The treatment of hypertension in people with dementia

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Abstract

Introduction

Current guidance on the treatment of high blood pressure provides the advice that co-pathology should be taken into account when treatment decisions are made, but does not specify the approach in people with dementia. A relationship between high blood pressure and dementia, all be it complex and variable over time, does exist, making dementia a relevant co-pathology in decisions around the treatment of hypertension. No trial evidence exists however to guide clinical decision making in this specific context and clinicians with theoretical concerns over adverse events or varying priorities may act differently while remaining within the scope of current guidance. To inform the design of potential future research examining the repercussions of different treatment approaches, the way high blood pressure is currently treated in people with dementia and the adverse events they experience need to be understood.

Aims

This thesis reports research which set out to describe the treatment of high blood pressure in people with dementia and the adverse events that this population experienced over a six month period.

Methods

(i) A systematic literature review of observational studies describing the treatment of hypertension in people with dementia was performed.

(ii) A multicentre cohort study, the Hypertension IN Dementia (HIND) study, of 181 participants, recorded information on dependency in activities of daily living (ADLs), cognition, medication, diagnoses, and healthcare use. It provided a detailed description of the treatment of high blood pressure in the study population and the adverse events experienced over a 6 month period.

Results

Literature review: The prevalence of hypertension in people with dementia was 45% (range 36%-84%), of whom 73% (range 48%-85%) were taking at least one antihypertensive. 55% of people with dementia achieved target blood pressure in the one study that reported this. The review found no studies that specifically set out to describe the treatment of high blood pressure in people with dementia in the UK.

Cohort study: 181 participants were recruited from general practices and via memory clinics. The rate of recruitment was low (8%) in the GP arm, resulting in potential selection bias. The study population were mildly cognitively impaired (median MMSE 23 (IQR 18-26)), 56% were dependent for at least one ADL, had a median of 5 (IQR 3-7) diagnoses and were treated with a median of 7 (5-9) medications. High blood pressure was treated in 87% (95% CI 82% - 92%) and target blood pressure was achieved in 57% (95% CI 49% - 64%) of those on treatment, no different from the general population (87% (95% CI 85% - 89%) treated and 52% (95% CI

49% - 55%) achieving target). ACEi/ARBs were the most frequently prescribed antihypertensive class (55%), followed by calcium channel blockers (33%), beta-blockers (30%) and diuretics (21%). Diuretics were less likely to be prescribed than in the general population (21% (95% CI 15%-26%) vs 34% (95% CI 31% - 37%)).

During 6 months follow up the study population reported 475 GP appointments, 65 hospital admissions, 214 falls, 1 myocardial infarction, 6 strokes and 8 deaths. Heart failure, stroke, recurrent falls, falls with fractures, death and GP appointments were more common in the study population than in benchmark populations.

Conclusion

In conclusion in an area where clinicians were acting without a firm evidence base and where there were theoretical concerns around the potential side effects of antihypertensive use, clinicians treated hypertension in people with dementia much as they did in people without dementia.

The same classes of antihypertensives were used to maintain blood pressure at a similar level to that achievable in the general population. Despite a potential selection bias that may have over recruited fitter and milder people with dementia than the overall population, the study population reported a higher level of cardiovascular events, recurrent falls, fractures and adverse symptomatology than those without dementia in benchmark populations. Although this finding could relate to reporting bias or a

higher intrinsic cardiovascular risk it raises the possibility that the benefits of antihypertensive treatment are attenuated, while the risks are increased, in people with dementia with implications for the risk-benefit ratio in this population.

Future specific research, using an approach that avoids selection bias, to explore the risk-benefit ratio of antihypertensive treatment in people with dementia is outlined and advice is provided to clinicians managing high blood pressure in people with dementia.

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Chapter 1

Hypertension in people with dementia

1.1 Introduction

Policy and guidelines across the globe stress the importance of the detection and treatment of high blood pressure, which is often regarded as the most important cardiovascular risk factor with the greatest impact on mortality[1-3]. High blood pressure is very common amongst older adults with a reported 56.1% of community dwelling older people, 43.7% of care home residents and 40.6% of nursing home residents having a diagnosis of hypertension[4]. Its prevalence increases with increasing age[5] with approximately 80% of those aged over 80 being hypertensive[6].

Current guidance on the treatment of high blood pressure provides the advice that co-pathology should be taken into account when treatment decisions are made, but does not specify the approach in people with dementia[1]. A relationship between high blood pressure and dementia, all-be-it complex and variable over time, does exist[7-10], making dementia a relevant co-pathology in decisions around the treatment of hypertension. No robust trial evidence exists however, to guide clinical decision making in this specific context and the approach currently adopted by clinicians is unknown. Clinicians with varying concerns or priorities may act differently while remaining within the scope of current guidance. For instance, those concerned

about the potential side effects of antihypertensive treatment might opt not to give any antihypertensive medication or use less stringent target blood pressures[11], while others might advocate tight blood pressure control[12]. Before future research can examine the repercussions of different treatment approaches, the way high blood pressure in people with dementia is currently treated needs to be understood. This thesis reports on research which aimed to describe the treatment of high blood pressure in people with dementia and proposes further specific research posited on this.

This chapter will define what is meant by hypertension and discuss the natural history of high blood pressure. It will describe the natural history of high blood pressure in people with dementia and make the case that dementia is a relevant co-pathology in the treatment of hypertension. It will outline current guidance on treatment and discuss potential adverse effects of antihypertensive treatment. It will outline the basis for the literature review and cohort study presented in subsequent chapters.

1.2 Defining hypertension

Blood pressure within the general population is a normally distributed continuous variable and so defining hypertension has always represented a challenge because any cut off is necessarily arbitrary. The risk of cardiovascular disease associated with high blood pressure doubles for every 20/10 mmHG rise in BP over 115/70[13] and so there is no natural cut off at which blood pressure can be said to be pathologically high. However, when faced with the

binary choice of whether or not to recommend intervention to lower blood pressure, a threshold is useful to facilitate decision making[14]. For guideline bodies making these recommendations, such as the National Institute for health and Care Excellence (NICE), European Society of Cardiology (ESC), European Society of Hypertension (ESH), American College of Cardiology (ACC) and American Heart Association (AHA), their recommended thresholds have been determined by examination of trial evidence showing treatment at these levels reduces the development or progression of disease[15]. However such decisions have not been without controversy, for instance, a significant minority of the guideline development group for Joint National Committee (JNC) 8 published their concerns about the interpretation of the evidence used in producing their own guidance[16]. The appropriateness of these recommended thresholds for a particular individual therefore relies on the applicability of the original research to that individual.

1.2.1 Measuring blood pressure

In addition to the challenges around defining blood pressure thresholds, different approaches to measuring blood pressure and variation in accuracy of measurements[17], add to the complexity of a definition. Clinic blood pressures, home blood pressures[18] and 24 hour ambulatory blood pressure monitoring[19] now all form part of the standard approaches used to measure blood pressure. This is reflected, for instance, in the 2011 update of the NICE guidance thresholds which have been modified to take into account the increasing use of ambulatory and home blood pressure monitoring[1].

1.2.2 Threshold blood pressures

A threshold of 140/90 mmHg or higher is recommended by NICE (age <80), ESC/ESH, and JNC8 (age <60) as a level at which to start therapy with the aim of reducing the BP to less than 140/90.

The precise thresholds recommended in different situations vary slightly between the different guideline bodies with ESC/ESH 2014 and JNC8 recommending <140/90 as the target BP despite comorbidities. In contrast NICE 2011 advises that with co-existent diabetes mellitus and chronic kidney disease the evidence base suggests different thresholds at which to intervene and hence different target blood pressures, these are described below. Both NICE and JNC8 advise different threshold in older adults, as well as a different categorisation of what should be regarded as "older". For JNC8 this is set at 60 years of age and for NICE at 80 years.

1.2.3 NICE 2011 thresholds

1.2.3.1 Type 1 diabetes mellitus

The recommended target BP is <135/85 mmHg unless the individual has albuminuria or two or more features of metabolic syndrome in which case the target is <130/80 mmHg[20].

1.2.3.2 Type 2 diabetes mellitus

The recommended target BP is <140/80 mmHg unless the individual has retinopathy or cerebrovascular disease or microalbuminuria in which case the recommendation is lower at <130/80 mmHg[21].

1.2.3.3 Chronic kidney disease

The recommended target is < 140/80 mmHg with a target range of 120–139mmHg unless there is co-existent diabetes, in which case

the diabetic target applies, or where the urinary albumin creatinine ratio is >70 mg/mmol where the recommendation is for a BP of <130/80 (target range 120–129 mmHg)[22].

1.2.3.4 Age over 80 years

For those aged over 80 the recommendation is that the clinic blood pressure should be brought down to below 150/90 (145/85 for ambulatory blood pressure monitoring (ABPM))[15].

As much of the research reported in this thesis is UK based, the NICE 2011 thresholds will be used throughout the thesis where discussion about target blood pressures occurs.

1.2.4 Causation

No single cause is identified in 90-95% of people with sustained high blood pressure and they are said to have primary hypertension (previously referred to as essential hypertension)[14]. In the remainder a cause can be identified, such as reno-vascular disease or Conn's adenoma, and in this case a label of secondary hypertension is applied[23]. Discussion of high blood pressure in this thesis focuses on primary hypertension only.

1.2.5 The diagnosis of primary hypertension

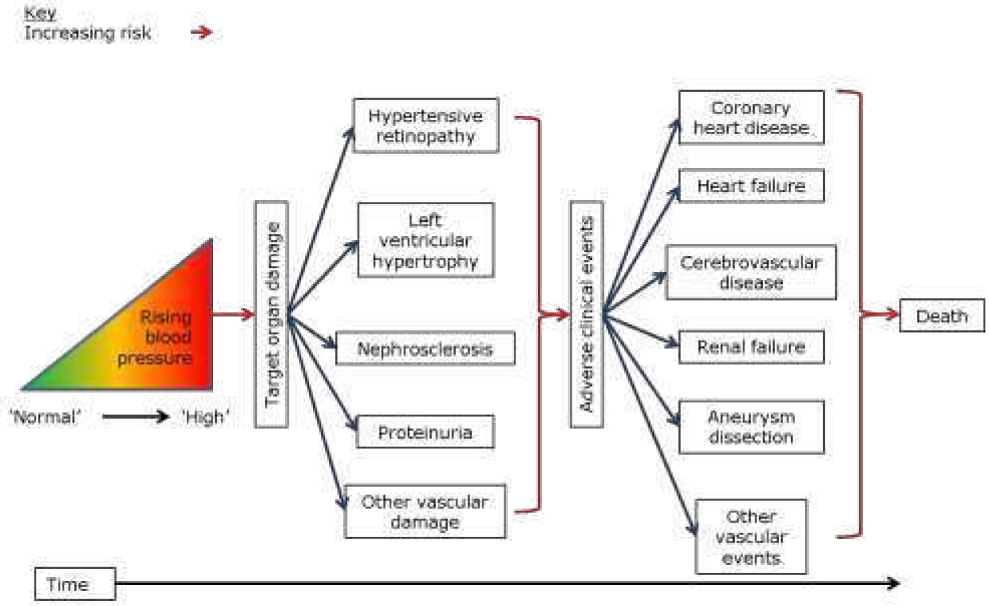
The label of primary hypertension therefore refers to a situation where blood pressure readings have been recorded to be sustained at a level over the threshold at which trial evidence suggests that therapy to lower blood pressure will reduce the chance of the development or progression of disease where no specific cause for the elevated blood pressure readings is found. Referring to this as a *diagnosis* of hypertension is a convenient short hand.

1.3 The natural history of hypertension

As someone ages, their systolic blood pressure tends to rise and in those with higher blood pressures the chance of it increasing over time is higher, even if they start below the diagnostic threshold for hypertension[24]. Diastolic blood pressure initially increases with increasing age before plateauing at around 50-55 years and then decreasing after 60-65 years of age[25]. This divergence in systolic and diastolic blood pressures results in the observed increase in the prevalence of isolated systolic hypertension in older age groups.

Higher blood pressure is associated with a higher risk of target organ damage, such as left ventricular hypertrophy[26], retinopathy[27], and proteinuria[28]. The presence of end organ damage is an important risk factor[14] for adverse clinical events such as MI, angina, cerebrovascular disease including vascular dementia, aneurysms, renal failure and heart failure[15]. Ultimately this results in an increased chance of death compared to people with lower blood pressures. Prior to the development of medical therapy for high blood pressure, individuals diagnosed with high blood pressure in their 30s were at high risk of dying in their early 50s from cardiovascular complications[28], and accelerated or 'malignant' hypertension was common[29]. Figure 1.1 summarises one model of the natural history of hypertension.

Figure 1.1 Model of the natural history of untreated hypertension



1.4 The natural history of hypertension in people with dementia

The natural history of blood pressure differs in people with dementia from their cognitively intact peers. Although diastolic blood pressure falls during ageing in cognitively intact people[25], this effect is more marked in people with dementia[7]. Systolic blood pressure, which normally climbs over time in cognitively intact people, falls in people with dementia[8]. A drop of between 22 and 8 mmHg in systolic BP and of between 13 and 7.3 mmHg in diastolic BP in those diagnosed with dementia during follow up has been observed compared to a drop of 2 mmHg systolic BP and 3.6 mmHg diastolic BP in those without dementia[7]. This fall in systolic blood pressure has been observed in a number of long term, large scale cohort studies, has been reported to have started between three[7,8] and six[9] years before clinically apparent dementia developed and has been

observed to continue to fall after diagnosis[7,8,30]. The magnitude of these changes in BP is such that they would potentially be enough to move an individual below a treatment threshold for their blood pressure.

In addition, increasing degrees of cognitive impairment are associated with increased prevalence of orthostatic hypotension – 4% in people with normal cognition, 12% in those with mild cognitive impairment, 15% in those with Alzheimer's disease, and 22% in those with vascular dementia. Higher numbers of antihypertensives were also associated with orthostatic hypotension in this study group[31].

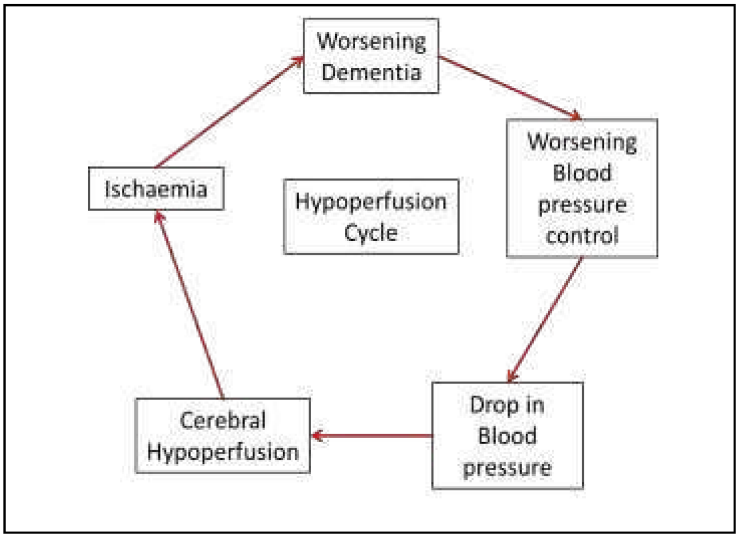
Both the changes in blood pressure over time and the increased prevalence of orthostatic hypotension have implications for the management of blood pressure in the context of coexisting dementia and may provide important information on the pathogenesis of dementia.

1.4.1 The hypoperfusion hypothesis

The hypoperfusion hypothesis attempts to explain how the observed fall in blood pressure and observed increase in orthostatic hypotension in people with dementia generates a self-perpetuating cycle of progressive cognitive deterioration. As cognitive impairment worsens orthostatic hypotension becomes more frequent, whilst age related and arteriosclerotic changes to cerebral blood flow auto-regulation occur concomitantly, thus reducing the ability of the body to minimise the effect of blood pressure fluctuation on the brain.

Fluctuations in blood pressure are therefore more likely to cause transient hypoperfusion and transient ischaemia which eventually may generate multiple white matter lesions. Systemic hypotension is associated with white matter lesions[32], and white matter lesions are associated with increasing cognitive impairment. A cycle of repeated insult leading to progressive cognitive decline can occur. This hypothetical mechanism is summarised in figure 1.2

Figure 1.2 The hypoperfusion cycle



If this hypothetical mechanism is correct then antihypertensives could potentially have a negative impact if used in an individual where this cycle is established.

1.5 The pharmacological management of high blood pressure

The major guideline bodies make a number of recommendations regarding the choice of specific pharmacological agents for high blood pressure. Broadly speaking the guidelines agree on the major classes that should be prioritised but they differ slightly in the

specifics. (The recommendations of the larger guideline bodies are summarised below.)

1.5.1 JNC 8 guidance

JNC 8 guidance advises initiating either a thiazide-type diuretic, a calcium channel blocker, or an ACEi/ARB in the non-black population, while in the black population they advise starting either a thiazide-type diuretic or a CCB. They advise that further agents be added from the initial lists until control is achieved.

1.5.2 ESH / ECS 2013 Guidance

No global recommendation for order of initiation is advised, however specific agents are recommended in the context of specific comorbidities. (Table 1.1)

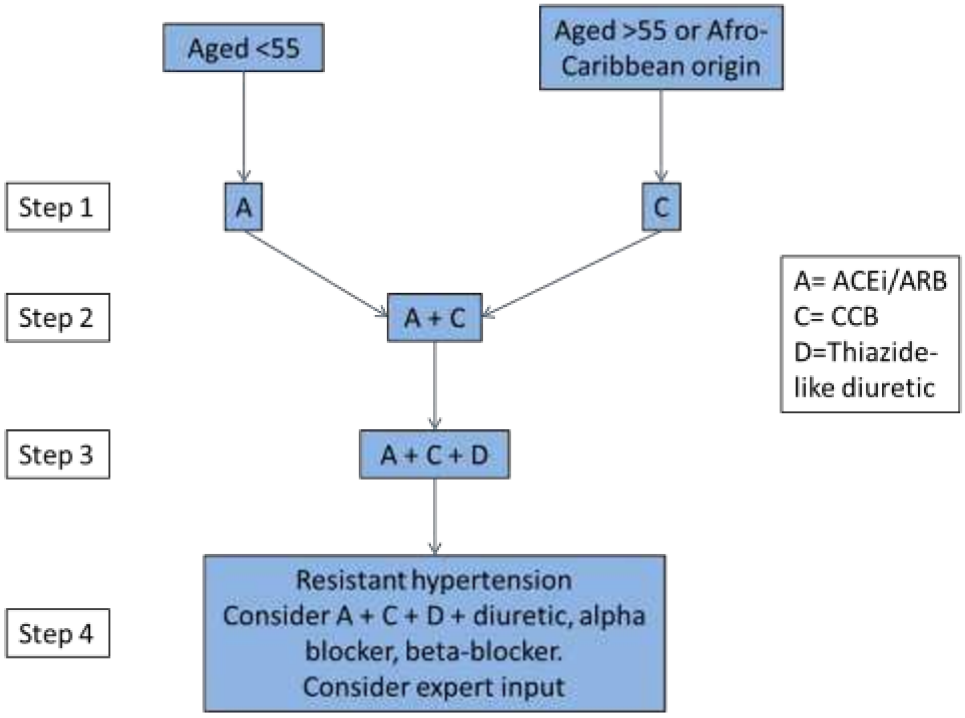
Table 1.1 ESH / ECS 2013 Guidance

Co-morbidity	**Agents(s)**
Asymptomatic organ damage	
LVH	ACEi/ARB, CCB
Asymptomatic atherosclerosis	CCB, ACEi
Microalbuminuria	ACEi/ARB
Renal dysfunction	ACEi/ARB
Clinical CV event	
Stroke	Any agent
MI	BB, ACEi/ARB
Angina	BB, CCB
Heart failure	D, BB, ACEi/ARB, mineralocorticoid
Aortic aneurysm	BB
ESRD /proteinuria	ACEi/ARB
Peripheral artery disease	ACEi /CCB
Other	
ISH	D, CCB
Metabolic syndrome	ACEi/ARB, CCB
DM	ACEi/ARB
Pregnancy	Methyldopa, BB, CCB
Blacks	D, CCB

1.5.3 NICE 2011

At odds with the ESC guidance, NICE 2011 recommends a specific order of medication initiation[3,15]. Figure 1.2 below summarises the recommended treatment regimen. The decision to commence treatment is based on a combination of blood pressure values and the presence of evidence of end organ damage or established cardiovascular disease.

Figure 1.2 Nice antihypertensive initiation schedule



The guidance recommends modifying this initiation schedule in the presence of certain comorbidities, such as using a diuretic rather than CCB in the presence of heart failure for instance.

Although the different guideline bodies' advice appears superficially different in practical terms the agents that would be advised for an individual patient vary little between them.

1.5.4 Quality and outcomes framework

The management of hypertension within the UK occurs largely within the constraints of the quality and outcomes framework (QOF) which is the annual reward and incentive scheme for GP practices originally introduced in April 2004[33] the purpose of which is to drive up the quality of healthcare. GP practices accumulate QOF points based on the achievement of multiple targets for which they are financially rewarded. Although the scheme is voluntary the majority of GP practices are signed up to it and derive a substantial part of their practice income from it. It includes targets for managing common chronic diseases such as diabetes, targets for managing major public health concerns such as smoking and targets for instigating disease prevention such as regular blood pressure checks. Hypertension has specific QOF targets, these include a requirement for a register of patients with a diagnosis of hypertension and financial incentives for increasing proportions achieving NICE recommended BP targets. The introduction of QOF increased the proportion of those diagnosed with hypertension achieving target blood pressures[33,34] but there has been concern that a target orientated approach is at odds with person centred care and has led to overtreatment of blood pressure[35]. In a survey of 427 UK GPs of their views on blood pressure control in people with and without dementia concern about QOF and compliance with guidelines formed a major theme in their responses[36]. A number of participants in the survey alluded to QOF influencing their management decisions while one specifically raised concern that QOF has led to overtreatment of blood pressure.

1.5.5 End organ damage and established cardiovascular disease

The presence or absence of risk factors such as end organ damage or established cardiovascular disease are used by all the major guideline bodies, partially to stratify individual cardiovascular risk and hence influence the decision to start pharmacological therapy, but also to prioritise specific antihypertensive classes when commencing treatment.

Given that high blood pressure is associated with an increased risk of asymptomatic brain damage, most commonly white matter hyper-intensities on MRI scan[37,38] and is a risk factor for the development of (all-cause) dementia[7,39,40] it might be anticipated that the presence of such end organ damage would be a factor which would be relevant to an individual's general cardiovascular risk and hence a factor to be considered in treatment decisions.

Indeed within the ESC guidelines hypertension is stated to be a risk factor for white matter lesions, cognitive impairment and dementia. However the presence of dementia per se is not regarded as a sufficient risk factor in treatment decision making within this guideline, while NICE 2011 and JNC8 make no specific mention of dementia at all[2,15].

The lack of specific guidance relates to the lack of an evidence base in people with established dementia. Dementia has often been used as an exclusion criterion in the major antihypertensive trials[41] and so there is limited data on which to base guideline recommendations. The only systematic review which describes the

evidence for treating high blood pressure in people with dementia identified only 6 small scale studies, the majority of which were looking into the effect of antihypertensive use on the progression of dementia rather than cardiovascular outcomes, and concluded that there was no overwhelming evidence of benefit or harm[42].

1.5.6 Prevention of dementia

Although not part of the antihypertensive guidelines' rationale control of blood pressure is a key element of dementia prevention strategies based on evidence from observational cohort studies that treatment of high blood pressure in mid-life is associated with a reduced chance of dementia in later life[43]. The emphasis placed on cardiovascular risk modification and lifestyle interventions over the last two decades, at least partly driven by QOF, may have contributed to the reported reduction in the incidence of dementia[44]. In later life however, this benefit appears to disappear with no compelling evidence from RCTs that treating high blood pressure in older age reduces the incidence or progression of dementia[45].

1.5.7 Dementia is a relevant co-pathology in the management of high blood pressure

The natural history of the fall in blood pressure and increased frequency of orthostatic hypotension in people with dementia has implications for treatment decisions and subsequent monitoring of blood pressure.

1.5.8 Potential benefits and hazards of antihypertensive therapy in people with dementia that may influence clinicians' decisions.

The decision to start treatment to lower blood pressure is ideally made when the evidence of benefit outweighs any evidence of harm. In the context of dementia this is a challenge due to the lack of a robust evidence base and clear guidance. Clinicians facing this problem at present have to make an individualised assessment and treatment plan. In addition, as multiple medical problems[46,47] as well as dementia[48] become more prevalent with increasing age, this decision is often made in the context of multiple medical pathologies as well as psychological and functional problems. In the UK these decisions are normally made by general practitioners who report that these are complex and often challenging to make[36].

Practitioners must weigh up the potential benefits and potential harms for each individual. As has been stated there is no robust evidence base for the treatment of hypertension in people with dementia, however, there is also no evidence that people with dementia would not experience similar cardiovascular risk reduction benefits from blood pressure lowering therapy as their cognitively intact peers. However, antihypertensive treatment is not risk free and unfortunately is associated with a number of adverse health problems[49]. One in ten people prescribed antihypertensives discontinue them and this is felt to be due to associated adverse events[50]. Medication side effects are more commonly overlooked in more dependent people with cognitive impairment[51] raising the hypothesis that such events may be more common in people with

dementia. Adverse events associated with antihypertensive use include increased risks of falls[52,53], hip fractures[54], orthostatic hypotension[55], hyponatraemia[56], hyperkalaemia[57], renal impairment[58], anaemia[58], angioedema[58,59], cough[58,60], headache[61,62], dizziness[63], swollen ankles[64], cold hands or feet[33,62], skin rash / itching[62], dry mouth[62], nausea[62], diarrhoea[62], constipation[62], palpitations[62], nervousness[33,62], tiredness[33,62], sleep problems[33,62] and frequent micturition[62].

In addition polypharmacy is contributed to by antihypertensive treatment and this remains a major cause of morbidity and mortality in older people[65,66]. Anticholinergic burden provides an a priori case for the risks of polypharmacy with many medications, which are not used primarily for an anti-cholinergic effect, having a mild effect. Alone this may not be an issue but when used in combination it is possible for a significant burden to be rapidly reached[67]. A number of agents used as antihypertensives have an anticholinergic effect including captopril, atenolol, metoprolol, and furosemide[68,69]. Increasing anticholinergic burden increases the risk of delirium and confusion[70] particularly in the case of someone with a pre-existing dementia[43], an effect which is potentially reversible, when anticholinergic medications are discontinued[71].

1.6 Describing the treatment of hypertension in people with dementia

This introduction has provided a working definition of hypertension and outlined the natural history of blood pressure in the context of dementia. It has given an overview of the guidelines which are used to help clinicians managing this condition and highlighted the lack of evidence specific to people with established dementia. It has demonstrated that the presence of dementia is a relevant factor in the management of high blood pressure.

Before future research can examine the repercussions of different treatment approaches for high blood pressure in people with dementia, the way it is currently treated needs to be understood. In order to ask appropriate questions to support future research it is necessary to know whether treatment practices for hypertension differ in dementia. Where people with dementia are treated for hypertension, it is important to understand how this influences attainment of recommended targets and incidence of adverse events. Clearly if current practice is to treat patients with dementia similarly to those without and there is no difference in terms of outcomes than it would be difficult to suggest sufficient equipoise to justify future interventional studies to modify recommended treatment regimes in this cohort.

This thesis reports research which sought to answer the following questions:

(i) How is hypertension in people with dementia treated in the UK and how does this compare to the treatment of hypertension in the general population?

(ii) Is hypertension in people with dementia more or less likely to be treated than in the general UK hypertensive population?

(iii) What factors are associated with treatment and non-treatment of blood pressure in people with dementia?

(iv) Is hypertension in people with dementia treated more or less effectively than in the general UK population?

(v) Are the adverse events and symptoms, including cardiovascular events, experienced by people with dementia on treatment for hypertension more or less frequent than in treated hypertensive people without dementia?

The first stage in this process was to conduct a review of the literature to determine whether these questions had previously been examined and to identify previous attempts to describe this population and its treatment. This process and its findings are described in chapter 2.

The second stage was to conduct an observational study to examine the approach to treatment within the UK and to compare the rates of adverse events experienced by this population with the general population. This is described in chapter 3.

Chapter 2

The treatment of hypertension in people with dementia: a systematic review

2.1 Introduction

The first stage in describing the treatment of hypertension in people with dementia was to conduct a systematic search to determine whether this area had been looked into previously and to identify previous attempts to describe this population. A systematic review of the literature was therefore carried out. This was a complex undertaking, in part due to the large volume of research which had been carried out looking at the potential prevention of dementia by the treatment of hypertension. This large volume of research, identified during preliminary work, tended to obscure the much smaller amount which had been carried out describing high blood pressure treatment in people with established dementia.

A review was designed to identify observational studies which reported the treatment of high blood pressure in people with established dementia. It was anticipated that this would encompass relatively few studies and, owing to the obscuration already alluded

to, it was essential that the search be as broad as possible to avoid missing any relevant studies.

2.2 General aims

This review set out to provide answers to some of the questions posited during the introduction, in particular:

(i) How is hypertension in people with dementia treated in the UK and how does this compare to the treatment of hypertension in the general population?

(ii) Is hypertension in people with dementia more or less likely to be treated than in the general hypertensive population?

(iii) Is hypertension in people with dementia treated more or less effectively than in the general UK population?

2.3 Methodology

2.3.1 Mode of literature review

A number of methods of literature review are in regular use and, although systematic reviews with or without a meta-analysis are often considered the gold standard, a review of the strengths and weaknesses of alternative methods was carried out to determine the most appropriate approach in this case. Grant and Booth describe

14 different types of literature review in their scoping review of 2009[72]. Approaches they describe include the very ad hoc 'an overview' to the very rigorous such as systematic review. After scrutinising the different review types described and considering the aims of this literature review it was felt that the systematic approach embodied in a systematic review was the most appropriate.

Although this approach does have some limitations, which largely cluster around the potential to exclude studies which may have some relevance but which do not meet selection criteria, there are many advantages of a systematic approach to a review. In addition to the reproducibility of the method[73], the principle advantage is that such an approach aims to avoid the potential for selection bias inherent in an ad hoc approach, while aiming to identify all relevant information to a question.

Overall therefore it was felt that conducting a systematic review would be the most appropriate approach here, and would effectively satisfy the aim.

2.3.2 Source choice

Electronic libraries provide a potentially excellent resource for conducting a systematic review. For a systematic review of observational studies Lemeshow and colleagues found that searching one or two databases was inadequate and located only 60-80% of relevant abstracts, they required four databases to identify 91% of papers relevant to their question[74]. Therefore, for the purposes of this review four databases would be searched to maximise retrieval rate while balancing this against the time and resource demands.

The Medline database is frequently used by biomedical researchers as the database of choice, this approach is supported by the Cochrane foundation[75], and in this case it formed the logical core to the search. In addition the Embase database, which is frequently used by non-US/UK researchers, provides and contains more pharmacological literature meaning that it would augment the search[76]. In addition to medical and pharmacological professionals, those working in the sphere of psychological medicine were also considered as potential contributors of relevant literature. The PsychInfo database was therefore also included in the list of sources. Finally the Cochrane database would be searched.

2.3.2.1 The 'grey' literature

Given the presumed scarcity of studies reporting the treatment of hypertension in people with dementia, consideration was given to additional searches within the grey literature. This body of work, including items such as conference proceedings, newspaper articles and government missives, is largely not indexed to the large electronic databases and so would require additional search strategies. Although concern has been raised that the exclusion of such work may bias the findings of a review, specifically a concern in RCTs rather than observational studies, the work of Egger and colleagues suggested that exclusion of this body is unlikely to have significant effects on the precision of review findings[77]. In addition the grey literature may not have undergone as rigorous a check as a peer reviewed publication, may be more open to publication bias or availability bias and, from a practical point of view, search strategies for locating work within the grey literature tend to be time and resource heavy. Given this, within the confines of a PhD project, it was decided that this area of the literature would not be investigated as part of the review process.

2.3.3 Developing a search protocol

The task of developing a robust search protocol which was broad enough to identify relevant but efficient enough to exclude irrelevant papers proved to be difficult. It was suspected, following preliminary scoping work, that the numbers of papers describing the treatment of hypertension in people with dementia would be small.

It was therefore important to keep the initial search terms broad so as to maximise the chance of identifying appropriate papers.

The first stage in developing the search terms was to review the question and to pull out the key elements. In this case these were felt to include 'dementia', 'hypertension' and 'treatment'. These were expanded to include associated MeSH terms, synonyms, and associated terms, thus 'hypertension' also included antihypertensive agents and 'treatment' therapeutics. The terms were altered as appropriate for each individual database.

To ensure that studies included in the review only reported standard practice only observational studies, rather than drug trials, were included.

Exclusion criteria were also applied, removing non-English language publications and studies published before 1990. The decision to focus on the English language literature was taken on a pragmatic basis on the grounds that within the restrictions of a PhD project translation costs could not be covered. It was decided to focus on more recent publications to try to avoid describing practice that has been superseded. An arbitrary date of 1990 was decided upon for this purpose.

2.4 Describing the treatment of hypertension in people with dementia

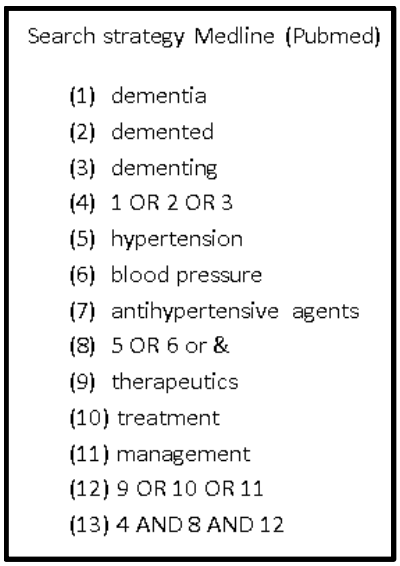
2.4.1 Aims

To describe the prevalence of, treatment of and change in treatment over time of hypertension in people with dementia

2.4.2 Methods

Medline (1946 – August 2015), Embase (1974 – August 2015), PsychInfo (1806- August 2015) and Cochrane databases were searched using the MeSH terms 'dementia', 'hypertension', 'antihypertensive agents' and 'therapeutics', and the non-MeSH terms 'treatment', 'management' and 'blood pressure'. These terms were altered as appropriate for the individual databases (an example search showing how the terms were combined is shown in figure 2.1). The search was then limited to English language articles, to studies involving humans and to studies involving adults.

Figure 2.1 Example search



The titles and abstracts of the identified citations were then reviewed and screened against the eligibility criteria. All observational studies of a population with dementia describing the prevalence of hypertension and treatments used were deemed eligible but non-English language articles and studies carried out prior to 1990 were excluded. Where there was uncertainty about eligibility the full article was reviewed. The bibliographies of eligible articles were searched for further relevant articles, which were again appraised against eligibility criteria.

2.4.3 Data collection and items

Based on the aim of describing this population a number of relevant pieces of data were identified. These related to study characteristics and to the individual study findings and are now listed. For the study characteristics: year published, year the study started, study methodology, population size, location, country, method of identification of hypertensive people, if BP was measured and selection method. For individual study's findings: prevalence of HTN, mean age, sex, comorbidities, antihypertensive types, mean number of antihypertensives, and proportion hitting target BP. Relevant data were extracted from the articles and used to populate a structured Microsoft® Excel database under the above headings.

2.4.4 Assessment of risk of bias

It was important to consider the impact of potential bias in the included studies. A systematic method of assessing this risk was sought and identified in the Agency for Healthcare Research and Quality's (AHRQ)[78] risk of bias tool. The information needed to populate this was therefore gathered simultaneously with the above data. Figure 2.2 summarises the headings.

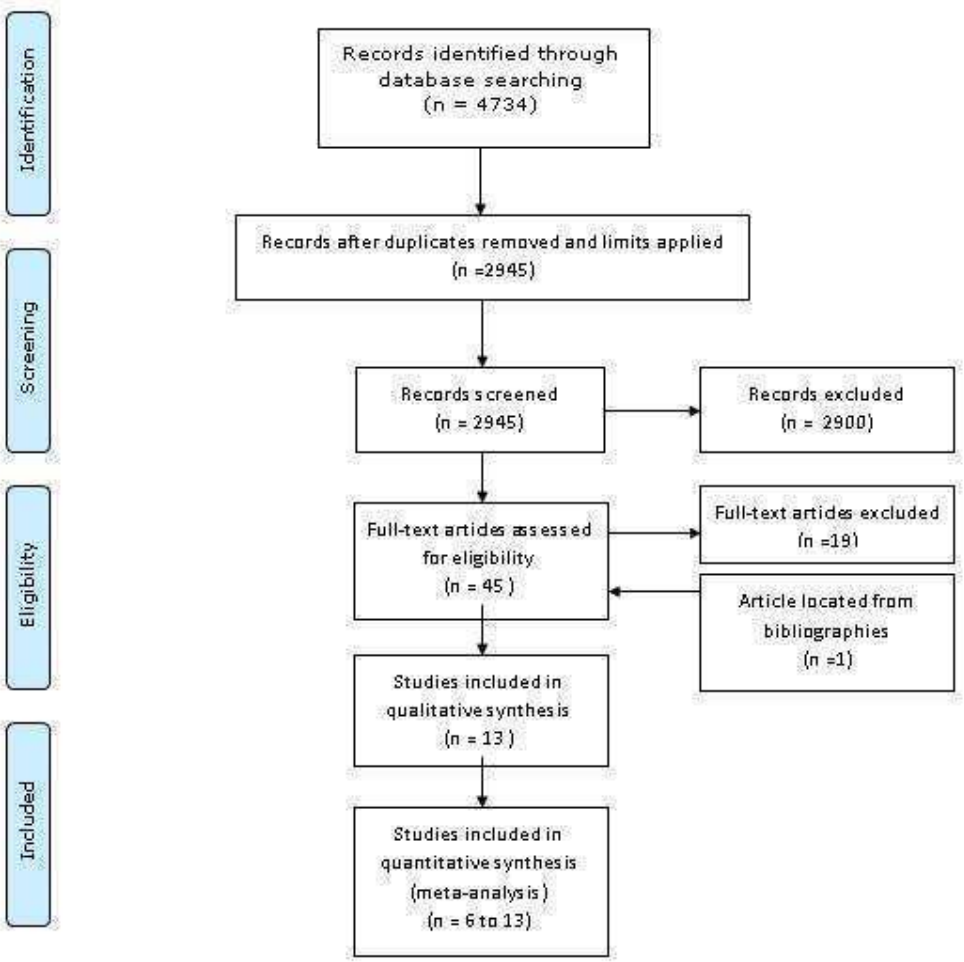
Figure 2.2 Agency for Healthcare Research and Quality's (AHRQ)[78] risk of bias tool headings

Source	Selection Bias				Performance bias	Attrition bias	Detection bias			Publication bias	Included in synthesis?
	Inclusion / exclusion criteria applied uniformly ?	Confounding accounted for?	Concurrent intervention accounted for?	Missing data handling ?	Outcome assessors blinded?	Diagnosis defined with valid and reliable measures?	Outcomes defined with valid and reliable measures?	Confounding variables assessed?	Outcomes pre-specified?	Suspicion of publication bias?	

2.5 Results

4734 citations were identified initially and, after applying limits and removing duplicates, this was reduced to 2945 citations. Of these 2900 articles were rejected after review of the abstract demonstrated that they did not meet the eligibility criteria. The full text of the remaining 45 articles was then reviewed in detail. 33 of these articles were then discarded after this review revealed that they were ineligible. One additional article was identified by review of the included articles' bibliographies which met the eligibility criteria. In total, therefore, 13 articles were included in the review (Figure 2.3). Periodic update searches (until August 2015) were undertaken to ensure no new reports were published.

Figure 2.3 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA[79]) flow diagram



2.5.1 Risk of bias

The risk of bias of each study is summarised in table A4.1 (see Appendix IV).

2.5.2 Characteristics of studies

(Table A4.2, appendix IV, summarises the studies' characteristics)

2.5.2.1 Country of origin

The number of articles published by different countries is summarised in Table 2.1. Of the 13 articles three reported studies which were conducted in the USA[80,81], two each in the UK[82,83] and France[84,85] and one each in Brazil[86], Canada[87], Finland[88], Germany[89], Nigeria[90] and Norway[91].

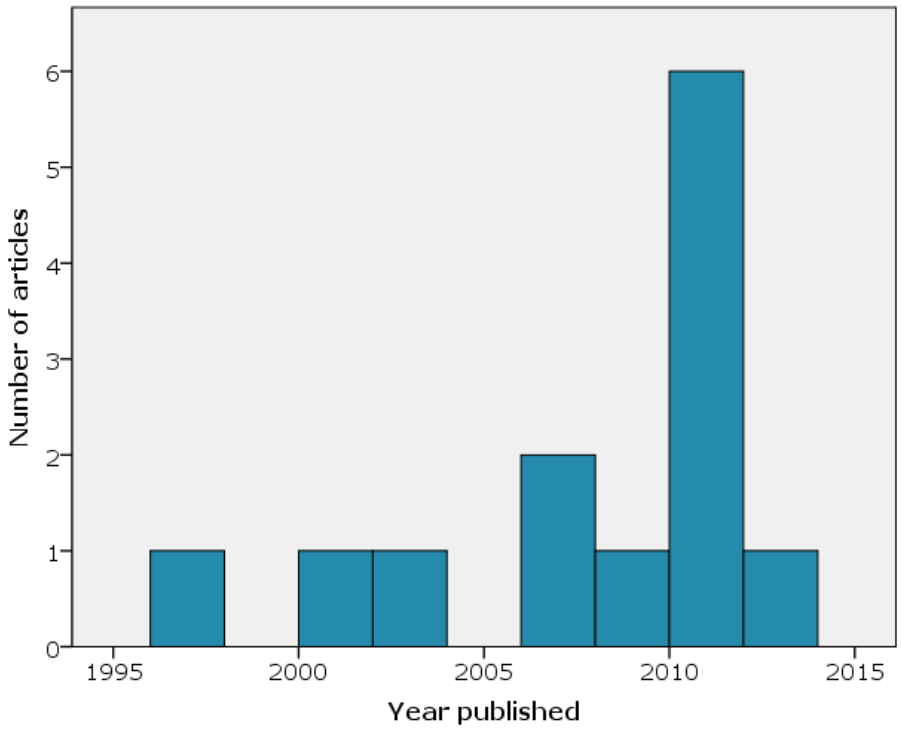
Table 2.1 Articles by country of origin

Country	Number of publications
USA	3
UK	2
France	2
Brazil	1
Canada	1
Finland	1
Germany	1
Nigeria	1
Norway	1

2.5.2.2 Year of publication

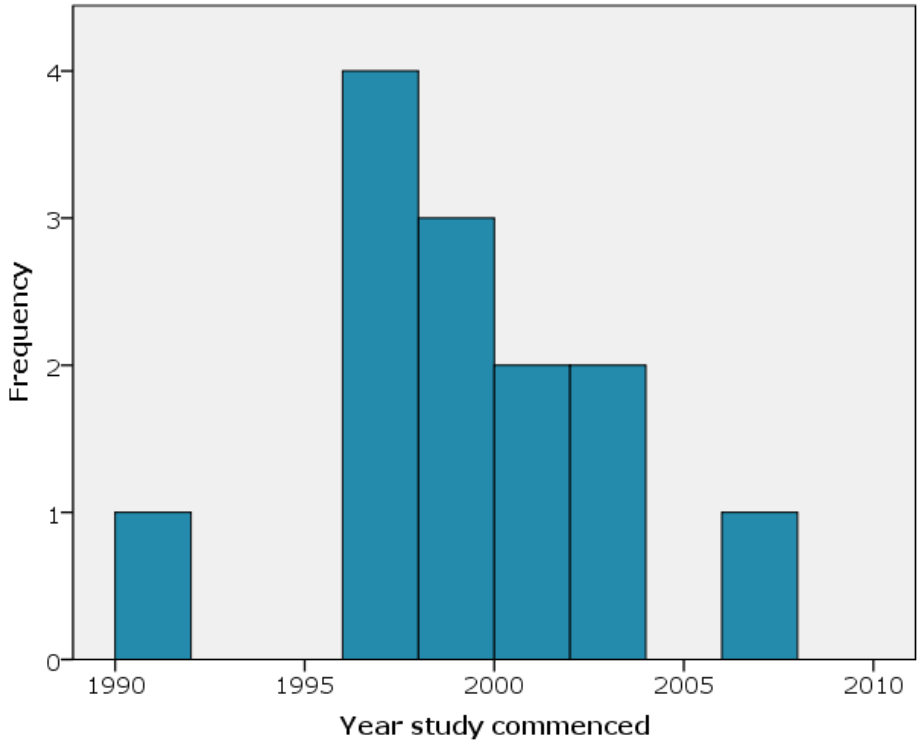
The articles were published between 1997 and 2013; more articles were published in 2011 than in any other year. See figure 2.4 below.

Figure 2.4 Number of articles published per year



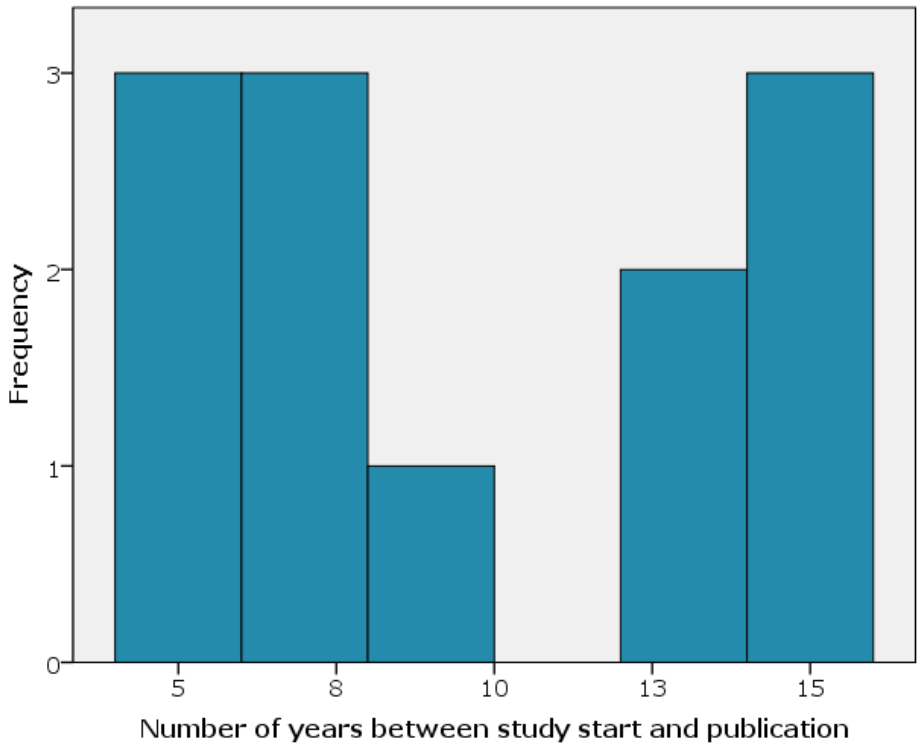
Data on the studies' dates of commencement was also gathered. The studies started between 1991 and 2006 with 1997 being the year with the most starters. No data was available on the start date for one of the studies[81]. Figure 2.5 summarises this information. For the purposes of more detailed temporal analysis the mid-point of data collection for the studies was used rather than the publication date, where this information was not available, the publication date was used.

Figure 2.5 Study start dates



Studies waited a mean of 9.25 (SD 4.0) years between starting and being published. (Figure 2.6).

Figure 2.6 Years between start date and publication



2.5.2.3 Methodology

All 13 studies were observational studies. 11 were cross-sectional and four of these were case-controlled[82,83,89,91]. The remaining two were cohort studies[85,92]. Of the 11 cross-sectional studies, six gathered prospective data and five did so retrospectively[80,82,83,89,90]. Of the five retrospective studies the two UK studies and the German study used databases built using data held by primary care doctors[82,83,89], and the remaining two retrospectively analysed digital and hard copy hospital data[80,90].

All of the studies described their sampling method. Six studies invited routine attendees to their clinic or hospital to take part in their study[80,84-86,90,92], three studies used information from primary care databases to identify participants[82,83,89] and four conducted population surveys[81,87,88,91].

2.5.2.4 Participants

15,921 people with hypertension out of a total population of 23,804 were studied.

2.5.2.5 Objectives

The objectives of the studies varied, although none set out to specifically describe the treatment of hypertension in people with dementia in the UK. Three set out to describe the clinical profile, including information on demographics, comorbidities and medications, of patients with dementia[86,90,92]. Four studies aimed to compare comorbidities and medication use between those with and without dementia[83,88,89 91], while one aimed to look specifically at

treatment in those with vascular cognitive impairment[87]. Two studies aimed to look at the association between antihypertensives and cognitive impairment[82 81]. Two set out to evaluate the effect of antihypertensive therapy on cognitive function[84,85] and one study aimed to compare blood pressure control and medication between different ethnic groups[80].

2.5.3 Individual study findings

The findings of each individual study are summarised in table A4.3. (Please see Appendix IV)

2.6 Synthesis of results

2.6.1 Characteristics of study participants

The mean age of the patients across the studies was 82 (figure 2.7), with the majority (65%) being female. Alzheimer's disease was the most common dementia subtype (63%), followed by vascular dementia (30%), unspecified dementia (7%) and mixed dementia (0.7%). The population had a high burden of comorbidity with 27% having ischaemic heart disease, 26% cerebrovascular disease, 12.7% diabetes mellitus and 9.3% heart failure (table 2.2).

Figure 2.7 Histogram showing mean age of participants in the different studies

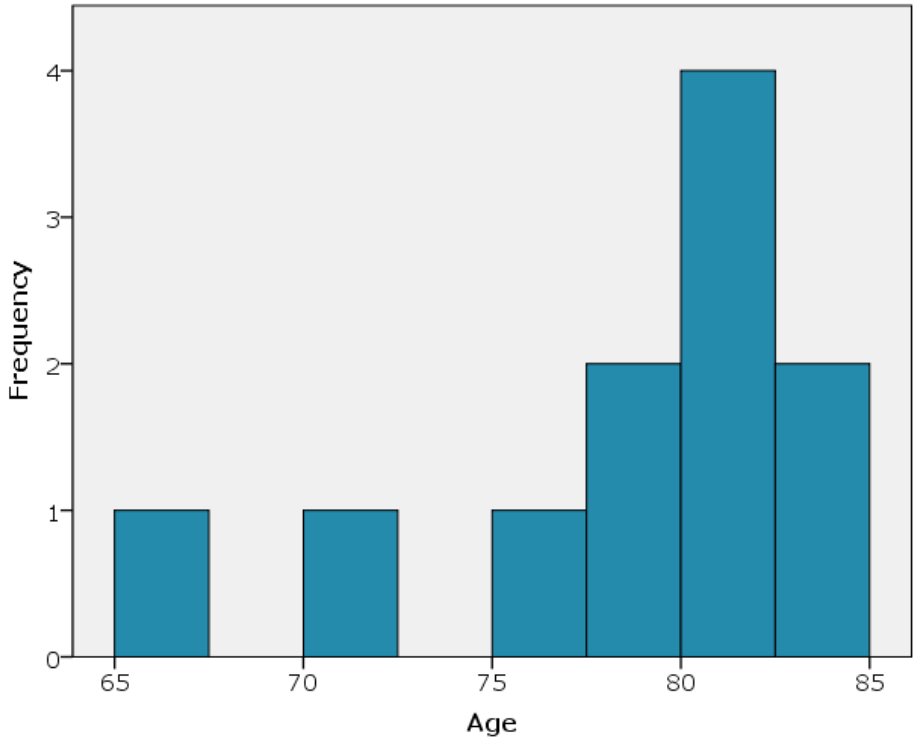


Table 2.2 Dementia subtypes and comorbidities

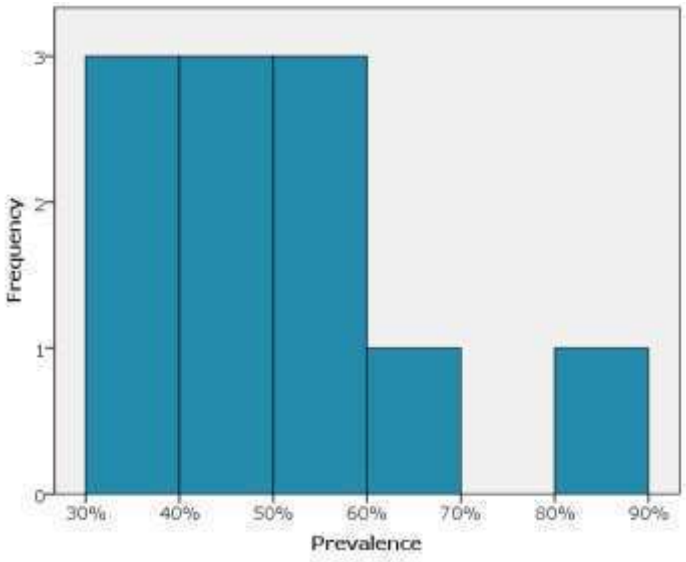
Comorbidity	Percentage (%)
Dementia subtype	
Alzheimer's dementia	63
Vascular dementia	30
Unspecified dementia	7
Mixed dementia	0.7
Ischaemic heart disease	27
Cerebrovascular disease	26
Diabetes Mellitus	12.7
Heart failure	9.3

2.6.2 Prevalence of hypertension

Two of the studies[80,84] selected people on the basis that they had hypertension meaning that 100% of their study population had hypertension. When these studies were excluded the reported

prevalence ranged between a minimum of 35.5%[92] and a maximum of 84%[89] with a mean prevalence of 46.5% (figure 2.8).

Figure 2.8 Histogram of the prevalence of hypertension in people with dementia



The prevalence of hypertension remained unchanged when more recent studies were compared to older studies (R^2=0.068, P=0.439).

2.6.3 Prescribing patterns

Of the eight studies[81,84-89,92] which reported details of treatment between 15% and 52% of their participants were not taking any antihypertensives. Across all studies a mean of 27% (95% CI 26% - 28%) were not taking any antihypertensives.

Diuretics (64%, range 30%-90%) were most commonly used, while calcium channel blockers (43%, range 27%-45%), ACEi/ARBs

(42%, range 12%-59%) and β-blockers (42%, range 8%-45%) were less common.

A higher proportion of the population took ACEi / ARBs (R^2 = 0.791, p=0.018), and calcium channel blockers (R^2 = 0.794, p=0.017) in later studies than in earlier studies, while the use of β -blockers and diuretics remained unchanged between later and earlier studies. (Figures 2.9.1-4)

Figure 2.9.1 Change in use of ACEi/ARBs

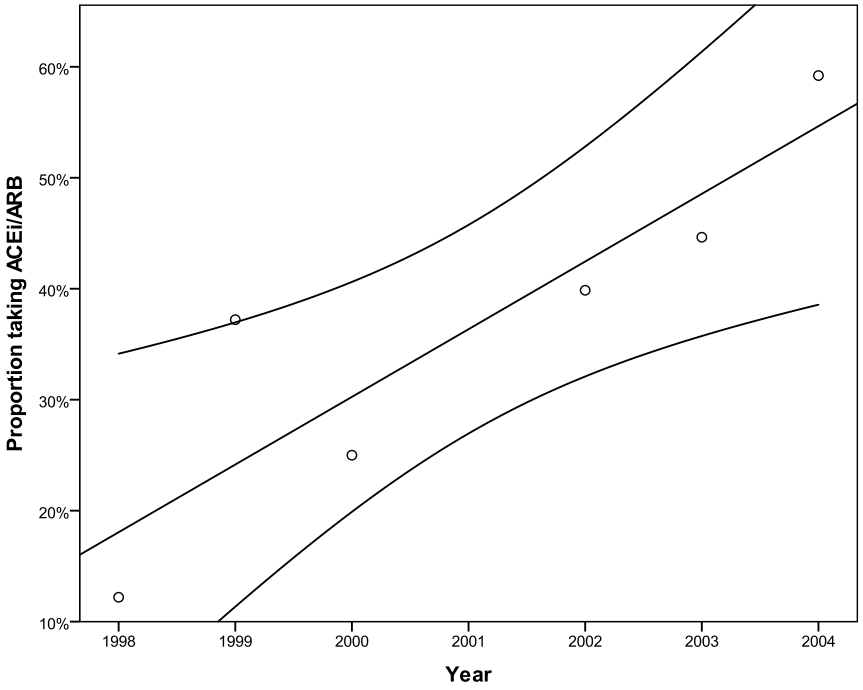


Figure 2.9.2 Change in use of CCBs

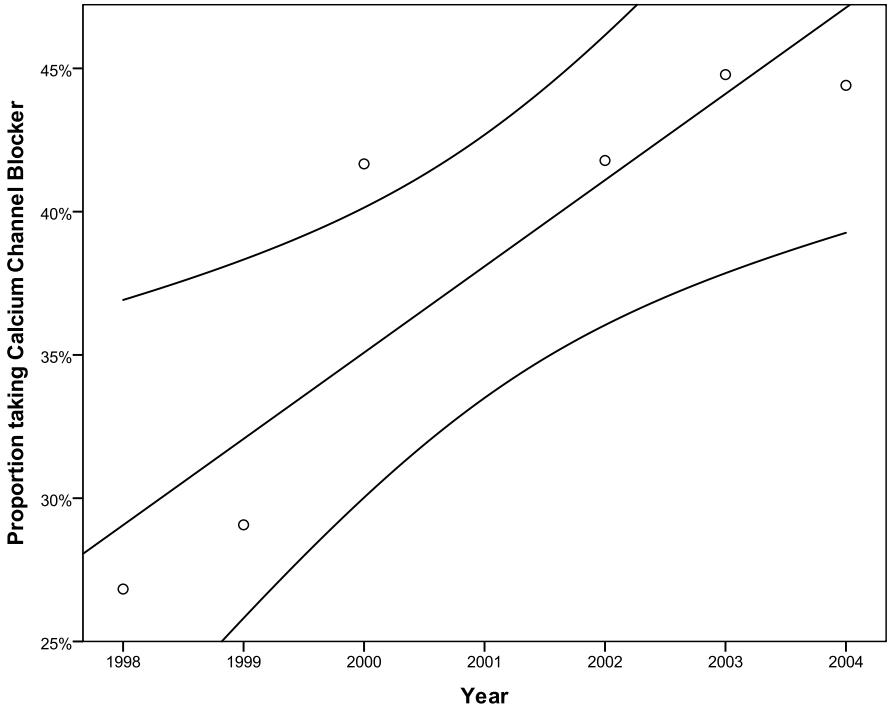


Figure 2.9.3 Change in use of diuretics

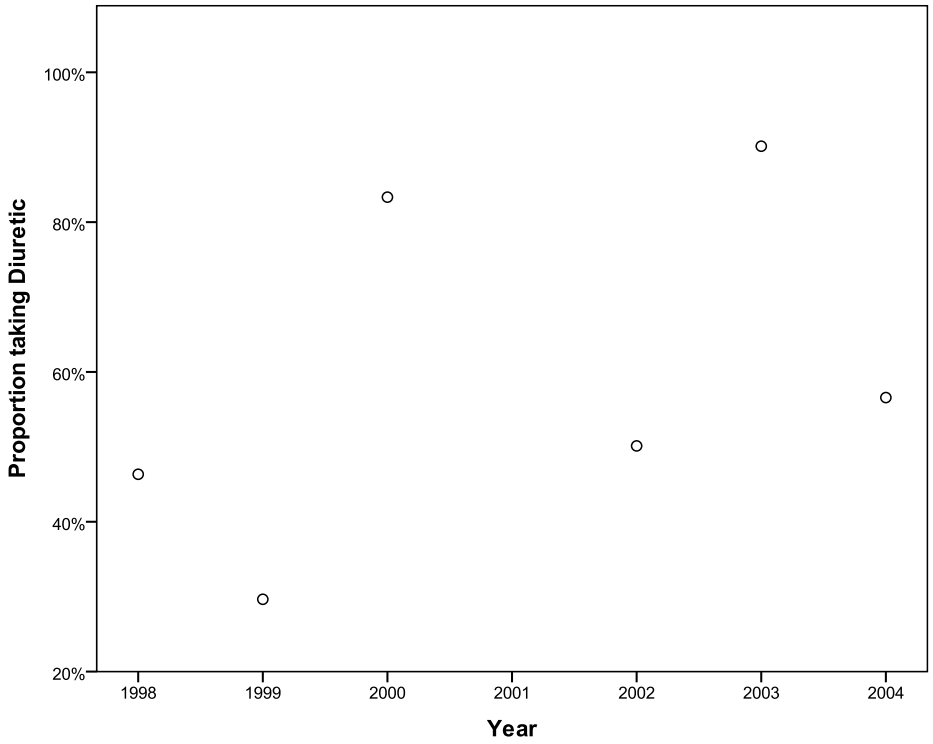
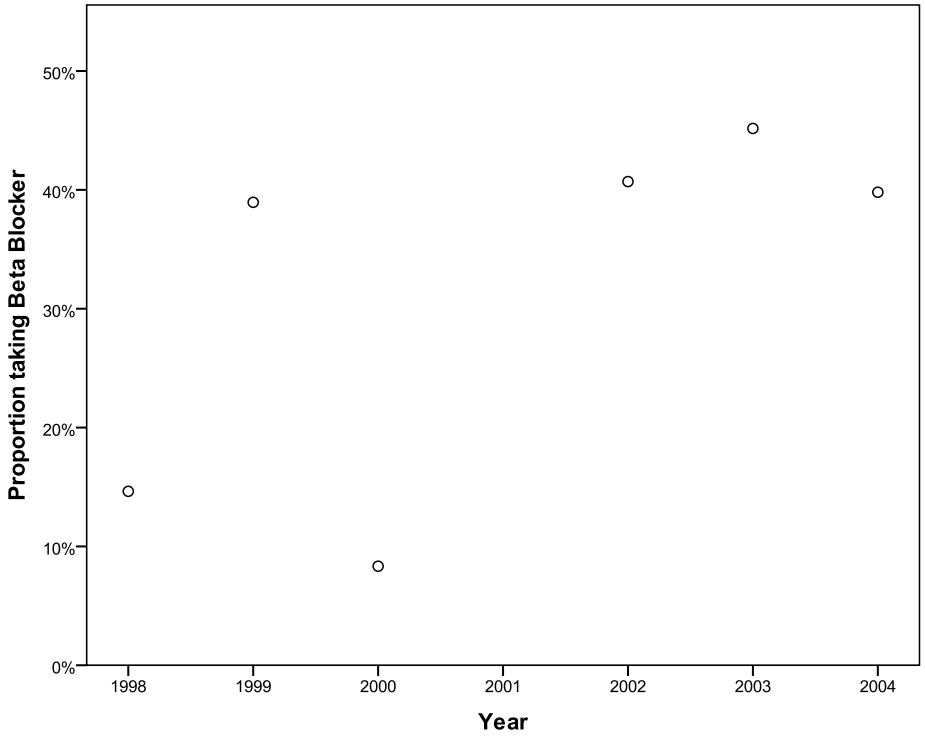


Figure 2.9.4 Change in use of beta-blockers



2.6.4 Number of antihypertensive agents and target blood pressure

Two studies reported details of the number of antihypertensives used[80,85]. The mean number of antihypertensives was 2.4. Only one study reported on the achievement of target blood pressure[80], with 55% achieving this. This study involved 304 people, almost all male, in a Veteran Affairs hospital.

2.7 Discussion

This review has demonstrated that hypertension is common in people with dementia with a prevalence of 45.6% and was treated in the majority, although a substantial minority (27%) were untreated. There was no evidence that the prevalence of hypertension in people with dementia changed over time. Although diuretics were the most frequently prescribed antihypertensive drug, ACE inhibitors / ARBs and calcium channel blockers were prescribed more frequently in more recent studies. There was no change in the prescription of diuretics or β-blockers over this 13 year period. Only one study reported on achievement of target blood pressure, with just over half of individuals achieving this.

No previous systematic review looking at the treatment of hypertension in people with dementia was identified. Similarly, no specific guidance for the treatment of hypertension in people with dementia with which to compare these findings was found. Over the study period the JNC, along with others, issued a number of reports (V-VII)[93-95] with changes in the generic guidance for the treatment of hypertension in older people. The rise over time in the use of ACE inhibitors / ARBs and calcium channel blockers is likely to reflect these changes in guidance.

The fact that the prevalence of hypertension did not change over time, despite lower blood pressure thresholds for diagnosis over time, is interesting. This apparently stable prevalence could be the result of a number of confounding factors such as changing

attitudes to treating high blood pressure in people with dementia or changing incentives for diagnosis and treatment. However, it raises the possibility that the true prevalence would have fallen over time had current, stricter, criteria for diagnosis been used throughout. It is not possible to comment from these findings whether this was the case, since several studies reported hypertension dichotomously as either present or absent using diagnostic criteria of the time, rather than presenting raw blood pressure data that could be re-analysed.

This review found no evidence that hypertension in people with dementia was being treated differently to the general population. Whereas 63% (95% CI 62% - 64%) of people in the general US population with hypertension were on treatment[96,97], this review found that 73% (95% CI 72%-74%) of hypertensive people with dementia were on treatment. Side-effects are recognised to be a potent contributor to non-compliance in antihypertensive therapy[98,99] and the higher rates of treatment raise the possibility that side effects of antihypertensive therapy in those with dementia may be either unrecognised or unreported. This raises the hypothesis that people with dementia on treatment for hypertension may be subject to additional risk and in the context of the poor evidence base in this group may mean that the favourable risk to benefit ratio observed in trials of the non-frail may not apply. In addition with theoretical concerns that, with impaired cerebral auto-regulation, this population are at increased risk of cerebral hypoperfusion[30] high rates of anti-hypertensive use, with the

potential to exacerbate this, may not be ideal. Blood pressure falls as part of the natural history of dementia, starting prior to clinically apparent dementia[8] and it is intriguing that while studies contemporaneous with the trials described here show that only 22-27% of the general hypertensive population achieve target blood pressures[96,97], 55% reached target blood pressures in the one study which reported on this in people with dementia.

2.7.1 Strengths and limitations

Although some of the study populations were atypical, for instance the Vale study recruited from a population with dementia and associated behavioural problems[86], several large database studies were included in the review, and so the overall findings are likely to be representative of ordinary practice. However, they were carried out almost entirely within North America and Europe, and so the findings may not apply to countries with other health systems and prescribing habits such as in Asia or non-English speaking countries. Two of the studies reported whether participants had ever been on an antihypertensive drug rather than their current treatment. The inclusion of these data in the synthesis will have had the effect of increasing the apparent proportion on each antihypertensive class. The studies used different criteria and different blood pressure thresholds to diagnose hypertension and several used recorded or self-reported diagnoses. This may have led to the inclusion of individuals who may not have had hypertension at the time of the studies who may have been diagnosed years previously, and exclusion of those who would meet current thresholds for a

diagnosis or who were undiagnosed at the time of the study. This may have impacted on the generalisability of the systematic review's findings.

2.8 Conclusions

The findings of this review imply that high blood pressure is being treated in the majority of cases and with standard antihypertensive classes. There is no evidence that people with dementia are less likely to receive treatment than the general population, if anything the opposite is the case with the review describing higher rates of people receiving treatment for hypertension and reaching target blood pressures compared to the contemporaneous general population. Medication adherence tends to increase in more dependant populations[100] and concern has been raised that this may be, in part, because side effects of treatment are overlooked particularly in those with cognitive impairment[51]. Recent work on the treatment of hypertension in care home residents by the PARTAGE group showed an association between increased mortality and a systolic BP below 130 in people taking two or more antihypertensive agents[101].

One important finding from these reviews is the dearth of research examining the treatment of hypertension in people with dementia in the UK. Only two of the studies identified were based in the UK, neither of which set out to specifically look at hypertension

treatment and neither of which included new clinical data - they were either based on database or case note review.

As has been discussed there is a lack of experimental data on which to base clinical decisions on treating hypertension in people with dementia. Before progress can be made to clarify this position we need to understand how high blood pressure is currently being managed in this group of people. The results of this literature review have provided some helpful information towards answering questions (i) *(How is hypertension in people with dementia treated in the UK and how does this compare to the treatment of hypertension in the general population?)*, (ii) *(Is hypertension in people with dementia more or less likely to be treated than in the general UK hypertensive population?)* and (iv) *(Is hypertension in people with dementia treated more or less effectively than in the general UK population?)*, but none of the studies identified have provided an up-to-date picture of practice within the UK or provided information on adverse events. The next step in understanding this problem in the UK would be to undertake observational work to record how hypertension is currently being treated, to describe the characteristics of this population and to describe the adverse events they experience.

The next chapter will go on to describe a cohort study setting out to do this.

Chapter 3

Hypertension in dementia – Cohort study

3.1 Introduction

The introductory chapter set out the aim of this thesis: to examine current treatment patterns, testing whether antihypertensive treatment and the rate of adverse events differs between those with dementia and the general population. Chapter two presented evidence that there was no difference in the way hypertension in people with dementia compared to the general population was treated and provided some evidence that achievement of target blood pressure might be higher. However it also demonstrated that the treatment of hypertension in people with dementia in the UK has not been extensively reported. Only two of the studies identified were based in the UK, neither of which set out to specifically look at hypertension treatment and neither of which included new clinical data - they were either based on database or case note review.

Chapter 3 sets out the next step in the process. This aimed to clarify current practice in the UK and to provide information on the rate of adverse events experienced by those with dementia treated for hypertension.

3.2 Aims

This study set out to provide answers to the questions posited during the introduction, supplementing the information already provided by the literature review. In particular:

(i) How is hypertension in people with dementia treated in the UK and how does this compare to the treatment of hypertension in the general population?

(ii) Is hypertension in people with dementia more or less likely to be treated than in the general UK hypertensive population?

(iii) What factors are associated with treatment and non-treatment of blood pressure in people with dementia?

(iv) Is hypertension in people with dementia treated more or less effectively than in the general UK population?

(v) Are the adverse events and symptoms, including cardiovascular events, experienced by people with dementia on treatment for hypertension more or less frequent than in treated hypertensive people without dementia?

3.3 Methodology

3.3.1 Study type

An observational study was thought most suitable to describe this population and follow up over a period of 6 months was also planned to quantify the frequency of adverse events which might be occurring. A prospective cohort study was therefore planned.

3.3.2 Assessment choices

In order to characterise this population in detail a number of measures would be needed to assess different aspects including cognition, dependency in ADLs, quality of life, healthcare resource use and symptoms.

3.3.2.1 Dependency in activities of daily living

For the purposes of this study a global measure of activities of daily living (ADL) was felt to give an appropriate assessment. The Barthel index is one of the most commonly used methods of assessing ADLs in the UK, is recommended for use in older people by the Royal College of Physicians[102] and is used in both research and clinical practice[103]. The Barthel Index is an ordinal scale that was originally developed in the 60s by Mahoney and Barthel[104] to help monitor performance in chronically unwell inpatients with paralytic conditions. In its original form it was scored from 0 (total dependence) to 100 (independence). The index has been modified by a number of people since its conception in attempts to increase its sensitivity to milder disability and to help clarify its scoring procedure. One of the more commonly used versions was introduced by Wade and colleagues and provides scores ranging between 0 and 20[105]. The index has good inter-rater reliability and is reliable when administered face-to-face or over the telephone[102].

As with any measure there are some issues with this scale. One which is commonly cited is the ceiling effect. This reflects the original setting of the scale, and its use in a relatively disabled population. In addition the index is an ordinal scale; the numerical

values assigned to different individuals do not always accurately reflect differences in dependency in basic ADLs. Thus someone with a score of 5 is not twice as dependent as someone with a score of 10. Finally there is some concern that self-reported BI may be less reliable in people with cognitive impairment[102].

On balance the Barthel index remains 'highly recommended'[102]. Although the ceiling effect was a concern, it was anticipated that the population likely to be recruited to this study would be dependent and so any ceiling effect would be minimised. It was felt that it would be an appropriate measure for the purposes of this study.

3.3.2.2 Cognition – MMSE

The mini-mental state examination (MMSE) was developed by Folstein and Folstein as a tool for rapidly, systematically and quantitatively assessing the severity of cognitive impairment and change in cognition over time of psychiatric inpatients[106]. The test itself is built of 30 questions which assess orientation, attention, recall and spacial awareness. Although developed 40 years ago and despite its use becoming more restricted after the copyright was enforced by Psychological Assessment Resources® in 2001, it remains the most commonly used cognitive test worldwide[107]. This widespread use remains its main advantage as well as the wealth of data on its reliability and validity which has been generated during this time period[108].

The disadvantages of the test have been well described and documented. They include problems around educational level bias,

the high verbal content and inter-rater variability in the scoring of certain sections, in particular the scoring of attention through serial sevens and spelling "world" backwards[109]. In addition the test shows both ceiling and floor effects and a maximum score of 30/30 does not exclude dementia[110]. The test is insensitive to mild cognitive impairment and the highly verbal content increases the risk of lower scores in those who have lower education levels or who are illiterate[111].

Overall however the fact the test has been extensively used for such a long time and in multiple countries and settings means that this was the natural choice for measuring cognition in this group. An alternative measure would have to have demonstrated significant advantages over the MMSE for it to be considered.

Other measures considered included the Montreal Cognitive Assessment (MOCA) and the Addenbrookes Cognitive Examination-III (ACE-III). Both have the advantage of not falling under the copyright restrictions imposed on the MMSE, and both are used in clinical practice and are advocated by the Alzheimer's society and department of Health. However, both take significantly longer to perform than the MMSE (10-20 minutes as opposed to 5-10 mins) and are still subject to the same educational bias as the MMSE[112,113]. On balance therefore these alternatives were rejected. Official MMSE assessments were obtained from Psychological Assessment Resources® for use in the study.

3.3.2.3 Quality of life

An important aspect of healthcare in older people, and in people with a chronic progressive condition like dementia in particular, is quality of life[114]. Quality of life is a broad concept which transects numerous academic disciplines incorporating more than just health and which is challenging to define and measure[115]. For the purpose of this study, focused as it was on hypertension in people with dementia, the narrower concept of health related quality of life was used.

Many tools are used to measure health related quality of life, but these face additional challenges in people with dementia. One of the most commonly used scales in the UK is the EQ-5D[116], as this forms part of the cost-utility calculations carried out by NICE, and hence has significant influence on UK healthcare. However there are issues in using this scale in people with dementia where it lacks validity and where there are reliability issues with the visual analogue scales even in those with mild dementia[117].

A number of health related quality of life scales have been developed specifically for use in people with dementia, these include the Alzheimer disease related quality of life (ADRQL)[118], the Cornell-Brown scale for quality of life in dementia (CBS)[119], dementia quality of life instrument (DQoL)[120], and DEMQoL[121]. The ADRQL was developed primarily for use in people with Alzheimer's disease, potentially limiting its use in other forms of dementia. Both CBS and DQoL have good evidence for use in those with mild to moderate

dementia, but not in those with severe disease[122]. DEMQoL, a more recent development, can be used across the whole spectrum of disease[121]. It was intended that this study involve people with the full range of degrees of cognitive impairment. It was therefore important that the scales be usable in these different settings for this reason DEMQoL was selected as the tool used to measure quality of life.

3.3.2.4 Measuring comorbidity – The Charlson index

The Charlson comorbidity index (ChI) was first published in 1987[123]. The index was based on the mortality rates of 607 patients admitted to a general medical service over a period of one month. It is comprised of 16 diseases all weighted on the strength of their association with mortality. The original aim was to develop this index for use in prospective studies as a means to classify comorbidities in terms of their risk of mortality. It has subsequently become the most researched comorbidity index[124]. The index shows moderate to good correlation with other comorbidity indices and shows moderate to very good intra class correlation. As such it is felt to be a valid and reliable measure of comorbidity[125] and is commonly used. For the purposes of this cohort study it was felt to be a reasonable measure.

3.3.2.5 Healthcare resource use and adverse health events

In order to help answer question (v) *(Are the adverse events and symptoms, including cardiovascular events, experienced by people with dementia on treatment for hypertension more or less frequent than in treated hypertensive people without dementia?)* information

on the rate adverse health events experienced by the study population was needed. Although NHS resource use is increasingly recorded in electronic databases it was beyond the scope of this project to access and use these datasets. A pragmatic decision was therefore made to collect information directly from study participants during the follow up period. A short questionnaire was developed asking about contact with healthcare providers (GPs, district nurses, paramedics and hospital admissions), newly diagnosed cardiovascular events (Stroke, TIA, MI, Heart failure) and newly diagnosed adverse health events associated with antihypertensive use (falls, falls with fractures and syncope). For the purpose of the study the WHO definition of a fall was used: "inadvertently coming to rest on the ground, floor or other lower level, excluding intentional change in position to rest in furniture, wall or other objects"[126].

3.3.2.6 Symptom questionnaire

As was discussed in chapter 1, use of antihypertensive medications has been associated with a number of adverse symptoms such as ankle swelling or angioedema. A questionnaire was developed for this study to collect data on the prevalence and frequency of adverse symptoms. The total number of potential side effects for the commonly used antihypertensives, as listed in the BNF, was felt to be too large for a fully comprehensive review of symptoms; the BNF lists 52 side effects for amlodipine alone[127]. To rationalise the list of symptoms the relevant literature was reviewed and a large scale cohort study describing adverse symptomatology was

identified. Kjelgren and colleagues reported the findings of an observational cohort study of 1013 people with hypertension on antihypertensives recruited from 66 sites[62]. They collected data on the prevalence of symptoms which were felt to be related to antihypertensive use, high blood pressure or a combination of the two. This study was used to derive a list of symptoms (headache, dizziness, swollen ankles, cold peripheries, flushing/sweating, skin rash / itching, cough, dry mouth, nausea, diarrhoea, constipation, palpitations, nervousness/restlessness, sleep problems and frequent micturition), which were then used to populate the questionnaire. Participants were asked whether or not they experienced the symptom and were asked to quantify the frequency according to a seven point scale.

3.4 The research team

This study was conceived of as part of a broader research programme and as such a team of people, specialising in research in frail older people were already collaborating. The core team involved in this cohort study comprised of the author (Dr Tomas Welsh (TW)), an academic geriatrician in training, Professor John Gladman (JG), a professorial level academic geriatrician and first PhD supervisor for TW, and Dr Adam Gordon (AG), an academic geriatrician and second PhD supervisor for TW. TW designed the research protocol, study paper work, obtained ethical approval and research funding. TW recruited 59 participants from GP practices in Nottinghamshire and followed them up for the duration of the study. TW orchestrated and organised the involvement of ultimately 6 additional study sites, above the original core of two sites, coordinating and overseeing their involvement over the course of the study. JG and AG provided supervision to TW at all stages of the project in keeping with their role as PhD supervisors. In addition the wider research group consisting of Dr Simon Conroy, an academic geriatrician, Professor Pip Logan, a professorial level academic occupational therapist, Dr Veronika van der Ward, a post-doctoral researcher, Dr Jennifer Harrison, an academic clinical fellow and Ms Lisa Woodhouse, a statistician working on her own PhD, all provided input, advice and support for the project from its conception. A number of researchers based at other sites performed data collection locally and are listed in table 3.1.

Table 3.1 Local teams at the different research sites

Site	Local Team
Leicester	PI: Dr Simon Conroy Mr Aidan Dunphy, Dr Jennifer Harrison, Dr Sabira Somani
Surrey and Borders NHS Trust	PI: Dr Ramin Nilforooshan Ms Ruth Charig Ms Jessica True
NHS Fife	PI: Dr Stella Clark Mrs Linsey Burd Mrs Sarah Gray
Southern Health NHS Trust	PI: Dr Maged Swelam Ms Amelia Abbott
South Essex Partnership University NHS Trust	PI: Dr J Schoeman Ms Elizabeth Slater
Solent NHS Trust	PI: Dr Kayode Osanaiye Mrs Sharon Simpson Ms Stephanie Grist
Leicestershire Partnership NHS Trust	PI: Dr Hari Subramaniam. Ms Deborah Glancy

3.4.1 Patient and public involvement (PPI)

As part of a larger programme of research PPI involvement occurred at various points during the development and management of this and associated projects. During this project's initial development the research questions and preliminary documentation (patient

information sheets and lay summaries) were presented at carers groups and local PPI groups and feedback was sort. This confirmed the relevance and importance of the research questions and improved the quality of the participant information sheets. Lay representation on the programme management board ensured ongoing oversight for the duration of the study.

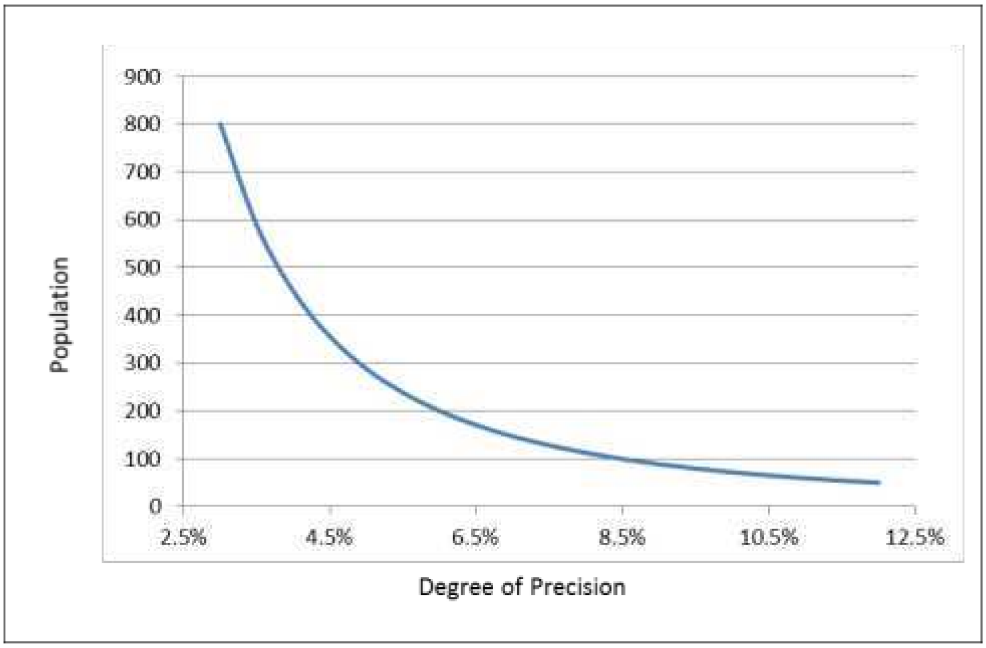
3.5 Method

3.5.1 Sample size considerations

As a descriptive study, the sample size estimation was based upon the objective of accurately describing this population and was therefore based on a desired degree of precision [128]. It was anticipated that, owing to the nature of this group, it would be difficult to recruit a large study population. Thus the degree of precision was necessarily balanced against realistic study sample sizes. Based upon the literature reviewed the proportion of the baseline sample receiving antihypertensive treatment (i.e. at least one antihypertensive) was used to calculate the required sample size.

Based upon the findings of the literature review it was anticipated that around 75% of the population with hypertension and dementia would be taking at least one antihypertensive[84,129,130]. Based on this anticipated proportion on treatment, it was calculated that a study population of 200 was required to achieve a degree of precision of +/- 6% 95% confidence intervals (Figure 3.1).

Figure 3.1 Varying Degree of Precision at Different Population Sizes for an expected proportion of 75%



3.5.2 Additional sites

The study, as originally planned, envisaged two sites – Leicester and Nottingham recruiting via GP practices. After funding was obtained the study was incorporated into the National Institute for Health Research (NIHR) portfolio. The NIHR portfolio consists of "high quality clinical research studies that are eligible for consideration for support from the Clinical Research Network (CRN)"[131]. With the study listed on the portfolio it became eligible for CRN support and after the study commenced a number of research centres contacted the project asking whether they could act as recruiting sites, funded via the portfolio for doing so. This was agreed to, and the study was amended to permit recruitment via memory clinic services to facilitate this. Over the course of the study the number of sites involved increased until, ultimately, a

total of 8 sites were involved. Table 3.2 below lists the sites and date at which they made contact.

Table 3.2 Recruitment sites and dates of involvement

Site	Date of involvement
Nottingham	From inception
Leicester	From inception
Surrey and Borders NHS Trust	26/7/13
NHS Fife	4/9/13
Southern Health NHS Trust	7/10/13
South Essex Partnership University NHS Trust	14/3/14
Solent NHS Trust	12/5/14
Leicestershire Partnership NHS Trust	2/6/14

3.5.2.1 Monitoring

Arrangements were made for two formal monitoring visits per study site over the course of the project. (An example of the standard monitoring report form is found in appendix V.) During a monitoring visit the local site file and storage facilities were inspected to ensure they met the appropriate standard. The documentation of consent was reviewed with particular attention and all data collection forms were inspected. This safeguarded against deviation from the study protocol at different sites.

3.5.2.2 A note on NHS Fife

Owing to the differences between the law on capacity in Scotland and in the rest of the UK a separate, new submission was required for review by a Scottish ethics committee. Because of this additional process there was a significant delay before this site was able to start recruiting. Thus although they were one of the earliest sites involved they were the last to start the recruitment process.

3.5.3 Selection of participants

3.5.3.1 Identification – Core sites

Participants at the Nottingham and Leicester sites were recruited via GP practices from the local clinical commissioning groups (CCGs). All general practices belonging to CCGs located within 10 miles of Queen's Medical Centre (QMC) in Nottingham or Leicester Royal Infirmary (LRI) in Leicester were contacted by letter asking about their interest in being involved in the study. This was then followed up with a telephone call to the practice manager or equivalent. To facilitate this process the primary care research network (PCRN) was involved in identifying and contacting practices. In addition the study was publicised at CCG training days and via primary care in-house publications (See appendix III figures A3.1-A3.3). In Leicester the PCRN was the primary means by which practices were identified and contacted, in Nottingham they were supplementary to the work of the local research team. A meeting was then arranged with interested practices to discuss things further and to answer any questions. Interested practices were then asked to use their practice

databases to identify people with diagnoses of hypertension and dementia.

One of the challenges facing the recruitment process was that only a limited number of GP practices could be involved at each site due to funding restrictions. It was therefore vital to maximise potential recruitment by prioritising those practices with a higher number of potential participants. Unfortunately only after practice involvement was agreed was the true number found. A method of predicting potential participants was therefore developed and was employed in the Nottingham site. This average number of potential participants identified in the Nottingham site was subsequently compared to that in the Leicester site to test this approach.

3.5.3.2 Developing a method of identifying practices with higher number of potential participants

The NHS choices website (www.nhs.uk) "*…the UK's biggest health website. It provides a comprehensive health information service to help put you in control of your healthcare...*" provides information about GP practice populations including the proportion aged over 65. Practices within the region as determined by the protocol were identified and population data was extracted from NHS Choices. Using these data the population over 65 in each practice was calculated and then using data from the Office of National Statistics (ONS) for the prevalence of dementia (5% of those aged over 65[132]) a prediction of the number of people with dementia at the practice was produced. Using the findings of the literature review a prediction of the number of these individuals with hypertension was

also made (approximately 50%). These data were then used to rank the practices in order and this order was then used to prioritize contacting and involving practices. The correlation between the predicted and actual numbers was tested.

3.5.3.3 Identification – Additional Sites

Sites wishing to act as recruiting centres for the study made initial contact via e-mail after learning about the study through the NIHR portfolio. In response to this initial enquiry written information about the study was sent to the local research team. If they continued to express an interest a meeting was subsequently arranged with the local team including the potential PI. If following this meeting the team remained interested formal agreement and regulatory approvals were sought. Once approvals were in place a training meeting was arranged with the local researchers to ensure that they understood the study protocol and data collection tool. Further queries were clarified through regular e-mail and telephone contact. Monitoring visits were arranged as previously discussed.

The local research teams were asked to screen referrals to memory clinics and any registers of research-interested people held locally to identify people with diagnoses of hypertension and dementia. These individuals were subsequently invited to participant in the study.

3.5.3.4 Recruitment

Letters were then sent to this sample of potential participants from the GP practice or from the memory clinic asking if they would agree to be contacted by one of the research team about the study. This letter was accompanied by a detailed information sheet and a

reply slip. Those who expressed an interest, via the reply slip, were then contacted by a member of the research team who arranged to meet with them or their consultee and to answer any questions. Where a consultee was involved a consultee information sheet was also sent prior to the meeting which included information about being a consultee and a duplicate of the information given to the potential participant. Where the individual was attending the memory clinic they were supplied with an invitation letter and information sheet on arrival to the clinic and were approached by a member of the research team during their clinic visit.

Where potential participants had linguistic problems related to their dementia, or had a visual or hearing impairment but had English as their first language, all efforts were made to communicate with them and to maximise their potential to understand what was being requested of them. This was achieved by using a combination of verbal and written communication, augmented by the involvement of family and carers.

Where the potential participant did not have English as a first language a translator was identified from the participant's family. If a translator was not available then they were excluded from the study.

3.5.4 Capacity and consent

Capacity to consent to participate in the study was assessed by the researcher at the time of the visit. Capacity was defined against the criteria of the Mental Capacity Act 2005 or, in the case of Scotland,

Adults with Incapacity Act (Scotland) 2000. All researchers involved in the study either had a healthcare background or a research background involving people without capacity and were therefore already experienced in making this assessment. They all had current Good Clinical Practice (GCP) certification. Additional and ongoing training was available if required.

3.5.4.1 Consent

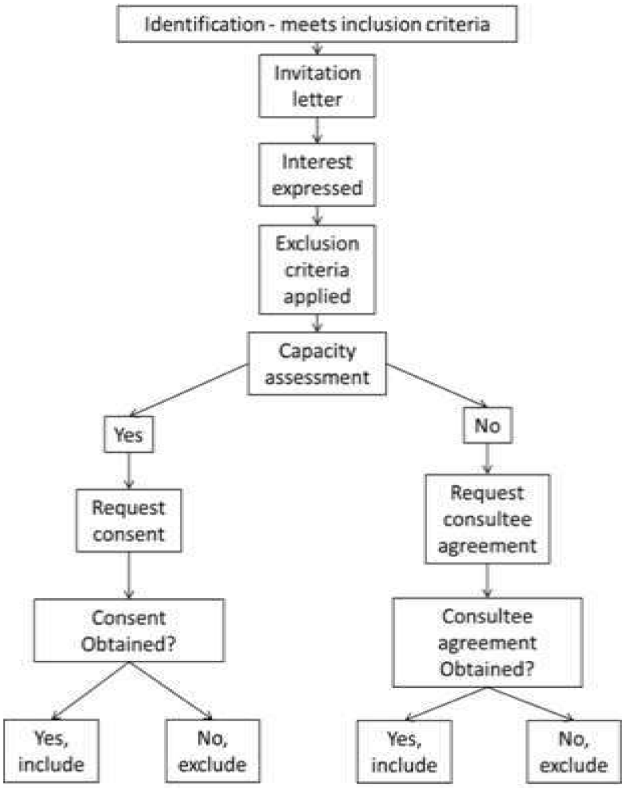
Informed consent was collected from each participant before they underwent any assessment related to the study. Consent was taken by one of the research team who was trained in taking consent. It was anticipated that a number of potential participants would lack the capacity to consent and so different arrangements were made for them. In those with capacity the researcher took the person through each step of the study answering any questions and consent was then sought. The option of an additional 24 hours for reflection was available if needed.

Where a potential participant was deemed not to have capacity to give consent, advice was sought from an appropriate personal consultee. If the consultee, having taken into account any previously expressed wishes or an advanced directive, felt that their relative or friend would have wanted to be involved then a consultee advice form was completed. The option of an additional 24 hours for reflection was available if needed. Participants who did not have capacity to give consent and for whom no consultee was available were excluded. Professional nominees were not used in the study. If

a participant's capacity was felt to have changed during the study then the consent process was repeated.

The recruitment algorithm can be seen in figure 3.2.

Figure 3.2 Recruitment algorithm



3.5.5 Summary of inclusion criteria

- Diagnosis of primary hypertension (as recorded in their medical records)
- Diagnosis of dementia (as recorded in their medical records)

3.5.6 Summary of exclusion criteria

- Non-English speakers without translators
- Individual without an involved family member or similar individual to speak as an independent informant and advocate.
- Consent/ consultee agreement unobtainable

3.5.7 Data collection - Baseline

A data collection form was developed to incorporate the indices discussed. See appendix V for a copy of a data collection sheet.

3.5.7.1 Demographics, health conditions, current medications

The participant's demographic details were documented along with current diagnoses and a list of medications from a combination of the participant's medical records and direct enquiry. During this part of the assessment the participant was asked to sit down comfortably for 10 minutes.

3.5.7.2 Blood pressure and orthostatic blood pressure

Brachial blood pressure was then measured in each arm and, if one measurement was more than 20mmHg higher, the readings were repeated. If this finding persisted then the arm with the higher readings was used subsequently for all measurements. The blood pressure one minute after standing was then measured. If the individual was unable to stand then lying and sitting blood pressures were used as a proxy. They were asked if they experienced any symptoms on standing or sitting up. All blood pressure measurements were taken by a validated automatic BP machine (OMRON M6 HEM-7211-E) with an appropriate cuff size, at all times the first reading was accepted, unless an error message occurred in which case the reading was repeated. If a participant was distressed by the blood pressure measurement, then attempts at further BP measurement were discontinued.

3.5.7.3 Questionnaires

The researcher then took the participant through the MMSE and the DEMQoL was completed by interviewing the participant's informant. A modified Barthel index was also compiled based upon the answers given by participant and informant. Where there was disagreement, the informant was taken as giving the correct response. Finally the side effect symptom questionnaire was completed by discussion with the participant and informant. Again, where there was disagreement, answers by the informant were taken to be correct.

The entire assessment took approximately 1 hour.

3.5.7.4 Abnormal Findings

Any concerns on behalf of the researcher at the time of the visit were discussed with the local (medically trained) Principle Investigator (PI). The participant's general practitioner was informed of abnormal findings such as low or high blood pressure, or symptomatic orthostatic hypotension in writing or immediately by telephone, depending on the degree of urgency, under the direction of the local PI.

3.5.8 Data collection - Monitoring phase

After baseline assessments were completed the participants entered the monitoring phase of the study. For the first month a weekly questionnaire was administered by a member of the research team, either in person or via the telephone to record any health related events. After the initial 4 weeks this was completed on a monthly basis for a further 5 months.

The questionnaire was split into two main sections. The first section recorded visits by health professionals such as the participant's GP, district nurse or a paramedic, hospital admissions, falls, fractures and cardiovascular events. The second section recorded the frequency of symptoms associated with the side effects of antihypertensive treatments. Finally if the participant had died since the last contact this was also recorded.

3.5.9 Planned data analysis

Data from the study were entered onto a Microsoft Excel database held on a secure computer at the University of Nottingham. Data was entered by individual research sites and then rechecked by TW against the original data collection forms at the study's completion to improve data accuracy.

The data were analysed using IBM SPSS version 22. Table 3.3 summarises the planned analysis.

Data from participants recruited via GPs and memory clinics were analysed together. Descriptive statistics were used to describe the recruitment process, study population and its antihypertensive treatment and adverse events in detail. Analysis of the recruitment process was undertaken. Differences between GP and memory clinic recruits, between those achieving and those not achieving target BP, and between those taking and not taking antihypertensive agents were explored using: the t-test for continuous and normally

distributed variables; the Mann-Whitney U test for continuous and non-normally distributed or ordinal variables and the Chi-Squared test for categorical variables. Comparisons of the use of antihypertensives, blood pressure levels, achievement of target blood pressure and experience of adverse events with a priori benchmarks derived from large scale studies and population surveys were carried out. The rationale and process of developing these benchmarks is discussed in the next section.

Table 3.3 Summary of planned analysis

Planned analysis
Recruitment - Descriptive data - Correlation between the predicted and actual number of potential participants per practice. - Comparison of the average number of potential participants identified in Nottingham compared to Leicester practices
Missing Data
Description of the study population **-** Whole population demographics - Comparison between GP and memory clinic recruits - Detailed description of the baseline characteristics
The use of antihypertensive agents **-** Number of antihypertensives used - Comparison with benchmark data - Combinations used - Classes and specific agents used

- Comparison with benchmark data

- Dosage

- Comparison with defined daily dose

- Adherence

- Anticholinergic burden score (Using the anticholinergic cognitive burden scale[69])

Blood pressure levels

- Levels achieved

- Comparison with benchmark data

- Target blood pressure

- Comparison between those achieving those not achieving target BP

- Comparison between target BP and benchmark data

Comparison of baseline metrics by antihypertensive use

Follow up data

- Health service use

- Adverse medical events

- Comparison with benchmark data

- Symptoms

- Comparison with benchmark data

3.5.9.1 Rationale for using benchmarks for comparison

The intention of this project was to compare the treatment and outcomes of people with hypertension and dementia with people with hypertension but no dementia to better understand the impact of the dementia diagnosis. Consideration was given to recruiting a control group of age-matched individuals with a recorded diagnosis

of hypertension but no dementia diagnosis. However, after consideration and in the context of anticipated challenges in recruiting older people with dementia and within the resource and time constraints of a PhD project it was felt that it would be more effective to target the population of people with dementia and hypertension and use benchmarks derived from the literature for comparison.

3.5.9.2 Determining benchmarks for comparison

Data from large scale studies or population surveys identified by reviewing the relevant literature were used to derive benchmarks to compare with the study data. An assumption of normal distribution was made and 95% confidence intervals based on the degree of precision of the relevant data were produced. This was done for treatment patterns, adverse events and daily defined dose as follows.

3.5.9.2.1 Treatment patterns

The Health Survey for England (HSE) 2011 was the latest in a series of national annual surveys about the health of people living in England to focus on cardiovascular disease[133]. The survey involved a multistage, stratified random probability sample, and data was collected from participants during a home visit by research staff. It featured a section dedicated to hypertension and provided detailed information on treatment patterns for the general population with hypertension. Relevant data from the HSE 2011 was used to provide

benchmarks, as listed in the table 3.4 together with estimated 95% CI, for comparison with the study population.

Table 3.4 summarises the variables and the HSE data

Variable	Value	95% CI
Treated	87%	85% - 89%
Target BP achieved (<140/90)	52%	49% - 55%
Mean blood pressure (on treatment)	Systolic 135 Diastolic 74	134 – 137 73 - 74
Number of antihypertensives		
1	45%	42% - 49%
2	36%	33% - 39%
3	15%	12% - 17%
4	4%	3% - 6%
Type of antihypertensives		
Diuretics	34%	31% - 37%
Beta blockers	24%	21% - 27%
ACEi / ARBs	63%	60% - 66%
CCB	37%	34% - 40%
Others	8%	6% - 10%

In people taking one antihypertensive		
Diuretics	15%	11% - 19%
Beta blockers	11%	8% - 14%
ACEi / ARBs	53%	48% - 58%
CCB	20%	16% - 24%
Others	1%	0% - 2%
In people taking two antihypertensives		
Diuretic and Beta blockers	3%	1% - 5%
Diuretic and CCB	11%	7% - 15%
Diuretic and ACEi/ARB	27%	22% - 32%
Beta blocker and ACEi/ARB	16%	12% - 20%
Beta blocker and CCB	10%	6% - 14%
ACEi / ARB and CCB	28%	23% - 33%
Other combination	5%	2% - 8%
In people taking three antihypertensives		

Diuretic and BB and CCB	6%	2% - 10%
Diuretic and BB and ACEi/ARB	22%	14% - 30%
Diuretic and ACEi/ARB and CCB	32%	23% - 41%
BB and ACEi/ARB and CCB	13%	7% - 19%
Other combination	27%	19% - 35%
In people taking four antihypertensives		
Diuretic and BB and CCB and ACEi/ARB	53%	36% - 70%
Diuretic and CCB and ACEi/ARB and Alpha-blocker	15%	3% - 27%
Diuretic and BB and ACEi/ARB and Alpha-blocker	11%	0% - 22%
Other combination	21%	7% - 35%

3.5.9.2.2 Adverse events

The large scale randomised control trials of antihypertensives involving older people were reviewed and relevant data on adverse events for use in benchmarking were extracted. Studies reviewed included the 'Swedish Trial in Old Patients with hypertension (STOP-Hypertension)'[134], 'Systolic Hypertension in the Elderly Programme (SHEP)'[135], 'MRC trial of treatment of hypertension in older adults'[136], 'the Systolic hypertension in Europe (Syst-Eur) Trial'[137], 'Study on Cognition and Prognosis in the Elderly (SCOPE)'[138] and the 'Hypertension in the Very Elderly Trial (HYVET)'[41].

Priority was given to data from HYVET[41], given its key relevance in the management of hypertension in older people and because being recruited entirely from older people >80 the population was expected to be most similar to that in this study.

Where data on adverse events was not available large scale observational studies and database studies were identified by literature review and relevant data was extracted.

HYVET

HYVET evaluated the effect of antihypertensives (indapamide +/- perindopril) in 3845 people aged over 80 and found a significant risk reduction in stroke, heart failure and death. The study was the first to demonstrate sustained benefit from blood pressure modification into extreme old age and as such has a key place in decisions around the management of hypertension in older people. It was the natural choice for comparison. Data from HYVET was used to

provide benchmarks, as listed in table 3.5, together with estimated 95% CI for comparison with the study population.

Table 3.5 HYVET derived comparators

Variable	Event rate per 1000 Patient-Years	CI (per 1000 Patient-Years)
MI	2.2	2.2 – 2.2
Heart Failure	5.3	5.3 – 5.3
Stroke	12.4	12.3 – 12.5
Death	47.2	47.1 – 47.3

Systolic Hypertension in the Elderly Program (SHEP)

The SHEP study was one of the earlier studies examining the usefulness of antihypertensives in older people. It studied the effect of chlorthalidone on 4736 participants aged over 60 over an average period of 4.5 years. They found a reduction in incident stroke of 36% in the treatment group. The study reported the prevalence of adverse symptoms in great detail and this was used to derive benchmark data (table 3.6).

Table 3.6 SHEP derived comparator

Variable	Event rate per 1000 Patient-Years	CI (per 1000 Patient-Years)
Black outs	4.9	4.9 – 4.9

REGARDS study comparator (Banach)

The REGARDS study was an observational study designed to explore geographic variation in the incidence of stroke[139]. Data on the proportion experiencing recurrent falls over 6 months in those aged over 75 on antihypertensives was collected for 2507 participants and was used to derive a benchmark and 95% CIs (table 3.7).

Table 3.7 REGARDS derived comparator

Variable	Proportion	CI
Recurrent falls	7.3%	6% - 8%

Medicare Current Beneficiary Survey (Tinetti)

Tinetti and colleagues conducted a sub-study of the Medicare current beneficiary survey involving 4961 older adults (mean age 80.2) taking antihypertensives[140]. They reported the rate of falls associated with fracture, head trauma or death. This was used as a comparator for the rate of falls with fracture in the HIND study (table 3.8).

Table 3.8 Medicare Current Beneficiary Survey derived comparator

Variable	Event rate per 1000 Patient-Years	CI (per 1000 Patient-Years)
Falls with fracture	30.8	30.8 - 30.8

Adverse symptoms

The same large multicentre study[62] which was used to develop the symptom questionnaire was used to extract relevant adverse symptom data. The prevalence and confidence intervals are listed in table 3.9.

Table 3.9 Prevalence of antihypertensive adverse symptoms

Variable	Prevalence	CI
Headache	29%	26% - 32%
Dizziness	34%	31% - 37%
Swollen ankles	30%	27% - 33%
Cold hands / feet	34%	31% - 37%
Flushing / sweating	26%	23% - 29%
Skin rash / itching	16%	14% - 18%
Cough	19%	17% - 21%
Dry mouth	32%	29% - 35%
Nausea	14%	12% - 16%
Diarrhoea	13%	11% - 15%
Constipation	11%	9% - 13%
Palpitations	25%	22% - 28%
Nervousness / restlessness	21%	18% - 24%
Tiredness	41%	38% - 44%
Sleep problems	26%	23% - 29%
Frequent micturition	38%	35% - 41%

3.5.9.2.3 Defined daily dose

The Defined Daily Dose (DDD) is "*the assumed average maintenance dose per day for a drug used for its main indication in adults".* The concept has been developed since the 1960s and popularised by the World Health Organization International Working Group for Drug Statistics Methodology from the early 80s[141]. Its chief use is in drug utilisation studies, but it has been applied in observational studies to standardise antihypertensive doses to facilitate analysis[140]. In this study the DDD was used as a benchmark for comparison with the doses prescribed for participants.

3.6 Results

3.6.1 Recruitment

Recruitment started on the 25/7/13 and finished on 31/10/14. In total 181 individuals were recruited and these were distributed between the sites as shown in table 3.10. Figures 3.3 and 3.4 show plots of recruitment over time and by recruitment site.

Table 3.10 Recruitment at different sites

Site	Number of recruits
Nottingham	59
Leicester	27
Surrey and Borders NHS Trust	40
NHS Fife	1
Southern Health NHS Trust	28
South Essex Partnership University NHS Trust	7
Solent NHS Trust	9
Leicestershire Partnership NHS Trust	10
Total	181

Figure 3.3 Plot of recruitment over time

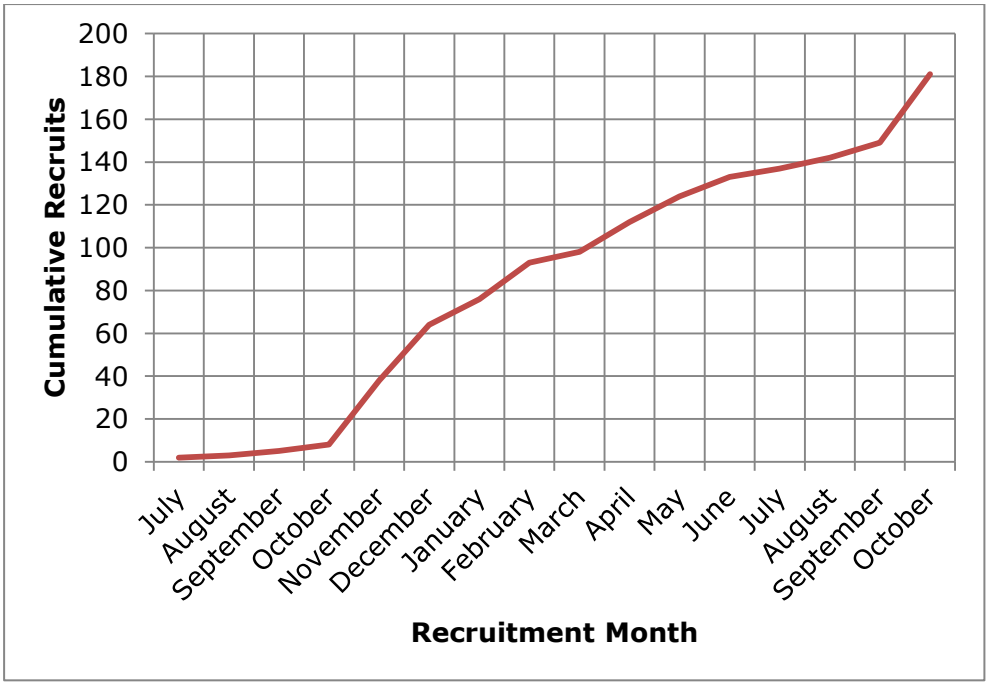
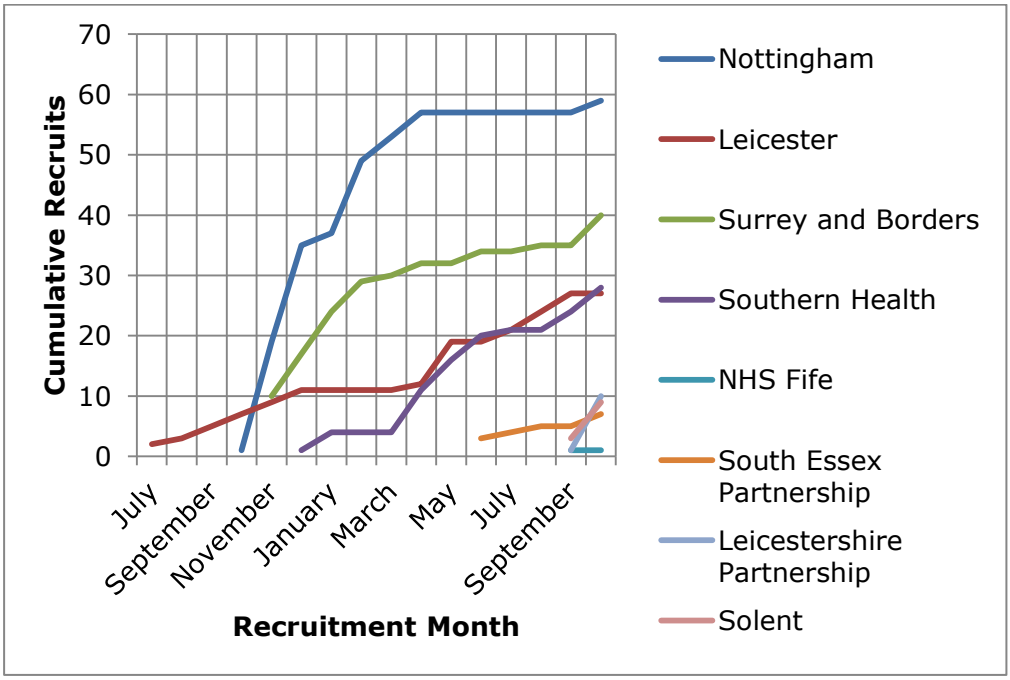


Figure 3.4 Plot of recruitment over time by recruitment site



3.6.1.1 Recruitment (Core sites)

3.6.1.1.1 GP practices

249 GP practices were identified and contacted. The mean practice size was 6550 individuals, ranging from 402 to 31452.

45 practices (18%) agreed to take part in the study.

3.6.1.1.2 Reasons for GP practices declining

Specific reasons were given by 14 practices for not wanting to participate. No reason was given by the remainder. The most common reason given was that the practice was too busy to take on additional work at the time. The reasons given are summarised in table 3.11.

Table 3.11 Reasons GP practices gave for not getting involved

Reason	Frequency	Percent
Not interested	4	29%
Too busy	5	36%
Not enough support funding	1	7%
Practice doesn't do research	1	7%
New computer system being installed	2	14%
Practice merging (too busy)	1	7%

3.6.1.1.3 Practices involved

The mean population per involved practice was 8482 (SD 3940), with a mean of 29 (SD 23) potential participants per practice. A total population of 390,175 was searched and 1337 individuals with recorded diagnoses of hypertension and dementia were identified and contacted.

3.6.1.1.4 Responses

Out of the 1337 invitations sent out 108 replies were received. Of these 93 were from people interested in taking part. Of these 93 seven were ultimately unable to take part. The reasons are summarised in tables 3.12 and 3.13. No data was available on the reasons for lack of response to 1229 invitations.

Table 3.12 Reason for declining / not able to take part

Reason	Frequency	Percent
No answer despite multiple attempts to contact	4	29%
No contact details given	2	14%
Not interested in taking part	2	14%
Too unwell	4	29%
Forgotten that they had responded	2	14%

Table 3.13 Reason for not consenting to take part at initial visit

Reason	Frequency
No consultee	1
After consideration didn't want to take part	1
Died prior to initial visit	1
Ineligible	4

3.6.1.1.5 Comparison of predicted and actual numbers (Nottingham)

The predicted number correlated with the actual number R^2 0.715 P<0.001. The method used to predict the number of potential participants had a tendency to overestimate the numbers. The mean absolute error was -3.4, mean percentage error -9.0%. Table 3.14 summarises the comparison.

Table 3.14 Comparison of predicted and actual numbers

Practice	Number	Prediction	Percentage error
Belvoir Group	90	101	-12.2%
Keyworth Medical Practice	41	67	-63.4%
Barnby Gate	63	66	-4.8%
Willowbrook Medical Practice	92	60	34.8%
Ravenshead and Blidworth	39	60	-53.8%
Torkard Hill	71	57	19.7%
Clipstone HC	61	57	6.6%
East Leake Health Centre	47	56	-19.1%
Radcliffe on Trent	44	51	-15.9%
Chilwell Valley and	36	47	-30.6%

Meadows Surgeries			
Rivergreen Medical Centre	31	42	-35.5%
Daybrook	30	41	-36.7%
Collingham Medical Practice	18	40	-122.2%
Brierley Park Medical Centre	30	37	-23.3%
St George's	42	37	11.9%
Hucknall Road	28	36	-28.6%
Leen View Surgery	55	34	38.2%
Derby Road Health Centre in Lenton	32	33	-3.1%
Drs Ward, Pearce & Partners (Churchside)	18	28	-55.6%
Family Medical Centre	29	22	24.1%
Bramcote	11	16	-45.5%
Fairfield	14	13	7.1%
Compton Acres Medical Centre	11	10	9.1%
Riverlyn Medical Centre	6	10	-66.7%
West Bridgford	6	9	-50.0%

3.6.1.1.6 Comparison with the Leicester site

There were significantly fewer potential participants on average at the GP practices involved at the Leicester site compared to the Nottingham site (p=0.03) (table 3.15).

Table 3.15 Comparison between Nottingham and Leicester

Site	Mean potential participants	SD	Significance
Nottingham	37.8	23.3	0.03
Leicester	18.7	16	

3.6.2 Missing Data (Baseline)

36 discrete variables were collected at baseline function from 181 participants. The 14 variables with missing data are listed in table 3.16.

Table 3.16 Variables with missing baseline data

Variable	Valid	Missing	Percent
Weight	173	8	4.4%
BP (standing)	174	7	3.9%
DemQol	177	4	2.2%
Height	178	3	1.7%
BP (sitting)	179	2	1.1%
Symptoms	180	1	0.6%
MMSE	180	1	0.6%
Concordance	180	1	0.6%
Medication history	180	1	0.6%
Dementia subtype	180	1	0.6%
Medical history	180	1	0.6%
Falls	180	1	0.6%
Age on finishing full time education	180	1	0.6%
Pack years	180	1	0.6%

One participant withdrew during the initial baseline assessment resulting in missing data from all the variables listed in table 3.16. Further discussion of the missing data will exclude this participant.

Comparison between participants with missing data, excluding equipment problems, to those without missing data revealed significantly lower MMSE and Barthel indices in those with missing data (table 3.17).

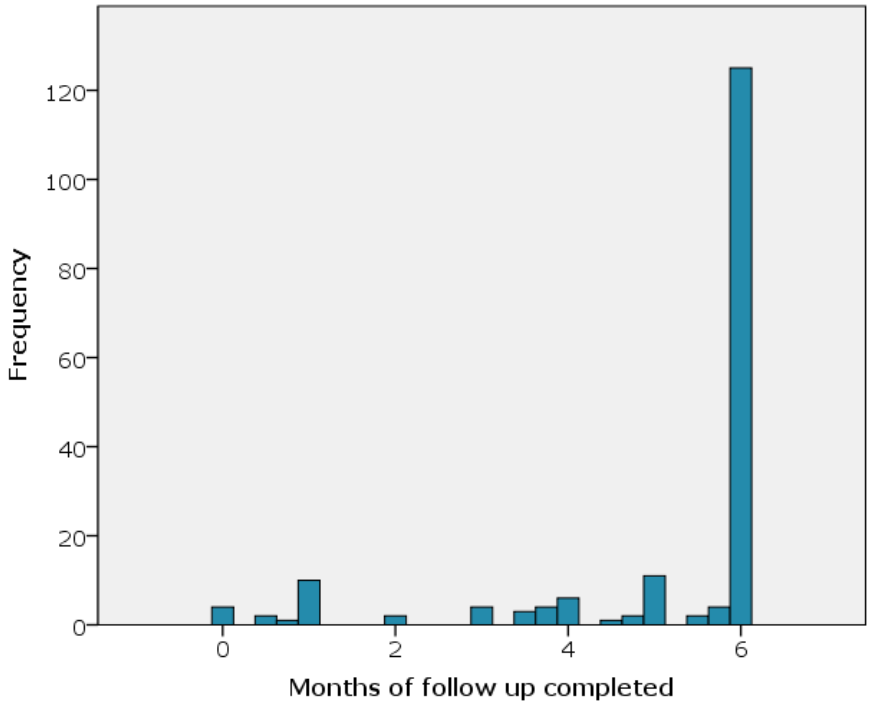
Table 3.17 Comparison of MMSE and BI between participants with and without missing data

Missing data	Frequency	Mean (SD) or Median (IQR)	Significance
MMSE			0.014
Complete	168	21.2 (6.8)	
Incomplete	12	15.92 (11.2)	
Barthel			0.001 (M-W)
Complete	168	19 (17-20)	
Incomplete	12	13 (7.5-18.5)	

3.6.3 Missing Data (Follow-up)

Of the 181 participants recruited 125 completed the full six months of follow ups with the median follow-up completed being 6 months (IQR 5-6).

Figure 3.5 Months of follow up completed



56 participants did not complete the full six months' worth of follow ups. The commonest reason for lack of completion of all follow up calls was missing one or more follow up calls, followed by withdrawal, being lost to follow up and death during the study. See table 3.18 below for detailed breakdown.

Table 3.18 Reason for not completing follow ups

Reason	Frequency	Percent
Missing one or more follow up calls	22	39%
Withdrawal	17	30%
Lost to follow up	9	16%
Died	8	14%
Total	56	100%

3.6.3.1 Missing follow-up time

Excluding deaths and withdrawals, data was missing from 31 participants. This equated to 46.5 months missing out of a total 930.25 months F/U data gathered (table 3.19).

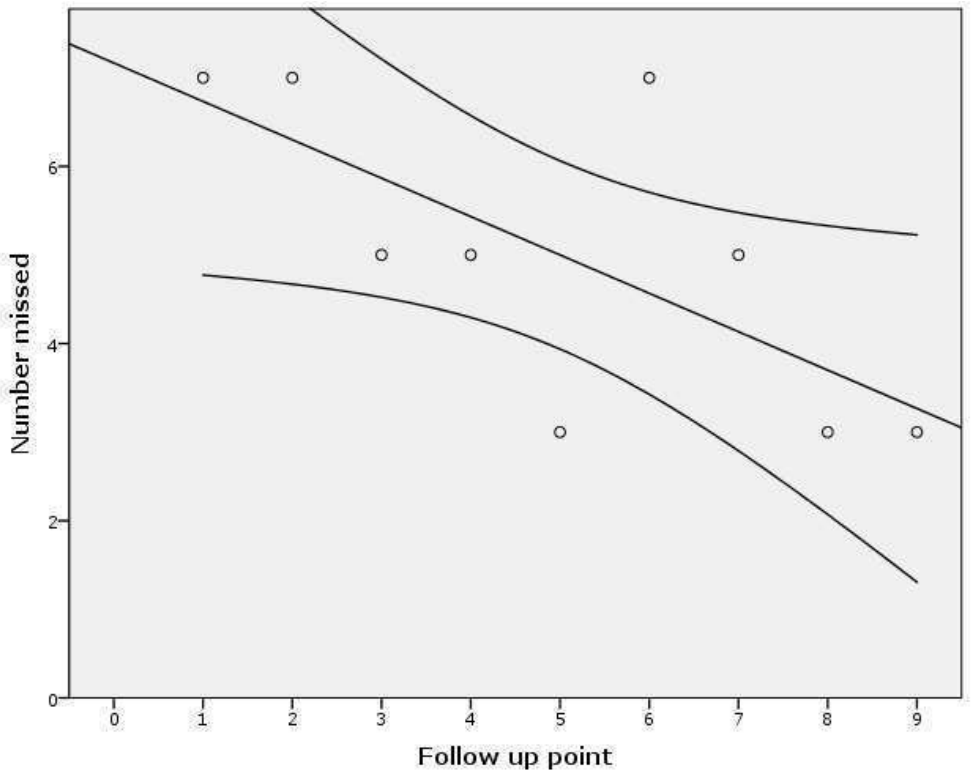
Table 3.19 Months of follow up missing

Months missing	Frequency	Totals
4	1	4
3	1	3
2.5	3	7.5
2.25	4	9
2	4	8
1.5	1	1.5
1.25	2	2.5
1	9	9
0.5	2	1
0.25	4	1
	Total:	**46.5**

3.6.3.2 Missed a follow up call

Participants received follow up phone calls on 9 occasions. The commonest reason for missing follow up data was that one or more follow ups had been missed due to challenges in contacting the participant. Earlier follow ups were more likely to be missed than later follow ups (p=0.042) (figure 3.6).

Figure 3.6 Missed follow up calls over time



3.6.3.3 Withdrawals

18 participants withdrew from the study. The median duration of involvement was 1 month (IQR 0.375-1). Figure 3.7 summarises the duration of involvement while table 3.20 summarises the reasons given for withdrawal.

Figure 3.7 Duration of involvement of participants who withdrew

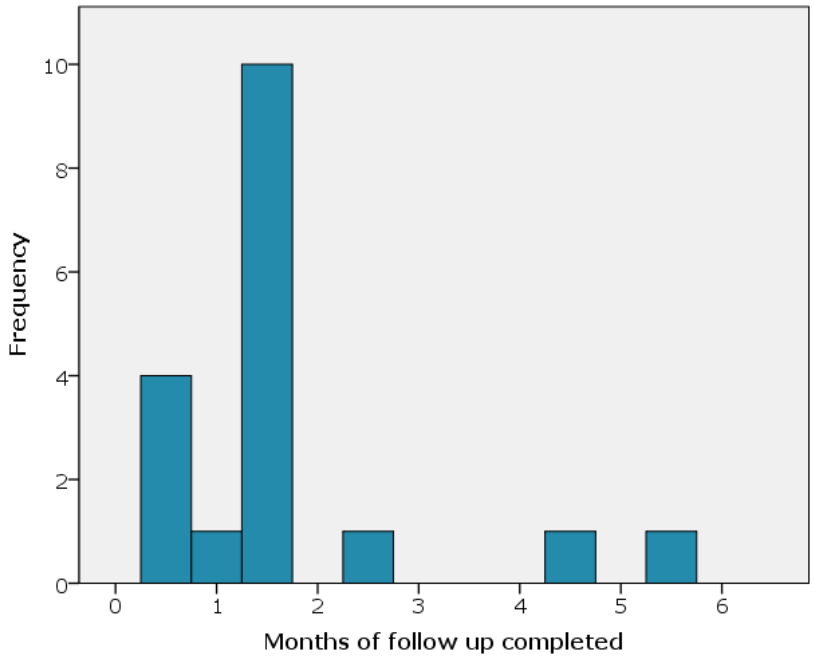


Table 3.20 Reasons for withdrawal

Reason for withdrawal	Frequency
No longer interested	6
Not what I expected	1
Too much effort	2
Ill health	4
Family issues	1
Terminal diagnosis	1
No reason given / available	2

3.6.3.4 Loss to follow up

These 9 participants completed a median of 4 months (IQR 3.75-5) before being lost to follow up.

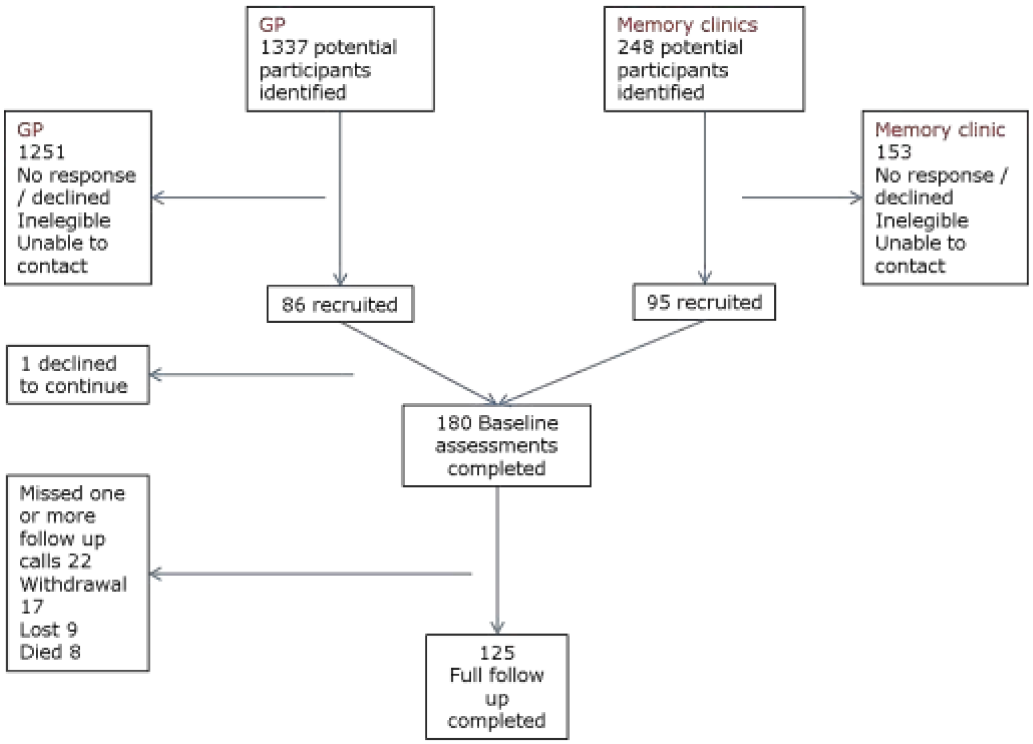
3.6.3.5 Deaths

Eight participants died during the study after a median follow up period of 3 months (IQR 1.5-4.75).

3.6.3.6 Participant losses

Figure 3.8 shows the participant losses from patient identification to completion of follow up for participants recruited both via GPs and via memory clinics.

Figure 3.8 Flow diagram showing participant losses



3.6.4 Description of the study population

3.6.4.1 Whole population demographics

Table 3.21 below summarises the baseline demographics of the whole study population. The study population was predominantly white, married and resident in their own homes. They had a median BI of 19 (IQR 16-20) and scored a median of 23 (IQR 18-26) on the MMSE suggesting a preponderance of mild to moderate dementia in this group. Their blood pressure appeared to be well controlled with a median of 1 (IQR 1-2) antihypertensive prescribed.

Table 3.21 Summary of baseline variables

Variable	Finding
Age (median (IQR))	83 (78-87)
Sex (%(n))	70.2% (127) female
Residence (%(n))	86.7% (157) Own home, 12.7% (23) Residential home, 0.8% (1) Nursing home
Packyears (Median (IQR))	1 (0-15.5)
Age on finishing full time education (Median (IQR))	15 (14-16)
Marital status (%(n))	3.9% (7) Single, 61.3% (111) Married, 31.5% (57) Widow /widower, 3.3% (6) Divorced
Ethnicity	94.5% (171) White British, 2.8% (5) White Irish, 1.1% (2) Any other white background, 1.1% (2) Indian,

	0.6% (1) Any other ethnic group
Falls / 1000 patientyears (Mean(SD))	1945 (5775)
Falls (prevalence) (n (%))	41 (23%)
Weight (kg) (Mean(SD))	68.2 (15.8)
Height (cm) (Mean(SD))	164 (10.1)
BMI (Mean (SD))	25.3 (5.1)
Blood pressure (mmHg) (Mean (SD))	140/78 (22.9/12.7)
Postural hypotension (n=174) (Prevalence)	19 (10.9%)
Number of antihypertensives (Median(IQR))	1 (1-2)
Number of medications (Median (IQR))	7 (5-9)
Polypharmacy (4 or more medications)	156 (86.7%)
Polypharmacy (10 or more medications)	38 (21.1%)
Charlson Score (age adjusted) (Median (IQR))	5.5 (5-6.75)
Number of medical diagnoses (Median (IQR))	5 (3-7)
MMSE (Median (IQR))	23 (18-26)
Barthel (Median (IQR))	19 (16-20)
DemQol (Median (IQR))	99 (85-106)

A comparison between the findings from the memory clinic population and from the GP population is summarised in table 3.22 below. People recruited via GP reported more falls, took fewer antihypertensives, had more medical diagnoses, were more likely to have a diagnosis of vascular or unspecified dementia, less likely to have a diagnosis of Alzheimer's and were more dependent with basic ADLs compared to those recruited via memory clinics. (More detailed examination of the difference in dependency is presented in section 3.6.4.6.)

Table 3.22 Comparison between memory clinic population and GP population

Variable	GP	Memory Clinic	Significance
Number	86	95	
Age (median (IQR))	84 (79.75-87)	81 (76-87)	NS
Sex (%(n))	73.3% (63) female	67.4% (64) female	NS
Residence (%(n))	82.6% (71) OH, 17.4% (15) RH	90.5% (86) OH, 8.4% (8) RH, 1.1% (1) NH	NS
Packyears (Mean (SD))	13.2 (25.6)	11.1(17.5)	NS
Age on finishing full time education (Median (IQR))	15 (14-16)	15 (14-17)	NS
Marital status (%(n))	5.8% (5) S, 58.1% (50) M, 34.9% (30) W, 1.2% (1) D	2.1% (2) S, 64.2% (61) M, 28.4% (27) W, 5.3% (5) D	NS

Ethnicity	94.2% (81) White British, 2.3% (2) White Irish, 2.3% (2) Indian, 0 (0) any other ethnic group, 1.2% (1) Any other white	94.7% (90) White British, 3.2% (3) White Irish, 0 (0) Indian, 1.1% (1) any other ethnic group, 1.1% (1) Any other white	NS
Falls / 1000 patientyears (Mean(SD))	2837 (7486)	1137 (3435)	0.014
Falls (prevalence) (n (%))	26 (30%)	15 (16%)	0.021
BMI (Mean (SD))	24.7 (4.8)	25.8 (5.4)	NS
Blood pressure (mmHg) (Mean (SD))	139/79 (21/12)	142/76 (25/13)	NS
Postural hypotension (Prevalence) (n= 174)	10 (12%)	9 (9.9%)	NS
Number of medications (Median (IQR))	6 (5-9)	7 (5-9)	NS
Polypharmacy (4 or more medications)	75 (88.2%)	81 (85.3%)	NS

Polypharmacy (10 or more medications)	17 (20.0%)	21 (22.1%)	NS
Number of Antihypertensives (Median (IQR))	1 (1-2)	2 (1-2)	0.008
Number of medical diagnoses (Median (IQR))	5.5 (4-8)	4 (3-5)	<0.001
Charlson Score (Age adjusted)	6 (5-7)	5 (5-6)	NS
Dementia subtypes	85	95	
Vascular	21 (24.7%)	11 (11.6%)	0.021
Alzheimer's	37 (43.5%)	64 (67.4%)	0.001
Mixed	10 (11.8%)	14 (14.7%)	NS
Unspecified	17 (20.0%)	3 (3.2%)	<0.001
Dementia with Lewy bodies	0 (0%)	1 (1.1%)	NS
Dementia in Parkinson's	0 (0%)	2 (2.1%)	NS
Dementia in Pick's	1 (1.2%)	0 (0%)	NS
MMSE (Median (IQR))	22 (16-25.25)	23 (19-26)	NS
Barthel (Median (IQR))	19 (14.75-20)	20 (17-20)	0.028
DemQol (Median (IQR))	96 (79-105)	101 (92.25-109)	NS

3.6.4.2 Medical diagnoses

159 different diagnoses within the study population were reported. A full list is available in appendix II (table A2.2), while the 20 most frequently occurring diagnoses are summarised in table 3.23. All study recruits had diagnoses of dementia and hypertension, osteoarthritis was the most common other diagnosis and cardio/cerebrovascular disease was also very common. Compared to the findings of the Health Survey for England 2005 stroke and diabetes were more common and arthritis less common in the study population in women (table 3.24).

Table 3.23 Top 20 diagnoses (excluding hypertension and dementia)

Diagnosis	Frequency n (%)
Osteoarthritis	48 (27%)
Type 2 diabetes mellitus	35 (19%)
Stroke (unspecified)	28 (16%)
Osteoporosis	27 (15%)
Chronic kidney disease stage 3	24 (13%)
Heart failure	23 (13%)
MI	23 (13%)
Atrial fibrillation	18 (10%)
Hypothyroidism	18 (10%)
Depression	10 (6%)
Hypercholesterolaemia	10 (6%)
Diverticular disease	10 (6%)
TIA	9 (5%)
Angina	9 (5%)
Age related macular degeneration	8 (4%)
Hysterectomy	7 (4%)
Falls	6 (3%)
Mitral regurgitation	6 (3%)
GORD	6 (3%)
Fracture of the radius	6 (3%)
Basal cell cancer (cutaneous)	6 (3%)

Table 3.24 Comparison between the study population and results of the Health Survey for England 2005

Condition	Health Survey for England 2005		HIND	
	Male	Female % (95%CI)	Male % (95%CI)	Female % (95%CI)
IHD	23%	16% (15%-17%)	16.7% (7%-27%)	22.2% (15%-29%)
Stroke	9%	7% (6%-8%)	7.4% (0-14%)	19.0%* (12%-26%)
Arthritis	32%	47% (45%-49%)	24.1% (13%-36%)	28.6%* (21%-36%)
Osteoporosis	2%	12% (11%-13%)	3.7% (0-9%)	19.8% (13%-27%)
Diabetes	13%	10% (9%-11%)	18.5% (8%-29%)	19.8%* (13%-27%)

*significant difference

Table 3.25 summarises the dementia subtypes reported. Alzheimer's was the most common subtype, occurring in the majority of participants, while vascular dementia was the second most common.

Table 3.25 Dementia diagnoses

Dementia Subtype	Frequency n (%)
Vascular	35 (19%)
Alzheimer's	101 (56%)
Mixed	23 (13%)
Pick's	1 (0.6%)
Dementia in Parkinson's	2 (1%)
Dementia with Lewy bodies	1 (0.6%)
Unspecified	16 (9%)

3.6.4.3 Medications (excluding antihypertensives)

164 different drugs were prescribed with a total of 941 prescriptions for the study population. A full list of medications is available in appendix II (table A2.1), but the 10 most frequently occurring prescriptions are summarised in table 3.26 below. Drugs for dementia were the most commonly prescribed class with 68.9% of the study population taking one. Antihypertensive drug use is described in detail in section 3.6.5.

Table 3.26 Top 10 most frequently occurring medications grouped as per BNF chapters.

Drug (n=180)	Frequency n (%)
Drugs for dementia	124 (68.9%)
Donepezil	73 (40.6%)
Galantamine	12 (6.7%)
Memantine	28 (15.6%)
Rivastigmine	11 (6.1%)
Lipid regulating drugs	97 (53.9%)
Statins	95 (52.8%)
Fibrates	2 (1.1%)
Analgesics	90 (50.0%)
Paracetamol	52 (28.9%)
NSAIDs (Oral)	4 (2.2%)
NSAIDs (Topical)	6 (3.3%)
Mebeverine	1 (0.6%)
Nefopam	1 (0.6%)
Codeine	15 (8.3%)
Dihydrocodeine	3 (1.7%)
Tramadol	4 (2.2%)
Meptazinol	1 (0.6%)
Buprenorphine	1 (0.6%)
Morphine	1 (0.6%)
Fentanyl	1 (0.6%)

Antiplatelets	81 (45.0%)
Aspirin	62 (34.4%)
Clopidogrel	17 (9.4%)
Dipyridamole	2 (1.1%)
Bone Protection	72 (40.0%)
Calcium + vitamin D combination	45 (25%)
Vitamin D	4 (2.2%)
Oral bis-phosphonate	22 (12.2%)
IV bis-phosphonate	1 (0.6%)
Antisecretory drugs and mucosal protectants	56 (31.1%)
PPIs	48 (26.7%)
Ranitidine	8 (4.4%)
Anti-depressants	47 (26.1%)

SSRIs	25 (13.9%)
SNRIs	2 (1.1%)
Tricyclics	11 (6.1%)
Mirtazapine	9 (5.0%)
Bronchodilators +/- inhaled corticosteroids	35 (19.4%)
Aminophylline	1 (0.6%)
Montelukast	1 (0.6%)
Inhaled beta agonist	12 (6.7%)
Inhaled antimuscarinic	7 (3.9%)
Compound inhalers	7 (3.9%)
Inhaled corticosteroids	7 (3.9%)
Diuretics	34 (18.9%)
Furosemide	24 (13.3%)
Bumetanide	5 (2.8%)
Amiloride	1 (0.6%)
Spironolactone	4 (2.2%)

Antidiabetic drugs	29 (16.1%)	**Sulfonylureas**	13 (7.2%)
Metformin	14 (7.8%)	**Pioglitazone**	1 (0.6%)
		Sitagliptan	1 (0.6%)

3.6.4.4 Falls

41 participants reported at least one fall in the three months preceding baseline data gathering with 3 participants experiencing 6 or more falls. These findings are summarised in table 3.27 below.

Table 3.27 Number of reported falls in the last three months

Number of falls (n=180)	**Frequency n (%)**
0	139 (77%)
1	22 (12%)
2	9 (5%)
3	7 (4%)
6	2 (1%)
More than 6	1 (1%)

3.6.4.5 Degree of cognitive impairment

Data was available from 180 participants. Scores were not normally distributed; the median score was 23, with an interquartile range of 18.25 to 26. Only 10% of participants had a MMSE compatible with severe dementia. The study population in general was mildly cognitively impaired. The breakdown is shown in table 3.28.

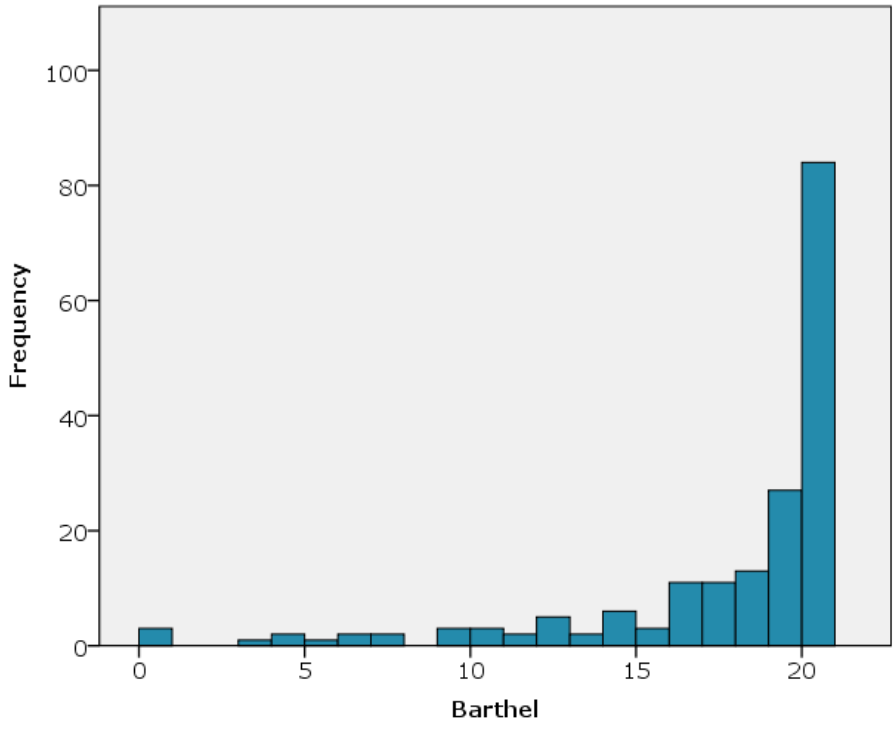
Table 3.28 MMSE scores

MMSE score	Frequency
Normal (27-30)	37 (21%)
Mild (21-26)	76 (42%)
Moderate (10-20)	49 (27%)
Severe (0-9)	18 (10%)

3.6.4.6 Dependency in basic ADLs

46% (84) of the participants had a BI of 20/20; figure 3.9 below shows the distribution of scores.

Figure 3.9 Barthel index



On detailed analysis of the components of the Barthel index a number of specific dependencies were highlighted. Data between those recruited via GP and those recruited via memory clinics were

also compared to further elucidate clues to the different make up of these populations. Table 3.29 summarises the data and differences by recruitment strategy.

A quarter of the total study population needed help with bathing and over 10% needed at least some help with grooming, dressing, transfers, mobility and using the stairs. Faecal and urinary incontinence occurred at least occasionally in over 10%.

Table 3.29 Detail of the Barthel Index

Barthel component	**Whole population (n=181)**	**Recruited via GP**	**Recruited via memory clinics**	**Significance**
Feeding				NS
Needs at least some help	10 (5.5%)	4 (4.7%)	6 (6.3%)	
Unable	5 (2.8%)	5 (5.8%)	0 (0%)	
Bathing				0.023
Dependent	45 (24.9%)	28 (32.6%)	17 (17.9%)	
Grooming				NS
Needs help with personal care	22 (12.2%)	14 (16.3%)	8 (8.4%)	

Dressing				0.01
Needs help, but can do about half	23 (12.7%)	14 (16.3%)	9 (9.5%)	
Dependent	17 (9.4%)	14 (16.3%)	4 (4.2%)	
Bowels				0.034
Occasional accident	20 (11%)	13 (15.1%)	7 (7.4%)	
Incontinent	9 (5%)	7 (8.1%)	2 (2.1%)	
Bladder				0.001
Occasional accident	26 (14.4%)	17 (19.8%)	9 (9.5%)	
Incontinent	22 (12.2%)	17 (19.8%)	5 (5.3%)	
Toilet use				0.039
Needs some help	7 (3.9%)	6 (7.0%)	1 (1.1%)	
Dependent	12 (6.6%)	8 (9.3%)	4 (4.2%)	
Transfers				NS
Minor help	21 (11.6%)	9 (10.5%)	12 (12.6%)	
Major help	4 (2.2%)	3 (3.5%)	1 (1.1%)	
Unable	3 (1.7%)	3 (3.5%)	0 (0%)	
Mobility				0.045

Walks with help of one >50yrds	26 (14.4%)	11 (12.8%)	15 (15.8%)	
Wheelchair independent	5 (2.8%)	1 1.2%)	4 (4.2%)	
Unable / <50yrds	12 (6.6%)	10 (11.6%)	2 (2.1%)	
Stairs				0.044
Needs help	24 (13.3%)	13 (15.1%)	11 (11.6%)	
Unable	34 (18.8%)	22 (25.6%)	12 (12.6%)	

Comparing between the populations recruited via GP and memory clinics, those recruited via GPs were more dependent in every aspect except feeding, grooming and transfers.

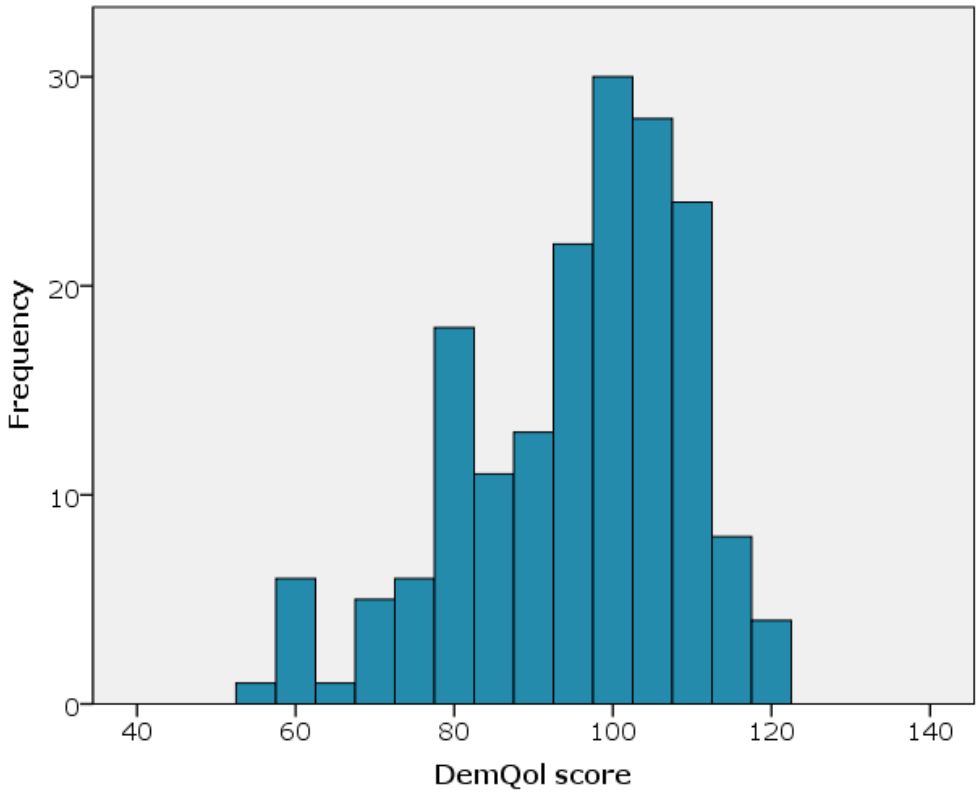
3.6.4.7 Health-related quality of life

The majority of participants reported a good or very good quality of life. This is summarised in table 3.30 and figure 3.10.

Table 3.30 Quality of life

DemQol rating (n=177)	Frequency n (%)
Poor	18 (10.2%)
Fair	45 (25.4%)
Good	69 (39.0%)
Very good	45 (25.4%)

Figure 3.10 DEMQol scores



3.6.4.8 Symptoms

95.6% of the population experienced at least one of the symptoms during the month prior to baseline data collection and 69.4% experienced at least one of the symptoms on a daily basis. Tiredness was the most commonly reported symptom with 28% experiencing this daily. Table 3.31 summarises the symptoms reported.

Table 3.31 Symptoms in the last month

Symptom	Not reported	Once	Twice	Thrice	Weekly	Most days	Daily
Headache	129	10	10	6	12	3	10
Dizziness	129	10	11	3	5	13	9
Swollen ankles	127	3	2	0	5	15	28
Cold hands / feet	103	4	6	8	8	16	35
Flushing / sweating	148	9	4	2	7	1	9
Skin rash / itching	123	8	7	3	2	18	19
Cough	125	6	4	8	8	13	16
Dry Mouth	127	3	12	4	4	12	18
Nausea	167	6	2	0	1	4	0
Diarrhoea	148	13	4	3	8	4	0
Constipation	148	6	3	3	10	6	4
Palpitations	164	3	6	4	1	1	1
Nervousness	124	6	7	5	12	9	17
Tiredness	61	5	7	3	12	42	50
Sleep Problems	120	6	4	3	13	20	14
Frequent Micturition	108	3	1	3	4	23	38
Any Symptom	8 (4%)	2 (1%)	7 (4%)	1 (0.6%)	6 (3%)	31 (17%)	125 (69%)

3.6.5 The use of antihypertensive agents

3.6.5.1 Antihypertensive classes

ACE inhibitors were the most commonly prescribed antihypertensive class, followed by calcium channel blockers and beta blockers. Table 3.32 below summarises this data.

Table 3.32 Frequency of antihypertensive classes

Class	Frequency	Percent
ACEi	68	38%
ARB	32	18%
Calcium Channel Blocker	60	33%
Beta-Blocker	54	30%
Diuretic	37	21%
Alpha Blocker	17	9%
Other	5	3%

Compared to the benchmark data study participants took significantly fewer diuretics, but other antihypertensive classes were equally represented. (Table 3.33)

Table 3.33 Comparison with benchmarked data

Class	Percent	CI	Bench - mark percent	Benchmark CI	Sig
ACEi/ARBs	56%	48% - 63%	63%	60% - 66%	NS
CCB	33%	26% - 40%	37%	34% - 40%	NS
BB	30%	23% - 37%	24%	21% - 27%	NS
Diuretic	21%	15% - 26%	34%	31% - 37%	S
Other	12%	7% - 17%	8%	6% - 10%	NS

3.6.5.2 Specific antihypertensives

Ramipril was the most frequently prescribed antihypertensive medication with 46 (26%) of the study population taking it.

Ramipril, losartan, bendroflumethiazide, bisoprolol, amlodipine and doxazosin were the most frequently prescribed ACEi, ARB, diuretic, beta-blocker, calcium channel blocker and alpha blocker respectively. Antihypertensives taken by 5% or more of the study population are listed in table 3.34. A full breakdown of the antihypertensives used is given in appendix II (table A2.3).

Table 3.34 antihypertensives taken by 5% or more of the study population

Drug	Frequency of prescription	Proportion (%)
Ramipril	46	26%
Lisinopril	9	5%
Perindopril	9	5%
Losartan	17	9%
Bendroflumethiazide	28	16%
Bisoprolol	32	18%
Atenolol	16	9%
Amlodipine	37	21%
Doxazosin	15	8%

3.6.5.3 Dosage of different antihypertensive classes

Data on the doses of the different antihypertensives used was collected and is presented in detail in appendix II (section A2.1). Table 3.35 below shows a comparison between the mean study dose and the Defined Daily Dose for specific agents that were taken by 5% or more of the study population.

Table 3.35 Comparison with DDD

Drug	Mean dose (mg)	95% CI		DDD (mg)	Significance
Ramipril	6.3	5.3	7.2	2.5	S
Lisinopril	11.4	3.6	19.2	10	NS
Perindopril	5.8	4.0	7.6	4	NS
Losartan	61.8	45.4	78.1	50	NS
Bendroflumethiazide	2.5	2.5	2.5	2.5	NS
Bisoprolol	3.0	2.3	3.7	10	S
Atenolol	50.0	39.0	61.0	75	S
Amlodipine	6.4	5.0	7.1	5	NS
Doxazosin	4.2	3.0	5.4	4	NS

The mean ramipril dose in the study cohort was 2.5 times higher than the DDD value, while the mean atenolol and bisoprolol study doses were lower.

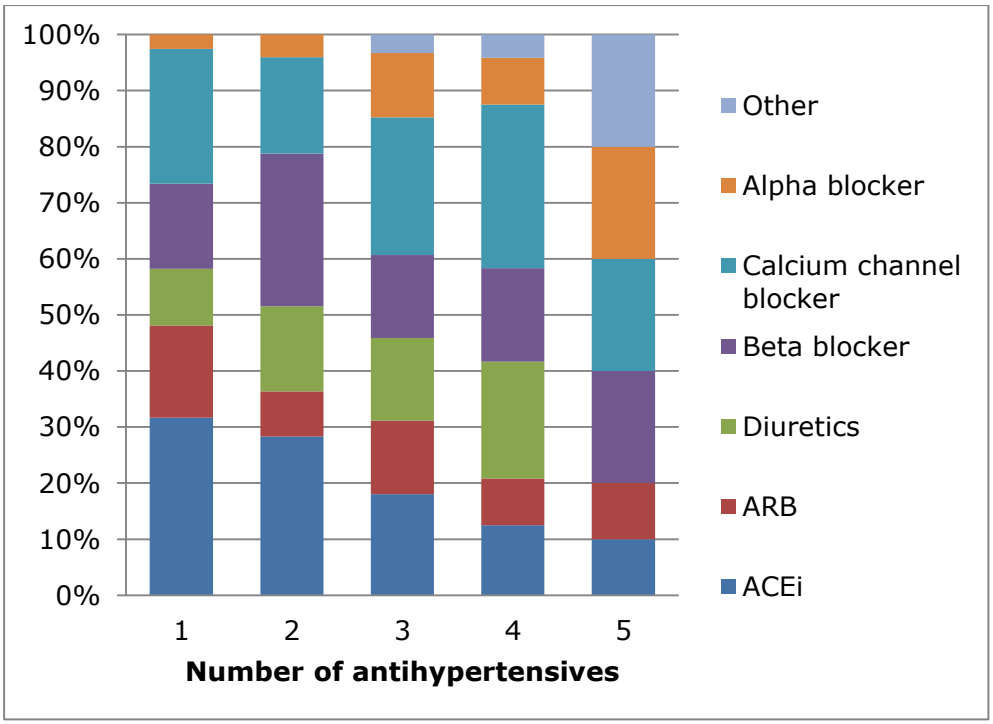
3.6.5.4 Number of antihypertensives

157 participants out of 180 (87%) were taking at least one antihypertensive. 23 (13%) were taking no agents, 79 (44%) were taking one, 50 (28%) were taking 2, 20 (11%) were taking 3, 6 (3%) were taking 4 and 2 (1%) were taking five agents. The classes used are summarised in table 3.36 and figure 3.11. Table A2.4 and figure A2.1, located in appendix II, provide summary information on specific antihypertensives and additional graphical representation of table 3.36 respectively.

Table 3.36 Summary of different antihypertensive classes by number of agents used

Drug Class	One (n=79)		Two (n=50)		Three (n=20)		Four (n=6)		Five (n=2)	
ACEi	25	31.6%	28	29.2%	11	17.2%	3	12.5%	1	10.0%
ARB	13	16.5%	8	8.3%	8	12.5%	2	8.3%	1	10.0%
Diuretic	8	10.1%	15	15.6%	9	14.1%	5	20.8%	0	0.0%
B-blocker	12	15.2%	27	28.1%	9	14.1%	4	16.7%	2	20.0%
CCB	19	24.1%	17	17.7%	15	23.4%	7	29.2%	2	20.0%
Alpha-blocker	2	2.5%	4	4.2%	7	10.9%	2	8.3%	2	20.0%
Others	0	0.0%	0	0.0%	2	3.1%	1	4.2%	2	20.0%

Figure 3.11 Summary of different antihypertensive classes by number of agents used



3.6.5.4.1 Comparison with benchmark data

Table 3.37 Comparison of proportion treated with benchmark data

Variable	Percent	CI	Bench - mark percent	Benchmark CI	Sig
Proportion Treated	87%	82% - 92%	87%	85% - 89%	NS
Number of antihyper-tensives					
1	44%	33% - 55%	45%	42% - 49%	NS
2	28%	16% - 40%	36%	33% - 39%	NS
3	11%	0-25%	15%	12% - 17%	NS
4	3%	0-17%	4%	3% - 6%	NS

There was no significant difference in the proportion of the study population on treatment or the number of antihypertensives used and the Health Survey for England (table 3.37).

3.6.5.5 Combinations

The data was further subdivided to examine the combinations of classes of antihypertensives used where participants were taking two or more agents with the intention of comparing this to population level data.

3.6.5.5.1 Two agents

The most common combination was of an ACEi/ARB and a beta blocker. In general an ACEi/ARB and another class of agent was the most commonly occurring combination for participants taking two agents (table 3.38).

Table 3.38 Combinations of two different classes of antihypertensives

Drug combination	Number taking	Percent
ACEi/ARB and Diuretic	8	16%
ACEi/ARB and BB	16	32%
ACEi/ARB and CCB	9	18%
ACEi/ARB and AB	3	6%
Diuretic and BB	4	8%
Diuretic and CCB	3	6%
BB and CCB	5	10%
BB and AB	2	4%

3.6.5.5.2 Three agents

The combination of an ACEi/ARB, a diuretic and a calcium channel blocker was the most frequently occurring combination. In general the combination of an ACEi/ARB, with a CCB and one other class was the most common combination (table 3.39).

Table 3.39 Combinations of three different classes of antihypertensives

Drug combination	Number taking	Percent
ACEi/ARB and BB and CCB	4	20%
ACEi/ARB and 2 BBs	1	5%
ACEi/ARB and D and CCB	6	30%
ACEi/ARB and D and Other	1	5%
2 ACEi/ARBs and CCB	1	5%
ACEi/ARB and CCB and AB	1	5%
ACEi/ARB and CCB and Other	1	5%
ACEi/ARB and BB and AB	3	15.0%
Diuretic and CCB and AB	2	10.0%

3.6.5.5.3 Four agents

The combination of ACEi/ARB, diuretic, beta blocker and CCB was the most common, in general though the combination of ACEi/ARB, diuretic and CCB with one other class was the most commonly occurring combination (table 3.40).

Table 3.40 Combinations of four different classes of antihypertensives

Drug combination	Number taking	Percent
ACEi/ARB and D and CCB and CCB	1	17%
ACEi/ARB and BB and CCB and AB	1	17%
ACEi/ARB and D and BB and CCB	2	33%
ACEi/ARB and D and CCB and AB	1	17%
Diuretic and BB and CCB and Other	1	17%

3.6.5.5.4 Five agents

Only two participants were taking five different antihypertensives. In both cases this consisted of a combination of ACEi/ARB, beta blocker, CCB, alpha blocker and one 'other' antihypertensive (table 3.41).

Table 3.41 Combinations of five different classes of antihypertensives

Drug combination	Number taking	Percent
ACEi/ARB and BB and CCB and AB and Other	2	100%

3.6.5.5.6 Comparison with benchmark data

Table 3.42 Participants taking one agent

Class	Percent	CI	Bench - marked percent	Bench - marked CI	Sig
Diuretics	10.1%	3% - 17%	15%	11% - 19%	NS
BB	15.2%	7% - 23%	11%	8% - 14%	NS
ACEi/ARBs	48.1%	37% - 59%	53%	48% - 58%	NS
CCB	24.1%	15% - 34%	20%	16% - 24%	NS
Other	2.5%	0% - 6%	1%	0% - 2%	NS

There was no difference in the proportions taking each class in those taking a single agent between the study population and the Health Survey for England findings (table 3.42).

Table 3.43 Participants taking two agents

Class	Percent	CI	Bench - marked percent	Bench - marked CI	Sig
D and BB	8%	0% - 16%	3%	1% - 5%	NS
D and CCB	6%	0% - 13%	11%	7% - 15%	NS
D and ACEi/ARBs	16%	6% - 26%	27%	22% - 32%	NS
BB and ACEi/ARBs	32%	19% - 45%	16%	12% - 20%	NS
BB and CCB	10%	2% - 18%	10%	6% - 14%	NS
ACEi/ARBs and CCB	18%	7% - 29%	28%	23% - 33%	NS
Other	10%	2% - 18%	5%	2% - 8%	NS

There was no difference in the proportions taking each class in those taking two antihypertensives between the study population and the Health Survey for England findings (table 3.43).

3.6.5.5.6 Participants taking 3 or more agents

A comparison for those taking 3 or more agents was not undertaken due to the small sample size (20, 6 and 2 participants respectively)

3.6.6 Blood pressure and achievement of target blood pressure

3.6.6.1 Blood pressure levels achieved

The mean blood pressure in those on treatment was 141/78 (95% CI 138-145/76-80). The blood pressure was significantly higher than the benchmark level reported in the Health Survey for England 135/74 (95% CI 134-137/73-74).

3.6.6.2 Association between treatment and blood pressure

Increasing number of antihypertensives was not associated with significantly lower systolic BP, but was associated with significantly lower diastolic BP (p=0.005). Table 3.44 summarises the mean BPs achieved by participants taking different numbers of antihypertensives.

Table 3.44 Mean systolic and diastolic BP by number of antihypertensives

Number of AHTN	Systolic BP Mean (SD)	Systolic BP Min - Max	Diastolic BP Mean (SD)	Diastolic BP Min - Max
0	141 (17)	114-173	78 (11)	62-106
1	139 (21)	92-189	78 (11)	48-109
2	142 (24)	90-204	79 (14)	52-117
3	146 (22)	114-185	77 (14)	58-100
4	138 (18)	120-172	68 (5.3)	58-73
5	137 (38)	110-164	65 (21)	51-80
Total	141 (22)	90-204	78 (12)	48-117

3.6.6.3 Achievement of target blood pressure

58% (95% CI 51%-66%) of the total study population achieved target blood pressure. More in the group not taking any antihypertensive achieved target BP compared to other groups. Increasing numbers of antihypertensives were not associated with increased achievement of target blood pressures. (Table 3.45)

Table 3.45 Proportion achieving target BP by number of antihypertensives prescribed

Number of AHTN	Target Systolic BP achieved	Target Diastolic achieved	Combined achievement
0 (n= 23)	16 (70%)	20 (87%)	16 (70%)
1 (n= 79)	52 (66%)	67 (85%)	48 (61%)
2 (n= 50)	29 (58%)	40 (80%)	28 (56%)
3 (n= 20)	12 (60%)	14 (70%)	9 (45%)
4 (n= 6)	3 (50%)	6 (100%)	3 (50%)
5 (n=2)	1 (50%)	2 (100%)	1 (50%)
Total (n=180)	113 (63%)	149 (83%)	105 (58%)
95% CI for Total	105-121 (56%-70%)	141-157 (77%-88%)	97-113 (51%-66%)

3.6.6.4 Comparison with benchmark figure

There was no significant difference in the proportion achieving target BP between the study population and benchmark figure. In those taking antihypertensive agents 57% (95% CI 49% - 64%) achieved target blood pressure compared to 52% (95 CI 49% - 55%) in the Health Survey for England.

Those achieving target BP were older, smoked more heavily, had a higher ChI and lower BI than those not achieving target BP. There was no difference in the number of antihypertensives used. Table 3.46 below summarises the differences in baseline variables.

Table 3.46 Comparison of baseline variables between those achieving and those not achieving target BP

Variable	Blood pressure < 140/90 or <150/90	Blood pressure > 140/90 or >150/90	Significance
Number	105 (58.3%)	75 (41.7%)	-
Site Type	55 (52.4%) GP 60 (47.6%) Memory clinic	30 (40%) GP 45 (60%) Memory clinic	NS
Age (mean (SD))	82.9 (5.6)	80.5 (7.1)	0.014
Sex (n (%))	73 (69.5%) female	53 (70.7%) female	NS
Residence (%(n))	90 (85.7%) OH, 14 (13.3%) RH, 1 (1%) NH	67 (89.3%) OH, 8 (10.7%) RH 0 (0) NH	NS
Packyears (Mean (SD))	15.8 (24.5)	7.08 (16.0)	0.004
Age on finishing full time education (Median (IQR))	15 (14 -16)	15 (14-17)	NS
Marital status (%(n))	3 (2.9%) S, 67 (63.8%) M, 31 (29.5%) W, 4 (3.8%) D	4 (5.3%) S, 44 (58.7%) M, 25 (33.3%) W, 2 (2.7%) D	NS
Ethnicity	100 (95.2%) White British, 3 (2.9%) White Irish, 1 (1.0%) Indian	70 (93.3%) White British, 2 (2.7%) White Irish, 1 (1.3%) Indian	NS

	1 (1.0%) Any other ethnic group 0 (0) Any other white background	0 (0) Any other ethnic group 2 (2.7%) Any other white background,	
Falls / 1000 patientyears (Mean(SD))	2480 (6960)	1230 (3480)	NS
Falls (prevalence) (n (%))	27 (26%)	14 (19%)	NS
Weight (Mean(SD))	68.1 (16.9)	68.4 (14.2)	NS
Height (Mean(SD))	164 (10.8)	165 (8.9)	NS
BMI (Mean (SD))	25.3 (5.6)	25.2 (4.2)	NS
Blood pressure	128/72 (14/9.2)	159/86 (16/12)	<0.001
Postural hypotension	15 (14.6%)	4 (5.6%)	NS
Number of antihypertensives (Median (IQR))	1 (1-2)	1 (1-2)	NS
Number of medications (Median (IQR))	7 (5-9.5)	6 (5-8)	NS
Polypharmacy (4 or more medications)	91 (86.7%)	65 (86.7%)	NS
Polypharmacy (10 or more medications)	26 (24.8%)	12 (16.0%)	NS

Charlson Score (age adjusted) (Median (IQR))	6 (5-7)	5 (4-6)	0.006
Number of medical diagnoses (Median (IQR))	4 (3 – 7)	5 (3-7)	NS
MMSE (Median (IQR))	23 (17-26)	22 (19-26)	NS
Barthel (Median (IQR))	19 (15 – 20)	20 (18-20)	0.007
DemQol (Median (IQR))	100 (83-108)	98.5 (85.25-107)	NS

3.6.6.5 Adherence

80% reported never missing a dose of antihypertensive, table 3.47 below summarises other reports.

Table 3.47 Frequency of missed doses

Frequency of missed doses in a month	**N (%)**
Never	144 (80%)
Once	18 (10%)
Twice	11 (6%)
Thrice	6 (3%)
Weekly	0
Most Days	0
Daily	1 (0.6%)

3.6.6.6 Anticholinergic burden

The median anticholinergic burden (ACB) score was 1 (IQR 0-2). 99 (55%) of the participants had an ACB score of one or more, while 33 (18%) had a cumulative ACB score of three or more. Antihypertensives contributed to the ACB score in 25 of the 99 participants with an ACB score of one or more. Where antihypertensives with anticholinergic effects were prescribed they accounted for a mean of 73% of the ACB score.

All the contributing antihypertensives had an ACB score of 1. Atenolol was the most frequently used antihypertensive with anticholinergic effects, table 3.48 summarises the contributing antihypertensives.

Table 3.48 Frequency of antihypertensives with anticholinergic burden scores

Antihypertensive	Frequency
Atenolol	16
Captopril	1
Chlorthalidone	2
Diltiazem	6
Hydralazine	2
Nifedipine	4

3.6.7 Comparison of baseline variables by antihypertensive use

The 157 participants taking antihypertensives were less likely to have a postural drop in blood pressure, and were more likely to have a higher MMSE and a higher BI than those not prescribed an antihypertensive. The differences in baseline variable by antihypertensive use are summarised in table 3.49 below.

Table 3.49 Comparison of baseline variables by antihypertensive use

Variable	Antihypertensive	Not on antihypertensive	Significance
Number	157 (86.7%)	23 (12.7%)	
Site type	70 (44.6%) GP 87 (55.4%) Memory clinic	15 (65.2%) GP 8 (34.8%) Memory clinic	NS
Age (mean (SD))	81.7 (6.4)	83.3 (5.8)	NS
Sex (n(%))	108 (68.8%) female	18 (78.3%) female	NS
Residence (n(%))	138 (87.9%) OH, 18 (11.5%) RH, 1 (0.6%) NH	19 (82.6%) OH, 4 (17.4%) RH 0 (0) NH	NS
Packyears (Mean (SD))	11.5 (20.0)	16.8 (31.4)	NS
Age on finishing full time education (Mean (SD))	15.8 (2.4)	15.4 (2.3)	NS

Marital status (n(%))	7 (4.5%) S, 98 (62.4%) M, 47 (29.9%) W, 6 (3.2%) D	0 (0) S, 13 (56.5%) M, 9 (39.1%) W, 1 (4.3%) D	NS
Ethnicity	149 (94.9%) White British, 4 (2.5%) White Irish, 2 (1.3%) Indian, 1 (0.6%) Any other ethnic group 1 (0.6%) Any other white background,	21 (91.3%) White British, 1 (4.3%) White Irish, 0 (0) Indian 0 (0) Any other ethnic group 1 (4.3%) Any other white	NS
Falls / 1000 patientyears (Mean(SD))	1960(6040)	1900 (3790)	NS
Falls (prevalence) (n (%))	35 (22%)	6 (26%)	NS
Weight (Mean(SD))	68.8 (15.9)	64.8 (14.2)	NS
Height (Mean(SD))	164 (10.0)	162 (10.1)	NS
BMI (Mean (SD))	25.4 (5.1)	24.4 (5.2)	NS
Blood pressure (Mean (SD))	141/78 (22/12)	141/78 (17/11)	NS

Postural drop (n=174)	13 (8.6%)	6 (26.1%)	0.009 (χ^2)
Number of medications (Median (IQR))	7 (5-9)	5 (3-8)	NS
Number of medical diagnoses (Median (IQR))	5 (3-7)	7 (3-8)	NS
Charlson Score (Age adjusted)	5 (5-7)	6 (5-6)	NS
MMSE (Median (IQR))	23 (19-26)	20 (14-24)	0.023
Barthel (Median (IQR))	20 (17-20)	18 (10-20)	0.027
DemQol (Median (IQR))	100 (85-106)	95.5 (81-104)	NS

3.6.8 Follow-up data

Data from the follow-up period for participants with missing follow ups was combined to produce average monthly values for each variable, this was then converted into a 6 months equivalent value to aid inclusion and analysis. 6 month values were used throughout unless otherwise stated. Four participants withdrew before any follow up data was collected therefore all follow-up data displayed is from a total population of 177 participants of whom 155 were taking at least one antihypertensive.

3.6.8.1 Contact with the health service

GPs were the most frequently encountered aspect of the health service in this group of people with a total of 475 contacts in 6 months. Hospital admissions and ambulance call-outs were relatively unusual (table 3.50).

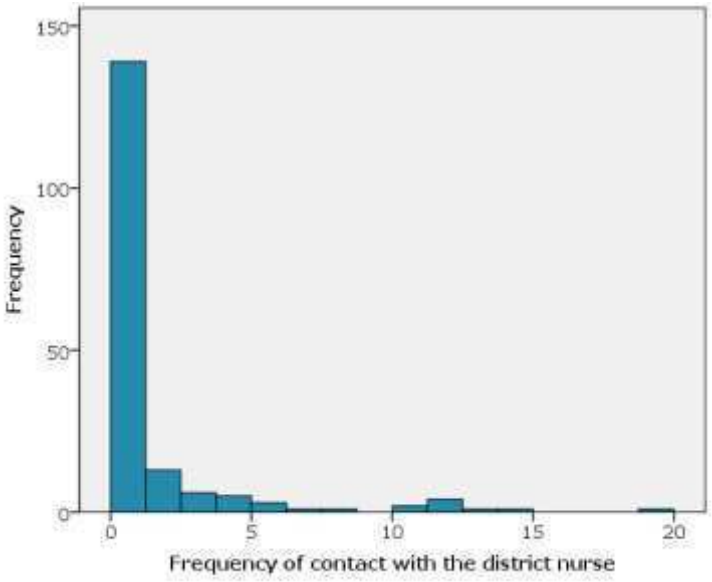
Table 3.50 Contact with the health service

Contact with	Total contacts in 6 months	Number of participants (%)	Median	IQR
District Nurse	243	68 (38%)	0	0-1
GP	475	135 (76%)	2	1-4
Ambulance	61	34 (19%)	0	0-0
Hospital admission	65	36 (20%)	0	0-0

3.6.8.1.1 District nurse

68 out of 177 participants (38%) saw the district nurse at least once during follow-up. For these 68 a median of 2 contacts (IQR 1-4) was made. Figure 3.12 summarises the frequency of contact.

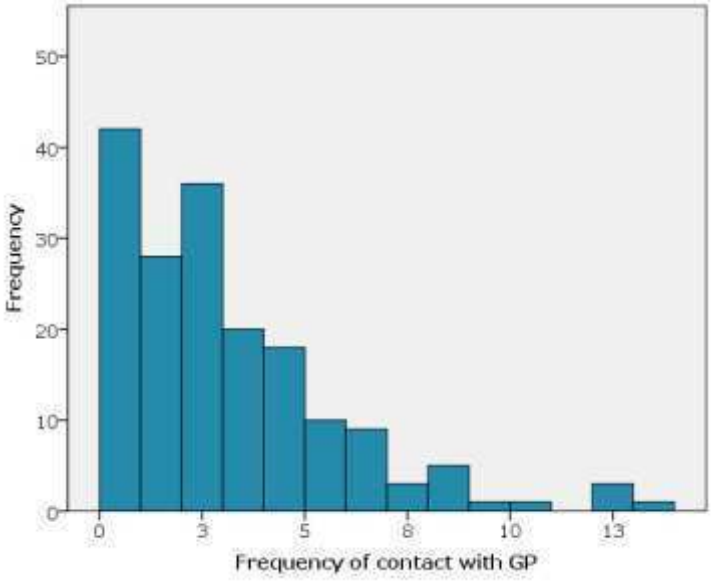
Figure 3.12 Frequency of contact with the district nurse



3.6.8.1.2 GP

135 participants out of 177 (76%) saw their GP at least once during follow-up. For these 135 a median of 3 (2-4) contacts occurred. Figure 3.13 summarises the frequency of contact.

Figure 3.13 Frequency of contact with GP



3.6.8.1.3 Ambulance and hospital admissions

34 (19%) participants reported contact with the ambulance service, either having called directly or following GP input. These 34 participants all ended up being admitted to hospital. Of these 34 a median of 1.2 (IQR 1-2) contacts occurred over 6 months. (Figure 3.14 summarises the frequency of contact with ambulance services)

An additional 2 participants were admitted to hospital without contact with the ambulance service, making a total of 36 (20%) participants admitted. Of these a median of 1.35 (1-2.345) admissions occurred over 6 months. (Figure 3.15 summarises the frequency of hospital admissions)

Figure 3.14 Frequency of contact with ambulance services (excluding no contact)

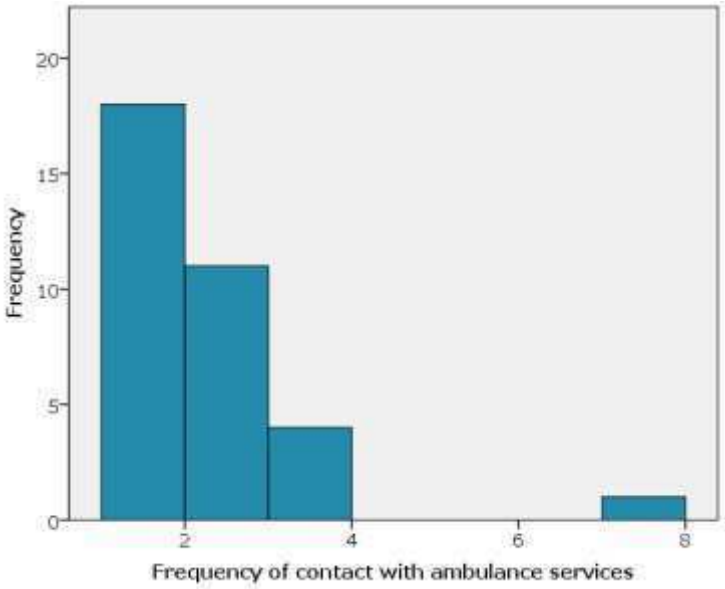
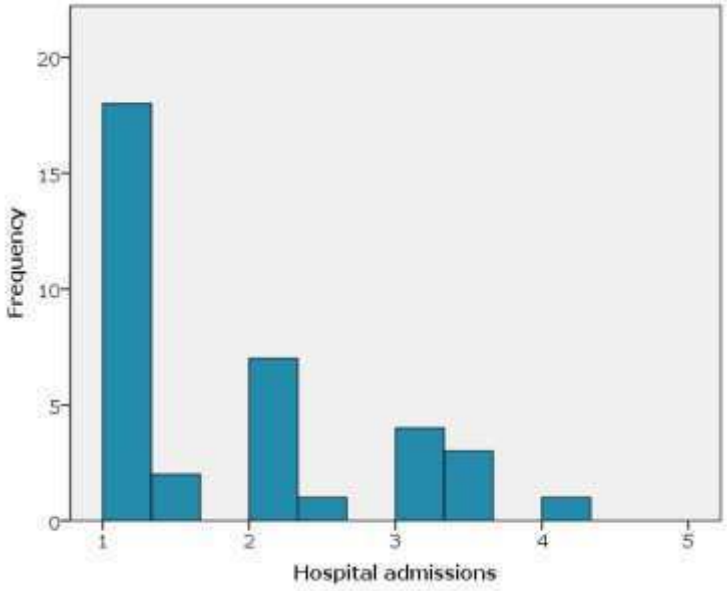


Figure 3.15 Frequency of hospital admissions (excluding no admissions)



3.6.8.2 Adverse medical events

Falls were the most commonly reported adverse event during follow up with a total of 214 occurring over 6 months. Table 3.51 below summarises the adverse medical events as reported.

Table 3.51 Frequency of adverse medical events

Event	Total events in 6 months	Number of participants (%)
Falls	214	71 (40%)
Recurrent Falls (≥2)	-	30 (17%)
Blackouts	17	8 (5%)
Fractures	3	3 (2%)
Heart attack	1	1 (0.6%)
Heart failure	5	3 (2%)
Stroke	6	4 (2%)
Death	8	8 (5%)

3.6.8.2.1 Comparison of adverse events in those taking antihypertensives (n=155) with benchmark figures

The rate per 1000 patient-years of heart failure, stroke and death in those on antihypertensives was higher in the study cohort than in the HYVET study. The rate of falls with fractures was higher in the cohort than in the Tinetti group and the rate of blackouts was significantly higher than the reported rate in the SHEP study. The proportion experiencing recurrent falls was higher than in the REGARDS study population. (See table 3.52).

Table 3.52 Comparison of adverse events with benchmark data

Event	Rate (per 1000ptyr) / proportion (%)	95% CI (per 1000ptyr) / proportion (%)	Bench - marked rate / proportion	Bench - marked 95% CI	Sig
Recurrent falls	17%	11% - 22%	7.3%	6% - 8%	S
Blackouts	168	157-178	4.9	4.9 – 4.9	S
Fractures	41	36-46	30.8	30.8 - 30.8	S
Heart attack	-	-	2.2	2.2 – 2.2	-
Heart failure	39	34-44	5.3	5.3 – 5.3	S
Stroke	39	34-44	12.4	12.3 – 12.5	S
Death	65	58-71	47.2	47.1 – 47.3	S

3.6.8.3 Symptoms

For the purposes of analysis the symptom scores were combined into an average monthly prevalence. Tiredness was the most prevalent symptom (63%).

3.6.8.3.1 Comparison with benchmark data

In comparison with the benchmark data participants taking antihypertensives reported a higher average monthly prevalence of skin rash / itchiness, constipation, nervousness / anxiety and tiredness and a lower prevalence of palpitations and flushing during follow up. The comparison is summarised in table 3.53.

Table 3.53 Comparison of symptom prevalence with benchmark data

Symptom	Prevalence (%)	95% CI (%)	Bench - mark Prevalence	Bench -mark 95% CI	Sig
Headache	23%	17%-30%	29%	26% - 32%	NS
Dizziness	26%	19%-33%	34%	31% - 37%	NS
Swollen ankles	25%	18%-32%	30%	27% - 33%	NS
Cold hands	34%	26% - 42%	34%	31% - 37%	NS
Flushing	15%	9% - 21%	26%	23% - 29%	S
Skin rash / itchiness	27%	20% - 34%	16%	14% - 18%	S
Cough	29%	21% - 37%	19%	17% - 21%	NS
Dry mouth	26%	18% - 33%	32%	29% - 35%	NS
Nausea	10%	5% - 14%	14%	12% - 16%	NS
Diarrhoea	17%	11% - 23%	13%	11% - 15%	NS
Constipation	22%	15% - 29%	11%	9% - 13%	S
Palpitations	7%	3% - 11%	25%	22% - 28%	S
Nervousness	40%	32% - 48%	21%	18% - 24%	S
Tiredness	63%	55% - 71%	41%	38% - 44%	S
Sleep problems	33%	25% - 41%	26%	23% - 29%	NS
Frequent micturition	38%	30% - 46%	38%	35% - 41%	NS

3.7 Discussion

3.7.1 Recruitment

The rate of recruitment to the study was low in the GP recruitment arm where 92% of the potential participants did not respond to the study invitation. This put the study population at high risk of significant selection bias and limited the generalisability of its findings. The study participants that were recruited were predominantly older, white, married and living in their own homes. The population reported high levels of medication use and multiple medical diagnoses. There was a preponderance of mild-moderate dementia in the study population. Although the majority (56%) of the participants were dependent for at least one ADL the remainder scored 20/20 on the BI suggesting independence in basic ADLs but also a significant ceiling effect. Application of the study's findings was therefore restricted to a community dwelling, mildly cognitively impaired and mildly disabled group.

The method used to identify and target GP practices with higher numbers of potential participants produced estimates that correlated well with the actual numbers. The practices involved in the Nottingham site, where practice involvement was prioritised using this method, had on average a higher number of potential participants.

Comparison between the groups recruited via GP practices and via memory clinics revealed a number of differences. People recruited via GP reported a higher falls rate, took fewer antihypertensives

(median 1 vs 2), had more medical diagnoses (median 5.5 vs 4), were more likely to have a diagnosis of vascular or unspecified dementia, less likely to have a diagnosis of Alzheimer's and were more dependent with basic ADLs (median BI 19 vs 20). However, with rates of dementia diagnosis varying (between 39% and 75%)[142] across the country, these observations are potentially confounded by geographical variation in practice.

3.7.2 Missing data

36 discrete variables were collected at baseline from 181 participants. Weight was the most commonly missing variable, in six cases this was missing due to unavailable or faulty equipment at two of the research sites (Leicester and Surrey and Borders), and in one case due to the participant's immobility. The two missing height measurements were due to the unavailability of measuring equipment. The seven missing blood pressure measurements occurred when patients were unable to stand (one) or did not tolerate having their BP measured (six). Excluding equipment problems, comparison between participants with missing data to those without, revealed lower MMSE scores and lower Barthel indices in those with missing data. No baseline variable had more than 5% missing values and so the impact of this missing data is unlikely to have been statistically significant.

Excluding deaths and withdrawals follow-up data was missing from 31 participants. This equated to 46.5 months missing out of a total 930.25 months F/U data gathered. Overall therefore 5.0% was

missing. Given the relatively small proportion of missing data it is unlikely that this will have produced significant bias in the results.

3.7.3 Description of the study population

3.7.3.1 Medical diagnoses

Multi-morbidity was common in the study population with a median of five diagnoses per participant. 13 out of the top 20 diagnoses reported were chronic diseases and cerebrovascular and cardiovascular diseases were common. Falls were no more common than in the general population with 23% (95% CI 17% - 29%) of study participants having reported at least one fall in the three months prior to baseline assessment compared to 23-29% of the general population aged over 65 (Health Survey for England 2005[143]). Those who did report falls fell a median of 2 (IQR 1-3) times.

When compared to the findings of the literature review, the study population had a higher prevalence of diabetes (19.4% vs 12.7%), and heart failure (12.8% vs 9.3%) but a lower prevalence of ischaemic heart disease (17.8% vs 27%) and cerebrovascular disease (20.6% vs 26%). However, all the study values lay within the range of reported values in the literature review studies, (diabetes 6-32%, heart failure 9-23%, ischaemic heart disease 6-57%, and cerebrovascular disease 12-26%), which suggested that these findings were not untypical for this population. Compared to the findings of the Health Survey for England 2005[143] stroke and

diabetes were more common and arthritis less common in the study population in women while there was no significant difference in men.

3.7.3.2 Medications

Study participants took a median of 7 medications. Polypharmacy, defined as 4 or more medications, was experienced by the majority (87%), while 21% took 10 or more medications. In comparison, the Health Survey for England 2013 reported that just over half of those aged over 65 in the general population took three or more tablets[144].

The same survey reported that lipid lowering medications, followed by antiplatelets, analgesics, PPIs, antidiabetic medications and antidepressants were commonly used drug classes; a similar finding to this study.

Within the study population the most commonly prescribed group of medications (excluding antihypertensives) were drugs for dementia, with 69% of the study population taking one. Donepezil was the most commonly prescribed drug (41%), followed by aspirin (34%), simvastatin (33%), paracetamol (29%) and calcium-vitamin D (25%). Given that the study population all had diagnoses of dementia, it is unsurprising that drugs for this condition were the most commonly prescribed. However it is curious that a diagnosis of Alzheimer's dementia was present in only 56% of the participants, and of those with a diagnosis of vascular dementia five were prescribed a drug for Alzheimer's dementia. This suggests that

either there is poor documentation of diagnoses or that these agents are being used outside of their standard remit.

The most commonly prescribed psychoactive agent was trazadone (3%). Risperidone, amisulpride, aripiprazole and quetiapine were also used. In total 9% of the study population were taking an anti-psychotic. This relatively low level is likely to reflect the predominance of mild-moderate dementia in the study group. Increasing severity of cognitive impairment, as measured by MMSE, was not associated with increased anti-psychotic use.

3.7.3.2.1 Anticholinergic burden

The majority, 99 (55%), of the participants had an ACB score of one or more. Antihypertensives contributed to this score in 25 of these 99 participants. Where antihypertensives contributed they accounted for a mean of 73% of the total ACB score in that individual. Potentially these medications could be replaced by alternative antihypertensives without anticholinergic effects.

3.7.3.3 Cognition

When the study population was grouped by MMSE score into normal (27-30), mild (21-26), moderate (10-20) and severe (0-9) the largest group was of people with a mild score (42%), then moderate (27%), normal (21%) and finally severe (10%). The fact that only a small minority of study participants had severe dementia had an important impact on the generalisability of the study's findings.

3.7.3.4 Dependency with basic ADLs

The majority (56% (95% CI 49%-63%)) of the study population needed help with at least one ADL in comparison to 28% (95% CI 26%-30%) of the general population over 65 (National Health Survey 2013)[144]. A substantial minority had ongoing problems which had the potential to have a significant impact on day-to-day living, including the 25% who needed help with bathing and the 12% with urinary incontinence. That 46% of participants scored 20/20 in the BI is likely to reflect the ceiling effect of the index. The population were not as dependent as had been anticipated when the study was designed but were more dependent than the general population.

3.7.4 The use of antihypertensive agents

3.7.4.1 Classes used and comparison with benchmark data

ACEi were the most commonly prescribed class of antihypertensive, and this may well reflect the high prevalence of comorbidities such as diabetes and heart failure where an ACEi or ARB would be mandated. The high prevalence of beta-blockers may similarly relate to comorbidities or potentially to a lag in treatment changes, particularly for those taking older agents such as atenolol and propranolol.

The numbers of agents and classes used was, apart from diuretics, no different to that used in the general population as described in the Health Survey for England 2011.

3.7.4.2 Dosage and comparison with the DDD

The doses of the majority of the antihypertensives used by participants were not significantly different from the average maintenance dose defined by the DDD. While all the doses prescribed were within the BNF limits, the mean ramipril dose prescribed was 2.5 times higher than the DDD, while the mean bisoprolol dose was a third of the DDD and the mean atenolol dose was slightly lower (50mg vs 75mg).

3.7.4.3 Proportion treated and number of antihypertensives used

There was no difference in the proportion of participants on treatment for hypertension compared to the general population as described in the Health Survey for England 2011. However, this was a higher proportion (87%) than had been anticipated from the literature review (73% range 48-85%) and this could be a result of selection bias.

3.7.4.4 Achievement of target BP and comparison with benchmark data

Over half (58%) of the study population had recorded BP below the target and this was not significantly different from the general population as reported in the Health Survey of England 2011. There was no significant difference in the number of antihypertensives used between those achieving and those not achieving target, but those achieving target BP took more medications overall. Although there was no difference in cognitive function between these groups, those achieving target BP were more functionally dependent with a lower BI. Falls and orthostatic hypotension were more prevalent in those achieving target blood pressures compared to those not

achieving target BP (26% vs 19% and 15% vs 6% respectively) but this was not statistically significant. Increasing numbers of antihypertensives were not associated with lower systolic blood pressures; this observation is compatible with ongoing careful management of treatment.

3.7.4.5 Comparison of baseline metrics by antihypertensive use

Those not taking antihypertensives were more dependent and cognitively more impaired than those taking antihypertensives and experienced more postural hypotension. This confirmed preliminary findings previously presented[145] (Appendix VI). There was no significant difference in mean blood pressure between the groups. Curiously there was also no significant difference in the overall number of medications being used between the groups.

3.7.5 Follow up data

3.7.5.1 Health service use

The study participants made substantial use of the health service during the 6 month follow up period with 475 GP appointments, 243 district nurse visits and 65 hospital admissions reported. In terms of GP appointments this equates to an average of 6.6 appointments per person per year (95% CI 6.6-6.7), this compares to a median rate of 5.4 (IQR 4.8-6.1) appointments per year in 2008[146] for the general population.

3.7.5.2 Adverse events

The rate of heart failure, stroke and death in those on antihypertensive treatment was higher in the study population than in the HYVET study. The rate of falls with fractures, blackouts and

recurrent falls in those on antihypertensives was higher in the study population than in the Tinetti study, SHEP study and REGARDS study respectively. Skin rash / itchiness, constipation, nervousness / anxiety and tiredness symptoms were more commonly reported in the study population than in the general population. In the original benchmark population, which compared symptom prevalence in treated and untreated people with hypertension, none of these symptoms was associated with antihypertensive use[62]. However all, with the exception of skin rash / itching, have been reported to be more common in people with dementia[147-149].

The rates of cardiovascular events seen in this study were higher than seen during the HYVET study, although the mean blood pressures were no different (HYVET 140/72 vs HIND 140/78 (SD +/- 23/13)). This is an important observation but one which may be due to a number of reasons.

Firstly, event data was based on patient reports rather than hard evidence and this may have resulted in over reporting and hence a higher apparent rate than in the benchmark trials.

Secondly, this population had a higher baseline prevalence of adverse cardiovascular events (stroke 16%, MI 13%, heart failure 13%) than the HYVET population (stroke 6.7%, MI 3.1%, heart failure 2.9%) [41] as well as dementia, thus potentially resulting in a higher underlying cardiovascular risk. It is possible that the cardiovascular event rate without antihypertensive treatment would have been even higher than that observed in this treated group.

Lastly the higher cardiovascular event rate raises the possibility that treatment to similar blood pressures as in the antihypertensive trials does not provide the same benefits in this population. Given, in addition, the high prevalence of recurrent falls and blackouts, which were reported in this study and which are commonly associated with antihypertensive treatment[52,53,150], the risk / benefit ratio of antihypertensive treatment in this population appears less certain.

3.7.6 Strengths and limitations of the study

The primary strength of this study is that it fills a gap in the literature surrounding the treatment of hypertension in people with dementia which, as was demonstrated in the literature review, has not been extensively investigated in the UK. The study has recruited participants from a variety of settings and geographical locations so its findings are likely to be applicable across the whole of the UK. The average age of participants is very similar to that of the two large UK database studies[82,83] and the proportion achieving target BP is almost identical to that in the only other study to report this[80]. In contrast to the database studies, this project has directly linked contemporaneous clinical assessment with current treatment, something which has not been done in the UK before.

The most important limitations affecting the study were issues around identification and recruitment and the significant potential for selection bias as a result. Firstly, participants were recruited on the basis of recorded diagnoses of hypertension and dementia. However, on average, 52% of people with dementia in England were undiagnosed in 2012/13[142]. Hypertension shows similar

difficulties with diagnosis and appears to have been undiagnosed in between 40% and 50% of people with high blood pressure when results of the GP Quality Outcomes Framework and Health Survey for England were compared in 2012[133]. Secondly, only 8% of those who were potentially eligible in the GP arm were recruited and recruitment from some study centres was very limited, for instance in Fife. It is likely that the study population is atypical of the bulk of people with hypertension and dementia, with people with severe cognitive impairment being particularly under-represented. The generalisability of these findings will therefore be restricted to those with milder cognitive impairment.

Blood pressure readings were based on a single visit. This increased the risk of an inaccurate measurement and affected the reliability of the blood pressure data.

The use of literature derived benchmarks as a comparison was not ideal. Although effort was taken to ensure that the comparison observational study populations were similar to the cohort population this method lacked the rigor of a contemporaneously recruited control group. Comparison to the outcomes reported in the large antihypertensive studies, although pertinent, may not have been ideal given that these study populations were physiologically fitter than the general population. Although this does again limit the usefulness of these findings, some helpful information was still derived from the comparison.

3.8 Conclusions

This study aimed to help answer the questions first set out in chapter 1. Some material had been provided by the literature review, but the lack of studies reporting on practice in the UK limited the usefulness of these findings in answering the research questions. The findings of this study are difficult to generalise due to the potential for selection bias produced by the recruitment method. However these findings do provide information relevant to a group of community dwelling older people with mild dementia and mild dependency.

This study has shown that despite the lack of a firm evidence base for antihypertensive treatment in people with dementia, there was no evidence that people with relatively mild dementia were less likely to be treated for hypertension than the general population and when treated were as likely to achieve target blood pressure. Thus helping to answer questions (ii) *(Is hypertension in people with dementia more or less likely to be treated than in the general UK hypertensive population?)* and (iv) *(Is hypertension in people with dementia treated more or less effectively than in the general UK population?)*.

In addition to a detailed description of the medications and combinations used to treat hypertension it showed that they received the same number of drugs from the same antihypertensive classes as the general population with hypertension helping to answer question (i) *(How is hypertension in people with dementia*

treated in the UK and how does this compare to the treatment of hypertension in the general population?).

Factors associated with treatment and non-treatment of hypertension were identified, answering question (iii) *(What factors are associated with treatment and non-treatment of blood pressure in people with dementia?)*.

During prospective follow up this population experienced adverse events at a higher rate and had a higher prevalence of adverse symptoms than the benchmark populations, thus helping to answer question (v) *(Are the adverse events and symptoms, including cardiovascular events, experienced by people with dementia on treatment for hypertension more or less frequent than in treated hypertensive people without dementia?)*

This study added to the literature by providing a detailed description of a UK population of people with hypertension and dementia, their treatment and experience of adverse events, and did so by using contemporaneous data for the first time.

These results imply that UK clinicians treat high blood pressure in people with mild-moderate dementia in the same way and to the same standard as the general population. This population reported higher rates of cardiovascular events, falls, and syncope than in the trials, this may relate to reporting bias or a higher intrinsic risk of cardiovascular events but it raises the possibility of treatment attenuation and also of increased risk of harm from treatment,

potentially unsettling the balance of risk and benefit observed in the trials in this population.

Chapter 4

Conclusions

4.1 The treatment of hypertension in people with dementia

Chapter 1 provided a working definition of hypertension and explored how the natural history of blood pressure differs in the context of dementia. It made the case that dementia was a relevant co-pathology in the treatment of hypertension. Of particular importance was the significant fall in blood pressure over time, starting before clinically apparent dementia, and continuing during the dementing process. This drop was of a degree that could move an individual from a treatment group to a non-treatment group according to guidelines and so had implications for clinicians. It hypothesised that the presence of dementia itself might indicate a higher general cardiovascular risk. It highlighted the lack of an evidence base in people with established dementia and considered the potential adverse effects of antihypertensive treatment. With a limited evidence base, guidelines made no specific recommendations in the context of dementia, apart from suggesting an individualised approach. Within the scope of this guidance and in the context of the reward and incentive scheme QOF, General Practitioners, who provide the majority of medical oversight of the management of hypertension in the UK, reported finding treatment decision making in people with dementia challenging.

This thesis reported on a period of research which formed part of a programme of research looking at hypertension in people with dementia. The purpose of the research presented in this thesis was to describe current treatment patterns and adverse event rates. It sought to answer the following questions:

(i) How is hypertension in people with dementia treated in the UK and in general and how does this compare to the treatment of hypertension in the general population?

(ii) Is hypertension in people with dementia more or less likely to be treated than in the general UK hypertensive population?

(iii) What factors are associated with treatment and non-treatment of blood pressure in people with dementia?

(iv) Is hypertension in people with dementia treated more or less effectively than in the general UK population?

(v) Are the adverse events and symptoms, including cardiovascular events, experienced by people with dementia on treatment for hypertension more or less frequent than in treated hypertensive people without dementia?

The first stage in this process was to conduct a review of the literature to determine whether these questions had previously been examined and to identify previous attempts to describe this

population and its treatment. This process and its findings were described in chapter 2.

The second stage was to conduct an observational study to examine the approach to treatment within the UK and to compare the rates of adverse events experienced by this population with the general population. This was described in chapter 3.

Chapter 2 presented a systematic review of observational studies describing the treatment of hypertension in people with dementia. The review identified 13 studies only two of which had been carried out in the UK. Neither of these had deliberately set out to describe the treatment of hypertension in people with dementia. Notwithstanding this point the review demonstrated that hypertension was common in people with dementia (46%) and was treated in the majority (73%) with standard antihypertensive classes. The review found no evidence that hypertension in people with dementia was treated any differently to that in the general population at the time. Only one study reported on the achievement of target blood pressure with just over half achieving this, a higher rate than in the general population at the time.

The literature review provided important information towards answering questions (i) (*How is hypertension in people with dementia treated in the UK and in general and how does this compare to the treatment of hypertension in the general population?*), (ii) (*Is hypertension in people with dementia more or*

less likely to be treated than in the general UK hypertensive population?) and (iv) (*Is hypertension in people with dementia treated more or less effectively than in the general UK population?*). However, the relative under-representation of the UK in the review meant a good understanding of practice within this country was still lacking. The specific detail of treatment methods and potential adverse events would need further work and a cohort study was proposed to help answer the remaining questions.

Chapter 3 reported the findings of the HIND cohort study, a multi-centre observational study involving 181 participants from 8 sites in the UK, followed up over a period of 6 months. The study provided a detailed description of a population of people with diagnoses of dementia and hypertension. The population described were largely community dwelling with mild to moderate dementia but with significant comorbidity and with the majority being dependant for at least one ADL.

There were challenges with the recruitment process and only a small fraction of potential participants that were identified via GP practices were recruited. People with more severe cognitive and physical dependency were not so well represented in the study population. These findings therefore should not be applied to people with severe dementia and dependency.

However the study did demonstrate that, for this group of people, there was no difference in the treatment rate between the study

population and the general population and no difference in the proportion achieving target blood pressures helping to provide an answer for questions (ii) (*Is hypertension in people with dementia more or less likely to be treated than in the general UK hypertensive population?*) and (iv) (*Is hypertension in people with dementia treated more or less effectively than in the general UK population?*). Participants were treated with standard antihypertensive classes, and, apart from a lower level of diuretic prescription, the proportions taking each class were no different from the general population. This helped to answer question (i) (*How is hypertension in people with dementia treated in the UK and in general and how does this compare to the treatment of hypertension in the general population?*).

The study explored the factors associated with treatment and non-treatment of blood pressure showing that participants who were not prescribed antihypertensives were more likely to experience orthostatic hypotension, had a lower MMSE score and a lower BI than those prescribed antihypertensives and thus helped to answer question (iii) (*What factors are associated with treatment and non-treatment of blood pressure in people with dementia?*).

The study demonstrated a higher rate of incident heart failure, stroke and death compared to the results of HYVET[41]. It presented evidence of a higher rate of falls with fractures than in the benchmark Tinetti study[140], a higher proportion reporting recurrent falls than in the REGARDS study[139] and a higher rate of blackouts

than in the SHEP study[135]. The study reported that over half (57.1%) of the participants experienced at least one adverse symptom daily or on most days. The study provided evidence that the average monthly prevalence of skin rash / itchiness, constipation, nervousness / anxiety and tiredness was higher in the cohort than in the benchmark population[62]. These findings helped to answer question (v) (*Are the adverse events and symptoms, including cardiovascular events, experienced by people with dementia on treatment for hypertension more or less frequent than in treated hypertensive people without dementia?)* but it also raised the possibility of treatment attenuation and of increased risk of harm from treatment, potentially unsettling the balance of risk and benefit observed in the original antihypertensive trials.

4.2 Conclusions

Although the findings of the cohort study have restricted generalisability the research presented in this thesis has provided answers to the questions posited in chapter 1. This study added to the literature by providing the first systemic review of observational studies describing the treatment of hypertension in people with dementia and by providing a detailed description of a UK population of people with hypertension and dementia, their treatment and experience of adverse events, and did so using contemporaneous data for the first time.

High blood pressure in people with mild-moderate dementia is treated no differently to high blood pressure in the general population and to a similar standard. However, the population of people with dementia experience higher rates of cardiovascular events and higher rates of recurrent falls, syncope and fractures than in benchmark studies despite similar blood pressures. This may reflect issues with reporting bias or an intrinsically higher cardiovascular risk in this group but it is possible that the benefits of lower blood pressures, achieved using antihypertensive treatment, might be attenuated, while the risks of treatment may be elevated.

One of the major failings of research in older people is the misapplication of findings from physiologically robust, non-comorbid older people who are not exposed to polypharmacy, to those who are frail, multi-morbid and on high doses of multiple drugs[151]. The HYVET study population was entirely community dwelling and

cognitively intact with a lower prevalence of stroke, IHD, heart failure and diabetes than the HIND study population. While it is on the basis of the findings of HYVET that the benefits of antihypertensive therapy are felt to extend to the oldest old the findings of the research presented here lead to some reservations that the assumptions justifying antihypertensive treatment apply in this less robust group- the population with co-existing dementia.

This research occurred in the context of a growing body of work which has provided evidence that suggests that the effect of blood pressure modification is altered in the presence of co-existing frailty. This evidence potentially supports the hypoperfusion hypothesis discussed in chapter 1.

Odden and colleagues found that walking speed (a simple measure of frailty) modified the association of high blood pressure with mortality such that in those unable to complete the walk test high blood pressure conferred a survival advantage, whilst in faster walkers the inverse was the case[152].

The PARTAGE group raised concern about the use of antihypertensive agents in less robust populations having found an association between increased mortality and a systolic BP below 130mmHg in care home residents taking two or more antihypertensive agents[101].

Ogliari and colleagues reported on a longitudinal outpatient cohort of adults aged over 75. They found that in those with impaired ADLs

and MMSE a higher systolic blood pressure was associated with reduced mortality[153].

The findings of the research presented here add to this picture and justify further work to better understand the risk-benefit ratio in people with dementia. Should further work confirm these findings then this will need to feed in to future updates of antihypertensive guidelines and would have important implications for any future changes to incentive schemes such as QOF and for dementia prevention strategies.

4.2.1 Implications for researchers

The findings of this research have implications mainly for researchers.

Firstly the cohort study demonstrated the difficulty in recruiting people with dementia. Future research in this area should explore alternative methods of recruitment or make use of alternative data sources such as large scale population databases to try to ensure that study findings are not invalidated by selection bias.

Secondly the population with more advanced dementia was under-represented in the research presented here, future attempts to describe the treatment of hypertension in people with dementia should focus on this group.

4.2.3 Implications for clinicians

There was no indication from the research presented here to modify the treatment of hypertension in people with dementia now. However some advice can be provided to clinicians managing high blood pressure in people with dementia based on the work covered in this thesis.

Firstly consent for antihypertensive treatment in people with dementia should be taken carefully and involve mention of the problems with the evidence base and the degrees of uncertainty around treatment benefit and risks which this study helps to illuminate through providing relevant data of the actual risks facing such patients.

Secondly clinicians should look carefully for orthostatic hypotension, which is more common in people with dementia, at diagnosis and during follow-up and modify treatment accordingly.

Thirdly clinicians managing hypertension in people with dementia should be aware of the natural history of blood pressure in dementia, i.e. that BP falls over time, and monitor blood pressure measurements more frequently than in those without dementia. Home blood pressure monitoring is a feasible approach in people with cognitive impairment[154] and may be a helpful resource to improve monitoring.

Fourthly clinicians should be aware that a number of antihypertensives contribute to anticholinergic burden. If possible antihypertensives with anticholinergic effects should be avoided in

people with dementia and ongoing prescriptions should be reviewed regularly.

4.2.4 Policy implications

On the basis of the research presented here there is no compelling indication to modify current policy approaches. However, should further work add to the evidence that the risk-benefit ratio of antihypertensive treatment in people with dementia, or in frailty syndromes generally, is not clear cut or even deleterious then guidelines, public health drivers such as QOF and dementia prevention strategies would need to be modified.

The evidence that treating high blood pressure in the physiologically robust is beneficial is substantial and QOF and similar systems have an important role to play in supporting this. However in physically and cognitively frailer individuals the evidence is not certain and until more definitive data are available policy and guidelines should continue to support an individualised approach.

4.3 Future work

As has been said, the finding that the rate of cardiovascular events and adverse events was higher in the cohort study than in the benchmark studies potentially has implications for the assumption that the beneficial risk-benefit ratio of antihypertensive treatment seen in the trials applies in the population of people with dementia. Definitive work to test this assumption further can only be justified should more robust evidence of uncertainty about the risk-benefit ratio be found. However the challenges of recruiting people with dementia, particularly of people with more advanced disease, need to be addressed if this question is to be resolved.

The next stage in examining the risk-benefit ratio in more detail but using an approach which circumvents the issues around recruitment and selection bias would be to use a primary care database such as The Health Improvement Network (THIN). The database includes a large number of people with dementia - 54816 people aged 60 to 89 with incident dementia (defined according to diagnosis or medication) from 2001 to 2010 were identified in a study on incontinence in patients with dementia using this database[155]. A similar method to that used by Tinetti's group when they reported fracture rates in older people with treated hypertension could be used[140]. This involved propensity score matching, with individual matching of treated and untreated patients according to their propensity score (likelihood) of receiving treatment to provide balance between treated and untreated groups. Data from a cohort derived from the database could then be interrogated to examine

the association between exposure to antihypertensive therapy and cardiovascular and adverse events.

To complement the database work and to explore the underlying ideas and concerns around current practice in more detail qualitative work looking at practitioners' and patients' understanding and beliefs around the treatment of high blood pressure could be undertaken. The design and specific research questions could be developed with integral PPI involvement and input from experienced qualitative researchers from inception to ensure relevance and quality.

If the database work were to provide further evidence of uncertainty and if the qualitative work confirmed the importance of this area to patients and practitioners, then it would provide further justification to continue to explore the risk-benefit ratio in this population.

4.4 Conclusion

In conclusion in an area where clinicians are acting without a firm evidence base and where there are theoretical concerns around the potential side effects of antihypertensive use, clinicians treat hypertension in people with dementia much as they do in people without dementia and to a similar standard. The higher rate of cardiovascular events and adverse events experienced by this population leads to some reservations that the assumptions justifying treatment hold in this group. Future research work should examine this and its implications in more detail.

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Appendix I

Glossary of abbreviations

ABPM= Ambulatory blood pressure monitoring

ACC= American College of Cardiology

ACEi= Angiotensin Converting Enzyme inhibitor

ACE-III= Addenbrooke's Cognitive Examination- III

AD= Alzheimer's disease

ADL= Activities of Daily Living

ADRQL= Alzheimer disease related quality of life

AHA= American Heart Association

AHRQ= Agency for Healthcare Research and Quality

ARB= Angiotensin Receptor Blocker

ARMD= Age Related Macular Degeneration

BB= Beta-blocker

BGS= British Geriatrics Society

BI= Barthel Index

BMI= Body Mass Index

BNF= British National Formulary

BP= Blood pressure

CBS= Cornell-Brown scale for quality of life in dementia

CCB= Calcium Channel Blocker

CCG= Clinical Commissioning Group

CGA= Comprehensive Geriatric Assessment

ChI= Charlson Index

CI= Confidence interval

CKD= Chronic Kidney Disease

CONSORT= Consolidated Standard of Supporting Trials

CRN= Clinical Research Network

D= diuretic antihypertensive

DDD= Defined Daily Dose

DEMQoL= Dementia Quality of Life assessment

DQol= Dementia quality of life instrument

DM= Diabetes mellitus

EQ-5D= EuroQoL 5 Dimension Quality of Life Scale

ESC= European Society of Cardiology

ESH= European Society of Hypertension

ESRD= End stage renal disease

GCP= Good Clinical Practice

GP= General Practitioner

HIND= Hypertension in dementia cohort study

HSE= Health Survey for England

HTN= Hypertension

HYVET= Hypertension in the Very Elderly Trial

IQR= Inter Quartile Range

ISH= Isolated systolic hypertension

JNC= Joint National Committee

LRI= Leicester Royal Infirmary

LVF= Left ventricular failure

MDT= Multidisciplinary Team

MeSH= Medical Subject Headings for Medline

MI= Myocardial infarction

MMSE= Mini-mental state examination

MOCA= Montreal Cognitive Assessment

MRC= UK Medical Research Council

MRI= Magnetic resonance imaging

NHS= National Health Service

NIHR= National Institute for Health Research

NICE= UK National Institute for health and Care Excellence

NS= Not significant

NSAID= Non-steroidal Anti-inflammatory Drug

ONS= Office of National Statistics

PARS= Psychological Assessment Resources®

PARTAGE= Predictive values of blood pressure and arterial stiffness in institutionalized very aged population

PCRN= Primary Care Research Network

PI= Principle Investigator

PPI= Patient and public involvement

PRISMA= Preferred Reporting Items for Systematic Reviews and Meta-Analyses

QMC=Queen's Medical Centre

RCT= Randomized Controlled Trial

SCOPE= Study on Cognition and Prognosis in the Elderly

SHEP= Systolic Hypertension in the Elderly Programme

STOP-Hypertension= Swedish Trial in Old Patients with hypertension

Syst-Eur= Systolic hypertension in Europe Trial

UTI= Urinary Tract Infection

VAD= Vascular Dementia

WHO=World Health Organisation

Appendix II

Additional data

Table A2.1 summary of medications used ordered by frequency (excluding antihypertensives)

Medication	n	%
Donepezil	73	41%
Aspirin	62	34%
Simvastatin	60	33%
Paracetamol	52	29%
Calcium-VitD	45	25%
Lansoprazole	29	16%
Memantine	28	16%
Atorvastatin	27	15%
Levothyroxine	19	11%
Omeprazole	18	10%
Clopidogrel	17	9.4%
Warfarin	17	9.4%
Alendronate	17	9.4%
Codeine	15	8.3%
Metformin	14	7.8%
Citalopram	13	7.2%
Galantamine	12	6.7%
Rivastigmine	11	6.1%
Tamsulosin	11	6.1%
Gliclazide	11	6.1%
ISMN	10	5.6%
Ferrous Fumerate	10	5.6%
Salbutamol Inhaler	10	5.6%
Multivitamin	10	5.6%
Mirtazapine	9	5.0%
Quinine	9	5.0%
Sertraline	8	4.4%
Ranitidine	8	4.4%
Folic Acid	8	4.4%
Allopurinol	8	4.4%
Amitriptyline	7	3.9%
Steroid inhaler	7	3.9%
Steroid and LABA inhaler	7	3.9%
Latanoprost Eye drops	7	3.9%
Digoxin	6	3.3%
Trazadone	6	3.3%
Zopiclone	6	3.3%
Finasteride	6	3.3%
NSAID Topical	6	3.3%
Laxido	6	3.3%
Senna	6	3.3%
Pravastatin	5	2.8%
Risedronate	5	2.8%
Tiotropium inhaler	5	2.8%
Steroid Nasal spray	5	2.8%
Insulin	5	2.8%
Nicorandil	4	2.2%
GTN Spray	4	2.2%
Risperidone	4	2.2%
Quetiapine	4	2.2%
Fluoxetine	4	2.2%
Pregabalin	4	2.2%
Gabapentin	4	2.2%
Cetirizine	4	2.2%
Vitamin D	4	2.2%
Tolterodine	4	2.2%
NSAID Oral	4	2.2%
Tramadol	4	2.2%
Cetraben	4	2.2%
Diazepam	3	1.7%
Lamotrigine	3	1.7%
Ferrous Sulphate	3	1.7%

Oxybutynin	3	1.7%
Tamoxifen	3	1.7%
Di-hydrocodeine	3	1.7%
Movicol	3	1.7%
Lactulose	3	1.7%
Docusate	3	1.7%
Carmellose Eye drops	3	1.7%
Steroid Topical	3	1.7%
Codliver Oil	3	1.7%
Dipyridamole	2	1.1%
Rosuvastatin	2	1.1%
Lithium	2	1.1%
Venlafaxine	2	1.1%
Nortriptyline	2	1.1%
Valproate	2	1.1%
Fexofenadine	2	1.1%
Cinnarizine	2	1.1%
B12	2	1.1%
Carbimazole	2	1.1%
Methotrexate	2	1.1%
Fybogel	2	1.1%
Carbocisteine	2	1.1%
Ipratropium inhaler	2	1.1%
LABA inhaler	2	1.1%
Dorzolamide eye drops	2	1.1%
Combigan eye drops	2	1.1%
Carbomer eye drops	2	1.1%
Aqueous Cream	2	1.1%
E45	2	1.1%
Diprobase	2	1.1%
Cavilon	2	1.1%
Prednisolone	2	1.1%
Trimethoprim	2	1.1%
Fluvastatin	1	0.6%
Fenofibrate	1	0.6%
Bezafibrate	1	0.6%
Naftidrofuryl	1	0.6%
Ivabradine	1	0.6%

Sotalol	1	0.6%
Amiodarone	1	0.6%
Amisulpride	1	0.6%
Aripiprazole	1	0.6%
Duloxetine	1	0.6%
Lofepramine	1	0.6%
Clomipramine	1	0.6%
Melatonin	1	0.6%
Zolpidem	1	0.6%
Clonazepam	1	0.6%
Temazapem	1	0.6%
Carbe-mazepine	1	0.6%
Levetiracetam	1	0.6%
Phenytoin	1	0.6%
Co-Beneldopa	1	0.6%
Co-Careldopa	1	0.6%
Levocetirizine	1	0.6%
Chlor-pheniramine	1	0.6%
Hyoscine	1	0.6%
Cyclizine	1	0.6%
Pro-chlorperazine	1	0.6%
Betahistine	1	0.6%
Zoledronate	1	0.6%
Pantoprazole	1	0.6%
Peptac	1	0.6%
Sulfasalazine	1	0.6%
Mesalazine	1	0.6%
Creon	1	0.6%
Loperamide	1	0.6%
Solefenacin	1	0.6%
Fesoterodine	1	0.6%
Dutesteride	1	0.6%
Alfuzosin	1	0.6%
Zoladex	1	0.6%
Anastrozole	1	0.6%
Mebeverine	1	0.6%
Nefopam	1	0.6%
Meptazinol	1	0.6%
Bu-prenorphine	1	0.6%

Morphine	1	0.6%
Fentanyl Patch	1	0.6%
Macrogol	1	0.6%
Aminophylline	1	0.6%
Montelukast	1	0.6%
Travaprost eye drops	1	0.6%
Bimatoprost eye drops	1	0.6%
Brinzolamide eye drops	1	0.6%
Azopt eye drops	1	0.6%
Macrogol eye drops	1	0.6%
Cromoglicate eye drops	1	0.6%
Glimepiride	1	0.6%
Glipizide	1	0.6%
Pioglitazone	1	0.6%
Sitagliptan	1	0.6%
Doublebase	1	0.6%
Epaderm	1	0.6%
Oxy-tetracycline	1	0.6%
Minocycline	1	0.6%
Doxycycline	1	0.6%
Azithromycin	1	0.6%
Co-trimoxazole	1	0.6%
Acetylcisteine	1	0.6%
Glucosamine	1	0.6%
Ginkgo Biloba	1	0.6%

Table A2.2 Summary of medical diagnoses ordered by frequency

Medication	Frequency	Percent
Osteoarthritis	48	27%
Diabetes (Type 2)	35	19%
Stroke	28	16%
Osteoporosis	27	15%
CKD 3	24	13%
Heart Failure	23	13%
Myocardial infarction	23	13%
Atrial Fibrillation	18	10%
Hypothyroidism	18	10%
Depression	10	5.6%
Hypercholesterolaemia	10	5.6%
Diverticular Disease	10	5.6%
Transient ischaemic attack	9	5.0%
Angina	9	5.0%
ARMD	8	4.4%
Hysterectomy	7	3.9%
Falls (as documented in the medical history)	6	3.3%
Mitral Regurgitation	6	3.3%
Gastro-oesophageal reflux disease	6	3.3%
Fractured Radius	6	3.3%
Basal Cell carcinoma	6	3.3%
Permanent pacemaker	5	2.8%
CKD 4	5	2.8%
Back Pain	5	2.8%
Chronic obstructive pulmonary disease	5	2.8%
Asthma	5	2.8%
Gastro-intestinal Ulcer	5	2.8%
Anaemia	5	2.8%
Breast cancer	5	2.8%
Glaucoma	5	2.8%
Anxiety	4	2.2%
Seizure/Epilepsy	4	2.2%
Impaired glucose tolerance	4	2.2%
Benign prostatic hypertrophy	4	2.2%
Gout	4	2.2%

Knee Replacement	4	2.2%
Fractured neck of femur	4	2.2%
Cataracts	4	2.2%
Pulmonary tuberculosis	4	2.2%
Atrial Flutter	3	1.7%
Coronary artery bypass graft	3	1.7%
Hyperthyroidism	3	1.7%
Hyperparathyroidism	3	1.7%
Renal Stones	3	1.7%
Polymyalgia rheumatica	3	1.7%
Pulmonary Embolus	3	1.7%
Gallstones	3	1.7%
Irritable Bowel	3	1.7%
Constipation	3	1.7%
Gastro-intestinal haemorrhage	3	1.7%
Bilateral salpo-oophrectomy	3	1.7%
Vertigo	3	1.7%
Migraine	2	1.1%
Sub arachnoid haemorrhage	2	1.1%
Aortic Stenosis	2	1.1%
Aortic Regurgitation	2	1.1%
Valve Replacement	2	1.1%
Coronary Stent	2	1.1%
Abdominal aortic aneurysm	2	1.1%
Peripheral Vascular Disease	2	1.1%
CKD 3B	2	1.1%
Urge Incontinence	2	1.1%
Spinal Stenosis	2	1.1%
Reynaud's	2	1.1%
Deep vein thrombosis	2	1.1%
Hiatus Hernia	2	1.1%
Oesophageal Stricture	2	1.1%
Vaginal Prolapse	2	1.1%
Hip Replacement	2	1.1%
Fractured Humerus	2	1.1%
Bladder cancer	2	1.1%
Bowel cancer	2	1.1%
Prostate cancer	2	1.1%
Lymphoma	2	1.1%

Myeloma	2	1.1%
Eczema	2	1.1%
Solar Keratoses	2	1.1%
Tinnitus	2	1.1%
Retinopathy	2	1.1%
Cellulitis	2	1.1%
Vascular Parkinsonism	1	0.6%
Parkinson's Disease	1	0.6%
Benign Tremor	1	0.6%
Adjustment Disorder	1	0.6%
Personality Disorder	1	0.6%
Complex Regional Pain Syndrome	1	0.6%
Insomnia	1	0.6%
Tension Headache	1	0.6%
Subdural Haemorrhage	1	0.6%
Postural Hypotension History	1	0.6%
Pericardial Effusion	1	0.6%
Femoral aneurysm	1	0.6%
Renal Artery stenosis	1	0.6%
Arterial embolisation	1	0.6%
Goitre	1	0.6%
Vitamin D Deficiency	1	0.6%
Hypercalcaemia	1	0.6%
Hyponatraemia	1	0.6%
Hypokalaemia	1	0.6%
Polycystic Kidneys	1	0.6%
Urethral Stricture	1	0.6%
Cramps	1	0.6%
Scoliosis	1	0.6%
Cervical Spondylosis	1	0.6%
Cervicalgia	1	0.6%
Spinal Nerve Compression	1	0.6%
Rheumatoid arthritis	1	0.6%
Bakers Cyst	1	0.6%
Hay fever	1	0.6%
Allergic Rhinitis	1	0.6%
Pneumoconiosis	1	0.6%
Pleural Effusion	1	0.6%
Pleurisy	1	0.6%

Pulmonary Fibrosis	1	0.6%
Pancreatitis	1	0.6%
Colitis	1	0.6%
Anal Fissure	1	0.6%
Achalasia	1	0.6%
Barrett's Oesophagus	1	0.6%
Folate deficiency	1	0.6%
Obesity	1	0.6%
Ovarian Cyst	1	0.6%
Nephrectomy	1	0.6%
Nephrostomy	1	0.6%
Urostomy	1	0.6%
TURP	1	0.6%
Inguinal hernia repair	1	0.6%
Colporrhaphy	1	0.6%
Endoscopic retrograde cholangiopancreatogram	1	0.6%
Cholecystectomy	1	0.6%
Thyroidectomy	1	0.6%
Anterior Resection	1	0.6%
Shoulder Replacement	1	0.6%
Osteotomy	1	0.6%
Fractured Shoulder	1	0.6%
Fractured Fibula	1	0.6%
Metastatic cancer of unknown primary	1	0.6%
Carcinoma in situ	1	0.6%
Renal cancer	1	0.6%
Liver cancer	1	0.6%
Cutaneous Squamous cell carcinoma	1	0.6%
Testicular cancer	1	0.6%
Clonal B Cell	1	0.6%
Chronic lymphocytic leukaemia	1	0.6%
Thymoma	1	0.6%
Haemangioma	1	0.6%
Cutaneous Vasculitis	1	0.6%
Psoriasis	1	0.6%
Lichen Planus	1	0.6%
Dry Eyes	1	0.6%
Retinal Vein Occlusion	1	0.6%
Sub Conjunctival	1	0.6%

Haemorrhage		
Rheumatic Fever	1	0.6%
Post-herpetic Neuralgia	1	0.6%
Pneumonia	1	0.6%
Urosepsis Or UTI	1	0.6%
Septicaemia	1	0.6%

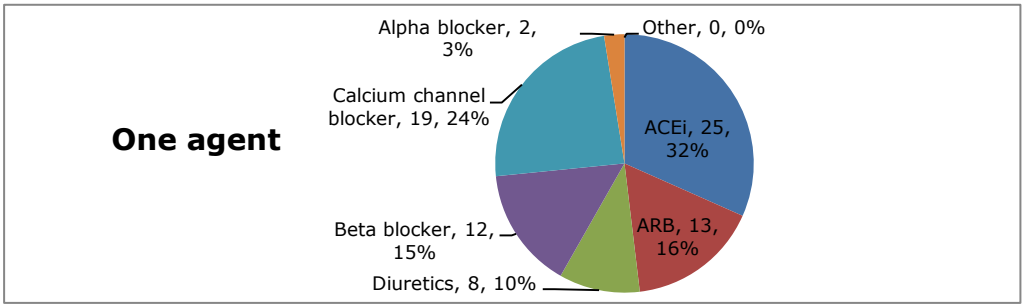
Table A2.3 Summary of antihypertensive use

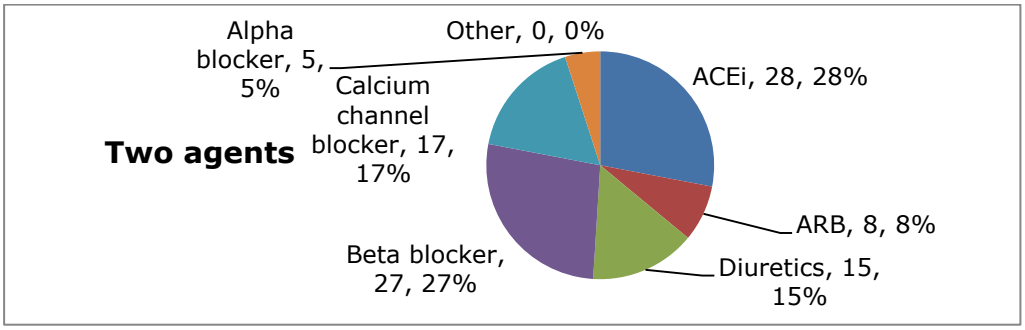
Antihypertensive	Frequency	Percent
ACEi		
Ramipril	46	68%
Lisinopril	9	13%
Enalapril	2	2.9%
Perindopril	9	13%
Captopril	1	1.8%
Cilazapril	1	1.8%
ARBs		
Losartan	17	53%
Valsartan	4	13%
Candesartan	7	22%
Irbesartan	4	13%
Diuretics		
Bendroflumethiazide	28	76%
Hydrochlorothiazide	2	5.4%
Chlorthalidone	2	5.4%
Indapamide	5	14%
Beta blockers		
Bisoprolol	32	59%
Nebivolol	1	1.9%
Atenolol	16	30%
Propranolol	5	9.3%
Calcium Channel Blockers		
Verapamil	1	1.7%
Amlodipine	37	62%
Lercanidipine	4	6.7%
Felodipine	3	5.1%
Lacidipine	4	6.7%
Nifedipine	4	6.7%
Nicardipine	1	1.7%
Diltiazem	6	10%
Alpha blockers		
Doxazosin	15	88%
Terazosin	2	12%
Others		
Minoxidil	1	20%
Hydralazine	2	40%
Moxonidine	1	20%
Aliskiren	1	20%

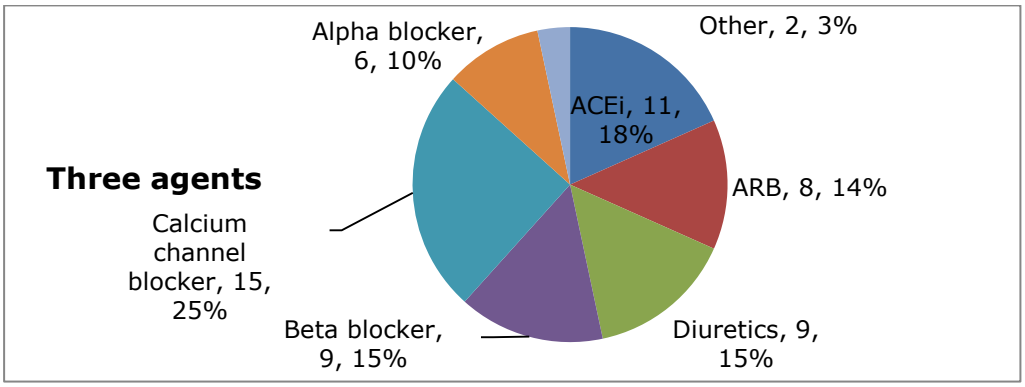
Table A2.4 Summary table of frequency of use of individual antihypertensive agents by total number per participant

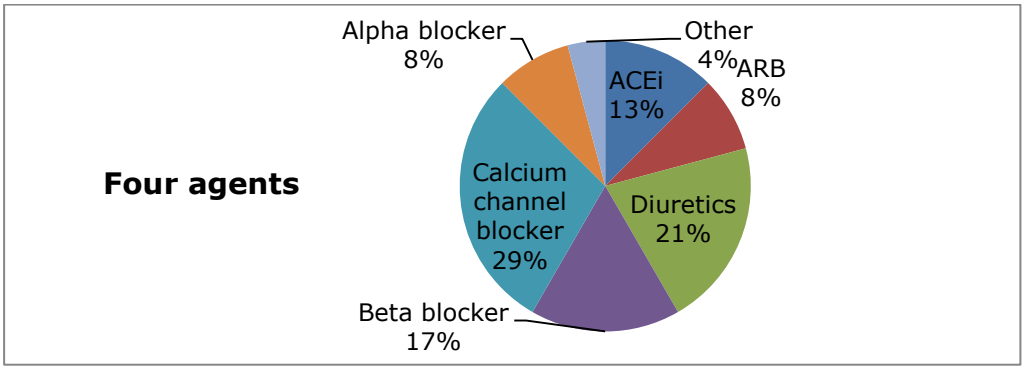
Number of agents	One	Two	Three	Four	Five
	n=76	n=50	n=20	n=6	n=2
Ramipril	18	21	6	0	1
Lisinopril	3	3	2	1	0
Enalapril	0	2	0	0	0
Perindopril	2	1	4	2	0
Captopril	1	0	0	0	0
Cilazapril	1	0	0	0	0
Losartan	4	7	4	1	1
Valsartan	2	1	1	0	0
Candesartan	4	0	2	1	0
Irbesartan	3	0	1	0	0
Bendro-flumethiazide	7	12	7	2	0
Hydro-chlorothiazide	0	1	1	0	0
Chlorthalidone	0	1	0	1	0
Indapamide	1	1	1	2	0
Bisoprolol	11	12	7	2	0
Nebivolol	0	1	0	0	0
Atenolol	1	8	3	2	2
Propranolol	0	4	1	0	0
Verapamil	1	0	0	0	0
Amlodipine	13	11	9	3	1
Lercanidipine	1	1	0	2	0
Felodipine	1	2	0	0	0
Lacidipine	0	2	2	0	0
Nifedipine	2	0	0	1	1
Nicardipine	0	0	1	0	0
Diltiazem	1	1	3	1	0
Minoxidil	0	0	1	0	0
Hydralazine	0	0	0	1	1
Doxazosin	1	4	7	1	2
Terazosin	1	0	0	1	0
Moxonidine	0	0	1	0	0
Aliskiren	0	0	0	0	1

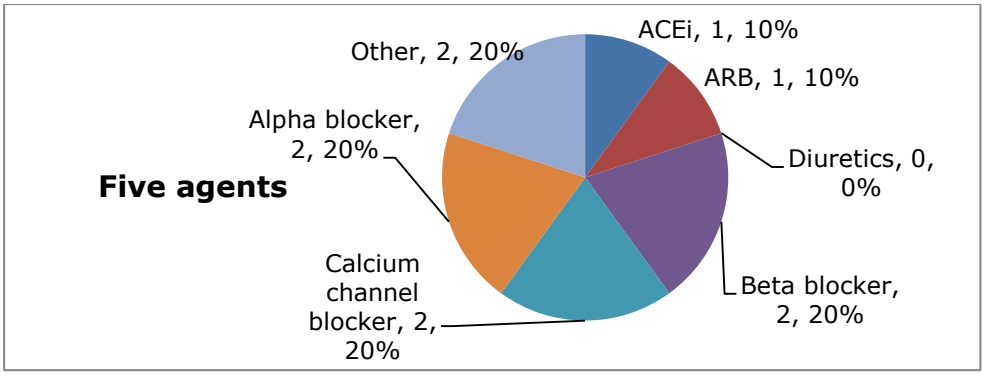
Figure A2.1 Frequency of different classes used by participants taking one to five agents











A2.1 Dosage of different antihypertensive classes

The total daily dose is presented here (thus Ramipril 5mg twice a day appears as 10mg).

A2.1.1 ACE inhibitors and angiotensin receptor blockers

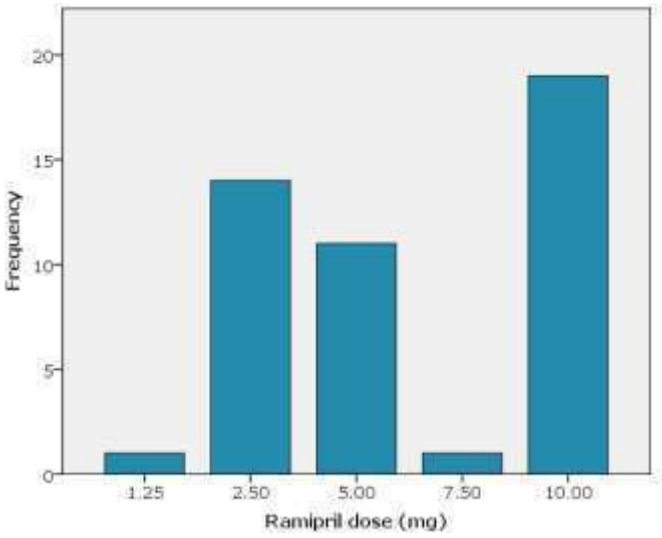
A2.1.1.1 Ramipril

The median dose prescribed was 5mg (IQR 2.5-10).

Table A2.5 Prescribed dose of Ramipril

Dose (mg)	Number taking	Percent (%)	Percent in group
1.25	1	0.6	2.2
2.5	14	7.7	30.4
5	11	6.1	23.9
7.5	1	0.6	2.2
10	19	10.5	41.3

Figure A2.2 Prescribed dose of Ramipril



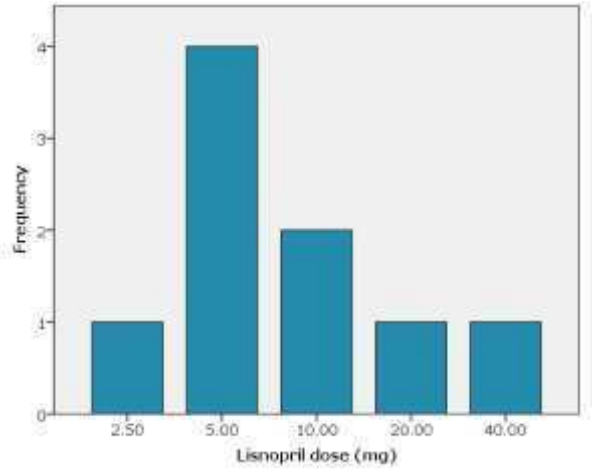
A2.1.1.2 Lisinopril

The median dose of lisinopril prescribed was 5mg (IQR 5-15).

Table A2.6 Prescribed dose of Lisinopril

Dose (mg)	Number taking	Percent (%)	Percent in group
2.5	1	0.6	11.1
5	4	2.2	44.4
10	2	1.1	22.2
20	1	0.6	11.1
40	1	0.6	11.1

Figure A2.3 Prescribed dose of Lisinopril



A2.1.1.3 Enalapril

Only two participants were taking this ACEi and both took the same dose (20mg).

Table A2.7 Prescribed dose of Enalapril

Dose (mg)	Number taking	Percent (%)	Percent in group
20	2	1.1	100

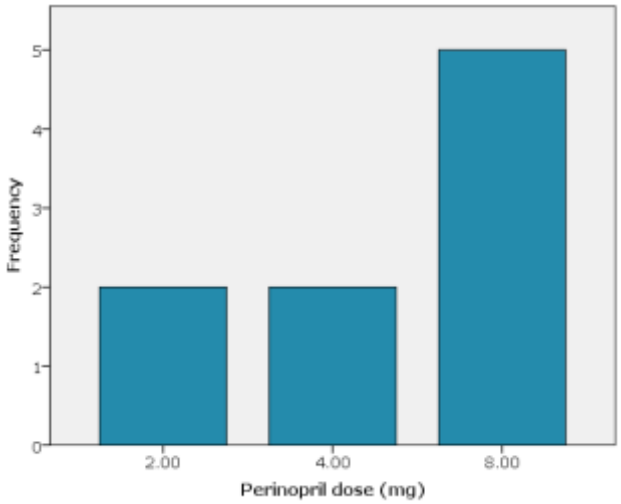
A2.1.1.4 Perindopril

The majority of participants were taking 8mg, the maximum advised antihypertensive dose. The median dose was 8mg (IQR 3-8).

Table A2.8 Prescribed dose of Perindopril

Dose (mg)	Number taking	Percent (%)	Percent in group
2	2	1.1	22.2
4	2	1.1	22.2
8	5	2.8	55.6

Figure A2.4 Prescribed dose of Perindopril



A2.1.1.5 Captopril and Cilazapril

Captopril and cilazapril were taking by one individual each.

Table A2.9 Prescribed dose of Captopril and Cilazapril

Dose	Number taking	Percent (%)	Percent in group
Captopril 25mg	1	0.6	100
Cilazapril 2.5mg	1	0.6	100

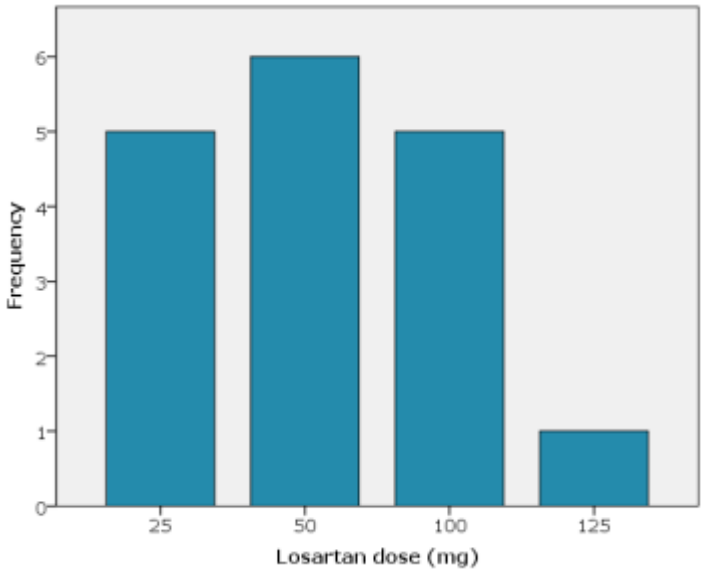
A2.1.1.6 Losartan

Losartan was the most frequently prescribed ARB. The median dose prescribed was 50mg (IQR 25-100) but a significant minority were taking the lowest dose.

Table A2.10 Prescribed dose of Losartan

Dose (mg)	Number taking	Percent (%)	Percent in group
25	5	2.8	29.4
50	6	3.3	35.3
100	5	2.8	29.4
125	1	0.6	5.9

Figure A2.5 Prescribed dose of Losartan



A2.1.1.7 Valsartan

The median dose prescribed was 80mg (IQR 80-140).

Table A2.11 Prescribed dose of Valsartan

Dose (mg)	Number taking	Percent (%)	Percent in group
80	3	1.7	75
160	1	0.6	25

A2.1.1.8 Candesartan

The median dose prescribed was 10mg (4-16).

Table A2.12 Prescribed dose of Candesartan

Dose (mg)	Number taking	Percent (%)	Percent in group
4	3	1.7	42.9
8	1	0.6	14.3
16	3	1.7	42.9

A2.1.1.9 Irbesartan

All participants taking Irbesartan took a dose of 300mg.

Table A2.13 Prescribed dose of Irbesartan

Dose (mg)	Number taking	Percent (%)	Percent in group
300	4	2.2	100

A2.1.2 Antihypertensive diuretics

A2.1.2.1 Bendroflumethiazide

This was the most commonly prescribed antihypertensive diuretic.

All participants taking this medication were prescribed 2.5mg.

Table A2.14 Prescribed dose of bendroflumethiazide

Dose (mg)	Number taking	Percent (%)	Percent in group
2.5	28	15.5	100

A2.1.2.2 Hydrochlorothiazide

Only two participants were taking this agent. The median dose prescribed was 12.5mg (IQR 8.8-18.8)

Table A2.15 Prescribed dose of hydrochlorothiazide

Dose (mg)	Number taking	Percent (%)	Percent in group
12.5	1	0.6	50
25	1	0.6	50

A2.1.2.3 Chlorthalidone

The two participants taking this agent were both prescribed 12.5mg.

Table A2.16 Prescribed dose of chlorthalidone

Dose (mg)	Number taking	Percent (%)	Percent in group
12.5	2	1.1	100

A2.1.2.4 Indapamide

The five participants taking this agent were all prescribed 2.5mg.

Table A2.17 Prescribed dose of indapamide

Dose (mg)	Number taking	Percent (%)	Percent in group
2.5	5	2.8	100

A2.1.3 Beta Blockers

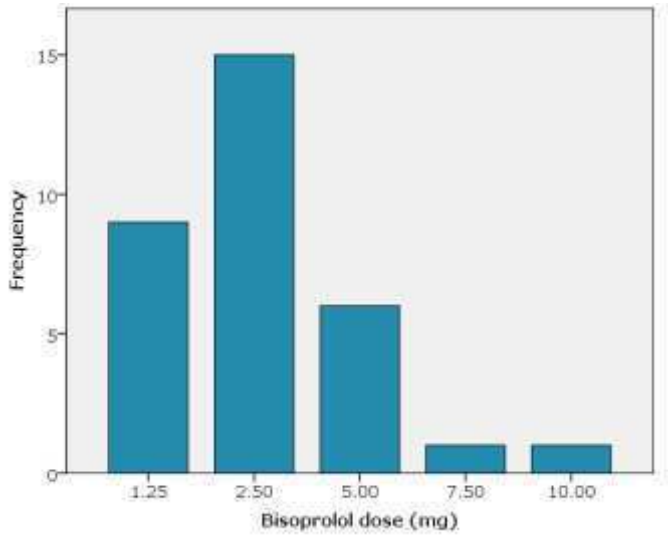
A2.1.3.1 Bisoprolol

The median dose prescribed was 2.5mg (IQR 1.25-4.375) and this was also the most frequently prescribed dose. The majority of participants taking bisoprolol took relatively low doses (2.5mg or below). Table A2.18 and figure A2.6 below show the breakdown of doses prescribed.

Table A2.18 Prescribed doses of bisoprolol

Dose (mg)	Number taking	Percent (%)	Percent in group
1.25	9	5.0	28.1
2.5	15	8.3	46.9
5	6	3.3	18.8
7.5	1	0.6	3.1
10	1	0.6	3.1

Figure A2.6 Prescribed doses of bisoprolol



A2.1.3.2 Nebivolol

Only one participant took this agent.

Table A2.19 Prescribed dose of nebivolol

Dose (mg)	Number taking	Percent (%)	Percent in group
2.5	1	0.6	100

A2.1.3.3 Atenolol

Atenolol was the second most frequently prescribed beta blocker.

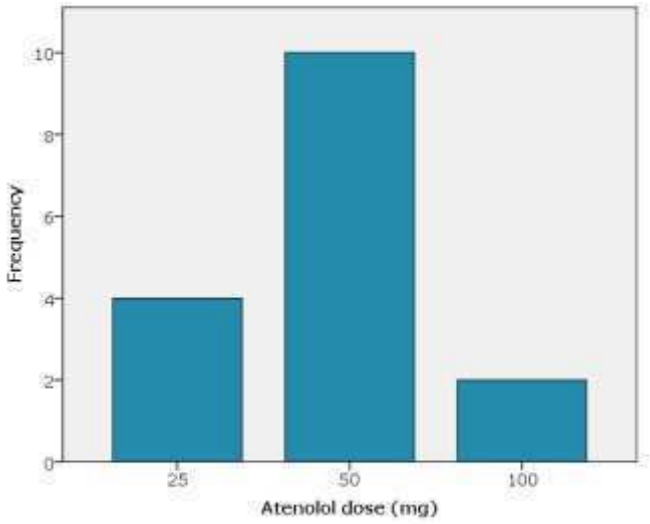
The majority of participants prescribed this agent took 50mg,

median dose 50mg (IQR 31.25-50).

Table A2.20Prescribed doses of atenolol

Dose (mg)	Number taking	Percent (%)	Percent in group
25	4	2.2	25
50	10	5.5	62.5
100	2	1.1	12.5

Figure A2.7 Prescribed doses of atenolol



A2.1.3.4 Propranolol

The median prescribed dose was 40mg (25-160).

Table A2.21Prescribed dose of propranolol

Dose (mg)	Number taking	Percent (%)	Percent in group
20	1	0.6	20
30	1	0.6	20
40	1	0.6	20
160	2	1.1	40

A2.1.4 Calcium Channel Blockers

A2.1.4.1 Verapamil

Only one participant took verapamil.

Table A2.22 Prescribed dose of verapamil

Dose (mg)	Number taking	Percent (%)	Percent in group
120	1	0.6	100

A2.1.4.2 Amlodipine

This was the most commonly prescribed calcium channel blocker. The median dose was 5mg (5-10).

Table A2.23 Prescribed doses of amlodipine

Dose (mg)	Number taking	Percent (%)	Percent in group
5	27	14.9	73
10	10	5.5	27

A2.1.4.3 Lercanidipine

The median dose was 20mg (12.5-20).

Table A2.24 Prescribed dose of lercanidipine

Dose (mg)	Number taking	Percent (%)	Percent in group
10	1	0.6	25
20	3	1.7	75

A2.1.4.4 Felodipine

The median dose was 5mg.

Table A2.25 Prescribed dose of felodipine

Dose (mg)	Number taking	Percent (%)	Percent in group
2.5	1	0.6	33.3
5	1	0.6	33.3
10	1	0.6	33.3

A2.1.4.5 Lacidipine

The median dose was 4mg (IQR 2.5-4).

Table A2.26 Prescribed dose of lacidipine

Dose (mg)	Number taking	Percent (%)	Percent in group
2	1	0.6	25
4	3	1.7	75

A2.1.4.6 Nifedipine

The median dose was 45mg (30-60).

Table A2.27 Prescribed dose of nifedipine

Dose (mg)	Number taking	Percent (%)	Percent in group
30	2	1.1	50
60	2	1.1	50

A2.1.4.7 Nicardipine

Only one participant took this agent.

Table A2.28 Prescribed dose of nicardipine

Dose (mg)	Number taking	Percent (%)	Percent in group
30	1	0.6	100

A2.1.4.8 Diltiazem

The median dose was 180mg (157-255).

Table A2.29 Prescribed dose of diltiazem

Dose (mg)	Number taking	Percent (%)	Percent in group
90	1	0.6	16.7
180	4	2.2	66.7
480	1	0.6	16.7

A2.1.5 Alpha blockers

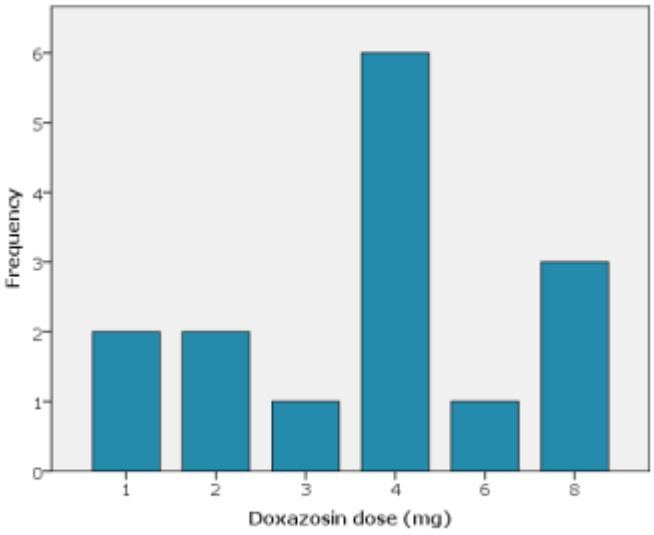
A2.1.5.1 Doxazosin

The median and most frequently prescribed dose of doxazosin was 4mg (IQR 2-6). Table A2.30 and figure A2.7 summarise the doses used.

Table A2.30 Prescribed dose of doxazosin

Dose (mg)	Number taking	Percent (%)	Percent in group
1	2	1.1	13.3
2	2	1.1	13.3
3	1	0.6	6.7
4	6	3.3	40
6	1	0.6	6.7
8	3	1.7	20

Figure A2.7 Prescribed dose of doxazosin



A2.1.5.2 Terazosin

Only two participants took terazosin, the median dose was 7.5mg.

Table A2.31 Prescribed dose of terazosin

Dose (mg)	Number taking	Percent (%)	Percent in group
5	1	0.6	50
10	1	0.6	50

A2.1.6 Other antihypertensive drugs

Only one participant was taking minoxidil, moxonidine and aliskiren. Two participants were taking hydralazine at different doses. The doses prescribed are summarised in table A2.32 below.

Table A2.32 Prescribed doses of other antihypertensives

Drug Dose (mg)	Number taking	Percent (%)	Percent in group
Minoxidil			
10mg	1	0.6	100
Hydralazine			
50mg	1	0.6	50
75mg	1	0.6	50
Moxonidine			
300mcg	1	0.6	100
Aliskiren			
300mg	1	0.6	100

Appendix III

Additional material for GPs

Figure A3.1 Poster used at CCG training meetings to advertise the study

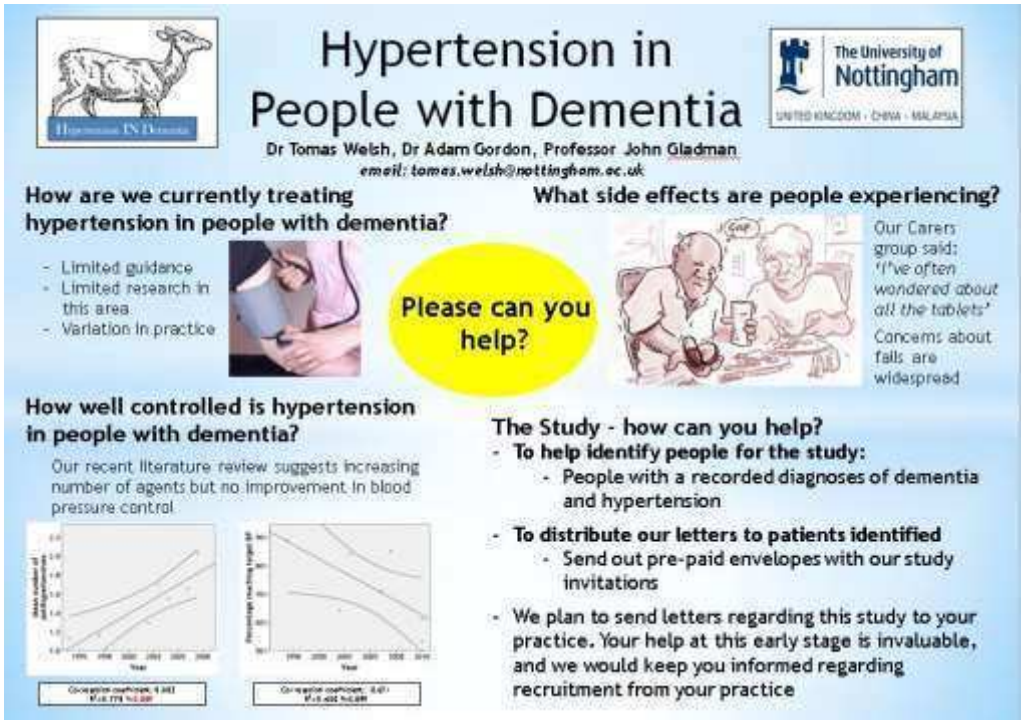


Figure A3.2 Handout for GPs

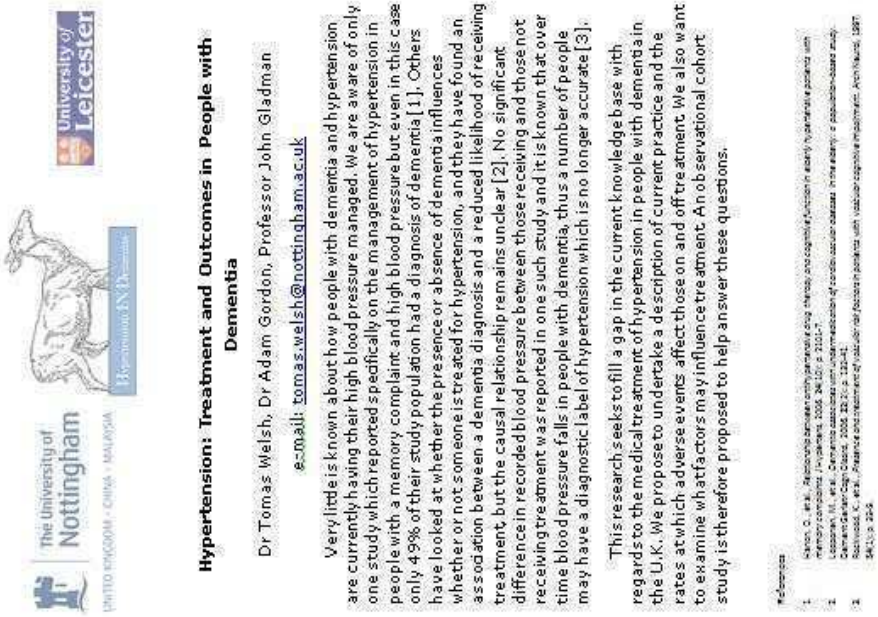
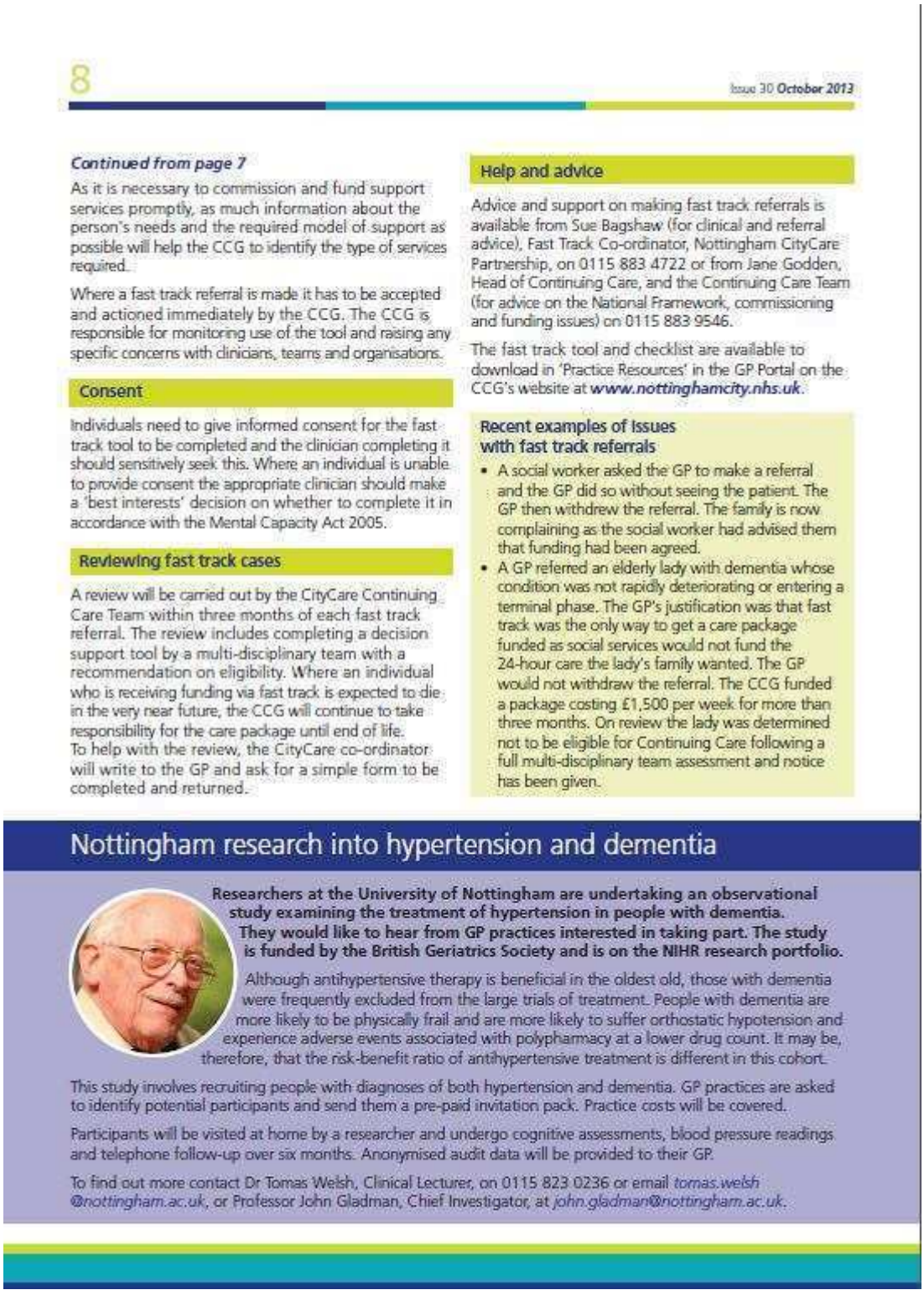


Figure A3.3 Article in CCG magazine - NHS Nottingham City 'Connect'



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Continued from page 7

As it is necessary to commission and fund support services promptly, as much information about the person's needs and the required model of support as possible will help the CCG to identify the type of services required.

Where a fast track referral is made it has to be accepted and actioned immediately by the CCG. The CCG is responsible for monitoring use of the tool and raising any specific concerns with clinicians, teams and organisations.

Consent

Individuals need to give informed consent for the fast track tool to be completed and the clinician completing it should sensitively seek this. Where an individual is unable to provide consent the appropriate clinician should make a 'best interests' decision on whether to complete it in accordance with the Mental Capacity Act 2005.

Reviewing fast track cases

A review will be carried out by the CityCare Continuing Care Team within three months of each fast track referral. The review includes completing a decision support tool by a multi-disciplinary team with a recommendation on eligibility. Where an individual who is receiving funding via fast track is expected to die in the very near future, the CCG will continue to take responsibility for the care package until end of life. To help with the review, the CityCare co-ordinator will write to the GP and ask for a simple form to be completed and returned.

Help and advice

Advice and support on making fast track referrals is available from Sue Bagshaw (for clinical and referral advice), Fast Track Co-ordinator, Nottingham CityCare Partnership, on 0115 883 4722 or from Jane Godden, Head of Continuing Care, and the Continuing Care Team (for advice on the National Framework, commissioning and funding issues) on 0115 883 9546.

The fast track tool and checklist are available to download in 'Practice Resources' in the GP Portal on the CCG's website at ***www.nottinghamcity.nhs.uk***.

Recent examples of issues with fast track referrals

- A social worker asked the GP to make a referral and the GP did so without seeing the patient. The GP then withdrew the referral. The family is now complaining as the social worker had advised them that funding had been agreed.
- A GP referred an elderly lady with dementia whose condition was not rapidly deteriorating or entering a terminal phase. The GP's justification was that fast track was the only way to get a care package funded as social services would not fund the 24-hour care the lady's family wanted. The GP would not withdraw the referral. The CCG funded a package costing £1,500 per week for more than three months. On review the lady was determined not to be eligible for Continuing Care following a full multi-disciplinary team assessment and notice has been given.

Nottingham research into hypertension and dementia

Researchers at the University of Nottingham are undertaking an observational study examining the treatment of hypertension in people with dementia. They would like to hear from GP practices interested in taking part. The study is funded by the British Geriatrics Society and is on the NIHR research portfolio.

Although antihypertensive therapy is beneficial in the oldest old, those with dementia were frequently excluded from the large trials of treatment. People with dementia are more likely to be physically frail and are more likely to suffer orthostatic hypotension and experience adverse events associated with polypharmacy at a lower drug count. It may be, therefore, that the risk-benefit ratio of antihypertensive treatment is different in this cohort.

This study involves recruiting people with diagnoses of both hypertension and dementia. GP practices are asked to identify potential participants and send them a pre-paid invitation pack. Practice costs will be covered.

Participants will be visited at home by a researcher and undergo cognitive assessments, blood pressure readings and telephone follow-up over six months. Anonymised audit data will be provided to their GP.

To find out more contact Dr Tomas Welsh, Clinical Lecturer, on 0115 823 0236 or email *tomas.welsh@nottingham.ac.uk*, or Professor John Gladman, Chief Investigator, at *john.gladman@nottingham.ac.uk*.

Appendix IV

Data tables for the literature review

Table A4.1. Risk of Bias

Source	Selection Bias				Performance bias	Attrition bias	Detection bias			Publication bias	Included in synthesis?
	Inclusion / exclusion criteria applied uniformly ?	Confounding accounted for?	Concurrent intervention accounted for?	Missing data handling?	Outcome assessors blinded?	Diagnosis defined with valid and reliable measures?	Outcomes defined with valid and reliable measures?	Confounding variables assessed?	Outcomes pre-specified?	Suspicion of publication bias?	
Amoo et al. (2011)[90]	Yes	Yes	N/A	N/A	N/A	Yes	N/A	Yes	Yes	No	Yes
Andersen et al. (2011)[91]	Yes	Yes	N/A	N/A	No	Yes	Yes	Yes	Yes	No	Yes
Davies et al. (2011)[82]	Yes	Yes	N/A	Yes	No	Yes	Yes	Yes	Yes	No	Yes
Duron et al. (2009)[85]	Yes	Yes	N/A	N/A	No	Yes	Yes	Yes	Yes	No	Yes
Hanon et al. (2006)[84]	Yes	Yes	N/A	N/A	No	Yes	Yes	Yes	Yes	No	Yes
Imfeld et al. (2013)[83]	Yes	Yes	N/A	Yes	No	Yes	Yes	Yes	Yes	No	Yes

Löppönen et al. (2006)[88]	Yes	Yes	N/A	No	No	Yes	Yes	Yes	Yes	No	Yes
Műther et al. (2010)[89]	Yes	Yes	N/A	Yes – Missing data for PWD	No	Yes	Yes	Yes	Yes	No	Yes
Poon et al. (2010)[80]	Yes	Yes	N/A	Yes – excluded	No	Yes	Yes	Yes	Yes	No	Yes
Richards et al. (2000)[81]	Yes	Yes	N/A	N/A	No	Yes	Yes	Yes	Yes	No	Yes
Rockwood et al. (1997)[87]	Yes	Yes	N/A	Yes *	No	Yes	Yes	Yes	Yes	No	Yes
Vale et al. (2002)[86]	Yes	Yes	N/A	Yes 58.8% enrolled	No	Yes	Yes	Yes	Yes	No	Yes
Zhu et al. (2011)[92]	Yes	Yes	N/A	N/A	No	Yes	Yes	Yes	Yes	No	Yes

* 11.4% not contactable, 27.9% refused (community) 3.2% not contactable, 18.3% refused (institutions); [- = data not available]

Table A4.2 Summary of the studies' characteristics

Source (year published)	Type of Study	Number of People with Dementia and Subtypes (%)	Number with HTN (%)	Mean Age (range)	Location	Country	Identification of Hypertensive Pts	BP measured	Selection method
Amoo et al. (2011)[90]	Cross-sectional Retrospective review of hospital records	108 AD 57 VaD 17 Mixed 4 Unsp. 22	39 (36.1)	70	Neuro-psychiatric Hospital	Nigeria	BP>140/90	No	All attendees with a diagnosis of dementia over a 10 year period
Andersen et al. (2011)[91]	Cross-sectional Case controlled	187 AD 100 VaD 0 Mixed 0 Unsp. 0	102 (54.5)	80.9 (SD 7)	76% community dwelling, 24% in long-term care	Norway	Self-reported medical history	No	Recent diagnosis of dementia and/or population screening. Randomly selected control group
Davies et al. (2011)[82]	Cross-sectional Case-controlled Retrospective	20,021 AD 63 VaD 24 Mixed 0 Unsp. 13	9197 (46)	82.2 (SD 7)	UK General Practice Research Database (GPRD)	UK	Having ever taken an antihypertensive for 6 months	No	Database. (Read codes for probable AD, possible AD, VaD and unspecified / other dementia searched)

Duron et al. (2009)[85]	Cohort	321 AD 100 VaD 0 Mixed 0 Unsp. 0	221 (68.8)	78.1 (SD 6)	Memory Clinic	France	BP>140/90	Yes	All patients diagnosed with Alzheimer's disease and on anti-cholinesterase treatment
Hanon et al. (2006)[84]	Cross-sectional	609 AD 86 VaD 14 Mixed 0 Unsp. 0	609 (100)	80.1 (70-86)	Community dwellers attending a memory clinic	France	BP>140/90 or taking an antihypertensive	Yes	Consecutive attendees
Imfeld et al. (2013)[83]	Cross-sectional Case controlled Retrospective	11,524 AD 61 VaD 39 Mixed 0 Unsp. 0	4926 (42.7)	-	UK General Practice Research Database (GPRD)	UK	Recorded diagnosis	No	Database. (Read codes for AD, VaD and unspecified dementia + selection algorithm)
Löppönen et al. (2006)[88]	Cross-sectional Population based	94 AD 43 VaD 37 Mixed 0 Unsp. 20	48 (51.1)	84.4 (SD 5.7)	Population based	Finland	Recorded diagnosis or BP >160/100	Yes	All residents >65 years of age, of Lieto, were invited to take part (82% took part)
Műther et al. (2010)[89]	Cross-sectional Case controlled Retrospective	216 AD 0 VaD 0 Mixed 0 Unsp. 100	181 (83.8)	82.7 (SD 6.2)	GP database	Germany	Recorded diagnosis	No	16 of 25 invited teaching GP practises. Patients with a recorded diagnosis of dementia and one of HTN, DM, hyperlipidaemia

Poon et al. (2010)[80]	Cross-sectional Retrospective	304 AD 60 VaD 35 Mixed 4 Unsp. 2	304 (100)	78.1	Outpatient attendees VA medical centre clinics.	USA	Recorded diagnosis	No	Recorded diagnoses of both HTN and dementia.
Richards et al. (2000)[81]	Cross-sectional	65 AD 75 VaD 0 Mixed 0 Unsp. 25	37 (56.9)	81.4 (6.4)	Urban dwellers	USA	Recorded diagnosis	No	Random sample of a population derived from 29 contiguous census tracts.
Rockwood et al. (1997)[87]	Cross sectional	792 AD 57 VaD 26 Mixed 17 Unsp. 0	281 (35.5)	-	Survey of institutionalised and community dwelling older people	Canada	Recorded diagnosis	Yes	Stratified comprehensive sample across the country
Vale et al. (2002)[86]	Cross-sectional	186 AD 31 VaD 19 Mixed 9 Unsp. 41	86 (46.2)	67.4 (13.21)	Behavioural Neurology Outpatients Clinic. Tertiary referral centre	Brazil	Recorded diagnosis	No	All first attendees between 1997 and 1999 were invited to take part
Zhu et al. (2011)[92]	Cohort	201 AD 100 VaD 0 Mixed 0 Unsp. 0	71 (35.5)	76 (SD 8.1)	84% community dwelling, 16% in long-term care.	USA	Recorded diagnosis	No	Consecutive outpatient attendees; Referrals; some long-term care residents MMSE >16, advocate available.

Table A4.3 Summary of the studies' findings

Source (year published)	Prevalence of HTN (%)	Sex (%)	Comorbidities (%)	Antihypertensive types (%)	Treated (%)	Effectiveness (meets target <140/90)
Amoo et al. (2011)[90]	36	47 M 53 F	Heart Failure: - IHD: - DM: 6 CVD: 12	ACEi/ARB: - Diuretic: - C C Blockers: - β-Blockers: - Other: -	108 (some on antihypertensives for other diagnoses)	-
Andersen et al. (2011)[91]	55	40 M 60 F	Heart Failure: - IHD: 40 DM: 11 CVD: 18	ACEi/ARB: - Diuretic: - C C Blockers: - β-Blockers: - Other: -	125 (some on antihypertensives for other diagnoses)	-
Davies et al. (2011)[82]	46	33 M 67 F	Heart Failure: - IHD: 34 DM: 15 CVD: 26	ACEi/ARB: 40 Diuretic: 50 C C Blockers: 42 β-Blockers: 41 Other: 10	100 (population selected to be on an antihypertensive)	-
Duron et al. (2009)[85]	69	32 M 68 F	Heart Failure: - IHD: 26 DM: 9 CVD: -	ACEi/ARB: 37 Diuretic: 30 C C Blockers: 29 β-Blockers: 39 Other: 6	78	-
Hanon et al. (2006)[84]	100	28 M 72 F	Heart Failure: - IHD: - DM: - CVD: -	ACEi/ARB: - Diuretic: - C C Blockers: - β-Blockers: - Other: -	55	-

Imfeld et al. (2013)[83]	43	35 M 65 F	Heart Failure: 9 IHD: 22 DM: 11 CVD: -	ACEi/ARB: 45 Diuretic: 90 C C Blockers: 45 β-Blockers: 45 Other: -		-
Löppönen et al. (2006)[88]	51	31 M 69 F	Heart Failure: 23 IHD: 57 DM: 18 CVD: 37	ACEi/ARB: 12 Diuretic: 46 C C Blockers: 27 β-Blockers: 15 Other: -	85	-
Műther et al. (2010)[89]	84	23 M 77 F	Heart Failure: - IHD: - DM: - CVD: -	ACEi/ARB: - Diuretic: - C C Blockers: - β-Blockers: - Other: -	85	-
Poon et al. (2010)[80]	100	98 M 2 F	Heart Failure: 11 IHD: 31 DM: 32 CVD: 19	ACEi/ARB: 59 Diuretic: 57 C C Blockers: 44 β-Blockers: 40 Other: 20	100 (2.95) (population selected to be on an antihypertensive)	55
Richards et al. (2000)[81]	57	35 M 65 F	Heart Failure: - IHD: - DM: 18 CVD: -	ACEi/ARB: 25 Diuretic: 83 C C Blockers: 42 β-Blockers: 8 Other: 13	65	-
Rockwood et al. (1997)[87]	35	29 M 71 F	Heart Failure: - IHD: - DM: - CVD: -	ACEi/ARB: - Diuretic: - C C Blockers: - β-Blockers: - Other: -	53	-

Vale et al. (2002)[86]	46	59 M 41 F	Heart Failure: - IHD: - DM: - CVD: -	ACEi/ARB: - Diuretic: - C C Blockers: - β-Blockers: - Other: -	88	-
Zhu et al. (2011)[92]	35	Not available	Heart Failure: - IHD: 6 DM: 11 CVD: -	ACEi/ARB: - Diuretic: - C C Blockers: - β-Blockers: - Other: -	48	-

[- = data not available]

Appendix V

Example study documents

Document A5.1 Data collection sheet

Data Collection Sheet Final Version 1.0

Researcher: _____

Identity Code Number: _____

Date: _____

ID Number_____

DOB ___/___/_____ **(format 01/01/1900)**

Sex: **Male** ☐ **Female** ☐

Residence Residential home ☐ Nursing home ☐ Own Home ☐

Smoker Never ☐ Ex ☐ Current ☐ **Packyears**_____

Age when finished full time education _____

Marital status: Single ☐ Married ☐ Widow/er ☐

Ethnicity

White	
A	British
B	Irish
C	Any other White background
Mixed	
D	White and Black Caribbean
E	White and Black African
F	White and Asian
G	Any other mixed background
Asian or Asian British	
H	Indian
J	Pakistani
K	Bangladeshi
L	Any other Asian background
Black or Black British	
M	Caribbean
N	African
P	Any other Black background
Other Ethnic Groups	
R	Chinese
S	Any other ethnic group
Z	Not stated

ID Number_____

Recorded medical diagnoses:

Heart failure ☐ IHD ☐ Stroke ☐

CKD ☐ Diabetes ☐ Osteoarthritis ☐

Number of falls in the last 3 months:

_____

Others: _____

_____

Weight:_____ **kg** **Height:** _____ **cm or Humeral Length**_____

Medications

Medication Name	Dose	Route
Total Number = _____		

Concordance

It is often difficult to remember to take medications especially if there are a large number.

In the last month how many times have you forgotten to take a medication? (circle the best approximation)

Daily Most Days Weekly Thrice Twice Once Never

Blood pressure measurements

Ensure participant has sat down in a relaxed environment for 10 minutes prior to measurements. Record the first measurement unless an error message is displayed, in which case a repeat measurement should be made.

Measurement	Blood pressure
Right Arm	
Left Arm	
Standing – 1 Minute	

MMSE

Please complete separate MMSE.

Result: _____/30

DEMQoL

Instructions: *Read each of the following questions (in bold) verbatim and show the respondent the response card.*

(N.B. ** items need to be reversed before scoring)

Practice
I would like to ask you about _____ *(your relative 's)* life, as you are the person who knows him/her best. There are no right or wrong answers. Just give the answer that best describes how _____ *(your relative)* has felt in the last week. If possible try and give the answer that you think _____ *(your relative)* would give. Don't worry if some questions appear not to apply to _____ *(your relative)*. We have to ask the same questions of everybody.

Before we start we'll do a practise question; that's one that doesn't count. *(Show the response card and ask respondent to say or point to the answer)*. In the last week how much has _____ *(your relative)* enjoyed watching television?

a lot quite a bit a little not at all

Follow up with a prompt question: Why is that? *or* Tell me a bit more about that.

Section 1
For all of the questions I'm going to ask you, I want you to think about the last week. First I'm going to ask you about _____ *(your relative 's)* feelings. In the last week, would you say that _____ *(your relative)* has felt……

1. cheerful? **	A lot	Quite a bit	A little	Not at all
2. worried or anxious?	A lot	Quite a bit	A little	Not at all
3. frustrated?	A lot	Quite a bit	A little	Not at all
4. full of energy? **	A lot	Quite a bit	A little	Not at all
5. sad?	A lot	Quite a bit	A little	Not at all
6. content? **	A lot	Quite a bit	A little	Not at all
7. distressed?	A lot	Quite a bit	A little	Not at all
8. lively? **	A lot	Quite a bit	A little	Not at all
9. Irritable?	A lot	Quite a bit	A little	Not at all
10. Fed-up?	A lot	Quite a bit	A little	Not at all
11. That he / she has things to look forward to?**	A lot	Quite a bit	A little	Not at all

Section 2
Next, I'm going to ask you about _____ *(your relative 's)* memory. In the last week, how worried would you say _____ *(your relative)* has been about……

12. His/her memory in general?	A lot	Quite a bit	A little	Not at all
13. Forgetting things that happened a long time ago?	A lot	Quite a bit	A little	Not at all
14. Forgetting things that happened recently?	A lot	Quite a bit	A little	Not at all
15. Forgetting people's names?	A lot	Quite a bit	A little	Not at all
16. Forgetting where he/she is?	A lot	Quite a bit	A little	Not at all
17. Forgetting what day it is?	A lot	Quite a bit	A little	Not at all

18. Difficult making decisions?	A lot	Quite a bit	A little	Not at all
19. Making him/herself understood?	A lot	Quite a bit	A little	Not at all

Section 3
Now, I'm going to ask about _____ *(your relative's)* everyday life. In the last week, how worried would you say _____ *(your relative)* has been about……

20. Keeping him/herself clean (e.g. washing and bathing)?	A lot	Quite a bit	A little	Not at all
21. Keeping him/herself looking nice?	A lot	Quite a bit	A little	Not at all
22. Getting what he/she wants from the shops?	A lot	Quite a bit	A little	Not at all
23. Using money to pay for things?	A lot	Quite a bit	A little	Not at all
24. Looking after his / her finances?	A lot	Quite a bit	A little	Not at all
25. Things taking longer than they used to?	A lot	Quite a bit	A little	Not at all
26. Getting in touch with people?	A lot	Quite a bit	A little	Not at all
27. Not having enough company?	A lot	Quite a bit	A little	Not at all
28. Not being able to help other people?	A lot	Quite a bit	A little	Not at all
29. Not playing a useful part in things?	A lot	Quite a bit	A little	Not at all
30. His / her physical health?	A lot	Quite a bit	A little	Not at all

Section 4
We've already talked about lots of things: _____ *(your relative's)* feelings, memory and everyday life. Thinking about all of these things in the last week, how would you say _____ *(your relative)* would rate……..

31. His / her quality of life overall? **	Very Good	Good	Fair	Poor

Modified Barthel Index

Activity	Score
Feeding 0 = unable 1 = needs help cutting, spreading butter etc, or requires modified diet 2 = Independent	0 1 2
Bathing 0 = dependent 1 = Independent (or in shower)	0 1
Grooming 0 = needs help with personal care 1 = independent face / hair / teeth / shaving	0 1
Dressing 0 = dependent 1 = needs help but can do about half unaided 2 = independent (including buttons, zips, laces etc)	0 1 2
Bowels 0 = incontinent (or needs to be given enemas) 1 = occasional accident 2 = continent	0 1 2
Bladder 0 = incontinent, or catheterised and unable to manage alone 1 = occasional accident 2 = continent	0 1 2
Toilet Use 0 = dependent 1 = needs some help, but can do something alone 2 = independent (on and off, dressing, wiping)	0 1 2
Transfers (bed to chair and back) 0 = unable, no sitting balance 1 = major help (one or two people – physical help), can sit 2 = minor help (verbal or physical) 3 = independent	0 1 2 3
Mobility (on level surface) 0 = immobile or <50yrds 1 = wheelchair independent, including corners, >50yrds 2 = walks with help of one person (verbal or physical) > 50yrds 3 = independent (but may use any aid, e.g. stick) >50 yrds	0 1 2 3
Stairs 0 = unable 1 = needs help (verbal, physical, carrying aid) 2 = independent	0 1 2
Total (0-20)	

ID Number_____

Symptom Checker

In the last month how often have you experienced any of the following symptoms? (Circle best approximation)

If participant unable to answer proxy answers via an informant should be used.

Symptom	How Often?
Headache	Daily Most Days Weekly Thrice Twice Once None
Dizziness	Daily Most Days Weekly Thrice Twice Once None
Swollen ankles	Daily Most Days Weekly Thrice Twice Once None
Cold hands / feet	Daily Most Days Weekly Thrice Twice Once None
Flushing / sweating	Daily Most Days Weekly Thrice Twice Once None
Skin rash / itching	Daily Most Days Weekly Thrice Twice Once None
Cough	Daily Most Days Weekly Thrice Twice Once None
Dry Mouth	Daily Most Days Weekly Thrice Twice Once None
Nausea	Daily Most Days Weekly Thrice Twice Once None
Diarrhoea	Daily Most Days Weekly Thrice Twice Once None
Constipation	Daily Most Days Weekly Thrice Twice Once None
Palpitations	Daily Most Days Weekly Thrice Twice Once None
Nervousness / restlessness	Daily Most Days Weekly Thrice Twice Once None
Tiredness	Daily Most Days Weekly Thrice Twice Once None
Sleep problems/ nightmares	Daily Most Days Weekly Thrice Twice Once None
Frequent Micturition	Daily Most Days Weekly Thrice Twice Once None

Document A5.2 Follow up data collection form (monthly)

Medical Events Questionnaire V1.0 (Monthly)

Identity Code Number: _____

Month: 2 3 4 5 6

If the participant is unable to answer, answers via an informant should be used.

In the last month have you…

(1) Seen a health professional?

a. District Nurse?
Yes No
How many times? 1 2 3 4 5 If more than 5 enter number _____
Why?_____

b. General Practitioner?
Yes No
How many times? 1 2 3 4 5 If more than 5 enter number _____
Why?_____

c. Paramedic?
Yes No
How many times? 1 2 3 4 5 If more than 5 enter number _____
Why?_____

(2) Been admitted to hospital?

Yes No

How many times? 1 2 3 4 5 If more than 5 enter number_____

Why_____

(3) Fallen?

Yes No

How many times? 1 2 3 4 5 If more than 5 enter number_____

Did you injury yourself? Yes No

(4) Blacked out?

Yes No

How many times? 1 2 3 4 5 If more than 5 enter number_____

(5) Broken any bones?

Yes No If Yes what? _____

How many times? 1 2 3 4 5 If more than 5 enter number_____

(6) Been told you have had a heart attack, heart failure, a stroke or TIA (mini-stroke)

No Heart attack Heart Failure Stoke TIA

(7) Experienced any of the following symptoms?

Symptom	**How Often?**
Headache	Daily Most Days Weekly Thrice Twice Once None
Dizziness	Daily Most Days Weekly Thrice Twice Once None
Swollen ankles	Daily Most Days Weekly Thrice Twice Once None
Cold hands /feet	Daily Most Days Weekly Thrice Twice Once None
Flushing / sweating	Daily Most Days Weekly Thrice Twice Once None
Skin rash / itching	Daily Most Days Weekly Thrice Twice Once None
Cough	Daily Most Days Weekly Thrice Twice Once None
Dry Mouth	Daily Most Days Weekly Thrice Twice Once None
Nausea	Daily Most Days Weekly Thrice Twice Once None
Diarrhoea	Daily Most Days Weekly Thrice Twice Once None
Constipation	Daily Most Days Weekly Thrice Twice Once None
Palpitations	Daily Most Days Weekly Thrice Twice Once None
Nervousness / restlessness	Daily Most Days Weekly Thrice Twice Once None
Tiredness	Daily Most Days Weekly Thrice Twice Once None

Symptom	How Often?
Sleep problems/ nightmares	Daily Most Days Weekly Thrice Twice Once None
Frequent Micturition	Daily Most Days Weekly Thrice Twice Once None

(8) Had any changes to your medication made?

Yes No

If Yes describe: _____

(9) If the participant has passed away please record the date:

___/___/___

Figure A5.3 Site monitoring form

Study Monitoring Report Form

Study Title: Hypertension in Dementia	PI Name:
Sponsor: University of Nottingham	Visit Date:
Previous Visit Date:	

Site Address	
Research team present	

Specify which patients notes were reviewed:

1. **Informed Consent**

	Yes	No	NA	Comments (If applicable include a comment and describe any corrective actions that were initiated)
1.1- Was consent obtained prior to any study procedures being conducted?				
1.2- Has consent been documented in the patient notes?				

2. **Source Data Verification / Data Consistency Checking / CRF Completion**

	Yes	No	NA	Comments (If applicable include a comment and describe any corrective actions that were initiated)
2.1- Is the source documentation adequate?				
2.2- Are only eligible patients being enrolled?				
2.3- Is the source data legible, original and accurate?				
2.4- Are there any repeated errors? If yes, please highlight these to relevant personnel to improve CRF completion & data quality				
2.5- Have all data queries been resolved?				

Monitoring Report Form V1.0

3. Study Conduct / Site Personnel, Facilities & Equipment / Study Supplies

	Yes	No	NA	Comments (if applicable include a comment and describe any corrective actions that were initiated)
3.1- Are site personnel adhering to the Protocol, patient visit and treatment schedule?				
3.2- Have any protocol compliance issues been detected?				
3.3- Have all protocol deviations been properly document & reported appropriately?				
3.4- Has there been a repeated breach of GCP or protocol?				
3.5- If yes, has this been reported appropriately?				
3.6- Have there been any changes in facilities or equipment?				
3.7- Do the facilities & equipment remain adequate for the conduct of the study?				
3.8- Are there adequate study supplies (CRFs, lab kits etc) available on site?				

4. Follow-Up Action Items None ☐

Action Item #	Patient Involved / NA	Date Issue Identified	Status	Action Item / Corrective Action Plan

5. Follow-Up Action Items Resolved from previous visit None ☐

Action Item #	Patient Involved / NA	Date Issue Identified	Date Issue Resolved	Action Item / Corrective Action Plan

6. General Comments

Signature of Monitor/Date	Printed Name and Title

Appendix VI

Outputs

Journal articles

Welsh TJ, Gladman JR, Gordon AL. The treatment of hypertension in people with dementia: a systematic review of observational studies. *BMC geriatrics.* 2014;14:19.

Welsh T, Gladman J, Gordon AL. The treatment of hypertension in care home residents: a systematic review of observational studies. *Journal of the American Medical Directors Association.* Jan 2014;15(1):8-16.

Letters

Welsh TJ, Gordon AL, Gladman JR. Letter of response to Dr Aronow. *Journal of the American Medical Directors Association.* Nov 2013;14(11):847-848.

Poster publications

Presented at the European Union Geriatric Medicine Society (EUGMS) September 2015

Welsh TJ, Gordon AL, Gladman JR. *Should the treatment of hypertension in people with coexisting dementia be attenuated?* European geriatric medicine. Sept 16-18 2015;6(S1)

Van der Wardt V, Conroy S, **Welsh T**, Logan P, Harrison J, Taggar J, Gladman J. *Recruitment of people with dementia in primary care – experiences from the HIND study.* European geriatric medicine. Sept 16-18 2015;6(S1)

Presented at the British Geriatrics Society Spring Conference 2015

Welsh TJ, Gladman JR, Gordon AL. *Hypertension is less likely to be treated in those with lower MMSE scores. Preliminary data from the HIND (Hypertension in dementia) study*. Age Ageing 2015 Sep; 44(Suppl 2): 1-28.

Welsh TJ, Gladman JR, Gordon AL. *Hypertension in care home residents: More medication but no better control*. Age Ageing 2015 Sep; 44(Suppl 2): 1-28.

Non-peer reviewed articles

Welsh TJ. Hypertension in people with dementia – what should we do? British Geriatrics Society Blog. 2013. (invited submission).
http://britishgeriatricssociety.wordpress.com/2013/08/28/hypertension-in-people-with-dementia-what-should-we-do/

Welsh TJ. Nottingham research into hypertension and dementia. CCG Connect, NHS Nottingham City CCG. Issue 30. October 2013. http://www.nottinghamcity.nhs.uk/news-projects/connect.html