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Investigating the cost-effectiveness of antiplatelet medications in patients with type 2 diabetes for the secondary prevention of acute coronary syndromes

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Abstract

Acute Coronary Syndrome (ACS)is a condition with very high clinical burden and financial burden worldwide and in the UK. ACS is more common in populations with Type 2 Diabetes Mellitus(T2DM), due to the vascular complications that people with T2DM face. This fact results in increased occurrence of ACS compared to the general population. ACS management is complex in T2DM populations because of the additional need for glycaemic control. Oral antiplatelet medication (clopidogrel, aspirin) is among the most important treatments for the secondary prevention of ACS.

New oral antiplatelet agents (ticagrelor, prasugrel) were compared as alternative treatments to clopidogrel in the general population. The new agents performed better than clopidogrel in terms of effectiveness and cost-effectiveness. The results of the effectivess of those agents in T2DM subgroups were available, but they were presented as an ad hoc analysis of the initial trials. This gap in research provided an opportunity for investigating effectiveness of antiplatelet medications in T2DM populations using real world data.

This study investigated the economic impact of different antiplatelet regimens in people with T2DM post-ACS, from the perspective of the NHS in England. The study aimed to gain an understanding of the characteristics of people with T2DM prescribed antiplatelet medications for secondary prevention post-ACS (demographics, clinical outcomes, medication usage, medication adherence, healthcare resource used, and costs), explain the variation in those clinical outcomes and costs, and investigate the effectiveness and cost-effectiveness of antiplatelet regimens in this population.

Using routinely collected data from the Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES), a cohort study was carried out in order to investigate the effect of different antiplatelet regimens in patients with T2DM. Inverse probability treatment weights were obtained from propensity score models, and those weights were used to address the confounding that arised from the non-random assignment in antiplatelet regimens in the retrospectively observed data.

The time to event analysis found that the newer antiplatelet medications had better results than aspirin-clopidogrel for the outcomes investigated. The time to reccurence of a major adverse cardiovascular event (MACE) in patients treated with aspirin-prasugrel was approximately 4.4 times longer [Time Ratio (TR): 4.42; 95%CI: 1.73 to 11.28] compared to that of patients on aspirin-clopidogrel. No effect was found in patients who were prescribed aspirin-ticagrelor. Aspirin-prasugrel was associated with a 96% decrease in the hazard rate of stroke [Hazard Ratio (HR): 0.04 ;95% CI: 0.01 to 0.32] and aspirin-ticagrelor with a 78% decrease [Hazard Ratio (HR): 0.22 ;95% CI: 0.05 to 0.95] when compared with aspirin-clopidogrel.

The time to recurrence of a bleeding event in patients on aspirin-ticagrelor was approximately 12 times longer compared to that of patients on aspirin-clopidogrel [TR:11.89; 95%CI: 0.95 to 148.03]. No effect in bleeding was found in patients who were prescribed aspirin-prasugrel. Patients on aspirin-ticagrelor and aspirin-prasugrel survived 2.6 times [TR: 2.57;95% CI: 1.61 to 4.12] and 1.4 times longer [TR: 1.43;95% CI: 1.01 to 2.06] compared to patients treated with aspirin-clopidogrel. The findings are in partial accordance with the literature around the effectiveness of newer antiplatelet agents versus aspirin-clopidogrel.

The cost association analysis found that, on average, patients on aspirin-ticagrelor and aspirin-clopidogrel incur annually £6345 in total care health care costs. Patients on aspirin-prasugrel incurred 35% less costs (£4098).

The adherence analysis found that the average proportion of days covered (PDC) for all regimens is high and above the cut-off point of 80%. Patients on dual antiplatelet therapy regimens started discontinuing their therapies after 180 days. For the groups of aspirin-ticagrelor and aspirin-prasugrel there where no patients continuing their prescription after 450 days. In the aspirin-clopidogrel group the number of patients with prescriptions lasting more than 450 days was decreasing and the number of patients continuing with therapy for more than 450 days and less than 720 days was very small.

A decision analytical model was used to estimate the cost-effectiveness of alternative dual antiplatelet regimens and aspirin only. The analysis demonstrated that aspirin-ticagrelor generated more QALYs [0.67;95% CI:0.05 to 1.22] compared with aspirin only and costs [£1459.96; 95% CI: -5797.66 to 10056.77] over the lifetime horizon. Aspirin-prasugrel and aspirin-clopidogrel were extendedly dominated.

The probabilistic model estimated that aspirin-ticagrelor had the highest probability of being cost-effective for willingness to pay levels higher than £2000 per QALY. For a maximum willingness-to pay of £20000 per QALY the probability of cost-effectiveness was 90%. These findings were in accordance with similar studies for the general population.

This study allowed for a head-to-head comparison of alternative antiplatelet regimens for T2DM patients who suffered an ACS. Study findings were relevant for England only and not UK wide, because of the linkage of primary and secondary care data. The time-to-event and the cost analyses, even though they were carried out with the use of doubly robust estimation methods, potentially did not sufficiently address some of the confounding. In the Markov model, it was not possible to use a more complex treatment pattern in the patients who were assigned in DAPT regimen, and that could result in the potential overestimation cost-effectiveness.

Many T2DM patients were on monotherapy regimens for secondary prevention, even though this is not suggested in the clinical guidelines. Further investigation for this specific group is needed. T2DM patients who are on a DAPT regimen, tend to discontinue the treatment from the sixth month. This practice implication indicates the need for interventions that reduce DAPT discontinuation.

Conference presentations

G. Gkountouras, R.A. Elliott, A.J. Avery, L .Tanajewski (2018) "Investigating Adherence in Adults with Type 2 Diabetes (T2DM) Prescribed Antiplatelet Medications for Secondary Prevention Following Acute Coronary Syndrome (ACS) Using Large UK Healthcare Databases"

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ACS	Acute Coronary Syndromes
ADP	Adenosine Diphosphate
AF	Atrial Fibrilation
AFT	Accelerated Failure Time Model
AIC	Akaike Information Criterion
AMP	Actual Medicinal Product
AMPP	Actual Medicinal Product Pack
ARBS	Angiotensin II Receptor Blockers
ASA	Acetylsalicylic Acid
ATE	Average Treatment Effect
ATT	Average Treatment Effect On The Treated
BHPS	British Household Panel Survey
BIC	Bayesian Information Criterion
BMI	Body Mass Index
BNF	British National Formulary
CABG	Coronary Artery Bypass Graft
CBPS	Covariate Balancing Propensity Scores
CEAC	Cost-Effectiveness Acceptability Curve
CHF	Congestive Heart Failure
CI	Confidence Interval
Clop-AM	Clopidogrel Active Metabolite
COX-1	Cyclooxygenase-1 Inhibitors
CPRD	Clinical Practice Research Datalink
CPT-4	Common Procedural Terminology Version 4
CREDO	Clopidogrel for the reduction of Events During Observation trial
CVD	Cardiovascular Disease
CURE	Clopidogrel in Unstable Angina to prevent Recurrent Events trial
DALY	Disability Adjusted Life Years
DAPT	Dual Antiplatelet Treatment
DBP	Diastolic Blood Pressure
DIN-Link	Doctors Independent Network
ECHO-T2DM	The Economic And Health Outcomes Model For T2DM
EEE	Extended Estimating Equations
EGFR	Estimated Glomerular Filtration Rate
EHR	Electronic Health Records
EMA	European Medicines Agency
EMIS	Egton Medical Information Systems Health
EU	European Union
FRISC	Fast Revascularisation In Instability In Coronary Disease
GBM	Generalised Boosted Models
GLM	Generalised Linear Models
GMM	Generalised method of moments
GP	General Practitioner

GRACE	Global Registry Of Acute Coronary Events
HDL	High Density Lipoprotein
HES	Hospital Episode Statistics
HR	Hazard Ratio
ICD	International Classification Of Diseases
ICER	Incremental Cost-Effectiveness Ratio
ICPC	International Classification Of Primary Care
IHD	Ischaemic Heart Diseases
IMD	Index Of Multiple Deprivation
IMS	Intercontinental Marketing Services
IMS-CORE	IMS Centre For Outcomes Research Model
INPS	In Practice Systems Ltd
IPTW	Inverse Probability Of Treatment Weighting
ISAC	Independent Scientific Advisory Committee
ITALIC	Is There A Life For Des After Discontinuation Of Clopidogrel
JADE	Januvia Diabetes Economic Model
LDL	Low Density Lipoprotein
LR	Likelihood Ratio
LYG	Life Year Gained
MACE	Major Adverse Cardiovascular Event
MHRA	Medicines & Healthcare Products Regulatory Agency
MI	Myocardial Infarction
MMW-S	Marginal Mean Weighting Through Stratification
MNPS	Multinomial Propensity Scores
MPR	Medication Possession Ratio
MPT	Modified Park Test
NHS	National Health Service
NHS IA	NHS Information Authority
NICE	The National Institute For Health And Care Excellence
NIHR	National Institute For Health Research
NIPPON	Nobori Dual Antiplatelet Therapy As Appropriate Duration
NMB	Net Monetary Benefit
NN	Nearest Neighbour
NOS	No Other Symptoms
NSTEMI	Non St-Segment Elevation Myocardial Infarction
OLS	Ordinary Least Squares
ONS	Office For National Statistics
OPCS	Office Of Population Censuses And Surveys
OXMIS	Oxford Medical Information System
PCI	Percutaneous Coronary Intervention
PDC	Proportion Of Days Covered
PH	Proportional Hazards
PLATO	Platelet Inhibition And Patient Outcomes Trial
pPCI	Primary Percutaneous Coronary
PSSRU	Personal Social Services Research Unit

PURSUIT	Platelet Glycoprotein Iib/Iiia In Unstable Angina: Receptor Suppression Using Integrilin (Eptifibatide) Therapy
PVD	Peripheral Vascular Disease
QALY	Quality Adjusted Life Year
RCT	Randomised Control Trial
SAIL	Secure Anonymised Information Linkage Databank
SBP	Systolic Blood Pressure
ST-ACS	St-Segment Elevation Acute Coronary Syndrome
STEMI	St-Segment Elevation Myocardial Infarction
SUTVA	Stable Unit Treatment Value Assumption
T2DM	Type 2 Diabetes Mellitus
THIN	The Health Improvement Network
TIA	Transient Ischaemic Attack
TIMI	Thrombolysis In Myocardial Infarction
TPP	The Phoenix Partership
TRITON-TIMI 38	Trial To Assess Improvement In Therapeutic Outcomes By Optimizing Platelet Inhibition With Prasugrel Thrombolysis In Myocardial Infarction 38
UKPDS	United Kingdom Prospective Diabetes Study
VMP	Virtual Medicinal Product
VMPP	Virtual Medicinal Product Pack
WHO	World Health Organisation
WTP	Willingness To Pay
YLD	Years Lost To Disability
YLL	Years Of Life Lost

1. Chapter One: Thesis Introduction

1.1 Introductory remarks

Acute coronary syndromes (ACS) represent a subgroup of ischaemic heart diseases (IHD) that range from unstable angina to transmural myocardial infarction. The classification of an ACS is based on information from three criteria; 1) previous clinical history; 2) the presence or absence of ST-segment elevation in electrocardiogram (ST-ACS, non ST-ACS); 3) changes in the serum concentration of cardiac enzymes and markers(1) such as troponin I and troponin T. The mechanism that causes ACS is atherosclerosis of coronary arteries, where formation of atheromatous plaques in arteries develops over time. Ischaemic heart disease is the leading cause of death globally, responsible for seven million deaths in 2010 and an age-standardised death rate of 106 per 100000(2). The main drivers of increasing cardiovascular mortality during the last 25 years according to Roth et al are population aging and population growth (3). As a result, IHD is the condition with the highest disease burden globally, being responsible for 129 million disability-adjusted life-years (DALYs), equivalent to 1884 DALYs per 100000 of population in 2010 (4). In the UK, IHD is responsible for the most years of life lost (YLL), it is in the top 25 causes of years lost to disability (YLD), and approximately 1.5 million DALYs in 2010 were attributed to IHD (5). In the US, IHD is the leading cause of disease burden and was responsible for 560000 deaths in 2010 (6).

Among the populations that suffer from ACS, people with T2DM are a particular priority. This is because of the increasing prevalence of T2DM over time and because T2DM has symptoms that can lay the foundations for heart disease if T2DM is consistently not well managed.

As a long-term condition, T2DM can lead to several comorbidities, which can be attributed to vascular complications. Those complications can be separated into two categories, microvascular and macrovascular. Among the macrovascular complications is cardiovascular disease (CVD), which incorporates ACS. Macro and microvascular complications can be attributed to symptoms found in people with diabetes such as increased glucose levels (hyperglycaemia), oxidative stress, insulin deficiency and resistance, imbalance in the expression of microRNAs involved in vascular repair, and vascular hyperglycaemic memory. All these mechanisms result in the dysfunction of platelets which lead to atherogenesis (7). Therefore, this connection between T2DM and abnormal platelet function puts T2DM populations at risk for CVD and ACS.

Furthermore, an additional link between T2DM and CVD has to do with the increase of T2DM prevalence over time. Several studies have been carried out with the objective to provide global estimates of T2DM prevalence with future population and prevalence estimates. Green reported a global prevalence estimate of 150 million patients in 2003, and expected prevalence to reach 300 million by 2025 (8). Wild et al report an estimated worldwide prevalence for all age-groups of T2DM to be 2.8% in 2000. Their projections suggest that in 2030 prevalence will be 4.4%, with diabetes affecting 366 million people (9). Zaini concurs with the findings of Wild et al. and suggests that the majority of increase in diabetes cases will occur in China and Southeast Asian nations (10). Shaw gives more up-to-date estimates of national diabetes prevalence for all countries on a 20-year period (2010-2030). According to their study, the total number of affected people in 2010 was 285 million (6.4%) and in 2030 would be 439 million (7.7%) (11). Danaei et al combined several sources in their analysis in order to estimate trends in prevalence of T2DM from 1980-2008 by gender, world region and country (12). Based on their review they estimated that the affected people with T2DM in 2008 are 347 million, a value much higher than the estimates of Wild et al and Shaw et al. Finally, the latest study that was using a method similar to Danaei and colleagues, estimated the number of people with diabetes in 2013 to be 382 million, and expected to increase in 592 million by 2035 with the highest increase in low and middle income countries (13). Based on the findings of Guariguata(13), it can be seen that the clinical burden of T2DM is quite high and increasing over time. T2DM is globally in the top ten causes of death globally, responsible for approximately 1.3 million deaths and a death rate of 20 per 100000 people in 2010. The numbers of DALYs in 2010 lost due to diabetes in UK were estimated to be 29.3 per 100000 of population (14).

The main finding from disease burden and epidemiological studies is the increase of prevalence of T2DM over time on a global scale, with increased population size, better living standards in low and middle income countries and the higher proportion of middle aged people attributing to this phenomenon (8-10). More diabetes sufferers over time means a higher number of complications, which inevitably will increase the number of CVD and ACS events. As a result of the increased events, higher clinical and financial disease burden in healthcare systems and society will be imposed in the future.

For the secondary prevention against the ACS a range of interventions have been suggested from the clinical guidelines, which include non-pharmaceutical and pharmaceutical interventions. There are suggestions for improving dietary habits, exercise reducing blood pressure and antithrombotic protection. Antiplatelet treatment is among the most important pharmaceutical treatments for the secondary prevention of ACS. Usually patients are treated with low dose aspirin and an additional antiplatelet medication, clopidogrel. Clopidogrel, was a medicine that improved the treatment of patients who suffered from ACS. Newer antiplatelet agents (ticagrelor, prasugrel) entered the market in order to substitute clopidogrel as the second medication of choice in dual antiplatelet therapy regimens (DAPT). In this thesis, the characteristics and outcomes of patients with T2DM who were treated with clopidogrel and the newer antiplatelet medications for the secondary prevention of ACS were investigated. This research was carried out with the use of information routinely collected from GP practice systems and hospital records.

1.2 Aim and objectives

Aim

To estimate the economic impact of different anti-platelet regimens in people with T2DM post-ACS, from the perspective of the NHS in England.

Objectives

1. To provide an overview of the characteristics of people with diabetes post-ACS, regarding their demographics, clinical outcomes, medication usage, medication adherence, health resource usage and costs, with the use of routinely collected health care data.
2. To explain variation in adherence, clinical outcomes (such as second ACS event), mortality and costs by using statistical analysis and investigate the effect of different antiplatelet regimens on key clinical outcomes and costs.
3. To estimate the cost-effectiveness of alternative antiplatelet regimens in post-ACS T2DM population.

1.3 Outline of thesis

The thesis, consisting of six chapters, presents the research that was carried out in order to investigate the clinical and economic impact of antiplatelet therapies used for secondary prevention of acute coronary syndromes in T2DM populations. Chapter 2 presents a summary of key literature about the treatment of ACS, and the effectiveness and cost-effectiveness of ACS treatments in general population and in populations with T2DM. Chapter 3 contains the methods used for the extraction of data from electronic health records, Clinical Practice Research Datalink and Hospital Episode Statistics, and ONS death registration data. Furthermore, the methods for addressing confounding, and the design of the statistical analysis are described, justified, and discussed.

Chapter 4 includes the results of the descriptive analysis, the results of the methods used for addressing confounding, and the results of time to event analysis used to evaluate the effectiveness of different antiplatelet regimens included in the study. Chapter 5 provides information about the methods and results of the cost-effectiveness analysis of alternative antiplatelet regimens in patients with T2DM. Chapter 6 (the discussion) summarises the findings of all the studies carried out in the thesis, discusses the strengths and weaknesses of the data and approaches used, discusses the implications for policy, and makes recommendations for future research.

2. Chapter Two: Literature about treatment for the secondary prevention of ACS

2.1 Chapter introduction and background

This chapter provides the findings in literature about the clinical and economic impact of antiplatelet therapy in acute coronary syndrome in general and T2DM population. A summary of the management of ACS in the general population follows this, and then focuses on how management of people with T2DM may differ or need to differ. Finally, the focus is shifted towards the treatment with antiplatelets for the secondary prevention of ACS, the available antiplatelet agents used, and the status of these treatments in general and T2DM populations in terms of effectiveness and cost-effectiveness, the optimal duration of antiplatelet treatment therapy, information about prescription costs in England of antiplatelet treatment, and adherence to those agents is presented.

2.2 ACS management

ACS management occurs at two main stages; the first is completed during within the first 12 hours from the onset of an ACS event. The second stage aims at post-ACS management and prevention.

2.2.1 Initial treatment

The first stage of management in the 12 hours post-ACS event includes treatment with antiplatelet agents, anticoagulant drugs and beta-blockers plus interventions for the unblocking of arteries (reperfusion therapy). In this stage, the main objectives are to stabilise the patient's condition, to relieve ischaemic pain and minimise myocardial damage with the help of antithrombotic therapy.

ACS treatment should be carried out in a specialist cardiology service (15, 16), where the patient will be under continuous heart monitoring (17). In terms of antiplatelet therapy, patients need to receive aspirin (300mg) immediately as the first step of treatment (18). Combination of aspirin and clopidogrel is recommended in cases where electrocardiographic changes or changes in biomarkers occur (19-22).

In patients that are considered as high risk for cardiovascular events, with NSTEMI and undergo percutaneous coronary intervention (PCI), treatment with an intravenous glycoprotein IIb/IIIa receptor antagonist is also suggested (23). Regarding anticoagulation therapy, the general recommendation is the use of low molecular weight heparins or fondaparinux and for those with STEMI, immediate treatment with synthetic pentasaccharides (fondaparinux) is suggested (24, 25). In patients with STEMI, there is recommendation for the immediate use of oral and intravenous beta-blockers (26).

2.2.2 Reperfusion therapies

Primary percutaneous coronary intervention (pPCI) is suggested as the main method of reperfusion therapy since it has been shown to be superior to thrombolysis in reducing mortality, stroke, re-infarction and the need for coronary artery bypass graft (CABG) (27, 28). During this intervention, treatment with a glycoprotein IIb/IIIa receptor antagonist (29) is suggested as adjuvant therapy combined with intracoronary stent implantation (30). If pPCI cannot be carried out during the first two hours after ACS diagnosis, then thrombolytic therapy treatment should be performed as an alternative method of reperfusion (31, 32). Fibrin-specific agents such as alteplase should be used for thrombolysis (33-35). "Rescue" PCI is recommended in cases of patients with ST-ACS where reperfusion with thrombolysis has failed (36-38). If patients have a high probability of one-year (>10%) or five-year (>20%) recurrent ACS or death, then they should be considered for coronary angiography and revascularisation either through vascular bypass or angioplasty (39). The risk estimation of either death or recurrent ACS of individual patients is based on scores like GRACE, TIMI (40), PURSUIT (41) and FRISK (42) and is used to detect those who could benefit most from coronary angiography and revascularisation interventions.

2.2.3 Management after ACS event

The summary of management after an ACS event was based on guidelines from Scotland and England (43-45) .

In the second stage (post-event), the main goal is to minimise the probability of an ACS recurrence. In order to achieve this goal, the patient needs to be treated via lifestyle interventions, pharmacological interventions and psychological support. Lifestyle interventions include alterations in the patient's diet, alcohol intake, smoking, and physical activity. Pharmacological interventions include the prescription of medications for blood pressure lowering, lipid lowering, and antiplatelet therapy.

Regarding their diet, patients are recommended to make alterations in their eating behaviour, where necessary in terms of reduction in saturated fat intake (46), reduction in salt intake(47) , and increase in fruit and vegetable intake (48, 49). Those who are overweight are advised to lose weight and maintain that loss in order to reduce cardiovascular risk (50, 51). Gradual increase in physical activity is suggested for all individuals (52) unless they are already taking recommended levels of exercise.

Those who are smokers or passive smokers are advised to stop smoking (53) and minimise their exposure to passive smoke (54). In terms of alcohol intake, moderation in consumption of alcohol, or abstinence, is suggested both to people with and without history of coronary heart disease.

Pharmacological treatment varies by the target that needs to be achieved (lower blood pressure, lower serum lipids, antiplatelet therapy) and the groups to which it is administered (previous CVD history, asymptomatic, other comorbidities). A daily dose of 75mg aspirin is suggested to individuals that are at risk of CVD, independent of previous CVD history, people with hypertension with high risk of CVD, and people with T2DM as a means of antiplatelet therapy (55, 56). Clopidogrel as a monotherapy is suggested in the case where the patient has aspirin hypersensitivity or intolerance, or aspirin creates side effects(57). In situations where people have had a transient ischaemic attack (TIA) or stroke, then a combination of dipyridamole and aspirin, or clopidogrel if aspirin is contraindicated, is suggested (58). Ticagrelor in combination with low-dose aspirin is recommended for up to 12 months as a treatment option in adults with non ST-ACS and people with ST-ACS treated with pPCI (45). For patients who have a pre-existing indication for anticoagulation, the continuation of anticoagulation therapy is suggested after taking into account factors such as bleeding risk, thromboembolic risk and cardiovascular risk(45).

Treatment with statins in high risk patients that haven't had a cardiovascular event is considered for the lowering of lipid levels, whereas a high-dose statin therapy is considered in patients with history of cardiac event (59). T2DM patients should be considered for treatment with statins if they are over 40 years of age, because they are at high risk of a CVD event. Treatment with nicotinic acid or fibrates is considered in cases of hypertriglyceridemia (60).

Blood pressure that is below a specific level can lead to lower risks of CVD. Treatment with anti-hypertensive drugs is considered when blood pressure is above thresholds that vary depending on the patients' characteristics. The optimal target for high risk CVD patients is less than 140/85mm Hg, whereas for patients with history of CVD, diabetes or chronic renal disease the limit is 130/80 mm Hg. In the UK, the choice of drugs for blood pressure regulation is based on the British Hypertension Society A/CD algorithm (61, 62). According to the algorithm people aged less than 55 years should be treated with ACE inhibitors or ARBs. People over 55 years or patients of African or Caribbean descent of any age should be treated with a calcium channel blocker or a thiazide-type diuretic drug. If this is not sufficient for blood pressure lowering, then a combination of ACE inhibitor or ARB with calcium channel blocker or thiazide-type diuretic is considered. As a third step for blood pressure regulation is the treatment with a combination of the previously mentioned drugs. Finally, if none of these steps is sufficient, then addition of alpha blockers, beta blockers or diuretics should be considered.

2.3 ACS treatment in populations with diabetes

In terms of ACS treatment during the initial management stage, recommended clinical management remains the same in T2DM as for the general population (63), with the additional need for intensive glycaemic control during the first 24 hours of the event(64, 65), and the use of glycoprotein IIb/IIIa receptor antagonists which has been shown to be beneficial in reducing the 30 day mortality from 6.2% to 4.6% (OR 0.74, 95% CI 0.59-0.92) in T2DM populations (66).

2.4 General info about antiplatelet agents

One of the key factors that contribute to the development of ACS is platelet activation and aggregation. Antiplatelet agents are the drugs that decrease platelet aggregation and they are used in early stages of ACS management, but also as a means of secondary prevention after ACS. The antiplatelet agents used in ACS management are cyclooxygenase-1 (COX-1) inhibitors (aspirin), ADP P2Y12 receptor antagonists (clopidogrel, prasugrel, ticagrelor), and glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban).

The antiplatelet medications that are used for secondary prevention of ACS are the following: aspirin, clopidogrel, prasugrel and ticagrelor. Aspirin (acetylsalicylic acid (ASA)) is a medication that is used for various conditions such as inflammation and fever, but also as an antiplatelet. Aspirin provides its cardio-protective effects by inhibiting irreversibly the platelet COX-1 and blockading subsequently the production of thromboxane A2 (TXA2), which is reducing thrombus formation (67). Clopidogrel, is an out of patent antiplatelet medicine that was authorised for market access in 1998 from European Medicines Agency (EMA) in its branded form (Plavix), whereas market access authorisations were given for clopidigrel in generic form from 2008 onwards. Clopidogrel is a prodrug, and the active metabolite targets the P2Y12 adenosine diphosphate (ADP) receptor. Ticagrelor and prasugrel belong to a new generation of antiplatelet drugs and are used as alternatives to clopidogrel, because they have the same mechanism of action. Prasugrel is marketed under the name Efient in Europe, was authorised for use in EU by the EMA in February 2009. Ticagrelor which is marketed in Europe under the name Brilique, was authorised for use in EU by the EMA in December 2010.

2.4.1 Effectiveness of antiplatelet agents

A literature search for the clinical studies investigating the effectiveness of antiplatelet agents and systematic reviews of those studies was carried out. The search was carried out using the Embase and the MEDLINE databases. The search strategy included the use of keyword combinations containing the names of antiplatelet agents (aspirin, clopidogrel, ticagrelor, prasugrel), the type of study (clinical trials, RCT, observational), and the types of outcomes of interest (cardiovascular events). The search included studies that were published between 2000 and 2018. After identifying relevant studies, the reference lists of those studies were scanned to spot any additional studies that could be relevant (ancestry search)(68). Before the introduction of clopidogrel, aspirin was found to reduce the number of atherothrombotic events in patients that were high risk for such events(18).The Clopidogrel in Unstable Angina to prevent Recurrent Events (CURE)(69) trial, and the Clopidogrel for the reduction of Events During Observation (CREDO) (70) trial were those that supported the use of dual antiplatelet therapy (DAPT) in patients with ACS, whereas the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) (71) trial, found no significant difference in effectiveness. An explanation for the findings of CHARISMA was that the population included in that trial was having lower risk of cardiovascular events than those on CURE and CREDO, and that in CHARISMA trial, nearly three quarters of the participants were having an additional treatment with statins, and statins as an independent treatment reduced the risk of cardiovascular problems(72). Finally, the systematic review of Squizzato et al (73), aspirin-clopidogrel was associated with a reduction of risk of myocardial infarction and ischaemic stroke, compared to aspirin only. In general, treatment with aspirin and clopidogrel became the standard antiplatelet therapy for the secondary prevention of ACS. Therefore, the trials for the new agents, were comparing dual antiplatelet therapies: aspirin plus new antiplatelet agent versus aspirin-clopidogrel. Two trials that compared the new agents versus clopidogrel were conducted recently: the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38)(74) and PLATelet inhibition and patient Outcomes trial (PLATO)(75). TRITON-TIMI 38, was a clinical trial of prasugrel versus clopidogrel in patients with scheduled PCI. According to this study, the patients in the prasugrel therapy group had lower rates of ischaemic events, but increased risks of bleeding (76). In PLATO, the clinical effectiveness of ticagrelor versus clopidogrel was studied in a multicentre, double-blind, randomised trial. In this trial, ticagrelor was better than clopidogrel in reducing the rates of MI (HR: 0.84, 95% CI:0.75-0.95) and deaths from vascular causes (HR:0.79, 95% CI:0.69-0.91) (75). In 2013, an article challenged the reliability of the PLATO trial(77). The main concerns of the authors were that the results in the centres controlled by the study sponsor were favouring ticagrelor, whereas in centres that were monitored by an independent third-party Contract Research Organisation the results were favouring clopidogrel. Furthermore almost 50% of all positive results for ticagrelor came from two countries (Poland and Hungary) (77). The authors of the PLATO study responded that the results showed consistent superiority of ticagrelor in all patient groups they tested (STEMI/NSTEMI, T2DM, smokers, elderly, previous stroke) (78). Overall, newer agents presented better protection against ACS but with the higher risk of bleeding events.

Table 1 Studies investigating the effectiveness of antiplatelet medications

Study	**Target population, setting, age**	**Type of intervention**	**Dose**	**Type of study**	**Sample size**
Yusuf 2001(69)	Patients who presented with acute coronary syndromes without ST-segment elevation, Hospitalised,>60 years	Aspirin and clopidogrel versus aspirin and placebo	300mg clopidogrel loading dose, followed by 75mg clopidogrel per day plus aspirin (recommended dose 75mg-325mg daily), 300mg placebo loading dose, followed by 75mg placebo per day plus aspirin (recommended dose 75mg-325mg daily)	Randomised, double-blind, placebo-controlled trial	12562 (6259 aspirin-clopidogrel, 6303 aspirin placebo)
Steinhubl 2002(70)	Patients referred for a planned PCI or coronary angiogram, US or Canada,>21 years	Aspirin and clopidogrel versus aspirin and placebo	300mg clopidogrel loading dose, followed by 75mg clopidogrel per day plus aspirin, 300mg placebo loading dose, followed by 75mg placebo per day plus aspirin	Randomised, double-blind, placebo-controlled trial	2116 (1053 aspirin-clopidogrel, 1063 aspirin placebo)
Bhatt 2006(71)	Patients who had: multiple atherothrombotic risk factors, documented coronary disease, documented cerebrovascular disease, or documented symptomatic peripheral arterial disease, multiple settings, multiple settings, >45 years	Aspirin and clopidogrel versus aspirin and placebo	Clopidogrel (75 mg per day) plus low-dose aspirin (75 to 162 mg per day), placebo plus low-dose aspirin	Prospective, multicentre, randomized, double-blind, placebo-controlled study	15603(7802 aspirin-clopidogrel, 7801 aspirin placebo)
Squizzato 2017(73)	Systematic review of clinical trials	Studies that compared aspirin and clopidogrel versus aspirin and placebo, or aspirin and clopidogrel versus aspirin alone	Clopidogrel (75 mg per day) plus low-dose aspirin, Aspirin only, aspirin plus placebo	Multiple randomised control trials	15 trials included with 33970 participants.

Study	Target population, setting, age	Type of intervention	Dose	Type of study	Sample size
Wiviott 2007(74)	Patients with moderate-to-high-risk acute coronary syndromes with scheduled percutaneous coronary intervention, multiple settings, >18 years	Aspirin and prasugrel versus aspirin and clopidogrel	60 mg loading dose prasugrel, then 10 mg prasugrel per day plus low-dose aspirin (75 to 162 mg per day), 300 mg loading dose clopidogrel, then 75 mg clopidogrel per day plus low-dose aspirin (75 to 162 mg per day)	Randomized, double-blind, controlled study	13608 (6813 aspirin-prasugrel, 6795 aspirin-clopidogrel)
Wallentin 2009(75)	Patients hospitalized for an acute coronary syndrome, with or without ST-segment elevation, with an onset of symptoms during the previous 24 hours, multiple settings,	Aspirin and ticagrelor versus aspirin and clopidogrel	ticagrelor (180-mg loading dose, 90 mg twice daily thereafter) plus low dose aspirin (75-100 mg daily), clopidogrel (300-to-600-mg loading dose, 75 mg daily thereafter) plus low dose aspirin (75-100 mg daily)	Multicentre, randomized, double-blind trial	18624 (9333 aspirin-ticagrelor, 9291 aspirin-clopidogrel)
Castini 2017(79)	Patients admitted to the Coronary Care Unit (CCU) of the San Paolo Hospital (Milan) with diagnosis of ACS between 2012 and 2014, no age restriction	Aspirin-clopidogrel versus novel P2Y12 inhibitors (prasugrel, ticagrelor)	No further information provided.	Observational study	470 treated with dual antiplatelet therapy (230 aspirin-clopidogrel, 92 with aspirin-prasugrel, 148 with aspirin-ticagrelor
Yudi 2016(80)	Patients undergoing percutaneous coronary intervention from 1st July 2009 to 30 November 2013 enrolled in Melbourne Interventional Group, no age restriction	Aspirin-clopidogrel versus aspirin-prasugrel, versus aspirin-ticagrelor	No further information provided.	Observational study	3882 patients (2775 aspirin clopidgorel, 554 aspirin-prasugrel, 553 aspirin-ticagrelor)
Kayata 2017(81)	Patients hospitalised for acute coronary syndrome at Cleveland Clinic Akron General, United states, no age restriction	Aspirin-clopidogrel versus aspirin-prasugrel, versus aspirin-ticagrelor	No further information provided.	Observational study	1388 patients (1012 aspirin-clopidogrel, 244 aspirin-prasugrel, 142 aspirin-ticagrelor)
Alexopoulos 2016(82)	Patients hospitalised for acute coronary syndrome in eight hospitals with percutaneous coronary intervention facilities between January 2012 and August 2013 in	Aspirin-clopidogrel versus aspirin-prasugrel, versus aspirin-ticagrelor	No further information provided.	Prospective, observational multicentre cohort study	2047 (959 aspirin-clopidogrel, 363 aspirin-prasugrel,717 aspirin-ticagrelor, 8 died in hospital

Study	Target population, setting, age	Type of intervention	Dose	Type of study	Sample size
	Greece, no age restriction				without exposure to antiplatelet medications)
James 2010(83)	Patients hospitalized for an acute coronary syndrome, with or without ST-segment elevation, with an onset of symptoms during the previous 24 hours, multiple settings, with cohort restricted to patients that have diabetes mellitus	Aspirin and ticagrelor versus aspirin and clopidogrel	ticagrelor (180-mg loading dose, 90 mg twice daily thereafter) plus low dose aspirin (75-100 mg daily), clopidogrel (300-to-600-mg loading dose, 75 mg daily thereafter) plus low dose aspirin (75-100 mg daily)	Substudy of multicentre, randomized, double-blind trial	4662 (2326 aspirin-ticagrelor, 2336 aspirin-clopidogrel)
Wiviott 2008(84)	Patients with moderate-to-high-risk acute coronary syndromes with scheduled percutaneous coronary intervention, multiple settings, >18 years, with cohort restricted to patients that have diabetes mellitus	Aspirin and prasugrel versus aspirin and clopidogrel	60 mg loading dose prasugrel, then 10 mg prasugrel per day plus low-dose aspirin (75 to 162 mg per day), 300 mg loading dose clopidogrlel, then 75 mg clopidogrel per day plus low-dose aspirin (75 to 162 mg per day)	Substudy of randomized, double-blind, controlled study	3146 (1570 aspirin-clopidogrel, 1576 aspirin-prasugrel

Apart from trials, several studies that were based on registry datasets were investigating the impact of DAPT therapies, based on real world evidence. The study of Castini in Italy (79) had shown that patients on aspirin-clopidogrel were having higher in hospital mortality than those on aspirin-prasugrel and aspirin-ticagrelor and increased bleeding events. The study of Alexopoulos et al in Greece(82), found lower MACE rates in patients treated with aspirin-prasugrel versus aspirin-clopidogrel (HR, 0.53; 95% confidence interval 0.30–0.91) and not significant difference in MACE between those on aspirin-ticagrelor versus aspirin-clopidogrel, increased bleeding events on patients treated with aspirin-prasugrel and aspirin-ticagrelor, and reduced death rates for newer agents versus aspirin-clopidogrel. The study by Yudi et al (80) in Australia, found no difference in unadjusted 30-day rates for mortality, myocardial infarction, MACE, and in hospital bleeding between patients treated with any DAPT therapies. The study by Khayata(81) in USA, found that when DAPT therapies were compared head to head, the aspirin-prasugrel combination was the one with lower rates of heart failure (aspirin-clopidogrel vs aspirin-prasugrel, OR, 2.96 ; 95%CI[1.47 – 5.94]) and lower rates of bleeding (aspirin-clopidogrel vs aspirin-prasugrel, OR, 5.5 ; 95%CI[1.32 - 22.85]). Some of those studies adjusted for non-random nature of the data (82) with the use of balancing techniques or regression methods (79), while others reported unadjusted estimates.

2.4.2 Effectiveness of antiplatelet agents in T2DM populations

From the literature research that was carried out for effectiveness studies of antiplatelet medications, an ancestry search was carried out(68); the bibliographies of antiplatelet studies were reviewed to find literature that was specifically about effectiveness of antiplatelet medications for T2DM populations. There have been sub studies of several clinical trials that were in progress and were part of larger clinical trials (PLATO and TRITON-TIMI 38 respectively). In the sub studies, the effect of aspirin-prasugrel versus aspirin-clopidogrel and aspirin-ticagrelor versus aspirin-clopidogrel was investigated just in the members of the cohort who had diabetes, irrespective of insulin dependence. In the sub-study of the PLATO trial, the clinical effectiveness of aspirin-ticagrelor versus aspirin-clopidogrel was investigated for the part of the initial cohort that had diabetes or long term persistently elevated glucose levels [HbA(1c) >= 9.5%/80 mmol/mol (poor glycaemic control)]. The aspirin-ticagrelor group had fewer ischaemic events, albeit not reaching statistical significance, maybe due to insufficient sample size (HR: 0.88, 95% CI: 0.76–1.03) and didn't present more major bleeding events than the aspirin-clopidogrel group (HR: 0.95, 95% CI: 0.81 – 1.12) (83). A similar sub study was published for aspirin-prasugrel versus aspirin-clopidogrel. The participants with diabetes were isolated from the main study (TRITON-TIMI 38) and the results showed that the diabetes subgroup on aspirin-prasugrel experienced greater reduction in cardiovascular events (HR: 0.70, 95% CI: 0.58–0.85) with a decreased risk of bleeding (HR: 0.74, 95% CI: 0.62–0.89) (84).

Regarding trials in progress, some relevant studies have been identified in the American Clinical Trials Register (clinicaltrials.gov), but only three of them contain results at the present time. All three presented pharmacodynamic comparisons between antiplatelet medications in populations with T2DM (85-87). Trials that investigated how alternative aspirin dosage can affect platelet aggregation(88) and how extended-release aspirin might affect the same outcome (89) were completed, but no published results were available at the time of writing. For agents such as clopidogrel, ticagrelor and prasugrel several studies are in the stage of completion without reported results or in the stage of recruiting (90, 91). With the exception of an industry funded large scale clinical trial that will investigate the cardiovascular effects of ticagrelor versus placebo in T2DM populations (92), the rest of the trials have small numbers of participants that range from 20 to 144, and they explore the effectiveness of the regimens in short term outcomes such as platelet inhibition(90) instead of longer term outcomes such as all-cause mortality, major bleeding or major cardiovascular events. Two trials which will make a head to head comparisons of clopidogrel versus ticagrelor and clopidogrel versus ticagrelor, prasugrel for T2DM populations are still in the phase of recruitment (91) or with an unknown status (93). There have been no large healthcare data based studies that were investigating the effectiveness of DAPT in populations with T2DM.

2.4.3 Cost-effectiveness of antiplatelet agents

A search for literature that included cost-effectiveness studies or reviews of cost-effectiveness studies for antiplatelet medications was carried out. The search was carried out using the MEDLINE and the Embase databases. The search strategy included terms that had keyword combinations with the names of antiplatelet agents (aspirin, clopidogrel, ticagrelor, prasugrel), and terms such as "cost-effectiveness analysis", "cost-utility analysis", and "systematic review". The search included studies that were published between 2000 and 2018. After identifying relevant studies, the reference lists of those studies were scanned to spot any additional studies that could be relevant (ancestry search). In a literature search by Heeg et al(72), cost-effectiveness and cost utility studies of antiplatelet medications were selected and a cost-effectiveness analysis from the NHS perspective was carried out. Findings of Heeg et al study supported NICE guidelines for the prevention of ACS events. Several cost-effectiveness studies in various healthcare settings have been conducted to investigate whether aspirin-ticagrelor or aspirin-prasugrel provide value for money versus aspirin-clopidogrel. The effectiveness information for these studies was provided by clinical trials that cover the general population. For both aspirin-ticagrelor and aspirin-prasugrel cost-effectiveness studies, each manufacturer prepared one model structure. The model structure was then adapted for the different health care settings with the use of input parameters that reflected the health care setting where the model was used. The results in the studies were expressed in costs/QALY gained. Section 5.1 of the thesis provides more information about the structure of the cost-effectiveness models for antiplatelet medications, which were found in the literature.

Aspirin-ticagrelor has been found to be a cost-effective treatment compared with aspirin-clopidogrel in the PLATO study (94) and in Singapore (95), Germany (96), Canada (97), United States (98), Switzerland (99) and Sweden(100).

Aspirin-prasugrel was found to be cost-effective versus aspirin-clopidogrel in Germany, Sweden, the Netherlands, Turkey (101), Spain (102) and the United States (103). Both aspirin-prasugrel and aspirin-ticagrelor were found to provide value for money versus aspirin-clopidogrel in many different health care settings. Three studies were found that provide a head-to-head comparison between aspirin-clopidogrel, aspirin-ticagrelor and aspirin-prasugrel. Among these were the study of Wisloff(104), where aspirin-ticagrelor was found to be cost-effective against aspirin-prasugrel, and against aspirin-clopidogrel in the Norwegian healthcare setting. The study of Abdel-Qadir (105) found aspirin-ticagrelor to be cost-effective in the health care setting of Canada. Finally the study of Zhao (106) found that aspirin-ticagrelor is more cost-effective than aspirin-prasugrel, and more cost-effective than aspirin-clopidogrel in reducing all-cause mortality in patients with ACS, but cost-effectiveness between aspirin-prasugrel and aspirin-ticagrelor was similar when the impact of dyspnoea was taken into account. All those studies were using information taken from clinical trials. This could potentially overestimate the cost-effectiveness because even though RCT results are 'gold standard' for efficacy, selected populations, idealised conditions and limited time horizons can have an impact in the assessment of effectiveness and costs(107).

Table 2 Studies investigating the cost-effectiveness of antiplatelet medications.

Study	**Target population, age**	**Type of intervention**	**Type of economic evaluation**	**Cost perspective**	**Source of resource use data**
Heeg 2007(72)	Multiple studies; Patients with acute coronary syndrome, patients undergoing primary percutaneous intervention, patients prescribed medications for secondary prevention, >18 years	Clopidogrel versus aspirin, clopidogrel (1 year) vs clopidogrel (28 days), Dipyridamole plus aspirin versus aspirin, Dipyridamole plus aspirin versus clopidogrel, aspirin versus placebo	Model based study (Markov model)	UK NHS perpective	Published literature

Study	Target population, age	Type of intervention	Type of economic evaluation	Cost perspective	Source of resource use data
Nikolic 2013(94)	Patients, hospitalised for an acute coronary syndrome, with or without ST-segment elevation, >18years	Aspirin-Ticagrelor vs Aspirin-Clopidogrel	Model based study (Markov model)	Swedish Health care sector perscpective	Medical records from PLATO study
Chin 2013(95)	Patients, hospitalised for an acute coronary syndrome, with or without ST-segment elevation, >18years	Aspirin-Ticagrelor vs Aspirin-Clopidogrel	Model based study (Markov model)	Singapore health care perspective	Medical records from the PLATO study
Theidel 2013(96)	Patients, hospitalised for an acute coronary syndrome, with or without ST-segment elevation, >18years	Aspirin-Ticagrelor vs Aspirin-Clopidogrel	Model based study (Markov model)	German health care sector perspective	Published literature, medical records from PLATO study
Grima 2014(97)	Patients, hospitalised for an acute coronary syndrome, with or without ST-segment elevation, >18years	Aspirin-Ticagrelor vs Aspirin-Clopidogrel	Model based study (Markov model)	Canadian health care sector perspective	Medical records from PLATO study
Crespin 2011(98)	Patients hospitalised for an acute coronary syndrome enrolled in Medicare, >65 years	Universal treatment with Aspirin-Ticagrelor versus genotype driven treatment with antiplatelet medications	Model based study (Markov model)	Cost perspective of Medicare	Literature, medical records for Medicare patients
Gasche 2013(99)	Patients, hospitalised for an acute coronary syndrome, with or without ST-segment elevation, >18years	Aspirin-Ticagrelor vs Aspirin-Clopidogrel	Model based study (Markov model)	Swiss health care sector perspective	Medical records from PLATO study
Henriksson 2014(100)	Patients, hospitalised for an acute coronary syndrome, with or without ST-segment elevation, >18years	Aspirin-Ticagrelor vs Aspirin-Clopidogrel	Model based study (Markov model)	Danish, Swedish health care sector	Medical records from PLATO study
Davies 2013(101)	Patients undergoing percutaneous	Aspirin-Prasugrel versus	Model based study (Markov model)	Perspective of the national health care	Medical records from the

Study	Target population, age	Type of intervention	Type of economic evaluation	Cost perspective	Source of resource use data
	coronary intervention without prior stroke or transient ischaemic attack	Aspirin-Clopidogrel		settings (Dutch, German, Swedish, Turkish)	TRITON-TIMI study
Davies Schulpher 2013(102)	Patients undergoing percutaneous coronary intervention without prior stroke or transient ischaemic attack	Aspirin-Prasugrel versus Aspirin-Clopidogrel	Model based study (Markov model)	Spanish health care sector	Medical records from the TRITON-TIMI study
Mahoney 2010(103)	Patients undergoing percutaneous coronary intervention	Aspirin-Prasugrel versus Aspirin-Clopidogrel	Model based study (Markov model)	US health care systems sector	Medical records from the TRITON-TIMI study, Literature
Wislof 2016(104)	Patients undergone percutaneous coronary intervention, >60 years	Aspirin-Ticagrelor vs Aspirin-Prasugrel vs Aspirin-Clopidogrel	Model based study (Markov model)	Norwegian health care sector	Medical records
Abel-Qadir 2015(105)	Patients undergone percutaneous coronary intervention, >60 years	Aspirin-Ticagrelor vs Aspirin-Prasugrel vs Aspirin-Clopidogrel	Model based study (Markov model)	Canadian health care sector	Literature
Zhao 2016(106)	Patients undergone percutaneous coronary intervention, >60 years	Aspirin-Ticagrelor vs Aspirin-Prasugrel vs Aspirin-Clopidogrel	Model based study (Markov model)	Patient perspective	Literature

2.4.3.1 Cost-effectiveness of antiplatelet agents in T2DM populations

Even though research into the cost-effectiveness of alternative antiplatelet agents for general populations is available, with published economic models for different health care settings, it was not possible to find any published studies for T2DM populations. As a result, there is no mention about T2DM populations in publications that contain cost-effectiveness analyses of alternative antiplatelet agents. In the NICE technology appraisal of prasugrel from Greenhalgh and colleagues, the appraisal team estimated the cost-effectiveness for prasugrel over 40 years of follow-up in patients with diabetes who experienced a STEMI was £1640/QALY gained and in patients with diabetes who experienced a NSTEMI, prasugrel dominated clopidogrel (108), and this was a subgroup analysis of the overall cohort. Overall, evidence about cost-effectiveness of antiplatelet agents for T2DM population is scarce, not only for the comparisons of newer agents with aspirin-clopidogrel but also with head to head comparisons among all DAPT therapies. There is a gap in the literature regarding this subject.

2.5 Antiplatelet response variability in T2DM populations

For the prevention of CVD in terms of antiplatelet therapy the guidelines suggest the same strategies for all patients (63, 109), irrespective of diabetes status. The problem is that in patients with T2DM, several mechanisms contribute in the dysfunction of antiplatelets (hyperglycaemia, deficient insulin action, cellular abnormalities) resulting in the increasing risk of ACS events(110). These mechanisms can also result in a decreased effect of antiplatelet therapies for T2DM populations. Aspirin and clopidogrel are the most common antiplatelet agents used for therapy and have been less effective in people with diabetes that have high platelet reactivity (HR MACE high platelet reactivity versus non high platelet reactivity 3.35; 95%CI 1.68-6.66) (111-113). One of the mechanisms that could explain the reduced clinical efficacy of aspirin in populations with diabetes ("aspirin resistance") is hyperglycaemia, where increased glycation of platelets and coagulation factors may interfere with acetylation by aspirin (114). Reduced platelet response of clopidogrel in T2DM populations, "clopidogrel resistance", has been attributed to the reduced levels of clopidogrel active metabolite (Clop-AM), leading to reduced P2Y12 inhibition (115-117). Those treatment limitations (resistance to aspirin and clopidogrel) could be overcome with modification of antiplatelet drug dose, use of adjunctive antiplatelet agents and use of novel and more potent antiplatelet agents (118).

Ticagrelor and prasugrel use the same mechanism as clopidogrel for platelet inhibition. Prasugrel, as clopidogrel, is a pro-drug but it has better pharmacokinetic profile than clopidogrel, because it needs a single cytochrome p450 metabolic step whereas clopidogrel needs two sequential steps (119). On the other hand, ticagrelor is an active drug and no pro-drug conversion is needed (120). Overall, there's a need for tailored regimens for patients with T2DM, because of the optimal level of platelet inhibition in this group is not the same as in general population (121).

2.6 Duration of antiplatelet therapies

The use of antiplatelet medications allows for the prevention of ACS, but it also increases the risk of bleeding. As a result of this trade-off that exists between the risks of bleeding and ACS, prescribers have to monitor their patients and adjust their treatment accordingly, so that a balance is struck between those risks. Overall European and US guidelines suggest dual antiplatelet treatment (DAPT) for up to twelve months with assessment by practitioners in case of prolonging therapy (122, 123). Overall, there is no clear consensus about the optimal duration of antiplatelet therapy, therefore systematic reviews of clinical trials regarding DAPT that compared shorter versus longer periods of treatment (6 vs 12 months, 3 vs 6 vs 12 months) were carried out(124, 125) and both found that prolonged duration of DAPT increased the risk of bleeding. According to the findings of Verdoia et al, shorter DAPT treatment strategies provide lower mortality risk of death and bleeding, but an increased risk of MI (126). Trials such as the NIPPON (Nobori Dual Antiplatelet Therapy as Appropriate Duration) study (127) and the ITALIC (Is There a Life for DES After Discontinuation of Clopidogrel) trial (128) found that 6 month DAPT is not inferior in terms of bleeding and thrombotic events to longer periods of DAPT. Tada et al also suggest that shorter than one year DAPT periods might be optimal (129). Paravattil and Kereiakes suggest that DAPT should be individualised with the help of a decision tool that determines, the DAPT-eligible patients who are more likely to derive benefit (vs. harm) from long-term antiplatelet therapy [DAPT score](130, 131), whereas Parker points out the need for studies that investigate the optimal personalised strategies for DAPT(132). In England the suggested duration for DAPT is one year, whereas in Scotland the suggested duration of DAPT is six months, and the considerations for longer of shorter durations of DAPT are based on comparison of bleeding risks versus the risks of atherothrombotic events (43).

2.7 Adherence to antiplatelet medications

The systematic review of Czarny et al (133) collected studies that investigated the adherence to DAPT after coronary stenting. The general finding of the review was that aspirin adherence was quite high throughout the time periods, whereas adherence to DAPT was high during the first month of treatment and declined by 12 months. Czarny et al concluded that DAPT adherence was suboptimal at 12 months, and there was need for interventions that increase adherence. The study of Rezaei et al (134) investigated the prescriptions of antiplatelet medications in Austria between the years 2009-2014, using data collected from Austrian health insurance funds. Razaei et al found that discontinuation of DAPT begun in 6 months after therapy initiation, and by 12 months 45.3% of patients on aspirin-clopidogrel, 45.7% on aspirin-prasugrel, and 57.0% on aspirin-ticagrelor discontinued therapy. In the study of Nakamura et al (127), where outcomes of patients in short-term versus long term DAPT were investigated, it was found that patients on the long term DAPT remain adherent for time periods beyond 12 months, and adherence in the long term DAPT group reduced over six months but remained stable afterwards. All those results were for general population only, and there was no study investigating the adherence in DAPT for populations with T2DM.

2.8 Costs of antiplatelet medications in England

The most current information for the overall cost to the NHS of the dispensed antiplatelet medications, was available in the 2017 prescription cost analysis from ONS (135). This statistical series provided information about the total costs of prescribed medicines, the total number of prescriptions, and the cost per prescription. For the antiplatelet medications in England, the total number of antiplatelet prescriptions that were dispensed in 2017 was 34,600,167(aspirin: 24,755,375, clopidogrel: 9,264,767, prasugrel: 71,617, ticagrelor: 508,408). The cost of antiplatelet prescriptions for the NHS (net ingredient cost) for 2017 was £64,356,270 (aspirin: £20,151,320, clopidogrel: £12,821,710, prasugrel: £3,749,505, ticagrelor: £27,633,736), with the total cost of ticagrelor prescriptions being the highest. The cost per prescribed item was £0.81 for aspirin, £1.38 for clopidogrel, £52.35 for prasugrel, and £54.35 for ticagrelor. Overall, the majority of antiplatelet prescriptions were for aspirin and clopidogrel, but the prescriptions of ticagrelor were the ones with the higher cost. Prasugrel prescriptions were as expensive as those of ticagrelor. This cost information, is on prescription level and for general population, therefore further analysis of large health care datasets is needed to find the cost of antiplatelet prescriptions for specific population groups.

2.9 Summary

ACS management tends to be complex during the early stages of the condition and afterwards in the general population, but for T2DM populations it can be even more complex, due to the additional demands for good glycaemic control. Among the most important treatments for the secondary prevention of ACS is the treatment with oral antiplatelet medication, more specifically clopidogrel and aspirin. New oral antiplatelet agents (ticagrelor, aspirin) in the place of clopidogrel have been tested and found effective and cost-effective in the general population. The findings of antiplatelet medication effectiveness were available for T2DM, but they were presented as an ad hoc analysis of the initial trials, even though there is antiplatelet response variability in the T2DM populations (see section 2.5). Furthermore, there were no studies that were investigating head to head all the antiplatelet therapies. As a result of that, this head to head comparison needs a large RCT in order to be resolved, but also leaves an opportunity for investigating effectiveness of antiplatelet medications in T2DM populations using real world data, after addressing the non-random nature of this kind of data. The results in terms of effectiveness in real world provided no clear result about which treatment is the most effective in general population, and those studies used different methods to address the selection bias caused by the non-random nature of the data. Cost-effectiveness results were based on trial data, and not in real world evidence, which could lead to overestimation. A cost-effectiveness model with parameters based on real world data could alleviate this problem. Furthermore, mixed results about adherence of general population in DAPT were found, and there was no information on this subject for people with T2DM. From the published evidence, we can conclude that there is an opportunity to investigate the effectiveness of antiplatelet regimens in patients with T2DM with the use of observational data. The findings of that investigation could be used to inform a cost-effectiveness model of antiplatelet medications in T2DM populations.

This study intends to investigate the clinical and economic impact of alternative antiplatelet regimens prescribed for secondary prevention of ACS events in adults with T2DM, and the factors affecting it. This allows the investigation of effectiveness of antiplatelet medications in patients with T2DM, allowing also the use of a cost—effectiveness model informed by real world evidence. Study findings could be used to inform the implementation of better practices and policies by practitioners, policy makers and patients.

2.10 Chapter conclusion

In this chapter, the way that ACS is managed in the general population and in T2DM population was presented. Furthermore, a brief overview of the range of treatments used during ACS was given. The focus was set on antiplatelet medications, since they are probably the most important pharmacological treatment in secondary prevention of ACS. Information about antiplatelet treatment effectiveness, and cost-effectiveness was given, about antiplatelet response variability of those treatments in T2DM populations, information about optimal treatment duration, cost of DAPT therapies, and adherence to DAPT. A case is made for the investigation of effectiveness of antiplatelet medications in T2DM populations with the use of routinely collected health care data. The following chapter, presents the methods used for carrying out for data extraction from the health care datasets, how the problem of non-random nature of data were addressed, what characteristics, outcomes, and measures were collected, and the ways that the data are analysed.

3. Chapter Three: Methods for data extraction, data analysis and estimation of treatment effect

3.1 Methods for data extraction, data analysis and estimation of treatment effect

The previous chapter focused on the initial acute management of ACS, and its management post-hospitalisation. Among the treatments for secondary prevention of ACS that were discussed was oral antiplatelet medication, the agents that were prescribed, and the reasons why antiplatelet treatment of T2DM populations post-ACS remains a challenge for clinicians ("aspirin resistance", "clopidogrel resistance", choice of agent, dose modification).

This chapter describes the methods that were used to extract, identify, select and analyse the data to allow the first two thesis objectives to be met, and use the results to populate the economic model mentioned in the third objective of thesis. Description of the datasets where health care data is collected and represent the data sources of the study, primarily Clinical Practice Research Datalink, Hospital Episode Statistics and the linked databases (Index of Multiple deprivation, ONS death registry) is provided, followed by the methods used for patient identification, generation of outcome variables, exposure variables and other covariates needed for later stages of analysis.

The description of the methods and the rationale for the use of balancing methods and time to event analysis is followed by information about the characteristics of the study cohort with the use of descriptive statistics. Then, the results of the balancing methods and the comparison between the methods are provided. Time to event analysis results for the outcomes presented in in the earlier parts of the chapter are described, followed by the discussion of overall strengths and weaknesses of the analyses.

3.2 Chapter Objectives

The objectives of this chapter are to:

1. Provide an overview and justification of the use of routinely collected electronic health care data for the study, the data structure, data management.
2. Describe the type of information that was extracted from the health care data and the methods used to extract it.
3. Provide information about how participants were assigned in medication groups, the overall cohort characteristics, and how participants were included in the study.
4. Describe the outcomes and the health care resource use data that are investigated in the study, and how were these retrieved using the extracted information (prescription patterns, medication adherence, all-cause death, MI, stroke, cardiovascular death, Major Adverse Cardiovascular Events-MACE, bleeding, inpatient costs, outpatient costs).
5. Provide an overview of the methods used to control for confounding arising from the non-random assignment into groups, and the strategy used for method selection to

adjust for the non-random assignment into comparison groups of alternative antiplatelet regimens.

6. Describe the methods used in time to event analysis and strategy used to select the best available estimate of the treatment effect among alternative antiplatelet medications for several health care outcomes (Bleeding, MI, stroke, MACE, all-cause death)

3.3 Comparators

In this study, the treatment with, and the treatment effect of, alternative antiplatelet regimens in adults with T2DM was investigated. Multiple antiplatelet regimens were compared: treatment with aspirin alone, clopidogrel and aspirin, prasugrel and aspirin, or ticagrelor and aspirin, with study participants assigned to the aforementioned groups. The reason for selecting these regimens was due to the fact that pharmacological therapy with aspirin and clopidogrel is considered as the cornerstone for secondary prevention against ACS(21, 22), and the prescription of aspirin combined with clopidogrel is in line with the recommendations of UK and European guidelines on the use of antiplatelet treatment for secondary prevention of cardiovascular disease. Aspirin only was included, in order to investigate the demographic characteristics of patients who were treated with this regimen (136).The other combination therapies were examined because they constitute the newer agents also being used in this patient group for this indication; they were reported to have better effectiveness versus aspirin and clopidogrel in general populations (76, 83, 84, 137), but these agents come with higher acquisition costs.

3.4 Background on healthcare databases

For this part of the study, the data source was the Clinical Practice Research Datalink (CPRD) linked with Hospital Episode Statistics (HES), and Office for National Statistics mortality data (ONS). The cohort was defined using information from CPRD and HES data respectively.

3.4.1 Use of large databases in healthcare research

Large administrative databases have been used as sources for research, apart from being used for administrative support and clinical purposes. The widespread introduction of IT in healthcare settings has allowed the recording and storing of routinely collected patient data. This has resulted in the development of healthcare databases, where healthcare records from healthcare providers can be systematically retrieved, anonymised, cleaned, standardised, and are provided in a format that can be used by researchers. These databases have been used for epidemiological research, pharmacoepidemiology or other types of observational research all over the world.

Databases such as the Veterans Affairs database (138), or the privately held MarketScan database(139) and the GE Healthcare’s Electronic Medical Records(140) database in the United States. United Network for Organ Sharing, National Health and Nutrition Examination Survey, Medicaid, as well as the PHARMO Database Network (141) database in the Netherlands are some examples widely used in research. Other databases that have been used extensively for research in the UK purposes include the Clinical Practice Research Datalink (formerly the General Practice Research Database (CPRD/GPRD) (142) QResearch(143), the Secure Anonymised Information Linkage (SAIL) Databank in Wales(144), Doctors Independent Network(DIN-Link) (145), commercial databases such as the UK IMS Disease Analyzer, the Health Improvement Network (THIN)(146), and Hospital Episode Statistics (HES)(147). The detailed information on episodes of care and diagnoses available in these databases could also complement existing sources of systematically collected data, such as the British Household Panel Survey (BHPS) (Taylor 2010), Office for National Statistics (ONS) mortality register and others in order to broaden the options for retrospective observational research in UK healthcare.

3.4.2 Advantages of large clinical databases

Large databases in research allow the use of a dataset that collects information about a population sample that is much larger than a primary data collection study is able to achieve. Furthermore, due to the routine collection of clinical data, clinical information is collected in a way that the risk of recall bias appearing in studies that bias data collection in questionnaires or interviews is reduced (148, 149).

Healthcare databases tend to collate large amounts of patient-level information over long periods of time, which makes them ideal sources for epidemiological and longitudinal studies. Furthermore, due to the long periods of complete follow up of patient data that are included in many of these databases, it is possible to conduct studies on rare exposures and diseases, something that couldn't be feasible otherwise (150). Over 98% of the population in the UK is registered in a GP practice (151), with GP practice visits free of charge. As a result the UK primary care databases have breadth of data, long term follow-up and not only represent the local population, but the national population as well, due to their geographical and socioeconomic spread (150, 152). For example, patients in CPRD are representative of the UK population in terms of age and gender, when compared with the UK census in 2011 (152). Ethnicity data recorded in CPRD, are representative of the population(153), whereas BMI measurements in CPRD are comparable to the Health Survey for England (154).

Large databases can be used for research because the stored patient records can be conveniently managed with the help of database software such as MySQL(155) or Hadoop® (156), and are convertible into formats usable by statistical software like SPSS® (157), Octave® (158), Stata® (159), R® (160), and Julia® (161), allowing researchers to answer different study questions. Due to the standardised format that large datasets have after data processing by database maintainers, less time for data management and cleaning is often needed, and more time can be devoted to analysis.

Due to the fact that text is not handled conveniently in computerised databases, patient information is recorded with the use of standard coding schemes for clinical events like prescriptions, diagnoses, treatments, and procedures of care. Those coding schemes include Read codes(162), Common procedural terminology version 4(CPT-4) (163), WHO International Classification of Diseases (ICD)(164), International Classification of Primary Care (ICPC) for classifying diagnoses(165), Office of Population Censuses and Surveys (OPCS-4) for procedures(166), Healthcare Resource Groups (HRGs) for diagnosis related group classification(167), BNF codes for medications (see section 3.6.4 for more details). The use of coding schemes results in the search and extraction of clinical data in a more streamlined and organised way. Furthermore, it allows researchers to create, refine, and share code lists or code list generation practices (168). This practice helps researchers make their studies comparable, due to standardised coding.

Another positive aspect of large clinical databases is the potential of having linkages with other databases that collect different types of information (census data, social care information). This allows the researchers to have a better overview of the patients' profile, allowing them to include all this additional information in their research questions, and generate hypotheses that combine clinical and any other additional data from the linked databases. In the case of CPRD in the UK, linkages to different datasets like ONS mortality data and a dataset of index of multiple deprivation scores are available.

Collected data in large databases represent real-life practice, and in terms of clinical research this is completely in contrast with the concept of the double blind randomised controlled trial (RCT). RCTs are considered the gold standard and the only appropriate way to get a true measurement of exposure effects (169, 170).The problem with RCTs though is that they are conducted in a relatively artificial environment, with many studies having very strict inclusion and exclusion criteria for participants, favouring mainly younger and healthier participants, with artificial processes of care (such as more diagnostic tests) and more intensive follow-up than normal care, which can influence adherence to the intervention(171). On the other hand, large databases of routinely collected data allow research for groups of patients that usually could be excluded from RCTs, in cases where the groups of interest are quite small, or in cases where interventions cannot easily be tested with the use of RCTs (a change in prescribing policies would be an example).

3.4.3 Limitations of large clinical databases

Even though in large databases a large amount of data is collected, the case is that the information was not collected with the primary purpose of data being used in studies. Therefore, researchers have to consider the completeness and the accuracy of the information(152). There is always the chance of missing data across patients and across time. As a result of this possibility, researchers have to evaluate the level of missing data and make decisions about the way that observations with missing data should be handled(170). Apart from missing values in collected information that are retained in the databases, there is a chance that the databases may lack key variables needed to answer research questions imposed (171, 172). As a result, researchers may need to consider alternative variables in the database that could be used as proxy variables.

Studies based on large clinical databases can be challenging when researchers need to combine information from multiple sources, like in studies where researchers have to combine information from primary, secondary, tertiary care sources to measure the overall effect of an intervention, or report the health outcomes and resource use from a wider perspective across the health care system. Clinical databases usually focus on specific sectors of healthcare, and they retrieve data from systems that use one type of software, for example CPRD retrieves data mainly from GP practices that use Vision software, and some practices that use EMIS software. This can generate problems due to lack of interoperability among databases that collect data from different healthcare sectors, but also due to lack of standardised formats among databases that focus on the same sector. For this reason studies taking a wide perspective across the healthcare system may opt for bespoke data collection (173), by not using a specific clinical database, but collecting the information from multiple different datasets, even if this decision means greater effort and higher data extraction costs, because of dealing with multiple agencies, different research governance practices, multiple data formats and a more lengthy process of ethics approval.

Data retrieval from large databases is considered a cost-effective way of conducting research, but researchers have to take into account several other aspects. Researchers may have limited access to large databases, because the maintainers charge fees for accessing the data. Another matter that can hinder access to datasets, is the need for compliance with data ethics and governance that the policy makers or the data maintainers put in place. Apart from that, due to the nature of the databases, researchers need some time to become familiarised with the structure of the datasets in order to extract information that is relevant to their research question. Additionally, the size of the datasets is usually large ("big data"), making the use of non-standard computational power (high performance computing) a prerequisite (150). The processing and analysis of large datasets is a complex task, which demands from the researcher to already have (or to develop during the study) a wide range of additional skills in data management and computer programming. Additionally access to clinical knowledge either based on the researcher's background or through cooperation with clinical experts is needed for coding and interpretation (149). Because of the range of expertise needed in different areas, the work around large clinical datasets is usually carried out by teams of experts with diverse backgrounds (statisticians, clinicians, IT professionals, health economists), or by researchers who have links with such teams. After taking into account all these additional costs (database access, time to get skills, hiring of experts), researchers who have no previous experience with large datasets, but still want to use those datasets, may opt for paying a third party to provide specialist services for data collection.

Coding systems in large databases tend to evolve or be replaced over time. This can result in variation in the way information about a condition is recorded over time. Changes in the methods of removing erroneous or duplicate data, and the variation in the way users of electronic systems import data to the systems to define a health condition can also affect data consistency over time. This is quite common in the GP systems of the UK, where Read codes are used for defining clinical conditions, and more than one code can be used to describe a condition (150). Additionally, from April 2018, Read codes are going to be substituted by SNOMED clinical terms (SNOMED CT) in phases, and until April 2020 both coding systems will coexist (174). Another example has to do with the definition of diabetes using Read codes. Although there are Read codes for type 1 and type 2 diabetes, there are also codes that don't specify the type of diabetes they refer to, a situation that makes it difficult for the researcher to select codes during cohort definition. Another issue that may arise in coding is the introduction of perverse incentives for biasing data entry. For example, if there's a GP practice performance indicator that is connected to information derived from the GP systems, there is a chance that data entry could be steered in a way so that this performance goal is achieved.

In summary, the use of large healthcare databases in research can have many advantages compared with other sources of data obtained from primary collection. Collected data represents real life practice, long periods of patient follow-up are available, information from much larger samples of population can be extracted, data are organised with the help of coding schemes, and there are potential linkages with other datasets. Researchers though need to take into account several limitations that exist in large datasets: (i) data might have been collected not for research purposes, (ii) difficulties in combining information from several datasets, (iii) additional effort and expertise needed to handle and analyse these data. Overall, after weighing the strengths and weaknesses, in many cases, it is worthwhile for researchers to carry out research using large databases.

3.5 Data sources in the study

3.5.1 General information

The Clinical Practice Research Datalink (CPRD) is a primary care database that contains anonymised medical records, covering 11.3 million patients from 674 practices in the United Kingdom, with 4.4 million active patients (alive and registered). The database covers nearly 7% of the total UK population(152). It is managed by the Medicines & Healthcare Products Regulatory Agency (MHRA) in collaboration with the National Institute for Health Research (NIHR)(175).

In the UK, GPs are the first point of contact for somebody who seeks non-emergency medical care treatment, and they act as "gatekeepers" to secondary care and specialist referrals. This structure of health care provision allows for having a comprehensive picture of population health, based on data recorded in primary care. Every contact has an electronic trail, and every electronic health record (EHR) is managed by one of the several clinical systems software. These include SystmOne by The Phoenix Partership(TPP) (176), EMIS web by EMIS Health (177), and Vision (178). CPRD includes EHRs managed by Vision, a system provided by In Practice Systems Ltd (INPS). The maintainers of CPRD are now including EHRs managed by EMIS web (CPRD Aurum), which would increase the number of practices available to CPRD. The users of CPRD are able to extract data from static monthly versions of the database, as CPRD maintainers prepare monthly snapshots of the database, based on the continuous update of the records received from practices. Every practice receives a set of guidelines regarding data entry about referrals, drug treatment and any other information during a consultation. Validity checks and quality control of received data are carried out by an auditing team in MHRA. This practice ensures the reliability and consistency of the data for research (179).

HES is an electronic records collection containing details of all admissions, outpatient appointments and accident and emergency (A&E) attendances at NHS hospitals in England, and is collected during a patient's time at hospital. Hospitals use these data for reimbursement purposes. HES data are designed to enable secondary use, that is, use for non-clinical purposes, of these administrative data. It is a records-based system that covers all NHS trusts in England, including acute hospitals, clinical commissioning groups and mental health trusts. HES information is stored as a large collection of separate records - one for each period of care - in a secure data warehouse. HES was conceived in 1987, following a series of reports on collection and use of hospital activity information published by a steering group chaired by Dame Edith Körner (180-185). Before 1987, only a 10% sample of admitted patient records was collected nationally, whereas HES aims to collect a detailed record for each 'episode' of admitted patient care delivered in England. HES data are collected monthly (147). HES data are split into episodes of care, diagnoses, procedures, inpatient care, outpatient care, and critical care.

3.5.2 Data structure in CPRD

The CPRD database contains information about practices, patients, consultations, treatments, medication prescriptions, and laboratory test results. All data are extracted and held in separate plain text, tab delimited files. Every file contains one record per row, and records can be linked together using consultation based or patient based unique identifiers. All the files except the "staff" and the "additional" file, contain information about patient unique identifier, date of event, and the date that the information was entered in the system.

The “additional” file should be considered as an extension of the “test” file, since all additional clinical details obtained during a consultation are stored here. Test results and measurements are stored here. The “clinical” file contains the medical diagnoses inserted by GP during consultation, the type of consultation, information about tests or measurements carried out during consultation (weight, height) , and a unique identifier that links the records of clinical file with the records of “additional” file. The “consultation” file contains information about some general information about the consultation occurred, such as type of consultation (surgery, night visit, out of hours, emergency), its unique identifier, and consultation duration. The “patient” file contains demographic information (gender, year of birth, marital status), information of patient registration status in the practice (registration date, transfer out date), and date of death. The “practice” file has information about the region that practices are located, the date that data was last collected from the practice, and the date since the practice was deemed to have data of research quality (up-to-standard practice). The “referral” file has information about the type of referral, its urgency, the specialty that the patient is referred to, the classification of it (day case, in patient), and what kind of attendance is the referral event (first visit, follow-up). The “staff” file contains information about the role of staff that add data to the system, staff’s gender, and staff’s unique identifier. The “test” provides information about the test results and measurements that are carried out during a consultation. Each measurement result is identified by a specific code (entity type) and is accompanied by information about the unit of measure and the normal ranged that this measure has. The “therapy” file contains information about the treatments prescribed by the GP during consultation, information about product code (CPRD unique code that describes the prescribed treatment quantity, number of packs, BNF code (in a CPRD specific format), and pack size or type of prescribed treatment. Finally, the “immunisation” file contains several details about the immunisations carried out on patients (compound given, location of vaccination, method of vaccination, reason for vaccination).

Figure 1 presents the link between the various records held in the database (152, 186). A snapshot of data in before (raw format) and after processing is presented in Figure 2 and Figure 3 respectively.

Figure 1.CPRD database overview (figure drawn based on Tate et al. 2014 and Herrett et al 2015)

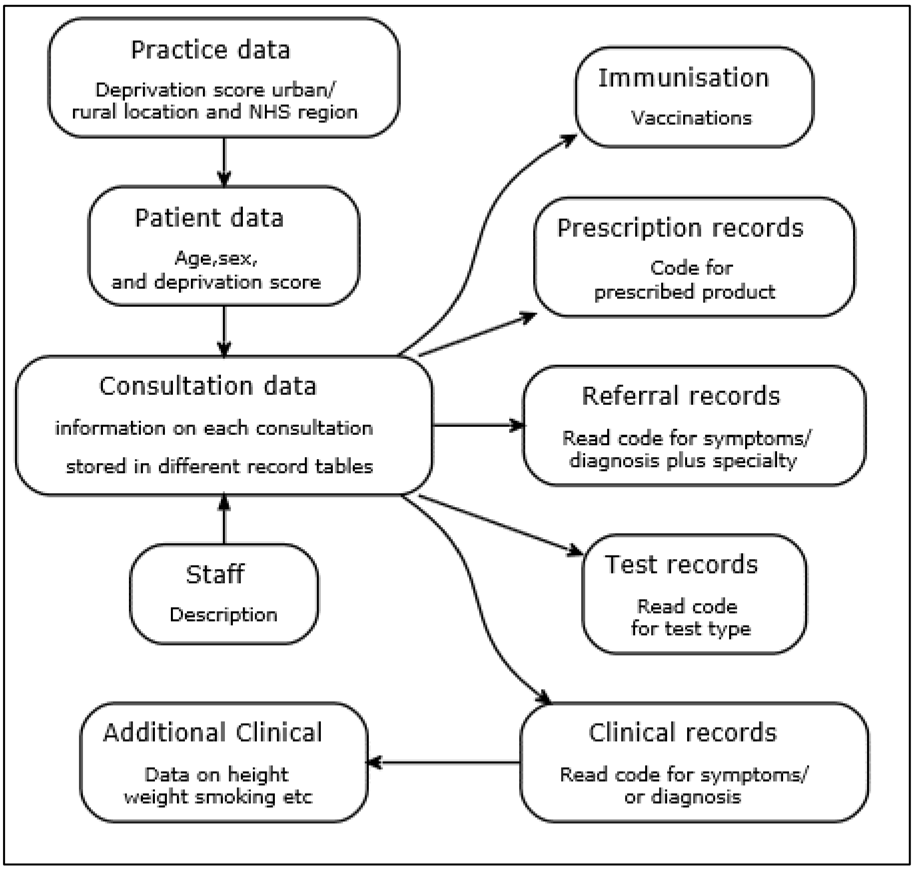
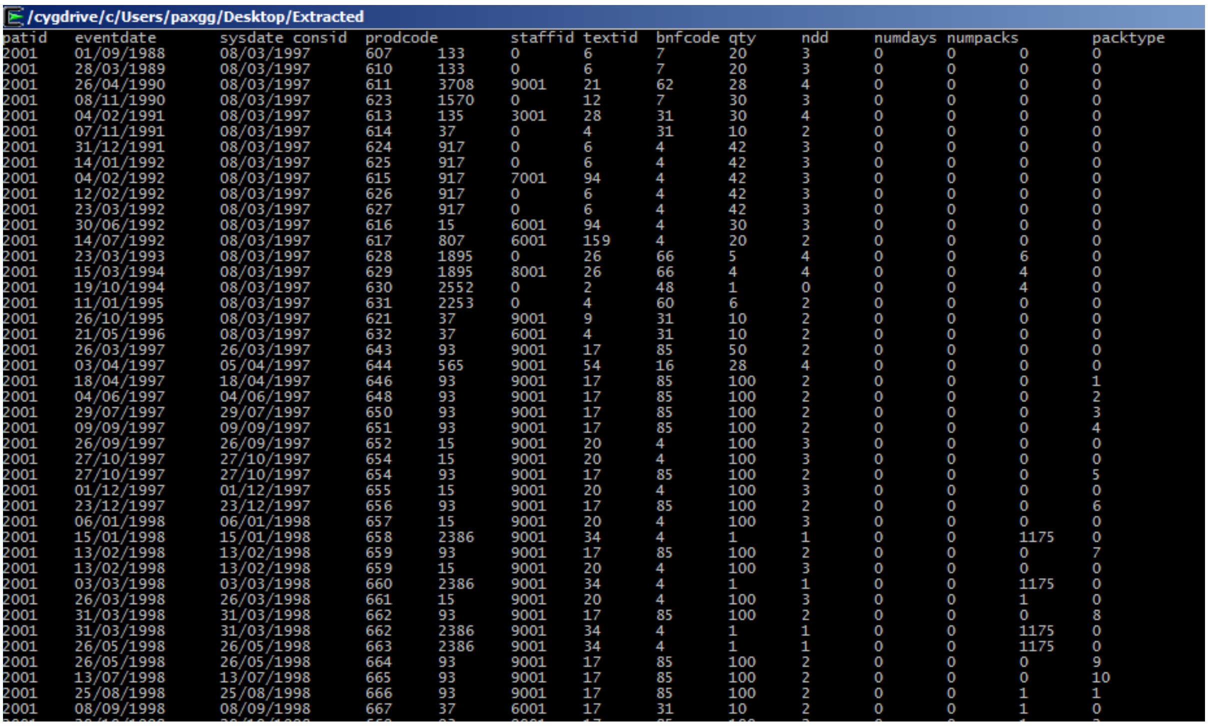


Figure 2. Raw plain text format of prescription data in CPRD



patid	eventdate	sysdate	consid	prodcode	staffid	textid	bnfcode	qty	ndd	numdays	numpacks	packtype	
2001	01/09/1988	08/03/1997	607	133	0	6	7	20	3	0	0	0	0
2001	28/03/1989	08/03/1997	610	133	0	6	7	20	3	0	0	0	0
2001	26/04/1990	08/03/1997	611	3708	9001	21	62	28	4	0	0	0	0
2001	08/11/1990	08/03/1997	623	1570	0	12	7	30	3	0	0	0	0
2001	04/02/1991	08/03/1997	613	135	3001	28	31	30	4	0	0	0	0
2001	07/11/1991	08/03/1997	614	37	0	4	31	10	2	0	0	0	0
2001	31/12/1991	08/03/1997	624	917	0	6	4	42	3	0	0	0	0
2001	14/01/1992	08/03/1997	625	917	0	6	4	42	3	0	0	0	0
2001	04/02/1992	08/03/1997	615	917	7001	94	4	42	3	0	0	0	0
2001	12/02/1992	08/03/1997	626	917	0	6	4	42	3	0	0	0	0
2001	23/03/1992	08/03/1997	627	917	0	6	4	42	3	0	0	0	0
2001	30/06/1992	08/03/1997	616	15	6001	94	4	30	3	0	0	0	0
2001	14/07/1992	08/03/1997	617	807	6001	159	4	20	2	0	0	0	0
2001	23/03/1993	08/03/1997	628	1895	0	26	66	5	4	0	0	6	0
2001	15/03/1994	08/03/1997	629	1895	8001	26	66	4	4	0	0	4	0
2001	19/10/1994	08/03/1997	630	2552	0	2	48	1	0	0	0	4	0
2001	11/01/1995	08/03/1997	631	2253	0	4	60	6	2	0	0	0	0
2001	26/10/1995	08/03/1997	621	37	9001	9	31	10	2	0	0	0	0
2001	21/05/1996	08/03/1997	632	37	6001	4	31	10	2	0	0	0	0
2001	26/03/1997	26/03/1997	643	93	9001	17	85	50	2	0	0	0	0
2001	03/04/1997	05/04/1997	644	565	9001	54	16	28	4	0	0	0	0
2001	18/04/1997	18/04/1997	646	93	9001	17	85	100	2	0	0	0	1
2001	04/06/1997	04/06/1997	648	93	9001	17	85	100	2	0	0	0	2
2001	29/07/1997	29/07/1997	650	93	9001	17	85	100	2	0	0	0	3
2001	09/09/1997	09/09/1997	651	93	9001	17	85	100	2	0	0	0	4
2001	26/09/1997	26/09/1997	652	15	9001	20	4	100	3	0	0	0	0
2001	27/10/1997	27/10/1997	654	15	9001	20	4	100	3	0	0	0	0
2001	27/10/1997	27/10/1997	654	93	9001	17	85	100	2	0	0	0	5
2001	01/12/1997	01/12/1997	655	15	9001	20	4	100	3	0	0	0	0
2001	23/12/1997	23/12/1997	656	93	9001	17	85	100	2	0	0	0	6
2001	06/01/1998	06/01/1998	657	15	9001	20	4	100	3	0	0	0	0
2001	15/01/1998	15/01/1998	658	2386	9001	34	4	1	1	0	0	1175	0
2001	13/02/1998	13/02/1998	659	93	9001	17	85	100	2	0	0	0	7
2001	13/02/1998	13/02/1998	659	15	9001	20	4	100	3	0	0	0	0
2001	03/03/1998	03/03/1998	660	2386	9001	34	4	1	1	0	0	1175	0
2001	26/03/1998	26/03/1998	661	15	9001	20	4	100	3	0	0	1	0
2001	31/03/1998	31/03/1998	662	93	9001	17	85	100	2	0	0	0	8
2001	31/03/1998	31/03/1998	662	2386	9001	34	4	1	1	0	0	1175	0
2001	26/05/1998	26/05/1998	663	2386	9001	34	4	1	1	0	0	1175	0
2001	26/05/1998	26/05/1998	664	93	9001	17	85	100	2	0	0	0	9
2001	13/07/1998	13/07/1998	665	93	9001	17	85	100	2	0	0	0	10
2001	25/08/1998	25/08/1998	666	93	9001	17	85	100	2	0	0	1	1
2001	08/09/1998	08/09/1998	667	37	6001	17	31	10	2	0	0	1	0

Figure 3.Formatted and cleaned prescription data in Stata 14

eventdate[27] 16/11/1999

	patid	pracid	edate	time	index	eventdate	prodcode	bnfcode	qty	ndd	numdays	numpacks
4	2001	001	16082007	7989	01101985	16/08/2007	3	15	56	1	0	0
5	2001	001	16102007	8050	01101985	16/10/2007	3	15	56	1	0	0
6	2001	001	22112007	8087	01101985	22/11/2007	3	15	56	1	0	0
7	2001	001	25022008	8182	01101985	25/02/2008	3	15	56	1	0	0
8	2001	001	25042008	8242	01101985	25/04/2008	3	15	56	1	0	0
9	2001	001	04062008	8282	01101985	04/06/2008	3	15	56	1	0	0
10	2001	001	20082008	8359	01101985	20/08/2008	3	15	56	1	0	0
11	2001	001	29122008	8490	01101985	29/12/2008	3	15	56	1	0	0
12	2001	001	09022009	8532	01101985	09/02/2009	3	15	56	1	0	0
13	2001	001	13052009	8625	01101985	13/05/2009	3	15	56	1	0	0
14	2001	001	14072009	8687	01101985	14/07/2009	3	15	56	1	0	0
15	2001	001	18052000	5343	01101985	18/05/2000	8	9	1	0	0	0
16	2001	001	06052010	8983	01101985	06/05/2010	9	7	21	3	0	0
17	2001	001	30061992	2464	01101985	30/06/1992	15	4	30	3	0	0
18	2001	001	26091997	4378	01101985	26/09/1997	15	4	100	3	0	0
19	2001	001	27101997	4409	01101985	27/10/1997	15	4	100	3	0	0
20	2001	001	01121997	4444	01101985	01/12/1997	15	4	100	3	0	0
21	2001	001	06011998	4480	01101985	06/01/1998	15	4	100	3	0	0
22	2001	001	13021998	4518	01101985	13/02/1998	15	4	100	3	0	0
23	2001	001	26031998	4559	01101985	26/03/1998	15	4	100	3	0	0

3.5.3 Data structure in HES database

HES data that are linked to the CPRD database are provided in two parts, the outpatient database and the inpatient databases. The inpatient HES database contains records of hospital admissions, diagnoses and procedures during hospital stay. The structure is similar to CPRD with separate tab delimited text files containing the information. The outpatient HES database has the same structure as the inpatient one, and contains detailed records of outpatient visits. The data contains patient demographics, episode information, outpatient visits information, events of critical care, diagnoses, procedures, and maternity care.

3.5.4 Coding systems

The majority of information in CPRD and HES databases is coded. In order to extract the relevant information for their study research questions, researchers have to consult dictionary and lookup files that match the information stored in the databases with its relevant explanations. Coding systems are used in the databases in order to reduce their overall size, and make the search of specific information easier for the researchers.

Clinical information in CPRD is coded in Read and Oxford Medical Information System (OXMIS) dictionaries. Read codes are the standard clinical terminology system used in General Practice in the United Kingdom, and support detailed clinical encoding of multiple patient phenomena including: occupation, social circumstances, ethnicity and religion, clinical signs, symptoms and observations, laboratory tests and results, diagnoses, diagnostic, therapeutic or surgical procedures performed, and a variety of administrative items. They were developed in during the 80’s by Dr James Read, and they were acquired for the NHS by the UK government. The use of codes allowed for standardised recording and retrieval of information from a clinical record, and facilitated the use of records for research purposes. The Read codes are five-character alphanumeric codes. At each level the code may be a lower (small) or upper case (capital) letter or a number. There are 58 available characters at each level and so a theoretical maximum of more than 650 million available codes (187). The codes are arranged in a hierarchical fashion, with the level of detail increasing down the hierarchy. Codes that have another level beneath them in the hierarchy are known as parent codes and the codes beneath them are their children (188). For example, G3011 stands for Acute anteroseptal myocardial infarction. The root G includes all circulatory system diseases, G3 represents ischaemic heart disease, G30 is acute myocardial infarction, and within that anterior myocardial infarction NOS is found (G301.).

In HES data, coding systems different from Read codes are used. Diagnoses are coded using the using the 10th revision of the International Classification of Diseases (ICD-10), an international standard diagnostic classification system created and maintained by WHO(189-192). Procedures are recorded using the 4th revision of the Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS-4) system (166). The OPCS-4 code system is currently maintained by NHS Information Authority (NHS IA).

Medication prescriptions in CPRD are coded according to the BNF chapter and section to which they belong, which allows the structure of queries that are based either on BNF chapter (BNF chapter structure up to BNF 69), name of medicine or both.

3.6 Study design, inclusion criteria, data extraction methods

3.6.1 Inclusion criteria and cohort definition

The study comprised adults with T2DM who had had an ACS episode and were prescribed antiplatelet medications as a secondary prevention measure. The definition of the cohort was carried out in four steps: 1) Identify adults with T2DM in CPRD 2) Generate a subset of adults with T2DM that were eligible to be linked in HES, ONS mortality and IMD score data. 3) Identify the adults who suffered an ACS after searching the HES data for events signalling inpatient admissions due to ACS. The events were identified by finding the inpatient admissions with a primary ICD-10 code that represented an ACS (Codes with disease type "MI" in Appendix 2), irrespective of admission type. 4) Identify the earliest prescription of antiplatelet medications that those patients had after the ACS event (index date), and group the patients based on the antiplatelet regimen they were prescribed.

In the first stage the CPRD database was interrogated with the help of the database built-in tool (DEFINE) using the specific inclusion and exclusion criteria. The patients included in the study were adults (≥ 18 years old) and they were registered in a CPRD-participating practice for at least 12 months prior to the index date (a standard practice in CPRD data analysis, in order to ensure the reliability of any diagnoses). Furthermore, the practice where patients were registered had to provide the CPRD database with research quality data (up-to-standard practice). The study included patients who had a record of a Read code that corresponded to T2DM (Read code located in the "clinical" file) and at least one prescription for an antidiabetic medication (Prescription information located in the "therapy" file). The combination of T2DM read codes and antidiabetic prescriptions allowed for identifying patients that have the condition and they are also treated for it with medication. Patients with Read codes that did not describe explicitly the type of diabetes, but had prescriptions for oral antidiabetic medication were included in the cohort because these medications are not used for any other indication, so excluding them would have reduced the cohort size unnecessarily. Patients with a Read code of undefined diabetes type and without oral antidiabetic prescriptions were excluded. Patients with a diagnosis of T1DM or other non-T2DM diabetes such as gestational diabetes or diabetes associated with malnutrition were excluded from the study.

After the completion of the first step, the list of patients with T2DM extracted from CPRD was compared with the list of patients whose records were eligible for linking with other databases (HES, ONS, IMD) in CPRD linkage eligibility scheme. Finally, the records of patients that were linked to HES data were investigated in order to find episodes of ACS. The following section describes how the records were kept based on the definition of observation period.

3.6.2 Observation period

Study participants were observed from the index date (date when a study participant was prescribed an antiplatelet medication for secondary prevention of ACS) to the end of observed follow up or the final recorded data (date of death, or date of switching antiplatelet regimen, or transfer out date, or end of study period). Characteristics of study participants (see 3.6.3 for more detail) were collected by observing CPRD diagnosis records, prescription records, and test records over a 12-month period prior to index date. The study covered a nine-year time period from January 2007 to December 2015. The main reason that January 2007 was selected had to do with the, alignment of datasets, introduction of the Quality Outcomes Framework (QOF), and the quality in the recording of potential key variables for the study after a specific time point. Because of the inclusion of outpatient HES data in the study, the absolute earliest date that patient observation could start was April 2003. The introduction of QOF on 1st April 2004, meant that the earliest date of data collection was moved to April 2005 in order to take into account the shift in GP coding practices of T2DM condition due to QOF criteria and the increased voluntary participation of GP practices in the scheme. Herrett et al pointed out that in CPRD, the recording of key variables such as smoking status, blood pressure, BMI, and alcohol intake has improved after the introduction of QOF criteria in 2004, but the rise in recording of those variables is visible after 2007(152). All patients with T2DM were included, irrespectively of being prevalent (had the condition before January 2007) or incident (diagnosis of the condition occurred during the study period) cases. The beginning of follow up is defined as the index date, that is when a patient in the cohort was prescribed an antiplatelet medication for the secondary prevention of ACS suffered from ACS. Every patient in the study had to have at least 12 months of records prior to the index date (a standard practice in CPRD data analysis, in order to ensure the reliability of any diagnoses). Patients were followed up until the transfer out date, last collection date in CPRD, death (deathdate), or 31 December 2015 (last date of study), whichever occurred first.

3.6.3 Patient characteristics

After the initial cohort definition, the definition of observation period, and the identification of adults that were eligible for inclusion in the study, data extraction was carried out. The reason for collecting information about patient characteristics serves several purposes: 1) To provide a better description of the study participants and help in drawing better conclusions about the regimens prescribed. 2) To use this information in order to estimate the probability of treatment assignment for the balancing among treatment groups. 3) To use this information for the inferential analysis in the later stages of the study. The information that was extracted comprised demographic characteristics, clinical information, and health care resource use information. Information representing patient demographics (gender, age) was retrieved from the patient file of CPRD, and patients' socioeconomic status were collected from the linked dataset that contains information about the index of multiple deprivation. Age was calculated at initiation of antiplatelet medication therapy using the date of birth and the index date. Additional variables extracted from the "patient" sheet were the patient gender and the number of the GP practice where the patient is registered. The GP practice number corresponds to the last 3 digits of the CPRD patient ID.

In order to derive information about health care indicators and lifestyle choices of the cohort participants, with the use of CPRD records, the laboratory test data were used to identify information about smoking status (Appendix 1) ,BMI calculation and Hba1C levels, blood pressure levels, and cholesterol levels. For the estimation of the body mass index of a patient, the measurements of body weight and height recorded in the "test" CPRD text file were used.

The list of the entity types that were relevant for the study was identified with the help of a GP (Prof. Anthony Avery).

Charlson comorbidity index was used as an indicator of multiple comorbidities among patients, and it was estimated from ICD-10 codes used to describe hospital admission episodes in inpatient HES data (193, 194). Section 3.9.3.12 describes which parts of the extracted information was used as covariates for balancing among treatment groups.

3.6.4 Study medications

Details of the patients for all prescribed medications were extracted, but the focus was only on antidiabetic medication and antiplatelet medications. The list of product codes which represent the medications that were used to identify patients on antidiabetic medication and antiplatelet medication regimens respectively, are included in Appendix 3.

3.6.4.1 Medications for diabetes

The medication list used for the extraction of data was compiled using the formulations listed in the BNF (195) chapter 06.01.01 and 06.01.02, including sulfonylureas, biguanides, and other antibiabetic drugs (acarbose, alogliptin, canagliflozin, dapagliflozin, empagliflozin, exenatide, linagliptin, liraglutide, lixisenatide, nateglinide, pioglitazone, repaglinide, saxagliptin, sitagliptin, and vildagliptin). Medication prescriptions together with Read codes identified patients with T2DM.

3.6.4.2 Antiplatelet medications

The medication list used for the identification of antiplatelet exposures was compiled using the formulations listed in the BNF chapter 02.09.00.00. The medications were: aspirin (as antiplatelet), clopidogrel, ticagrelor, and prasugrel.

3.6.5 Exposure

Antiplatelet prescription is the exposure of interest. Initially, several separate exposures were identified; exposure to aspirin, exposure to aspirin and clopidogrel, to clopidogrel only, exposure to aspirin and prasugrel, to prasugrel only, aspirin and ticagrelor, and exposure to ticagrelor only. The reason for selecting these combinations was to include patients that were on dual antiplatelet therapy and those who were prescribed one medication only, because of intolerance to aspirin. In the case where exposure groups had very small patient numbers (equal or less than five), those exposure categories were removed from the analysis, because the terms and conditions of CPRD use, do not allow the publication of results of such small groups, due to potential loss of anonymity.

3.6.6 Outcomes

3.6.6.1 Prescribing patterns

The trends of antiplatelet usage among patients in different regimens were reported over time, from treatment initiation and afterwards. CPRD therapy files were used to identify all the needed information about antiplatelet prescriptions.

3.6.6.2 Medication adherence

Prescription information as recorded from CPRD was used to estimate patients' adherence to antiplatelet medicines (aspirin only, clopidogrel only, aspirin-ticagrelor, aspirin-prasugrel, aspirin-clopidogrel). Two measures of adherence were considered, proportion of days covered (PDC) and medication possession ratio (MPR), which are the most common adherence measures used in studies utilising routinely collected data.

The variation in adherence was observed for every exposure group from the index date over several monthly time intervals (1 month to 1 year post-ACS) using the Proportion of Days Covered (PDC) as a measuring unit; PDC is a more conservative measure compared to medication possession ratio (MPR) and it takes into account medications that are in the same therapeutic class, making it more appropriate as measure of adherence in medications regimens. Following the suggestions of Karve et al who suggest that a PDC value cut-off point of 0.8 for classifying a patient as "adherent" is reasonable (196). PDC calculation was carried out in four steps as specified by the Pharmacy Quality Alliance: 1) Determine the patient's measurement period, defined as the index prescription date to the end of the calendar year, disenrollment, or death; 2) Within the measurement period, count the days the patient was covered by the drug (monotherapy regimen) or the drugs (if the regimen has more than one medications) based on the prescription fill date and days of supply. If prescription fills for the same drug overlap, then adjust the prescription start date to be the day after the previous fill has ended; 3) Divide the number of covered days found in Step 2 by the number of days found in Step 1. Multiply this number by 100 to obtain the PDC (as a percentage) for each patient; 4) Count the number of patients who had a PDC greater than 80% and then divide by the total number of eligible patients (197).

During PDC estimation the gaps between prescriptions were considered. When there was a gap between prescriptions that was equal or longer than 60 days, it was assumed that the patients had discontinued their therapy (198-200). Prescription information after the time of discontinuation was not considered.

3.6.6.3 All-cause mortality

Mortality information was extracted from CPRD and linked databases. That included the death date variable in CPRD database, the dod (date of death) entry in the ONS linked dataset, and the discharge method information recorded in inpatient HES dataset. In case of multiple death records for the same patient, the hierarchy of information was as follows: the ONS record was at the top of the hierarchy, followed by the record in CPRD, and the HES record at the bottom. The same hierarchy of information was followed, in the case of multiple death records per patient that have mismatched dates of death reported. The reason for having CPRD and ONS death records above in the hierarchy was because mortality information in these sources was recovered from death certificates.

3.6.6.4 Cardiovascular disease (CVD) related death

Every mortality record was investigated for cause of death and deaths that were related to CVD were grouped as a separate outcome. In the cases where the main cause of death was an MI or stroke, based on the list of ICD-10 codes in Appendix 4, then the death was classified as a CVD-related death.

3.6.6.5 Non-Fatal Myocardial Infarction (MI)

In the study, myocardial infarction (MI) events were collected, because they were part of the composite outcome (MACE). The reporting of MI was based on the records of HES inpatient admission data, where the first diagnosis ICD-10 code was relevant to MI. The events that were included as MI in the study, represented a range of ACS conditions, from unstable angina to transmural MI (NSTEMI, STEMI). Only the non-fatal events are included in this outcome. The full list of conditions that represent MI are listed in Appendix 2.

3.6.6.6 Non-Fatal stroke

All stroke events of any type (ischemic, haemorrhagic, transient ischaemic attack), that are not fatal were included, with information sourced from ICD-10 codes from HES inpatient data. The reporting of stroke was based on the records of HES data, where events with the first diagnosis ICD-10 code relevant to stroke, were considered as stroke events. The full list of conditions that represent the types of stroke are listed in Appendix 2.

3.6.6.7 Major adverse cardiovascular events (MACE)

MACE was the composite outcome of interest in the analysis. It was generated using the findings of separate reporting of nonfatal MI, nonfatal stroke, and CVD related death in the HES inpatient linked dataset. Events of nonfatal MI, nonfatal stroke, and CVD related death, as defined in sections 3.6.6.4,3.6.6.5,3.6.6.6 and previously identified through the ICD-10 codes reported in HES inpatient episode admission data from the HES inpatient linked dataset, were included in this outcome (201). MACE was used because it was the primary endpoint reported by studies investigating the clinical effectiveness of newer agents versus clopidogrel. Furthermore, this outcome is commonly used in studies that involve the assessment of cardiovascular treatments(202).

3.6.6.8 Bleeding

Information about bleeding events was collected because internal bleeding is a common side effect that occurs in patients treated with antiplatelet medications. It is an outcome that is used as a safety endpoint in studies that assess the clinical effectiveness of antiplatelet treatments (75). In the study only bleeding events leading to hospitalisations were considered. Those events were obtained from the records of HES inpatient admission data. Admissions due to a range of causes of internal bleeding were considered. The full list of ICD-10 codes that were relevant for the study and represent bleeding events was identified with the help of a clinically active GP (Prof. Anthony Avery), and is provided in Appendix 2.

3.7 Study approval

The study protocol was submitted for reviewing to the Independent Scientific Advisory Committee (ISAC) for Medicines and Healthcare products Regulatory Agency in line with requirements for the extraction and dissemination of CPRD data and it was accepted in November 2016 (protocol code: 16_188R). Linked data from the HES database and ONS mortality data was additionally requested.

3.8 Data management and cleaning

3.8.1 General information

In this section, information about the steps that were taken for the preparation of analysis datasets is provided. The main purpose of the data management strategy was to:

1. Discard unwanted information from the initially extracted data, allowing for faster processing at the analysis stage
2. Select pieces of information in the initially extracted data that would help us identify exposures, outcome events and additional covariates for use in the quantitative analyses.
3. Generate variables required for the analysis

3.8.2 Data cleaning-data management of CPRD text files

Data from CPRD database were obtained, and extracted from compressed tab delimited text files in a non-interactive way with the use of unzip software (203) and a text processing programming language (AWK)(204). An initial visual inspection of files was performed with vim (205).

The extracted CPRD text files contained variables that were not relevant to the analysis. Columns of data that were containing the date that information was inserted in the system (sysdate) and the unique ID number (textid) that corresponded to text comments made during consultation by software users (GP, nurses, administrative staff) were removed, in order to decrease the size of text files. Furthermore, in this initial stage, the full unique id numbers for consultations were generated. This was made possible by extracting the last three digits from the CPRD patient ID, and combining it with the "consid" variable.

In the therapy file, the type of antiplatelet medication regimen that patients were following was based on the BNF codes that were used in the database and the product codes representing the medications. CPRD lookup files were used to identify the product codes and the BNF codes that correspond to antiplatelet medications. Information on the date of death was obtained from the "patient" sheet, HES data (in a case of a fatal event), and linked ONS mortality data.

Dates are recorded on CPRD as string values in DD/MM/YYYY format. In order to facilitate data cleaning and identification of clinical events, all dates were converted using Stata code into a numeric format consisting of the number of days elapsed since 1960, and transformed into human readable format.

3.8.3 Data cleaning-HES data management

The first step in HES data management was to identify the patients in the cohort who had an inpatient or outpatient event recorded on HES. This was made possible after merging the "patient" file from CPRD with the several text files that HES database consists of. Dates were recorded in the HES database as string values and were treated in the same way as dates in CPRD. HES inpatient data were used for the identification of the date when the patients had their first ACS episode. This date was used as the index date of patient follow-up. In order to generate the hospital episode dataset that would be used for analysis of outcomes and costs, the initial HES inpatient dataset parts were formatted in order to be used with the HRG reference costs grouper software. This procedure involved the merging of the separate text files that were containing the ICD-10 codes and OPCS-4 codes respectively for every inpatient episode, and the transformation of the data contained in those files from "long" format into "wide" format.

3.8.4 Data cleaning-Index date generation for patient follow-up

The study included adults (>18 years old) with T2DM who suffered an ACS event and were prescribed antiplatelet medications post-ACS as a secondary prevention measure. Patient identification was carried out in four steps: 1) Identification of the patients with T2DM in CPRD 2) Find those who were eligible to be linked in HES, ONS mortality and IMD score datasets. This information is stored in the linkage eligibility file. 3) Finding the patients who suffered an ACS using HES inpatient data, and 4) retrieve the earliest prescription of antiplatelet medications they had post-event (index date). Patient identification during the first step was carried out by including patients who either had a record of a Read code that corresponded to T2DM and at least one prescription for an antidiabetic medication or a Read code record that did not describe explicitly the type of diabetes, and a prescription for oral antidiabetic medication. Tables in Appendix 3 provide lists of indicative Read codes and medication codes used for identification of study population. Patients with either a Read code of undefined diabetes type and without oral antidiabetic prescriptions records, or a diagnosis of T1DM or other non-T2DM diabetes such as gestational diabetes or diabetes associated with malnutrition were excluded. Then, with the use of linkage eligibility files, patients who had linked records to HES, ONS mortality, and IMD score datasets were selected. Every patient ought to have at least 12 months of records, and should have been registered in a CPRD-participating practice for at least 12 months prior to the index date (standard practice in the use of CPRD data handling,in order to ensure the reliability of any diagnoses). The study period for tracing the diabetes condition in patients was from 1987 until the 30 September 2015. The beginning of follow up was defined as the date when a patient in the cohort was prescribed an antiplatelet medication after an ACS event (index date), and the inclusion period is set between 1 January 2007 and 30 September 2015. Patients were followed up until the transfer out date, last collection date in CPRD, regimen switch, death (deathdate), or 30 September 2015 (end of HES and ONS data collection), whichever occurred first.

3.9 Data analysis

3.9.1 Characteristics of costs, outcomes and population description

Descriptive characteristics about population age, gender, duration of T2DM, number of medications, blood pressure, BMI, HbA1c levels, smoking status, drinking status, comorbidity score based on Charlson index were provided (section 3.6.1 and 3.9.3.12 for details). Information about medication adherence, and prescribing patterns was also provided. The results of descriptive characteristics were presented in groups according to antiplatelet exposure patients belong (aspirin only, clopidogrel only, aspirin and clopidogrel, aspirin and prasugrel, aspirin and ticagrelor).

The outcomes that constitute MACE were presented separately and for every exposure group. All cause death was presented as a sum of all disease related deaths in the cohort. Results for MACE and all cause death were provided only for the linkage eligible population.

3.9.2 Selection bias and balancing for non-random group classification

A common problem that occurs in non-experimental observational studies is selection bias. When a researcher is trying to estimate treatment effects in outcomes among patients in different treatment groups, these effects are likely to be biased because other patient characteristics or treatments might affect the outcome. This bias can be overt, meaning that it can be seen from the data available at hand; for example, before treatment the treated subjects have higher socioeconomic status than controls. A hidden bias is similar, but it is not observable, because the information needed for this type of bias to be seen is neither recorded or available (206). The selection bias problem is usually treated during the study design stage with the help of randomisation and in the study analysis stage by using regression techniques for confounding adjustment. In cases where data are collected from patients that are not randomised, methods that balance patients in their pre-treatment characteristics are used.

The balancing methods are used in order to allow comparison of patients with similar characteristics who belong to different treatment groups. Those methods allow for the allocation of patients, in such a manner that the only difference among patients should be the treatment group they belong to. Using these methods, a researcher can estimate treatment effects among patients in non-randomised studies. In the case of this study, balancing methods were used to create comparable groups among adults with T2DM undergoing secondary prevention after an ACS event with different antiplatelet agents.

3.9.3 Overview of methods for addressing non-random assignment

3.9.3.1 Regression analysis

Regression analysis is a very common method for addressing confounding. Statistical models that include several known confounding factors in their specifications are used to estimate treatment effects. Various model specifications can be used to in order to address linear or non-linear relationships among outcomes and treatment assignment. In regression analysis, the treatment is included as an explanatory (exposure) variable in the model(207). The use of different regression models depends on the nature of the dependent and the treatment variables, which can be continuous, binary or categorical. The coefficient of the exposure variable represents the treatment effect, which can be expressed as marginal value, odds ratio or hazard ratio, depending on the type of regression model used (linear, logistic, time-to-event). Regression analysis allows the researcher to investigate the goodness of fit of the model in the data with the use of measures such as R-squared, likelihood ratio test, and Akaike information criterion. These measures present the proportion of variation explained by the models (R-squared) and help the researcher assess the reliability of the model drawing inferences from existing data. Another advantage that lies in the use of regression analysis is that results can be easily interpreted, since they are presented in the form of variable coefficients. This way treatment effect can be presented as a marginal change on the outcome (ordinary least squares models) or a change in risk or hazard ratio (logistic models, time-to-event models)(207). Regression analysis can be problematic when the model goodness-of-fit is poor due to incorrect model specification or selection of variables, or when the balance in baseline characteristics among treatment groups is low. Another problem that frequently occurs is the correlation between two or more explanatory variables in the model (multicollinearity). This can result in coefficients becoming very sensitive to small changes in the model together with a reduction of their precision (208).

Difference-in-difference methods is a strategy for evaluating the impact of policies or programs that commence in a specific period of time, such as the introduction of legislation. The changes over time occurring in the group affected by the policy are compared with changes in the group that is not affected, and the effect of an intervention is measured as difference-in-differences(209). This method was not considered as a candidate for addressing confounding, because it was not relevant for the analysis. This study investigates the costs and outcomes in patients treated with different antiplatelet therapies, and not the impact before and after the introduction of new antiplatelet therapies, where such a method could be relevant.

Instrumental variables to control confounding is a method for addressing confounding used in econometrics with a potential use in epidemiological studies. An instrumental variable is a variable associated with the exposure of interest but not associated with the outcome either directly or indirectly. Few variables have these characteristics in studies, but in pharmacoepidemiological studies, a potential instrumental variable may be preference in drug choice by the treating physician or hospital(210). This method was not considered for the study due to the fact that it is more developed in the linear regression framework but not as developed in analyses that are using non-linear models (211)

For the rest of the methods which address non-random assignment, several steps for method selection need to be taken. The steps for method selection and the methods them selves are described in the following sections.

3.9.3.2 Balancing methods selection

In order to implement the balancing across the patients in different treatment regimens general steps as described in Stuart (212) were used:

1. Define closeness: what distance measure is going to be used for deciding whether participants have close characteristics. The two steps are:
    a. Inclusion of variables that are going to be used to measure the distance among patients.
    b. Distance measure selection (Exact, Mahalanobis, Propensity score, Linear Propensity score.)
2. Selecting a balancing method after measuring distance (matching, weighting, stratification, combinations of balancing methods).
3. Balance assessment on the covariates; Repeat of steps 1-3 if balance is poor.
4. Estimate the treatment effect on the balanced sample.

3.9.3.3 Balancing methods overview

3.9.3.3.1 Exact matching

When exact matching is used as a method of balancing, then the distance among individuals is zero for the same values of covariates **X**, whereas the distance is equal to infinity when covariate values differ. This balancing method is the ideal because participants that have identical baseline characteristics except the allocated treatment can be compared. This strategy though can result in the high reductions in sample size by excluding patients that are not matched. An advance in this method is the coarsened exact matching (CEM), where each variable is coarsened. That is, observations with different values are grouped and are assigned the same value, for example putting patients into age groups instead of using their age for balancing purposes(213). Exact matching is performed using the values of the coarsened variables, and in the post balancing analysis stage the values of the original variables are used.

3.9.3.3.2 Mahalanobis distance matching

Mahalanobis distance(214) is calculated using the following equation

$$D_{ij} = \left(X_i - X_j\right)^T \sum^{-1} \left(X_i - X_j\right).$$

The distance D_{ij} between individuals *i* and j is measured based on the covariate values X_i and X_j.Depending on the treatment effect of interest the variance covariance matrix **Σ** can be either that of **X** in the full control group in the case of average treatment effect on the treated (ATT), or that in the full sample in the case of average treatment effect (ATE). Matching using Mahalanobis distance can be selected when the number of baseline variables is relatively low. In cases where the covariate number is high or the covariates are not normally distributed, this matching method does not perform well.

3.9.3.4 Propensity scores

Propensity scores are defined as the summary of all pre-treatment covariates into one value: the probability of being assigned in a treatment(215). The probability of an individual *i* being assigned to a treatment T_i is given from a specific set of covariates X_i

$$e_i(X_i) = P(T_i = 1|X_i).$$

Propensity scores have two main properties; they are balancing scores, so when patients are grouped based on their propensity scores, the effect of a randomised experiment is emulated. Additionally, when the assumptions of strong ignorability for treatment assignment hold, matching of patients using propensity scores instead of the full set of pre-treatment covariates is justified (212). Several balancing methods, such as nearest neighbour matching or stratification, are based on propensity scores.

3.9.3.4.1 Assumptions of balancing using propensity score methods

All the balancing techniques used for the estimation of treatment effects in non-experimental studies use the following assumptions:

1. Unconfoundedness: $\boldsymbol{Y(0), Y(1)} \coprod \boldsymbol{D} \mid \boldsymbol{X}$, with $\coprod$ denoting independence, and **D** being the treatment, **X** the set of observable covariates, and **Y** the outcome,
2. Overlap or common support: $\boldsymbol{0 < P(T = 1 \mid X) < 1.}$
3. Stable Unit Treatment Value Assumption (SUTVA) (216)

The unconfoundedness assumption denotes that potential outcomes are independent of treatment assignment, for a set of observable covariates **X** (215).

The common support assumption rules out the phenomenon that treatment T can be perfectly predicted given the values of X covariates. This way patients with the same values on **X** covariates have a positive probability of being assigned under any treatment(202)(217). When assumptions 1 and 2 hold then "strong ignorability" exists; treatment effects can be estimated without bias (212).

The third assumption states that the outcomes of one patient are not influenced by the treatment selection of other patients, that is no spill-over effects can occur between patient interactions (216).

3.9.3.4.2 Nearest neighbour matching (NN)

In this matching method, the person from the comparison group is matched with a person from the control group based on the closeness of the propensity scores. NN matching can be carried out 'with replacement', where a person that is on the control grouped can be used as a match more than once, or 'without replacement'. In that case controls are used as a match only once. Another variation in this method is to match treatment participants with more than one NN control ('oversampling'). Decisions regarding 'oversampling' is used or if matching is performed with or without replacement depend on the trade-off between variance and bias. Smith (218), and Smith and Todd (219) describe the trade-offs in more detail.

3.9.3.4.3 Caliper and Radius matching

When NN matching is used, there is a possibility of achieving bad matches when the closest neighbouring observation is far away in terms of propensity score. This can be avoided if the researcher imposes a limit in the maximum propensity score distance (caliper). With the use of caliper matching the participants among comparison groups are matched only when their distance in terms of propensity score ranges from very close to the imposed maximum (caliper). A variant of caliper matching is radius matching. In radius matching, all the closest neighbours within the selected caliper are matched, not only the NN. This method combines the advantages of oversampling with those of caliper matching, allowing for the use of more observations, without the risk of bad matches. The disadvantage of both methods is that the researcher is not aware a priori what the optimal maximum distance is (220).

3.9.3.4.4 Kernel matching, local linear matching

In kernel matching, propensity scores are used as a method to define the distance of characteristics between those who had the treatment and their controls in a study. Propensity scores are estimated using non-linear multivariate regression models. In kernel matching estimation every matched pair receives a weight and the weighted average treatment effect is generated with the kernel function as the weighting function(221, 222). The local linear regression matching is an extension of the kernel matching, and instead of estimating a weighted average treatment effect, creates a weighted least squares regression.

3.9.3.5 Weighting adjustments

Another option of balancing treatment groups involves the use of propensity score as inverse weights in estimates of treatment effects. This method is known as inverse probability of treatment weighting (IPTW). The weights obtained from this method are used in all observations, in a manner similar to the way that survey sampling weights adjust a sample. The weights w_i for the average treatment effect for every individual *i* are calculated as follows (223)

$$w_i = \frac{T_i}{e_i} + \frac{1 - T_i}{1 - e_i}$$

with $T_i$representing the treatment assignment (T_i =1: treated, T_i =0: control) and e_i the propensity score for every individual. The weight value is equal to $1/e_i$ for treated patients and to $1/(1 - e_i)$ for non-treated patients. This method is designed for binary cases of exposure (intervention and control). In the case of this study where, the number of treatment options is not binary, an extension of this method is required for the investigation of treatment effects. Methods such as marginal mean weighting through stratification, multinomial propensity scores and covariance balance propensity scores allow for obtaining weights for multiple exposures.

The results of weighting adjustments can be used for the generation of doubly robust estimators. Those estimators are generated by using two models: a model for the investigating the relationship between treatment and covariates (propensity score model) and a model for the relationship between the outcome, the covariates and treatment. Doubly robust estimators are consistent when one of the two models is correct, allowing for some protection in the case of model misspecification(224).

3.9.3.5.1 Marginal mean weighting through stratification (MMW-S)

This balancing method is one that combines several key elements from propensity score stratification and IPTW (225). Estimated propensity scores are used to stratify observations within the sample. Instead of comparing balance within strata as in propensity score stratification, weights for every observation that belongs to the treated group are generated within stratum. This method is suitable for balancing not only among binary treatments, but also for ordinal and multinomial treatments. The weight for observations in treatment $\mathbf{z}$ in stratum $\mathbf{s_z}$ is calculated as

$$\frac{n_{s_z} \times P(Z = z)}{n_{z=z,s_z}}$$

with $\mathbf{n_{s_z}}$ the number of patients in stratum $\mathbf{s_z}$, $\mathbf{P(Z = z)}$ the probability of assignment to treatment $\mathbf{z}$, and $\mathbf{n_{z=z,s_z}}$ the number of patients in stratum $\mathbf{s_z}$, actually assigned to treatment $\mathbf{z}$.

3.9.3.6 Multinomial propensity scores using generalised boosted models (MNPS)

This method uses multiple simple regression models that predict the probability of treatment assignment(226). Those simple models are combined in iterative manner, so that an overall multivariate model is generated. The algorithm works in such a manner that every new propensity score model fits the covariates better than the previous models. Treatment assignment balance for M treatments (M>1) is achieved using the generalised boosted models (GBM) method M times and obtaining the propensity scores for every treatment group. The IPTW $w_i[t]$ for every patient *i* of being assigned treatment t, that is having a propensity score $p_t(X_i)$ is calculated as

$$w_i[t] = 1/p_t(X_i)$$

MNPS models perform better in propensity score estimation compared to logistic regression models whose variables are selected iteratively. In the case where no covariate balance is achieved, MNPS allows the researchers to use doubly robust methods for the estimation of treatment effects.

3.9.3.7 Covariate balancing propensity scores (CBPS)

Propensity score estimation is dependent on model specification. In practice, researchers have to adjust propensity score models until those models provide results that balance covariates. Imai called this issue "propensity score tautology"(227), that a score is appropriate when it balances covariates. CBPS, is a method where the model that estimates the propensity scores is also achieving covariate balance at the same time. In CBPS, the fact that propensity scores are both scores that balance covariates and conditional probabilities of treatment assignment is exploited(228). The CBPS allows to estimate propensity score models that achieve optimal covariance balance. This method has several advantages: 1) Better balancing results when the propensity score model is misspecified. 2) It can be used for balancing among multiple treatments. 3) Balancing methods that use propensity scores such as weighting and matching can be selected without making any further modifications(228).

3.9.3.8 Stratification

In stratification matching, also known as interval matching, blocking, or subclassification, the main idea is to split the common support of the propensity scores into strata, and then make direct comparisons among treated and control patients in every stratum(229). The percentage bias that is removed increases when a high number of strata is used, but an increased number of subclasses decreases the observations within each stratum, affecting statistical power. According to Cochran, usually five subcategories are enough to remove 95% of bias associated with a single covariate(230). The main advantage of this method is that it removes the bias simultaneously on multiple pre-treatment covariates used on the propensity score estimation, by splitting the sample into a small number of subcategories(231). This method also allows for identifying treatment effect among subpopulations. The problem with this method is that very dependent on the correct specification of the propensity score model, because there is the chance of achieving balance in propensity scores, and having the covariates among treatment groups within strata unbalanced. If this occurs a different model specification that includes interactions or higher order terms is needed.

3.9.3.9 Selection of balancing methods

CBPS, MNPS and MMW-S were the candidate methods for balancing implementation, and the method that achieved the best balance was selected. All three methods had to be used, because it was impossible to know a priori which method achieved the best balance. In order to compare the achieved balance from every method, an add-on (cobalt) program that is available in R software(160) and generates covariates balance tables and graphs was used(232). The use of the add-on allowed for the comparison of the propensity scores and weights in a standardised manner across methods, since every balancing method generated different measures of balance assessment. This add-on allowed the import of balancing results generated from different statistical packages. In the case where after the use of balance tables and graphs, no clear conclusion about the method that performed the best balancing has been achieved, the next steps of analysis (time to event analysis, cost analysis) were carried out using balancing weights from all the implemented methods. The same strategy was followed if the add-on fails to produce any comparison tables and plots.

In propensity scores the assessment of covariate balance is carried out by examining the the absolute standardized differences between groups for each covariate, instead of using other statistical tests. The absolute standardized difference (ASD) is defined as

$$ASD = \frac{\overline{|x_T} - \overline{x_C|}}{\sqrt{\frac{S_T^2}{2} + \frac{S_C^2}{2}}}$$

where $\overline{x_T}$ and S_T are the sample mean and standard deviation, respectively, for subjects in the treated group and $\overline{x_C}$ and S_C are the sample mean and standard deviation for the control group. Larger values of ASD indicate greater imbalance in covariate values(233). The assessment of covariate balance using ASD can be carried out graphically with the use of Love plots(234), where the ASDs for every covariate are provided for every balancing method as data points in a scatter plot. Points that are closer to zero or below a specific threshold, indicate better covariate balance.

The suggestion of Stuart (212) for balancing method selection is based on the comparison of the standardised differences of means generated from the various balancing methods. The best method could be selected using as a guide one of the three alternative criteria: 1) choice of the method that yields the smallest standardized difference of means across the largest number of covariates, or 2) the method that minimizes the standardized difference of means of a few particularly prognostic covariates, and 3) the method that results in the fewest number of "large" standardized differences of means (greater than 0.25). The first and the third criterion were used to assess the balancing methods in the study.

Due to the fact that in the MNPS method, all the relevant balancing variables were included, the same strategy was followed for the CBPS method. This way the sampling weights generated from both methods would be derived from models that contained the same variables. For that reason, no specific strategy for the inclusion or exclusion of model variables like backward elimination or forward elimination was carried out. Overall, even though the model provides us with an overview of how a range of factors affect the treatment assignment of antiplatelet regimens, the model itself is used to derive sampling weights that are used for the time to event and costing analysis, and not specifically to interpret the prescription behaviour of the GPs. It is not possible to interpret fully the factors affecting prescribing behaviour from this analysis, some associations can be seen that are worthy of note.

During the use of MNPS, the final model that was used to derive the propensity scores was estimated automatically, and it was providing the best model that could fit the data, based on the stopping rule that was set in the beginning (effect size between the pairs of treatments). There was no need for manual introduction of interaction or polynomial terms, because this procedure was carried out by the machine learning algorithm. As a result of the automated process of the final model generation, according to the software authors (226), the algorithm of the MNPS method after multiple iterations, produced a model which contained variables (polynomial variables, interactions between variables) that could not be interpreted. The automated process of model generation constitutes the default behaviour of the MNPS software. Therefore, no results of the final MNPS equation are presented, because the software itself is programmed not to provide any model output by default, since the output of interest is the propensity scores and the balancing weights. For balancing purposes, only the propensity scores and the inverse treatment weights were obtained and used, as it was suggested by the software authors (226).

3.9.3.10 Covariate selection for propensity score estimation

In the estimation of propensity score models the selection of covariates to be included is driven by the tradeoff in the effect that the variable has in bias (difference between estimated effect and true effect) and efficiency (precision of estimated effect). If a variable is thought to be related to the outcome but not the treatment, including it in the propensity score should reduce bias; on the other hand, variables that are assumed to have associations with treatment but not outcome, can decrease precision. Covariates that are affected by treatment assignment should not be included in propensity score estimation models.(235)

All three methods generate propensity scores. The set of covariates used in all methods was the same, and the covariates selected for propensity score estimation models had the objective of identifying three aspects of treatment assignment:

1) Variation in the introduction and adoption of antiplatelet medications in England. Prasugrel and ticagrelor were introduced later than aspirin and clopidogrel (historical variations in treatment availability). More information about historical differences in authorisation is provided in Chapter 2.

2) Expected prescription variations among GP practices in different regions of England.

3) Factors affecting GP prescription behaviour. GPs prescribe medications to patients after considering patient safety. From a GP point of view, patient safety during medication prescription could be thought as an effort to avoid any adverse drug reactions, which means that before prescribing, the GP is considering patient factors, social factors, interactions of prescribed medicines with other medicines the patient is taking, and comorbidities. The covariates were selected after discussing with a clinical practicioner who had experience in prescribing antiplatelet medications (personal communication, Prof. Tony Avery)

In order to capture the historical variations in treatment availability, variables indicating the year of cohort entry, and the number of annual follow-up periods were used. This way, adjustment for two facts was made: 1) Patients on older medications entered the cohort earlier. 2) Patients on newer regimens had shorter follow-up periods than patients on older medications. A variable representing the area of England in which each GP practice was located, was used to capture prescription variations across GP practices in different regions of England. Finally, a set of variables that were associated with the factors that a GP may take into account during medication prescription were added. For patient characteristics, patients' gender and age at the time of prescription of antiplatelet were included. Social factors such as smoking status (Smoker, non-Smoker, ex-Smoker) and alcohol consumption status (Drinker, Non-Drinker, Ex-drinker) were also included. The information about alcohol consumption was obtained from the records in the "additional" files that were linked to the "clinical" files in CPRD. A grouped Charlson comorbidity index with three levels calculated over the year prior to index ACS event (no comorbidity, one comorbidity, two or more comorbidities) was used as a categorical variable representing patient comorbidity burden (236). Due to the way that the algorithm for the Charlson comorbidity estimation works (based on primary ICD-10 codes of inpatient admissions that are relevant for the score estimation), no adjustments for T2DM were made, meaning that the diabetes condition was not included in the Charslon comorbidity index.

The same set of covariates was used for both balancing methods that generated the sampling weights needed for the next steps of the analysis (time to event analysis, analysis of cost associations).

During the propensity score estimation two specification issues arise: the inclusion of relevant variables for the model and the functional form of the model. The usual approach is that when a specific variable is unbalanced, then the propensity score model is respecified using higher order terms or interactions (237). This approach can result in overfitting the propensity score model. A consequence of this can be either a more efficient estimator, or an estimator that performs no worse than the correctly specified model. In the case where a relevant covariate is excluded this can result in a worse treatment effect estimator but even in that case the result of overfitting has little consequence when not relevant variables are included in the model. The MNPS method follow this approach in the specification of propensity score models.

An alternative method to test specification of a propensity score model is to check whether the propensity scores balance the covariates, and it was suggested by Imai and Ratkovic. They suggested that the equations for the parameters of the propensity score model represent a generalised method of moments (GMM) estimator, with the conditions imposed by mean covariate balance as overidentifying conditions. As a result, an overidentifying test, known as Hansen's J test can be used as a test for assessing covariate balance(228). The CBPS method implements this approach for the specification of the propensity scores.

3.9.3.10.1 Definition of polypharmacy

Polypharmacy measurement was carried out using the prescription records from therapy files in CPRD. This measurement was used as an indicator that could affect GP prescription behaviour, and a variable indicating polypharmacy was used as a covariate in the models for the estimation of propensity scores. GPs who prescribe for patients with multiple medications have to take into account potential interactions between medications and potential adverse drug reactions. A variable indicating the number of medications from different BNF chapters was created. Polypharmacy was defined as the status where patients that had five or more prescribed medications from different BNF chapters(238). Five or more prescribed medications were selected as a cut-off point because this is the usual cut-off point for such a definition (239). Ten drugs from different BNF chapters or more are considered to represent 'major' or 'excessive' polypharmacy.

3.9.4 Time to event analysis

In order to identify the treatment effect occurring between the groups of different antiplatelet regimens, time to event analysis is needed to be carried out.

3.9.4.1 Time-to-event analysis-Justification

In the context of retrospective cohort studies, it is quite common that patients drop out of the study before the date set by the researcher as end of follow up date. This can happen because patients can withdraw from the study prematurely (death before the end of follow-up), they may be lost during follow-up (patients may relocate or change health care providers), or experience an outcome that makes them ineligible for further follow-up, before the end of the study. In these situations, the information about the time of follow-up is incomplete, meaning that these observations are censored. This type of censoring where the participant is observed for a time period and then it no longer observed is called "right censoring". Standard regression techniques are not capable of handling censored data, because those techniques cannot take into account the information provided from both censored and uncensored observations during parameter estimation. A key feature of time to event analysis is that ability to handle right censoring, and it is the preferred analysis method for data that have three characteristics: 1) the dependent variable is the time waiting for an event to occur, 2) observations are censored, and 3) existence of variables with effect on the waiting time, that researchers want to assess.

3.9.4.2 Dataset preparation for time to event analysis

The datasets for time to event analysis preparation were dependent on the outcome that was investigated. In the case of all-cause death, all relevant patient information was included in one row, with other columns representing patient characteristics such as gender, age, medication regimen, index date and end of follow-up date. The length of analysis period for every patient was from the date of first antiplatelet prescription (index date) until the transfer out date, last collection date in CPRD, death (deathdate), or 30 September 2015, whichever happened first. In the case where outcomes occurring multiple times could happen such as bleeding or stroke, multiple rows per patient were prepared in the datasets after following Therneau's suggestions (240) about event classification and using the counting process of Andersen and Gill (241). In that case, when a patient had one event, patient information was spread into two rows, one covering the period from index date to the date of event and the other row the period after the event till the end of follow-up. Datasets also contained the variables that were used in the balancing step. Those variables, which were described in section 3.9.3.10, were included in the dataset, in case where "doubly robust" model adjustment was needed.

The parameters of a time to event analysis model in Stata can be estimated after declaring the data as time to event with the use of stset command, and then fitting a time-to-event model using the streg command.

3.9.4.3 Strategy for the selection of the time to event analysis

In time to event analysis, there are several methods for estimating the treatment effect on the hazard rate of a particular event. The standard approaches to the regression models of survival data are proportional hazards models and accelerated failure time models. A proportional hazards model (PH) assumes that covariates are multiplicative with respect to the hazard (242). An accelerated failure time model (AFT) assumes covariates are multiplicative with respect to baseline hazard. Furthermore, the models can be parametric or semiparametric depending on the assumptions made for the baseline hazard function. Cox proportional hazards model(243) is a very common option for time to event analysis. In a Cox model, there is no need to make any assumptions about the underlying baseline hazard function, because the hazard function is assumed to have no particular parameterisation. If the proportional hazards assumption did not hold in Cox models, this would be true also for parametric proportional hazards models. This meant that fully parametric models expressed in AFT metric would be used.

The strategy for selecting the appropriate time to event model for every outcome (MI, stroke, MACE, bleeding, all-cause death) initially involved the estimation of Cox models and testing whether the proportional hazards assumption held. The assumption of proportional hazards was assessed with a global test based on Schoenfeld residuals (244). If the proportional hazards assumption did not hold, then alternative models were tested, in PH and AFT metric. For the fully parametric models several distributions of baseline hazard have to be tested (Generalised gamma, Weibull, Gompertz, Lognormal, Exponential, Loglogistic). Usually a generalised gamma model is fitted assuming that baseline hazard is expressed by the function:

$$t_j \sim GenGamma(\beta_0, \kappa, \sigma)$$

$H_0: \kappa = 0$, meaning that if H_0 was true, then the model was Lognormal

$H_0: \kappa = 1$, meaning that if H_0 was true, then the model was Weibull

$H_0: \kappa = 1, \sigma = 1$, meaning that if H_0 was true, then the model was exponential (constant baseline hazard function)

If the previously mentioned hypothesis tests were not allowing the exclusion of any functional form, then the models based on all functional forms were fitted, and the one with the lowest value of Akaike Information Criterion was selected (245).

3.9.4.4 Selection of the time to event model

The strategy for selecting the appropriate time to event model was dependent on the results of the balancing step. If there was no clear decision about which of the three methods achieved the best covariate balancing, then the step described in section 3.9.4.3, would be repeated for all three balancing methods, resulting in three candidate models. The selection of the final model was based on the Akaike Information Criterion (245). All time to event models contained the antiplatelet regimen as the main explanatory variable. In the case where the balancing methods were not providing sufficient balance in baseline characteristics among treatment groups, then the models included those baseline characteristics as well, so that the existing imbalances could be accounted for (doubly robust estimation).

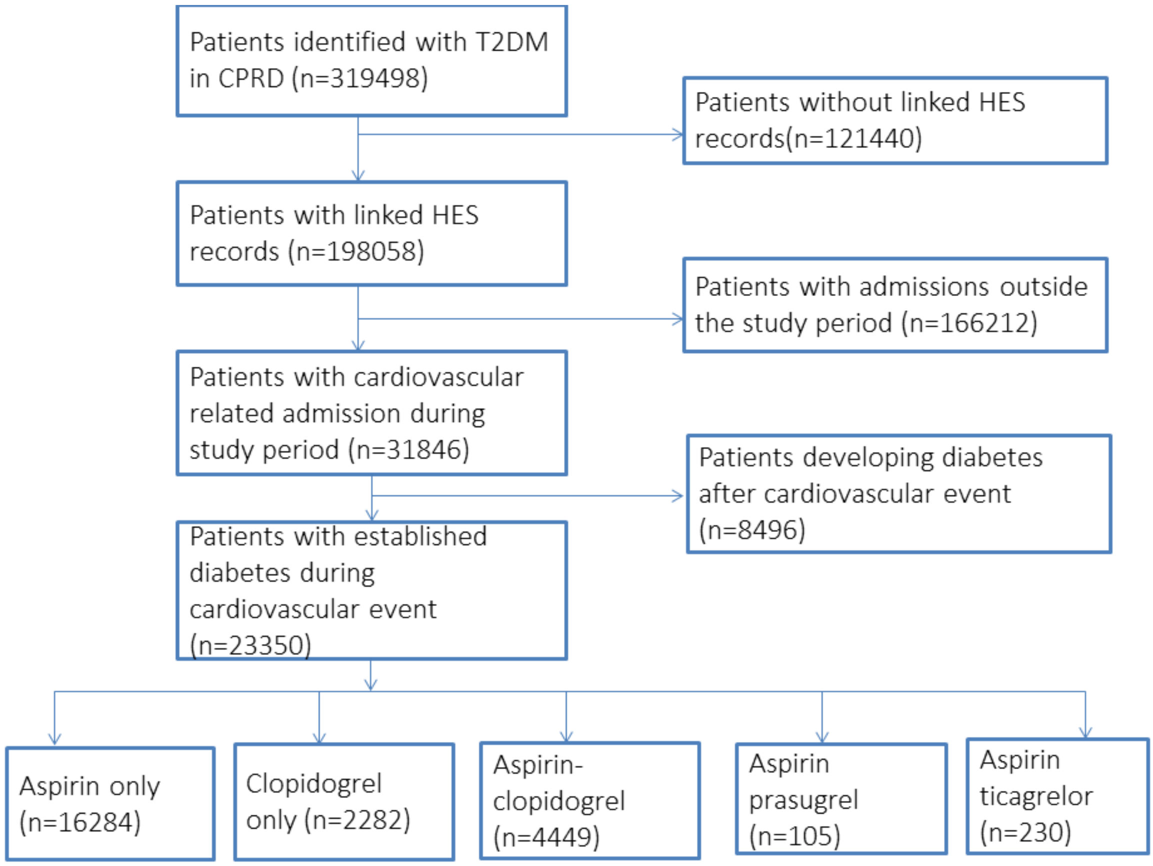
The results of time to event analysis are structured as follows. For every outcome analysed (Bleeding, stroke, MI, MACE, all-cause death), the results of the proportional hazards tests are provided. Based on those results, and by taking into account if the proportional hazards assumption holds, the results of investigating the presence of nested models (use of generalised gamma time distribution model, and investigating if the time distribution of the model is Weibull, lognormal, or exponential with the help of Wald tests) are provided. Then, the results of diagnostic measures of all the fully parametric models that were balanced with the MNPS and the CBPS method (see 3.9.4.3 for more details). Finally, the selected model with the parameters that present the impact of antiplatelet therapies on the discussed outcome is shown and interpreted. The full list of the model parameters is presented in the Appendix 4(8.4). For the time to event models, the effect that various coefficients have on the outcomes, is expressed either in accelerated failure time (AFT) or proportional hazards (PH) metrics, depending on the time distribution of every time to event model (AFT for loglogistic and lognormal models, PH for Gompertz models). As a result of the difference in the metrics, the interpretation of coefficients will differ depending on the metric used. No interpretation is given for the coefficients additional to the exposure variable (age, gender, number of follow-up periods, region, polypharmacy, Charlson index, year of cohort entry). These variables were introduced in the analysis models as a way to further reduce the imbalance among treatment groups that was not sufficiently controlled from the balancing methods (doubly robust estimation). When any coefficient of those balancing variables was statistically significant, it meant that further correction for that characteristic was achieved.

3.10 Results of balancing and time-to-event analysis.

3.11 Study cohort selection results

In total, 319,498 patients with T2DM were initially identified in CPRD, using the medical and product codes. After taking into account the fact that patients needed to be registered in practices that participated in the CPRD/HES linkage scheme, the number of patients was reduced to 62% of the initial sample (198,058). During the second stage of cohort definition, where patients that had records in HES data and had a cardiovascular-related admission between January 2007 and September 2015, the number of patients included was 16% of the linked sample (31,846). Finally, patients who had records signalling diabetes only after the initial prescription of antiplatelet agents were also excluded, because this meant that they had developed T2DM after a cardiovascular problem. As a result, the number of included patients was 23,350, and this cohort was used for the first stages of the descriptive analysis (patient demographics, patient adherence). The sample for the later stages of analysis (balancing, time to event analysis, cost association analysis), was restricted to patients that were following dual antiplatelet regimens, which in total was 4,784.Figure 4 presents the CONSORT flow chart of the study.

Figure 4 CONSORT flow chart of the study



From Table 3, we can see that the largest group of patients are those on the aspirin only regimen, with the aspirin-clopidogrel group the second largest. The number of patients on newer antiplatelet regimens is much smaller in comparison. The cohort population is predominantly male, and this is observed in every regimen. In terms of follow-up time, we see that on average patients on aspirin and clopidogrel related regimens contribute information for longer time periods (more than two years) than patients on newer antiplatelet medications. Patients who are on aspirin and clopidogrel regimens tend to be older when they start antiplatelet therapy, they are diagnosed at an older age with diabetes, and the period between T2DM diagnosis and first antiplatelet prescription is longer than patients taking newer antiplatelet agents. In terms of clinical characteristics, patients among all groups on average have baseline cholesterol readings that are above the cut-off point of 4, the cholesterol value that indicates controlled cholesterol levels. Overall, 44% of the total cohort had cholesterol readings higher than 4 (uncontrolled cholesterol levels) at baseline. Regarding BMI and using WHO obesity definitions(246), all patients can be classified as overweight or obese class I, and findings are similar to those of the study of Khunti et al (234)(247). The blood pressure among different treatment groups is at similar levels. Many patients have been smokers in the past. Smoking status information is missing for 18% of total population, whereas for alcohol consumption status, the information is missing for approximately 8% of the population. In terms of comorbidity as expressed in Charlson index scores, we see that patients on dual antiplatelet therapies and clopidogrel-only usually have one or more comorbidities other than T2DM at baseline. On the other hand, in the aspirin-only group, patients who have no comorbidities other than T2DM at baseline constitute the majority in that group. In the table, there are patients reported to have no comorbidities. In the results, the patients are reported to have Charlson indices equal to zero. The reason for that is because the patients are reported, is because no minimum value of one for having T2DM was introduced (see 3.9.3.10 for Charlson index estimation details).

3.11.1 Adherence to antiplatelet medications

From Table 4, it can be seen that patients across all regimens have high average PDC values across all time periods. Except for the 90-day time point for the aspirin-clopidogrel group, the average PDC for all regimens is above the cut-off point of 0.80 that was set. For the groups of aspirin-ticagrelor and aspirin-prasugrel, no information about PDC is available after the 450-day time point. This is a signal that there was no continuation of prescription for those two regimens after 450 days, something that is in accordance with the fact that these DAPT regimens are recommended to be prescribed for a year, and then a change in regimen should occur. In Figure 5, it can be seen how the number of people that are adherent drops for all DAPT regimens, during 30 and 90 days then becomes stable between 90 days and 360 days, and then increases between 360 and 450 days. From 450 days onwards it can be seen that the percentage of patients that were adherent increased, and this is suggested to happen because fewer people contributed with prescription information during the later stages of PDC time points. Figure 6 shows the percentage of people that keep on getting prescriptions on their regimens. Overall, it can be seen that over time the percentage of patients that continue with their prescriptions decreases. The decrease is much higher in the DAPT regimens than in the monotherapy regimens. After 450 days patients on aspirin-ticagrelor and aspirin-prasugrel are no longer continuing with their regimens. For the aspirin-clopidogrel group this decrease continues after 450 and during 450 and 720 days a very small number of patients continues with that therapy.

Table 3 Baseline characteristics of study cohort.

	Aspirin	**Clopidogrel**	**Asp-Clop**	**Asp-Pras**	**Asp-Tica**	**Total**
Number of patients	16,284	2,282	4,449	105	230	23,350
Age at index date (years) (SD)	71.98 (*10.99*)	73.66 (*10.51*)	69.61 (*11.98*)	58.07 (*9.92*)	63.85 (*11.84*)	71.55 (*11.26*)
Age at index date not identified	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
Age at diabetes onset (years) (SD)	61.64 (*12.57*)	62.91 (*12.29*)	59.79 (*12.95*)	51.81 (*11.45*)	56.18 (*12.13*)	61.31 (*12.66*)
Age at diabetes onset not identified	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
Follow-up time (years) (SD)	2.96 (*2.19*)	2.47 (*2.09*)	3.14 (*2.34*)	1.73 (*1.45*)	1.05 (*0.85*)	2.92 (*2.21*)
Follow-up time not identified	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)

	Aspirin	Clopidogrel	Asp-Clop	Asp-Pras	Asp-Tica	Total
Years since diabetes onset (SD)	10.34 (*8.03*)	10.75 (*7.87*)	9.82 (*8.35*)	6.26 (*6.12*)	7.67 (*6.46*)	10.23 (*8.06*)
Years since diabetes onset not identified	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
No. of male patients	10,134	1,277	2,938	84	165	14,598
IMD decile (No.)						
1	1,249	164	375	7	16	1,811
2	1,425	204	386	5	21	2,041
3	1,596	264	452	9	24	2,345
4	1,652	229	458	9	23	2,371
5	1,753	260	500	16	17	2,546
6	1,629	195	471	8	24	2,327
7	1,686	217	478	15	23	2,419
8	1,784	255	444	18	26	2,527
9	1,685	240	497	9	21	2,452
10	1,815	252	386	9	35	2,497
Baseline HbA1C (mmol/mol) (SD)	58.97 (16.76)	58.85 (17.61)	61.67 (18.05)	66.26 (20.96)	65.40 (18.81)	59.56 (17.18)
Baseline HbA1C not identified	1,237(7.60%)	172(7.54%)	376(8.45%)	22(20.95%)	15(6.52%)	1822(7.80 %)
Lipid profile						
Total Cholesterol (mmol/L)	4.09	4.19	4.38	4.64	4.71	4.16
No. with Cholesterol > (4%)	6,798 (42.85%)	1,005 (44.04%)	2,318 (52.00%)	65 (61.90%)	144 (62.60%)	10,330 (44.23%)
No. with Cholesterol < (4%)	8,312 (51.04%)	1,109 (48.59%)	1,837 (41.29%)	25 (23.80%)	72 (31.30%)	11,355 (48.62%)
Not identified	1,174(7.21%)	168(7.36%)	294(6.61%)	15(14.29%)	14(6.09%)	1,665(7.13 %)
Blood pressure (mmHg)						
Average SBP (SD)	133.82 (17.73)	133.72 (18.16)	134.38 (18.99)	128.81 (16.33)	131.54 (20.14)	133.87 (18.04)
Average DBP (SD)	73.27 (10.57)	72.92 (11.37)	74.02 (11.07)	76.72 (9.91)	74.63 (10.50)	73.41 (10.75)
Not identified	445(2.73%)	57(2.50%)	101(2.27%)	5(4.76%)	*	838(3.59%)
Average BMI(SD)	30.62 (6.38)	30.19 (6.33)	30.20 (6.13)	31.40 (5.90)	30.67 (6.13)	30.50 (6.33)
BMI not identified	734(4.51%)	138	163	5(4.76%)	8(3.48%)	1048(4.49 %)

	Aspirin	Clopidogrel	Asp-Clop	Asp-Pras	Asp-Tica	Total
Smoking status (number of patients)						
Ex-Smoker	10,218 (62.76%)	1,429 (62.62%)	2,704 (60.78%)	*	115 (50.00%)	14,466 (61.95%)
Smoker	2,057 (12.63%)	282 (12.36%)	664 (14.92%)	*	61 (26.52%)	2,864 (12.27%)
Non-Smoker	1,054 (6.47%)	143 (6.27%)	317 (7.13%)	*	12 (5.22%)	1,526 (6.54%)
Not identified	2,955 (18.15%)	428 (18.76%)	764 (17.17%)	*	42 (18.26%)	4,189 (17.94%)
Alcohol consumption status (number of patients)						
Ex-Drinker	1,003 (6.16%)	151 (6.62%)	259 (5.82%)	*	14 (6.09%)	1,431 (6.13%)
Drinker	9,561 (58.72%)	1,246 (54.60%)	2,705 (60.80%)	*	144 (62.61%)	13,725 (58.78%)
Non-Drinker	4,468 (27.44%)	683 (29.93%)	1,168 (26.25%)	*	62 (26.96%)	6,400 (27.41%)
Not identified	1,252 (7.69%)	202 (8.85%)	317 (7.13%)	*	10 (4.35%)	1,794 (7.68%)
Charlson index (number of patients)						
0	9,344 (57.39%)	932 (40.84%)	1,452 (32.64%)	25 (23.81%)	24 (10.43%)	11,777 (50.44%)
1	4,190 (25.73%)	802 (35.14%)	2,206 (49.58%)	71 (67.62%)	172 (74.78%)	7,441 (31.87%)
≥2	2,750 (16.89%)	548 (24.01%)	791 (17.78%)	9 (8.57%)	34 (14.78%)	4,132 (17.70%)
Not identified	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
* Less than five patients were included; therefore, results were not reported						
Asp-Clop: Aspirin-Clopidogrel dual therapy, **Asp-Pras:** Aspirin-Prasugrel dual therapy, **Asp-Tica:** Aspirin-Ticagrelor dual therapy **BMI:** Body Mass Index, **DBP:** Diastolic Blood Pressure, **HbA1C:** Haemoglobin A1C, **IMD:** Index of Multiple Deprivation, **No.** Number of Patients, **SD:** Standard Deviation, **SBP:** Systolic Blood Pressure						

Figure 5 Adherence to antiplatelet regimens (PDC>0.8) in adults with T2DM, over time.

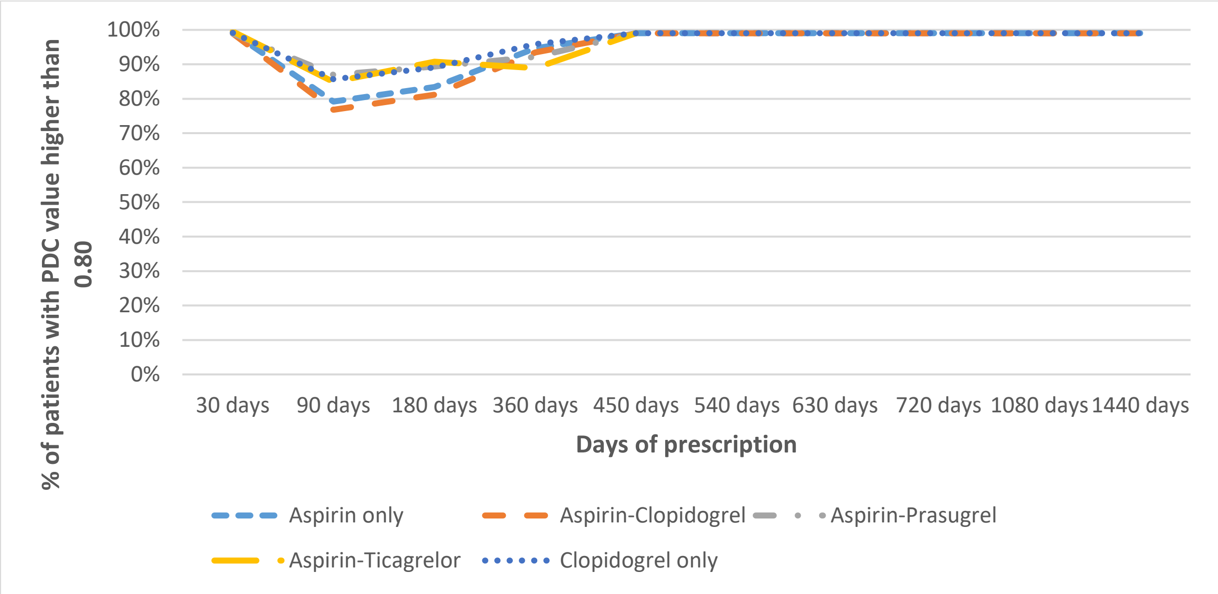


Figure 6 Percentage of patients who continue therapy over time.

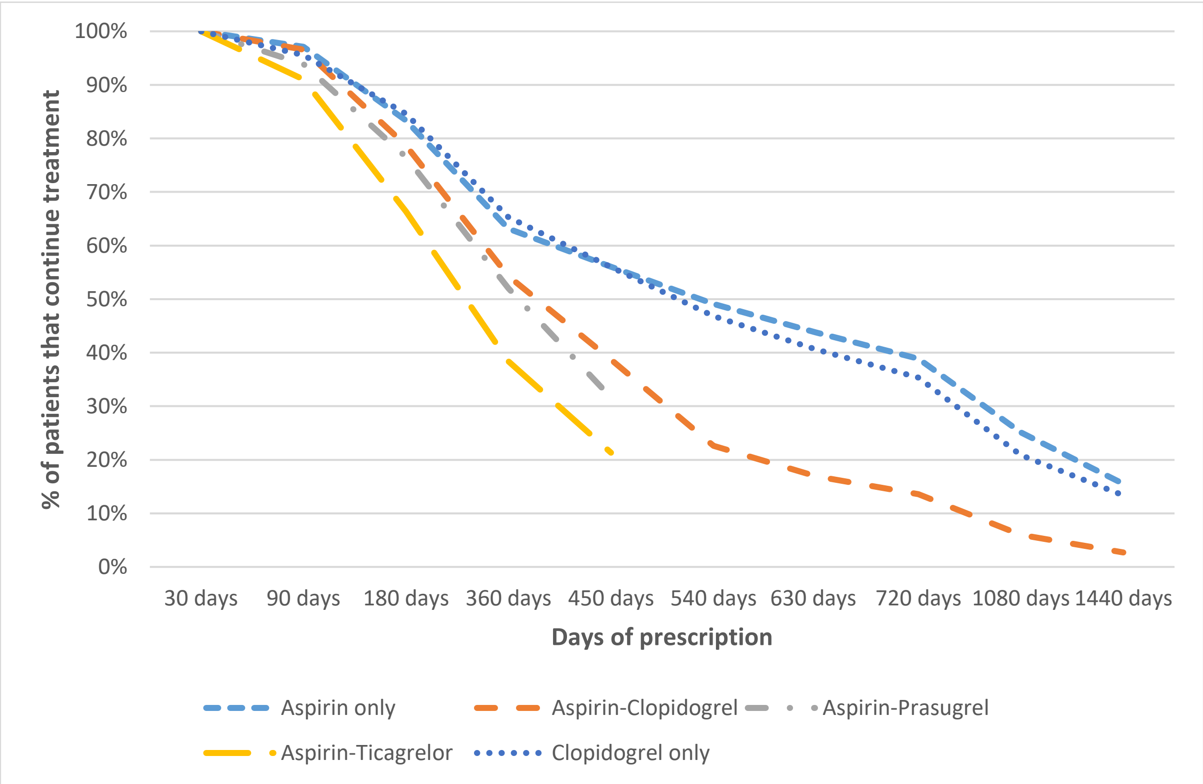


Table 4 Medication regimen adherence based on proportion of days covered by the Medication (PDC)

Days since antiplatelet initiation		Aspirin only	Asp-Clop	Asp-Pras	Asp-Tica	Clopidogrel only
30 days	No. of Patients	15239	4293	98	211	2095
	Mean PDC (SD)	0.98(0.05)	0.98(0.06)	0.97(0.08)	0.98(0.05)	0.98(0.04)
90 days	No. of Patients	14798	4147	92	192	2002
	Mean PDC (SD)	0.89(0.16)	0.88(0.17)	0.93(0.10)	0.91(0.13)	0.92(0.13)
180 days	No. of Patients	12701	3378	75	140	1773
	Mean PDC (SD)	0.91(0.11)	0.90(0.12)	0.93(0.10)	0.92(0.10)	0.93(0.10)
360 days	No. of Patients	9627	2332	51	81	1368
	Mean PDC (SD)	0.94(0.06)	0.93(0.06)	0.93(0.10)	0.92(0.07)	0.95(0.05)
450 days	No. of Patients	8539	1662	31	45	1172
	Mean PDC (SD)	0.95(0.05)	0.93(0.06)	0.91(0.06)	0.90(0.06)	0.95(0.05)
540 days	No. of Patients	7481	971	-	-	981
	Mean PDC (SD)	0.96(0.04)	0.95(0.05)			0.96(0.04)
630 days	No. of Patients	6672	726	-	-	851
	Mean PDC (SD)	0.96(0.04)	0.95(0.04)			0.96(0.04)
720 days	No. of Patients	5928	582	-	-	740
	Mean PDC (SD)	0.96(0.03)	0.96(0.04)			0.96(0.03)
1080 days	No. of Patients	3824	258	-	-	437
	Mean PDC (SD)	0.97(0.02)	0.97(0.02)			0.97(0.02)
1440 days	No. of Patients	2364	116	-	-	280
	Mean PDC (SD)	0.98(0.02)	0.97(0.02)			0.97(0.02)
***** Less than five patients were included; therefore, results were not reported						
Asp-Clop: Aspirin-Clopidogrel dual therapy, **Asp-Pras:** Aspirin-Prasugrel dual therapy, **Asp-Tica:** Aspirin-Ticagrelor dual therapy, **No.** Number, **PDC**: Proportion Of Days Covered, **SD**: Standard Deviation						

3.11.2 Outcome results

Table 5 presents the unadjusted (crude) incidence rates results for all the outcomes. The results are reported only for the DAPT regimens and aspirin because in the economic evaluation analysis, the results of the bleeding events, the incidence rates are the same for patients on aspirin-clopidogrel and aspirin-prasugrel, and lower for patients on aspirin-ticagrelor. Patients on aspirin-prasugrel have the lowest incidence rates for non-fatal MI, whereas patients on aspirin-clopidogrel and aspirin-ticagrelor have rates that are quite similar. The incidence of stroke is lower in patients on aspirin-ticagrelor and aspirin-prasugrel, compared to patients on aspirin-clopidogrel. For MACE events the findings are similar as in MI events with patients on aspirin-prasugrel having the lowest rates and aspirin-clopidogrel and aspirin-ticaglelor having similar rates. Furthermore, the incidence rates in MI and MACE have quite close values, which suggests that MI outcomes are the ones that the most influence in the MACE composition. Patients prescribed with aspirin-clopidogrel had much higher incidence of death compared to those on aspirin-prasugrel and aspirin-ticagrelor, who had similar incidence rates for all cause death. The incidence rates for all outcomes are lower in patients that are following newer DAPT regimens.

Table 5 Incidence rates of disease outcomes across treatment groups.

Incidence rates (events per 100 patient years)				
Outcome	**Treatment group**			
	Aspirin only (N=16284)	**Aspirin-clopidogrel (N=4449)**	**Aspirin-prasugrel (N= 230)**	**Aspirin-ticagrelor (N=105)**
Bleeding	0.96(0.88-1.05)	1.10(0.94-1.29)	1.10(0.27-4.40)	0.83(0.21-3.31)
Non-fatal MI	8.01 (7.76-8.27)	21.95(21.19-22.74)	11.01(7.10-17.07)	24.91(19.34-32.09)
Non-fatal Stroke	1.61 (1.50-1.73)	1.95 (1.73-2.19)	1.10 (0.27-4.40)	0.83 (0.21-3.31)
MACE	10.76 (10.47-11.05)	25.67(24.85-26.52)	13.22(8.86-19.72)	27.29(21.44-34.74)
All-cause death	7.72(7.48-7.98)	7.44(7.00-7.90)	2.20(0.82-5.86)	2.07(0.86-4.98)
95% CI in parentheses				

3.12 Balancing methods results

From this point onwards, and with the exception of the section where the descriptive statistics of health care costs is described, the treatment groups that are investigated are only those of patients on dual antiplatelet regimens.

Implemented balanding methods

Implemented balancing methods took into account that treatment allocation was not binary and that the focus was on DAPT only. Therefore, the balancing methods that were assessed were marginal mean weighting through stratification (MMW-s), multinomial propensity scores (MNPS) with the use of generalised boosted models (GBM) and covariate balancing propensity scores (CBPS).

3.12.1 MMW-s model results

In order to estimate propensity scores for the MMW-s method of balancing, multinomial logit and multinomial probit models were selected. During the stratification stage, the MMW-s algorithm was stopped, because the number of patients in several propensity score strata was not sufficient for the algorithm to make comparisons for every stratum-specific treatment group, and it was not possible to provide balancing weights for every stratum-specific treatment group. A second solution that could be followed by collapsing the treatment groups would defeat the purpose of generating separate balancing weights for every treatment group, therefore the MMW-s method was abandoned. For this reason, the results of the models for propensity scores are not presented.

3.12.2 CBPS model results

Table 6 summarises the results of the multinomial multivariate model that was used for deriving propensity scores during the implementation of the CBPS method.

From Table 6, it can be seen that the probability of being prescribed aspirin-ticagrelor versus being prescribed aspirin-clopidogrel was affected by the year adults entered the cohort. Adults entering the cohort from 2009 onwards, were more likely to be prescribed aspirin-prasugrel. The year of patient cohort entry affected the choice between aspirin-ticagrelor and aspirin-prasugrel as well. Patients entering the cohort after 2011 were more likely to be prescribed aspirin-prasugrel or aspirin-ticagrelor instead of aspirin-clopidogrel. Another factor that affected the probability of being prescribed aspirin-ticagrelor versus being prescribed aspirin-ticagrelor, was the region where GP practices were located. Patients who were registered in GP practices located in the Midlands, the East of England, and the South were less likely to be prescribed aspirin-clopidogrel compared with patients registered in GP practices located in the North East (reference group). However, the probability of being prescribed aspirin-prasugrel was not affected by the region of the GP practice where the patient was registered. The probability of being prescribed aspirin-ticagrelor versus aspirin-clopidogrel was not affected by the age and gender of patients. The probability of prescribing aspirin-prasugrel versus aspirin-clopidogrel, was not affected by age or the number of years that the observed patient was followed up. The J-statistic that is shown in Table 6, is used to control if an over-identified model that combines the propensity score and covariate balancing conditions for the estimation of CBPS weights, is selected. A value of the J-statistic close to zero means that, even if the model is misspecified, the scores produced can be still used because they achieve covariate balance.

Table 6 Results of the multivariate multinomial CBPS model with categorical treatment assignment

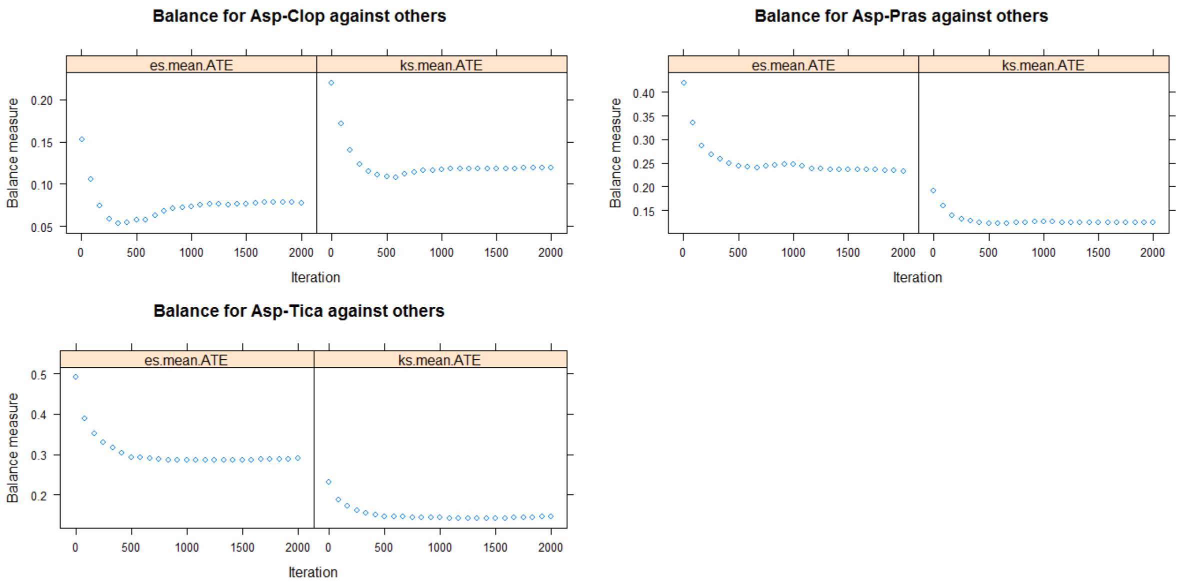
(N=4784)	**Probability of being prescribed prasugrel Pr(Y=1)**		**Probability of being prescribed ticagrelor Pr(Y=2)**	
	Odds ratio	**P>|z|**	**Odds ratio**	**P>|z|**
Follow-up periods	0.828	0.485	0.595	<0.001
Age at index date	0.922	0.669	0.958	0.668
Female	0.596	<0.001	0.905	0.269
Grouped Charlson Index				
0	Ref	-	Ref	-
1	1.835	0.004	4.068	<0.001
2	1.069	0.765	2.734	<0.001
Polypharmacy	0.604	0.004	0.555	<0.001
Region				
North	Ref	-	Ref	-
Midlands & East	0.835	0.584	0.358	<0.001
South	0.920	0.809	0.286	<0.001

(N=4784)	Probability of being prescribed prasugrel Pr(Y=1)		Probability of being prescribed ticagrelor Pr(Y=2)	
Year of cohort entry				
Entry after 2009	94.490	<0.001	0.792	0.07
Entry after 2011	3.531	<0.001	1262.620	<0.001
Constant	0.032	<0.001	0.004	<0.001
J-statistic : 0.00003335409				
Asp-Clop: Aspirin-Clopidogrel dual therapy, **Asp-Pras:** Aspirin-Prasugrel dual therapy, **Asp-Tica:** Aspirin-Ticagrelor dual therapy, **Pr :** probability				

3.12.3 MNPS model results

The algorithm used to derive the propensity score models converged after 2000 iterations, meaning that beyond that number of iterations no better balancing results from the MNPS method could be produced. Figure 7 shows the number of iterations that were needed for the algorithm to converge, and the stopping rule, which is the effect size between the pairs of treatments, summarised by the mean across the variables used for the balancing (es.mean ATE) and not the Kolmogorov Smirnoff statistic (ks.mean.ATE). The graph serves as an indicator of the iterations needed for the algorithm to generate. As it can be seen from the optimisation plots in Figure 7, as the number of iterations increases, the steepness of the curve is decreasing and then becomes flat, meaning that the effect size cannot decrease more after 2000 iterations. Section 3.12.4 compares the performance of the MNPS and the CBPS methods in terms of balancing for this study.

Figure 7 Optimization plot for estimating the propensity scores for the paired comparison of the available treatment combination of the other two to generate propensity score derived weights for analysis dataset.



3.12.4 Balancing methods comparison

Figures show the difference in absolute standardised means of the covariates used in the balancing procedure among the patients prescribed aspirin-clopidogrel and aspirin-ticagrelor. When the difference is zero or close to zero for a specific covariate, it means that there is balance between the groups for the specific covariate, and in the graph is presented with points closer to the vertical line. It was previously mentioned that two criteria were going to be used for comparing the achieved balance for both MNPS and CBPS; a)the method that yields the smallest standardized difference of means across the largest number of covariates, and b) the method that results in the fewest number of "large" standardized differences of means (greater than 0.25). By using the first method of achieved balance assessment, the CBPS method is the one that provides better balance for patients on clopidogrel and ticagrelor (Figure 8). CBPS achieved lower standardised difference in nine out of twelve covariates. By using the second method is to compare MNPS and CBPS, no clear conclusion about which is the better balancing method can be provided, because both methods provide the same number of "large" standardised differences of means. Therefore, the better method for balancing patients on clopidogrel and ticagrelor was decided to be CBPS.

Figure 8 Covariate balance among patients on clopidogrel and ticagrelor

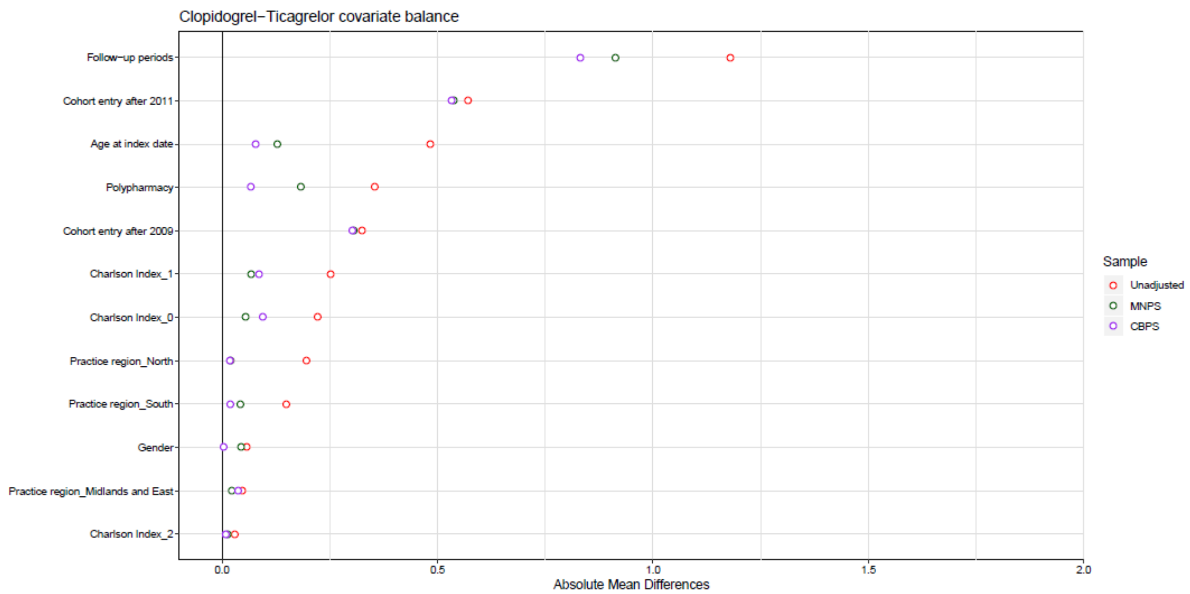


Table 7 Covariate balance of variables among patients on clopidogrel and ticagrelor

Absolute standardised mean difference Clopidogrel-Ticagrelor			
	Unadjusted	**MNPS**	**CBPS**
Follow-up periods	1.180	0.913	0.831
Age at index date	0.483	0.128	0.078
Female	0.057	0.044	0.004
Charlson Comorbidity Index			
0	0.222	0.054	0.095
1	0.252	0.067	0.086
2	0.030	0.013	0.009
Polypharmacy	0.354	0.183	0.067
Region			
North	0.196	0.020	0.018
Midlands & East	0.047	0.023	0.038
South	0.149	0.043	0.019
Year of cohort entry			
Entry after 2009	0.325	0.306	0.302
Entry after 2011	0.571	0.538	0.533

Figure 9 presents the difference in absolute standardised means among the patients prescribed clopidogrel and prasugrel. In this Love plot, the CBPS method is the one that achieved better balance in most covariates. CBPS also results in fewest number of "large" standardized differences of means for multiple covariates. The best balance among patients on clopidogrel and prasugrel was achieved with CBPS, no matter which assessment criterion was used.

Figure 9 Covariate balance among patients on clopidogrel and prasugrel

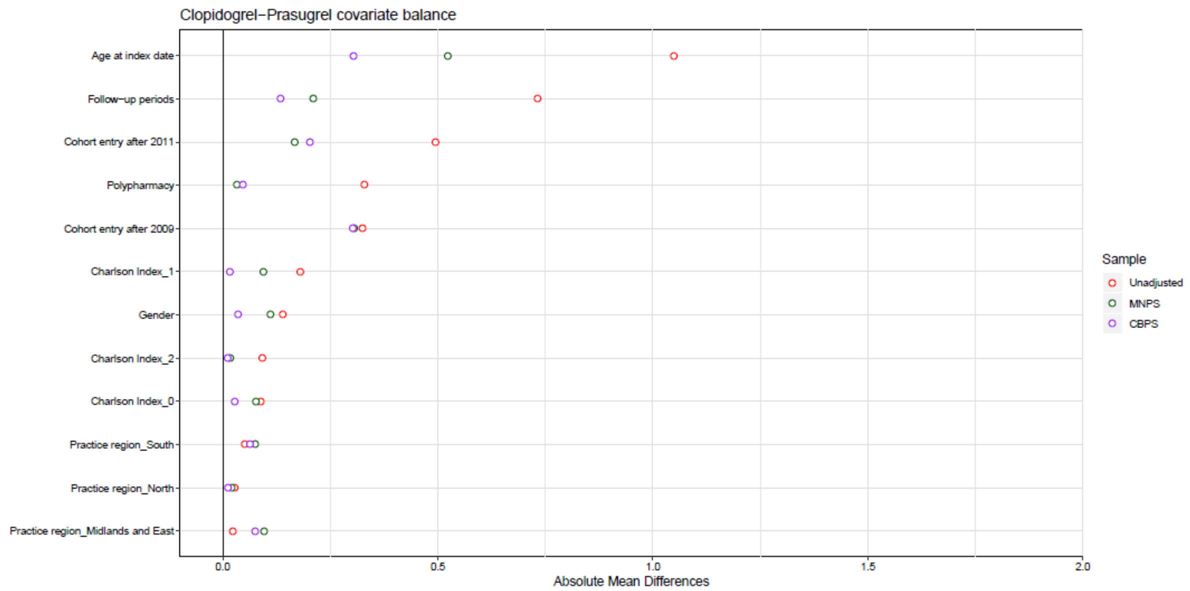


Table 8 Covariate balance of variables among patients on clopidogrel and prasugrel

Absolute standardised mean difference Clopidogrel-Prasugrel			
	Unadjusted	**MNPS**	**CBPS**
Follow-up periods	0.732	0.210	0.134
Age at index date	1.049	0.524	0.304
Female	0.140	0.111	0.035
Charlson Comorbidity Index			
0	0.088	0.077	0.028
1	0.180	0.095	0.017
2	0.092	0.018	0.011
Polypharmacy	0.329	0.033	0.047
Region			
North	0.028	0.021	0.012
Midlands & East	0.024	0.096	0.076
South	0.051	0.075	0.064
Year of cohort entry			
Entry after 2009	0.325	0.306	0.302
Entry after 2011	0.495	0.167	0.203

Figure 10 presents the Love plot of absolute standardised means among the patients prescribed prasugrel and ticagrelor. CBPS provided smaller standardised means in four out of seven covariates (year of cohort entry, follow-up periods, age at index date and polypharmacy). Both methods provided standardised means over 0.25 for three covariates (year of cohort entry, follow-up periods and age at index date). Based on those findings, the CBPS method achieved better covariate balance among patients on prasugrel and ticagrelor.

Figure 10 Covariate balance among patients on prasugrel and ticagrelor

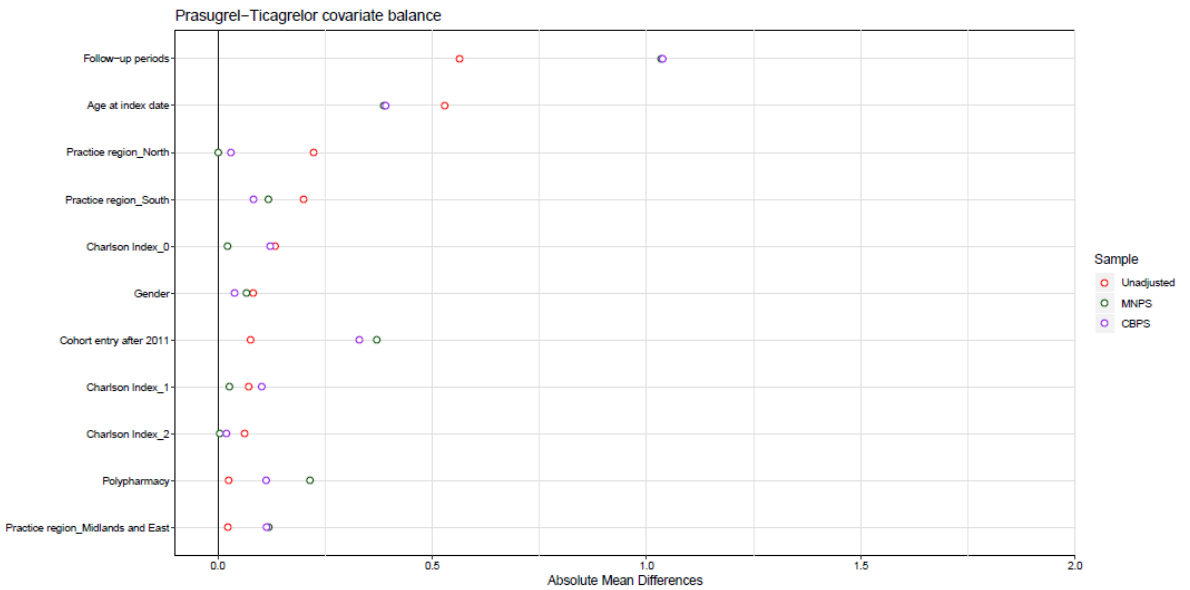


Table 9 Covariate balance of variables among patients on prasugrel and ticagrelor

Absolute standardised mean difference Prasugrel-Ticagrelor			
	Unadjusted	**MNPS**	**CBPS**
Follow-up periods	0.564	1.034	1.037
Age at index date	0.529	0.388	0.392
Female	0.083	0.067	0.039
Charlson Comorbidity Index			
0	0.134	0.023	0.123
1	0.072	0.027	0.103
2	0.062	0.004	0.020
Polypharmacy	0.025	0.215	0.113
Region			
North	0.223	0.001	0.030
Midlands & East	0.023	0.119	0.113
South	0.200	0.118	0.083
Year of cohort entry			
Entry after 2009			
Entry after 2011	0.076	0.371	0.331

3.12.5 Balancing method selection

It is clear from the Love plots and the covariate balancing tables, that there is not one method achieving the best balance across all groups. For every pair of treatments, a different balancing method achieves better results. This means that it is not possible to select a method that can be used across all groups. Balancing diagnostics themselves allow for the comparison of groups in pairs only, and not across all treatment groups. Furthermore, both methods reduce imbalances on baseline characteristics among treatment groups, but they do not eliminate those differences completely. Based on these findings two decisions were made for the later stages of analysis. First, "doubly robust" estimation methods had to be used in the further stages of the analysis. "Doubly robust" estimation meant that all the models for time to event and cost associations analyses were estimated using models that took into account sampling weights derived from the balancing methods, and those models included the variables which were used to derive propensity scores a priori, as a measure of further reducing the imbalance on baseline characteristics among the treatment groups. Second, since it was not clear which balancing method was the best, all time to event and costing analyses were carried out twice, using the MNPS and the CBPS sampling weights. In order to indicate which models (models with MNPS derived weights versus models with CBPS derived weights) provided the best estimates, additional criteria were used (Wald tests, information criteria for time to event models, and Modified park test, Pregibon link test, information criteria for cost analysis models)

3.13 Results of time-to-event analysis

The results of time to event analysis are structured as follows. For every outcome analysed (Bleeding, stroke, MI, MACE, all-cause death), the results of the proportional hazards tests are provided. Based on those results, and by taking into account if the proportional hazards assumption holds, the results of investigating the presence of nested models are provided. Then, the results of diagnostic measures of all the fully parametric models that were balanced with the MNPS and the CBPS method (see 3.9.4.3 for more details). Finally, the selected model with the parameters that present the impact of antiplatelet therapies on the discussed outcome is shown and interpreted

3.13.1 Time to bleeding event models

The Cox proportional hazards test that was run in models with the CBPS and MNPS sampling weights has shown that the PH assumption does not hold, not only for the Cox model but also for the parametric proportional hazards models. Table 10 presents the results of the proportional hazards test for models with CBPS and MNPS sampling. As a result of that, parametric models that are expressed in the PH metric (exponential in PH, Weibull in PH, Gompertz) were not run. A generalised gamma model was fitted using both the CBPS and the MNPS sampling weights to test the hypotheses of whether the bleeding time to event model had a lognormal, or Weibull or exponential distribution. The generalised gamma distribution with shape parameters **κ, σ** includes as special cases the Weibull distribution when **$\kappa=1$**, the lognormal distribution when **$\kappa=0$**, and the exponential distribution when **$\kappa=\sigma=1$** (248).

Table 11 summarises the Wald test results for nested models. From the results of the Wald tests, we can reject the hypothesis that the model is exponential. Further testing about the model's distributional assumptions were carried out. Models were fitted using all parametric assumptions except the exponential, and they were included using sampling weights from MNPS and CBPS methods. The best model in terms of AIC and BIC among those estimated using the CBPS sampling weights was the lognormal model. The same was true for the models that were fitted using the MNPS sampling weights. By comparing the lognormal models of both MNPS and CBPS sample weights using the AIC and BIC, the lognormal MNPS model was selected as the one fitting the data best.

Table 10 Test for the proportional hazards assumption in the time to bleeding models

	MNPS		**CBPS**	
H_0 assumption	**X^2 value**	**Prob > X^2**	**X^2 Value**	**Prob > X^2**
H_0: PH holds	77.26	<0.001	159.67	<0.001
CBPS: Covariate Balancing Propensity Scores, **MNPS**: Multinomial Propensity Scores, **Prob**: Probability				

Table 11 Wald test for nested models in the bleeding time to event models

	MNPS		**CBPS**	
H_0 assumption	**X^2 value**	**Prob > X^2**	**X^2 Value**	**Prob > X^2**
H_0: $\kappa=0$	0.89	0.3465	2.13	0.1441
H_0: $\kappa=1$	0.99	0.3189	0.26	0.6079
H_0: $\kappa=1$ $\sigma=1$	19.77	<0.001	12.49	<0.001
CBPS: Covariate Balancing Propensity Scores, **MNPS**: Multinomial Propensity Scores, **Prob**: Probability				

Table 12 summarises the diagnostics of the full parametric time to bleeding models generated using the sampling weights of CBPS balancing method. Loglogistic model was the model that fitted the data the best according to AIC and BIC.

Table 12 Diagnostics of bleeding time to event models with CBPS-derived sampling weights

	Weibull	**Loglogistic**	**Lognormal**
Log Likelihood	-1714.025	-1605.387	-1616.032
AIC	3456.050	3238.774	3260.063
BIC	3547.116	3329.840	3351.129
LR X^2	67.339	72.234	104.474
Prob > X^2	<0.001	<0.001	<0.001
AIC: Akaike Information Criterion, BIC: Bayesian Information Criterion, **LR**: Likelihood Ratio, **Prob**: Probability			

Table 13 summarises the diagnostics of the full parametric time to bleeding models generated using MNPS balancing method sampling weights. The model that fitted the data best according to AIC and BIC was the loglogistic model.

Table 13 Diagnostics of bleeding time to event models with MNPS-derived sampling weights

	Weibull	**Loglogistic**	**Lognormal**
Log Likelihood	-1471.462	-1409.483	-1411.744
AIC	2970.925	2846.967	2851.487
BIC	3061.991	2938.033	2942.553
LR X^2	43.170	45.128	68.984
Prob > X^2	<0.001	<0.001	<0.001
AIC: Akaike Information Criterion, BIC: Bayesian Information Criterion, **LR**: Likelihood Ratio, **Prob**: Probability			

After comparing the time to event models from the CBPS and MNPS method using AIC/BIC statistics, the model that is used for the interpretation of bleeding events is the loglogistic model with MNPS sampling weights, which is expressed in accelerated failure time metrics, and the coefficients are interpreted as time ratios. Table 14 presents the coefficients of the model. The time ratio coefficients represent the ratio between the time that members of one group experience an outcome and the time members of the other group experience the same outcome, which in this case is a bleeding event. From the table we see that the time ratio coefficient is very close to statistical significance The median time until patients on aspirin-ticagrelor experience a bleeding event was almost 12 times longer than that of patients on aspirin-clopidogrel, which meant that by observing the two groups for a specific time period for a bleeding event, the patients on aspirin-ticagrelor needed longer time to have a bleeding event. As a result of this the probability of patients treated with aspirin-ticagrelor experiencing a bleeding event in a defined time period is lower than that of patients in the aspirin-clopidogrel group. No significant effect for the patients on aspirin-prasugrel versus those on aspirin-clopidogrel was found, meaning that the probability of having a bleeding event is the same for patients prescribed aspirin-clopidogrel and those that are prescribed aspirin-prasugrel.

Table 14 Final model of time to bleeding events

Bleeding model loglogistic				
Time ratios*				
	Coefficient	**P>|z|**	**[95% Conf. Interval]**	
Regimen				
Asp-Clop	Reference category			
Asp-Pras	0.290	0.315	0.026	3.227
Asp-Tica	11.893	0.054	0.955	148.034
Number of events	158			
Number of person years	14410			
Asp-Clop: Aspirin-Clopidogrel dual therapy**, Asp-Pras:** Aspirin-Prasugrel dual therapy, **Asp-Tica:** Aspirin-Ticagrelor dual therapy				
*Coefficients presented in exponentiated form				

3.13.2 Models for time to non-fatal stroke events

The Cox proportional hazards test that was run in models with the CBPS and MNPS sampling weights has shown that the PH assumption holds for the model with the MNPS weights, but not for that with the CBPS weights. Table 15 presents the results of the test. As a result of that, parametric models that are expressed in the PH metric (exponential in PH, Weibull in PH, Gompertz) were not run with CBPS sampling weights, but they were run with the MNPS weights. A generalised gamma model was fitted using both the CBPS and the MNPS sampling weights to test the hypotheses of whether the stroke time to event model had a lognormal, or Weibull or exponential distribution. From the results of the Wald tests for nested models (Table 16), we cannot reject the hypothesis that the model can be Weibull when using NMPS weights. From the same table we see that if the CBPS weights are used, the hypothesis of the model being lognormal or Weibull cannot be rejected. Further testing about the model's distributional assumptions were carried out. Models were fitted using all parametric assumptions and they were included using sampling weights from MNPS and CBPS methods. The best model in terms of AIC and BIC among those estimated using the CBPS sampling weights was the Weibull model. The same was true for the models that were fitted using the MNPS sampling weights. By comparing the Gompertz models using either MNPS or CBPS sampling weights, the Gompertz MNPS model was selected as the one fitting the data best.

Table 15 Test for the proportional hazards assumption in the time to stroke models

	MNPS		**CBPS**	
H_0 assumption	**X^2 value**	**Prob > X^2**	**X^2 Value**	**Prob > X^2**
H_0: PH holds	20.50	0.058	21.32	0.045
CBPS: Covariate Balancing Propensity Scores, **MNPS**: Multinomial Propensity Scores, **Prob**: Probability				

Table 16 Test for nested models in the non-fatal stroke time to event models

	MNPS		CBPS	
H_0 assumption	**X^2 value**	**Prob > X^2**	**X^2 Value**	**Prob > X^2**
H_0: κ=0	6.40	0.011	0.84	0.359
H_0: κ=1	1.75	0.185	0.13	0.715
H_0: κ=1 σ=1	17.47	<0.001	7.62	0.022
CBPS: Covariate Balancing Propensity Scores, **MNPS**: Multinomial Propensity Scores, **Prob**: Probability				

Table 17 summarises the diagnostics of the full parametric time to non-fatal stroke models generated using the sampling weights of CBPS balancing method. The model that fits the data best according to Akaike information criterion and BIC is the Weibull model.

Table 17 Diagnostics of non-fatal stroke time to event models which have sampling weights through the CBPS method

	Weibull	Loglogistic	Lognormal
Log Likelihood	-1508.705	-1513.652	-1528.418
AIC	3045.410	3055.304	3084.835
BIC	3136.821	3146.714	3176.246
LR X^2	225.737	226.576	227.255
Prob > X^2	<0.001	<0.001	<0.001
AIC: Akaike Information Criterion, BIC: Bayesian Information Criterion, **LR**: Likelihood Ratio, **Prob**: Probability			

Table 18 summarises the diagnostics of the full parametric time to non-fatal stroke models generated using the sampling weights of MNPS balancing method. The model that fits the data best according to Akaike information criterion and BIC is the Gompertz model.

Table 18 Diagnostics of non-fatal stroke time to event models which have sampling weights through MNPS method.

	Cox PH	Weibull	Loglogistic	Gompertz
Log Likelihood	-2398.525	-1449.426	-1454.495	-1438.888
AIC	4821.050	2926.853	2936.991	2905.776
BIC	4899.401	3018.263	3028.401	2997.186
LR X^2	202.682	206.287	206.103	211.942
Prob > X^2	<0.001	<0.001	<0.001	<0.001
AIC: Akaike Information Criterion, BIC: Bayesian Information Criterion, **LR**: Likelihood Ratio, **Prob**: Probability				

After comparing the time to event models from the CBPS and MNPS method using AIC statistics, the model that is used for the interpretation of non-fatal stroke is the Gompertz model with MNPS sampling weights. The model is expressed using the proportional hazards metric. Table 19 presents the coefficients of the model. The hazard of experiencing a non-fatal stroke in patients prescribed aspirin-ticagrelor is almost one twentieth of that of patients on aspirin-clopidogrel, meaning that the risk of stroke in aspirin-ticagrelor treated patients is much lower than the risk in patients treated with aspirin-clopidogrel. For the patients on aspirin-prasugrel the hazard of stroke is one fifth compared to that of the patients on aspirin-clopidogrel. Overall, patients treated with aspirin-ticagrelor and those treated with aspirin-prasugrel have lower chances of experiencing a stroke event than patients on aspirin-clopidogrel.

Table 19 Time to non-fatal stroke (coefficients expressed in proportional hazards)

Stroke model Gompertz				
Hazard ratio*				
	Coefficient	**P>|z|**	**[95% Conf. Interval]**	
Regimen				
Asp-Clop	Reference category			
Asp-Pras	0.222	0.044	0.051	0.957
Asp-Tica	0.044	0.002	0.006	0.321
Number of events	277			
Number of person years	14411			
Asp-Clop: Aspirin-Clopidogrel dual therapy**, Asp-Pras:** Aspirin-Prasugrel dual therapy, **Asp-Tica:** Aspirin-Ticagrelor dual therapy *Coefficients presented in proportional hazards form				

3.13.3 Models for time to non-fatal MI models

The Cox proportional hazards test that was run in models with the CBPS and MNPS sampling weights has shown that the PH assumption does not hold neither for CBPS nor for MNPS weights. Table 20 presents the results of the test. As a result of that, parametric models that are expressed in the PH metric (exponential in PH, Weibull in PH, Gompertz) were not run. A generalised gamma model was fitted using both the CBPS and the MNPS sampling weights to test the hypotheses of whether the non-fatal MI time to event model was lognormal, or Weibull or exponential. From the results of the Wald tests, we cannot reject the hypothesis that the model can be Weibull or lognormal when either the MNPS or the CBPS sampling weights were used. (Table 21). Further testing about the model's distributional assumptions were carried out. Models were fitted using all parametric assumptions and they were included using sampling weights from MNPS and CBPS methods. The best model in terms of AIC among those estimated using the CBPS sampling weights was the lognormal model. This was also true when the MNPS weighting method was used. By comparing the models of both MNPS and CBPS sampling weights using the AIC and BIC values, the lognormal MNPS model was selected as the one fitting the data best.

Table 20 Test for the proportional hazards assumption in the time to MI models

	MNPS		CBPS	
H_0 assumption	**X^2 value**	**Prob > X^2**	**X^2 Value**	**Prob > X^2**
H_0: PH holds	3746.43	<0.001	4429.87	<0.001
CBPS: Covariate Balancing Propensity Scores, **MNPS**: Multinomial Propensity Scores, **Prob**: Probability				

Table 21 Test for nested models in the non-fatal MI time to event models

	MNPS		CBPS	
H_0 assumption	**X^2 value**	**Prob > X^2**	**X^2 Value**	**Prob > X^2**
H_0: κ=0	1.11	0.2910	0.14	0.7126
H_0: κ=1	1.50	0.2214	1.53	0.2162
H_0: κ=1 σ=1	226.63	<0.001	238.95	<0.001
CBPS: Covariate Balancing Propensity Scores, **MNPS**: Multinomial Propensity Scores, **Prob**: Probability				

Table 22 summarises the diagnostics of the full parametric time to non-fatal MI models generated using the sampling weights of CBPS balancing method. The model that fits the data best according to AIC and BIC is the lognormal model.

Table 22 Diagnostics of time to non-fatal MI models which have sampling weights through the CBPS method

	Weibull	Loglogistic	Lognormal
Log Likelihood	-14560.352	-12953.143	-12884.786
AIC	29148.704	25934.286	25797.571
BIC	29246.288	26031.871	25895.156
LR X^2	78.347	70.729	60.708
Prob > X^2	<0.001	<0.001	<0.001
AIC: Akaike Information Criterion, BIC: Bayesian Information Criterion, **LR**: Likelihood Ratio, **Prob**: Probability			

Table 23 summarises the diagnostics of the full parametric time to non-fatal MI models generated using the sampling weights of MNPS balancing method. The model that fits the data best according to AIC and BIC is the lognormal model.

Table 23 Diagnostics of time to non-fatal MI that have sampling weights through the MNPS method

	Weibull	Loglogistic	Lognormal
Log Likelihood	-12581.127	-11608.438	-11560.040
AIC	25190.254	23244.875	23148.080
BIC	25287.840	23342.461	23245.666
LR X^2	75.364	67.095	57.158
Prob > X^2	<0.001	<0.001	<0.001
AIC: Akaike Information Criterion, BIC: Bayesian Information Criterion, **LR**: Likelihood Ratio, **Prob**: Probability			

After comparing the time to event models from the CBPS and MNPS method using AIC statistic, the model that has been used for the interpretation of non-fatal MI is the lognormal model with MNPS sampling weights.

Table 24 presents the coefficients of the model. The time when patients on aspirin-prasugrel experience a non-fatal MI is 4 times longer than that of patients on aspirin-clopidogrel, meaning that the probability of experiencing a non-fatal MI in a set time period is lower for patients on aspirin-prasugrel than those on aspirin-clopidogrel No significant difference was found between the patients taking aspirin-ticagrelor compared with aspirin-clopidogrel, which means that the probability of experiencing a non-fatal MI event is similar for both groups.

Table 24 Final model of time to non-fatal MI event

Non fatal MI lognormal				
Time ratio*				
	Coefficient	**P>|z|**	**[95% Conf. Interval]**	
Regimen				
Asp-Clop	Reference category			
Asp-Pras	4.071	0.010	1.394	11.882
Asp-Tica	1.170	0.680	0.553	2.476
Number of events	3143			
Number of person years	14364			
Asp-Clop: Aspirin-Clopidogrel dual therapy**, Asp-Pras:** Aspirin-Prasugrel dual therapy, **Asp-Tica:** Aspirin-Ticagrelor dual therapy *Coefficients presented in exponentiated form				

3.13.4 Models for time to MACE

The Cox proportional hazards test that was run in models with the CBPS and MNPS sampling weights has shown that the PH assumption does not hold neither for CBPS nor for MNPS weights. Table 25 presents the results of the test. As a result of that, parametric models that are expressed in the PH metric (exponential in PH, Weibull in PH, Gompertz) were not run. A generalised gamma model was fitted using both the CBPS and the MNPS sampling weights to test the hypotheses of whether the MACE time to event model was lognormal, or Weibull or exponential. From the results of the Wald tests, we cannot reject the hypothesis that the model can be Weibull, when the MNPS sampling weights were used. When the CBPS sampling weights were used only the hypothesis that the model could be exponential is rejected. Further testing about the model's distributional assumptions were carried out. Models were fitted using all parametric assumptions and they were included using sampling weights from MNPS and CBPS methods. The best model in terms of AIC among those estimated using the CBPS sampling weights was the lognormal model, whereas for the models that were fitted using the NMPS sampling weights the loglogistic was the best. By comparing the parametric models of both MNPS and CBPS sampling weights, the loglogistic MNPS model was selected as the one fitting the data best.

Table 25 Test for the proportional hazards assumption in the time to MACE models

	MNPS		**CBPS**	
H_0 assumption	**X^2 value**	**Prob > X^2**	**X^2 Value**	**Prob > X^2**
H_0: PH holds	3062.29	<0.001	4309.71	<0.001
CBPS: Covariate Balancing Propensity Scores, **MNPS**: Multinomial Propensity Scores, **Prob**: Probability				

Table 26 Test for nested models in the MACE time-to-event models

	MNPS		**CBPS**	
H_0 assumption	**X^2 value**	**Prob > X^2**	**X^2 Value**	**Prob > X^2**
H_0: κ=0	6.00	0.0143	0.79	0.3755
H_0: κ=1	1.69	0.1941	0.07	0.7905
H_0: κ=1 σ=1	102.09	<0.001	73.21	<0.001
CBPS: Covariate Balancing Propensity Scores, **MNPS**: Multinomial Propensity Scores, **Prob**: Probability				

Table 27 summarises the diagnostics of the full parametric time to MACE models generated using the sampling weights of CBPS balancing method. The model that fits the data best according to AIC and BIC was the lognormal model.

Table 27 Diagnostics of time to MACE models which have sampling weights through the CBPS method

	Weibull	Loglogistic	Lognormal
Log Likelihood	-15619.625	-14147.382	-14102.672
AIC	31267.250	28322.764	28233.345
BIC	31365.520	28421.034	28331.615
LR X^2	105.208	80.587	66.515

Prob > X^2	<0.001	<0.001	<0.001
AIC: Akaike Information Criterion, BIC: Bayesian Information Criterion, **LR**: Likelihood Ratio, **Prob**: Probability			

Table 28 summarises the diagnostics of the full parametric time to MACE models generated using the sampling weights of MNPS balancing method. The model that fits the data best according to AIC and BIC was the loglogistic model.

Table 28 Diagnostics of time to MACE models which have sampling weights through the MNPS method

	Weibull	Loglogistic
Log Likelihood	-13537.328	-12683.088
AIC	27102.656	25394.177
BIC	27200.927	25492.447
LR X^2	105.009	75.332
Prob > X^2	<0.001	<0.001
AIC: Akaike Information Criterion, BIC: Bayesian Information Criterion, **LR**: Likelihood Ratio, **Prob**: Probability		

After comparing the time to event models from the CBPS and MNPS method using AIC statistic, the model that is used for the interpretation of non-fatal MI is the loglogistic model with MNPS sampling weights. Table 29 presents the coefficients of the model, expressed in time ratios. The time when patients on aspirin-prasugrel experience a MACE is approximately 4.4 times longer than that of patients on aspirin-clopidogrel. No significant was observed for patients taking aspirin-ticagrelor compared with aspirin-clopidogrel.

Table 29 Final model of time to MACE event

MACE loglogistic model				
Time ratio*				
	Coefficient	**P>|z|**	**[95% Conf. Interval]**	
Regimen				
Asp-Clop	Reference category			
Asp-Pras	4.418	0.002	1.730	11.280
Asp-Tica	1.305	0.454	0.649	2.626
Number of events	3720			
Number of person years	14385			
Asp-Clop: Aspirin-Clopidogrel dual therapy**, Asp-Pras:** Aspirin-Prasugrel dual therapy, **Asp-Tica:** Aspirin-Ticagrelor dual therapy *Coefficients presented in exponentiated form				

3.13.5 Models for time to all cause death

The Cox proportional hazards test that was run in models with the CBPS and MNPS sampling weights has shown that the PH assumption does not hold neither for CBPS nor for MNPS weights. Table 30 presents the results of the test. As a result of that, parametric models that are expressed in the PH metric (exponential in PH, Weibull in PH, Gompertz) were not run.A generalised gamma model was fitted using both the CBPS and the MNPS sampling weights to test the hypotheses of whether the time to all cause death model was lognormal, or Weibull or exponential. From the results of the Wald tests, we can reject the hypothesis that the model can be Weibull, lognormal or exponential when the MNPS sampling weights were used (Table 31). When the CBPS sampling weights were used only the hypothesis that the model could be Weibull is not rejected. Further testing about the model's distributional assumptions were carried out. Models were fitted using all parametric assumptions and they were included using sampling weights from MNPS and CBPS methods. The best model in terms of AIC among those estimated using the CBPS sampling weights was the Weibull model. The only model that was fitted using the NMPS sampling weights was the loglogistic one. By comparing the Weibull model of CBPS weights with the loglogistic model of the MNPS weights, the Weibull CBPS model was selected as the one fitting the data best.

Table 30 Test for the proportional hazards assumption in the time to death models

	MNPS		**CBPS**	
H_0 assumption	**X^2 value**	**Prob > X^2**	**X^2 Value**	**Prob > X^2**
H_0: PH holds	1080.61	<0.001	2126.08	<0.001
CBPS: Covariate Balancing Propensity Scores, **MNPS**: Multinomial Propensity Scores, **Prob**: Probability				

Table 31 Test for nested models in time to death models

	MNPS		**CBPS**	
H_0 assumption	**X^2 value**	**Prob > X^2**	**X^2 Value**	**Prob > X^2**
H_0: κ=0	67.17	<0.001	32.58	<0.001
H_0: κ=1	10.32	<0.001	3.63	0.0569
H_0: κ=1 σ=1	122.13	<0.001	109.58	<0.001
CBPS: Covariate Balancing Propensity Scores, **MNPS**: Multinomial Propensity Scores, **Prob**: Probability				

Table 32 summarises the diagnostics of the full parametric time to all-cause death models generated using the sampling weights of CBPS balancing method. The model that fitted the data best according to AIC and BIC was the Weibull model.

Table 32 Diagnostics of time to death event models which have sampling weights through the CBPS method

	Weibull	Loglogistic
Log Likelihood	-2529.862	-2846.190
AIC	5087.724	5720.381
BIC	5178.347	5811.003
LR X^2	1024.870	972.142
Prob > X^2	<0.001	<0.001
AIC: Akaike Information Criterion , BIC: Bayesian Information Criterion, **LR** : Likelihood Ratio, **Prob**: Probability		

Table 33 summarises the diagnostics of the full parametric time to non-fatal MI models generated using the sampling weights of MNPS balancing method. The model that fitted the data best according to AIC and BIC was the Loglogistic model.

Table 33 Diagnostics of time to death event models which have sampling weights through the MNPS method

	Loglogistic
Log Likelihood	-2665.847
AIC	5359.693
BIC	5450.316
LR X^2	1040.797
Prob > X^2	<0.001
AIC: Akaike Information Criterion, BIC: Bayesian Information Criterion, **LR**: Likelihood Ratio, **Prob**: Probability	

After comparing the time to event models from the CBPS and MNPS method using AIC statistic, the model that is used for the interpretation of all cause death is the Weibull model with CBPS sampling weights, expressed in accelerated failure time (AFT) metric. Table 34 presents the coefficients of the model. Patients on aspirin-ticagrelor and aspirin-prasugrel survive 2.5 times and 1.4 times longer than patients on aspirin-clopidogrel.

Table 34 Final model of time to death event

Death Weibull model				
Time ratio				
	Coefficient	P>|z|	[95% Conf. Interval]	
Regimen				
Asp-Clop	Reference category			
Asp-Pras	1.439	0.047	1.005	2.062
Asp-Tica	2.579	<0.001	1.613	4.125
Number of events	1050			
Number of person years	14411			
Asp-Clop: Aspirin-Clopidogrel dual therapy**, Asp-Pras:** Aspirin-Prasugrel dual therapy, **Asp-Tica:** Aspirin-Ticagrelor dual therapy *Coefficients presented in exponentiated form				

3.13.6 Summary of time to event analysis

From the time to event analyses, we can see that always one of the newer antiplatelet medications has better results than aspirin-clopidogrel for the outcomes investigated.

The study results of time to non-fatal stroke could be directly compared with the findings from the literature, because the treatment effect was expressed in hazard ratio metrics. The rest of the findings cannot be compared with the published studies in terms of magnitude, because the results were expressed in AFT metric, thus making it impossible to transform results in HR metric (treatment effects only from Weibull models can be expressed in both metrics;in the case of all-cause death analysis, the proportional hazards assumption did not hold). The reason for comparing study results with the literature was to find out if study results were similar or very different with the literature, since this study covers only T2DM population. Table 35 presents the findings of the study and literature side by side for interpretation purposes.

For the comparison of aspirin-prasugrel versus aspirin-clopidogrel, the results for non-fatal stroke were statistically significant, which was in discordance with the TRITON-TIMI study findings (HR aspirin-prasugrel vs aspirin-clopidogrel for non-fatal stroke: 1.02 [95% CI 0.71-1.45], p-value:0.93) (74). For aspirin-ticagrelor versus aspirin-clopidogrel, the findings for the non-fatal stroke were also in discordance with those of the PLATO study (HR:0.04 vs HR:1.17) (75).

Table 35 Study coefficients and results from the literature

Aspirin-prasugrel vs aspirin-clopidogrel				Aspirin-ticagrelor vs aspirin-clopidogrel			
Outcome	**Study estimate (95%CI), p-value**	**Literature estimate (95%CI), p-value**	**Source of Literature**	**Outcome**	**Study estimate (95%CI), p-value**	**Literature estimate (95%CI), p-value**	**Source of Literature**
Stroke	0.22(0.05-0.95), 0.04	1.02 (0.71-1.45),0.93	(74)	**Stroke**	0.04(0.006-0.32),0.002	1.17 (0.91-1.52),0.22	(75)

3.14 Summary

In this chapter, information about the data sources, data analysis and statistical methods that was used in the study has been provided. This study employed CPRD as its main source of electronic health records (EHR), which is a representative collection of primary care records from over 600 practices in England. The various data files of CPRD and HES databases were used to identify exposure to antiplatelet drug therapy, and outcomes, for a cohort of patients with T2DM that suffered an ACS episode. CPRD was linked to secondary care data contained on the HES database, which were used to identify outcomes and resource use of patients on alternative antiplatelet regimens post-ACS.

The methods of investigating associations between antiplatelet regimens and health outcomes were reported. The methods for balancing according to baseline characteristics, and the strategy for selecting the most appropriate method were presented, compared and discussed. The selection of three candidate methods was qualified because it was unknown which method would provide optimal balancing. The advantage of this strategy is that it takes into account all potential methods that can deal with multinomial treatment assignments.

Due to the nature of the extracted data, the use of least squares linear regression was not recommended in duration data for the time to event analysis. Time to event regression analysis was used to deal with the problem of censoring in the duration data, and to investigate the relationships between antiplatelet regimens and health event outcomes.

Overall, patients on ticagrelor and prasugrel were younger than patients on clopidogrel at start of prescribing, and they were predominantly male. Patients started on ticagrelor or prasugrel had had the condition for a shorter time than the patients started on clopidogrel.

Patients on antiplatelet regimens were adherent to therapies, and the fact that patients on aspirin-ticagrelor and aspirin-prasugrel, had no continuation of prescription after 450 days, meant adherence to guidelines. Another finding from this analysis was that patients on DAPT start discontinuing their medications after 180 days, meaning that the true treatment effect of those regimens starts decreasing after the six-month time period. Therefore, the results of this analysis are in accordance with the findings of the review of Czarny regarding the overall adherence(133). Furthermore, the discontinuation in DAPT after six months was also found in the study of Rezaei et al. in Austria(134) , and with the study of Nakamura et al. in Japan (127).

CBPS MMW-s and MNPS methods were the ones selected as candidate methods for balancing across groups. The MMW-s method was abandoned because the algorithm was stopped during the stratification stage. CBPS and MNPS methods produced sampling weights and they were compared with the help of Love plots.

In the CBPS model the probabilities of treatment assignment to different antiplatelet regimens were presented. The model presented a high probability of patients being prescribed aspirin-ticagrelor if they entered the cohort after 2011. This makes sense because aspirin-ticagrelor was not available before 2010.

The results of the comparison did not help in selecting the method that was providing the best balance, because no method presented the best balance across all groups. Furthermore, even though imbalances across groups were reduced by both methods, they were not eliminated. This resulted in using “doubly robust” methods in the later stages of the analysis, and that all analyses in the later stages would be carried out twice, with the MNPS and the CBPS sampling weights.

The time to event analyses, have shown that the newer antiplatelet medications has better results than aspirin-clopidogrel for the outcomes investigated. Aspirin-prasugrel is better than aspirin-clopidogrel in the protection against MI, and MACE, death and stroke, whereas patients on aspirin-ticagrelor experience fewer events of stroke, fewer event of bleeding and survive longer than patients treated with aspirin-clopidogrel.

Overall, for the models where treatment effect is measured in AFT, it can be said that for patients on aspirin-ticagrelor it takes longer to experience a bleeding event than those on aspirin-clopidogrel, meaning that for a set time period, the probability of a bleeding event is lower in aspirin-ticagrelor patients than those in aspirin-clopidogrel treatment. This result was diifferent result from that of the PLATO study (75), where probability of bleeding events higher in the aspirin-ticagrelor group. Using this type of interpretation for the non-fatal MI and MACE outcomes, it can be said that patients on aspirin-prasugrel treatment have lower probability of experiencing an MI, a MACE event, and death than those on aspirin-clopidogrel, which is in accordance with the TRITON-TIMI study (74).

The findings of the time to event analyses indicate that prasugrel is the treatment that provides better protection from cardiovascular events and death for patients with T2DM, with bleeding risks being similar to the treatment with aspirin-clopidogrel. Aspirin-ticagrelor could be considered as an alternative treatment when prescribers have to compare the tradeoffs of patients having increased bleeding risks and increased cardiovascular events.

3.14.1 Use of findings in the Markov model

It was not feasible to use the findings of the time to event analysis in the Markov model. The reasons for that were as follows; Transition probabilities had to be estimated for every single subgroup that could be defined from the time to event models. This meant that the estimations had to be carried out for every subgroup defined, and after that, a population weight that represented the size of the subgroup in the total cohort had to be assigned, so that a transition probability weighted by the subgroup size. For every time to event model, the amount of variable combinations was quite high for such an attempt to be made.

The second reason is the findings of the time to event models. There were models where both ticagrelor and prasugrel had statistically significant results versus clopidogrel, but the magnitude of the effects was quite high. This phenomenon was also true in models where only ticagrelor or prasugrel had statistically significant results. The magnitude of effects in the models could indicate that there was confounding which was not addressed. Additionally, the findings for the bleeding events, non-fatal MI, MACE, and death could not be compared directly with the findings in the literature because of the different way the treatment effect was expressed in this study (AFT versus hazard ratios). A potential use of the time to event analysis findings could be the use of the statistically significant relationships among treatment groups in stroke and all cause death from the analysis as a way of sensitivity analysis in the Markov Model.

4. Chapter Four: Costs of health care in T2DM patients treated with antiplatelet medications for ACS secondary prevention.

4.1 Introduction to the chapter

In this chapter, the results of the second part of the quantitative analysis are presented. The methods for costing of health care resource use from the clinical databases and the steps followed in the econometric analysis of associations between healthcare costs and antiplatelet therapies are presented, followed by the results of the cost analysis.

4.2 Methods for cost analysis

In the following sections the methods for obtaining information about resource use in primary and secondary care from CPRD and HES datasets is discussed, followed by the additional steps that were carried out in order to investigate the associations between different healthcare cost categories and antiplatelet treatments

4.2.1 Healthcare resource usage and costs

In order to get an overview about health care resource usage and the costs incurred to the NHS for every antiplatelet regimen mentioned in the study, information was collected from CPRD and HES linked datasets. The CPRD therapy, clinical, additional, and consultation files were used to obtain information about prescriptions, diagnostic tests and primary care contacts. The HES inpatient and outpatient linked datasets were used to obtain information about outpatient visits in secondary care and hospitalisations. This way the health care resource use and the cost to the NHS could be reported as descriptive characteristic for every antiplatelet regimen, and used for the later stages of cost analysis.

4.2.1.1 Healthcare resource usage

Resource use in primary care included information about general practice consultations that were obtained from the consultation files and the clinical files of CPRD. Consultation costs were assigned based on the staff role and consultation duration available on staff and consultation files of CPRD. Therapy items such as diagnostic tests were identified in the clinical and additional files of CPRD. The CPRD therapy file was used for sourcing information about antiplatelet prescription costs, and the prescription costs of all other medications that don’t fall into the antiplatelet category (rest of medications prescription costs).

Resource use in secondary care included information about outpatient visits and hospital inpatient admissions. The source for outpatient attendances in secondary care was the outpatient linked HES dataset. Based on the type of visit (first visit, follow up visit, consultant led visit, non-consultant led visit) the appropriate unit cost was assigned. Visits during the index year and in consecutive years were considered. Hospital admissions were identified in the HES inpatient linked dataset. The cost of every inpatient admission was adjusted based on the type of admission (elective, non-elective, day case) and the type of admission length (long stay, short stay).

4.2.1.2 Unit costs

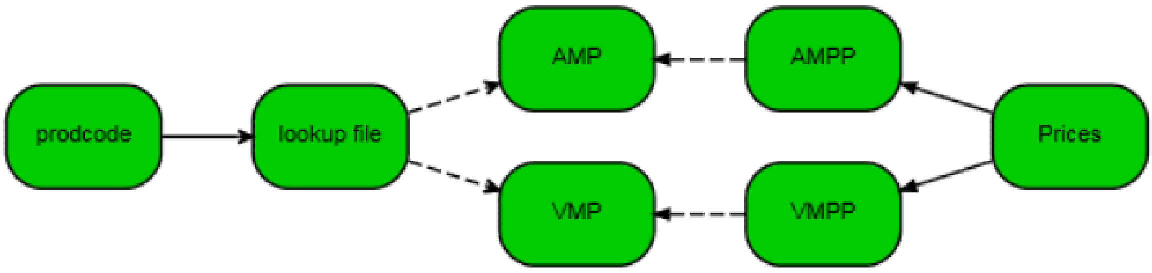
Unit costs were taken from publically available sources for UK health care. For primary care, the latest PSSRU publication (249) was the source, whereas for the inpatient and outpatient admissions recorded in HES data the latest national reference cost schedule was used (250). Costs of admissions were assigned after being processed with the latest Healthcare Resource Group (HRG) grouper and receiving an HRG code. The cost of prescriptions was obtained from the latest British National Formulary (BNF) publication. All costs were expressed in 2016 prices. If the most up-to-date unit cost sources were not available for this year, then inflation adjustment was carried out with the use of the Healthcare inflation price index (HCHS) (249). Total costs per patient during the first and consecutive years post-ACS were estimated.

4.2.1.3 Attaching unit costs across the various healthcare resource use elements-Prescription costs

In order to estimate the prescription costs, two sources of information were required: the patient prescription records in therapy files, and the prescription price information that was recorded in the NHS Dictionary of Devices and Medicines (dm+d), a list that was available by the Technology Reference Data Update Distribution. Prescription records from therapy files for the period between index date and end of follow up were selected. After grouping and selection of records in therapy files, a list containing all the product codes that appeared at least once in the prescription records was generated. This list was combined with the product code lookup file, so that descriptions of medications in the lookup file were matched to the product codes in the list. Medication description fields were used to match the product codes with corresponding prices in dm+d. The dm+d consisted of records that are stored in five different levels. These levels contain information about medicines and devices in a hierarchical way. In each level, medicine and device information is stored with different detail. The records of dm+d were available as Extensible Markup Language (xml) files, and a tool available from HSIC was used to transform the files in Excel format.

Figure 12 presents the levels of dm+d and the relationships between those levels. The only levels that contained pricing information were the Actual Medicinal Product Pack (AMPP) and the Virtual Medicinal Product Pack (VMPP) level respectively, whereas the Actual Medicinal Product (AMP) and the Virtual Medicinal Product (VMP) had descriptions of devices and medications that could be matched with the description field product code lookup file. There was also partial connection between VMP and VMPP and AMP and AMPP respectively. By exploiting these partial connections between the lookup file and the several levels of dm+d, a very indirect matching of product codes with prices was carried out, without the need for manual investigation of prices and product codes (Figure 11). The fact that not all product codes in therapy file were matched with a price from dm+d, meant that the prescription costs were underestimated, thus leading to underestimation of primary care costs.

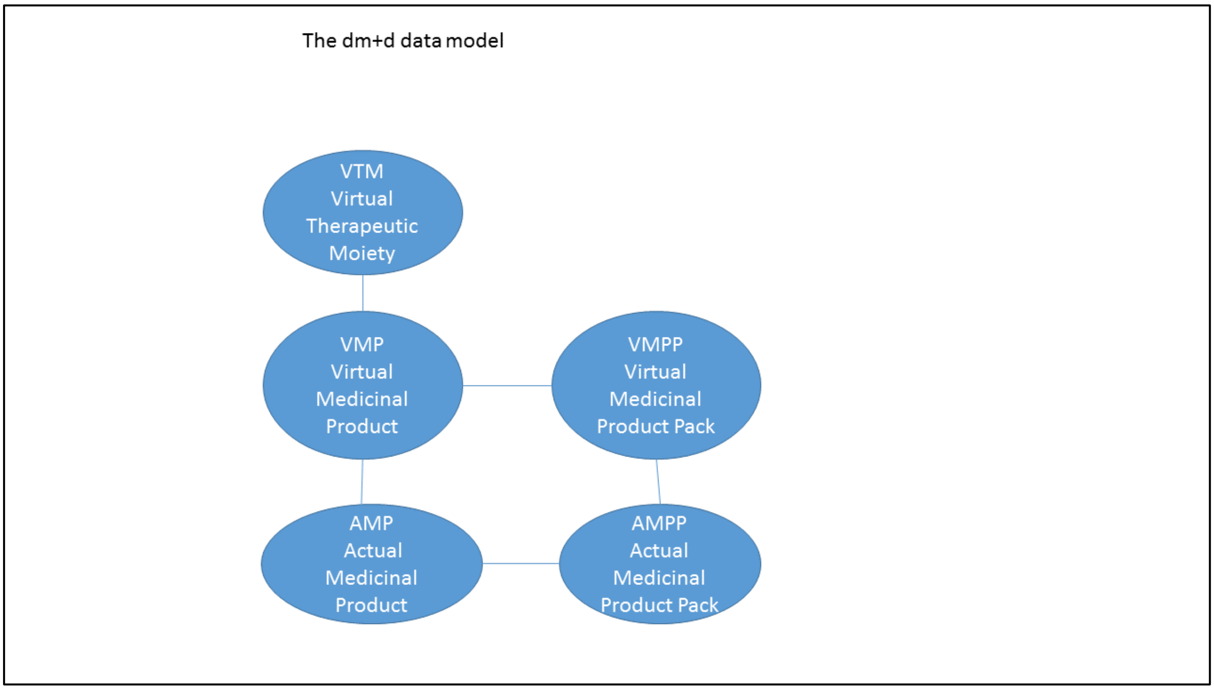
Figure 11.Relationships between product codes, prices and levels of dm+d data.



Solid arrows: 1:1 match, Dashed arrows: partial match

AMP: Actual Medicinal Product, **AMPP:** Actual Medicinal Product Pack, **VMP:** Virtual Medicinal Product, **VMPP:** Virtual Medicinal Product Pack

Figure 12.The structure of the dm+d data model.



4.2.1.4 Attaching unit costs across the various healthcare resource use elements-Primary care consultations

For the costs of primary care consultations, the records stored in consultation file were used. A selection and grouping of records during the follow-up period and during the first and subsequent years post-ACS was performed. Every record in the consultation file contained information about the role of staff, type of action, and duration of action during the interaction of clinical staff and the patient. In CPRD the duration of every action, was downrounded to the closest minute, meaning that actions lasting less than a minute would take the value of zero. In cases where the recorded actions lasted more than what could be considered as a normal period of interaction, resulted in records of having duration time of more than an hour. For those records, specific assumptions for the adjustment of duration time were made. The assumptions followed in the analysis are the same made by Hobbs et al (251), that is records with zero minute duration were assumed to last 0.5 minutes and a maximum cut-off value of 60 minutes was imposed for all the records. The consultation files were also merged with the staff files of the dataset. This allowed for the identification of the role of every staff member and the proper distribution of hourly rates or payment from PSSRU. In CPRD there are 60 different types of consultation and 68 roles of staff. Tables that show the groupings of consultations and the correspondence of staff roles to descriptions of clinical staff in PSSRU respectively are available in Appendix 6 Primary care resource use was costed by taking into account the role of staff and the duration of action, and not the type of consultation.

4.2.2 Associations between costs and treatment regimens

In order to find out whether patients who followed different antiplatelet treatments incurred additional costs, and if the assignment of antiplatelet treatment affected any type of healthcare cost, further analysis, beyond that of descriptive nature, had to be carried out. Regression analysis of costs was selected as a method to identify any significant difference in costs between patients on different antiplatelet regimens.

4.2.2.1 Regression analysis of costs

Data about health care resource use, and health care costs have specific characteristics. Cost information contains non-negative values, a large fraction of zero values in the sample and population, and resource use and cost values are usually positively skewed. The non-normality of healthcare costs has to do with the nature of costs themselves, since patients who have more severe conditions and comorbidities, tend to accrue higher costs (252). Furthermore, it is the case where a low number of patients are responsible for a high proportion of costs. As a result of those characteristics, regression analysis using the method of ordinary least squares (OLS) can be problematic, because the method cannot always cope with the skewness and the potential non-linearity of the data. Several alternatives for addressing those problems have been used, where one involves the logarithmic transformation of costs and the use of OLS method, the use of generalised linear models (GLM) (253), or the use of extended estimating equations (EEE) which is an extension of GLM (254).

4.2.2.2 Dataset preparation for cost analysis

The information in the dataset was in wide format, meaning that every row contained all the information needed for analysis. Various columns showed the costs that were incurred during the first year post-ACS in various primary and secondary care resource use. There was only use of the first-year information post-ACS data, because the information in the subsequent years is less complete. Futhermore, the cost of the initial ACS admission, that led to the prescription of antiplatelet medications for secondary prevention, is excluded from the analysis. The inclusion of additional years of information would result in introducing a time element in the dataset (longitudinal data), meaning that the methods for cost analysis would have to address for missing data and the longitudinal structure of the dataset, thus the analysis was not extended for multiple years post-ACS. More details in preparing cost information was provided in section 4.2.1. As in dataset preparation for time to event analysis, the dataset included the variables that were used for balancing purposes, in the case where doubly robust model adjustments were needed.

4.2.2.3 Specifying the cost model

In order to specify the model, we needed to select in the GLM framework the family of distributions that the dependent variable would follow and the linkage power. The family could be gamma, Gaussian, inverse Gaussian, Poisson, binomial, negative binomial. Regarding the link power we could select identity, log, probit, logit, or a custom value. To select the family, the modified Park test was implemented as suggested by Manning (252). In order to run the Modified Park Test correctly, the GLM model that is used for the test needs to be specified correctly. For that reason, multiple GLM models with specific link functions (log, Gaussian, Inverse Gaussian, square root), and different distribution families were estimated. The models were not fit with the identity link (253), because this type of link for non-negative costs is conceptually flawed. The cost dependent variable can never be negative, whereas a model with identity link would allow this kind of possibility. In that case the log link (exponentiates the linear index) and the square root link never estimate conditional mean of the dependent variable to be negative (253).

For the selection of linkage power several tests were performed and based on the results of Pregibon link test (255), the Pearson correlation test and the modified Hosmer and Lemeshow test (256).

Patients have different follow-up times in the dataset, something that during the analysis of cost associations can lead to biased results, because patients can be censored during different time points during the time period in the first year post-ACS. In order to overcome this problem two solutions can be followed; 1) Include in the analysis only the patients who post-ACS have a full year of follow up data. 2) Adjust for the follow-up time of every patient using an offset variable; the offset variable is equal to the log of time that every patient is followed up. In the analysis the second option was selected.

4.3 Results of cost analysis

4.3.1 Description of costs among patients in antiplatelet regimens

For the description of total costs among patients during the first year post-event, information about all the medication regimens was reported. The cost association analysis included only the dual antiplatelet regimens, because the balancing step was carried out with the DAPT regimens only. During the first year post-event, the total costs were the highest in patients who were on aspirin-clopidogrel (Table 36); those patients had the highest inpatient, critical care, and non-elective costs during the same period. Patients who were on the clopidogrel-only regimen had the second highest total costs. Similar levels of total costs were found for patients on aspirin-ticagrelor and aspirin-only regimens. In general, the total primary care costs were similar among patients, whereas the prescription costs were higher in patients that were on newer antiplatelet regimens. This difference in prescription costs is mainly attributed to the prescription costs of ticagrelor and prasugrel which are much higher than the costs of aspirin and clopidogrel respectively. Secondary care costs represent the majority of health care costs among all patient groups. Day case costs were similar for all patients, but elective inpatient costs were lower in the aspirin-prasugrel and aspirin-ticagrelor group.

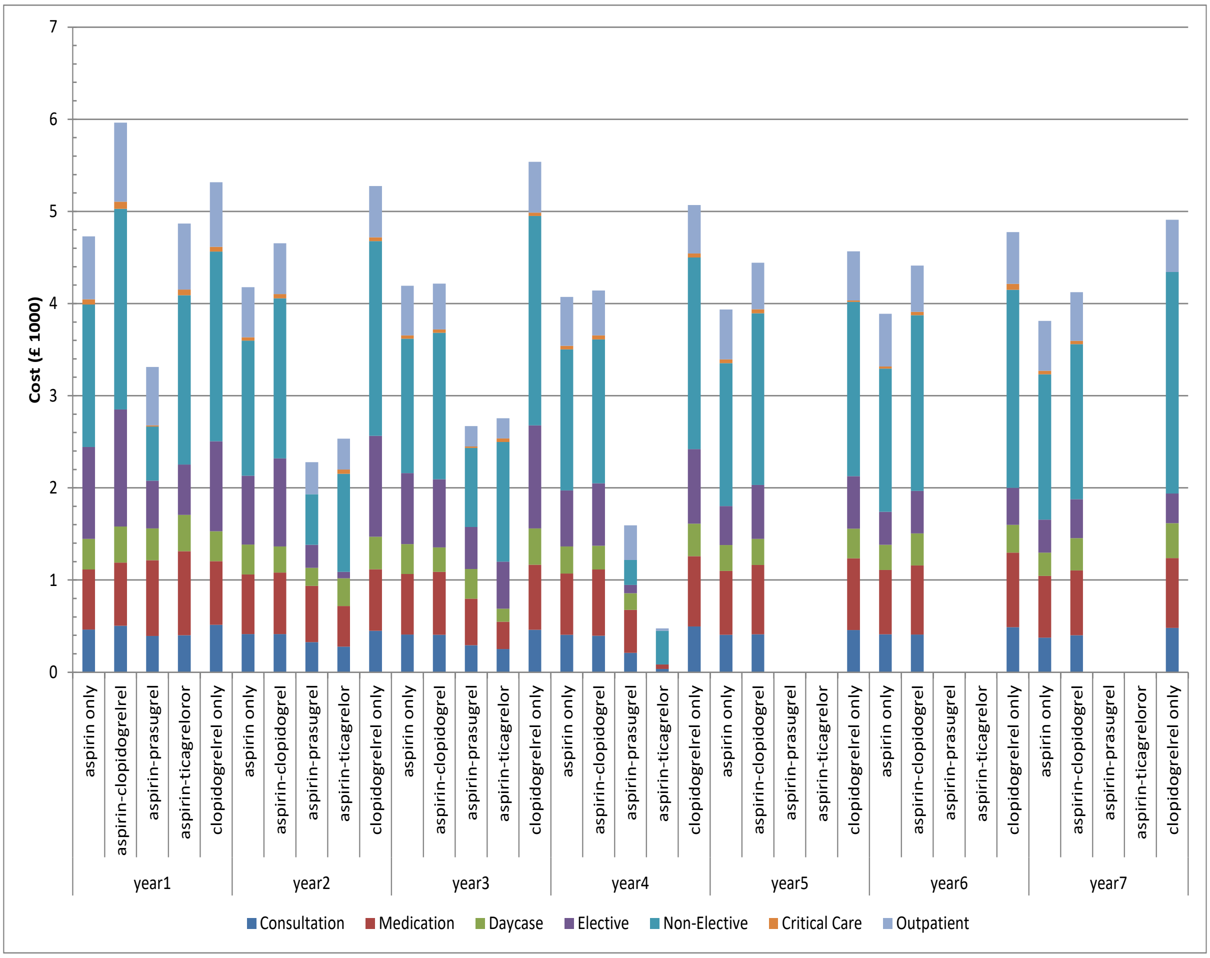
Cost of patients over longer time periods (two to seven years post-ACS) remain at similar levels as the costs during the first year (Figure 12). Primary care costs are similar between all patient groups, beyond the first year post event. This can be attributed to the fact that patients with long-term conditions need primary care support to manage their condition over time, irrespective of which antiplatelet regimen they follow. Secondary care needs remain high in the subsequent years after the initial ACS event. Non-elective care costs constitute the largest part of secondary care costs among all patients during the subsequent years post-ACS. For the patients who are on aspirin-ticagrelor or aspirin-prasugrel there is no cost information after the fifth year post-ACS and later on, due to the smaller size of these groups and the shorter period those patients are followed up.

Table 36 Total costs per patient during the first year post event, by cost category and antiplatelet regimen

Cost Category		Aspirin	Clopidogrel	Asp-Clop	Asp-Pras	Asp-Tica
Total Primary care	**Mean**	1115.38	1203.51	1189.33	1215.91	1312.46
	N/SU	16284/16284	2282/2282	4449/4449	105/105	230/230
	Median	875.93	957.34	923.18	1089.03	1047.85
	Min	1.79	1.53	5.06	53.85	69
	Max	107773.08	10756.79	17129.14	5792.85	4579.6
	95% CI	1095.46-1135.31	1161.63-1245.39	1157.57-1221.09	1038.53-1393.29	1181.47-1443.45

Cost Category		Aspirin	Clopidogrel	Asp-Clop	Asp-Pras	Asp-Tica
Consultation	**Mean**	462.3	514.21	504.98	393.62	401.15
	N/SU	16284/16284	2282/2282	4449/4449	105/105	230/230
	Median	358.01	389.08	399.58	324.22	317.73
	Min	0	0	0	0	0
	Max	14834.97	4209.61	4880.32	1922.55	2055.88
	95% CI	455.96-468.63	495.55-532.88	492.45-517.51	326.34-460.91	354.73-447.56
Prescriptions	**Mean**	653.08	689.29	684.35	822.28	911.31
	N/SU	16284/16284	2282/2282	4449/4449	105/105	230/230
	Median	420.84	457.07	431.92	681.66	664.02
	Min	1.13	1.44	5.06	52.95	59.88
	Max	102115.11	10077.12	16467.57	4911.15	4162.82
	95% CI	635.90-670.27	657.22-721.36	658.69-710.01	679.72-964.85	804.6-1018.03
Total inpatient	**Mean**	2875.04	3359.83	3837.9	1448.79	2777.98
	N/SU	16284/8205	2282/1304	4449/2644	105/43	230/118
	Median	216.56	759.51	1067.15	0	331.5
	Min	0	0	0	0	0
	Max	331653.53	319898.66	329969.56	17963.87	25507.48
	95% CI	2697.52-3052.56	2901.62-3818.05	3473.84-4201.95	847.07-2050.51	2157.46-3398.5
Day-case	**Mean**	330.13	325.55	392.09	343.79	393.43
	N/SU	16284/3746	2282/549	4449/1092	105/16	230/57
	Median	0	0	0	0	0
	Min	0	0	0	0	0
	Max	307386.19	13491.78	46512.39	14651.15	6987.92
	95% CI	285.51-374.74	287.3-363.8	355.52-428.66	39.92-647.66	263.78-523.08
Elective inpatient stays	**Mean**	997.79	975.77	1269.55	518.71	546.18
	N/SU	16284/2221	2282/311	4449/820	105/14	230/31
	Median	0	0	0	0	0
	Min	0	0	0	0	0
	Max	319519.88	317753.22	325586.69	16469.19	14812.1
	95% CI	844.32-1151.27	559.93-1391.6	944.07-1595.03	149.43-887.99	317.24-775.12
Non-elective inpatient stays	**Mean**	1547.12	2058.52	2176.26	586.29	1838.37
	N/SU	16284/5058	2282/867	4449/1789	105/28	230/76
	Median	0	0	0	0	0
	Min	0	0	0	0	0
	Max	163258.39	36939.67	51888.84	8044.77	25507.48
	95% CI	1483.27-1610.97	1881.65-2235.38	2036.36-2316.15	313.12-859.46	1284.8-2391.94

Figure 13. Costs by type, regimen and years after initial ACS event



4.3.2 Investigation of cost associations

The investigation of cost associations was initially carried out for the total care costs, for total primary care costs, for total secondary care costs, and finally for subcategories of primary care and secondary care costs respectively. The primary care cost subcategories were the primary care contacts costs and the medication prescription costs. For the secondary care cost associations, total inpatient care, and total outpatient care costs were investigated. Although, further classification of secondary care costs was made by splitting the inpatient costs into day case costs, elective inpatient costs, non-elective inpatient costs, the Modified Park Test (MPT) was not possible to be carried out for those cost categories, and the analysis could not be completed. The reason for not carrying out the MPT was the non-convergence of the MPT algorithm which led to the inability of result generation. Information about those cost categories is only provided in terms of descriptive statistics. The cost analysis is restricted in the total amount of health care costs that are incurred during the first year post-index date because of the smaller time period that patients on aspirin-ticagrelor and aspirin-prasugrel are followed up in the dataset. Extending the cost analysis period beyond the first year would have resulted in very small numbers of patients on aspirin-ticagrelor and aspirin-prasugrel contributing data.

4.3.3 Modified Park Test (MPT) results

As mentioned previously, the ability to carry out the MPT was the criterion that affected which cost categories would be used for testing their association with antiplatelet regimens. The specification of the GLM models used for the MPT for every cost category is presented in Table 37. This MPT based assessment resulted in the inclusion of cost categories reported in Table 38, which summarises the coefficients that were generated from the MPT for the selection of a probability distribution from the exponential family conditional on a particular link function. Due to being unable to select a specific balancing method in earlier stages of analysis, the test was carried out twice, using MNPS followed by CBPS sampling weights. The coefficients generated were rounded to the first decimal point, and based on that, the appropriate probability distribution was selected. When the MPT coefficient ranged from zero to three there were clear instructions for probability distribution selection, but not when the coefficient was higher than three. In the case where the MPT coefficient was over three, it was treated as if it was equal to three and an inverse Gaussian family was assumed for the model. Coefficient results of the test were not affected by the choice of sampling weights. Decisions over probability distribution from the exponential family were the same irrespective of sampling weights.

Table 37 Transformation and family selection for the specification of the GLM equations used for the Modified Park Test for every cost type and sampling weights.

Cost type	**MNPS**		**CBPS**	
	Transformation	**Family**	**Transformation**	**Family**
Total Primary care	Log	Gamma	Log	Gamma
Primary care consultations	Log	Gamma	Log	Gamma
Prescribed medication costs	Log	Gamma	Log	Gamma
Inpatient costs	Square	Gamma	Square	Gamma
Outpatient costs	Log	Gamma	Log	Gamma
Total patient costs	Square	Gamma	Square	Gamma

Table 38 Results of the Modified Park Test for the selection of probability distribution from the exponential family

	Modified park test coefficients		**Family of models based on MPT**	
Sampling weights	**MNPS**	**CBPS**	**MNPS**	**CBPS**
Cost type				
Total	0.051	0.050	gaussian	gaussian
Total primary care	1.62	1.62	gamma	gamma
Primary care consultations	1.41	1.42	gamma	gamma
Prescriptions	1.73	1.74	gamma	gamma

	Modified park test coefficients		Family of models based on MPT	
Sampling weights	**MNPS**	**CBPS**	**MNPS**	**CBPS**
Cost type				
Total outpatient	1.79	1.80	gamma	gamma
Total inpatient	0.044	0.043	gaussian	gaussian
CBPS: Covariate Balancing Propensity Scores, **MNPS:** Multinomial Propensity Scores, **N/A:** Not Applicable				

4.3.3.1 Total patient cost associations

In this cost category, the total health care costs incurred by patients during the first year post-ACS are combined and their association with the antiplatelet regimens is presented. Table 39 provides an overview of the associations between total patient costs and the medication regimen the patients follow. Both MNPS and CBPS models were estimated, and the one with the MNPS sampling weights, a Gaussian family and a square root link function $\boldsymbol{X\beta} = \mu^{0.5}$ was selected. On average, patients on ticagrelor and clopidogrel incur annually £6345 in total care. Patients on aspirin-prasugrel incur 35% less total costs (£4098).

Table 39 Associations between total patient healthcare costs and antiplatelet regimens

Total Patient Costs				
	Coefficient	**P val.**	**[95% Conf. Interval]**	
Regimen				
Asp-Clop	Ref.			
Asp-Pras	-2247.22	<0.001	-3077.69	-1416.74
Asp-Tica	510.2904	0.528	-1073.74	2094.322
Asp-Pras: Aspirin-Prasugrel dual therapy**, Asp-Tica:** Aspirin-Ticagrelor dual therapy,				

From the analysis that was carried out for the total health care costs, we found that there were different costs incurred by patients on aspirin-prasugrel and those on aspirin-clopidogrel or aspirin-ticagrelor. For that reason, additional analyses by cost categories had to be carried out, in order to be able to see where the difference in costs was occurring. The results of analyses on the cost categories that represent on aggregate the total health care costs are presented in the following sections.

4.3.3.2 Total primary care cost associations

In this cost category, the total medication prescription costs and the total primary care contact costs are combined and their association with the antiplatelet regimens is presented. Table 40 provides an overview of the associations between the prescription costs and the medication regimen the patients belong. Both the MNPS and the CBPS models were estimated using the log link function $\boldsymbol{X\beta} = \ln(\mu)$. From the information criterion the model with the MNPS derived sampling weights was selected. According to the model the patients on aspirin-clopidogrel incur during the first year post-ACS total primary care costs equal to £1226, whereas patients on aspirin-ticagrelor and aspirin-prasugrel incur around £120 more and £410 more per year respectively. This increase in total primary care costs for patients on aspirin-ticagrelor and aspirin-prasugrel could be attributed to the increased cost of medications.

Table 40 Associations between total primary care costs and antiplatelet regimens

Total Primary Care Costs				
	Coefficient	**P val.**	**[95% Conf. Interval]**	
Regimen				
Asp-Clop	Ref.			
Asp-Pras	120.62	0.059	-4.41	245.67
Asp-Tica	410.11	<0.001	239.78	580.44
Asp-Pras: Aspirin-Prasugrel dual therapy**, Asp-Tica:** Aspirin-Ticagrelor dual therapy,				

4.3.3.3 Primary care consultations cost associations

Table 41 provides an overview of the associations between the primary care contacts costs and the medication regimen the patients belong. The MNPS model was estimated using a log link function $\boldsymbol{X\beta} = \ln(\mu)$. From the information criterion the model with the MNPS derived sampling weights was selected. From the model, we can conclude that the antiplatelet regimen that patients follow does not affect the cost of primary care contacts, meaning that the cost of primary care contacts are the same among all patients. The annual costs of primary care consultations are approximately £530.

Table 41 Associations between primary care contacts costs and antiplatelet regimens

Primary Care Consultation Costs				
	Coefficient	**P val.**	**[95% Conf. Interval]**	
Regimen				
Asp-Clop	Ref.			
Asp-Pras	-82.41	0.058	-161.56	-3.27
Asp-Tica	6.95	0.862	-71.26	85.17
Asp-Pras: Aspirin-Prasugrel dual therapy**, Asp-Tica:** Aspirin-Ticagrelor dual therapy,				

4.3.3.4 Association between antiplatelet regimen and prescribed medication cost

Table 42 provides an overview of the associations between the prescription costs and the medication regimen the patients belong. The MNPS model was estimated using the log link function $\boldsymbol{X\beta} = \ln(\mu)$. Based in the results of both information criteria (AIC, BIC) the model with the MNPS derived sampling weights was selected. Patients on aspirin-prasugrel or aspirin-ticagrelor incur on average £211 and £406 higher medication prescription costs during the first year post-ACS compared with patients on aspirin-clopidogrel. This additional cost burden could be explained from the fact that both aspirin-prasugrel and aspirin-ticagrelor are still on patent and just the treatment with these new agents increases the total prescription costs.

Table 42 Associations between prescribed medications costs and antiplatelet regimens

Prescription Costs				
	Coefficient	**P val.**	**[95% Conf. Interval]**	
Regimen				
Asp-Clop	Ref.			
Asp-Pras	211.83	<0.001	94.70	328.96
Asp-Tica	406.88	<0.001	263.38	550.38
Asp-Pras: Aspirin-Prasugrel dual therapy**, Asp-Tica:** Aspirin-Ticagrelor dual therapy,				

4.3.3.5 Secondary care outpatient cost associations

In this cost category, the total outpatient care contact costs are combined and their association with the antiplatelet regimens is presented. Table 43 provides an overview of the associations between the outpatient costs and the medication regimen the patients belong. The MNPS model was estimated using the gamma family and the log link function $\boldsymbol{X\beta} = \ln(\mu)$. From the information criterion the model with the MNPS derived sampling weights was selected. The estimated annual cost in outpatient visits is £1042 for patients in aspirin-clopidogrel and not statistically significant difference was found for the patiens on other antiplatelet regimens.

Table 43 Associations between outpatient costs and antiplatelet regimens

Total Outpatient Costs				
	Coefficient	**P val.**	**[95% Conf. Interval]**	
Regimen				
Asp-Clop	Ref.			
Asp-Pras	-266.48	0.058	-509.71	-23.25
Asp-Tica	-88.26	0.412	-293.89	117.35
Asp-Pras: Aspirin-Prasugrel dual therapy**, Asp-Tica:** Aspirin-Ticagrelor dual therapy,				

4.3.3.6 Inpatient cost associations

In this cost category, the total medication prescription costs and the total primary care contact costs are combined and their association with the antiplatelet regimens is presented. Table 44 provides an overview of the associations between the prescription costs and the medication regimen the patients belong. The MNPS model was estimated using the square root link function $\boldsymbol{X\beta} = \mu^{0.5}$. From the information criterion the model with the MNPS derived sampling weights was selected. Patients who were prescribed aspirin-prasugrel incurred lower inpatient costs compared to those prescribed aspirin-clopidogrel or aspirin-ticagrelor (£3223 versus £7591)

Table 44 Associations between inpatient admission costs and antiplatelet regimens

Total Inpatient Costs				
	Coefficient	**P val.**	**[95% Conf. Interval]**	
Regimen				
Asp-Clop	Ref.			
Asp-Pras	-4367.95	<0.001	-6004.45	-2731.46
Asp-Tica	12.55783	0.993	-2709.61	2734.723
Asp-Pras: Aspirin-Prasugrel dual therapy**, Asp-Tica:** Aspirin-Ticagrelor dual therapy,				

4.3.4 Discussion

In this chapter the relationship between various health care costs and antiplatelet treatments is presented. The attachment of unit costs in the resource use information from primary and secondary datasets is described, followed by description of methods for the statistical analysis of health care costs.

Due to the specific characteristics of the health care cost data (non-negative values, a large fraction of zero values, positive skewness) the use of least squares linear regression could be problematic. Generalised linear models were used to investigate the relationships between antiplatelet regimens and various primary and secondary care cost categories. In the dataset, patients had different follow-up times, and this could lead to biased analysis results. Adjustments for the follow-up time was carried out with the use of an offset variable.

In terms of total health care costs, patients on aspirin-prasugrel incur less costs than those on aspirin-ticagrelor and aspirin-clopidogrel. For aspirin-prasugrel patients, the increased costs that they incur in medication prescriptions are balanced by the reduced costs in inpatient admissions.For patients on aspirin-ticagrelor, the increased medication costs was counterbalanced by the outpatient care costs they incurred during the year, resulting in a non-significant difference in total health care costs with patients on aspirin-clopidogrel.

The cost association analysis of the separate cost categories showed that patients who are prescribed with aspirin-prasugrel tend to incur similar costs with patients on aspirin-clopidogrel in three cost categories (primary care contacts, total primary care costs,outpatient visits), and more costs in one category (prescription costs).On the other hand, patients that were prescribed aspirin-ticagrelor incurred higher costs than those on aspirin-clopidogrel in two cost categories (medication prescription, total primary care) and similar costs with patients on clopidogrel in three categories (primary care contacts, outpatient visits, inpatient admissions).

The cost analysis presented that comparing between aspirin-clopidogrel and aspirin-ticagrelor regimens, aspirin-clopidogrel patients are those who incur similar or less costs than those on aspirin-ticagrelor. Finally, patients on aspirin-prasugrel are those that incur the least costs compared to those on aspirin-clopidogrel and aspirin-ticagrelor. The study of Kim (257)that made comparisons among patients treated with DAPT in the US health care setting, found that the higher price of prasugrel and ticagrelor was partially offset by a decrease in hospital admission compared with generic clopidogrel over a 6-month post discharge period, and that aggregated medical costs and resource utilization were not significantly different between prasugrel and ticagrelor patients.

4.3.4.1 Use of the findings in the Markov model.

The results of the costs analysis for the inpatient and outpatient health care costs could be used as estimates for the costs per cycle in the various stages of the Markov model. The problem with this approach though, is the fact that the analysis could provide cost estimates only for the aspirin-clopidogrel group in both outpatient and inpatient costs, since this was the reference category in the analysis. The analysis of outpatient costs has shown that there was no difference among treatment groups, allowing us to use the same outpatient cost estimates for every group in the Markov model. The analysis of inpatient costs has shown that patients on aspirin-prasgurel had significantly lower inpatient costs than the other two groups. Using the same inpatient cost estimates for all groups in the states of Markov model, by having the aspirin-clopidogrel as reference group, would result in the overestimation of costs for the aspirin-prasugrel group.

The models that were used in the estimation of total health care costs and the estimation of costs of several cost categories in primary and secondary care, were not taking into account the presence of a condition or the history of a previous event. This meant that in the various health states of the Markov model, every state that described a different condition could have the same annual inpatient and outpatient costs of treatment, if the current findings of the analysis were used.

Due to the focus that the current cost analyses have (associations between different treatment groups) the results of the analyses can’t be used in the economic evaluation.

5. Chapter Five: Economic evaluation of antiplatelet therapies used for secondary prevention of ACS in a T2DM population.

5.1 Introduction

This chapter outlines a cost-effectiveness analysis where the relative costs and benefits of alternative antiplatelet regimens in patients with T2DM who have experienced ACS are compared. At the time of writing, I am not aware of any equivalent study that compares, head-to-head, the key regimens for this population group. The commonly used dual antiplatelet therapy of aspirin and clopidogrel is compared with the relatively newer combinations of aspirin and prasugrel, aspirin and ticagrelor, and aspirin monotherapy. This chapter describes the development of a model that compares the costs of the three antiplatelet regimens from a UK NHS perspective at 2016 prices, and outcomes in terms of quality adjusted life years (QALYs) over a lifetime horizon. The analysis carried out included the comparison of expected values for incremental costs and QALYs, using one way and probabilistic sensitivity analyses for the assessment of the uncertainty around the values of model parameters. The reporting of the model is structured according to the CHEERS criteria (258) and validated according to the AdViSHE guidelines (259). Completed checklists for both guidelines, outlining how and where the economic evaluation follows the guidelines, are in Appendices 6-7 (8.6,8.7)

In order to model the use of antiplatelet regimens in T2DM, various approaches to structuring of the model were considered. T2DM is a condition that can lead to multiple complications, so the models that simulate the progression of this condition tend to have multiple states that represent those complications (patient level simulation). The Economic and Health Outcomes model for T2DM (ECHO-T2DM)(239)(260), the IMS Centre for Outcomes Research model (CORE) model (261), the Januvia Diabetes Economic model (JADE)(262), and the United Kingdom Prospective Diabetes Study (UKPDS) model (263) fall into this category, by simulating the complications that occur in patients with diabetes over time (264). In those models, microvascular complications, macrovascular complications, and adverse events such as hypoglycaemia, peripheral oedema and osteoporosis are described as events due to diabetes or due to other reasons. A second approach to economic modelling in T2DM is that followed by studies that were used for the evaluation of various antidiabetic treatments and the impact those treatments have in the reduction of complication risk. In those models, which can be either Markov cohort models or decision tree models, and for the transition probabilities (Markov models) or the probabilities in the branches of decision trees, the risk equations from the UKPDS 68 study (263) are used and they are combined with the treatment effects of the medications in question. A systematic review from Charokopou et al provides an overview of models that have been used for health technology assessment purposes and follow the second approach. (265). The third approach that was considered was the one that was followed in a set of economic models that have been structured for the evaluation of antiplatelet medications. These models are Markov cohort models, and they focus mainly on the cardiovascular events that may occur (Stroke, MI, cardiovascular death) and potential adverse events due to the medication use (dyspnoea, bleeding) in general populations. Chapter Two provides an overview and results of the cost-effectiveness models that used the third approach.

In order to create a model that compares antiplatelet medications in a T2DM population, a model structure that combined elements from the three previously mentioned approaches was used. Following a structure like that of ECHO-T2DM or IMS-CORE would not allow for the comparison of antiplatelet medications, because the information about how the antiplatelet regimens affect all the T2DM complications, is not available, so using an all-encompassing diabetes model would be not appropriate. For that reason, the final model combined elements from the second and the third approach. For this study, a Markov cohort model was created, which had a structure that was similar the structure of the models used for the evaluation of antiplatelet medications, and the model parameters for the Markov cohort were selected to fit a population of adults with T2DM in the United Kingdom.

5.2 Aims and objectives of the model

The model's main aim is to compare the several antipatlet regimens that are prescribed in patients with T2DM for secondary prevention of cardiovascular events. In this case, the treatment options under investigation were patients prescribed aspirin only, aspirin and clopidogrel, aspirin and ticagrelor or aspirin and prasugrel, in terms of incremental costs and utility, over a lifetime horizon, from the perspective of the NHS in England. The model's aim was achieved through the following specific objectives:

1. Describe the clinical pathway of adults with T2DM post-ACS event hospitalisation and how patients were treated in primary and secondary care with the help of a state transition model for the representation of the progression;
2. Identify used resource and costs associated with the treatment of various outcomes that could occur in patients after their first hospitalisation, from an NHS England perspective;
3. Value the impact of the various outcomes on patient health in terms of QALYs;
4. Assess the costs and outcomes in patients by making all the possible comparisons between those prescribed aspirin only, aspirin and clopidogrel, aspirin and prasugrel and aspirin and ticagrelor;
5. Carry out an incremental cost-effectiveness analysis of cost per QALY over a lifetime period;
6. Determine key areas of uncertainty with the use of one-way sensitivity analysis and identify the overall effect of uncertainty across all model parameters with the use of probabilistic sensitivity analysis.

5.3 Model population

The source population was adults with T2DM, who had an ACS event are receiving DAPT or aspirin only for the secondary prevention of further ACS events. It was assumed that after they had an ACS event they were prescribed antiplatelet medications for the secondary prevention of ACS, according to current practice guidelines (266-269).

5.4 Model structure and input parameters

5.4.1 Structure overview

A state transition Markov model was designed with the purpose of reflecting the progression of adults with T2DM prescribed antiplatelet medication for the secondary prevention of ACS, and the events that impact the resource use and patient utility over the life time of the patient cohort. Markov model was selected instead of a patient level simulation because the patient level simulation models are data demanding, and the events needed to capture are specific. Furthermore, using a Markov model is sufficient to capture the main effect of which antiplatelet treatment is more cost-effective. The model estimated mean costs and effects as hypothetical patients progressed through the model states until they reach an absorbing state (death). Utility gains are measured using quality adjusted life years (QALYs) and for every cycle the patient is alive, since the QALYs that are gained every time a patient is in the non-absorbing state are positive. When a patient reached an ill health state (e.g. bleeding), QALY payoff reduction was based on published literature, representing the impact of illness on overall patient health status. QALYs were selected as an outcome measure, because it could combine the reductions in mortality and morbidity in a single index, and facilitate the comparison of treatments (270). Costs were estimated in GBP using 2016 price levels from the perspective of the NHS, with total cost for every state being estimated by multiplying resource use associated with every state with unit costs obtained from published UK sources. The NHS perspective was selected because in the UK, the most important constraint in decisions about healthcare is that of the NHS budget. The NHS budget constraint is fundamental for setting up the ranges of cost-effectiveness thresholds by NICE to reach any of its decisions (271).

All cost and QALY payoffs were discounted using the HM Treasury's benchmark discounting rate of 3.5%, assuming a positive rate of time preference in relation to all costs and outcomes. Costs and effectiveness of alternative antiplatelet regimens were modelled using a Markov process design. According to Markov chain design, all patients are assumed to move through a series of finite health states until a stopping rule is implemented. This rule could be either the reaching of an absorbing state (death) or a situation where a specific number of patients reach a specific state. The movement of patients through the various states of the Markov chain represents the natural progression of the condition that the patients face (e.g. macrovascular and microvascular complications occurring in adults with T2DM) and the way that the treatment is provided in every state.

The period which the health outcomes and costs occur (analytic horizon) needs to be sufficient to capture differences in cost-effectiveness between alternative treatments. Usually this period is equal to the lifetime of the cohort investigated in the model. This approach (lifetime analytic horizon) was followed in the current model, because an analytic horizon smaller than cohort's lifetime, could provide results which would potentially ignore important outcomes (272). The cycle length selection was driven by the fact that the treatment with DAPT lasted for one year, according to the guidelines for the secondary prevention of ACS. Since the suggested use of DAPT regimens was for a year, an annual cycle length was adopted for the model.

Utilities and costs for the time spent in every state are finally aggregated after the model running and reaching its stopping rule. This modelling method allows for the use of treatment effect results of the different antiplatelet regimens on the several outcomes sourced from the literature. A limitation of the implemented modelling method is that there is no "memory" among state transitions. This means that cost, utility and the probability of transition in a health state is independent of the time spent in that specific state or in previous states. The fact that this modelling method is "memoryless", is usually overcome with the use of temporary ("tunnel") states, which measure the time spent by every patient in each state.

The effect of every antiplatelet regimen in this analysis was assessed via the impact on the probability of developing any cardiovascular event or bleeding. More specifically the events of interest were myocardial infarction (MI), stroke, bleeding, or all cause death. Table 45 provides a summary of the state definitions.

Table 45 States of the decision analytical model and their definition

State	Description
Post-Event	In this state, the patient is assumed to be event free
Non-fatal MI	The state includes a range of ACS conditions, from unstable angina to transmural MI (NSTEMI, STEMI)
Post MI	The state after the MI event (tunnel state)
Non- fatal Stroke	The state includes all stroke events of any type (ischemic, haemorrhagic, transient ischaemic attack), that are not fatal
Post-Stroke	The state after the stroke event (tunnel state)
Bleeding	The state includes internal bleeding events that lead to hospitalisation
Post-Bleeding	The state after the bleeding event (tunnel state)
Death	Death from any cause
ACS: Acute Coronary Syndromes, **MI:** Myocardial Infarction, **NSTEMI:** Non St-Segment Elevation Myocardial Infarction, **STEMI:** St-Segment Elevation Myocardial Infarction	

The cohort in the analysis consisted of adults with T2DM. Those patients, during the time period they live with the condition could develop several macrovascular and microvascular complications which could lead to stroke, MI, renal disease, amputation, blindness and other diabetes related events. The model was structured in such a manner, that only specific selected macrovascular diabetes complications were taken into account (non-fatal stroke, non-fatal MI). The structure represents the clinical pathway that focuses on complications that can be affected by the use of antiplatelet medications in a T2DM population. It did not incorporate other T2DM microvascular and macrovascular complications whose occurrence was not affected by the use of antiplatelet agents. Bleeding events were also incorporated in the model because it was a quite common adverse event caused by the use of antiplatelet medications. The structure is the result of combining elements from the first and the third modelling approach for this model, where diabetic complications had been included, and they were also relevant with the protective effect that antiplatelet medications provide.

Patients entering the model were assumed to be in a steady state where they were already treated for a cardiovascular event (ACS) and they are prescribed one of the three dual antiplatelet combinations or aspirin only. As a result of this assumption all patients were starting in the "post-event" state, where the initial ACS event has already occurred (index event) and patients were receiving antiplatelet medications for the secondary prevention of cardiovascular events. This structure was selected to reflect the research question at hand.

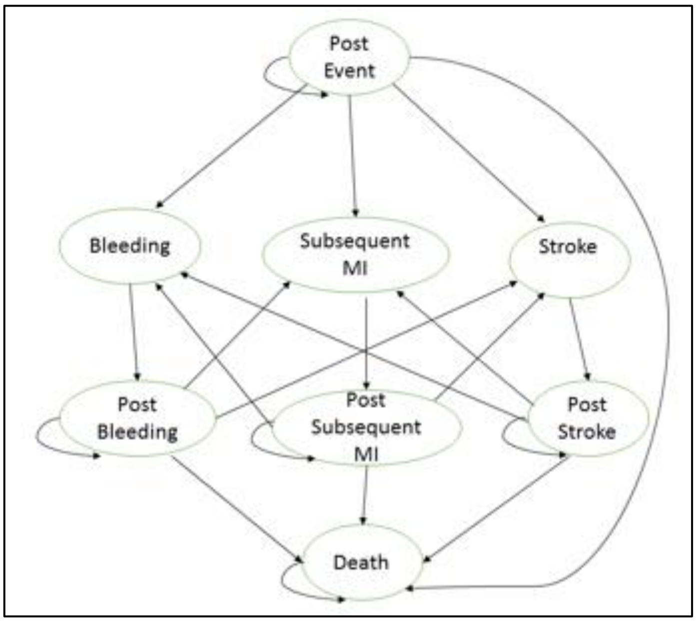
A limitation of the cost-effectiveness models prepared by the manufacturers of prasugrel (103) and ticagrelor (97) was that the patients might have only one macrovascular event and after that event they could not proceed to another state except death, which does not reflect reality and can underestimate the morbidity associated with CV events subsequent to the initial CV event. In order to overcome this limitation of previous model structures, patients in this model, were allowed to transition between macrovascular events and bleeding states. This way, in theory, patients could have multiple macrovascular events or adverse events during the time horizon of the model.

Patients in the model may progress from the steady state (post-event) to "bleeding", "subsequent MI", "stroke", or "all-cause death". The probabilities of progression from "post event" to "subsequent MI", "stroke", and "all-cause death" were estimated using the parameters of the time-to-event models from the UKPDS 82 study (273). For the estimation of the transition probability from post event to "bleeding", the crude incidence rates from the results in Chapter 4 were used. The treatment effect of every antiplatelet regimen was represented by the change in the estimated transition probabilities for every state. Patients that progressed to "bleeding", "subsequent MI", "stroke" states within a cycle were assumed to be treated within that cycle and stay in that state during that cycle. In the next cycle patients could move to another state or stay in the same state.

In a transition model where the states are discrete, the number of patients that move to another state or remain in the same state after each cycle, is recalculated during the end of the cycle based on the transition probabilities for every state. In real life though, patients can progress from one state to another at any time during the cycle. For example, if all patients from the post-event state progress to stroke, and this happens in the end of the cycle (and not at any point during the cycle), this can result in the overestimation of utility and costs in the post event state and thus increased QALY accumulation and increased cost accumulation for that stage. To adjust for these increased accumulations of costs and QALYs in the model, half-cycle correction was applied to all cost and utility values attached to health states. A half payoff was assigned in the first cycle for overestimation adjustment purposes. The half payoff was reassigned in the case where the patient is still alive in the end of the last cycle.

The state transition model that was used in the cost-effectiveness analysis is presented in Figure 14. Table 45 represents all the possible transitions that can occur within the model.

Figure 14 States and transitions of the decision analytical model. All patients start in the post event stage



5.4.2 State transitions

The model consists of two parts: the first includes the transitions from the "post-event" (initial) stage to all the potential outcomes that are covered as presented in ("stroke", "subsequent MI", "bleeding", "all-cause death"), with patients either remaining in the "post-event" state or moving to the outcome states. When patients transition to "stroke", "subsequent MI, or "bleeding", it is assumed to experience the event and in the following cycle, they remain in a maintenance (tunnel) state ("post bleeding", "post subsequent MI", "post stroke") for one or more cycles, and then they either move to another outcome state or in "all-cause death"). Figure 14 presents the states and the progression that can occur in the cost-effectiveness model.

For the various transitions across states, transition probabilities were obtained from the time to event models of the UKPDS 82 study (273), and literature. The assumptions used in the time to event equations of the UKPDS 82 study are explained in section 5.4.2.1

5.4.2.1 Estimation of transition probabilities from the parametric time to event models of UKPDS study

For the MI outcomes, the distribution of time to event models obtained from the UKPDS 82 study was exponential, for stroke it was Weibull and for all cause death outcome the distribution of time to event model was Gompertz (273). In order to estimate transition probabilities, the relationships between survivor function, cumulative hazard functions and transition probabilities were exploited. As a first step, the cumulative hazard function was derived from the survivor function for every model. The time to event models of the UKPDS 82 study were used for the estimation of transition probabilities and had exponential, Weibull, and Gompertz distributions and the procedure was as follows:

For the estimation of transition probabilities from exponential models:

- The survivor function of the exponential distribution is presented in Equation 1 where

$$\boldsymbol{S(t) = e\,xp[-\lambda t]\,(1)}$$

- The cumulative hazard function can be written as

$$\boldsymbol{\Lambda(t) = -ln[S(t)]\ \ (2)}$$

- The transition probabilities can be provided based on the general Equation 3, with $\boldsymbol{tp}$ representing transition probability, $\boldsymbol{u}$ the cycle length that the probability is estimated for and $\boldsymbol{\Lambda(t)}$ representing the cumulative hazard function of the parametric distribution.

$$\boldsymbol{tp(t,u) = 1 - exp[\Lambda(t-u) - \Lambda(t)](3)}$$

- Which for the exponential model can be transformed into

$$\boldsymbol{tp(t,u) = 1 - exp[-\lambda u](4)}$$

The model that was used to derive those transition probabilities was the UKPDS-OM2 time to second MI equation.

For the Weibull models:

The survivor function for the Weibull distribution with $\boldsymbol{k}$ as shape parameter and $\boldsymbol{\lambda}$ as the scale parameter is:

$$\boldsymbol{S(t) = exp\,[-(\frac{t}{\lambda})^{k}](5)}$$

- The cumulative hazard function

$$\boldsymbol{\Lambda(t) = -ln[S(t)]\ (2)}$$

- The Weibull model can be written as

$$\boldsymbol{\Lambda(t) = (1/\lambda^{k})t^{k}\ (7)}$$

- Finally, the transition probabilities derived from the Weibull time to event models can be estimated using the following equation

$$\boldsymbol{tp(t,u) = 1 - exp\big[(1/\lambda^{k})(t-u)^{k} - (1/\lambda^{k})t^{k}\big]\,(8)}$$

For Gompertz models:

The general equation, as previously mentioned, for deriving transition probabilities is as follows

$$\boldsymbol{tp(t,u) = 1 - \mathbf{exp}[\Lambda(t-u) - \Lambda(t)]\,(3)}$$

With $\boldsymbol{tp}$ representing transition probability, $\boldsymbol{u}$ the cycle length that the probability is estimated for, $\boldsymbol{t}$ the time point when the transition probability is estimated and $\boldsymbol{\Lambda(t)}$ representing the cumulative hazard function of the parametric distribution

- For the Gompertz distribution, the survivor function is

$$\boldsymbol{S(t) = exp[\,-\lambda\gamma^{-1}(e^{\gamma\tau} - 1)]\ (9)}$$

- The cumulative hazard function is

$$\boldsymbol{\Lambda(t) = -ln[S(t)]\,(2)}$$

- The Gompertz distribution can be translated as

$$\boldsymbol{\Lambda(t) = \lambda\gamma^{-1}(e^{\gamma\tau} - 1)(10)}$$

- By using equation 10 in equation 3

$$\boldsymbol{tp(t,u) = 1 - exp[\lambda\gamma^{-1}\big(e^{\gamma(\tau-u)} - 1\big) - \lambda\gamma^{-1}(e^{\gamma\tau} - 1)]}$$

- Which can be rearranged into equation 11

$$\boldsymbol{tp(t,u) = 1 - exp\big[\lambda\gamma^{-1}\big(e^{\gamma(\tau-u)} - e^{\gamma\tau}\big)\big](11)}$$

Where $\boldsymbol{\lambda = exp\{x\beta\}}$ and $\boldsymbol{\gamma}$ is the ancillary parameter. Both $\boldsymbol{\lambda}$ and $\boldsymbol{\gamma}$ values were the ones reported in the Gompertz time to event models of the UKPDS 82 study

5.4.2.2 Assumptions about the patient characteristics in the time to event equations, about characteristics in the cost equations, and about treatment effect

In the UKPDS 82 study (273), the long-term progression of diabetes, is calculated using time to event equations that estimate the probability of patients suffering from microvascular or macrovascular complications, or other complications such as blindness and leg amputation. The equations of the UKPDS 82 study, contained covariates about age of diabetes diagnosis, current age, duration of diabetes, variables for gender, Afro-Caribbean ethnicity, Indian ethnicity, smoking status, body mass index, categorical variables for BMI classification, level of Hba1c, systolic blood pressure, high and low density lipoprotein cholesterol (HDL, LDL), presence of micro or macro albuminuria, heart rate, estimated glomerular filtration rate (eGFR), presence of atrial fibrillation (AF), presence of peripheral vascular disease (PVD), white blood cell count, and binary variables for the presence of first amputation, the presence of second amputation, and the history of amputation. Additional variables that indicated whether the patients had a macrovascular complication (myocardial infarction, stroke, ischaemic heart disease (IHD), congestive heart failure (CHF), ulcer, blindness, renal failure) for the first or second time and history of other macrovascular complications first or second presence and the history of other macrovascular complications were also included in the time to event models.

For the estimation of transition probabilities in the model of this study it was attempted to In the case where multiple variables had to be taken into account, then transition probabilities had to be generated for every subgroup that those variables defined, and a weighted transition probability with weights from every subgroup to be estimated, and this would result in an impracticably large number of subgroups. Therefore, in this model, the patients were assumed to have no previous history of amputations, renal failure, blindness, AF, PVD, IHD or CHF or albuminuria, they were non-smokers, they were 65 years old, they had diabetes for 10 years, and the age of diabetes diagnosis was 55 years. The assumptions about age at treatment initiation, duration of diabetes, and diagnosis of diabetes were selected so that they would reflect the characteristics of the cohort presented in Chapter 4. For variables that were continuous and contained spline values (eGFR, LDL) a value equal to the spline point was used in the time to event equations, in order to minimise the impact of that variable in the time to event equation. Furthermore, it was assumed that patients had controlled blood pressure and cholesterol levels.

It was assumed that the cohort consisted of 62.3% male and 37.7% female patients, and this assumption is used in transition probabilities estimation and in the estimation of cost in every state. The gender split in the Markov model is that same as that in the total cohort of the study in Chapter 4 and was selected to reflect the characteristics of that cohort. Table 46 presents the variables of the UKPDS models and the assumptions about their values that were used.

Table 46 Variables used in prediction of diabetes complications and death

Covariate label	**Definitions/ Values**	**Transformat-ion applied**	**Assumption s made**
AGE DIAG	Age in years at diagnosis of diabetes	None	55
CURR AGE	Current age in years	None	65
YEAR	Duration of diabetes (years)	None	10
FEMALE	1 for female; 0 for male	None	1/0

Covariate label	Definitions/ Values	Transformat-ion applied	Assumptions made
INDIAN	1 for Asian Indian ethnicity; 0 otherwise	None	0
SMOKER	1 for current smoker; 0 otherwise	None	0
BMI CAT1	Body mass index < 18.5m/kg2	None	0
BMI CAT3	Body mass index > 25m/kg2	None	1
HbA1C	HbA1c (%)	None	6.5
SBP	Systolic blood pressure (mm Hg)	÷ 10	130
HDL	High density lipoprotein cholesterol (mmol/l)	x 10	1
LDL	Low density lipoprotein cholesterol (mmol/l)	x 10	3
HEART R	Heart rate (beats per minute) determined from inspiration/expiration RR on ECG	÷ 10	80
eGFR<60 eGFR>60	Estimated glomerular filtration rate (ml/min/1.73m2) from Modification of Diet in Renal Disease (MDRD) formula	÷ 10	60
MIC ALB	Presence of micro- or macro-albuminuria. 1 for urine albumin ≥50mg/l; 0 otherwise	None	0
ATFIB	1 for atrial fibrillation; 0 otherwise. Defined from Minnesota codes 831 and 833	None	0
PVD	1 for peripheral vascular disease; 0 otherwise. Defined from presence of intermittent claudication or ankle brachial pressure index < 0.9	None	0
WBC	White blood cell count	None	7
AMP2 EVENTa	1 for second amputation; 0 otherwise	None	0
AMP HIST a	1 for history of amputation; 0 otherwise	None	0
MI	1 for history of MI; 0 otherwise	None	1

[a] equivalent format for 1st and 2nd events and histories for other complications (MI =myocardial infarction, STROKE =stroke, IHD=ischaemic heart disease, CHF=congestive heart failure, ULCER= ulcer, BLIND=blindness, RENAL=renal failure)

Assumptions about the costs of the model states

In their study, Alva et al (274) provided models that allow the calculation of hospitalisation costs and primary care consultation (non-hospitalisation costs). The reason for using this study was due to the fact that the research was carried out for a UK population, from a long-term study of diabetes population (UKPDS), and it included diabetic comorbidities that are relevant to the model states. The models estimated by Alva et al. allowed for flexibility in the cost estimation because the user can adjust for patient demographic characteristics (age, gender) and history of complications such as stroke, myocardial infarction and amputation. The assumptions about age and gender split were used as well in the cost equations from the Alva et al study.

Assumptions for the treatment effect of antiplatelet medications.

In Chapter 2, it was mentioned that there is still no clear consensus about the duration that patients should be prescribed with antiplatelet medications. Even though in clinical guidelines it is suggested that duration of antiplatelet treatment should be one year, and then an evaluation for further continuation of treatment afterwards should be carried out, there is still research about the optimal duration of antiplatelet therapy.

In this model, it was assumed that patients were prescribed antiplatelet medications during the first year after the initial ACS event. This assumption was made after consulting with a general practitioner (Prof. Tony Avery). After the first year of the event, it is assumed that all patients revert to the prescription of aspirin alone as a means of antiplatelet therapy. In order to implement this assumption, sets of probabilities that indicated the treatment effect of a specific DAPT regimen during the first cycle were used. In the subsequent cycles all patients were assumed to revert to aspirin, and for that reason, patients across all the treatment arms had the same set of transition probabilities. The same was the case for patients on aspirin only. Furthermore, the results of the previous clinical trials of prasugrel and ticagrelor were also used for the generation of transition probabilities in the current model, allowing for the indirect comparison of prasugrel and ticagrelor. Those results were derived from the trials which were carried out in the general population. The sub studies of those trials were also publishing results, but they were not used, because they were ad hoc analyses, and they were not set up beforehand to identify treatment effect of DAPT therapies in T2DM populations. Furthermore, the reasons for not using the result from the time to event analysis in Chapter 4 are mentioned in section 4.3.4.1

5.4.2.3 Transition probabilities

Figure 15 summarises the sources of transition probabilities.

From "Post-event" to "Stroke", "Bleeding", "Subsequent MI", "All-cause death"

The transition probabilities from "Post-event" to "Stroke", to "Subsequent MI", and to "All-cause death" were estimated using the UKPDS 82 study time to event equations, with hazard ratios attached so that every treatment arm has its own transition probability set. For the "Post-event" to "Bleeding" the crude incidence rates from the CPRD study were used. With the use of the literature (74, 75), transition probabilities are estimated for the different treatment arms of the model.

Remain in "Post-Event" state

The probability of remaining in this state is equal to 1 minus the sum of probabilities of transitioning to the other states ("Stroke", "Bleeding", "Subsequent MI", and "All-cause death").

From "Subsequent MI" to "Bleeding", "Stroke", "All-cause death"

It was assumed that the probability of bleeding when a patient was in the subsequent MI state was the same as in the "Post-Event state". The "time to stroke" equation from the UKPDS 82 study (273) was used to estimate this transition probability, and a history of index MI was used as an explanatory variable. The transition probability from "Subsequent MI" to "All-cause death" was estimated using from the UKPDS 82 study the equation that estimated the probability of death after experiencing an MI, with history of MI included as an explanatory variable in the equation.

Remain in "Subsequent MI" state

Patients who enter the subsequent MI state, during the following cycle, they remain in a maintenance post-subsequent MI state (tunnel state), in order to account for the fact that after being treated from MI, patients will not accrue the same costs as when they entered the "Subsequent MI" state during the following cycles. From that maintenance state, patients can either remain in that state, or transition to other states (Stroke, Bleeding, All-cause death). The probability of staying in this state was complementary to the rest of the states (Stroke, Bleeding, All-cause death)

From "Stroke" to "All-cause death", "Bleeding", "Subsequent MI"

For the estimation of transition probability from stroke to "All-cause death", the estimates of a time to event model from the UKPDS 82 study were used. For the aspirin-prasugrel and the aspirin-ticagrelor groups the hazard ratios of CVD causes, non-fatal MI, non-fatal stroke or rehospitalisation for ischaemia were used (74). For the estimation of "Stroke" to "Bleeding" probability, the study of Coleman (275) was used, and it was selected because it evaluated the use of aspirin-clopidogrel for stroke prevention. By having the information about aspirin-clopidogrel and combining it with the result of other studies that compared aspirin-clopidogrel versus other antiplatelet agents, allowed to have transition probabilities for the rest of the treatment arms. In the same study, the annual baseline rate of major haemorrhage that is not intracranial was used to estimate the transition from stroke to bleeding. In order to estimate the "Stroke" to Subsequent MI" transition probability, the time to event models from the UKPDS 82 (273) study were used.

Remain in "Stroke" state

It is assumed that patients are treated for an acute stroke event the first time they entered that state, and afterwards they remained in a maintenance post-stroke state unless they experienced another event, in which case they transitioned to that state. This assumption is made in order to depict that patients suffered a stroke during the cycle they entered the stroke state, and in the next cycle they were recovering from the stroke event. Afterwards they either remained in this post-stroke state or experience another event (Bleeding, subsequent MI, or all cause death)

Remain in "Bleeding" state

The remaining in bleeding state is expressed with a state in which patients remain in a maintenance post-bleeding state. In this state, patients have recovered from the bleeding event and they either stay for multiple cycles, or they transition to other states ("Stroke", "Subsequent MI", "All-cause death"). The probability of remaining in bleeding state was equal to the net of the sum of transition to the rest of the states ("Stroke", "Subsequent MI", "All-cause death").

From "Bleeding" to "Subsequent MI", "Stroke", "All-cause death"

The estimation of transition probability of Bleeding to All-cause death was sourced from the study of Wisloff, which compared the cost-effectiveness of clopidogrel, ticagrelor, and prasugrel (104). From that source, the 6-month probability of death after bleeding was transformed into an annual probability. This probability remains constant over the years.

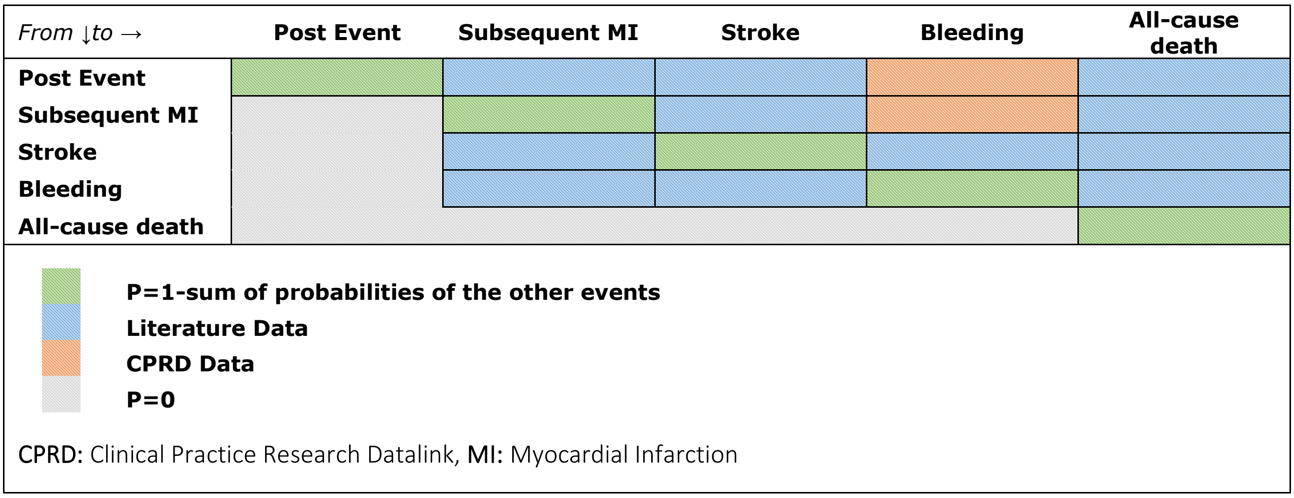
This transition probability from "Bleeding" to "Subsequent MI" was obtained from the Coleman study (275) and it was assumed that the probability was the same for all treatment groups.

The probability of patients experiencing a stroke after being in the bleeding state was obtained from Coleman (275). The study was selected because it evaluated the use of aspirin-clopidogrel for stroke prevention. Based on the findings of the meta-analysis from Gouya et al. (276), where they mention that other antiplatelet medications such as ticagrelor and prasugrel do not provide any further protective effect from stroke compared to clopidogrel, the assumption was made that the probability of stroke from the bleeding state was equal across all treatment groups.

Use of the UKPDS 82 equations to estimate the probability of All-cause death

In the model, the death state represents all-cause death, meaning that any death occurring, irrespective of its type (natural causes, cardiovascular causes, any other reason) is represented in that state. The transition to the death state was assumed to happen from every state in the model. The probability of all-cause death from the "event free" state was estimated in such a manner that reflects the probability of death during the first year after the event and afterwards, in patients who suffer from T2DM. During the first year after hospitalisation for an ACS event (while patients remain in the post-event state) the probability of death increases, and then it reduces to lower levels after the first year. In order to implement this variability in the risk of death in the model, the two survival equations from the UKPDS 82 study (273) were used: the logistic model that estimated the probability of death during the first year after an ACS event, and the Gompertz model that estimated the probability of death in years with history but no events was used to estimate the probability of death in subsequent years

Figure 15 Description of data sources used to populate state transition probabilities



Sources of treatment effect

Several hazard ratios were used in order to estimate transition probabilities for the aspirin-ticagrelor and the aspirin-prasugrel group. The literature that compared aspirin-clopidogrel versus aspirin only was used for the estimation of transition probabilities during the cycles where patients in the model revert to aspirin monotherapy.

Table 47 Hazard ratios used in the derivation of transition probabilities across the treatment groups

Hazard ratio	Value (95% CI)	Source
Aspirin-Prasugrel Vs Aspirin-Clopidogrel		
Any cause death	0.95 (0.78-1.16)	(76)
Death from cardiovascular causes	0.89 (0.7-1.12)	(104)
Bleeding	1.03 (0.93-1.15)	(104)
Non-fatal MI	0.76 (0.67-0.85)	(76)

Hazard ratio	Value (95% CI)	Source
Non-fatal Stroke	0.98 (0.67-1.42)	(277)
Aspirin-Ticagrelor Vs Aspirin-Clopidogrel		
Any cause death	0.78 (0.69-0.89)	(75)
Death from cardiovascular causes	0.79 (0.69-0.91)	(104)
Bleeding	1.32 (1.03-1.68)	(104)
Non-fatal MI	0.84 (0.75-0.95)	(104)
Non-fatal Stroke	1.09 (0.80-1.49)	(97)
Aspirin-Clopidogrel vs Aspirin only		
Any cause death	0.99(0.86-1.14)	(71)
Death from cardiovascular causes	0.93(0.79-1.08)	(69)
Bleeding	1.25(0.97-1.61)	(71)
Non-fatal MI	0.77(0.67-0.89)	(69)
Non-fatal Stroke	0.79(0.64-0.98)	(71)
CI: Confidence Intervals, **MI:** Myocardial Infarction		

There were two death Hazard ratios, one for all-cause death and one for death from cardiovascular causes. The second hazard ratio was used during transitions such as "Stroke" to "All-cause death". Table 47 presents the hazard ratios and the literature where this information was sourced. All the treatment effects were sourced from studies that were carried out in general populations.

Model validation

Validity of the model was assessed by the members of the supervision team (Prof. Tony Avery, Prof. Rachel Elliott, Dr Lukasz Tanajewski) and the structure was based on conceptual models that evaluated the cost-effectiveness of antiplatelet medications. The input data were sourced by the relevant literature. The Advishe checklist provides further details about the validation checks.

5.4.3 Health state utility tariffs

The utility values were used to generate QALYs. QALYs were calculated by multiplying the number of years alive with utility weights ranging from 0 (dead) to 1 (full health). QALY weights for every health state in the model were sourced from studies that reported the health status of adults with T2DM on a scale between 0-1. The studies that were preferred were those that reported the health utility based on preference-based health status measures, such as EQ-5D (278, 279).

The baseline utility weight in the post event state was based on the findings of the UKPDS 62 study. The utility weights were generated using the EuroQOL EQ-5D instrument in UKPDS patients with T2DM (280). In Clarke et al., adults from the UKPDS that suffer from T2DM and are free of microvascular and macrovascular complications have an average utility value of 0.77 (SD: 0.27). The cohort entering the model in this study comprises adults with T2DM that have already experienced an MI. The utility decrement of an MI event available from the same study [-0.055, (95% CI: -0.067, -0.042)] was used and it was implemented in the initial post-event stage. For the health states of "Stroke" and "Subsequent MI" it was assumed that the utility weights were related to the utility weights of the post-event state, and that the impact of utility decrements was additive. For the "Stroke" state, the utility value that was attached was equal to that of post-event state after implementing the utility decrement of a stroke event that was available from the UKPDS 62 study [-0.164, (95% CI: -0.222, -0.105)]. For the bleeding state there was not any information available from the UKPDS-82 study. Therefore, an alternative assumption was made. The utility decrement for a bleeding event was estimated based on the assumption of Wechowski et al (281). In that study, authors assumed that a bleeding event resulted in 25% decrement of utility for a disutility period lasting two weeks. This assumption was adopted by the prasugrel manufacturer in their submission to NICE (108) and the prasugrel cost-effectiveness model for the Spanish health care setting (102). Therefore, the overall utility decrement for a bleeding event was -0.00697 and assumed to be the same across each treatment arm.

Table 48 Utility tariffs and decrements used in the model

State	**Value (SD),[95% CI]**	**Source***
Well	0.77(0.27)	(280)
Utility Decrements		
MI decrement	-0.055 (-0.067, -0.042)	(280)
Stroke decrement	-0.164 (-0.222, -0.105)	(280)
Bleeding decrement	-0.00697†	(281)
***** Full references are provided at the references list † CI was not reported CI: Confidence Intervals, MI: Myocardial Infarction		

5.4.4 Cost incurred of model states

The total costs in each stage of the model reflect the secondary prevention of ACS (antiplatelet costs), primary and secondary care management of subsequent events (stroke and MI) and adverse events associated with DAPT (bleeding). Costs in the model were estimated for every state, and included the annual costs of antiplatelet medication prescription, and the costs of a potential hospitalisation, and the primary care consultation costs. For the estimation of annual prescription costs, prices were retrieved from the BNF. The hospitalisation costs and the primary care consultation costs, were estimated using the cost estimation models from the study of Alva et al (274). This study was selected because it was recent (published in 2015), and it was investigating the costs incurred in patients from the UKPDS study, representing the UK treatment practice. For that reason, the study of Alva was considered relevant for the population in this Markov model (patients with T2DM in United Kingdom prescribed with antiplatelets). In the study of Alva et al, the hospitalisation costs were estimated based on the admissions that the patients had, and the primary care consultation costs (non-hospitalisation costs) were including general practice attendances and check-ups, but not costs of laboratory tests and costs of prescriptions. In the post-event state, it was assumed that patients incur only prescription costs and primary care consultation costs, because it is the state where they have recovered from the index ACS event and are free of events that could lead them to hospitalisation. For the bleeding state, the stroke state and the subsequent MI state, there were two sets of cost estimates, one set used during the cycle when the event occurred, and a second set for the subsequent cycles. The only difference between those two sets of costs was that the second set did not include any hospitalisation costs, because it was used in states where patients were recovering from the hospitalisation event in the community, with primary care support. When a patient entered any of the bleeding state, the stroke state or the subsequent MI state, the first set of cost estimates was used in order to include the cost of hospitalisation during entering the state. In the next cycle, the patient was entering in states (post bleeding, post subsequent MI, post stroke) where he incurred only maintenance costs, and these in these states the second cost set was used. Table 49 shows the annual costs for every antiplatelet medication and Table 50 the annual medication costs that are incurred by patients depending the antiplatelet regimens they follow.

Table 49 Annual costs of antiplatelet medications

Medications			**Source**
Aspirin	**Description**	Aspirin 75mg tablets	BNF online accessed 10/June/2017
	MAH	AAH Pharmaceuticals Ltd	
	Daily Dose	once daily	
	Annual costs/£	14.69	
Clopidogrel	**Description**	Clopidogrel 75mg tablets	BNF online accessed 10/June/2017
	MAH	AAH Pharmaceuticals Ltd	
	Daily Dose	once daily	
	Annual costs/£	17.29	
Ticagrelor	**Description**	Brilique® 60 or 90 mg tablets	BNF online accessed 10/June/2017
	MAH	AstraZeneca UK Ltd	
	Daily Dose	twice daily	
	Annual costs/£	709.80	
Prasugrel	**Description**	Efient® 5 or 10 mg tablets	BNF online accessed 10/June/2017
	MAH	Eli Lilly and Company Ltd	
	Daily Dose	once daily	
	Annual costs/£	618.28	
BNF: British National Formulary, **MAH:** Marketing Authorisation Holder			

Table 50 Cost of medication and treatment

Type of cost	**Annual costs***	**Source****
Regimen costs		
Asp only	14.69	BNF online (accessed 10/June/2017)
Asp-Clop	31.98	BNF online (accessed 10/June/2017)
Asp-Pras	632.97	BNF online (accessed 10/June/2017)

Type of cost	Annual costs*	Source**
Asp-Tica	724.49	BNF online (accessed 10/June/2017)
Hospitalisation costs		
Non-fatal MI	8394.80	(274)
Non-fatal stroke	11682.79	(274)
Bleeding	2457.58	(282)
Non hospitalisation costs		
Event free	752.58	(274)
Non-Fatal MI	1182.84	(274)
Non-Fatal MI maintenance	873.81	(274)
Non-Fatal stroke	1311.28	(274)
Non-Fatal stroke maintenance	976.38	(274)
Bleeding	1135.75	(282)

*****Standard deviation of costs assumed to be equal to the mean **Full references are provided at the references list
Asp-Clop: Aspirin-Clopidogrel dual therapy, **Asp-Pras:** Aspirin-Prasugrel dual therapy, **Asp-Tica:** Aspirin-Ticagrelor dual therapy, **BNF:** British National Formulary, **MI:** Myocardial Infarction

5.5 Base case analysis

In the base case economic evaluation, a lifetime horizon was assumed for the model. A discount rate of 3.5% for both costs and outcomes was assumed. During the estimation of mean costs and QALYs across treatments, four possible alternatives occur: 1) Higher costs and lower QALYs for the intervention (aspirin-prasugrel, aspirin-ticagrelor) versus standard care (aspirin-clopidogrel); Intervention is dominated. 2) Lower costs and higher QALYs for the intervention versus standard care Intervention dominated standard care. 3) The intervention costs more and generates more QALYs than standard care. 4) The intervention is less costly and accrues less QALYs than standard care. In the case that events 3 or 4 occurred (that is no scenarios of dominance), then pairwise incremental analyses had to be carried out in order of effectiveness using the incremental cost-effectiveness ratio (ICER), which is the ratio of the differential between the accumulated costs and QALYs for every pair of treatments. For example, if aspirin-clopidogrel, aspirin - prasugrel, and aspirin-ticagrelor are in ascending order of QALYs generated, then the head to head comparisons are aspirin-prasugrel versus aspirin-clopidogrel, and aspirin - ticagrelor versus aspirin-prasugrel. In cases where events 1 or 2 happened costs and outcomes were presented separately.

5.6 Sensitivity analysis in deterministic model

The expected value analysis was carried out to investigate the cost per unit of outcome across the treatments in order to allow decision makers select the optimal strategy.

The analysis outlined above assumed that all model input parameters were represented with the use of expected values. This way, point estimates of ICERs were obtained through deterministic analysis. The investigation of variables that would affect the ICER estimate was conducted with the use of one-way sensitivity analyses. Parameters that were considered to have an impact on costs per QALY gained and therefore in ICER rankings, were varied, and the results were compared with the base case. If the change in the parameter changed the conclusions made during the base case, then this parameter was considered to have impact in the overall result.

The uncertainty in the model parameters was investigated in three areas of the model's input parameters: effect of treatment in the probability of death (via the hazard ratios sourced from the literature), treatment costs and utility weight of the well state. The treatment effect in the probability of death was selected because during the first year, the probability of death was far higher than during the rest of the years. Furthermore, it was the only period where the effect of medications manifests. The utility weight in the well state is the anchor value for the rest of the utility tariffs in the model states, therefore any change in that value could have smaller or higher impact in the QALYs accrued during the lifetime horizon.

5.7 Probabilistic sensitivity analysis-methods

A probabilistic sensitivity analysis was performed in order to assess the overall impact of uncertainty around input parameters. It was assumed that all input parameters were associated with some level of uncertainty and distributional assumptions about the transition probabilities, costs and utility values were made (see sections 5.8.1-5.8.3). The uncertainty around the mean for ICER values was represented by estimating the 2.5th and the 97.5th percentile of ICER. The incremental costs and outcomes were plotted on cost-effectiveness planes, where points in SE quadrant are considered always cost-effective. Points that are placed in NW quadrant are considered always non cost-effective. The points that are in NE and SW quadrants can be considered either cost or non cost-effective, depending on the maximum amount of monetary unit per unit change of outcome that a policy maker is willing to pay.

In order to represent the uncertainty that a decision maker is facing during the selection of an intervention, a cost-effectiveness acceptability curve (CEAC) was generated. The curve presents the probability of an intervention being cost-effective for different levels of a decision-maker's ceiling willingness-to-pay (WTP). The National Institute for Health and Care Excellence generally accepts interventions as cost-effective when the cost per QALY is below £20000 and when cost-effectiveness ranges between £20000 and £30000, interventions are cost-effective under specific circumstances.

5.7.1 Probabilities

For the probabilistic sensitivity analysis, all transition probabilities were modelled using the Dirichlet distribution. This distribution can be considered as the most appropriate for data that are multinomial. In the case of the current model, patients can either progress from one state to others, or remain in the same state. These transitions have data that are multinomial with multiple categories. The Dirichlet distribution is a generalisation of the beta distribution. This way, probabilities are restricted between 0 and 1, and the number of parameters that are needed to inform the distribution is equal to the number of the multiple categories of events that are modelled.

All transition probabilities were assigned distribution parameters. The alpha values needed to inform the Dirichlet distribution were based on the total number of patients in the UKPDS 82 outcome study that experienced their first MI, which were in total 1014. For every probability $\pi 1, \pi 2, \ldots, \pi k$ that represents an individual transition, the Dirichlet distribution of is as follows :

$$\boldsymbol{\pi \sim Dirichlet(a_1, a_2, \dots, a_k)}$$

$$\boldsymbol{p(\pi) = \frac{\Gamma(\alpha_1 + \dots + \alpha_\kappa) * (\pi_1^{[\alpha_1 - 1]} \dots \pi_\kappa^{[\alpha_\kappa - 1]})}{\Gamma(\alpha_1) \dots \Gamma(\alpha_\kappa)}}$$

Where $\boldsymbol{\alpha_1, \dots, \alpha_\kappa > 0; \sum_{j=1}^{k} \pi_j = 1}$

5.7.2 Costs

The costs in every state were assumed to follow the gamma distribution. This type of distribution allows for modelling variables that are typically strongly positively skewed, as in the case of healthcare costs. The costs that were derived from the NHS reference cost schedule are reported with lower and upper quartile estimates.

Based on those estimates and their 95% CI the standard errors were derived to calculate the gamma distribution parameters. Other costs that were reported without confidence intervals or ranges, like the medication costs, were assumed to have standard errors equal to the mean(262)(283), and based on this assumption the gamma parameters were fitted.

5.7.3 Utilities

As in the case with probabilities, utility values range only between zero and one. Therefore, the beta distribution was selected as the most appropriate distribution to model the uncertainty around utility values. The utility tariffs from the study of Clarke (259)(280), which were representative of a UK population with diabetes, and their reported means and standard deviations were used. Based on the literature values the $\boldsymbol{a}$ and $\boldsymbol{\beta}$ parameters of the beta distribution were calculated with the use of the following equations:

$$\boldsymbol{a = \frac{\mu^2(1-\mu)}{\sigma^2 - \mu}}$$

$$\boldsymbol{\beta = \frac{\mu(1-\mu)^2}{\sigma^2 - \mu}}$$

With $\boldsymbol{\mu}$ equal to the mean value and $\boldsymbol{\sigma^2}$the variance.

5.8 Results

5.8.1 Base case analysis

Table 51 summarises the lifetime costs and QALYs generated by each of the treatment arms. The treatment combination of aspirin-ticagrelor generated the most QALYs per patient over the lifetime horizon of the model at the highest mean cost per patient, whereas the aspirin-only treatment provided the lowest QALYs and the lowest cost per patient.

From

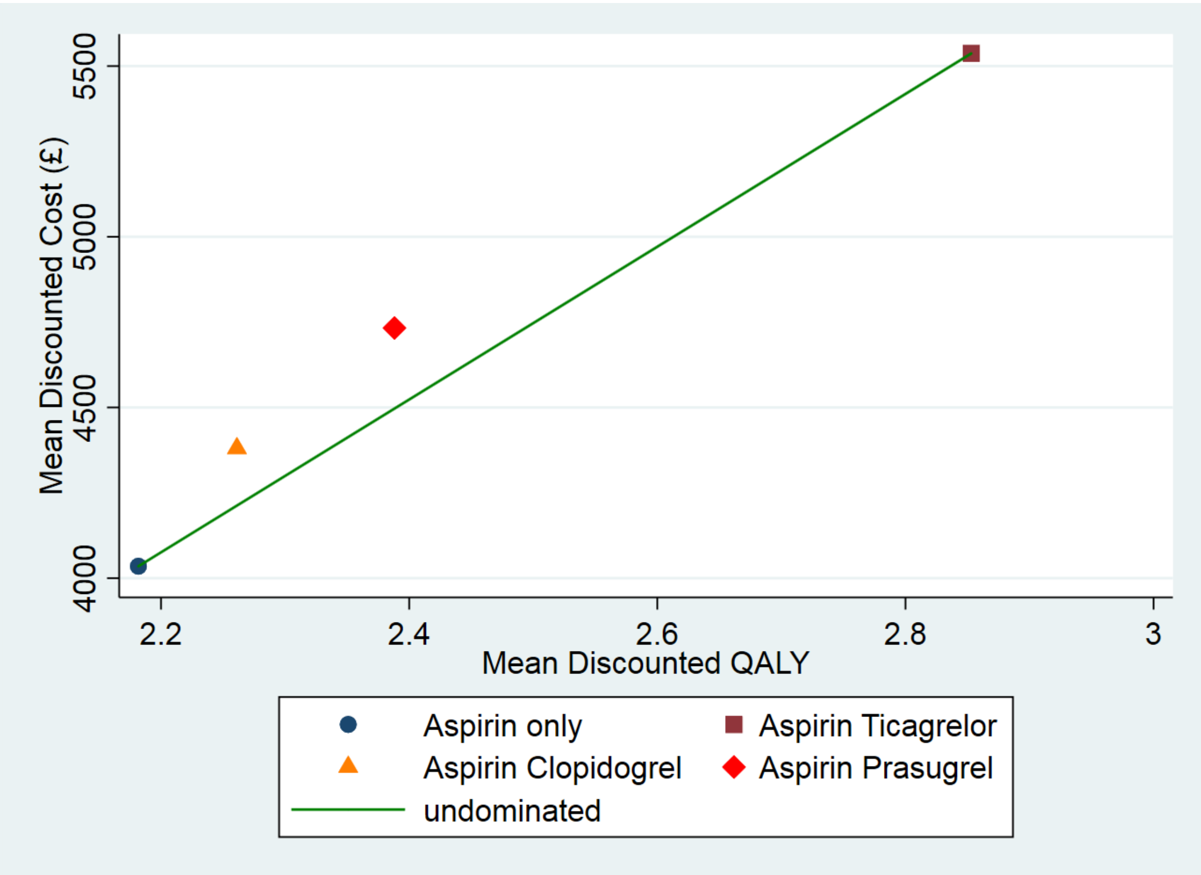
Figure 16 we see that the cost-effectiveness frontier begins with the aspirin-only treatment (the least effective and the least costly option) and ends in the aspirin-ticagrelor treatment. The aspirin-prasugrel and the aspirin-clopidogrel treatments are extendedly dominated.

Table 51 Lifetime costs and effects

Strategy	Lifetime cost (£)	Incremental cost(£)	Total QALYs	QALYs gained	ICER
Asp-only	4034.93	N/A	2.18	N/A	N/A
Asp-Clop*	4380.27	N/A	2.26	N/A	-
Asp-Pras*	4732.99	N/A	2.39	N/A	-
Asp-Tica	5537.24	1502.31	2.85	0.67	2237.99
Asp-Clop: Aspirin-Clopidogrel dual therapy, **Asp-Pras:** Aspirin-Prasugrel dual therapy, **Asp-Tica:** Aspirin-Ticagrelor dual therapy**, ICER:** Incremental Cost-Effectiveness Ratio, **N/A:** Not applicable, **QALY:** Quality Adjusted Life Year ***Extendedly dominated , removed from ICER calculation					

In terms of expected values, the aspirin-ticagrelor treatment was the most effective in terms of QALYs over the lifetime horizon. It yielded 0.67 QALYs per patient more than aspirin only. Aspirin-clopidogrel and aspirin-prasugrel were extendedly dominated and were excluded from the calculateion of ICER.

Figure 16 Mean discounted values of costs and QALYs accumulated over lifetime horizon for every treatment



5.8.2 Sensitivity analysis

The impact of changing the values of key variables in the model on the ICER for every treatment was assessed with the help of several sensitivity analyses.

The following table presents the results of one-way sensitivity analysis for several different scenarios. All the parameters were changed in to the lowest and their upper bound of their 95% CI, as suggestd by Briggs et al (284) The parameters that had impact in the cost-effectiveness rankings derived from the model, is the change in probability of death during the first year for patients on ticagrelor, and the change in the same probability for patients on prasugrel. The setting of hazard ratio of death for prasugrel patients to 0.78 (lowest CI bound) made equal the probabilities of death during the first year for patients on prasugrel and patients on ticagrelor. This change resulted in prasugrel being the most cost-effective treatment. When the hazard ratio of death for ticagrelor patients was varied according to its 95% CI limits, ticagrelor remained the most cost-effective option.

Table 52 Sensitivity analysis cases and the impact on costs, effectiveness and ICER

Sensitivity analysis	**Strategy**	**Cost**	**Incr. Cost**	**Effectiveness**	**Incr. Effectiveness**	**ICER**
Base case						
	Asp-only	4034.93	N/A	2.18	N/A	N/A
	Asp-Clop*	4380.27	N/A	2.26	N/A	-
	Asp-Pras*	4732.99	N/A	2.39	N/A	-
	Asp-Tica	5537.24	1502.31	2.85	0.67	2237.99
Discount rate						
2.95%	**Asp-only**	4171.15	N/A	2.25	N/A	N/A
	Asp-Clop*	4536.48	N/A	2.34	N/A	-
	Asp-Pras*	4890.51	N/A	2.47	N/A	-
	Asp-Tica	5728.49	1557.34	2.95	0.70	2224.77
4.01%	**Asp-only**	3918.84	N/A	2.12	N/A	N/A
	Asp-Clop*	4247.18	N/A	2.20	N/A	-
	Asp-Pras*	4598.78	N/A	2.32	N/A	-
	Asp-Tica	5374.44	1455.60	2.77	0.65	2239.38
Probability of death during the first year for ticagrelor patients						
HR=0.69	**Asp-only**	4034.93	N/A	2.18	N/A	N/A
	Asp-Clop*	4380.27	N/A	2.26	N/A	-
	Asp-Pras*	4732.99	N/A	2.39	N/A	-
	Asp-Tica	6017.14	1982.21	3.12	0.94	2108.73
HR=0.89	**Asp-only**	4034.93	N/A	2.18	N/A	N/A
	Asp-Clop*	4380.27	N/A	2.26	N/A	-
	Asp-Pras*	4732.99	N/A	2.39	N/A	-
	Asp-Tica	5010.26	975.33	2.56	0.38	2566.65
Probability of death during the first year for prasugrel patients						
HR=0.78	**Asp-only**	4034.93	N/A	2.18	N/A	N/A
	Asp-Clop*	4380.27	N/A	2.26	N/A	-
	Asp-Pras*	5528.00	N/A	2.83	N/A	-
	Asp-Tica	5537.24	1502.31	2.85	0.67	2237.99
HR=1.16	**Asp-Pras**	3931.38	N/A	1.94	N/A	N/A
	Asp-only*	4034.93	N/A	2.18	N/A	-
	Asp-Clop*	4380.27	N/A	2.26	N/A	-
	Asp-Tica	5537.24	1605.86	2.85	0.91	1764.68
Utility in the well state						
0.761	**Asp-only**	4034.93	N/A	2.15	N/A	N/A
	Asp-Clop*	4380.27	N/A	2.23	N/A	-
	Asp-Pras*	4732.99	N/A	2.36	N/A	-
	Asp-Tica	5537.24	1502.31	2.82	0.67	2237.99
0.779	**Asp-only**	4034.93	N/A	2.21	N/A	N/A
	Asp-Clop*	4380.27	N/A	2.29	N/A	-
	Asp-Pras*	4732.99	N/A	2.42	N/A	-

Sensitivity analysis	Strategy	Cost	Incr. Cost	Effectiveness	Incr. Effectiveness	ICER
	Asp-Tica	5537.24	1502.31	2.89	0.68	2209.28
Asp-Clop: Aspirin-Clopidogrel dual therapy, **Asp-Pras:** Aspirin-Prasugrel dual therapy, **Asp-Tica:** Aspirin-Ticagrelor dual therapy**, ICER:** Incremental Cost-Effectiveness Ratio, **N/A:** Not applicable, **QALY:** Quality Adjusted Life Year *****Extendedly dominated , removed from ICER calculation						

5.8.3 Probabilistic sensitivity analysis

In order to demonstrate the effect of parametric uncertainty on ICERs, estimates of incremental costs and incremental QALYs were presented in cost-effectiveness planes. Using the results of expected values and costs from the PSA, the aspirin-ticagrelor treatment generated more QALYs [0.67;95% CI:0.05 to 1.22] compared with aspirin only and costs [£1459.96; 95% CI: -5797.66 to 10056.77] over the lifetime horizon. Aspirin-prasugrel and aspirin-clopidogrel were extendedly dominated.

Table 53 Results of probabilistic sensitivity analysis (95% CI in brackets)

Strategy	Lifetime Cost (£)	Incremental Cost(£)	Total QALYs	Gained QALYs	ICER
Asp only	4043.68(987.12-9909.70)	N/A	2.18 (0.16-3.07)	N/A	N/A
Asp-Clop*	4383.63(1242.63-10140.41)	N/A	2.26 (0.16-3.19)	N/A	-
Asp-Pras*	4728.53(1236.69-11214.60)	N/A	2.39 (0.18-3.36)	N/A	-
Asp-Tica	5503.64(1419.58-13278.24)	1459.96(-5797.66-10056.77)	2.85 (0.21-3.99)	0.67 (0.05-1.22)	2170.79
Asp-Clop: Aspirin-Clopidogrel dual therapy, **Asp-Pras:** Aspirin-Prasugrel dual therapy, **Asp-Tica:** Aspirin-Ticagrelor dual therapy**, ICER:** Incremental Cost-Effectiveness Ratio, **N/A:** Not Applicable, **QALY:** Quality Adjusted Life Year,*****Extendedly dominated , removed from ICER calculation					

The two-way comparisons were made according to increasing effectiveness for every regimen; aspirin-prasugrel versus aspirin-clopidogrel, and aspirin-ticagrelor versus aspirin-prasugrel. The following figures, Figure 17 and Figure 18, present the cost-effectiveness planes. In order to illustrate decision uncertainty when all four treatment strategies were compared, a cost-effectiveness acceptability curve was generated (

Figure 19). This shows which treatment option has the probability of being cost-effective for various levels of willingness to pay.

In the figure, we see that the aspirin-ticagrelor treatment becomes the strategy that had the highest probability of being cost-effective for every willingness to pay per additional QALY gained level that is higher than 2000£/QALY. For WTP of 2000£/QALY the probability of the aspirin-ticagrelor treatment being cost-effective was 32% and this probability increased to 90% for a WTP equal to 20000£/QALY.

Figure 17 Cost-effectiveness plane: aspirin-prasugrel relative to aspirin-clopidogrel

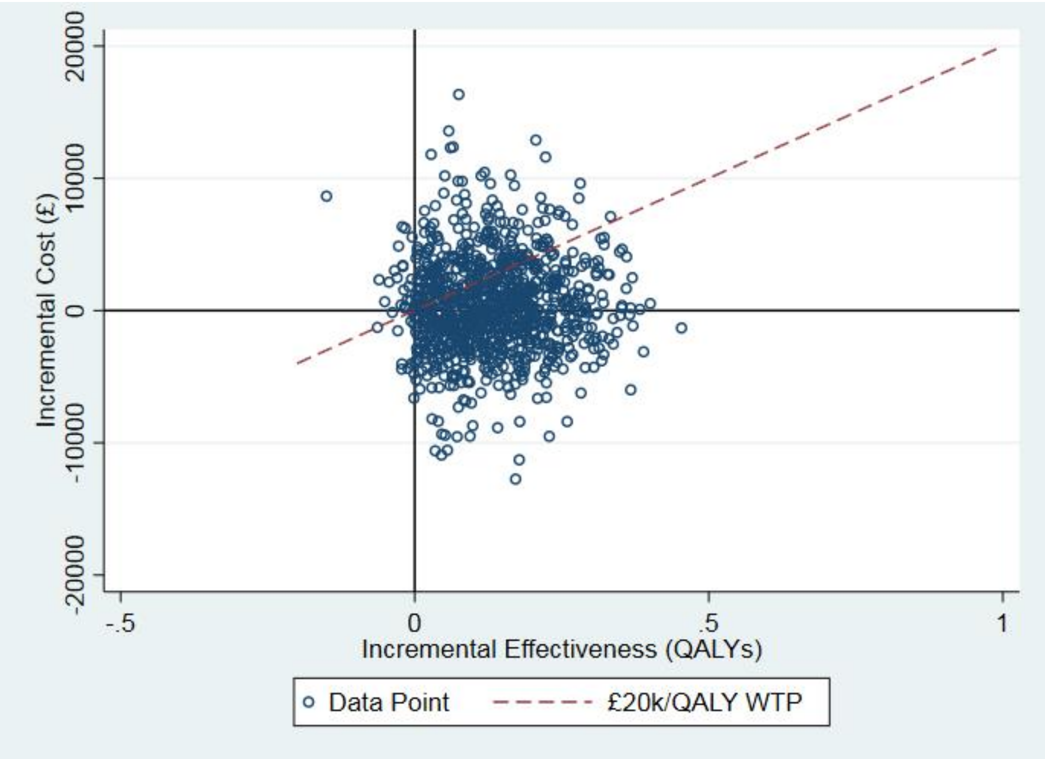


Figure 18 Cost-effectiveness plane: aspirin-ticagrelor relative to aspirin-prasugrel

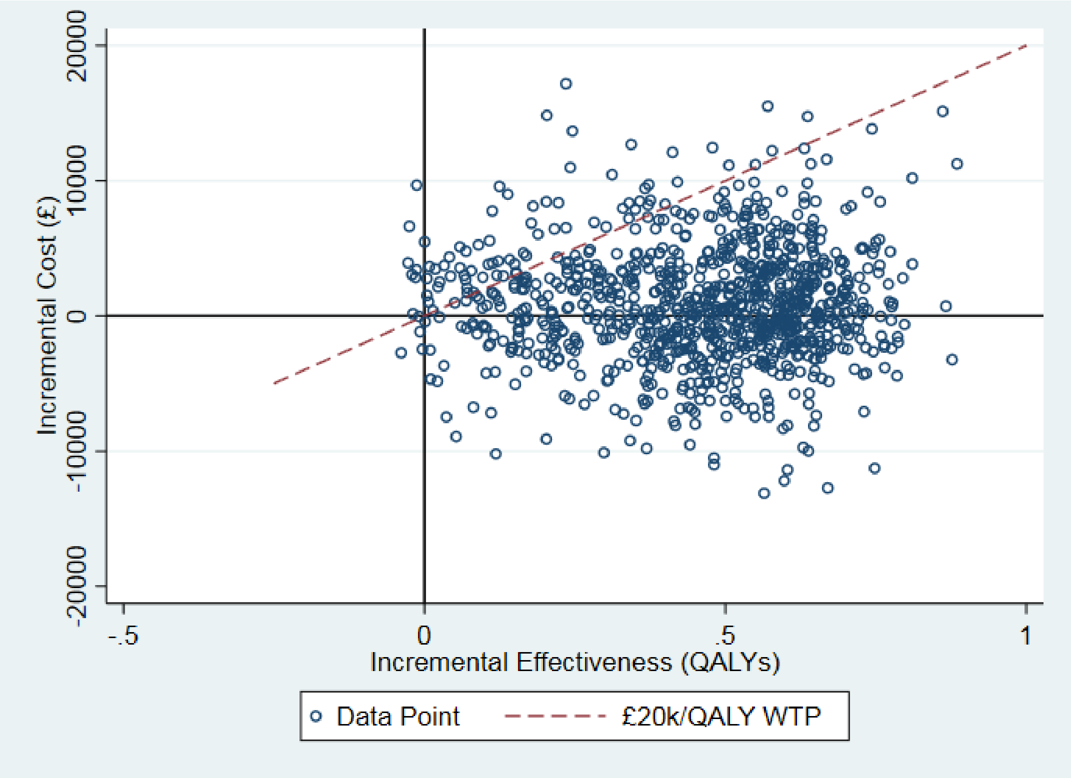
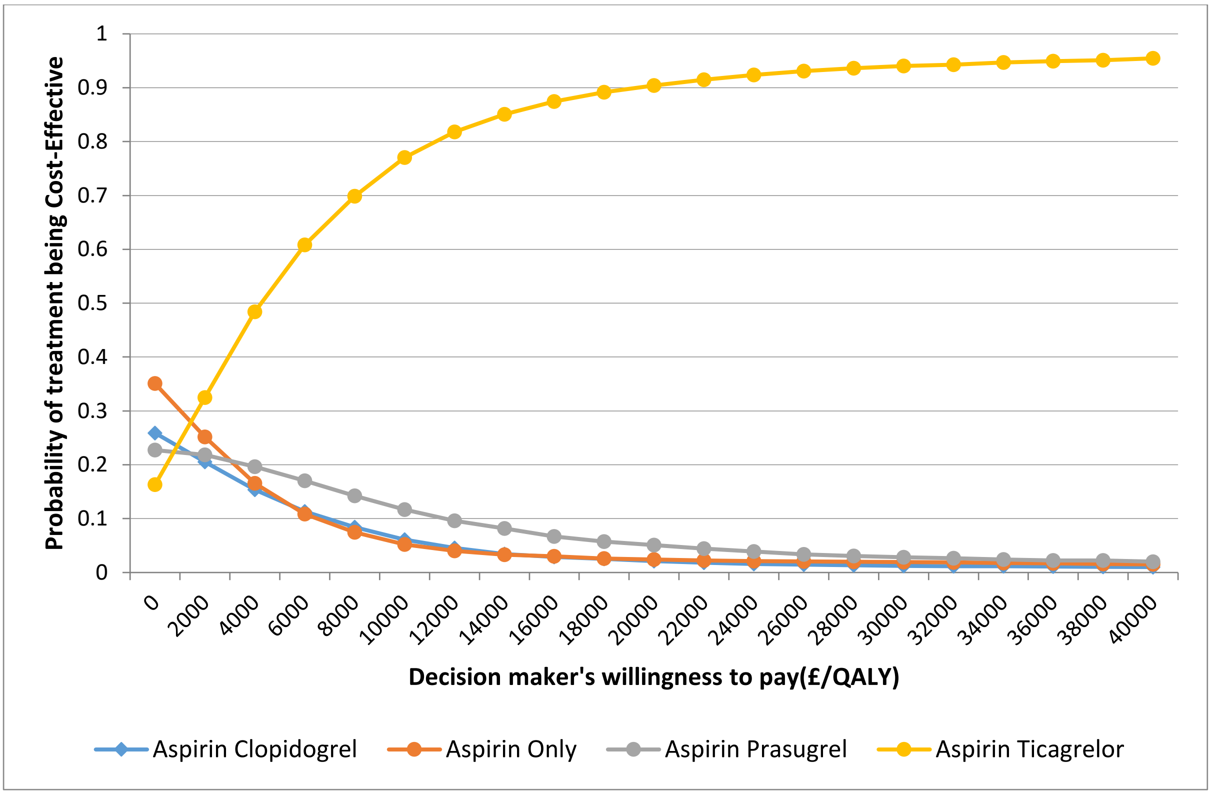


Figure 19 Cost-effectiveness acceptability curve, lifetime horizon



5.9 Discussion

In this chapter, the cost-effectiveness of alternative antiplatelet regimens in patients with T2DM with the use of a decision analytical model was investigated. Using the expected values of incremental cost and effectiveness, the use of the aspirin-ticagrelor regimen for the secondary prevention of ACS resulted in higher costs and higher accumulated QALYs during the lifetime horizon. In the deterministic analysis, the aspirin-ticagrelor treatment generated a mean of 2.85 discounted QALYs over a lifetime, with a mean discounted cost of £5537.24 and ICER versus aspirin only £2237.99/QALY. Both aspirin-prasugrel and aspirin-clopidogrel treatments were extendedly dominated. During the PSA, again there was increasing effectiveness and costs among treatments; the aspirin-ticagrelor treatment generated more QALYs [0.67;95% CI:0.05 to 1.22] compared with aspirin only and costs [£1459.96; 95% CI: -5797.66 to 10056.77] over the lifetime horizon, with aspirin-prasugrel and aspirin-clopidogrel becoming extendedly dominated.

A change of a value of a single parameter in the model, can result in differences in effectiveness and costs between the treatments investigated. This can result in changing the decision about the most optimal antiplatelet treatment in the population.

Investigation of variables that had such impact in the change of optimal treatment was carried out with the help of one-way sensitivity analyses. In this set of analyses, the parameters that had the highest impact in the final results were the probabilities of death during the first year for patients on ticagrelor and prasugrel. Even when the probability of death in aspirin-ticagrelor was increased, it was still the most cost-effective therapy. Any difference in the effect of all cause death, was going to have impact in the lifetime horizon. Patients on ticagrelor or prasugrel, were having lower risk of mortality than patients on clopidogrel and those on aspirin only during the first year, this difference resulted in higher QALY gains during the lifetime horizon. The rest of OSA did not have any inpact in the cost-effectiveness rankings of the base case. The overall uncertainty was investigated with the help of probabilistic sensitivity analyses.

The PSA was carried out in order to assess the relative cost-effectiveness of antiplatelet treatments when all input parameters were varied simultaneously across plausible ranges using appropriate sampling distributions. The introduction of this level of uncertainty resulted in identifying the aspirin-ticagrelor treatment as the most cost- effective treatment for WTP values that were £2000/QALY gained (32% probability of being cost-effective) or higher. The probability that the aspirin-ticagrelor treatment compared to aspirin-prasugrel, aspirin-clopidogrel and aspirin only was cost-effective increased for higher values of WTP thresholds and reached 90% probability of cost-effectiveness in WTP equal to £20000/QALY.

By using only the cost-effectiveness argument in the selection of antiplatelet therapy during the first year post ACS, the aspirin-ticagrelor is the best option for patients with T2DM. In the NHS health care setting, the health gains that aspirin-ticagrelor provides, come at a price which is below the WTP threshold of cost-effectiveness in United Kingdom.

Strengths and Weaknesses

The main strength of this study is that it compared the effectiveness of alternative antiplatelet medications in diabetic population. The structure of the model also allowed for transitions between cardiovascular events, whereas in the models that were constructed for the evaluation of the new medications (ticagrelor, prasugrel) versus clopidogrel patients were assuming that patient could suffer only one cardiovascular event. Compared to the previous models, this study provides a Markov model that provides a still simplified but better depiction of reality, since a patient with T2DM, during lifetime, can have multiple cardiovascular events, and not of just one type.

In the case where a decision from a health care perspective had to be made for the optimal antiplatelet therapy for T2DM patients for the first year after an ACS event, then using the base case analysis of this study, the combination of aspirin-ticagrelor should be considered as such. The decision would remain the same even after incorporating uncertainty around costs and outcomes, since the PSA presented in section 5.8.3 has shown that for a WTP threshold higher than £2000/QALY, the aspirin-ticagrelor treatment has the highest probability of being cost-effective.

In the model, platelet response was not taken into account. It was assumed that all patients when assigned in a treatment, did not have any signs of either "aspirin resistance" or "clopidogrel resistance". The study of Angiolillo (113), investigated the relationship between platelet reactivity and MACE and did not have any specific results by regimen.

Overall, the model results overestimate the cost-effectiveness of the various regimens, because they assume treatment effect for a year. This assumption is made because the English guidelines suggest treatment with DAPT for a year, but from the results on Chapter 3, we saw that patients on DAPT started discontinuing therapy after six months.

For the patients who were assigned in one of the DAPT regimens in the model, it was assumed that they were prescribed DAPT for the first year and aspirin only afterwards. This assumption could be challenged, because in the population there would be patients that continued to be high risk after the first year of DAPT therapy, and their GPs would decide to extend DAPT therapy. If it was known what happens to patient treatment after the first year of antiplatelet prescriptions, and how extended treatment is selected for which patients, we would be able to better model the use of antiplatelet medication treatment over time in high risk groups.

Other studies that made head to head comparisons between the antiplatelet regimens for the general population, were of Wisloff (104), where they used a modified version of a cardiac disease progression model and they estimated the ICER of prasugrel compared with clopidogrel to be 7505 eur/LYG (6683£/LYG) and the ICER of ticagrelor compared with prasugrel was 7820 eur/LYG (6963£/LYG). In their simulations the treatment with ticagrelor was the most cost-effective strategy, as in the study reported in this chapter. Zhao and colleagues (105) (106) in their study also found that ticagrelor is cost-effective against prasugrel, but they pointed out that this result was more sensitive when the hazard ratio for all cause death was changing, and when the utility value for the state of dyspnoea was varied. When changes in those parameters happened, the cost-effectiveness rankings changed. Changes in ICER were also found in this study when the hazard ratio for death changed, which is in agreement with the findings of Zhao and colleagues when one way sensitivity analysis was carried out, but when PSA was carried out aspirin-ticagrelor was still the most cost-effective treatment.

6. Chapter Six: Thesis Discussion

6.1 Chapter introduction

Antiplatelet medications are the cornerstone of pharmaceutical treatment for the secondary prevention of ACS. People with T2DM have a higher risk of suffering macrovascular complications than the general population. This thesis aimed to investigate the cost-effectiveness of different antiplatelet regimens in adults with T2DM. To achieve this, a retrospective cohort study was carried out with the use of routinely collected health care data such as prescriptions, GP consultations and hospital admissions. Time to event analyses were performed to assess the impact that different antiplatelet regimens had on outcomes of interest. The economic effect of being treated with a specific antiplatelet regimen was examined with the use of a cost-effectiveness model that used the evidence about treatment effect of antiplatelet regimens with cost data and utility tariffs sourced from the literature.

6.2 Summary of study and study findings

In Chapter 1, an overview about the relationship between T2DM and ACS, the clinical and economic burden of T2DM and ACS treatment was presented.

In Chapter 2, an overview of how ACS should be managed, before, during and after hospitalisation according to national guidelines was provided. Regarding the secondary prevention of ACS, the focus of the study steered to antiplatelet treatments. The evidence for effectiveness and cost-effectiveness of treatments was examined. The general message from those studies was that clopidogrel in addition to aspirin was providing better protection against ACS than aspirin only, and that the combinations of newer agents with aspirin were having better treatment effect than aspirin-clopidogrel in ACS protection, but with higher risk of bleeding. Similar results for the newer antiplatelet agents were found in studies that were using real world data. The trials were carried out by including the general population. The sub studies of those trials that were reporting the effectiveness of medications in T2DM populations were ad hoc analyses, and they were not set up for T2DM populations. Furthermore, no study that investigated the effectiveness of DAPT using real world data was available. Regarding the cost-effectiveness of DAPT therapies, all the studies were using the results of trials for the general population, and no cost-effectiveness analysis of DAPT was carried out for T2DM population. There was a gap regarding the cost-effectiveness of DAPT regimens in T2DM populations.

Issues that were relevant to T2DM population being treated with antiplatelet medications, such as "aspirin resistance" and "clopidogrel resistance" were discussed. Another aspect discussed was the optimal duration of antiplatelet therapy and what treatments should be considered after DAPT, where still there was no clear consensus among clinicians. Some studies found that prolonged DAPT therapy increased the risk of bleeding, others that by shortening DAPT therapy period can increase the risk of MI and decrease the risk of bleeding, or that a six month DAPT cand have the same results as longer therapy periods. Suggestions for the individualisation of DAPT and the need for further research on optimal personalised DAPT therapies was mentioned in the literature.

In terms of adherence in DAPT therapies, the published studies reported high adherence during the early months and suboptimal adherence afterwards. All these studies were giving information about the general population and not for a population with T2DM. The gap literature allowed for a study that would investigate the effectiveness and cost-effectiveness of DAPT in populations with T2DM with the use of real world data.

In Chapter 3, the methods for data extraction from routinely collected health care data, how health care datasets like CPRD and HES are structured were discussed. Large electronic health care records were considered suitable for this study.

In order to observe the characteristics of patients prescribed with different antiplatelet regimens, selected outcome variables and patient covariates were generated with information from CPRD records. CPRD records were used to define age, gender, and other variables such as smoking status, alcohol consumption status. The same records were used to identify the resource use and the costs or primary care. HES data were used to identify outcomes of interest and the secondary care resource use and costs.

In the same chapter, it was outlined how data from CPRD and HES were used to estimate the effect of antiplatelet agents on the risk of specific outcomes included in the study. It was also discussed how the estimation of treatment effect could be carried out with the use of non-randomised data like those from electronic health care records. Balancing methods such as propensity scores or inverse probability treatment weights were used to identify treatment effect (82). Balancing methods suitable for multiple groups were selected, due to the comparison between three DAPT treatments.

Time to event analysis was used as the most appropriate method to estimate the effect of antiplatelet regimens on the risk of several outcomes, against which those medications are protecting patients. This type of analysis was also selected for estimating the impact on hazard rate, and it was suitable for data that included different time periods of observation.

The same chapter summarised the findings of the cohort in adults with T2DM who were treated with antiplatelet medications for secondary management of ACS, in terms of demographic characteristics (region of GP practice, gender, age), in terms of adherence, and outcomes. Furthermore, the confounding problems arising from the non-random nature of the data were addressed with the help of balancing methods. The first study objective was achieved by carrying out those analyses.

Overall, patients prescribed aspirin-ticagrelor or aspirin-prasugrel were younger than patients on aspirin-clopidogrel at start of prescribing, and predominantly male. Also, the patients prescribed aspirin-ticagrelor or aspirin-prasugrel had T2DM for a shorter time than the patients started on clopidogrel.

Patients on antiplatelet regimens were adherent to therapies, and patients on aspirin-ticagrelor and aspirin-prasugrel, had no continuation of prescription after 450 days. Furthermore, patients on DAPT started discontinuing their medications after 180 days.

Three balancing methods were selected as candidates to address confounding (CBPS, MMW-s, MNPS). The MMW-s method was abandoned because the algorithm was stopped during the stratification stage. CBPS and MNPS methods produced sampling weights, but no method produced the best balance across all groups. In the later stages of the analysis, “doubly robust” methods of estimation methods were used. All analyses were carried out twice, with MNPS and CBPS sampling weights, because both balancing methods reduced, but didn’t eliminate the imbalances across groups.

The time to event analyses, indicated that the newer antiplatelet medications have better results than aspirin-clopidogrel for the outcomes investigated. Aspirin-prasugrel is better than aspirin-clopidogrel in the protection against stroke, MI, MACE, and all cause death, whereas patients on aspirin-ticagrelor experience fewer events of stroke, bleeding, and all cause death.

In time to event analyses, the data related limitations had to do with the small follow-up period for the patients on newer antiplatelet agents, and that those groups were smaller in size compared to the aspirin-clopidogrel group. Additionally, the use of the balancing methods, reduced the confounding among treatment groups but it didn't eliminate it. Only one safety outcome measure (bleeding) was considered in the outcome analysis, but not other adverse events, which could occur during the use of antiplatelet medications (hematuria, ticagrelor induced dyspnea).

The use of doubly robust methods resulted in findings that were in accordance with the findings in the literature in terms of effect sign but not in magnitude.

Both newer antiplatelet therapies performed better than the aspirin-clopidogrel. From the analysis findings it is indicated that prasugrel provided better protection against cardiovascular events and death, with the same risk of bleeding as the aspirin-clopidogrel regimen. This could suggest that prasugrel for patients with T2DM could be the most effective treatment.

The results of time to event analysis were not used in the Markov model analysis, because the transition probabilities needed to populate the model, had to be estimated for an impractically large number of subgroups. Furthermore, the effect magnitude was quite high, indicating still existing confounding that was not addressed. The time to event analyses after balancing across treatment groups were carried out in order to meet the second objective of the study.

Chapter 4 presented the methods used to attach costs in the resource use recorded in the electronic clinical data used in the study, analysis methods used for the investigation of association between clinical costs and antiplatelet treatments, and the results of this analysis. The work presented in this chapter was carried out so that the first and the second objective of the study was met.

Cost analysis with the use of generalised linear models was selected as the most suitable analysis method to investigate the associations between health care costs and antiplatelet regimens. GLM was chosen because health care costs are non-normally distributed, they contain non-negative values, and they are usually positively skewed. The models contained adjustments for patient follow-up time. The adjustments were introduced in order to avoid biased analysis results, which could happen due to the different follow-up time period every patient had.

The cost association analysis presented that in terms of total health care costs, patients on aspirin-prasugrel incurred less costs than those on aspirin-ticagrelor and aspirin-clopidogrel. For aspirin-prasugrel patients, the increased costs they incurred in medication prescriptions were offset by the reduced costs in inpatient care. For patients on aspirin-ticagrelor, the increased medication costs were counterbalanced by the outpatient care costs they incurred during the year, resulting in a non-significant difference in total health care costs with patients on aspirin-clopidogrel.

It was not feasible to carry out a cost analysis using more years of follow-up in a longitudinal analysis, because of the short period of follow-up in patients treated with aspirin-ticagrelor or aspirin-prasugrel. The cost analysis models had a specification that did not include variables such as the presence of a condition or the history of a previous event. Due to the focus that the current cost analyses have (associations between different treatment groups) and the way the models were specified, the results of the analyses could not be used in the economic evaluation.

Chapter 5 described a model-based cost-effectiveness evaluation. The evaluation was carried out in order to assess the economic impact of alternative antiplatelet medications in patients with T2DM for the secondary prevention of ACS events. A lifetime horizon and the NHS/PSS perspective were used in the evaluation. The reason behind this study was to find out which antiplatelet regimens were more cost-effective than the standard DAPT therapy (treatment with aspirin-clopidogrel).

The model in the analysis, was a Markov cohort model, which focused mainly on the cardiovascular events that may occur (Stroke, MI, cardiovascular death, death from any cause) and potential adverse events due to the antiplatelet medication use (bleeding) for a population with T2DM in the United Kingdom.

The deterministic base-case analysis concluded that the aspirin-ticagrelor regimen had the highest lifetime costs (£5537.24) and the highest number of QALYS (2.85) and an ICER of £2237.99/QALY. The results were assessed by using the principles of strong and extended dominance. Aspirin-prasugrel and aspirin-clopidogrel were extendedly dominated, and they were excluded from the ICER calculation

One-way sensitivity analyses showed that aspirin-ticagrelor remained the most cost-effective treatment option.In a probabilistic sensitivity analysis that took into account all the uncertainty across all input parameters in the model, the aspirin-ticagrelor treatment generated more QALYs [0.67;95% CI:0.05 to 1.22] compared with aspirin only and costs [£1459.96; 95% CI: -5797.66 to 10056.77] over the lifetime horizon. Aspirin- prasugrel and aspirin-clopidogrel were again extendedly dominated.

A cost-effectiveness acceptability curve was used to identify which of the antiplatelet regimens had the higher probability of being cost-effective for several levels of willingness to pay. For intervals that ranged from £0-£40000/QALY, the treatment with aspirin-ticagrelor was the most cost-effective option for thresholds of £2000/QALY and beyond. The treatment with aspirin-ticagrelor had 90% chance of being cost-effective for WTP equal to £20000/QALY.

The Markov model in the study did not include additional health states representing adverse events that were related to the use of antiplatelet medications (ticagrelor related dyspnea, hematuria). The treatment effects used in the model were sourced from studies that were related to the general population.

6.3 Strengths and limitations

This study provided an overview of T2DM patients that were prescribed antiplatelet medications for secondary prevention of ACS in England. Quasi experimental methods were used to overcome the problems of non-random treatment assignment in the cohort.

This study allowed for a head-to-head comparison of alternative antiplatelet regimens for T2DM patients who suffered an ACS, with the use of routinely collected healthcare data.

This study focused on adults with T2DM that are prescribed antiplatelet medications for secondary prevention of ACS in England. The work reported here focused on understanding the relative effectiveness and safety of different DAPT regimens after ACS, given that current randomised studies do not focus specifically on this group. Rather than carry out an RCT, quasi experimental methods were applied to routinely collected health care data for the head to head comparison of alternative DAPT regimens for patients with T2DM and suffered an ACS. The key advantage of this approach is that a costly, time-consuming RCT did not have to be carried out. Also, RCTs do not always reflect real clinical practice in terms of target cohort or treatment pathways. However, there are necessarily limitations associated with the use of non-randomised data to identify reliable treatment effects. Given the absence of an RCT-based economic evaluation, the second key approach in this work was to use published evidence to design and populate an economic evaluation of four alternative antiplatelet regimens (aspirin monotherapy and DAPT regimens) in this cohort.

Real world data have a non-random nature, and this can have impact when a study is carried out. The treatment allocation of DAPT in this study was affected by several factors, such as historical differences, regional variations, and factors related to patient's safety as considered by the GPs. Also, other factors such as gender, age, and time with diabetes had to be considered. Furthermore, the group size in the prescribed newer antiplatelet agents was much smaller compared to the group in the aspirin and clopidogrel groups. As a result, treatment allocation, which was driven by these factors, introduced confounding and imbalances among groups. For that reason, methods for balancing differences in characteristics among groups were introduced. Those methods can reduce imbalances but may not be able to completely eliminate them. The use of CPRD and HES resulted in the inclusion of GP practices of England only, because those practices are providing HES linked data. Therefore, study findings were relevant for England only and not UK wide. Additionally, there was a chance of misclassification of the type of diabetes that patients suffered from, because the description of some of the Read codes for diabetes description was vague.

The time-to-event and the cost analyses were carried out with the use of doubly robust estimation methods, but there was the possibility that some of the confounding could be not sufficiently addressed.

6.3.1 Strengths and limitations in economic evaluation

The model in the analysis, was a Markov cohort model, and that focused mainly on the cardiovascular events that may occur (Stroke, MI, cardiovascular death, death from any cause) and potential adverse events due to the antiplatelet medication use (bleeding) for a population with T2DM in the United Kingdom.

This allowed for having a cost-effectiveness model that could assess the impact of antiplatelet medications for T2DM population. Furthermore, compared to the models that were used for the assessment of antiplatelets in the general population, it allowed for the fact that multiple complications could occur during the lifetime horizon that the model was run.

One limitation for the model, was that for the patients in DAPT regimens was that only one strategy of treatment could be assessed (dual antiplatelet regimen during the first year, aspirin only during the rest of the time) and we could not incorporate the fact that some patients might have to stop DAPT before the end of the year, or they had to continue the DAPT for longer than a year, or that a proportion of patients could have problems with the use of aspirin or clopidogrel. Another issue was that for the treatment effect, the results of clinical trials were used, instead of real world evidence. This could also result in potential overestimation of the overall cost-effectiveness. The cost-effectiveness in the Markov model was potentially overestimated, since the treatment effect of DAPT was assumed to last for 12 months, whereas in prescription analysis that was carried out, people were discontinuing DAPT after the six month period.

6.4 Comparisons with the literature

In chapter 4, the descriptive analysis of the groups of patients that were on antiplatelet medications has shown that the patients who were treated on clopidogrel were older than those on prasugrel and ticagrelor. It was also found that the majority of patients on those medications was male. Those findings that are in accordance with those of Rezaei et al (134), Alexopoulos et al (82) and Yudi et al (80), even though the studies were carried out for the general population and not for patients with T2DM, and they were for non UK clinical settings (Austria, Greece, and Australia).

In the analysis of adherence in DAPT, the analysis findings were in accordance with the findings of the review of Czarny (133) regarding the overall adherence. Furthermore, the discontinuation in DAPT after six months was also found in the study of Razaei et al. (134) in Austria, and with the study of Nakamura et al. (127) in Japan.

The time to event analysis found that for every outcome assessed the newer antiplatelet agents are better than aspirin-clopidogrel. Aspirin-prasugrel is better than aspirin-clopidogrel in the protection against MI, and MACE, whereas patients on ticagrelor experience fewer events of stroke, bleeding, and all cause death. The results were in accordance with the findings of TRITON-TIMI 38 and for aspirin-ticagrelor the findings are in accordance with the PLATO study for all-cause death and in discordance for non-fatal stroke.

For the cost analysis there was no study investigating the costs accrued in patients with T2DM that were prescribed antiplatelet medications. The most recent studies that made comparisons between T2DM patients on different medications and are making annual cost estimations similar to those of the study are those of Farr et al. (285), and Reed et al (286). The study or Reed estimated the average annual cost of a patient with T2DM not on sitagliptin to be £6258 and that of a patient on sitagliptin at £7130, which were much higher than the estimates of £4400 found in this study.

The comparison of the findings of the cost-effectiveness analysis is difficult, because no cost-effectiveness analysis that included all three antiplatelet regimens for the T2DM population was carried out in the health care setting of UK or a setting of any other country. The only cost-effectiveness analyses that included all three antiplatelet regimens were those of Wisloff (104) and Zhao (106). By comparing the findings of the cost-effectiveness analysis with those studies, we see that they were in accordance with the findings of Zhao et al and that of Wisloff et al., since they also found that the most cost-effective treatment is that of aspirin and ticagrelor. The models differed in structure compared to that of the thesis (no state for stroke in both studies, inclusion of dyspnoea state in the study of Zhao), but overall, the findings concurred.

6.5 Implications for policy and practice

Antiplatelet therapy is the most important pharmaceutical intervention for the secondary prevention of acute coronary syndromes. The main challenge that clinicians face when prescribe antiplatelet therapies to patients is about striking a balance between the risk of the patient having a cardiovascular event (MI, stroke, or death due to MI or stroke) and the risk of side effects.

A finding of the study that has implication in practice is that many T2DM patients are on monotherapy regimens for secondary prevention, event though this is not suggested in the clinical guidelines. A further analysis of the groups that belong in monotherapy groups in order to find the reason why practitioners don’t follow the guidelines could be of help.

A possible finding that may have implication in practice is the fact that T2DM patients who are on a DAPT regimen, tend to discontinue the treatment from the sixth month. This could impact clinical practice in two ways: if the guidelines continue to suggest the treatment with DAPT for at least 12 months, then interventions that could reduce DAPT discontinuation among T2DM populations should be introduced. In the case where guidelines are going to suggest a six month time period of DAPT, then a revision about the cost-effectiveness of DAPT therapies, either for T2DM population or the general population might be necessary.

The time to event analysis has shown that the regimens of newer antiplatelet agents provide better atherothrombotic protection compared with clopidogrel. Based on the findings, ticagrelor provides lower risk of bleeding in this specific population. A possible implication of this could be that for T2DM populations, the use of newer agents instead of clopidogrel to be encouraged, and the use of ticagrelor in T2DM patients with higher bleeding risk. This could be a cost-effective solution, based on the findings of the study, but this would require an increase in the budget allocated for antiplatelet medications, since the cost of treatment with prasugrel or ticagrelor versus treatment with clopidogrel is much higher. In the case of budgetary expansion for the NHS, a decision for more frequent prescription of newer antiplatelet agents could be implemented, otherwise such a decision could be made when prasugrel and ticagrelor go “off-patent”, and those medications can be procured from the NHS in a more discounted price.

6.6 Implications for research

The studies that investigate the impact of alternative antiplatelet regimens have to take into account all the risks and side effects that might occur. Additionally, the impact of alternative antiplatelet treatment durations should be considered.

An additional work that could be carried out is the identification of the ideal cut-off point for adherence in antiplatelet medications for T2DM populations. The study of Karve et al (196) identified specific cut-off points of adherence measures that could be used as indicators for hospitalisations for several types of medications, but not for antiplatelet medications.

Since the duration of DAPT in general population is still open for debate, a research that focus on groups of general population or in populations with T2DM and investigates outcomes of those who are on longer or short term DAPT therapy could be carried out. It could be a natural experiment study, since users of DAPT could be prescribed therapy for a specific time period but they may not stay adherent, or they may discontinue therapy. A cohort study based on real world evidence could be feasible.

Cost-effectiveness analyses that could assess different antiplatelet strategies with the use of inputs from real world evidence, could help inform guidelines include more cost-effective strategies.

6.6.1 Use of real world data and lessons learned

During the study, a significant amount of time and effort was spent in the analysis and use of non-randomised data. The datasets used in the study weren't able to answer sufficiently the multiple questions the study posed.

The selected cohort was a subset of the general population who were treated for the secondary prevention of ACS with multiple alternative treatments. Furthermore, two of the treatments were available for a smaller time period compared to the older and established ones. As a result of this situation, the groups of patients treated with the newer antiplatelet agents were smaller in size, and they had information for a shorter time period. There was also difference in size among the groups compared, with the group of aspirin-clopidogrel having more patients than those of aspirin-prasugrel and aspirin-ticagrelor. This could signal that the dataset itself was not able to capture the treatment with newer antiplatelets as good as treatment with older antiplatelets. A way to address this problem, is to rerun the analysis in a newer version of CPRD data cut. An alternative solution could be the extension of the analysis using the SAIL database for the same observation period as that used in CPRD. The SAIL database has similar characteristics to CPRD and covers health care facilities in Wales, allowing the researchers to compare findings from England and Wales.

Several outcomes were investigated for the time to event analysis, and the analysis of cost associations was carried out for several cost categories. This resulted in a dataset where multiple small groups were analysed for every part of the study. The strategy for the use of data was to extract and keep all the information that was available. That was the reason for using balancing techniques which didn't drop observations. This resulted in analysis of outcomes that could indicate an effect but couldn't provide certainty in the observed magnitude of the effect.

For the use of real world data, the ideal strategy for designing a study would be have a population that could be divided in two groups during the analysis stage (a group with one condition versus the group without/general population or investigating the same group before and after the implementation of a policy or a new guideline for treatment). The study should have a small number of outcomes that could be easily defined using healthcare records (all cause death, fractures). Finally the study should be carried out in a time period when the real world datasets were able to have captured information about the subject that is going to be investigated, for example datasets that have enough follow-up information for patients who were treated with recently introduced medications, or datasets which have information about patients for several months before and after the introduction of a new healthcare policy or a new clinical guideline.

7. References

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8. Appendices

8.1 Appendix 1. Cost of Staff in primary care

CPRD code	Role Of Staff	£/hr	£/min	Reference	Comments
0	Data Not Entered				
1	Senior Partner	179	2.98	10.3b p.145 pssru 2016	Excluding direct care costs/without qualification costs
2	Partner	179	2.98	10.3b p.145 pssru 2016	Excluding direct care costs/without qualification costs
3	Assistant	179	2.98	10.3b p.145 pssru 2016	Excluding direct care costs/without qualification costs
4	Associate	179	2.98	10.3b p.145 pssru 2016	Excluding direct care costs/without qualification costs
5	Non-commercial local rota of less than 10 GPs	179	2.98	10.3b p.145 pssru 2016	Excluding direct care costs/without qualification costs
6	Commercial Deputising service	179	2.98	10.3b p.145 pssru 2016	Excluding direct care costs/without qualification costs
7	Locum	179	2.98	10.3b p.145 pssru 2016	Excluding direct care costs/without qualification costs s
8	GP Registrar	48	0.80	15 p.190 pssru 2016	Assuming 40hr week/without qualification costs
9	Consultant	104	1.73	15 p.190 pssru 2016	Without qualification costs/ Consultant:medical
10	Sole Practitioner	179	2.98	10.3b p.145 pssru 2016	Excluding direct care costs/without qualification costs
11	Practice Nurse	36	0.60	10.2 p.143 pssru 2016	Without qualification costs
12	Health Visitor	44	0.73	10.1 p.142 pssru 2016	Assuming band 6 nurse
13	Community Nurse	44	0.73	10.1 p.142 pssru 2016	Assuming band 6 community nurse
14	Midwife	36	0.60	10.2 p.143 pssru 2016	Assuming GP nurse salary, no qualification cost
15	Community Psychiatric Nurse	44	0.73	10.1 p.142 pssru 2016	Assuming band 6 community nurse
16	Social Worker	40	0.67	11.2 p.156 pssru 2016	Without qualification costs

CPRD code	Role Of Staff	£/hr	£/min	Reference	Comments
17	Pharmacist	44	0.73	13 p.185 pssru 2016	Assuming band 6 hospital pharmacist, no qualification costs
18	Dispenser	11.66	0.19	17.5 p199 pssru 2016	Assuming Agenda for change band 3 worker, working the same hours as hospital pharmacist
19	Non-qualified Dispenser	10.45	0.17	17.5 p199 pssru 2016	Assuming Agenda for change band 2 worker, working the same hours as hospital pharmacist
20	Practice Manager	16.29	0.27	17.4 p.199 pssru 2016	Assuming band 5 worker with 1565 hours of work
21	Fund Manager	16.29	0.27	17.4 p.199 pssru 2016	Assuming band 5 worker with 1565 hours of work
22	Business Manager	16.29	0.27	17.4 p.199 pssru 2016	Assuming band 5 worker with 1565 hours of work
23	Administrator	11.85	0.20	17.4 p.199 pssru 2016	Assuming band 3 worker with 1565 hours of work
24	Secretary	13.66	0.23	17.4 p.199 pssru 2016	Assuming band 4 worker with 1565 hours of work
25	Receptionist	10.75	0.18	17.4 p.199 pssru 2016	Assuming band 2 worker with 1565 hours of work
26	Physiotherapist	34	0.57	13 p.185 pssru 2016	Assuming band 5 hospital physiotherapist, no qualification costs
28	Dentist	96	1.60	10.5 p.148 pssru 2016	NHS dentist, performing only, no qualification costs
29	Dietician	33	0.55	13 p.185 pssru 2016	Assuming band 5 hospital dietician role, no qualification costs
30	Counsellor	33	0.55	13 p.185 pssru 2016	Assuming band 5 hospital speech therapist role, no qualification costs
31	Osteopath	33	0.55	13 p.185 pssru 2016	Assuming band 5 hospital speech therapist salary, no qualification costs
32	Maintenance staff	10.67	0.18	17.4 p.199 pssru 2016	Assuming band 2 admin and estates worker with 1565 hours of work
33	Other Health Care Professional	22	0.37	10.1 p.142 pssru 2016	Assuming clinical support worker nursing (band 2 community nurse), no qualification costs
34	Hospital Nurse	35	0.58	14 p.188 pssru 2016	Assuming band 5 nurse
35	Community Medical Officer	179	2.98	10.3b p.145 pssru 2016	Excluding direct care costs/without qualification costs

CPRD code	Role Of Staff	£/hr	£/min	Reference	Comments
36	School Nurse	44	0.73	14 p.188 pssru 2016	Assuming band 6 nurse
37	Health Education Officer	24	0.40	13 p.185 pssru 2016	Assuming allied health professional band 2 support worker, no qualifications
38	Contact Tracing Nurse	36	0.60	10.2 p.143 pssru 2016	Assuming GP nurse salary, no qualification cost
39	Stomatherapist	53	0.88	14 p.188 pssru 2016	Assuming nurse advanced , band 7
40	Computer Manager	16.29	0.27	17.4 p.199 pssru 2016	Assuming band 5 worker with 1565 hours of work
42	Chiropractor	34	0.57	13 p.185 pssru 2016	Assuming the payment of hospital physiotherapist
45	Mental Handicap Nurse	44	0.73	10.1 p.142 pssru 2016	Assuming band 6 nurse
47	Salaried Partner	179	2.98	10.3b p.145 pssru 2016	Excluding direct care costs/without qualification costs
48	Occupational Therapist	41	0.68	11.5 p.159 pssru 2016	Without qualification costs
49	Speech Therapist	33	0.55	13 p.185 pssru 2016	Assuming hospital speech therapist, no qualification costs
50	GP Retainer	179	2.98	10.3b p.145 pssru 2016	Excluding direct care costs/without qualification costs
51	Phlebotomist	10.67	0.18	17.5 p.199 pssru 2016	Assuming band 2 worker with 1565 hours of work
52	Other Medical & Dental	96	1.60	10.5 p.148 pssru 2016	Without qualification costs
54	Other Nursing & Midwifery	36	0.60	10.2 p.143 pssru 2016	Assuming GP nurse salary, no qualification cost
55	Other Allied Health Professionals	24	0.40	13 p.185 pssru 2016	Assuming allied health professional band 2 support worker, no qualifications
56	Other Professional Scientific & Technical	24	0.40	13 p.185 pssru 2016	Assuming allied health professional band 2 support worker, no qualifications
57	Other Healthcare Scientists	24	0.40	13 p.185 pssru 2016	Assuming allied health professional band 2 support worker, no qualifications
59	Other Admin & Clerical	11.85	0.20	17.4 p.199 pssru 2016	Assuming band 3 worker with 1565 hours of work

CPRD code	Role Of Staff	£/hr	£/min	Reference	Comments
60	Clinical Practitioner Access Role	33	0.55	13 p.185 pssru 2016	Assuming hospital speech therapist, no qualification costs
61	Nurse Access Role	36	0.60	10.2 p.143 pssru 2016	Assuming GP nurse salary, no qualification cost
62	Nurse Manager Access Role	44	0.73	10.1 p.142 pssru 2016	Assuming band 6 nurse
63	Health Professional Access Role	33	0.55	13 p.185 pssru 2016	Assuming hospital speech therapist salary, no qualification costs
64	Healthcare Student Access Role	33	0.55	13 p.185 pssru 2016	Assuming hospital speech therapist salary, no qualification costs
65	Biomedical Scientist Access Role	33	0.55	13 p.185 pssru 2016	Assuming hospital speech therapist salary, no qualification costs
66	Clinical Coder Access Role	33	0.55	13 p.185 pssru 2016	Assuming hospital speech therapist salary, no qualification costs
67	Optometrist	33	0.55	13 p.185 pssru 2016	Assuming hospital speech therapist salary, no qualification costs
68	Radiographer	35	0.58	13 p.185 pssru 2016	Assuming the payment of band 5 hospital radiographer

8.2 Appendix 2. ICD-10 codes for outcomes

ICD-10 codes for the conditions that consist the Major cardiovascular event outcome.

ICD-10 codes	Descriptions	Disease type
I60.0	Subarachnoid haemorrhage from carotid siphon and bifurcation	stroke
I60.1	Subarachnoid haemorrhage from middle cerebral artery	stroke
I60.2	Subarachnoid haemorrhage from anterior communicating artery	stroke
I60.3	Subarachnoid haemorrhage from posterior communicating artery	stroke
I60.4	Subarachnoid haemorrhage from basilar artery	stroke
I60.5	Subarachnoid haemorrhage from vertebral artery	stroke
I60.6	Subarachnoid haemorrhage from other intracranial arteries	stroke
I60.7	Subarachnoid haemorrhage from intracranial artery, unspec	stroke

ICD-10 codes	Descriptions	Disease type
I60.8	Other subarachnoid haemorrhage	stroke
I60.9	Subarachnoid haemorrhage, unspecified	stroke
I61.0	Intracerebral haemorrhage in hemisphere, subcortical	stroke
I61.1	Intracerebral haemorrhage in hemisphere, cortical	stroke
I61.2	Intracerebral haemorrhage in hemisphere, unspecified	stroke
I61.3	Intracerebral haemorrhage in brain stem	stroke
I61.4	Intracerebral haemorrhage in cerebellum	stroke
I61.5	Intracerebral haemorrhage, intraventricular	stroke
I61.6	Intracerebral haemorrhage, multiple localized	stroke
I61.8	Other intracerebral haemorrhage	stroke
I61.9	Intracerebral haemorrhage, unspecified	stroke
I62.0	Subdural haemorrhage (acute)(nontraumatic)	stroke
I62.1	Nontraumatic extradural haemorrhage	stroke
I62.9	Intracranial haemorrhage (nontraumatic), unspecified	stroke
I63.0	Cerebral infarct due to thrombosis of precerebral arteries	stroke
I63.1	Cerebral infarction due to embolism of precerebral arteries	stroke
I63.2	Cereb infarct due unsp occlusion or stenos precerebrl arts	stroke
I63.3	Cerebral infarction due to thrombosis of cerebral arteries	stroke
I63.4	Cerebral infarction due to embolism of cerebral arteries	stroke
I63.5	Cerebrl infarct due unspec occlusion or stenos cerebrl arts	stroke
I63.6	Cereb infarct due cerebral venous thrombosis, nonpyogenic	stroke
I63.8	Other cerebral infarction	stroke
I63.9	Cerebral infarction, unspecified	stroke
I64	Stroke, not specified as haemorrhage or infarction	stroke
G45.0	Vertebro-basilar artery syndrome	stroke

ICD-10 codes	Descriptions	Disease type
G45.1	Carotid artery syndrome (hemispheric)	stroke
G45.2	Multiple and bilateral precerebral artery syndromes	stroke
G45.3	Amaurosis fugax	stroke
G45.8	Other transient cerebral ischaemic attacks and related synd	stroke
G45.9	Transient cerebral ischaemic attack, unspecified	stroke
H34.1	Central retinal artery occlusion	stroke
I21.0	Acute transmural myocardial infarction of anterior wall	MI
I21.1	Acute transmural myocardial infarction of inferior wall	MI
I21.2	Acute transmural myocardial infarction of other sites	MI
I21.3	Acute transmural myocardial infarction of unspecified site	MI
I21.4	Acute subendocardial myocardial infarction	MI
I21.9	Acute myocardial infarction, unspecified	MI
I22.0	Subsequent myocardial infarction of anterior wall	MI
I22.1	Subsequent myocardial infarction of inferior wall	MI
I22.8	Subsequent myocardial infarction of other sites	MI
I22.9	Subsequent myocardial infarction of unspecified site	MI
I23.0	Haemopericardium as curr comp folow acut myocard infarct	MI
I23.1	Atral sept defect as curr comp folow acut myocardal infarct	MI
I23.2	Ventric sep defect as curr comp fol acut myocardal infarc	MI
I23.3	Rup cardac wal withou haemopercard as cur comp fol ac MI	MI
I23.4	Rup chordae tendinae as curr comp fol acut myocard infarct	MI
I23.5	Rup papilary muscle as curr comp fol acute myocard infarct	MI
I23.6	Thromb atrium/auric append/vent as curr comp foll acute MI	MI
I23.8	Oth current comp following acute myocardial infarction	MI

ICD-10 codes	Descriptions	Disease type
I25.2	Old myocardial infarction	MI
I20.0	Unstable angina	Angina
I20.1	Angina pectoris with documented spasm	Angina
I20.8	Other forms of angina pectoris	Angina
I20.9	Angina pectoris, unspecified	Angina
I24.0	Coronary thrombosis not resulting in myocardial infarction	IHD
I24.1	Dressler's syndrome	IHD
I24.8	Other forms of acute ischaemic heart disease	IHD
I24.9	Acute ischaemic heart disease, unspecified	IHD
I25.0	Atherosclerotic cardiovascular disease, so described	IHD
I25.1	Atherosclerotic heart disease	IHD
I25.6	Silent myocardial ischaemia	IHD
I25.8	Other forms of chronic ischaemic heart disease	IHD
I25.9	Chronic ischaemic heart disease, unspecified	IHD
I51.6	Cardiovascular disease, unspecified	IHD
I51.7	Cardiomegaly	IHD
I70.0	Atherosclerosis of aorta	Atherosclerosis
I70.1	Atherosclerosis of renal artery	Atherosclerosis
I70.2	Atherosclerosis of arteries of extremities	Atherosclerosis
I70.8	Atherosclerosis of other arteries	Atherosclerosis
I70.9	Generalized and unspecified atherosclerosis	Atherosclerosis

ICD-10 codes for specifying internal bleeding.

ICD 10	ICD 10 description	Condition
K920	Haematemesis	Bleeding
K921	Melaena	Bleeding
K922	Gastrointestinal haemorrhage unspecified	Bleeding
K264	Duodenal ulcer chronic or unspecified with haemorrhage	Bleeding
K226	Gastro-oesophageal laceration-haemorrhage syndrome	Bleeding

ICD 10	ICD 10 description	Condition
K254	Gastric ulcer chronic or unspecified with haemorrhage	Bleeding
K260	Duodenal ulcer acute with haemorrhage	Bleeding
K290	Acute haemorrhagic gastritis	Bleeding
K228	Haemorrhage of oesophagus	Bleeding
K250	Gastric ulcer acute with haemorrhage	Bleeding
K274	Peptic ulcer chronic or unspecified with both haemorrhage and perforation	Bleeding
K266	Duodenal ulcer chronic or unspecified with haemorrhage	Bleeding
K262	Duodenal ulcer acute with both haemorrhage and perforation	Bleeding
K256	Gastric ulcer acute with chronic or unspecified with both haemorrhage and perforation	Bleeding
K270	Peptic ulcer acute with haemorrhage	Bleeding
K252	Gastric ulcer acute with both haemorrhage and perforation	Bleeding
K284	Gastrojejunal ulcer chronic or unspecified with haemorrhage	Bleeding
K280	Gastrojejunal ulcer acute with haemorrhage	Bleeding
K276	Peptic ulcer chronic or unspecified with haemorrhage	Bleeding
K286	Gastrojejunal ulcer chronic or unspecified with haemorrhage	Bleeding
K282	Gastrojejunal ulcer with both haemorrhage and perforation	Bleeding

8.3 Appendix 3. List of product and medical codes used for data extraction in CPRD

Read codes for smoking status

code	Description	Category
137T.00	Date ceased smoking	Ex-smoker
137O.00	Ex cigar smoker	Ex-smoker
137N.00	Ex pipe smoker	Ex-smoker
137l.00	Ex roll-up cigarette smoker	Ex-smoker
137S.00	Ex smoker	Ex-smoker
137j.00	Ex-cigarette smoker	Ex-smoker
137A.00	Ex-heavy smoker (20-39/day)	Ex-smoker
1378	Ex-light smoker (1-9/day)	Ex-smoker

code	Description	Category
1379	Ex-moderate smoker (10-19/day)	Ex-smoker
137F.00	Ex-smoker - amount unknown	Ex-smoker
1377	Ex-trivial smoker (<1/day)	Ex-smoker
137B.00	Ex-very heavy smoker (40+/day)	Ex-smoker
1371.11	Non-smoker	Non smoker
137K.00	Stopped smoking	Non smoker
137D.00	Admitted tobacco cons untrue ?	Smoker
137Y.00	Cigar consumption	Smoker
137J.00	Cigar smoker	Smoker
137X.00	Cigarette consumption	Smoker
137P.00	Cigarette smoker	Smoker
137R.00	Current smoker	Smoker
137m.00	Failed attempt to stop smoking	Smoker
1375	Heavy smoker - 20-39 cigs/day	Smoker
137C.00	Keeps trying to stop smoking	Smoker
1373	Light smoker - 1-9 cigs/day	Smoker
137h.00	Minutes from waking to first tobacco consumption	Smoker
1374	Moderate smoker - 10-19 cigs/d	Smoker
137d.00	Not interested in stopping smoking	Smoker
137H.00	Pipe smoker	Smoker
137a.00	Pipe tobacco consumption	Smoker
137b.00	Ready to stop smoking	Smoker
137f.00	Reason for restarting smoking	Smoker
137M.00	Rolls own cigarettes	Smoker
137V.00	Smoking reduced	Smoker
137e.00	Smoking restarted	Smoker
137Q.11	Smoking restarted	Smoker
137c.00	Thinking about stopping smoking	Smoker
137..11	Smoker - amount smoked	Smoker
137Z.00	Tobacco consumption NOS	Smoker
1372	Trivial smoker - < 1 cig/day	Smoker
137G.00	Trying to give up smoking	Smoker
1376	Very heavy smoker - 40+cigs/d	Smoker

Medication list for T2DM condition.

prodcode	productname
23	Metformin 500mg tablets
93	Metformin 850mg tablets
735	Metformin 100mg/ml Oral solution
7048	Metformin 500mg modified-release tablets
7166	Glucophage 500mg tablets (Merck Serono Ltd)
7610	Glucophage 850mg tablets (Merck Serono Ltd)
11990	Metformin 500mg/5ml oral solution sugar free
16044	Glucophage SR 500mg tablets (Merck Serono Ltd)
25678	Glucamet 500mg Tablet (Opus Pharmaceuticals Ltd)
26258	Glucamet 850mg Tablet (Opus Pharmaceuticals Ltd)
27501	Orabet 500mg Tablet (Lagap)
31146	Metsol 500mg/5ml oral solution (Kappin Ltd)
33087	Metformin 500mg tablets (Actavis UK Ltd)
33674	Metformin 850mg tablets (A A H Pharmaceuticals Ltd)
34004	Metformin 500mg tablets (IVAX Pharmaceuticals UK Ltd)
34020	Metformin 850mg tablets (IVAX Pharmaceuticals UK Ltd)
34135	Metformin 500mg Tablet (M & A Pharmachem Ltd)
34323	Metformin 500mg tablets (A A H Pharmaceuticals Ltd)
34504	Metformin 500mg tablets (Wockhardt UK Ltd)
34598	Metformin 500mg tablets (Generics (UK) Ltd)
34697	Metformin 850mg tablets (Wockhardt UK Ltd)
34742	Metformin 850mg tablets (Teva UK Ltd)
34836	Metformin 850mg tablets (Actavis UK Ltd)
34917	Metformin 500mg tablets (Teva UK Ltd)
38355	Metformin 750mg modified-release tablets
38400	Glucophage SR 750mg tablets (Merck Serono Ltd)
39560	Bolamyn SR 500mg tablets (Teva UK Ltd)
39598	Metformin 1g modified-release tablets
39729	Glucophage SR 1000mg tablets (Merck Serono Ltd)
39988	Metformin 500mg oral powder sachets sugar free
40007	Glucophage 1000mg oral powder sachets (Merck Serono Ltd)
40110	Glucophage 500mg oral powder sachets (Merck Serono Ltd)
40233	Metformin 1g oral powder sachets sugar free
42161	Orabet 500mg Tablet (Sandoz Ltd)

prodcode	productname
43270	Metformin 500mg/5ml oral solution sugar free (Rosemont Pharmaceuticals Ltd)
44250	Metformin 500mg/5ml Oral solution (Hillcross Pharmaceuticals Ltd)
45581	Metabet SR 500mg tablets (Morningside Healthcare Ltd)
46989	Metabet SR 1000mg tablets (Morningside Healthcare Ltd)
47939	Glucient SR 500mg tablets (Consilient Health Ltd)
48149	Metformin 500mg tablets (Almus Pharmaceuticals Ltd)
49502	Glucophage SR 500mg tablets (Mawdsley-Brooks & Company Ltd)
49738	Metformin 1g modified-release tablets (A A H Pharmaceuticals Ltd)
50570	Glucophage SR 500mg tablets (Lexon (UK) Ltd)
50821	Metformin 850mg tablets (Pfizer Ltd)
50970	Metformin 500mg tablets (Bristol Laboratories Ltd)
51080	Metabet SR 1000mg tablets (Actavis UK Ltd)
51135	Metformin 500mg modified-release tablets (A A H Pharmaceuticals Ltd)
51527	Metformin 500mg tablets (Boston Healthcare Ltd)
52221	Diagemet XL 500mg tablets (Thornton & Ross Ltd)
52442	Metformin 500mg tablets (Pfizer Ltd)
52634	Glucophage SR 500mg tablets (DE Pharmaceuticals)
53478	Metformin 500mg modified-release tablets (Kent Pharmaceuticals Ltd)
53774	Metabet SR 500mg tablets (Actavis UK Ltd)
53867	Metformin 500mg tablets (Zentiva)
54442	Metformin (roi) 1000mg Tablet
54898	Metformin 850mg tablets (Almus Pharmaceuticals Ltd)
55270	Duformin 500mg Tablet (Dumex Ltd)
55711	Metformin 500mg tablets (Alliance Healthcare (Distribution) Ltd)
55739	Metformin 500mg tablets (Tillomed Laboratories Ltd)
57147	Bolamyn SR 1000mg tablets (Teva UK Ltd)
57457	Metformin 500mg tablets (Aurobindo Pharma Ltd)
58051	Metformin 500mg/5ml oral solution
58607	Metformin 500mg/5ml oral solution sugar free (Zentiva)
59620	Glucophage SR 500mg tablets (Waymade Healthcare Plc)
60012	Dapagliflozin 5mg / Metformin 1g tablets
60074	Metformin 1g modified-release tablets (Waymade Healthcare Plc)
60286	Metformin 500mg/5ml oral suspension
60643	Xigduo 5mg/1000mg tablets (AstraZeneca UK Ltd)

prodcode	productname
60968	Metformin 500mg modified-release tablets (Actavis UK Ltd)
61043	Sukkarto SR 1000mg tablets (Morningside Healthcare Ltd)
61559	Sukkarto SR 500mg tablets (Morningside Healthcare Ltd)
62144	Metformin 500mg modified-release tablets (DE Pharmaceuticals)
62265	Metformin 500mg modified-release tablets (Mawdsley-Brooks & Company Ltd)
62605	Metformin 850mg tablets (Kent Pharmaceuticals Ltd)
11609	Metformin with rosiglitazone 500mg + 1mg Tablet
11610	Metformin with rosiglitazone 500mg + 2mg Tablet
11737	Metformin with rosiglitazone 1000mg + 4mg Tablet
11760	Metformin with rosiglitazone 1000mg + 2mg Tablet
30316	Metformin with pioglitazone 850mg + 15mg Tablet
50682	Jentadueto 2.5mg/1000mg tablets (Boehringer Ingelheim Ltd)
52445	Linagliptin 2.5mg / Metformin 1g tablets
52449	Linagliptin 2.5mg / Metformin 850mg tablets
54150	Jentadueto 2.5mg/850mg tablets (Boehringer Ingelheim Ltd)
1589	U100 Insulin syringe 0.5ml
1591	U100 Insulin syringe 1ml
5620	U100 Insulin syringe 0.3ml
5962	Humapen inj device Injection device (Eli Lilly and Company Ltd)
6724	U100 Insulin syringe 0.3ml
7412	U100 Insulin syringe 0.5ml
9363	U100 Insulin syringe 0.5ml
9619	Bd Ultra Pen 1.5ml Insulin pen (Becton, Dickinson UK Ltd)
10133	U100 Insulin syringe 1ml
10145	Humapen luxura insulin pen 3ml/1-60 units Insulin pen 3ml/1-60 units (Eli Lilly and Company Ltd)
11086	B-d u-100 0.5ml Insulin syringe (Becton, Dickinson UK Ltd)
11245	B-d u-100 0.3ml Insulin syringe (Becton, Dickinson UK Ltd)
11271	B-d u-100 1ml Insulin syringe (Becton, Dickinson UK Ltd)
11345	Bd Ultra Pen 3ml Insulin pen (Becton, Dickinson UK Ltd)
11346	B-d u-100 0.3ml Insulin syringe (Becton, Dickinson UK Ltd)
12840	B-d u-100 0.5ml Insulin syringe (Becton, Dickinson UK Ltd)
12892	Clinipak u100 single use ins syr+12mm need28g 0.5ml [rand] 0.5ml Insulin syringe with 28gauge needle 12mm (Rand Rocket Ltd)
13274	Clinipak u100 single use ins syr+12mm need28g 1ml [rand] 1ml Insulin syringe with 28gauge needle 12mm (Rand Rocket Ltd)

prodcode	productname
13474	U100 Insulin syringe Sp.36 [2A] 1ml
13969	U100 Insulin syringe 0.3ml
14642	Bd m 0.3ml Insulin syringe with 29gauge needle 12mm (Becton, Dickinson UK Ltd)
17377	Novopen inj device Injection device (Novo Nordisk Ltd)
17405	Novopen classic inj device Injection device (Novo Nordisk Ltd)
18149	Monoject u100 insulin syringe 12mm(29g)0.5ml 12mm29G 0.5ml Insulin syringe (Covidien (UK) Commercial Ltd)
21223	U100 Insulin syringe 0.3ml
22328	Unifine single use Insulin syringe with 30gauge needle 8mm 0.5ml (Owen Mumford Ltd)
24554	Unifine single use Insulin syringe with 30gauge needle 8mm 0.3ml (Owen Mumford Ltd)
25422	Hypoguard u100 click/count 1ml Insulin syringe (Hypoguard Ltd)
29090	Novopen fun inj device Injection device (Novo Nordisk Ltd)
33914	Omnican 30 12mm 29G 0.3ml Syringe (B.Braun Medical Ltd)
35017	Optipen pro 1 white insulin pen 3ml/1-60 units 3ml/1-60 units Insulin pen (Aventis Pharma)
35078	Optipen pro 1 blue insulin pen 3ml/1-60 units 3ml/1-60 units Insulin pen (Aventis Pharma)
35218	Optipen pro 1 yellow insulin pen 3ml/1-60 units 3ml/1-60 units Insulin pen (Aventis Pharma)
49506	Insujet needle free starter kit Starter kit (European Pharma Group BV)
1273	Monolet type A Lancet sterile single use 0.8mm/21gauge (Sherwood Davis & Geck)
1275	Softclix Lancet sterile single use 0.8mm/21gauge (Roche Diagnostics Ltd)
1779	Unilet G superlite type A Lancet sterile single use 0.66mm/23gauge (Owen Mumford Ltd)
1800	Ames type B Lancet sterile single use 0.5mm/25gauge (Bayer Diagnostics Manufacturing Ltd)
2024	Micro-Fine Lancet sterile single use (Becton, Dickinson UK Ltd)
2809	Unilet type B Lancet sterile single use (Owen Mumford Ltd)
3770	Novofine Hypodermic needle 12mm/28gauge (Novo Nordisk Ltd)
4686	Unilet superlite type B Lancet sterile single use 0.66mm/23gauge (Owen Mumford Ltd)
4774	Unilet universal comfortouch type A and B Lancet sterile single use 0.45mm/26gauge (Owen Mumford Ltd)
5120	Unilet GP Lancet sterile single use Type A 0.81mm/21gauge (Owen Mumford Ltd)
5222	Softclix Lancing device (Roche Diagnostics Ltd)

prodcode	productname
5285	Unilet GP Lancet sterile single use Type A 0.38mm/28gauge (Owen Mumford Ltd)
5726	Unilet general purpose type A Lancet sterile single use 0.38mm/28gauge (Owen Mumford Ltd)
7113	Unistik 2 Lancet sterile single use (Owen Mumford Ltd)
8939	Carrying case spec 17a hypodermic syringe
9260	BD Micro-Fine Plus type A Lancet sterile single use 0.36mm/28gauge (Becton, Dickinson UK Ltd)
9287	Baylet Lancet sterile single use 0.5mm/25gauge (Bayer Diagnostics Manufacturing Ltd)
9297	Baylet Lancet sterile single use 0.5mm/25gauge (Bayer Diagnostics Manufacturing Ltd)
9302	Sterile single use hypodermic Needle 0.5mm/25gauge
9388	Luer Mount Hypodermic needle Sp15[Sp2B]
9998	Pen Injector screw on hypodermic needle 6.2mm to 9.9mm
11155	Unilet G superlite type A Lancet sterile single use AT0450 0.66mm/23gauge (Owen Mumford Ltd)
11343	Unilet universal comfortouch type A Lancet sterile single use AT460 0.45mm/26gauge (Owen Mumford Ltd)
11617	Pen Injector screw on hypodermic needle < or = 6.1mm
11877	Pen Injector snap on hypodermic needle < or = 6.1mm
11936	Sharpsguard orange Container 1 litre (Daniels Pharmaceutical Ltd)
12676	General purpose lancet
12686	Unilet type B Lancet sterile single use (Owen Mumford Ltd)
13203	Pen Injector snap on hypodermic needle 6.2mm to 9.9mm
14589	Microlance sterile Hypodermic single use needle 0.45mm/26gauge/16mm (Becton, Dickinson UK Ltd)
15147	Cleanlet 25 type A Lancet sterile single use 0.5mm/25gauge (Zygo Medica)
15358	Pen Injector screw on hypodermic needle = or > 10mm
16155	Vitalcare auto safety soft (blue) 1.8mm/21gauge Lancets (VitalCare (UK))
16825	General purpose lancet
20567	Ames type B Lancet sterile single use 0.65mm/23gauge (Bayer Diagnostics Manufacturing Ltd)
22957	Pen Injector snap on hypodermic needle = or > 10mm
28645	Milward steri-let type A Lancet sterile single use 0.66mm/23gauge (Entaco Ltd)
29677	Cleanlet 25 xl type B Lancet sterile single use 0.5mm/25gauge (Gainor Medical Europe)

prodcode	productname
30074	Sabre single use Hypodermic single use needle 0.4mm 27G 12mm (Sabre International)
31567	Neoject Hypodermic needle 0.5mm/25gauge (Neomedic Ltd)
33964	Unilet universal comfortouch type B Lancet sterile single use AT460 0.45mm/26gauge (Owen Mumford Ltd)
34158	Unilet G superlite type A Lancet sterile single use AT0455 0.66mm/23gauge (Owen Mumford Ltd)
35325	Microlance sterile Hypodermic needle 0.5mm/23G/inch (Becton, Dickinson UK Ltd)
35551	Neoject Hypodermic needle 0.45mm/26gauge/16mm (Neomedic Ltd)
35552	Neoject Hypodermic needle 0.4mm/27gauge (Neomedic Ltd)
36648	Sterile single use hypodermic Needle 0.5mm/23gauge
37216	Sharpsguard purple Container 1 litre (Daniels Pharmaceutical Ltd)
37585	Sharpsguard yellow Container 1 litre (Daniels Pharmaceutical Ltd)
40389	Unilet universal comfortouch type B Lancet sterile single use AT465 0.45mm/26gauge (Owen Mumford Ltd)
44248	Unilet G superlite type A Lancet sterile single use AT0450 0.66mm/23gauge (Owen Mumford Ltd)
44405	Unistik 2 extra Lancets (Owen Mumford Ltd)
45858	U100 Screw cap
58961	Mylife Penfine Classic hypodermic insulin needles for pre-filled / reusable pen injectors screw on 4mm/32gauge (Ypsomed Ltd)
59004	Mylife Penfine Classic hypodermic insulin needles for pre-filled / reusable pen injectors screw on 6mm/32gauge (Ypsomed Ltd)
59005	Mylife Penfine Classic hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/31gauge (Ypsomed Ltd)
1274	Glucotrend colorimetric strips Colorimetric strips (Roche Diagnostics Ltd)
4249	Dextrostix colorimetric strips [bayer] Colorimetric strips (Bayer Diagnostics Manufacturing Ltd)
5213	Glucotrend plus colorimetric strips Colorimetric strips (Roche Diagnostics Ltd)
5286	Advantage ii Biosensor strips (Roche Diagnostics Ltd)
5507	Medisense optium biosensor strips Biosensor strips (Abbott Laboratories Ltd)
15692	Ga Colorimetric strips (Hypoguard Ltd)
19388	Glucose vt colorimetric strips Colorimetric strips (BioCare Ltd)
5691	Multistix GP Reagent strips (Bayer Diagnostics Manufacturing Ltd)
6394	Uristix Strips (Bayer Diagnostics Manufacturing Ltd)
8802	Albym test Strips (Boehringer Mannheim UK Ltd)

prodcode	productname
9556	Clinitest urine sugar analysis Set (Bayer Diagnostics Manufacturing Ltd)
11472	Medi-test combi 5s strips Strips (BHR Pharmaceuticals Ltd)
11558	Medi-test combi 10l strips Strips (BHR Pharmaceuticals Ltd)
21303	Labstix Strips (Bayer Diagnostics Manufacturing Ltd)
21729	Multistix 10 s.g. Reagent strips (Bayer Diagnostics Manufacturing Ltd)
22065	Micral-test strips Strips (Roche Diagnostics Ltd)
37301	Phenistix 50 Strips (Bayer Diagnostics Manufacturing Ltd)
40375	Micral-test ii strips Strips (Roche Diagnostics Ltd)
1593	Insulatard penfill 100 100iu/ml Penfill (Novo Nordisk Ltd)
1595	Insulatard NovoLet 100units/ml suspension for injection (Novo Nordisk Ltd)
1649	Human actraphane 100iu/ml Injection (Novo Nordisk Ltd)
1805	Mixtard 30/70 100unit/ml Injection (Novo Nordisk Ltd)
1806	Penmix 30/70 100iu/ml Penfill (Novo Nordisk Ltd)
1886	Insulatard 100iu/ml GE injection (Novo Nordisk Ltd)
2220	Penmix 20/80 Pen (Novo Nordisk Ltd)
2454	Mixtard 30 penfill 100 100iu/ml Penfill (Novo Nordisk Ltd)
2929	Mixtard 30 100iu/ml GE injection (Novo Nordisk Ltd)
3396	Penmix 10/90 Penfill (Novo Nordisk Ltd)
3439	Penmix 10/90 Pen (Novo Nordisk Ltd)
3550	Mixtard 40 penfill 100 100iu/ml Penfill (Novo Nordisk Ltd)
3551	Mixtard 20 penfill 100 100iu/ml Penfill (Novo Nordisk Ltd)
4163	Rapitard MC 100unit/ml Injection (Novo Nordisk Ltd)
4198	Humulin m3 100unit/ml M3 injection (Eli Lilly and Company Ltd)
4199	Humulin m1 100unit/ml M1 injection (Eli Lilly and Company Ltd)
4715	Humalog mix 25 25/75 100units/ml Injection (Eli Lilly and Company Ltd)
4760	Humulin i 100unit/ml Injection (Eli Lilly and Company Ltd)
4784	Lentard mc 100unit/ml Injection (Novo Nordisk Ltd)
4790	Mixtard 50 penfill 100 100iu/ml Penfill (Novo Nordisk Ltd)
5250	Insulin biphasic lispro human prb 25:75; 100 units/ml Injection
5255	Mixtard 10 penfill 100 100iu/ml Penfill (Novo Nordisk Ltd)
5501	Insuman basal 100iu/ml Injection (Aventis Pharma)
5891	Insulatard FlexPen 100units/ml suspension for injection (Novo Nordisk Ltd)

prodcode	productname
5953	Insulin glargine 100iu/ml Injection
6057	Lantus 100iu/ml Injection (Aventis Pharma)
6061	Novomix 30 30/70 100units/ml Injection (Novo Nordisk Ltd)
6958	Levemir FlexPen 100units/ml solution for injection 3ml pre-filled pen (Novo Nordisk Ltd)
6965	Levemir Penfill 100units/ml solution for injection 3ml cartridges (Novo Nordisk Ltd)
7237	Lantus 100units/ml solution for injection 3ml pre-filled OptiSet pen (Sanofi)
7266	Lantus 100units/ml solution for injection 3ml cartridges (Sanofi)
7350	Insulin isophane porcine 100units/ml suspension for injection 10ml vials
7393	Insulin glargine 100units/ml solution for injection 3ml cartridges
7400	Insulin glargine 100units/ml solution for injection 3ml pre-filled disposable devices
7402	Lantus 100units/ml solution for injection 10ml vials (Sanofi)
7771	Human protaphane penfill 100 100unit/ml Penfill (Novo Nordisk Ltd)
7772	Human protaphane 100unit/ml Injection (Novo Nordisk Ltd)
8118	Humaject i 100iu/ml Pen (Eli Lilly and Company Ltd)
8203	Penmix 50/50 100iu/ml Penfill (Novo Nordisk Ltd)
8322	Insulin zinc suspension mixed human pyr 100unit/ml Injection
8895	Initard 50/50 100unit/ml Injection (Novo Nordisk Ltd)
9341	Insulin biphasic isophane human prb 30:70; 100 units/ml Injection
9376	Insulin zinc suspension crystalline human pyr 100unit/ml long acting Injection
9503	Hypurin Bovine Protamine Zinc 100units/ml suspension for injection 10ml vials (Wockhardt UK Ltd)
9737	Insulatard innolet 100iu/ml Injection (Novo Nordisk Ltd)
10001	Humalog Mix50 Pen 100units/ml suspension for injection 3ml pre-filled pen (Eli Lilly and Company Ltd)
10067	Insulin biphasic aspart human pyr 30:70; 100 units/ml Injection
10184	Insulin detemir 100 iu/ml Solution for injection
10207	Insulin isophane human 100units/ml suspension for injection 3ml cartridges
10208	Insulatard InnoLet 100units/ml suspension for injection 3ml pre-filled pen (Novo Nordisk Ltd)
10225	Lantus 100units/ml solution for injection 3ml OptiClik cartridges (Sanofi)
10229	Humulin I Pen 100units/ml suspension for injection 3ml pre-filled pen (Eli Lilly and Company Ltd)

prodcode	productname
10243	Humalog Mix25 100units/ml suspension for injection 3ml cartridges (Eli Lilly and Company Ltd)
10259	Insulin glargine 100units/ml solution for injection 10ml vials
10484	Penmix 20/80 Penfill (Novo Nordisk Ltd)
10887	Penmix 40/60 100iu/ml Penfill (Novo Nordisk Ltd)
10910	Humaject m2 100iu/ml M2 pen (Eli Lilly and Company Ltd)
10915	Humaject m1 100iu/ml M1 pen (Eli Lilly and Company Ltd)
11055	Insulin biphasic isophane human pyr 20:80; 100 units/ml Injection
11056	Insulin biphasic isophane human pyr 30:70; 100 units/ml Injection
11080	Insulin isophane human prb 100iu/ml Injection
11107	Humulin m4 100unit/ml M4 injection (Eli Lilly and Company Ltd)
12035	Insulin zinc mixed bovine 100units/ml suspension for injection 10ml vials
12299	Semitard mc 100unit/ml Injection (Novo Nordisk Ltd)
13416	Insulin biphasic 100 units/ml Injection
13516	Hypurin bovine isophane 100unit/ml Injection (C P Pharmaceuticals Ltd)
13729	Insulin isophane human emp 100unit/ml Injection
13837	Insulin biphasic isophane human prb 10:90; 100 units/ml Injection
14270	Humalog Mix25 Pen 100units/ml suspension for injection 3ml pre-filled pen (Eli Lilly and Company Ltd)
14290	Insulatard Penfill 100units/ml suspension for injection 3ml cartridges (Novo Nordisk Ltd)
14301	Insulin detemir 100units/ml solution for injection 3ml cartridges
14330	Insulin detemir 100units/ml solution for injection 3ml pre-filled disposable devices
14340	Hypurin Bovine Isophane 100units/ml suspension for injection 10ml vials (Wockhardt UK Ltd)
14357	Humulin I 100units/ml suspension for injection 3ml cartridges (Eli Lilly and Company Ltd)
14505	Insulin protamine zinc bovine 100units/ml suspension for injection 10ml vials
14644	Insulin biphasic isophane human prb 20:80; 100 units/ml Injection
14649	Insulin biphasic isophane human pyr 10:90; 100 units/ml Injection
14918	Humulin I 100units/ml suspension for injection 10ml vials (Eli Lilly and Company Ltd)
14925	Insulin isophane human vial 100unit/ml Sterile suspension injection
14928	Insulatard 100units/ml suspension for injection 10ml vials (Novo Nordisk Ltd)
14933	Hypurin Porcine Isophane 100units/ml suspension for injection 3ml cartridges (Wockhardt UK Ltd)

prodcode	productname
15199	Insuman comb 25 100iu/ml Injection (Aventis Pharma)
15961	Insulin isophane human crb 100iu/ml Injection
16682	Tempulin 100unit/ml Injection (Knoll Ltd)
16700	Insulin zinc mixed bovine vial 100unit/ml Sterile suspension injection
17712	Hypurin Bovine Lente 100units/ml suspension for injection 10ml vials (Wockhardt UK Ltd)
17731	Penmix 50/50 100iu/ml Injection (Novo Nordisk Ltd)
17809	Humaject m4 100iu/ml M4 pen (Eli Lilly and Company Ltd)
18590	Insulin isophane bovine 100units/ml suspension for injection 10ml vials
18593	Humalog Mix50 100units/ml suspension for injection 3ml cartridges (Eli Lilly and Company Ltd)
20422	Insuman comb 15 100iu/ml Injection (Aventis Pharma)
21110	Insulin biphasic isophane human prb 50:50; 100 units/ml Injection
21347	Penmix 40/60 100iu/ml Injection (Novo Nordisk Ltd)
21374	Insulin biphasic isophane human prb 40:60; 100 units/ml Injection
21395	Insulin biphasic isophane human pyr 40:60; 100 units/ml Injection
21554	Insuman comb 50 100iu/ml Injection (Aventis Pharma)
22058	Pur-in mix 15/85 Injection (C P Pharmaceuticals Ltd)
22155	Humaject m5 100iu/ml M5 pen (Eli Lilly and Company Ltd)
23992	Insuman Basal 100units/ml suspension for injection 3ml pre-filled OptiSet pen (Sanofi)
25812	Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices
26403	Pur-in mix 25/75 Injection (C P Pharmaceuticals Ltd)
26498	Insulin zinc suspension mixed bovine and porcine 100unit/ml Injection
27177	Insulin biphasic lispro human prb 50:50; 100 units/ml Injection
27461	Insuman Basal 100units/ml suspension for injection 3ml cartridges (Sanofi)
27614	Penmix 30/70 100iu/ml Injection (Novo Nordisk Ltd)
28183	Hypurin Porcine Isophane 100units/ml suspension for injection 10ml vials (Wockhardt UK Ltd)
28185	Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml cartridges
28588	Hypurin Bovine Isophane 100units/ml suspension for injection 3ml cartridges (Wockhardt UK Ltd)
29837	Insulin biphasic isophane human prb 25:75; 100 units/ml Injection
30236	Isophane insulin 100iu/ml Injection

prodcode	productname
30686	Insulin isophane porcine 100units/ml suspension for injection 3ml cartridges
31258	Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices
33167	Insulin biphasic isophane human crb 25:75; 100 units/ml Injection
33966	Insulatard 100unit/ml Injection (Novo Nordisk Ltd)
34031	Monotard mc 100unit/ml Injection (Novo Nordisk Ltd)
34097	Human initard 50/50 100unit/ml Injection (Novo Nordisk Ltd)
35260	Levemir InnoLet 100units/ml solution for injection 3ml pre-filled pen (Novo Nordisk Ltd)
35468	Insuman Basal 100units/ml suspension for injection 5ml vials (Sanofi)
35701	Insulin lispro biphasic 50/50 100units/ml suspension for injection 3ml pre-filled disposable devices
36066	Insulin isophane bovine 100units/ml suspension for injection 3ml cartridges
36146	Insulin lispro biphasic 50/50 100units/ml suspension for injection 3ml cartridges
36853	Lantus 100units/ml solution for injection 3ml pre-filled SoloStar pen (Sanofi)
38422	Isophane 100iu/ml Injection (Celltech Pharma Europe Ltd)
39006	Humalog Mix25 KwikPen 100units/ml suspension for injection 3ml pre-filled pen (Eli Lilly and Company Ltd)
39086	Humalog Mix50 KwikPen 100units/ml suspension for injection 3ml pre-filled pen (Eli Lilly and Company Ltd)
41834	Insulin zinc suspension lente 100iu/ml Injection (Celltech Pharma Europe Ltd)
42395	Humalog Mix25 100units/ml suspension for injection 10ml vials (Eli Lilly and Company Ltd)
43950	Humulin I KwikPen 100units/ml suspension for injection 3ml pre-filled pen (Eli Lilly and Company Ltd)
43953	Insulin lispro biphasic 25/75 100units/ml suspension for injection 10ml vials
44251	Insulin zinc suspension mixed porcine 100unit/ml Injection
46001	Insuman Basal 100units/ml suspension for injection 3ml pre-filled SoloStar pen (Sanofi)
47856	Neuphane 100unit/ml Injection (Wellcome Medical Division)
49831	Lantus 100units/ml solution for injection 3ml pre-filled SoloStar pen (Necessity Supplies Ltd)
50633	Lantus 100units/ml solution for injection 3ml cartridges (Necessity Supplies Ltd)
52522	Humalog Mix50 KwikPen 100units/ml suspension for injection 3ml pre-filled pen (DE Pharmaceuticals)

prodcode	productname
52748	Insulatard Penfill 100units/ml suspension for injection 3ml cartridges (Waymade Healthcare Plc)
54462	Insulin biphasic isophane human emp 25:75; 100 units/ml Injection
55234	Tresiba FlexTouch 200units/ml solution for injection 3ml pre-filled pen (Novo Nordisk Ltd)
55462	Tresiba FlexTouch 100units/ml solution for injection 3ml pre-filled pen (Novo Nordisk Ltd)
55517	Insulin isophane human 100units/ml suspension for injection 10ml vials
55618	Levemir FlexPen 100units/ml solution for injection 3ml pre-filled pen (Waymade Healthcare Plc)
55687	Insulin degludec 100units/ml solution for injection 3ml pre-filled disposable devices
55907	Insulin degludec 100units/ml solution for injection 3ml cartridges
55910	Tresiba Penfill 100units/ml solution for injection 3ml cartridges (Novo Nordisk Ltd)
56691	Insulin degludec 200units/ml solution for injection 3ml pre-filled disposable devices
57622	Humalog Mix50 KwikPen 100units/ml suspension for injection 3ml pre-filled pen (Waymade Healthcare Plc)
59500	Insulin isophane human 100units/ml suspension for injection 5ml vials
479	Acarbose 50mg tablets
548	Pioglitazone 15mg tablets
3740	Guar gum 90% granules
4307	Guarina Sachets (Norgine Pharmaceuticals Ltd)
5174	Acarbose 100mg tablets
5621	Glucobay 50mg tablets (Bayer Plc)
5678	Nateglinide 120mg tablets
5989	Nateglinide 180mg tablets
7695	Guarem Sachets (Shire Pharmaceuticals Ltd)
9105	Glucobay 100mg tablets (Bayer Plc)
9699	Pioglitazone 30mg tablets
9707	Repaglinide 1mg tablets
9748	Repaglinide 2mg tablets
9865	Repaglinide 500microgram tablets
10051	Pioglitazone 45mg tablets
11316	NovoNorm 500microgram tablets (Novo Nordisk Ltd)
11321	NovoNorm 1mg tablets (Novo Nordisk Ltd)
11366	NovoNorm 2mg tablets (Novo Nordisk Ltd)

prodcode	productname
11483	Nateglinide 60mg tablets
13628	Romozin 400mg Tablet (Glaxo Wellcome UK Ltd)
15955	Starlix 120mg tablets (Novartis Pharmaceuticals UK Ltd)
18220	Pioglitazone 15mg / Metformin 850mg tablets
19472	Actos 45mg tablets (Takeda UK Ltd)
20287	Actos 15mg tablets (Takeda UK Ltd)
20889	Actos 30mg tablets (Takeda UK Ltd)
23945	Starlix 60mg tablets (Novartis Pharmaceuticals UK Ltd)
27125	Starlix 180mg tablets (Novartis Pharmaceuticals UK Ltd)
31077	Competact 15mg/850mg tablets (Takeda UK Ltd)
35022	Sitagliptin 100mg tablets
35144	Byetta 5micrograms/0.02ml solution for injection 1.2ml pre-filled disposable devices (AstraZeneca UK Ltd)
35149	Exenatide 10micrograms/0.04ml solution for injection 2.4ml pre-filled disposable devices
35150	Byetta 10micrograms/0.04ml solution for injection 2.4ml pre-filled disposable devices (AstraZeneca UK Ltd)
35251	Exenatide 5micrograms/0.02ml solution for injection 1.2ml pre-filled disposable devices
35462	Januvia 100mg tablets (Merck Sharp & Dohme Ltd)
35561	Prandin 2mg tablets (Novo Nordisk Ltd)
36774	Prandin 1mg tablets (Novo Nordisk Ltd)
36948	Prandin 0.5mg tablets (Novo Nordisk Ltd)
37617	Rosiglitazone 2mg tablet
37874	Vildagliptin 50mg / Metformin 850mg tablets
37902	Vildagliptin 50mg / Metformin 1g tablets
38551	Eucreas 50mg/1000mg tablets (Novartis Pharmaceuticals UK Ltd)
39203	Eucreas 50mg/850mg tablets (Novartis Pharmaceuticals UK Ltd)
40642	Victoza 6mg/ml solution for injection 3ml pre-filled pen (Novo Nordisk Ltd)
40693	Liraglutide 6mg/ml solution for injection 3ml pre-filled disposable devices
41204	Saxagliptin 5mg tablets
41431	Onglyza 5mg tablets (AstraZeneca UK Ltd)
43619	Metformin 1g / Sitagliptin 50mg tablets
43684	Janumet 50mg/1000mg tablets (Merck Sharp & Dohme Ltd)
45775	Saxagliptin 2.5mg tablets
45821	Onglyza 2.5mg tablets (AstraZeneca UK Ltd)

prodcode	productname
46458	Exenatide 2mg powder and solvent for suspension for injection vials
46469	Bydureon 2mg powder and solvent for suspension for injection vials (AstraZeneca UK Ltd)
46665	Linagliptin 5mg tablets
46716	Trajenta 5mg tablets (Boehringer Ingelheim Ltd)
48120	Avandia 2mg Tablet (GlaxoSmithKline UK Ltd)
48139	Pioglitazone 30mg tablets (A A H Pharmaceuticals Ltd)
48401	Sitagliptin 50mg tablets
48533	Sitagliptin 25mg tablets
50087	Januvia 50mg tablets (Merck Sharp & Dohme Ltd)
50124	Januvia 25mg tablets (Merck Sharp & Dohme Ltd)
52203	Enyglid 0.5mg tablets (Consilient Health Ltd)
54182	Dapagliflozin 10mg tablets
54203	Forxiga 10mg tablets (AstraZeneca UK Ltd)
54265	Dapagliflozin 5mg tablets
54480	Forxiga 5mg tablets (AstraZeneca UK Ltd)
54891	Saxagliptin 2.5mg / Metformin 1g tablets
54973	Saxagliptin 2.5mg / Metformin 850mg tablets
55413	Lixisenatide 20micrograms/0.2ml solution for injection 3ml pre-filled disposable devices
55459	Lixisenatide 10micrograms/0.2ml solution for injection 3ml pre-filled disposable devices
55723	Lixisenatide 10micrograms/0.2ml solution for injection 3ml pre-filled disposable devices and Lixisenatide 20micrograms/0.2ml solution for injection 3ml pre-filled disposable devices
55728	Lyxumia 10micrograms/0.2ml solution for injection 3ml pre-filled pen (Sanofi)
55729	Lyxumia 20micrograms/0.2ml solution for injection 3ml pre-filled pen (Sanofi)
55767	Lyxumia 10micrograms/0.2ml solution for injection 3ml pre-filled pen and Lyxumia 20micrograms/0.2ml solution for injection 3ml pre-filled pen (Sanofi)
56208	Pioglitazone 15mg tablets (A A H Pharmaceuticals Ltd)
56831	Troglitazone 200mg Tablet
56965	Komboglyze 2.5mg/1000mg tablets (AstraZeneca UK Ltd)
57659	Pioglitazone 30mg tablets (Actavis UK Ltd)
58865	Komboglyze 2.5mg/850mg tablets (AstraZeneca UK Ltd)
60073	Canagliflozin 100mg tablets
60211	Canagliflozin 100mg tablets

prodcode	productname
60379	Invokana 300mg tablets (Janssen-Cilag Ltd)
60386	Canagliflozin 300mg tablets
60430	Invokana 100mg tablets (Janssen-Cilag Ltd)
61756	Empagliflozin 10mg tablets
61925	NovoNorm 500microgram tablets (Waymade Healthcare Plc)
62172	Empagliflozin 25mg tablets
62426	Pioglitazone 30mg tablets (Accord Healthcare Ltd)
62661	Bydureon 2mg powder and solvent for suspension for injection pre-filled pen (AstraZeneca UK Ltd)
5021	NovoRapid Penfill 100units/ml solution for injection 3ml cartridges (Novo Nordisk Ltd)
5892	NovoRapid FlexPen 100units/ml solution for injection 3ml pre-filled pen (Novo Nordisk Ltd)
6209	NovoRapid 100units/ml solution for injection 10ml vials (Novo Nordisk Ltd)
6447	Insulin aspart human pyr 100 iu/ml Injection
7318	Humalog 100units/ml solution for injection 3ml cartridges (Eli Lilly and Company Ltd)
7349	Actrapid 100units/ml solution for injection 10ml vials (Novo Nordisk Ltd)
9521	Pork Actrapid 100units/ml solution for injection 10ml vials (Novo Nordisk Ltd)
10264	Humalog Pen 100units/ml solution for injection 3ml pre-filled pen (Eli Lilly and Company Ltd)
14299	Insulin glulisine 100units/ml solution for injection 3ml cartridges
14313	Insulin lispro 100units/ml solution for injection 3ml cartridges
14339	Hypurin Bovine Neutral 100units/ml solution for injection 10ml vials (Wockhardt UK Ltd)
14345	Apidra 100units/ml solution for injection 3ml cartridges (Sanofi)
14362	Insulin lispro 100units/ml solution for injection 3ml pre-filled disposable devices
14930	Hypurin Porcine Neutral 100units/ml solution for injection 3ml cartridges (Wockhardt UK Ltd)
14944	Humulin S 100units/ml solution for injection 3ml cartridges (Eli Lilly and Company Ltd)
16129	Insulin soluble human 100units/ml solution for injection 3ml cartridges
16142	Insulin aspart 100units/ml solution for injection 3ml cartridges
18224	Humalog 100units/ml solution for injection 10ml vials (Eli Lilly and Company Ltd)
18592	Insulin soluble bovine 100units/ml solution for injection 10ml vials

prodcode	productname
19491	Apidra 100units/ml solution for injection 10ml vials (Sanofi)
19877	Insulin aspart 100units/ml solution for injection 3ml pre-filled disposable devices
21235	Humulin S 100units/ml solution for injection 10ml vials (Eli Lilly and Company Ltd)
21583	Apidra 100units/ml solution for injection 3ml pre-filled OptiSet pen (Sanofi)
21590	Insulin glulisine 100units/ml solution for injection 3ml pre-filled disposable devices
22983	Insuman Rapid 100units/ml solution for injection 3ml cartridges (Sanofi)
23231	Hypurin Bovine Neutral 100units/ml solution for injection 3ml cartridges (Wockhardt UK Ltd)
23993	Insuman Rapid 100units/ml solution for injection 3ml pre-filled OptiSet pen (Sanofi)
25479	Insulin soluble porcine 100units/ml solution for injection 3ml cartridges
26060	Insulin lispro 100units/ml solution for injection 10ml vials
26098	Hypurin Porcine Neutral 100units/ml solution for injection 10ml vials (Wockhardt UK Ltd)
27396	Insulin soluble porcine 100units/ml solution for injection 10ml vials
27402	Insulin soluble human 100units/ml solution for injection 10ml vials
28101	Insulin glulisine 100units/ml solution for injection 10ml vials
28442	Insulin glulisine 100unit/ml Solution for injection
29567	Insulin aspart 100units/ml solution for injection 10ml vials
29953	Apidra 100units/ml solution for injection 3ml OptiClik cartridges (Sanofi)
36430	Insulin soluble human 100units/ml solution for injection 3ml pre-filled disposable devices
36920	Apidra 100units/ml solution for injection 3ml pre-filled SoloStar pen (Sanofi)
38986	Humalog KwikPen 100units/ml solution for injection 3ml pre-filled pen (Eli Lilly and Company Ltd)
46666	NovoRapid FlexTouch 100units/ml solution for injection 3ml pre-filled pen (Novo Nordisk Ltd)
49108	NovoRapid Penfill 100units/ml solution for injection 3ml cartridges (Necessity Supplies Ltd)
51743	NovoRapid Penfill 100units/ml solution for injection 3ml cartridges (Sigma Pharmaceuticals Plc)
53118	NovoRapid FlexPen 100units/ml solution for injection 3ml pre-filled pen (Mawdsley-Brooks & Company Ltd)
53251	NovoRapid Penfill 100units/ml solution for injection 3ml cartridges (DE Pharmaceuticals)

prodcode	productname
55603	Humalog KwikPen 100units/ml solution for injection 3ml pre-filled pen (DE Pharmaceuticals)
57529	Humalog 100units/ml solution for injection 10ml vials (Dowelhurst Ltd)
57564	Humalog KwikPen 100units/ml solution for injection 3ml pre-filled pen (Waymade Healthcare Plc)
59533	NovoRapid FlexPen 100units/ml solution for injection 3ml pre-filled pen (Sigma Pharmaceuticals Plc)
61845	NovoRapid PumpCart 100units/ml solution for injection 1.6ml cartridges (Novo Nordisk Ltd)
62180	Insulin aspart 100units/ml solution for injection 1.6ml cartridges
1588	Actrapid 100iu/ml Injection (Novo Nordisk Ltd)
1592	Actrapid penfill 100 100iu/ml Penfill (Novo Nordisk Ltd)
1840	Humulin s 100unit/ml Injection (Eli Lilly and Company Ltd)
1842	Pork velosulin 100unit/ml Injection (Novo Nordisk Ltd)
10572	Insulin soluble bovine 100unit/ml Injection
12297	Hypurin bovine neutral 100unit/ml Injection (C P Pharmaceuticals Ltd)
12638	Insulin soluble human pyr 100unit/ml Injection
12654	Insulin soluble human prb 100unit/ml Injection
13622	Hypurin porcine neutral 100unit/ml Injection (C P Pharmaceuticals Ltd)
14938	Insulin soluble bovine cartridge 100unit/ml Solution for injection
15710	Insulin soluble human emp 100unit/ml Injection
17336	Novopen 100unit/ml Injection device (Novo Nordisk Ltd)
22945	Insuman rapid 100iu/ml Injection (Aventis Pharma)
24593	Neutral insulin bovine 100unit/ml Injection
24846	Pur-in neutral 100unit/ml Injection (C P Pharmaceuticals Ltd)
26621	Insulin soluble human crb 100iu/ml Injection
30209	Actrapid mc 100unit/ml Injection (Arun Products Ltd)
36513	Velosulin cartridge 100unit/ml Injection (Novo Nordisk Ltd)
41959	Penject 100unit/ml Injection device (Hypoguard Ltd)
47360	Neutral insulin 100unit/ml Injection (Celltech Pharma Europe Ltd)
32	Gliclazide 80mg tablets
1253	Chlorpropamide 100mg tablets
1254	Glibenclamide 5mg tablets
1847	Chlorpropamide 250mg tablets
1964	Diamicron 80mg tablets (Servier Laboratories Ltd)

prodcode	productname
1965	Tolbutamide 500mg tablets
2219	Glibenclamide 2.5mg tablets
4862	Diabetamide 2.5mg tablets (Ashbourne Pharmaceuticals Ltd)
5276	Glimepiride 1mg tablets
5316	Glimepiride 4mg tablets
5353	Glimepiride 2mg tablets
5627	Gliclazide 30mg modified-release tablets
5636	Glipizide 5mg tablets
6337	Glimepiride 3mg tablets
7284	Amaryl 2mg tablets (Zentiva)
7332	Amaryl 1mg tablets (Zentiva)
7409	Amaryl 3mg tablets (Zentiva)
7744	Daonil 5mg tablets (Sanofi)
7912	Semi-Daonil 2.5mg tablets (Sanofi)
8034	Diabinese 100mg Tablet (Pfizer Ltd)
8168	Diabinese 250mg Tablet (Pfizer Ltd)
8976	Euglucon 2.5mg tablets (Aventis Pharma)
10427	Tolazamide 250mg Tablet
11284	Amaryl 4mg tablets (Zentiva)
11695	Diamicron 30mg MR tablets (Servier Laboratories Ltd)
11946	Tolbutamide 50mg/ml Injection
12245	Glutril 25mg Tablet (Roche Products Ltd)
12259	Glibornuride 25mg Tablet
12455	Rastinon 500mg Tablet (Hoechst Marion Roussel)
12513	Glibenese 5mg tablets (Pfizer Ltd)
13331	Euglucon 5mg tablets (Sanofi)
15374	Gliclazide 40mg/5ml oral suspension
16602	Calabren 2.5mg Tablet (Berk Pharmaceuticals Ltd)
17343	Gliclazide 80mg tablets (A A H Pharmaceuticals Ltd)
17698	Minodiab 5mg tablets (Pfizer Ltd)
19336	Tolazamide 100mg Tablet
21424	Glibenclamide 5mg/5ml oral suspension
21489	Tolanase 250mg Tablet (Pharmacia Ltd)
21564	Gliclazide 80mg tablets (Wockhardt UK Ltd)
21832	Diabetamide 5mg tablets (Ashbourne Pharmaceuticals Ltd)

prodcode	productname
21892	Diaglyk 80mg tablets (Ashbourne Pharmaceuticals Ltd)
22145	Tolanase 100mg Tablet (Pharmacia Ltd)
22858	Acetohexamide 500mg tablets
24848	Glymidine sodium 500mg Tablet
25636	Libanil 2.5mg Tablet (Approved Prescription Services Ltd)
26118	Dimelor 500mg Tablet (Eli Lilly and Company Ltd)
26218	Calabren 5mg Tablet (Berk Pharmaceuticals Ltd)
27969	Glymese 250mg Tablet (DDSA Pharmaceuticals Ltd)
28708	Malix 2.5mg Tablet (Lagap)
29326	Glipizide 5mg tablets (Generics (UK) Ltd)
29939	Gliclazide 80mg tablets (Generics (UK) Ltd)
30460	Malix 5mg Tablet (Lagap)
31212	Gliclazide 80mg tablets (Actavis UK Ltd)
31474	Libanil 5mg Tablet (Approved Prescription Services Ltd)
33562	Duclazide 80mg Tablet (Dumex Ltd)
33673	Tolbutamide 500mg tablets (Actavis UK Ltd)
34399	Gliclazide 80mg tablets (IVAX Pharmaceuticals UK Ltd)
34507	Glibenclamide 2.5mg tablets (Wockhardt UK Ltd)
34563	Glibenclamide 5mg tablets (Wockhardt UK Ltd)
34676	Glibenclamide 2.5mg tablets (A A H Pharmaceuticals Ltd)
34706	Glibenclamide 2.5mg tablets (IVAX Pharmaceuticals UK Ltd)
34802	Glipizide 5mg tablets (IVAX Pharmaceuticals UK Ltd)
34932	Gliclazide 80mg tablets (Genus Pharmaceuticals Ltd)
34957	Tolbutamide 500mg tablets (A A H Pharmaceuticals Ltd)
36856	Gliclazide 80mg tablets (Sandoz Ltd)
40365	Glimepiride 1mg tablets (Actavis UK Ltd)
40425	Nazdol MR 30mg tablets (Teva UK Ltd)
41558	Glibenclamide 5mg tablets (Teva UK Ltd)
41559	Glibenclamide 5mg tablets (A A H Pharmaceuticals Ltd)
41593	Glibenclamide 2.5mg tablets (Teva UK Ltd)
42790	Gliclazide 80mg Tablet (Merck Generics (UK) Ltd)
43065	Gliclazide 40mg tablets
43465	Zicron 40mg tablets (Bristol Laboratories Ltd)
44304	Glyconon 500mg Tablet (DDSA Pharmaceuticals Ltd)
44473	Edicil MR 30mg tablets (Ratiopharm UK Ltd)

prodcode	productname
44738	Niddaryl 1mg tablets (Dee Pharmaceuticals Ltd)
45215	Gliclazide 80mg Tablet (Neo Laboratories Ltd)
45831	Dacadis MR 30mg tablets (Generics (UK) Ltd)
46927	Tolbutamide 500mg tablets (Teva UK Ltd)
47074	Gliclazide 80mg/5ml oral suspension
47894	Nazdol MR 30mg tablets (Consilient Health Ltd)
48056	Gliclazide 80mg tablets (Sovereign Medical Ltd)
51955	Gliclazide 80mg tablets (Accord Healthcare Ltd)
53288	Gliclazide 30mg modified-release tablets (A A H Pharmaceuticals Ltd)
54764	Gliclazide 80mg tablets (Arrow Generics Ltd)
55862	Gliclazide Oral solution
56008	Gliclazide 80mg tablets (Almus Pharmaceuticals Ltd)
56437	Gliclazide 60mg modified-release tablets
57601	Daonil 5mg tablets (Dowelhurst Ltd)
57830	Gliclazide 30mg modified-release tablets (Alliance Healthcare (Distribution) Ltd)
58882	Gliclazide 120mg/5ml oral suspension
60495	Gliclazide 80mg tablets (Teva UK Ltd)
61311	Glimepiride 4mg tablets (Sigma Pharmaceuticals Plc)
61957	Gliclazide 40mg tablets (A A H Pharmaceuticals Ltd)
62014	Glimepiride 2mg tablets (Accord Healthcare Ltd)
62034	Laaglyda MR 60mg tablets (Consilient Health Ltd)
56376	Rosiglitazone 4mg with glimepiride 4mg tablet
804	Glucagon 1mg powder and solvent for solution for injection vials
4156	Hypostop Gel (Bio-Diagnostics Ltd)
4362	Glucagon novo 1mg Injection (Novo Nordisk Ltd)
4813	GlucaGen Hypokit 1mg powder and solvent for solution for injection (Novo Nordisk Ltd)
6005	Glucose 40% oral gel
6265	Diazoxide 50mg tablets
7220	GlucoGel 40% gel original (BBI Healthcare Ltd)
17770	Glucagon novo 10mg Injection (Novo Nordisk Ltd)
19425	Glucagon 10mg Injection
22239	Glucagon lilly 1mg Injection (Eli Lilly and Company Ltd)
25887	Eudemine 50mg tablets (Focus Pharmaceuticals Ltd)
31417	Diazoxide 50mg/ml oral solution

prodcode	productname
35960	Diazoxide 50mg/5ml oral suspension
38542	Hypo-fit Oral solution (Arctic Medical Ltd)
39306	Sucrose with glucose & fructose oral solution
39956	Diazoxide 250mg/5ml oral suspension
40348	Dextrogel 40% gel (Neoceuticals Ltd)
42677	Diazoxide 250mg/5ml oral solution
48579	Glucojuice liquid (BBI Healthcare Ltd)
49317	Glucose 15g liquid
51018	Diazoxide 50mg/5ml oral solution
51228	GlucoBoost 40% gel (Ennogen Healthcare Ltd)
51757	Rapilose 40% gel (Galen Ltd)
54340	Diazoxide 10mg/5ml oral solution
55989	Diazoxide 25mg/5ml oral solution
56391	GlucoGel 40% gel berry (BBI Healthcare Ltd)
4361	Glucose 50% Infusion
6813	Glucose 5% Infusion
17397	Glucose Injection
18741	Dextrose IV 50% infusion
18813	Glucose 20% Infusion
22707	Dextrose IV 50% infusion
23265	Glucose strong Injection (Phoenix Healthcare Distribution Ltd)
25356	Glucose 25% Intravenous infusion
25424	Dextrose IV 25% infusion
38393	Dextrose 50% Injection (Celltech Pharma Europe Ltd)
42508	Glucose 10% Infusion
43258	Glucose 40% Infusion
44710	Dextrose IV 20% infusion
16140	Glucose liquid BPC 1963
26054	Glucose liquid BPC 1963 (A A H Pharmaceuticals Ltd)
55606	GSF-Syrup oral gel 18g sachets
58925	GSF-Syrup oral gel 18g sachets orange (Arctic Medical Ltd)
59994	GSF-Syrup oral gel 18g sachets mixed (Arctic Medical Ltd)
52465	Rapilose OGTT solution (Aspire Pharma Ltd)
54002	Glucose 75g/300ml oral solution

READ code list for T2DM condition.

code	Description
13AB.00	Diabetic lipid lowering diet
13AC.00	Diabetic weight reducing diet
13B1.00	Diabetic diet
14F4.00	H/O: Admission in last year for diabetes foot problem
2126300	Diabetes resolved
212H.00	Diabetes resolved
2BBF.00	Retinal abnormality - diabetes related
2BBk.00	O/E - right eye stable treated prolif diabetic retinopathy
2BBl.00	O/E - left eye stable treated prolif diabetic retinopathy
2BBL.00	O/E - diabetic maculopathy present both eyes
2BBM.00	O/E - diabetic maculopathy absent both eyes
2BBo.00	O/E - sight threatening diabetic retinopathy
2BBP.00	O/E - right eye background diabetic retinopathy
2BBQ.00	O/E - left eye background diabetic retinopathy
2BBR.00	O/E - right eye preproliferative diabetic retinopathy
2BBS.00	O/E - left eye preproliferative diabetic retinopathy
2BBT.00	O/E - right eye proliferative diabetic retinopathy
2BBV.00	O/E - left eye proliferative diabetic retinopathy
2BBW.00	O/E - right eye diabetic maculopathy
2BBX.00	O/E - left eye diabetic maculopathy
2G51000	Foot abnormality - diabetes related
2G5A.00	O/E - Right diabetic foot at risk
2G5B.00	O/E - Left diabetic foot at risk
2G5C.00	Foot abnormality - diabetes related
2G5E.00	O/E - Right diabetic foot at low risk
2G5F.00	O/E - Right diabetic foot at moderate risk
2G5G.00	O/E - Right diabetic foot at high risk
2G5H.00	O/E - Right diabetic foot - ulcerated
2G5I.00	O/E - Left diabetic foot at low risk
2G5J.00	O/E - Left diabetic foot at moderate risk
2G5K.00	O/E - Left diabetic foot at high risk
2G5L.00	O/E - Left diabetic foot - ulcerated
2G5V.00	O/E - right chronic diabetic foot ulcer
2G5W.00	O/E - left chronic diabetic foot ulcer
42c..00	HbA1 - diabetic control
42c0.00	HbA1 < 7% - good control
42c1.00	HbA1 7 - 10% - borderline control
42c2.00	HbA1 > 10% - bad control
42W..00	Hb. A1C - diabetic control
42W1.00	Hb. A1C < 7% - good control
42W2.00	Hb. A1C 7-10% - borderline

code	Description
42W3.00	Hb. A1C > 10% - bad control
42WZ.00	Hb. A1C - diabetic control NOS
66A..00	Diabetic monitoring
66A1.00	Initial diabetic assessment
66A2.00	Follow-up diabetic assessment
66A3.00	Diabetic on diet only
66A4.00	Diabetic on oral treatment
66A5.00	Diabetic on insulin
66A6.00	Last hypo. attack
66A7.00	Frequency of hypo. attacks
66A7000	Frequency of hospital treated hypoglycaemia
66A7100	Frequency of GP or paramedic treated hypoglycaemia
66A8.00	Has seen dietician - diabetes
66A9.00	Understands diet - diabetes
66Aa.00	Diabetic diet - poor compliance
66AA.11	Injection sites - diabetic
66Ab.00	Diabetic foot examination
66Ac.00	Diabetic peripheral neuropathy screening
66Ad.00	Hypoglycaemic attack requiring 3rd party assistance
66AD.00	Fundoscopy - diabetic check
66AG.00	Diabetic drug side effects
66Ah.00	Insulin needles changed for each injection
66AH.00	Diabetic treatment changed
66AH000	Conversion to insulin
66Ai.00	Diabetic 6 month review
66AI.00	Diabetic - good control
66Aj.00	Insulin needles changed less than once a day
66AJ.00	Diabetic - poor control
66AJ.11	Unstable diabetes
66AJ000	Chronic hyperglycaemia
66AJ100	Brittle diabetes
66AJ200	Loss of hypoglycaemic warning
66AJ300	Recurrent severe hypos
66AJz00	Diabetic - poor control NOS
66Ak.00	Diabetic monitoring - lower risk albumin excretion
66AK.00	Diabetic - cooperative patient
66Al.00	Diabetic monitoring - higher risk albumin excretion
66AL.00	Diabetic-uncooperative patient
66AM.00	Diabetic - follow-up default
66AN.00	Date diabetic treatment start
66Ao.00	Diabetes type 2 review
66AP.00	Diabetes: practice programme
66AQ.00	Diabetes: shared care programme

code	Description
66AR.00	Diabetes management plan given
66AS.00	Diabetic annual review
66AT.00	Annual diabetic blood test
66At111	Type 2 diabetic dietary review
66AU.00	Diabetes care by hospital only
66AV.00	Diabetic on insulin and oral treatment
66AW.00	Diabetic foot risk assessment
66AX.00	Diabetes: shared care in pregnancy - diabetol and obstet
66AY.00	Diabetic diet - good compliance
66AZ.00	Diabetic monitoring NOS
68A7.00	Diabetic retinopathy screening
68A9.00	Diabetic retinopathy screening offered
68AB.00	Diabetic digital retinopathy screening offered
8A12.00	Diabetic crisis monitoring
8A13.00	Diabetic stabilisation
8B3l.00	Diabetes medication review
8BL2.00	Patient on maximal tolerated therapy for diabetes
8H2J.00	Admit diabetic emergency
8H3O.00	Non-urgent diabetic admission
8H4F.00	Referral to diabetologist
8H7C.00	Refer, diabetic liaison nurse
8H7f.00	Referral to diabetes nurse
8H7r.00	Refer to diabetic foot screener
8HBG.00	Diabetic retinopathy 12 month review
8HBH.00	Diabetic retinopathy 6 month review
8HHy.00	Referral to diabetic register
8Hj0.00	Referral to diabetes structured education programme
8Hl1.00	Referral for diabetic retinopathy screening
8Hl4.00	Referral to community diabetes specialist nurse
8HLE.00	Diabetology D.V. done
8HME.00	Listed for Diabetology admissn
8HTe.00	Referral to diabetes preconception counselling clinic
8HTi.00	Referral to multidisciplinary diabetic clinic
8HTk.00	Referral to diabetic eye clinic
8HVU.00	Private referral to diabetologist
8I3W.00	Diabetic foot examination declined
8I3X.00	Diabetic retinopathy screening refused
93C4.00	Patient consent given for addition to diabetic register
9N0m.00	Seen in diabetic nurse consultant clinic
9N0n.00	Seen in community diabetes specialist clinic
9N0o.00	Seen in community diabetic specialist nurse clinic
9N1i.00	Seen in diabetic foot clinic
9N1o.00	Seen in multidisciplinary diabetic clinic

code	Description
9N1Q.00	Seen in diabetic clinic
9N1v.00	Seen in diabetic eye clinic
9N2d.00	Seen by diabetologist
9N2i.00	Seen by diabetic liaison nurse
9NM0.00	Attending diabetes clinic
9NN8.00	Under care of diabetologist
9NN9.00	Under care of diabetes specialist nurse
9NND.00	Under care of diabetic foot screener
9OL1.00	Attends diabetes monitoring
9OL2.00	Refuses diabetes monitoring
9OLA.11	Diabetes monitored
9OLD.00	Diabetic patient unsuitable for digital retinal photography
C10..00	Diabetes mellitus
C100.00	Diabetes mellitus with no mention of complication
C100000	Diabetes mellitus, juvenile type, no mention of complication
C100011	Insulin dependent diabetes mellitus
C100100	Diabetes mellitus, adult onset, no mention of complication
C100111	Maturity onset diabetes
C100112	Non-insulin dependent diabetes mellitus
C100z00	Diabetes mellitus NOS with no mention of complication
C101.00	Diabetes mellitus with ketoacidosis
C101000	Diabetes mellitus, juvenile type, with ketoacidosis
C101100	Diabetes mellitus, adult onset, with ketoacidosis
C101y00	Other specified diabetes mellitus with ketoacidosis
C101z00	Diabetes mellitus NOS with ketoacidosis
C102.00	Diabetes mellitus with hyperosmolar coma
C102000	Diabetes mellitus, juvenile type, with hyperosmolar coma
C102100	Diabetes mellitus, adult onset, with hyperosmolar coma
C102z00	Diabetes mellitus NOS with hyperosmolar coma
C103.00	Diabetes mellitus with ketoacidotic coma
C103000	Diabetes mellitus, juvenile type, with ketoacidotic coma
C103100	Diabetes mellitus, adult onset, with ketoacidotic coma
C103y00	Other specified diabetes mellitus with coma
C103z00	Diabetes mellitus NOS with ketoacidotic coma
C104.00	Diabetes mellitus with renal manifestation
C104.11	Diabetic nephropathy
C104000	Diabetes mellitus, juvenile type, with renal manifestation
C104100	Diabetes mellitus, adult onset, with renal manifestation
C104y00	Other specified diabetes mellitus with renal complications
C104z00	Diabetes mellitus with nephropathy NOS
C105.00	Diabetes mellitus with ophthalmic manifestation
C105000	Diabetes mellitus, juvenile type, + ophthalmic manifestation
C105100	Diabetes mellitus, adult onset, + ophthalmic manifestation

code	Description
C105y00	Other specified diabetes mellitus with ophthalmic complicatn
C105z00	Diabetes mellitus NOS with ophthalmic manifestation
C106.00	Diabetes mellitus with neurological manifestation
C106.11	Diabetic amyotrophy
C106.12	Diabetes mellitus with neuropathy
C106.13	Diabetes mellitus with polyneuropathy
C106000	Diabetes mellitus, juvenile, + neurological manifestation
C106100	Diabetes mellitus, adult onset, + neurological manifestation
C106y00	Other specified diabetes mellitus with neurological comps
C106z00	Diabetes mellitus NOS with neurological manifestation
C107.00	Diabetes mellitus with peripheral circulatory disorder
C107.11	Diabetes mellitus with gangrene
C107.12	Diabetes with gangrene
C107000	Diabetes mellitus, juvenile +peripheral circulatory disorder
C107100	Diabetes mellitus, adult, + peripheral circulatory disorder
C107200	Diabetes mellitus, adult with gangrene
C107300	IDDM with peripheral circulatory disorder
C107400	NIDDM with peripheral circulatory disorder
C107z00	Diabetes mellitus NOS with peripheral circulatory disorder
C108.00	Insulin dependent diabetes mellitus
C108.11	IDDM-Insulin dependent diabetes mellitus
C108000	Insulin-dependent diabetes mellitus with renal complications
C108100	Insulin-dependent diabetes mellitus with ophthalmic comps
C108200	Insulin-dependent diabetes mellitus with neurological comps
C108300	Insulin dependent diabetes mellitus with multiple complicatn
C108400	Unstable insulin dependent diabetes mellitus
C108500	Insulin dependent diabetes mellitus with ulcer
C108600	Insulin dependent diabetes mellitus with gangrene
C108700	Insulin dependent diabetes mellitus with retinopathy
C108800	Insulin dependent diabetes mellitus - poor control
C108900	Insulin dependent diabetes maturity onset
C108A00	Insulin-dependent diabetes without complication
C108B00	Insulin dependent diabetes mellitus with mononeuropathy
C108C00	Insulin dependent diabetes mellitus with polyneuropathy
C108D00	Insulin dependent diabetes mellitus with nephropathy
C108E00	Insulin dependent diabetes mellitus with hypoglycaemic coma
C108F00	Insulin dependent diabetes mellitus with diabetic cataract
C108G00	Insulin dependent diab mell with peripheral angiopathy
C108H00	Insulin dependent diabetes mellitus with arthropathy
C108J00	Insulin dependent diab mell with neuropathic arthropathy
C108y00	Other specified diabetes mellitus with multiple comps
C108z00	Unspecified diabetes mellitus with multiple complications
C109.00	Non-insulin dependent diabetes mellitus

code	Description
C109.11	NIDDM - Non-insulin dependent diabetes mellitus
C109.12	Type 2 diabetes mellitus
C109000	Non-insulin-dependent diabetes mellitus with renal comps
C109012	Type 2 diabetes mellitus with renal complications
C109100	Non-insulin-dependent diabetes mellitus with ophthalm comps
C109112	Type 2 diabetes mellitus with ophthalmic complications
C109200	Non-insulin-dependent diabetes mellitus with neuro comps
C109212	Type 2 diabetes mellitus with neurological complications
C109300	Non-insulin-dependent diabetes mellitus with multiple comps
C109400	Non-insulin dependent diabetes mellitus with ulcer
C109412	Type 2 diabetes mellitus with ulcer
C109500	Non-insulin dependent diabetes mellitus with gangrene
C109512	Type 2 diabetes mellitus with gangrene
C109600	Non-insulin-dependent diabetes mellitus with retinopathy
C109612	Type 2 diabetes mellitus with retinopathy
C109700	Non-insulin dependent diabetes mellitus - poor control
C109712	Type 2 diabetes mellitus - poor control
C109800	Reaven's syndrome
C109900	Non-insulin-dependent diabetes mellitus without complication
C109A00	Non-insulin dependent diabetes mellitus with mononeuropathy
C109B00	Non-insulin dependent diabetes mellitus with polyneuropathy
C109C00	Non-insulin dependent diabetes mellitus with nephropathy
C109C12	Type 2 diabetes mellitus with nephropathy
C109D00	Non-insulin dependent diabetes mellitus with hypoglyca coma
C109D12	Type 2 diabetes mellitus with hypoglycaemic coma
C109E00	Non-insulin depend diabetes mellitus with diabetic cataract
C109E12	Type 2 diabetes mellitus with diabetic cataract
C109F00	Non-insulin-dependent d m with peripheral angiopath
C109F12	Type 2 diabetes mellitus with peripheral angiopathy
C109G00	Non-insulin dependent diabetes mellitus with arthropathy
C109G12	Type 2 diabetes mellitus with arthropathy
C109H00	Non-insulin dependent d m with neuropathic arthropathy
C109H12	Type 2 diabetes mellitus with neuropathic arthropathy
C109J00	Insulin treated Type 2 diabetes mellitus
C109J11	Insulin treated non-insulin dependent diabetes mellitus
C109K00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C10A.00	Malnutrition-related diabetes mellitus
C10A000	Malnutrition-related diabetes mellitus with coma
C10A100	Malnutrition-related diabetes mellitus with ketoacidosis
C10A500	Malnutritn-relat diabetes melitus wth periph circul complctn
C10B.00	Diabetes mellitus induced by steroids
C10B000	Steroid induced diabetes mellitus without complication
C10C.00	Diabetes mellitus autosomal dominant

code	Description
C10C.11	Maturity onset diabetes in youth
C10D.00	Diabetes mellitus autosomal dominant type 2
C10D.11	Maturity onset diabetes in youth type 2
C10E.12	Insulin dependent diabetes mellitus
C10E012	Insulin-dependent diabetes mellitus with renal complications
C10E112	Insulin-dependent diabetes mellitus with ophthalmic comps
C10E212	Insulin-dependent diabetes mellitus with neurological comps
C10E312	Insulin dependent diabetes mellitus with multiple complicat
C10E412	Unstable insulin dependent diabetes mellitus
C10E512	Insulin dependent diabetes mellitus with ulcer
C10E712	Insulin dependent diabetes mellitus with retinopathy
C10E812	Insulin dependent diabetes mellitus - poor control
C10E912	Insulin dependent diabetes maturity onset
C10EA12	Insulin-dependent diabetes without complication
C10EC12	Insulin dependent diabetes mellitus with polyneuropathy
C10ED12	Insulin dependent diabetes mellitus with nephropathy
C10EE12	Insulin dependent diabetes mellitus with hypoglycaemic coma
C10EF12	Insulin dependent diabetes mellitus with diabetic cataract
C10ER00	Latent autoimmune diabetes mellitus in adult
C10F.00	Type 2 diabetes mellitus
C10F000	Type 2 diabetes mellitus with renal complications
C10F100	Type 2 diabetes mellitus with ophthalmic complications
C10F200	Type 2 diabetes mellitus with neurological complications
C10F300	Type 2 diabetes mellitus with multiple complications
C10F400	Type 2 diabetes mellitus with ulcer
C10F500	Type 2 diabetes mellitus with gangrene
C10F600	Type 2 diabetes mellitus with retinopathy
C10F700	Type 2 diabetes mellitus - poor control
C10F800	Reaven's syndrome
C10F811	Metabolic syndrome X
C10F900	Type 2 diabetes mellitus without complication
C10FA00	Type 2 diabetes mellitus with mononeuropathy
C10FB00	Type 2 diabetes mellitus with polyneuropathy
C10FC00	Type 2 diabetes mellitus with nephropathy
C10FD00	Type 2 diabetes mellitus with hypoglycaemic coma
C10FE00	Type 2 diabetes mellitus with diabetic cataract
C10FF00	Type 2 diabetes mellitus with peripheral angiopathy
C10FG00	Type 2 diabetes mellitus with arthropathy
C10FH00	Type 2 diabetes mellitus with neuropathic arthropathy
C10FJ00	Insulin treated Type 2 diabetes mellitus
C10FK00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C10FL00	Type 2 diabetes mellitus with persistent proteinuria
C10FM00	Type 2 diabetes mellitus with persistent microalbuminuria

code	Description
C10FN00	Type 2 diabetes mellitus with ketoacidosis
C10FP00	Type 2 diabetes mellitus with ketoacidotic coma
C10FQ00	Type 2 diabetes mellitus with exudative maculopathy
C10FR00	Type 2 diabetes mellitus with gastroparesis
C10G.00	Secondary pancreatic diabetes mellitus
C10G000	Secondary pancreatic diabetes mellitus without complication
C10H.00	Diabetes mellitus induced by non-steroid drugs
C10H000	DM induced by non-steroid drugs without complication
C10J.00	Insulin autoimmune syndrome
C10K.00	Type A insulin resistance
C10K000	Type A insulin resistance without complication
C10M.00	Lipoatrophic diabetes mellitus
C10N.00	Secondary diabetes mellitus
C10N000	Secondary diabetes mellitus without complication
C10N100	Cystic fibrosis related diabetes mellitus
C10y.00	Diabetes mellitus with other specified manifestation
C10y100	Diabetes mellitus, adult, + other specified manifestation
C10yy00	Other specified diabetes mellitus with other spec comps
C10yz00	Diabetes mellitus NOS with other specified manifestation
C10z.00	Diabetes mellitus with unspecified complication
C10z000	Diabetes mellitus, juvenile type, + unspecified complication
C10z100	Diabetes mellitus, adult onset, + unspecified complication
C10zy00	Other specified diabetes mellitus with unspecified comps
C10zz00	Diabetes mellitus NOS with unspecified complication
Cyu2.00	[X]Diabetes mellitus
Cyu2000	[X]Other specified diabetes mellitus
Cyu2300	[X]Unspecified diabetes mellitus with renal complications
F171100	Autonomic neuropathy due to diabetes
F345000	Diabetic mononeuritis multiplex
F35z000	Diabetic mononeuritis NOS
F372.00	Polyneuropathy in diabetes
F372.11	Diabetic polyneuropathy
F372.12	Diabetic neuropathy
F372000	Acute painful diabetic neuropathy
F372100	Chronic painful diabetic neuropathy
F372200	Asymptomatic diabetic neuropathy
F381300	Myasthenic syndrome due to diabetic amyotrophy
F381311	Diabetic amyotrophy
F3y0.00	Diabetic mononeuropathy
F420.00	Diabetic retinopathy
F420000	Background diabetic retinopathy
F420100	Proliferative diabetic retinopathy
F420200	Preproliferative diabetic retinopathy

code	Description
F420300	Advanced diabetic maculopathy
F420400	Diabetic maculopathy
F420500	Advanced diabetic retinal disease
F420600	Non proliferative diabetic retinopathy
F420700	High risk proliferative diabetic retinopathy
F420800	High risk non proliferative diabetic retinopathy
F420z00	Diabetic retinopathy NOS
F440700	Diabetic iritis
F464000	Diabetic cataract
G73y000	Diabetic peripheral angiopathy
K01x100	Nephrotic syndrome in diabetes mellitus
Kyu0300	[X]Glomerular disorders in diabetes mellitus
L180500	Pre-existing diabetes mellitus, insulin-dependent
L180600	Pre-existing diabetes mellitus, non-insulin-dependent
L180X00	Pre-existing diabetes mellitus, unspecified
M037200	Cellulitis in diabetic foot
M271000	Ischaemic ulcer diabetic foot
M271100	Neuropathic diabetic ulcer - foot
M271200	Mixed diabetic ulcer - foot
N030000	Diabetic cheiroarthropathy
N030011	Diabetic cheiropathy
N030100	Diabetic Charcot arthropathy
R054200	[D]Gangrene of toe in diabetic
R054300	[D]Widespread diabetic foot gangrene
ZL22500	Under care of diabetic liaison nurse
ZL62500	Referral to diabetes nurse
ZL62600	Referral to diabetic liaison nurse
ZLA2500	Seen by diabetic liaison nurse
ZV65312	[V]Dietary counselling in diabetes mellitus

List of antiplatelet medications included in the study.

prodcode	Description
3	Aspirin 75mg dispersible tablets
16	Aspirin 75mg tablets
34	Aspirin 75mg gastro-resistant tablets
254	Aspirin 300mg tablets
377	Aspirin 300mg dispersible tablets
393	Disprin 300mg dispersible tablets (Reckitt Benckiser Healthcare (UK) Ltd)
434	Aspirin 300mg gastro-resistant tablets

prodcode	Description
489	Clopidogrel 75mg tablets
572	Ticlopidine 250mg tablets
645	Aspirin 300mg suppositories
657	Aspirin 500mg granules sachets sugar free
836	Plavix 75mg tablets (Sanofi)
1049	Nu-seals aspirin 600mg Tablet (Eli Lilly and Company Ltd)
1137	Nu-seals aspirin ec 300mg Gastro-resistant tablet (Eli Lilly and Company Ltd)
1902	Aspirn 600mg gastro-resistant tablets
2105	Solprin 300mg Tablet (Reckitt Benckiser Healthcare (UK) Ltd)
2607	Paynocil Tablet (Beecham Research Laboratories)
2628	Nu-seals aspirin ec 75mg Gastro-resistant tablet (Eli Lilly and Company Ltd)
6006	Nu-Seals 75 gastro-resistant tablets (Alliance Pharmaceuticals Ltd)
6007	Nu-Seals 300 gastro-resistant tablets (Alliance Pharmaceuticals Ltd)
6696	Micropirin 75mg gastro-resistant tablets (Dexcel-Pharma Ltd)
7516	Aspirin 300mg effervescent tablets sugar free
8185	Disprin CV 300mg modified-release tablets (Reckitt Benckiser Healthcare (UK) Ltd)
8186	Aspirin 300mg modified-release tablets
8645	Aspirin 300mg effervescent tablets
9144	Caprin 75mg gastro-resistant tablets (Wockhardt UK Ltd)
9301	Aspirin 100mg modified-release tablets
9939	Aspirin 500mg effervescent tablets sugar free
10305	Aspirin 162.5mg capsules
10310	Aspirin powder
11977	Aspro clear maximum strength tablets
15364	Aspirin 150mg suppositories
17449	Ticlid 250mg tablets (Sanofi-Synthelabo Ltd)
17704	Platet 100mg Effervescent tablet (Roche Products Ltd)
17920	Disprin cv 100mg Modified-release tablet (Reckitt Benckiser Healthcare (UK) Ltd)
18217	Aspirin 300mg orodispersible tablets sugar free
18329	Enprin 75mg gastro-resistant tablets (Galpharm International Ltd)
19189	Micropirin 75mg Gastro-resistant tablet (Ratiopharm UK Ltd)
21019	ReoPro 10mg/5ml solution for injection vials (Eli Lilly and Company Ltd)
21921	Postmi ec 300mg Gastro-resistant tablet (Ashbourne Pharmaceuticals Ltd)
22138	Aspirin 324mg modified-release tablets
22232	Disprin Direct 300mg orodispersible tablets (Reckitt Benckiser Healthcare (UK) Ltd)

prodcode	Description
22618	Solprin 75mg Tablet (Reckitt Benckiser Healthcare (UK) Ltd)
23488	Claradin 300mg Tablet (Nicholas Laboratories Ltd)
23593	PostMI 75 dispersible tablets (Ashbourne Pharmaceuticals Ltd)
23878	Nu-seals cardio ec 75mg Gastro-resistant tablet (Genus Pharmaceuticals Ltd)
23932	Aspro Clear 300mg effervescent tablets (Bayer Plc)
24025	Caprin 300mg gastro-resistant tablets (Pinewood Healthcare)
24960	Aspirin 300mg tablets (Vantage)
25335	PostMI 75 EC tablets (Ashbourne Pharmaceuticals Ltd)
25718	Angettes 75 tablets (Bristol-Myers Squibb Pharmaceuticals Ltd)
28810	Aspirin 300mg with Glycine 133mg soluble tablets
29759	Aspro Tablet (Roche Consumer Health)
29848	Aspirin 300mg with Glycine 150mg chewable tablets
30554	Abciximab 10mg/5ml solution for injection vials
30920	Aspirin 300mg Dispersible tablet (M & A Pharmachem Ltd)
31210	Aspirin 300mg Tablet (Co-operative)
31211	Aspirin 75mg Dispersible tablet (A A H Pharmaceuticals Ltd)
31858	Caspac xl 162.5mg Capsule (Pharmacia Ltd)
31870	Aspirin 320mg tablets
31938	Aspirin 75mg gastro-resistant tablets (Sandoz Ltd)
31953	Aspirin 75mg dispersible tablets (IVAX Pharmaceuticals UK Ltd)
31954	Aspirin 75mg dispersible tablets (Teva UK Ltd)
31956	Aspirin 75mg gastro-resistant tablets (Kent Pharmaceuticals Ltd)
32036	Aspirin 75mg dispersible tablets (Actavis UK Ltd)
32210	Aspirin 300mg dispersible tablets (Actavis UK Ltd)
32992	Aspirin 75mg gastro-resistant tablets (Generics (UK) Ltd)
33293	Aspirin 75mg gastro-resistant tablets (Sterwin Medicines)
33320	Aspirin 75mg Dispersible tablet (Sovereign Medical Ltd)
33656	Aspirin 75mg dispersible tablets (A A H Pharmaceuticals Ltd)
33662	Aspirin 300mg Dispersible tablet (A A H Pharmaceuticals Ltd)
33668	Aspirin 300mg Dispersible tablet (Rusco Ltd)
33676	Aspirin 75mg dispersible tablets (Kent Pharmaceuticals Ltd)
33877	Aggrastat 12.5mg/250ml infusion bags (Correvio GmbH)
34309	Aspirin 300mg dispersible tablets (A A H Pharmaceuticals Ltd)
34385	Aspirin 75mg Soluble tablet (Co-operative)
34386	Aspirin 300mg tablets (Actavis UK Ltd)

prodcode	Description
34434	Aspirin 75mg dispersible tablets (Thornton & Ross Ltd)
34485	Aspirin 75mg gastro-resistant tablets (IVAX Pharmaceuticals UK Ltd)
34611	Aspirin 75mg gastro-resistant tablets (C P Pharmaceuticals Ltd)
34666	Aspirin ec 300mg Gastro-resistant tablet (A A H Pharmaceuticals Ltd)
34762	Aspirin 300mg Gastro-resistant tablet (Galen Ltd)
34796	Aspirin 75mg Gastro-resistant tablet (Galen Ltd)
34797	Aspirin 75mg gastro-resistant tablets (Actavis UK Ltd)
34942	Aspirin 75mg Dispersible tablet (Nucare Plc)
35809	Tirofiban hydrochloride 12.5mg/250ml infusion bags
36521	Aspirin 500mg modified-release tablets
36543	Aspirin 100mg effervescent tablets
37541	Aspirin 227mg medicated chewing-gum
38349	Clopidogrel 300mg tablets
38998	Plavix 300mg tablets (Sanofi)
39738	Aspirin 162.5mg modified-release capsules
39932	Prasugrel 10mg tablets
40114	Prasugrel 5mg tablets
40144	Aspirin 300mg Dispersible tablet (Thornton & Ross Ltd)
40381	Aspirin 75mg Soluble tablet (C P Pharmaceuticals Ltd)
40591	Efient 5mg tablets (Eli Lilly and Company Ltd)
40913	Grepid 75mg tablets (Beacon Pharmaceuticals Ltd)
41229	Efient 10mg tablets (Eli Lilly and Company Ltd)
41512	Aspirin 75mg gastro-resistant tablets (Teva UK Ltd)
41569	Aspirin 300mg tablets (A A H Pharmaceuticals Ltd)
41594	Aspirin 300mg Dispersible tablet (Teva UK Ltd)
41766	Maximum Strength Aspro Clear 500mg effervescent tablets (Bayer Plc)
42750	Clopidogrel 75mg tablets (Actavis UK Ltd)
43060	Aspirin 300mg Soluble tablet (Celltech Pharma Europe Ltd)
43434	Aspirin 300mg gastro-resistant tablets (A A H Pharmaceuticals Ltd)
43679	Flamasacard 162.5mg Modified-release capsule (Abbey Pharmaceuticals Ltd)
43709	Aspirin 75mg gastro-resistant tablets (Almus Pharmaceuticals Ltd)
43806	Aspirin 300mg gastro-resistant tablets (Sandoz Ltd)
44639	Aspirin 300mg Dispersible tablet (Nucare Plc)
45576	Ticagrelor 90mg tablets
45643	Aspirin 75mg Soluble tablet (Celltech Pharma Europe Ltd)

prodcode	Description
45840	Aspirin 300mg Dispersible tablet (Numark Management Ltd)
45851	Aspirin 300mg Soluble tablet (Ranbaxy (UK) Ltd)
45905	Clopidogrel 1mg/ml oral suspension
46891	Clopidogrel 75mg/5ml oral suspension
47895	Brilique 90mg tablets (AstraZeneca UK Ltd)
47992	Aspirin 75mg gastro-resistant tablets (A A H Pharmaceuticals Ltd)
48000	Aspirin 300mg tablets (Sigma Pharmaceuticals Plc)
48021	Aspirin 75mg Tablet (Hillcross Pharmaceuticals Ltd)
48165	Aspirin 300mg tablets (Aspar Pharmaceuticals Ltd)
48974	Aspirin 75mg tablets (Phoenix Healthcare Distribution Ltd)
49060	Aspirin 75mg dispersible tablets (Alliance Healthcare (Distribution) Ltd)
49220	Aspirin 300mg tablets (Kent Pharmaceuticals Ltd)
49685	Aspirin 75mg dispersible tablets (Sigma Pharmaceuticals Plc)
49799	Aspirin 150mg suppositories (A A H Pharmaceuticals Ltd)
50555	Aspirin 300mg dispersible tablets (DE Pharmaceuticals)
50926	Aspirin 75mg dispersible tablets (The Boots Company Plc)
50949	Aspirin 75mg tablets (A A H Pharmaceuticals Ltd)
51474	Aspirin 150mg suppositories (Martindale Pharmaceuticals Ltd)
51561	Aspirin 75mg gastro-resistant tablets (Zanza Laboratories Ltd)
52044	Aspirin 300mg caplets (The Boots Company Plc)
52280	Aspirin 300mg Tablet (Wockhardt UK Ltd)
52618	Aspirin 75mg dispersible tablets (Bristol Laboratories Ltd)
52761	Clopidogrel 75mg tablets (Dr Reddy's Laboratories (UK) Ltd)
52905	Aspirin 300mg tablets (Lloyds Pharmacy Ltd)
53178	Aspirin 75mg gastro-resistant tablets (Wockhardt UK Ltd)
53622	Aspirin 300mg Tablet (M & A Pharmachem Ltd)
53711	Aspirin 300mg Tablet (Nucare Plc)
53751	Clopidogrel 75mg tablets (Phoenix Healthcare Distribution Ltd)
53791	Aspirin 150mg suppositories (Alliance Healthcare (Distribution) Ltd)
53804	Aspirin 300mg gastro-resistant tablets (Alliance Healthcare (Distribution) Ltd)
53816	Aspirin 300mg dispersible tablets (Alliance Healthcare (Distribution) Ltd)
54284	Aspirin 75mg dispersible tablets (Almus Pharmaceuticals Ltd)
54430	Aspirin 75mg tablets (Alliance Healthcare (Distribution) Ltd)
54526	Aspirin 300mg tablets (Alliance Healthcare (Distribution) Ltd)
54565	Aspirin 75mg dispersible tablets (Lloyds Pharmacy Ltd)

prodcode	Description
54700	Clopidogrel 75mg tablets (A A H Pharmaceuticals Ltd)
54734	Aspirin 300mg tablets (Wockhardt UK Ltd)
54997	Aspirin 75mg dispersible tablets (Dowelhurst Ltd)
55161	Clopidogrel 75mg tablets (Wockhardt UK Ltd)
55230	Aspirin 300mg dispersible tablets (Kent Pharmaceuticals Ltd)
56007	Aspirin 300mg dispersible tablets (Sigma Pharmaceuticals Plc)
56736	Aspirin 300mg tablets (Waymade Healthcare Plc)
56807	Clopidogrel 75mg tablets (Teva UK Ltd)
56883	Aspirin 75mg tablets (Waymade Healthcare Plc)
56995	Aspirin 75mg dispersible tablets (Phoenix Healthcare Distribution Ltd)
56996	Aspirin 75mg dispersible tablets (Waymade Healthcare Plc)
57036	Clopidogrel 75mg tablets (Generics (UK) Ltd)
57057	Aspirin 75mg dispersible tablets (Wockhardt UK Ltd)
58331	Aspirin 300mg gastro-resistant tablets (Generics (UK) Ltd)
58347	Clopidogrel 75mg tablets (DE Pharmaceuticals)
58448	Clopidogrel 75mg tablets (Aspire Pharma Ltd)
59021	Aspirin 75mg gastro-resistant tablets (Bristol Laboratories Ltd)
59244	Aspirin 100mg capsules
59253	Aspirin 75mg gastro-resistant tablets (Waymade Healthcare Plc)
59728	Aspirin 75mg tablets (Alissa Healthcare Research Ltd)
59791	Aspirin 75mg dispersible tablets (Aspar Pharmaceuticals Ltd)
59904	Clopidogrel 75mg/5ml oral solution
60127	Aspirin 75mg tablets (DE Pharmaceuticals)
60278	Aspirin 300mg tablets (DE Pharmaceuticals)
60693	Aspirin 15mg/5ml oral solution
60694	Aspirin 25mg/5ml oral solution
60777	Aspirin 75mg gastro-resistant tablets (DE Pharmaceuticals)
62334	Aspirin 300mg caplets (Wockhardt UK Ltd)
62430	Aspirin 300mg suppositories (A A H Pharmaceuticals Ltd)

8.4 Appendix 4. Tables from Time to event analysis

Final model for the time to non-fatal MI events

Non-fatal-MI Lognormal				
Time ratios				
	Coefficient	**P>|z|**	**[95% Conf. Interval]**	
Regimen				
Asp-Clop	Reference			
Asp-Pras	4.07024	0.01	1.394683	11.87858
Asp-Tica	1.170864	0.68	0.553545	2.476622
Follow-up periods	1.04344	0.416	0.941867	1.155967
Age at index date	1.012535	0.192	0.993753	1.031672
Female	1.43301	0.121	0.909453	2.257969
Grouped Charlson Index				
0				
1	2.046394	0.009	1.192843	3.510711
2	1.253583	0.525	0.624076	2.518077
Polypharmacy	0.717142	0.179	0.441393	1.16516
Region				
North				
Midlands & East	1.364523	0.33	0.730499	2.548837
South	1.779065	0.036	1.039107	3.045956
Year of cohort entry				
Entry after 2009	1.767832	0.02	1.093192	2.858811
Entry after 2011	0.971534	0.937	0.475663	1.98434
Constant	0.358814	0.132	0.09466	1.360105
Natural logarithm of scale parameter (ln σ)	0.939554	0	0.858473	1.020634
sigma	2.558839		2.359554	2.774955
Asp-Clop: Aspirin-Clopidogrel dual therapy, **Asp-Pras:** Aspirin-Prasugrel dual therapy, **Asp-Tica:** Aspirin-Ticagrelor dual therapy,				

Final model for the time to non-fatal stroke events

Stroke Gompertz				
Hazard ratio				
	Coefficient	**P>|z|**	**[95% Conf. Interval]**	
Regimen				
Asp-Clop	Reference			
Asp-Pras	0.222926	0.044	0.051877	0.957956
Asp-Tica	0.044581	0.002	0.006176	0.321814
Follow-up periods	0.571512	<0.001	0.490944	0.665302
Age at index date	1.007332	0.481	0.98708	1.027999
Female	1.169339	0.411	0.805154	1.698251
Grouped Charlson Index				
0				
1	1.500036	0.028	1.04419	2.154883
2	2.266118	0.003	1.315728	3.903001
Polypharmacy	1.333748	0.202	0.856883	2.075994
Region				
North				
Midlands & East	1.072236	0.768	0.675156	1.702851

South	1.11027	0.649	0.707507	1.742313
Year of cohort entry				
Entry after 2009	0.730021	0.164	0.468676	1.137098
Entry after 2011	0.798902	0.35	0.498661	1.279918
Constant	0.026917	<0.001	0.006409	0.113051
Gamma	0.301557	0	0.164938	0.438175
Asp-Clop: Aspirin-Clopidogrel dual therapy, **Asp-Pras:** Aspirin-Prasugrel dual therapy, **Asp-Tica:** Aspirin-Ticagrelor dual therapy,				

Final model for the time to MACE events

MACE Loglogistic				
Time ratios				
	Coefficient	**P>|z|**	**[95% Conf. Interval]**	
Regimen				
Asp-Clop	Reference			
Asp-Pras	4.418081	0.002	1.730301	11.28095
Asp-Tica	1.305815	0.454	0.649169	2.626669
Follow-up periods	1.146508	<0.001	1.058393	1.241959
Age at index date	1.010237	0.207	0.994396	1.026331
Female	1.336093	0.13	0.918245	1.944084
Grouped Charlson Index				
0				
1	1.678039	0.027	1.061675	2.652239
2	1.02104	0.943	0.578726	1.801412
Polypharmacy	0.734531	0.14	0.487541	1.106649
Region				
North				
Midlands & East	1.222803	0.466	0.711888	2.100397
South	1.543565	0.055	0.991292	2.403524
Year of cohort entry				
Entry after 2009	1.884676	0.002	1.272049	2.792348
Entry after 2011	1.027478	0.928	0.570921	1.849136
Constant	0.284744	0.02	0.098786	0.820754
Ln gamma	0.298211	<0.001	0.20015	0.396272
Gamma	1.347446		1.221586	1.486273
Asp-Clop: Aspirin-Clopidogrel dual therapy, **Asp-Pras:** Aspirin-Prasugrel dual therapy, **Asp-Tica:** Aspirin-Ticagrelor dual therapy,				

Final model for the time to all cause death event

Death Weibull
Time ratios

	Coefficient	P>|z|	[95% Conf. Interval]	
Regimen				
Asp-Clop	Reference			
Asp-Pras	1.439846	0.047	1.005009	2.062823
Asp-Tica	2.579944	<0.001	1.613265	4.125862
Follow-up periods	1.756524	<0.001	1.686302	1.829671
Age at index date	0.985516	<0.001	0.981158	0.989894
Female	1.058388	0.116	0.986156	1.13591
Grouped Charlson Index				
0	Reference			
1	0.940915	0.176	0.861499	1.027651
2	0.747463	<0.001	0.67936	0.822393
Polypharmacy	1.004032	0.892	0.947249	1.064219
Region				
North				
Midlands & East	1.166272	<0.001	1.076514	1.263513
South	1.179807	<0.001	1.08394	1.284153
Year of cohort entry				
Entry after 2009	1.050086	0.279	0.961113	1.147295
Entry after 2011	1.681249	<0.001	1.520744	1.858693
Constant	2.528676	<0.001	1.763857	3.625126
Ln pi	0.961626	<0.001	0.715166	1.208087
pi	2.615948		2.044525	3.347076
1/pi	0.382271		0.298768	0.489111
Asp-Clop: Aspirin-Clopidogrel dual therapy, **Asp-Pras:** Aspirin-Prasugrel dual therapy, **Asp-Tica:** Aspirin-Ticagrelor dual therapy,				

Final model for the time to bleeding events

Bleeding Lologistic				
Time ratios				
	Coefficient	**P>|z|**	**[95% Conf. Interval]**	
Regimen				
Asp-Clop	Reference			
Asp-Pras	0.290778	0.315	0.026196	3.227729
Asp-Tica	11.89366	0.054	0.955583	148.0345
Follow-up periods	1.222915	0.079	0.977089	1.530587
Age at index date	0.931427	0.009	0.882764	0.982772
Female	4.447342	0.132	0.638037	30.99952
Grouped Charlson Index				
0	Reference			
1	0.21414	0.193	0.021011	2.182522
2	0.918733	0.922	0.167179	5.048903
Polypharmacy	0.120604	<0.001	0.033026	0.440419
Region				
North	Reference			
Midlands & East	0.177425	0.073	0.026857	1.172116
South	0.272768	0.153	0.045932	1.619848
Year of cohort entry				
Entry after 2009	0.440074	0.21	0.121782	1.590256
Entry after 2011	3.21405	0.29	0.370517	27.88026

Constant	1481734	0.001	402.7275	5.45E+09
Ln Gamma	0.462627	0.004	0.14502	0.780234
Gamma	1.588241		1.156063	2.181982
Asp-Clop: Aspirin-Clopidogrel dual therapy, **Asp-Pras:** Aspirin-Prasugrel dual therapy, **Asp-Tica:** Aspirin-Ticagrelor dual therapy,				

8.5 Appendix 5. Tables from Cost analysis

Model for total patient costs

Total Costs				
	Coefficient	**P>|z|**	**[95% Conf. Interval]**	
Regimen				
Asp-Clop	Reference			
Asp-Pras	-15.8776	<0.001	-22.3808	-9.37431
Asp-Tica	3.177615	0.52	-6.50902	12.86425
Follow-up periods	-3.1403	<0.001	-4.46952	-1.81107
Age at index date	0.382438	<0.001	0.202818	0.562058
Female	-1.00341	0.714	-6.37199	4.365162
Grouped Charlson Index				
0	Reference			
1	0.939967	0.742	-4.65166	6.531597
2	15.97616	0.003	5.563031	26.38928
Polypharmacy	13.83421	<0.001	8.056342	19.61209
Region				
North	Reference			
Midlands & East	3.469728	0.383	-4.33383	11.27328
South	-0.85928	0.789	-7.16158	5.443029
Year of cohort entry				
Entry after 2009	-5.45871	0.079	-11.5511	0.633714
Entry after 2011	-5.26853	0.092	-11.3895	0.852409
Constant	57.52179	<0.001	42.33278	72.71081
Asp-Clop: Aspirin-Clopidogrel dual therapy, **Asp-Pras:** Aspirin-Prasugrel dual therapy, **Asp-Tica:** Aspirin-Ticagrelor dual therapy,				

Model for total inpatient costs

Total Inpatient Costs				
	Coefficient	**P>|z|**	**[95% Conf. Interval]**	
Regimen				
Asp-Clop	Reference			
Asp-Pras	-30.7485	<0.001	-44.5886	-16.9084
Asp-Tica	0.072641	0.993	-15.6676	15.81284
Follow-up periods	-4.57129	<0.001	-6.78446	-2.35811
Age at index date	0.301877	0.126	-0.08466	0.688413
Female	-4.9086	0.327	-14.7187	4.901534
Grouped Charlson Index				
0	Reference			

1	2.705902	0.53	-5.72939	11.14119
2	11.80267	0.175	-5.26752	28.87286
Polypharmacy	1.017167	0.88	-12.1463	14.18064
Region				
North	Reference			
Midlands & East	4.84252	0.475	-8.43602	18.12106
South	-1.39223	0.809	-12.6905	9.906001
Year of cohort entry				
Entry after 2009	-6.34546	0.23	-16.7171	4.02621
Entry after 2011	-13.5763	0.08	-28.7567	1.604132
Constant	85.47351	<0.001	43.58932	127.3577
Asp-Clop: Aspirin-Clopidogrel dual therapy, **Asp-Pras:** Aspirin-Prasugrel dual therapy, **Asp-Tica:** Aspirin-Ticagrelor dual therapy,				

Model for total outpatient costs

Total Outpatient Costs				
	Coefficient	**P>|z|**	**[95% Conf. Interval]**	
Regimen				
Asp-Clop	Reference			
Asp-Pras	-0.29534	0.058	-0.60124	0.010555
Asp-Tica	-0.08851	0.412	-0.29985	0.122829
Follow-up periods	-0.05188	0.006	-0.08882	-0.01494
Age at index date	-0.00735	0.044	-0.01451	-0.00018
Female	-0.01353	0.877	-0.18535	0.158283
Grouped Charlson Index				
0	Reference			
1	0.107343	0.171	-0.04631	0.261
2	0.282085	0.033	0.022866	0.541304
Polypharmacy	0.053603	0.551	-0.1227	0.229902
Region				
North	Reference			
Midlands & East	0.201223	0.033	0.01665	0.385795
South	0.121049	0.226	-0.07472	0.316815
Year of cohort entry				
Entry after 2009	0.24438	0.025	0.030836	0.457924
Entry after 2011	-0.0268	0.845	-0.29484	0.241238
Constant	7.259234	<0.001	6.727283	7.791186
Asp-Clop: Aspirin-Clopidogrel dual therapy, **Asp-Pras:** Aspirin-Prasugrel dual therapy, **Asp-Tica:** Aspirin-Ticagrelor dual therapy,				

Model for total prescription costs

Prescription Costs				
	Coefficient	**P>|z|**	**[95% Conf. Interval]**	
Regimen				
Asp-Clop	Reference			
Asp-Pras	0.264951	<0.001	0.133072	0.396831

Asp-Tica	0.459134	<0.001	0.323218	0.595051
Follow-up periods	-0.11619	<0.001	-0.13871	-0.09368
Age at index date	-0.00321	0.065	-0.00661	0.000196
Female	0.079903	0.06	-0.00337	0.163178
Grouped Charlson Index				
0	Reference			
1	0.07797	0.099	-0.01459	0.170532
2	0.372705	<0.001	0.249279	0.496131
Polypharmacy	0.388884	<0.001	0.295004	0.482764
Region				
North	Reference			
Midlands & East	-0.18371	0.003	-0.30324	-0.06419
South	-0.10157	0.058	-0.20673	0.00359
Year of cohort entry				
Entry after 2009	-0.15286	<0.001	-0.24711	-0.0586
Entry after 2011	0.100881	0.063	-0.0053	0.207067
Constant	6.989597	<0.001	6.690486	7.288708
Asp-Clop: Aspirin-Clopidogrel dual therapy, **Asp-Pras:** Aspirin-Prasugrel dual therapy, **Asp-Tica:** Aspirin-Ticagrelor dual therapy,				

Model for primary care consultation costs

Primary care consultation Costs				
	Coefficient	**P>|z|**	**[95% Conf. Interval]**	
Regimen				
Asp-Clop	Reference			
Asp-Pras	-0.16873	0.058	-0.34346	0.005997
Asp-Tica	0.013021	0.861	-0.13261	0.158656
Follow-up periods	-0.11155	<0.001	-0.13557	-0.08752
Age at index date	0.000932	0.604	-0.00259	0.00446
Female	0.083883	0.111	-0.01924	0.187004
Grouped Charlson Index				
0	Reference			
1	0.065521	0.153	-0.02442	0.155458
2	0.083094	0.198	-0.04356	0.209746
Polypharmacy	0.301507	<0.001	0.19752	0.405494
Region				
North	Reference			
Midlands & East	0.037537	0.619	-0.11038	0.185451
South	-0.04001	0.548	-0.17047	0.090446
Year of cohort entry				
Entry after 2009	-0.00257	0.956	-0.09335	0.088219
Entry after 2011	0.007732	0.9	-0.11233	0.12779
Constant	6.392089	<0.001	6.105762	6.678416
Asp-Clop: Aspirin-Clopidogrel dual therapy, **Asp-Pras:** Aspirin-Prasugrel dual therapy, **Asp-Tica:** Aspirin-Ticagrelor dual therapy,				

Model for total primary care costs

Total primary care Costs				
	Coefficient	**P>|z|**	**[95% Conf. Interval]**	
Regimen				
Asp-Clop	Reference			
Asp-Pras	0.093826	0.05	-2.3E-05	0.187674
Asp-Tica	0.288505	<0.001	0.181082	0.395928
Follow-up periods	-0.11391	<0.001	-0.12911	-0.0987
Age at index date	-0.00148	0.241	-0.00395	0.000992
Female	0.084497	0.009	0.02113	0.147865
Grouped Charlson Index				
0	Reference			
1	0.071641	0.049	0.000158	0.143123
2	0.266928	<0.001	0.166116	0.36774
Polypharmacy	0.346792	<0.001	0.279454	0.414131
Region				
North	Reference			
Midlands & East	-0.09629	0.036	-0.18608	-0.0065
South	-0.07026	0.071	-0.14658	0.006051
Year of cohort entry				
Entry after 2009	-0.0861	0.013	-0.15389	-0.01831
Entry after 2011	0.056057	0.148	-0.01998	0.132095
Constant	7.419545	<0.001	7.204531	7.63456
Asp-Clop: Aspirin-Clopidogrel dual therapy, **Asp-Pras:** Aspirin-Prasugrel dual therapy, **Asp-Tica:** Aspirin-Ticagrelor dual therapy,				

8.6 Appendix 6. CHEERS criteria form

CHEERS Checklist

Items to include when reporting economic evaluations of health interventions

Section/item	**Item No**	**Recommendation**	**Reported on page No/ Line No**
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Chapter title
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	N/A
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	5.1 second, third paragraph, 5.2
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	5.3

Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	5.4.1, _rst paragraph
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	5.4.1, _rst paragraph
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Methods,Clinical trials, 3rd paragraph
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	5.4.1, third paragraph
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	5.4.1, second paragraph
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	N/A
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	5.4.2.2 (Assumptions), Table 5.2 (sources)
Measurement of valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	5.4.3
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	N/A
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost Describe any adjustments made to approximate to opportunity costs	5.4.2.1, assumptions about the costs of model states
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	5.4.1 _rst paragraph
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	5.4.2 _rst paragraph
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	5.4.1, pars 7-10
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	5.4.2.1, 5.4.2.2
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty	Results, intervention cost section

		where appropriate. Providing a table to show the input values is strongly recommended.	
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	
Characterising uncertainty	20a	Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	N/A
	20b	Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	5.8.3
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	N/A
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	5.9
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	None, model prepared for PhD thesis
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	None declared

8.7 Appendix 7. AdViSHE criteria for the model

AdViSHE

Assessment of the Validation Status of Health-Economic decision models

AdViSHE is a questionnaire that modellers can complete to report on the efforts performed to improve the validation status of their health-economic (HE) decision model. It is not intended to replace validation by model users but rather to inform the direction of validation efforts and to provide a baseline for replication of the results. In addition to using it after a model is finished, the modellers can use AdViSHE to guide validation efforts during the modelling process.

The modellers are asked to comment on the validation efforts performed while building the underlying HE decision model and afterwards. Many of the questions simply refer to the model documentation. AdViSHE is divided into five parts, each covering an aspect of validation:

- Part A: Validation of the conceptual model (2 questions)
- Part B: Input data validation (2 questions)
- Part C: Validation of the computerized model (4 questions)
- Part D: Operational validation (4 questions)
- Part E: Other validation techniques (1 question)

No final validation score is calculated, as the assessment of the answers and the overall validation effort is left to the model users. It is assumed that the model has been built according to prevailing modelling and reporting guidelines. For instance, the model builders would presumably adhere to the ISPOR-SMDM[†] Modeling Good Research Practices (Caro et al., 2010) and/or CHEERS[†] Statement (Husereau et al., 2013). Some questions may not be applicable to a particular model. If this is the case, the model builder should take the opt-out option and provide a justification of why this item is not deemed applicable.

Part A: Validation of the conceptual model (2 questions)

Part A discusses techniques for validating the conceptual model. A conceptual model describes the underlying system (e.g., progression of disease) using a mathematical, logical, verbal, or graphical representation. Please indicate where the conceptual model and its underlying assumptions are described and justified.

A1/ Face validity testing (conceptual model): Have experts been asked to judge the appropriateness of the conceptual model?
If yes, please provide information on the following aspects:
- Who are these experts?
- What is your justification for considering them experts?
- To what extent do they agree that the conceptual model is appropriate?

If no, please indicate why not.

Anthony Avery GP, GP experienced in prescribing DAPT medications, Lukasz Tanajewski ,health economist with experience in decision analytical models

Aspects to judge include: appropriateness to represent the underlying clinical process/disease (disease stages, physiological processes, etc.); and appropriateness for economic evaluation (comparators, perspective, costs covered, etc.).

A2/ Cross validity testing (conceptual model): Has this model been compared to other conceptual models found in the literature or clinical textbooks?
If yes, please indicate where this comparison is reported.
If no, please indicate why not.

The model has been structured based on the cost-effectiveness models that evaluate antiplatelet medications and is quite similar to those ones

Part B: Input data validation (2 questions)

Part B discusses techniques to validate the data serving as input in the model. These techniques are applicable to all types of models commonly used in HE modelling.

Please indicate where the description and justification of the following aspects are given:

- search strategy;
- data sources, including descriptive statistics;
- reasons for inclusion of these data sources;
- reasons for exclusion of other available data sources;
- assumptions that have been made to assign values to parameters for which no data was available;
- distributions and parameters to represent uncertainty;
- data adjustments: mathematical transformations (e.g., logarithms, squares); treatment of outliers; treatment of missing data; data synthesis (indirect treatment comparison, network meta-analysis); calibration; etc.

B1/ Face validity testing (input data): Have experts been asked to judge the appropriateness of the input data?
If yes, please provide information on the following aspects:
- Who are these experts?
- What is your justification for considering them experts?
- To what extent do they agree that appropriate data has been used?

If no, please indicate why not.

Anthony Avery GP, GP experienced in prescribing DAPT medications, Lukasz Tanajewski ,health economist with experience in decision analytical models

Aspects to judge may include but are not limited to: potential for bias; generalizability to the target population; availability of alternative data sources; any adjustments made to the data.

B2/ Model fit testing: When input parameters are based on regression models, have statistical tests been performed?
If yes, please indicate where the description, the justification and the outcomes of these tests are reported.
If no, please indicate why not.

No, because the sources of the regression models were already sourced from published studies and they were available as estimation tools that had already been validated

Examples of regression models include but are not limited to: disease progression based on survival curves; risk profiles using regression analysis on a cohort; local cost estimates based on multi-level models; meta-regression; quality-of-life weights estimated using discrete choice analysis; mapping of disease-specific quality-of-life weights to utility values.
Examples of tests include but are not limited to: comparing model fit parameters (R^2, Akaike information criterion (AIC), Bayesian information criterion (BIC)); comparing alternative model specifications (covariates, distributional assumptions); comparing alternative distributions for survival curves (Weibull, lognormal, logit); testing the numerical stability of the outcomes (sufficient number of iterations); testing the convergence of the regression model; visually testing model fit and/or regression residuals.

Part C: Validation of the computerized model (4 questions)

Part C discusses various techniques for validating the model as it is implemented in a software program. If there are any differences between the conceptual model (Part A) and the final computerized model, please indicate where these differences are reported and justified.

C1/ External review: Has the computerized model been examined by modelling experts?
If yes, please provide information on the following aspects:
- Who are these experts?
- What is your justification for considering them experts?
- Can these experts be qualified as independent?
- Please indicate where the results of this review are reported, including a discussion of any unresolved issues.

If no, please indicate why not.

The model was judged by Lukasz Tanajewski, who has been and experienced modeller and user of the Treeage software, which was used to construct the model.

Aspects to judge may include but are not limited to: absence of apparent bugs; logical code structure optimized for speed and accuracy; appropriate translation of the conceptual model.

C2/ Extreme value testing: Has the model been run for specific, extreme sets of parameter values in order to detect any coding errors?
If yes, please indicate where these tests and their outcomes are reported.
If no, please indicate why not.

The tests that were carried out were with testing hazard ratios across the different branches of the models. HR=1 was used as a testing method to indicate potential problems with the transition probabilties

Examples include but are not limited to: zero and extremely high (background) mortality; extremely beneficial, extremely detrimental, or no treatment effect; zero or extremely high treatment or healthcare costs.

C3/ Testing of traces: Have patients been tracked through the model to determine whether its logic is correct? If yes, please indicate where these tests and their outcomes are reported. If no, please indicate why not.

Testing of traces was used when the results of the deterministic analysis and those of probabilistic sensitivity analysis were not in accordance, as a way of finding out the differences between the analyses

In cohort models, this would involve listing the number of patients in each disease stage at one, several, or all time points (e.g., Markov traces). In individual patient simulation models, this would involve following several patients throughout their natural disease progression.

C4/ Unit testing: Have individual sub-modules of the computerized model been tested? If yes, please provide information on the following aspects: - Was a protocol that describes the tests, criteria, and acceptance norms defined beforehand? - Please indicate where these tests and their outcomes are reported. If no, please indicate why not.

The model was built branch by branch and every treatment arm was prepared and run afterwards

Examples include but are not limited to: turning sub-modules of the program on and off; altering global parameters; testing messages (e.g., warning against illegal or illogical inputs), drop-down menus, named areas, switches, labelling, formulas and macros; removing redundant elements.

Part D: Operational validation (4 questions)

Part D discusses techniques used to validate the model outcomes.

D1/ Face validity testing (model outcomes): Have experts been asked to judge the appropriateness of the model outcomes? If yes, please provide information on the following aspects: - Who are these experts? - What is your justification for considering them experts? - To what extent did they conclude that the model outcomes are reasonable? If no, please indicate why not.

Lukasz Tanajewski ,health economist with experience in decision analytical models

Outcomes may include but are not limited to: (quality-adjusted) life years; deaths; hospitalizations; total costs.

D2/ Cross validation testing (model outcomes): Have the model outcomes been compared to the outcomes of other models that address similar problems? If yes, please provide information on the following aspects: - Are these comparisons based on published outcomes only, or did you have access to the alternative model? - Can the differences in outcomes between your model and other models be explained? - Please indicate where this comparison is reported, including a discussion of the comparability with your model. If no, please indicate why not.

In the models that were comparing the similar interventions across different populations and different health care settings, the results were similar. Ticagrelor was found to be cost-effective but a change in the death risk could result in different selection of cost-effective treatment

Other models may include models that describe the same disease, the same intervention, and/or the same population.

D3/ Validation against outcomes using alternative input data: Have the model outcomes been compared to the outcomes obtained when using alternative input data? If yes, please indicate where these tests and their outcomes are reported. If no, please indicate why not.

No , because it was not possible to obtain an alternative set of input parameters

Alternative input data can be obtained by using different literature sources or datasets, but can also be constructed by splitting the original data set in two parts, and using one part to calculate the model outcomes and the other part to validate against.

D4/ Validation against empirical data: Have the model outcomes been compared to empirical data? If yes, please provide information on the following aspects: - Are these comparisons based on summary statistics, or patient-level datasets? - Have you been able to explain any difference between the model outcomes and empirical data? - Please indicate where this comparison is reported. If no, please indicate why not. **D4.A/** Comparison against the data sources on which the model is based (dependent validation).

No, this was not possible because no alternative data source for the model existed

D4.B/ Comparison against a data source that was not used to build the model (independent validation).

N/A

Part E: Other validation techniques (1 question)

E1/ Other validation techniques: Have any other validation techniques been performed? If yes, indicate where the application and outcomes are reported, or else provide a short summary here.

No further validation techniques were carried out

Examples of other validation techniques: structured “walk-throughs” (guiding others through the conceptual model or computerized program step-by-step); naïve benchmarking (“back-of-the-envelope” calculations); heterogeneity tests; double programming (two model developers program components independently and/or the model is programmed in two different software packages to determine if the same results are obtained).