

During the study period, 371,605 prescribing episodes of the six antihypertensive drug classes were identified from 176,835 adults with primary hypertension, who contributed 850,310.4 person-years of follow-up time. The majority of patient's first-ever antihypertensive drug prescription was ACEIs (36.4%), followed by CCB (24.4%). The mean age for the study cohort at index date was 60.8±13.6 years, with more than half being female (55.6%), and the median follow-up time was 5.3 years. Mean SBP and DBP at first-ever antihypertensive prescription was 157.4±17.9 and 90.1±10.3 mmHg, respectively. The majority of the patients were new drug users (51.0%), 53.4% were existing hypertensive patients and 62.5% had no comorbidity. More than half of the patients had a deprivation score quintile ≤3 (25.2%, 24.2% and 20.8% with a score quintile of 1, 2 and 3, respectively).

Of the 371,605 antihypertensive drug class episodes (Table 4.6), the most commonly prescribed antihypertensive drug class of those episodes was ACEIs (29.7%) and CCB (25.1%). There were statistically significant differences in all patients' demographic and clinical characteristics across the prescribing episodes of the six antihypertensive drug classes. The mean age of patients at the start of an antihypertensive drug class episode was 62.2±12.9 years. Mean SBP and DBP was 155.3±19.4 and 89.7±12.2 mmHg, respectively, with the highest mean SBP in the CCB class and the lowest in the BB class. In contrast, the highest DBP was in the ACEIs class and the lowest in the BB class. Slightly over half of patients at first-ever antihypertensive drug class episodes were new drug users (52.2%), with the highest percentage in ACEIs class, and more than half of them (55.5%) were existing hypertensive patients, with the highest in ACEIs class. More than half of the patients at first-ever, antihypertensive drug class episode had a deprivation score quintile of ≤3, for all antihypertensive drug classes.

Table 4.6 Characteristics of the 371,605 first-ever antihypertensive drug class prescribing episodes

Covariates	ACEIs	CCBs	Diuretics	BBs	ARBs	"Others"	Total
Number of episodes (%)	110,493 (29.7)	93,119 (25.1)	71,883 (19.3)	42,164 (11.4)	39,862 (10.7)	14,084 (3.8)	371,605 (100)
Age (mean± SD, years)	57.9 (12.4)	64.8 (12.0)	67.4 (12.1)	61.5 (13.1)	62.2 (12.6)	64.7 (14.1)	62.2 (12.9)
Age categories (%)[a]							
< 50 years	30,717 (27.8)	10,895 (11.7)	6,110 (8.5)	8,095 (19.2)	6,856 (17.2)	1,986 (14.1)	68,004 (18.3)
50-59 years	33,369 (30.2)	19,183 (20.6)	12,508 (17.4)	10,667 (25.3)	10,245 (25.7)	2,620 (18.6)	90,672 (24.4)
60-69 years	26,629 (24.1)	31,195 (33.5)	21,924 (30.5)	11,637 (27.6)	11,241 (28.2)	3,986 (28.3)	10,5164 (28.3)
70-79 years	14,585 (13.2)	22,069 (23.7)	19,912 (27.7)	8,222 (19.5)	8,132 (20.4)	3,662 (26.0)	71,720 (19.3)
≥ 80 years	5,193 (4.7)	9,777 (10.5)	11,429 (15.9)	3,542 (8.4)	3,388 (8.5)	1,831 (13.0)	36,046 (9.7)
Gender (%)[a]							
Male	61,655 (55.8)	46,839 (50.3)	23,865 (33.2)	17,709 (42.0)	18,695 (46.9)	6,648 (47.2)	177,627 (47.8)
Female	48,838 (44.2)	46,280 (49.7)	48,018 (66.8)	24,455 (58.0)	21,167 (53.1)	7,436 (52.8)	193,978 (52.2)
Townsend deprivation score (quintile) (%)[b]							
1 (Least deprived)	28,176 (25.5)	22,535 (24.2)	17,252 (24.0)	11,131 (26.4)	11,042 (24.5)	3,451 (24.5)	97,361 (26.2)
2	26,739 (24.2)	22,162 (23.8)	17,539 (24.4)	10,372 (24.6)	10,045 (25.2)	3,324 (23.6)	86,212 (23.2)
3	22,983 (20.8)	18,996 (20.4)	15,455 (21.5)	8,728 (20.7)	81,72 (20.5)	3,042 (21.6)	73,578 (19.8)
4	19,889 (18.0)	17,227 (18.5)	13,298 (18.5)	7,547 (17.9)	6,418 (16.1)	2,577 (18.3)	63,544 (17.1)
5 (Most deprived)	12,707 (11.5)	12,292 (13.2)	8,338 (11.6)	4,385 (10.4)	4,186 (10.5)	1,648 (11.7)	50,910 (13.7)
Median follow up time (IQR, years)[b]	4.6 (2.9, 6.4)	4.4 (2.6, 6.4)	5.6 (3.6, 6.9)	6.8 (4.6, 7.0)	6.5 (4.4,6.9)	6.5 (4.2, 6.9)	5.1 (3.2, 6.8)
Follow up time categories (%)[a]							
≤2 years	14,364 (13.0)	14,247 (15.3)	5,391 (7.5)	2,150 (5.1)	2,073 (5.2)	845 (6.0)	40,877 (11.0)
>2-3 years	15,248 (13.8)	13,502 (14.5)	7,404 (10.3)	2,741 (6.5)	2,830 (7.1)	986 (7.0)	44,221 (11.9)
>3-4 years	16,021 (14.5)	13,409 (14.4)	8,195 (11.4)	3,500 (8.3)	34,28 (8.6)	1,422 (10.1)	47,194 (12.7)
>4-5 years	16,242 (14.7)	12,944 (13.9)	9,201 (12.8)	4,048 (9.6)	4,345 (10.9)	1,451 (10.3)	49,052 (13.2)
>5 years	48,617 (44.0)	39,017 (41.9)	41,620 (57.9)	29,726 (70.5)	27,226 (68.3)	9,380 (66.6)	18,6917 (50.3)

(Continued) **Table 4.6 Characteristics of the 371,605 first-ever antihypertensive drug class prescribing episodes**

Covariates	ACEIs	CCBs	Diuretics	BBs	ARBs	"Others"	Total
BP*							
SBP (mean+SD)	156.7 (19.4)	161.4 (21.0)	153.8 (19.7)	145.4 (18.7)	148.4 (18.8)	150.9 (19.0)	155.3 (20.4)
DBP (mean+SD)	92.5 (12.2)	91.3 (12.8)	87.0 (11.1)	84.8 (11.0)	86.1 (11.3)	85.0 (11.4)	89.7 (12.3)
BP categories (%)[a]							
Normal	4,972 (4.5)	2,980 (3.2)	4,385 (6.1)	5,523 (13.1)	3,867 (9.7)	1,028 (7.3)	22,296 (6.0)
High normal	9,281 (8.4)	6,798 (7.3)	9,129 (12.7)	8,391 (19.9)	6,936 (17.4)	2,099 (14.9)	41,248 (11.1)
Grade 1	36,573 (33.1)	27,749 (29.8)	28,538 (39.7)	18,299 (43.4)	17,300 (43.4)	6,183 (43.9)	13,2663 (35.7)
Grade 2	40,330 (36.5)	33,523 (36.0)	20,487 (28.5)	6,915 (16.4)	8,212 (20.6)	3,436 (24.4)	11,5941 (31.2)
Grade 3	19,336 (17.5)	21,790 (23.4)	9,273 (12.9)	2,994 (7.1)	3,588 (9.0)	1,352 (9.6)	59,828 (16.1)
CCI (%)[a]							
0	65,412 (59.2)	58,292 (62.6)	44,208 (61.5)	30,400 (72.1)	22,522 (56.5)	7,535 (53.5)	229,280 (61.7)
1	24,529 (22.0)	18,251 (19.6)	14,520 (20.2)	6,072 (14.4)	9,288 (23.3)	3,451 (24.5)	75,807 (20.4)
≥2	20,552 (18.6)	16,575 (17.8)	13,155 (18.3)	5,692 (13.5)	8,052 (20.2)	3,098 (22.0)	66,517 (17.9)
Hypertension status (%)[a]							
Incident cases	62,650 (56.7)	51,960 (55.8)	26,165 (36.4)	7,252 (17.2)	6,458 (16.2)	2,225 (15.8)	165,364 (44.5)
Prevalent cases	47,843 (43.3)	41,159 (44.2)	45,718 (63.6)	34,912 (82.8)	33,404 (83.8)	11,859 (84.2)	206,241 (55.5)
Drug use status (%)[a]							
Incident users	72,925 (66.0)	60,993 (65.5)	29,184 (40.6)	9,698 (21.0)	9,328 (23.4)	3,606 (25.6)	193,978 (52.2)
Prevalent users	37,568 (34.0)	32,126 (34.5)	42,699 (59.4)	33,310 (79.0)	30,534 (76.6)	10,478 (74.4)	177,627 (47.8)

(Note) ***p<0.001 from One-way repeated ANOVA; **a: p<0.001 from McNemar test; **b**: p<0.001 Kruskal-Wallis test; **IQR**: Interquartile range; **BP**: Blood pressure; **CC**I: Charlson comorbidity index; **SBP**: Systolic blood pressure; **DBP**: Diastolic blood pressure; **ACEIs**: Angiotensin converting enzyme inhibitors; **ARBs**: Angiotensin receptor blockers; **CCBs**: Calcium channel blockers; **BBs**: Beta-blockers

4.5.2. Management of prescription overlapping

Of the 11,116,920 prescriptions included in the study period, there were 3,468,479 (31.2%) prescriptions with overlapped days of supply, of which 1,892,536 (54.5%) overlaps were between the same drug classes and the rest between two different antihypertensive drug classes. Prior to managing overlapping days of supply, ~35.2% (n=62,305) and 68.3% (n=120,866) of patients had class and therapy PDC values greater than 100%, respectively. However, the proportion declined to 25.4% and 41.0%, respectively, after accounting for overlapped days of supply.

Accounting for overlapping had no effect on median class PDC, but it led to a reduction in the median therapy PDC to 98.3% (IQR: 86.5–103.0%). Furthermore, truncation of PDC at 100% had no impact on median class and therapy PDC (Table 4.7).

Table 4.7 Median class and therapy PDC before and after accounting for overlapped days of supply and truncation at 100%

	Class PDC (median, IQR)			Therapy PDC (median, IQR)		
	Overlapped	**Not overlapped**	**Not overlapped and truncated**	**Overlapped**	**Not overlapped**	**Not overlapped and truncated**
ACEIs	95.7 (51.3, 103.1)	95.7 (51.3, 103.1)	95.7 (51.3, 100)	106.7 (95.0, 166.7)	98.3 (85.8,103.2)	98.3 (85.8,103.2)
CCBs	94.3 (50.4, 102.3)	94.3 (50.4, 102.3)	94.3 (50.4, 100)	109.4 (96.5, 180.0)	98.6 (86.5, 103.3)	98.6 (86.5, 103.3)
Diuretics	90.6 (44.2, 101.2)	90.6 (44.2, 101.2)	90.6 (44.2, 100)	117.5 (96.7, 185.0)	97.8 (85.9, 102.3)	97.8 (85.9, 102.3)
BBs	86.7 (24.3, 101.0)	86.7 (24.3, 101.0)	86.7 (24.3, 100)	115.8 (97.8, 184.6)	98.5 (88.0, 102.4)	98.5 (88.0, 102.4)
ARBs	97.4 (74.2, 102.4)	97.4 (74.2, 102.4)	97.4 (74.2, 100)	111.8 (97.6, 178.7)	98.3 (88.7, 102.5)	98.3 (88.7, 102.5)
"Others"	84.4 (267, 101.6)	84.4 (267, 101.6)	84.4 (267, 100)	165.4 (101.1, 255.3)	98.6 (86.8, 103.4)	98.6 (86.8, 103.4)
Overall	94.0 (47.3, 102.2)	94.0 (47.3, 102.2)	94.0 (47.3,100)	110.0 (96.3, 178.2)	98.3 (86.5, 103.0)	98.3 (86.5, 103.0)

(Note) PDC: proportion days covered; **IQR**: interquartile range **; ACEIs**: Angiotensin converting enzyme inhibitors; **ARBs**: Angiotensin receptor blockers; **CCBs**: Calcium channel blockers; **BBs**: Beta-blockers

4.5.3. Associations between covariates and PDC as a continuous variable

4.5.3.1. Univariate analysis of covariates, and class and therapy PDC

The overall class and therapy PDCs were non-normally distributed (Figure 4.4, Figure 4.5). The overall mean class and therapy PDC was 73%±33.8 and 87%±22.2, respectively; whereas the overall median PDC was 93.3% (IQR: 47.3–100%) and 98.3 (IQR: 86.5–100%), respectively.

The univariate analysis indicated that all study covariates were significantly associated with both class and therapy PDC (Table 4.8). The highest-class PDC was in ARBs episodes, followed by ACEIs, and the lowest was in “Others”. On the other hand, therapy PDC varied only slightly across the six drug classes with the highest in patients started on CCB and the lowest in diuretics. Higher class and therapy PDCs were associated with increasing age, lower deprivation quintile, increasing follow-up time, prevalent drug users and with ≥2 CCI. Male and prevalent hypertensive patients were associated with higher class PDC, but lower therapy PDC. Compared with least deprived patients, the most deprived patients had lower class and therapy PDC.

Figure 4.4 Distribution and cumulative frequency of class PDC

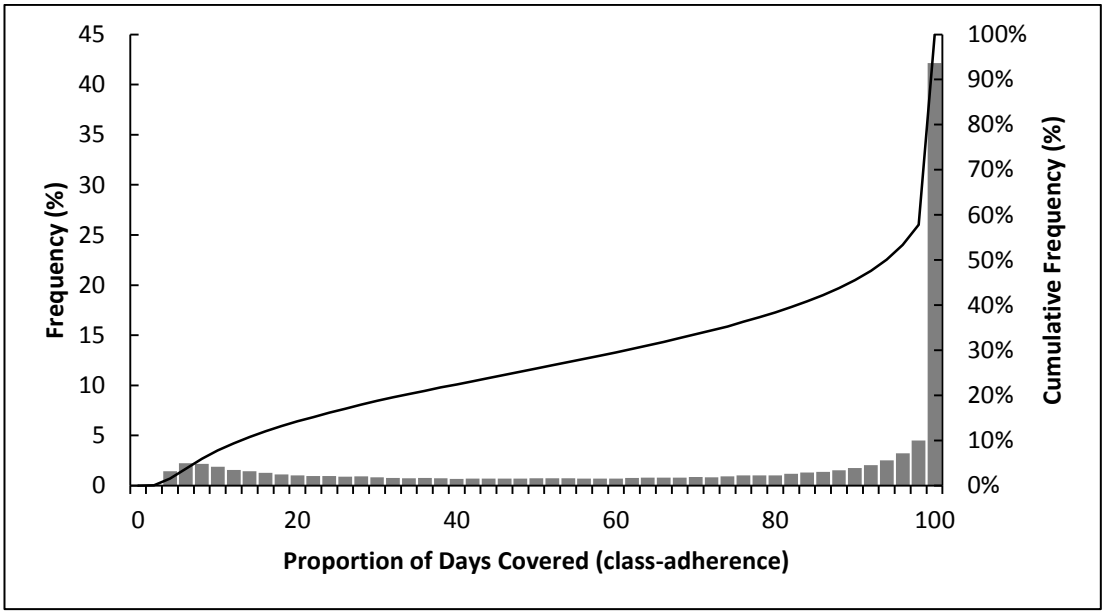


Figure 4.5 Distribution and cumulative frequency of therapy PDC

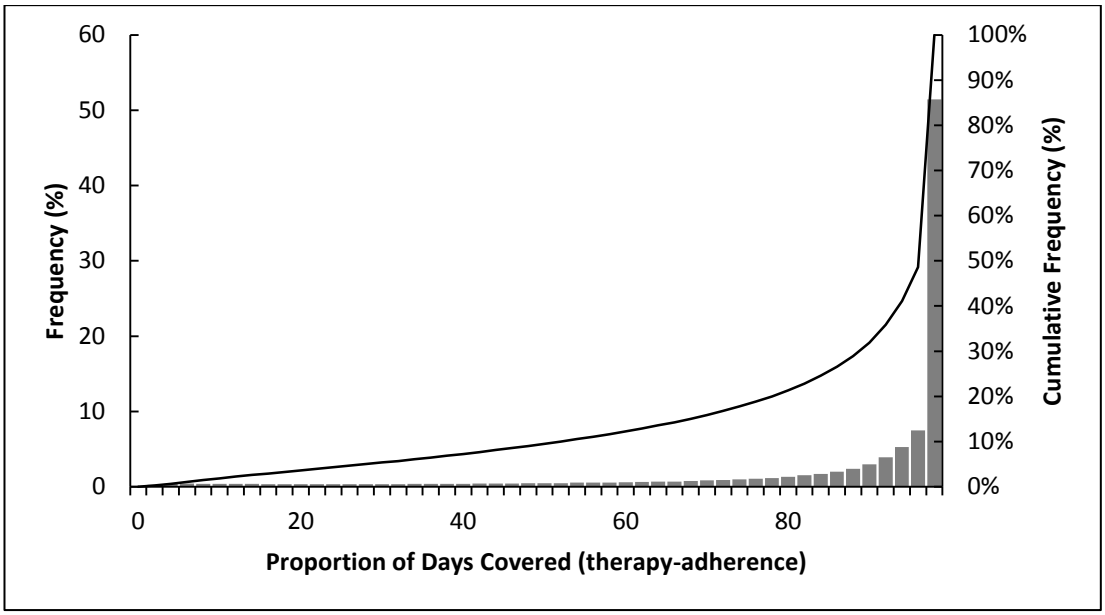


Table 4.8 Univariate analysis of covariates, and class and therapy PDC as continuous variables

Covariates	Class PDC		Therapy PDC		Statistical test
	Median (IQR)	p-value	Median (IQR)	p-value	
Overall	93.9 (47.3, 100)		98.3 (86.5, 100)		
Index drug class					
ACEIs	95.7 (51.3, 100)		98.3 (85.8, 100)		
CCBs	94.3 (50.4, 100)		98.6 (86.5, 100)		
Diuretics	90.6 (44.2, 100)	P=0.001	97.8 (85.9, 100)	P=0.0001	Kruskal-Wallis test
BBs	86.7 (24.3, 100)		98.5 (88.0, 100)		
ARBs	97.4 (74.2, 100)		98.3 (88.7, 100)		
"Others"	84.4 (26.7, 100)		98.5 (86.8, 100)		
Gender					
Male	94.2 (51.1,100)	P<0.001	97.9 (85.7, 100)	P<0.001	Wilcoxon rank sum (Mann-Whitney) test
Female	93.6 (43.7, 100)		98.7 (87.2, 100)		
Townsend deprivation score (quintile)					
1 (Least deprived)	95.3 (48.3, 100)		98.8 (89.4, 100)		
2	94.6 (47.8, 100)	P=0.001	98.6 (88.2)	P=0.0001	Kruskal-Wallis test
3	94.2 (47.7, 100)		98.3 (86.8, 100)		
4	93.0 (46.9, 100)		97.9 (84.1, 100)		
5 (Most deprived)	89.6 (45.1, 100)		96.6 (78.1, 100)		
Drug use status					
Incident users	92.7 (37.9, 100)		98.2 (82.7, 100)		Wilcoxon rank sum (Mann-Whitney) test
Prevalent users	94.9 (57.0, 100)	P<0.001	98.4 (89.4, 100)	P<0.001	
Hypertension status					
Incident cases	93.3 (39.3, 100)	P<0.001	98.5 (84.0, 100)	P= 0.0079	Wilcoxon rank sum (Mann-Whitney) test
Prevalent cases	94.3 (53.1, 100)		98.2 (88.0, 100)		
Switching index drug					
No	NA	NA	98.7 (88.9, 100)	P<0.001	Wilcoxon rank sum (Mann-Whitney) test
Yes			96.7 (78.4, 100)		
CCI					
0	93.7 (45.5, 100)	P=0.001	98.1 (85.8, 100)	P=0.0001	Kruskal-Wallis test
1	94.3 (50.6, 100)		98.5 (87.1, 100)		
≥2	94.3 (49.1, 100)		98.9 (87.7, 100)		
Age (years)	0.08*	P<0.001	0.15*	P<0.001	Spearman's rank correlation test
Follow up time (years)	0.03*	P<0.001	0.02*	P<0.001	Spearman's rank correlation test

(Note) PDC: Proportion days covered; **IQR**: Interquartile range**; ACEIs**: Angiotensin converting enzyme inhibitors; **ARBs**: Angiotensin receptor blockers; **CCBs**: Calcium channel blockers; **BBs**: Beta-blockers; **CCI**: Charlson comorbidity index; **NA**: Not applicable

4.5.3.2. Multivariate analyses of covariates associated with class and therapy PDC

After adjusting for the other covariates, all the study covariates were significantly associated with class and therapy PDC (Table 4.9). Compared with diuretics, patients on ARBs had the highest-class PDC value (13% higher, p<0.001), followed by ACEIs (8% higher, p<0.001), and “Others” had the lowest class PDC (11% lower, p<0.001). In contrast, for therapy PDC, patients with ACEIs had the highest value (4% higher, p<0.001), followed by ARBs (3% higher, p<0.001). Female gender was associated with significantly lower class PDC by 3.4% compared with male, but higher therapy PDC by 0.4%. Prevalent or existing drug users had both higher class and therapy PDC compared with new drug users.

Prevalent or existing hypertensive patients were associated with higher class and therapy PDC (2% and 3% higher, respectively) compared with newly diagnosed hypertensive patients. Compared with patients with no comorbidity, having low comorbidity score (CCI score=1) was not significantly associated with class and therapy PDC; however, having a comorbidity score of ≥2 was associated with significantly lower class and therapy PDC. Increasing age was associated with higher class and therapy PDC – for each one-year increase in age, class and therapy PDC was increased by 0.3%.

Adherence to index drug class (class PDC) was higher earlier in the course of therapy such that PDC was significantly declining by 1.4% for each one-year increase in the course of therapy. In contrast, adherence to antihypertensive therapy (therapy PDC) was higher in the later course of therapy, such that its value was significantly increasing by 0.7% for each one-year increase in the course of therapy. Switching index drug class had therapy PDC level of 4.3% lower compared

with those who stayed on their index drug class. Higher level of deprivation was associated with both lower class and therapy PDC.

Table 4.9 Multivariate analyses of covariates associated with class and therapy PDC as continuous variables

Covariates	Class PDC		Therapy PDC	
	Coefficients (95% CI)	**p-value**	**Coefficients (95% CI)**	**p-value**
Index drug class				
Diuretics	1.0		1.0	
ACEIs	0.08 (0.074, 0.087)	<0.001	0.04 (0.035, 0.043)	<0.001
CCBs	0.052 (0.04, 0.06)	<0.001	0.02 (0.017, 0.025)	<0.001
BBs	-0.09 (-0.10, 0.-0.084)	<0.001	0.016 (0.011, 0.020)	<0.001
ARBs	0.13 (0.12, 0.14)	<0.001	0.03 (0.023, 0.032)	<0.001
"Others"	-0.11(-0.13, -0.09)	<0.001	-0.008 (-0.011, 0.0096)	0.869
Gender				
Male	1.0		1.0	
Female	-0.034 (-0.38, -0.029)	<0.001	0.004 (0.0012, 0.0060)	<0.001
Townsend deprivation score (quintile)				
1 (Least deprived)	1.0		1.0	
2	-0.003 (-0.009, 0.002)	0.294	-0.009 (-0.012, -0.01)	<0.001
3	-0.002 (-0.009, 0.004)	0.452	-0.013 (-0.02, 0.01)	<0.001
4	-0.008 (-0.012, -0.001)	0.022	-0.025 (-0.03, -0.02)	<0.001
5 (Most deprived)	-0.02 (-0.03, -0.01)	<0.001	-0.05 (-0.06, -0.04	<0.001
Drug use status				
Incident users	1.0		1.0	
Prevalent users	0.13 (0.12, 0.14)	<0.001	0.06 (0.055, 0.065)	<0.001
Hypertension status				
Incident cases	1.0		1.0	
Prevalent cases	0.02 (0.008, 0.025)	0.02	0.03 (0.028, 0.04)	<0.001
CCI				
0	1.0		1.0	
1	0.0006 (-0.0049, 0.006)	0.837	0.03 (-0.00002, 0.0059)	0.052
≥2	-0.02 (-0.021, -0.0092)	<0.001	-0.046 (-0.078, - 0.0020)	0.004
Age (years)	0.003 (0.0028, 0.0033)	<0.001	0.0032 (0.0032, 0.0033)	<0.001
Follow up time (years)	-0.014 (-0.016, -0.013)	<0.001	0.007 (0.006, 0.0073)	<0.001
Switching index drug				
No	NA	NA	1.0	
Yes			-0.043 (-0.046, -0.040)	<0.001

(Note) PDC: Proportion days covered; **ACEIs**: Angiotensin converting enzyme inhibitors; **ARBs**: Angiotensin receptor blockers; **CCBs**: Calcium channel blockers; **BBs**: Beta-blockers; **CCI**: Charlson comorbidity index; **NA**: Not applicable

4.5.4. Association between covariates, and class and therapy PDC as a binary variable

4.5.4.1. Univariate analysis of covariates associated with class and therapy PDC<80%

Overall, 38.4% (n=142,696) of the episodes were non-adherent (class PDC<80%) to their index drug (Figure 4.4); whereas only 20.0% (n=35,343) of the patients were non-adherent (therapy PDC<80%) to their antihypertensive therapy (Figure 4.5). The proportion of episodes or patients with class or therapy PDC<80% was lower in those with ARBs as index drug class, prevalent drug users, prevalent hypertensive patients, having higher comorbidity, were older, were least deprived, followed up for a longer time and did not switch their index drug class (Table 4.10). Females, compared with males, were associated with higher proportion of class PDC<80%, but lower proportion of therapy PDC<80%. Univariate logistic regression analysis showed that all the study covariates were significantly associated with class and therapy PDC<80%.

Table 4.10 Covariates associated with the proportion of episodes and patients with antihypertensive drug class and therapy PDC<80%

Covariates	Class non-adherence (%)	Therapy non-adherence (%)
Index drug class		
Diuretics	41.5*	20.4*
ACEIs	35.9	20.6
CCBs	37.7	20
BBs	46.5	19
ARBs	28.5	17.3
"Others"	47.3	20.4
Gender		
Male	37.3*	20.5*
Female	39.3	19.5
Townsend deprivation score (quintile) (%)		
1 (Least deprived)	37.0*	17.3*
2	37.7	18.5
3	37.9	19.6
4	39.2	21.9
5 (Most deprived)	42.3	26.4
Drug use status		
Incident users	40.8*	23.2*
Prevalent users	35.7	16.5
Hypertension status		
Incident cases	40.1*	22.2*
Prevalent cases	36.9	18.2
CCI		
0	38.8*	20.5*
1	37.5	19.4
≥2	37.9	18.9
Age (years)		
<50	48*	34.1*
50-59	37.6	20
60-69	33.9	14.2
70-79	35.9	14.6
≥80	40.3	21.4
Follow up time (years)		
≤2	34.8*	22.1*
>2-3	38.1	23.5
>3-4	39.2	22.7
>4-5	40.5	22.3
>5	38.4	17.3
Switching index drug		
No	NA	17.6*
Yes		26.8

(Note) ACEIs: Angiotensin converting enzyme inhibitors; **ARBs**: Angiotensin receptor blockers; **CCBs**: Calcium channel blockers; **BBs**: Beta-blockers; **CCI**: Charlson comorbidity index; **NA**: Not applicable

4.5.4.2. Multivariate analyses of covariates associated with class and therapy PDC<80%

Multivariate logistic regression indicated that all study covariates were significantly associated with both class and therapy PDC<80%. Episodes with ARBs as index

drug class were the least likely to be associated with class PDC<80% (OR: 0.55, 95%CI: 0.53, 0.58) in comparison with diuretics (Table 4.11), followed by ACEIs (OR: 0.66, 95%CI: 0.64, 0.68); whereas “Others” were 28% more likely to be associated with class PDC<80% (OR: 1.28, 95%CI: 1.19, 1.39). Likewise, prevalent drug users (OR: 0.66, 95%CI: 0.64, 0.68), prevalent hypertensive patients (OR: 0.92, 95%CI: 0.89, 0.95) and increasing age were associated with lower likelihood of class PDC<80%. On the other hand, female gender (OR: 1.07, 95%CI: 1.05, 1.09), higher comorbidity (CCI≥2) (OR: 1.07, 95%CI: 1.04, 1.1), higher deprivation and longer follow-up time were associated with higher likelihoods of class PDC<80%.

For therapy PDC<80%, compared with diuretics, patients with other drug classes were less likely to be associated with PDC<80% of antihypertensive drug therapy; the least likelihood was with ACEIs (OR: 0.71, 95%CI: 0.69, 0.74), followed by ARBs (OR: 0.79, 95%CI: 0.75, 0.84) (Table 4.11). Lower likelihoods to therapy PDC<80% were also associated with female (OR: 0.96, 95%CI: 0.94, 0.99), prevalent drug users (OR: 0.61, 95%CI: 0.59, 0.63), prevalent hypertensive patients (OR: 0.76, 95%CI: 0.73, 0.79), follow-up time longer than five years (OR: 0.82, 95% CI: 0.79, 0.86) and increasing age. However, higher likelihoods of therapy PDC<80% were associated with CCI≥2 (OR: 1.05, 95%CI: 1.01, 1.08), higher deprivation and switching index drug class (OR: 1.71, 95%CI: 1.67, 1.76).

Table 4.11 Adjusted odds ratios of covariates associated with antihypertensive drug class and therapy PDC<80%

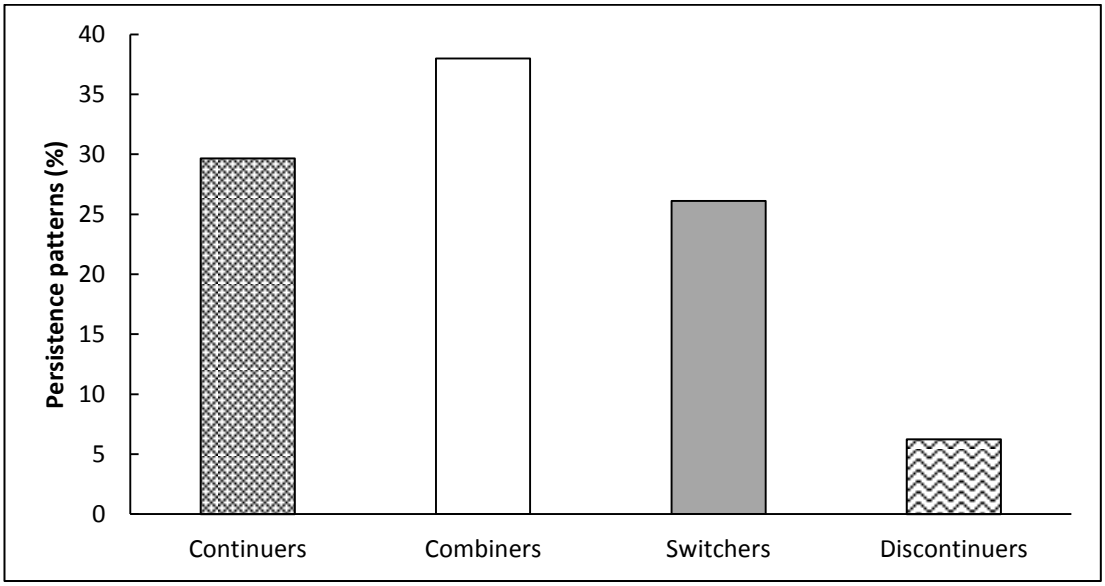
Covariates	Class non-adherence (PDC<80%)		Therapy non-adherence (PDC<80%)	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Index drug class				
Diuretics	1.0		1.0	
ACEIs	0.66 (0.64, 0.68)	<0.001	0.71 (0.69, 0.74)	<0.001
CCBs	0.80 (0.78, 0.82)	<0.001	0.87 (0.83, 0.9)	<0.001
BBs	1.23 (1.19, 1.27)	<0.001	0.81 (0.78, 0.85)	<0.001
ARBs	0.55 (0.53, 0.58)	<0.001	0.79 (0.75, 0.84)	<0.001
"Others"	1.28 (1.19, 1.39)	<0.001	0.90 (0.81, 0.99)	0.028
Gender				
Male	1.0		1.0	
Female	1.07 (1.05, 1.09)	<0.001	0.96 (0.94, 0.99)	<0.001
Townsend deprivation score (quintile)				
1 (Least deprived)	1.0		1.0	
2	1.03 (1.01, 1.06)	0.042	1.10 (1.04, 1.13)	<0.001
3	1.02 (1.0, 1.05)	0.175	1.13 (1.08, 1.17)	<0.001
4	1.06 (1.03, 1.10)	<0.001	1.25 (1.20, 1.30)	<0.001
5 (Most deprived)	1.20 (1.15, 1.23)	<0.001	1.52 (1.45, 1.58)	<0.001
Drug use status				
Incident users	1.0		1.0	
Prevalent users	0.66 (0.64, 0.68)	<0.001	0.61 (0.59, 0.63)	<0.001
Hypertension status				
Incident cases	1.0		1.0	
Prevalent cases	0.92 (0.89, 0.95)	<0.001	0.76 (0.73, 0.79)	<0.001
CCI				
0	1.0		1.0	
1	1.01 (0.99, 1.04)	0.294	0.99 (0.96, 1.02)	0.579
≥2	1.07 (1.04, 1.1)	<0.001	1.05 (1.01, 1.08)	0.006
Age (years)				
<50	1.0		1.0	
50-59	0.64 (0.62, 0.66)	<0.001	0.48 (0.47, 0.50)	<0.001
60-69	0.52 (0.51, 0.54)	<0.001	0.31 (0.30, 0.32)	<0.001
70-79	0.56 (0.54, 0.58)	<0.001	0.32 (0.30, 0.33)	<0.001
≥80	0.68 (0.65, 0.71)	<0.001	0.49 (0.47, 0.52)	<0.001
Follow up time (years)				
≤2	1.0		1.0	
>2-3	1.17 (1.12, 1.22)	<0.001	1.08 (1.03, 1.14)	0.001
>3-4	1.24 (1.19, 1.30)	<0.001	1.04 (0.99, 1.09)	0.148
>4-5	1.35 (1.30, 1.40)	<0.001	1.02 (0.97, 1.07)	0.756
>5	1.34 (1.30, 1.39)	<0.001	0.82 (0.79, 0.86)	<0.001
Switching index drug				
No	NA	NA	1.0	
Yes			1.71 (1.67, 1.76)	<0.001

(Note) PDC: proportion days covered; ACEIs: Angiotensin converting enzyme inhibitors; ARBs: Angiotensin receptor blockers; CCBs: Calcium channel blockers; BBs: Beta-blockers; CCI: Charlson comorbidity index; NA: Not applicable

4.5.5. Association between covariates and persistence patterns

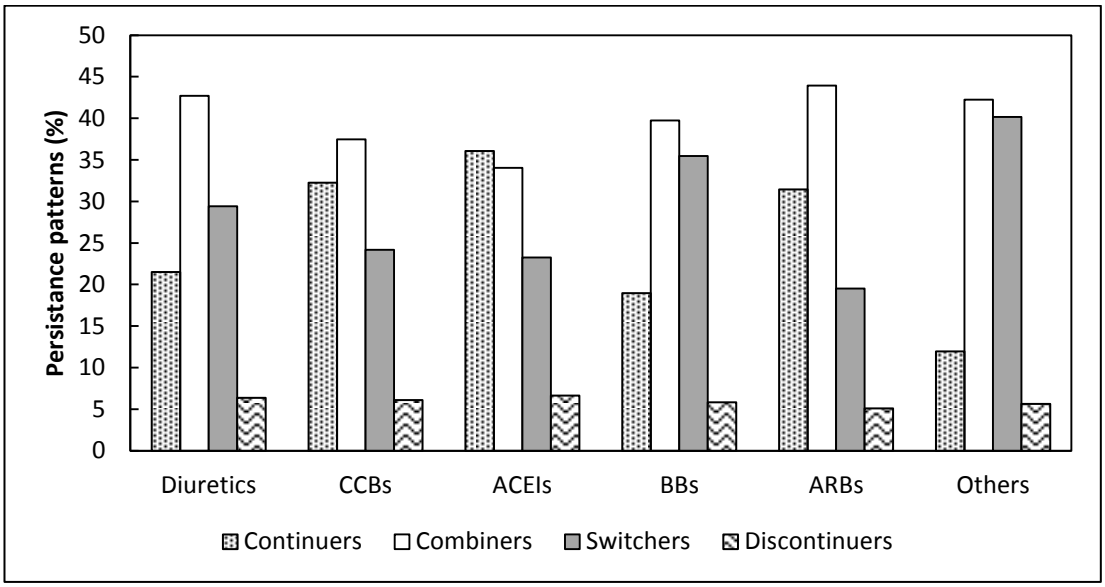
More than one-third (38%, n=67,173) of the study cohort were combiners, 30% (n=53,051) were continuers, 26% (n=46,193) were switchers and 6% (n=10,418) were discontinuers (Figure 4.6).

Figure 4.6 Overall persistence patterns of the study cohort



Proportion of drug continuation was greater in patients whose index drug class was ACEIs (36%), CCBs (32%) and ARBs (31%) and was lower in those with diuretics (21.5%), BBs (19%) and “Others” (12%) (Figure 4.7). The combination of index drug class with other antihypertensive classes was highest in those patients with ARBs (44%) as index drug class, followed by diuretics (43%) and was lowest in ACEIs (34%). Switching of index drug class was most common in patients with “Others” as index drug class (40%), followed by BBs (35%) and was least frequent with ARBs (20%).

Figure 4.7 Overall persistence patterns of the study cohort stratified by index drug class



4.5.5.1. Association between covariates, and class and therapy discontinuation

Of all the antihypertensive drugs episodes (n=371,605), there were 189,518 discontinuation episodes and the overall discontinuation rate was 1.69 (95%CI: 1.68, 1.70) per 10-person-years. The highest proportion of overall discontinuation was in the early course of therapy (19.5%, 95%CI: 19.3%, 19.7%) at six months and 28.5% (95%CI: 28.3%, 28.8%) at one year, and by the end of follow-up time after six years, the proportion of discontinuation reached 56.1% (95%CI: 55.8%, 56.4%). The median time for discontinuation of drug class was 4.4 years, and the longest median time for discontinuing a drug class was for episodes with ARBs (6.5 years), followed by ACEIs (5.1 years), CCBs (4.3 years), diuretics (3.7 years), BBs (3.2 years) and “Others” (3.1 years). One-year discontinuation rate was lowest for episodes with ARBs (18%, 95%CI: 17.6%, 19.0%) and highest for “Others” episodes (31.5%, 95%CI: 29.8%, 33.2%).

For discontinuation of any antihypertensive drug therapy (therapy non-persistence), there were 55,959 discontinuation episodes of first-ever antihypertensive drug therapy among the study cohort, with an overall discontinuation rate of 8.4 (95%CI: 8.3, 8.5) per 100-person-years. The highest proportion of antihypertensive therapy discontinuation was at the early stage of drug therapy: 10.3% (95%CI: 10.1%, 10.4%) at six months and 15.6% (95%CI: 15.5%, 15.8) at one year, and by the end of follow-up time after six years, only one-third (35.5%, 95%CI: 35.3%, 35.8%) of the patients discontinued their antihypertensive drug therapy. One-year discontinuation rate ranged from 12.6% (95%CI: 12.1%, 13.3%) for patients who started treatment with ARBs to 16.7% (95%CI: 16.2%, 16.9%) for CCBs.

Univariate Cox regression analysis indicated that all study covariates were significantly associated with class and therapy discontinuation (non-persistence). Likewise, multivariate Cox regression also showed significant association between all covariates and class and therapy discontinuation (non-persistence) after adjusting for other covariates (Table 4.12).

The results of multivariate Cox regression indicated that all the studied covariates were independent significant risk factors of class and therapy discontinuation (non-persistence) (Table 4.12). The results of Schoenfeld residual statistical test revealed that PH assumption was not held for all the studied covariates, except for hypertension status, Townsend deprivation score (for class non-persistence) and CCI (for therapy non-persistence) (Appendix 6) and all those covariates interacted with time, and interaction terms were included in the model. Consequently, these covariates had two HRs, one for main variable effect and one for the time-varying effect.

Compared with diuretics, prescribing episodes of ARBs (HR: 0.65, 95%CI: 0.62, 0.68), ACEIs (HR: 0.82, 95%CI: 0.80, 0.85) and CCBs (HR: 0.95, 95%CI: 0.93, 0.98) had a lower risk associated with class discontinuation; whereas BBs (HR: 1.30, 95%CI: 1.26, 1.34) and "Others" (HR: 1.25, 95%CI: 1.18, 1.34) had a higher risk of discontinuation (Table 4.12). However, risk of discontinuation for all drug classes was declining over time, except for ARBs (time-varying HR: 1.03, 95%CI: 1.02, 1.05).

The risk of discontinuing index drug class was also lower with prevalent drug users (HR: 0.57, 95%CI: 0.56, 0.59), prevalent hypertensive patients (HR: 0.96, 95%CI: 0.93, 0.98) and increasing age; however, over time, these covariates tend to be associated with higher discontinuation rate. Female gender (HR: 1.08, 95%CI: 1.06, 1.10) and having high comorbidity, i.e., CCI≥2, (HR: 1.05, 95%CI: 1.03, 1.08) and higher deprivation score quintiles were associated with an increased risk of class drug discontinuation. Nevertheless, the increased risk associated with women was decreasing by 3% for each year increase in follow-up time (time-varying HR: 0.97, 95%CI: 0.96, 0.98).

Unlike class discontinuation, for therapy discontinuation, patients with any of the antihypertensive drug classes as index drug had lower therapy discontinuation risk, in comparison with diuretics (Table 4.12); however, over time, ACEIs (time-varying HR: 1.05, 95%CI: 1.03, 1.06) and ARBs (time-varying HR: 1.06, 95%CI: 1.04, 1.08) were associated with increased risk of therapy discontinuation. Similar to the class discontinuation, prevalent drug users (HR: 0.59, 95%CI: 0.57, 0.61), prevalent hypertensive patients (HR: 0.88, 95%CI: 0.85, 0.91) and increasing age were associated with lower risk of therapy discontinuation, although prevalent drug users and increasing age were associated with increased risk over time.

However, unlike class discontinuation, female gender was associated with 6% lower risk of therapy discontinuation (HR: 0.94, 95%CI: 0.92, 0.96), but with a 2% annual increase in risk over time (time-varying HR: 1.02, 95%CI: 1.01, 1.03). Higher comorbidity, i.e. CCI≥2 (HR: 1.07, 95%CI: 1.05, 1.10), switching of index drug (HR: 1.50, 95%CI: 1.47, 1.52) and high deprivation score quintiles were independent factors for increased risk of therapy discontinuation. However, over time, the increased risk of switching index drug class was further increasing by 4% a year (time-varying HR: 1.04, 95%CI: 1.03, 1.05), while those associated with deprivation was decreasing.

Table 4.12 Adjusted hazard ratios of covariates associated with antihypertensive drug class and therapy discontinuation

Covariates	Class discontinuation		Therapy discontinuation	
Main effects	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Index drug class				
Diuretics	1.0		1.0	
ACEIs	0.82 (0.80, 0.85)	<0.001	0.74 (0.71, 0.76)	<0.001
CCBs	0.95 (0.93, 0.98)	<0.001	0.95 (0.91, 0.98)	<0.001
BBs	1.30 (1.26, 1.34)	<0.001	0.82 (0.79, 0.86)	<0.001
ARBs	0.65 (0.62, 0.68)	<0.001	0.77 (0.73, 0.81)	<0.001
“Others”	1.25 (1.18, 1.34)	<0.001	0.88 (0.80, 0.97)	<0.001
Gender				
Male	1.0		1.0	
Female	1.08 (1.06, 1.10)	<0.001	0.94 (0.92, 0.96)	<0.001
Townsend deprivation score (quintile)				
1 (Least deprived)	1.0		1.0	
2	1.01 (0.99, 1.03)	0.158	1.08 (1.05, 1.12)	<0.001
3	1.03 (1.01, 1.05)	0.001	1.16 (1.12, 1.20)	<0.001
4	1.08 (1.05, 1.10)	<0.001	1.29 (1.25, 1.34)	<0.001
5 (Most deprived)	1.17 (1.15, 1.20)	<0.001	1.54 (1.48, 1.60)	<0.001
Drug use status				
Incident users	1.0		1.0	
Prevalent users	0.57 (0.56, 0.59)	<0.001	0. 59 (0.57, 0.61)	<0.001
Hypertension status				
Incident cases	1.0		1.0	
Prevalent cases	0.96 (0.93, 0.98)	<0.001	0.88 (0.85, 0.91)	<0.001
CCI				
0	1.0		1.0	
1	1.001 (0.98, 1.02)	0.958	1.02 (0.99, 1.04)	0.436
≥2	1.05 (1.03, 1.08)	<0.001	1.07 (1.05, 1.10)	0.019
Age (years)				
<50	1.0		1.0	
50-59	0.76 (0.74, 0.78)	<0.001	0.63 (0.61, 0.65)	<0.001
60-69	0.64 (0.62, 0.65)	<0.001	0.44 (0.42, 0.45)	<0.001
70-79	0.60 (0.59, 0.62)	<0.001	0.41 (0.39, 0.42)	<0.001
≥80	0.66 (0.64, 0.68)	<0.001	0.46 (0.44, 0.48)	<0.001
Switching index drug				
No	NA	NA	1.0	
Yes			1.5 (1.47, 1.52)	<0.001

(Continued) **Table 4.12 Adjusted hazard ratios of covariates associated with antihypertensive drug class and therapy discontinuation**

Covariates	Class discontinuation		Therapy discontinuation	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Time-varying effect				
Index drug class				
Diuretics	1.0		1.0	
ACEIs	0.94 (0.93, 0.95)	<0.001	1.05 (1.03, 1.06)	<0.001
CCBs	0.95 (0.93, 0.96)	<0.001	0.99 (0.98, 1.01)	0.089
BBs	0.89 (0.88, 0.90)	<0.001	0.97 (0.96, 0.99)	<0.001
ARBs	1.03 (1.02, 1.05)	<0.001	1.06 (1.04, 1.08)	<0.001
"Others"	0.94 (0.92, 0.97)	<0.001	0.97 (0.94, 1.01)	0.135
Gender				
Male	1.0		1.0	
Female	0.97 (0.96, 0.98)	<0.001	1.02 (1.01, 1.03)	0.003
Townsend deprivation score				
1 (Least deprived)	NA	NA	1.0	
2			0.99 (0.97, 0.99)	0.044
3			0.98 (0.96, 0.99)	0.003
4			0.96 (0.95, 0.98)	<0.001
5 (Most deprived)			0.94 (0.92, 0.96)	<0.001
Drug use status				
Incident users	1.0		1.0	
Prevalent users	1.18 (1.17, 1.19)	<0.001	1.13 (1.11, 1.14)	<0.001
Hypertension status				
Incident cases	NA	NA	1.0	
Prevalent cases			1.01 (0.99, 1.03)	0.316
CCI				
0	1.0		NA	NA
1	1.02 (1.001. 1.03)	0.004		
≥2	1.02 (1.01, 1.03)	0.002		
Age (years)				
<50	1.0		1.0	
50-59	1.004 (0.99, 1.018)	<0.001	1.02 (1.01, 1.04)	<0.001
60-69	1.02 (1.004, 1.03)	<0.001	1.05 (1.03, 1.07)	<0.001
70-79	1.05 (1.03, 1.06)	<0.001	1.06 (1.05, 1.08)	<0.001
≥80	1.11 (1.10, 1.12)	<0.001	1.16 (1.14, 1.17)	<0.001
Switching index drug				
No	NA	NA	1.0	
Yes			1.04 (1.03, 1.05)	<0.001

(Note) ACEIs: Angiotensin converting enzyme inhibitors; **ARBs**: Angiotensin receptor blockers; **CCBs**: Calcium channel blockers; **BBs**: Beta-blockers; **CCI**: Charlson comorbidity index; **NA**: Not applicable

4.5.5.2. Association between covariates, and combining and switching of index drug class

For the whole study cohort, there were 67,173 combination episodes identified, with an overall combination rate of 1.14 (95%CI: 1.13, 1.15) per 10-person-years. By the end of follow-up time at six years, ~41.9% (95%CI: 41.6%, 42.1%) of patients had combined their index drug class with other antihypertensive classes, with nearly half of those combinations (18.5%, 95%CI: 18.3%, 18.6%) happening in the first six months of therapy. One-year combination rate was lowest in patients with ACEIs as index drug class (15.0%, 95%CI: 14.7%, 15.2%), followed by BBs (18.0%, 95%CI: 17.5%, 18.5%) and highest in “Others” (29.4%, 95%CI: 27.7%, 31.1%).

In terms of switching index drug classes, overall, there were 46,193 switching episodes, with an overall switching rate of 6.4 (95%CI: 6.3, 6.5) per 100-person-years. The lowest switching rate was in patients with ARBs as index drug class (3.9, 95%CI: 3.7, 4.0), followed by ACEIs (6.1, 95%CI: 5.9, 6.5); while the highest rate was in “Others” (9.5, 95%CI: 8.9, 10.0). By the end of follow-up time at six years, the cumulative incidence of switching was 30.3% (95%CI: 30.0%, 30.5%), with about one-third (10.2%, 95%CI: 10.0%, 10.3%) occurring at one year of therapy. One-year switching rate was lowest in patients started on ARBs (3.1%, 95%CI: 2.8%, 3.4%), followed by diuretics (7.5%, 95%CI: 7.2%, 7.8%); whereas the highest rate was in BBs (15.1%, 95%CI: 14.6%, 15.6%).

The univariate Cox regression results showed that all the study covariates were significantly associated with combining and switching index drug class. Similarly, the adjusted HRs from multivariate Cox regression indicated that all the study covariates were independent risk factors for combining and switching index drug class (Table 4.13). The results from Schoenfeld residual's statistical test (Appendix 6) revealed that PH assumption was not held for all the study covariates, except for

gender, drug use status and Townsend deprivation score (for combining index drug class), and the blood pressure category (for switching index drug class). Therefore, all these covariates interacted with time, and the interaction terms were included in the Cox model, and these covariates considered as having time-varying effects. Consequently, these covariates had both main and time-varying HRs and the estimated covariate effect at any time point could be obtained by using the equation described in Appendix 6.

For combining index drug class, compared with diuretics, all antihypertensive drug classes, except “Others” were significantly associated with a lower risk of combining index drug class (Table 4.13); however, ACEIs (time-varying HR: 1.11, 95%CI: 1.10, 1.13) and ARBs (time-varying HR: 1.08, 95%CI: 1.06, 1.10) were associated with a higher risk of combination over time. Similarly, females (HR: 0.92, 95%CI: 0.91, 0.94) and prevalent hypertensive patients (HR: 0.96, 95%CI: 0.93, 0.98) were less likely to combine index drug class. Prevalent drug users (HR: 1.56, 95%CI: 1.52, 1.61), higher deprivation scores quintiles, those with comorbidity, those with high normal to grade-III hypertension stage, or age ≥50 were at greater risk of combining their index drug class, and their risk was changing over time.

In terms of switching index drug class, all antihypertensive drug classes were associated with increased risk of switching the index drugs except ARBs (HR: 0.59, 95%CI: 0.54, 0.64), although over time their risk of switching was significantly decreasing, except for ARBs (Table 4.13). Females (HR: 1.10, 95%CI: 1.08, 1.12), prevalent hypertensive patients (HR: 1.16, 95%CI: 1.11, 1.22), hypertension stage I-III and increasing age were significantly associated with increased risk of switching the index drugs, but their risk of switching decreased over time. In contrast, prevalent drug users (HR: 0.75, 95%CI: 0.73, 0.78), those with low comorbidity i.e., CCI=1 (HR: 0.94, 95%CI: 0.91, 0.98) and higher deprivation score quintiles were

associated with lower risk of switching, although their risks of switching were increasing over time.

Table 4.13 Adjusted hazard ratios of covariates associated with combining and switching the index drugs

Covariates	Combining index drug classes		Switching index drug classes	
Main effects	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Index drug class				
Diuretics	1.0		1.0	
ACEIs	0.74 (0.72, 0.76)	<0.001	1.24 (1.19, 1.29)	<0.001
CCBs	0.93 (0.90, 0.95)	<0.001	1.02 (0.97, 1.07)	0.095
BBs	0.90 (0.87, 0.93)	<0.001	2.30 (2.19, 2.41)	<0.001
ARBs	0.88 (0.84, 0.92)	<0.001	0.59 (0.54, 0.64)	<0.001
"Others"	1.32 (1.23, 1.42)	<0.001	1.95 (1.77, 2.16)	<0.001
Gender				
Male	1.0		1.0	
Female	0.92 (0.91, 0.94)	<0.001	1.10 (1.08, 1.12)	<0.001
Townsend deprivation score (quintile)				
1 (Least deprived)	1.0		1.0	
2	1.01 (0.99, 1.03)	0.195	0.95 (0.91, 0.99)	0.008
3	1.05 (1.02, 1.07)	<0.001	0.93 (0.89, 0.97)	0.001
4	1.07 (1.05, 1.10)	<0.001	0.86 (0.82, 0.89)	<0.001
5 (Most deprived)	1.09 (1.07, 1.12)	<0.001	0.79 (0.75, 0.83)	<0.001
Drug use status				
Incident users	1.0		1.0	
Prevalent users	1.56 (1.52, 1.61)	<0.001	0.75 (0.73, 0.78)	<0.001
Hypertension status				
Incident cases	1.0		1.0	
Prevalent cases	0.96 (0.93, 0.98)	0.001	1.16 (1.11, 1.22)	<0.001
CCI				
0	1.0		1.0	
1	1.10 (1.08, 1.13)	<0.001	0.94 (0.91, 0.98)	<0.001
≥2	1.11 (1.08, 1.14)	<0.001	1.001 (0.97, 1.05)	0.821
BP categories				
Normal	1.0		1.0	
High normal	1.14 (1.08, 1.20)	<0.001	1.03 (0.98, 1.08)	0.186
Grade 1 hypertension	1.36 (1.30, 1.43)	<0.001	1.11 (1.06, 1.16)	<0.001
Grade 2 hypertension	1.95 (1.85, 2.10)	<0.001	1.25 (1.20, 1.31)	<0.001
Grade 3 hypertension	3.50 (3.32, 3.70)	<0.001	1.34 (1.28, 1.41)	<0.001
Age (years)				
<50	1.0		1.0	
50-59	1.13 (1.10, 1.17)	<0.001	1.08 (1.03, 1.13)	<0.001
60-69	1.20 (1.16, 1.24)	<0.001	1.09 (1.05, 1.16)	<0.001
70-79	1.29 (25, 1.33)	<0.001	1.04 (0.99, 1.09)	0.09
≥80	1.26 (1.22, 1.30)	<0.001	1.03 (0.98, 1.08)	0.211

(Continued) **Table 4.13 Adjusted hazard ratios of covariates associated with combining and switching the index drugs**

Covariates	Combining index drug classes		Switching index drug classes	
Main effects	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Time varying effect				
Index drug class				
Diuretics	1.0		1.0	
ACEIs	1.11 (1.10, 1.13)	<0.001	0.83 (0.82, 0.85)	<0.001
CCBs	0.99 (0.98, 1.01)	0.147	0.93 (0.92, 0.94)	<0.001
BBs	0.99 (0.98, 1.01)	0.146	0.81 (0.79, 0.82)	<0.001
ARBs	1.08 (1.06, 1.10)	<0.001	1.02 (0.99, 1.04)	0.223
"Others"	0.77 (0.73, 0.80)	<0.001	0.90 (0.87, 0.93)	<0.001
Gender				
Male	NA	NA	1.0	
Female			0.95 (0.94, 0.96)	<0.001
Townsend deprivation score (quintile)				
1 (Least deprived)	NA		1.0	
2			1.02 (1.01, 1.03)	0.002
3			1.02 (1.01, 1.03)	0.004
4			1.06 (1.04, 1.07)	<0.001
5 (Most deprived)			1.09 (1.07, 1.11)	<0.001
Drug use status				
Incident users	NA	NA	1.0	
Prevalent users			1.18 (1.17, 1.20)	<0.001
Hypertension status				
Incident cases	1.0		1.0	
Prevalent cases	1.02 (1.002, 1.03)	0.026	0.95 (0.94, 0.97)	<0.001
CCI				
0	1.0		1.0	
1	0.99 (0.97, 0.99)	<0.001	1.03 (1.02, 1.05)	<0.001
≥2	0.97 (0.96, 0.99)	<0.001	1.04 (1.03, 1.05)	<0.001
BP categories				
Normal	1.0			
High normal	1.02 (0.99, 1.05)	0.112		
Grade 1 hypertension	1.001 (0.99, 1.03)	0.213	NA	NA
Grade 2 hypertension	0.91 (0.89, 0.93)	<0.001		
Grade 3 hypertension	0.74 (0.72, 0.76)	<0.001		
Age (years)				
<50	1.0		1.0	
50-59	0.99 (0.97, 1.002)	0.465	0.94 (0.92, 0.96)	<0.001
60-69	0.97 (0.96, 0.99)	0.001	0.93 (0.92, 0.95)	<0.001
70-79	0.97 (0.96, 0.99)	<0.001	0.96 (0.95, 0.98)	<0.001
≥80	0.95 (0.93, 0.97)	<0.001	1.03 (1.02, 1.05)	<0.001

(Note) ACEIs: Angiotensin converting enzyme inhibitors; **ARBs**: Angiotensin receptor blockers; **CCBs**: Calcium channel blockers; **BBs**: Beta-blockers; **CCI**: Charlson comorbidity index; **NA**: Not applicable

4.6. Discussion

4.6.1. Key findings

Overall, the study results showed suboptimal adherence and persistence to antihypertensive drug therapy. Additionally, about one-third of the patients either combined or switched their index drug class. Many demographic and clinical characteristics were associated with antihypertensive drug adherence and persistence.

4.6.2. Association between the study covariates and adherence to antihypertensive drugs

The results indicated a higher adherence to any antihypertensive drug therapy than antihypertensive drug classes. Adherence to antihypertensive drug classes was suboptimal, i.e., the overall mean class PDC was 73% and only 61.6% of the episodes were adherent (class PDC≥80%), although the median class PDC was 93.3%. These results were comparable with the results of a systematic review[327], which reported an average one-year adherence to antihypertensive drug classes of 67% with only 64% patients being categorised as adherent. A recent observational study of patient characteristics and medication adherence found an overall median class adherence of ~96%, with <75% being considered adherent[301], even though the study analysed all antihypertensive drugs as one class.

In contrast to adherence to antihypertensive drug classes, adherence to antihypertensive drug therapy was higher, with mean therapy PDC of 87% and 80% being classified as adherent (therapy PDC≥80%). Such higher therapy adherence has also been reported by other studies. One study reported mean therapy PDC value of 86.2%[208], and a more recent retrospective cohort study found that ~96.9% of included patients had adherence value >80% over two years of follow up[213].

Many demographic and clinical characteristics were identified as independent predictors for both class and therapy adherence. Type of antihypertensive drug class was a significant determinant for both class and therapy adherence, with highest adherence value for ARBs and ACEIs, and the lowest for diuretics and BB. This finding has been consistently demonstrated in many other studies[207, 208, 214, 328-330] and has been largely attributed to the more favourable safety profile of these drugs compared with other drug classes.

Although ARBs have been associated with higher adherence than ACEIs, a meta-analysis of 17 studies argued that this small difference in adherence between ARBs and ACEIs could be due to publication bias[203]. Moreover, a recent observational study claimed that the higher adherence level in ARBs and ACEIs could not be exclusively explained by their favourable safety profile, rather associated with their relatively new market availability[216]. However, it is unclear yet whether this observed statistical difference in the adherence profile between ARBs and ACEIs has any significant clinical implication; further studies are needed to evaluate this in the future.

Newly diagnosed hypertensive patients and new antihypertensive drug users were less adherent to both antihypertensive drug class and any antihypertensive drug therapy, compared with prevalent hypertension patients and prevalent drug users. This difference in adherence behaviour between incident and prevalent hypertension patients has been pointed out by Halpern *et al* (2006)[283] and was considered as a potential confounder for adherence, which should be controlled for in any adherence study. This disparity in adherence between new and established patients could be explained, partly, by differences in beliefs, and disease perceptions and attitudes as established HT patients may have passed the stage of lack of belief in their diagnosis of hypertension[303]. Additionally, fears of a drug's side

effects in the early stages of treatment (i.e., new patients) may act as a barrier for good adherence to antihypertensive drugs, especially when the patient believes that the drug's adverse effects outweigh any potential future benefits[304].

The finding that class and therapy adherence was lower in patients with higher comorbidity is consistent with that of prior studies[213, 331]. A study investigating the effects of non-cardiovascular comorbidity (asthma, chronic obstructive pulmonary disorders, depression, gastrointestinal tract disorders, osteoarthritis) on antihypertensive drug use in hypertensive patients[331], found that all these comorbidities were associated with lower antihypertensive drug use, in addition to a negative association between CCI and antihypertensive drug use (OR: 0.98 per one-unit increase in CCI). Furthermore, patients with no comorbidity were 29% more likely to be adherent than those with a high comorbidity score among newly treated hypertensive patients[213].

It is clear from the current study results that the negative comorbidity effect was significant only for those with high CCI score (≥2), suggesting that comorbidity would negatively influence adherence only when it reaches a certain extent. This negative effect of high comorbidity on adherence could be explained partially by comorbidity-induced poly pharmacy through the necessity of using additional drugs with increasing comorbid conditions[204], which has been found to decrease adherence[286]. Furthermore, a recent review has meta-analysed 44 studies to evaluate adherence to cardiovascular therapy, including antihypertensive agents, and comorbidity has been reported as a key factor for non-adherence[305].

Switching of the index drug class was one of the most significant predictors for therapy non-adherence because switching could be associated with many factors that may decrease a patient's adherence[3] such as changes in product packaging

and tablet appearance[332] and taste[204], differences in adherence profiles of the various antihypertensive drug classes[203], and impairing patients' confidence in drug therapy[333, 334]. For example, a National Consumers League survey in the USA revealed significant concerns about therapeutic switching and found that 40% of patients who experienced switching reported that the new drug was not as effective; 30% reported more side effects and 47% were not satisfied with the switching process[335]. Furthermore, it has been reported that patients' concerns about switching may produce a nocebo effect[205, 206] (i.e. patients' negative perceptions may cause negative outcomes). Other studies have also demonstrated lower adherence rate in patients following antihypertensive drug switching[200, 202].

Certain demographic factors were also found to be significantly associated with adherence such as age and gender. Increasing age was found to be associated with higher class and therapy adherence. Many studies have found better and higher adherence levels in older patients [199, 302, 306, 307, 336-338], including a recent meta-analysis to study adherence to cardiovascular therapy[305].

The study results also showed that women were less adherent to antihypertensive drug class compared with any antihypertensive drug therapy, which may imply greater switching of antihypertensive drug classes in women (HR for switching was 1.10, $p<0.001$) and this was in agreement with another study[213]. The observed lower class adherence in women was also observed in other studies[300, 331].

Consistent with other studies, high deprivation, indicated by high deprivation score quintiles, was associated with lower adherence to antihypertensive drug medications. The WHO's report on adherence to long-term therapies[279] has recognised poor SES as a potential factor for non-adherence to antihypertensive drug therapy. In a study of antihypertensive drug compliance among newly treated

elderly hypertensive patients[213], increase in income quintile, as an indicator for lower deprivation, was associated with a 10% increase in the proportion of adherent patients (OR: 1.10, 95%CI: 1.08, 1.12). A recent retrospective cohort study of more than 30,000 adult patients that assessed the association between patients' characteristics and medication adherence across eight diseases, including hypertension, found higher a adherence rate in those living in higher SES areas (lower deprivation)[301].

As the patients had different follow-up times, it was necessary to account for this when potential risk factors on adherence were investigated. The study results revealed an inverse relationship between class adherence and follow-up time; however, therapy adherence was affected differently, such that it was declining at early stages of follow-up, then reduced insignificantly until year five of follow-up when it started to rise again. This gradual decline of adherence with increasing follow-up time has been reported in a recent meta-analysis of 20 studies to estimate adherence for drugs that prevent cardiovascular disease, including antihypertensive agents, which found a 0.15% decline in adherence for each monthly increase in follow-up time[214].

The fitted multivariate GLM regression model can be used to estimate the predicted mean class and therapy PDC. For example, the predicted mean class PDC for patients with ACEIs as index class was 78.7% (95%CI: 78.4%, 79.0%) having all other covariates in the model at baseline. Whereas for diuretics, the predicted mean class PDC was 70.7% (95%CI: 70.3%, 71.1%), and the difference between predicted mean class for ACEIs and diuretics would be 0.08 (8.0)%, which equals the regression coefficient of ACEIs in the model.

Furthermore, the fitted multivariate GLM regression model can be used also to estimate the predicted mean class or therapy PDC for any patient with a set of demographic and clinical characteristics. For example, the predicted mean class PDC for a patient with the following demographics and characteristics: index drug class – diuretics, female, deprivation score quintile – 2, new drug user, prevalent or existing hypertensive patient, CCI ≥2, 50 years old, and four years of follow-up time, would be 67.7% (95%CI: 66.8%, 69.5%); whereas the predicted mean class PDC for the same patient with index drug class of ACEIs would be 75.7% (95%CI: 75.1%, 76.3%).

Likewise, the same principle could be applied to predict mean therapy PDC. For example, the predicted mean therapy PDC for the same patient in the above example would be 83% (95%CI: 82.5%, 83.4%) for diuretics as index drug class and 87% (95%CI: 86.5%, 87.7%) for ACEIs as the index drug class.

4.6.3. Association between covariates and discontinuation of antihypertensive drugs

Persistence to both index drug class and antihypertensive therapy was poor and suboptimal, with only 49% and 68% patients showing class and therapy persistence, respectively. Different persistence rates have been reported by other studies depending on study follow-up times, ranging from 14%[339] to 73%[285] at one year, 9%[340] to 59%[285] at three years, and 16% to 51%[341] at four years. A recent retrospective cohort study of 207,473 newly treated hypertensive patients found two-year class and therapy persistence rates of 54.8% and 66.1%, respectively[213].

Many clinical and demographic factors were found to be significant determinants for class and therapy non-persistence (discontinuation). Type of index drug class was a significant predictor for class and therapy discontinuation, with the lowest discontinuation rate for ARBs and ACEIs, followed by CCBs, and the highest for

BBs and "Others". This has been consistently observed across studies over time[208, 210-212, 339-346]. The low discontinuation rates in ARBs and ACEIs could be partially related to their better tolerability compared with BBs and diuretics[209, 211, 212, 308, 347], although other factors, such as dosing frequency, health behaviour and patients' beliefs, that vary between antihypertensive drug classes might also be contributing factors[210].

Prevalent drug users and established hypertensive patients were also associated with lower discontinuation rate compared with new drug users and new hypertensive patients. This is in line with findings from other studies[210, 302, 342]. For instance, a cohort study[302] found higher persistence rates in established hypertensive patients (one year and 4.5 year persistence rates of 97% and 82%, respectively, compared with 78% and 46% in new patients)[302]. The difference in discontinuation rate between incident and prevalent drug users could be partly due to the lack of awareness or beliefs in hypertension diagnosis[303], and the subsequent consequences of long-term high BP[209] and fear of drugs' side effects[215, 304] in new patients. However, the previous study[302] also indicated that the difference in discontinuation rates between incident and prevalent drug users tended to decline over time, which may suggest that patients may change their beliefs and overcome their fears of a drug's side effects as their disease progresses. However, the possibility of survival bias in explaining the difference between prevalent and incident patients could not be excluded.

The current results also agree with results of prior research[208, 209, 213, 215] in terms of positive association between discontinuation rate and existence of comorbidity. However, this finding was in contrast with the results of one study[286], which could be related to the different methods used (in the latter study) in terms of the study population (new patients), short follow-up time (12 months), definition of persistence

(having treatment continued for more than 273 days), use of comorbidity index other than CCI and using analysis method other than time-to-event analysis. The impact of comorbidity was significant at a CCI score index of ≥2, which similarly to its impact on adherence may be related to poly pharmacy and regimen complexity associated with the increase in medications required to treat the other comorbidities[204], which in turn may be associated with higher discontinuation rate[286]. One of the most significant determinants for discontinuing antihypertensive therapy was switching of index drug class, and this was consistent with other studies, which reported that switching could negatively influence long-term persistence to antihypertensive drug therapy[217, 233, 348].

Age and gender were also significantly associated with class and therapy discontinuation. An inverse relationship between increasing age and discontinuation rate was observed, which has been reported in many other previous studies[209, 211, 213, 215, 286, 302, 341, 349, 350]. One study[208], in contrast, reported the opposite result to this study. This disparity could be attributed to the fact that the study was not designed to assess determinants of persistence to antihypertensive therapy, rather it was aimed at assessing one-year persistence and adherence rates to most commonly used antihypertensive monotherapy (hydrochlorothiazide, amlodipine, lisinopril, valsartan), which is a completely different research question. In terms of gender, females were more likely to discontinue their index drug class but less likely to discontinue antihypertensive therapy, which may be attributed to the greater switching between antihypertensive drug classes in females[213]. A higher discontinuation of initial drug class in women was reported in prior studies[208, 211, 341, 349, 350], which was attributed to the fact that women, in general, report higher rates of side effects than men[351, 352], given that tolerability is considered one of the likely driving factors for drug discontinuation[341]. However, the gap difference in

discontinuing index drug class was declining over time, as previously reported in another study[302].

The inverse associations of SES with class and therapy persistence are consistent with those of another study, which found lower class and therapy persistence to antihypertensive drug class or therapy, respectively[213]. This also has been confirmed in other studies[353, 354]. The consistent reported finding of lower antihypertensive drug adherence and persistence in patients with poor SES could be explained, partly, by their poorer knowledge of cardiovascular risk factors[355]; hence poorer perceptions about hypertension-related health risks and the beneficial effect of antihypertensive drug therapy, which has been considered important for patients' adherence and persistence to drug treatment[347, 356-358].

In addition, it was suggested that patients with higher SES could have better collaboration with healthcare professionals[359], with pharmacists, for example, which in turn could play an important role for better adherence and persistence[279]. Furthermore, it has been reported that patients with higher SES tend to show greater responsibility for their own health, which motivates them to adhere to and persist with the medical regimen instructions[359].

4.6.4. Association between covariates and combination of antihypertensive drug classes

Overall, the study results showed that ~40% of the study cohort required at least an additional antihypertensive drug class during their follow-up time, which was consistent with results of the Antihypertensive and Lipid Lowering to Prevent Heart Attack Trial[360]. In this trial, 40% of patients require two or more antihypertensive drugs to control their high blood pressure. A similar proportion of 38.5% was also

reported in a previous study of persistence patterns with antihypertensive medications in newly diagnosed hypertensive patients in Italy[215].

All of the investigated clinical and demographic factors were found to be significant determinants for combining index drug class. Lower risk of combining antihypertensive drugs was found in those who prescribed any type of antihypertensive drug classes, except “Others”, females and prevalent hypertensive cases, although this lower likelihood of combination was declining over time for both those prescribed ACEIs or ARBs and for prevalent cases. It was not possible from the current results to explain the lower tendency of combining index drug class in the above patient groups. However, it may be, partially, because most drugs classes, for example, ACEIs, ARBs, can also be indicated for the treatment of other potential conditions that hypertensive patients may develop in the future as hypertension-related complications, such as chronic kidney disease, left ventricular dysfunction and coronary artery disease. Therefore, the initial index drug class would be able to treat both conditions without the need for an additional drug. Furthermore, the higher tendency of females to switch index drug class[213] than combining antihypertensive drug classes may imply that they seem to follow sequential therapy approach rather than stepped-care approach in treating their hypertension, which in turn may explain the lower combination rate in females.

In contrast, patients with high baseline blood pressure, high comorbidity and older age were most likely to combine their index drug class, which is consistent with a previous study in Italy[215] of patterns of persistence with antihypertensive drugs in 13,303 hypertensive patients. The observed high proportion of combination in patients with high baseline BP value – a 3.5-fold increase tendency of requiring an additional drug in patients with grade-III hypertension – is in line with reports about the limited ability of monotherapy to achieve target BP value in many patients,

particularly those with high baseline BP level[92] because it can reduce SBP and DBP only by an average of 10 or 5 mmHg, respectively[105].

Therefore, it is necessary to introduce additional antihypertensive drugs to patients with high baseline BP value to achieve the required BP target. Likewise, achieving BP target may be more difficult in patients with certain comorbid conditions, and they usually require more than two antihypertensive agents to control their BP. For example, ≥3 agents may be required in patients with diabetes, heart diseases and chronic kidney diseases[187, 361]; thus, this could explain the higher combination rate in patients with high baseline comorbidity.

Furthermore, the positive association of increasing age with combination rate could be related to the difficulty of controlling BP as age increases[204], given that comorbidity increases[362] with increasing age; thus, the increase in antihypertensive drug use with increasing age[362]. The higher association of antihypertensive drug combination with higher deprivation score could be explained by the reported higher BP values in those with poor socioeconomic status[363-365], which necessitate the prescribing of more than one antihypertensive drug class to be controlled. The high BP in people with poor SES was claimed to be more related to the specific stressful aspects of poor SES such as unemployment or job insecurity[363-365].

4.6.5. Association between covariates and switching of antihypertensive drug classes

The study results showed that 26% of patients switched from their index drug class, which is comparable to the 19.7% four-year switching rate reported by a previous study[341] of four-year persistence patterns among hypertensive patients. All the investigated potential factors were significantly associated with switching index drug class.

Type of index drug class was the most determinant factor for switching, such that, compared with diuretics, patients started on all the other types of antihypertensive agents, except ARBs, were more likely to switch; this is in agreement with other studies, which reported lowest switching rates with ARBs[211, 217, 341]. Given that, tolerability is the most likely driving factor for switching[341, 366], and the wide inter-class variations in drug tolerability[204], the placebo-like tolerability of ARBs[367-369] may at least partly explain the low switching rate in ARBs users. Furthermore, it has been reported that drug side effects often cause early switching[283]; thus, patients who tolerated the drug early in the course of therapy are often unlikely to switch later, and this fact was clearly shown in the observed over-time reduction in switching risk in all antihypertensive class users. The fact that women, in general, report higher rates of drug side effects than men[351, 352], may explain why females had a higher switching rate initially, which started to decline over time by 5% annually, which was comparable with results from other studies[213, 286, 341].

Moreover, higher risk of switching was found in patients who had established hypertension, high baseline BP and were older. These patient groups had a higher risk of developing other comorbid diseases, such as chronic kidney disease or chronic heart failure, as a complication of hypertension, for which a new antihypertensive drug, i.e. switching, may be required either to treat both hypertension and the new condition or to avoid contraindications associated with the new condition. This may explain the higher switching rate in these patient groups; however, further studies are needed for confirmation.

On the other hand, prevalent users and patients with high comorbidity were less likely to switch their index drug initially, though switching risk started to rise over time. Switching of antihypertensive drugs after a long period of starting the drug therapy may indicate either treatment failure or treatment of new developing

condition[283]; however, treatment failure may be the more relevant cause for switching in this case since lowering of BP is more difficult to control in patients with comorbid conditions[187, 361].

Poor SES was associated with lower switching rate when compared with those with higher SES. This finding could be explained in part by the lack of patients' awareness of risk of uncontrolled hypertension and antihypertensive drug benefits owing to poor knowledge of cardiovascular risk factors[359], accepting responsibility of their health to a lower extent[370] and reduced access to medical care[371]. All these issues in patients with poor SES could be considered essential for the recognition of the three most possible causes for antihypertensive drug switching, i.e. drug intolerance, ineffectiveness, or treating a comorbid condition[283], which may then explain the lower switching rate in those with poor socioeconomic status.

4.6.6. Strengths and limitations of the current study

This study overcame most of the observed limitations in previous studies. The findings of other studies that focused solely on adherence and persistence of individual antihypertensive drug classes without considering the totality of antihypertensive drug therapy may not be generalised and applied to the whole hypertensive patient population. This is because monotherapy can effectively achieve BP target in only a limited number of hypertensive patients, and the majority of patients are prescribed at least two antihypertensive drugs to achieve their BP target[89] (more than one-third [40%] in the current study). It was, therefore, crucial to study patients' medication-taking behaviour of both individual antihypertensive drug class and subsequent total antihypertensive drug therapy so that the results can be applied to clinical practice of managing hypertension.

Additionally, adherence and persistence patterns were measured longitudinally over a long follow-up period in both incident and prevalent hypertensive patients, and adherence was analysed as a continuous outcome variable. Furthermore, included patients were identified based on the presence of both clinical diagnosis of primary hypertension and prescription of antihypertensive drugs, which ensured that the prescribed antihypertensive drugs were prescribed at least for treating hypertension. Due to the use of CPRD data, which include information related to patients' demographics, clinical and medication history, a wide range of factors was studied and their associations with antihypertensive drug adherence and persistence patterns were then determined.

However, a number of limitations need to be acknowledged. This study was conducted in the UK with its publicly funded healthcare system, and thus the findings may not be generalisable to countries with a different healthcare system. Nevertheless, the observed adherence and persistence patterns were quite similar to those reported in other studies. Although a wide range of factors related to patients' demographics, clinical features and medication were included, the role of unmeasured confounders cannot be ruled out due to the retrospective nature of the study design.

The CPRD contains only prescribed data and adherence, therefore, was measured indirectly by PDC as a proxy; thus, obtaining prescriptions was assumed to be equivalent to the actual use of medication and that any prescribed dose was dispensed and taken by patients, which may not reflect the real consumption. This assumption could lead to overestimation of medication adherence. However, measuring adherence using secondary databases has been validated with other methods of adherence measurement such as electronic devices, patients' self-

reports and pill counts[372, 373], with no substantial differences between dispensing and prescribing datasets[374].

Given the multiple metrics to measure medication adherence using secondary databases, it could be argued that different metrics may produce different results. However, Hess *et al* (2006)[295] in their comparison of the various methods of adherence measurement using secondary databases found that all measures provide comparable values. Furthermore, among all the adherence measures, MPR and PDC were the best predictors of patients' hospitalisations[296], even though PDC is considered preferable to MPR as it provides more conservative estimates of adherence, especially in the presence of therapeutic switching or concurrent drug therapy[290, 291].

4.6.7. Conclusions

A set of patient characteristics was identified as potential determinants of adherence and persistence patterns of antihypertensive medications. This knowledge will provide valuable information on the potential confounders that should be accounted for while investigating the impact of ARBs switching on patients' adherence and clinical outcomes in the next chapter. Furthermore, conducting this chapter has resulted in preparing the data for the next chapter in terms of data management and cleaning. Finally, patients who have been identified as switchers will form the basis of the study cohort for the next chapter.

Chapter 5. Clinical and economic consequences of switching from ARBs to ACEIs in patients with primary hypertension

5.1. Introduction

Switching of antihypertensive drugs is often due to either clinical or non-clinical reasons. The clinical reasons include patients' intolerance, treatment failure and/or development of comorbid conditions[283, 375]. On the other hand, antihypertensive drugs may be switched for economic purposes to save money by switching to drugs with a lower acquisition cost.

In terms of ARBs switching to ACEIs, which is promoted by the BCBV indicator, it is likely that switching is for non-medical reasons due to the lack of any potentially relevant clinical justifications. As ARBs have been shown to have a better safety and tolerability profile than ACEIs[134, 204, 207-214], or at least similar[203, 217], it is unlikely that patients would be switched due to intolerance to ARBs. Furthermore, given the comparable clinical efficacy of ARBs and ACEIs in lowering BP and cardiovascular mortality and morbidity, switching ARBs due to treatment failure or ineffectiveness is not likely either. Finally, ARBs have similar licence indications to ACEIs, and ACEIs have even wider indications than ARBs; therefore, it is unlikely that a GP would switch patients from ARBs to ACEIs in response to the development of new comorbid conditions.

Switching of antihypertensive drugs in general has been shown to be associated with clinical and economic issues (Chapter 2, section 2.9.4, page 48). However, there are several possible reasons why switching from ARBs to ACEIs in the UK might not be associated with those clinical and economic issues that are often associated with switching of antihypertensive drugs.

Firstly, despite the lack of evidence-based switching guidance on dose equivalence, some healthcare authorities across the UK provided guidelines on dose equivalence and drug selection when switching from ARBs to ACEIs[161, 184]. This general guidance coupled with the evidence on the comparable or even better clinical efficacy of ACEIs compared with ARBs may therefore eliminate or at least minimise the risk of losing BP control after switching. Furthermore, the reported similar adherence profile of ARBs and ACEIs[13, 14] would also eliminate the issue of post-switching reduction in adherence due to switching to a drug with lower adherence profile, despite other studies presenting conflicting results[134, 204, 207-214] and suggesting superiority of ARBs over ACEIs in terms of tolerability and adherence profile. However, these conflicting findings could be related to unmeasured confounders or methodological flaws (Chapter 2, section 2.9.4.1.3, page 52).

Additionally, the importance of patients' involvement in health decisions in the modern NHS and "no decision about me, without me"[229], would likely play a crucial role in minimising patients' confusion and negative expectations about switching, and thus may reduce the possibility of post-switching reduction in adherence. In fact, involving patients in prescribing decisions has been emphasised in NICE guidelines about medication adherence[228] and considered an essential indicator for prescribers' good prescribing practice by the General Medical Council[231] in the UK.

Collectively, these factors may minimise the likelihood of incurring additional costs from compromising patients' adherence and clinical outcomes, and thus switching from ARBs to ACEIs could result in an overall cost saving. However, these assumptions need further research to validate them; there is only one small study[183] that has evaluated patients' switching from ARBs to ACEIs in the UK, but this study had major flaws (Chapter 2, section 2.9.4.2, page 58). Therefore, further research is needed to investigate whether patients' switching from ARBs to ACEIs in the UK is

associated with any negative clinical or economic consequences and whether it results in an overall financial saving for the NHS.

However, since patients' switching from ARBs to ACEIs could have happened before the introduction of the BCBV indicator, it is important to assess whether the impact of the switching differed before and after the policy's introduction with the hypothesis of positive effect of the policy on the switching impact. This can be performed by selecting a cohort of patients with primary hypertension who switched their antihypertensive drug therapy from ARBs to ACEIs and then comparing the clinical and resources utilisations in the pre-switching period to those in the post-switching period.

5.2. Aim and objectives

This chapter aimed to investigate the clinical (adherence, BP and HT-related complications) and economic (HT-related healthcare resource utilisation and costs) consequences of the BCBV policy's promoted switching of antihypertensive drug treatment from ARBs to ACEIs. Additionally, the impact of ARBs switching before and after the introduction of the BCBV indicator was also examined.

The objectives of this chapter include identifying the following measures at patient level and comparing them before and after patients' antihypertensive treatment switching from ARBs to ACEIs (pre-switching and post-switching period), using a multilevel modelling:

1. Patients' adherence to ARBs and ACEIs
2. Patients' blood pressure
3. Incidence of HT-related clinical outcome episodes (stroke, MI, angina, atherosclerosis and other ischaemic heart disease [IHD], heart failure [HF], and chronic renal failure (CRF)

4. HT-related healthcare resource utilisation and total costs, including both primary and secondary resources

The impact of the switching on the study outcomes will then be compared in patients who switched before the BCBV policy with those who switched after the policy.

5.3. Methods

5.3.1. Study design and data source

This retrospective cohort study used CPRD database linked with the Hospital Episode Statistics (HES) from April 2006 to March 2012 (Figure 5.1), i.e., the last available date for HES data at the time of this study.

5.3.2. Structure and contents of HES dataset

The HES dataset contains detailed information of hospital admissions, outpatient appointments, accident and emergency (A&E) attendances to NHS hospitals in England and is managed by the Northgate Information Solutions on behalf of the NHS Information Centre for health and social care. It includes patients treated in all NHS trusts in England as well as private patients treated in treatment centres funded by the NHS. The data are collected during the patient's stay in a hospital, and are then submitted allowing hospitals to be paid for the care they deliver[376].

Data about inpatient hospitalisations included in HES are available from 1989 onwards; whereas outpatient attendance data are available from 2003 onwards and A&E data from 2007 onwards[377]. The data are recorded for each British government fiscal year (from 1 April one year to 31 March the next year), with more than 12 million and 40 million of new admission and outpatient attendance records being added each year, respectively. The HES data contain patients' demographics, such as age, gender, residency and ethnicity, as well as clinical details of diagnosis,

operations and administrative information, such as date and methods of hospitalisation admission and discharge[377].

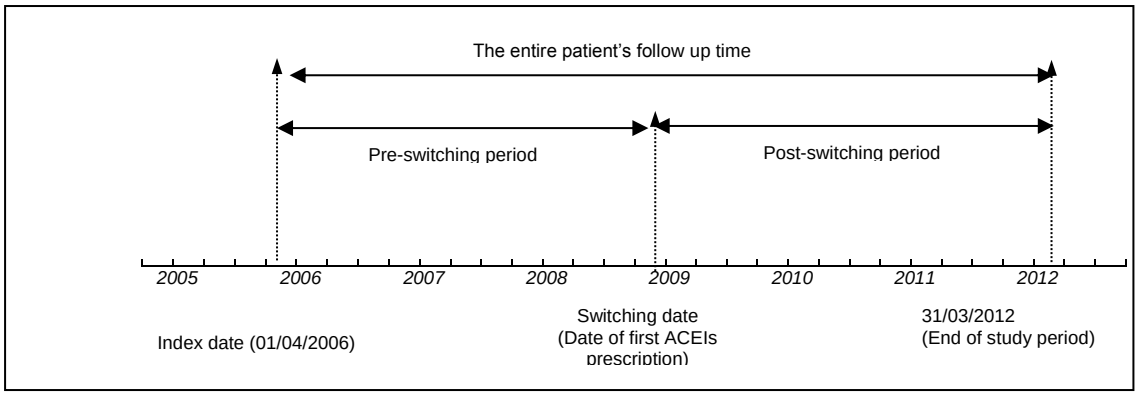
The data in HES are obtained through routine exchanges of information between healthcare providers and commissioners of healthcare for NHS patients in England. The data are submitted to the Secondary Uses Services (SUS) where the information is copied into a database. The SUS, at predetermined dates during the year on a monthly basis, takes an extract of their database and sends it to HES, where validation and cleaning of the extract are performed before the availability of the information in the data warehouse. Then, during various stages of data cleaning and processing cycle, data quality reports and checks are completed[378].

The HES dataset that is linked with CPRD consists of five main files (Appendix 7). In the HES dataset, "hospitalisation" refers to the total time of inpatient hospital stay from admission to discharge; whereas "episode" refers to a time period within a hospitalisation corresponding to the period where the patient is treated under a particular consultation's care. Individual patients may have more than one hospitalisation and each hospitalisation may consist of one or more episodes[379].

In the HES dataset, diagnosis data are coded using the International Classification of Diseases-tenth revision (ICD-10)[5, 6]; while procedure data are coded using the fourth revision of the Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS-4)[380, 381]. Each episode may have up to 20 ICD-10 diagnoses and 24 OPCS-4 procedure codes, among which one is a primary code, referring to the main condition investigated or treated during this episode, and the rest are secondary diagnosis codes[379].

This study used the HES dataset to extract HT-related clinical outcomes, and healthcare resource utilisation, as the majority of HT-related outcomes – such as MI and stroke – are acute events and managed primarily in hospitals.

Figure 5.1 Framework of the study time



5.3.3. Study cohort

Adults with primary hypertension who identified as switchers in Chapter 4 (page, 116) formed the basis of the cohort for this study. To be eligible for the study, the patients were required to be switched from ARBs to ACEIs before March 2012 and were registered in GP practices that had consented to data linkage with HES secondary data. This was so that patients could be linked to the HES dataset to extract their secondary care activities to enable the impact of switching ARBs to ACEIs on HT-related clinical complications and resource use in secondary care to be evaluated. The HES-consenting patients were identified by a two-step process. Firstly, the practice identifiers for eligible patients were obtained from the last three digits of patients' identifiers. Afterwards, these practice identifiers were matched with the list of HES-consenting practices, provided by CPRD, and those patients registered with HES-consenting practices were then identified and represented the final study cohort included in the analysis.

The included patients were then identified in HES data using the same CPRD patient identifier, which was generated by the CPRD team during the linkage process of CPRD with HES using a combination of criteria, including the patient's NHS number, gender and partial date of birth[379]. After identification of patients in the HES dataset, their activity data were extracted. Switching, as described in Chapter 4 (section 4.3.5.3, page 129) was defined as stopping of the index drug (ARBs) with subsequent prescribing of ACEIs within 30 days after finishing prescription day supply of last ARBs prescription.

It was observed that some patients were prescribed other antihypertension drug classes in additional to ACEIs during their follow-up time after the switching. Subsequently, the study cohort was stratified into two subgroups based on whether they had been prescribed additional antihypertensive drugs other than ACEIs in the post-switching period (ACEIs-combined group) or prescribed only ACEIs (ACEIs-monotherapy group). This was in order to avoid confounding by co-prescribing of ACEIs with other antihypertensive drugs.

5.3.4. Study outcome measures

The primary outcome measures of this study were: (1) antihypertensive drug adherence (ARBs and ACEIs); (2) short-term clinical outcome (BP level); (3) long-term hypertension-related major complications, including stroke, MI, angina, atherosclerosis and other IHD, HF, CRF; and (4) healthcare resource utilisation.

Individual patients were followed up from the date of ARBs prescription (index date) until the end of follow-up time, which consisted of either end of the study period (31 March 2012), patient transferred out of the dataset, or patient's death, whichever occurred first. Switching date (the date of the first ACEIs prescription after stopping ARBs) divided patients' follow-up times into two study periods (pre-switching and

post-switching period). Patients in the pre-switching period were followed up from the index date until the switching date; while those in the post-switching period were followed up from the switching date until the end of follow-up time.

All of these outcomes were measured for each individual patient in both pre- and post-switching periods. To describe the distribution of patients' index date and switching date in relation to the date of BCBV indicator implementation, the numbers of patients who started or switched their index drug before or after the BCBV policy were calculated.

5.3.4.1. Antihypertensive drug adherence before and after switching

PDC (Chapter 4, section 4.3.5.1, page 126) was used as the proxy for measuring patients' adherence to ARBs or to ACEIs (class adherence) using prescribing data from the CPRD. The PDC in the pre-switching period for ARBs was derived from dividing the number of days covered by ARBs (class adherence) by the number of days in the follow-up period (from the index date to switching date) and then multiplied by 100 and truncated at 100.

In the post-switching period, some patients (ACEIs-combined group) were prescribed other antihypertensive drugs in addition to ACEIs. Therefore, PDC for both ACEIs (class adherence) and for any antihypertensive drug therapies (therapy adherence) were calculated by dividing the number of days covered by ACEIs (for class adherence) or any antihypertensive drug therapy (for therapy adherence) by the number of days in the follow-up period (from switching date to end of follow-up time) and then multiplied by 100 and truncated at 100. Patients were then classified into adherent or non-adherent by applying the conventional 80% cut-off point of PDC[283, 296, 305, 322-325, 327], and the proportion of non-adherent patients in both pre- and post-switching time periods was then estimated.

5.3.4.2. Short-term clinical outcomes

To assess the short-term clinical outcomes that may be associated with ARBs switching, individual patients' BP records during the study period were identified by using the "entity type" variable in the additional clinical file of CPRD, which identifies the structured area in the computer system where the data were entered. The entity type value that corresponds to BP records was deciphered from the CPRD lookup file for entity type, March 2014 version[382].

The patients' mean BPs were calculated in both the pre-and post-switching periods. Since patients' mean BP in the pre- and post-switching periods could have been affected by the number and time gap between BP measurements, number of BP measurements and the mean time gap between the measurements were also calculated in order to avoid confounding by these factors. For the ACEIs-combined group, the BP value before the addition of a new antihypertensive drug class to ACEIs therapy was extracted and compared with the BP value in the pre-switching period.

5.3.4.3. Long-term clinical outcomes

Data on hospitalisation episodes due to HT-related complications[198, 233] were identified from the records within the HES database via the extraction of all the hospitalisation episodes with HT-related complications ICD-10 diagnosis codes (Appendix 8), regardless of whether the codes were recorded as primary or secondary diagnosis. The number and proportion of patients who developed any of those individual complications were calculated. Furthermore, number of and proportion of patients who developed any of those complications collectively (composite outcome measure) was also calculated.

5.3.4.4. Healthcare resource use and costs

The healthcare resource use and cost for managing individual patient's hypertension and complications in primary and secondary care during the study period were identified and calculated before and after switching.

5.3.4.4.1. Healthcare resource use

Primary care resource utilisation included GP visits and consultations, and antihypertensive drug prescriptions. The number and duration of GP consultations and visits for diagnosing hypertension, monitoring and reviewing hypertension treatment, and measuring BP that occurred within surgery, out of surgery (clinics, home visits) or via telephone, was identified from clinical files and consultation files within the CPRD using Read codes (Appendix 9). Antihypertensive drug prescriptions during the study period were identified and extracted from the therapy file using product codes (Appendix 3).

Secondary care resources for treating hypertension complications, including outpatient attendance and inpatient hospitalisation, were identified and extracted from HES and CPRD data, respectively. Outpatient attendances to cardiology, general medicine, A&E, and nephrology clinics were identified from the NHS speciality variable recorded in the CPRD referral file[382] because these are the most likely to be involved in the treatment, monitoring or reviewing hypertension and its complications. Of all the identified attendances, only those with medication Read codes for hypertension diagnosis and managements (Appendix 10) were included in this study.

Of all hospitalisation episodes identified for the study cohort, those with ICD-10 diagnosis for any of the hypertension complications (Appendix 8) were included in this study. Common sequelae of hypertension[195], such as MI and stroke, were

included in this study to avoid underestimation of hypertension-related resource utilisation[198], because it is a common practice to use the ICD-10 codes for those cardiovascular diseases instead of hypertension codes as diagnostic codes for patients with complicated hypertension at hospitalisations and emergency visits[198].

Detailed information about each hospitalisation episode, such as the date of admission and discharge, causes of admission, length of stay, the speciality, and any operations or procedures during each episode, was also extracted from HES dataset. All procedures for hypertension complications were identified in each episode using OPCS-4 codes (Appendix 11).

5.3.4.4.2. Assigning unit cost to the utilised healthcare resources

Resource use data were assigned a unit cost. The costs of antihypertensive drugs were obtained from the BNF, March 2012[176]. The costs of GP visits and consultations were obtained from PSSRU-Unit Costs of Health and Social Care 2012[383], based on whether the consultation was within surgery, out of surgery (clinics and home visits) or via telephone, including direct care staff costs without qualification (Table 5.1). The unit cost of outpatient attendance at the various outpatient clinics (cardiology, general medicine, A&E and nephrology) was estimated based on the mean costs provided by the NHS reference cost-2012 for each speciality clinic (Table 5.1).

Table 5.1 Unit cost of GP consultations and outpatient attendances

Healthcare resource	Number	Cost (£)	Source
GP consultations			
Within surgery consultation	1 minute	3.1	PSSRU-2012
Out of surgery consultation	1 minute	3.9	PSSRU-2012
Telephone consultation	1 minute	3.1	PSSRU-2012
Outpatient attendance			
Cardiology clinic	1 visit	130	NHS reference costs 2012
General medicine clinic	1 visit	150	NHS reference costs 2012
Accident and emergency	1 visit	119	NHS reference costs 2012
Nephrology clinic	1 visit	164	NHS reference costs 2012

Inpatient hospitalisation episodes related to hypertension complications were assigned unit costs using NHS reference cost-2012[384], based on the Healthcare Resource Groups-4 (HRGs)[384] code for each episode, and the type of hospitalisation admission (day case, elective or non-elective admission). HRG codes for each hospitalisation episode were derived using the NHS healthcare resource grouper software (NHS HRG-4 grouper, 2011/2012), whereby the most relevant HRG-4 code was assigned to each episode based on ICD-10 diagnostic and OPCS-4 procedure codes for the episode[385].

In addition, the assigned unit costs were adjusted for the episode's average length of stay (LOS) using excess bed days costs provided by the NHS reference costs[384]. The adjustment was performed by subtracting the episode's duration from the mean length of stay for that particular type of episode, and then the cost of any excess days was added to or subtracted from the episode's total cost.

5.3.4.4.3. Estimation of total direct costs of healthcare resources utilised

The total direct cost of healthcare resource utilisation was calculated by multiplying the quantities of the used resources by their unit cost. In addition, the total cost of each category of the healthcare resources (GP consultations, antihypertensive

drugs, inpatient hospitalisations and outpatient attendance) was calculated for each patient. Estimating total cost alone may be misleading[233] as different follow-up time results in varied healthcare resource utilisation. Therefore, total direct costs and annual total cost of each healthcare resource category were also calculated for each patient before and after switching.

5.3.5. Cohort characteristics

The patients' demographic and clinical characteristics that were found to be significantly associated with adherence and switching of antihypertensive drug classes in Chapter 4 (page 116) were included in this study. Those characteristics were age, gender, medication status, whether they were new or existing drug users, and medical and clinical status, such as whether they were a new or existing hypertensive patient, SBP and DBP, and CCI. Additional factors that were known to be clinically relevant as risk factors for BP control and hypertension were also included, such as body mass index (BMI), serum cholesterol and smoking status. Information about these additional factors was also measured at index date and extracted from CPRD additional clinical files using information recorded in "entity type" variable based on the lookup file provided by the CPRD[382]. For instance, based on the lookup file, an entity type value of "four" indicates smoking status. Furthermore, the proportion of patients who started their index drug before or after the BCBV policy (denoted by the index date variable) was also calculated, as well as the proportion of patients who switched their index drug before or after the BCBV policy (denoted by switching date variable).

5.4. Data analysis

5.4.1. Analyses framework

Primary outcomes (adherence [PDC], BP level, HT-related complications and healthcare resource utilisation) were compared before and after switching; hence,

patients act as their own control, and the analysis was stratified by two study groups, i.e., ACEIs-combined and ACEIs-monotherapy groups. To investigate the impact of BCBV policy on ARBs switching and its related clinical outcomes, the two study groups (ACEIs-combined and ACEIs-monotherapy groups) were further divided into those who switched before the BCBV policy (pre-BCBV group) and those who switched after the BCBV policy (post-BCBV group).

The impact of the switching on study outcomes in the pre-BCBV group was compared with those in the post-BCBV group to indicate a possible policy effect. Patients' demographic and clinical characteristics were compared between ACEIs-combined and ACEIs-monotherapy groups, and between pre- and post-BCBV groups to explore any significant variations in patient characteristics that might explain or bias any observed effect of the switching or the BCBV policy, respectively, on the study outcomes.

Descriptive statistics were used to report continuous variables (age, SBP, DBP, BMI, serum cholesterol and follow-up time) as means±SD. Unpaired t-tests were used to compare the continuous variables between the two study groups; whereas, categorical variables were reported as a proportion and compared using chi-squared tests. To determine whether the BCBV policy had affected the extent of switching patients from ARBs to ACEIs, the proportions of patients who switched ARBs as well as other antihypertensive drug classes to the various antihypertensive drug classes were calculated and compared before and after the BCBV policy.

5.4.2. Comparison of study outcomes before and after ARBs switching

Crude PDC values before and after switching are presented as medians (IQR), and compared using the non-parametric Wilcoxon signed-rank sum test, as they were non-normally distributed. SBP and DBP are presented as means±SD and were

compared using paired t-test. Crude proportions of non-adherent patients (PDC<80%) and proportion of patients with any major or composite of hypertension-related complications were compared using McNemar test (a type of paired chi-squared test)[386].

Multilevel modelling was used to analyse the study outcomes before and after ARBs switching since the observations were correlated and non-independent as patients were followed up longitudinally and outcomes were repeatedly measured in the same patients. Consequently, the standard regression methods, such as linear and logistic regression, were inappropriate to explore the association between study outcomes and ARBs switching since such non-independency would violate the independence assumption of standard regression methods. Multilevel modelling provides an alternative univariate and multivariate analysis of repeated measurements to the standard regression methods, with the study outcomes being considered as level one data; whereas, the individual patients as level two data[387].

The association between the study outcomes before and after switching was explored using univariate multilevel analysis, and the analysis was adjusted for potential confounders that likely appeared to affect the study outcomes, using multivariate multilevel modelling. One binary variable indicating whether the study outcomes were measured before or after switching was included in the models. Different study outcomes were adjusted for different confounders (Table 5.2). Only the results from the multivariate multilevel modelling are presented in this study.

Table 5.2 Confounders included in the multivariate multilevel modelling

Study outcomes	Confounders for which models were adjusted
Adherence	Patient's follow-up time in the pre- and post-switching period
BP	Patient's follow-up time in the pre- and post-switching period
	PDC level in the pre- and post-switching period Number of annual BP records
HT-related complications	Patient's follow-up time in the pre- and post-switching period
	SBP value in the pre- and post-switching period
	DBP value in the pre- and post-switching period
	Whether the patient developed any HT-related complications in the pre-switching period or not

(Note) BP: Blood pressure; **HT**: Hypertension; **PDC**: Proportion of days covered; **SBP**: Systolic blood pressure; **DBP**: Diastolic blood pressure

5.4.3. Comparison of healthcare resources used and costs incurred before and after ARBs switching

Descriptive statistics (median, IQR) was used to report the total number of individual elements of the healthcare resources utilised by patients, as well as the annual number of utilised healthcare resources per patient, and then compared before and after switching of antihypertensive drug treatment, using the Wilcoxon signed-rank test.

Total annual costs per patient and cost of each element were compared before and after switching via parametric paired t-test, using the data generated from bootstrapping. A non-parametric bootstrapping approach with replacement was used to achieve the approximate normality of data distribution, which in turn allowed the comparison of arithmetic means using a parametric test. Bootstrapping is a database simulation method for evaluating statistical precision that allows comparing arithmetic means while avoiding assumptions about the distribution of cost data. The bootstrapping process includes selecting random values from the original sample with replacement to produce a bootstrap sample then the statistic of interest (mean) was calculated for this new sample. This sampling process was

repeated 1000 times to create a sample of bootstrapped means with a distribution, and then mean cost was calculated for the bootstrap distribution[388].

Cost data are usually non-normally distributed and highly positively skewed, as was the case in this study; this is because a small number of patients usually incur high treatment cost, whereas others may have no costs[389]. Conventional approaches, such as log transformations and non-parametric tests, are not appropriate for analysing skewed cost data as they do not compare arithmetic means of all patients, which is mostly preferred and required by policy makers[390]. Transformation of cost data, mostly log transformation, may achieve approximate normality of data; however, parametric tests on a log transformed data compare geometric means, rather than arithmetic means, which are always less than arithmetic means[390]. Similarly, non-parametric tests, such as the Mann–Whitney test, compare the shape and location of distribution of the data, though are often interpreted as a comparison of median[391], which is also always less than the arithmetic mean in right-skewed data.

As pre and post analyses were performed on individual patient's cost data, each individual patient worked as a control for their data; therefore, there was no need to account for any potential confounders and hence no requirement to analyse the cost data using multivariate regression methods.

5.5. Results

5.5.1. Selection of the study cohort

Overall, 46,193 adults with primary hypertension, who switched their index drug to another antihypertensive drug class, were identified during the study period, of which 32.4% switched from ACEIs, 22.6% from CCBs, and only 5% switched from ARBs (Table 5.3). More than two-thirds of the identified patients (80%, n=36,964) started their index drug before the implementation of BCBV policy in April 2009 and more than half of them (61.2%, n=28,283) switched their index drug before the BCBV policy (Table 5.3).

Table 5.3 Characteristics of the switching episodes of antihypertensive drug classes from April 2006 to March 2012

Type of index drug	Number of patients (%)	Date of starting index drug class		Date of switching index drug class	
		Before policy	After policy	Before policy	After policy
ACEI	14,966 (32.4)	10,734 (71.7)	4,232 (28.3)	7,899 (52.8)	7,067 (47.2)
CCB	10,426 (22.6)	7,478 (71.7)	2,948 (28.3)	5,577 (53.5)	4,849 (46.5)
Diuretics	9,737 (21.1)	8,454 (86.8)	1,283 (13.2)	6,562 (67.4)	3,175 (32.6)
BB	7,630 (16.5)	7,158 (93.8)	472 (6.2)	5,916 (77.5)	1,714 (22.5)
ARB	2,304 (5.0)	2,118 (91.9)	186 (8.1)	1,474 (64.0)	830 (36.0)
"Others"	1,130 (2.5)	1,022 (90.4)	108 (9.6)	855 (75.7)	275 (24.3)
Total	46,193 (100)	36,964 (80.0)	9,229 (20.0)	28,283 (61.2)	17,910 (38.8)

(Note) ACEIs: Angiotensin converting enzyme inhibitors; **ARBs**: Angiotensin receptor blockers; **CCBs**: Calcium channel blockers; **BBs**: Beta-blockers

Patients who switched their index antihypertensive drug class before the policy were mostly switched to ACEIs regardless of their index drug class, except for patients with ARBs as their index drug class who switched to CCBs (Table 5.4). Likewise, patients who switched after the policy were mostly switched to ACEIs regardless of their index drug classes including ARBs. However, the proportion of patients who switched from ARBs to ACEIs increased by 27.6% – from 16.9% in those who switched before the policy to 44.5% in those who switched after the policy.

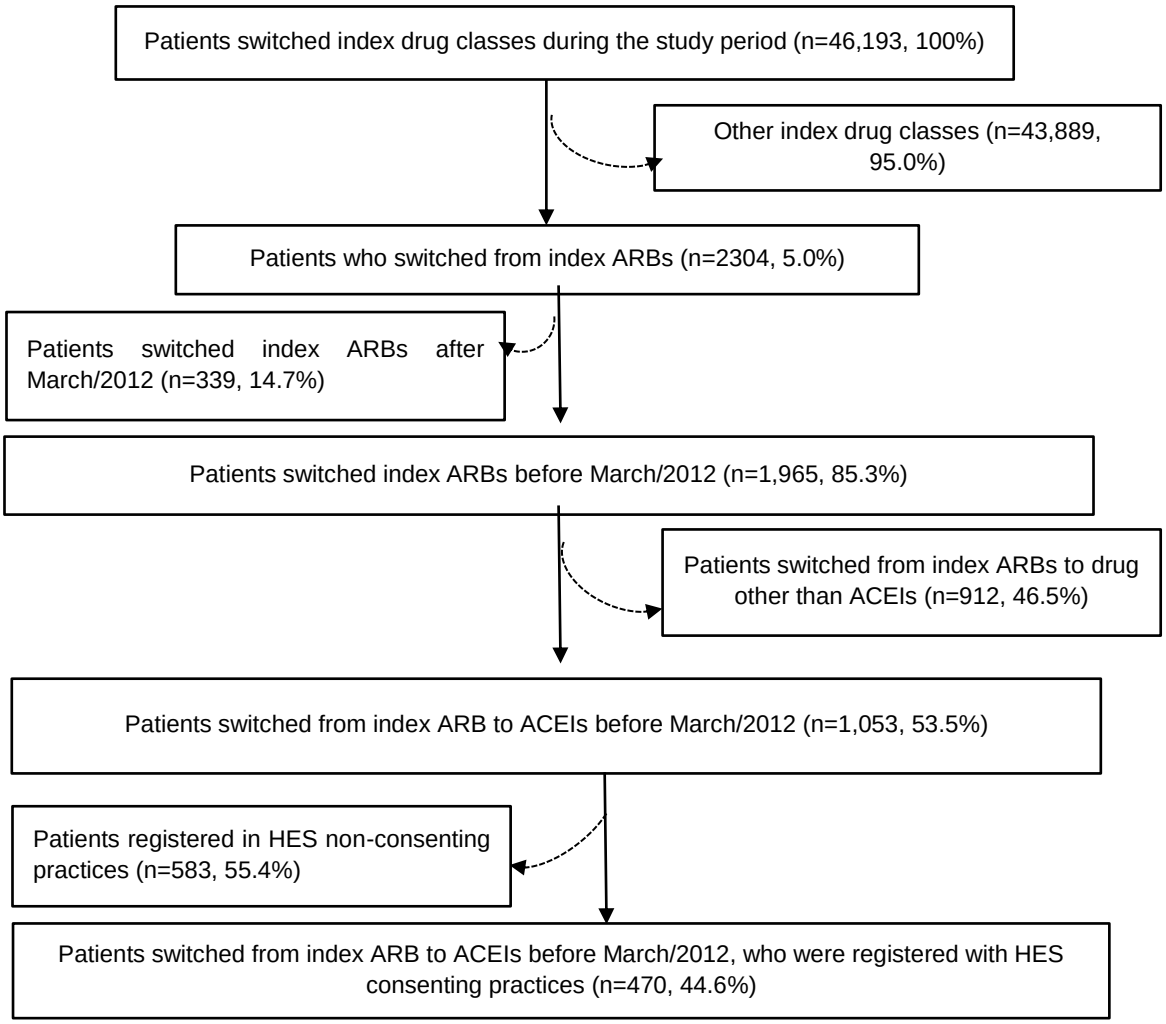
Table 5.4 The number and proportion of patients who switched their index drug class to other antihypertensive drug classes before and after the BCBV policy

	Patients switched before the BCBV policy, N (%)						Patients switched after the BCBV policy, N (%)					
	Type of index drug class											
	ACEIs	**CCBs**	**Diuretics**	**BBs**	**ARBs**	**"Others"**	**ACEIs**	**CCBs**	**Diuretics**	**BBs**	**ARBs**	**"Others"**
Switched-to												
ACEIs	___	2,470 (44.3)	3,222 (49.1)	2,845 (48.1)	249 (16.9)*****	250 (29.2)	___	2,426 (50.0)	1,411(44.4)	738 (43.1)	369 (44.5)*****	78 (28.4)
CCBs	2,577 (32.6)	___	2,087 (31.8)	1,557 (26.3)	532 (36.1)	168 (19.7)	2,454 (34.7)	___	1,276 (40.2)	609 (35.5)	219 (26.4)	89 (32.4)
Diuretic	1,666 (21.1)	1,899 (34.1)	___	926 (15.7)	455 (30.9)	239 (28.0)	892 (12.6)	1,513 (31.2)	___	241 (14.1)	149 (18.0)	50 (18.2)
BBs	564 (7.1)	463 (8.3)	551 (8.4)	___	153 (10.4)	106 (12.4)	453 (6.4)	393 (8.1)	241 (7.6)	___	71 (8.6)	32 (11.6)
ARBs	2,946 (37.3)	601 (10.8)	585 (8.9)	505 (8.5)	___	92 (10.8)	3,158 (44.7)	408 (8.4)	210 (6.6)	105 (6.1)	___	26 (9.5)
"Others"	146 (1.9)	144 (2.6)	117 (1.8)	83 (1.4)	85 (5.8)	___	110 (1.6)	109 (2.3)	37 (1.2)	21 (1.2)	22 (2.7)	___
Total	7,899 (100)	5,577 (100)	6,562 (100)	5,916 (100)	1,474 (100)	855 (100)	7,067 (100)	4,849 (100)	3,175 (100)	1,714 (100)	830 (100)	275(100)

(Note) ACEIs: Angiotensin converting enzyme inhibitors; **ARBs**: Angiotensin receptor blockers; **CCBs**: Calcium channel blockers; **BBs**: Beta-blockers; **BCBV**: Better Care Better Value; *****: Denote the proportion of patients who switched from ARBs to ACEIs

Of the 46,193 patients who switched their drug therapy, only 5% (n=2,304) were switched from ARBs to other antihypertensive drugs (Figure 5.2). Furthermore, of the 2,304 patients, only 85.3% (n=1,965) were switched from their index ARBs before the last available date of HES data (March 2012), of which only 53.3% (n=1,053) were switched from ARBs to ACEIs. Of those 1,053 patients, only 44.6% (n=470) were registered in HES-consenting practices. Accordingly, the final study cohort consisted of 470 patients (Figure 5.2).

Figure 5.2 Flowchart of the study cohort selection



5.5.2. Baseline characteristics of the study cohort

In the post-switching follow-up period, 78.5% (n=369) of the final study cohort (n=470) were prescribed other antihypertensive drug classes with ACEIs (ACEIs-combined group), and the remaining 101 patients (21.5%) were prescribed only ACEIs (ACEIs-monotherapy group).

The basic characteristics of the ACEIs-combined group were similar to those of the ACEIs-monotherapy group (Table 5.5), except for the follow-up time, smoking status and switching date. Patients in the ACEIs-combined group had a shorter pre-switching mean follow-up time, with a longer post-switching follow-up, a higher proportion of non-smokers, and a higher proportion of patients who were switched from their index ARBs drug class before the introduction of the BCBV policy.

Forty-three percent of the study cohort (n=202) were switched from their index ARBs drug before the introduction of the BCBV policy, among which 174 patients (86.0%) were ACEIs-combined and 28 patients (14%) were ACEIs-monotherapy group. Of the remaining 57% of the cohort (n=268), who switched their index ARBs drug after BCBV policy, 195 (72.8%) were in the ACEIs-combined group and 73 patients (27.2%) in the ACEIs-monotherapy group.

Table 5.5 Baseline characteristics of the study cohort

	Total (n=470)	ACEIs-combined group (n=369, 78.5%)	ACEIs-monotherapy group (n=101, 21.5%)
Mean age±SD	59.1±12.5	59.4±12.8	57.9±11.5
Gender			
Male	281 (59.8%)	225 (61.0%)	56 (55.5%)
Female	189 (40.2%)	144 (39.0%)	45 (44.5%)
BP (mmHg)			
Mean SBP±SD	147.2±18.4	147.3±18.6	146.8±17.8
Mean DBP±SD	86.6±11.5	86.6±11.5	86.6±11.8
Mean BMI±SD	28.6±5.4	28.8±5.2	28.0±6.1
Mean serum cholesterol±SD	5.1±1.1	5.1±1.2	5.2±1.0
Mean Follow-up time±SD (years)			
Before switching	2.5±1.7	2.3±1.7[a]	3.1±1.6[a]
After switching	2.6±1.7	2.8±1.7[b]	1.9±1.4[b]
Hypertension status			
Incident case	116 (24.7%)	89 (24.1%)	27 (26.7%)
Prevalent case	354 (75.3%)	280 (75.9%)	74 (73.3%)
CCI			
0	286 (60.9%)	218 (59.1%)	68 (67.3%)
1	112 (23.8%)	92 (24.9%)	20 (19.0%)
≥2	72 (15.3%)	59 (16.0%)	13 (12.9%)
Smoking status			
Non smokers	262 (55.7%)	214 (58.0%)[c]	48 (47.5%)[c]
Smokers	75 (16.0%)	52 (14.1%)	23 (22.8%)
Ex.smokers	133 (28.3%)	103 (27.9%)	30 (29.7%)
Drug use status			
Incident user	146 (31.1%)	117 (31.7%)	29 (28.7%)
Prevalent user	324 (68.9%)	252 (68.3%)	72 (71.3%)
Index date			
Before policy	428 (91.1%)	355 (90.8%)	93 (92.0%)
After policy	42 (8.9%)	34 (9.2%)	8 (8.0%)

(Note) a, b: p<0.05 using an unpaired t-test; **c, d**: p<0.05 using chi-square test; **CCI**: Charlson comorbidity index; **ACEIs**: Angiotensin converting enzyme inhibitors; **ARBs**: Angiotensin receptor blockers; **CCBs**: Calcium channel blockers; **BBs**: Beta-blockers; **CCI**: Charlson comorbidity index; **BP**: Blood pressure; **BMI**: Body mass index

5.5.3. Baseline characteristics of patients who switched their index drug ARBs before and after the BCBV policy

Compared with patients who switched ARBs after the BCBV policy, patients who switched before the policy had significantly higher mean age (60.8 vs. 57.8 years), higher mean SBP (149.7 vs. 145.3 mmHg), shorter mean pre-switching follow-up time (1.1 vs. 3.4 years) but longer mean post-switching follow-up time (4.2 vs. 1.3 years), higher proportion of prevalent hypertensive patients (82.2% vs. 70.2%) and lower proportion of patients with no comorbidity (53% vs. 66.8%) (Table 5.6).

In the ACEIs-combined groups, patients who switched before BCBV policy compared with those who switched after had significantly higher mean SBP (150.3 vs. 144.7 mmHg), shorter mean pre-switching follow-up time (1.1 vs. 3.3 years), longer mean post-switching follow-up time (4.3 vs. 1.4 years), higher proportion of prevalent hypertensive patients (82.2% vs. 70.3%) but lower proportion of patients with no comorbidity (52.3% vs. 65.1%) (Table 5.6).

In contrast, the characteristics of patients in the ACEIs-monotherapy group were similar in terms of those who switched before and after the policy, except for follow-up time, as those who switched before the policy had significantly shorter mean pre-switching follow-up time (1.4 years vs. 3.7 years) but longer mean post-switching follow-up time (3.7 years vs. 1.2 years) (Table 5.6).

Table 5.6 Baseline characteristics of the study cohort, stratified by whether switching happened before or after the BCBV policy

	Total (n=470)		**ACEIs-combined group** (n=369)		**ACEIs-monotherapy group** (n=101)	
	Before policy (n=202)	**After policy** (n=268)	**Before policy** (n=174)	**After policy** (n=195)	**Before policy** (n=28)	**After policy** (n=73)
Mean age±SD	60.8±13.8*	57.8±11.4*	60.7±14.1	58.3±11.5	61.5±11.7	56.6±11.2
Gender						
Male	117 (57.9%)	164 (61.2%)	103 (59.2%)	122 (62.6%)	14 (50.0%)	42 (57.5%)
Female	85 (42.1%)	104 (38.8%)	71 (40.1%)	73 (37.4%)	14 (50.0%)	31 (42.5%)
BP (mmHg)						
Mean SBP±SD	149.7±20.1*	145.3±16.8*	150.3±20.4*	144.7±16.4*	146.0±17.7	147.0±17.9
Mean DBP±SD	86.1±11.9	86.9±11.2	86.3±11.8	86.8±11.2	84.8±12.9	87.2±11.4
Mean BMI±SD	28.6±5.7	28.6±5.1	28.7±5.5	28.8±4.8	27.6±7.1	28.2±5.7
Mean serum cholesterol±SD	5.1±1.2	5.1±1.1	5.1±1.1	5.1±1.2	5.1±1.1	5.2±1.0
Mean Follow-up time±SD (years)						
Beforeswitching	1.1±0.8*	3.4±1.5*	1.1±0.8*	3.3±1.7*	1.4±0.7*	3.7±1.4*
After switching	4.2±1.1*	1.3±0.8*	4.3±1.1*	1.4±0.8*	3.7±1.2*	1.2±0.8*
Hypertension status						
Incident case	36 (17.8%)**	80 (29.9%)**	31 (17.8%)**	58 (29.7%)**	5 (17.9%)	22 (30.1%)
Prevalent case	166 (82.2%)**	188 (70%)**	143 (82%)**	137 (70.3%)**	23 (82.1%)	51 (69.9%)
CCI						
0	107 (53.0%)**	179 (66%)**	91 (52.3%)**	127 (65.1%)**	16 (57.1%)	52 (71.2%)
1	53 (26.2%)**	59 (22.0%)**	46 (26.4%)**	46 (23.6%)**	7 (25.0%)	13 (17.8%)
≥2	42 (20.8%)**	30 (11.2%)**	37 (21.3%)**	22 (11.3%)**	5 (17.9%)	8 (11.0%)
Smoking status						
Non smokers	114 (56.4%)	148 (55.2%)	103 (59.2%)	111 (56.9%)	11 (39.3%)	37 (50.7%)
Smokers	34 (16.8%)	41 (15.3%)	26 (14.9%)	26 (13.3%)	8 (28.6%)	15 (20.6%)
Ex.smokers	54 (26.7%)	79 (29.5%)	45 (25.9%)	58 (29.7%)	9 (32.1%)	21 (28.8%)
Drug use status						
Incident user	56 (27.7%)	90 (33.6%)	50 (28.7%)	67 (34.4%)	6 (21.4%)	23 (31.5%)
Prevalent user	146 (72.3%)	178 (66.4%)	124 (71.3%)	128 (65.6%)	22 (78.6%)	50 (68.5%)
Index date						
Before policy	202 (100%)**	226 (84%)**	174(100%)**	161 (82.6%)**	28(100%)**	65 (89.0%)**
After policy	0 (0.0%)**	42 (15.7%)**	0 (0.0%)**	34 (17.4%)**	0 (0.0%)**	8 (11.0%)**

(Note) *: p<0.05 (t-test); **: p<0.005 (chi-square test); **ACEIs**: Angiotensin converting enzyme inhibitors; **ARBs**: Angiotensin receptor blockers; **CCBs**: Calcium channel blockers; **BBs**: Beta-blockers; **CCI**: Charlson comorbidity index

5.5.4. Proportion of patients with PDC<80% in the post-switching compared with the pre-switching period

Switching of ARBs to ACEIs was associated with a statistically significant reduction in median class PDC (98.5% vs. 97.9%). However, after stratifying by the subgroups, significant reduction in the class median PDC was observed only in the ACEIs-combined group (99.2% vs. 97.9%); whereas patients in the ACEIs-monotherapy group had a non-significant difference in their class median PDC following the switching of ARBs (Table 5.7). In contrast, post-switching therapy PDC (a proxy of patients' adherence to any antihypertensive drugs) was not significantly different from the pre-switching period in both the ACEIs-combined and ACEIs-monotherapy group (Table 5.7). The proportion of class PDC<80% for drug class was significantly higher in the post-switching period than the pre-switching period (Table 5.7); however, the significantly higher proportion was only observed in the ACEIs-combined group. On the other hand, the proportion of PDC<80% for antihypertensive drugs therapy in the post-switching period was not significantly different from the pre-switching period in both ACEIs-combined and ACEIs-monotherapy groups (Table 5.7).

Table 5.7 PDC for class and therapy adherence in the post-switching compared with the pre-switching period

	Total (n=470)		**ACEIs-combined group** (n=369, 78.5%)		**ACEIs-monotherapy group** (n=101, 21.5%)	
	Before switch	**After switch**	**Before switch**	**After switch**	**Before switch**	**After switch**
Antihypertensive drug class						
Median PDC (IRQ)	98.5% (89.5-100%)*	97.9% (74.7-100%)*	99.2% (89.5-100%)*	97.9% (70-100%)*	95.7% (90.5-100%)	98.0% (86.0-100%)
Proportion of patients with PDC<80%	17.0%**	27.0%**	17.3%**	29.0%**	15.8%	19.8%
Antihypertensive drug therapy						
Median PDC (IRQ)	98.5% (89.5, 100%)	97.8% (86.9, 100%)	99.2% (89.5, 100%)	97.8% (84.9, 100%)	95.7% (90.5-100%)	98.0% (86.0-100%)
Proportion of patients with PDC<80%	17.4%	19.4%	17.9%	19.2%	15.8%	19.8%

(Note) * p<0.001 (Wilcoxon signed-rank test); ** p<0.001(McNemar test); **PDC**: Proportion of days covered

5.5.4.1. Multivariate analysis comparing the proportion of patients with PDC<80% in the post- and pre-switching periods

Compared with the pre-switching period, the proportion of patients with PDC<80% for antihypertensive drug class in the post-switching period was more than two-fold higher (OR: 2.4, 95%CI: 1.6, 3.7) after adjusting for follow-up time in the multivariate analysis (Table 5.8). After stratification, a similar likelihood was observed in the ACEIs-combined group (OR: 2.6, 95%CI: 1.6, 4.1) but not in the ACEIs-monotherapy group.

On the contrary, the proportion of patients with PDC<80% to any antihypertensive drug therapy was not significantly different between the pre- and post-switching period (Table 5.8), and the result remained consistent after stratifying to ACEIs-combined and ACEIs-monotherapy groups.

Table 5.8 Adjusted odds ratios for the proportion of patients with PDC<80% comparing the post- and pre-switching periods

Study cohort groups	Class PDC<80%		Therapy PDC<80%	
	OR (95%CI)	P-value	OR (95%CI)	P-value
Total (n=470)	2.4 (1.6, 3.7)	0.001	1.2 (0.8, 1.8)	0.376
ACEIs-combined group (n=369)	2.6 (1.6, 4.1)	0.001	1.1 (0.7, 1.8)	0.622
ACEIs-monotherapy group (n=101)	1.9 (0.6, 5.6)	0.247	1.9 (0.6, 5.6)	0.247

(Note) Models were adjusted for patients' follow-up time

In summary, switching of antihypertensive drug therapy from ARBs to ACEIs was associated with a statistically significant reduction in class PDC as patients were ~2.5 times more likely (OR: 2.4, 95%CI: 1.6, 3.7) to be non-adherent in the post-switching period compared with the pre-switching period. However, stratifying the analysis by whether the patients combined ACEIs with other antihypertensive drugs (ACEIs-combined group) or not (ACEIs-monotherapy group) in the post-switching

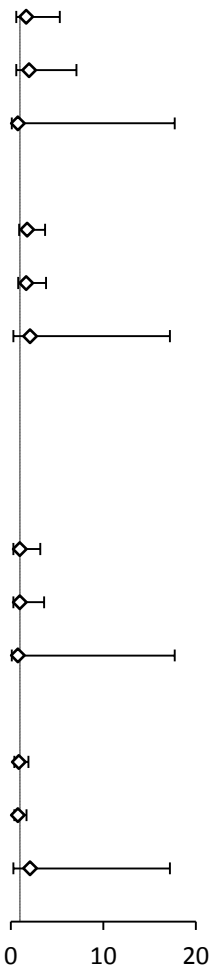
period demonstrated a statistically significant reduction in class PDC only in the ACEIs-combined group (OR: 2.6, 95%CI: 1.6, 1.4), but not in ACEIs-monotherapy group. On the other hand, ARBs switching was not associated with significant changes in therapy PDC, regardless of stratifying the analysis to ACEIs-combined and ACEIs-monotherapy groups.

5.5.4.2. Multivariate analysis comparing the proportion of patients with PDC<80% in the post- and pre-switching periods stratified by pre- and post-BCBV policy

Overall, the proportion of patients with PDC<80% for both antihypertensive drug class and therapy was not significantly different when comparing the post-switching and pre-switching periods, regardless of whether ARBs switching occurred before or after the BCBV policy (Table 5.9). Similar results were found when stratifying the patients to those who combined their ACEIs during the post-switching period (ACEIs-combined group) and those who did not (ACEIs-monotherapy group) (Table 5.9).

Table 5.9 Adjusted odds ratios for the proportion of patients with PDC<80% comparing the post- and pre-switching periods stratified by pre- and post-BCBV policy

The Study groups	OR (95%CI)
Class PDC<80%	
Patient switched before the BCBV policy (pre-BCBV policy group) (n=202)	
Total (n=202)	1.7 (0.6, 5.3)
ACEIs-combined group (n=174)	2.0 (0.6, 7.1)
ACEIs-monotherapy group (n=28)	0.8 (0.1,17.7)
Patient switched after the BCBV policy (post-BCBV policy group) (n=268)	
Total (n=268)	1.8 (0.9, 3.7)
ACEIs-combined group (n=195)	1.7 (0.8, 3.8)
ACEIs-monotherapy group (n=73)	2.1 (0.3,17.2)
Therapy PDC<80%	
Patient switched before the BCBV policy (pre-BCBV policy group) (n=202)	
Total (n=202)	1.0 (0.3, 3.2)
ACEIs-combined group (n=174)	1.0 (0.3, 3.6)
ACEIs-monotherapy group (n=28)	0.8 (0.1,17.7)
Patient switched after the BCBV policy (post-BCBV policy group) (n=268)	
Total (n=268)	0.9 (0.4, 1.9)
ACEIs-combined group (n=195)	0.8 (0.4, 1.7)
ACEIs-monotherapy group (n=73)	2.1 (0.3,17.2)



(Note) * models were adjusted for patient's follow-up time

5.5.5. Blood pressure in the post-switching compared with the pre-switching period

Although not significantly different, patients in the post-switching period appeared to have more BP measurements and a shorter time gap between any two consecutive records in comparison with the pre-switching period. The same patterns were found after stratifying patients into ACEIs-combined and ACEIs-monotherapy groups (Table 5.10).

Table 5.10 Number of BP records and time gap between records in the pre- and post-switching periods

	Total (n=470)		ACEIs-combined group (n=369, 78.5%)		ACEIs-monotherapy group (n=101, 21.5%)	
	Before switch	After switch	Before switch	After switch	Before switch	After switch
Median annual number of BP records (IQR)*	2.9 (1.9, 4.4)	3.2 (2.4, 4.6)	3.0 (1.9, 5.0)	3.7 (2.5, 4.8)	2.4 (1.7, 3.4)	2.6 (1.9, 3.8)
Median time (days) between BP records (IQR) *	120.0 (73.1, 176.5)	104.6 (64.2, 143.0)	115.4 (67.3, 173)	97.4 (63.9,139.3)	137.3 (94.4, 183)	120.9 (78.1, 180.7)

(Note) * p>0.05 using Wilcoxon signed-rank test; **BP**: blood pressure; **IQR**: interquartile range

Compared with the pre-switching period, overall, the mean SBP and DBP were significantly lower in the post-switching period (Table 5.11). However, after stratifying for the subgroups, a significant reduction in the SBP and DBP in the post-switching period was observed only in the ACEIs-combined group. The mean SBP and DBP just before the additions of the other antihypertensive drug classes in the post-switching period for patients in the ACEIs-combined group were not significantly different from those of the pre-switching period (144.2 vs. 146.1 mm Hg, p=0. 078; and 84.6 vs. 84.9 mmHg, p=0.645, respectively).

Table 5.11 Mean SBP and DBP before and after switching of ARBs

	Total (n=470)		ACEIs-combined group (n=369, 78.5%)		ACEIs-monotherapy group (n=101, 21.5%)	
	Before switch	After switch	Before switch	After switch	Before switch	After switch
SBP±SD	143.2±13.1*	141.3±12.8*	144.2±13.4*	141.9±12.5*	139.8±11.4	138.8±13.8
DBP±SD	84.1±8.8*	82.5±8.6*	84.6±8.7*	82.6±8.3*	82.4±8.7	81.9±9.5

(Note) * p<0.001 (paired t-test) ; **SBP**: systolic blood pressure (mmHg); **DBP**: diastolic blood pressure (mmHg); **SD**: standard deviation

Overall, compared with the pre-switching period, post-switching mean SBP and DBP were significantly lower, regardless of whether the patients were switched before or after the BCBV policy (Table 5.12). However, when stratifying for the subgroups, this significant reduction was only demonstrated in the ACEIs-combined

group but not in ACEIs-monotherapy group, irrespective of whether the switching occurred before or after the BCBV policy.

Table 5.12 Mean SBP and DBP before and after switching of ARBs stratified by pre- and post-BCBV policy groups

	Before switch	After switch	Before switch	After switch	Before switch	After switch
Patient switched before the BCBV policy (Pre-BCBV policy group) (n=202)						
	Total (n=202)		**ACEIs-combined group** (n=174, 86.1%)		**ACEIs-monotherapy group** (n=28, 13.7%)	
Mean SBP±SD	146.1±14.9*	142.7±12.4*	147.0±14.6*	143.4±12.0*	140.4±15.8	138.6±14.4
Mean DBP±SD	84.9±9.5*	82.7±8.7*	85.3±9.2*	83.0±8.5*	82.5±10.7	81.1±9.6
Patient switched after the BCBV policy (Post-BCBV policy group) (n=268)						
	Total (n=268)		**ACEIs-combined group** (n=195, 72.8%)		**ACEIs-monotherapy group** (n=73, 27.3%)	
Mean SBP ±SD	141.1±11.1*	140.2±13.1*	141.6±11.6*	140.6±12.8*	139.6±9.4	138.8±13.7
Mean DBP±SD	83.5 ±8.1*	82.3±8.5*	84.0±8.3*	82.3±8.0*	82.3±7.9	82.3±9.6

(Note) *** p<0.001 (paired t-test); **SBP: Systolic blood pressure; **DBP**: Diastolic blood pressure; **SD**: Standard deviation

5.5.5.1. Multivariate analysis comparing blood pressure in the post- and pre-switching periods

Comparing the post-switching period with the pre-switching period, there was a significant reduction in both mean SBP and DBP of the overall study cohort (Table 5.13), after adjusting for patients' follow-up time, number of BP records, class and therapy PDC in the multivariate analysis. However, after stratifying by study subgroups, the significant reduction in mean SBP and mean DBP was only found in the ACEIs-combined group but not in ACEIs-monotherapy group (Table 5.13).

Table 5.13 Adjusted mean differences and 95% confidence intervals in SBP and DBP between post- and pre-switching periods

		Total (n=470)	ACEIs-combined group (n=369, 78.5%)	ACEIs-monotherapy group (n=101, 21.5%)
Model 1[a]	SBP	–2.3 (–3.4, –1.2)*	–2.2 (–3.5, –1.0)*	–2.0 (–4.8, 0.4)
	DBP	–1.9 (–2.6, –1.2)*	–2.1 (–2.9, –1.4)*	–1.0 (–2.7, 0.7)
Model 2[b]	SBP	–1.9 (–3.0, –0.8)*	–1.8 (–3.0, –0.6)*	–2.0 (–4.8, 0.4)
	DBP	–1.7 (–2.4, –1.0)*	–1.9 (–2.6, –1.1)*	–1.0 (–2.7, 0.7)

(Note) a: Models were adjusted for follow-up time, number of annual BP records and class PDC; **b:** Models were adjusted for follow-up time, number of annual BP records and therapy PDC; * p<0.005; **SBP**: Systolic blood pressure; **DBP**: Diastolic blood pressure; Data presented in mean differences (95%CI)

5.5.5.2. Multivariate analysis comparing blood pressure in post- and pre-switching periods stratified by pre- and post-BCBV policy

There was no significant difference in both mean SBP and DBP when comparing the post-switching period with the pre-switching period for patients who switched ARBs therapy before the BCBV policy, regardless of the subgroups of ACEIs-combined or ACEIs-monotherapy groups (Table 5.14). In contrast, patients who switched ARBs therapy after the BCBV policy had a significantly lower mean SBP and DBP in the post-switching period compared with the pre-switching period (Table 5.14). However, after stratifying, the significant reduction in mean SBP and DBP was only found in the ACEIs-combined group but not in the ACEIs-monotherapy group (Table 5.14).

Table 5.14 Adjusted mean difference and 95% confidence interval in SBP and DBP between post- and pre-switching periods stratified by pre- and post-BCBV policy groups

Patient switched before the BCBV policy (Pre- BCBV policy group) (n=202)				
		Total (n=202)	**ACEIs-combined group** (n=174, 86.1%)	**ACEIs-monotherapy group** (n=28, 13.7%)
Model 1[a]	SBP	–0.5 (–3.7, 2.8)	0.3 (–3.2, 3.7)	–3.2 (–11.5, 5.1)
	DBP	0.4 (–1.6, 2.4)	1.0 (–1.1, 3.1)	–2.3 (–8.0, 3.3)
Model 2[b]	SBP	–0.2 (–3.5, 3.0)	0.6 (–2.9, 4.0)	–3.2 (–11.5, 5.1)
	DBP	0.5 (–1.4, 2.5)	1.2 (–1.0, 3.3)	–2.3 (–8.0, 3.3)
Patient switched after the BCBV policy (Post-BCBV policy group) (n=268)				
		Total (n=268)	**ACEIs-combined group** (n=195, 72.8%)	**ACEIs-monotherapy group** (n=73, 27.3%)
Model 1[a]	SBP	–3.4 (–5.4, –1.4)*	–3.2 (–5.4, –0.9)*	–2.4 (–8.1, 0.7)
	DBP	–2.8 (–4.0, –1.6)*	–3.3 (–4.7, –1.9)*	–0.5 (–3.3, 2.3)
Model 2[b]	SBP	–3.0 (–5.0, –1.0)*	–2.8 (–5.0, –0.5)*	–2.4 (–8.1, 0.7)
	DBP	–2.7 (–3.8, –1.3)*	–3.1 (–4.4, –1.7)*	–0.5 (–3.3, 2.3)

(Note) a: Models were adjusted for follow-up time, number of annual BP records and class PDC; **b:** Models were adjusted for follow-up time, number of annual BP records and therapy PDC; * p<0.005; **SBP**: Systolic blood pressure; **DBP**: Diastolic blood pressure; Data presented in mean differences (95%CI)

5.5.6. Incidence of long-term hypertension-related complications comparing the post- and pre-switching periods

Overall, 40 patients developed at least one of the six HT-related complications (composite outcome) (Table 5.15). Compared with the pre-switching period, the incidence of composite outcome measure was not significantly different in the post-switching period, regardless of whether the patients were in the ACEIs-combined or in the ACEIs-monotherapy group.

Likewise, the incidence of the individual HT-related complications (stroke, MI, angina, atherosclerosis and other IHD, HF and CRF) in the post-switching period was not significantly different from that of the pre-switching period, except for MI, regardless of the ACEIs-combined or ACEIs-monotherapy subgroups. The incidence of MI was significantly lower in the post-switching period in the overall

study cohort as well as in the ACEIs-combined group, but not in the ACEIs-monotherapy group (Table 5.15).

Table 5.15 Number and incidence of hypertension-related complications comparing post- and pre-switching periods

Events	Total (n=470)		ACEIs-combined group (n=369, 78.5%)		ACEIs-monotherapy group (n=101, 21.5%)	
	Before switch	After switch	Before switch	After switch	Before switch	After switch
Composite	19 (4.0%)	21 (4.5%)	18 (4.9%)	18 (4.9%)	1 (1.0%)	3 (3.0%)
Stroke	1 (0.2%)	2 (0.4%)	0 (0.0%)	1 (0.3%)	1 (1.0%)	1 (1.0%)
MI	13 (2.8%)*	3 (0.6%)*	13 (3.5%)*	3 (0.8%)*	0 (0.0%)	0 (0.0%)
HF	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
CRF	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Angina	6 (1.3%)	7 (1.5%)	6 (1.6%)	6 (1.6%)	0 (0.0%)	1 (1.0%)
Atherosclerosis and other IHD	4 (0.9%)	11 (2.3%)	4 (1.1%)	10 (2.7%)	0 (0.0%)	1 (1.0%)

(Note) * p<0.001 (McNemar test); **MI**: Myocardial infarction; **HF**: Heart failure; **CRF**: Chronic renal failure; **IHD**: Ischaemic heart diseases

Thirty of the 40 patients who developed the composite outcome switched ARBs before the BCBV policy (Table 5.16). Compared with the pre-switching period, the incidence of composite outcome as well as the other six HT-related complications in the post-switching period was comparable between patients who switched their ARBs drug therapy before and after the BCBV policy, except for atherosclerosis and other IHD, for which a significant increase in its incidence was observed in the post-switching period for those who switched before the BCBV policy (Table 5.16).

Furthermore, the subgroup analysis indicated that there was no significant difference in the incidence of composite outcome and the other HT-related complications when comparing the post-switching with the pre-switching periods (Table 5.16). Similar results were observed in the ACEIs-combined group except

the incidence of atherosclerosis and other IHD were significantly lower in the post-switching period for those who switched before the policy.

Table 5.16 Number and incidence of hypertension-related complications comparing post- and pre-switching periods stratified by pre- and post-BCBV policy groups

	Before switch	After switch	Before switch	After switch	Before switch	After switch
Patient switched before the BCBV policy Pre-BCBV policy group) (n=202)						
	Total (n=202)		**ACEIs-combined group** (n=174, 86.1%)		**ACEIs-monotherapy group** (n=28, 13.7%)	
Composite	12 (5.9%)	18 (8.9%)	11 (6.3%)	15 (8.6%)	1 (3.6%)	3 (10.7%)
Stroke	1 (0.5%)	2 (1.0%)	0 (0.0%)	1 (0.6%)	1 (3.6%)	1 (3.6%)
MI	7 (3.5%)	3 (1.5%)	7 (4.0%)	3 (1.7%)	0 (0.0%)	0 (0.0%)
HF	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)
CRF	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)
Angina	6 (3.0%)	7 (3.5%)	6 (3.5%)	6 (3.5%)	0 (0.0%)	1 (3.5%)
Atherosclerosis and other IHD	0 (0.0%)*	8 (4.0%)*	0 (0.0%)*	7 (4.2%)*	0 (0.0%)	1 (3.5%)
Patient switched after the BCBV policy (Post-BCBV policy group) (n=268)						
	Total (n=268)		**ACEIs-combined group** (n=195, 72.8%)		**ACEIs-monotherapy group** (n=73, 27.3%)	
Composite	7 (2.6%)	3 (1.1%)	7 (3.6%)	3 (1.5%)	0 (0.0%)	0 (0.0%)
Stroke	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
MI	6 (2.2%)	0 (0.0%)	6 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
HF	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CRF	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Angina	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Atherosclerosis and other IHD	4 (1.5%)	3 (1.1%)	4 (2.1%)	3 (1.5%)	0 (0.0%)	0 (0.0%)

(Note) * p<0.001 (McNemar test); **MI**: Myocardial infarction; **HF**: Heart failure; **CRF:** Chronic renal failure; **IHD**: Ischaemic heart diseases

5.5.6.1. Multivariate analysis comparing the incidence of HT-related complications in the post- and pre-switching periods

There was no significant difference in the incidence of composite outcome or other HT-related complications when comparing the post-switching to the pre-switching period after adjusting for potential confounders (patients' follow-up time, adherence, systolic and diastolic BP, and whether the patient developed the outcome in the pre-

switching period or not) in the multivariate analysis. This result was consistent after stratifying by ACEIs-combined and ACEIs-monotherapy groups, except for the incidence of MI was significantly lower in post-switching period in the overall study cohort as well as the ACEIs-combined group, but not in the ACEIs-monotherapy group (Table 5.17).

Table 5.17 Adjusted odds ratios and 95% confidence intervals of hypertension-related complications comparing post- and pre-switching periods

	Total (n=470)		ACEIs-combined group (n=369, 78.5%)		ACEIs-monotherapy group (n=101, 21.5%)	
	OR (95%CI)	**P-value**	**OR (95%CI)**	**P-value**	**OR (95%CI)**	**P-value**
Composite	0.9 (0.4 2.0)	0.844	0.7 (0.3, 1.6)	0.380	4.4 (0.4, 50.2)	0.238
Stroke	1.2 (0.08, 17.8)	0.894	NA		1.0 (0.08, 14.1)	1.000
MI	0.1 (0.04, 0.6)	0.009	0.1 (0.04, 0.6)	0.009	NA	
HF	NA		NA		NA	
CRF	NA		NA		NA	
Angina	0.9 (0.2, 3.9)	0.953	0.7 (0.1, 3.3)	0.618	NA	
Atherosclerosis and other IHD	2.1 (0.6, 7.3)	0.233	1.7 (0.5, 6.2)	0.419	NA	

(Note) Models adjusted for patients` follow up time, adherence, systolic and diastolic BP, whether the patient developed the outcome in the pre-switch period; **MI**: Myocardial infarction; **HF**: Heart failure; **CRF**: Chronic renal failure; **IHD**: Ischaemic heart diseases; **NA**: Non-applicable as study subgroups did not develop the complications before or after the switching

5.5.6.2. Multivariate analysis comparing the incidence of HT-related complications in the post- and pre-switching periods stratified by pre- and post-BCBV policy

In comparison with the pre-switching period, the likelihood of developing the composite outcome and other individual HT-related complications was not significantly different in the post-switching period for the overall study cohort, as well as for the ACEIs-combined and ACEIs-monotherapy groups, irrespective of whether the patients were switched before or after the BCBV policy (Table 5.18).

Table 5.18 Adjusted odds ratios and 95% confidence intervals of hypertension-related complications comparing post- and pre-switching periods stratified by pre- and post-BCBV policy groups

	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value
Patient switched before the BCBV policy (Pre-BCBV policy group) (n=202)						
	Total (n=202)		**ACEIs-combined group** (n=174, 86.1%)		**ACEIs-monotherapy group** (n=28, 13.7%)	
Composite	0.7 (0.1, 4.0)	0.685	0.3 (0.03, 2.0)	0.199	8.2 (0.3, 204.4)	0.199
Stroke	0.04 (0.001, 11.6)	0.263	NA		1.0 (0.05, 14.4)	1.0
MI	0.5 (0.04, 6.4)	0.604	0.5 (0.04, 6.4)	0.604	NA	
HF	NA		NA		NA	
CRF	NA		NA		NA	
Angina	0.6 (0.1, 5.4)	0.675	0.1 (0.01, 1.9)	0.132	NA	
Atherosclerosis and other IHD	NA		NA		NA	
Patient switched after the BCBV policy (Post-BCBV policy group) (n=268)						
	Total (n=268)		**ACEIs-combined group** (n=195, 72.8%)		**ACEIs-monotherapy group** (n=73, 27.3%)	
Composite	0.1 (0.01, 1.5)	0.101	0.1 (0.01, 1.5)	0.101	NA	
Stroke	NA		NA		NA	
MI	NA		NA		NA	
HF	NA		NA		NA	
CRF	NA		NA		NA	
Angina	NA		NA		NA	
Atherosclerosis and other IHD	0.3 (0.04, 1.9)	0.191	0.3 (0.04, 1.9)	0.930	NA	

(Note) Models adjusted for patients` follow up time, adherence, systolic and diastolic BP, whether the patient developed the outcome in the pre-switch period; **MI**: Myocardial infarction; **HF**: Heart failure; **CRF**: Chronic renal failure; **IHD**: Ischaemic heart diseases; **NA**: Non-applicable as study subgroups did not develop the complications before or after the switching

5.5.7. Healthcare resources utilised and costs incurred comparing post- and pre-switching periods

5.5.7.1. Total number of healthcare resources utilised

Overall, 10,093 hypertension-related GP consultations were identified from the study cohort, of which 8,968 (88.9%) encounters were within the surgery, 1,083 (10.7%) were out of surgery and the remainder were telephone consultations (Table 5.19). More than half of the GP consultations (56.8%, n=5,734) occurred in the post-switching period. In the ACEIs-combined group, of all the hypertension-related consultations (n=8,352), over half (60.8%, n=5,075) occurred in the post-switching period. In contrast, over half of the consultations (62.1%, n=1,082) in the ACEIs-monotherapy group occurred in the pre-switching period (Table 5.19).

Overall, 79 episodes of inpatient hospitalisations were observed, 55 of them were non-elective and 16 were elective, and there were eight day case admissions. Over half (n=46, 58.2%) of inpatient hospitalisations happened in the pre-switching period (Table 5.19). In the ACEIs-combined group, the majority (n=45, 61.6%) of inpatient hospitalisations episodes (n=73) occurred in the pre-switching period. In contrast, only six episodes were observed in the ACEIs-monotherapy group, of which five episodes occurred in the post-switching period. Of the total 79 identified hospitalisation episodes, MI (n=29, 36.7%), angina (n=23, 29.1%) and atherosclerosis and other IHD (n=21, 26.6%) constituted the majority.

Of the total 61 HT-related outpatient attendances identified, 34 (55.7%) were to the cardiology outpatient clinic, 25 (41.0%) to general medicine and the remaining (3.1%, n=2) were to A&E (Table 5.19). Most of the 61 outpatient attendances occurred in the post-switching period in the overall study cohort (n=44, 72.1%) and ACEIs-combined group (n=42, 77.8%). On the other hand, most of the outpatient

attendances (n=5/7, 71.4%) occurred in the pre-switching period for the ACEIs-monotherapy groups.

Table 5.19 Total number of healthcare resources utilised comparing post- and pre-switching periods

Events	Total number of events	Total (n=470)		ACEIs-combined group (n=369, 78.5%)		ACEIs-monotherapy group (n=101, 21.5%)	
		Before switch	After switch	Before switch	After switch	Before switch	After switch
GPs consultations	10,093	4,359	5,734	3,277	5,075	1,082	659
Hospitalisations							
Composite	79	46	33	45	28	1	5
Stroke	4	1	3	0	1	1	2
MI	29	26	3	26	3	0	0
HF	1	0	1	0	1	0	0
CRF	1	0	1	0	1	0	0
Angina	23	12	11	12	10	0	1
Atherosclerosis and other IHD	21	7	14	7	12	0	2
Outpatient attendance	61	17	44	12	42	5	2

(Note) MI: Myocardial infarction; **HF**: Heart failure; **CRF**: Chronic renal failure; **IHD**: Ischemic heart diseases

In total, 23,467 antihypertensive drug prescriptions were issued during the study period; unsurprisingly ARBs (n=9,347, 39.8%) and ACEIs (n=8,964, 38.2%) were the most frequently prescribed drug classes in the pre-switching and post-switching periods, respectively (Table 5.20). In the ACEIs-combined group, of the total antihypertensive drug prescriptions (n=19,417), ARBs prescriptions in the pre-switching period accounted for about one-third of them (n=6,909, 35.6%); whereas post-switching prescribing of ACEIs and other antihypertensive drugs constituted 37.9% (n=7,352) and 26.6% (n=5,156), respectively. In contrast, in the ACEIs-monotherapy group, ARBs prescriptions in the pre-switching period accounted for over half of the 4,050 antihypertensive drug prescriptions (n=2,438, 60.2%); while the remainder were for ACEIs (n=1,612, 39.8%) in the post-switching period.

Table 5.20 Number of antihypertensive drug prescriptions comparing post- and pre-switching periods

Study groups	Total number of antihypertensive drug prescriptions	Antihypertensive drugs		
		Before switching	After switching	
		ARBs prescriptions	ACEIs prescriptions	Other antihypertensive drug prescriptions
Total (n=470)	23,467	9,347	8,964	5,156
ACEIs-combined group (n=369)	19,417	6,909	7,352	5,156
ACEIs-monotherapy group (n=101)	4,050	2,438	1,612	0

5.5.7.2. Annual healthcare resources utilised

Overall, although not significantly different from the pre-switching period, patients had a higher median annual number of GPs consultations in the post-switching period (Table 5.21). Likewise, patients in ACEIs-combined group and ACEIs-monotherapy group had a comparable median annual number of GPs consultations in the pre- and post-switching periods. Similarly, the post-switching median annual number of the other healthcare elements, including hospitalisations and outpatient attendances, was not significantly different from the pre-switching period, regardless of whether the patients were in the ACEIs-combined or ACEIs-monotherapy groups. However, in comparison with the pre-switching period, median annual number of antihypertensive drug prescriptions was significantly higher in the post-switching period for the overall study cohort, and remained so in both the ACEIs-combined and ACEIs-monotherapy groups (Table 5.21).

Table 5.21 Annual median number of healthcare resources utilised per patient comparing post- and pre-switching periods

Events	Total (n=470)		ACEIs-combined group (n=369, 78.5%)		ACEIs-monotherapy group (n=101, 21.5%)	
	Before switch	After switch	Before switch	After switch	Before switch	After switch
GPs consultations (IQR)	3.6 (2.3, 5.9)	4.1 (2.9, 6.3)	3.8 (2.3, 6.4)	4.5 (3.1, 6.8)	3.4 (2.5, 4.3)	3.3 (2.0, 5.1)
Antihypertensive drugs (IQR)	7.5 (6.2,12.4)*	9.8 (6.8,14)*	7.7 (6.3, 12.7)*	10.8 (7.0,14.8)*	6.8 (5.8,11.7)*	8.1 (6.4, 12.1)*
Hospitalisations (IQR)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Outpatient attendance (IQR)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)

(Note) * p<0.001 (Wilcoxon signed-rank test); **IQR**: interquartile range

5.5.7.3. Annual number of healthcare resources utilised comparing post- and pre-switching periods stratified by pre- and post-BCBV policy groups

Patients, who switched their ARB drug before the BCBV policy, had a comparable median annual number of GP consultations in both post- and pre-switching periods, irrespective of whether they were in the ACEIs-combined or ACEIs-monotherapy group. Whereas patients who switched after the BCBV policy had a significantly higher median annual number of GP consultations in the post-switching period compared with the pre-switching period, and upon stratification, this was observed only in those in the ACEIs-combined group (Table 5.22).

In contrast, patients in the post-switching period appeared to have a significantly higher median annual number of antihypertensive drug prescriptions compared with the pre-switching period in the overall study cohort as well as in both the ACEIs-combined and ACEIs-monotherapy groups, irrespective of whether they switched their index ARB drug before or after the BCBV policy (Table 5.22).

There was no significant difference in both median annual numbers of hospitalisations and outpatient attendances when comparing post- and pre-

switching periods in the overall study cohort or in the ACEIs-combined and ACEIs-monotherapy subgroups (Table 5.22).

Table 5.22 Annual median number of healthcare resources utilised per patient comparing post- and pre-switching periods stratified by pre- and post-BCBV policy groups

	Before switch	After switch	Before switch	After switch	Before switch	After switch
Patient switched before the BCBV policy (Pre-BCBV policy group) (n=202)						
Events	**Total** (n=202)		**ACEIs-combined group** (n=174, 86.1%)		**ACEIs-monotherapy group** (n=28, 13.7%)	
GPs consultations (IQR)	4.2 (2.4, 8.5)	4.1 (3.0, 5.8)	4.4 (2.4, 9.6)	4.2 (3.1, 6.1)	3.6 (2.8, 4.6)	3.3 (2.1, 4.1)
Antihypertensive drugs (IQR)	9.0 (6.5, 13.1)*	11.3 (6.5,15)*	9.0 (6.5, 13.2)*	12.3 (6.7, 16.2)*	9.3 (6.1, 12.3)*	8.7 (5.0, 12.3)*
Hospitalisations (IQR)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Outpatients attendance (IQR)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Patient switched after the BCBV policy (Post-BCBV policy group) (n=268)						
	Total (n=268)		**ACEIs-combined group** (n=195, 72.8%)		**ACEIs-monotherapy group** (n=73, 27.3%)	
GPs consultations (IQR)	3.4 (2.3, 5.1)*	4.2 (2.7, 7.1)*	3.5 (2.3, 5.3)*	4.6 (3.0, 7.6)*	3.3 (2.5, 4.3)	3.3 (1.9, 5.2)
Antihypertensive drugs (IQR)	6.8 (6.0, 11.8)*	9.5 (6.9, 14)*	6.9 (6.2, 12.0)*	10.3 (7.2, 14.2)*	6.6 (5.7, 10.6)*	8.0 (6.6, 11.7)*
Hospitalisations (IQR)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Outpatients attendance (IQR)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)

(Note) * p<0.001 (Wilcoxon signed-rank test); **IQR**: interquartile

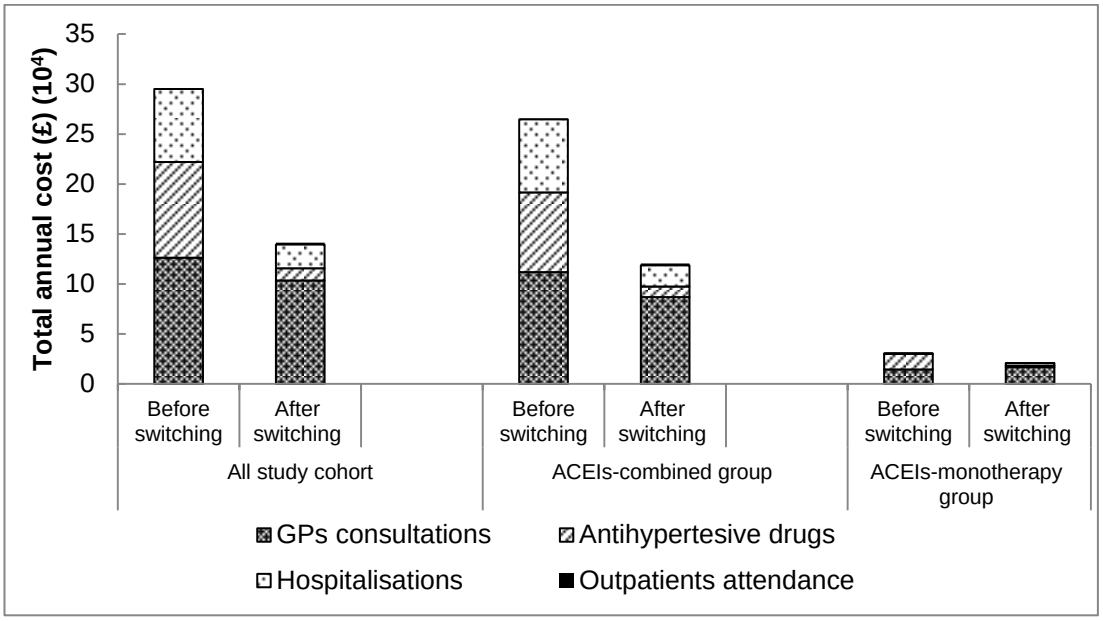
5.5.8. Costs of healthcare resources utilised comparing post- and pre-switching periods

5.5.8.1. Total annual costs of healthcare resources utilised

The total annual cost of healthcare resources was lower in the post-switching period compared with the pre-switching period in the overall study cohort and the two stratified study subgroups (ACEIs-combined and ACEIs-monotherapy) (Figure 5.3). Compared with the pre-switching period, the cost of antihypertensive drug prescriptions, GPs consultations and hospitalisations was lower in the post-

switching period for all study subgroups, except for higher cost of GPs consultations and hospitalisations in the ACEIs-monotherapy group (Figure 5.3).

Figure 5.3 Total annual cost of healthcare resources utilised comparing post- and pre-switching periods



Similar results were found for the total annual cost of healthcare resources when stratifying the study subgroups by pre- and post-BCBV policy groups (Table 5.23). Likewise, the post-switching annual cost of antihypertensive drugs prescriptions, hospitalisations and outpatient attendances, in general, were also lower compared with the pre-switching period. However, patients who switched after the BCBV policy incurred higher annual costs of GPs consultations in the post-switching compared with the pre-switching period; whereas those who switched before the BCBV policy had lower annual costs of GPs consultations in the post-switching compared with the pre-switching period (Table 5.23).

Table 5.23 Total annual cost of healthcare resources utilised comparing post- and pre-switching periods stratified by pre- and post-BCBV policy groups

	Before switch	After switch	Before switch	After switch	Before switch	After switch
Patient switched before the BCBV policy (Pre-BCBV policy group) (n=202)						
	Total (n=202)		**ACEIs-combined group** (n=174, 86.1%)		**ACEIs-monotherapy group** (n=28, 13.7%)	
GPs consultations	82,824	39,162	78,424	35,752	4,400	3,400
Antihypertensive drugs prescriptions	54,198	6,216	49,546	5,850	4,652	367
Hospitalisations	57,000	20,208	57,784	17,645	216	2,563
Outpatient attendance	473	1,552	394	1,447	79	105
Total costs	194,495	67,138	186,148	60,694	9,347	6,435
Patient switched after the BCBV policy (Post-BCBV policy group) (n=268)						
	Total (n=268)		**ACEIs-combined group** (n=195, 72.8%)		**ACEIs-monotherapy group** (n=73, 27.3%)	
GPs consultations	43,537	64,331	33,292	51,018	10,244	13,314
Antihypertensive drugs prescriptions	41,345	6,000	30,433	4,753	10,911	1,247
Hospitalisations	16,147	3,592	16,147	3,592	0	0
Outpatients attendance	587	339	484	339	103	0
Total costs	101,616	74,262	80,356	59,702	21,258	14,561

(Note) Cost data are presented in British pounds

5.5.8.2. Mean annual costs of healthcare resources utilised per patient comparing post- and pre-switching periods

Compared with the pre-switching period, patients in the post-switching period had significantly lower mean total annual cost of all healthcare resources collectively in the study cohort (mean difference: –£329.2, p=0.011), as well as those in the ACEIs-combined (mean difference: –£393.2, p=0.01) and ACEIs-monotherapy (mean difference: –£95.1, p=0.002) groups (Table 5.24) (Figure 5.4). The highest reduction was observed in the mean annual cost of antihypertensive drug prescriptions, which reduced significantly by £177.3 (p=0.025) in the overall study cohort, by £188 (p=0.021) in the ACEIs-combined group, and by £38.1 (p<0.001) in the ACEIs-monotherapy group (Table 5.24). Furthermore, there was also significant reduction in the mean annual hospitalisation cost in the post-switching period in the

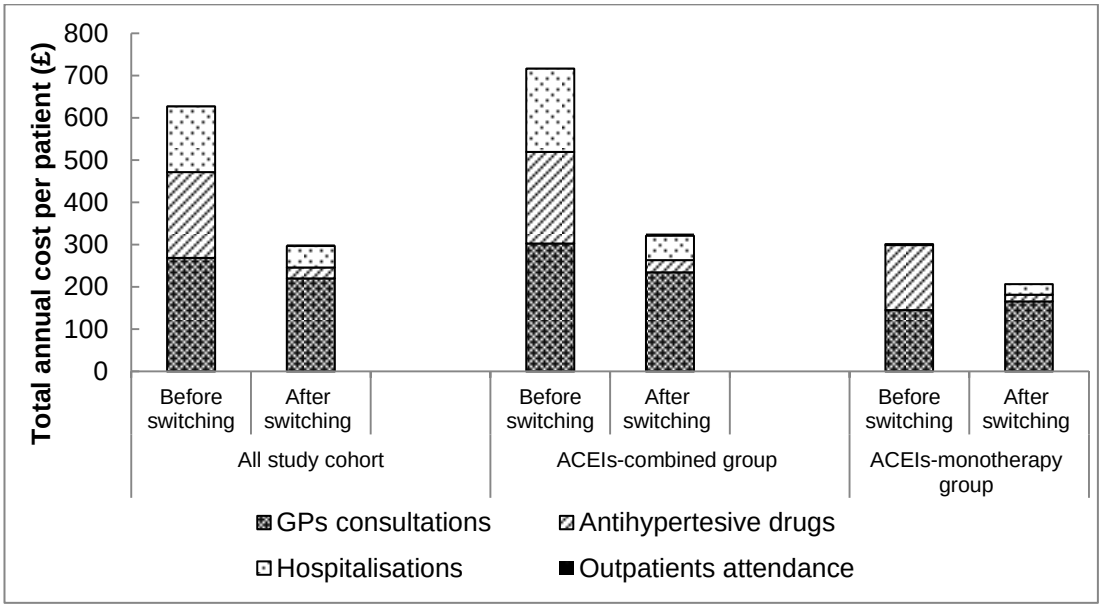
overall study cohort and ACEIs-combined group, but not in the ACEIs-monotherapy group.

Table 5.24 Mean annual cost of healthcare resources utilised per patient comparing post- and pre-switching periods

	Total (n=470)		ACEIs-combined group (n=369, 78.5%)		ACEIs-monotherapy group (n=101, 21.5%)	
	Before switch	After switch	Before switch	After switch	Before switch	After switch
GPs consultations						
Mean cost (95%CI)*	268.9 (212.2, 457.4)	220.2 (202.4,248.5)	302.8 (227.5, 520.9)	235.2 (212.5, 264.5)	145.0 (125.7, 172.8)	165.5 (136.2, 210.6)
Cost difference (95%CI)*	–48.7 (–227.4, 10.0)		–67.6 (–283.8, 14.4)		20.5 (–14.7, 64.5)	
p-value**	0.382		0.348		0.315	
Antihypertensive drugs prescriptions						
Mean cost (95%CI)*	203.3 (173.8, 272.1)	26.0 (27.0, 28.5)	216.7 (181.8, 317.8)	28.7 (26.1, 31.8)	154.1 (146.4, 162.0)	16.0 (14.6, 18.1)
Cost difference (95%CI)*	–177.3 (–246.6, –148.0)		–188.0 (–288.0, –153.4)		–138.1 (–146.3, –131.1)	
p-value**	0.025		0.021		<0.001	
Hospitalisations						
Mean cost (95%CI)*	155.6 (86.9, 304.2)	50.6 (27.3, 93.4)	197.6 (106.3, 367.2)	57.6 (27.1, 108.2)	2.2 (0.0, 12.9)	25.4 (7.7, 82.3)
Cost difference (95%CI)*	–105.0 (–251.0, –31.1)		–140.1 (–308.2, –49.0)		23.2 (–6.0, 52.5)	
p-value**	0.028		0.021		0.117	
Outpatients attendance						
Mean cost (95%CI)*	2.3 (1.2, 4.3)	4.0 (2.6, 6.7)	2.4 (1.1, 4.9)	4.8 (2.9, 8.6)	1.8 (0.4, 4.8)	1.0 (0.3, 4.3)
Cost difference (95%CI)*	1.8 (–0.5, 4.2)		2.4 (–0.2, 5.4)		0.8 (–3.6, 1.6)	
p-value**	0.138		0.10		0.585	
Total cost						
Mean cost (95%CI)*	630.0 (506.7, 844.5)	300.9 (269.3, 350.2)	719.5 (565.8, 979.0)	326.3 (288.8, 387.0)	303.0 (281.6, 329.4)	207.9 (172.6, 274.3)
Cost difference (95%CI)*	–329.2 (–534.6, –205.7)		–393.2 (–665.3, –242)		–95.1 (–132.1, –39.0)	
p-value**	0.011		0.01		0.002	

(Note) *Bootstrapped bias-corrected and accelerated confidence interval; ** Bootstrapped paired t-test p-value; Cost data are presented in British pounds

Figure 5.4 Mean annual cost of healthcare resources utilised per patient comparing post- and pre-switching periods



5.5.8.3. Mean annual cost of healthcare resources utilised per patient comparing post- and pre-switching periods stratified by pre- and post-BCBV policy groups

Compared with the pre-switching period, the mean annual total cost per patient was significantly lower in the post-switching period for all the study groups regardless of whether the switching occurred before or after the BCBV policy (Table 5.25). Compared with patients whose ARBs were switched after the policy, the extent of reduction in the mean annual total cost was smaller in those patients who were switched before the policy. There was a significant decrease in mean annual cost per patient of antihypertensive drugs prescriptions in the post-switching period, in those who switched both before and after the policy in pre-and post-BCBV policy groups. The mean annual costs of hospitalisations and outpatients' attendances per patient in the post-switching period were not significantly different from those of the pre-switching period, irrespective of whether patients were switched before or after the policy (Table 5.25).

However, patients who switched before the BCBV policy had significantly lower mean annual cost of GPs consultations in the post-switching period compared with the pre-switching period in the overall study cohort (mean difference: –£216.1, p=0.031) and in the ACEIs-combined group (mean difference: –£245.2, p=0.032), but not in the ACEIs-monotherapy group (mean difference: –£35.7, p=0.250) (Table 5.25). In contrast, the mean annual cost of GPs consultations in the post-switching period compared with the pre-switching period in those patients who switched after the BCBV policy was significantly higher by £77.6 (p=0.001) for the overall study cohort, by £90.9 (p<0.001) for the ACEIs-combined group, but not significantly higher for the ACEIs-monotherapy group (mean difference: £42.0, p=0.131) (Table 5.25).

Table 5.25. Mean annual cost of healthcare resources utilised per patient comparing post- and pre-switching periods stratified by pre- and post-BCBV policy groups

	Before switch	After switch	Before switch	After switch	Before switch	After switch
Patient switched before the BCBV policy (Pre-BCBV policy group) (n=202)						
	Total (n=202)		**ACEIs-combined group** (n=174, 86.1%)		**ACEIs-monotherapy group** (n=28, 13.7%)	
GPs consultations						
Mean cost (95%CI)*	410.0 (277.9, 798.0)	193.8 (174.9, 218.3)	450.7 (292.8, 924.4)	205.5 (182.3, 231.9)	157.1 (116.3, 231.4)	121.4 (95.5, 155.3)
Cost difference (95%CI)*	–216.1 (–596.2, –84.3)		–245.2 (–714.6, –86.3)		–35.7 (–119.8, 7.0)	
p-value**	0.031		0.032		0.25	
Antihypertensive drugs prescriptions						
Mean cost (95%CI)*	268.3 (203.1, 429.6)	30.7 (26.9, 25.4)	284.7 (207.9, 489.1)	33.6 (29.6, 38.6)	166.1 (150.0, 183.9)	13.1 (10.9, 16.0)
Cost difference (95%CI)*	–237.5 (–399.6, –172.9)		–251.1 (–458.4, –174.2)		–153.0 (–170.1, –136.5)	
p-value**	0.04		0.021		0.001	
Hospitalisations						
Mean cost (95%CI)*	282.2 (125.5, 553.5)	100.1 (50.2, 192.2)	326.3 (153.8, 661.6)	101.4 (45.9, 203.9)	7.7 (0.0, 23.0)	91.5 (27.8, 245.8)
Cost difference (95%CI)*	–182.1 (–389.8, 25.5)		–224.9 (–465.1, 15.3)		83.8 (–23.0, 190.6)	
p-value**	0.085		0.0663		0.1193	
Outpatients attendance						
Mean cost (95%CI)*	2.3 (0.8, 5.0)	7.7 (4.6, 13.7)	2.3 (0.6, 6.1)	8.3 (5.0, 15.3)	3.8 (1.2, 14.0)	2.8 (0.0, 19.6)
Cost difference (95%CI)*	5.3 (–2.2, 11.4)		6 (–2.4, 12.5)		1 (–8.4, 7.7)	
p-value**	0.061		0.052		0.846	
Total cost						
Mean cost (95%CI)*	962.8 (677.4,1448.6)	332.4 (276.3, 436)	1064.1 (735,1602.1)	348.9 (288.3, 468.4)	333.8 (288.0, 398.4)	229.8 (288.0, 398.4)
Cost difference (95%CI)*	–630.5 (–1095.6, –345.7)		–751.2 (–1241.9, –390)		–104.0 (–199.2, –8.8)	
p-value**	0.024		0.026		0.0335	

(Continued) Table 5.25. Mean annual cost of healthcare resources utilised per patient comparing post- and pre-switching periods stratified by pre- and post-BCBV policy groups

	Before switch	After switch	Before switch	After switch	Before switch	After switch
Patient switched after the BCBV policy (Post-BCBV policy group) (n=268)						
	Total (n=268)		**ACEIs-combined group** (n=195, 72.8%)		**ACEIs-monotherapy group** (n=73, 27.3%)	
GPs consultations						
Mean cost (95%CI)*	162.5 (145.7, 183.8)	240.0 (212.3, 281.3)	170.7 (149.5, 201.0)	261.6 (222.4, 317.7)	140.3 (120.1, 169.6)	182.4 (143.1, 235.9)
Cost difference (95%CI)*	77.6 (45.7, 120.7)		90.9 (47.7, 148.0)		–42.0 (–8.8, 92.9)	
p-value**	0.001		<0.001		0.131	
Antihypertensive drugs prescriptions						
Mean cost (95%CI)*	154.3 (148.6, 161)	22.4 (20.5, 25.6)	156.1 (148.9, 163.8)	24.4 (21.8, 28.8)	149.5 (141.0, 157.6)	17.1 (15.4, 19.7)
Cost difference (95%CI)*	–131.9 (–138.4, –125.3)		–131.7 (–140.2, –123.2)		–132.4 (–139.7, –124.1)	
p-value**	<0.001		<0.001		<0.001	
Hospitalisations						
Mean cost (95%CI)*	60.2 (25.7, 147.9)	13.4 (1.4, 44.2)	82.8 (28.7, 183.7)	18.4 (3.9, 67.8)	NA	NA
Cost difference (95%CI)*	–46.8 (–98.9, 5.2)		–64.4 (–135.9, 7.1)			NA
p-value**	0.130		0.130			NA
Outpatients attendance						
Mean cost (95%CI)*	2.2 (0.8, 5.7)	1.3 (0.3, 3.7)	2.5 (0.8, 8.3)	1.7 (0.4, 5.1)	1.4 (0.0, 4.4)	0
Cost difference (95%CI)*	–0.9 (–3.7, 1.3)		–0.7 (–5.0, 2.2)		–1.4 (–3.4, 0.6)	
p-value**	0.150		0.710		0.167	
Total cost						
Mean cost (95%CI)*	379.2 (337.4, 461.6)	277.1 (243.1, 323.2)	412.1 (354.1, 505.7)	306.2 (263.1, 373.3)	291.2 (268.9, 320.1)	199.5 (160.8, 254.1)
Cost difference (95%CI)*	–102.1 (–166.1, –40.5)		–105.9 (–203.0, –34.9)		–91.8 (–136.0, –27.5)	
p-value**	0.03		0.022		0.006	

(Note) *Bootstrapped bias-corrected and accelerated confidence interval; ** Bootstrapped paired t-test p-value; Cost data are presented in British pounds

5.6. Discussion

5.6.1. Key findings

Although the switching of antihypertensive drug therapy from ARBs to ACEIs was uncommon, it was not associated with alterations in patients' adherence to antihypertensive medication, BP level or the incidence of HT-related complications. However, the switching was associated with an overall reduction in direct HT-related medical costs. The potential cost saving due to switching to cheaper ACEIs was not offset by any increase in costs incurred in other areas, because the switching was not associated with significantly higher utilisation of the HT-related healthcare resources (GP consultations, hospitalisations and outpatients' attendance).

The proportion of patients who switched from ARBs to ACEIs was higher after the implementation of BCBV policy. However, the impact of ARBs switching on the primary outcome measures was similar and comparable between patients who switched before and after the BCBV policy. The BCBV policy, generally, had neither clinical nor economic implications.

The observed low proportion of patients switching from ARBs (5%) was expected possibly due to the good tolerability[367, 368], strong pharmaceutical marketing of ARBs[217], and lack of nationally effective cost-containment switching policies to actively prompt the switching from ARBs – apart from the BCBV, which was shown to be ineffective in this study (Chapter 3). Similarly, Thayer and Dastani (2009)[200] found only a small percentage patients (n=4,941, 8.5%) who switched from ARBs in their cohort study of evaluating clinical and cost impact of switching between ARBs classes.

In addition, two studies[217, 241] that evaluated the persistence patterns of antihypertensive drugs in newly diagnosed hypertensive patients found a relatively

higher ARBs switching proportion of ~13.1%. Mohamed *et al* (2012)[375], who aimed to assess switching and continuation of care using the NHS primary care database, also reported a higher proportion (30.6%) of patients switching ARBs.

However, the reported higher proportion of ARBs switching in the three aforementioned studies[217, 241, 375] could be due to variations in the study populations, and type and definition of switching. The first two studies[217, 241] involved newly diagnosed patients with hypertension; whereas the third study[375] was not restricted to patients with hypertension but included any patients prescribed antihypertensive drugs. All of the studies defined switching as changing initial prescribed antihypertenisve drug class to another class, and only the third study[375] identified a switching period of 120 days, which is wider than the 30-day switching period used in this chapter; thereby, inevitably more patients were identified and classified as switchers. It has been suggested that using a wide switching period would probably introduce the risk of misclassifying patients as switchers when they might have discontinued ARBs and started the new drug for reasons other than switching[375], and consequently, a switching period of 30 days or the duration of one prescription supply, as recommended by Halpern *et al* (2006)[283], was used in this study.

5.6.2. Switching of ARB drug therapy and patients' adherence

Patients' post-switching drug class adherence, i.e., comparing post-switching PDC of ACEIs to pre-switching PDC of ARBs, decreased significantly only in those patients who combined ACEIs with other antihypertensive drugs in the post-switching period; while patients maintained on ACEIs alone in the post-switching period showed non-significant changes in adherence. Given the comparable adherence profile of ARBs and ACEIs[203, 216, 217], and the negative association between increasing therapeutic regimen complexity and adherence[293, 301, 392], one could hypothesise that the observed reduction in adherence to ACEIs after

switching – in the ACEIs-combined but not in the ACEIs-monotherapy group – could be due to the complexity of the therapeutic regimen resulted from the increased number of antihypertensive drugs after combining ACEIs with other drugs[195, 301], rather than the switching process itself.

Although this has not been proven, as no previous studies have evaluated the impact of ARBs switching on medication adherence, the non-significant change in adherence level in the ACEIs-monotherapy group supports this explanation. Furthermore, patients' adherence to any antihypertensive drug therapy (therapy adherence) in the post-switching period was not significantly different from that in the pre-switching period, which may further support the notion that patient's adherence was not affected by the switching of ARBs drug.

In general, antihypertensive drug switching has been shown to impede patients' adherence[200-202, 348]. This association between antihypertensive drug switching and adherence reduction could be attributed to many issues (Chapter 2, section 2.9.4.1.3, page 52). However, the contradictory finding of comparable patients' adherence after the switching in this current study implies that most of the issues associated with antihypertensive drug switching in general may not be applied to ARBs switching to ACEIs in the UK. One possible reason could be the active involvement of patients in any decisions about their healthcare in the UK[227], which may have made some of the issues related to the switching – such as changes in the appearance, taste and packaging of the new drug, and patients' negative expectations – less problematic. It has been shown that patients' confusion could be addressed and minimised by educating and counselling[202, 393] patients, and involving them in the switching decision by obtaining their consent before the switching process[220, 225].

Patients' involvement in their healthcare decisions has been clearly observed in many UK studies. For instance, Watman (2013)[183] developed a pharmacist-led clinic to implement a switching programme for actively switching patients from ARBs to ACEIs, and after careful screening of patients' medical files to select the eligible patients, all the selected patients were sent an invitation letter to attend the clinic to discuss the switching decision, which is then made only after the patient consents.

Similarly, Usher-Smith *et al* (2007)[394] conducted a prospective cohort study to evaluate the cost-saving and clinical outcomes of switching patients from atorvastatin to simvastatin, and losartan to candesartan, in a UK primary care setting, in which patients' medical records were screened carefully, and the eligible patients were sent a letter informing them about the proposed switching and asked them to contact their GPs in case of any concerns. Both studies found a potential cost saving with no significant difference in patients' clinical outcomes after the switching.

Furthermore, in a survey of 194 patients (65% response rate), who switched their branded cardiovascular drugs to generics, in a UK PCT, to evaluate patients' satisfaction with switching medications[224], 83% of the participants considered the notion of switching patients' medication to provide better value for money in the NHS was an appropriate and accepted action, and 91% reported no problems following the switching. Moreover, 68% of respondents remembered that they had received a letter informing them about the switching, which indicates that patients felt involved in the switching decision, which in turn may explain the high satisfaction (83%) observed in the survey.

5.6.3. Switching of ARB drug therapy and BP level

This study found that the BCBV policy had no impact on BP level and that patients' switching from ARBs to ACEIs was associated with a significantly small reduction in SBP and DBP in the ACEIs-combined group, but not in ACEIs-monotherapy group. This suggests that the observed reduction in BP values is more likely to be caused by the combination of more than one antihypertensive drug in the ACEIs-combined group. It has been proven in literature that a combination of two antihypertensive drugs increases the reduction in BP levels much more than a single antihypertensive drug class[395].

Although it was not possible to know exactly the reason for adding another antihypertensive drug in this group of patients, it is likely that the BP level in the pre-switching period played an important role. Patients, on average, in both ACEIs-combined and ACEIs-monotherapy groups had uncontrolled baseline BP level at the index date, using a target BP of <140/90 mmHg[89] as the patients in general were of low-moderate risk (no cerebrovascular, cardiovascular or renal diseases). However, with ARBs therapy in the pre-switching period, patients' mean BP level decreased to below the target level in the ACEIs-monotherapy group but was above the target in the ACEIs-combined group. After switching, the mean BP level remained above the target in the ACEIs-combined group (146.1/84.9 mmHg before adding the other antihypertensive drug), which may rationalise the addition of another antihypertensive drug class in this group – to decrease BP level to the required target of <140/90 mmHg, in concordance with evidence that two or more antihypertensive drugs are usually required to achieve the BP target in ~75% of hypertensive patients[396].

Watman (2013)[183] is the only UK study to evaluate the clinical and economic implications of switching from ARBs to ACEIs, in which 319 patients were switched

from ARBs to ACEIs with a follow-up period of one year; the results showed a significantly lower BP value after switching from ARBs to ACEIs, which is similar to findings of the current study. The author has attributed this significant reduction in BP values, partly due to patients' relaxation with the examiner, increased adherence to medication and lifestyle changes, and/or the addition of other antihypertensive drugs and dose escalations.

The current study found a significant BP reduction in the ACEIs-combined group despite a statistically significant reduction in patient adherence to ACEIs (class PDC). At first glance, this seems to contradict the well-known fact that poor adherence is associated with suboptimal control of BP[89, 191, 197, 397]. One possible explanation is that the statistically significant reduction in class adherence was clinically insignificant (only 1.3% reduction in median class PDC from pre-switching value of 99.1% to post-switching value of 97.9%). This has also been shown in a recent clinical trial[398], to evaluate the impact of fixed-dose combination of antihypertensive drugs on patients' self-reported adherence and risk factor control (BP and cholesterol level), which found that despite the significant improvement in patients' adherence in those who received the fixed-dose combination regimen at 12 months (relative risk:1.75, 95%CI: 1.52, 2.03) in comparison with usual care, no significant improvements in risk factor control and BP values were observed.

Another possible explanation for the observed BP reduction despite reduction in drug adherence in this study may be related to the association between BP values and adherence to antihypertensive drug therapy, rather than adherence to an antihypertensive drug class. Most of the studies that evaluated the association between adherence and BP control measured adherence to an antihypertensive drug class and BP control in patients treated with single drug therapy, which is clinically relevant. However, in the current study, patients in the ACEIs-combined

group were prescribed more than one antihypertensive drug class; consequently, the observed non-significant change in therapy adherence (i.e., adherence to any antihypertensive drug regimen) and the reduction in BP level after ARBs switching in the ACEIs-combined group, along with the non-significant change in class adherence and BP level after ARBs switching in the ACEIs-monotherapy group, are in line with the well-known notion of the positive association between drug adherence and BP control reported in the literature.

5.6.4. Switching of ARB drug therapy and incidence of HT-related complications

This study showed that only small proportion of patients had suffered at least one of the HT-related complications, which could be because the study cohort patients in general were at relatively low cardiovascular risk. This low cardiovascular risk was reflected by patient's normal baseline mean serum cholesterol, low proportion of smokers and being non-obese, and this is consistent with findings from previous research[198], which indicated that treated hypertensive patients have relatively low risk of HT-related complications.

This study confirms the findings from Watman (2013)[183] that there was no major cardiovascular events after the switching from ARBs to ACEIs. This study also showed a non-significant change in the incidence of composite or individual HT-related complications after antihypertensive drug switching from ARBs to ACEIs. Furthermore, the BCBV policy had no impact on the incidence of HT-related complications. Since BP is the major risk factor for many cardiovascular diseases (stroke, MI, HF, end-stage CRF)[89, 284, 399, 400], and non-adherence is positively associated with cardiovascular events[192, 282, 284, 401], the comparable adherence and BP level in the post-switching period compared with the pre-switching period found in this study makes the study's findings of non-significant change in the incidence of HT-related complication rather expected.

Interestingly, patients in the ACEIs-combined group showed significant reduction in the risk of developing MI after the switching to ACEIs. A possible explanation for this might be the significant reduction in BP level in this group of patients attributed mainly to the addition of other antihypertensive drug classes in the post-switching period, and this is consistent with the findings of the INTERHEART study[402], which identified hypertension as one of the important risk factors for first-time MI.

5.6.5. Switching of ARB drug therapy and healthcare resources utilised and costs incurred

In this study, switching of antihypertensive drug therapy from ARBs to ACEIs was not associated with an increase in the utilisation of healthcare resources and costs; instead it resulted in a potential reduction. This cost saving was driven primarily by substantial reduction in the antihypertensive drugs' cost, which resulted from the switching of antihypertensive drug therapy from drugs with a high acquisition cost (ARBs) to drugs with a lower acquisition cost (ACEIs). Furthermore, the significant reduction in hospitalisation costs after the switching in the ACEIs-combined group likely resulted from the significant reduction in the incidence of MI hospitalisations, which also contributed to the overall cost saving in this group of patients.

These findings support the results of Watman (2013)[183], who reported an annual total saving of £42,475 for the 319 patients being switched from ARBs to ACEIs. Although Watman (2013)[183] included the cost of staff involved in implementing the switching, which was not included in the current study, other sources of incurring costs such as GP visits, outpatient referral and inpatient hospitalisations, which contribute largely to the overall medical cost, were not included; but this current study considered all these sources making the findings presented here more clinically relevant.

No previous study in the UK has evaluated the full economic impact of switching from ARBs to ACEIs. The comparison of the current study's findings with those of previous research was difficult due to either the inclusion of different resources[235], involvement of within-class switching[200, 233, 394], and/or studies being conducted in other countries – mainly the USA – with different healthcare systems[235, 239, 403]. Despite differences in healthcare systems, resources utilised and considering switching other than switching of ARBs to ACEIs, the results from the current study generally support the switching-related implications highlighted in a number of previous studies. It has been reported that the cost saving of medication switching can be potentially offset by incurring costs in other areas such as in the process of implementing the switching or managing the consequence of the switching, including additional GP visits (to increase patient's education and reassurance), and possibly hospitalisations (resulted from poorly controlled BP either due to patient's poor adherence or ineffectiveness of the switched-to drug, relative to the original drug)[2, 3].

However, none of these led to additional costs to offset the cost saving from switching ARBs to ACEIs in the current study. This could be because involving patients in the switching decision in the UK, prompted mainly by the adoption of patient choice approach in the modern NHS, plays an important role in educating and reassuring patients about their medication switching, which could reduce the number of extra GP visits after switching[2, 3]. This was clearly illustrated in the observed non-significant increase in GPs visits after the switching, which had no significant cost implications.

The comparable adherence profile[203, 216, 217] and clinical efficacy[127, 131, 134] of ARBs and ACEIs, as reflected in the current study by no reduction in post-switching adherence and BP control, could explain in part the lack of any significant difference

in hospitalisations events and costs observed in the current study. This is in the presence of evidence that adherence is a well-known recognised factor for uncontrolled BP[57, 59-61] and hence additional hospitalisations and costs[194, 198, 401].

The current results suggest that the BCBV policy had no significant impact on the total direct costs since both groups of patients in the pre-policy and the post-policy switching group showed significant reduction in total direct costs, although the overall cost saving in the post-policy switching group was lower than in the pre-policy switching group, especially for the ACEIs-combined group. A possible explanation for this could be the significant increase in the post-switching cost of GPs in the ACEIs-combined group in the post-BCBV policy group, compared with a significant decrease in those in the pre-BCBV policy group. The increase in the number of GPs consultations in the post-BCBV policy group in comparison with the general reduction in the pre-BCBV policy group may be due to either careful attention or monitoring of patients, as a possible unintended policy consequence, or more frequent follow-up, possibly driven by having a worse condition. However, the latter could be excluded given the significantly lower baseline SBP, higher proportion of no comorbidity and higher proportion of incident hypertensive patients in those who switched after the policy in the ACEIs-combined group. Further studies are required to investigate and establish this association.

The observed post-policy increase in the number of GP consultations resulted in a significant increase in the cost of GP consultations only in those who were in the ACEIs-combined group, but not in ACEIs-monotherapy group. This would suggest that the switching, in fact, was not the primary reason for this observed increase in GPs' consultation cost; rather it might be related to the complexity of the antihypertensive drug regimen in this group of patients, resulting from being prescribed more than one antihypertensive drug classes.

It has been reported that patients on complex drug regimens are at higher risk of poor adherence[293, 404, 405]. Therefore, it is clinically relevant to offer more follow-up visits, education, motivation and support to maximise their adherence, given the clear evidence of the effectiveness of these measures in improving patients' adherence[209, 405, 406], and hence more GP consultations; however, this needs to be confirmed in future studies.

5.6.6. Strengths and limitations of the current study

This study, to my knowledge, is the only population-based study that has evaluated the full clinical and economic implications of antihypertensive drug switching from ARBs to ACEIs – the switching recommended by the BCBV indicator – using data from primary and secondary care databases. Inclusion of both surrogate markers (adherence and BP) and longer-term clinical outcomes has provided deeper insight into the long-term clinical consequences of antihypertensive drug switching. The study also included drug acquisition costs and costs of other healthcare resources, providing an overall economic picture of the implications of switching from ARBs to ACEIs.

There were a number of limitations of the current study. Given the retrospective nature of the study design and data collection, complete identification of clinical events and healthcare resource use might not have been attained, and thus results might reflect an underestimation of some resources. However, this is likely to be similar for all study cohorts before and after switching. In addition, it was not possible to determine the exact cause of the switching; therefore, it could be argued that the observed results were biased by the cause of switching, assuming that patients respond differently to various types of switching (medical versus non-medical switching). However, given the comparable clinical efficacy of ARBs and ACEIs and the better tolerability profile of ARBs, it is unlikely that the switching was

due to adverse effects, treatment failure or development of comorbid conditions; therefore, it was assumed that reduced cost was the main motivation for this direction of the switch.

Since the current study population consisted of hypertensive patients with no previous cardiovascular disease, it may not be possible to generalise the study findings to hypertensive patients with comorbidities such as previous MI, even though both ARBs and ACEIs have been shown to have comparable clinical efficacy in treating hypertension in the presence of a history of MI and other cardiovascular conditions. Furthermore, the study findings may not be generalisable to patients prescribed additional antihypertensive drugs together with ARBs as patients on complex therapeutic regimens could behave differently and may be systematically different from those on single antihypertensive drug regimens.

Moreover, caution should be taken in interpreting the study findings given the relatively small number of patients included in this study, especially for the ACEIs-monotherapy group. In fact, the number of patients included in this study was higher than that included in previous studies[183, 235, 236, 394], which evaluated the clinical and economic impact of antihypertensive drug switching, including two randomised clinical trials[235, 236]. Furthermore, the ability of identifying significant differences in some of the study outcomes, such as total direct and antihypertensive drug cost, SBP and DBP, suggests that by definition, the study had a sufficient sample size to detect these differences[407]. Additionally, the before and after comparison design used in this study has been shown to have higher study power compared with the two parallel sample design (intervention versus control)[408, 409].

Although alternative approaches could have been used to answer the research question such as comparing patient who switched to a control group (patients who

did not switch), it was not possible to elicit the cognition behind the decision of switching from the CPRD data. This is likely to systematically bias the results as it is possible that patients' refusal to switch might be one of the reasons for non-switching in the control group, which in turn affects patients' medication-taking behaviour and hence determines the successfulness of the switching in terms of maintaining patients' adherence and clinical effectiveness.

5.6.7. Conclusions

Although antihypertensive drug switching from ARBs to ACEIs is uncommon, it has not resulted in impeding patients' adherence, BP control or incidence of HT-related clinical outcomes. Importantly, it resulted in reduced direct total costs associated with treating hypertension, driven primarily by a reduction in the costs of antihypertensive drugs. The BCBV policy in general had no impact on any of the study outcomes, although the results suggested that the policy led to more GP consultations but without any significant cost implications.

In conclusion, switching patients with primary hypertension from ARBs to ACEIs in this setting, assuming careful consideration of patients' perspectives, can be considered as an effective cost-containment strategy. This is based on the fact that the switching of medications is considered a cost-containment strategy only if the potential cost savings resulting from the medication switching outweigh the costs of healthcare resources utilised as a consequence of the switching[3].

Ideally, the question of whether considering antihypertensive drug switching from ARBs to ACEIs as an effective cost-saving strategy would be investigated by randomised clinical trials before recommending such a policy in clinical practice[3]. However, observational studies of real-world patient data can also provide important information on the possible implications of antihypertensive drug switching[2].

Chapter 6. Prescribers' perspectives on the ineffectiveness of the BCBV prescribing policy

6.1. Introduction

Although it was not possible to identify the reasons underpinning the ineffectiveness of the BCBV policy in the secondary database analysis (Chapter 3), inappropriate policy implementation was hypothesised to be the main barrier for the ineffectiveness of the BCBV policy, which can be explored in more detail by other study designs (Chapter 3). As the policy continued to offer cost-saving opportunity even years after the availability of several generic ARBs (Chapter 3), it is still necessary to consider and reinforce the BCBV indicator. A comprehensive and detailed understanding of why the policy was ineffective would help to understand the barriers that contributed to the ineffectiveness of the policy and to improve its effectiveness in the future.

Conducting a qualitative study offers the opportunity to understand why the BCBV policy was ineffective in improving the prescribing efficiency of ACEIs/ARBs. Qualitative interview is considered one of the most powerful methods of understanding people and provides authentic insights into the perspectives of the study participants[410] by discovering what people think of a particular issue, assessing their experiences and understanding why they behave in the way they do[411], and their beliefs of a given subject[412]. However, qualitative interviews only provide information about what people say they are doing but not what they actually do[412]. For instance, participants may tend to give answers that appear to be socially acceptable behaviours in an attempt to reduce the extent to which their behaviour could be judged negatively by the researcher, or they may tend to please the researcher or even show interest in the research topic, which does not reflect their real thoughts.

In semi-structured interviews, the researcher follows an interview schedule, which involves mostly several open-ended questions and the sequence of asking questions is changeable in response to participants' reply[413] to enable the researcher to explore in more detail any issues raised by participants[414]. Although the researcher assigns the interview agenda in terms of included topics, it is the interviewee's response that shapes the information produced about the covered topics[412] and this flexibility assures that almost the same range of topics are covered within each interview[413, 415, 416].

To understand why the policy failed, it is imperative to explore in-depth the views and opinions of the personnel who are involved in implementing the policy and prescribing ACEIs/ARBs, such as GPs. Therefore, semi-structured interviews were conducted with GPs to explore their views about the BCBV policy. This qualitative study was built and designed based on the results from the interrupted time-series analysis (Chapter 3) to answer predetermined questions regarding the potential reasons for the policy ineffectiveness that would help in explaining why the policy failed.

6.2. Aim and objectives

The aim of this chapter was to understand and explain why the BCBV prescribing policy failed to have an effect on changing the prescribing efficiency of ACEIs/ARBs, and to identify lessons learned for future prescribing policy implementation by determining the exact reason(s) and barrier(s) for the policy failure as well as the potential strategies to improve the policy's effectiveness.

The objectives were to explore GPs' and prescribing advisers' views and perceptions on:

1. Antihypertensive drug utilisation and prescribing, in particular ACEIs/ARBs, including patients' switching between ACEIs and ARBs
2. Prescribing indicators, in particular the BCBV prescribing indicator for ACEIs/ARBs
3. Barriers for the uptake and implementation of the BCBV prescribing indicator for ACEIs/ARBs
4. Potential strategies for improving the future effectiveness of the BCBV policy
5. Why the current national proportion of ACEIs prescription is not as high as expected, based on the small proportion of patient who cannot tolerate ACEIs

6.3. Methods

6.3.1. Study design and participants

In-depth semi-structured interviews were conducted from 1st August/2014 to 31st January 2015 after ethical approval was granted. Any GP and prescribing advisers, who are involved in the management and treatment of primary hypertension in primary care, and in the developing, monitoring and evaluating of any prescribing efficiency policies of antihypertensive drugs within the CCG, respectively, were eligible to participate in the study. All study participants were aged 18 years or older and able to give informed consent.

To explore antihypertensive drug prescribing and prescribing indicators implementations, a purposive sampling strategy was used to recruit the study participants from GP practices within various CCGs in Nottinghamshire, Leicestershire and Derbyshire. The name of CCGs in each of those three areas were identified from

the NHS England website and included six CCGs in Nottinghamshire, four in Derbyshire and three in Leicestershire[417]. Subsequently, the names of all the GP practices within each CCG were identified from the Public Health England website[418] and the demographic characteristics and profiles of each practice (population size, practice deprivation index, prevalence of hypertension and number of GPs) were then extracted.

For each CCG, five to ten GP practices were purposively selected such that they ensured maximum variation in terms of demographic and clinical characteristics such as population size, number of GPs, practice deprivation index, prevalence of hypertension and location (urban, sub-urban or rural). For instance, based on the average population size and HT prevalence of each CCG, GP practices with high, medium and low population size, and HT prevalence were selected. The same principle was applied to deprivation index and number of GPs; the selected practices included a mixture of practices with high, medium and low deprivation index and number of GPs. Overall, 41 GP practices were selected in Nottinghamshire, 29 in Derbyshire and 21 in Leicestershire.

6.3.2. Recruitment strategies

GPs were recruited in each selected practice using three approaches. Firstly, practice managers and senior GPs of the selected practices within each CCG were approached, by post, with an invitation letter (Appendix 12, Appendix 13), participant information sheet (Appendix 14), reply slip and a pre-paid envelope. Practice managers and senior GPs were asked to share and distribute the invitation letter to all GPs in their practices to ask them to take part in this study. GPs who were willing to participate and returned the reply slip with their contact information were contacted by the researcher (either via

phone, post or email) to arrange interviews. Non-responding managers and senior GPs were sent a reminder letter 14 days after the first letter.

Secondly, the study was advertised in the CCGs newsletter by sending an advertising letter (Appendix 15) containing a short summary of the study to each CCG asking for GPs to participate in the study. Finally, personal contact and snowballing strategies (participants recommending other GPs to participate) were also used to recruit GPs.

To recruit prescribing advisers, names and contact details of the heads of prescribing adviser teams in each CCG were obtained through direct contact with the CCG. A pack containing an invitation letter (Appendix 16), participant information sheet (Appendix 17), reply slip and pre-paid envelope was then mailed to invite them to participate in a 20–30 minutes semi-structured interview. Prescribing advisers who agreed to take part by sending back the reply slip were then contacted by the researcher (either via phone, post or email) to arrange an interview. Prescribing advisers, who did not reply within 14 days, were sent a reminder letter. Personal contact was also used for recruiting prescribing advisers, with the allowance for snowballing. This study planned to recruit at least 10 GPs and up to 10 prescribing advisers or until thematic saturation within the collected data is achieved.

6.3.3. Conducting the interviews

The interviews were conducted at the most convenient time and venue (mostly at GP practices, apart from two interviews which were at the researcher's office). Both face-to-face and telephone interviews were offered to participants due to accommodate their busy schedules. However, all of the interviews were face to face in this study. Before conducting the interviews, the participants were informed that entry into the study is

entirely voluntary, withdrawal from the study is available at any time, and that the interview would last for 20–30 minutes. All study participants were ensured confidentiality and anonymity, were asked for their permission for audio-recording of the interviews and their consent was sought just before the start of the interview.

The semi-structured interviews were conducted using interview schedules (Appendix 18, Appendix 19) with open-ended and semi-structured questions. The interview schedules were constructed and developed based on previous literature around the uptake of policy and guidelines and implementation in clinical practice, strategies to translate guidelines into practice, and factors influencing GPs' prescribing behaviour[419-422]. Furthermore, the interview schedule was developed with the assistance of a GP colleague and then piloted with one GP; however, there were minor adjustments of the interview schedule after the piloting and the results of the pilot interview are included in the main analysis.

The interviews of GPs firstly started by asking GPs about their experience in prescribing antihypertensive drugs in general, but focusing on ACEIs/ARBs in particular, and their views on switching patients from ACEIs to ARBs and vice versa. Secondly, GPs' views on prescribing indicators – in general and BCBV – were explored, including their awareness of the BCBV policy, barriers and motivations for implementing the BCBV policy, and their views on the policy's theory represented by the proposed 80% ACEIs target. Finally, GPs' views on the up-to-date value of the national percentage of ACEIs as a proportion of all ACEIs/ARBs items in June 2014 (70.1%) were explored, and then they were asked about potential strategies that would improve the policy uptake and implementation.

Prescribing advisers' interviews started with questions about their general responsibilities, and then their views about utilisation of antihypertension drugs and prescribing indicators with focus on ACEIs/ARBs prescribing and the BCBV indicator, respectively, were explored. Finally, implementation of the BCBV indicator and any associated barriers were explored.

6.4. Data analysis

All interviews were audio-recorded and transcribed verbatim by a professional transcriber. Each transcript was checked carefully against the original recording by the researcher to correct any omissions or mistakes, if applicable. Any personal identifiers were removed and replaced by a study ID known only to the researcher before sending the recordings to the transcriber. Confidentiality consent was also obtained from the transcriber to maintain confidentiality of the participants during the transcription process.

Text data obtained from the transcribed audio-records were analysed using the thematic analysis approach, a most commonly used approach for analysing qualitative data[423]. Thematic analysis usually involves identifying, analysing and reporting of themes inductively (themes are grounded in the data and obtained from the data gradually)[424]; but it also includes the identification of themes deductively[425] (themes that are predetermined and anticipated based on previous literature) as well as those obtained from the data inductively[423]. In general, thematic analysis includes coding data, dividing the text data into small units, assigning a label to each unit and then grouping the codes into themes.

6.4.1. Data organisation and management

To explore and become familiarised with the data, the recordings were listened to several times, with repeated reading and re-reading of the transcripts carefully line by line. The transcribed data were then divided and organised into sections under the key headings of the interview schedule, which focused on topics and themes to answer and achieve the study aims. For instance, for GP interviews, the transcribed data were collected under key headings such as GPs' prescribing decision of antihypertensive drugs, GPs' views on prescribing indicators, and their motivation and barriers for policy implementation. However, since the study aimed to explore the understanding and perspectives of the participants, the analysis was not limited to those issues or headings related to study aims; topics or issues that emerged from the data were also included. Organising the data in this way allowed linking the participants' response to each question and specific topic individually and made it easier to identify themes and concepts.

6.4.2. Data analysis process

Data organised into sections under the headings covered in the interview schedule were coded to identify connections and over-arching themes. Coding of the data involved labelling and grouping ideas to reflect wider perspectives, and this process is the core feature of analysing qualitative data[244].

A focus by question approach[426] was used in the coding process whereby participants' response to an individual question was systematically checked and coded. Responses related to a specific code including specific words, ideas, attitudes or phrases used by the participants were identified and the same language or terminology was used for labelling the initial codes. Coding and labelling were inclusive to reflect as many of the

concepts in the data as possible. Similar codes were grouped and organised into coherent categories and themes that summarised them and made the text meaningful.

Once all the text data were coded and grouped into broader categories, the "one sheet of paper" (OSOP) approach[427] was used to make connections between themes and categories. All the anticipated and emerged codes and categories that arose from the participants' response to each individual question were organised on a large single paper sheet with the respondents' identifiers next to them.

Those codes and categories for each question were grouped together into broader themes using axial coding. Axial coding is the process of making connections between codes and categories by rearranging the coded text data together under a broader category[428]. Axial coding helped to develop an explanation and understanding of coded text that accounted for all the issues that arose from the code extracts. Furthermore, the OSOP strategy enabled the identification of any negative evidence or deviant cases that did not match or fit with the emerging story as it involved thorough searching of all text data.

The process of data analysis started at the early stage of the data collection. The collected interview data from the initial interviews and their analysis and subsequently identified codes shaped the ongoing process of data collection (sequential analysis). This sequential analysis allowed not only for refining the questions in the interview schedules to identify areas that require deeper investigation but also continually checking and interpreting the data to build up hypotheses for subsequent examination in the later interviews[423]. For instance, after the first few interviews, the issue of over-switching patients from ACEIs to ARBs due to ACEIs-induced dry cough was brought

up by the participants; accordingly, this issue was explored further in the later interviews by asking the participants to quantify the incidence of ACEIs-related dry cough based on their experience.

Furthermore, the importance of presenting the interrupted time-series results of this study (Chapter 3) to the study participants for better understanding of the barriers for the failure of the BCBV policy was evident from the initial interviews; therefore, this topic was included in the subsequent interviews. Data collection and analysis were continued until saturation was reached within the data with no further themes emerging. The analysis processes were all performed under close supervision from my supervisors to assure high quality of the data coding and analysis.

6.5. Ethics approvals and confidentiality consideration

All the study documents (protocol, consent form, invitation letters, participant information sheets, interview schedule) were reviewed and approved by the University of Nottingham, Faculty of Medicine and Health Sciences Research Ethics Committee (Appendix 20), as well as by the NHS Research & Development (R&D) department in Nottinghamshire (Appendix21), Derbyshire (Appendix 22) and Leicestershire (Appendix 23).

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, and the Department of Health Research Governance Framework for Health and Social care, 2005.

Confidentiality was assured during all stages of the study. Access to the study forms and study information was restricted to the researcher and his supervisors. Study forms were held securely, in a locked room, locked cupboard or cabinet. A university computer was used to store and analyse the data, which was held securely and password protected.

6.6. Results

6.6.1. Characteristics of study participants

Of the 91 GP practices selected and invited to participate in the study, 32 GPs replied and returned the reply slip, but only 16 GPs and GP practices agreed to participate in the study, which represents a response rate of 17.6% (16/91). The mean age of the participants was 43.4±7.4 years. Participants had a range of characteristics in terms of gender, ethnicity and employment type, and most of the GPs were from Nottinghamshire (n=9, 56%) (Table 6.1).

Table 6.1 Characteristics of the study participants

	Total	Area		
		Nottinghamshire	Derbyshire	Leicestershire
Number of GPs	16 (100%)	9 (56%)	5 (31%)	2 (13%)
Age (Mean±SD, years)	43.4±7.4	41.3±6.1	46.6±8.8	44.5±10.6
Duration of work experience (Mean±SD, years)	13.7±8.2	12.2±7.2	19.4±8.0	5±2.8
Gender				
• Male	13 (81.2%)	8 (88.9%)	3 (60%)	2 (100%)
• Female	3 (18.8%)	1 (11.1%)	2 (40%)	0 (0%)
Ethnicity				
• White	12 (75%)	5 (55.6%)	5 (100%)	2 (100%)
• Mixed/Multiple	1 (7%)	1 (11.1%)	0 (0%)	0 (0%)
• Asian/British Asian	3 (18%)	3 (33.3%)	0 (0%)	0 (0%)
Employment type				
• Salaried	5 (32.0%)	3 (33.3%)	0 (0%)	2 (100%)
• Partner	9 (56.0%)	4 (44.5%)	5 (100%)	0 (0%)
• Locum	1 (6.0%)	1 (11.1%)	0 (0%)	0 (0%)
• Self-employed	1 (6.0%)	1 (11.1%)	0 (0%)	0 (0%)

(Note) SD: standard deviation

Only seven of the 13 prescribing advisers across the 13 CCGs in the three areas returned the reply slip, but unfortunately, none of them agreed to participate in the study due to their tight schedules. Therefore, this chapter only presents results from GP interviews.

The interview schedule covered questions and themes about GPs' views around antihypertensive drugs prescribing, in particular ACEIs/ARBs, including switching patients between ACEIs and ARBs. Then they were asked about their opinions about prescribing indicators, in particular BCBV, including the policy uptake and implementation. Finally, GPs' views on the current national value of ACEIs prescription proportion were explored to understand why it is not as high as been expected based on the low number of patients who cannot tolerate ACEIs.

6.6.2. Prescribers' views and perceptions on prescribing antihypertensive drugs

All of the participants had experience in prescribing antihypertensive drugs as common routine work in their daily practice, except one participant who had less experience in prescribing antihypertensive drugs – due to the very low prevalence of patients with hypertension in his practice.

> *"We do it [prescribing antihypertensive drugs] a lot. It's bread and butter general practice stuff isn't it?"*
>
> *(35-year-old, male, partner GP)*

> *"Well, first of all, I probably have less experience of prescribing antihypertensive drugs in terms of the amount I prescribe than GPs in other practices"*
>
> *(43-year-old, male, salaried GP)*

Participants reported a wide range of factors affecting their decision of prescribing different classes of antihypertensive drugs, which were categorised into guidelines, patient-related factors, prescriber-related factors and prescriber's cost-consciousness.

6.6.2.1. Influence of national guidelines

The NICE guidelines and/or British Hypertension Society guidelines for treating hypertension were considered as an important source of guidance for selecting among the various antihypertensive drug classes. All participants stated that they usually try to prescribe in accordance with the latest updates of these guidelines.

> *"We currently normally try and prescribe according to the latest NICE guidance"*
>
> *(52-year-old, male, partner GP)*

6.6.2.2. Patient-related factors

Many patient-related factors were reported to influence participants' prescribing decision including patients' demographics (age, ethnicity), past medication history, and medical and clinical conditions, such as BP level and comorbidities, e.g., diabetes mellitus and chronic kidney diseases.

> *"If it was a first treatment for antihypertensive I start with their age and their sort of ethnic background, following NICE guidelines. But I'd also look at what other tablets they're taking because if they're already on an antihypertensive or if they're diabetic or if they've got some impaired renal function or if there's CKD then that would affect my choice of antihypertensive"*
>
> *(35-year-old, male, partner GP)*

Although participants tried adhering to guidelines, the individualised patient-centred care approach appeared to be central to GPs' philosophy and practice of their prescribing. They adopt this approach to achieve the ultimate goal of maximising treatment outcomes for individual patients through selecting the most appropriate drug that suits each individual patient, even if it required deviating from guidelines, particularly in the case of hypertension due to its asymptomatic nature.

> *"Really I choose the one that will suit the patient best, depending on how old they are, what other medical conditions they might have like diabetes, what other medication they're already on, what they might have tried before, what they've had problems with. So all the clinical factors first and choose the one that's most appropriate"*
>
> *(37-year-old, female, partner GP)*

> *"The option of the treatment is to find something that suits you that works for your blood pressure. If we find something that suits you that doesn't work for your blood pressure, there's no point in continuing. If we find something that works for your blood pressure but doesn't suit you, there's no point in continuing"*
>
> *(58-year-old, male, partner GP)*

6.6.2.3. Other factors affecting prescribing

GPs' characteristics, such as their familiarity with certain groups of drugs, and personal preferences, also influenced GPs' prescribing decisions. Some participants were cautious and reluctant to prescribe new drugs as they were concerned about the possibility of withdrawing them from the market due to clinical or safety issues. Rather, they preferred prescribing a drug with clinically established effectiveness. Furthermore, some participants preferred to use a particular drug based on their personal perception of the drug's evidence base of efficacy and safety profile.

"I don't tend to jump on the bandwagon of anything particularly new. I've been stung in the past. There were several drugs that have come in a blaze of glory, really pushed and then some way down the line they've actually been withdrawn for whatever reason. So I'm a little bit reluctant, when there are drugs with equal enough efficacy available that I'm very familiar with. So I tend to keep my prescribing, I try to keep it as conservative as possible, just to work with drugs that I'm used to working with"

(58-year-old, male, partner GP)

"Most patients of course who I'm treating for hypertension are older so I'll tend to go for calcium antagonists or thiazide diuretics. I personally like the thiazide diuretics. I think the evidence base is good for them. They seem to have somehow fallen a little bit out of favour but particularly for women who are older patients, the thiazide diuretics I think have some advantages"

(50-year-old, male, partner GP)

6.6.2.4. Prescribers' cost awareness

Most of the participants reported drug cost as one of the elements affecting their prescribing decision; even though all participants prioritised effectiveness and safety profiles of a drug over its cost and usually considered cost as the last element. The extent to which cost of drug was considered in GPs' prescribing decision varied widely among the participants ranging from reluctance in considering cost to complete consideration.

"I would probably more think of efficacy and safety first over cost I suppose, yeah, I suppose I would think about it in that order"

(37-year-old, male, salaried GP)

"So all the clinical factors first and choose the one that's most appropriate and then if I'm going to choose a particular group of drugs like calcium channel blockers or ACE inhibitors then I'll choose probably the cheapest"

(37-year-old, female, partner GP)

The role within an organisation in a CCG or GP practice, such as involvement in a prescribing committee appeared to affect the extent to which GPs were aware of drug cost and hence its consideration in their prescribing decision.

> *"I'm probably more cost aware than most people because of my role as prescribing lead"*
>
> *(49-year-old, male, partner GP)*

Three GPs clearly pointed out that they prescribe cheap antihypertensive drugs and it became expensive only when patients do not adhere to them, which emphasises the importance of practicing individual patient-centred care approach through selecting the most appropriate drug for individual patients.

> *"I would consider efficacy and safety. I mean, I don't bear cost in mind, no.1, because the antihypertensive that I tend to use tend to be those that have been around for a long time and they are relatively inexpensive"*
>
> *(58-year-old, male, partner GP)*

> *"There's plenty of evidence of efficacy but overall I think that often comes in secondary to side effects and suitability for individual patients. [What about cost?] They are all cheap these days. The only time they are expensive is when you don't use them"*
>
> *(50-year-old, male, partner GP)*

One participant suggested that drug cost has been indirectly or subconsciously considered via following NICE guidelines since he believed that NICE only recommends cost-effective drugs.

"I mean I think they all [efficacy, safety, cost] play a role. I suppose the cost side of things I would say partly comes into play but in a way is already done in terms of NICE. So the medications that NICE recommend are obviously the kind of cost-effective. So cost is a consideration but actually in terms of NICE guidelines, you know, if I'm kind of sticking to those anyway then I probably don't tend to pay a lot of attention to a cost within that"

(32-year-old, male, salaried GP)

6.6.3. Prescribers' views on prescribing ACEIs and ARBs

Participants' views and perceptions on prescribing ACEIs/ARBs were explored in this section, which supported the understanding of how GPs think of ACEIs/ARBs and why ARBs might be prescribed as a first-line treatment instead of ACEIs.

Participants reported that they would often initiate treatment with ACEIs as first-line treatment for hypertension and ARBs were only prescribed in cases where patients are intolerant to ACEIs, mainly due to ACEIs-induced dry cough. With one exception, all participants had never prescribed ARBs as a first-line treatment. A wide range of reasons underpinned the prescribing of ACEIs as the first-line treatment including guidelines, prescribers' perceptions and knowledge of ACEIs, which affected their prescribing behaviour. Most participants considered more than one of these three factors that collectively affected their views on prioritising ACEIs over ARBs.

In addition to national guidelines, such as NICE, local guidelines implemented by local pharmacy advisers were also mentioned by participants as the main factor influencing their choice of using ACEIs as the first-line treatment while preserving ARBs for ACEIs-intolerant patients.

"I'd start with the ACE inhibitor but only if they developed a cough would I then think of an ARB because, well, I'm pretty sure that we were told by guidelines and a visit by one of the regional practice pharmacists, we should always start with ACE inhibitors and only go to ARBs if there was a contraindication to them"

(37-year-old, male, salaried GP)

In addition to guideline recommendations, prescribers' perceptions and attitudes on ACEIs as having more clinical evidence, being more effective, having wider licence indications and being a cheaper option also supported participants' choice of prescribing ACEIs as the first-line treatment.

"So first line, ACE inhibitors. I would always try an ACE inhibitor first. I'd only use ARBs if there is a side effect with the ACE inhibitor. That's because we've been taught that it's a cost issue and I think also there's more evidence of the ACE inhibitors being more effective than the ARBs in things like heart failure and for CKD; still the ACE inhibitors are the best at their job but if they can't be tolerated, the ARBs are the sort of secondary"

(41-year-old, female, partner GP)

Participants also reported that their choice of ACEIs over ARBs was shaped by their familiarity with the use of ACEIs. They felt more confident and comfortable with prescribing ACEIs since they have been prescribing ACEIs for a long period of time.

"I'm more used to prescribing ACE inhibitors and they've probably got a longer track record than ARBs, so I suppose it's what you're comfortable prescribing. I suppose it's around confidence that ARBs I've not widely prescribed in the past and also because of cost and pressure from various prescribing advisers around the use of ARBs, and the fact that ACEIs seem to have more evidence behind them"

(52-year-old, male, partner GP)

Most prescribers perceived ACEIs as more effective than ARBs due to more effectiveness evidence, but some prescribers viewed both drug classes as having equal efficacy. Consistently, most prescribers viewed both drug classes as having similar safety profiles, apart from a higher incidence of dry cough associated with ACEIs. Only one prescriber regarded ARBs to have a better safety profile than ACEIs. ACEIs were regarded as cheaper by most of the participants and only a minority of them did not differentiate ACEIs and ARBs by cost as they usually prescribed generic ACEIs or ARBs that have similar costs.

> *"In terms of efficacy, as far as I know there's no difference. In terms of safety, no difference, but ACE inhibitors as we know have this annoying side effect in cough probably in 10% of patients which sometimes can preclude their use and cost, ARBs are obviously more expensive"*
>
> *(52-year-old, female, partner GP)*

In contrast to all other participants, one participant reported prescribing ARBs instead of ACEIs as first-line treatment for hypertension due to his concerns about the ACEIs-induced dry cough and the high possibility of patients switching ACEIs at later stages due to this ACEIs side effect, which may then lead to poor medication adherence. This participant's specified risk and benefit justification was solely applied for treating hypertension, as ARBs (namely candesartan) are regarded as having good evidence for BP reduction. However, for renal protection or HF treatment, ACEIs were still selected over ARBs due to evidence on superiority of ACEIs over ARBs for these indications.

> *"I was always keen to enalapril, it was nice and cheap as well. These days however quite a lot of patients do get side effects with ACEIs. They do tend to get irritable cough, certainly in women. Longer term it's a good 20% or more and in clinical practice that's a problem because very often you will*

see patients – you think it's just going to be a viral cough but they're on an ACEI, you end up changing them. I find myself too often having to – if I start with an ACEI, I end up swapping it. It's more whether you manage to get the patients to take it. If the patient has side effects then the one that they take's going to be more efficacious. So I do tend to use ARBs. Candesartan is the main one. I think the evidence again is very good for that; it's got good blood pressure lowering effects. But It depends what the indication is. It's for pure hypotension in a youngish person I'll go for candesartan. Perhaps for heart failure, the evidence is really more supportive of using ACE inhibitors rather than ARBs and I like the evidence for enalapril particularly for heart failure and for renal dysfunction"

(50-year-old, male, partner GP)

On two occasions, participants mentioned that their prescribing choice might change under a consultant or a specialist doctor's request as they regarded consultants as having a higher level of knowledge than themselves.

"I can't think of any time I've started with ARB before ACE inhibitors, because in my head I see them as the same. I know they're slightly different but I see them as the same but the ACE inhibitor is better and more cost-effective than the ARB, so why wouldn't you always go with that one first? So unless a consultant has said start an ARB, I would just use the ACE inhibitor first. So if I'm told by a consultant start someone on an ARB rather than an ACE inhibitor, I'd do what they say because I think well they must know something I don't"

(41-year-old, female, partner GP)

6.6.4. Prescribers' views on switching patients between ACEIs and ARBs

Since the implementation of the BCBV indicator involves switching established ARBs to ACEIs, it was necessary to explore GPs' views on this issue, which would help to highlight any potential issues that GPs are facing regarding this topic.

6.6.4.1. Switching from ACEIs to ARBs

Switching patients' medication from ACEIs to ARBs was reported as a frequent and common practice by participants since many patients are intolerant to ACEIs, largely due to dry cough and occasionally other side effects.

> *"So the most common reason I suppose I would do that would be when someone appears to have developed a cough on an ACE inhibitor and that's certainly the most common side effect or problem that I have come across personally"*
>
> *(32-year-old, male, salaried GP)*

> *"We do that [switching from ACEIs to ARBs] quite frequently. Most commonly due to coughs and occasionally other side effects. We'll try an ARB with them"*
>
> *(32-year-old, male, partner GP)*

Two participants also reported that they would switch ACEIs-intolerant patients to other antihypertensive drugs that are cheaper than ARBs when the indication is appropriate. This is due to their cost awareness and willingness to save the NHS money through avoiding the prescribing of a relatively more expensive drug class. In fact, such level of cost awareness seemed to be associated with their roles a prescribing leads.

> *"Generally if somebody's got a problem with an ACE inhibitor I would probably change to something like a calcium channel blocker instead rather than ARB really. As long as they're not contraindicated or there's no other reason not to, due to the cost more than anything else really. I'm probably a bit out of touch with what the costs are but I have the impression that ACE inhibitors are now next to nothing, you know, £1, £2 a month and ARBs are still £10, £20"*
>
> *(49-year-old, male, partner GP)*

> *"I mean if a patient is on an ACE inhibitor, these days generally it depends on what the indication's for. So let's say if they can't tolerate it [ACEIs] and it's for hypertension then I'd probably try the next step. I'd probably go for either a beta blocker or calcium antagonist rather than ARB, mainly because of guidelines which I guess they're based on a cost issue"*
>
> *(41-year-old, male, self-employed GP)*

Although ACEIs-induced dry cough was the main reported side effect of ACEIs, participants expressed a wide range of views on its prevalence that ranged mostly from 10% to 20%, but a much higher rate of 30–40% was mentioned by one participant. This is much higher than the evidence-based prevalence rate of up to 10%[132].

Several GPs recognised and acknowledged two primary issues with this side effect, which might contribute to its higher rate in their daily clinical practice, hence higher switching rate of ACEIs to ARBs: GPs' uncertainty about the cause of the cough, and patient's pressure to switch from ACEIs. Some participants pointed out the difficulty and uncertainty in diagnosing the exact cause of cough in patients receiving ACEIs, in particular the development of dry cough at the later stages of ACEIs treatment (delayed reaction) makes the diagnosis even harder.

> *"Well, everybody gets a cough every year and it's always difficult at some times to say is this suddenly because of an ACEI or not? Especially with a delayed reaction. Personally, I tend to believe it's just a cough and wait and see. If it's somebody who's adamant that it's the ACEI that's causing it, I quite often ask them to have a drug holiday, where they just stop it for a month or so, see if the cough goes away and then ask them to restart it and if the cough comes back I'll say well, maybe it was. The trouble with ACE inhibitors doing that is there's such a delayed reaction to the drug it's a difficult one. I mean some side effects, they go when you stop and they come back when you start; that's easy. But with a delayed side effect, it's*

very difficult to do. So it usually comes down to the fact that if the patient believes that their cough has gone away with their ACE inhibitors then they'll go to an ARB"

(52-year-old, male, salaried GP)

Prescribers adopted various approaches to deal with patients' dry cough; some followed a firmer strategy such as stopping ACEIs and giving a drug holiday to monitor whether the cough would be relieved or not; while others directly stopped ACEIs and switched patients to ARBs. As the dry cough is a subjective symptom, patients' beliefs of whether the cough subsided after stopping or switching ACEIs were reported as a factor that affects prescribers' judgement on the association of a dry cough with ACEIs.

Patients' beliefs and perceptions on the association between their ACEIs treatment and occurrence of dry cough also imposed pressure on prescribers to switch to ARBs. However, one participant perceived that patients' knowledge about the dry cough makes the consultation easier and smoother.

"I use an ARB for those who are intolerant to an ACE; for example, a patient today had a cough, he talked to a friend, knew that ramipril quite often caused a cough, he had stopped his ramipril, his cough had got better, he hadn't re-challenged and restarted understandably but he came to see me today and said "my friend had a cough on ramipril, my friend changed to losartan do you think I ought to do that". You know yes I think the word on the street. It was a very easy consultation because he had been talking to his friend who had had a similar experience. So, I think a lot of patients do know quite a lot about their drug"

(55-year-old, female, salaried GP)

6.6.4.2. Switching from ARBs to ACEIs

Participants reported no experience of switching patients from ARBs to ACEIs because most patients are prescribed with ARBs due to their intolerance to ACEIs or their ARBs were prescribed by a consultant in secondary care, and GPs did not feel confident in switching their ARBs in this circumstance.

> *"I don't think I've ever done that, because I would have – normal practice would be to see that somebody has already been on an ACE before they're ever on an ARB. I do not think I have ever seen it that they're on an ARB first. It would be incredibly rare to find somebody on an ARB that has not already had an ACE"*
>
> *(52-year-old, male, salaried GP)*

> *"I don't think I have [done that] routinely. Normally it's the other way round so I can't think of an occasion when I've switched somebody from an ARB to an ACE. Often historical ARB patients have been prescribed from secondary care, in which case I don't feel particularly confident to change the treatment if it's been prescribed by a consultant really"*
>
> *(52-year-old, male, partner GP)*

Three participants reported several instances of switching patients from ARBs to ACEIs in the past either due to cost-saving initiatives, GPs' willingness to try a relatively new class of antihypertensive drug or screening the medication history of a patient who recently joined the practice. The increased number of patients who received ARBs as first-line treatment also contributed to the marketing of ARBs by drug companies.

> *"We have audited that and done that, mainly because when the ARBs came in we had a big drive from drug companies and also our own experience of trying and seeing how they go. So we changed over and reviewed all those cases and the majority of them were switched back to an ACE inhibitor of a different choice. Some of them still remain but many of*

them have been changed to other classes of agents, for cost saving and quality purposes as well"

(41-year-old, male, self-employed GP)

6.6.4.3. GPs' reluctance to switch patients from ARBs to ACEIs

Given a scenario that an ARB user without previous history of using ACEIs, who is well tolerant to ARBs and whose BP is well controlled, all participants expressed their unwillingness to change the patient's medication from ARBs to ACEIs, due to a variety of reasons, including GPs' lack of motivators, their concerns of compromising the patient's quality of care and patient's resistance to the switching.

The most common reason for participants' reluctance to switch patients from ARBs to ACEIs was the concern that switching may risk and compromise the patient's quality of care and health, as it usually takes a long time and effort to find an appropriate antihypertensive drug that works and suits patients. Participants were also concerned that patients' compliance could be impeded by switching from ARBs to ACEIs, in particular ACEIs were perceived to have a poorer safety profile than ARBs.

"No, I would keep him on the ARB, because if it ain't broke, why fix it. If it isn't broken, why do you fix it, why do you mess about? We spend so long in starting people off on a drug, gradually increasing it, getting blood pressure controlled. Why do we actually, once we've got it controlled, why do we want to change things? -[for cost saving for example]-That is not at the top of my list. If I found something that works for a particular individual, I would much prefer to stick with that, I wouldn't change it on the basis purely of cost, there has to be another reason"

(58-year-old, male, partner GP)

Several participants mentioned that there is a lack of motivation, such as policies or initiatives, to encourage switching from ARBs to ACEIs in particular given the loss of cost differential between ARBs and ACEIs due to the availability of low-cost generic ARBs.

> *"No. I think nowadays I wouldn't. I don't see a reason why I should do. Nobody pushes me at the moment to change this back. I'm happy to prescribe an ARB"*
>
> *(45-year-old, male, partner GP)*

> *"No, because the cost is minimal now because most patients are on losartan or Valsartan and they're generic and so the cost is not such an issue"*
>
> *(36-year-old, male, partner GP)*

Participants also pointed out patients' general resistance to frequently switching drugs when a drug has been effective and accepted by the patient. Participants suggested that this resistance to switching appeared to be associated with a patient's demographics; for example, elderly patients appeared to be more resistant to changing drugs.

> *"A lot of people are quite sensitive about their tablets and I think don't like having them switched. A lot of people get used to brands, used to side effects and a lot of the elderly patients don't like the change. So, often patients will say 'I accept it's not the first line but it works for me. I don't want to rock the boat, it works, can I leave it as it is?' and I think that's quite a reasonable thing to say"*
>
> *(32-year-old, male, partner GP)*

> *"No, normally a patient would be very strong about it and they can get a bit sensitive about it. So I can't remember that I did that but I did consider it, I did sort of try to do that with a patient or two in my mind and I think I*

remember I offered it a long time ago but they said 'oh no, we're happy with that, we don't want to change it'."

(43-year-old, male, locum GP)

In terms of patients' response to the switching decision, participants suggested that patients may accept the drug's switching when the purpose of it (whether it is for medical or non-medical reasons) can be justified. In general, patients tend to accept switching for medical reasons and drug intolerance due to side effects as the switching will benefit their health.

"It's not usually a problem because as I say, the main reason is they've got side effects with the ACE inhibitor, so often it's the dry cough and obviously they're happy if they think it's the ACE inhibitor then they want to get off it"

(37-year-old, female, salaried GP)

On the other hand, patients' response to non-medical switching was reported to be varied depending on the level of patients' cost awareness, and the way that GPs explain the switching to patients. Patients who are aware of the budget constrain in the NHS tend to accept the non-medical switching. Furthermore, explaining the rationale of the switching by GPs to patients in terms of treatment appropriateness and guidelines appeared to positively affect patients to accept the switching. However, justifying the switching in terms of monetary values reported to be unacceptable by patients due to patients' negative perceptions of cheaper drugs as being of poorer efficacy compared with expensive drugs.

"The conversations you can have with patients sometimes is to say 'look, there's a much cheaper alternative to this that's supposed to work equally

as well, are you prepared to try it?'. Now some patients will say 'yeah, great, the NHS needs the money, do whatever you like' and other patients will say 'I'm not having anything cheap, you horrible doctor, I hate you', because they just perceive expense to be good"

(52-year-old, male, salaried GP)

"In the most part I think they react reasonably well, as long as you can explain to them why it is that you're switching the medication. I don't tend to say to people specifically this alternative treatment is a cheaper treatment because I don't think patients always react to that very well, but I will explain to people that in terms of the guidelines for current treatment that I think it might be more appropriate for them to be on a slightly different medication. Generally they respond very well to that. I can think of one patient who ended up in a more in-depth conversation and the patient specifically asked about cost and I explained that the alternative was a cheaper alternative and they were not impressed by mention of that fact."

(32-year-old, male, salaried GP)

These extracts clearly demonstrate patients' involvement in any switching decision by GPs and only those who accept the change were actually switched.

6.6.5. Views about prescribing indicators

In order to understand the reasons underpinning the ineffectiveness of the BCBV indicator, it was necessary first to explore GPs' perceptions regarding prescribing indicators in general but the BCBV indicator in particular. Overall, there were consistent, positive views about prescribing indicators, even though one participant had different views.

All participants had positive opinions toward the general principle underpinning prescribing indicators. They regarded prescribing indictors as a good and useful way to

make GPs more focused in practice and to prescribe in a more cost-effective way. Given the current budget constrains in the NHS, they realised that overspending in certain areas would lead to healthcare shortage or disinvestment elsewhere.

> *"As a general principle, I think that's a good idea because it focuses people to deliver; otherwise it's, you know, if you don't measure things you tend not to achieve them."*
>
> *(52-year-old, male, salaried GP)*

> *"A big fan of them [prescribing indicators] because I think if they're appropriately referenced and reviewed and set then they are things we should be aiming to do which represents good practice – good, safe, cost-effective practice. It's the NHS, it's the real world, you know, if we overspend on something we haven't got the money for doing something else."*
>
> *(49-year-old, male, partner GP)*

Despite the overall positive views, one participant disliked prescribing indicators and believed they are mostly cost-oriented rather than quality-oriented, with the objective of saving money, which was considered a short-term focus.

> *"I think the biggest problem is all too often they're obsessed by trying to save trivial sums of money rather than looking at the bigger picture."*
>
> *(50-year-old, male, partner GP)*

After explaining the principles of the BCBV indictor to the participants, their views were positive, supportive and almost identical with their views on prescribing indicators in general. All participants acknowledged that they were practising the right principle through following NICE guidelines in prescribing ACEIs as first-line treatment and preserving ARBs only for those patients who cannot tolerate ACEIs.

"I think that's OK because I'd go along with that. Myself I'd try and go for ACE inhibitors preferentially, as long as it's based on evidence then I don't think there's a problem with it. I think it's a good idea, definitely"

(37-year-old, female, partner GP)

"I think it's good to have guidelines and targets because it makes you think and that data will be presented to you at times so you can compare yourself with other practices"

(41-year-old, female, partner GP)

"No, I have not heard of it, I do not think so, but it's obviously been converted and adopted into our guidelines that we follow, I might not know where that initiative came from but I certainly know that that's what I'm supposed to be doing, if you can see the difference. I've never heard of those phrases that you used, but am I supposed to be using the cheapest things that work and would I tell you exactly what I'm doing with ACEs and ARBs and be right, then yes"

(52-year-old, male, salaried GP)

6.6.6. Barriers for the effectiveness of the BCBV prescribing indicator for ACEIs/ARBs

Participants pointed out a variety of reasons as potential barriers for the effectiveness of the BCBV indicator, which can be categorised under four main themes: lack of GP awareness of the policy, GPs' resistance to guidelines and prescribing indicators, lack of incentives and scepticism about the BCBV proposed target.

6.6.6.1. Lack of GP awareness

Overall, a very low level of awareness and knowledge of the policy were reported by all the participants. The majority of participants had not heard about BCBV and were completely unaware of such an initiative – even those who were cost-conscious and

had a role within the organisation (such as lead of prescribing committee). Such unawareness was reported across participants from the three regional areas.

Participants contributed their unawareness of the policy to the poor advertisement and communication of the policy. Given the overloaded information that GPs receive, a good and more structured method to publicise and disseminate the policy is necessary. Furthermore, most participants attributed their unawareness also to the lack of initiatives to implement or push the policy from CCGs, primarily due to the lack of prioritising of ACEIs/ARBs prescribing efficiency. This lack of priority was due to the presence of other potential areas for efficiency improvement within CCGs, which took priority over ACEIs/ ARBs.

> *"Not specifically that one for ACEIs [Why?] because presumably badly advertised. It sounds very much as though it's what we're doing anyway. I suppose the other thing that might have happened is, you know, when information comes through whoever agenda's the meetings might have looked at it and said 'well we already do that anyway'"*
>
> *(49-year-old, male, partner GP)*

> *"No, I have not heard of it [Why?] I think it's just information overload or it's not well advertised. It's not being pushed by the CCG"*
>
> *(36-year-old, male, partner GP)*

> *"I've heard of the idea behind better care, better value but I wasn't aware it was a prescribing indicator [Why?] perhaps because we're achieving nationally quite a lot or perhaps because there's other areas to focus prescribing energies on and resources in terms of time and if you're going to pick a more important one so that the targets we perhaps get given by the cluster prescribing team are different from the national ones"*
>
> *(32-year-old, male, partner GP)*

However, a small minority of participants expressed their awareness of the principles underpinning the BCBV policy in general, but they were either vaguely aware of it as a prescribing indicator for ACEIs/ARBs or not familiar of the details of it.

> *"I'm aware of it. I'm more aware of the proton pump inhibitors, the statins, because we've really concentrated on those. I know in that pack of data there's the ACE inhibitor ones as well. Have I concentrated on it? No. Why not? Because as a practice we've talked more about the statins and the other one, which makes me think we might hit the indicator already. If we already hit target, we're doing it fine, don't change anything"*
>
> *(41-year-old, female, partner GP)*

> *"I have heard of them. I have to say I get slightly confused or muddled as to perhaps which indicator might be related to which target or something like that. So I'm not sure I would be able to tell you specifically what came from where but I am aware of them"*
>
> *(32-year-old, male, salaried GP)*

In addition to this unawareness, difficulty in remembering the policy was also pointed out as one of potential contributing barrier to the policy's failure, unless some reminding tools, such as an inbuilt computer reminding or alerting tool, were provided to constantly remind them of the policy,

> *"My general comment on the NHS and policies and initiatives is that it's difficult to go through a day at the moment without there being five initiatives. So remembering one from morning till the afternoon is hard enough, far less the next week. Initiatives should be – a bit of saying what's good with QoF, I get flashy alerts on my screen because it's all been put into the system properly so I can see oh, I should be thinking about this, I should be thinking about that. If it relies on me remembering all these initiatives, you haven't got a hope in hell because you'd need a computer in your head to keep on top of all the millions of different things that are*

> *changing every day that they want us to do. it's impossible unless they build it into the systems and make it easy for people to quickly go 'oh, that's what I'm supposed to be doing'"*
>
> *(52-year-old, male, salaried GP)*

A possibility of regional variations in the level of GP awareness of the BCBV indicator could exist depending on what kind of input various GP practices have. For instance, the presence of a peer GP, who is actively involved in CCGs' prescribing committee, would continually remind all the other GPs of any prescribing policies; hence enhancing the policy uptake and effectiveness.

> *"You'd have to break it down into practice level. That's the only way because you need to see what each practice is doing. Why one practice will do one and one wouldn't? I can't think of any reason why, other than some practices try and follow the guidelines more strictly than others and Again, why? Awareness. Don't forget, Dr Tom* is on the JPC [Joint Prescribing Committee], he's on the board, so we get a lot of feedback from him. So constantly being told things and you have this constant awareness here, with Tom* being on the prescribing committee, you have this constant awareness of what's changing, what you should be doing, what you shouldn't be doing"*
>
> ***(Note) *** Names in the above quote have been changed
>
> *(41-year-old, female, partner GP)*

6.6.6.2. GPs' resistance to guidelines and prescribing indicators

Overall, the participants had positive views about the prescribing indicators, but they speculated that other GPs might resist the BCBV indicator. This resistance could possibly have also contributed to the failure of the policy. Participants reported that other GPs might resist the BCBV indicator because they consider it as rigid and non-flexible, jeopardising prescribing autonomy, lack of authors' credibility and being mostly

cost-oriented. Furthermore, the BCBV indicator was also viewed as being non-sustainable, having a short-term focus and changed quickly with the same targeted cohort, and recurrent switching that may negatively influence GPs' credibility. Considering patients as their first priority and adopting patient-centred care was also reported as a possible reason for not following the BCBV indicator.

> *"I think a number of GPs probably don't like being told what to prescribe by prescribing indicators, largely written by people who aren't seeing patients face to face. I think there probably are a small number of patients where they don't fit the guidelines and sometimes there are reasons within individual patients why you might not want to change them, even if on the guideline it says so"*
>
> *(52-year-old, male, partner GP)*

> *"I have to admit, a lot of these targets can be quite, sort of, I want to say demoralising or depressing because you just feel like you're being watched and looked at all of the time and yeah, it is very good to have to justify all our decisions and it's important that we do but at the same time it can feel like a sort of a Big Brother watching you, you naughty person, why could you think of prescribing that ARB, that's really hideous"*
>
> *(37-year-old, male, salaried GP)*

6.6.6.3. Lack of incentives

Some participants attributed the ineffectiveness of the BCBV indicator to the lack of any financial incentives linked to it. They believed that financial incentive is an important strategy to make GPs interested in this policy, under their current workload.

> *"It could be because it's not financially incentivised. I suppose in a way, as cynical as it is and I don't think this perhaps personally works for me so much, but I certainly have heard colleagues say that if you want GPs to do something, if you financially incentivise it then people will tend to do it"*
>
> *(32-year-old, male, salaried GP)*

"They have to have some form of funding and resource allocation for the work that needs to be involved, there has to be an incentive there. So if people buy into that incentive then they're more likely to work hard at it because what's actually happened in this case, you're asking people who are already working full time to do something over and above what they normally do. But all these things tend to be unpaid and so there's a bit of unwillingness for a GP to go out of his way to do these things"

(41-year-old, male, self-employed GP)

6.6.6.4. Scepticism about the proposed BCBV target

Only one participant showed her doubts about the foundation theory of the policy target, i.e., number of people who cannot tolerate ACEIs due to dry cough or other side effects. She suggested reasons other than dry cough for switching patients from ACEIs to ARBs, and conditions requiring prescribing ARBs as first line instead of ACEIs should also be considered.

"I would be thinking of the policy itself. Are they being realistic in actually how many people are affected by side effects from the ACE inhibitors. So, I would say, if my personal data showed that I was prescribing more than the 20% of ARBs, I would then feel that the policy was wrong because I feel I do stick to the guidelines quite well, which means I'd be saying 'is the policy just looking at dry cough? Are there other side effects we change it for which they're not taking into account?' Such as, yeah, I've just thought of one, here we go! It's very uncommon but what would I use first line in a less than 55 year old male with erectile dysfunction? I'd use an ARB first because the ARBs are less likely to affect erectile function. So that is one of the few times that I would pick an ARB without trying an ACE inhibitor"

(41-year-old, female, partner GP)

Participants expressed a range of views on the suggested 80% target. The majority felt that the proposed target is an easy achievable target based on their reported prevalence of ACEI-induced dry cough of 10–20%; a target >80% was suggested by one participant based on the infrequent occurrence of ACEIs-induced dry cough. Some participants identified factors other than the dry cough that could influence GPs' prescribing of ARBs as first-line treatment, such as GPs' prescribing habit and preference of prescribing ARBs, especially specialist or consultant doctors.

> *"It's probably an achievable target. When you think that probably 10%-ish of patients have intractable cough on an ACE, which is the biggest problem, that's probably an achievable target"*
>
> *(52-year-old, male, partner GP)*

> *"Yes, I think that's not unreasonable. Just reflecting on my own experience, most of the patients that are on that drug, one or the other, are on ACE inhibitors and a small proportion will be on ARBs and 20/80 seems reasonable"*
>
> *(58-year-old, male, partner GP)*

> *"I don't think it's high enough. I'd go for higher. Personally, and this is personal now, I'm not sure why that many people should be on ARBs rather than ACE inhibitors because I don't see there's a significant difference in cost-effectiveness really, with the exception of people who have tried an ACE inhibitor and cannot tolerate it for various reasons"*
>
> *(49-year-old, male, partner GP)*

6.6.7. Strategies to enhance the effectiveness of the BCBV prescribing indicator for ACEIs/ARBs

After exploring the barriers for the ineffectiveness of the BCBV policy, participants suggested a wide range of approaches that would potentially improve the future effectiveness of the policy. The suggested strategies emerged from the identified

barriers and can be grouped under four themes: strategies to increase GPs' awareness of the policy, linking the policy to financial incentives, GPs' education and benchmarking, and strategies to facilitate patients' switching from ARBs to ACEIs.

6.6.7.1. Strategies to improve GPs' awareness of the policy

Increasing GPs' awareness of the policy was considered crucial for the policy uptake and implementation. This increase in awareness was suggested to be achieved through adoption of effective methods for advertising, disseminating and communicating the policy. For instance, adopting the policy by local personnel such as the prescribing committee in a CCG then disseminating it down to individual GP practices was seen as an effective method for policy uptake. This local adoption was seen not only to increase GPs' awareness and uptake of the policy, but also would potentially address GPs' doubts about the credibility of the policy's authors. Furthermore, another implementation strategy highlighted by the participants was the incorporation of a reminding or alerting tool in GPs' computers to remind them of the policy whenever they attempt to prescribe ACEIs/ARBs.

> *"I think there's an ownership thing to any protocol or advice and that's why I strongly believe in local protocol. I mean personally it's me that's there making them but for my partners and people in the CCG, they can actually contact me, they can access me rather than somebody over in London that's an obtuse organisation. It needs to be easily accessible but also more locally peer referenced that you can, you know, people that you sort of trust I suppose may have formulated them. If it's a local cardiologist on the committee that you've got a good relationship with that's suggesting that protocol then I would personally very strongly follow that rather than Professor somebody down in London that I've never met. I think it needs to go through some sort of local organisation such as the joint area prescribing*

committee in Derbyshire or a hospital prescribing committee in secondary care, that sort of thing and be disseminated top down"

(49-year-old, male, partner GP)

"I think obviously they have to be publicised, if I don't know about them I think there is a good chance that quite a lot of other GPs don't know about them. I think they have to be championed possibly by somebody in their vicinity so a sort of local person that can speak to GPs individually or as a practice might be helpful"

(43-year-old, male, salaried GP)

6.6.7.2. Linking of the policy to financial incentives

More than half of the participants strongly suggested and supported the idea of financially incentivising the policy, as a potential strategy to increase the policy uptake by GPs. Participants believed that financial incentives would increase GPs' willingness to take up the policy, as was the case for the QoF indicators. This fact was emphasised by participants who disliked the idea of using financial incentives to increase the policy uptake.

"I suppose in an ideal world we should all be striving to do the best for our patients within the limited resource, but in reality I think unless you incentivise people to go and look for groups of patients who are clinically appropriate to switch and cost saving, I think if you don't incentivise people it just won't happen"

(52-year-old, male, partner GP)

"If there are good reasons to give incentives to prescribe certain medications and this is evidence based on wide studies, I think yes this is a way to try and achieve, for example, certain prescribing patterns and I think this is not a new way out to try to bring doctors to prescribe certain classes of medications that can be done with budgeting and can be done with penalising of prescribing, it can be done by incentives of prescribing"

(45-year-old, male, partner GP)

"Yeah. I don't have a problem with that [giving incentives]. I think QoFs revolutionised general practice"

(52-year-old, male, salaried GP)

However, some other participants expressed an opposite opinion and actually disliked the idea of linking the policy to any kind of financial incentive or legislation enforcement. They believed that GPs should practice to achieve the best for patients' health and prescribe the most appropriate medicines, regardless of any incentive. Some of these participants also expressed their concerns that incentivising the policy as a measure to increase its uptake may have negative consequences on the quality of patients' care and be considered morally unacceptable. Nevertheless, they admitted that this measure, despite their personal dislike to it, would work for most of their GP colleagues.

"It [giving incentives] works for some people. I'm a bit insulted by it because I feel that I would do the best for the patients, regardless of what money was thrown at me, but I know there are perhaps some people that are more motivated by money"

(37-year-old, female, partner GP)

"I think there's too much of that [giving incentives] now, sadly. I think there's a danger that you wouldn't do the best thing for your patient, just trying to hit that target. You see, we're talking about what's the best thing for the patient and if the patient comes in – let's say it's more often that I'm changing someone to an ARB but I don't know how often I'd do it but I would be saying it's necessary for the patient and actually leaving them on a medication that doesn't suit them means they're less likely to take it, which is actually doing them more harm"

(41-year-old, female, partner GP)

"I'm not sure personally that I do like that way of doing things. I know obviously in terms of QoF and things like that certainly for the last however many years it has been a key part of how GPs are paid and I suppose I can understand the performance level of it in that if GPs are doing things entirely inappropriately, then it would seem sensible to try and coerce them into doing things more appropriately by making it financially incentivised"

(32-year-old, male, salaried GP)

"I don't particularly like that idea but I'm sure it will get done. Yeah, I think it happens a lot but I don't think it's necessary but I'm sure it will end up happening"

(37-year-old, male, salaried GP)

6.6.7.3. GPs' education and peer pressure

A small minority of participants suggested that educating GPs about the evidence base underpinning the policy is another alternative approach to enhance the policy uptake. In addition, the ability to compare and discuss the prescribing patterns of ACEIs/ARBs by benchmarking each other's prescriptions, for instance, comparing prescriptions among GP practices in a quarterly or annual basis might also help improving the prescribing efficiency of these drugs due to the pressure from other peer practices and the natural tendency to avoid being out of the norms or an outlier.

"I think most of the time rather than enforcement it's better to try and educate GPs, put the evidence base for them because if there's reason for having guidelines there's usually an evidence base and most doctors are quite happy to follow an evidence base"

(50-year-old, male, partner GP)

"What we did was we actually could look, analyse the prescribing per GP within the practice and we publicised that just to the partners on a quarterly basis and what we found was we'd had a discussion about alpha-blockers for instance, and we found out that some partners were prescribing a lot,

some partners weren't prescribing enough and we'd agreed that perhaps the mean should be about there and over time, because we all knew what everybody was doing, we found that everybody regressed to the mean. The ones that were high prescribers reduced the ones that were lower prescribers increased. So it's being aware of what your peers are doing is the thing"

(58-year-old, male, partner GP)

6.6.7.4. Strategies to facilitate patients' switching from ARBs to ACEIs

Switching patients from ARBs to ACEIs is an essential component of the BCBV policy, and therefore, strategies that enhance this action are of great importance for improving the policy's effectiveness. Accordingly, some participants suggested approaches that would encourage patients switching from ARBs to ACEIs, including providing support from other healthcare professionals, improving GP-patient communication methods and provision of guidance on how to perform the switching.

6.6.7.4.1. Support from other healthcare professionals

Due to GPs' heavy workload, limited time and perceiving switching as an additional duty, two participants suggested that other healthcare professionals, such as pharmacists and pharmacy technicians, could play important roles in simplifying the switching process through screening and identifying patients who are eligible for switching. Identification of eligible patients may make the switching easier as it saves GPs' time. Furthermore, these two participants viewed the employment of other healthcare professionals to run this active switching programme as a cheaper alternative than incentivising GPs to perform the switching.

"I think you've got to be careful with the swaps, you know, having some support, like here we've got pharma techs' support who will come in and

say 'this is where we can perhaps make a saving by changing this to this and this is the evidence', and we'll say 'yeah, fine'. If she does most of the work for us on say a swap and makes it a lot easier. If you have to leave it to individual doctors to try and do it in the surgeries when we're already busy, well I think you're going to have to incentivise us more. It's cheaper I think to have pharma techs to do the swaps than it is to incentivise GPs to do it in their surgeries"

(50-year-old, male, partner GP)

"They need to be funded and they need to be incentivised. Not necessarily doctors need to be incentivised but people or pharmacists need to be incentivised to go in there and drive that, which is what our CCG is doing. We have employed a pharmacist. That money has to come from somewhere and that's what I'm talking about, resources. Once you get these people in it makes our life a lot easier and so it's just a very simple thing."

(41-year-old, male, self-employed GP)

6.6.7.4.2. Improving communication between GPs and patients

It was pointed out that the communications style of GPs with patients regarding the switching would have a great impact on patients' acceptance of the switching. Participants reported that involving patients in the switching decision and explaining the switching rationale in terms of guidelines or appropriateness, instead of relating it to cost would potentially improve patients' acceptance of the switching. Furthermore, using face-to-face consultations to explain the justification of the switching rather than sending letters (the most traditional way of communication), was also considered a promoting factor for patients' acceptance of the switching.

"I can't remember which switch it was but one of our patients came in and said 'look, I've had this letter from you' – the practice – 'about the fact that you're just changing one of my drugs. I think it's outrageous'. So I suppose

the way things are done can be problematic as well. If it's to do with changing people off drugs, ways in which we can bring our patients on board with that and not make it just look like it's a government edict or a cost-cutting measure or something. So ways in which we can maybe promote it to our patients better than just a letter in the post saying 'oh' 'the NHS are saying we should change your drug from this to that, so we have'. I suppose it's maybe more involvement with the patients in the way things are done"

(37-year-old, male, partner GP)

6.6.7.4.3. Providing guidance on the switching

One participant highlighted the necessity of having switching guidance to assist GPs in implementing the switching in terms of dose equivalence of ACEIs and ARBs, and patients' clinical eligibility for the switching given their clinical conditions.

"For that [the BCBV policy] to be implemented, it should have a plan in place for GPs of how to kind of implement the change. So for example, say if they wanted to change everybody from simvastatin to atorvastatin because there's less interactions, because the cost has now come down of atorvastatin and it's a better statin. So they should give guidance on actually if somebody is on simvastatin and their cholesterol's less than four then don't change them. If their cholesterol's more than five or if it's between 4 to 5 but they've had previous heart attacks then change them to atorvastatin. So there should be just proper guidance"

(36-year-old, male, partner GP)

6.6.8. GPs' views on the national data of ACEIs prescription proportion

Since all the participants reported that their prescribing of ACEIs and ARBs was in line with NICE recommendations in terms of prescribing ACEIs as first-line treatment, it was imperative to explore their views on the current national value of the ACEIs prescription

proportion (70.1% at June 2014), being lower than the expected target (80.0%). Participants pointed out three possible factors related to switching patients from ACEIs to ARBs associated with GPs and patients that could contribute to the lower proportion of ACEIs being prescribed.

6.6.8.1. Over-switching of patients from ACEIs to ARBs

Few participants attributed the low proportion of ACEIs users to the over-switching of patients from ACEIs to ARBs, primarily due to an unconfirmed cause of cough. The difficulties in correctly diagnosing ACEIs-associated dry cough were due to the lack of a diagnostic test and the drug cough often occurs at a later stage of ACEIs therapy. Subsequently, cough from other origins, such as flu or acid reflex, may be confused with ACEIs-induced dry cough and thus GPs may over-switch ACEIs users to ARBs.

Patients with hypertension were reported to be at higher risk of cough due to acid reflex because of some antihypertensive drugs they make take or other conditions (e.g., obesity) they may suffer from. Participants also mentioned patients' pressure that originated from patients' knowledge about this side effect of ACEIs acquired from friends, media or the drug's leaflet is another potential source of over-switching patients from ACEIs to ARBs. Patients' knowledge could produce negative perceptions about ACEIs, which may affect the actual prevalence and diagnosis of the ACEIs-induced cough.

> *"You can think of lots of reasons. I'm guessing though, this is a wild thing, if you tell people that there is a possible side effect of a cough and you write it in the drug sheet, there are people that will come back with that cough, whether they're even taking the tablet or not. Statins is a great example of that isn't it? 'I've got these muscle aches, doctor, they started since the statins', 'you only started it yesterday', 'oh, but it's definitely that, doctor',*

you know, because they've read it and they've heard it in the paper so they'll have it. So there's a percentage of people that will have the side effect, no matter what you say – because they have all the side effects for everything."

(52-year-old, male, salaried GP)

"Patient factors could be things like they haven't actually got an ACE inhibitor cough, they just happen to have a bit of a cough but they've heard about the ACE inhibitor cough and so they don't ever want to be on this hideous ACE inhibitor drug."

(37-year-old, male, salaried GP)

"Well I think it's going to be because we mainly use these drugs for heart failure for hypertension and patients get side effects on ACE inhibitors. Over a period of time, you will often see people with irritable cough and whether it's all due to the ACE or not – a lot of the time we will see people with irritable cough because of coughs and colds and viruses. We often see them because they're getting reflux, acid reflux symptoms and then the question is well, is it acid reflux symptoms or is it the ACE inhibitors? You're going to swap but two-thirds of hypertension is driven by obesity. Obese people get reflux. We use loads and loads of PPIs on them. Part of that is irritable cough. But the other one of course with hypertension is that we use a lot of amlodipine. Something like 20, 25% of patients within a year of starting amlodipine will have reflux symptoms and again, a lot will get a bit of a cough and you end up swapping them. I think that's the main driver"

(50-year-old, male, partner GP)

"From a personal level I think because if somebody comes to the practice and the patient usually complains from cough and they've heard about that it's caused this cough then they really insist, they wouldn't leave the room without having to try to see how it goes with the cough, if the cough settles or whatever, they want to change straightaway. And also some of my colleagues or the doctors a patient comes with a cough and say 'oh it must be because of ramipril' we'll change that."

(43-year-old, male, locum GP)

6.6.8.2. GP-related factors

Most of the participants attributed the lower proportion of ACEIs to the preference of prescribing ARBs as first-line treatment by some other GPs. This preferential prescribing was regarded to be associated with pharmaceutical companies' heavy marketing of ARBs and GPs' positive views toward ARBs. Some participants also mentioned prescribing ARBs in secondary care also leading to the increase of ARBs prescribing in primary care, contributed possibly to the cost in secondary care.

> *"For various reasons, but sartans were very very heavily pushed by drug companies, by drug reps, a few years ago. There was significant incentivisation to practices, to prescribers from drug companies. And I do strongly believe a lot of people were started through that. I'm a big believer that certain groups of prescribers are more easily influenced as well. Nurse prescribers, pharmacy prescribers, people like that I think are more heavily influenced because they haven't got responsibility for the drug budgets necessarily."*
>
> *(49-year-old, male, partner GP)*

> *"I think sometimes it can be prescribing from secondary care although that is probably more likely for heart failure than that would be for hypertension. I think doctors are influenced by Drug Company advertising. I think you would be a fool if you thought that companies would spend the amount of sums they do if it didn't affect doctors' behaviour or prescriber behaviour."*
>
> *(52-year-old, female, salaried GP)*

> *"I know that ARBs over the years have been heavily marketed. And there is always a temptation to go for the easiest most effective option. We have been very target driven over the years in terms of our management of hypertension and the fewer visits here the fewer blood tests, the few appointments to discuss side effects the better in many ways and I suspect that ARBs have been seen as an easier option in that respect, which is probably why in general practice in general throughout the UK they tend to be prescribed more first line than one would hope."*

(43-year-old, male, salaried GP)

"Some of it [ARBs prescribing] of course is driven by hospital prescribing and things like Esomeprazole, virtually all the Esomeprazole in this practice was all started by hospital consultants. Why are they using it? I've no idea. It's totally unjustifiable for the amount of cost but I don't think hospital consultants are really anything like aware of the cost of the drugs as we are and they don't have it impacting upon when people don't go along and badger them and say 'look at the price of the drugs you're prescribing and the effects on the community.'"

(50-year-old, male, partner GP)

6.6.8.3. Patient preference and resistance to switching from ARBs to ACEIs

A small minority of participants pointed out patients' preference as another contributing factor for the higher proportion of ARBs users; thus, some patients prefer expensive, brand ARBs over cheaper ACEIs. It was also reported that moving patients from their preferred choice is hard and thus it would be difficult to switch ARBs users to ACEIs in the absence of any clinical reasons.

"When I have talked about changes [ARBs to ACEIs], some patients can be quite suspicious 'why are you changing this? Are you getting paid for doing this? You're only doing this to save money. Aren't I important? I pay my taxes, I want the more expensive drug', so there can be pressure from that side."

(37-year-old, male, salaried GP)

"I think a lot of guidelines don't really take into account the fact that most patients struggle with multiple comorbidities, that you're trying to discuss the options to the patient in a ten minute appointment, usually with other things and on top of that, patient preference probably plays a large proportion to what we do. A large proportion is perhaps expected in the guidelines so quite frequently patients will want a branded version rather than a generic

and it's very hard to move people away from that. I think with guidelines we're looking at numbers, whereas patients we see the people and it's someone sat opposite you and it's very hard to say no and follow a guideline to the T when a patient says 'I don't want that.'"

(32-year-old, male, partner GP)

6.7. Discussion

6.7.1. Key findings

This study revealed several influences on GPs' prescribing of antihypertensive drugs, including ACEIs/ARBs. Participants reported that their prescribing of ACEIs/ARBs was consistent with NICE guidelines in terms of prescribing ACEIs as first-line therapy. This may be encouraging for the future uptake of the first part of the BCBV indicator. However, the second BCBV component of switching established ARBs to ACEIs appears to be challenging as most participants were reluctant to switch patients from ARBs to ACEIs in the absence of any clinical reason (i.e., non-medical switching).

Participants frequently switched patients from ACEIs to ARBs, largely due to ACEIs-associated cough. However, over-switching of ACEIs to ARBs could potentially have contributed to the lower ACEIs prescription proportion reported here. Additionally, factors influencing GPs prescribing behaviour and patients' preference, such as pharmaceutical companies' heavy marketing of ARBs, may also contribute to the low ACEIs prescription proportion. Although participants had positive views on prescribing indicators, including BCBV, they suggested the ineffectiveness of the BCBV policy may be related to the policy uptake and implementation, potentially due to barriers including lack of GP awareness and lack of incentives. Furthermore, participants suggested potential strategies to improve the future uptake and effectiveness of the BCBV indicator such as enhancing GPs' awareness of the policy and linking the policy to financial incentives.

6.7.2. GPs' experience and factors influencing their prescribing of antihypertensive drugs

The study findings indicated that prescribing decision-making is a complex and multifactorial process as several influential factors were reported to affect

prescribing decisions. This finding is consistent with results from other studies [70, 429]. In addition, the prescribing decision usually involves an interaction among many factors, including drug-related factors (efficacy, safety, cost) and patient-related factors (adherence, patient demand and preference)[429]. The National Audit Office (NAO) reported more than 15 influential factors on GPs' prescribing decision, that included guidelines, peer pressure, patients, drug companies and various other information sources[70]. Therefore, it is not surprising that a single prescribing policy such as the BCBV indicator often fails to influence prescribing behaviour, but rather multiple measures and a combination of policies would be required to effectively alter GPs' prescribing habits as discussed in Chapter 2.

Most participants prioritised drugs' efficacy and safety profiles over cost and adopted a patient-centred care approach. Participants considered the patient to be at the core of their decision and believed that prescribing a drug that patients may not take or take inappropriately as "cost-ineffective" prescribing. Prioritisation of drugs' efficacy and safety over its cost and adoption of a patient-centred care approach were found consistently with results demonstrated in a systematic review of 28 studies, primarily in the UK, to explore the influence of drugs' cost on prescribing behaviours and uptake of new medicines[51]. Furthermore, Prosser and Walley (2005)[430] conducted a focused group and in-depth interviews with GPs and stakeholders in the UK to explore their views on the importance and influence of cost on prescribing and found that GPs often considered cost but only secondary to clinical efficacy and safety, whereas patients' needs were prioritised over cost.

The extent of considering cost by GPs in their prescribing decision appeared to be dependent on their level of cost awareness, even though cost-awareness might not be translated into GPs' prescribing decision. GPs who are involved in organisational roles such as prescribing lead appeared to be more aware of the cost implication of

their prescribing to the NHS compared with those who are not involved in any organisational role. The cost-conscious GPs prescribed for individual patient's benefits but also considered the cost element.

6.7.3. GPs' experience and views on prescribing ACEIs and ARBs

Participants' prescribing of ACEIs/ARBs was reported to be in accordance with NICE guidelines in terms of prescribing ACEIs as first-line treatment. ACEIs were perceived to have more evidence base, especially in treating patients with HF and diabetes, in line with NICE guidelines for treating HF[110] and diabetes[36, 37]. Most participants expressed their preference of prescribing ACEIs over ARBs as first-line treatment for hypertension due to their beliefs on the stronger evidence for ACEIs. In fact, the stronger evidence for ACEIs was concluded recently by a Cochrane systematic review group[124], which found evidence for the effectiveness of only ACEIs, but not ARBs, on total and cardiovascular mortality compared with placebo. However, the NICE guidelines for treating hypertension[91] regarded both ACEIs and ARBs equivalent in terms of their effects on clinical outcomes and recommended either ACEIs or a low-cost generic ARBs as first-line treatment in patients aged <55 years.

It is worth mentioning that one participant preferred to prescribe ARBs as first-line treatment for hypertension due to the better safety profile (no incidence of dry cough) and loss of cost differential between ACEIs and ARBs. This view matches the suggestion from McInnes (2013)[178]; however, ARBs' better tolerability profile should be weighed against its weaker evidence for effectiveness in treating hypertension compared with ACEIs[124]. In addition, GPs might prescribe ARBs as first-line treatment under the influence of a consultant or specialist doctor, an important influencing factor on GPs' prescribing decision. GPs interviewed seemed

reluctant to challenge a consultant's prescribing decision[51, 68, 431], due to the beliefs that consultants have a higher level of knowledge.

6.7.4. GPs' views on switching patients between ACEIs and ARBs

6.7.4.1. Switching patients from ACEIs to ARBs

The majority of the study participants reported switching patients from ACEIs to ARBs frequently, primarily due to ACEIs-associated dry cough. Only a minority of participants switched patients to other antihypertensive drugs instead of ARBs due to an awareness of ARBs' higher cost.

Most participants estimated the incidence of the dry cough associated with ACEIs to be around 10–20%, although a higher incidence rate of 30–40% was also reported. These rates were higher than that reported in a clinical trial (10%)[132], but comparable with results from other observational studies. In practice, the incidence of ACEIs-associated dry cough has been reported as high as 25% in a selected population, in particular those who were prescribed high doses of ACEIs for treating heart failure[432].

6.7.4.2. Reasons why the national value of ACEIs prescription proportion is lower than expected

The national value of ACEIs prescription proportion (70.1%) in June 2014[179] seems to contradict participants' practice of prescribing ACEIs over ARBs as first-line treatment and switching patients who are intolerant to ACEIs-associated dry cough (10–20%). One plausible reason could be due to frequently switching patients from using ACEIs to ARBs; in fact, two of the three reasons potentially contributing to the higher proportion of ARB users reported by the participants were related to over-switching of patients from ACEIs to ARBs.

Difficulties and misdiagnosis of ACEIs-associated dry cough by GPs has also been reported by another study as it may be the main factor for the link with over-switching[433]. The ACEIs-associated dry cough is usually resolved within 1–4 weeks after stopping ACEIs, although the cough may take up to three months in some patient groups to be resolved[434]. GPs may straightaway switch any patients who are on ACEIs and present with a dry cough to ARBs before confirming the cause of the cough due to GPs' limited time and resources[68, 430]. Poor and/or loss of blood pressure control during the ACEIs discontinuation period may increase the risk of cardiovascular events[185].

Avoidance of possible clinic visits from patients complaining of ACEIs-associated cough and hence saving the NHS money was one of the reasons for some participants to justify their preference of initiating patients on ARBs as first-line treatment. Other studies have also demonstrated that drugs' characteristics, in particular drugs' safety profile, affect GPs' prescribing behaviours[51] and this is largely applied to ARBs' better tolerability profile compared with ACEIs in terms of incidence of dry cough. In another study[435], some participants' personal views on the better effectiveness of ARBs in lowering blood pressure and promotional activities from pharmaceutical companies could also contribute to the use of ARBs.

In additional to the difficulties in diagnosing ACEIs-associated cough, participants also mentioned pressure from patients as another reason for over-switching patients from ACEIs to ARBs. Patients' knowledge and perceptions about ACEIs possible causing a dry cough may accelerate GPs' decisions on switching ACEIs to ARBs, regardless of whether or not the cough is associated with ACEIs. Patients' negative perceptions regarding the possible ACEIs-related cough may enhance their chance of developing the cough. The expectation of side effects by patients results in them experiencing those side effects is a well-recognised health phenomena –the nocebo

effect[218]. It has been reported that expectation of drugs' side effects can emphasise patients' attention on these symptoms leading to higher detection and reporting of these expected side effects[436], and this may partly explain the higher incidence of ACEIs-associated dry coughs in clinical practice compared with clinical trials.

Patients can get information about drugs' side effects from various sources including drugs leaflets, friends, media or directly from their GPs. Informing patients about the possible side effects of a prescribed medicine by their GPs during a consultation could substantially increase the number of patients who would experience those side effects[218, 436]. For instance, patients who were prescribed beta-blockers or a hair loss medication and being informed that they might experience sexual side effects were found to report these symptoms 3–4 times more frequently than those who were not told about these symptoms[437, 438]. Likewise, getting information about drugs' side effects from television news or the internet was also found to influence patients' experiences of those side effects. For example, the formulation of a widely used thyroid replacement hormone was changed in New Zealand prior to 2008 and this was covered in television news; subsequently, the frequency of reporting of the side effects mentioned in the news coverage increased more than those side effects that were not mentioned in the television news[439].

Participants also suggested that preference in the prescribing of ARBs by some other GPs was attributed to the effect of the promotional activities of pharmaceutical companies on those GPs. The influence of pharmaceutical companies on GPs' prescribing behaviour is well recognised and has been confirmed by many other studies, including systematic reviews[51, 70, 431, 435, 440], and is considered a key factor in explaining the uptake of new medicines, including ARBs[51, 435]. In a systematic review of 28 studies of factors affecting the prescribing of new medicines in primary

care[13], pharmaceutical company representatives were one of the key influencing factors in the uptake of new medicines. This finding was applicable both in the UK and internationally.

A study that examined the determinants of the adoption of ARBs by GPs in primary care in the Netherlands found that the variation in the adoption of ARBs among GPs was mainly due to the marketing efforts of pharmaceutical companies[38]. In fact, marketing by pharmaceutical companies was identified as the main explanatory variable for adopting ARBs by GPs in the Netherlands[435], with the adoption rate increasing as contacts of GPs with pharmaceutical representatives was increasing.

In the UK, the efforts of pharmaceutical companies can be clearly observed in the amount of money they spend annually on marketing activities. It has been reported that pharmaceutical companies spend more than £850 million a year on promotional and marketing activities in the UK[70], with ~8,000 pharmaceutical representatives visiting GPs and marketing their drugs across the country[441], through their contacts with GPs. In a questionnaire survey of 1000 GPs and 158 prescribing advisers in 2006 in the UK, conducted for the NAO, the results illustrated that 87% of the GP respondents reported to have contact with pharmaceutical representatives and that the majority of them saw representatives between once a week to once every three months[70].

Some participants also suggested that hospital doctors' preference in prescribing ARBs as first-line treatment is another contributing factor for the lower prescription proportion of ACEIs. Although one participant attributed the preference of ARBs' prescribing by hospital doctors to the lack of cost-consciousness and prescribing auditing, the exact reason is not clear.

In a qualitative interview of 23 UK hospital doctors about the factors affecting their prescribing of new drugs[442], four forms of knowledge including scientific, social, patient and experiential knowledge, were identified as determinants of prescribing new drugs. Interestingly, there was no reporting of drugs' cost as an influencing factor, which may suggest their lack of cost-consciousness and awareness of the cost implications of their prescribing on the community.

However, other factors influencing prescribing, such as promotions from pharmaceutical companies cannot be excluded, in particular, pharmaceutical companies were found to be influential on hospital doctors' prescribing behaviour in the UK[443]. The impact of hospital doctors' prescribing on the prescription proportion of ACEIs users in community may become more important as GPs often continue with the drugs prescribed by hospital doctors without challenging their decision[70]. In previous studies, hospital doctors reported their upset at GPs in switching their patients to a cheaper equivalent drug[444, 445].

Patients' preference of using ARBs is a possible contributing factor for deviating from prescribing recommendations and thus prescribing ARBs as first-line treatment. This concept of considering patients' choice and preference in GPs' clinical decisions, including prescribing decisions, has been re-emphasised by the principle of "no decision about me, without me" introduced by the King's Fund report[229], subsequently to the Department of Health's white paper[180], which promoted the concept of patients' choice. In the modern NHS, giving people more choice is a priority[227], and this based on evidence that shows better treatment effectiveness by enabling patients to choose, understand and control their care [182]. Although there are concerns about the cost implications of allowing patients' choice, given the finite resources within NHS[182], GPs, through their communications with patients, could possibly enhance patients' cost-consciousness and make them more

willing to accept GPs' prescribing decisions – including switching them from ARBs to ACEIs – which in turn would contribute to assuring efficient prescribing of ACEIs/ARBs.

6.7.4.3. Switching patients from ARBs to ACEIs

This study found an overall reluctance and unwillingness of GPs to switch patients for non-medical reasons primarily because patients' adherence might be negatively affected by switching and hence leading to poor clinical outcomes. Previous studies also found that patients were concerned about switching their medication for cost-saving purposes in the absence of clinical reasons[224], and these concerns could negatively affect patients' adherence and hence patients' clinical outcomes. It has also been found that changing drug packaging and/or tablets' appearance, as a result of the switching, often evoke confusion and anxiety in patients[2], which could have negative consequences on their health[3, 204, 221]. In a questionnaire asking patients about their views on therapeutic substitution in the USA[335], about 40% perceived the new drug as not as effective, 30% reported more side effects and 47% were unsatisfied with the switching process.

Patients' resistance to switch was also reported as one of the barriers for GPs' reluctance to switch patients to different treatments. The switching of ARBs to ACEIs involves both therapeutic switching as well as generic switching (switching from branded to generic product). Surveys of public and patient opinions indicated various views on both generic and therapeutic switching, with the latter being more contentious due to lack of evidence to support clinical equivalence of the newly switched-to drug[182].

In a survey (65% response rate) of 194 patients from a PCT in England, who had undergone generic switching in the previous 12 months, >90% of the respondents

were satisfied with their switching[224]. The authors highlighted that such a high satisfaction rate was expected because the switching did not involve changing the drug's active ingredient. From this, it could be predicted that such a high level of patient satisfaction would not be the case for therapeutic switching, as it involves changing of drug's active ingredient.

6.7.5. Barriers and facilitators for the effectiveness of the BCBV prescribing indicator

6.7.5.1. GPs' awareness of the BCBV policy

Given all the encouragement from the NHS to maximise cost-effective prescribing, which is crucial for the NHS to be able to provide the same quality of care with the limited available resources[222], it is rather surprising that almost all the study participants were unaware of this BCBV indicator, which aims to save NHS money while maintaining quality of care. The lack of awareness was not influenced either by participants' geographical area or level of cost-consciousness as even GPs with organisation role as prescribing lead were unaware of the policy. Participants contributed their unawareness of the policy to the poor advertisement and dissemination methods used to transfer and communicate the BCBV policy.

Lack of awareness is a well-known barrier for policy uptake. In a systematic review of 76 studies about the barriers for policy uptake, lack of GP awareness of the policy was considered one of the major barriers for the policy failure, given the expanding body of research which makes it hard for any GP to be aware of every guideline[446]. A survey of GPs found that about two-thirds of the respondents read less than half of the prescribing information they received in the previous year, with 40% reading less than a quarter, due to GPs' limited time to process all the materials received[70], which influenced GPs' prescribing decisions[68, 430].

Prioritisation among prescribing areas is a well-recognised operational approach, with the ability of most practices to focus only on two or three prescribing issues at any one time[70]. Some participants commented that the poor transferring mechanism of the policy could be related to the lack of priority in CCGs when compared against other areas of efficient prescribing, and this might lead to the lack of any local strategies to promote the policy's dissemination, uptake and implementation within CCGs. Therefore, it is evident that improving GPs' awareness of the policy should be the first step for promoting the uptake of the policy.

Participants showed their preference of adopting the policy locally (i.e., national guidelines in the local context) by a local prescribing committee or medicine management team; for example, being championed by a local peer colleague or advertising to individual GP practices. This local adoption would make the national policies less technical and clearer to follow by removing any ambiguities, prioritising, and/or removing some options according to the clinical needs for the local population and budgetary constraints of the CCG[70].

Participants also highlighted the important roles of automatic computerised systems in the uptake of the policy. Some participants attributed the success and uptake of QoF indicators to the effective and continual reminding system it involves. Prescribing supporting systems and reminders were perceived by GPs to play key roles in improving prescribing quality and efficiency. In a survey of primary care physicians' views in seven countries (UK, Australia, Canada, Germany, New Zealand, the Netherlands and USA) about their experience of the primary care's office system, the use of reminding tools and decision-support systems, which alert and prompt GPs, were viewed as essential elements for providing high quality and efficient care management[447]. In another study[435], which aimed to identify the determinants for the adoption of ARBs by GPs in the Netherlands, a negative

association was found between the use of a prescribing decision-support system and the adoption of ARBs, which highlights the important role of such a system in improving efficient prescribing of ACEIs/ARBs.

6.7.5.2. Linking the BCBV indicator to financial incentives

The lack of financial incentives was also reported as one of the important barriers to the policy's uptake and effectiveness. However, there were variations in participants' views on the roles of financial invectives in promoting the policy uptake. The discrepancy seems to be related to GPs' employment type, i.e., whether the incentives affect GPs' income or not. Partner GPs supported incentivising GPs, likely because their income is affected substantially by incentives through achieving certain quality and prescribing targets; whereas the salaried GPs disliked the notion as their income is not affected by such incentives. A case study reported by the UK NAO[70] found that financial incentives provided for achieving four prescribing targets have motivated improvement in the value for money in prescribing in two PCTs in England. A survey of GPs published by the UK NOA[443] showed that three-quarters of the participants reported that financial incentives to achieve efficient prescribing incentivised them to stay within their prescribing budgets.

It is evident that a single policy or initiative, such as BCBV indicator, would often fail to achieve any marked change in GPs' prescribing behaviour[25, 32, 59, 67, 448], given the complexity of the prescribing process. In a meta-review of 12 systematic reviews of factors influencing clinical guideline implementation[421], the authors concluded that effective policies often possess multiple components and policies with multiple components appeared to be more effective than a single component policy. The linking of policies to financial incentives is one of the well-recognised approaches to enhance policy uptake and effectiveness[22, 25, 449]. In many European countries (Austria, Croatia, Austria, Serbia, Scotland, Sweden and Spain), it has been found

that multiple intensive policies, such as combination of prescribing guidance, prescribing targets and financial incentives, was mostly required to maximise prescribing efficiency, including ACEIs/ARBs[35, 63, 151, 449]. On the other hand, countries, such as Portugal, with limited policies, failed to obtain efficient prescribing of ACEIs/ARBs[32, 63].

As an alternative to linking the policy with financial incentives, some participants suggested other potential strategies including GPs' education, through academic detailing, and benchmarking of the policy's target among GP practices. Benchmarking usually involves the comparison of the prescribing indicator among GP practices, and subsequently, those GP practices whose prescribing pattern differs from their local colleagues might change their prescribing behaviour positively, and adopt more mainstream prescribing practice to improve their prescribing efficiency under the increased peer pressure[450].

A survey of factors influencing GPs' prescribing decision among 1000 GPs in England indicated that comparison of prescribing patterns among practices was an effective method to positively affect GPs' prescribing behaviour as a result of the increased pressure on practices[70]. Furthermore, in a survey of 158 prescribing advisers across England, the respondents ranked benchmarking of prescribing patterns among GP practices as the fourth best approach to influence prescribing behaviour of GPs[70]. Therefore, benchmarking could be an alternative option to financial incentives to promote the uptake of the policy.

6.7.5.3. GPs' views on guidelines and prescribing indicators

Although participants initially expressed their positive views about the underlying theory of the prescribing indicator, their resistance to follow those indicators appeared to outweigh these positive views when it came to clinical practice.

Prescribing indicators, including BCBV, were perceived as reducing prescribing autonomy, not flexible to fit individual patients, lacking authorship credibility, cost-oriented and being non-sustainable with short-term focus. These findings are consistent with those barriers for guidelines' non-adherence identified from international studies[419, 451].

The lack of GPs' agreement with guidelines due to their impracticality, reducing GPs' autonomy and lack of credible authors, are well-known barriers for guideline non-adherence and uptake as they negatively affect GPs' attitudes toward guidelines[446, 452]. In a survey of 300 USA paediatricians about their attitudes and awareness of four clinical guidelines[453], reducing doctors' prescribing autonomy and hence promotion of 'cookbook medicine' was one of the most commonly reported barriers for guidelines' uptake. Authors of guidelines were found to influence their credibility. GPs' acceptance is higher with guidelines issued by peers or those developed and approved by a local medical committee[419, 454]. In a recent systematic review of 278 studies[455] to identify factors associated with uptake and implementation of guidelines, one factor identified as a potential determinant for guidelines' uptake was credibility of guidelines, and it was found that involving a range of stakeholders and experts in developing guidelines or indicators promoted their implementation.

Furthermore, it was reported that GPs often dislike cost-oriented prescribing indicators as they were perceived to have no face validity regardless of whether they are based on patient or practice level data[429, 456]. This study finding is in agreement with literature in that cost-oriented policies were considered by GPs to be of short-term focus and they were disinclined to undertake systematic switching unless sustainable and substantial financial benefits were maintained[430]. Moreover, GPs expressed their resistance to adhere to cost-oriented policies unless evidence

for quality assurance was provided[430]. Therefore, to improve the uptake of the BCBV indicator, it is important to adopt measures that decrease GPs' resistance to the policy, such as local adoption of the policy by the local prescribing committee and/or providing GPs with quality assurance.

6.7.5.4. GPs' reluctance to switch established ARBs users

This study also revealed the issue of balancing the relatively long time required to explain the switching for the patient against the financial gain; unless a strong clinical reason is present, GPs are still reluctant to switch drugs. In qualitative interviews of 21 UK GPs' perceptions on patients' influence on their prescribing[457], it was also found that GPs' strategy and willingness to change people's medications were explained in terms of the necessity to balance the required time between explaining and discussing the changes against the cost difference and hence cost gain between the original and generic medicine.

Since switching established ARB users to ACEIs is an important component for succeeding the BCBV indicator, participants' resistance and reluctance to switch established ARBs users could be considered an important potential barrier for the effectiveness of the BCBV policy. Therefore, appropriate measures would be required to alter GPs' reluctance and negative perceptions about switching established ARB users to ACEIs, which would potentially improve the uptake and effectiveness of BCBV indicator.

This study identified several strategies that could facilitate or motivate GPs to switch ARBs, including the provision of support from other healthcare professionals, improvement of GP-patient communication and providing GPs with guidance on how to perform the switching. The technical and scientific support from other healthcare professionals, such as pharmacists, to simplify the switching process

and decrease the workloads of GPs by screening and identifying eligible patients for the switching, for instance, was regarded as an effective approach to facilitate and encourage switching patients from ARBs to ACEIs. The effectiveness of this approach has been proven in two PCTs in England in 2005–2006 (the New Forest PCT, and Eastleigh and Test Valley South PCT), where dedicated pharmacist support was provided for each of 38 PCT practices via eight full-time employed pharmaceutical supports who assisted with the PCTs' medicine management policy[70]. The two PCTs spent about £400,000 on the appointed pharmacist, and in return, they created a saving of more than £1.1 million by supporting practices to prescribe efficiently as well as improving patients' compliance with medication. Furthermore, it was also found that providing administrative support also encouraged GPs' participation in medication switching as it played a role in decreasing the workload required to switch the patient.

Prescribing support could also be given by prescribing advisers from the prescribing committee. Previous literature has shown that prescribing advisers strongly influence GPs' prescribing[450], although the methods used at local levels to positively change GPs' prescribing were not entirely clear.

Prescribing advisers were also found to have influential roles in reinforcing the implementation of national guidelines[51]. The influence of prescribing advisers on GPs' prescribing habits has also been found in a survey of 1000 GPs across England[70]; in fact, about two-thirds of the respondents perceived prescribing advisers to be more influential than pharmaceutical companies in changing their prescribing behaviour.

Prescribing committees, which often involve representatives of various healthcare sectors, were also considered effective in improving efficient use of medicines

through the development of local prescribing policies and encouragement of GP practices to comply with those policies[70]. In a case study published by the UK NAO about prescribing costs in primary care[70], the prescribing committee in New Forest and Eastleigh and Test Valley South PCTs developed a formulary for use in hospitals and GP practices and they were monitoring practices' prescribing patterns. This action has encouraged GPs to follow the guidance on efficient prescribing, as it required the involvement of a senior PCT leader in medicine management. Therefore, it is possible for a prescribing committee to develop local strategies to increase the uptake of the BCBV indicator. This local adoption of strategies indeed is consistent with what our study participants suggested to increase their awareness of the policy as described in section 6.7.5.1.

Participants reported that patients' response and acceptance of the switching were determined by GPs' communication method with the patients, in terms of explaining the rationale for the switching decision, and patients' level of cost-consciousness. Furthermore, explaining the switching rationale from clinical and best evidence perspectives would improve patients' acceptance of the switching compared with explaining it in fiscal terms. A qualitative study that explored pharmacists' and patients' perceptions on one of the BCBV indicators for lipid modifying medication (switching from atorvastatin to simvastatin) in a PCT in England[222], found that patients' views on the switching varied based on how they were informed about the switching. Patients often accepted the switching when it was explained in terms of evidence base rather than because of guideline recommendations and even fewer accepted the switching because of saving money. These results are consistent with the findings in this study.

Patients' dissatisfaction with medication switching was found to be associated with communication about the switching rather than the switching itself[458]. Consistently,

Stevenson *et al*[457] pointed out that to improve patients' acceptance of the switching, GPs usually tend to avoid explaining and discussing the switching in financial terms; alternatively, they explain it in other terms such efficacy.

To engage patients with the switching decision, the methods used to inform and communicate the decision to patients was also regarded as an important factor. It appears that most practices send letters to inform patients about their medication changes as a way of communication, which often included the opportunity of contacting their healthcare professionals to discuss the changes if they wanted[183, 222, 224, 237]. Participants preferred communicating the switching rationale and decision via methods that include better patient involvement. Indeed, patient involvement is an essential component of any successful medication switching. Research evidence has demonstrated an increase in patients' acceptance of switching by informing patients about the switching through better communication with their GPs[459].

The UK Department of Health's guidelines[230] for PCTs and CCGs in 2010 suggested strategies to achieve cost-effective prescribing, including therapeutic switching, by informing and involving patients in the switching process. Patient involvement is one of the essential principles for any local strategy, and patients should be given the opportunity to discuss the switching decision.

Although the guidelines recommended the development of local standard operating procedures by each PCT, they did not specify a preferred way of communication with patients for their involvement in the switching process. However, in a survey of 248 patients' views and experiences on therapeutic switching of atorvastatin to simvastatin in the UK[29], more than half (53%) were unhappy with sending letters as a method of communicating the switching, rather, they preferred face-to-face consultation, which assures better involvement of patients. In contrast, a survey of

194 patients in the UK to evaluate patients' satisfaction with generic medication switching[25] found that 88% of respondents agreed with sending a letter as the most appropriate way of informing them of the switch.

Although it may not be possible to completely explain this contradiction between the two studies, each evaluated two different types of switching, i.e., therapeutic switching in the first study[29] versus generic switching in the second[25]. As therapeutic switching is considered more contentious[182], it is possible that patients included in the first study[29] were more concerned about their switching and medication change, and needed further clarification and discussion with their healthcare professionals, as the change involved changing of their drugs' active ingredient. This is indicated by the fact that 24% of the respondents were unhappy with the switching[29]. However, those in the second study[25] may have had less concerns about the change as it did not involve changing the active ingredient but only a change from branded to generic; subsequently, perhaps they did not feel the necessity for further clarification, which is indicated by the fact that 83% agreed with the principle of generic switching in this study[25]. This explanation is plausible in the UK context since generic substitution by pharmacists is standard practice in UK hospitals[182], with more than 83% of the prescribed prescriptions being for generics in England in 2013[460].

Arguably, given the number of eligible patients for switching, offering face-to-face consultation with GPs to all the eligible patients to discuss the switching decisions would likely have significant time and cost implications. Therefore, some other mechanisms of communications might be required. One possible option is to involve community pharmacists, who can explain the reasons for switching at the time of dispensing, provided that the practice has fully informed them in advance about the switching; this option has been studied as an alternative option for communicating

switching[222]. However, further studies are needed to prove the effectiveness of this approach.

Involving patients in their healthcare decisions, including prescribing, has been re-emphasised by the principle of "no decision about me, without me", introduced by the King's Fund report[229], and subsequently to the Department of Health's white paper[180], which promotes the concept of patients' choice. In the modern NHS, 'giving people more choice' is a priority[227] and this is based on evidence that better treatment effectiveness can be achieved by enabling patients to choose, understand and control their care[182]. Although there are concerns about the cost implications of allowing patients' choice, explanations on GPs' prescribing decision in terms of efficacy and appropriateness would hopefully moderate patients' concerns about medication switching, and thus positively influence patients' responses.

The final suggested strategy to facilitate patients switching from ARBs to ACEIs was providing guidance to GPs on how to implement the switching in terms of dosage equivalence and patients' eligibility. This view reflects the current situation where there is no central guidance or any officially published evidence-base guidance on switching from ARBs to ACEIs and the information about this is rather poor[3, 183], apart from some guidance provided by some local health authorities about dose equivalence to ensure the maintenance of blood pressure control after the switching[161].

In general, it has been reported that during therapeutic switching of antihypertensive medications, e.g., switching ARBs to ACEIs, the new drug is likely to be administered at low dose then increased gradually[3], due to the lack of clear guidance on the switching and inter-patient variation in response to different antihypertensive drug classes[461]. Subsequently, switching medicines could lead to

delay in regaining blood pressure control, which could negatively affect patients' clinical outcomes, especially those who are at high cardiovascular risk[3]. Therefore, based on these facts, it appears that it is important to have clear guidance about ARBs switching to ACEIs to encourage GPs' engagement with the switching.

6.7.5.5. Scepticism about the BCBV proposed 80% target

All participants viewed the 80% target as an easily achievable target based on the most commonly reported 10–20% incidence rate of the ACEIs-associated dry cough, despite one participant expressing doubts about the achievability of the proposed 80% target. This interviewee believed that side effects other than a dry cough or even some clinical conditions may affect patients' switching to ARBs or initiating ARBs instead of ACEIs. However, this is unlikely to be a barrier for the policy's effectiveness given the lower documented rate of ACEIs-associated dry cough from clinical trials and observation studies[132], 10% and 2%, respectively.

6.7.6. Strengths and limitations of the current study

This study employed a qualitative design to explore and answer different types of questions, which quantitative approaches could not answer. The purposive sampling strategy used in this study ensured and provided a diversity of the study participants in terms of their demographic characteristics, including age, gender and employment type, work experience and ethnicity. This diversity provided the opportunity to explore the research questions from participants with various characteristics, which helped to give a more complete understanding of the study topic. Furthermore, the participants were sampled from three different geographical areas, giving the opportunity of wider insight into GPs' views from various organisational perspectives.

By interviewing GPs who are the primary responsible personnel involved in the policy adoption and uptake, it was possible to explore the most current issues surrounding the BCBV policy from a relevant and practical point. Moreover, all the interviews were conducted by the same researcher, which ensured a modicum of comparability in the interview style. Although it is usually challenging to recruit GPs into qualitative studies, using multiple recruitment strategies enabled the recruitment of enough GPs across the three study areas.

However, there are a number of limitations that need to be acknowledged in this study. The GPs who were interviewed may represent a biased sample of engaged and interested GPs in treating hypertension, and thus their views may be different from GPs who did not participate. Furthermore, it is also possible that those who were interviewed were more engaged in research and policy, so their prescribing was in accordance with guideline recommendations, but this may not bias the reporting of barriers for the policy's failure. A general limitation inherent to qualitative interviews was the inability to assure whether the study participants were telling the truth. However, almost all the reported views and perceptions in this study were supported and in agreement with findings from other studies on similar topics. Although speculating views on how other GPs would behave were also reported, participants' views reflected their real opinions. It would have been better if prescribing advisers had been interviewed, but none of them in all the three study areas agreed to participate. Even though understanding the views and perceptions of GPs, who are primarily involved in the adoption and implementation of the policy, has likely provided insights into the subject, prescribing advisers are likely to have different perspectives to GPs and hence it is recommended to explore their views in future studies.

6.7.7. Conclusions

The study interviews revealed four main possible reasons for the policy failure that were mostly related to poor uptake and implementation of the policy, despite participants' overall positive views on the principles underpinning the prescribing indicators.

In addition, other factors were also found to counteract the policy's aim of increasing the proportion of ACEIs prescriptions, including over-switching of patients from ACEIs to ARBs due to dry cough potentially attributed to ACEIs. Given the lack of a specific diagnostic test, there was a relatively higher incidence rate of ACEIs-associated cough reported in this study that could be partly related to patients' negative expectations about ACEIs side effects and nocebo effect. GPs would directly switch ACEIs users with dry cough to ARBs to avoid the potential follow-up visits and the possibility of losing BP control that could result from a trial period of stopping ACEIs, which is required to confirm the ACEIs-associated dry cough.

Initiating new patients on ARBs as first-line treatment instead of ACEIs was one of the potential reasons for the lower prescription proportion of ACEIs. Promotional efforts from pharmaceutical companies were the primary factor for GPs' preference prescribing of ARBs as first-line treatment. However, since the majority of study participants reported their preference of prescribing ACEIs as first-line treatment in accordance with recommendations, it is most likely that over-switching of patients from ACEIs to ARBs rather than initiating new patients on ARBs is the potential responsible factor for the relatively low proportion of ACEIs prescriptions compared with the proposed target of 80%.

Effective advertising and disseminating strategies are considered crucial to increase GPs' awareness of the policy, which can be achieved through local adoption of the

policy by local organisations such as medicine management teams. The local organisations then can develop local strategies to enhance the uptake and implementation of the policy. Given the complex nature of the prescribing process, combining prescribing policy with additional measures is often required to effectively alter GPs' prescribing behaviours.

Therefore, combining the BCBV indicator with other measures, such as financial incentives and benchmarking, was perceived crucial to increase the policy uptake. Since both actions of initiating new patients on ACEIs and switching established ARBs users to ACEIs are required for the policy's effectiveness, measures to encourage GPs' engagement with ARBs switching are imperative for the policy to be successful.

Given GPs' existing heavy workload and limited time, provision of support from other healthcare professionals, such as pharmacists, was viewed important to facilitate patients' switching from ARBs. Furthermore, enhancing patients' involvement in the switching decision through offering better methods of communicating the switching, such as face-to-face consultation, and appropriate explanation of switching rationale were also perceived to improve patients' acceptance and response to the switching decision. Finally, participants also perceived the availability of guidance on how to perform the switching important to facilitate the switching. Although the issue of over-switching might not have directly contributed to the policy failure, developing strategies to overcome this issue is necessary to augment and support the BCBV policy.

The findings of this study have a number of important implications for future practice. Through understanding of the barriers for the policy failure and the subsequent possible suggested solutions, it is possible to not only improve the

future effectiveness of the BCBV policy but also provide lessons on how to improve the uptake and implementation of other health policies, including prescribing policies in particular.

Chapter 7. General discussion and implications of the findings

This chapter discusses the key results emerged from both quantitative and qualitative research approaches and the implications to policy, clinical practice, and future research based on the reflections and the generalisability of study results.

7.1. Summary of the key findings

7.1.1. Poor policy uptake and implementation underpinning the ineffectiveness of the BCBV indicator

Inappropriate policy implementation and uptake were hypothesised as the most likely reasons for the ineffectiveness of the BCBV indicator in improving the prescribing efficiency of ACEIs/ARBs (Chapter 3) and this hypothesis was later corroborated by the results from the qualitative interviews.

Four main barriers were pointed out by the study participants as potential reasons for the ineffectiveness of the BCBV policy (Chapter 6), including lack of GPs' awareness, lack of incentives and GPs' reluctance of switching established ARBs users and all of them are related to implementation of the policy and demonstrated a lack of potential, central strategies for implementing the policy.

The mostly likely reason for the ineffectiveness of the BCBV indicator appeared to be related to issues of the policy's second component (switching established ARBs users to ACEIs) rather than the policy's first component (initiating new patients on ACEIs) since most GPs prescribed ACEIs as the first line treatment; whereas they were reluctant to switch established ARBs users to ACEIs, especially in the presence of over-switching of ACEIs to ARBs due to doubts about ACEIs-induced dry cough (Chapter 6).

Switching established ARBs users to ACEIs is one of the important components to implement the BCBV indicator. It is, therefore, unsurprised that GPs' reluctance to switch ARBs is one of the potential barriers for the ineffectiveness of the BCBV indicator as GPs were concerned that switching could compromise patients' quality of care through impeding patients' adherence, especially with ACEIs, as unlike ARBs, could induce a dry cough. Indeed, this may reflect the known issue of post-switching reduction in patients' adherence following the switching of antihypertensive drugs that has been observed in several studies[200-202, 348]. Given the potential clinical and economic issues associated with switching of antihypertensive drugs, patients' negative perceptions of switching, and the necessity of patients' involvement in the prescribing decision in the UK (Chapter 2, section 2.9.4.1, page 50), it may be reasonable for GPs to resist switching patients from ARBs to ACEIs if it is clinically non-justifiable and for cost-saving purposes.. This indicates that switching for cost-containment purpose is difficult and challenging in clinical practice, which has been demonstrated in other studies[182, 462] as well.

7.1.2. Switching ARBs to ACEIs is a cost-saving strategy, without compromising patients' quality of care

Despite switching appears to be practically difficult and challenging, it is still possible and may be necessary for a wide range of medical and non-medical reasons such as intolerance, treatment failure, development of comorbid conditions and/or cost-saving purposes[283, 375];. In fact, this was shown in the current study (Chapter 4) as about 26% of the study cohort switched their antihypertensive drug class. However, only 5% of the switchers were switched from ARBs (Chapter 5). This low switching rate in ARBs users was rather expected since ARBs drug class was the most significant factor against switching of antihypertensive drugs in comparison with the other identified factors, as it

was associated with 41% reduction in the likelihood of switching antihypertensive drug classes (Chapter 4) and this finding was consistent with those of many other studies that found the lowest switching rate with ARBs use compared with other antihypertensive drug classes[211, 217, 341].

Switching might not necessarily and always be associated with worsening of patient clinical outcomes. Prior to this PhD study, it was unknown whether the issues that associated with switching in general would be applicable to patients' switching from ARBs to ACEIs, especially in UK settings, due to a lack of studies that specifically evaluated patients switching from ARBs to ACEIs. There are reasonable factors to hypothesise that switching patients from ARBs to ACEIs in the UK is unlikely to be associated with such clinical and cost issues (Chapter 5). Importantly, this thesis has indicated a non-association of ARBs switching to ACEIs with any deterioration of patient's clinical outcomes but rather resulted in an overall cost saving in total medical cost.

Interestingly, the findings from the qualitative interviews also supported the factors that were hypothesised to account for the non-association of ARBs switching with clinical and cost issues in the UK. Almost all the study participants expressed their preference toward prescribing ACEIs over ARBs as they viewed ACEIs to have stronger evidence for their efficacy with a similar safety profile to ARBs. This perceived superiority of ACEIs over ARBs would have contributed to maintaining the same clinical treatment efficacy post-switching. Furthermore, the qualitative data suggested that GPs would most likely involve patients in the switching decision and discuss the rationale for the switching with them, and then would perform the switching only in those patients who accepted the switching decision. This action of involving patients in the prescribing

decision may have played a role in overcoming patients' confusion and negative attitudes toward the switching and thus contributed to maintaining patients' adherence post-switching.

7.1.3. Strategies to improve the future effectiveness of the BCBV indicator

In the GP interviews, the participants suggested several measures to potentially enhance the future effectiveness of the BCBV indicator, building on the reported barriers for the policy failure, including effective dissemination strategies and linking the policy to financial incentives.

Effective dissemination strategies are crucial for improving the uptake of a policy. A systematic meta-review of 33 systematic reviews to evaluate the effectiveness of various implementation strategies in the uptake of guidelines[463], found that passive dissemination strategies, such as posting the guideline on a website or sending a printed version to GPs, were ineffective in promoting the uptake of policies. Therefore, more effective dissemination strategies such as active involvement of GPs and the local adoption of the policy by local organisational committees would be required to create awareness among GPs[421]. However, it has been suggested that awareness alone is not sufficient for the uptake and implementation of guidelines or policies[464]. Therefore, an effective dissemination strategy to improve GPs' awareness of the policy should be combined with other strategies such as a reminder tool loaded in GPs' computer systems to continually alert them whenever they attempt to prescribe ACEIs/ARBs – as suggested by some participants in this study. Computer-based reminders and decision-support systems have been consistently shown to be effective in improving guideline uptake and implementation[463].

Furthermore, linking the policy to financial incentives was also a suggested strategy to motivate and promote GPs to implement the policy and achieve the proposed policy target of 80% ACEIs, building on the experiences from the QoF programme, even though financial incentives might be associated with negative consequences alongside its positive impact on the policy uptake The linking could be in the form of allocating drug budgets to GPs or, as in QoF, it could be a performance-based system with financial rewards for GPs achieving the 80% ACEIs policy target. Incentive schemes and allocation of drug budgets to GPs have been proposed as an effective strategy to influence GPs' prescribing behaviour and increase the cost-effectiveness of prescribing[35, 465]. Furthermore, financial incentives have been shown to reduce healthcare resources use, and improve adherence with practice guidelines or achieve certain health targets[449]. In Sweden, financial incentives schemes – ranging from financial rewards linked to a certain targets to drug budgets – were introduced to increase GPs' adherence to regional guidelines to improve quality and efficiency of prescribing[449]. The incentive schemes significantly increased GPs' adherence to the regional guidelines, which in turn achieved a significant cost saving that, was five times greater than the cost of implementing the programme.

Although the effectiveness of financial incentives in improving the efficiency and quality of prescribing has been shown in several studies[48, 49, 52, 53, 466, 467], their impact can be short lived[468], with their long-term effects on quality of care being less well researched. Concerns have been reported about the potential negative impact of financial incentives on quality of care and the patient–GPs relationship[50]. In a systematic review of seven studies to evaluate the effect of financial incentives on the provided quality of care[469], no conclusive evidence was found on the impact of financial incentives on

quality of care, even though six of the seven included studies demonstrated a positive but moderate effect on quality of care for some but not all primary outcome measures.

However, risks of negative consequences of linking the BCBV indicator with financial incentives could be considered low given the clinical equivalence of ACEIs and ARBs in terms of treating hypertension and cardiovascular morbidity and mortality[132, 134]. Furthermore, the proposed target for the policy requires only 80% of total ACEIs plus ARBs prescriptions to be for ACEIs, thereby leaving enough flexibility for GPs to preserve their autonomy and deviate from the indicator when necessary.

Finally, to encourage GPs to switch established ARBs users to ACEIs, when appropriate, requires support from other members of healthcare professionals – such as pharmacists, provision of guidance on how to implement the switching, and improving their communication methods with patients. Including pharmacists and other administrative support in the switching programme is likely to simplify the process and support GPs in performing the switching, which has shown its effectiveness in a case study of two PCTs in England[70] (Chapter 6, section 6.7.5.4). It is also necessary to encourage GPs to explain the rationale of their switching decision in terms of evidence base and clinical appropriateness rather than in monetary terms to enhance patients' acceptance of the switching[222]. As patients are thought to prefer face-to-face consultations for communicating the switching over sending letters[222], potentially other healthcare professionals – such as pharmacists – should perform these consultations as a cheaper alternative than GPs[222], as suggested by one of the study participants here.

Although over-switching of patients from ACEIs to ARBs, due to suspected ACEIs-associated cough, was not directly reported by the study participants as a barrier for the effectiveness of the BCBV policy, it is clear that it would have affected the policy's effectiveness indirectly by counteracting the policy's effect through increasing the proportion of ARBs users. Therefore, in addition to the suggested strategies to increase the future effectiveness of the BCBV policy, it is necessary to adopt measures to tackle this issue of over-switching in order to get the optimum efficiency in ACEIs/ARBs prescribing.

Although the study participants proposed multiple potential strategies to increase the future uptake and effectiveness of the BCBV policy, they neither indicated their preference of a particular strategy nor which strategy would be the most effective one. Therefore, from the current study findings, it is not possible to clearly indicate and recommend one particular strategy in favour of the others. However, previous studies have demonstrated the greater effectiveness of multiple measures over single measures in enhancing the uptake, implementation and hence effectiveness of clinical guidelines and policies[421, 463]. .

Accordingly, a combination of effective dissemination strategies, providing a reminder tool, linking to financial incentives, and/or strategies to encourage and engage GPs in switching patients from ARBs to ACEIs is recommended to improve the future uptake and effectiveness of the BCBV indicator. However, since the study participants reported their preference for prescribing ACEIs as first-line treatment, which is already consistent with the first component of the BCBV indicator – starting new patients with ACEIs, it may be reasonable to recommend that more efforts should be focused on the second component of the BCBV indicator – of switching established ARBs users to

ACEIs. Therefore, emphasis should be on those measures that promote this second element, especially in the presence of reported reluctance among the study participants regarding patients' switching from ARBs to ACEIs, even though the cost implication of these measures on the overall cost-saving consequences on the switching is unclear.

7.2. Implications of the study findings

7.2.1. Implications for policy makers and NHS's recent strategy of medicine optimisation

This thesis represents a case study of an ineffective or failed prescribing policy, attributed primarily to inappropriate implementation of the policy. Therefore, this study provides key learning lessons to healthcare authorities that effective implementation strategies are integral to the uptake and effectiveness of healthcare policies and that failure of a policy to produce demonstrable benefits may be related to the failure of the implementation approaches rather than the policy itself.

The missed opportunity of potential cost saving from achieving the policy target of 80%, despite the availability of several low-cost generic ARBs and the findings that patients' switching from ARBs to ACEIs was associated with neither deterioration in patients' clinical outcomes nor with incurring of extra costs but rather an overall net cost saving in total medical expenditure should, therefore, reassure policy makers that there would be no inadvertent effects of the BCBV policy.

Importantly, at the same time, the current study also pointed out the potential reasons for the ineffectiveness of the BCBV policy as well as the potential strategies that could possibly enhance its future implementation and effectiveness. Therefore, it is important for policy makers to initiate central measures nationally building on the strategies

suggested by the current study and use them as a platform to facilitate the uptake and implementation of the BCBV indicator almost uniformly across the country.

Furthermore, the study findings also indicated a relatively low level of cost-consciousness among GPs with drug cost being inferior to drugs' efficacy and safety. It is, therefore, necessary to initiate measures, such as a combination of basic cost education, relative and absolute cost information, integrated into GPs' point of prescribing system, and continual audit-feedback and education[471], to increase the cost-consciousness of GPs, which would improve their prescribing efficiency, especially in case of ACEIs/ARBs due to their comparable efficacy and safety profiles. Nevertheless, hospital doctors and consultants were found to be an important source of starting patients on ARBs and had an influential effect on GPs' prescribing behaviour, which is consistent with other studies[68, 70, 431]. This could, at least partly, be related to specialists' cost-unawareness, as one GP pointed out in the interviews. Therefore, the cost awareness programme should not only target GPs but also hospital doctors to ensure optimal and efficient use of medicines, especially, although a contentious point, that the pressure to prescribe high-cost drugs often comes from hospital doctors[182]. Increasing the level of cost awareness among GPs and hospital doctors would not only potentially improve the prescribing efficiency of ACEIs/ARBs but also prescribing in other areas where there is an opportunity for improving the value for money while maintaining quality of care – as in the case of statins and proton pump inhibitors.

Since GPs' reluctance to switch patients from ARBs to ACEIs was one of the reported barriers for the ineffectiveness of the BCBV policy, active switching programmes are required to be initiated and encouraged by policy makers to motivate GPs to switch ARBs users. These active switching programmes should be encouraged and supported

further following the current study's findings of no evidence to suggest any negative clinical consequences of switching ARBs to ACEIs in patients with primary hypertension.

This case study evaluated the impact of the BCBV indicator for ACEIs/ARBs (a particular NHS prescribing policy); the thesis's findings and implications, however, are equally important as they can be generic and applied in a wider context to any NHS policy aimed at improving the quality and efficiency of prescribing as well as policies to improve the quality of provided care such as NHS's recent principle of medicine optimisation.

Medicine optimisation is defined as a "person-centred approach to safe and effective medicines use, to ensure people obtain the best possible outcomes from their medicines"[472]. Although the NICE guideline on medicine optimisation[472] provides recommendations in eight areas to implement medicine optimisation, these general recommendations were lacking specific details which would carry a potential risk of inconsistency and ineffectiveness of the various policies employed by different organisations[473]. For instance, potential medicine optimisation strategies might include active switching programme between drugs which are therapeutically equivalent but with different prices. This active switching programme needs to be comprehensive, and provides detailed information about how to implement the switching, including guidance on the dose equivalence as well as the criteria for patients' eligibility to switch. The switching process should also be in accordance with Department of Health[230] guidelines about the strategies of achieving cost-effective prescribing in primary care in terms of applying the concept of shared decision making with active involvement of

patients in the switching decision, which is considered an essential indicator for GPs' good prescribing practice by the UK's General Medical Council[231].

Therefore, the thesis's finding of the importance of having effective implementation strategies alongside any policy should be considered as well as the necessity of using multiple initiatives to promote the uptake and implementation of any medicine optimisation strategy. Passive dissemination strategies such as email or post should be discouraged; alternatively, active disseminations strategies should be used and the potential strategies, as qualitative data has shown, include local adoption of the strategy by involving local healthcare professionals to develop the policy, who can then champion its dissemination through educations forums and medicine management team.

The study findings also indicated suboptimal adherence and persistence of hypertensive patients to antihypertensive drugs, consistent with what has been reported in other studies[89, 327, 474], with identification of potential determinant factors for antihypertensive drugs' non-adherence and discontinuation. Consequently, knowledge about these factors, therefore, would be of great importance for healthcare professionals and policy makers for identifying patients at risk of being non-adherent or discontinuing, who then could be targeted for any adherence-improving interventions.

The thesis's finding of the potential roles that pharmacists and pharmacy technicians could have in communicating the prescribing decision to patients fits with medicines reconciliation, one of the key priorities areas for implementation in NICE's guideline on medicine optimisation, that identified pharmacists as the ideal health care professional to carry out medicine reconciliation[472].

7.2.2. Implications for practice

The findings from this PhD project have several important implications for clinical practice. Since successful implementation of the BCBV indicator includes switching patients from ARBs to ACEIs as an essential component, it is crucial to encourage GPs to perform such switching in order to achieve the BCBV target.

Prior to this PhD project, GPs' resistance to switching, at first glance, appeared to be plausible given the evidence on the potential clinical issues that might be associated with antihypertensive drug switching in general, and lack of any evidence related to switching from ARBs to ACEIs in particular. However, the evidence from the current study (Chapter 5) should potentially quell GPs' concerns about the switching and hence make them more confident in performing the switching.

The study findings also highlighted the importance and the type of communication style that GPs should potentially adopt to communicate the switching decision to patients effectively, which would potentially increase patients' acceptance of the switching, and thus, minimise the possibility of impeding patients' subsequent adherence and quell any negative expectations about the switching.

A previous study has reported that patients who have been involved in the switching were more likely to accept it, since any concerns about the switching could be discussed with the GP during their communication with the patient[459]. Nevertheless, the potential determinant factors for antihypertensive drugs' adherence and persistence identified in the current study (Chapter 4) could be used by GPs to predict patients' risk of drugs' non-adherence and/or discontinuation while performing the ARBs switching. This could be achieved by converting this information into a prescribing tool

incorporated into GP's computer system. Prediction of patients' risks would then allow GPs to potentially identify those patients who are at higher risk of drug discontinuation and non-adherence and this could help to alert GPs to communicate or deal with them differently so as to decrease their chance of being non-adherent, or perhaps even consider them ineligible for switching.

To overcome the issue of over-switching of patients from ACEIs to ARBs identified in this thesis, GPs are required to follow more strict approaches in investigating and diagnosing any symptom of cough in patients using ACEIs, rather than switching them directly to ARBs. The diagnosis of ACEIs-associated cough is recommended to be made only if the cough resolves 1–4 weeks after stopping ACEIs[434]. This approach often requires multiple visits of the patient to GP to check both patients' cough status and BP level as well, and these additional visits are likely associated with more resource use in terms of GPs' time; however, this extra cost may outweigh the cost of switching the cheaper ACEIs to the more expensive ARBs for life-long treatment; but this needs further investigation. Furthermore, stopping patients' antihypertensive drug therapy (ACEIs) during the 1–4-week check-up period may carry the risk of losing BP control, especially if the patient was not receiving any other antihypertensive medications, which may have negative clinical consequences[185]. Perhaps losing BP control may not be an issue, however, because the majority of patients with hypertension require and receive combination therapy to control their BP[89, 396], and thus stopping ACEIs for few weeks may not be associated with any risk for patients in terms of losing BP control. Therefore, this approach is recommended and GPs should be encouraged to adopt it in diagnosing ACEIs-associated dry cough.

Furthermore, since ACEIs users may develop a cough as a result of nocebo effect (Chapter 6, section 6.7.4.2), following this side effect of ACEIs being mentioned by GPs during a consultation[218, 436, 470], GPs should try to formulate their ways of disclosing this information to patients such that the nocebo effect is minimised. This could, perhaps, reduce the incidence of ACEIs-associated cough and thus potentially decrease unnecessary switching of ACEIs to ARBs.

Possible suggested strategies that GPs could adopt to reduce the risk of nocebo response include positive framing of the information (for instance, by emphasising that the majority of patients do not develop this side effect), and authorised concealment approach – whereby GPs educate the patient about potential nocebo responses and ask that the patient therefore gives their permission not to receive the information about the side effects[436, 470].

One of the medicine optimisation's principles is to understand the patients' experience in those who may or may not take their medicines effectively[472]. This thesis highlights the effective way on how to communicate with patients in terms of the importance of communicating the prescribing decision in terms of evidence base rather than fiscal terms as it is more acceptable to patients, and this would positively affect patients' attitudes about the prescribed medicine which in turn would potentially improve their adherence; hence optimises patients' outcome from the prescribed medicine. Furthermore, conveying the communication through methods that involve direct interaction between patients and healthcare professionals such as face-to-face consultation was considered more effective and acceptable than sending letters as a method of communication. Moreover, the importance of involving patients in the prescribing decision (shared decision making) and its impact on the treatment

outcomes were also highlighted in this thesis as it has been suggested as one of the reasons behind the non-association of ARBs switching with any negative clinical outcomes.

7.2.3. Implications for future research

This thesis evaluated the impact and implementation of the BCBV indicator for ACEIs/ARBs, which no previous study has investigated before, in an innovative way through mixing both quantitative and qualitative approaches, which allowed thorough and deep insights into this policy to be determined. Furthermore, advanced statistical techniques were used in this thesis such as time-series analysis, GLM, and multilevel modelling to evaluate the impact of this policy using a large, high-quality patient level database (CPRD) in linkage with secondary care database, enabling the collection of almost complete information about patients' activities and resource uses in both primary and secondary care. Moreover, national dispensing datasets were also used to validate the study findings and to ensure that they are reflective of national figures.

This is the first study to evaluate the short and long-term clinical impact of ARBs switching to ACEIs while including the costs of all healthcare resources used. The strength of this thesis lies partly in using a mixed-method approach to answer the research questions, which combined both quantitative and qualitative study designs. Both approaches were used because it was neither possible to appropriately answer the research questions nor to achieve the thesis aims by using either approach separately. The quantitative design assisted in quantifying the clinical and economic impact of the BCBV indicator. However, the reasons why the policy had such impact were lacking. On the other hand, the qualitative design allowed understanding the implementation of the policy in real clinical practice. Using either approach separately

would not give such complete insights into the impact and implementation of the BCBV indicator. Therefore, results from both approaches provided a complete picture about the real impact of the policy and the mechanisms through which the policy produced its effects.

The study population included in Chapter 3 consisted of patients with primary hypertension who had been prescribed ACEIs/ARBs for treating high BP; however, it is unknown whether the same study findings – in terms of the impact of the BCBV indicator – would be observed in other ACEIs/ARBs users who had been prescribed these drugs for indications other than HT, such as renal protection in diabetic patients, or heart failure. Therefore, evaluating the impact of the BCBV indicator in these patient groups could be the focus of further research.

Furthermore, patients included in the cohort studies in Chapter 4 and Chapter 5 consisted of patients with primary hypertension with no previous history of cardiovascular disease and who were prescribed a single antihypertensive drug class as a monotherapy; therefore, assessing adherence and persistence patterns among patients with primary hypertension together with cardiovascular diseases and/or those prescribed more than one antihypertensive drug classes could be the basis of future studies. This is especially pertinent given the evidence on the potential effect of comorbid conditions and complex treatment regimens on patients' behaviour in taking medications.

In addition, investigating the effect of switching from ARBs to ACEIs in the presence of other cardiovascular diseases, in addition to hypertension, and additional antihypertensive drugs co-prescribed with ARBs could be a focus for further research.

Although the current study (Chapter 5) included both primary and secondary care resources in evaluating the impact of switching from ARBs to ACEIs, the cost of staff involved in implementing the switching was not included due to the unavailability of such data in CPRD. Therefore, evaluating the impact of switching ARBs to ACEIs while accounting for the costs of implementing the switching programme in future studies would provide more comprehensive insights into the economic consequences of the switching.

The qualitative findings highlighted several possible strategies that could possibly improve the future implementation and effectiveness of the BCBV indicator. However, neither the efficacy nor the cost-effectiveness of the suggested measures is known. Therefore, comparing the efficacy and the cost-effectiveness of the various implementation strategies in enhancing the effectiveness and uptake of the BCBV policy could be investigated in future studies. This would identify the most cost-effective strategy that could be initiated nationally to ensure uniform uptake and implementation of the BCBV indicator in improving the prescribing efficiency of ACEIs/ARBs. Further research is also necessary to assess the net cost-saving impact of the BCBV policy while accounting for the cost of designing, implementing and monitoring the policy in order to estimate the overall cost-effectiveness of the BCBV indicator.

The qualitative chapter of the current study included interviews with GPs who, as prescribers, are primarily responsible for implementing the BCBV policy. However, although huge efforts were spent to recruit prescribing advisers in the current study, understanding their views and opinions, given their role in monitoring, prioritising and auditing various prescribing areas as well as designing potential strategies to implement policies, would provide a more in-depth understanding of both the

ineffectiveness of the BCBV indicator and possible strategies to enhance its future effectiveness. Therefore, interviewing prescribing advisers in a future study would be of useful value.

7.3. Conclusions

The study findings indicated the failure of the BCBV indicator to improve the efficiency of ACEIs/ARBs prescribing as well as to achieve the 80% ACEIs target, which led to a missed opportunity to make substantial cost savings. This failure was found to be related mainly to the poor implementation and uptake of the policy rather than the policy's underlying theory. There is an ongoing necessity to consider and reinforce this policy through instigating multiple initiatives to promote the policy's uptake and implementation, overcoming the identified barriers and building on the recommendations. This ongoing necessity is indicated by both the current association of achieving the 80% ACEIs target with a substantial cost-saving opportunity, even several years after the availability of generic ARBs, and the fact that the policy's promoted switching of ARBs to ACEIs was not linked to any negative clinical or cost consequences, which should reassure policy makers and GPs that implementing the BCBV indicator for ACEIs/ARBs would not be associated with inadvertent clinical effects, but instead would result in cost saving.

As a case study of an ineffective and failed prescribing policy, this thesis provides policy makers and healthcare authorities with key lessons on the necessity of considering and adopting effective implementation strategies as an integral component of the success of any healthcare policy.

References

1. The NHS Institute for Innovation and Improvement. 2012, Better Care Better Value indicators. Available at: http://www.institute.nhs.uk/quality_and_value/high_volume_care/better_care_better_value_indicators.html. Accessed 25th April, 2012.

2. Johnston, A. Challenges of therapeutic substitution of drugs for economic reasons: Focus on CVD prevention. *Current Medical Research & Opinion* 2010;**26**:871-878.

3. Johnston, A, Stafylas, P and Stergiou, G. Effectiveness, safety and cost of drug substitution in hypertension. *British Journal of Clinical Pharmacology* 2010;**70**:320-334.

4. phizackerley, D. Achieving savings will not be striaghtforward. *British Medical Journal* 2010;**341**:c7161.

5. National Institute for Health and Care Excellence. 2015, Medicines optimisation: the safe and effective use of medicines to enable the best possible outcomes. Available at: http://www.nice.org.uk/guidance/ng5/resources/medicines-optimisation-the-safe-and-effective-use-of-medicines-to-enable-the-best-possible-outcomes-51041805253. Accessed 6th March, 2015.

6. World Health Organization. 2011, Medicines: rational use of medicines. Available at: http://www.who.int/mediacentre/factsheets/fs338/en/index.html#. Accessed 15Th September, 2012.

7. Department of Health. 2012, Long term conditions compendium of information: third edition. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/216528/dh_134486.pdf. Accessed 5th May, 2015.

8. IMS Institute for Healthcare Informatics. The Global Use of Medicines:OutlookThrough 2016. IMS Institute for Healthcare Informatics. 2012. Available at:http://www.imshealth.com/deployedfiles/ims/Global/Content/Insights/IMS%20Institute%20for%20Healthcare%20Informatics/Global%20Use%20of%20Meds%202011/Medicines_Outlook_Through_2016_Report.pdf. Accessed

9. Simoens, S. Creating Sustainable European Health-Care Systems through the Increased Use of Generic Medicines: A Policy Analysis. *Journal of Generic Medicines* 2010;**7**:131-137.

10. IMS Institute for Healthcare Informatics. The Global Use of Medicines: Outlook through 2017. IMS Institute for Healthcare Informatics. 2013. Available Accessed

11. Sketris, I, Fisher, J, Langille, I, Bergman, U, Andersen, M and Vlahović-Palčkevski, V. Prescribing indicators: what can Canada learn from European countries? *Journal of population therapeutics and clinical pharmacology* 2011;**19**:e78-98.

12. Cutler, DM. Are the benefits of medicine worth what we pay for it? *Available at SSRN 1822511* 2004;

13. Tamblyn R. Appropriate prescribing. In: *Safe and Effective: The Eight Essential Elements of an Optimal Medication-use System*. By: MacKinnon NJ (Editors). 2007, Canadian Pharmacists Association: Ottawa, ON:161-185.

14. Pirmohamed, M, James, S, Meakin, S, Green, C, Scott, AK, Walley, TJ, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ* 2004;**329**:15-19.

15. Zuvekas, S and Cohen, J. Prescription drugs and the changing concentration of health care expenditures. *Health Affairs* 2007;**26**:249-257.

16. Mousnad, M, Shafie, A and Ibrahim, M. Systematic review of factors affecting pharmaceutical expenditures. *Health Policy* 2014;**116**:137-146.

17. Organisation for Economic Co-operation and Development. 2011, “Pharmaceutical expenditure”, in Health at a Glance 2011: OECD Indicators, OECD Publishing. Available at: http://apps.who.int/medicinedocs/documents/s19848en/s19848en.pdf. Accessed 13th June, 2014.

18. Cameron, A, Ewen, M, Ross-Degnan, D, Ball, D and Laing, R. Medicine prices, availability, and affordability in 36 developing and middle-income countries: a secondary analysis. *Lancet* 2009;**373**:240-249.

19. Wettermark, B, Persson, M, Wilking, N, Kalin, M, Korkmaz, S, Hjemdahl, P, et al. Forecasting drug utilization and expenditure in a metropolitan health region. *BMC Health Services Research* 2010;**10**:128.

20. Garattini, L, Motterlini, N and Cornago, D. Prices and distribution margins of in-patent drugs in pharmacy: A comparison in seven European countries. *Health Policy* 2008;**85**:305-313.

21. Godman B, Wettermark B, Bishop L, Burkhardt T, Fürst J., Garuoliene K, et al. European payer initiatives to reduce prescribing costs through use of generics. *Generics and Biosimilars Initiative Journal* 2012;**1**:22-27.

22. Godman, B, Shrank, W, Andersen, M, Berg, C, Bishop, I, Burkhardt, T, et al. Policies to enhance prescribing efficiency in Europe: findings and future implications. *Frontiers in Pharmacology* 2011;**1**:1-16.

23. Godman, B, Bennie, M, Baumgärtel, C, Sović-Brkičić, L, Burkhardt, T, Fürst, J, et al. Essential to increase the use of generics in Europe to maintain comprehensive health care? *Health economics and therapeutic pathways* 2012;**13**:5-20.

24. Godman, B, Shrank, W, Andersen, M, Berg, C, Bishop, I, Burkhardt, T, et al. Comparing policies to enhance prescribing efficiency in Europe through increasing generic utilization: changes seen and global implications. *Expert review of pharmacoeconomics & outcomes research* 2010;**10**:707-722.

25. Godman, B, Campbell, S, Suh, H, Finlayson, A, Bennie, M and Gustafsson, L. Ongoing measures to enhance prescribing efficiency across Europe: Implications for other countries. *Journal of Health Technology Assessment* 2013;**1**:27-42.

26. Godman, B, Paterson, K, Malmström, R, Selke, G, Fagot, J and Mrak, J. Improving the managed entry of new medicines: sharing experiences across Europe. *Expert Review of Pharmacoeconomics & Outcomes Research* 2012;**12**:439-441.

27. Klemp, M, Frønsdal, K and Facey, K. What principles should govern the use of managed entry agreements? *International journal of technology assessment in health care* 2011;**27**:77-83.

28. Wettermark, B, Godman, B, Jacobsson, B and Haaijer-Ruskamp, F. Soft regulations in pharmaceutical policy making: an overview of current approaches and their consequences. *Applied Health Economics and Health Policy* 2009;**7**:137-147.

29. McGinn, D, Godman, B, Lonsdale, J, Way, R, Wettermark, B and Haycox, A. Initiatives to enhance the quality and efficiency of statin and PPI prescribing in the UK: impact and implications. *Expert Review of Pharmacoeconomics & Outcomes Research* 2010;**10**:73-85.

30. Sermet, C, Andrieu, V, Godman, B, Van Ganse, E, Haycox, A and Reynier, J. Ongoing pharmaceutical reforms in France: implications for key stakeholder groups. *Applied Health Economics and Health Policy* 2010;**8**:7-24.

31. Coma, A, Zara, C, Godman, B, Agustí, A, Diogène, E, Wettermark, B, et al. Policies to enhance the efficiency of prescribing in the Spanish Catalan region: impact and future direction. *Expert Review of Pharmacoeconomics & Outcomes Research,* 2009;**9**:569-581.

32. Godman, B, Bishop, I, Finlayson, A, Campbell, S, Kwon, H and Bennie, M. Reforms and initiatives in Scotland in recent years to encourage the prescribing of generic drugs, their influence and implications for other countries. *Expert Review of Pharmacoeconomics & Outcomes Research* 2013;**13**:469-482.

33. Wettermark, B. Drug Utilization Research. In: *Pharmacoepidemiology and therapeutic risk management*. By: Hartzema, A, Tilson, H, and Chan, K (Editors). 2008, Harvey Whitney Books: Cincinnati, OH.

34. Rice, R and Atkin, C (Editors). *Public communication campaigns*. 3rd ed. 2001, SAGE Publications Inc: London.

35. Godman, B, Wettermark, B, Hoffmann, M, Andersson, K, Haycox, A and Gustafsson, L. Multifaceted national and regional drug reforms and initiatives in ambulatory care in Sweden: global relevance. *Expert Review of Pharmacoeconomics & Outcomes Research* 2009;**9**:65-83.

36. Godman, B, Shrank, W, Wettermark, B, Andersen, M, Bishop, I, Burkhardt, T, et al. Use of Generics—A Critical Cost Containment Measure for All Healthcare Professionals in Europe? *Pharmaceuticals* 2010;**3**:2470-2494.

37. Grimshaw, J, Thomas, R, MacLennan, G, Fraser, C, Ramsay, C, Vale, L, et al. Effectiveness and efficiency of guideline dissemination and implementation strategies. 2004;

38. Bero, L, Grilli, R, Grimshaw, J, Harvey, E, Oxman, A and Thomson, M. Closing the gap between research and practice: an overview of systematic reviews of interventions to promote the implementation of research findings. *British Medical Journal* 1998;**317**:465-468.

39. O'Brien, M, Rogers, S, Jamtvedt, G, Oxman, A, Odgaard-Jensen, J, Kristoffersen, D, et al. Educational outreach visits: effects on professional practice and health care outcomes. *Cochrane Database Systematic Reviews* 2008;**4**:1-62.

40. Busse, R. Disease management programs in Germany's statutory health insurance system. *Health affairs* 2004;**23**:56-67.

41. Villagra, V and Ahmed, T. Effectiveness of a disease management program for patients with diabetes. *Health Affairs* 2004;**23**:255-266.

42. Martin, A, Godman, B, Miranda, J, Tilstone, J, Saleem, N, Olsson, E, et al. Measures to improve angiotensin receptor blockers prescribing efficiency in the UK: findings and implications. *Journal of Comparative Effectiveness Research* 2014;**3**:41-51.

43. Walshe, K and Freeman, T. Effectiveness of quality improvement: learning from evaluations. *Quality and Safety in Health Care* 2002;**11**:85-87.

44. McGavock, H. Strategies to improve the cost effectiveness of general practitioner prescribing. An international perspective. *Pharmacoeconomics* 1997;**12**:307.

45. Godman, B, Schwabe, U, Selke, G and Wettermark, B. Update of recent reforms in Germany to enhance the quality and efficiency of prescribing of Proton Pump Inhibitors and lipid-lowering drugs. *Pharmacoeconomics* 2009;**27**:435-438.

46. Martikainen, J, Saastamoinen, L, Korhonen, M, Enlund, H and Helin-Salmivaara, A. Impact of restricted reimbursement on the use of statins in Finland: a register-based study. *Medical care* 2010;**48**:761-766.

47. The NHS Information Centre. 2012, Quality and Outcomes Framework : Online GP practice results database. Available at: www.qof.ic.nhs.uk. Accessed 19th March, 2012.

48. Martens, J, Werkhoven, M, Severens, J and Winkens, R. Effects of a behaviour independent financial incentive on prescribing behaviour of general practitioners. *Journal of evaluation in clinical practice* 2007;**13**:369-373.

49. Mason, A, Drummond, M, Hunter, J, Towse, A and Cooke, J. Prescribing incentive schemes. A Useful Approach? *Applied Health Economics and Health Policy* 2005;**4**:111-117.

50. Chaix-Couturier, C, Durand-Zaleski, I, Jolly, D and Durieux, P. Effects of financial incentives on medical practice: results from a systematic review of the literature and

methodological issues. *International Journal for Quality in Health Care* 2000;**12**:133-142.

51. Mason, A. New medicines in primary care: a review of influences on general practitioner prescribing. *Journal of clinical pharmacy and therapeutics* 2008;**33**:1-10.

52. Sturm, H, Austvoll-Dahlgren, A, Aaserud, M, Oxman, A, Ramsay, C, Vernby, A, et al. Pharmaceutical policies: effects of financial incentives for prescribers. *Cochrane Database Systematic Reviews* 2011;**10**:CD006731.

53. Mason, A, Towse, A, Drummond, M and Cooke, J. Influencing prescribing in a primary care led NHS: a review of the management of prescribing and findings from the MANMED survey. Office of Health Economics: 2002

54. Ess, S, Schneeweiss, S and Szucs, T. European healthcare policies for controlling drug expenditure. *Pharmacoeconomics* 2003;**21**:89-103.

55. Wallack, S, Weinberg, D and Thomas, C. Health plans' strategies to control prescription drug spending. *Health Affairs* 2004;**23**:141-148.

56. Abuelkhair, M, Abdu, S, Godman, B, Fahmy, S, Malmström, R and Gustafsson, L. Imperative to consider multiple initiatives to maximize prescribing efficiency from generic availability: case history from Abu Dhabi. *Expert review of pharmacoeconomics & outcomes research* 2012;**12**:115-124.

57. Garuoliene, K, Godman, B, Gulbinovic, J, Wettermark, B and Haycox, A. European countries with small populations can obtain low prices for drugs: Lithuania as a case history. *Expert review of pharmacoeconomics & outcomes research* 2011;**11**:343-349.

58. Godman, B, Bucsics, A, Burkhardt, T, Haycox, A, Seyfried, H and Wieninger, P. Insight into recent reforms and initiatives in Austria: implications for key stakeholders. 2008;**8**:357-371.

59. Godman, B, Malmström, R, Bennie, M, Sakshaug, S, Burkhardt, T, Campbell, S, et al. Prescribing restrictions–a necessary strategy among some European countries to enhance future prescribing efficiency? *Reviews in Health Care* 2011;**3**:5-16.

60. Pettersson, B, Hoffmann, M, Wändell, P and Levin, L. Utilization and costs of lipid modifying therapies following health technology assessment for the new reimbursement scheme in Sweden. *Health policy* 2012;**104**:84-91.

61. Godman, B, Bucsics, A, Burkhardt, T, Schmitzer, M, Wettermark, B and Wieninger, P. Initiatives to enhance renin-angiotensin prescribing efficiency in Austria: impact and implications for other countries. *Expert Review of Pharmacoeconomics & Outcomes Research* 2010;**10**:199-207.

62. Vončina, L, Godman, B, Vlahović-Palčevski, V, Bennie, M and Bishop, I. Recent policies to enhance renin-angiotensin prescribing efficiency in Europe; implications for the future. In: *International Conference on Pharmacoepidemiology*. 2011.

63. Voncina, L, Strizrep, T, Godman, B, Bennie, M, Bishop, I, Campbell, S, et al. Influence of demand-side measures to enhance renin-angiotensin prescribing efficiency in Europe: implications for the future. *Expert review of Pharmacoeconomics & Outcomes Research* 2011;**11**:469-479.

64. Preblick, R and Frech-Tamas, F. Effects of a step-therapy program for angiotensin receptor blockers on antihypertensive medication utilization patterns and cost of drug therapy. *Journal of Managed Care Pharmacy* 2007;**13**:235-244.

65. Wettermark, B, Godman, B, Andersson, K, Gustafsson, L, Haycox, A and Bertele, V. Recent national and regional drug reforms in Sweden. *Pharmacoeconomics* 2008;**26**:537-550.

66. Atella, V, Schafheutle, E, Noyce, P and Hassell, K. Affordability of medicines and patients' cost-reducing behaviour: empirical evidence based on SUR estimates from Italy and the UK. *Applied Health Economics and Health Policy* 2005;**4**:23-35.

67. Szecsenyi, J. Influence of attitudes and behaviour of GPs on prescribing costs. *Quality & safety in health care* 2003;**12**:6.

68. Prosser, H, Almond, S and Walley, T. Influences on GPs' decision to prescribe new drugs—the importance of who says what. *Family Practice* 2003;**20**:61-68.

69. Denig, P, Witteman, C and Schouten, H. Scope and nature of prescribing decisions made by general practitioners. *Quality and Safety in Health Care* 2002;**11**:137-143.

70. National Audit Office. 2007, Prescribing costs in primary care. Report by the Comptroller and Auditor General (HC 454 Session 2006-2007). Available at: http://www.nao.org.uk/wp-content/uploads/2007/05/0607454es.pdf. Accessed 15th July, 2013.

71. Pegler C and Underhill J. Evaluating promotional material from industry: an evidence-based approach. *Pharmaceutical Journal* 2005;**274**:271–274

72. Godman, B, Burkhardt, T, Bucsics, A, Wettermark, B and Wieninger, P. Impact of recent reforms in Austria on utilization and expenditure of PPIs and lipid-lowering drugs: implications for the future. *Expert review of pharmacoeconomics & outcomes research* 2009;**9**:475-484.

73. Wettermark, B, Godman, B, Neovius, M, Hedberg, N, Mellgren, T and Kahan, T. Initial effects of a reimbursement restriction to improve the cost-effectiveness of antihypertensive treatment. *Health Policy* 2010;**94**:221-229.

74. Barton, S. Using clinical evidence. *British Medical Journal* 2001;**322**:503-504.

75. Grol, R and Grimshaw, J. From best evidence to best practice: effective implementation of change in patients' care. *Lancet* 2003;**362**:1225-1230.

76. Voncina, L and Strizrep, T. Croatia: 2009/2010 pharmaceutical pricing and reimbursement reform. *Eurohealth* 2011;**16**:20-22.

77. Godman, B, Abuelkhair, M, Vitry, A, Abdu, S, Bennie, M and Bishop, I. Payers endorse generics to enhance prescribing efficiency: impact and future implications, a case history approach. *Generics and Biosimilars Initiative Journal* 2012;**1**:69-83.

78. Pichetti, S, Sermet, C, Godman, B, Campbell, S and Gustafsson, L. Multilevel Analysis of the Influence of Patients' and General Practitioners' Characteristics on Patented Versus Multiple-Sourced Statin Prescribing in France. *Applied health economics and health policy* 2013;**11**:205-218.

79. Tilson, L, Bennett, K and Barry, M. The potential impact of implementing a system of generic substitution on the community drug schemes in Ireland. *European Journal of Health Economics* 2005;**6**:267-273.

80. Opie, L, Poole-Wilson, P and Pfeffer, M. Angiotensin-converting enzyme inhibitors (ACEIs), Angiotensin-II receptor blockers (ARBs) and Aldosterone antagonist In: *Drugs for the Heart*. By: Opie, L and Gersh, B (Editors). 2005, Elsevier Saunders: Philadelphia, Penn.

81. Jackson, E and Garrison, J. Renin and Angiotensin. In: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. By: Hardman, J and Limbird, L (Editors). 2001, McGraw-Hill Education New York:733-758.

82. Ruggenenti, P, Iliev, I, Costa, G, Parvanova, A, Perna, A, Giuliano, G, et al. Preventing left ventricular hypertrophy by ACE inhibition in hypertensive patients with type 2 Diabetes. *Diabetes Care* 2008;**31**:1629-1634.

83. Schmieder, R, Martus, P and Klingbeil, A. Reversal of left ventricular hypertrophy in essential hypertension. *Journal of the American Medical Association* 1996;**275**:1507-1513.

84. Mann, J, Gerstein, H, Yi, Q, Franke, J, Lonn, E, Hoogwerf, B, et al. Progression of renal insufficiency in type 2 diabetes with and without microalbuminuria: results of the Heart Outcomes and Prevention Evaluation (HOPE) randomized study. *American Journal of Kidney Disorders* 2003;**42**:936-942.

85. Centers for Disease Control and Prevention. Prevalence of actions to control high blood pressure-20 states, 2005. *Morbidity and Mortality Weekly Report* 2007;**56**:420-423.

86. World Health Organization. Global status report on noncommunicable diseases 2010. 2011. Available Accessed

87. Kearney, P, Whelton, M, Reynolds, K, Muntner, P, Whelton, P and He, J. Global burden of hypertension: Analysis of worldwide data. *Lancet* 2005;**365**:217-223.

88. Tu, K, Chen, Z and Lipscombe, L. Prevalence and incidence of hypertension from 1995 to 2005: a population-based study. *Canadian Medical Association Journal* 2008;**178**:1429-1435.

89. Mancia, G, Fagard, R, Narkiewicz, K, Redon, J, Zanchetti, A, Böhm, M, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *European Heart Journal* 2013;**34**:2159-2219.

90. National Prescribing Centre. 2012, Health Survey for England - 2011. Available at: http://www.ic.nhs.uk/catalogue/PUB09302. Accessed 21th December, 2012.

91. The National Institute of Health and Clinical Excellence. 2011, Hypertension: The clinical management of primary hypertension in adults, clinical guideline 127. Available at: http://www.nice.org.uk/nicemedia/live/13561/56008/56008.pdf. Accessed 15th May, 2012.

92. Saseen, J. Essential Hypertension. In: *Applied therapeutics: the clinical use of drugs*. By: Koda-Kimble, M, Young, L, Corelli, B, Guglielmo, B, Kradjan, W, and Williams, B (Editors). 2008, Lippincott Williams & Wilkins:13.01-13.41.

93. Prospective-Studies-Collaboration. Age-specific relevance of usual BP to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;**306**:983-987.

94. Kaplan, W and Laing, R. 2004, Priority Medicines for Europe and the World Project."A Public Health Approach to Innovation". Available at: http://whqlibdoc.who.int/hq/2004/WHO_EDM_PAR_2004.7.pdf. Accessed 15th May, 2012.

95. Roger, V, Go, A, Lloyd-Jones, D, Adams, R, Berry, J, Brown, T, et al. Executive Summary: Heart Disease and Stroke Statistics—2011 Update. *Circulation* 2011;**123**:459-463.

96. Mathers, C and Loncar, D. Projections of global mortality and burden of disease from 2002 to 2030: a systematic analysis for the Global Burden of Disease Study 2010. *PLoS medicine* 2006;**3**:e442.

97. World Health Organization. The global burden of disease: 2004 update. 2008. Available Accessed

98. Leal, J, Luengo-Fernández, R, Gray, A, Petersen, S and Rayner, M. Economic burden of cardiovascular diseases in the enlarged European Union. *European Heart Journal* 2006;**27**:1610-1619.

99. British Heart Foundation. 2011, Heart Statistics. Available at: www.heartstats.org.uk. Accessed 5th March, 2013.

100. Centre for Economics and Business Research. The economic cost of cardiovascular disease from 2014-2020 in six European economies. 2014. Available at:http://www.cebr.com/reports/the-rising-cost-from-cvd/. Accessed

101. James, P, Oparil, S, Carter, B, Cushman, W, Dennison-Himmelfarb, C, Handler, J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *Journal of American Medical Association* 2014;**311**:507-520.

102. Psaty, B, Lumley, T, Furberg, C, Schellenbaum, G, Pahor, M, Alderman, M, et al. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. *Journal of American Medical Association* 2003;**289**:2534-2544.

103. Law, M, Morris, J and Wald, N. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *British Medical Journal* 2009;**338**:1245-1253.

104. Trialists'Collaboration. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus. Results of prospectively designed overviews of randomized trials. *Arch Intern Med* 2005;**165**:1410-1419.

105. Law, M, Wald, N, Morris, J and Jordan, R. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. *British Medical Journal* 2003;**326**:1427.

106. Skeggs, L, Dorer, F, Kahn, J, Lentz, K and Levine, M. The biochemistry of the renin-angiotensin system and its role in hypertension. *American journal of medicine* 1976;**60**:737-748.

107. Van Vark, L, Bertrand, M, Akkerhuis, K, Brugts, J, Fox, K, Mourad, J, et al. Angiotensin-converting enzyme inhibitors reduce mortality in hypertension: a meta-analysis of randomized clinical trials of renin–angiotensin–aldosterone system inhibitors involving 158 998 patients. *European Heart Journal* 2012;2088-2097.

108. Sciarretta, S, palano, F, Tocci, G, Baldini, R and Volpe, M. Antihypertensive treatment and development of heart failure in hypertension. *Archives of Internal Medicine* 2010;**8**:427-438.

109. Whitworth, J. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. *Journal of Hypertension* 2003;**21**:1983-1992.

110. The National Institute of Health and Clinical Excellence. 2010, Chronic heart failure: management of chronic heart failure in adults in primary and secondary care. Clinical guideline 108. . Available at: http://www.nice.org.uk/nicemedia/live/13099/50517/50517.pdf. Accessed 13th May, 2013.

111. The National Institute of Health and Clinical Excellence. Myocardial infarction: secondary prevention. Clinical guideline 48. The National Institute of Health and Clinical Excellence. 2007. Available at: www.nice.org.uk/cg48. Accessed

112. The National Institute of Health and Clinical Excellence. 2004, Type 1 diabetes: diagnosis and management of type 1 diabetes in children, young people and adults. Clinical guideline 15. Available at: www.nice.org.uk/CG15. Accessed 10th March, 2012.

113. The National Institute of Health and Clinical Excellence. 2009, Type 2 diabetes: the management of type 2 diabetes. Clinical guideline 87. Available at: www.nice.org.uk/cg87. Accessed 8th June, 2014.

114. The National Institute of Health and Clinical Excellence. 2008, Chronic kidney disease: early identification and management of chronic kidney disease in adults in primary and secondary care. Clinical guideline 73. Available at: www.nice.org.uk/cg73. Accessed 10th July, 2014.

115. Marketou, M, Kintsurashvili, E, Papanicolaou, K, Lucero, H, Gavras, I and Gavras, H. Cardioprotective effects of a selective B2 receptor agonist of bradykinin post-acute myocardial infarct. *American journal of hypertension* 2010;**23**:562-568.

116. Reboldi, G, Angeli, F, Cavallini, C, Gentile, G, Mancia, G and Verdecchia, P. Comparison between angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on the risk of myocardial infarction, stroke and death: a meta-analysis. *Journal of hypertension* 2008;**26**:1282-1289.

117. Unger, T and Stoppelhaar, M. Rationale for double renin-angiotensin-aldosterone system blockade. *American journal of cardiology* 2007;**100**:S25-S31.

118. Lévy, B. Can angiotensin II type 2 receptors have deleterious effects in cardiovascular disease? Implications for therapeutic blockade of the renin–angiotensin system. *Circulation* 2004;**109**:8-13.

119. Vacanti L. Could angiotensin receptor blockers and activation of AT2 induce plaque rupture, rather than repair? . *British Medical Journal* 2004;**Rapid Response** December 23.

120. Fournier, A, Achard, J, Boutitie, F, Mazouz, H, Mansour, J, Oprisiu, R, et al. Is the angiotensin II type 2 receptor cerebroprotective? *Current hypertension reports* 2004;**6**:182-189.

121. Li, J, Culman, J, Hörtnagl, H, Zhao, Y, Gerova, N, Timm, M, et al. Angiotensin AT2 Receptor Protects Against Cerebral Ischemia-Induced Neuronal Injury. *Journal of the Federation of American Scocieties for Experimental Biology* 2005;**19**:617-619.

122. Ruschitzka, F and Taddei, S. Angiotensin-converting enzyme inhibitors: first-line agents in cardiovascular protection? *European heart journal* 2012;ehs108.

123. Heran, B, Wong, M, Heran, I and Wright, J. Blood Pressure Lowering Efficacy of Angiotensin Receptor Blockers For Primary Hypertension. *Cochrane Database Systematic Reviews* 2008;**4**:CD003822.

124. Li, C, Heran, S and Wright , M. Angiotensin Converting Enzyme (ACE) Inhibitors versus Angiotensin Receptor Blockers for Primary Hypertension. *Cochrane Database of Systematic Reviews* 2014;**8**:CD009096.

125. Strauss, M and Hall, A. Angiotensin Receptor Blockers May Increase Risk of Myocardial Infarction Unravelling the ARB-MI Paradox. *Circulation* 2006;**114**:838-854.

126. Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure-dependent and independent effects of agents that inhibit the renin–angiotensin system. *Journal of hypertension* 2007;**25**:951-958.

127. Bangalore, S, Kumar, S, Wetterslev, J and Messerli, F. Angiotensin receptor blockers and risk of myocardial infarction: meta-analyses and trial sequential analyses of 147 020 patients from randomised trials. *British Medical Journal* 2011;**342**:d2234.

128. Beckett, N, Peters, R, Fletcher, A, Staessen, J, Liu, L, Dumitrascu, D, et al. Treatment of hypertension in patients 80 years of age or older. *New England Journal of Medicine* 2008;**358**:1887-1898.

129. Lithell, H, Hansson, L, Skoog, I, Elmfeldt, D, Hofman, A, Olofsson, B, et al. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. *Journal of hypertension* 2003;**21**:875-886.

130. Patel, A. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet* 2007;**370**:829-840.

131. Savarese, G, Costanzo, P, Cleland, J, Vassallo, E, Ruggiero, D, Rosano, G, et al. A meta-analysis reporting effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients without heart failure. *Journal of the American College of Cardiology* 2013;**61**:131-142.

132. Matchar, D, McCrory, D, Orlando, L, Patel, M, Patel, U, Patwardhan, M, et al. Systematic review: Comparative effectiveness of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers for treating essential hypertension. *Annals of Internal Medicine* 2008;**148**:16-29.

133. Sanders, G, Coeytaux, R, Dolor, R, Hasselblad, V, Patel, U, Powers, B, et al. Angiotensin-Converting Enzyme Inhibitors (ACEIs), Angiotensin II Receptor Antagonists (ARBs), and Direct Renin Inhibitors for treating essential hypertension: an update. Rockville (MD): Agency for Healthcare Research and Quality (US). 2011. *Comparative Effectiveness Reviews, No. 34*. Available at:http://www.ncbi.nlm.nih.gov/books/NBK61789/. Accessed 26th June 2015

134. The ONTARGET investigators. Telmisartan, ramipril or both in patients at high risk for vascular events. *New England Journal of Medicine* 2008;**358**:1547–1559.

135. Timbie, J, Hayward, R and Vijan, S. Variation in the net benefit of aggressive cardiovascular risk factor control across the us population of patients with diabetes mellitus. *Archives of Internal Medicine* 2010;**170**:1037-1044.

136. National Prescribing Centre. NPC rapid review: NICE updates its guidance on management of hypertension. National Prescribing Centre. 2011. Available at:http://www.npc.nhs.uk/rapidreview/?p=4470. Accessed

137. López-Sendón, J, Swedberg, K, McMurray, J, Tamargo, J, Maggioni, A, Dargie, H, et al. Expert consensus document on Angiotensin Converting Enzyme Inhibitors in cardiovascular disease. *European Heart Journal* 2004;**25**:1454-1470.

138. Lombardi, C, Crivellaro, M, Dama, A, Senna, G, Gargioni, S and Passalacqua, G. Are Physicians Aware of the Side Effects of Angiotensin-Converting Enzyme Inhibitors? *Chest* 2005;**128**:976-979.

139. National Prescription Centre. 2010, MeReC Bulletin, Angiotensin-II Receptor Antagonist: What is the evidence for their place in therapy? Available at: http://www.npc.nhs.uk/merec/cardio/cdhyper/resources/merec_bulletin_vol20_no2.pdf. Accessed 15th January, 2013.

140. Frisk, P, Mellgren, TO, Hedberg, N, Berlin, A, Granath, F and Wettermark, B. Utilisation of Angiotensin Receptor Blockers in Sweden: combining survey and register data to study adherence to prescribing guidelines. *European Journal of Clinical Pharmacology* 2008;**64**:1223-1229.

141. Fletcher, A, Palmer, A and Bulpitt, C. Cough with Angiotensin Converting Enzyme Inhibitors: how much of a problem? *Journal of hypertension* 1994;**12**:S43.

142. Weber, M and Messerli, F. Angiotensin-Converting Enzyme Inhibitors and Angioedema. *Hypertension* 2008;**51**:1465-1467.

143. Bas, M, Adams, V, Suvorava, T, Niehues, T, Hoffmann, T and Kojda, G. Nonallergic angioedema: role of bradykinin. *Allergy* 2007;**62**:842-856.

144. Siragy, H. A current evaluation of the safety of Angiotensin Receptor Blockers and Direct Renin Inhibitors. *Vascular Health and Risk Management* 2011;**7**:297-313.

145. Mazzolai, L and Burnier, M. Comparative safety and tolerability of Angiotensin II Receptor Antagonists. *Drug safety* 1999;**21**:23-33.

146. Dickstein, K, Cohen-Solal, A and Filippatos, G, et al. On behalf of the task force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. . *European heart journal* 2008;**29**:2388-2442.

147. Makani, H, Messerli, F, Romero, J, Wever-Pinzon, O, Korniyenko, A, Berrios, R, et al. Meta-Analysis of Randomized Trials of Angioedema as an Adverse Event of Renin–Angiotensin System Inhibitors. *American Journal of Cardiology* 2012;**110**:383-391.

148. Ma, T, Kam, K, Yan, B and Lam, y. Renin-angiotensin-aldosterone system blockade for cardiovascular diseases: current status. *British Journal of Pharmacology* 2010;**160**:1273-1292.

149. IMS Health. 2012, Top theraputic classes by U.S. dispensed prescriptions. Available at: http://www.imshealth.com/deployedfiles/ims/Global/Content/Corporate/Press%20Room/Top-Line%20Market%20Data%20&%20Trends/2011%20Top-line%20Market%20Data/Top_Therapy_Classes_by_RX.pdf. Accessed 10th March, 2012.

150. Bian, B, Kelton, C, Guo, J and Wigle, P. ACE Inhibitor and ARB utilization and expenditures in the Medicaid Fee-For-Service Program from 1991 to 2008. *Journal of Managed Care Pharmacy* 2010;**16**:671-679.

151. Kalaba, M, Godman, B, Vuksanovic, A, Bennie, M and Malmström, R. Possible ways to enhance Renin-Angiotensin prescribing efficiency: Republic of Serbia as a case history? *Journal of comparative effectiveness research* 2012;**1**:539-549.

152. Tomasik, T, Windak, A, Jozwiak, J, Oleszczyk, M, Seifert, B, Kersnik, J, et al. Treatment of hypertension in central and eastern European countries: self-reported practice of primary care physicians. *Journal of Hypertension* 2012;**30**: 1671–1678.

153. Serumaga, B. *The impact of "pay-for-performance" and clinical guidelines on the quality of care and outcomes for patients with hypertension in primary care in the United Kingdom* [Ph.D]. Nottingham: University of Nottingham, 2010

154. NHS Business Services Authority. 2009, PCT Prescribing Report: Prescribing of Angiotensin-Converting Enzyme (ACE) Inhibitors and Angiotensin-II Receptor Antagonists (AIIRAs)-Prescribing Guidance and Discussion Points. Available at: http://www.nhsbsa.nhs.uk/PrescriptionServices/Documents/PPDPCTReports/pctreport_20092.pdf. Accessed 24th September, 2014.

155. Moon, J, Flett, A, Godman, B, Grosso, A and Wierzbicki, A. Getting better value from the NHS drug budget. *British Medical Journal* 2010;**341**:30-32.

156. Bennie, M, Bishop, I, Godman, B, Campbell, S, Miranda, J, Finlayson, AE, et al. Are prescribing initiatives readily transferable across classes: the case of generic losartan in Scotland? *Quality in primary care* 2013;**21**:7-15.

157. Health and Social Care Information Centre. 2012, Prescription Cost Analysis England 2011. Available at: http://www.hscic.gov.uk/catalogue/PUB05807/pres-cost-anal-eng-2011-rep.pdf. Accessed 24th September, 2014.

158. Tomlinson, L, Abel, G, Chaudhry, A, Tomson, C, Wilkinson, I, Roland, M, et al. ACE Inhibitor and Angiotensin Receptor-II Antagonist prescribing and hospital admissions with acute kidney injury: A longitudinal ecological study. *PloS one* 2013;**8**:e78465.

159. Barber, N. What constitutes good prescribing? *British Medical Journal* 1995;**310**:923-925.

160. British Medical Association. British National Formulary, 67 Royal Pharmaceutical Society of Great Britain: London, September 2014

161. London New Drugs Group. 2008, ACE Inhibitors and Angiotensin II Receptor-Antagonists for hypertension. Available at: http://www.medicinesresources.nhs.uk/upload/documents/Evidence/Drug%20Specific%20Reviews/AIIA%20final%20Jan%2008.pdf. Accessed 10th January, 2015.

162. Voncina L, Strizrep T and Godman B. Influence of prescribing restrictions compared with other demandside measures to enhance Renin-Angiotensin prescribing efficiency: implications for other countries. *Expert Review of Pharmacoeconomics & Outcomes Research* 2011;**11**:469-479.

163. Markovic-Pekovic, V, Škrbic, R, Godman, B and Gustafsson, L. Ongoing initiatives in the Republic of Srpska to enhance prescribing efficiency: influence and future directions. *Expert review of pharmacoeconomics & outcomes research* 2012;**12**:661-671.

164. Lafond, S, Arora, S, Charlesworth, A and McKeon, A. 2014, Into the Red? The State of the NHS' Finances. An analysis of NHS expenditure between 2010 and 2014. Available at: http://www.nuffieldtrust.org.uk/publications/red-state-nhs-finances. Accessed 10th January, 2015.

165. NHS England. 2013, The NHS belongs to the people: a call to action. Available at: http://www.england.nhs.uk/2013/07/11/call-to-action/. Accessed 4th October, 2014.

166. HM Treasury. Public Expenditure Statistical Analyses 2014. 2014. Available Accessed

167. Taunt, R, Lockwood, A and Berry, N. More than money: closing the NHS quality gap. The Health Foundation Inspiring Improvement. 2014. Available Accessed

168. Monitor. NHS Foundation Trusts Consolidated Account 2013-14. 2014. Available at:https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/331166/Consolidated_Accounts_2013-14.pdf. Accessed

169. The NHS Institute for Innovation and Improvement. 2009, MeReC Stop Press; NPC Rapid Review- Resources relating to Better Care Better Value indicators. Available at: http://www.npc.nhs.uk/rapidreview/?p=328. Accessed 23rd June, 2012.

170. The Department of Health. 2010, The NHS Quality, Innovation, Productivity and Prevention Challenge: an introduction for clinicians. Available at: http://somaxa.com/docs/file/QIPP_2010.pdf. Accessed 02ed October, 2014.

171. The National Institute for Health and Care Excellence. 2013, Key Theraputic Topics- Medicines managemenet options for local implementation: Interim process statement. Available at: http://www.nice.org.uk/article/pmg7/resources/non-guidance-key-therapeutic-topics-medicines-management-options-for-local-implementation-interim-process-statement-pdf. Accessed 10th June, 2014.

172. National Prescribing Centre. 2009, Renin-Angiotensin system drugs: Data focused commentary. Available at: http://www.npc.nhs.uk/therapeutics/cardio/cd_hyper/resources/dfc_hypertension.pdf. Accessed 10th August, 2012.

173. Office of Fair Trading (UK). 2007, Annexe M: Current price inefficiencies and potential benefits of value-based pricing Available at: http://www.oft.gov.uk/shared_oft/reports/comp_policy/oft885m.pdf. Accessed 15th January, 2014.

174. The NHS Business Services Authority. 2013, PCT charts and data: ACE inhibitor % items. Available at: http://www.nhsbsa.nhs.uk/PrescriptionServices/3424.aspx. Accessed 25th September, 2013.

175. National Institute for Health and Clinical Excellence. 2014, Key Theraputic Topics: Medicines managemenet options for local implementation, September 2014. Available at: http://www.nice.org.uk/Media/Default/About/what-we-do/NICE-advice/Key-therapeutic-topics/key-therapeutic-topics-2014-consultation-document.pdf. Accessed 5th Januray, 2015.

176. British Medical Association. British National Formulary, 63. Royal Pharmaceutical Society of Great Britain: London, March 2012

177. British Medical Association. British National Formulary, 64. Royal Pharmaceutical Society of Great Britain: London, September 2012

178. McInnes, G. Are ARBs now first-line therapy for hypertension? *Prescriber* 2013;**24**:51-52.

179. National Institute for Health and Care Excellence. 2015, Key Theraputic Topics: Medicines managemenet options for local implementation, January 2015. Available at: http://www.nice.org.uk/Media/Default/About/what-we-do/NICE-advice/Key-therapeutic-topics/Key-therapeutic-topics-2015-1.pdf. Accessed 20th February, 2015.

180. The Departmnet of Health. 2010, "Equity and excellence: Liberating the NHS". Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/213823/dh_117794.pdf. Accessed 25th January, 2015.

181. Food and Drug Administration. Orange book: approved drug products with therapeutic equivalence evaluations USA, 2004

182. Duerden, M and Hughes, D. Generic and therapeutic substitutions in the UK: are they a good thing? *British journal of clinical pharmacology* 2010;**70**:335-341.

183. Watman, G. Clinic to implement patient change from an Angiotensin Receptor Blocker (ARB) to an Angiotensin Converting Enzyme Inhibitor (ACEI) in general medical practices. *Pharmacy Management* 2013;**29**:19-24.

184. Leicestershire Medicines Strategy Group. 2008, Leicestershire ACE inhibitor /ARB Choices for Primary Care. Available at: http://www.lmsg.nhs.uk/LMSGDocs%5CGuidelines%5CACE_ARB_200803.pdf. Accessed 15th June, 2014.

185. Julius, S, Kjeldsen, SE, Weber, M, Brunner, HR, Ekman, S, Hansson, L, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *The Lancet* 2004;**363**:2022-2031.

186. Stergiou, G, Karotsis, A, Symeonidis, A and Vassilopoulou, V. Aggressive blood pressure control in general practice (ABC-GP) study: can the new targets be reached? *Journal of human hypertension* 2003;**17**:767-773.

187. Chobanian, A, Bakris, G, Black, H, Cushman, W, Green, L, Izzo, J, et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension* 2003;**42**:1206-1252.

188. Heran, S, Musini, M, Bassett, K, Taylor, S and Wright , M. Angiotensin receptor blockers for heart failure. *Cochrane Database of Systematic Reviews* 2012;**4**:CD003040.

189. Cheng, J, Zhang, W, Zhang, X and et al. Effect of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers on all-cause mortality, cardiovascular deaths, and cardiovascular events in patients with diabetes mellitus: A meta-analysis. *JAMA Internal Medicine* 2014;**174(5)**:773-785.

190. Vrijens, B, De-Geest, S, Hughes, D, Przemyslaw, K, Demonceau, J, Ruppar, T, et al. A new taxonomy for describing and defining adherence to medications. *British journal of clinical pharmacology* 2012;**73**:691-705.

191. Krousel-Wood, M, Thomas, S, Muntner, P and Morisky, D. Medication adherance: a key factor in achieving blood pressure control and good clinical outcomes in hypertensive patients. *Current Opinion in Cardiology* 2004;**19**:357-362.

192. Corrao, G, Parodi, A, Nicotra, F, Zambon, A, Merlino, L, Cesana, G, et al. Better compliance to antihypertensive medications reduces cardiovascular risk. *Journal of hypertension* 2011;**29**:610-618.

193. Kettani, F, Dragomir, A, Côté, R, Roy, L, Bérard, A, Blais, L, et al. Impact of a better adherence to antihypertensive agents on cerebrovascular disease for primary prevention. *Stroke* 2009;**40**:213-220.

194. Muszbek, N, Brixner, D, Benedict, A, Keskinaslan, A and Khan, Z. The economic consequences of noncompliance in cardiovascular disease and related conditions: a literature review. *International journal of clinical practice* 2008;**62**:338-351.

195. Hilleman, D. Adherence and health care costs with single-pill fixed-dose combination in hypertension management. *Journal of Managed Care Pharmacy* 2014;**20**:93-100.

196. Breekveldt-Postma, N, Penning-van Beest, F, Siiskonen, S, Falvey, H, Vincze, G, Klungel, O, et al. The effect of discontinuation of antihypertensives on the risk of acute myocardial infarction and stroke. *Current Medical Research and Opinion* 2007;**24**:121-127.

197. Halpern M, Khan Z, Daley W and W, S. Impact of compliance (adherence) and persistence of treatment with valsartan on hypertension clinical outcomes. *Value in health* 2005;**8**:A104.

198. Sokol, M, McGuigan, K, Verbrugge, R and Epstein, R. Impact of Medication Adherence on Hospitalization Risk and Healthcare Cost. *Medical Care* 2005;**43**:521-530.

199. Monane, M, Bohn, R, Gurwitz, J, Glynn, R, Levin, R and Avorn, J. The effects of initial drug choice and comorbidity on antihypertensive therapy compliance. *American Journal of Hypertension* 1997;**10**:697-704.

200. Thayer, S and Dastani, H. Can switching among the ARB class impact medical costs and medication adherence. *Journal of Managed Care Pharmacy* 2009;**15**:179.

201. Wilson, J, Axelsen, K and Tang, S. Medicaid prescription drug access restrictions: exploring the effect on patient persistence with hypertension medications. *Am J Manag Care* 2005;**11**:27-34.

202. Yiannakopoulou, E, Papadopulos, J, Cokkinos, D and Mountokalakis, T. Adherence to antihypertensive treatment: a critical factor for blood pressure control. *European Journal of Cardiovascular Prevention & Rehabilitation* 2005;**12**:243-249.

203. Kronish, I, Woodward, M, Sergie, Z, Ogedegbe, G, Falzon, L and Mann, D. Meta-analysis: impact of drug class on adherence to antihypertensives. *Circulation* 2011;**123**:1611-1621.

204. Munger, M, Van, B and LaFleur, J. Medication nonadherence: an unrecognized cardiovascular risk factor. *Medscape general medicine* 2007;**9**:58-68.

205. Himmel, W, Simmenroth-Nayda, A, Niebling, W, Ledig, T, Jansen, R, Kochen, M, et al. What do primary care patients think about generic drugs? *International journal of clinical pharmacology and therapeutics* 2005;**43**:472-479.

206. Barsky, A, Saintfort, R, Rogers, M and Borus, J. Nonspecific medication side effects and the nocebo phenomenon. *Journal of the American Medical Association* 2002;**287**:622-627.

207. Lachaine, J, Petrella, R, Merikle, E and Ali, F. Choices, persistence and adherence to antihypertensive agents: evidence from RAMQ data. *Canadian Journal of Cardiology* 2008;**24**:269-273.

208. Elliott, W, Plauschinat, C, Skrepnek, G and Gause, D. Persistence, adherence, and risk of discontinuation associated with commonly prescribed antihypertensive drug monotherapies. *Journal of the American Board of Family Medicine* 2007;**20**:72-80.

209. Elliott, W. Improving Outcomes in Hypertensive Patients: Focus on Adherence and Persistence With Antihypertensive Therapy. *Journal of Clinical Hypertension* 2009;**11**:376-382.

210. Bourgault, C, Senecal, M, Brisson, M, Marentette, M and Gregoire, J. Persistence and discontinuation patterns of antihypertensive therapy among newly treated patients: a population-based study. *J Hum Hypertens* 2005;**19**:607-613.

211. Erkens, J, Panneman, M, Klungel, O, Boom, G, Prescott, M and Herings, R. Differences in antihypertensive drug persistence associated with drug class and gender: a PHARMO study. *Pharmacoepidemiology and drug safety* 2005;**14**:795-803.

212. Burke, T, Sturkenboom, M, Lu, S, Wentworth, C, Lin, Y and Rhoads, G. Discontinuation of antihypertensive drugs among newly diagnosed hypertensive patients in UK general practice. *Journal of hypertension* 2006;**24**:1201-1208.

213. Friedman, O, McAlister, F, Yun, L, Campbell, N and Tu, K. Antihypertensive drug persistence and compliance among newly treated elderly hypertensives in Ontario. *American Journal of Medicine* 2010;**123**:173-181.

214. Naderi, S, Bestwick, J and Wald, D. Adherence to drugs that prevent cardiovascular disease: meta-analysis on 376,162 patients. *American Journal of Medicine* 2012;**125**:882-887.

215. Mazzaglia, G, Mantovani, L, Sturkenboom, M, Filippi, A, Trifirò, G, Cricelli, C, et al. Patterns of persistence with antihypertensive medications in newly diagnosed hypertensive patients in Italy: a retrospective cohort study in primary care. *Journal of hypertension* 2005;**23**:2093-2100.

216. Evans, C, Eurich, D, Lu, X, Remillard, A, Shevchuk, Y and Blackburn, D. The association between market availability and adherence to antihypertensive medications: an observational study. *American Journal of Hypertension* 2013;**26**:180-190.

217. Vegter, S, Nhu Ho, N, Visser, S, Postma, M and Boersma, C. Compliance, persistence, and switching patterns for ACE inhibitors and ARBs. *American Journal of Managed Care* 2011;**17**:609-616.

218. Faasse, K and Petrie, K. The nocebo effect: patient expectations and medication side effects. *Postgraduate medical journal* 2013;**0**:1-7.

219. Cote, B and Petersen, E. Impact of therapeutic switching in long-term care. *American Journal of Managed Care* 2008;**14**:SP23-28.

220. Kjoenniksen, I, Lindbaek, M and Granas, A. Patients' attitudes towards and experiences of generic drug substitution in Norway. *Pharmacy World and Science* 2006;**28**:284-289.

221. Kesselheim, A, Bykov, K, Avorn, J, Tong, A, Doherty, M and Choudhry, N. Burden of changes in pill appearance for patients receiving generic cardiovascular medications after myocardial infarction: cohort and nested case–control studies. *Annals of internal medicine* 2014;**161**:96-103.

222. Krska, J, Allison, K, Delargy, M, Murray, L and Smith, H. Implementing a statin switching programme in primary care: patients' views and experiences. *British journal of clinical pharmacology* 2012;**74**:147-153.

223. Al Ameri, M, Whittaker, C, Tucker, A, Yaqoob, M and Johnston, A. A survey to determine the views of renal transplant patients on generic substitution in the UK. *Transplant International* 2011;**24**:770-779.

224. Thompson, A, Green, S, Dubois, S, Ansell, A, Harewood, E and Ayre, J. Evaluation of patient satisfaction with switching medication. *Prescriber* 2006;**17**:27-35.

225. Hassali, M, Shafie, A, Jamshed, S, Ibrahim, M and Awaisu, A. Consumers' views on generic medicines: A review of the literature. *International Journal of Pharmacy Practice* 2009;**17**:79-88.

226. Greenhalgh, T, Howick, J and Maskrey, N. Evidence based medicine: a movement in crisis? *British Medical Journal* 2014;**348**:g3725.

227. The Department of Health. 2003, Building on the best: choice, responsiveness and equity in the NHS. Available at: https://www.gov.uk/government/publications/building-on-the-best-choice-responsiveness-and-equity-in-the-nhs. Accessed 4th April, 2014.

228. National Institute for Health and Care Excellence. 2009, Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence. Available at: http://www.nice.org.uk/guidance/CG76. Accessed 25th February, 2015.

229. Coulter;, A and Collins, A. MAKING SHARED DECISION-MAKING A REALITY: No decision about me, without me. The King's Fund. 2011. Available at:http://www.kingsfund.org.uk/sites/files/kf/Making-shared-decision-making-a-reality-paper-Angela-Coulter-Alf-Collins-July-2011_0.pdf. Accessed

230. The Departmnet of Health. 2010, Strategies to achieve cost-effective prescribing: guidance for primary care trusts and clinical commissioning groups. Available at: https://www.gov.uk/government/publications/strategies-to-achieve-cost-effective-prescribing-guidance-for-primary-care-trusts-and-clinical-commissioning-groups. Accessed 15th January, 2015.

231. General Medical Council. 2013, Good practice in prescribing and managing medicines and devices. Available at: http://www.gmc-uk.org/static/documents/content/Prescribing_guidance.pdf. Accessed 15th January, 2015.

232. Schroeder, S and Cantor, J. On squeezing balloons. Cost control fails again. *New England journal of medicine* 1991;**325**:1099-1100.

233. Signorovitch, J, Zhang, J, Wu, E, Latremouille-Viau, D, Yu, A, Dastani, H, et al. Economic impact of switching from valsartan to other angiotensin receptor blockers in patients with hypertension. *Current Medical Research & Opinion* 2010;**26**:849-860.

234. Hughes, D and McGuire, A. The direct costs to the NHS of discontinuing and switching prescriptions for hypertension. *Journal of human hypertension* 1998;**12**:533-537.

235. Lindgren-Furmaga, E, Schuna, A, Wolff, N and Goodfriend, T. Cost of switching hypertensive patients from enalapril maleate to lisinopril. *American Journal of Health-System Pharmacy* 1991;**48**:276-279.

236. McDonough, K, Weaver, R and Viall, G. Enalapril to lisinopril: economic impact of a voluntary Angiotensin-Converting Enzyme-Inhibitor substitution program in a staff-model health maintenance organization. *Annals of pharmacotherapy* 1992;**26**:399-404.

237. Usher-Smith, J, Ramsbottom, T, Pearmain, H and Kirby, M. Evaluation of the clinical outcomes of switching patients from atorvastatin to simvastatin and losartan to candesartan in a primary care setting: 2 years on. *International Journal of Clinical Practice* 2008;**62**:480-484.

238. Hilleman, D, Reyes, A, Wurdeman, R and Faulkner, M. Efficacy and safety of a therapeutic interchange from high-dose calcium channel blockers to a fixed-dose combination of amlodipine/benazepril in patients with moderate-to-severe hypertension. *Journal of human hypertension* 2001;**15**:559-565.

239. Murawski, M and Abdelgawad, T. Exploration of the impact of preferred drug lists on hospital and physician visits and the costs to Medicaid. *Am J Manag Care* 2005;**11**:SP35-42.

240. Belsey, J. Switch strategies in the management of hypertension: a cost minimisation analysis of Angiotensin Receptor Blocker based regimen. *Curr Med Res Opin* 2008;**24**:581-589.

241. Esposti, L, Martino, M, Saragoni, S, Sgreccia, A, Capone, A, Buda, S, et al. Pharmacoeconomics of antihypertensive drug treatment: an analysis of how long patients remain on various antihypertensive therapies. *Journal of Clinical Hypertension* 2004;**6**:76-82.

242. Stankus, V, Hemmelgarn, B, Campbell, N, Chen, G, McAlister, F and Tsuyuki, R. Reducing costs and improving hypertension management. *Canadian Journal of Clinical Pharmacology* 2009;**16**:e151-155.

243. Aronson, B. Mixed methods: A methodological smorgasbord for social pharmacy research. *Research in Social and Administrative Pharmacy* 2013;**9**:647-650.

244. Creswell, J and Plano, V. Designing and Conducting Mixed Methods Research. Sege Publications: Thousand Oaks, California, 2011

245. Guy, M. Prescribing Incentive Scheme 2009/10. NHS North of Tyne,. 2009. Available at:http://www.northoftyne.nhs.uk/about-us/the-board-the-pec/commissioning-board-

agenda-and-papers/july-28/prescribing-incentive-scheme/Agenda-Item-No-17.pdf. Accessed 10th March 2014

246. Milton Keynes PCT. Prescribing Incentive Scheme 2010-2011. 2010. Available at:http://www.miltonkeynesccg.nhs.uk/. Accessed 5th April 2013

247. NHS Bury PCT. Prescribing Incentive Scheme 2009-2010. 2010. Available at:http://www.buryccg.nhs.uk/Library/Board_Papers/2009/AI%202.6%20CB%202009%202010%20PIS%20Apr%2009%2001042009.pdf. Accessed 24th May 2014

248. Harris, A, McGregor, J, Perencevich, E, Furuno, J, Zhu, J, Peterson, D, et al. The use and interpretation of quasi-experimental studies in medical informatics. *Journal of the American Medical Informatics Association* 2006;**13**:16-23.

249. Rothwell, P. Factors that can affect the external validity of randomised controlled trials. *PLoS Clinical Trials* 2006;**1**:e9.

250. Rockers, P, Røttingen, J, Shemilt, I, Tugwell, P and Bärnighausen, T. Inclusion of quasi-experimental studies in systematic reviews of health systems research. *Health Policy* 2015;**119**:511-521.

251. Higgins, J and Green, S (Editors). *Cochrane handbook for systematic reviews of interventions*. Vol. 5.1.0. 2011, The Cochrane Collaboration.

252. William, S, Cook, T and Campbell, D. Quasi-experimental: interrupted time-series designs. In: *Experimental and quasi-experimental designs for generalized causal inference*. By: William, S, Cook, T, and Campbell, D (Editors). 2002, Houghton Mifflin Company: Boston:171-206.

253. Wagner, A, Soumerai, S, Zhang, F and Ross-Degnan, D. Segmented regression analysis of interrupted time series studies in medication use research. *Journal of Clinical Pharmacy and Therapeutics* 2002;**27**:299-309.

254. Fretheim, A, Zhang, F, Ross-Degnan, D, Oxman, A, Cheyne, H, Foy, R, et al. A reanalysis of cluster randomized trials showed interrupted time-series studies were valuable in health system evaluation. *Journal of Clinical Epidemiology* 2015;**68**:324-333.

255. Herrett, E, Thomas, S, Schoonen, M, Smeeth, L and Hall, A. Validation and validity of diagnoses in the General Practice Research Database: A systematic review. *British Journal of Clinical Pharmacology* 2010;**69**:4-14.

256. Herrett, E, Gallagher, A, Bhaskaran, K, Forbes, H, Mathur, R, van Staa, T, et al. Data resource profile: Clinical Practice Research Datalink (CPRD). *International Journal of Epidemiology* 2015;**44**:827-836.

257. The Medicines and Healthcare Products Regulatory Agency (MHRA). 2013, The Clinical Practice Research Datalink (CPRD). Available at: https://cprdcw.cprd.com/downloads/FileDownloads.aspx#ReleaseNotes. Accessed 10th November, 2013.

258. Guidelines for ATC Classification and DDD Assignment 2012. Norwegian Institute of Public Health, WHO Collaborating Centre for Drug Statistics Methodology: Oslo, Norway 2012

259. World Health Organization (WHO). 2003, Introduction to Drug Utilization Research. Available at: http://apps.who.int/medicinedocs/en/d/Js4876e/6.html. Accessed 5th February, 2012.

260. World Health Organization Collaborating Centre for Drug Statistics and Methodology. 2011, ATC/DDD Index 2012. Available at: http://www.whocc.no/atc_ddd_index/. Accessed 25th July, 2012.

261. Ronning, M, Blix, H, Harbo, B and Strom, H. Different versions of the anatomical therapeutic chemical classification system and the defined daily dose– are drug utilisation data comparable? *European Journal of Clinical Pharmacology* 2000;**56**:723-727.

262. Vlahović-Palčevski, V, Gantumur, M, Radošević, N, Palčevski, G and Vander, R. Coping with changes in the Defined Daily Dose in a longitudinal drug consumption database. *Pharmacy world and science* 2010;**32**:125-129.

263. Mauskopf, J, Sullivan, S, Annemans, L, Caro, J, Mullins, C, Nuijten, M, et al. Principles of good practice for budget impact analysis: Report of the ISPOR task force on good research practices—Budget impact analysis. *Value in Health* 2007;**10**:336-347.

264. NHS Business Services Authority. 2014, Prescription Cost Analysis (PCA) Data: Monthly Drug Data. Available at: http://www.nhsbsa.nhs.uk/PrescriptionServices/3494.aspx. Accessed 15th October, 2014.

265. Eliopoulos, G, Shardell, M, Harris, A, El-Kamary, S, Furuno, J, Miller, R, et al. Statistical analysis and application of quasi experiments to antimicrobial resistance intervention studies. *Clinical Infectious Diseases* 2007;**45**:901-907.

266. Escanciano, C and Lobato, N. An automatic Portmanteau test for serial correlation. *Journal of Econometrics* 2009;**151**:140-149.

267. NHS Business Services Authority. 2012, Prescription cost analysis - England. Available at: http://www.nhsbsa.nhs.uk/PrescriptionServices/3494.aspx. Accessed 2ed April, 2013.

268. National Prescribing Centre. 2006, Hypertension data-focussed commentary. Available at: http://www.npc.nhs.uk/therapeutics/cardio/cd_hyper/resources/dfc_hypertension.pdf. Accessed 8th August, 2012.

269. Health and Social Care Information Centre. 2013, GP Practice Prescribing Presentation-level Data. Available at: http://www.hscic.gov.uk/searchcatalogue?q=title%3a%22presentation+level+data%22&sort=Relevance&size=10&page=3#top. Accessed 1st April, 2013.

270. Kutner, M, Nachtsheim, C and Neter, J. Applied linear regression models. McGraw-Hill/Irwin: Boston, 2004

271. NHS Business Services Authority. 2013, Prescription Cost Analysis (PCA) Data: Monthly Drug Data. Available at: http://www.nhsbsa.nhs.uk/PrescriptionServices/3494.aspx. Accessed 20th January, 2014.

272. Soumerai, S, Ross-Degnan, D, Gortmaker, S and Avorn, J. Withdrawing payment for nonscientific drug therapy. *Journal of the American Medical Association* 1990;**263**:831-839.

273. Patton, C and Sawicki, D. Basic methods of policy analysis and planning. Prentice Hall: Englewood Gliffs, NJ, 1993

274. Milton Keynes PCT. 2007, Prescribing Incentive Scheme 2007-08. Available at: http://www.mkchs.nhs.uk/assets/_managed/editor/file/QMK/Prescribing/PIS/PISpaper2007-08%20Practices.pdf. Accessed 24th April, 2013.

275. Lakhani, R. 2008, Prescribing Incentive scheme 2008-2009. Available at: http://www.nice.org.uk/media/sharedlearning/327_327FinalPrescribingIncentivescheme 2008-2009.pdf. Accessed 25th April, 2013.

276. Health and Social Care Information Centre. 2004, The quality and outcomes framework. Available at: http://www.hscic.gov.uk/qof. Accessed 5th May, 2012.

277. Health and Social Care Information Centre. 2013, Quality and outcomes framework Available at: http://www.hscic.gov.uk/qof. Accessed 2ed April, 2013.

278. The National Institute for Health and Clinical Excellence. 2006, Hypertension: The clinical management of primary hypertension in adults. clincal guideline 34. Available at: http://guidance.nice.org.uk/CG34/Guidance/pdf/English Accessed 15th March, 2013.

279. World Health Organization. Adherence to long-term therapies: evidence for action. World Health Organization. 2003. Available at:http://www.who.int/chp/knowledge/publications/adherence_full_report.pdf. Accessed

280. Horne, R, Weinman, J, Barber, N, Elliott, R, Morgan, M and Cribb, A. Concordance, adherence and compliance in medicine taking. National Co-ordinating Centre for NHS Service Delivery and Organisation R & D (NCCSDO). 2005. Available Accessed

281. Cherry, S, Benner, J, Hussein, M, Tang, S and Nichol, M. The clinical and economic burden of nonadherence with antihypertensive and lipid-lowering therapy in hypertensive patients. *Value in Health* 2009;**12**:489-497.

282. Dragomir, A, Côté, R, Roy, L, Blais, L, Lalonde, L, Bérard, A, et al. Impact of adherence to antihypertensive agents on clinical outcomes and hospitalization costs. *Medical care* 2010;**48**:418-425.

283. Halpern, M, Khan, Z, Schmier, J, Burnier, M, Caro, J, Cramer, J, et al. Recommendations for evaluating compliance and persistence with hypertension therapy using retrospective data. *Hypertension* 2006;**47**:1039-1048.

284. Mazzaglia, G, Ambrosioni, E, Alacqua, M, Filippi, A, Sessa, E, Immordino, V, et al. Adherence to antihypertensive medications and cardiovascular morbidity among newly diagnosed hypertensive patients. *Circulation* 2009;**120**:1598-1605.

285. Perreault S, Lamarre D, Blais L, Dragomir A, Berbiche D, Lalonde L, et al. Persistence with treatment in newly treated middle-aged patients with essential hypertension. *Annals of Pharmacotherapy* 2005;**39**:1401-1408.

286. Degli Esposti, L, Degli Esposti, E, Valpiani, G, Di Martino, M, Saragoni, S, Buda, S, et al. A retrospective, population-based analysis of persistence with antihypertensive drug therapy in primary care practice in Italy. *Clinical therapeutics* 2002;**24**:1347-1357.

287. Little, R. A test of missing completely at random for multivariate data with missing values. *Journal of the American Statistical Association* 1988;**83**:1198-1202.

288. Little, R and Rubin, D. Statistical Analysis with Missing Data. Wiley: New York, 2002

289. Raebel, M, Schmittdiel, J, Karter, A, Konieczny, J and Steiner, J. Standardizing terminology and definitions of medication adherence and persistence in research employing electronic databases. *Medical care* 2013;**51**:S11-21.

290. Martin, B, Wiley-Exley, E, Richards, S, Domino, M, Carey, T and Sleath, B. Contrasting measures of adherence with simple drug use, medication switching, and therapeutic duplication. *Annals of Pharmacotherapy* 2009;**43**:36-44.

291. Nau, D. Proportion of Days Covered (PDC) as a Preferred Method of Measuring Medication Adherence. The Pharmacy Quality Alliance. 2012. Available at:http://ep.yimg.com/ty/cdn/epill/pdcmpr.pdf. Accessed 17th June 2015

292. Yen, L, Wu, J, Hodgkins, P, Cohen, R and Nichol, M. Medication use patterns and predictors of nonpersistence and nonadherence with oral 5-aminosalicylic acid therapy in patients with ulcerative colitis. *Journal of Managed Care Pharmacy* 2012;**18**:701-712.

293. Choudhry, N, Fischer, M, Avorn, J, Liberman, J, Schneeweiss, S, Pakes, J, et al. The implications of therapeutic complexity on adherence to cardiovascular medications. *Archives of internal medicine* 2011;**171**:814-822.

294. Wang, S, Huang, Z and Traubenberg, S. 2013, Measuring Medication Adherence with Simple Drug Use and Medication Switching Available at: http://support.sas.com/resources/papers/proceedings13/168-2013.pdf. Accessed 20th September, 2013.

295. Hess, L, Raebel, M, Conner, D and Malone, D. Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. *Annals of Pharmacotherapy* 2006;**40**:1280-1288.

296. Karve, S, Cleves, M, Helm, M, Hudson, T, West, D and Martin, B. An empirical basis for standardizing adherence measures derived from administrative claims data among diabetic patients. *Medical care* 2008;**46**:1125-1133.

297. Karve, S, Cleves, M, Helm, M, Hudson, T, West, D and Martin, B. Good and poor adherence: optimal cut-point for adherence measures using administrative claims data. *Current medical research and opinion* 2009;**25**:2303-2310.

298. Ho, M, Bryson, C and Rumsfeld, J. Medication Adherence: Its Importance in Cardiovascular Outcomes. *Circulation* 2009;**119**:3028-3035.

299. DiMatteo, MR. Social support and patient adherence to medical treatment: a meta-analysis. *Health psychology* 2004;**23**:207-218.

300. Van-Wijk, B, Klungel, O, Heerdink, E and de-Boer, A. The association between compliance with antihypertensive drugs and modification of antihypertensive drug regimen. *Journal of hypertension* 2004;**22**:1831-1837.

301. Rolnick, S, Pawloski, P, Hedblom, B, Asche, S and Bruzek, R. Patient Characteristics Associated with Medication Adherence. *Clinical Medicine & Research* 2013;**11**:54–65.

302. Caro, J, Salas, M, Speckman, JL, Raggio, G and Jackson, J. Persistence with treatment for hypertension in actual practice. *Canadian Medical Association Journal* 1999;**160**:31-37.

303. Cramer, J, Scheyer, R and Mattson, R. Compliance declines between clinic visits. *Archives of internal medicine* 1990;**150**:1509-1510.

304. Richardson, M, Simons-Morton, B and Annegers, J. Effect of perceived barriers on compliance with antihypertensive medication. *Health Education and Behavior* 1993;**20**:489-503.

305. Chowdhury, R, Khan, H, Heydon, E, Shroufi, A, Fahimi, S, Moore, C, et al. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. *European Heart Journal* 2013;**34**:2940-2948.

306. Siegel, D, Lopez, J and Meier, J. Antihypertensive medication adherence in the Department of Veterans Affairs. *American journal of medicine* 2007;**120**:26-32.

307. Ren, X, Kazis, L, Lee, A, Zhang, H and Miller, D. Identifying patient and physician characteristics that affect compliance with antihypertensive medications. *Journal of clinical pharmacy and therapeutics* 2002;**27**:47-56.

308. Burnier, M. Medication adherence and persistence as the cornerstone of effective antihypertensive therapy. *Am J Hypertens* 2006;**19**:1190-1196.

309. Bramlage, P and Hasford, J. Blood pressure reduction, persistence and costs in the evaluation of antihypertensive drug treatment -A review. *Cardiovascular Diabetology* 2009;**8**:18-31.

310. Thorpe, C, Bryson, C, Maciejewski, M and Bosworth, H. Medication acquisition and self-reported adherence in veterans with hypertension. *Medical Care* 2009;**47**:474-481.

311. Bovet, P, Burnier, M, Madeleine, G, Waeber, B and Paccaud, F. Monitoring one-year compliance to antihypertension medication in the Seychelles. *Bulletin of the World Health Organization* 2002;**80**:33-39.

312. Graham, M and Allcock, N. Irbesartan substitution for valsartan or losartan in treating hypertension. *Annals of pharmacotherapy* 2002;**36**:1840-1844.

313. Charlson, M, Pompei, P, Ales, K and MacKenzie, R. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of chronic diseases* 1987;**40**:373-383.

314. Liu, P and Wang, J. Antihypertensive medication prescription patterns and time trends for newly-diagnosed uncomplicated hypertension patients in Taiwan. *BMC Health Services Research* 2008;**8**:133-143.

315. Gartner, A and Lester, N. 2008, LSOA Townsend deprivation scores calculated from unadjusted Census data. Available at: http://www2.nphs.wales.nhs.uk:8080/hiatdocs.nsf/61c1e930f9121fd080256f2a004937ed/17fdbca9920051368025772f003b5a35/$FILE/TownsendBriefing.pdf. Accessed 26th June, 2014.

316. MacCallum, R, Zhang, S, Preacher, K and Rucker, D. On the practice of dichotomization of quantitative variables. *Psychological methods* 2002;**7**:19-40.

317. Wetzels, G, Nelemans, P, Schouten, J and Prins, M. Facts and fiction of poor compliance as a cause of inadequate blood pressure control: a systematic review. *Journal of hypertension* 2004;**22**:1849-1855.

318. Shentu, Y and Xie, M. A note on dichotomization of continuous response variable in the presence of contamination and model misspecification. *Statistics in medicine* 2010;**29**:2200-2214.

319. Royston, P, Altman, D and Sauerbrei, W. Dichotomizing continuous predictors in multiple regression: a bad idea. *Statistics in medicine* 2006;**25**:127-141.

320. Taylor, A, West, S and Aiken, L. Loss of power in logistic, ordinal logistic, and probit regression when an outcome variable is coarsely categorized. *Educational and psychological measurement* 2006;**66**:228-239.

321. Peterson, A, Nau, D, Cramer, J, Benner, J, Gwadry-Sridhar, F and Nichol, M. A checklist for medication compliance and persistence studies using retrospective databases. *Value in Health* 2007;**10**:3-12.

322. Steiner, J and Earnest, M. The language of medication-taking. *Annals of internal medicine* 2000;**132**:926-930.

323. Woltmann, E, Valenstein, M, Welsh, D, Lee, T, Wolschon, P, Grabowski, J, et al. Using pharmacy data on partial adherence to inform clinical care of patients with serious mental illness. *Psychiatric Services* 2007;**58**:864-867.

324. Benner, J, Pollack, M, Smith, T, Bullano, M, Willey, V and Williams, S. Association between short-term effectiveness of statins and long-term adherence to lipid-lowering therapy. *American journal of health-system pharmacy* 2005;**62**:1468-1475.

325. Lau, D and Nau, D. Oral antihyperglycemic medication nonadherence and subsequent hospitalization among individuals with type 2 diabetes. *Diabetes Care* 2004;**27**:2149-2153.

326. ISPOR Medication Compliance Special Interest Group (Med Comp). Draft-Appendix A. Medication compliance special interest group checklist for medication compliance studies using retrospective drug utilization data. Available at: http://www.ispor.org/sigs/eval_checklistdraft.asp. Accessed 24th May, 2014.

327. Cramer, J, Benedict, A, Muszbek, N, Keskinaslan and Khan, Z. The significance of compliance and persistence in the treatment of diabetes, hypertension and dyslipidaemia: a review. *Int J Clin Pract* 2008;**62**:76-87.

328. Wogen, J, Kreilick, C, Livornese, R, Yokoyama, K and Frech, F. Patient adherence with amlodipine, lisinopril, or valsartan therapy in a usual-care setting. *Journal of Managed Care Pharmacy* 2003;**9**:424-429.

329. Höer, A, Gothe, H, Khan, Z and Häussler, B. Patients on ARBs (and valsartan as a representative) experience higher persistence and compliance (adherence) with therapy compared to other antihypertensive classes in a german sickness fund population. *Value in Health* 2005;**8**:A108-A109.

330. Sung, S, Lee, S, Lee, K, Kim, D, Kim, K and Kim, K. First-year treatment adherence among outpatients initiating antihypertensive medication in Korea: results of a retrospective claims review. *Clinical therapeutics* 2009;**31**:1309-1320.

331. Wang, P, Avorn, J, Brookhart, A, Mogun, H, Schneeweiss, S, Fischer, M, et al. Effects of noncardiovascular comorbidities on antihypertensive use in elderly hypertensives. *Hypertension* 2005;**46**:273-279.

332. Gerbino, P and Joseph, A. Multisource drugs: Implications and concerns in the geriatric population. *Hospital pharmacy* 1993;**28**:96-98;101-102.

333. Düsing, R. Adverse events, compliance, and changes in therapy. *Current Hypertension Reports* 2001;**3**:488-492.

334. Håkonsen H., Eilertsen M., Borge H. and Toverud E. Generic substitution: additional challenge for adherence in hypertensive patients. *Informa Healthcare* 2009;**25**:2515-2521.

335. Burkholder, R. 2008, Consumers' views on therapeutic substitution. Available at: http://nclnet.org/images/PDF/therapeutic_substitution_survey.pdf. Accessed 28th October, 2013.

336. Shea, S, Misra, D, Ehrlich, M, Field, L and Francis, C. Correlates of nonadherence to hypertension treatment in an inner-city minority population. *American Journal of Public Health* 1992;**82**:1607-1612.

337. Monane, M, Bohn, R and Gurwitz, J. A population-based study of compliance with antihypertnsive therapy: role of age, gender, and race. *American Journal of Public Health* 996;**86**:1805-1809.

338. Marentette, M, Gerth, W, Billings, D and Zarnke, K. Antihypertensive persistence and drug class. *Canadian journal of cardiology* 2002;**18**:649-656.

339. Höer, A, Gothe, H, Khan, Z, Schiffhorst, G, Vincze, G and Häussler, B. Persistence and adherence with antihypertensive drug therapy in a German sickness fund population. *Journal of human hypertension* 2007;**21**:744-746.

340. Hasford, J, Schröder-Bernhardi, D, Rottenkolber, M, Kostev, K and Dietlein, G. Persistence with antihypertensive treatments: results of a 3-year follow-up cohort study. *European journal of clinical pharmacology* 2007;**63**:1055-1061.

341. Conlin, P, Gerth, W, Fox, J, Roehm, J and Boccuzzi, S. Four-year persistence patterns among patients initiating therapy with the angiotensin II receptor antagonist losartan versus other antihypertensive drug classes. *Clinical therapeutics* 2001;**23**:1999-2010.

342. Perreault, S, Lamarre, D, Blais, L, Dragomir, A, Berbiche, D, Lalonde, L, et al. Persistence with treatment in newly treated middle-aged patients with essential hypertension. *Annals of pharmacotherapy* 2005;**39**:1401-1408.

343. Hasford, J, Mimran, A and Simons, W. A population-based European cohort study of persistence in newly diagnosed hypertensive patients. *Journal of Human Hypertension,* 2002;**16**:569–575.

344. Bloom, B. Continuation of initial antihypertensive medication after 1 year of therapy. *Clinical therapeutics* 1998;**20**:671-681.

345. Patel, B, Remigio-Baker, R, Mehta, D, Thiebaud, P, Frech-Tamas, F and Preblick, R. Effects of initial antihypertensive drug class on patient persistence and compliance in a usual-care setting in the United States. *Journal of clinical hypertension* 2007;**9**:692-700.

346. Elliott, W, Meyer, P and Basu, S. One-year persistence with initial antihypertensive drug therapy: a comparison of network and Bayesian meta-analysis. *Journal of clinical hypertension* 2008;**10** A113-A114.

347. Grégoire, J, Moisan, J, Guibert, R, Ciampi, A, Milot, A, Gaudet, M, et al. Determinants of discontinuation of new courses of antihypertensive medications. *Journal of clinical epidemiology* 2002;**55**:728-735.

348. Caro, J, Speckman, J, Salas, M, Raggio, G and Jackson, J. Effect of initial drug choice on persistence with antihypertensive therapy: the importance of actual practice data. *Canadian Medical Association Journal* 1999;**160**:41-46.

349. Van Wijk, B, Klungel, O, Heerdink, E and de Boer, A. Rate and determinants of 10-year persistence with antihypertensive drugs. *Journal of hypertension* 2005;**23**:2101-2107.

350. Degli-Esposti, E, Sturani, A, Di-Martino, M, Falasca, P, Novi, M, Baio, G, et al. Long-term persistence with antihypertensive drugs in new patients. *Journal of Human Hypertension* 2002;**16**:439–444.

351. Bowman, L, Carlstedt, B, Hancock, E and Black, C. Adverse drug reaction (ADR) occurrence and evaluation in elderly inpatients. *Pharmacoepidemiology and drug safety* 1996;**5**:9-18.

352. Bowman, L, Carlstedt, B and Black, C. Incidence of adverse drug reactions in adult medical inpatients. *Canadian journal of hospital pharmacy* 1994;**47**:209-216.

353. Van-Wijk, B, Shrank, W, Klungel, O, Schneeweiss, S, Brookhart, A and Avorn, J. A cross-national study of the persistence of antihypertensive medication use in the elderly. *Journal of Hypertension* 2008;**26**:145-153.

354. Bautista, L. Predictors of persistence with antihypertensive therapy: results from the NHANES. *American journal of hypertension* 2008;**21**:183-188.

355. Shea, S, Stein, A, Basch, C, Freudenheim, J, Lantigua, R, Maylahn, C, et al. Independent associations of educational attainment and ethnicity with behavioral risk factors for cardiovascular disease. *American Journal of Epidemiology* 1991;**134**:567-582.

356. Kirscht, J and Rosenstock, I. Patient adherence to antihypertensive medical regimens. *Journal of Community Health* 1997;**3**:115-124.

357. Ross, S, Walker, A and MacLeod, M. Patient compliance in hypertension: role of illness perceptions and treatment beliefs. *Journal of human hypertension* 2004;**18**:607-613.

358. Becker, M. Role of patient attitudes and beliefs in patient compliance. *Combining psychological and drug therapy. Hypertension, depression and diabetes. Health and behavior: A research agenda interim report* 1981;67-73.

359. Chabot, I, Moisan, J, Grégoire, J and Milot, A. Pharmacist Intervention Program for Control of Hypertension. *Annals of Pharmacotherapy* 2003;**37**:1186-1193.

360. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *Journal of the American Medical Association* 2002;**288**:2998-3007.

361. Rosendorff, C, Black, HR, Cannon, C, Gersh, B, Gore, J, Izzo, J, et al. Treatment of hypertension in the prevention and management of ischemic heart disease: a scientific statement from the American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention. *Circulation* 2007;**115**:e28-e55.

362. Borzecki, A, Glickman, M, Kader, B and Berlowitz, D. The effect of age on hypertension control and management. *American journal of hypertension* 2006;**19**:520-527.

363. Grotto, I, Huerta, M and Sharabi, Y. Hypertension and socioeconomic status. *Current opinion in cardiology* 2008;**23**:335-339.

364. Steptoe, A, Feldman, P, Kunz, S, Owen, N, Willemsen, G and Marmot, M. Stress responsivity and socioeconomic status. A mechanism for increased cardiovascular disease risk? *European Heart Journal* 2002;**23**:1757-1763.

365. Colhoun, H, Hemingway, H and Poulter, N. Socio-economic status and blood pressure: an overview analysis. *Journal of human hypertension* 1998;**12**:91-110.

366. Lip, G and Beevers, D. Doctors, nurses, pharmacists and patients-the Rational Evaluation and Choice in Hypertension (REACH) survey of hypertension care delivery. *Blood Pressure* 1996;**1**:6-10.

367. Böhm, M, Baumhaekel, M, Mahfoud, F and Werner, C. From evidence to rationale: cardiovascular protection by Angiotensin II Receptor Blockers compared with Angiotensin-Converting Enzyme Inhibitors. *Cardiology* 2010;**117**:163-173.

368. Cicardi, M, Zingale, L, Bergamaschini, L and Agostoni, A. Angioedema associated with Angiotensin-Converting Enzyme Inhibitor use: outcome after switching to a different treatment. *Archives of internal medicine* 2004;**164**:910-913.

369. Goldberg, A, Dunlay, M and Sweet, C. Safety and tolerability of losartan potassium, an Angiotensin II Receptor Antagonist, compared with hydrochlorothiazide, atenolol, felodipne ER, and Angiotensin-Converting Enzyme Inhibitors for the treatment of systemic hypertension. *American journal of cardiology* 1995;**75**:793-795.

370. Cockerham, WC, Lueschen, G, Kunz, G and Spaeth, JL. Social stratification and self-management of health. *Journal of Health and Social Behavior* 1986;1-14.

371. Williams, D, Mohammed, S, Leavell, J and Collins, C. Race, socioeconomic status, and health: complexities, ongoing challenges, and research opportunities. *Annals of the New York Academy of Sciences* 2010;**1186**:69-101.

372. Hansen, R, Kim, M, Song, L, Tu, W, Wu, J and Murray, M. Comparison of methods to assess medication adherence and classify nonadherence. *Annals of Pharmacotherapy* 2009;**43**:413-422.

373. Choo, P, Rand, C, Inui, T, Lee, M-L, Cain, E, Cordeiro-Breault, M, et al. Validation of patient reports, automated pharmacy records, and pill counts with electronic monitoring of adherence to antihypertensive therapy. *Medical care* 1999;**37**:846-857.

374. Mabotuwana, T, Warren, J, Harrison, J and Kenealy, T. What can primary care prescribing data tell us about individual adherence to long-term medication?—comparison to pharmacy dispensing data. *Pharmacoepidemiology and drug safety* 2009;**18**:956-964.

375. Mohamed, I, Helms, P and McLay, J. Using primary care prescribing databases to determine drug switching and continuation of care. *Basic and clinical pharmacology and toxicology* 2012;**111**:396-401.

376. Health and Social Care Information Centre. 2014, Hospital Episode Statistics. Available at: http://www.hscic.gov.uk/hes. Accessed 13th March, 2014.

377. Health and Social Care Information Centre. 2014, What HES data are available? Available at: http://www.hscic.gov.uk/hesdata. Accessed 13th March, 2014.

378. Health and Social Care Information Centre. 2014, The processing cycle and HES data quality. Available at: http://www.hscic.gov.uk/article/1825/The-processing-cycle-and-HES-data-quality. Accessed 13th March, 2014.

379. The Clinical Practice Research Datalink (CPRD). 2014, Hospital Episode Statistic Data [HES]. Available at: https://cprdcw.cprd.com/datalinkages/hesdata.aspx. Accessed 13th March, 2014.

380. Health and Social Care Information Centre. 2014, Hospital Episode Statistics (HES) Analysis Guide. Available at: http://www.hscic.gov.uk/media/1592/HES-analysis-guide/pdf/HES_Analysis_Guide_Jan_2014.pdf. Accessed 13th March, 2014.

381. Health and Social Care Information Centre. 2014, Background to OPCS-4 development. Available at: http://systems.hscic.gov.uk/data/clinicalcoding/codingstandards/opcs4/background. Accessed 13th March, 2014.

382. The Clinical Practice Research Datalink (CPRD). 2014, File Downloads. Available at: https://cprdcw.cprd.com/downloads/FileDownloads.aspx#ReleaseNotes. Accessed 14th March, 2014.

383. Personal Social Services Research Unit. 2012, Unit Costs o Health and Social Care. Available at: http://www.pssru.ac.uk/project-pages/unit-costs/2012/#sections. Accessed 14th March, 2014.

384. Department of Health. 2012, NHS reference costs: financial year 2011 to 2012. Available at: https://www.gov.uk/government/publications/nhs-reference-costs-financial-year-2011-to-2012. Accessed 14th March, 2014.

385. Health and Social Care Information Centre. 2012, HRG4 2011/12 Local Payment Grouper. Available at: http://www.hscic.gov.uk/article/2328/HRG4-201112-Local-Payment-Grouper. Accessed 14th March, 2014.

386. Dawson, B and Trapp, R (Editors). *Basic and clinical biostatistics*. 4th ed. 2004, Lange Medical Books/McGraw-Hill: New York.

387. Tabachnick, B and Fidell, L (Editors). *Using Multivariate Statistics*. 5th ed. 2008, Montreal: Pearson/A & B: Boston.

388. Briggs, A and Gray, A. The distribution of health care costs and their statistical analysis for economic evaluation. *Journal of health services research & policy* 1998;**3**:233-245.

389. Barber, J and Thompson, S. Analysis and interpretation of cost data in randomised controlled trials: review of published studies. *British Medical Journal* 1998;**317**:1195-1200.

390. Thompson, S and Barber, J. How should cost data in pragmatic randomised trials be analysed? *British Medical Journal* 2000;**320**:1197-1200.

391. Bradley, J. Distribution-free statistical tests. Englewood Cliffs: NJ:Prentice-Hall, 1968

392. Fung, V, Huang, J, Brand, R, Newhouse, J and Hsu, J. Hypertension treatment in a medicare population: adherence and systolic blood pressure control. *Clinical therapeutics* 2007;**29**:972-984.

393. Vallès, J, Barreiro, M, Cereza, G, Ferro, J, nez, M, Escribà, J-M, et al. A prospective multicenter study of the effect of patient education on acceptability of generic prescribing in general practice. *Health Policy* 2003;**65**:269-275.

394. Usher-Smith, J, Ramsbottom, T, Pearmain, H and Kirby, M. Evaluation of the cost savings and clinical outcomes of switching patients from atorvastatin to simvastatin and losartan to candesartan in a Primary Care setting. *International Journal of Clinical Practice* 2007;**61**:15-23.

395. Wald, D, Law, M, Morris, J, Bestwick, J and Wald, N. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. *American journal of medicine* 2009;**122**:290-300.

396. Gradman, A, Basile, J, Carter, B and Bakris, G. Combination therapy in hypertension. *Journal of Clinical Hypertension* 2011;**13**:146-154.

397. Bramley, T, Gerbino, P, Nightengale, B and Frech-Tamas, F. Relationship of blood pressure control to adherence with antihypertensive monotherapy in 13 managed care organizations. *Journal of Managed Care Pharmacy* 2006;**12**:239-245.

398. Selak, V, Elley, C, Bullen, C, Crengle, S, Wadham, A, Rafter, N, et al. Effect of fixed dose combination treatment on adherence and risk factor control among patients at high risk of cardiovascular disease: randomised controlled trial in primary care. *British Medical Journal* 2014;**348**:g3318.

399. Lewington, S, Clarke, R, Qizilbash, N, Peto, R and Collins, R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;**360**:1903-1913.

400. Go, A, Mozaffarian, D, Roger, V, Benjamin, E, Berry, J, Borden, W, et al. Heart disease and stroke statistics-2013 update: a report from the American Heart Association. *Circulation* 2013;**127**:e6-e245.

401. Rihal, C, Ryan, J, Singh, M, Lennon, R, Bresnahan, J, Liesinger, J, et al. Antihypertensive medication adherence and subsequent healthcare utilization and costs. *Am J Manag Care* 2010;**16**:568-576.

402. Yusuf, S, Hawken, S, Ôunpuu, S, Dans, T, Avezum, A, Lanas, F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;**364**:937-952.

403. Schneeweiss, S, Walker, A, Glynn, R, Maclure, M, Dormuth, C and Soumerai, S. Outcomes of reference pricing for Angiotensin-Converting–Enzyme Inhibitors. *New England Journal of Medicine* 2002;**346**:822-829.

404. Sherrill, B, Halpern, M, Khan, S, Zhang, J and Panjabi, S. Single-Pill vs Free-Equivalent Combination Therapies for Hypertension: A Meta-Analysis of Health Care Costs and Adherence. *Journal of Clinical Hypertension* 2011;**13**:898-909.

405. Schroeder, K, Fahey, T and Ebrahim, S. How can we improve adherence to blood pressure–lowering medication in ambulatory care? Systematic review of randomized controlled trials. *Archives of Internal Medicine* 2004;**164**:722-732.

406. Düsing, R. Overcoming barriers to effective blood pressure control in patients with hypertension. *Current Medical Research and Opinion* 2006;**22**:1545-1553.

407. Storm, B. Sample Size Considerations for Pharmacoepidemiology Studies. In: *Textbook oF pharmacoepidemiology*. By: Storm, B and Kimmel, S (Editors). 2006, John Wiley & Sons Ltd: West Sussex, England:25-33.

408. Dupont, W and Plummer, W. Power and sample size calculations: a review and computer program. *Controlled clinical trials* 1990;**11**:116-128.

409. Lerman, J. Study design in clinical research: sample size estimation and power analysis. *Canadian journal of anaesthesia* 1996;**43**:184-191.

410. Silverman, D. Interpreting Qualitative data- Methods for analysing talk, text and interaction. Sage Publications: Thousand Oaks, California, 2001

411. Murphy, E, Dingwall, R, Greatbatch, D, Parker, S and Watson, P. Qualitative research methods in health technology assessment: a review of the literature. *Health technology assessment* 1998;**2**:3-9.

412. Green, J and Thorogood, N. Qualitative methods for health research. Sage Publications: London, 2004

413. Bryman, A. Social Research Methods. Oxford University Press: Oxford, 2008

414. Smith, F. Conducting your Pharmacy Practice Research Project. Pharmaceutical Press: London, 2005

415. Smith, F. Research methods in pharmacy practice. Pharmaceutical Press: London, 2002

416. Fontana, A and Frey, J. The interview: From neutral stance to political involvement. In: *Strategies of qualitative enquiry*. By: Denzin, N and Lincoln, Y (Editors). 2005, Sage: London.

417. NHS England. 2014, CCG Directory. Available at: http://www.england.nhs.uk/resources/ccg-directory/. Accessed 15th August, 2014.

418. Publich Health England. 2014, National General Practice Profiles. Available at: http://fingertips.phe.org.uk/profile/general-practice/data. Accessed 20th August 2014.

419. Carlsen, B, Glenton, C and Pope, C. Thou shalt versus thou shalt not: a meta-synthesis of GPs' attitudes to clinical practice guidelines. *British Journal of General Practice* 2007;**57**:971-978.

420. Toner, R, Snape, C, Acton, S and Blenkiron, P. Do general practitioners adhere to NICE guidelines for depression? Systematic Questionnaire Survey. *Primary Health Care Research & Development* 2010;**11**:123-131.

421. Francke, A, Smit, M, de Veer, A and Mistiaen, P. Factors influencing the implementation of clinical guidelines for health care professionals: a systematic meta-review. *BMC medical informatics and decision making* 2008;**8**:38-49.

422. Davis, D and Taylor-Vaisey, A. Translating guidelines into practice: a systematic review of theoretic concepts, practical experience and research evidence in the adoption of clinical practice guidelines. *Canadian Medical Association Journal* 1997;**157**:408-416.

423. Pope, C, Zeibland, S and Mays, N. Analysing qualitative data. In: *Qualitative research in health care*. By: Pope, C and Mays, N (Editors). 2006, BlackWell: Oxford:63-81.

424. Guest, G, MacQueen, K and Namey, E. Applied thematic analysis. Sage Publications: London, 2012

425. Spencer L, Ritchie J and O'Connor, W. Analysis: practices, principles and processes. In: *Qualitative research practice*. By: Ritchie J and Lewis J. (Editors). 2004, Sage Publications: London:199-218.

426. Auerbach, C and Silverstein, L. Qualitative data: An introduction to coding and analysis. NYU press: 2003

427. Ziebland, S and McPherson, A. Making sense of qualitative data analysis: an introduction with illustrations from DIPEx (personal experiences of health and illness). *Medical Education* 2006;**40**:405-414.

428. Strauss, A and Corbin, J. Basics of qualitative research: grounded theory procedures and techniques. Thousand Oaks: California, 1990

429. Rasmussen, H, Søndergaard, J, Kampmann, J and Andersen, M. General practitioners prefer prescribing indicators based on detailed information on individual patients: a Delphi study. *European journal of clinical pharmacology* 2005;**61**:237-241.

430. Prosser, H and Walley, T. A qualitative study of GPs' and PCO stakeholders' views on the importance and influence of cost on prescribing. *Social science & medicine* 2005;**60**:1335-1346.

431. Prosser, H and Walley, T. New drug uptake: qualitative comparison of high and low prescribing GPs' attitudes and approach. *Family practice* 2003;**20**:583-591.

432. Elliott, H. Focus on the ONTARGET results. *Journal of Hypertension* 2009;**27**:S8-S10.

433. Vegter, S and de Jong-van, L. Misdiagnosis and mistreatment of a common side-effect-Angiotensin-Converting Enzyme Inhibitor-induced cough. *British Journal of Clinical Pharmacology* 2010;**69**:200-203.

434. Dicpinigaitis, P. Angiotensin-Converting Enzyme Inhibitor-induced cough. *Chest* 2006;**129**:169S-173S.

435. Greving, J, Denig, P, Van der Veen, W, Beltman, F, Sturkenboom, M and Haaijer-Ruskamp, F. Determinants for the adoption of Angiotensin II Receptor Blockers by general practitioners. *Social Science & Medicine* 2006;**63**:2890-2898.

436. Colloca, L and Miller, F. The nocebo effect and its relevance for clinical practice. *Psychosomatic medicine* 2011;**73**:598-603.

437. Cocco, G. Erectile dysfunction after therapy with metoprolol: the Hawthorne effect. *Cardiology* 2009;**112**:174-177.

438. Mondaini, N, Gontero, P, Giubilei, G, Lombardi, G, Cai, T, Gavazzi, A, et al. Finasteride 5 mg and sexual side effects: how many of these are related to a nocebo phenomenon? *Journal of Sexual Medicine* 2007;**4**:1708-1712.

439. Faasse, K, Gamble, G, Cundy, T and Petrie, K. Impact of television coverage on the number and type of symptoms reported during a health scare: a retrospective pre–post observational study. *British Medical Journal* 2012;**2**:e001607.

440. Carthy, P, Harvey, I, Brawn, R and Watkins, C. A study of factors associated with cost and variation in prescribing among GPs. *Family Practice* 2000;**17**:36-41.

441. House of Commons Health Committee. The influence of the pharmaceutical industry, Fourth Report of Session 2004-05*.* 2005. Available Accessed

442. Prosser, H and Walley, T. New drug prescribing by hospital doctors: the nature and meaning of knowledge. *Social Science & Medicine* 2006;**62**:1565-1578.

443. Jones, M, Greenfield, S and Bradley, C. Prescribing new drugs: qualitative study of influences on consultants and general practitioners. *British Medical Journal* 2001;**323**:378-384.

444. Goldsmith, D and Duerden, M. Statins: to switch or not to switch? *Prescriber* 2008;**19**:35-41.

445. Deedwania, P, Barter, P, Carmena, R, Fruchart, J, Grundy, S, Haffner, S, et al. Reduction of low-density lipoprotein cholesterol in patients with coronary heart disease and metabolic syndrome: analysis of the Treating to New Targets study. *Lancet* 2006;**368**:919–928.

446. Cabana, M, Rand, C, Powe, N, Wu, A, Wilson, M, Abboud, P, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. *Journal of the American Medical Association* 1999;**282**:1458-1465.

447. Schoen, C, Osborn, R, Huynh, P, Doty, M, Peugh, J and Zapert, K. On the front lines of care: primary care doctors' office systems, experiences, and views in seven countries. *Health Affairs* 2006;**25**:w555-w571.

448. Godman, B, Wettermark, B, Van Woerkom, M, Fraeyman, J, Alvarez-Madrazo, S, Berg, C, et al. Multiple policies to enhance prescribing efficiency for established medicines in Europe with a particular focus on demand-side measures: findings and future implications. *Frontiers in Pharmacology* 2014;**5**:106-115.

449. Wettermark, B, Pehrsson, A, Juhasz-Haverinen, M, Veg, A, Edlert, M, Tornwall-Bergendahl, G, et al. Financial incentives linked to self-assessment of prescribing patterns: a new approach for quality improvement of drug prescribing in primary care. *Quality in Primary Care* 2009;**17**:179-189.

450. Ashworth, M, Golding, S and Majeed, A. Prescribing indicators and their use by primary care groups to influence prescribing. *Journal of clinical pharmacy and therapeutics* 2002;**27**:197-204.

451. Johnson, D. Clinicians' attitudes to clinical practice guidelines. *Medical Journal of Australia* 2003;**178**:354-355.

452. Carlsen, B and Bringedal, B. Attitudes to clinical guidelines—do GPs differ from other medical doctors? *British Medical Journal Quality & Safety* 2011;**20**:158-162.

453. Christakis, D and Rivara, F. Pediatricians' awareness of and attitudes about four clinical practice guidelines. *Pediatrics* 1998;**101**:825-830.

454. Cranney, M, Warren, E, Barton, S, Gardner, K and Walley, T. Why do GPs not implement evidence-based guidelines? A descriptive study. *Family Practice* 2001;**18**:359-363.

455. Kastner, M, Bhattacharyya, O, Hayden, L, Makarski, J, Estey, E, Durocher, L, et al. Guideline uptake is influenced by six implementability domains for creating and communicating guidelines: a realist review. *Journal of Clinical Epidemiology* 2015;**68**:498–509.

456. Campbell, S, Cantrill, J and Roberts, D. Prescribing indicators for UK general practice: Delphi consultation study. *British Medical Journal* 2000;**321**:425-430.

457. Stevenson, F, Greenfield, S, Jones, M, Nayak, A and Bradley, C. GPs' perceptions of patient influence on prescribing. *Family Practice* 1999;**16**:255-261.

458. Dowell, J, Snadden, D and Dunbar, J. Rapid prescribing change, how do patients respond? *Social Science & Medicine* 1996;**43**:1543-1549.

459. Weissenfeld, J, Stock, S, Lüngen, M and Gerber, A. The nocebo effect: A reason for patients' non-adherence to generic substitution? *International Journal of Pharmaceutical Sciences* 2010;**65**:451-456.

460. Health and Social Care Information Centre. 2014, Prescriptions Dispensed in the Community, Statistics for England - 2003-2013 Available at: http://www.hscic.gov.uk/catalogue/PUB14414/pres-disp-com-eng-2003-13-rep.pdf. Accessed 10th March, 2015.

461. Attwood, S, Bird, R, Burch, K, Casadei, B, Coats, A, Conway, J, et al. Within-patient correlation between the antihypertensive effects of atenolol, lisinopril and nifedipine. *Journal of hypertension* 1994;**12**:1053-1060.

462. Makani, H, Bangalore, S, Desouza, KA, Shah, A and Messerli, FH. Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomised trials. *British Medical Journal* 2013;**346**:

463. Prior, M, Guerin, M and Grimmer-Somers, K. The effectiveness of clinical guideline implementation strategies–a synthesis of systematic review findings. *Journal of evaluation in clinical practice* 2008;**14**:888-897.

464. Heneghan, C, Perera, R, Mant, D and Glasziou, P. Hypertension guideline recommendations in general practice: awareness, agreement, adoption, and adherence. *British Journal of General Practice* 2007;**57**:948-952.

465. Walley, T and Mossialos, E. Financial incentives and prescribing. In: *Financial incentives and prescribing in regulating pharmaceuticals in Europe: striving for efficiency, equity and quality*. By: Walley, T, Mossialos, E, and Mrazek, M (Editors). 2004, Open University Press: Buckingham:177-195.

466. Wettermark, B, Pehrsson, Juhasz-Haverinen, M, Veg, A, Edlert, M, Trnwall-Bergendahl, G, et al. Improving the quality and efficiency of drug prescribing in primary care by means of financial incentives. *Pharmacoepidemiology and Drug Safety* 2009;**18**:S261.

467. Marteau, T, Ashcroft, R and Oliver, A. Using financial incentives to achieve healthy behaviour. *British Medical Journal* 2009;**338**:b1415.

468. Walley, T, Mrazek, M and Mossialos, E. Regulating pharmaceutical markets: improving efficiency and controlling costs in the UK. *International journal of health planning and management* 2005;**20**:375-398.

469. SScott, A, Sivey, P, Ait Ouakrim, D, Willenberg, L, Naccarella, L, Furler, J, et al. The effect of financial incentives on the quality of health care provided by primary care physicians. *Cochrane Database of Systematic Reviews* 2011;**9**:CD008451.

470. Häuser, W, Hansen, E and Enck, P. Nocebo phenomena in medicine: their relevance in everyday clinical practice. *Deutsches Ärzteblatt International* 2012;**109**:459-465.

471. Allan, M, Lexchin, J and Wiebe, N. Physician Awareness of Drug Cost: A Systematic Review. *PLoS Med* 2007;**4**:e283.

472. National Institute for Health and Care Excellence. 2015, Medicines optimisation: the safe and effective use of medicines to enable the best possible outcomes. Available at: https://www.nice.org.uk/guidance/ng5/resources/medicines-optimisation-the-safe-and-effective-use-of-medicines-to-enable-the-best-possible-outcomes-51041805253. Accessed 5th December, 2015.

473. Payne, R. NICE on medicines optimisation. *Prescriber* 2015;**26**:6-6.

474. Vrijens, B, Vincze, G, Kristanto, P, Urquhart, J and Burnier, M. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. *British Medical Journal* 2008;**336**:1114-1117.

Appendices

Appendix 1 Description of the CPRD database

See supplementary file_1 in the accompanying CD at the end of the thesis.

Appendix 2 List of Read codes for primary hypertension

See supplementary file_2 in the accompanying CD at the end of the thesis.

Appendix 3 List of product codes for the six antihypertensive drug classes

See supplementary file_3 in the accompanying CD at the end of the thesis.

Appendix 4 Segmented regression model to estimate the impact of the BCBV policy

$Yt = \beta_0 + \beta_1$*time + β_2*BCBV intervention + β_3*time after BCBV intervention + β_4*launch of generic losartan + β_5*time after launch of generic losartan + β_6*launch of generic perindopril + β_7*time after launch of generic perindopril + e_t

Y_t : monthly outcome variable

e_t: error term at the time t which describes the random variability in outcome not explained by the model

time: continuous variable referring to time, in months, from start of the observation period, range from 1 to 72 from the start to end of the study period

BCBV intervention: binary variable, takes the value of zero and one for the time before and after intervention implementation, respectively, i.e. zero from start till month 36, then one afterward

time after BCBV intervention: a continuous variable counting the number of months after the BCBV intervention at time t, coded 0 before the intervention and (time-36) after the intervention

launch of generic losartan: binary variable, takes the value of zero and one for the time before and after intervention implementation, respectively, i.e. zero from start till month 51, then one afterward

time after launch of generic losartan: a continuous variable counting the number of months after the launch of generic losartan at time t, coded 0 before the intervention and (time-51) after the intervention

launch of generic perindopril: binary variable, takes the value of zero and one for time before and after intervention implementation, respectively, i.e. zero from start till month 18, then one afterward

time after launch of generic perindopril: a continuous variable counting the number of months after the launch of generic perindopril at time t, coded 0 before the intervention and (time-18) after the intervention

Appendix 5 Diagnostic tests for the GLM model

See supplementary file_4 in the accompanying CD at the end of the thesis.

Appendix 6 Model diagnostics for Cox regression

See supplementary file_5 in the accompanying CD at the end of the thesis.

Appendix 7 Description of the five main files within the HES dataset

See supplementary file_6 in the accompanying CD at the end of the thesis.

Appendix 8 List of ICD-10 codes for hypertension-related complications

See supplementary file_7 in the accompanying CD at the end of the thesis.

Appendix 9 List of Read codes for hypertension-related medical visits and consultations

See supplementary file_8 in the accompanying CD at the end of the thesis.

Appendix 10 List of Read codes for hypertension-related outpatient referrals

See supplementary file_9 in the accompanying CD at the end of the thesis.

Appendix 11 List of OPCS-4 codes for hypertension-related procedures

See supplementary file_10 in the accompanying CD at the end of the thesis.

Appendix 12 Invitation letter to the practice manager of the selected GP practices

See supplementary file_11 in the accompanying CD at the end of the thesis.

Appendix 13 Invitation letter to the senior GP of the selected GP practices

See supplementary file_12 in the accompanying CD at the end of the thesis.

Appendix 14 Participant information sheet for the GPs

See supplementary file_13 in the accompanying CD at the end of the thesis.

Appendix 15 Advertising letter to the CCGs

See supplementary file_14 in the accompanying CD at the end of the thesis.

Appendix 16 Invitation letter for the prescribing advisers to the CCGs

See supplementary file_15 in the accompanying CD at the end of the thesis.

Appendix 17 Participant information sheet for the prescribing advisers

See supplementary file_16 in the accompanying CD at the end of the thesis

Appendix 18 Interview schedules for the GPs

See supplementary file_17 in the accompanying CD at the end of the thesis.

Appendix 19 Interview schedules for the prescribing advisers

See supplementary file_18 in the accompanying CD at the end of the thesis.

Appendix 20 Ethics approval letter from the Faculty of Medicine and Health Sciences Research Ethics Committee at University of Nottingham

See supplementary file_19 in the accompanying CD at the end of the thesis.

Appendix21 Ethics approval letter from the NHS Research & Development Department at Nottinghamshire Healthcare Trust

See supplementary file_20 in the accompanying CD at the end of the thesis.

Appendix 22 Ethics approval letter from the NHS Research & Development Department at Derbyshire Healthcare Trust

See supplementary file_21 in the accompanying CD at the end of the thesis.

Appendix 23 Ethics approval letter from the NHS Research & Development Department at Leicestershire CCG

See supplementary file_22 in the accompanying CD at the end of the thesis.