

**Factors affecting blood pressure control in primary
care**

Lena Isabel Barrera Vergara

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**Department of Primary Care and Public Health
School of Public Health
Imperial College London**

Declaration of originality

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Abstract

Background

Hypertension is the main cardiovascular risk factor. Worldwide, 40% of adults aged 25 years and over have hypertension. Only around 25% of hypertensive patients had controlled hypertension (CH). I assessed the association between individual factors, physician factors and health system factors with having CH

Methods

Population included 17252 hypertensive adults (HA) registered with 28 general practices in Wandsworth, London between 1998 and 2007. Comparison of two blood pressure targets was performed by cross-sectional analysis. Changes in antihypertensive prescribing were evaluated using logistic models. A Bayesian frailty survival model was developed to assess the relationship between potential risk factors and CH with blood pressure $\leq 140/90$ mm Hg.

Results

In 2007, 26 (93%) practices had more than 70% HA with CH using the QOF target. Using the NICE target of 140/90 mm Hg 4 (14.2%) of practices had more than 70% HAs with CH. In 1998 49.0% HA were not prescribed antihypertensive medication but only 14.8% in 2007. The introduction of the 2006 NICE guidelines was associated with an increase in recommended monotherapy prescribing. 37% of 11373 HA used for survival analysis had CH in 1998 and 62.4% had CH in 2007. Being older, increases in body mass index and higher levels of cholesterol were negatively associated with having CH, hazard ratio (HR) 0.99 (95% credible interval 0.99 – 0.99), HR 0.93 (95% credible interval 0.88 – 0.99) and HR 0.89 (95% credible interval 0.79 – 0.99) respectively. HA registered after the introduction of Quality and Outcomes Framework (QOF) were more likely to have CH, HR 2.05 (95% credible interval 1.94 – 2.16).

Conclusion

In this cohort of HA being treated in primary care, individual factors were mainly associated with not having CH. Blood pressure control rates increased over the period. The use of national hypertension guidelines and the QOF could contribute to this improvement.

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Abbreviations

AASK	African American Study of Kidney Disease
ASCPTT-LLA	The Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA) trial
ACCORD	The Action to Control Cardiovascular Risk in Diabetes trial
ABCD-H	The Appropriate Blood Pressure Control in Diabetes tria (H = hypertensive patients)
ABCD- N	The Appropriate Blood Pressure Control in Diabetes Trial (N= normotensive patients)
ABCD-2V	The Appropriate Blood Pressure Control in Diabetes Trial
ARB	Angiotensin receptor blockers
ACEI	Angiotensin-Converting Enzyme inhibitor
ACCOMPLISH	The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension Trial
ADVANCE	The Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation trial
AFR	African region
ALLHAT	The Antihypertensive Lipid-Lowering Treatment to Prevent Heart Attack Trial
AMR	Region of Americas
ARB	Angiotensin receptor blockers
AOR	Adjusted Odds Ratio
ABPM	Ambulatory blood pressure monitoring
BB	Beta blockers
BHS	British Hypertension Society
BP	Blood pressure
BMI	Body Mass Index
BRFSS	The Behavioural Risk Factor Surveillance System Survey
CASE-J	The Candesartan Antihypertensive Survival Evaluation trial
CCB	Calcium channels blockers

CKD	Chronic kidney disease
CI	Confidence Interval
CHD	Coronary heart disease
CH	Controlled hypertension
DAG	Direct acyclic graph
DASH	Dietary Approaches To Stop Hypertension
DBP	Diastolic blood pressure
DD	Diuretics
DM	Diabetes mellitus
ESKD	End stage kidney disease
EMR	Eastern Mediterranean
ENCORE	The Exercise and Nutrition interventions for CardiOvasculaR hEalth study
ESH-ESC	European Society of Hypertension-European Society of Cardiology
FEVER	The Felodipine Event Reduction study
GEE	Generalized estimating equations
GMS	General Medical Services
GP	General Practitioner
GPRD	General Practice Research Database
gr	grams
HBPM	Home blood pressure monitoring
HDFP	The hypertension detection and follow-up program
HR	Hazard ratio
HSE	Health Survey for England
HTA	Hypertension
HOT	The Hypertension Optimal Treatment study
HYVET	The Hypertension in the Very Elderly Trial
IDH	Isolated diastolic hypertension
IMD	Index of Multiple Deprivation

INVEST	The International VErapamil SR-Trandolapril study
IOM	Institute of Medicine
ISH	Isolated systolic hypertension
JATOS	The Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients
JNC 7	The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
J-Health study	The Japan Hypertension Evaluation with Angiotensin II Antagonist Losartan Therapy
LDL	Low-Density Lipoprotein
mmHg	millimetres of mercury
MCMC	Markov chain Monte Carlo
MONICA	Monitoring Trends and Determinants in Cardiovascular Disease
MDRD	The modification of Diet in Renal Disease study
MRC	The Medical Research Council's trial of drug treatment of mild hypertension
MRC2	The Medical Research Council trial of treatment of hypertension in older adults
MRFIT	The Multiple Risk Intervention Trial
NHANES	National Health and Nutrition Examination Survey
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
ONTARGET	The Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial
PRA	Plasma rennin activity
PREMIER	The Life Interventions for Blood Pressure Control trial
ProFESS	The Prevention Regimen for Effectively Avoiding Second Strokes trial
PROGRESS	The perindopril protection against recurrent stroke study
PC	Primary Care
PHC	Primary Health Care
PCH	Patient with controlled hypertension
PCT	Primary Care Trust

PSA	Public Service Agreement
QMAS	Quality Management and Analysis System
QOF	Quality and Outcomes Framework
QMAS	The Quality and Outcomes Framework
REGARDS	The Reasons for Geographic and Racial Differences in Stroke study
REIN-2	The Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease multicentre, randomised controlled trial
SHEP	The Systolic Hypertension in the Elderly Program
SBP	Systolic blood pressure
SDH	Systolic/diastolic hypertension
STOP-hypertension 2	The Swedish Trial in Old Patients with Hypertension-2 study
Syst-Eur	The Multicenter Trial on the Treatment of Isolated Systolic Hypertension in the Elderly
sd	Standard deviation
SOA	Super output areas
THIN	The Health Improvement Network
TONE	Trial of Non-pharmacologic Interventions in the Elderly
TROPHY	The trial of preventing hypertension
TRASCEND	The Telmisartan Randomized Assessment Study in ACE-Intolerant Subjects With Cardiovascular Disease
UR	European Region
UK	The United Kingdom
UKPDS	United Kingdom Prospective Diabetes Study
VA	Department of Veterans Affairs
VALISH	The Valsartan in Elderly Isolated Systolic Hypertension Study
VALUE	The Valsartan Antihypertensive Long-term Use Evaluation study
WHO	World Health Organisation
WPR	Western Pacific Region

Chapter 1 Introduction

1.1 Definition of hypertension

Blood pressure is the force that vascular volume exerts on the vascular system. It is the product of cardiac output and peripheral vascular resistance. Cardiac output determines the highest level of blood pressure, which is called systolic blood pressure (SBP); and peripheral resistance determines the lowest level of blood pressure, called diastolic blood pressure (DBP) (1).

A raised blood pressure has been linked to an increased risk of developing cardiovascular diseases (2-4). Initially the term hypertension emerged to classify raised blood pressure as a disease (5). However, this classification is debatable because symptoms or signs of organ damage are not always evident in the early stages of a mild raise of blood pressure (6). Moreover, the hypertension-related cardiovascular risk is still present at a lower blood pressure level of 115/75 mm Hg (7) and increases in blood pressure levels are an independent risk factor for cardiovascular diseases (8). Therefore, hypertension has been mainly considered as cardiovascular risk factor (9). For adults aged 18 years and over, essential hypertension, primary hypertension, raised blood pressure or high blood pressure is defined as idiopathic increases in blood pressure levels which are associated with increases in the risk of cardiovascular diseases. These increases may or may not be associated with symptoms or evidence on damaged organ (6, 9-10). I will use hypertension as a term referring either to high blood pressure or raised blood pressure.

The definition of hypertension is based upon a blood pressure threshold. The threshold is a matter of uncertainty due to the presence of the hypertension-related cardiovascular risk at lower blood pressure levels (7-8). This cardiovascular risk also increases linearly with increases in blood pressure levels (7, 11). Hence, blood pressure levels have been established to set intervention thresholds. The threshold for defining hypertension is considered to be the point at which the reduction of blood pressure should be more beneficial than dan-

gerous (12). However, using these thresholds may lead to exclude hypertensive individuals from interventions because some individuals with particular cardiovascular risk could also have blood pressure below these thresholds. As a result, different definitions of hypertension have been postulated in the current hypertension guidelines (Table 1) (13-17). Despite these differences, a blood pressure equal to or above 140/90 mmHg in adults aged 18 years and over is accepted as the minimum limit required for the diagnosis of hypertension. The England hypertension guidelines will be mentioned in a separate section.

Based on the National Health and Nutrition Examination Survey (NHANES) III, Franklin et al described three age-related sub-types of hypertension presented in Western populations. The most common subtype in individuals aged below 50 years was isolated diastolic blood pressure (IDH) (SBP<140 mm Hg, DBP >90 mm Hg); in those aged 60 years and over it was isolated systolic blood pressure (ISH) (SBP>140 mm Hg, DBP <90 mm Hg); and in those aged 50 to 60 years it was systolic/diastolic hypertension (SDH) (SBP>140 mm Hg, DBP>90 mm Hg) (18). Some definitions used in the guidelines reflect these patterns.

Diagnosis of hypertension

The measurement of blood pressure is influenced by two sources of error. One is due to the random error attributed to individual variability of blood pressure. Blood pressure fluctuates constantly during a day dipping during the first periods of sleep (19). Extreme values taken in an occasional measure tend to be lower in repeated measurements (8). The other source of error is explained by conditions affecting the technique used for the measurement. Failure to identify the Korotkoff sounds and the tendency of health workers to round readings up or down and to bias the reading towards an expected value are common errors in the measurement of blood pressure (20-21). For example, in an analysis of clinical records from patients being attended in primary care Fishman et al found that systolic blood pressure and diastolic blood pressure registered in clinical records were 3.7 mmHg and 2.8 mmHg lower compared to that reported by an external assessment (22).

The measurement of blood pressure is also affected by a transitory increase in blood pressure levels during the clinical assessment of blood pressure, named the “white coat effect” observed in some individuals (16). This response occurs in individuals who have lower am-

bulatory blood pressure levels which usually fall into a normotensive category. The cause of this response has not been totally clarified but it has been understood as a hyperactive reaction to the presence of clinical staff which is enhanced by aging arterial changes (23). In a study of 600 ambulatory individuals, Hong et al reported that the hypertension rates taken in the presence of physicians were nearly 15% higher than those taken in their absence ($p<0.05$) (24). Moreover, the use of automated devices in the assessment of blood pressure may reduce the frequency of these transitory blood pressure readings (25).

The standard method for the diagnosis of hypertension is based on the measurement of blood pressure using mercury or aneroid sphygmomanometers during clinical visits (13-15, 26-27). Alternatively automated device have been used (28). Two other methods have also been standardized for the measurement of blood pressure such as home blood pressure monitoring (HBPM) and ambulatory blood pressure monitoring (ABPM). The correlation coefficient between clinic and ambulatory measurement has been reported around 0.7 (29). Clinic blood pressure measurements tend to be higher than those observed in ambulatory assessment (30).

Table 1 Classification of blood pressure levels in hypertension guidelines

	WHO 2003			ESH-ESC 2007-2009-2013			JNC VII 2003‡		
	Systolic		Diastolic	Systolic		Diastolic	Systolic		Diastolic
Category	mm Hg		mm Hg	mm Hg		mm Hg	mm Hg		mm Hg
Optimal	<120	and	<80	<120 and	and	<80	NA		
Normal	120-129	and	80-84	120-129	and/or	80-84	120 and	and	<80
High normal	130-139	and/or	85-89	130-139	and/or	85-89	NA		
Prehypertension	NA			NA			120-139	or	80-89
Grade 1 Hypertension mild	140-159	and/or	90-99	140-159	and/or	90-99	140-159	or	90-99
Grade 2 Hypertension moderate	160 - 179	and/or	100-109	160-179	and/or	100-109	>=160	or	>=110
Grade 3 Hypertension severe	>180	and/or	>110	>=180	and/or	>=110	NA		
Isolated systolic hypertension	>=140	and	<90	>=140	and	<90			
Grade 1	NA			NA			NA		
Grade 2	NA			NA			NA		

‡ Grade 1 and Grade 2 are defined as Stage 1 and Stage 2 respectively

From reference WHO(14), ESH-ESC (15-17) , JNC VII (13)

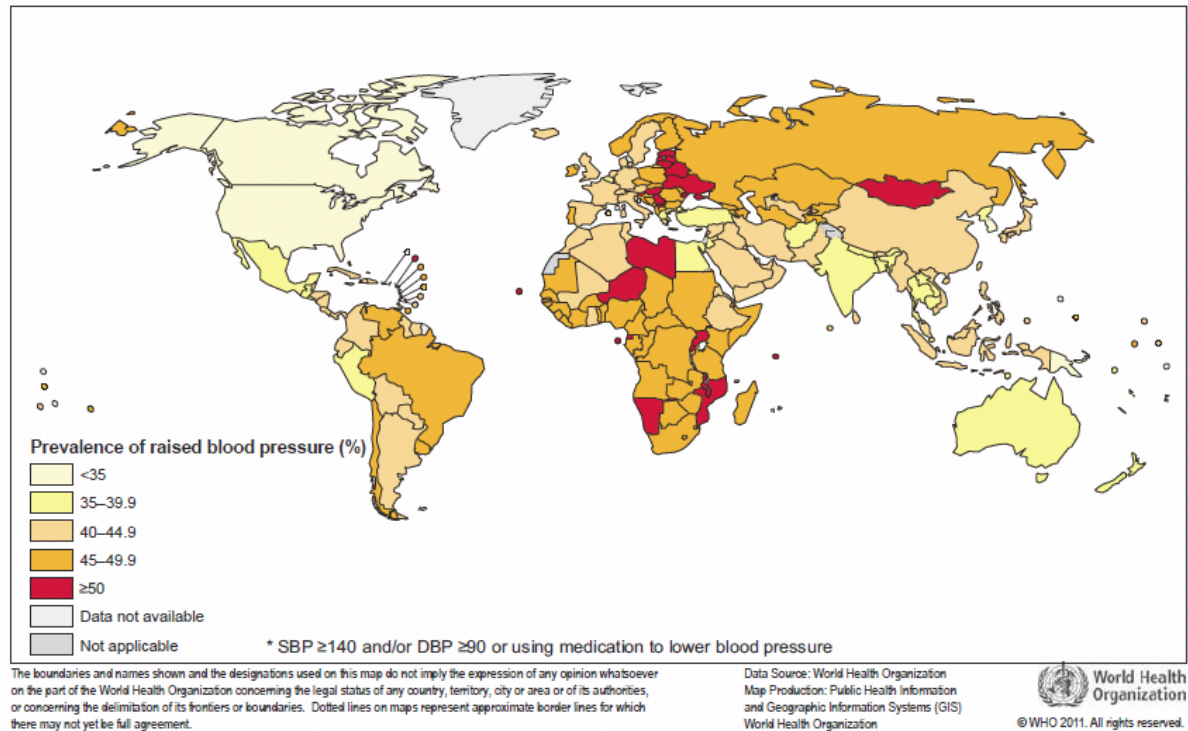
1.2 Epidemiology of hypertension

1.2.1 Global trends

Worldwide the prevalence of hypertension ranged from 20% to 45%, averaging 40%, among adults aged 25 years and over in 2008 (31-32). From 1980 to 2008 the prevalence of hypertension and blood pressure levels have decreased in developed countries (32-33). Conversely, in developing countries both the prevalence of hypertension and blood pressure levels rose during the same period (32, 34). The highest reduction has been observed in Europe and the highest increase was observed in Africa (32, 34). Prevalence rises with age so the number of people with hypertension may increase over the next few decades due to improvements in life expectancy and the ageing of the population (35) (Figure 1 -3)

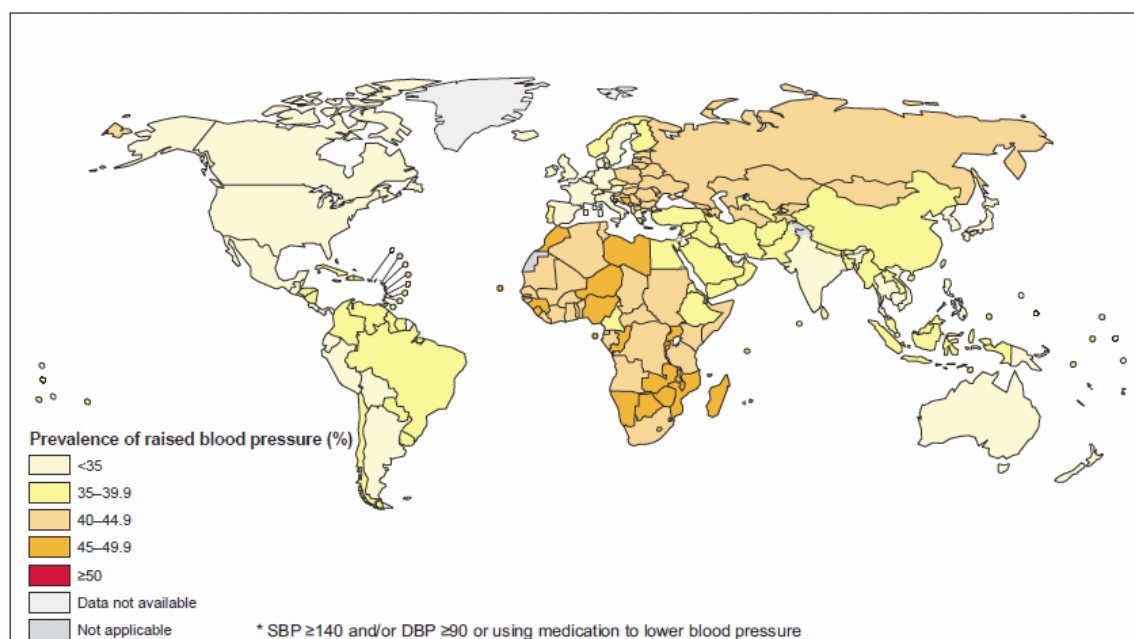
At population level blood pressure follows a log normal distribution with a positive skew towards high levels (36). For each 1 mmHg variation in the mean population blood pressure, there may be a 0.74% variation in the prevalence of hypertension in the population (37). Blood pressure levels vary across countries and between sex. Surveys from 22 countries collected from 1985 to 1993 as part of the MONICA project revealed that for men mean systolic blood pressure ranged from 124 mmHg to 148 mmHg and mean diastolic blood pressure from 75 to 93 mmHg, while for women mean systolic blood pressure ranged from 128 mmHg to 145 mmHg and mean diastolic blood pressure from 74 mmHg to 90 mmHg. 14% of population blood pressure variance was attributed to BMI (38). In an analysis of 23796 men and 24986 women from the MONICA project Merlo et al, also found that individual blood pressure levels are influenced by population conditions. The population component could explain about 7-8% of the differences in blood pressure between individuals. The contribution of the population factors to individual blood pressure levels was higher in those hypertensive individuals on treatment and/or who were overweight (39). In a systematic review of data from 786 countries, Danaei et al reported that between 1980 and 2008 mean systolic blood pressure decreased from 130.5 mmHg to 128.1 mmHg in men and from 127.2 mmHg to 124.4 mmHg in women (34). The highest mean systolic blood pressure was reported in men from Western Europe with 131.3 mmHg and the lowest systolic blood pressure was reported in women from Australasia with 117.6 mmHg.

Figure 1 Prevalence of hypertension in men aged 25 years over, standardised by age 2008



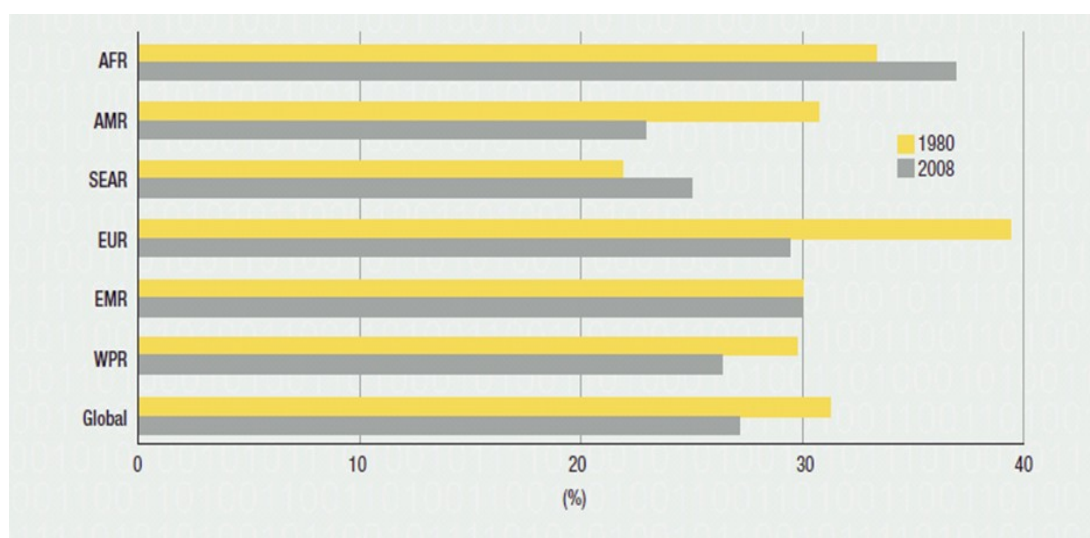
Source Global Status Report on Non-communicable Diseases, WHO 2010 (40)

Figure 2 Prevalence of hypertension in women aged 25 years over, standardised by age 2008



Source Global status report on noncommunicable diseases, WHO 2010 (40)

Figure 3 1 Percentage of adults aged 25 years and over with high blood pressure by WHO region*, 1980 and 2008



*WHO regions

AFR African region AMR Region of the Americas EUR European Region SEAR South-East Asia Region EMR Eastern Mediterranean Region WPR Western Pacific Region

Source World Health Statistics (32)

The reasons for the observed reductions in blood pressure levels have not been totally elucidated. In their analysis of the national survey from Japan, Ikeda et al partially attribute the decline to an increase in antihypertensive prescribing and lowered mean body mass index in the young population (41). In an analysis of data from the MONICA project, Tunstall-Pedoe et al found that the decline in blood pressure levels may have been driven by interventions different from antihypertensive medication (42). In Finland, the decline in blood pressure has been associated with national health promotion initiatives. The most relevant initiatives included the introduction of comprehensive primary care services, massive education on diet habits, salt labelling regulation in some products and mass promotion of physical activity (42-44).

Globally hypertension accounts for 13%, 51% and 45% of total deaths, stroke cases and ischaemic heart disease cases respectively (45-46). It is the biggest contributor to the total cardiovascular mortality and so the most important modifiable risk factor worldwide (46). 80% of hypertension-related mortality occurs in low and middle income countries. In 2006, Lawes et al reported that population with mean systolic blood pressure higher than 115 mm Hg contributed to 62% of stroke, 49% of ischemic cardiac, 76% of hypertensive disease and 14% of other cardiovascular disease worldwide (47). Although the hypertension cardiovascular risk increased with blood pressure levels, the largest amount of deaths is observed in those with lower blood pressure levels.

1.2.2 The relationship between hypertension and cardiovascular diseases

The association between blood pressure and cardiovascular diseases has been well established (7-8). The dose-response association is strong and log-linear across all blood pressure levels down to levels of 115/75 mm Hg (7-8). Hypertension-related cardiovascular risk increases with increases in blood pressure levels but the association varies with age. Among those aged between 40 and 69 years, for each difference of 20 mm Hg in usual systolic blood pressure or 10 mm Hg in usual diastolic blood pressure, there is a twofold difference in vascular mortality and a twofold difference in stroke rate. This association is about half for older (80-89 years) and younger (40 – 49 years) individuals (7). In other words, the strength of the association is lower at extreme ages and declines with increasing age (2).

Systolic blood pressure and diastolic blood pressure are both predictors of cardiovascular diseases. However systolic blood pressure and pulse blood pressure become stronger predictors than diastolic blood pressure after 50 years (48 , 49-50). The relationship between blood pressure and cardiovascular morbidity and mortality is independent of age, sex, body mass index, smoking and cholesterol (48). These associations have been consistent across different populations (8, 51-52).

Hypertension-related damage evolves over a long time (53). Initially, hypertension produces variations in lipid and glucose metabolism (54). It accelerates the age-related changes in the vascular wall leading to an increase large artery thickening and stiffness and endothelial dysfunction (55). The damage compromises all arterial system but vascular tissues located in myocardium, brain and kidney are particularly affected. The long-term effect results in organ-related diseases such myocardium infarct, stroke or chronic kidney disease (53, 56). The final impact on health is a reduction of at least five years in life expectancy which is also observed in patients with antihypertensive medication (57-58).

Hypertension is a risk factor for stroke (2, 59), coronary heart disease (50, 60), congestive heart failure (53), renal failure (56) and peripheral vascular disease (61). It has also been associated with non-cardiovascular diseases such as cognitive decline (62-63) and all-cause mortality (64). The strength of the association is stronger for stroke than for other cardiovascular diseases (8, 65). The size of hypertension-related cardiovascular risk varies between

sex, age and populations. In a review of eight trials that included hypertensive individuals aged 60 years and over, Staessen et al showed that the risk for stroke was 1.12 ($p=0.02$) and 1.04 ($p=0.37$) for coronary events with each 10 mm Hg increase in baseline systolic blood pressure (64). By comparison, middle aged individuals are more likely to suffer from ischemic cardiovascular disease (66). In the Chinese population, stroke is a more common hypertension complication rather than coronary heart diseases, and may account up to 45% of total deaths attributable to hypertension (67). Opposite association has been observed in population of Caucasian origin for whom coronary heart diseases are the most important cause of hypertension-related mortality (68). The relative risk of any hypertension related event is lower in women aged below 55 years than men of the same age. Individuals aged below 40 and those over 80 have lower risk of cardiovascular event than those aged between 40 and 80 (7, 68). The differences in follow-up and in the definition of hypertension may contribute to explaining the variations in the size of the association observed in some studies (69) (Table 2-4).

Table 2 Associated hazard risk of stroke mortality with each 20 mmHg lower systolic blood pressure

Age	Western cohort (7) (95% CI)	Asian pacific cohort (52) (95% CI)
50 – 59 years	0.38 (0.35 – 0.40)	0.46 (0.44 – 0.47)
60 – 69 years	0.43 (0.41 – 0.45)	0.64 (0.62–0.66)
70 – 79 years	0.50 (0.48-0.52)	0.75 (0.72–0.78)*
80 – 89 years	0.67 (0.63 – 0.71)	NA

*Age category 70 years and over

Table 3 Associated hazard risk of coronary heart disease mortality with each 20 mmHg lower systolic blood pressure by sex*

Age	Male (95% CI)	Female (95% CI)
40 – 59 years	0.50 (0.46 – 0.54)	0.40 (0.32 – 0.49)
50 – 59 years	0.50 (0.42 – 0.52)	0.49 (0.45 – 0.54)
60 – 69 years	0.55 (0.54 – 0.57)	0.50 (0.47 – 0.53)
70 – 79 years	0.62 (0.60 – 0.64)	0.55 (0.53 – 0.58)
80 – 89 years	0.69 (0.65 – 0.73)	0.64 (0.60 – 0.68)

*Reference (7)

Table 4 Risk of cardiovascular events in individuals aged 35-64 years with blood pressure >140/90 mmHg**

Cardiovascular events	Age-adjusted biennial rate per 1000		Age-adjusted risk ratio	
	Men	Women	Men	Women
Coronary heart disease	45	21	2.0*	2.2*
Stroke	12	6	3.8*	2.6*
Peripheral arterial disease	10	7	2.0*	3.7*
Cardiac failure	14	6	4.0*	3.0*
Cardiovascular events	65	35	2.2*	2.5*

*p<0.001

****From Framingham study (68)**

Hypertension coexists with other cardiovascular disease risk factors. In the Framingham study a clustering of risk factors such as adiposity, elevated blood sugar, elevated triglyceride, high cholesterol and alcohol intake was observed in newly hypertensive individuals (68). It was found that at least 25% of hypertensive individuals have an additional cardiovascular risk factor and moreover the prevalence of others risk cardiovascular factors increased with age. 49% of men with systolic blood pressure equal to or above 138 mm Hg and 54% of women with systolic blood pressure equal to or above 130 mm Hg had more than two additional cardiovascular risk factors (68). Similar findings have been observed in other longitudinal studies. For instance, in a cohort of 8686 women and 10503 men, Lowe et al found that 37% of men and 33.9 % of women had more than one cardiovascular risk factor such as hypertension, smoking and high cholesterol (70).

Hypertension is an independent cardiovascular risk factor. However the hypertension-related cardiovascular risk is modifiable by the presence of other cardiovascular risk factors. Individuals with two or more risk factors are at higher cardiovascular risk than those with one cardiovascular risk factor. In the Framingham study, the probability of suffering from stroke

was 20% for a 70 year old hypertensive individual on antihypertensive treatment without other cardiovascular risk factors but 40% for those of the same age with four additional risk factors such as diabetes, smoking, previously diagnosed coronary heart disease and atrial fibrillation (71). Then although the hypertension-related cardiovascular relative risk slightly varied with the presence of other cardiovascular risk factors, the hypertension cardiovascular absolute risk measured as percent of event risk per year varied with the presence of other cardiovascular risk factors (72).

1.2.3 Risk factors for hypertension

There are variations in blood pressure levels across age categories and sex. Studies carried out in Western societies have revealed that whereas systolic blood pressure rises continually with age starting at 30 years; diastolic blood pressure rises continually until 50 years and then remains stable or slightly decreases (73). This increase is related to initial value of blood pressure and occurs in a stepwise fashion over a period of at least four years (74). Men develop higher systolic blood pressure levels up to the age of 50 in comparison with women of the same age, but women aged over 50 years have higher systolic blood pressure levels than men (73, 75). However these trends have not been observed in populations living in rural areas (76). Hence these patterns have been considered to be related to environmental factors occurred in western societies rather than only as a result of physiological changes (77).

Individuals of different racial origin have different patterns of blood pressure. Adults of African origin living in developed countries have higher blood pressure levels in comparison with individuals of white origin (78-80). They also have a higher prevalence of hypertension (81) and higher incidence of hypertension-related cardiovascular disease (82). Unlike African descendents living in Western societies, African citizens living in rural African areas have lower blood pressure levels (83). In Africa, rural populations have lower blood pressure levels than urban populations (83-84). However a similar prevalence of hypertension in African and white populations living in a developing country has also been reported (85-86). Then genetic and environmental conditions have been associated with raised high blood in migrant individuals with African origin (87-89). In contrast migrants from South Asia living in

developed countries tend to have lower blood pressure levels than white population (90-91). Other migrant populations such as Chinese and Hispanic residents in developed countries have developed patterns of blood pressure levels similar to those observed in the white population (81, 92-94).

Parental raised blood pressure is a risk factor for developing high blood pressure levels (95). High correlation of blood pressure levels among twins also supports a familial pattern (96). A variety of genetic determinants associated with blood pressure levels have been identified (97-99). Recently, Ehret et al described a genetic risk score which included 29 genome variants linked to blood pressure regulation. It explained up to 2.5% of the variation in blood pressure level and was also associated with developing hypertension, left ventricular wall thickness, stroke and coronary heart disease (100). This evidence established that there are multiple genes which have contributed to the increment of blood pressure in adults (101). However, the association between blood pressure levels in childhood and in adulthood has not been completely understood possibly due to differences in the method used measure blood pressure in infants and adolescences (102). Additionally, the association has also been weak (103) though multiple measurements may improve the prediction (104). Then genetic determinants are not a sufficient cause in themselves as environmental factors also play a significant causal role in the development of hypertension (105).

Sodium intake has been also linked to raise blood pressure. The lower the salt consumption, the lower the blood pressure level (106-107). Levels of sodium excretion have also been found to have significant and independent positive association with systolic blood pressure (108). This association has also favoured increases in systolic blood pressure levels with age (109). Populations who migrate from low salt to higher salt intake environments evolve to hypertensive status (110-111). The relationship between salt and hypertension has also been demonstrated by interventions aimed at reducing salt intake. A decline of 3 mm Hg systolic blood pressure was associated with a decrease of 2g in daily urine sodium chloride excretion in volunteers exposed to a diet education program (112-113). Hypertensive individuals under a sodium restricted diet significantly lowered their blood pressure levels (114).

Population strategies reducing salt consumption were followed by a reduction of 10 mmHg in the population-average systolic and diastolic blood pressure (115). These observations have also been documented in non-human primates. Providing a diet with a progressively higher content of sodium significantly elevated their blood pressure in chimpanzees (116). In a cohort of 3681 individuals recruited for the FLEMENGHO study, Stolarz-Skrzypek et al also found that for each 100-mmol increase in sodium excretion, there was a 1.71 mmHg increase in systolic blood pressure (117). Hence excess salt intake is an independent causal but not sufficient factor of raised blood pressure.

Body index mass has been associated with an increasing probability of having higher blood pressure levels. The incidence of hypertension appears to increase linearly with increases in body index masses (83, 118). This association has been identified across different ethnicity groups (119-120). However the strength of the association may differ between ethnic groups and also starts at a different body mass index thresholds using for the definition of overweight (120). This may be explained by genetic predisposition in different ethnicities (121-123). Reassuring a higher body index mass is a risk factor for raised blood pressure, though the causal pathway has not been clarified yet.

Others factors have been associated with raised blood pressure. For instance, having a low birth weight increased the probability of being hypertensive in adulthood. The strength of the association varies across different studies but the association is consistent (124-126). Another factor is the concentration of potassium in daily diets. Low potassium intake has been related to increases in blood pressure levels (127-128). A paternal hypertensive response to low potassium intake has been described (129). Consequently, diets with low salt content and higher potassium content have been recommended to lower blood pressure (130). An association between other nutrients such as magnesium, calcium and phosphorus and higher blood pressure levels has been less well established (131-132). Diverse habits have also linked to hypertension. The risk of being hypertensive increases in alcohol drinkers (133). The association is positive but seems to follow a J-shape pattern (134-135). Smoking has mainly been related to a temporary increase in blood pressure though this effect could potentially be a determinant of hypertension (136-137).

Socio-economic conditions have been additionally associated with increases in blood pressure levels. In their analysis of the MONICA project, Merlo et al found a positive gradient between education and high blood pressure levels. Thus women and men with the lowest educational background had 3 and 2 mm higher systolic blood pressure respectively compared to those with the highest education background (39). By contrast, Orduñez et al found the effect of education on blood pressure levels was sex-dependent (85). Regardless of race/ethnicity women with highest level of education were less likely to have hypertension compared to those with lowest level of education. But an opposite association was observed in men (85). In a study of 11357 individuals with genetic ancestry, Non et al found that differences in blood pressure between whites and blacks were due to differences in education rather than genetic factors (87). Prince et al found a heterogeneity effect of education on blood pressure levels across 12 population samples of older individuals from 8 non-developed countries. Participants with higher education scores living in Cuba, China, Dominican Republic and China were less likely to have hypertension. By contrast those with a similar level of education living in Peru, rural Mexico and India were more likely to have hypertension. The association also varied between women and men (138).

1.2.4 Treatment of hypertension

Pharmacological intervention

The aim of hypertension treatment is to reverse hypertension-related cardiovascular risk. Evidence from clinical trials extensively supports the benefit of lowering blood pressure produced by pharmacological interventions. For each 10 mm reduction in systolic blood pressure or 5 mm Hg reduction in diastolic blood pressure, there is a 22% reduction in coronary heart diseases and a 35% reduction in stroke (139). This effect seems to be similar among all antihypertensive drug classes with slight differences. Calcium channels blockers (CCB) seem to produce a higher reduction in the relative risk of suffering from stroke (139) and a lower reduction in heart failure. Beta blockers (BB) class drug had a greater effect in preventing recurrent coronary heart diseases in those with a history of coronary heart disease. (139)

The reduction in cardiovascular hypertension associated risk is correlated with reductions in blood pressure levels (140). This effect has been observed regardless of baseline blood pressure levels. In a meta-analysis of 32 clinical trials, Czernichow et al demonstrated that the relative reduction in cardiovascular outcome was similar across all range of baseline blood pressure levels (141). The impact of hypertensive treatment has also been observed across all age groups. In a meta-analysis of 37 clinical trials, Turnbull et al found that the relative risk reduction in cardiovascular events is similar in patients aged above and below 65 years (142). This reduction has not varied between antihypertensive drug classes. Differences in the lowering blood pressure effect have been observed between ethnic groups. Black patients tended to have a lower response to ACEI and BB (143). However the guidelines do not establish any particular recommendation about the first line recommendation related to race/ethnicity. Only the England hypertension guidelines has established an ethnic-age algorithm (144). The main antihypertensive drug classes and their mechanism of action are shown in box 1.

Box 1 Main classes of lowering blood pressure drugs

Drug class	Main antihypertensive mechanism of action
Diuretics (Thiazide class) (DD)	To block renal sodium absorption in the early part of distal tubule (145)
Beta blockers (BB)	To block postsynaptic receptors of noradrenaline system (145)
Angiotensin converting enzyme inhibitors (ACEI)	To inhibit angiotensin converting enzyme resulting in lower levels of angiotensin II and aldosterone levels (145)
Angiotensin receptor blockers (ARB)	To inhibit the angiotensin II receptor producing vasodilatation lead to a reduction in peripheral resistance (145)
Calcium channel blockers (CCB) (Dihydropyridines class)	To block L type calcium channels in vascular cells producing vasodilatation (145)

The initiation of antihypertensive medication is based on the level of blood pressure and the assessment of the individual absolute cardiovascular risk (13-17). The threshold for commencing treatment varies among guidelines (Table 5). There are different scores to assess the absolute cardiovascular risk but the Framingham score is the one most commonly recommended. The drawback of using the Framingham score is the potential overestimation of cardiovascular risk in populations different from Americans (146). Despite differences between guidelines, patients are classified at low cardiovascular risk, middle cardiovascular risk and high cardiovascular risk with regard to cardiovascular scores and/or the presence of an additional cardiovascular comorbidity. Patients at low cardiovascular risk are those with hypertension but without other cardiovascular risk factors and/or other established cardiovascular diseases. Those at middle cardiovascular risk have more than one cardiovascular risk factor and patients at higher cardiovascular risk have more than 2 or cardiovascular risk factors and/or additional cardiovascular diseases (13-16).

Table 5 Thresholds for starting antihypertensive treatment established in hypertension guidelines

Guidelines	Assessment of cardiovascular risk	Blood pressure threshold mmHg*
WHO (14)	Framingham score Target-organ damage Other cardiovascular comorbidities	$\geq 140/90$ mmHg
ESH-ESC (15-17)	Chart based on blood pressure levels, cardiovascular risk factors, diabetes, renal disease and established cardiovascular disease	140-150/90-99 mmHg
JNC 7 (13)	Framingham score Evaluation of damaged organ	$\leq 140/90$ mmHg

*Threshold for patients without other comorbidities and no other cardiovascular risk factors and without response to non-pharmacological interventions

Non-pharmacological treatment

Non-pharmacological interventions have been demonstrated to be effective in lowering blood pressure. These interventions include low salt consumption, weight reducing diet, regular exercise, maintaining adequate BMI and moderate alcohol consumption (147-148). Salt intake reduction has consistently led to low blood pressure. In a meta-analysis of twenty nine clinical trials, He et al showed that a reduction of 4.6 gram in salt intake correlated with a 4.6 mmHg reduction in systolic blood pressure (149). The effect on lowering blood pressure was observed in a short time after starting a salt restriction diet. Among those studies including only hypertensive patients, the salt intake fell from 9.5 gr/day (7.3– 11.2 g/day) to 4.4 gr/day (3.1-6.8g/day). A reduction in 6gr/day salt intake was associated with a decrease of 10.8 mm Hg (3.5 mm Hg – 18.2 mm Hg) in systolic blood pressure. There was no association between salt intakes and diastolic blood pressure (12). Bray et al observed that the salt-related blood pressure reductions are higher in individuals of black origin and older patients than in white and younger individuals (150). The guidelines differ in the recommendations about salt consumption. The JNC 7 report recommends 2gr/day in salt intake and the 2011 NICE guidelines establish a minimal consumption between 3 and 7 gr/day for all hypertensive patients (13, 144).

Exercise has the potential to reduce blood pressure levels independently of weight loss. In a meta-analysis of 54 clinical trials testing the impact of aerobic exercise on blood pressure, Whelton et al found that regardless of hypertension status and race/ethnicity participants exposed to aerobic exercise achieved a reduction of 3.8 mm Hg and 2.6 mm Hg in systolic and diastolic blood pressure respectively (151). Similarly, Cornilesen et al found that any type of physical activity was associated with a reduction of between 1.8 mm Hg and 10.9 mm Hg in systolic blood pressure. The effect was observed in hypertensive and non-hypertensive patients (152). There may a threshold in the effect of exercise on blood pressure. In a clinical trial comparing groups with different frequencies in physical activity, Ishikawa et al found that those doing physical activity during 61 and 90 minutes per week achieve lower blood pressure than those doing 30-60 minutes per week. However, those doing more than 90 minutes did not achieve longer reductions (153). A regular aerobic exercise with a minimum duration of 30 minutes almost every day of the week has been recommended as a part of the non pharmacological treatment for hypertensive patients (13).

Losing weight has been associated with reductions in blood pressure levels. In a clinical trial assessing the benefit of exercise and losing weight in participants without high blood pressure or with stage 1 or 2 hypertension, Blumenthal et al demonstrated that those who lost weight experienced a higher reduction in blood pressure than those who did not modify weight though they both following the exercise recommendation (154). The level of adherence to interventions was 84%. Reducing weight using diet results in lower blood pressure levels than those produced by pharmacological interventions (155). Lowering weight is also associated with a lower incidence of hypertension (156). For instance, Stevens et al reported that even small reductions in weight as low as 0.2 kilograms reduced the risk of developing hypertension (157). In the TONE trial hypertensive patients aged 66 years and over attaining only small reductions in weight were less likely to reach reduced blood pressure levels compared to those who achieved the mean weight reduction of 4.7 kilograms (151).

Interventions aimed at lowering weight usually concurred with diet and exercise interventions. The DASH trial demonstrated the independent effect of a diet based on fruits, vegetables and reduced saturated fat in lowering blood pressure levels (158). Hypertensive participants who were assigned the recommended diet achieved blood pressure reductions between 5 and 11 mm Hg. From a review of eighteen clinical trials, Mulrow et al concluded that the impact of weight loss diets on lowering blood pressure is modest but may be enough to reduce the use of antihypertensive medication (159). However, the long term effect of weight loss diets is uncertain. The clinical trials testing these diets have usually included small numbers of patients with hypertension at early stages. Additionally, the studies were conducted over short follow-up periods (160). Some guidelines advice is to maintain a BMI between 18.5 and 24.5 kg/m² and regular consumption of DASH diet (13)

Reduction in alcohol consumption has also led to reductions in blood pressure. In a meta-analysis of fifteen clinical trials testing interventions for alcohol reduction in hypertensive and normotensive individuals, Xin et al found a mean reduction of -3.31 mmHg (-2.52 to -4.1 mm Hg and -2.04 mm Hg (-1.49 to -2.58 mm hg) in systolic blood pressure and diastolic blood pressure respectively to be associated with a 67% reduction in alcohol consumption (161). However among the included trials only seven reported significant reductions in blood pressure. Moreover, the studies had a short follow up period so that the effect of cardiovascular morbidity was not evaluated. Evidence of the relationship between cardiovascular morbidity

and alcohol consumption has been contradictory. Whereas some studies have revealed that alcohol consumption increases the risk of stroke (162), others have reported that light consumption of alcohol reduces the risk of coronary disease (163). Nevertheless, hypertension guidelines advise drinking moderate amount of alcohol (13).

Other non-pharmacological interventions for the management of hypertension have been less well supported. Steffen et al performed a review and meta-analysis of clinical trials and cohort studies to assess the effect of caffeine and blood pressure. They included ten clinical trials and five cohort studies. Their analysis of clinical trials did not reveal significant differences in blood pressure between groups with and without consumption of coffee and neither did the cohort studies reveal a higher incidence of hypertension in those exposed to coffee intake compared to those not being exposed (164). The heterogeneity observed across the studies limit the extent to which a definite answer may be given about the association between coffee and blood pressure.

Evidence supported potassium supplement has been contradictory. In an analysis of thirty three clinical trials testing the effect of potassium on blood pressure reduction, Whelton et al reported that supplementing with oral potassium led to significant reductions in blood pressure levels (165). By contrast, in a review of six clinical trials, Dickinson et al did not find a significant effect of potassium supplementation on blood pressure levels (166). However, the short follow-up in the clinical trials prevent from establishing the relationship between potassium and blood pressure. Similarly, there is no supportive evidence on the association between blood pressure and calcium or magnesium. That may be due to the small number of included patients, the short follow-up period and the lack of adequate randomised allocation observed in some studies testing the effect of diets with calcium and magnesium supplementation on hypertension (167-169).

Relaxation therapies have also been intended to lower blood pressure. In a meta-analysis of 24 clinical trials testing meditation techniques in hypertensive population, Ospina et al found that Tai Chi, yoga, and yoga combined with biofeedback reduced systolic blood pressure significantly compared to no treatment. Yoga with biofeedback was superior at reducing blood pressure than education. Transcendental meditation was better than progressive muscular relaxation in lowering blood pressure. The Zen Buddhist relaxation method resulted in lower reductions in diastolic blood pressure than blood pressure assessments (170). However the small numbers of patients with a short follow-up included in the studies prevent conclusions being drawn with regard to the benefits of this techniques for the management of hypertension (170).

Key points

- ✓ There is no threshold to define normal blood pressure
- ✓ The hypertension-related cardiovascular risk is presented across the whole of range of blood pressure levels down to levels of 115/75 mmHg.
- ✓ For adults aged 18 years and over hypertension is a level equal to or above 140/90 mmHg of blood pressure
- ✓ In Western societies, blood pressure levels increase with age.
- ✓ Excess salt intake and higher body mass index have been positively associated with increased levels of blood pressure across different social and environmental conditions.
- ✓ Differences in blood pressure levels between race/ethnic groups have been described. Globally, African-descendent individuals living in western societies have higher blood pressure levels than other race/ethnic groups.
- ✓ Hypertension is a risk factor for stroke, coronary heart disease, heart failure and chronic kidney disease.
- ✓ Nearly 40% of individuals aged 25 years and over suffer from hypertension worldwide
- ✓ Since 1980 there has been a reduction in blood pressure levels in developed countries and an increase in blood pressure levels in developing countries.
- ✓ 50% of total cardiovascular mortality is attributed to hypertension worldwide.
- ✓ 80% of hypertension-related cardiovascular diseases occur in middle and low income countries.
- ✓ Hypertension is a modifiable cardiovascular risk factor.
- ✓ For each 10 mmHg reduction in systolic blood pressure or 5 mmHg reduction in diastolic blood pressure, there is a 22% reduction in coronary heart diseases and a 35% reduction in stroke.

1.3 Definition of Blood Pressure Control

The aim of lowering blood pressure is to reverse the hypertension-related cardiovascular risk (171). Reductions in blood pressure lead to reductions in hypertension-related cardiovascular risk. With a 10 mm Hg reduction in systolic blood pressure or 5 mmHg in diastolic blood pressure, the risk of coronary heart disease and stroke events drops by 24% and 33% respectively (139, 172). However, to what extent blood pressure levels must be lowered is a matter of controversy (173). Clinical guidelines have postulated that the achievement of a recommended blood pressure level, i.e. defined targets, determines the control of blood pressure. Hypertensive patients are classified into those with controlled or uncontrolled hypertension based upon whether or not they achieve that target (13-14, 16, 144, 174). This section reviews the definition of targets for blood pressure control.

1.3.1 The definition of blood pressure targets

Blood pressure should be reduced to a level at which the reduction is more beneficial than harmful (12). The association between blood pressure and cardiovascular risk however creates uncertainty over the definition of that level. On the one hand, observational studies conducted at a population level have demonstrated that the association between blood pressure levels and cardiovascular mortality and morbidity exists across all ranges of blood pressure levels even at low values of 110/70 mmHg (7-8). This evidence therefore supports the idea that the lower the blood pressure, the better. On the other hand, clinical trials carried out on hypertensive patients have consistently shown that reductions in blood pressure levels result in significant reductions in the hypertension-associated cardiovascular risk (172, 175). This effect has also been shown to be independent from the patient's baseline blood pressure (139, 172, 175). In other words, data from clinical trials reinforce the findings from cohort studies in showing that there is no a blood pressure threshold at which cardiovascular risk is not longer associated with blood pressure.

Despite the known benefits from lowering blood pressure, the relationship between blood pressure reductions and cardiovascular mortality seems to follow a J curve pattern (176-177). Thus extreme reductions in blood pressure levels could lead to cardiovascular mortality. Messerli et al illustrated this relationship in a secondary analysis of the INVEST trial (178). They found that hypertensive patients with coronary heart disease who achieved a blood pressure levels below 129/74 mmHg had a higher risk of dying from all cause mortality in comparison to those with higher blood pressure levels. Patients with a lower baseline systolic blood pressure were found to have a higher prevalence of myocardial infarction, heart failure and cancer. The presence of heart failure was the most significant comorbidity associate with the outcome (178).

In a cohort of elderly patients, Merlo et al found that hypertensive patients on treatment who achieved diastolic blood pressure below 90 mmHg had fourfold increase in incidence of ischaemic cardiac events (179). The nadir of the J curve seems to appear at levels below 135/85 mm Hg (179-180). Bangalore et al reported that the achievement of systolic blood pressure below 135 mm Hg is associated with a slight but significant reduction in stroke and heart failure. They warned that this modest benefit may be counterbalanced by the higher risk of hypotension (181). However, in the Cardiovascular Health Study, Psaty et al did not find that systolic blood pressure between 125 and 135 mmHg increased the risk of stroke and/or myocardial infarction among elderly hypertensive individuals (182). Similarly, Hansson et al report that hypertensive adults can achieve diastolic blood pressure below 80 mmHg without increases in adverse effects (183). Aronow et al recommend that a target of below 140/90 mmHg for the management of hypertensive elderly adults. They advised that this target is based on expert opinions rather than evidence from clinical trials (184). Additionally, the increase in cardiovascular risk associated with lower blood pressure has mainly been documented in patients with established coronary heart diseases (178, 185). Consequently, there are questions over whether this adverse effect is due to antihypertensive treatment or the patient's conditions. Nevertheless, these observations have raised doubts upon using the idea of "the lower, the better", for the management of hypertensive patients and particularly in those with coronary heart diseases.

Regarding the limitations of defining a blood pressure threshold, there has been a need to identify a level to which blood pressure should be lowered. Randomised clinical trials comparing patients allocated to different blood pressure targets have been considered the goal standard for establishing that level (186-187). Two systematic reviews, using similar sources

of information, summarised the results from clinical trials assessing two or more blood pressure targets (188-189). Arguedas et al searched articles in MEDLINE (1966- April 2008), EMBASE (1980 – April 2008) and Cochrane Central Register of Controlled Trial (CENTRAL) (until April 2008) (188) and Lv et al did in MEDLINE via OVID (1950 – July 2011) EMBASE (1966 – July 2011) and the Cochrane Library database (189). Whereas Arguedas et al did not find significant reductions in total and cardiovascular mortality and morbidity associated with lower blood pressure targets (188), Lv et al reported that lower blood pressure targets produced reductions in cardiovascular morbidity such as stroke and end stage kidney disease (ESKD) but not in total and cardiovascular mortality (189).

A comparison of both reviews is presented in table 6. The period of both reviews overlaps until April 2008. The number of articles included by Lv et al is higher because they used wider inclusion criteria for blood pressure targets, a longer time period and full age range of patients including children (189). They also included all the studies selected by Arguedas et al (188-189). None of the reviews found significant heterogeneity in the mortality cardiovascular and total mortality outcomes between the studies included. Thus, in all clinical trials included the rate of total and cardiovascular mortality observed in the group with less intensive targets was similar to that of in the group with the standard target. Lv et al attributed the difference in the other results to the lower power of the review conducted by Arguedas et al (188-189). However, I present other potential explanations for the observed discrepancies. I also take into consideration other possible reasons for interpreting the lack of differences in cardiovascular mortality between groups with intensive and standard blood pressure targets.

A summary of all clinical trials included in both reviews is presented in appendix B. I have excluded the SCAPE trial because it was conducted in patients below 18 years (190) and the current review only applied to hypertensive patients aged 18 years and over. The age of the included patients ranges from 17 to 90 years but most of them were over 40 years. The percentage of men was higher in the studies with a population aged mainly below 60 years. By contrast the percentage of females increased in those trials carried out on patients over 60 years. Except for two trials (191-192), the race/ethnic origin of the included population was mainly white. Patients were mainly at high cardiovascular risk with five out of all trials conducted only in patients with diabetes.

Table 6 Description of systematic reviews assessing blood pressure control targets

Characteristic	Arguedas et al (188)	Lv et al (189)
Period	1966 - April 2008	1950 - July 2011
Research question	Determine the association between lower blood pressure targets and reduction in total mortality and morbidity	Assess evidence for using lower blood pressure targets
Language	No language restriction	No language restriction
Population	Adults (No age was defined)	No age restriction
Interventions	Comparisons between two targets (135/85 mmHg vs 140/90 mmHg)	Comparisons between targets
Type of studies	Randomised clinical trials	Randomised clinical trials
Outcomes		
Primary	All-cause mortality (Cardiovascular and non- cardiovascular mortality) Total serious adverse events	Major cardiovascular mortality (myocardial infarction, stroke, heart failure and cardiovascular death)
Secondary	Systolic and diastolic blood pressure achieved Withdrawals due to adverse effects	Mortality by each cause included in primary outcome End stage kidney disease Adverse outcomes
Bias assessment	Cochrane Reviewers Handbook	Cochrane Reviewers Handbook
Individual data included	No	No
Test for heterogeneity	I ₂	I ₂
Outcome assessment	RR	RR

Continuation table 6		
Characteristic	Arguedas et al (188)	Lv J et al (189)
Statistical methods	Fixed effects model Random effects model if heterogeneity was significant	Random effects model
Results		
Total clinical trials included	7	15
Total patients included	22089	37894
Total mortality events	384	1584
Total major cardiovascular events	998	1984
Total end stage renal disease cases	252	941
End achieved blood pressure levels	Lower blood pressure group Mean systolic blood pressure 139.3 mm Hg Mean diastolic blood pressure 81.5 mm Hg Standard blood pressure group Mean systolic blood pressure 143.2 mm Hg Mean diastolic blood pressure 85.1 mm Hg	Not reported

The trials included in the reviews used different definitions of targets. Six trials used diastolic blood pressure (185, 191, 193-196), four used systolic blood pressures (197-200), two used systolic and diastolic blood pressure (193, 201) and two used mean blood pressure (192, 202). The trials using diastolic blood pressure may have underestimated the effect of lowering blood pressure particularly in patients aged over 55 years. Diastolic blood pressure tends to decrease with age such that the strength of the association between diastolic blood pressure and cardiovascular mortality becomes weak with age (48-49, 65, 73, 203). Compared with diastolic blood pressure, systolic blood pressure contributes more to predicting the risk of hypertension-related cardiovascular mortality particularly in those at the age of 55 years and over (48, 50, 65, 204). Therefore, using systolic blood pressure has been recommended as a target for the management of hypertension (10, 60, 204-205). Some Clinical trials report mean achieved blood pressure as an outcome of the interventions. Using mean blood pressure as a target may not accurately identify who is achieving lower blood pressure levels. That is because of by calculating mean blood pressure as $2/3$ diastolic plus $1/3$ systolic, it is possible that two different measurements of blood pressure can produce the same mean blood pressure (188). Consequently, the trials assessing reductions in systolic blood pressure may provide more appropriate conclusions on the impact of using a specific blood pressure target.

The changes in blood pressure levels over the follow up period varied across the studies. Five of the included trials reported the percentage of patients who achieved blood pressure targets (185, 197-198, 201-202). Among them, the percentage of hypertensive patients randomised to the intensive blood pressure target who achieved the expected target ranged from 56% to 72 %. Except for one study (197), lower percentages of hypertensive patients with controlled blood pressure were observed in patients allocated to intensive blood pressure targets. The mean difference in systolic and/or diastolic blood pressure between a standard blood pressure target group and an intensive blood pressure target group was significant in six of the included trials (191, 197, 199-202). Five trials reported significant differences in the achieved blood pressure based on the comparison of mean achieved systolic and/or diastolic blood pressure between both groups (193-194, 196, 198, 206). The reported differences are mainly based on p values with three trials reporting confidence intervals of the comparing estimators. Although the p value provides certainty that the probability of the difference is not due to chance, use of confidence interval is recommended to establish the magnitude of the differences (207-209). The distribution of blood pressure achieved by in-

tensive and standard blood pressure values was described in two trials (185, 192, 210). The distributions have similar ranges of values but with a different mean. Hence it seems that the distribution of blood pressure levels achieved by intensive and standard blood pressure control may overlap despite significant differences in the mean end blood pressure.

Therefore using blood pressure achieved by patients included in clinical trials as a blood pressure target has been questioned. The associations between final achieved blood pressure and clinical outcomes may have been influenced by confounding variables (210). Davis et al illustrated this potential limitation in the interpretation of the African American Study of Kidney Disease (AASK) clinical trial results (210). This study was included in both reviews. Davis et al analysed data from AASK trial by using two approaches: intention to treat analysis and analysis based upon stratification by final achieved blood pressure regardless of allocation to the treatment or control group. The intention to treat analysis revealed that there were no significant differences in the rate of decline in glomerular filtration rate and total composite outcome (dialysis, transplantation or death) in spite of the treatment and control groups achieving different mean blood pressure. By contrast, the analysis based on stratification by final achieved mean blood pressure regardless of treatment allocation showed faster decline in the glomerular filtration rate and increased risk of total composite outcome for each 10 mmHg increase in achieved mean blood pressure. Although there were no differences in baseline characteristics between the two randomised groups, there were differences in patient characteristics between those with lower mean blood pressure and those with higher mean blood pressure at the end of the study. Patients with less comorbidity, higher adherence and less severe disease were more likely to achieve lower blood pressure targets and this may have driven the different conclusions reached by the two different methods of analysis.

Arguedas et al also reported that the effect of the assessed interventions on lowering blood pressure varied between studies (188). In other words there was a significant heterogeneity in blood pressure reductions across studies. The authors did not report the reasons for this observation. Lv et al did not mention whether blood pressure reductions were heterogeneous across the selected trials (189). As far as is known the blood pressure lowering effect is similar among all classes of antihypertensive drugs (139, 211). Therefore the observed differences in achieved blood pressure reductions may be attributed to differences in patient

characteristics in the different clinical trials. Lower baseline blood pressure levels may favour a particular group of patients for example those without additional comorbidity or those with advanced renal disease (210, 212-213). Similarly, patients with higher systolic blood pressure levels may attain lower reductions in blood pressure. Reductions in systolic blood pressure have been more difficult to reach than reductions in diastolic blood pressure (18, 214). Differences in follow-up periods may also affect to what extent blood pressure has been lowered.

The association between cardiovascular mortality and blood pressure targets varies between each meta-analysis. Arguedas et al did not find significant differences in cardiovascular mortality between intensive target group and standard target groups in spite of reporting significant differences of 6.8 mmHg in achieved systolic blood pressure and 5.4 mmHg in achieved diastolic blood between both groups (188). This negative result may differ from that has been observed in clinical trials evaluating the efficacy on antihypertensive drugs. In 17 clinical trials conducted before 1994 the mean diastolic blood pressure difference ranged from 4 to 6 mmHg. These differences were associated with an average 21% reduction in cardiovascular mortality (215). A 2001 meta-analysis of 9 clinical trials showed that differences in systolic blood pressure as low as 5 mm Hg between experimental groups produced a significant reduction in the risk of cardiovascular mortality (216). Lv et al reported a reduction of 11% in the relative risk of cardiovascular events associated with using intensive blood pressure targets. However they did not find differences in cardiovascular mortality risk between both groups (189). Two of the included studies report a lack of statistical power to detect significant differences in cardiovascular mortality between both groups (199-200). The results of the AASK trial corresponded to the period after finishing the original trial, in which less than 50% of the initially included patients remained (217). Because the authors did not establish the criteria for defining the intensive blood pressure targets, the reported findings mainly strengthen the idea that reductions in blood pressure lead to reductions in cardiovascular mortality rather than there being any benefit from using intensive blood pressure targets.

Arguedas et al reported no associations between intensive blood pressure targets and reductions in the risk of stroke (188). The finding was mainly due to the results from the HOT trial. As mentioned in this trial the achieved blood pressure levels between the randomised groups overlapped (185). By contrast Lv et al documented that using intensive blood pres-

sure targets was associated with reductions in the risk of stroke (189). The result was expected due to the strong association between stroke and blood pressure (7). In clinical trials, the achievement of systolic blood pressure to levels of 140 mm Hg and as low as 120 mm Hg has consistently been associated with a reduction in the risk of stroke (218-221). It seems that the lower the better apply to achieving the highest reduction in the risk of stroke.

The reviews also differ in their findings concerning the association between using intensive blood targets and the risk of end stage kidney disease. The difference is essentially explained by the analysis of the MDRD trial (202). Whereas Arguedas et al included the results from the original trial (188, 202). Lv et al included the results of the study which used the extended follow-up period. This complementary analysis was done without taking into account the original randomization procedure and including less than 50% of the original number of patients (189, 222). Hence the conclusion from this analysis may be biased.

Given the evidence provided by these two reviews, it appears that the definition of the blood pressure target for the management of hypertensive patients is a matter of uncertainty. The lack of associations reported by Arguedas et al may be due to the blood pressure targets used in the included studies, mainly diastolic blood pressure, and the low numbers in the patient with the expected outcome. Lv et al reported some benefits associated with the use of intensive blood pressure targets. The analysis of mixed population, one study includes patients below 18 years and the inclusion of trials using data from post hoc analysis may detract from drawing any conclusions regarding a target level for the management of hypertension. However this review provided additional evidence regarding the benefit of intensifying the lowering of blood pressure, particularly in hypertensive patients at a high cardiovascular risk.

1.3.2 Targets for specific populations

Patients at high cardiovascular risk

Lower blood pressure targets have been recommended for patients at a high cardiovascular risk. This patient group includes hypertensive patients with at least one of the following conditions: diabetes, chronic renal disease, stroke, coronary heart disease or heart failure. Patients with an additional cardiovascular risk and blood pressure levels over 180/100 mmHg are also considered within this category (13-15, 223). A blood pressure level of 135/85 or below 130/80 mmHg has been recommended as a target for patients at higher cardiovascular risk (13, 16, 224-226). The 1993 WHO hypertension guidelines initially advised using lower blood pressure targets without considering any particular level (227). The recommendation was supported by the SHEP study in which lowering blood pressure in patients over 60 years with baseline diastolic blood pressure of 77 mmHg led to reduction in major cardiovascular events (219, 227). Early clinical trials carried out mainly in hypertensive patients at a higher cardiovascular risk reported mean achieved blood pressure between 138/82 mmHg and 149/92 with percentages of patients achieving blood pressure below 140/90 mmHg ranging between 49% and 64% (185, 220-221, 228-234). Globally, these studies showed that patients with lower blood pressure levels experienced a greater reduction in hypertension-related cardiovascular risk than those with higher blood pressure levels. None of the studies aimed to assess any particular target except for the HOT trial (185).

Recent clinical trials are inconclusive with regards to the definition of blood pressure targets. The FEVER study reported that hypertensive patients at a high cardiovascular risk achieving a blood pressure of 138.1/82.3 mmHg experience a 27% reduction in the relative risk of stroke in comparison with those achieving a blood pressure of 142.5/85 mmHg (235). The findings may not totally apply to other populations because the study includes only a Chinese population. The association between blood pressure and stroke is stronger in a Chinese population than that observed in other populations (52, 236). In the ONTARGET trial, hypertensive patients at a high cardiovascular risk with mean achieved blood pressure of 132/75.8 mmHg had no differences in the risk of cardiovascular mortality compared to those with mean achieved blood pressure of 135.4/77.8 mmHg (237). Those patients with higher reductions in blood pressure also exhibited higher rates of hypotensive symptoms, syncope

and renal dysfunction. The side effects were associated with the combination of telmisartan and ramipril (237). The ProFESS trial showed that there were no differences in the stroke or major cardiovascular events between patients who achieved mean blood pressure of 136.8/78.0 mmHg and those who achieved 140.3/80 mmHg. The follow-up period was 2.5 years and stroke events that occurred during the first six months were excluded from the total outcome (238). The aim of the study was to compare the effects on stroke between telmisartan and placebo (238). Similar results were found in the TRANSCEND trial (239).

The ACCOMPLISH trial found that hypertensive patients on Benazepril plus amlodipine treatment who achieved mean blood pressure of 131.6/73.3 mmHg had a 16% relative risk reduction in all cardiovascular events and death from cardiovascular cause than those on benazepril plus hydrochlorothiazide who achieved mean blood pressure of 132.5/74.4 mmHg (240). Although the difference in mean blood pressure between both groups was significant, the authors attributed the results to the effect of the drug beyond blood pressure reductions. 72.5% of hypertensive patients achieved blood pressure below 140/90 mmHg without reporting side effects due to lower blood pressure levels. 60% of included patients were diabetic (240). In the VALUE study there were no differences in the risk of cardiovascular mortality between patients who achieved a mean blood pressure of 139.3/79.2 mmHg and those patients who achieved 137.5/77.7 mmHg (241). The trial reported a mean difference of 2.1/1.6 mmHg between both groups over the follow-up period. The percentage of patients with a blood pressure below 140/90 mmHg was 60.5% (242). It is worth noting, these levels were observed in patient with mean age of 67.2 years and no major side effects were reported (241).

Evidence from post hoc analyses of clinical trials has also been considered for the definition of targets (243). Mancia et al reported that hypertensive patients at a higher cardiovascular risk who achieved blood pressure levels below 130/80 mmHg have lower significant hazard ratio of stroke than those who achieved blood pressure levels above 140/90 mmHg. However, there are no significant differences in the hazard ratio of cardiovascular diseases. This was a secondary analysis of the ONTARGET trial in which patients with lower baseline blood pressure levels tended to have higher blood pressure control rates (244). A post analysis of the CASE-J trial showed that hypertensive patients with diabetes or chronic kidney disease who achieved systolic blood pressure above 130 mmHg had higher incidence of cardiovascular diseases than those with systolic blood pressure below 130 mmHg. The analysis also showed that the association is stronger for this group of patients than for those at a lower

cardiovascular risk (245). Hence the study supports the concept of using lower blood pressure targets in the management of hypertensive patients at high cardiovascular risk. A post hoc analysis of the PROGRESS trial showed that hypertensive patients who have cerebrovascular disease with a baseline systolic blood pressure less than 120 mmHg have similar reductions in the risk of stroke to those with a higher baseline systolic blood pressure. Hence the achievement of systolic blood pressure below 120 mmHg seems to have a beneficial effect on the prevention of stroke without an increase in mortality or side effects (218).

Diabetic patients

For hypertensive patients with diabetes, the use of targets below 140/90 mmHg have been promoted by different guidelines (13, 243). Whereas, the JNC 7 recommends a blood pressure below 130/80 mmHg (13), the European Society of Hypertension recommends a blood pressure target between 130-139/80-85 mmHg (15). The recommendation initially arose from the analysis of subgroups in the SHEP and HOT trials (246-247). The HOT trial showed that diabetic patients who achieved diastolic blood pressure below 80 mmHg have a 30% lower risk of total cardiovascular mortality than those without diabetes with similar diastolic blood pressure (246). Ghaede et al reported that diabetic patients exposed to a multifactorial intervention who achieved blood pressure below 135/85 mmHg had 47% lower risk of cardiovascular morbidity than those who received the standard intervention and achieved 150/86 mmHg blood pressure (248). The more intensive blood pressure target of systolic blood pressure below 130 mmHg was achieved by 45% of patients allocated to the intensive blood pressure intervention group. The aim of the study was to evaluate the impact of an intensive program for the management of diabetic patients (248).

The ADVANCE study reported that diabetic patients who achieved mean blood pressure of 134/74 mmHg experienced a 9% reduction in the relative risk of macrovascular and microvascular complications compared with those who achieved 140/76 mmHg blood pressure (249). The mean difference between both groups in systolic and diastolic blood pressure was 5.6 mmHg and 2.2 mmHg respectively (249). The ABCD trials compared the benefit of using a lower blood pressure target in diabetic patients with and without hypertension (193, 196). The ABCD-N trial reported lower incidence of stroke and slower progression of nephropathy in participants who achieved blood pressure below 128/75 mmHg than those who

achieved 37/81 mmHg (193). The ABCD-2V (ABCD part 2 with VALSARTAN) trial showed that diabetic patients without hypertension who achieved blood pressure below 120/80 mmHg had lower progression of urinary albumin excretion over the follow-up period. This trial was stopped early and included only 129 patients (196).

In contrast, the ACCORD trial and the ABCD-H trial found that diabetic lowering systolic blood pressure below 130 mmHg in diabetic patients was not associated with higher reductions in hypertension-related mortality and morbidity than those attained with blood pressure levels above 130 mmHg (194, 199). In the ACCORD trial also there were no differences in the total and cardiovascular mortality between the diabetic patients who achieved systolic blood pressure below 119.3 mmHg and those who achieved 133.5 mmHg. Nonetheless, a significant difference in the rate of stroke between both groups was observed (199). However the study had a low incidence of cardiovascular events reducing its statistical power to evaluate the differences in outcomes between both groups (199). In the ABCD-H trial there were no differences in total cause mortality between diabetic patients with end blood pressures of 132/78 mmHg and those with 156/98 mmHg (194). This trial did not report the total number of patients who completed the follow up period (194).

Evidence from observational studies also did not completely support the benefit of using lower blood pressure targets in individuals with diabetes. A post hoc analysis of 6400 patients with diabetes and coronary artery disease revealed that the mortality rate of all cause mortality did not vary significantly between patients with diabetes and coronary heart disease who achieved systolic blood pressure below 130 mmHg and those who achieved systolic blood pressure between 131 mmHg and 140 mmHg. The results may be confounded because of the significant differences in baseline characteristics between the groups (250). In an observational study of 126092 diabetic patients, Vamos et al additionally reported that the achievement of blood pressure target below 130/80 mmHg was not associated with a reduction in the risk of all mortality causes (251). Two meta-analyses documented that diabetic patients who achieved blood pressure below 130/80 mmHg tended to have a lower incidence of stroke compared with those who achieved higher blood pressure levels. However, the beneficial effect on total and cardiovascular mortality was not significant and the side effects tended to increase (252-253). Hence the effects of achieving systolic blood pressure below 130 mmHg pressure seem to be heterogeneous (181, 244, 252).

Patients with chronic kidney disease

A blood pressure target below 130/80 mmHg has been recommended for patients with chronic kidney disease (13). The strength of evidence supporting this target is questionable. I previously referred to the MDRD trial and the AASK trial. The REIN-2 trial compared the effect of two targets on time to end-stage renal disease in hypertensive patients with non-diabetic proteinuric nephropathy. Thus patients were randomly allocated either to a target of diastolic blood pressure below 90 mmHg or a blood pressure below 130/80 mmHg. The study did not find significant differences between the two groups. However neither the patients nor the investigators were blinded. Additionally, the percentage of patients' lost was around 35% during the follow-up period. Hence, the conclusions derived from the study may be biased (195).

Elderly patients

The blood pressure target for the elderly population has also been questioned. The MRC2 trial earlier documented that lowering blood pressure to or below 155/85 mm Hg in hypertensive patients with a mean age of 70.2 years resulted in a reduction of 25% and 17% in the rate of stroke and all cardiovascular events respectively (254). The SHEP trial reported that patients with mean age of 72 years who achieved an average blood pressure of 143/68 mmHg had a 36% lower risk of stroke than those who achieved average blood pressure of 155/68 mm Hg (219). In addition, they had a reduction in all cause mortality and cardiovascular events without increases in adverse events (219). The Syst-Eur trial reported that elderly hypertensive patients with end mean blood pressure of 150.8/78.5 mmHg had a lower incidence of stroke but not of cardiovascular mortality than those with mean blood pressure of 160.9/83.5. The follow-up period in this study was two years what may affect the probability of finding differences in total cardiovascular mortality (255). The HYVET trial showed that patients with age of 80 years and over who achieved mean blood pressure of 144.7/78.4 mmHg had significantly lower rates of total mortality and stroke than those who achieved 159.4/83.8 mmHg blood pressure (256-257). The researchers used a target of systolic blood pressure less than 150 mmHg in elderly patients who also had low frequency of cardiovascular disease (257). The STOP-hypertension 2 trial reported reductions in blood pressure from 187/100 to 159/80 in hypertensive patients with mean age of 72 years. These reduc-

tions were observed in the group on conventional antihypertensive therapy and those with newer antihypertensive drugs. There were no differences in all cardiovascular events between both groups (232).

Recent clinical trials have shed light on the benefit of lowering blood pressure in elderly. In the JATOS study, elderly hypertensive patients who achieved systolic blood pressure below 140 mmHg did not have significant improvements in cardiovascular mortality in comparison with those who achieved systolic blood pressure over 140 mmHg (198). An interaction effect between age and blood pressure reduction was reported. Thus patients aged over 75 years could benefit less from using lower targets than those aged below 75 years (198). However, the trial lacked statistical power to show significant differences in the outcome (198). In the VALISH trial, patients over 60 years were randomised either to systolic blood pressure target of less than 140 mmHg or systolic blood pressure target of 140-150 mmHg (200). Patients on the lower target achieved a mean blood pressure of 136.6/74.8 mmHg and those on the higher target achieved 142.0/76.5 mmHg. Despite the differences, there were no significant differences in mortality but the authors adverted that the study is underpowered to identify differences in outcome. Of note, patients with lower blood pressure level did not have excess in side effects (200).

Using lower targets for elderly patients could also be harmful. In the INVEST trial, a sub-analysis of the oldest hypertensive patients with coronary heart disease illustrated that the achievement of blood pressure below 140 mmHg was associated with a higher risk of total cause of mortality in those aged 80 years and over. The authors suggested that the threshold for safe reductions in systolic blood pressure decreases with increases in age (258). Fagard et al also provided evidence on the association between an increase of all causes of mortality and the achievement of diastolic blood pressure below 55 mmHg in elderly patients with coronary heart disease. The result came from the follow-up period of the Systolic Hypertension in Europe (Syst-Eur) Trial (176). The J-Health study presented same associations between blood pressure reductions and cardiovascular mortality in a cohort of 26512 Japanese patients with the mean age at 62 years (259). A similar association was observed among hypertensive patients of white and African-American ethnicity in the NANHES survey (260).

To sum up, the blood pressure target for elderly hypertensive patients is still uncertain. The differences in patient profile between studies and the potential side effects of lowering blood pressure limit the ability to definite a potential target for this patients group.

The 140/90 mm Hg blood pressure as blood pressure control target

The clinical guidelines recommend the level of 140/90 mmHg as the blood pressure target for the management of hypertensive patients particularly in those at middle and low cardiovascular risk (13-15, 261). The guidelines acknowledge that this target is based on consensus views of experts assessing the available evidence. To date, there is no a clinical trial supporting the use of this threshold as a blood pressure target. By contrast, the use of this level is under scrutiny (262).

The use of 140/90 mmHg has been recommended as blood pressure target mainly for patients at low and middle cardiovascular risk since 1993 (263-265). The criteria for selecting this threshold relied mainly on observational studies (38-39, 266). The studies revealed that 25% of population seems to be above its mean population systolic and diastolic blood pressure levels (39). The level of 140 mm systolic blood pressure and 90 mmHg diastolic blood pressure seems to be the cut off over this percentage are located (39). Port et al suggested that a systolic blood pressure of 140 mmHg may be the threshold below which the relationship between all cause mortality and systolic blood pressure seems to be linear and constant. The conclusion arose from performing a logistic spline model rather than linear logistic model to assess the relationship between mortality and systolic blood pressure (267). Evidence from observational studies including a large number of patients demonstrated that even a blood pressure of 115/75 mmHg is associated with cardiovascular risk (7). Van den Hoogen et al reported that having a usual systolic blood pressure of 140/90 mmHg is consistently associated with similar relative risk of dying from coronary heart disease though the absolute risk is variable worldwide (51). Vasan et al also documented that individuals with blood pressure in the range of 130–139 mmHg systolic blood pressure and 80–85 mmHg diastolic blood pressure are more likely to have a cardiovascular events over a 10 years follow-up period compared with those with blood pressure below these levels (11). These associations have also been observed in younger people aged between 18 and 39 years (268).

Clinical trials supporting the use of this target for the management of hypertensive patients at low or middle cardiovascular risk are scarce with early clinical trials accounting for most of them. The hypertension detection and follow-up program (HDFP) revealed that hypertensive patients with a baseline blood pressure between 90 and 104 mmHg who achieved diastolic blood pressure below 90 mmHg in a stepped care had 20% lower mortality than those in referred care (269). The Multiple Risk Factor Intervention Trial (MRFIT) showed that men with blood pressure as low as 115/75 mmHg were benefit from reductions in blood pressure. The protocol did not establish a particular threshold for the management of patients (270). The MRC trial assessed the management of hypertension in younger patients mean aged 35 and 64 years (271-272). The trial compared patients randomised to bendrofluazide or propranolol with placebo. A diastolic equal or below 90 mmHg was used as the target for the management of patients. The trial reported that the treatment group had lower stroke rates compared to that observed in the placebo group. The lower rates were associated with the higher reductions in blood pressure attained by those with active treatment. There was no difference in the rate of cardiovascular mortality between both groups. The TRHOPY trial evaluated the effect of using antihypertensive therapy in patients aged between 30 and 65 years with systolic blood pressure between 130 mmHg and 139 mmHg and diastolic blood pressure below 90 mmHg on the development of hypertension. Although patients on treatment have lower blood pressure levels, the associations with cardiovascular mortality were not reported (273). A secondary analysis of the FEVER trial revealed that hypertensive patients aged 65 years and over without other cardiovascular diseases or diabetes and patients who achieved blood pressure levels below 140/90 mmHg had lower incidence of stroke and other cardiovascular events (262). However the reported associations come from a post hoc analysis of the original trial so that need to be confirmed by other studies.

Currently, there is a lack of evidence from randomised controlled trials supporting a specific target for hypertensive patients at low or middle cardiovascular risk. The limitations for assessing blood pressure targets in this patient group risk are attributed to the high sample size and the long follow-up period needed to find differences between intervened groups. That are due to the lower incidence of cardiovascular events occur in this population in comparison to what is observed in hypertensive patients at higher cardiovascular risk. .

Summary

Most of the available evidence for the management of hypertension has been derived from studies conducted in patients at high cardiovascular risk. The majority of studies aim at comparing pharmacological interventions with few studies comparing blood pressure targets. The achieved blood pressure reported in these studies has commonly been translated into potential thresholds for the management of hypertensive patients.

There are also some doubts as to what extent targets derived from these clinical trials can be applied to whole range of hypertensive patients. Clinical trials have been conducted mainly in populations of Caucasian origin so that patients of different ethnic background may need a different approach. Blood pressure levels vary between different ethnic groups (34, 38, 51). The number of women included in these studies has been considered low particular in studies with patients below 60 years. Variations in blood pressure levels between the sex also raise questions about the use of equal targets for women and men (73, 274).

Summarizing the currently available evidence, the extent to which blood pressure should be lowered is still a matter of uncertainty. Clinical guidelines recommend differential targets for blood pressure reductions in hypertensive patients according to the classification of their cardiovascular risk. The targets are based on an appraisal of the available evidence. This evidence mainly came from clinical trials testing pharmacological interventions to reduce blood pressure. There is a lack of randomised clinical trials comparing blood pressure targets that producing definite results. It seems that lowering blood pressure down to a systolic blood pressure of 135 mmHg or diastolic blood pressure of 75 mmHg leads to significant reductions in hypertension-related cardiovascular risk in hypertensive patients regardless of age, sex or their cardiovascular risk. Evidence supporting higher reductions is contradictory. Some studies, mainly observational or post hoc analysis, showed that reducing blood pressure below these levels may result in an increase of cardiovascular mortality particularly in those with coronary heart disease and elderly patients.

1.3.3 Current definition of targets

The use of blood pressure targets for the management of hypertensive patients is established in clinical guidelines worldwide. Table 7 shows the current guidelines being used in the different geographical areas. The definitions of blood pressure targets used in England will be presented in a separate section.

The guidelines agree on recommending the blood pressure targets for the management of hypertensive patients at low and middle cardiovascular risk without additional cardiovascular comorbidity. Globally they recommend a blood pressure equal to or below 140/90 mm Hg as the aim of the therapy. The guidelines mainly differ in the recommended targets for patients at high cardiovascular risk. The JNC 7 proposed a lower blood pressure target for these patients compared to that proposed in other guidelines (13) (Table 7).

The use of blood pressure targets

Despite the described limitations, the achievement of a blood pressure target is regarded as a standard of care in the management of hypertensive patients. Blood pressure targets have been used for different purposes.

In the clinical context, the guidelines established thresholds to help doctors guide the management of hypertensive patient (13-14, 174). Decisions on drug therapy are based on the achievement of the recommended target. Physicians classify patients into a hypertensive patients with controlled or uncontrolled hypertension based on the achievement of that threshold (13-14, 174, 261). The classification may not accurately reflect the concept of blood pressure control in the sense of the achievement of the maximal reduction in blood pressure-related cardiovascular risk. Patients classified as those with controlled hypertension are still at higher risk than those patients without hypertension with similar characteristics (58, 275-277).

In primary care services blood pressure targets have also been used as indicators to measure the quality of care provided by health services (278). The performance of services is assessed based on the amount of hypertensive patients had blood pressure below the de-

fine blood pressure target (279). The use of this measurement relies on placing its accountability for blood pressure control with health care providers (279-280).

Table 7 Blood pressure targets for hypertensive patients on antihypertensive treatment

Guideline	WHO (14)	ESH-ESC (15-17)	JNC 7 (13)
Patients at low and middle cardiovascular risk	<140/90 mmHg	<140/90 mmHg	<140/90 mmHg
Patients at higher cardiovascular risk	<130/85 mmHg ₁	130-139/80/85 mmHg ₂	<130/80 mmHg ₃
₁ Referred to patients with diabetes, renal insufficiency and established cardiovascular disease ₂ Referred to patients with diabetes and should be considered for patients with established cardiovascular diseases. ₃ Referred to patients with diabetes or chronic kidney disease			

Key points

- ✓ The hypertension guidelines recommend blood pressure thresholds as a target for the management of hypertension.
- ✓ The recommended targets have been mainly based on the blood pressure levels achieved by hypertensive patients included in clinical trials.
- ✓ The clinical trials mainly aimed to assess the efficacy of antihypertensive drugs.
- ✓ Patients included in clinical trials have mainly been patients at a high cardiovascular risk.
- ✓ Few trials have compared the efficacy of using blood pressure targets for the management of hypertensive patients.
- ✓ Hypertension guidelines agree on a target equal to or below 140/90 mmHg as a blood pressure target for hypertensive patients at a low and middle cardiovascular risk.
- ✓ Hypertensive guidelines recommend lower blood pressure targets for hypertensive patients at high cardiovascular risk. Guidelines differ in these targets.
- ✓ There is a need of evidence on blood pressure thresholds for hypertensive patients at low cardiovascular risk and middle cardiovascular risk.

Chapter 2 Factors affecting blood pressure control

Despite the available interventions, the target of 140/90 mmHg is not attained by the majority of hypertensive patients. The proportion of patients achieving this target is still below 50% worldwide (281). The proportion of hypertensive patients achieving this target varies between different countries. The lowest rates of blood pressure control have been observed in developing countries. For instance in a survey from Asian countries, Van Minh et al reported that only 5.4% of hypertensive participants had blood pressure below 140/90 mmHg (282). By contrast, in a comparison between the NHANES 1988-1994 and 1999-2008 Egan et al found the percentage of hypertensive patients with controlled blood pressure increased from 27.3% to 50.1% over the period (283). A similar trend has been observed in England (283-284).

In studies from countries with advanced primary care services, the percentage of hypertensive patients with blood pressure below or equal to 140/90 mm Hg has been shown to vary from 20.3% to 54% among those receiving care within these settings (285-287). The achievement of controlled blood pressure depends upon individual conditions, social conditions and the quality of care from health providers. Then diverse factors have been associated with poor blood pressure control. These factors have been classified into patient-related factors, physician-related factors and health system-related factors (288-289). This chapter presents a summary of factors affecting blood pressure control.

I identified the potential factors from studies assessing blood pressure control in hypertensive patients aged 18 years and older using a target of 140/90 mmHg. The studies were either conducted at population level or in primary care services from January 2000 up to December 2012. The source for the review was PUBMED database. I excluded studies that reported blood pressure control rates without information about factors affecting blood pressure control.

I selected 64 studies conducted in 47 countries. 24 studies were carried out at population level. Among these, except for three studies (138, 282, 290), population were selected based on a sample sized calculation. 40 studies were conducted in primary care. In these studies, the study populations were hypertensive patients being treated in primary care or the community. In three studies the population was selected using other sources such as those participating in another community study (205), and sample sized based on a census (291-292). Blood pressure was mainly measured using a mercury sphygmomanometer or Omron monitor. The studies reported a diverse range of factors as discussed below (Table 8-9)

2.1 Patient-related factors

Patient-related factors constitute the most frequent factors reported in the studies. Among these are age, sex, race/ethnicity, the presence of other comorbidities, adherence to interventions and socio-economic conditions.

2.1.1 Adherence to interventions

The WHO defines adherence to long term therapy as “ the extent to which a person’s behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider” (293). The definition incorporates the two concepts of adherence and persistence with therapy (294). Adherence is considered as the adequate use of therapy that follows physician recommendations. Persistence is defined as the continuous use of antihypertensive medication for a defined period of time (294). Poor adherence to antihypertensive medication is commonly observed among antihypertensive patients. In a population survey from China, Tian et al found that only 27.7% of hypertensive patient were taking antihypertensive medications regularly. The reasons for not taking medications were not having enough money to purchase them and not being aware of

the health risk related to hypertension (295). In an analysis of prescribing records from 22918 hypertensive patients, Caro et al detected that only around 50% of patients continued on antihypertensive treatment six months after starting therapy (296). In a review of 20 studies assessing adherence to antihypertensive medication Fitz-Simon et al reported that the percentage of patients regularly taking antihypertensive medication varied between 4% and 86 % (297).

In an analysis of clinical records of 4378 hypertensive patients Vrijens et al, found that up to 50% of patients stopped taking antihypertensive medication over one year (298). They also reported that among patients continually taking antihypertensive medication at least 10% of scheduled prescriptions were omitted. In a study of 82824 hypertensive patients aged 65 years and over, Morgan et al found that only 50% of newly treated hypertensive patients reported continue use of antihypertensive drugs after having the initial prescription (299). By comparison, some authors have been reported good adherence to antihypertensive medications. In a cohort of 207473 patients with mean age 74 years, Friedman et al reported that adherence and compliance with antihypertensive medication increased up to levels between 50% and 75% over a seven year follow-up period (300). Similarly, Inkster et al reported a 91% level of adherence among hypertensive patients in primary care (301). Then although adherence is commonly reported, its frequency varies across studies.

The consequences of poor and/or good adherence varied between different studies. In a review of adherence to medication including nine studies related to antihypertensive treatment, DiMatteo et al reported that hypertensive patients with good adherence were more likely to have controlled blood pressure compared to those with poor adherence, odds ratio 3.5 (95% CI 1.60 – 7.37) (302). By contrast, in an analysis of 110 outpatients, Nuesch et al also established that the level of compliance did not explain the failures in lowering blood pressure (303). From a review of 30 studies assessing adherence to antihypertensive medication, Wetzels et al concluded that the association between poor adherence and poor blood pressure control is not totally supported by the available evidence (304). Some studies did not find differences in adherence between those with good and poor blood pressure control. Those studies which support the association between poor adherence and poor blood pressure control did not have a control group. Grezzana et al reported that despite having adequate adherence to antihypertensive medication, hypertensive patients did not achieve

blood pressure targets (305). The lack of a standard method for assessing adherence to medication is one the reasons for these divergences between studies. It also results in different estimations of adherence to antihypertensive medications between studies (293, 306-307). Therefore, although a lack of adherence to antihypertensive medications is frequently among hypertensive patients, its impact on blood pressure control has not precisely been estimated.

The consequences of poor adherence to antihypertensive medication go beyond poor blood pressure control. Bailey et al reported that there was a reduction in the risk of stroke associated with increases in the level of adherence to antihypertensive medication. Thus for each 15% increase in the adherence score, there was a reduction of 0.91 (CI 95% 0.86-0.97) in the hazard ratio of stroke (306). Corrao et al reported that compared to those patients stopping antihypertensive medication at any time, those who did not stop medication had a reduction of 37% in coronary or cerebrovascular outcomes (308). This evidence came from data collecting from general practices and so can be considered to reflect possible achievements within current clinical practice (308). From analysing medical records of 18806 newly diagnosed hypertensive patients receiving care in 700 general practices in Italy, Mazzaglia et al reported that those with higher levels of adherence had a nearly 40% reduction in their risk of having acute cardiovascular events (309). Similarly from analysing a cohort of 59647 hypertensive patients, Dragomir et al reported that those with poor adherence to medication had an increased risk of having coronary disease, cerebrovascular disease and chronic renal failure (310). Hence, adherence to medication should be considered an important factor for improving blood pressure control.

2.1.2 Individual factors

Being older is commonly associated with poor controlled blood pressure. This association has reported either in studies conducted at population level or the community (18, 205, 282-283, 287, 295, 311-328). It may be due to age-related increases in blood pressure leading to a higher prevalence of isolated systolic hypertension in individuals over 50 years (73). The association has been observed regardless of race/ethnic origin, socio-economic and education status. By contrast, only a few studies have reported that younger patients such those below 40 years have been less likely to have controlled blood pressure (283, 318, 328-330).

The relationship between sex and poor blood pressure control has been contradictory. Some studies revealed a negative association between women and blood pressure control (205, 313, 315, 320, 331-334). By contrast others studies revealed that women were more likely to have controlled blood pressure (287, 311, 334-343). In one study the relationship between women and blood pressure control changed with age. Compared to men, younger women were more likely to have controlled blood pressure and older women were less likely to have controlled blood pressure (328). Moreover, some studies reported being male as a predictor for inadequate blood pressure control (290, 312, 316-317, 344-350). Due to these discrepancies, there does not seem to be strong evidence supporting any particular association between sex and poor blood pressure control.

Race/ethnic origin has been associated with variation in the probability of having controlled blood pressure. Black patients living in Western societies have been reported less likely to have controlled blood pressure compared to those of white origin (283, 313, 329, 347, 351-352). Wong et al found that hypertension is the most significant contributor to differences in mortality between black and white race/ethnicity. It accounts for 15% of total difference in year lost between both groups (353). In an assessment of NHANES trends between 1998 and 2008, Egan et al reported that there has been a constant increase in the percentage of hypertensive patients with controlled hypertension in all ethnic groups. But white patients remain with higher blood pressure control rates than black patients and those of Hispanic origin (283). Similarly, Howard et al revealed that despite being aware of hypertension and having antihypertensive treatment, hypertensive patients of black origin were less likely to have controlled blood pressure than those of white origin (354). The association declines but remains significantly after adjustment for demographic and socio-economic conditions (354). Despite these trends, Wyatt et al pointed out that better blood pressure control in African Americans is achievable. In a cohort of 5249 American African they found that 66% of hypertensive patients on treatment had controlled blood pressure (355). They argued that this sample of African American population had a high level of education and better access to health than other African American populations.

Some factors have been associated with lower blood control rates in patients of black origin. Analysing data from a retrospective cohort of hypertensive patients managed in primary care, Kressin et al suggested that social conditions such as health benefits, patient's beliefs and adherence to medication accounted for lower blood pressure control rates in patients of black origin (352). In an analysis of 608 patients of white and black race/ethnicity, Bostworth et al found that age, worry about hypertension and poor adherence to antihypertensive medication were associated with poor blood pressure control in black patients (356). Similarly, in analysis of 40492 hypertensive patients on antihypertensive medication, Siegel et al reported that the lowest rates of blood pressure control were in those of black origin and those suffer from depression (357). However in a cross sectional of the REGARDS study, Durant et al showed that lower adherence to medications did not totally explain the lower blood pressure rates observed in black patients (358). Lower blood pressure control rates in black patients have been documented despite receiving an intensification of treatment (359).

Rehman et al explored the impact of health care services on black hypertensive patients. They found that black men receiving care at the Department of Veterans Affairs (VA) had better blood pressure control than those who received care in non-VA services. However, in both clinical settings patients of white origin were more likely to achieve blood pressure control targets (360). In an observational study using medical registers from 51722 hypertensive patients, Ishisaka et al identified that those of non-white race/ethnic origin (Asian American/Pacific, Islander, black, Hispanic and other ethnicities) had lower adherence to anti-hypertensive medication (361). In the ALLHAT clinical trial which included 33357 hypertensive patient recruited from the community, Cushman et al found that patients of black origin were less likely to achieve controlled blood pressure than those of other race/ethnic origin, odds ratio 0.69 (95% CI 0.65 – 0.73) (362). Glymour et al found that differences in stroke incidence between patients of black origin and those of white origin disappear when the analysis takes into account social economic conditions (363).

Life style

Among the studies presented in table 8, two studies reported positive associations between non-pharmacological interventions such as low salt intake, weight loss, doing physical 70es-pecity with having controlled blood pressure (311, 317). The negative impact of not using

these interventions was also documented in four studies (290, 327, 344, 346). The associations were observed taken into account age, sex and/or race/ethnicity. Consequently, these non-pharmacological interventions have been proved to reduce blood pressure levels (364). However, these interventions may be underused. In a national survey conducted in China, Gu et al reported that only 55% of hypertensive individuals were advised on using non pharmacological interventions (330). 45% of them were currently using more than one intervention and salt reduction was the most frequently non-pharmacological intervention used (330). Additionally the assessment of these interventions has not frequently been reported in the cited studies. The majority of the studies reported antihypertensive prescribing as the indicator for assessing the management of hypertension using a structured interview.

Poor adherence to non-pharmacological interventions has also been reported. In an open intervention study carried out with individuals with mildly elevated blood pressure, Korhonen et al found that despite having received intense counselling and low salt content products, only 20% of total participants reduced salt consumption to less than 5g/day (365). The PREMIER clinical trial of 810 hypertensive patients with mean blood pressure of 135/85 mm Hg showed that patients who were either under an intense education intervention or DASH diet plus intense education, achieved lower blood pressure levels than those who receive only advice. But only 28%, 34% and 34% of included participants were adherent to salt reduction, weight reduction and fruit and vegetable consumption recommendations respectively (366). In a longitudinal study of 389 hypertensive patients, Otha et al found that only 2.3% of included patients met the target of consuming less than 6 gr/day salt consumption over a 3.5 years follow up period (367). Therefore the effectiveness of salt reduction in current clinical practice may be unknown and also confounded by the presence of other interventions (368).

Different associations between smoking and having controlled blood pressure have been reported. McNagny et al reported that compared to patients with controlled hypertension, those with uncontrolled hypertension were more likely to be current smokers (369). In an analysis of 122 hypertensive patients, Chmiel et al found that smoking was positively associated with having uncontrolled blood pressure (370). In a Swiss survey the rate of blood pressure control was higher in non-smokers (286).

Presence of comorbidity

Increases in BMI have been associated with poor blood pressure control. The association has been consistently reported across the studies (205, 282, 287, 290, 292, 311, 315, 325, 370-374). Lloyd et al revealed that those with higher BMI were less likely to have controlled pressure (205). Sandoval et al found that those with high BMI were less likely to have controlled blood pressure (292). Chmiel et al reported that increases in BMI was highly correlated with higher blood pressures in hypertensive patients with uncontrolled blood pressure (370). Similar associations have been reported using BMI categories. Labeit et al found that patients with a body index mass (BMI) above 30kg/m² had a nearly 30% lower probability of having controlled blood pressure (287). Abaci et al also reported that a BMI over 25 kg/m² was negatively associated with having controlled blood pressure (325). Because increases in body mass index are a risk factor for hypertension (120), patients with a higher body mass index may experience more limitations in lowering blood pressure.

The association between the presence of other comorbidities and blood pressure control varied across the studies. 24 studies reported that having an additional cardiovascular comorbidity reduced the probability of having controlled blood pressure below 140/90 mmHg (205, 285-286, 292, 313, 323, 325-327, 332, 344, 349, 372, 374-384). These studies mainly included older hypertensive patients being prescribed more than one antihypertensive drug. Diabetes and chronic renal disease are of the most frequently cardiovascular comorbidity occurring in these patients. It seems that this patient group have longstanding hypertension and also higher baseline blood pressure levels. Patients with long established hypertension have been found more likely to have uncontrolled blood pressure (344). This may indicate that a simultaneous control of more than one cardiovascular risk factor is hardly achieved. By contrast, eight studies found that hypertensive patients having an additional cardiovascular comorbidity were more likely to have controlled blood pressure (287, 292, 344, 349, 373, 384-386). Within these studies coronary heart disease and stroke were the most commonly associated cardiovascular comorbidity reported. Patients on antihypertensive treatment were also older. That could be due to the quality of care provided to these patients. Petersen et al revealed that hypertensive patients with an additional comorbidity received better or equal care than those without other comorbidities and so they were more likely to have controlled hypertension (387).

Other non-cardiovascular comorbidities have also been related to blood pressure control. The relationship between depression and blood pressure control has been contradictory. Bautista et al in a longitudinal study of 178 patients reported that hypertensive patients with depression and anxiety were more likely to be non-adherent to antihypertensive medication (388). Michal et al assessed the relationship between depression and hypertension in a cross-sectional study of 5000 patients from Germany general practices. Compared to those without hypertension, patients unaware of hypertension were less likely to have depression or symptoms of depression (389). There was no association between having controlled hypertension and depression (389). In a meta-analysis of eight observational studies which assessed the relationship between depression and adherence to antihypertensive medication, Eze-Nliam et al found that a positive association between depression and poor adherence to antihypertensive medication. Additionally patients with both poor adherence and depression were more likely to have uncontrolled blood pressure in all the studies. However, the methodological differences observed between the studies prevented from establishing a conclusive association between both conditions (377).

Some surveys revealed that patients receiving a high number of hypertensive medication were less likely to have controlled blood pressure (312, 322). Hypertensive patients receiving more than two hypertensive drugs may have associated comorbidity and also higher blood pressure levels that make it difficult to achieve blood pressure targets. Poor adherence to greater number of antihypertensive medications could also explain the finding. Claxton et al in a review of 76 studies using electronic monitoring to assess patient adherence to antihypertensive medication found that the higher the number of drugs prescribed, the lower the adherence (390). Similarly in a meta-analysis of 51 studies of drug prescription for chronic diseases, Coleman et al found that patients are more adherent to one prescribed drug than two or more drugs (391). Dennison et al revealed that patients with few antihypertensive medications were more likely to have blood pressure below 140/90 mmHg (342). However, Hedblad et al did not observe an association between the number of hypertensive drugs and reductions in blood pressure levels (314).

Social and economic conditions

Socio economic status is a complex concept which depends on the interaction of variables such as education, occupation, income, wealth and place of residence (392). These conditions have been found as determinant of blood pressure control and hypertension-related morbidity. In an ecological study of 3.5 millions death occurred in Europe between 1990 and 2000, Mackenbach et al pointed out that inequalities in all cause mortality rates, including hypertension, may be due differences in access to health care and healthy habits across socio economic strata (393). From the NHANES, Fryar et al reported that there has been a reduction in the percentage of individuals with uncontrolled hypertension from 1999 to 2010. However, that reduction was less evident for lower income adults who had the highest percentage of individuals with uncontrolled hypertension (394). Of note, a consistent association between low socio economic status and stroke incidence has been observed (395). By comparison, Kagamimori et al showed that the effect of socio economic status on health outcomes is less marked in Japan than in Western societies. They considered that the smaller socio economic differences across social strata could explain this finding in Japan (396).

A high level of education was associated with better blood pressure control (292, 311, 313, 321, 324, 384). In study conducted in 184 general practices with free access to care, Paulsen et al identified that patients with less than 10 years education were less likely to achieve blood pressure control compared to those with higher levels of education (384). In the analysis of NHANES 1999-2004, Ostchega et al found that hypertensive patients with lower levels of education and in the lowest socio-economic category were less likely to have controlled blood pressure (313). Sandoval et al found that low education was associated with poor blood pressure control (292). Wong et al found that individuals with lower education background had 3.5 times higher life years lost than those with higher education. Ischemic heart disease was the most important contributor to this disparity accounting for 11.7% the total difference in years lost between both groups. Hypertension accounted for 3.5% of that difference (353). This association was found regardless of age and sex condition (311). However in a population survey taking in Cienfuegos (Cuba) Ordunez-Garcia et al did not find an association between education and blood pressure control. This observation may be attributed to universal access based on an extensive primary care services presented in that country (334).

Other social factors have also been associated with poor blood pressure control. In an analysis of 222 patients from outpatient clinics, Morgado et al identified that those living alone were less likely to have controlled blood pressure (375). In addition, those who were single were less likely to have controlled blood pressure than those who had a partner (384). In a longitudinal study of 6083 hypertensive patients aged 65 to 84 years, Chowdhury et al found that those living in inner regional areas were more likely to have uncontrolled blood pressure than those living in major cities (397).

Other individual aspects have also been associated with poor blood pressure control. Hypertensive individuals unaware of a blood pressure target, with hypertension-related morbidity and with poor knowledge about hypertension could be more likely to have uncontrolled blood pressure. Personal perceptions about hypertension may also explain poor blood pressure control (322, 398-399). In a qualitative study, Ogedegbe et al found that hypertensive patients believed that antihypertensive medications can cure high blood pressure levels, antihypertensive drugs can be stopped and these drugs are only needed to relieve symptoms (400).

2.2 Physician-related factors

Physician performance is a key factor for the attainment of controlled hypertension (401). Physician communication skills, physician acknowledgment on the management of hypertension and clinical inertia are part of relevant physician-related factors which have been directly associated with blood pressure control.

Clinical inertia, the lack of treatment intensification and/or initiation when needed by patients with regard to blood pressure levels, has been considered one of the most common factors to prevent the achievement of better blood pressure control rates in primary care settings (402-403). The percentage of clinical visits in which physicians have not intensified the antihypertensive treatment for hypertensive patients with high blood pressure levels may vary between 20% and 45% (402, 404-406). In an analysis of 169 patients receiving care from different providers, Hyman et al found that physician did not intensify treatment despite observing systolic blood pressure levels above 140 mmHg (401). Similarly Guthrie et al found

that in a range of 16%–30% consultations physicians did not intensify treatment. Additionally, physician took decisions on changing treatment based on a higher target than that recommended in the guidelines (402). In an assessment of clinical records from 3742 treated in primary care, Viera et al documented that 53% of patients did not achieve blood pressure control despite being continually treated. Physicians intensified treatment only in 46% of the time even though blood pressure measurements were above the expected target (407).

Intensification of treatment has been associated with better blood pressure control. Hicks et al reported that intensification of treatment had a positive effect on blood pressure control regardless of race/ethnicity (347). Physician may dismiss assessing patient adherence to medication to adjust antihypertensive treatment. In an analysis of pharmacy records from 38327 hypertensive patients, Heisler et al demonstrated the frequency of intensifying treatment was between 31% and 34% among hypertensive patients with moderate or poor adherence to antihypertensive medication (408).

Clinical guidelines intend to assist physicians on antihypertensive therapeutic decisions. Some surveys have revealed that physicians neither used the guidelines as resource for prescribing antihypertensive drug therapy or considered the information contained within the guidelines as a useful source (409). Physician criteria on commencing treatment, drug efficacy and/or blood pressure targets may differ from the recommendations established in the guidelines (385, 405, 410–417). Physicians also argued that universal prescriptions may not apply to all range of hypertensive patients visiting primary care services and a one size fits all prescription may reduce medical autonomy (416, 418–421).

Physician adherence to guidelines may however have been underestimated (422). There is no standard measurement to estimate the level of physician adherence to the former guidelines. Hence, the lack of standards makes it difficult to accurately estimate the level of physician adherence. (423–425). The assessment on how physicians used hypertension guidelines has not always used the recommendations established in the time-related guideline (426). The presence of other diseases may detract physicians from using the recommendations established in the guidelines (405, 427). In fact, some reports showed that physicians are in favor of using guidelines for the management of hypertension (428–430).

Moreover, some physicians consider waiting to achieve the total drug effect before intensifying antihypertensive treatment even observing high blood pressure levels in hypertensive patients (403). Some evidence also illustrated that physician knowledge on the management of hypertension is appropriate (403).

During clinical visits, the instructions given to the patients directly influence patient adherence to antihypertensive medication (431). For instance, through interviewing antihypertensive patients Svensson, et al found that compliance with antihypertensive prescription was highly dependent on the patient-physician relationship (432). Qureshi et al conducted a clinical trial in the community to assess the impact of a program which provides general practitioners with education about hypertension management and communication skills regarding blood pressure control. They demonstrated that patients who received care from general practitioners allocated to an education program achieved lower blood pressure levels. Better physician communication skills, which resulted in more explanations about hypertension to the patient, was the most influential part of the program (433). In an observational study of 2621 hypertensive patients being treated in primary care, Ferrari et al showed that the blood pressure target used for the management of each individual patient is highly dependent on physician criteria (420). In fact Banegas et al documented that physicians did not consider intensifying treatment when blood pressure levels are slightly above the blood pressure target (434).

The effect of physician advice has also been recognised. In a survey of two hundred patients participating in a clinical trial, Jones et al reported that patients with a higher level of trust in their physician's recommendations were more likely to participate in loss weight activities recommended for lowering blood pressure (435). However the association between patient trust in physician and blood pressure has not been consistently documented. Durant et al reported that trust in a physician did not modify the probability of having controlled pressure among patients of white and black origin (358).

2.3 Health system factors

Health system factors included those related to access to health care and the performance of health services. Access to services, which involve health care supply and service use, has been a determinant of blood pressure control (436). The impact of health services on blood pressure control has been observed worldwide regardless of health system organization. Duru et al assessed the impact of insurance on blood pressure control using data from the NHANES survey carried out between 1999 and 2002 (437). They found that hypertensive patients without insurance were less likely to have controlled blood pressure than those with private health insurance, odds ratio (0.63 95% CI 0.44-0.92). In an independent analysis of NHANES III survey (1998-2004), Ostchega et al and He et al also reported that individuals with health insurance and with frequent health care visits had better blood pressure control compared to those without health coverage and fewer health care visits (313, 317). Durant et al additionally found that patients suffering from stroke and hypertension without insurance were less likely to have controlled blood pressure compared to those with insurance. The association was positive despite variations in medical supply present in the area (438). In analysis of civil participants in the Framingham cohort, Brooks et al found a similar association (439).

Similarly, improving access to health care by developing primary care services has resulted in a better blood pressure control (440-441). Sandoval et al reported an increase in blood pressure control rates among hypertensive patients with access to primary care centres after the implementation of program supported by local government (292). Souza et al reported a reduction in hospitalizations due primary care-sensitive cardiovascular conditions, which includes hypertension, associated with the introduction of Family Health Program in Southern Brazil (442). Ordunez-Garcia et al also reported higher blood pressure rates in a low-income country with a well organized primary care compared to those rates observed in high income countries (334). Although a set of initiatives have led to a reduction in cardiovascular mortality in Finland, the first step of the program was the development of comprehensive primary health care (44).

However access to health services is not a sufficient condition to improve blood pressure control. The availability of antihypertensive medication affects the probability of having controlled blood pressure. For instance, Cameron et al reported that the availability of medications for chronic conditions such as hypertension was lower in public health services than in private health services compared to the availability of medications for acute diseases. This gap was observed in low income and middle income countries (443). In an analysis of data from the third NHANES 1992-1994 survey, Hyman et al did not find an association between having insurance and having frequently visited a physician and increases in the probability of having controlled blood pressure (316). In a survey conducted among a working population in Japan, Tanaka et al observed that the percentage of hypertensive patients on treatment was 41% despite being periodically assessed by an employment medical advisor (444).

Variations in the performance of services also affect the probability of having controlled blood pressure. In an evaluation of 1100 federally funded health centre services in the USA, Lebrun et al reported that centres with high volume of patients, longer established funding and with more than 5% of patient involved in hypertension control programs not only had better blood pressure control rates but also less inequalities in their outcomes (445). By comparison in the UK, a country which has universal access to health care and a strong primary care system, Ashworth et al found that general practices located in less deprived areas provides patients with better quality of care compared to those located in most deprived areas. The assessment of the performance was based on the QOF indicators which included blood pressure control rates (446). Hence, there is no standard strategy to organize health services to improve blood control. A diverse range of interventions has been postulated to improve the process of care offered to hypertensive patients in primary care settings, community services or outpatient clinics.

Strategies used to improve blood pressure control in primary care

Multiple strategies have been used to improve blood pressure control in primary care settings. The strategies are oriented to improve the performance of physicians, patient behaviour and knowledge about hypertension and health services organization.

Glynn et al carried out a systematic review of clinical trials evaluating at least one of the following interventions: 1) self-monitoring, 2) educational interventions directed at the patient, 3) educational interventions directed at the health professional, 4) health professional (nurse or pharmacist) led care, (5) organisational interventions that aimed at improving the delivery of care and (6) appointment reminder systems. The authors included 72 clinical trials mainly conducted in primary care. Improvements in blood pressure control were largely attributed to regular follow-up of patients and an increase in the use of antihypertensive drugs. There was no conclusive evidence of the benefit of self-monitoring and appointment reminders (447). By contrast, Stéphane Rinfret et al attributed a significant increase in the proportion of patients with controlled hypertension to a multidisciplinary information technology-supported program. The program included both self-monitoring and a software warning the physician about the inadequate management of hypertensive patients (448).

Clark et al examined the role of nurses in blood pressure control by analysing 32 randomised clinical trials (449). In these studies, the nurses supported the blood pressure control program by giving telephone monitoring, conducting community monitoring, prescribing antihypertensive medication or leading the established program. The authors concluded that the higher reduction in blood pressure levels reported in nurse intervention groups may be explained by the use of a treatment algorithm. Regarding the clinical scenario in which those studies were conducted, a nurse prescribing antihypertensive drugs seems to be a potential intervention for improving blood pressure control in both primary care and community settings.

Similarly, Walsh et al evaluated 44 interventions which reported using quality improvement strategies to improve blood pressure control (450). These strategies included provider education, provider reminders, facilitated relay of clinical information, patient education, self-management, patient reminders, audit and feedback, team change or financial incentives.

Patients included in the intervention groups regardless of the type of strategy achieved higher reductions in blood pressure levels. None of the reported interventions was independently associated with that reduction. Fernandez et al conducted a quasi-experimental study to assess the impact of physician education on the management of hypertension in five primary care centres. After the intervention patients assigned to intervention groups had a 92% increase in the odds of having controlled blood pressure (451).

Schroeder et al assessed 38 studies which evaluated 58 interventions for improving adherence to treatment in patients with high blood pressure (452). These interventions included simplification of drug regimens, patient education, patient motivation, support reminders and complex interventions. Adherence was mainly measured by electronic monitors. Improvements in blood pressure control were only identified in seven studies. The authors concluded that reducing the number of antihypertensive drugs was the most significant intervention in improving adherence to medication though the impact on blood pressure control was unknown.

Team-based care has been one of the strategies used to improve blood control in primary care settings. The team care made up of pharmacist nurses and physicians. In a meta-analysis of 37 studies Carter et al showed that after involving team groups in the management of blood pressure, there has been a reduction in blood pressure levels (453). The impact of each member of the team varied between studies but was consistently. Thus, the associated odds ratio for the effect of nurses and pharmacists on the improvement of blood pressure control was 1.69 (95% CI 1.48 – 1.93) and 2.89 (95% 1.83 – 4.85) respectively. The function of these team members varies. Pharmacists both advise physicians on medication use and also provide life style recommendations to patients, while nurses give lifestyle advice and education on self-management to patients (453). Walsh et al performed a systematic review of forty four studies evaluating quality improvement strategies for the improvement of blood pressure control. They found that those including team groups result in the highest reduction of blood pressure levels compared to other interventions (450).

Community health workers (CHW), defined as those without formal health education, have been considered a strategy to improve access to health in community and rural areas.

Brownstein et al carried out a systematic review of fourteen studies including eight randomised clinical trials and six observational studies assessing the impact of community health workers in blood pressure control mainly in underserved communities with population belonging to minorities. The roles of CHW were to provide patients with health education; offer health services such making referrals, taking blood pressure or social support. Although the studies are not comparable, it seems that CHW result in improving on adherence to treatment. (454). Jafar et al conducted a clinical trial that compared the effectiveness of CHW plus physicians to only physician for the management of hypertension in a community services in Pakistan. Patients assigned to the group including CHW achieved an average 10.8 mm Hg (95% CI 8.9 – 12.8 mm Hg) lower blood pressure than those who received care only by physicians (454). Farzadfar et al evaluated a national program for diabetes and blood pressure control base on CHW offering health care in a rural community in Iran. The program led to significant improvements in diabetes control with less impact on blood pressure. However the study suggested the lack of standardised hypertension guidelines may reduce the impact of CHW (455). Tuner et al reported a positive effect on blood pressure reduction in an intervention that used a peer coach to call patients with uncontrolled hypertension (456). Jungling et al reported a positive impact of group visit in the management of blood pressure control in primary care (457).

Home blood pressure monitoring (HBPM) has been identified as a strategy to improve blood pressure control. In a clinical trial conducted in primary care, Halme et al demonstrated that hypertensive patients who used an automatic device to measure blood pressure at home achieved significant reductions in systolic blood pressure of 7.8 mm Hg. The group under standard blood pressure who achieved a reduction of 4.5 mm Hg in systolic blood pressure but the difference between the baseline blood pressure levels and end blood pressure levels was not significant (458). The percentage of patients who achieved a blood pressure target of 140/85 mm Hg was higher in those using self-monitoring though that difference was observed comparing only home blood pressure records. The percentage of patients with controlled blood pressure was similar using proportions based on office measurements. They also reported that physicians intensified antihypertensive more frequently in patients who have home blood pressure records (458). In a review of 38 studies, Argarwal et al found that using HBPM resulted in lower systolic blood pressure compared with control group. However there was a significant heterogeneity in the outcome and the studies were conducted in different clinical settings (459).

The implementation of non-pharmacological interventions for the management of hypertension has led to improvements in blood pressure control. Kastarinen et al in a clinical trial carried out in primary care settings found that providing advice on salt reduction, lowering weight, moderate alcohol consumption, exercise and quitting smoking led to reductions in blood pressure levels as low as with pharmacological interventions (460). Patients were given formal education about the mentioned factors by a physician; a nurse and a nutritionist over two years follow up. Similarly, in a clinical trial conducted in general practices Reid et al found that the introduction of lifestyle modification interventions in diet and exercise led to a reduction in antihypertensive medication (461).

In a cross sectional study of 27 family practices, Putnam et al also identified that patients with diabetes and controlled hypertension were those that reported low salt consumption and higher adherence to medication (462). Churilla et al determined the prevalence of physical activity patterns between hypertensive and non-hypertensive patients using the 2007 Behavioural Risk Factor Surveillance System (BRFSS) Survey. They found that hypertensive individuals were less active than non-hypertensive individuals (463)

In the ENCORE trial hypertensive patients were recruited from the general community to assess the independent impact of the DASH diet on blood pressure (464). They found that differences in cultural patterns affected adherence to the interventions as African American participants were less likely to follow the recommendations compared to white participants (464). Some cultural patterns presented in the African-American population could affect adherence to the diet. Historically, the African-American population had high consumption of salt and high-fat products and low consumption of vegetables (465-466). These diet patterns have been associated with familial habits and ancestral traditions (467-468). The diet has also been called soul food meaning a spiritual and satisfactory food among the African American population (469).

2.4 Considerations that should be taken into account when interpreting studies assessing factors affecting blood pressure control

The studies presented in the review are not completely comparable. Populations differ in age, race/ethnicity, social conditions and health care provision. For instance, hypertensive patients from South Africa are younger (mean age 52 years) (342) than those from countries such as France (mean age 60 years) (372). Race/ethnicity represent those of black, white or Hispanic origin in studies from US (283) but individuals of Chinese, Malay and Indian origin in a study from Singapore (348). Whereas primary care is a public service with universal access in some European countries (349, 384), private and public health providers are responsible for primary care services in US (326). Differences in blood pressure control between public and private services have been reported. It seems that blood pressure control rates are higher in private services than that in public services (437).

The studies used different methods to measure blood pressure such as the mercury sphygmomanometer and the Omron blood pressure monitor with a standard protocol. Ostchega et al comparing the blood pressure measurements obtaining from these methods in participants from a national survey. They used an Omron HEM-907XL device. They found a higher correlation for systolic blood pressure (0.94) and lower correlation for diastolic blood pressure (0.83) between both measurements. The levels reported by OMRON device were lower than those produced by the sphygmomanometer (470). That could influence the differences in blood pressure control rates between countries and also the reported associations.

The associations between factors and blood pressure control have mainly derived from cross sectional studies conducted at population level or in primary care. Some considerations may have been taken. Firstly although these studies give information about blood pressure control across factor categories, they cannot assess the causal relationship between some factors and blood pressure control. The measurement of factors simultaneously with the outcome could overestimate the association between factors presented by the time the study was conducted. In contrast, the association between those factors with a time lag effect may be underestimated (471). Studies conducted in primary care could be affected by

selection bias. That is because those registered with or visited providers may not account for all hypertensive patients. They also may have particular conditions. Additionally in some studies patients and/or practices were recruited based on voluntary participation. Thirdly studies used a level of blood pressure measured at one occasion to define blood pressure control. One measure could not properly identify who has controlled blood pressure due to the individual variability in blood pressure (19).

Populations differ in health system characteristics. Whereas in some countries primary care services are a universal service with free access (328, 334), in others primary care services are offered by both private and public providers (317, 342). Although blood pressure control rates are reported low in both scenarios, differences in blood pressure control between public and private services have been reported. Studies seem to reveal that blood pressure control rates are higher in private sectors (437).

Summary

The achievement of controlled blood pressure depends on the interaction between patient factors, physician factors and health system factors. Studies analysing the importance of each factor are mainly national surveys and cross sectional studies conducted at primary care settings. The associations between some factors and blood pressure control varied across the studies. Becoming older has been the most frequent and consistent factor associated with poor blood pressure control. The relationship between sex and blood pressure control varied between studies and also has been contradictory. Although studies at population level revealed that some race/ethnic groups such as black groups are less likely to have controlled blood pressure, this association have not been replicated in context with different social structure. There seems that factors different from race/ethnicity account for some of this association. Increases in BMI/overweight have been consistently associated with poor blood pressure control. The relationship between socio economic aspects and blood pressure control varied across studies. However lower education levels have been more consistently associated with poor blood pressure control.

Patient adherence to recommendations for lowering blood pressure does not seem to be sufficient to achieve the expected efficacy of pharmacological interventions. For instance, up

to 50% of hypertensive patients who started taking antihypertensive medication stopped it over the first year of use. Patients with low adherence to antihypertensive medication are at higher risk of having hypertension-related cardiovascular diseases. Hence the benefit of using antihypertensive is lower than that observed in clinical trials may be due to non-compliance with the medical indications. Moreover, patient adherence to pharmacological and non pharmacological interventions have not frequently assessed in the studies conducted at population level or primary care services.

Physician related factors have been assessed in observational studies aimed at assessing physician performance. They have not always being incorporated in the assessment of individual factors. Inertial clinical, unaware of clinical recommendations, poor adherence to hypertension guidelines and a low strength of the relationship between physician and patient have been associated with not to have controlled blood pressure. However, clinical inertia has consistently been found as an explanation of having uncontrolled hypertension. The association between other physician factors and blood pressure control varied across the studies.

Health system factors refer to access to health services and the performance of service. Access to service may be the first step to improve blood pressure control. There is no one a consistent health system factor associated with blood pressure control. However it seems that offering regular visits to hypertensive patients, periodical physician education about hypertension guidelines, provide patient with education about blood pressure and team managed approaches are of more successful interventions to improve blood pressure control in primary care services.

Table 8 Characteristics of included studies reporting factors affecting blood pressure control

Study	Type of study	Setting	Sample sized method	Blood pressure method	Blood pressure control rates	Factors associated with blood pressure control Type of association	
Studies at population level						Poor control	Good control
Hyman et al (316) 2001	Cross sectional	NANHES III US Population aged 25 years and old	Sample including oversampling for race/ethnic minorities	Using mercury sphygmomanometer with standard protocol	23% among treated	Male Age 65 years and over Not visiting a physician in the previous 12 months	
He J et al 2002 (317)	Cross sectional survey	NANHES III US Population aged 18 years and over National Population	As ref 316	As ref 316		Mexican American origin Men Those aged 75 years and older	Regular access to health services/same provider Private insurance Having blood pressure measurement before six months Any modification of lifestyle (Weight loss, sodium reduction or exercise) Former married

Study	Type of study	Setting	Sample sized method	Blood pressure method	Blood pressure control rates	Type of association	
						Poor control	Good control
Gu et al (330) 2002	Cross sectional survey	China population Aged 35 to 74 years	Stratified sampling	Using mercury sphygmomanometer with standard protocol	8.1% among all hypertensive population.	Comparison frequencies Those between 35 and 44 years	Check non pharmacological interventions
Cifkova et al(472) 2004	Four Cross sectional surveys	National survey Czech Republic Population aged 25 – 64 years	Randomly selected from the General Health Insurance Company register	Using mercury sphygmomanometer with standard protocol	Increase from 3.9% to 17% in all hypertensive patients Increased 13.2% to 34.6% Among hypertensive on treatment		Women
Wang et al (318) 2004	Cross sectional survey (1992-1994) 1998	Population based China Aged 35 to 59 years	Subsample from national survey	Using mercury sphygmomanometer with standard protocol	6% controlled among all hypertensive population	Urban areas better than rural In Urban areas those aged 35-39 years had lower blood pressure control rates. In rural areas older patients had lower blood pressure control rates.	

Study	Type of study	Setting	Sample sized method reported	Blood pressure method	Blood pressure control rates	Type of association	
						Poor control	Good control
Agyemang et al (319)	Prevalence study	Ghana population	Random selection of residents in a village	Omron M5-I monitor	6.2% among those on treatment	Age >= 50 years	Being trader
Agyemang et al (311)	Cross sectional study	Population from South Amsterdam	Random sample	Omron M4 device	48.5% had systolic<140 mm Hg among those on treatment	For Dutch race/ethnicity Over-weight/obesity/abdominal obesity For African Surinamese Obesity/Abdominal obesity For Hindustani Surinamese Older age	For Dutch race/ethnicity High education Physical activity For African Surinamese Female Family history of hypertension
Ordunez-Garcia et al (334) 2006	Survey	Population Cienfuegos (Cuba) Aged 15 – 74 years	Sample designed considering equal probability for all groups	Using mercury sphygmomanometer with standard protocol	65.3% among treated 39.9% total population		Women

Study	Type of study	Setting	Sample sized method	Blood pressure method	Blood pressure control rates	Type of association	
						Poor control	Good control
De Macebo et al (343) 2007	Cross sectional	Population based Portugal 18 and 90 years	Multistage cluster sampling method	OMRON M4-1 sphygmomanometer	11.2% among all hypertensive individuals		Women Being younger Lower waist-hip ratio
Ostchega et al (313)	National survey 2008	Subsample from NHANES (Hypertensive patients)	Sample including oversampling for race/ethnic minorities	Using mercury sphygmomanometer with standard protocol	NA	Women Diabetes Poverty income Old or very old patients Non-Hispanic blacks Fewer visits to doctor	
Gu et al 2008 (320)	Cross sectional National survey	NANHES	Subanalysis of hypertensive patients	Using mercury sphygmomanometer with standard protocol	Men 53.7% Women 42.9% On treated	Women Becoming older Non-Hispanic black Mexican American	
Victor et al (329) 2008	Cross sectional	Population based Dallas Aged 18 – 64 years	Sample population with oversampling for minorities groups	Electronic oscillometric monitor	26.9% all hypertensive patients		Having a regular physician Being on treatment Perception on a good health

Study	Type of study	Setting	Sample sized method	Blood pressure method	Blood pressure control rates	Type of association	
						Poor control	Good control
Damasceno et al 2009 (339)	Cross sectional	Population Mozambique Aged 25 and 64 years	Sample based on census	Semiauto-matic sphygmomanometer (Omron 3)	3.1% all hypertensive patients		Women
Van Minh et al (282) 2009	Cross sectional study	Bangladesh, Indonesia, Vietnam, Thailand and India Aged 25 to 64 years	Surveillance system Not to mention on sample size strategy	Omron M3	5.4% all hypertensive patients	Become older High level of education Overweight	
Malthotra et al 2010 (345)	Cross sectional	Elderly participants in national survey Singapore Aged 60 years and over	Sampling from national registers	Omron HEM-780N	24.1% all hypertensive patients	Malay ethnic/race Men	
Ebrahimi et al (321)	Cross sectional 2010	National survey Iran Aged 15 to 64 years	Multistep cluster sampling	Aneroid sphygmomanometer	34.5% among treated patients	Men Increases in age	Middle educated people Academic education

Study	Type of study	Setting	Sample sized method	Blood pressure method	Blood pressure control rates	Type of association	
						Poor control	Good control
Egan et al (283)	Cross sectional national survey 2010	US Population	NANHES III Population aged 18 years and old	Sample including over-sampling for race/ethnic minorities	50.1% among treated hypertensive individuals	Those age 18 to 39 years Those aged 60 years and older Those of Hispanic origin and black race/ethnicity	
Tian et al 2011 (295)	Survey	Urban population China	Three stage stratified sample	A standardized mercuric-column sphygmomanometer	3.7% all patients	Becoming older Smoke	
Godet-Mardirossian et al (312)	Cross sectional survey 2012	France population Aged 18 to 74 years	Multistep sample design	OMRON M5-I	25.6% all hypertensive patients	Men Become older Those with more than three antihypertensive medication	
Guessous et al (346) 2012	Cross sectional	Geneva	Representative stratified sample	Omron HEM-907	60% among treated patients	Male Sedentary	

Study	Type of study	Setting	Sample sized method	Blood pressure method	Blood pressure control rates	Type of association	
						Poor control	Good control
Dzudie et al (290) 2012	Cross sectional	Cameron Urban areas Population aged 15 years and over	Sample size not to define Participates were invited by social communication media	Omron m3 hem-7200-e	24.6% among treated patients	Male gender High BMI Physical inactivity	Being from regions different from Centre and Littoral
Prince et al (138)	Cross sectional survey 2012	Sample population aged 65 years and over from Cuba, Dominican Republic, Puerto Rico, Peru, Venezuela, Mexico, China, India.	Sample were taking from a dementia survey	Not reported	Puerto Rico 58% Peru (71% in urban; 84% in rural) Others between 22%-39% among all hypertensive patients		Lower blood pressure levels observed in some populations were attributed to health care factors such as detection and blood pressure control

Study	Type of study	Setting	Sample size method	Blood pressure method	Blood pressure rates	Type of association	
						Poor control	Good control
Son et al 2012 (336)	Cross sectional survey	National population Vietnam Population aged 25 years and over	Stratified sample	Omron device	10% among treated patients		Women

NA Not applied

Studies at community services or ambulatory services							
Study	Type of study	Setting	Sample sized method	Blood pressure method	Blood pressure control rates	Type of association	
						Poor control	Good control
Lloyd Jones et al (205) 2000	Cross sectional	Hypertensive patients Community Mean age 66 years	Population from the Framingham Heart study US	Mercury sphygmomanometer	29.% all patients 47.8% among treated patients	Older age Left ventricular hypertrophy Obesity	
Westheim et al (315) 2001	Cross sectional	General practices Norway	Hypertensive patients Aged 18 years and over	Not reported	26% among treated patients	Increasing body mass index Increasing age	
Knight et al 2001(322)	Cross sectional	Ambulatory services US	Used registers from antihypertensive patients Mean age 65 years	Not reported	39% among treated patients	Older age Multi-antihypertensive prescription Poor patient knowledge about hypertension Reported antihypertensive side effects	

Study	Type of study	Setting	Sample sized method	Blood pressure method	Blood pressure control rates	Type of association	
						Poor control	Good control
Fagard et al 2002 (385)	Cross sectional	General practices Belgium	Physicians recruited hypertensive men aged 55 years and over	Omron hem-705	31% all hypertensive patients	Hypertensive patients at higher cardiovascular risk	
Jackson et al (379) 2002	Cross sectional	Managed care/Advance physician organizations		Not mentioned	36% among treated patients	Diabetes	
Ornstein et al (340) 2004	Cross sectional	General practices US	Hypertensive patients aged 18 years and over	Not mentioned	50% among all hypertensive patients		Younger below 59 years Female Visit periodically same the practice Antihypertensive treatment
Majernick et al (332)	Cross sectional 2004	Family practices US	Hypertensive patients on treatment visiting primary care centres Aged 18 years and over	Mercury sphygmomanometer	38.8% among all hypertensive patients	Higher Framingham score Female Diabetes	Patient knowledge about hypertension

Study	Type of study	Setting	Sample sized method	Blood pressure method	Blood pressure control rates	Type of association	
						Poor control	Good control
Hicks et al 2004(347)	Cross sectional	Community health services	Used registers from hypertensive patients on treatment Mean age 61.3 years	Not reported	36.6% among all hypertensive patients	Men Hispanic Patients without insurance	Intensification of therapy
Degli Espositi et al 2004 (323)	Longitudinal	General practices Italy	Practices accepted invitation recruited hypertensive patients Mean age 64 years	Automatic BP device	39.5% among all patients	Increasing patient age Increasing physician age Increase in the number of antihypertensives Previous myocardial infarction	
Mancia et al(324)	Longitudinal study 2005	Ambulatory clinic Italy	Hypertensive patients collected by open invitation Mean age 61 years	Omron 705 CP	37.5% among all patients	Becoming older	Management offered by cardiologist Use Monotherapy High education level

Study	Type of study	Setting	Sample sized method	Blood pressure method	Blood pressure control rates	Type of association	
						Poor control	Good control
Roux (372) 2006	Cross sectional	Primary care centres France Age 18 years and older	Representative sample hypertensive patients on treatment	Mercury or aneroid sphygmomanometer	18% among all hypertensive patients	Male Increases in age Increases in weight Increases in heart rate	Young age Female
King et al (350)	Cross sectional	General practices	Not referred Mean age 55.4 years	Not mentioned	Not reported	African American male Being from an urban setting	
Abaci et al (325) 2006	Cross sectional	Primary care units Turkey Aged 18 years and over	Hypertensive patients recruited from primary care centres. Sample size was defined for each centre.	Mercury sphygmomanometer	30.2% among hypertensive patients on treatment	Age ≥ 65 years Diabetes BMI >25 kg/m ²	Having a cardiovascular disease Smoking
Hedblad et al (314) 2006	Cross sectional 2006	Primary health care centres Skane Sweden	Hypertensive patients Aged 39 years and over	Not reported	22% among all hypertensive patients	Becoming older	

Study	Type of study	Setting	Sample sized method	Blood pressure method	Blood pressure control rates	Type of association	
						Poor control	Good control
Senior et al 2006 (386)	Survey	General practices New Zealand	Hypertensive patients aged 80 years and over	Blood pressure measurement taken from records Target 140/85 mmHg	54% (<150/90 mmHG) and 31% (<149/85 mmHG) among treated hypertensive patients		Stroke Heart failure Hypercholesterolemia
Dennison et al (342) 2007	Cross sectional	Public and private primary care services Cape Town (South Africa)	Hypertensive patients of black origin aged 35 to 65 years	Omron M4 device	38% among all hypertensive patients		Taking lower number of antihypertensive medications Women Higher adherence to antihypertensive medication
Petrella et al 2007 (373)	Longitudinal study	Family practice clinics Canada	Population selected from those registered in general practices Aged 18 years and over	Aneroid devices Mercury Sphygmomanometer Automated devices	17.3% among treated patients	Overweight patients	Older patients with diabetes People with two comorbidities Smokers

Study	Type of study	Setting	Sample sized method	Blood pressure method	Blood pressure control rates	Type of association	
						Poor control	Good control
Ma et al 2008 (326)	Cross sectional	Medical care US	Hypertensive patients aged 18 years and over	Information from registers	39% among treated patient visits	Patients aged 75 years and older Hypertension related – comorbidities	
Kim et al (344) 2008	Cross sectional	Primary care services Korea	Hypertensive patients from practices randomly selected	Standard electronic sphygmomanometer	51% among all hypertensive patients	Male Cardiovascular comorbidity Long duration of hypertension Unhealthy life style	
Rosenberger et al (341) 2008	Cross sectional	General practices North Carolina	Random charts from patients aged 21 to 84 years	Not reported	41% among all hypertensive patients	Being attended by one health provider	Female
Journath et al (333) 2008	Cross sectional	Swedish general practice	Hypertensive patients registered in general practices Mean age 64 years	Not reported	30% among treated hypertensive patients	Women	

Study	Type of study	Setting	Sample sized method	Blood pressure method	Blood pressure control rates	Type of association	
						Poor control	Good control
Varis et al (473) 2009	Cross sectional	General practices Finland	Hypertensive patients aged 18 years and over	Mercury sphygmomanometer	24% all hypertensive patients on target (140/85 mm Hg)		Being prescribed two or more antihypertensive drugs
Buckely et al 2009 (380)	Cross sectional	Ireland primary care practices	Hypertensive patients on treatment Mean age 64.7 years	Blood pressure records from registers	48.6% among all hypertensive patients without diabetes	Diabetic patients	
Tan et al (348) 2009	Cross sectional	Primary care services Singapore	Hypertensive patients Mean age 60 years	Omron hem-705cp	37.7% among all hypertensive patients	Male	
Filippi et al (474) 2009	Retrospective survey Controlled	Italian general practice Voluntary participation	Hypertensive patients Mean age 63.5 years	Automatic BP device (Dinamap)	28% among all hypertensive patients	Low rate patient attendance Under-recording blood pressure	
Ohta et al (475) 2009	Longitudinal study 54%	Japan Hospital clinic	Hypertensive patients Mean 68 years	Mercury sphygmomanometer	52% and 68.1% among younger and older hypertensive patient 101espectively		Increases in antihypertensive medication

Study	Type of study	Setting	Sample sized method	Blood pressure method	Blood pressure control rates	Type of association	
						Poor control	Good control
Saleheen et al (327) 2010	Cross sectional	Pakistan Primary care health centres	Hypertensive patients Mean age 59 years	Not reported	6.4% among those on treatment	Become older Hypercholesterolemia Physical inactivity	
Skliros et al et al (291)	Cross sectional 2012	Primary Health Care Nemea Health program Greek	Sample size defined based on census Older hypertensive patients	Mercury sphygmomanometer	49% among hypertensive patients on treatment	Heavy drinking	
Qvarnstrom et al 2011(328)	Cross sectional 2011	Primary care centres Swedish	Hypertensive patients aged 30 years and older	Not reported	27% among all hypertensive patients	Women at older age	Women at younger age
Brenner et al 2011 (286)	Cross sectional Survey	Swiss General practice	Hypertensive patients aged 20 years and over Practice randomly selected	Not reported	56.9% all hypertensive patients	Diabetes Nephropathy	

Study	Type of study	Setting	Sample sized method	Blood pressure method	Blood pressure control rates	Type of association	
						Poor control	Good control
Paulsen et al (349) 2011	Cross sectional	Denmark Primary care	Hypertensive patients invited to participate Mean age 65.9 years	Not reported	29.1% among all hypertensive patients	Diabetes Men	Patients with other cardiovascular comorbidity
Listerri et al 2011 (381)	Cross sectional	Women Primary care settings Spain	Hypertensive patients Sample size calculated based on heart failure prevalence Mean age 65 years	Mercury-based or aneroid sphygmomanometer	29% among all hypertensive patients	Patients being diagnosed with hypertension recently High cholesterol Monotherapy HbA1c	
Al Saadi 2011(382)	Cross sectional	Primary care services Oman	Hypertensive patients Aged 18 years and over	Not reported	39% among all hypertensive patients	Diabetes Renal disease	
Labeit et al (287) 2012	Cross sectional	Germany Primary care Services	Hypertensive patients Aged 18 years and old from representative primary care services	Sphygmomanometer or Automated validated devices.	20.3% among treated hypertensive patients	Increasing age Obesity	Coronary heart disease Antihypertensive medication Women

Study	Type of study	Setting	Sample sized method	Blood pressure method	Blood pressure control rates	Type of association	
						Poor control	Good control
Paulsen et al (383) 2012	Longitudinal study	Denmark General practices	Hypertensive patients Aged between 25 and 80 years	Mercury sphygmomanometer or home blood pressure measurement	33.2% among patients on treatment	Those with diabetes or those with diabetes plus other cardiovascular diseases	
Paulsen et al (384) 2012	Cross sectional	Denmark General practices	Hypertensive patients Mean age 65.9 years	Mercury sphygmomanometer	29.1% among all hypertensive patients	Diabetes	For patients aged 65 years and over: being married/cohabiting For patients aged below 65 years: High level of education For all presence of cardiovascular disease
Sandonval et al 2012 (292)	Cross sectional	Primary care centres Chile	Hypertensive patients aged 20 years and over Multicenter cross-sectional Systematically randomized sample	Mercury sphygmomanometers	59.7% among all hypertensive patients	Diabetes Obesity High cholesterol levels	Smoking Presence of stroke, heart failure and/or ischaemic heart disease

Study	Type of study	Setting	Sample sized method	Blood pressure method	Blood pressure control rates	Type of association	
						Poor control	Good control
Schaffer et al 2012 (285)	Cross sectional	Primary care practices Swiss	Hypertensive patients aged 18 years and old	Auscultatory or Oscillatory method	54% among all hypertensive patients	Diabetes Chronic renal disease	
Suarez et al (374) 2013	Longitudinal retrospective study	General practices Spain	Hypertensive patients aged 18 years and over	Aneroid or mercury sphygmomanometer or a validated automatic device	NA	Weight gain High baseline LDL cholesterol No reduction in fasting glucose	No smoking Absence of diabetes Reduction in cholesterol Low baseline cholesterol No weight gain

Table 9 Factors associated with blood pressure control

Factors	Good control	Poor control
Patients factors	Reference	Reference
Age		
Become older or Age >65 years	(373)	(18, 205, 282-283, 287, 295, 311-328)
Younger age	(340, 343)	(283, 318, 328-330)
Ethnicity		
Black		(283, 313, 329, 347, 351-352)
Mexican American		(283, 317, 347)
Malay ethnicity		(345)
Sex		
Women	(287, 311, 334, 336-343)	(205, 313, 315, 320, 331-334)
Men		(290, 312, 316-317, 344-350)
Presence of comorbidity		
Obesity Higher BMI/Overweight		(205, 282, 287, 290, 292, 311, 315, 325, 370-374)
Low waist hip ratio	(343)	
Presence of other cardiovascular comorbidity (Diabetes, left ventricular hypertrophy, hypercholesterolemia)	(287, 292, 344, 349, 373, 384-386)	(205, 285-286, 292, 313, 323, 325-327, 332, 344, 349, 372, 374-384)
Consumption of other medications		(476)
The severity of hypertension		(385)

Factors	Good control	Poor control
Long duration of hypertension		(344)
Family history of hypertension	(311)	
Being diagnosed recently		(381)
Multiple antihypertensive medication		(312, 322)
Few antihypertensive drugs	(342)	
Life style		
Smoking		(295, 369)
Not smoking	(374)	
Diet Lower salt consumption	(317)	
Doing physical activity	(311, 317)	
Unhealthy life style (Physical inactivity)		(290, 327, 344, 346)
Weight loss	(317)	
Higher adherence to antihypertensive medication	(342)	
Heavy physical work		(477)
Heavy drinking		(291)
Misunderstood prescription		(478)
Being on antihypertensive treatment	(287, 340, 473)	
Socio economic conditions		
Living alone		(375, 479)
Lack of social support		(479)
Being married/cohabiting	(384)	
High level of education	(292, 311, 313, 321, 324, 384)	
Being trader	(319)	
Poverty income		(313)

Factors	Good control	Poor control
Perception of a good health	(329)	
Poor knowledge about hypertension		(322, 398)
Physician factors		
Intensification of therapy	(475)	(347)
Clinical inertia		(359, 402, 408, 480-483)
Poor adherence to guidelines		(327, 405-406, 413, 415, 484)
Lack of continuing education for physician		(340, 485)
Continuing education for physician	(485-486)	
Increasing physician age		(323)
Health system factors		
Having good access	(317)	
Not visiting regularly a physician		(313, 316, 474)
Having a regular clinical visit	(317, 329, 340)	
Type of health plan	(317)	(347)
Not having an insurance		
Being attended by one provider		(341)

Key points

- ✓ The percentage of hypertensive individuals who achieved a blood pressure level below 140/90 mm Hg is below 50% worldwide
- ✓ The management of hypertensive patients mainly relies on primary care services.
- ✓ Within patients receiving care in well developed primary care services the percentages of hypertensive of patients who achieved a target of 140/90 mmHg ranged from 25% to 42%.
- ✓ In primary care settings, the achievement of a target of 140/90 mmHg depends on individual factors, physician factors and health system factors.
- ✓ The most frequent individual factors are age, race/ethnicity, BMI, adherence to pharmacological and non-pharmacological interventions and social conditions.
- ✓ The physician-related factors are mainly related to inertia clinical, physician knowledge about the management of hypertension and physician communication skills.
- ✓ The health system factors include access to health care and performance of services.
- ✓ Patient attending regularly health care services seem to have better blood pressure control
- ✓ Multiple initiatives have been proposed and implemented in primary care services to improve blood pressure control in primary care.
- ✓ Among these initiatives the team based management approach seems to produce the better improvement on blood pressure control

Chapter 3 Epidemiology of hypertension in England

3.1 General trends

In England the prevalence of raised blood pressure is assessed through the Health Survey for England (HSE) (487). The survey includes individuals over 16 years sampled from the general population living in a private house. Since 2003, the survey has defined a hypertensive individual as one who meets at least one the follow criteria: a) having systolic blood pressure equal or above 140mm Hg and/or diastolic blood pressure equal or above 90 mm Hg with or without taking antihypertensive medication; b) taking medicaments for hypertension regardless of blood pressure levels. The measurement of blood pressure was taken using Omron monitor. Since 2003 the protocol for measuring blood pressure has not been changed. To assess blood pressure control four categories of patients have been defined (Box 2).

The prevalence of hypertension has slightly changed over the last seven years. The prevalence was 30.6% in 2003 and 30.2% in 2010 among those aged 16 years and over (284, 487). Prevalence increases with age and the highest rates are in those over 55 years. Overall, the prevalence is higher in men than women across all age categories. In 2006, mean blood pressures were 131.4/74.5 mmHg and 125.7/73.3 mmHg for men and women respectively (488).

Differences in blood pressure levels between racial/ethnic groups in the UK population have been reported. In a systematic review of 14 studies conducted between 1966 and 2002, Agyemang et al reported that mean systolic and diastolic blood pressure was higher in men and women of African descent compared to those of white origin among population living in UK. Compared to white population, the African population had higher prevalence of hypertension (489). Similarly in the analysis of Health Survey for England between 1991 and 1996, Primatesta et al found that individuals of black origin had higher blood pressure levels

than those of white origin among those aged 40 years and over (490). Using data from people resident in the West Midlands, Lane et al found that participants of black origin had higher prevalence of hypertension than those of Caucasian or South Asian origin (491). By contrast, individuals of South Asian origin tend to have lower blood pressure levels than their white counterpart (90).

Box 2 Classification of individuals by blood pressure levels in Health Survey for England

Category	Definition
Normotensive untreated	Systolic blood pressure<140 mmHg and Diastolic blood pressure <90 mmHg, not currently taking medication specifically prescribed to treat high blood pressure
Hypertensive controlled	Systolic blood pressure<140 mmHg and Diastolic blood pressure <90 mmHg, currently taking medication specifically prescribed to treat high blood pressure
Hypertensive uncontrolled	Systolic blood pressure≥140 mmHg and Diastolic blood pressure ≥90 mmHg, currently taking medication specifically prescribed to treat high blood pressure
Hypertensive untreated	Systolic blood pressure≥140 mmHg and Diastolic blood pressure ≥90 mmHg, not currently taking medication specifically prescribed to treat high blood pressure

Source (487)

3.2 Blood pressure control in England

In England the percentage of hypertensive patients with blood pressure below 140/90 mm Hg has increased between 2003 and 2010. An opposite trend has been observed in the percentage of untreated patients over the same period (487, 492). In 2010 among those classified as hypertensive individuals (30.2%), 10% had controlled hypertension, 7.1% had uncontrolled hypertension and 12.4% were not being given antihypertensive treatment (487) (Table 10).

According to the last published national survey, the proportion of hypertensive patients with blood pressure below or at 140/90 mm Hg was 28% in 2006. Among those on antihypertensive treatment the proportion of patients with controlled hypertension rose from 46% in 2003 to 52% in 2006 (284). In 2009 that proportion was 58% for men and 50% for women including only those aged 35 years and over (493). A sub analysis of the surveys carried out between 2005 and 2007 revealed that the percentage of hypertensive people on treatment varied across the country. Hypertensive patients living in London suffering with others co-

morbidities are more likely to be on treatment than those living in the rest of the country (494).

The 2006 survey has not produced blood pressure control rates by ethnic groups or social strata (284). In an analysis of 1999 to 2004 Health Surveys for England, Nazroo did not find significant differences in blood pressure control rates between hypertensive individuals belong to ethnic minorities (Irish, Caribbean, Indian, Pakistani, Bangladeshi or Chinese) and those of white origin. Caribbean patients were more likely to have controlled blood pressure (495). The authors commented that the low response rate found in ethnic minorities may bias the results. Other reports have shown that African hypertensive patients were less likely to have their blood pressure controlled (496-497). Reductions in ethnic disparities of blood pressure control have been published though using a higher target of 159/90 mm Hg (498).

Table 10 Trends in hypertension prevalence and control. 2003 -2010 England

	2003	2005	2006	2007	2008	2009	2010
Normotensive untreated*	69.4	69.8	70.6	70.0	69.9	70.6	69.8
Hypertensive controlled	5.7	7.7	7.3	8.2	8.7	7.7	10.6
Hypertensive uncontrolled	7.0	7.5	6.7	6.6	6.7	6.6	7.1
Hypertensive untreated	17.9	15.0	15.3	15.3	14.7	15.0	12.5
All with high blood pressure	30.6	30.2	29.4	30.0	30.1	29.4	30.2

*Values in percentage

Source HSE (492)

Definition of clinical hypertension

The definitions of hypertension for clinical assessment in primary care are established by NICE (Table 11). The definition has been changed mainly due to variation in hypertension categories and the methods recommended for the measurement of blood pressure. However the level equal to or above 140/90 mm Hg remains as the level used for defining hypertension in the last clinical guideline (144, 499). The recommendations applied to adults aged 18 years and over of all patients regardless of race/ethnic origin and sex.

Table 11 Classification of blood pressure levels in England hypertension guidelines

Category	2004 BHS /2004-2006 NICE*		2011 NICE	
	Systolic mm Hg	Diastolic mm Hg	Systolic mm Hg	Diastolic mm Hg
Optimal	<120	<80	Normotensive	
Normal	<130	<85	Clinic blood pressure ABPM**/HBPM**	<140 <135 <90 <85
High normal	130-139	85-89	Stage 1 Hypertension	
Prehypertension	NA		Clinic blood pressure ABPM/HBPM	>=140 >=135 >=90 >=85
Grade 1 Hypertension mild	140-159	90-99	Stage 2 Hypertension	
Grade 2 Hypertension moderate	160-179	100-109	Clinic blood pressure	>=160 >=100
Grade 3 Hypertension severe	>=180	>=110	ABPM/HBPM	>=150 >=95
Isolated systolic hypertension			Severe Hypertension	
Grade 1	140-150	<90	Clinic blood pressure	>=180 >=110
Grade 2	>=160	<90		

*The classification is based on the highest valued when systolic blood pressure and/or diastolic blood pressure fall into different categories

**Ambulatory blood pressure monitoring

***Home blood pressure monitoring

3.3 The blood pressure targets for the management of hypertension

The blood pressure targets for the management of hypertensive patients have been established in national guidelines since 1993 (Table 12). Blood pressure targets are established based on the initial blood pressure and the individual cardiovascular risk assessment. There has been a reduction in the level of blood pressure target particularly for those at a higher cardiovascular risk. The following section describes the background used to establish the recommendations on blood pressure targets in the former guidelines. The review mainly is focused on the guidelines orienting the management of hypertensive patients without additional cardiovascular comorbidity.

3.3.1 The assessment of cardiovascular risk

Current guidelines advised on assessing the absolute cardiovascular risk of cardiovascular of the hypertensive patients without cardiovascular complications or target organ damage. The first step is to evaluate whether or not the patient has another established cardiovascular disease. The second is to determine if there are signs of hypertensive damage to target organs such as heart, kidneys or retina. Then the assessment of the probability of having a cardiovascular event over a long term period usually 10 years is indicated. The 1999 BHS guidelines recommended assessing the risk of coronary heart disease (CHD) based on the Framingham risk function. Then patients are classified into a high, middle and low cardiovascular risk category dependent upon a score of $\geq 30\%$, $\geq 15\%$ or $<15\%$ in the Framingham risk scale respectively.

The 2004 BHS hypertension guidelines and the 2004 hypertension NICE guidelines encouraged physicians to calculate the absolute risk of cardiovascular disease (CVD) rather than the risk of CHD (174). The change is based on the need for estimating as much as possible the total hypertension-related cardiovascular risk present in each hypertensive patient. The interventions should aim at preventing hypertensive patients from having any hypertension-

related cardiovascular event not only one in particular. The assessment of the CVD risk was again based on the Framingham risk function. A modification is introduced for the assessment of age-related risk. Patients aged 50 years and below were considered as having the risk of those aged 49 years and those aged 60 years and over are considering as having the risk of those aged 69 years. This modification intends to correct the underestimation of the risk in patients at extreme ages, younger and older. Patients with a Framingham risk score $\geq 20\%$ were classified as those at high cardiovascular risk.

Table 12 Blood pressure targets recommended in England hypertension guidelines between 1999 and 2011

	1999 BHS (500)	2004 BHS (174)	2004 NICE (501)	2011 NICE (144)
Patients at low and middle cardiovascular risk	<140/85 mmHg	<140/85 mmHg	<=140/90 mmHg	<140/90 mmHg‡ Patients > 80 years <150/90 mmHg¥
Patients at higher cardiovascular risk	<140/80 ₁ mmHg	<= 130/80 ₂ mmHg	See section 3.3.3	See section 3.3.3
‡ Clinic blood pressure measurement. Below 135/85 mm Hg using ABPM or HBPM ¥ Clinic blood pressure measurement. Below 145/85 mm Hg using ABPM or HBPM ₁ Referred to diabetic patients ₂ Referred to patients with diabetes, renal impairment or established cardiovascular diseases				

The 2011 NICE hypertension guidelines discouraged physicians to use the Framingham risk function as the standard score to assess cardiovascular risk (144). That is because the Framingham score has the potential to overestimate the cardiovascular risk in UK population (146). However the use of Framingham score is upon physician criteria in that the guidelines provide recommendations on interpreting the Framingham score in UK population. There are also other scores to assess the risk of cardiovascular diseases such as QRISK and AS-SIGN. However, the NICE guidelines advised on the need for validating these scores. The QRISK score has undergone additional validation. Because it is derived from UK data (unlike Framingham), it is being used much widely for the measurement of CVD risk in UK primary care. The assessment of cardiovascular risk aims to determine the therapeutic interventions and blood pressure targets more suitable for each individual (144, 174, 499). The threshold to which blood pressure should be lowered is based on the following criteria:

3.3.2 Patients at low and middle cardiovascular risk

The 1999 and 2004 BHS guidelines advised on achieving a level of blood pressure below 140/85 mm Hg in hypertensive patients without diabetes (174, 502). The recommendation required the achievement of both systolic blood pressure below 140 mmHg and diastolic blood pressure below 90 mmHg to define the control of blood pressure. The diastolic blood pressure target is mainly based on the findings reported in the HOT clinical trial (185). The study found that there were no differences in cardiovascular mortality between patients achieved diastolic blood pressure below 90 mmHg and those achieved diastolic blood pressure below 85 mm Hg or below 80 mmHg. 93% of the patients achieved diastolic blood pressure below 90 mm Hg (185). The systolic blood pressure target was based on the results from the VALUE trial (242) and the ASCOTT-LLA trial (503). Both trials reported that more than 80% of patients achieved systolic blood pressure below 140 mm Hg. In these studies hypertensive patients were mainly at high cardiovascular risk.

The 2004 NICE guidelines recommend a target of or below 140/90 mmHg for all hypertensive patients who are at middle or low cardiovascular risk (501). The target is recommended for all hypertensive patients regardless of age, sex and ethnicity. The target is supported by the following considerations. The proportion of patients who achieved blood pressure targets

ranged from 21% to 80% in the 24 clinical trials referred in the guideline. These trials used different blood pressure targets and some of them assessed only the achievement of a diastolic blood pressure target (178, 185, 228-229, 254-255, 504-509). The lack of significant differences in cardiovascular mortality between patients randomised to intensive blood pressure control and those to standard blood pressure control. Finally, the statement is mainly based on the HOT clinical trial (185). None of the clinical trials aimed to test the 140/90 mmHg target against other blood pressure target.

The 2011 NICE hypertension guidelines advocate a target blood pressure below 140/90 mm Hg for the hypertensive patients aged below 80 years and at low or middle cardiovascular risk. This level is the measurement of blood pressure taking in clinical settings. This blood pressure level corresponds to a target of 135/85 mm Hg when blood pressure is measured by using ABPM or HBPM. The recommendation is grounded in a review of fifteen studies (142, 197-198, 200, 218-219, 234, 510-525). The studies are two meta-analysis (142, 524), one systematic review (525), six clinical trials (197-198, 200, 510-512), five post hoc analyses (176, 218, 245, 258, 526) and one observational study (259). None of the studies aim to compare the 140/90 mmHg blood pressure target with other blood pressure target. The two meta-analysis concur on the benefit of reducing systolic and diastolic blood pressure regardless of patient age (142, 524). The systematic review assessed the reduction in cardiovascular risk in hypertensive patients but not the association with lower blood pressure targets (525). The six clinical trials differ in the follow up period and patients characteristics. Two trials do not have power to detect differences between intensive and standard target (198, 200). Two trials report a follow up period less than two years (510-511) and one does only 24 weeks (512). There is no level proposed as a blood pressure target in any of the trials. The five post hoc studies agreed on the significant impact of achieving blood pressure levels below 140/90 mm Hg. However three of them also report a high incidence of mortality in hypertensive patients with coronary disease when they achieved blood pressure levels below 65 mmHg diastolic blood pressure (176, 245, 258). The authors of the guideline concluded that the available evidence cannot prove the use of specific threshold as a blood pressure target. Hence they recommend preserving the target established in the 2004 hypertension guidelines.

3.3.3 Targets for specific groups

The 1999 and 2004 BHS guidelines did not establish a specific blood pressure target for elderly patients; it did highlight the lack of evidence about prescribing antihypertensive medication for those with systolic blood pressure levels between 140-150 mmHg and diastolic blood pressure below 90 mmHg. For diabetic patients and patients with renal disease a blood pressure level less than 130/80 mmHg is the recommended target (174, 502).

The hypertension NICE guidelines do not include recommendations for patients with diabetes or renal diseases because a disease-related guideline is produced for these conditions. The 2008 NICE guidelines for diabetes establishes a target of blood pressure below 140/80 mmHg for all diabetic patients and a target of blood pressure below 130/80 mmHg for those at particular risk for example patients with albuminuria (225). The 2008 NICE guideline establishes a blood pressure target below 140/90 mm Hg with systolic blood pressure between 120-139 mm Hg for hypertensive patients with chronic kidney disease (CKD). For hypertensive patients with CKD and other conditions such as diabetes a blood pressure target of systolic blood pressure between 120/129 mmHg and diastolic blood pressure below 80 mmHg is recommended (226).

The 2011 hypertension NICE guidelines also added a new blood pressure target for hypertensive patients aged 80 years and over. The guideline recommends a blood pressure target below 150/90 mm Hg. The recommendation is mainly based on the meta-analysis of eight trials conducted by Bejan-Angoulvant et al (527). The meta-analysis revealed that hypertensive patients with mean age of 83 years on antihypertensive treatment had a higher reduction in the risk of stroke, heart failure and cardiovascular events compare to those without treatment. The finding was observed in the least and lowest blood pressure levels achieved by the patients on treatment. However there was not reduction in all cause mortality. That may due to differences in patient characteristic between studies producing heterogeneity in this outcome. Hence this variability may detract from establishing a conclusive statement about the benefit of achieving a blood pressure below 150/90 mmHg.

The assessment of blood pressure control in primary care

Since 2004 the assessment of blood pressure control in primary care in England has been based on the Quality and Outcome Framework (QOF). The description of the QOF is presented in the section 4.4. For hypertension the percentage of patients with blood pressure equal to or less than 150/90 mmHg is the criterion of performance (528). The criteria used to select the threshold were not well supported in the guidance. However this level was the audit standard recommended by the BHS in 1999 (174).

Comparisons of performance between general practices are based on the achievement of the QOF indicators. According to Ashworth et al, the blood pressure control has improved across all general practices after the introduction of QOF (498). Moreover there has been reduction in disparities in blood pressure control between general practices. The last report of QOF indicators also showed that nearly 98% of general practices achieved the indicator in 2012 (529) .

3.4 Factors affecting blood pressure control: evidence from studies carried out in England

In England, associations between different factors and blood pressure control have been quantified. For instance adherence to medication may vary over the time. In a study including 37643 hypertensive patients, Jones et al found that for patients who were prescribed with a new antihypertensive drug, 50% of the initial prescriptions had been modified or discontinued after six months (530). In an analysis of medical records from 21024 hypertensive patients, Walley et al identified that the rate of using the same first line antihypertensive medication was 69% in the first year (531). Using information from 109454 hypertensive patients registered with the UK General Practice Research Database (GPRD), Burke et al identified that the rate of antihypertensive drug discontinuation was 20% and 28.5% over six months and one year follow-up period respectively (532).

The relevance of sex, age and race/ethnic in blood pressure control has been assessed in different studies conducted in general practices. In a study carried out in 16 general practices located in Wandsworth, London, Millett et al identified that hypertensive patients of black origin were less likely to have controlled blood pressure compared to those of white origin (496). Similarly, in a study conducted in Lambeth, London, Schofield et al reported that hypertensive patients of black origin were less likely to have controlled blood pressure compared to those of white origin (497). In analysis of 41250 patients registered with general practices in West Midlands (UK), Sheppard et al did not find differences in antihypertensive prescription between sex. They also identified that the percentage of patients who received antihypertensive medication increased with age (533). In a study of 4195 hypertensive patients, Tabenkin et al revealed that there were no differences in the management of hypertension between the sexes (534). In a cross-sectional study conducted in 148 general practices, Mathur et al identified that hypertensive patients of South Asian origin were more likely to have controlled blood pressure compared to those of white origin (535). They also found that hypertensive patients with an additional cardiovascular comorbidity were more likely to have controlled blood pressure (535).

Inister et al. performed an analysis of 536 hypertensive patients being treated in eight general practices to assess the relative importance of patient-factors, physician-factors and service performance in blood pressure control (536). They found that being treated with more than two antihypertensive drugs was not associated with blood pressure control. Similarly, continuity of care as a measurement of the number of clinical visits was not associated with blood pressure control (536). In the Whitehall II cohort of men and women aged between 42 and 63 years, Sabia et al found that healthy behaviours was associated with better systolic blood pressure levels among those being prescribed antihypertensive medication (537).

Chapter 4 Primary care

The origin of the term is not completely known but the concept was probably illustrated initially in the Dawson Report released in the UK in 1920 (538). The report described a pyramidal structure of health care services with three levels of complexity. The first level of complexity led to the origin of primary care. In 1961 White et al pointed out the concept of the ecology of medical care. The review described that the majority of health problems can be solved by local health services (539). Since then the concept of primary care has evolved further. I will describe the definition of primary care and its impact on the control of chronic diseases. A particular reference to the model of primary care in England will be presented.

4.1 Primary care concept

A definition of primary care was formally established in the Alma-Ata declaration in 1978 (540). Subsequently, the term has been modified (Box 3). From this historical background two terms have emerged: Primary Care (PC) and Primary Health Care (PHC). These terms have often been interchangeable depending on the country and the strategy used to deliver services at the community level.

Similarities and differences between both terms are presented in box 4. One difference between PHC and PC is that the former integrates some public health aspects into its definition. For instance the Alma-Ata declaration and the following WHO reports included activities such as improving the potable water supply or basic sanitation as part of the Primary Health Care strategy (541). The role of the local community in health decision-making forms a component of PHC and also represents another difference (541). These aspects are not clearly stated under the definition of PC (542).

The concepts are also context-dependent. Within PC, strengthening the role of the family doctor or general practitioner has mainly been the predominant strategy to expand health services at community level in some high income countries from Europe (440, 543). On the other hand, PHC, with its broad approach that includes community participation and environmental interventions, has delivered a strategy to develop health services at community level in low and some middle income countries (544-545). Moreover, selective primary health care, defining a PHC focused on managing particular health conditions in order to use resources efficiently, has also been implemented in some of low income countries (546-547).

In essence both PC and PHC aim to provide care for individuals in the context of the family and community in which the patient lives. PHC integrates the functions of health policy to thus influence the strategies used by PC to deliver care to individuals within a specific population (548-549).

Box 3 Definitions of Primary Care

Report	Definition
Lalonde (550)	The report introduced the term of health field which identified four elements that the health population status depends upon: human biology, environment, lifestyle and health care organization. Health field incorporated the following criteria: a) the equal importance of the four elements in determining health population status, b) a comprehensive approach in that the cause of any health problems should take into account one or all elements, c) measuring the contribution of each element in the analysis of any health problem, d) the identification of factors susceptible to intervene. There were not specific mentions of the primary care concept but it was implied that there was a need for seeking health solutions outside the hospital environment.
Alma-Ata (540)	The term Primary Health Care was defined as “Primary health care is essential health care based on practical, scientifically sound and socially acceptable methods and technology made universally accessible to individuals and families in the community through their full participation and at a cost that the community and country can afford to maintain at every stage of their development in the spirit of self-reliance and self-determination. It is the first level of contact of individuals, the family and community with the national health system bringing health care as close as possible to where people live and work, and constitutes the first element of a continuing health care process”.
WHO (551)	The report preserved the definition of Primary Health Care established in the Alma-Ata declaration. In addition to this, the report defined the essential elements of Primary Health Care. These elements arose from integrating activities such as the proper use of water and sanitary facilities and other related to environment and health technology development into the concept of Primary Health Care
IOM (552)	The document used the term Primary Care as it was established in the 1996 definition. “Primary care is the provision of integrated, accessible health care services by clinicians who are accountable for addressing a large majority of personal health care <i>needs</i> , developing a sustained partnership with patients, and practicing in the context of family and community”.
Barbara S. (553)	Primary Care is “is that level of a health service system that provides entry into the system for all new needs and problems, provides person-focused (nor disease-oriented) care over time, provides care for all but very uncommon or unusual conditions, and coordinates or integrates care provide elsewhere by others” Primary care connotes conventional primary medical care striving to achieve the goals of primary care health care”
WHO (554)	The report neither did establish a new definition of Primary Health Care nor Primary Care . The document defined what is called “the features of primary care” which including effectiveness and safety, person-centred care, comprehensive and integrated responses, continuity of care and longitudinality.

4.2 Definition of Primary Care attributes

The attributes of PC services are described below. I divide these attributes into two categories; the essential features of primary care services (542) and attributes added as a result of the progressive changes in clinical practice (554) (Box 4).

Essential features of primary care

The essential features of PC have been postulated by Starfield (542). PC services built on these features have improved the health conditions at community level (440, 554-556). The definition of each feature is below:

First contact access: this feature implies two dimensions. One is accessibility meaning that individuals can benefit from primary care interventions without financial, geographical, language or cultural limitations. The other is the role of PC as the entry point to the health system whereby people must use PC for each new health need.

Longitudinality of care (Long term-person care/continuity of care): it includes the following aspects: a) the process of care for each patient is delivered either until the resolution of health problem or until a health risk needed a follow-up to be eliminated; b) a person centred care approach whereby the solution for each health problem integrates, patient needs, patient beliefs and patient preferences on treatments.

Coordinated care: it is the requirement of the system to provide continuity and identify individuals with conditions which require follow-up. In other words health systems should systematically record patient information, including all levels of attention, to provide access to data regarding patients' medical history.

Comprehensive and integrated responses: PC services have the potential to offer to each patient an integrated management plans which may include not only drug prescription but also health promotion and prevention advice. The final solution for the health need could be beyond the primary health care service with which PC services are working.

Additional attributes of primary care

Effectiveness: the capability of solving health problems presented in the referred population.

Quality of care: ability to achieve defined health outcomes which can be measurable

Safe: medical interventions must be evidence-based regarding patient-values. In addition primary care health providers will pursue standards of care that assures high quality and safety care.

Box 4 Similarities and differences between Primary Care and Primary Health Care

Attribute	Primary Care	Primary Health Care
First entry point to the health system	(553-554)	(540, 551, 554)
Person-centred care	(553-554)	(555)
Long term continuity person care	(552-554)	
Comprehensive	(553-554)	
Essential services and health programs based on local epidemiology		(540)
Provided services affordable by each country		(540, 551)
Universal access	(552-553)	(540, 554)
Family doctor approach	(552)	
Community participation in establishing health priorities and health interventions		(540, 551)
Coordination	(553-554)	

4.3 Impact of primary care on the management of cardiovascular diseases

A positive impact of PC upon the population's health status has been documented. (440, 557-559). Thus access to primary care has resulted in lower mortality rates and a higher life expectancy for population involved. Moreover available primary care services have also prevented excessive hospitalizations mainly due to the better management of ambulatory primary care sensitive conditions (556, 560-562). Similarly improvements on health promotion such as vaccination, cancer screening, maternity health has been associated with the development of primary care (563). These impacts have been achieved regardless of the population characteristics such as ethnicity, income, education, urban-rural population dynamics and unemployment rates. They have also been reported worldwide.

Similarly the implementation of PC has led to improvements in the control of cardiovascular diseases (564-566). Lower mortality rates of heart disease and stroke have been associated with improves on the development of PC services (557-559). Advances in the management of chronic kidney disease (CKD) have been attained by incorporating PC services into CKD control (567-569). The use of patient centred strategies has also improved the management of chronic diseases (570). Similarly PC services which have integrated a chronic care model have provided better control for those with chronic diseases, particularly diabetes (571-572).

Blood pressure control in primary care

PC also has a central function in the management of patients with hypertension. The care of hypertensive patients is essentially provided in PC settings (573). Well established PC services have led to reductions in the number of admissions due to hypertension (441, 574-575), and increases in the number of hypertensive people having regular blood pressure monitoring (576). By contrast hypertensive patients in regions with lack of primary care physician have an increased probability of having uncontrolled blood pressure (577). Comparisons between the management of hypertensive patients provided by GPs and specialists have been found not being significantly different (578). Hence the management of blood

pressure is currently considered as a measure of performance of primary care services (579-581).

Despite the significant impact of PC services on the management and prevention of chronic diseases, benefits derived from interventions delivered in PC have not been equally distributed across the population. Both geographical and financial barriers to access PC as well as unequal distribution of resources across population account for dominating factors reducing the impact of PC (562). On the other hand, individual preferences, life style and low social class are the most relevant individual factors that have been reported as conditions which detract people from maximally benefiting of PC services (562, 582-583).

4.4 Primary care in England

In England, primary care has been changed continuously along with the transformations in the health system (584). I will present the current organization of primary care in England.

There is no consensus on the definition of primary care. PC has mainly constituted the health services provided by general practices, dental practices, community pharmacies and high street optometrist in the settings operating in local areas (585-586). The last reform of PC services was performed in 2002 but a new revision of PC services is undertaking since 2010 (587). The following features are considered the essential elements of PC in England (586, 588):

First contact care: PC is the first level of contact between citizens and the health system regardless of the type of health service they required. Therefore PC is the entry point to the system. Patients with accidents and emergencies are excluded from this definition in that they can receive their initial care at any level of health system.

Equity: it means that there is an equal access for equal health needs.

Access: the service is free at the point of entry to all citizens.

Location: services are as closer as possible to the citizen residence.

Continuity of care: long term care is delivered by general practice for patients suffering from the most common conditions. It is intended that the general practitioners working in the same practice manage the same patients registered within the practice.

Registration: almost all citizens are registered with a general practitioner. Currently, the registration is taken with general practices.

4.4.1 Organization of Primary care in England

In England PC service -like other NHS services- are funded from general taxation. The National Health Service (NHS) provides primary care services for a defined geographical population through the Primary Care Trust (PCT) (589). Thus, the PCT contracts with general practices and private providers to deliver essential primary care services to a defined population (590). The PCT pays for the services mainly based on two criteria. One is the annual amount of payment associated with each individual registered with a practice (capitation). The other criterion is an extra payment linked to a measure of quality of care assessed with the parameters defined in the Quality and Outcome Framework (QOF) (591). The QOF accounts for up to 25% of the total payment. Other extra payments are considered when the provider offers out of hours care and/or some additional services (e.g. Local Enhanced Services) (592).

In England there have been 152 primary care trusts (PCT) (565). They have been the local health units responsible for assessing the health needs in a defined population since 2002 (590). The PCT developed local public health strategies and planned primary care health services. The primary care health services are mainly purchased with general practices. PCTs can also contract or commissioning independent providers: such as Personal Medical Services (PMS), which includes Specialist PMS (SPMS); Primary Care Trust-Led Medical Services (PCTMS); Alternative Provider Medical Services (APMS) to provide primary care services. Currently, the PCT structure is changing and they will no longer operate with the same functions. Since April 2013, the PCT have been abolished and replaced by clinical commissioning groups integrated to local health system (593).

The general practice is the health service unit directly responsible to provide citizens with primary care services (594-595). The services offered are diagnostic, acute illness, long-term conditions care, prescribing, referrals and health promotion services. Other services may also be offered such as out of hour's service. Each general practice is composed of one or more general practitioners or a group of them working with a primary care health team (PHCT) that generally includes practice nurses, managers, administrative staff and health care assistants.

The general practitioner has been at the core of the development of PC in England since the start of NHS in 1948 (595). The role of the GP has evolved from being medical doctors regulating referrals into medical doctors with formal training in general practice. The training included not only clinical education but also health promotion and prevention subjects. A GP now also receives training on working with other health professionals and in multi-disciplinary teams (596).

The PCHT is an interdisciplinary health group (597). The PC team includes a combination of district nurses, health visitors, social and community workers, pharmacists, dentists, opticians, physiotherapists, counsellors among others. It intends to provide care beyond that provided by medical doctors (598). For instance community pharmacists provide patients suffering from chronic diseases with their prescription drugs and can also advise patients on the use of medication. The pharmacist also gives patient's advice on health promotion, assesses the prescription against the national protocols and examines potential drug side effects (599).

Each practice is committed to register clinical data into an electronic medical record system. Clinical diseases are codified using the Clinical Term (The Read Codes) (600). Data from these electronic medical records systems are used in national datasets such as the General Practice Research Database (GPRD), QResearch, and the Health Improvement Network (THIN) which are available for research purposes. Grouped data sets are also constructed to record the QOF indicators and prescribing data. The QOF includes incentives for maintaining registers of patients with chronic diseases such as diabetes or hypertension. The data on

patient outcomes is reported to the Quality Management and Assessment System (QMAS) (601-602).

The performance of general practices is oriented by national regulations. On the one hand clinical guidelines are provided by the National Institute for Health and Clinical Excellence (NICE). The guidelines formulate recommendations on how to prescribe drug therapy, use health technology and implement preventive interventions. The guidelines are developed by multi-disciplinary groups of experts assessing clinical evidence (603). On the other hand, the quality of care is assessed according to indicators established in the Quality and Outcomes Framework (QOF) (591).

4.4.2 The Quality and Outcome Framework

The Quality and Outcomes Framework (QOF) was an initiative launched in 2004 (591). This initiative aimed at improving both health worker satisfaction and the quality of care at primary care level (592). Since then the QOF has been a part of the contract between the Department of Health and general practices. The participation is voluntary but almost all general practices are part of the QOF agreement. The QOF is annually revised so that the 2011/2012 QOF differs from the original 2004/2005 version (604). Thus variations in the indicators and modifications in the formula payments have been made since QOF was first introduced in 2004 (595).

The 2011/2012, QOF guidance defines indicators to measure four dimensions of quality, called domains. The established domains are clinical domain, organizational domain, patient experience domain and additional services domain. Each domain is measured by a set of indicators Box 6. The indicators are calculated after excluding patients for whom the indicator is inappropriate (exception reporting). The annual result of the each indicator is translated into points. The sum of all points results in a maximum achievable of 1000 points. The final financial reward is adjusted for disease local prevalence and the number of patients registered with the practice (595, 604).

The clinical domain represents the majority of the framework. It accounts for 69.7% of the total points. It consists of a group of 20 diseases. Disease-related indicators are used to assess the quality of care provided by the practice. The indicators have been modified and since 2009 NICE has been contributed to these updates (279). For hypertension, there has been a reduction in the number of indicators. The current indicator for blood pressure control is the percentage of hypertensive patients having blood pressure equal or less than 150/90 mm Hg. This indicator was established in 2004 but it is under revision (605). (Box 5-6).

Box 5 The 2007/2008 hypertension QOF indicators

Indicator	Points	Payment thresholds
Records		
BP 1. The practice can produce a register of patients with established hypertension	6	
Ongoing management		
BP 4. The percentage of patients with hypertension in whom there is a record of the blood pressure in the previous 9 months	16	40 – 90%
BP 5. The percentage of patients with hypertension whom the last blood pressure (measured in the previous 9 months) is 150/90 or less	57	40-70%

Box 6 The 2011/201 QOF indicators

Domain	Number of Indicators	Number of points
Clinical domain		
Asthma	4	45
Atrial Fibrillation	3	27
Cancer	2	11
Cardiovascular disease primary prevention	2	13
Chronic Kidney Disease	5	38
Chronic Obstructive Pulmonary Disease	5	30
Coronary heart disease	8	76
Dementia	3	26
Depression	3	31
Diabetes	15	92
Epilepsy	4	14
Heart Failure	4	29
Hypertension	3	79
Hypothyroidism	2	7
Learning disability	2	7
Mental Health	10	40
Obesity	1	8
Palliative Care	2	6
Smoking	2	60
Stroke or Transient Ischemic Attacks	7	22
Clinical total	87	661
Organisational domain		
Education and Training	7	28
Medicines Management	8	36
Patient Communication	1	2
Practice Management	7	13,5
Quality and Productivity	11	96,5
Records and Information about patients	11	86
Organisational Total	45	262
Patient Experience		
Length of Consultations	1	33
Additional Services		
Cervical Screening	4	22
Child Health Surveillance	1	6
Contraceptive Services	3	10
Maternity Services	1	6
Additional Services Total	9	44
Total	142	1000

4.5 Impact of primary care on the management of cardiovascular diseases in England

In England there has been a significant reduction in coronary heart disease mortality over the last 20 years (606-607). A similar decline has been documented in cardiovascular related-hospitalizations rates (608). Moreover, the number of patients with cardiovascular diseases within the control outcomes such as diabetes and hypertension has continually increased (609). Both population and individual interventions account for these improvements. On the one hand, the ban on tobacco advertising (610), comprehensive smoke-free legislation (611), and voluntary agreements to reduce salt intake (612) are of the most significant population interventions to reduce cardiovascular risk factors. On the other hand improvements on access to treatment are the most significant intervention at individual level (606, 613). Since the individual interventions are mainly delivered in primary care settings (614), these achievements also reflect the impact of primary care on cardiovascular diseases in England (615-618).

In England different characteristics of primary care have been associated with these improvements (617). The introduction of Primary Care Groups, and then the PCTs, have led to a greater development of community and population based services (619). The model provides a comprehensive approach to the provision of care and the continuity of care particularly for those suffering from chronic diseases (620). The progressive use of clinical registers has also been associated with reductions in both total and coronary heart disease mortality (615, 621). Finally, the PCTs have provided integral interventions to those suffering from chronic diseases (622-623).

Despite these improvements, inequalities in the management of cardiovascular diseases across PCTs have been reported (446, 624). Cardiovascular mortality rates and hospitalizations rates due to chronic diseases have been higher in the most deprived areas than in the least deprived areas (608, 625). The introduction of QOF has been associated with reductions in health inequalities among the PCTs (498, 626-627). However the reasons for these discrepancies have not always been linked to PC services. Social determinants such as economic deprivation and low education may explain these differences (446, 582-583, 608,

628). Recently air pollution and extremes of temperature have been associated with discrepancies in coronary heart disease mortality rates across the country (629).

Key points

- ✓ The control of hypertensive patients is mainly carried out at community level.
- ✓ Primary Health Care is the WHO strategy to deliver health services at community level. It includes some public health actions.
- ✓ Primary care is the strategy to deliver medical health services at community level.
- ✓ Well established primary care services have been positively associated with better health outcomes at population level.
- ✓ Population with good access to primary care services have better control rates of chronic cardiovascular diseases.
- ✓ In England primary care is the core of the national health system.
- ✓ England PC covers almost entirely population and it is free access.
- ✓ England PC is delivered through general practices.
- ✓ In England the control of hypertensive patients are mainly relied on primary care services.
- ✓ The development of England PC has led to improvements in cardiovascular diseases control.

Chapter 5 Aim and objectives

Justification

Hypertension is the main cardiovascular risk factor. Nearly 40% of adults aged 25 years and over have hypertension worldwide. It accounts for almost 50% of total cardiovascular mortality worldwide. Despite available interventions to reduce blood pressure, the percentage of hypertensive patients with controlled blood pressure is around 25%. Improvements on blood pressure control have been observed in developed countries over the last ten years.

The control of hypertensive patients largely takes place in primary care settings. The definition of control is based on the achievement a blood pressure target. The interaction between patient-related factors, physician-related factors and health system factors determine the probability of having controlled blood pressure. The relative contribution of each factor is context-dependent.

Main objective

To assess the association between patient-related factors, physician related factors and health system factors and blood pressure control in hypertensive patients managed in primary care practices located in Wandsworth, London between 1998 and 2007.

Objectives

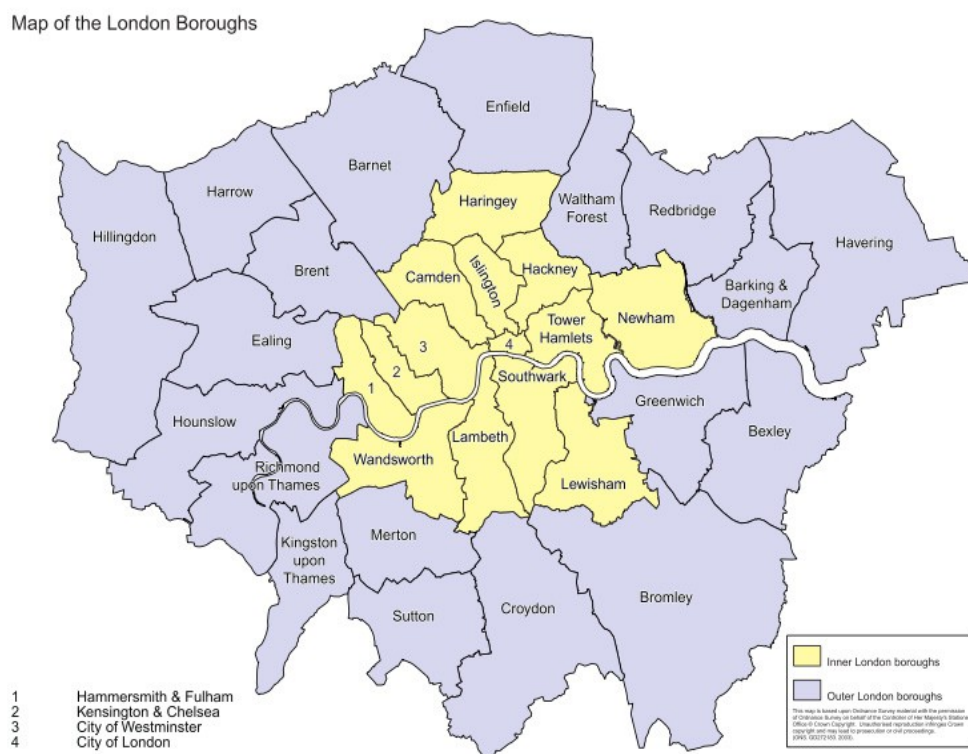
- To determine differences in the classification of patients with and without controlled hypertension using the National Institute for Health and Care Excellence (NICE) blood pressure target and the Quality and Outcome Framework (QOF) blood pressure target.
- To estimate the effect of national hypertension guidelines on antihypertensive prescribing patterns between 1998 and 2007.
- To estimate the association between patient factors, health provider characteristics and blood pressure control.
- To develop a Bayesian model for the analysis of hypertensive patient data using electronic medical registers.

Chapter 6 Description of study setting and sample characteristics

6.1 Study setting

The study was carried out in 28 general practices located in Wandsworth, South West London (Figure 4). These general practices provide primary care services to the local population. Population living in Wandsworth increased from 260380 in 2001 to 307.000 in 2011. The population is younger than both London population and England population. In 2011, mean age for Wandsworth population was 34.5 years whereas for London population was 35.6 years and for England population was 39.4 years (Table 13) (630). Among those aged between 16 and 74 years, 37.4% and 39.3% were men in 2001 and 2011 respectively. Between 2001 and 2011, there was an increase in the percentage of residents aged 33 to 64 years.

Figure 4 Wandsworth location in London



Source www.ons.gov.uk

Table 13 Distribution of population resident in Wandsworth by age, 2001 and 2011

Table Population: All usual residents

2011 Census Table KS102 Age structure	Wandsworth			Inner London		London		England & Wales	
	No.	%	Rank/348 LAs	No.	%	No.	%	No.	%
Age 0 to 4	21,670	7.1	46	225,908	7.0	591,495	7.2	3,496,750	6.2
Age 5 to 7	9,230	3.0	286	110,881	3.4	301,095	3.7	1,927,039	3.4
Age 8 to 9	5,344	1.7	339	66,358	2.1	181,714	2.2	1,208,672	2.2
Age 10 to 14	12,521	4.1	344	160,150	5.0	456,865	5.6	3,258,677	5.8
Age 15	2,241	0.7	345	31,751	1.0	93,599	1.1	687,994	1.2
Age 16 to 17	4,621	1.5	345	61,718	1.9	186,626	2.3	1,391,235	2.5
Age 18 to 19	5,541	1.8	344	75,690	2.3	191,434	2.3	1,460,156	2.6
Age 20 to 24	23,699	7.7	59	291,156	9.0	629,972	7.7	3,807,245	6.8
Age 25 to 29	47,217	15.4	2	421,780	13.1	832,966	10.2	3,836,609	6.8
Age 30 to 44	93,803	30.6	1	904,622	28.0	2,070,954	25.3	11,515,165	20.5
Age 45 to 59	43,539	14.2	346	493,863	15.3	1,389,882	17.0	10,886,135	19.4
Age 60 to 64	10,658	3.5	343	110,445	3.4	342,590	4.2	3,377,162	6.0
Age 65 to 74	14,455	4.7	343	151,216	4.7	473,058	5.8	4,852,833	8.7
Age 75 to 84	8,763	2.9	343	91,997	2.8	308,661	3.8	3,115,552	5.6
Age 85 to 89	2,355	0.8	340	22,678	0.7	80,574	1.0	825,671	1.5
Age 90 and over	1,338	0.4	335	11,688	0.4	42,456	0.5	429,017	0.8
Total	306,995	100		3,231,901	100	8,173,941	100	56,075,912	100
Mean age	34.5		336	34.0		35.6		39.4	
Median age	32.0		328	32.0		33.0		39.0	

Source (631)

Distribution of Wandsworth population by race/ethnicity

The definition of ethnicity is a complex concept. According to Bhopal ethnicity is a multidimensional individual characteristic meaning “the group to which people belong, and/or perceived to belong, as a result of certain shared characteristics including geographical and ancestral origins, but particularly cultural traditions and languages” (632). By comparison, the term race has been initially associated with biological characteristics (633). However, because the high genetic variation within individuals with same race origin (634), race was questioned as a measure of sub-population groups (635-636). Consequently, race has evolved to include the social background associated with a defined population group (637). Hence, currently both terms seem to represent the same concept.

The need for including race/ethnicity in the analysis of population health is because the patterns of some diseases varied between individuals with different ethnic background. For instance, Harper et al reported that individuals of white origin continue having higher life expectancy than those of black origin between 1983 and 2003 in the US population (638). That difference was mainly due to cardiovascular diseases mortality follow by homicide, HIV

and infant mortality (638). In the REACH study, which included data from 49602 patients registered with 5587 general practices from 44 countries, a significant difference in the prevalence of risk factors between the seventh ethnic categories used in the analysis was observed (639). Those of black origin had the highest prevalence of hypertension and patients of South Asian origin had the highest prevalence of diabetes. Whites had the lowest prevalence of hypertension and diabetes (639). Therefore race/ethnicity as a variable could help to trace populations with particular health risk factors.

The categorization of ethnicity has been controversial. The interaction between genetic traits, family ancestry and cultural heritage ancestry to define a specific ethnic group is still only partially understood. There are no gene clusters which define a particular race or cultural group (640). For instance, a significant heterogeneity in genetic markers among African populations has been described indicating that they did not form a homogenous population (641-642). By contrast, strong genetic correlations between some European population and African population have been observed (642-644). African populations living in East Africa have been found to be genetically similar to European-Middle Eastern populations (642, 644). African Caribbean populations also exhibited a diverse genetic ancestry. Populations from Barbados had a higher level of West African ancestry than those from Jamaica (645). But populations from Jamaica had higher European ancestry than those from Barbados (645). Hence, the definition of ethnic groups is beyond genetic patterns and without a specific genetic pattern defining race/ethnicity.

Similarly differences in morbidity and cultural characteristics among populations closely located have been documented. Populations from India, Pakistan, Bangladesh and Sri Lanka, commonly named as those of South Asian origin, could differ in some cultural aspects. For example individuals of Bangladeshi origin living in the UK have found having a higher prevalence of smoking than those of Pakistani or India origin (646). Individuals of Indian origin are less likely to have coronary heart disease than those of Pakistan and Bangladeshi background (647). They also differ in the language use and religious beliefs (648-649).

Differences in traditions between African Caribbean and African American populations have also been reported. Those of African Caribbean origin seem to have lower adherence to

some religious habits than the African American population (650). The English Caribbean population had a higher prevalence of smoking than the English African population (651). Moreover a wide diversity of eating habits and religious beliefs have been observed among the African English population with different African ancestry (652). Therefore, as for South Asian population, grouping all people of African descent into one category has been questioned (632, 653). It may detract from understanding mechanisms through race/ethnicity influences on health outcomes.

The criteria used for categorizing individuals into race/ethnicity has not totally been standardised worldwide. The 2000 US census established the following categories for race/ethnicity white, black/African American including African Caribbean, American Indian/Alaska Native, Asian including Chinese, Japanese, Korean, Vietnamese and Asian Indian, and Native Hawaiian/other Pacific Islander (654). Others authors suggested using the category Caucasian to refer to those of European and West Asian origin. This category also includes the population of Indian subcontinent, Middle East and North Africa (655). These categories mainly consider the geographical distribution of the population which could have a high genetic correlation (655). By comparison the UK census established categories of South Asian including those of Indian, Pakistani or Bangladeshi origin and those of China or other Asian background in an different category (631).

Terms used in the current study

In the UK the ethnic classification is based on that established in the national census conducted by the The Office for National Statistics. The classification is based on self assignment to previous groups described in the census. A comparison of the classification between 2001 and 2011 is presented in box 7. According to 2001 census, in Wandsworth white ethnicity configures the highest percentage of population (77.9%) and this percentage slightly decreased in the 2011 census (71.4%). Population of South Asian origin and black origin also increased from 6.9% in 2001 to 10.9% in 2011 and from 9.6% in 2001 to 10.6% in 2011 respectively. Population of mixed origin increased from 3.35% in 2001 to 5.0% in 2011. Population living in Wandsworth looks less diverse than that living in London in 2011. Of total 28.6% of residents were other ethnicity different from white in 2001, compare to 49.2% living in London (Table 14-15).

The assessment of ethnicity is controversial. Currently a self-reported measure based on the pre-established census categories has been commonly used (632). The classifications used in the current analysis were based on the classifications of ethnicity established in the 2001 UK census (656). The categories of ethnicity were provided by the patient as a self-report and registered by a health worker. I grouped the patients into six race/ethnic categories according to the ethnic origin and the numbers of patients in each category registered in the data. Because the patients were registered progressively, the samples of ethnic groups different from white were smaller particularly at the beginning of the study period. Therefore, the small numbers make it difficult to quantify significant differences of some outcomes between subgroups.

I used the main categories established in the 2001 UK census with the following labels white, South Asian for those of Indian, Pakistani or Bangladeshi origin, black for those of African or Caribbean origin, other Asian origin for those of Chinese, Taiwan or Hong Kong origin, other ethnicity for those of Hispanic origin or other ethnic category and unknown for those without any register of ethnicity (Table 16) (631). This classification might fail to identify particular conditions occurring in some ethnic groups such as African Caribbean and African British or those of South Asian from India and from Pakistan associated with blood pressure control. However it provides light about how the control of blood pressure could vary across the main ethnic categories living in Wandsworth. They were also exposed to similar health interventions for improving blood pressure control occurring in the area over the study period.

Box 7 Race/Ethnicity classification in the 2001 and 2011 England census

2001 census	2011 Census
White	White
A British	01 English/Welsh/Scottish/Northern Irish/British
B Irish	02 Irish
	03 Gypsy or Irish Traveler
C Any other White background	04 Other White
Mixed	Mixed/multiple ethnic group
D White and Black Caribbean	05 White and Black Caribbean
E White and Black African	06 White and Black African
F White and Asian	07 White and Asian
G Any other mixed background	08 Other Mixed
Asian or Asian British	Asian/Asian British
H Indian	09 Indian
J Pakistani	10 Pakistani
K Bangladeshi	11 Bangladeshi
L Any other Asian background	12 Chinese
	13 Any other Asian background
Black or Black British	Black or Black British
M Caribbean	14 African
N African	15 Caribbean
P Any other Black background	16 Any other Black/African/Caribbean background
Other ethnic categories	Other ethnic group
R Chinese	17 Arab
S Any other ethnic category	18 Any other group
Not stated	
Z Not stated	

Table 14 Distribution of population resident in Wandsworth by race/ethnicity, 2001

Migration Percentage of all People:	Wandsworth	London	England & Wales
	2001	2001	2001
All people ¹	260,380	7,172,091	52,041,916
%: Who are migrants	21.00	14.20	12.18
% Who moved into the area: From within the UK	10.52	N/A	N/A
%: Who moved into the area: From outside the UK	2.44	1.69	0.71
%: With no usual address one year before Census	1.70	1.39	0.81
%: Who moved within the area	6.34	N/A	N/A
%: Who moved out of the area ²	11.06	N/A	N/A
All people in ethnic groups other than 'White' ¹	57,402	2,068,888	4,521,050
%: in ethnic groups other than 'White' who are migrants	14.89	14.65	16.10
%: in ethnic groups other than 'White': Who moved into the area: From within the UK	5.22	N/A	N/A
%: in ethnic groups other than 'White': Who moved into the area: From outside the UK	2.33	2.03	2.51
%: in ethnic groups other than 'White': With no usual address one year before Census	1.88	1.91	1.84
%: in ethnic groups other than 'White': Who moved within the area	5.46	N/A	N/A
%: in ethnic groups other than 'White': Who moved out of the area ²	7.86	N/A	N/A

Source (631) Office for National Statistics.

Table 15 Distribution of population resident in Wandsworth by race/ethnicity, 2011

<i>Table Population: All usual residents</i>									
2011 Census Table KS201 Ethnic group	Wandsworth			Inner London		London		England & Wales	
	No.	%	Rank/348 LAs	No.	%	No.	%	No.	%
White: English/Welsh/Scottish/Northern Irish/British	163,739	53.3	319	1,240,266	38.4	3,669,284	44.9	45,134,686	80.5
White: Irish	7,664	2.5	10	75,165	2.3	175,974	2.2	531,087	0.9
White: Gypsy or Irish Traveller	163	0.1	254	3,055	0.1	8,196	0.1	57,680	0.1
White: Other White	47,650	15.5	12	534,723	16.5	1,033,981	12.6	2,485,942	4.4
TOTAL White	219,216	71.4		1,853,209	57.3	4,887,435	59.8	48,209,395	85.9
Mixed/multiple ethnic group: White and Black Caribbean	4,642	1.5	26	56,900	1.8	119,425	1.5	426,715	0.8
Mixed/multiple ethnic group: White and Black African	2,034	0.7	23	32,203	1.0	65,479	0.8	165,974	0.3
Mixed/multiple ethnic group: White and Asian	3,887	1.3	19	42,114	1.3	101,500	1.2	341,727	0.6
Mixed/multiple ethnic group: Other Mixed	4,678	1.5	15	58,531	1.8	118,875	1.5	289,984	0.5
TOTAL Mixed/multiple ethnic group	15,241	5.0		189,748	5.9	405,279	5.0	1,224,400	2.2
Asian/Asian British: Indian	8,642	2.8	59	109,933	3.4	542,857	6.6	1,412,958	2.5
Asian/Asian British: Pakistani	9,718	3.2	42	59,890	1.9	223,797	2.7	1,124,511	2.0
Asian/Asian British: Bangladeshi	1,493	0.5	72	163,838	5.1	222,127	2.7	447,201	0.8
Asian/Asian British: Chinese	3,715	1.2	36	65,983	2.0	124,250	1.5	393,141	0.7
Asian/Asian British: Other Asian	9,770	3.2	28	115,549	3.6	398,515	4.9	835,720	1.5
TOTAL Asian/Asian British	33,338	10.9		515,193	16.0	1,511,546	18.4	4,213,531	7.5
Black/African/Caribbean/Black British: African	14,818	4.8	24	276,513	8.6	573,931	7.0	989,628	1.8
Black/African/Caribbean/Black British: Caribbean	12,297	4.0	14	173,959	5.4	344,597	4.2	594,825	1.1
Black/African/Caribbean/Black British: Other Black	5,641	1.8	15	89,709	2.8	170,112	2.1	280,437	0.5
TOTAL Black/African/Caribbean/Black British	32,756	10.6		540,181	16.8	1,088,640	13.3	1,864,890	3.4
Other ethnic group: Arab	2,350	0.8	29	50,821	1.6	106,020	1.3	230,600	0.4
Other ethnic group: Any other ethnic group	4,094	1.3	26	82,749	2.6	175,021	2.1	333,096	0.6
TOTAL Other ethnic group	6,444	2.1		133,570	4.2	281,041	3.4	563,696	1.0
Total	306,995	100		3,231,901	100	8,173,941	100	56,075,912	100

Source (631)

Socio economic status in Wandsworth population

In 2004 the Department of Communities and Local government updated the measurement of socio economic conditions. In a commissioned work, an index of deprivation was developed by the Department Social Policy Work at the University of Oxford. This index is used in the analysis of the current data.

The index of deprivation is composed of seven domains (Box 8). The assessment of this index was performed at Super Output Areas (SOA) regarding population density. Each domain is measured by several items and given a score between 0 and 100. A higher score reflects higher deprivation conditions. The score is additionally transformed into a rank score which ranges from 1 to 500 units. Similarly, higher levels represent higher levels of deprivation (657).

In 2004, Wandsworth Borough was at 114th rank score of the most deprived area related to the maximal national rank score of 355. None of the SOA was in the 10% most deprived nationally. Similarly there was no SOA at the 10% worst rank of the national employment or education score distribution. However, 11 SOAs were at 10% worst income domain deprivation (658).

Box 8 Domains of deprivation index

Domain of deprivation	Domain weight
Income deprivation	22.5%
Employment deprivation	22.5%
Health deprivation and disability	13.5%
Education, skills and training deprivation	23.5%
Barriers to Housing and Services	9.3%
Living environment deprivation	9.3%
Crime	9.3%

Hypertension prevalence in Wandsworth

The estimated prevalence of hypertension was 21.8% in 2008 and 22.6% in 2011. Of total hypertensive population only 8.3% and 8.8% were registered with general practices in 2008 and 2011 respectively (659-660). The prevalence is lower than estimated for England 30.2% in the last Health Survey for England (284). The percentage of hypertensive patients registered with general practices was 10.9% and 13.4% in 2008 and 11.1% and 13.6% in 2011 for London and England respectively (659-660). Then there has been a higher gap between the number of hypertensive registered with general practices and the total of hypertensive patients in Wandsworth compared to that observed in London and England (660-661). Considering data using registers in the QOF reports, the prevalence of hypertension was 84.76 per 1000 habitants lower than observed in London 108.19 and in England 131.33 (662).

6.2 Study design

Sample population

The data for this study corresponded to hypertensive patients registered with 28 general practices. To obtain the data an ethical approval was gained from the Wandsworth local research ethics committee. Each practice gave consent to download the data. All included practices had electronic patient records used by general practitioners and other members of the primary care health team to register clinical data. The data was extracted from each practice computer using an algorithm linking patient information by a patient code. The code was an anonymised number which did not allow for identifying the patient. Then the files from all practices were merged in a macro data set in which patients were nested within each practice. Similarly to patient level data, each practice were given a number which preventing me for identifying the name of the practice. The process was described by Curcin et al (663)

Patient inclusion criteria

Individuals aged 18 years and older with hypertensive diagnosis in the registers of the 31st of December 2007 formed the included population. The diagnosis was based on the Read clinical classification codes (600). For essential hypertension and/or primary hypertension in non-pregnant women the code was G20. Data for all included patients was retrospectively and annually retrieved between 1998 and 2007.

Definition of study variables

Patient level variables

Information about patient variables was provided by the patient. Blood pressure level was recorded once as the last annual measurement registered in data set. The measurement of blood pressure was taken using either sphygmomanometer by listening Korotkoff sounds (auscultatory method) or an electronic device (oscillatory method). The former was more commonly used in years before 2004. The definition of race/ethnicity was based on self-report taken during the clinic visit and registered based on the 2001 census classification. It was grouped in six categories due to the small number in some of those established in the referred census. The date of registration was used for identifying the first record of each patient in the data set. The definitions of all variables are established in table 16.

Practice level variables

There were two practice level variables. The deprivation index which was based on the practice post code as the individual data was not linked to the individual post code. The deprivation index was based on the criteria described above and the one reported in 2004 was used for the study period. The number of patients registered with each practice was annually recorded. There was an annual increased in the number of patients registered with each practice over the study period.

Table 16 Definition of study variables

Variable	Definition
Date of birth	Day/month/year
Date of registration	Day/month/year on which the patient record was registered in the database
Age	Years
Sex	Men or Women
Race/Ethnicity	It was based on 2001 UK census
White	White British White Irish Other White
Black	Black British-Caribbean Black British-African Black or Black British-Other Black
South Asian	Asian British Indian Asian British Pakistani Asian British Bangladeshi
Other Asian	Chinese , Tawain
Other ethnicity	Those whose ethnicity was not classified in the groups above. For example those of Hispanic origin
Unknown	Not registered
Systolic blood pressure	mmHg
Diastolic blood pressure	mmHg
Cardiovascular comorbidities	Diabetes mellitus Atrial fibrillation Heart Failure Chronic renal disease Coronary Heart disease Stroke
Non-cardiovascular comorbidities	Depression Asthma COPD
Smoking	Correspond to Current smoker: those who reports active smoking
Cholesterol categories mmol /L	Based on the classification established in 2008 NICE guideline 67
Acceptable level	<=5
High cholesterol	5.1 to 6.0
Vey high cholesterol	>6.0
Treatment	Information on yes or no being prescribed one the following antihypertensive drugs ACE/BB/CCB/DD
Body mass index kg/m²	Based on the classification established in 2006 NICE guideline 43
Healthy weight	18.5 to 24.9
Overweight	25 – 29.9
Obesity I	30 – 34.9
Obesity II	35 – 39.9
Obesity III	40 or more
Practice level variables	
Deprivation index	Indicator based on the area where practice is located using the 2007 IMD
Practice list	Number of patients registers with each practice

COPD: Chronic Obstructive Pulmonar Disease

ACE Angiotensin converting enzyme inhibitor

CCB Calcium channels blocker

DD Diuretic

BB Betablockers

IMD Index of deprivation

Chapter 7 Differences in the classification of patients with controlled hypertension between the Quality and Outcome Framework and the National Institute for Health and Clinical Excellence blood pressure targets

7.1 Background

Despite the known limitations of blood pressure targets, these outcomes define the standard of care for hypertensive adults. The classification of having controlled pressure relies on a target definition. The use of two target definitions for hypertension control in England provides an opportunity to determine how blood pressure control varies with different targets. I analysed information on hypertensive patients managed in primary care to examine differences in the classification of patients with controlled hypertension by using two target definitions, one based on the QOF guidance (664) and other in the NICE hypertension guideline (499, 501).

Secondary objectives

1. To describe patient's characteristics of those with and without controlled blood pressure.
2. To describe blood pressure levels by patient's characteristics.
3. To assess the relationship between patients's characteristics and having controlled blood pressure.

7.2 Methods

I performed a cross-sectional study using data from hypertensive patients registered with 28 general practices located in Wandsworth, South London in 2007.

Outcome variables

The classification of hypertensive control patient was based on the former definitions established in the 2007/8 QOF and in 2006 NICE guidelines (499). The QOF guidance establishes a level of blood pressure equal to or less than 150/90 mm Hg as the recommended target for patients classified into hypertension disease category (528). Additional blood pressure targets for patients classified into other cardiovascular disease categories are specified by the QOF guidance Box 9 (528).

Box 9 Clinical QOF blood pressure indicators for cardiovascular diseases

Disease category	Clinical target
Hypertension (BP)	BP 5. The percentage of patients with hypertension whom the last blood pressure (measured in the previous 9 months) is 150/90 or less
Diabetes mellitus (DM)	DM 12. The percentage of patients with diabetes in whom the last blood pressure is 145/85 or less
Coronary heart disease (CHD)	CHD 6. The percentage of patients with coronary heart disease in whom the last blood pressure reading (measured in the previous 15 months) is 150/90 or less
Stroke	STROKE 6. The percentage of patients with a history of TIA or stroke in whom the last blood pressure reading (measured in the previous 15 months) is 150/90 or less
Chronic kidney disease (CKD)	CKD 3: The percentage of patients on the CKD register in whom the last blood pressure reading, measured in the previous 15 months, is 140/85 or less

Reference (528)

This analysis used the definitions of blood pressure targets established in the period-related hypertension national guidelines. In 2004, NICE produced guidelines on the management of hypertension in adults in England primary care (501). For hypertensive patients without pre-existing clinical disease a level equal to or below 140/90 mm Hg blood pressure is defined as the target of therapy. In addition, lower blood pressure targets for hypertensive patients with diabetes or other cardiovascular disease are established in each NICE disease-related guideline (223, 665). The targets established in both the QOF guidance and the NICE guide-

line applied for hypertensive adults 18 years or over, males and females, and patients of all ethnic origin.

Independent variables

I identified hypertensive patients who had a record of blood pressure in 2007. The independent variables were defined as follows: a category of patients with additional cardiovascular comorbidity for those with diabetes or coronary heart disease or stroke or atrial fibrillation or renal failure or heart failure. Patients with chronic obstructive pulmonary disease, depression or asthma were classified as patients with other no cardiovascular comorbidity. Ethnicity origin was grouped into white, black, South Asian, Other Asian, other ethnic and unknown. The data on treatment was based on drug prescription available over the current year.

Dependent variables

For each individual the dependent variable was having controlled blood pressure based on the NICE target and the QOF target. The NICE target of equal to or below 140/90 mmHg and the QOF target equal to or below 150/90 mmHg were use for all hypertensive patients. In the analysis of hypertensive patients with diabetes the 2008 NICE target of less than 140/80 mmHg and the QOF target of less than 145/85 mmHg were used. The 2008 NICE target was the recommended audit target for diabetic patients in the 2004 BHS hypertensive guidelines.

Statistical methods

Characteristics of patients were reported as percentages for categorical variables and mean with standard deviation for continuous variables. I tested differences in continuous variables between different strata using Student's t-test or analyses of variance (ANOVA) for comparisons of three or more groups. Categorical variables were assessed using the Chi-squared test. The main outcome was the proportion of patients who achieved blood pressure targets as defined in both QOF and NICE guidelines (501, 528). The percentage was reported as the number of controlled patients divided by the total number of hypertensive patients included in the analysis. We additionally stratified the percentage of patients with controlled

blood pressure by age, sex, ethnicity, antihypertensive prescribing and the presence of cardiovascular comorbidity.

I used a multiple logistic regression to assess the relationship between patient characteristics and the odds of being classified as a patient with controlled hypertension (PCH). A separate logistic model for each target definition was performed. The patient characteristics included in each model were based on the following criteria: 1) those which have been previously shown to influence blood pressure levels such age, sex and ethnicity (34, 73, 143, 666). We stratified age into three groups younger 17 -44 years, middle age 15 – 64 years and older 65 years and over. 2) Those variables which are used in the guidelines to classify patients at high cardiovascular risk as lower targets are established for these patients. Patients with at least one of the following clinical conditions diabetes, renal failure, stroke, heart failure, atrial fibrillation and coronary heart disease were classified as patients with cardiovascular comorbidity (501) 3) Those which directly modify blood pressure levels such as number of prescribed drugs. I grouped patients into being or not being prescribed antihypertensive medication (140) 4) Those which could modify blood pressure levels and/or drug prescription such as the presence of other comorbidities, patients with at least one of the following conditions COPD, depression or asthma were classified as patients with other comorbidity. The standard errors were adjusting for the cluster of 28 practices to take into account intragroup correlation. In the model the main explicatory variable was sex. I assessed whether or not the probability of being with controlled hypertension varies between the sexes across the age categories by including a term for interaction. A logistic model including only hypertensive patients with diabetes was also performed.

The data was analysed using STATA version 11 (Stata Corporation, College Station, TX, USA).

7.3 Results

In 2007, 17252 hypertensive patients aged 17 years and over were registered with 28 general practices. Of these 15751 (91.4%) with a valid record of blood pressure were included in the analysis. 8433 (53.5%) were of white origin, 8753 (56%) were female, and 5985 (38%) had at least an additional cardiovascular comorbidity. Diabetes was the most frequent disease comorbidity followed by coronary heart disease 1816 (11.5%), stroke 1141 (7.3%), atrial fibrillation 753 (4.7%), renal failure 671 (4.2%) and heart failure 395 (2.5%). 3977 (25.2%) patients had other comorbidities such as depression 2367 (15.0%), chronic obstructive pulmonary disease (COPD) 2054 (13.0%) and asthma 1646 (10.4%). 1608 (10%) of patients were not prescribed antihypertensive medication and 9103 (57.8%) were prescribed more than two antihypertensive drugs. Patients with cardiovascular comorbidity were older and more likely to be males than those without cardiovascular comorbidity. Patients with cardiovascular comorbidity were more likely to be on antihypertensive therapy than those without comorbidity (Table 17).

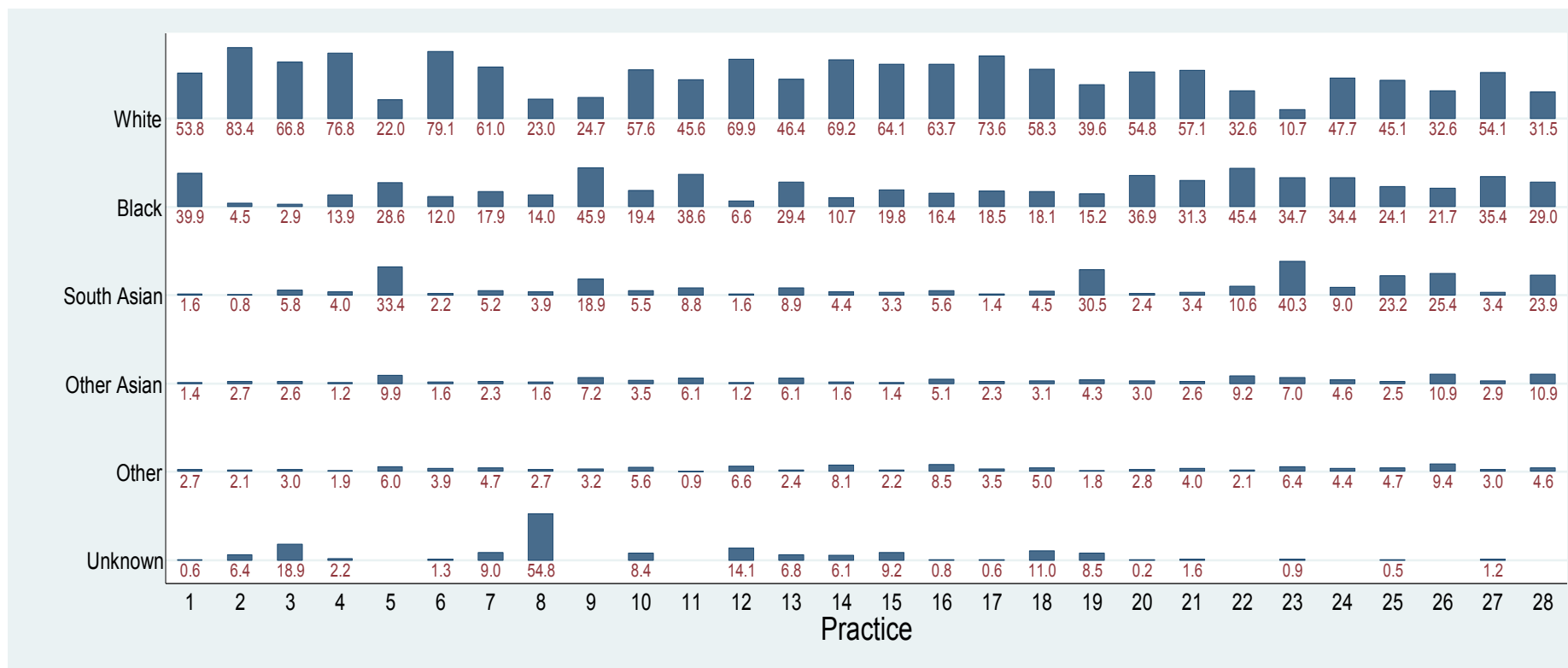
Table 17 Characteristics of hypertensive patients, 2007

	White	Black	South Asian	Other Asian	Other	Unknown	All	p value
	8433	3610	1440	554	687	1037	15761	
Age mean (sd)	66.7 (14.5)	60.7 (13.1)	62.6 (12.2)	61.6 (12.5)	61.6 (12.6)	61.8 (13.9)	64.3(14.1)	<0.0001
Male number (%)	3868 (48.9)	1450 (40.2)	701 (48.7)	269 (48.6)	296 (43.1)	424 (40.9)	7008 (44.5)	<0.0001
Patients with other cardiovascular comorbidity number (%)								
Diabetes	1410 (16.7)	984 (27.3)	540 (37.5)	181 (32.7)	168 (24.5)	77 (7.4)	3360 (21.3)	<0.0001
Coronary heart disease	1119 (13.3)	221 (6.1)	287 (19.9)	74 (13.4)	73 (10.3)	42 (4.1)	1816 (11.5)	<0.0001
Stroke	677 (8.0)	229 (6.3)	103 (7.5)	29 (5.2)	45 (6.5)	59 (5.6)	1142 (7.3)	0.001
Atrial fibrillation	598 (7.1)	62 (1.7)	35 (2.4)	11 (1.9)	14 (2.0)	33 (3.2)	753 (4.8)	<0.0001
Renal failure	336 (3.9)	170 (4.7)	74 (5.1)	31 (5.6)	31 (4.5)	29 (2.8)	671 (4.3)	0.015
Heart failure	256 (3.0)	50 (1.4)	49 (3.4)	10 (1.8)	14 (2.4)	16 (1.5)	395 (2.5)	<0.0001
Patients without cardiovascular comorbidity number (%)	4555 (54.0)	2051 (56.8)	615 (42.7)	255 (46.0)	381 (56.5)	759 (73.2)	9776 (62.3)	<0.0001
Patients with other comorbidities number (%)								
Depression	1537 (18.2)	380 (10.5)	156 (10.8)	53 (9.6)	112 (16.3)	129 (12.4)	2367 (15.0)	<0.0001
COPD *	1261 (14.9)	341 (9.5)	196 (13.6)	87 (17.5)	78 (11.4)	91 (8.8)	2054 (13.0)	<0.0001
Asthma	914 (10.8)	328 (9.1)	184 (12.8)	78 (14.1)	69 (10.4)	73 (7.0)	1646 (10.4)	<0.0001
Patients not taking antihypertensive therapy number (%)	895 (10.6)	309 (8.6)	120 (8.3)	47 (8.5)	93 (13.5)	144 (13.9)	1608 (10.2)	<0.0001

95.5% had a record of race/ethnicity. Patient's characteristics vary between race/ethnicity groups (Table 17). Patients of black origin were younger and predominantly female in comparison to patients with others ethnic origin. South Asian and Other Asian patients were more likely to have diabetes and renal failure. Those of white origin had the highest prevalence of stroke. Patients with unidentified race/ethnicity were less likely to have other cardiovascular comorbidity and not being prescribed antihypertensive medication,

Practices differed in the patient's characteristics. (Figure 5) The number of hypertensive patients registered with each practice ranged from 114 to 1096. The youngest population was in the practice number 5. The highest percent of females was in the practice number 11, 71 (62.3%). White was the most frequent race/ethnicity in all practices except for practices 5, 9, 22, 23. In practices 5 and 23 the highest race/ethnicity group was South Asian with 111(33.4%) and 472 (40.3) respectively. In practice 9 and 22 was Black with 260 (45.9%) and 64 (45.4%) respectively. The practice 8 had the highest percentage of patients without record of race/ethnicity, 369 (54.8%). In most practices the percentage of patients without antihypertensive medication was nearly 10% or below with the exception of practice 12, 71 (27.7%). Practices are mainly located in areas with median deprivation index of 21.3. The practice 2 is located in the wealthiest area, deprivation index 8.1 and the practice 17 in the less wealthy, deprivation index 38.5.

Figure 5 Distribution of patients by race/ethnicity in each practice, 2007



Blood pressure levels

For all included hypertensive patients mean systolic blood pressure and mean diastolic blood pressure were 137.8 mmHg (sd 16.3) (95% CI 137.5 – 138.0) and 79.8 mmHg (sd 10.7) (79.6 – 79.9), respectively. Of total patients 63.2% had systolic blood pressure equal to or below 140 mmHg and 88.6% had diastolic blood pressure equal to or below 90 mmHg. Patients aged between 17-44.9 years had lower mean systolic blood pressure 134.8 mmHg (sd16.7) (95% CI 133.9 – 135.6) than patients aged 45 – 64.9 years 137.0 mmHg (sd15.7) (95% CI 136.6 – 137.4) and patients aged 65 years and over 138.8 mmHg (sd 16.5) (95% CI 138.5 – 139.1). Conversely, patients aged 65 years and over had the lowest mean diastolic blood pressure 76.3 mmHg (sd 9.9) (95% CI 76.0 – 76.5), of whom almost 40% had diastolic blood pressure between 70 mmHg and 80 mmHg. Hence, whereas diastolic blood pressure levels decreased with age, systolic blood pressure levels rose with age (Figure 6-7).

Figure 6 Distribution of systolic blood pressure mmHg by age, 2007 N=15761

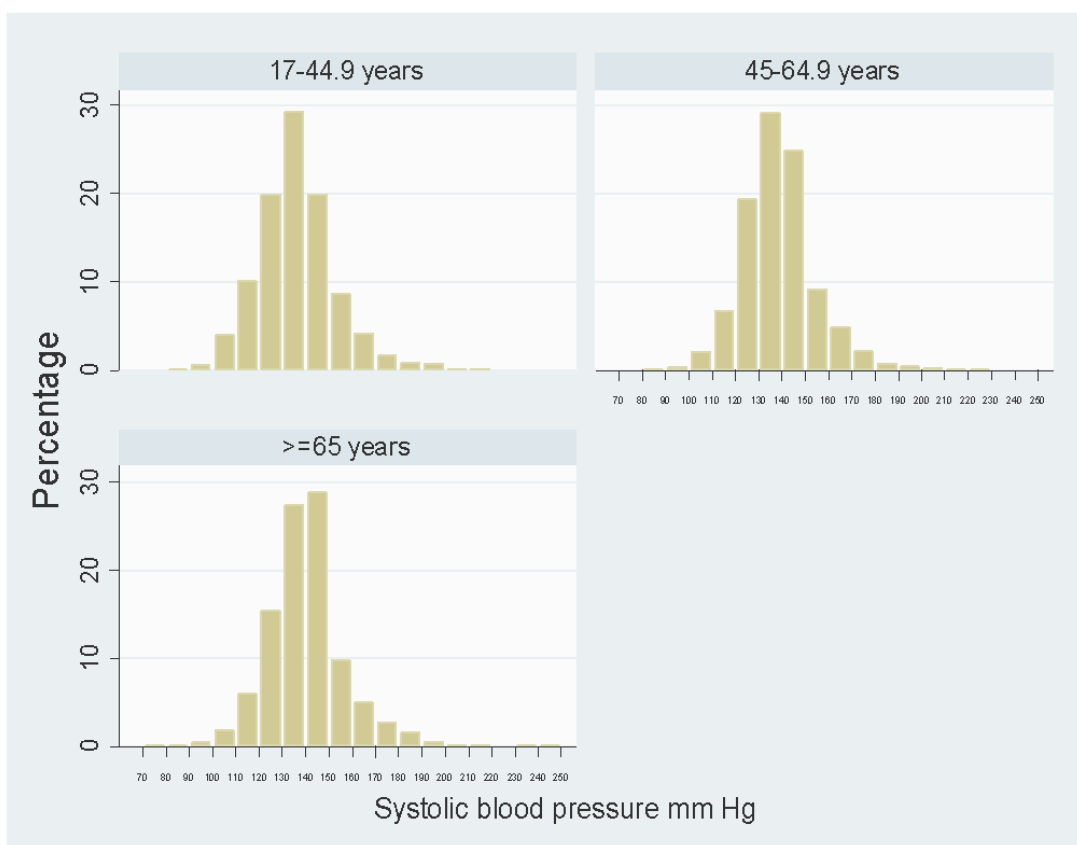
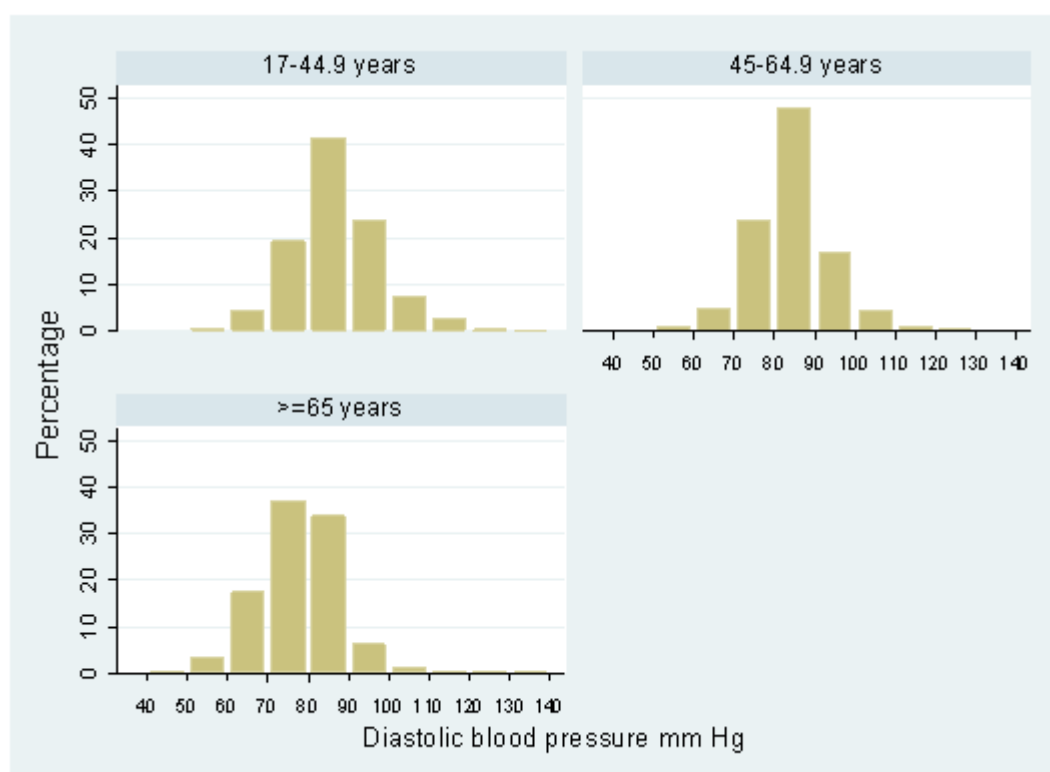


Figure 7 Distribution of diastolic blood pressure mmHg by age, 2007 N=15761



Men aged 65 years and over had lower mean diastolic blood pressure 76.1 mmHg sd (10.2) 95% CI 75.7 – 76.4) compared to those aged 45 to 64.9 years 83.8 mmHg sd (10.2) (95% CI 83.4 – 84.2) and those aged 17-44 years 86.5 sd (10.8) mmHg (95% CI 85.7 – 87.3) ($P < 0.0001$). By contrast, there was not a significant difference in mean systolic blood pressure between age groups. Globally, mean systolic blood pressure was 138.2 mmHg (sd 16.49) (95% CI 137.8 – 138.5). Regardless of age group systolic and diastolic blood pressure levels were lower in those with cardiovascular comorbidity. The overall differences in mean systolic and diastolic blood pressure were 4.6 mmHg and 6.3 mmHg between both groups respectively. (Figure 8 –Table 18)

Figure 8 Distribution of systolic and diastolic blood pressure for men, 2007

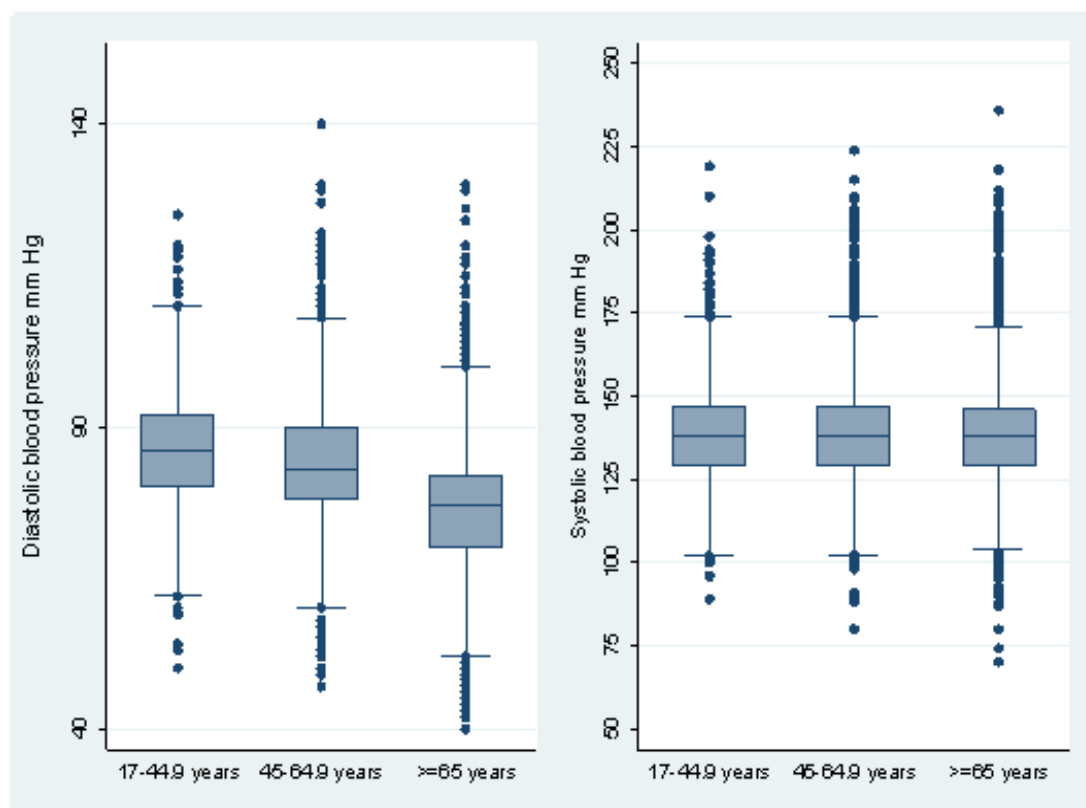


Table 18 Comparison of mean systolic blood pressure and mean diastolic blood pressure mmHg in men by age and cardiovascular comorbidity, 2007

		<u>Without comorbidity</u>		<u>With comorbidity</u> ‡			
Diastolic		Mean (sd *)	95% CI		Mean (sd)	95% CI	p value
Age	Number			Number			
17 - 44	571	87.5 (10.4)	86.6 - 88.4	125	82.2 (11.2)	80.2 - 84.2	<0.0001
45 - 64.9	1873	85.3 (10.1)	84.8 - 85.7	1017	81.1 (9.8)	80.5 - 81.7	<0.0001
>= 65	1478	78.5 (9.5)	78.0 - 78.9	1944	74.2 (10.2)	73.7 - 74.7	<0.0001
Total	3922	83.1 (10.6)	87.2 - 83.4	3086	76.8 (10.5)	75.9 - 76.6	<0.0001
		<u>Without comorbidity</u>		<u>With comorbidity</u>			p value
Systolic		Mean (sd)	95% CI		Mean (sd)	95% CI	
Age	Number			Number			
17 - 44	571	140.1 (15.7)	138.8 - 141.4	125	130.8 (17.5)	127.8 - 133.9	<0.0001
45 - 64.9	1873	140.1 (15.7)	139.4 - 140.8	1017	135.8 (16.2)	134.8 - 136.8	<0.0001
Total	2444	140.2 (15.8)	139.7 - 140.7	1142	135.6 (16.7)	135.0 - 136.2	<0.0001

‡ Patients with at least one of the follow disease: coronary heart disease, diabetes mellitus, heart failure, atrial fibrillation, stroke or renal failure.

CI confidence interval

*Standard deviation

For women, those aged 65 years and over had the lowest diastolic blood pressure with the highest systolic blood pressure. Women with additional cardiovascular comorbidity had lower blood pressure levels than those without cardiovascular comorbidity. Thus, those with an additional cardiovascular comorbidity had 4.6 mm Hg lower diastolic blood pressure and 0.9 mm Hg lower systolic blood pressure than those without additional cardiovascular comorbidity. However neither mean systolic blood pressure nor mean diastolic blood pressure were different between women with and without cardiovascular comorbidity aged 17 to 44 years. That may be due to the small number of patients in these patient groups (Figure 9, Table 19).

Figure 9 Distribution of systolic and diastolic blood pressure mmHg for women, 2007

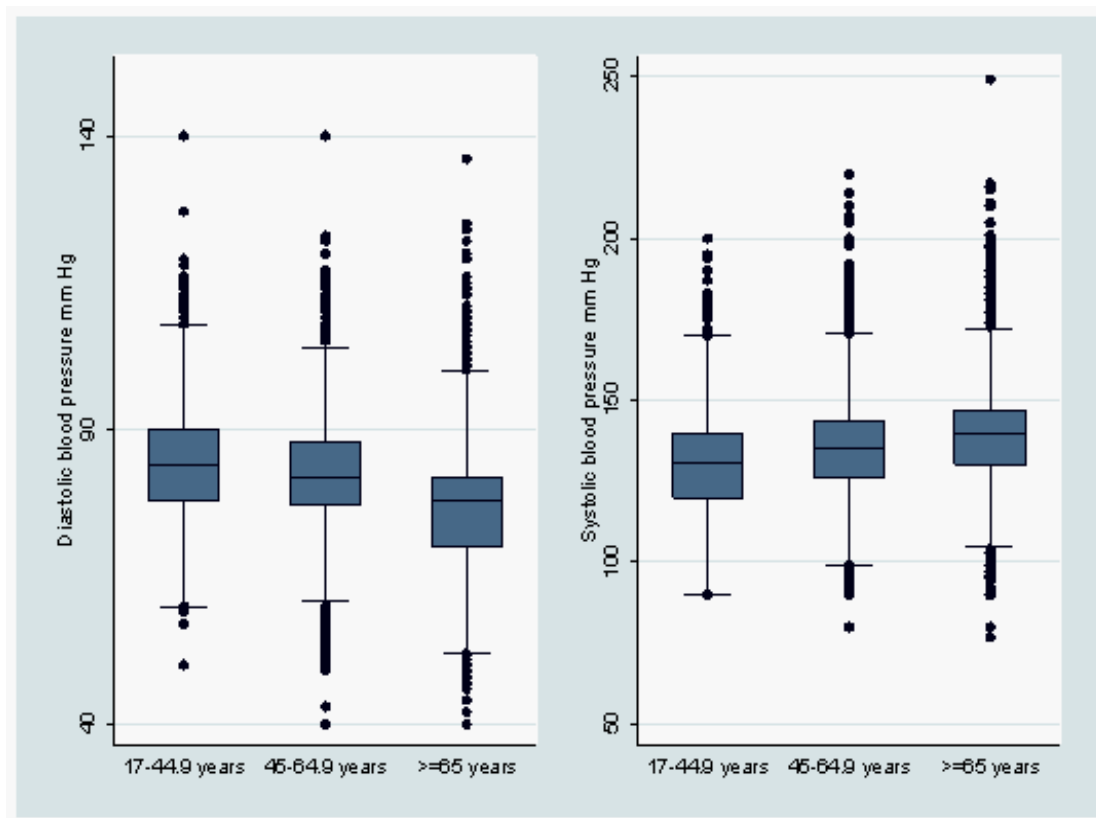


Table 19 Comparison of mean systolic blood pressure and mean diastolic blood pressure mmHg in women by age and cardiovascular comorbidity, 2007

Without comorbidity				With comorbidity‡			
Diastolic	Number	Mean (sd*)	95% CI	Number	Mean (sd)	95% CI	p value
Age group							
17 - 44	696	84.8 (10.8)	84.0 - 85.6	89	83.8 (12.3)	81.2 - 86.4	0.409
45 - 64.9	2399	83.3 (9.1)	82.9 - 83.7	802	79.4 (9.7)	78.7 - 80.0	<0.0001
>= 65	2759	77.7 (9.2)	77.7 - 78.1	2008	74.7 (10.3)	74.2 - 75.1	<0.0001
Total	5854	80.9 (9.8)	80.6 - 81.1	2899	76.3 (10.7)	76.4 - 76.12	<0.0001
Systolic		Mean (sd)	95% CI		Mean (sd)	95% CI	
Age group							
17 - 44	696	131.6 (15.8)	130.4 - 132.7	89	131.4 (19.3)	127.3 - 135.5	0.908
45 - 64.9	2399	136.2 (14.7)	135.6 - 136.8	802	134.1 (16.2)	132.9 - 135.2	0.0006
>= 65	2759	140.5 (15.9)	139.8 - 141.1	2008	138.2 (16.9)	137.4 - 138.9	<0.0001
Total	5854	137.7 (15.8)	137.3 - 138.1	2899	136.8 (16.9)	136.2 - 137.5	0.024

‡ Patients with at least one of the follow disease: coronary heart disease, diabetes mellitus, heart failure, atrial fibrillation, stroke or renal failure.

*Standard deviation

CI confidence interval

Differences in blood pressure levels between men of different race/ethnic origin were observed. Black patients aged 17 to 44 years and those aged 45 to 64.9 years had the highest systolic blood pressure levels, 143.3 mmHg (sd 16.2) and 141.3 mmHg (sd 16.4) respectively. The lowest level of systolic blood pressure was observed in men of South Asian origin, mean systolic blood pressure 134.6 (sd 17.1) mmHg. Among patients aged 65 years and older there were significant differences in diastolic blood pressure between all race/ethnic groups. Again those of south Asian origin had the lowest pressure levels with mean diastolic blood pressure of 77.7 (sd 10.6) mmHg (Tables 20-21).

Women of South Asian origin and other Asian origin had the lowest systolic blood pressure levels, 135.6 mmHg (sd 17.9) and 135.0 mmHg (sd 16.7) respectively. Among those women aged 17 to 44 years without cardiovascular comorbidity there were significant differences in systolic blood pressure between race/ethnic groups. Thus women of black origin had the highest level of systolic blood pressure 133.4 mmHg (sd 16.2). The analysis did not reveal significant variations in systolic blood pressure across other age groups between ethnic groups. On the contrary, higher variations were found in diastolic blood pressure across age groups except for those aged 17 to 44 years. Consistently higher diastolic blood pressure was observed in women of black origin, mean diastolic blood pressure 81.3 mmHg (sd 10.2) and lower diastolic blood pressure levels in those of South Asian origin, mean diastolic blood pressure 78.2 mmHg (sd 10.4). (Tables 22-23)

Table 20 Comparison of systolic blood pressure mmHg for men by race/ethnicity and presence of cardiovascular comorbidity, 2007

Men	White			Black			South Asian			Other Asian			Other race/ethnicity			Unknown race/ethnicity		
	mean (sd)	CI 95%	number	mean (sd)	CI 95%		mean (sd)	CI 95%		mean (sd)	CI 95%	number	mean (sd)	CI 95%	number	mean (sd)	CI 95%	number p value
Without comorbidity																		
17 - 44	140.1 (14.4)	139.0 - 142.3	(299)	143.3 (16.2)	140.6 - 146.0	(140)	129.9 (15.2)	125.6 - 134.4	(49)	142.6 (15.1)	135.9 - 149.3	(22)	132.8 (18.2)	125.4 - 140.4	(25)	139.7 (17.4)	133.8 - 145.6	(36) <0.0001*
45 - 64.9	140.5 (15.4)	139.5 - 141.5	(1044)	141.3 (16.4)	139.5 - 142.9	(355)	134.7 (13.1)	132.5 - 136.9	(138)	138.9 (19.6)	134.3 - 143.6	(70)	138.5 (16.0)	134.8 - 142.1	(75)	140.3 (16.3)	138.0 - 142.6	(191) 0.0013
>= 65	140.6 (16.3)	139.5 - 141.7	(864)	141.3 (15.7)	139.5 - 143.0	(312)	137.8 (17.2)	134.4 - 141.1	(105)	137.1 (17.2)	133.3 - 140.1	(43)	140.4 (15.2)	136.2 - 144.6	(53)	141.1 (16.1)	137.9 - 144.3	(101) 0.3217
With comorbidity†																		
17 - 44	133.2 (17.4)	128.6 - 137.8	(57)	128.8 (17.0)	122.4 - 135.2	(30)	123.3 (12.2)	116.2 - 130.3	(14)	135.4 (28.1)	111.9 - 158.9	(8)	129.4 (12.4)	121.4 - 137.4	(12)	134.4 (24.5)	NS	(4) 0.2630 **
45 - 64.9	135.6 (15.1)	134.2 - 136.9	(513)	138.5 (16.9)	136.1 - 140.8	(202)	135.1 (17.2)	132.4 - 137.6	(157)	131.7 (18.3)	126.9 - 136.6	(57)	133.4 (16.9)	128.7 - 138.1	(52)	136.5 (18.6)	130.2 - 142.8	(36) 0.1722***
>= 65	135.7 (16.7)	134.7 - 136.7	(1091)	136.9 (16.3)	135.3 - 138.5	(411)	134.3 (19.1)	131.9 - 136.8	(238)	132.5 (17.1)	128.4 - 136.7	(69)	137.9 (17.0)	134.1 - 141.7	(79)	137.8 (16.1)	133.5 - 142.1	(56) 0.2645
Global mean	138.4 (16.1)	137.9 - 138.9	(3868)	139.6 (16.5)	138.7 - 140.4	(1450)	134.6 (17.1)	133.3 - 135.8	(701)	135.7 (17.8)	133.5 - 138.8	(269)	136.9 (16.5)	135.1 - 138.8	(296)	139.8 (16.5)	138.2 - 141.3	(424) <0.0001

*Comparison between white, black and south asian

**Comparison between white and black

***Comparison between white, black and south Asian

Sd Standard deviation

† Patients with at least one of the follow disease: coronary heart disease, diabetes mellitus, heart failure, atrial fibrillation, stroke or renal failure

Table 21 Comparison of diastolic blood pressure mmHg for men by race/ethnicity and presence of cardiovascular comorbidity, 2007

Men	White			Black			South Asian			Other Asian			Other race/ethnicity			Unknwon race/ethnicity			p value
Without comorbidity	mean (sd)	CI 95%	number	mean (sd)	CI 95%	number	mean (sd)	CI 95%		mean (sd)	CI 95%	number	mean (sd)	CI 95%	number	mean (sd)	CI 95%	number	
17 - 44	88.0 (10.1)	86.9 - 89.9	(299)	88.0 (11.2)	86.2 - 89.9	(140)	83.5 (10.3)	80.5 - 86.4	(49)	92.5 (9.7)	88.2 - 96.8	(22)	84.6 (11.4)	79.8 - 89.4	(25)	85.4 (8.5)	82.5 - 88.2	(36)	0.0152*
45 - 64.9	85.3 (9.8)	84.7 - 85.9	(1044)	85.7 (10.9)	84.6 - 86.9	(355)	83.3 (8.7)	81.9 - 84.8	(138)	85.7 (14.1)	82.3 - 89.1	(70)	83.9 (9.1)	81.8 - 86.1	(75)	86.1 (9.8)	84.6 - 87.4	(191)	0.1374
>= 65	78.2 (9.8)	77.5 - 78.8	(864)	78.9 (8.9)	78.9 - 79.9	(312)	76.0 (8.7)	74.4 - 77.7	(105)	80.1 (8.6)	77.4 - 82.7	(43)	79.3 (10.4)	76.5 - 82.2	(53)	80.9 (7.9)	79.4 - 82.5	(101)	0.0042
With comorbidity‡																			
17 - 44	83.2 (10.7)	80.3 - 86.0	(57)	80.9 (11.8)	76.5 - 85.4	(30)	79.4 (8.5)	74.5 - 84.3	(14)	81.8 (16.4)	74.5 - 84.3	(8)	83 (10.5)	76.3 - 89.7	(12)	86.0 (15.5)	NS	(4)	0.3805 **
45 - 64.9	81.4 (9.1)	80.6 - 82.2	(513)	82.1 (10.9)	80.6 - 83.6	(202)	78.9 (10.4)	77.4 - 80.5	(157)	79.1 (11.4)	76.0 - 82.1	(57)	81.7 (10.7)	78.7 - 84.6	(52)	81.9 (7.7)	79.3 - 84.5	(36)	0.0058***
>= 65	74.1 (10.3)	73.5 - 74.6	(1091)	75.0 (9.9)	74.0 - 75.9	(411)	72.9 (10.6)	71.6 - 74.3	(238)	74.3 (9.4)	72.0 - 76.6	(69)	74.8 (9.7)	72.6 - 76.9	(79)	74.9 (11.4)	71.9 - 78.0	(56)	0.2356
Global mean	80.2 (11.0)	79.9 - 80.6	(3868)	80.9 (11.2)	80.3 - 81.4	(1450)	77.7 (10.6)	76.9 - 78.5	(701)	80.9 (12.5)	79.4 - 82.4	(269)	80.3 (10.7)	79.1 - 81.5	(296)	82.9 (10.1)	81.9 - 83.9	(424)	<0.0001

S (sample size): total of included patients less than 10

*Comparison only between white, black and south asian race/ethnicity

**Comparison only between white and black race/ethnicity

***Comparison only between white, black and south Asian race/ethnicity

Sd Standar deviation

‡Patients with at least one of the follow disease: coronary heart disease, diabetes mellitus, heart failure, atrial fibrillation, stroke or renal failure

Table 22 Comparison of systolic blood pressure mmHg for women by race/ethnicity and presence of cardiovascular co-morbidity, 2007

Women	White			Black			South Asian			Other Asian			Other race/ethnicity			Unknwon race/ethnicity			p value
Without comorbidity	mean (sd)	CI 95%	number	mean (sd)	CI 95%	number	mean (sd)	CI 95%	number	mean (sd)	CI 95%	number	mean (sd)	CI 95%	number	mean (sd)	CI 95%	number	
17 - 44	128.9 (14.8)	127.2 - 130.7	(276)	133.4 (16.2)	131.5 - 135.4	(262)	128.2 (16.9)	128.2 - 133.9	(37)	135.3 (16.2)	126.8 - 143.6	(17)	132.9 (15.9)	128.3 - 137.7	(46)	135.8 (16.6)	131.5 - 149.2	(58)	0.0022*
45 - 64.9	135.8 (14.3)	134.9 - 136.7	(1060)	137.1 (16.5)	135.9 - 138.2	(729)	136.2 (16.5)	133.8 - 138.6	(193)	132.5 (15.2)	129.3 - 135.8	(88)	137.8 (13.8)	135.2 - 140.4	(112)	135.8 (14.8)	133.8 - 137.3	(217)	0.0758
>= 65	140.9 (15.9)	140.2 - 141.7	(1722)	139.7 (15.0)	138.4 - 141.1	(466)	138.4 (18.1)	135.7 - 141.2	(173)	139.1 (14.7)	135.4 - 142.8	(62)	141.8 (18.1)	138.5 - 145.2	(117)	139.6 (15.3)	137.6 - 141.7	(219)	0.1936
With comorbidity																			
17 - 44	133.6 (16.2)	127.8 - 139.3	(33)	127.3 (14.0)	121.7 - 133.0	(26)	125.9 (23.9)	113.6 - 138.2	(17)	155.7 (38.4)	S	(3)	134.7 (10.0)	S	(7)	141.3 (42.3)	S	(3)	0.1262**
45 - 64.9	134.6 (15.8)	132.5 - 136.3	(269)	134.6 (14.7)	132.8 - 136.4	(259)	132.9 (17.8)	130.0 - 135.9	(147)	131.4 (15.9)	127.3 - 135.4	(61)	135.5 (21.1)	128.9 - 142.1	(42)	135.8 (16.4)	128.9 - 142.7	(24)	0.5663***
>= 65	137.8 (16.3)	136.8 - 138.7	(1205)	139.9 (17.6)	138.2 - 141.6	(418)	136.8 (18.1)	134.1 - 139.6	(172)	137.3 (19.3)	132.0 - 142.6	(54)	138.7 (19.3)	134.0 - 143.4	(67)	139.0 (16.7)	135.6 - 142.5	(92)	0.2645
Global mean	137.8 (15.9)	137.3 - 138.2	(4565)	137.3 (16.0)	136.7 - 138.0	(2160)	135.6 (17.9)	134.3 - 136.8	(739)	135.0 (16.7)	133.1 - 136.9	(285)	138.3 (17.3)	136.6 - 140.0	(391)	137.7 (15.7)	136.4 - 138.9	(613)	0.0019

*Comparison between white, black and south asian

**Comparison between white and black

***Comparison between white, black and south Asian

Table 23 Comparison of diastolic blood pressure mmHg for women by race/ethnicity and presence of cardiovascular co-morbidity, 2007

Women	White			Black			South Asian			Other Asian			Other race/ethnicity			Unknwon race/ethnicity			p value
Without comorbidity	mean (sd)	CI 95%	number	mean (sd)	CI 95%	number	mean (sd)	CI 95%	number	mean (sd)	CI 95%	number	mean (sd)	CI 95%	number	mean (sd)	CI 95%	number	
17 - 44	83.9 (11.4)	82.6 - 85.3	(276)	85.3 (10.0)	84.0 - 86.5	(262)	82.1 (12.4)	77.9 - 86.2	(37)	88.2 (9.2)	83.4 - 92.9	(17)	83.4 (10.2)	80.4 - 86.5	(46)	89.1 (11.2)	86.1 - 92.0	(58)	0.1437*
45 - 64.9	82.7 (9.0)	82.2 - 83.2	(1060)	84.2 (8.4)	83.5 - 84.9	(729)	82.2 (9.3)	80.8 - 83.5	(193)	83.1 (8.8)	81.3 - 85.0	(88)	82.9 (9.1)	81.3 - 84.7	(112)	84.6 (8.7)	83.4 - 85.7	(217)	0.0023
>= 65	77.3 (9.1)	76.9 - 77.8	(1722)	79.1 (8.9)	78.3 - 79.9	(466)	77.1 (10.7)	75.5 - 78.7	(173)	77.3 (7.7)	75.3 - 79.2	(62)	77.2 (9.8)	75.4 - 78.9	(117)	78.9 (8.8)	77.8 - 80.1	(219)	0.0025
With comorbidity																			
17 - 44	85.2 (11.1)	81.3 - 89.1	(33)	80.6 (9.2)	76.8 - 84.4	(26)	83.5 (17.9)	74.3 - 92.7	(17)	89.0 (19.3)	S	(3)	87.4 (11.8)	S	(7)	83.7 (5.5)	S	(3)	0.0945**
45 - 64.9	79.3 (9.1)	78.2 - 80.4	(269)	80.4 (9.9)	79.2 - 81.6	(259)	77.3 (10.0)	75.6 - 78.9	(147)	77.4 (8.9)	75.1 - 79.7	(61)	81.2 (10.8)	77.8 - 84.6	(42)	83.7 (9.2)	79.8 - 87.6	(24)	0.0077***
>= 65	73.8 (10.2)	73.2 - 74.4	(1205)	76.7 (10.6)	75.7 - 77.7	(418)	74.2 (9.3)	72.8 - 75.6	(172)	72 (9.2)	69.5 - 74.5	(54)	77.3 (10.4)	74.9 - 79.8	(67)	77.1 (11.6)	74.7 - 79.5	(92)	<0.0001
Global mean	78.2 (10.2)	77.9 - 78.5	(4565)	81.3 (10.2)	80.8 - 81.7	(2160)	78.2 (10.4)	77.4 - 78.9	(739)	78.9 (9.9)	77.8 - 80.3	(285)	80.2 (10.2)	79.2 - 81.2	(391)	81.8 (10.2)	81.0 - 82.6	(613)	<0.0001

S (sample size): total of included patients less than 10

*Comparison between white, black and south asian

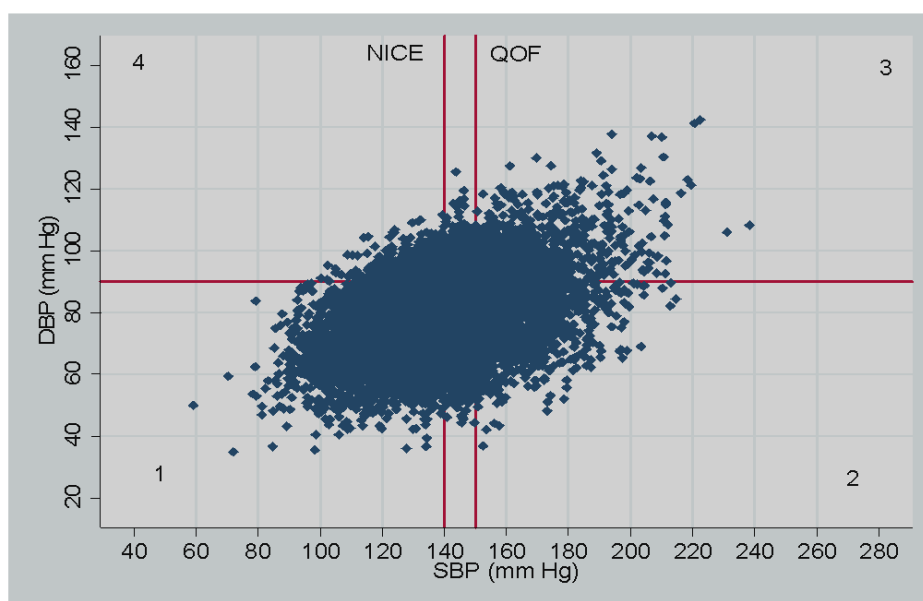
**Comparison between white and black

***Comparison between white, black and south Asian

Blood pressure control

Overall 12536 (79.5%) and 9568 (60.7%) of patients were classified as a PCH using the QOF and NICE target respectively. (Figure 10-11, Table 25) Regardless of the target, the percentage of men with controlled hypertension increase with age. Thus men aged 65 years and over had the highest percentage of those with controlled hypertension, 83.3% using the QOF target and 61.1% using the NICE target. The percentage of women with controlled hypertension rose with age using the QOF target but decreased using the NICE target. Thus the percentage of women aged 65 years and over with controlled hypertension was 81.1% and 58.2% using the QOF target and the NICE target respectively. Men aged below 65 years had lower blood pressure control rates than women at same age but men aged 65 years and over had higher blood control than women at similar age. Between race/ethnic groups, the highest percentage of percentage of PCHs was in those of South Asian origin, 1184 (82.2%) and 990 (68.8%) using the QOF target and the NICE target respectively.

Figure 10 Distribution of hypertensive patients by blood pressure levels



The classification of hypertensive patients is plotted according by the target definitions. The left vertical line represents the systolic blood pressure target of 140 mmHg recommended by NICE guidelines and the right the level of 150 mmHg recommended by the QOF guidance. The horizontal line is at 90 mmHg diastolic blood pressure. 1. Patients with controlled hypertension. 2. Patients with uncontrolled hypertension due to higher systolic blood pressure levels. 3. Patients with uncontrolled hypertension due to both higher systolic and diastolic blood pressure levels. 4. Patients with uncontrolled hypertension due to higher diastolic blood pressure levels.

Table 24 Cross-tabulation between NICE and QOF targets

NICE target	QOF target		Total
	No	Yes	
No	3225	2698	6193
Yes	0	9568	9568
Total	3225	12536	15761

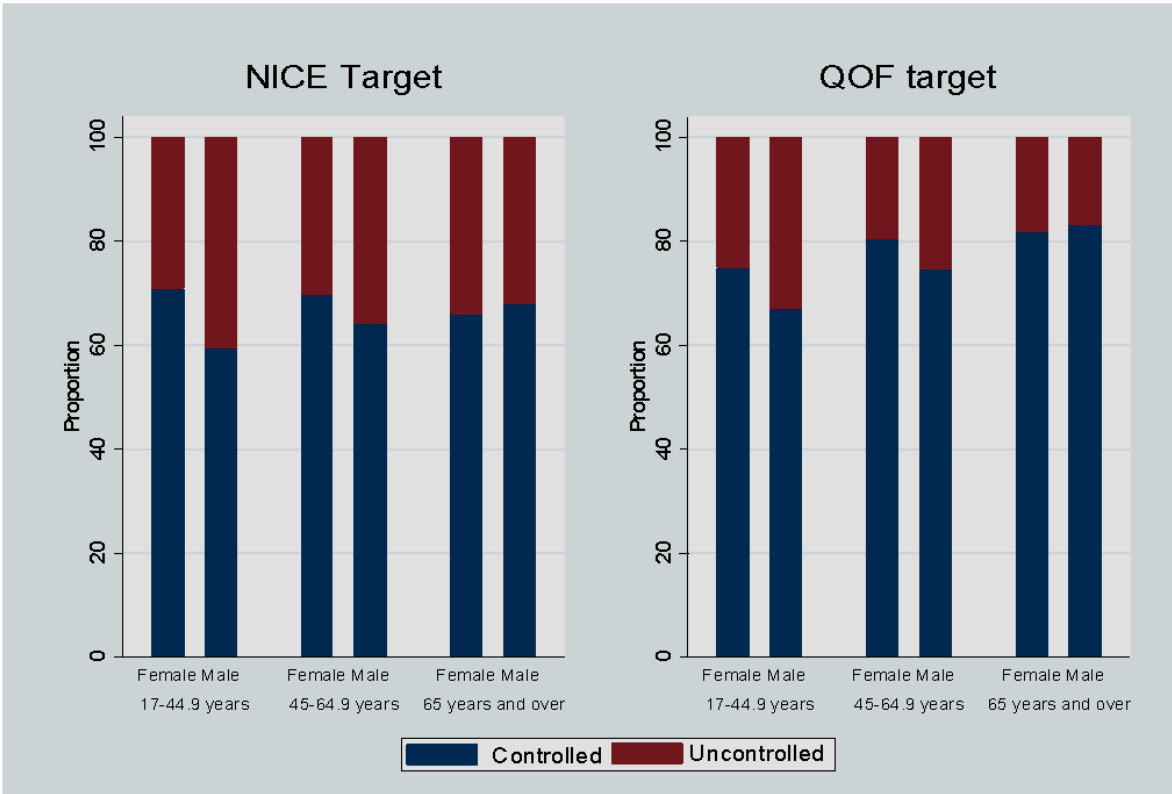
Fisher's exact <0.0001

The comparison between the QOF and NICE targets showed the percentage of patients classified as having controlled blood pressure is significantly different. There was one category with zero frequencies because it is not possible to be classified as patient with controlled blood pressure by the NICE target but not by the QOF target simultaneity. The QOF target thresholds include those of the NICE target (Table 24).

Table 25 Percentages of patients with controlled hypertension by age, sex and race/ethnicity

	QOF target		NICE target	
	% (number)	p value	% (number)	p value
Male		<0.0001		0.001
17 - 44 yr	466 (66.9)		377 (54.1)	
45 - 64 yr	2154 (74.5)		1691 (58.5)	
>= 65 yr	2850 (83.3)		2092 (61.1)	
Female		<0.0001		<0.0001
17 - 44 yr	589 (75.0)		543 (69.2)	
45 - 64 yr	2578 (80.5)		2093 (65.4)	
>= 65 yr	3899 (81.8)		2772 (58.2)	
Ethnic group		0.016		<0.0001
White	6740 (79.9)		5013 (59.5)	
Black	2824 (78.2)		2187 (60.6)	
South Asian	1184 (82.2)		990 (68.8)	
Other Asian	442 (79.8)		381 (68.8)	
Other ethnicity	543 (79.0)		407 (59.2)	
Unknown	803 (77.4)		590 (56.9)	
Overall	12536 (79.5)		9568 (60.7)	

Figure 11 Distribution of patients with controlled hypertension by sex and age



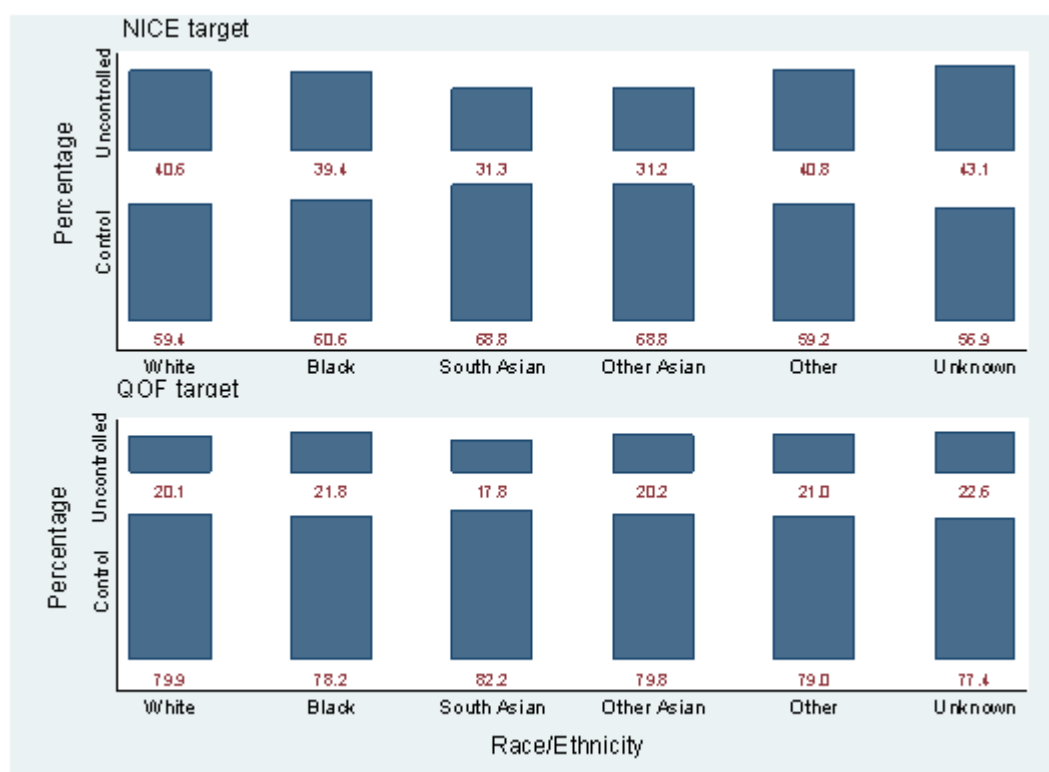
Whereas the percentages of PCH with additional cardiovascular comorbidity were 4955 (82.8%) and 3893 (65.1%), the percentages of PCH without cardiovascular comorbidity were 7581 (77.6%) and 5675 (58.1%) using the QOF target and the NICE target ($p < 0.0001$), respectively. The percentage of women aged 65 years and over with controlled hypertension was similar between those with and without cardiovascular comorbidity using the QOF target 82.3% and 81.4% respectively. In contrast, this percentage was higher in women with cardiovascular comorbidity than in those without cardiovascular comorbidity using the NICE target, 61.3% vs. 55.9% (Table 26, Figure 12).

Table 26 Comparison of patients with controlled hypertension between those with and without cardiovascular comorbidity*

	QOF target			NICE target		
	Without comorbidity Number (%)	With comorbidity * Number (%)	p value	Without comorbidity Number (%)	With comorbidity * Number (%)	p value
Male						
17 - 44	370 (64.8)	96 (76.8)	0.010	288 (50.4)	89 (71.2)	<0.0001
45 - 64.9	1350 (72.1)	804 (79.1)	<0.0001	1017 (54.3)	674 (66.3)	<0.0001
>= 65	1193 (80.7)	1657 (85.2)	<0.0001	818 (55.4)	1274 (65.5)	<0.0001
Female						
17 - 44	521 (74.9)	68 (76.4)	0.751	481 (69.1)	62 (69.7)	0.915
45 - 64.9	1900 (79.2)	678 (85.5)	0.001	1529 (63.7)	564 (70.3)	0.001
>= 65	2247 (81.4)	1652 (82.3)	0.464	1542 (55.9)	1230 (61.3)	<0.0001
Ethnic group						
White	4093 (77.7)	2647 (83.6)	<0.0001	2962 (56.3)	2051 (64.7)	<0.0001
Black	1736 (76.7)	1088 (80.8)	0.003	1333 (58.9)	854 (63.5)	0.007
South Asian	562 (80.9)	622 (83.5)	0.193	473 (68.1)	517 (69.4)	0.584
Other Asian	229 (75.8)	213 (84.5)	0.011	193 (63.1)	188 (74.6)	0.007
Other	333 (77.8)	210 (81.1)	0.306	247 (57.7)	160 (61.8)	0.293
Unknown	628 (76.4)	175 (81.4)	0.119	467 (56.8)	123 (57.2)	0.917
Overall	7581 (77.6)	4955 (82.8)	<0.0001	5675 (58.1)	3893 (65.1)	<0.0001

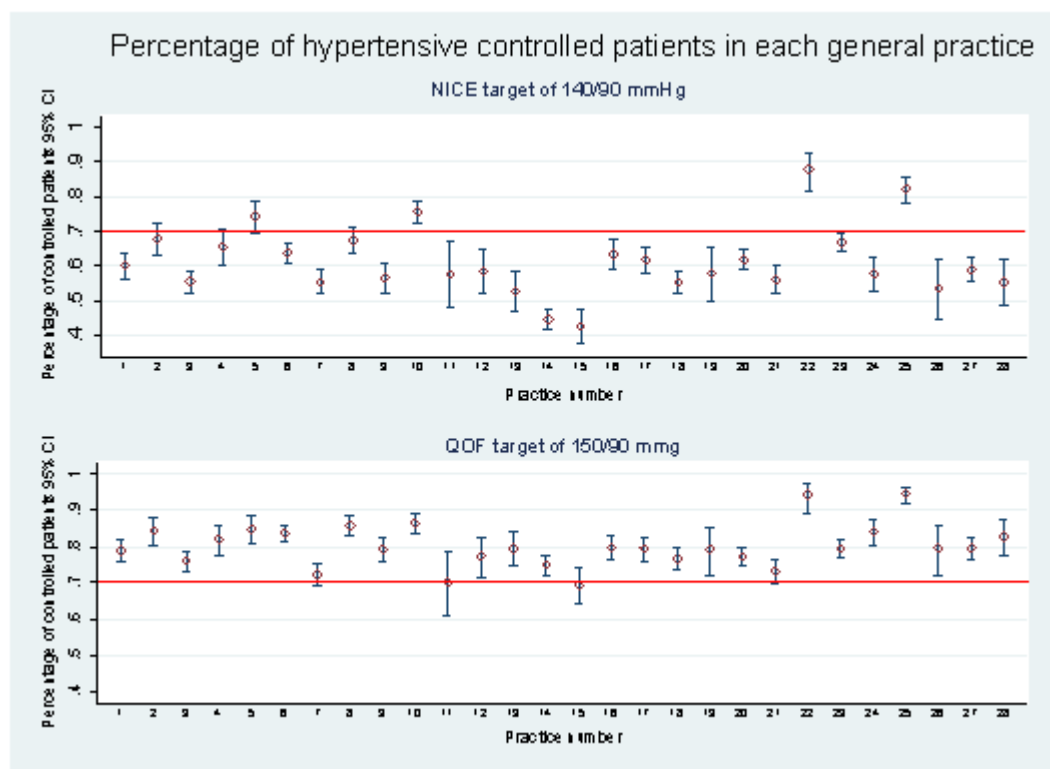
* Patients with at least one of the follow disease: coronary heart disease, diabetes mellitus, heart failure, atrial fibrillation, stroke or renal failure

Figure 12 Distribution of patients with controlled hypertension by race/ethnicity



The assessment of blood pressure control varied across the 28 practices with the target used. Almost all practices, 26 practices (92.8%) reported having more than 70% of patients with controlled hypertension by using the QOF target. On the contrary, only 5 practices (14.3%) had more than 70% of patients classified as a PCH by using the NICE target (Figure 8). Of these 4 practices had the higher percentages of patients of south Asian origin (practice 5 (33.4%), practice 22 (10%), practice 25 (24.1%) and practice 26 (25.4%)) compared to what observed in all practices. Practice 22 had the highest percentage of black patients (45.4%) and also the highest percentage of patients with an additional cardiovascular co-morbidity (51.7%). The practices 14 and 15 had the lowest proportion of PCHs. Patients of white origin represent the highest percentage of all registered patients with these practices, 69.2% and 64.1% respectively (Figure 13).

Figure 13 Percentage of hypertensive patients with controlled blood pressure by practice



Using the QOF target there were no significant differences in the proportion of PCHs between practices in the least deprived and the most deprived areas. By contrast, using the NICE target practices located at the least deprived areas had lower percentage of patients with blood pressure controlled compared to those located at the most deprived areas (57.1 vs 61.6%). Except for two practices (practice 22 and practice 23), the practices located at the least deprived had a higher percentage of hypertensive patients without additional cardiovascular comorbidity than those located at the most deprived areas (Figure 14-15). The reported differences in blood pressure control also were observed when only patients without cardiovascular comorbidity were compared. Patients registered with practices located at least deprived areas were more likely to be younger, male and belonging to other ethnicity different from white.

Figure 14 Distribution of patients with controlled hypertension by deprivation index

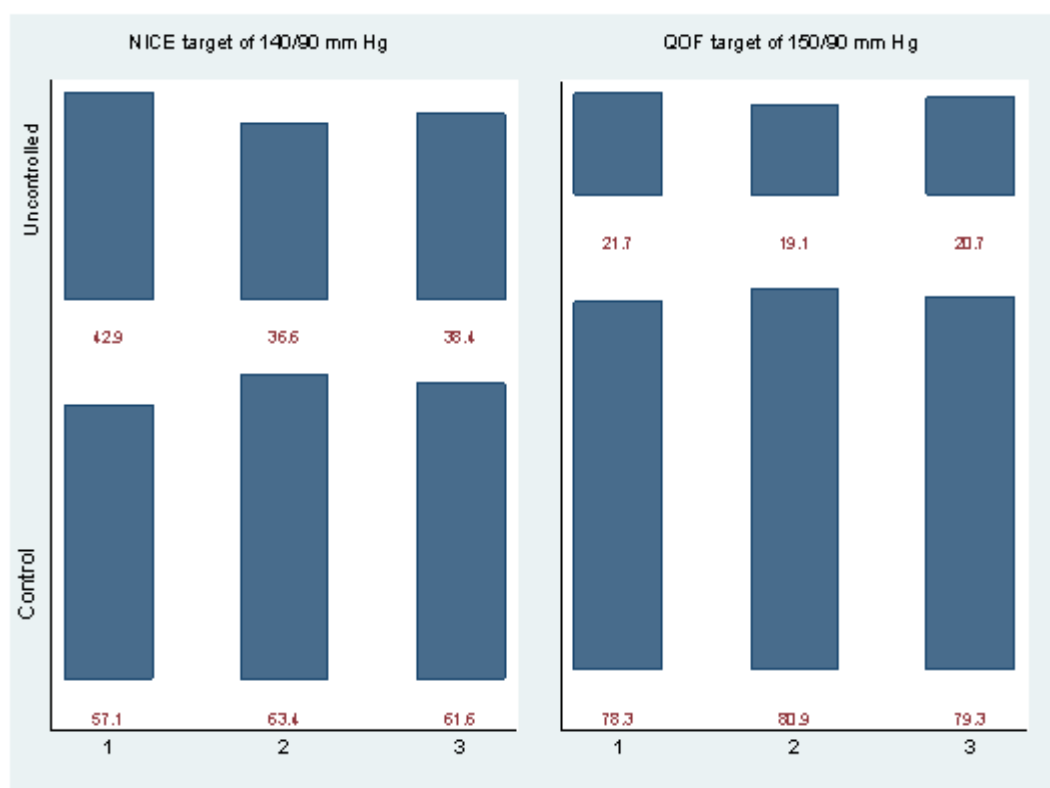
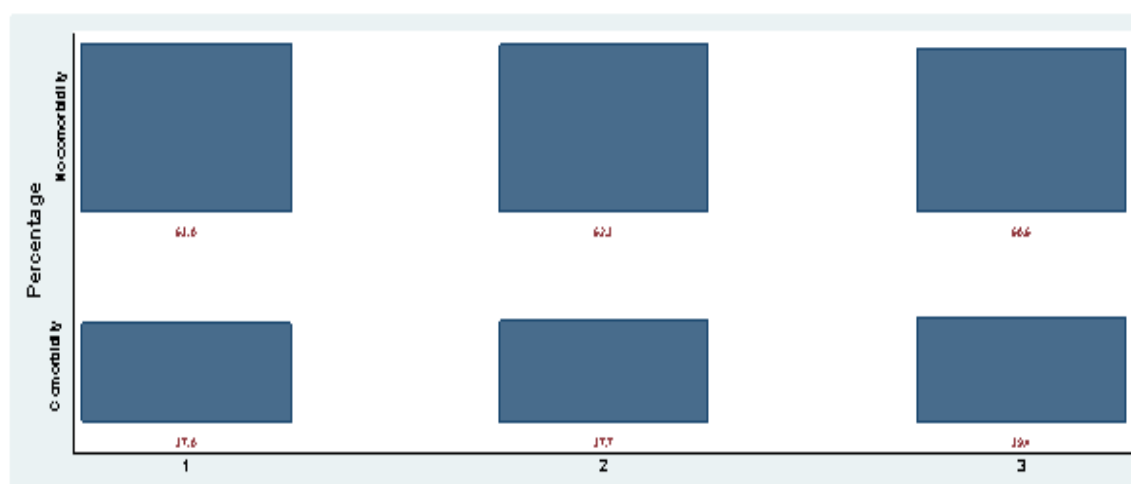


Figure 15 Distribution of patient with and without cardiovascular comorbidity by deprivation index



Variations in the odds ratio of being classified as a PCH by target definition in all patients included

The QOF target model

Overall men were less likely to be classified as a PCH (OR 0.64 95% CI 0.52 – 0.81) compared to women using the QOF target of 150/90 mm Hg. However men aged 45–64 years and those aged 65 years and over were more likely to be classified as a PCH (OR 1.34 95% CI 1.08 – 1.65) and (OR 2.15 95% CI 1.61 – 2.87) respectively related to men and women aged 17 to 44 years. A similar pattern was observed in women. There were no significant differences in the odds of being classified as a PCH between hypertensive patients of different origin. Patient with an additional cardiovascular comorbidity had a higher odds of being classified as a PCH (OR 1.25 95% CI 1.15 – 1.36) in comparison to those without an additional cardiovascular comorbidity (Table 27).

The NICE target model

Similar to what observed in the QOF target model, by using the NICE target of 140/90 mm Hg men were less likely to be classified as a PCH (OR 0.50 95% CI 0.41 – 0.62). However men at the age of 45 to 65 years and 65 years and over were more likely to be classified as a PCH (OR 1.31 95% CI 1.08 – 1.58) and (OR 1.61 95% CI 1.26 – 2.06) respectively compared to women and men aged 17 to 44 years. Conversely women were less likely to be classified as a PCH with increases in age. Thus those aged 65 years and over were less likely to be classified as a PCH (OR 0.77 95% CI 0.60 – 0.99). Patients of South Asian origin and other Asian origin were more likely to be classified as a PCH (OR 1.36 95% CI 1.23 – 1.57) and (OR 1.39 95% CI 1.16 – 1.68) respectively compared to those of white race/ethnicity. Those with an additional comorbidity were also more likely to have controlled blood pressure (OR 1.33 95%CI 1.24 – 1.42) (Table 27).

Interaction effect

The probability of being classified as a PCH varied between men and women across age groups. By using the QOF target, men aged 65 years and over had almost equal probability of being classified as a PCH as women, nearly 80%. However, men aged between 17 and 44 years had a lower probability of being classified as a HCP than women, 72% vs. 80.0%. Similar findings were also produced by the NICE target model but with lower probabilities of being classified as a HCP (Figure 16).

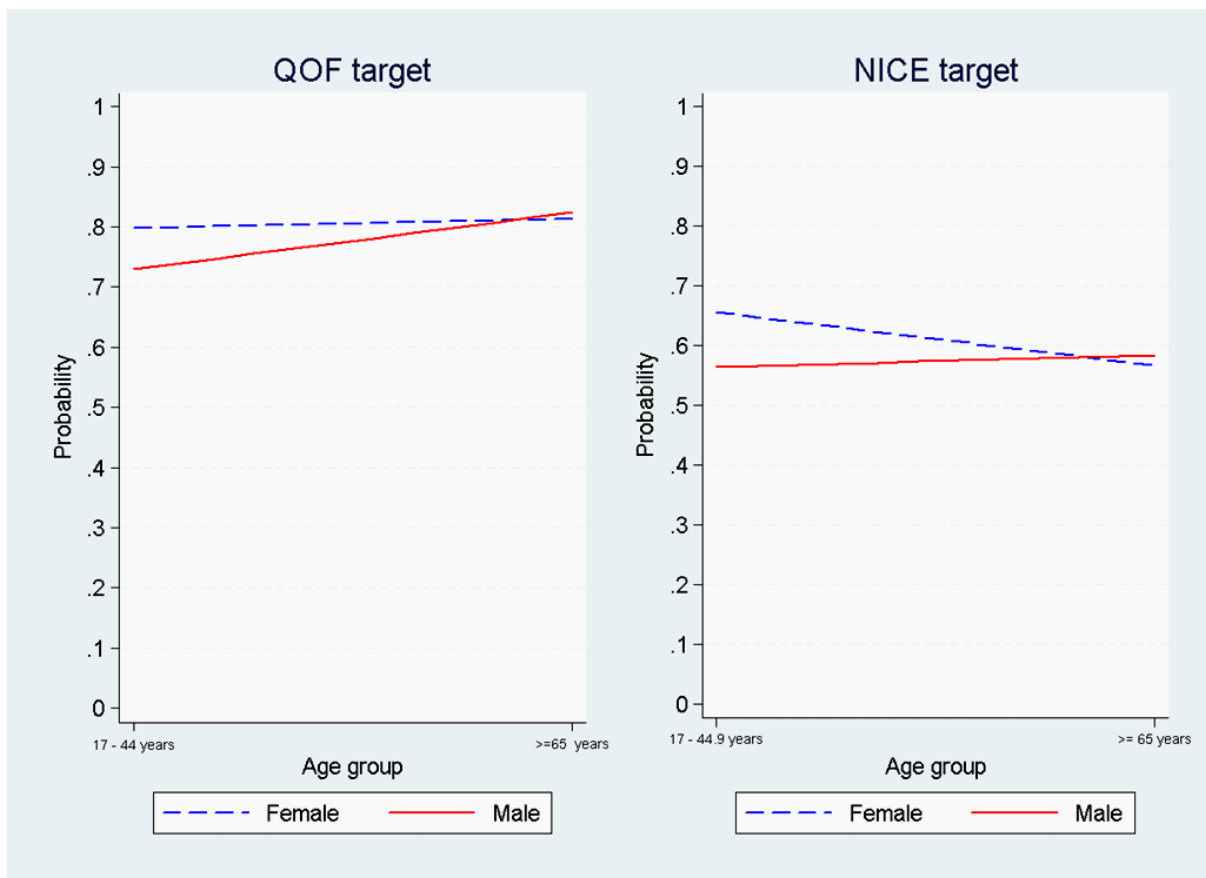
Table 27 Odds ratio of patient characteristics associated with being classified as a patient with controlled hypertension

	<u>QOF target</u>		<u>NICE target</u>	
Patient characteristics	Odds ratio 95% CI ^a	P value	Odds ratio 95% CI	p value
Men Referent women	0.64 (0.51 - 0.81)	<0.0001	0.50 (0.41 - 0.62)	<0.0001
Age (years)	1.00 (0.99 - 1.00)	0.904	0.99 (0.98 - 0.99)	<0.0001
Age-Sex *Interaction				
Men*Age 45-64 years	1.34 - (1.08 - 1.65)	0.006	1.31 (1.08 - 1.58)	0.005
Men*Age 65 years and over	2.15 (1.61- 2.87)	<0.001	1.61 (1.26 -2.06)	<0.0001
Women*Age 45-64 years	1.26 (1.01 - 1.57)	0.033	0.91 (0.75 - 1.11)	<0.367
Women*Age 65 years and over	1.29 (1.03-1.64)	0.027	0.77 (0.60 - 0.99)	0.0047
Referent group Men and Women age 17-44 years				
Ethnic group				
Black	0.91 (0.82 - 1.00)	0.067	0.97 (0.89 - 1.05)	0.485
South Asian	1.14 (0.98 - 1.32)	0.073	1.36 (1.23 - 1.56)	<0.0001
Other Asian	1.00 (0.81 - 1.24)	0.978	1.39 (1.23 - 1.56)	<0.0001
Other	0.97 (0.81 - 1.24)	0.824	0.94 (0.80 - 1.10)	0.473
Unknown Referent White	0.92 (0.79 - 1.08)	0.338	0.91 (0.79 - 1.04)	0.171
Presence of cardiovascular comorbidity‡ Referent Patient without cardiovascular comorbidity	1.25 (1.15 - 1.36)	<0.0001	1.33 (1.24 - 1.42)	<0.0001
Being prescribed any antihypertensive drug Referent group Not being prescribed antihypertensive	1.17 (1.04 - 1.33)	<0.0001	1.01 (0.98 - 1.22)	0.084

^aCI confidence interval

‡Patients with at least one of the follow disease: coronary heart disease, diabetes mellitus, heart failure, atrial fibrillation, stroke or renal failure.

Figure 16 Variation in the probability of being classified as patient with controlled blood pressure*



***Interaction effect**

Blood pressure control in hypertensive patients with diabetes

Of 3360 patients with both diabetes and hypertension, 1318 (39.2) and 2373 (66.9) were classified as patients with controlled blood pressure by the NICE target of less than 140/80 mmHg and the QOF target of equal to or less than 145/85 mmHg respectively. Regardless of the target, higher percentages of patients with controlled blood pressure were present in those aged 45 years and over. An exception was observed in females where I did not find differences in the percentages between age groups when the NICE target was used. There were no significant differences in the percentages of blood pressure control between race/ethnic groups (Table 28).

By using the NICE target, 473 (44.9%) and 845 (36.6%) diabetic patients with hypertension and other cardiovascular comorbidity and without an additional comorbidity had controlled blood pressure, respectively ($p < 0.001$). Higher proportions of patients with controlled blood pressure were observed in men aged 65 years and over and in those of South Asian and other Asian origin. Comparisons of the percentage of those with controlled blood pressure across sex, age categories and each ethnic group did not produce significant differences; except for male aged 45 to 65 years, whites and those of South Asian origin with an additional comorbidity who had higher percentages of those with controlled blood pressure than their counterparts without comorbidity. By using the QOF target, there were not significant differences in the percentages across age, sex and ethnic groups (Table 29).

The NICE logistic model including all diabetic patients with hypertension showed that for one year increase in age there was an increase in the risk of having controlled blood pressure OR 1.01 (95% CI 1.00 – 1.02). Compared to whites, those of other Asian origin were more likely to have controlled blood pressure OR 1.59 (95% CI 1.09 – 2.29). Having an additional cardiovascular comorbidity was positively associated with the control of blood pressure OR 1.19 (95% CI 1.05 – 1.37). In the model using the QOF target, none of the included variables were significant associated with having controlled blood pressure (Table 30).

When only patients with hypertension and diabetes were included in the NICE logistic model, again being older was significantly associated with having controlled blood pressure OR 1.02 (1.00 – 1.04). Those of other Asian origin were more likely to have controlled pressure related than whites OR 1.84 (95% CI 1.29 – 2.63). In the model using the QOF target, patients of other Asian origin were also more likely to have controlled blood pressure compared to whites OR 1.55 (95% CI 1.03 – 2.33) (Table 31).

Globally the sample of diabetic patients becomes smaller particularly in some patient groups. For instance, the number of hypertensive patients with diabetes aged 17 to 44 years is 142 but those aged 65 years and over is 1973. This distribution may limit the ability to make inferences about the results. However, the QOF targets consistently produced a higher percentage of hypertensive patients with diabetes with controlled blood pressure than that produced by the NICE target. It seems that the achievement of lower blood pressure targets was not completely satisfactory. Becoming older and those of other Asian origin were patient characteristics positively associated with having controlled blood pressure. However, the results should be interpreted cautiously because of the limitations of the sample size.

Table 28 Percentage of diabetic patients with controlled blood pressure by age, sex and race/ethnicity (N=3360)

	QOF target		NICE target	
	number (%)	p value	number (%)	p value
Male		<0.0001		<0.0001
17-44 years	40 (53.3)		19 (25.3)	
45 - 64 years	412 (63.3)		204 (31.2)	
>= 65 years	709 (74.9)		441 (46.2)	
Female		0.006		0.109
17-44 years	38 (56.7)		20 (29.9)	
45 - 64 years	416 (70.4)		218 (36.9)	
>= 65 years	758 (73.8)		416 (40.5)	
Ethnic group		0.062		0.059
White	1016 (72.1)		570 (40.5)	
Black	675 (68.6)		349 (35.5)	
South Asian	391 (72.4)		234 (43.3)	
Other Asian	134 (74.0)		89 (49.2)	
Other	106 (63.1)		52 (30.9)	
Unknown	51 (66.2)		24 (31.2)	
Overall	2373 (70.6)		1318 (39.2)	

Table 29 Comparison of diabetic patients with controlled hypertension between those with and without cardiovascular comorbidity N(3360)

	QOF target			NICE target		
	Without comorbidity Number (%)	With comorbidity Number (%)	p value	Without comorbidity Number (%)	With comorbidity Number (%)	p value
Male						
17 - 44	31 (50)	9 (69.2)	0.169	16 (25.8)	3 (23.8)	0.837
45 - 64.9	313 (61.7)	99 (67.4)	0.215	141 (27.8)	63 (42.9)	0.001
>= 65	375 (75.4)	334 (74.4)	0.706	224 (45.1)	217 (48.3)	0.316
Female						
17 - 44	34 (55.7)	4 (66.7)	0.606	18 (29.5)	2 (33.3)	0.845
45 - 64.9	350 (71.3)	66 (66.0)	0.292	173 (35.2)	45 (45.0)	0.645
>= 65	509 (73.8)	249 (73.9)	0.967	273 (39.6)	143 (42.4)	0.379
Ethnic group						
White	649 (70.4)	367 (75.2)	0.055	333 (36.1)	237 (48.6)	<0.0001
Black	511 (68.1)	164 (70.1)	0.574	262 (34.9)	87 (37.2)	0.531
South Asian	231 (70.9)	160 (74.8)	0.320	128 (39.3)	106 (49.5)	0.019
Other Asian	98 (77.8)	36 (65.5)	0.082	62 (49.2)	27 (49.1)	0.989
Other	81 (67.5)	25 (52.1)	0.061	39 (32.5)	13 (27.1)	0.493
Unknown	42 (65.6)	9 (69.2)	0.802	21 (32.8)	3 (23.1)	0.49
Overall	1612 (69.8)	761 (72.3)	0.141	845 (36.6)	473 (44.9)	<0.0001

‡ Patients with at least one of the follow disease: coronary heart disease, heart failure, atrial fibrillation, stroke or renal failure

Table 30 Odds ratio of patient characteristics associated with being classified as a patient with controlled hypertension for all diabetic patients (N 3360)

	QOF target		NICE target	
Patient characteristics	Odds ratio 95% CI		Odds ratio 95% CI	p value
Men Referent women	0.86 (0.53 - 1.41)	0.555	0.77 (0.38 - 1.55)	0.465
Age (years)	1.01 (0.99 - 1.02)	0.184	1.01 (1.00 - 1.02)	0.027
Sex *Interaction				
Men*Age 45-64 years	1.23 (0.53 - 2.95)	0.575	1.02 (0.47 - 2.20)	0.960
Men*Age 65 years and over	1.87 (0.82 - 4.23)	0.134	1.54 (0.67 - 3.51)	0.307
Women*Age 45-64 years	1.51 (0.79 - 2.87)	0.210	1.04 (0.63 - 1.72)	0.888
Women*Age 65 years and over Referent group	1.45 (0.69 - 3.22)	0.300	0.94 (0.49 - 1.79)	0.844
Men and Women age 17-44 years				
Ethnic group				
Black	0.84 (0.69 - 1.03)	0.090	0.84 (0.69 - 1.00)	0.056
South Asian	1.08 (0.74 - 1.59)	0.694	1.19 (0.92 - 1.54)	0.185
Other Asian	1.19 (0.82 - 1.74)	0.355	1.59 (1.09 - 2.29)	0.014
Other ethnic group	0.71 (0.49 - 1.03)	0.069	0.71 (0.54 - 0.94)	0.015
Unknown Referent White	0.77 (0.56 - 1.06)	0.112	0.72 (0.49 - 1.05)	0.089
Presence of cardiovascular Referent Patient without cardiovascular comorbidity	0.96 (0.82 - 1.15)	0.728	1.19 (1.05 - 1.37)	0.009
Being prescribed any antihypertensive drug Referent group Not being prescribed	0.83 (0.62 - 1.08)	0.166	0.79 (0.53 - 1.18)	0.252

*CI confidence interval

†Patients with at least one of the follow disease: coronary heart disease, heart failure, atrial fibrillation, stroke or renal failure.

Table 31 Odds ratio of patient characteristics associated with being classified as a patient with controlled hypertension for all diabetic patients without cardiovascular comorbidity (N=2308)

	QOF target		NICE target	
Patient characteristics	Odds ratio 95% CI		Odds ratio 95% CI p value	
Men	0.78 (0.44 - 1.36)	0.379	0.82 (0.42 - 1.59)	0.551
Referent women				
Age (years)	1.01 (0.99 - 1.03)	0.077	1.02 (1.00 - 1.04)	0.020
Sex *Interaction				
Men*Age 45-64 years	1.29 (0.61 - 2.71)	0.500	0.83 (0.35 - 1.94)	0.664
Men*Age 65 years and over	1.97 (0.87 - 4.48)	0.102	1.33 (0.50 - 3.51)	0.567
Women*Age 45-64 years	1.55 (0.80 - 3.00)	0.190	0.94 (0.52 - 1.72)	0.844
Women*Age 65 years and over	1.40 (0.67 - 2.93)	0.369	0.86 (0.39 - 1.89)	0.567
Referent group				
Men and Women age 17-44 years				
Ethnic group				
Black	0.88 (0.72 - 1.07)	0.191	0.95 (0.79 - 1.15)	0.630
South Asian	1.09 (0.73 - 1.65)	0.667	1.25 (0.91 - 1.70)	0.161
Other Asian	1.55 (1.03 - 2.33)	0.035	1.84 (1.29 - 2.63)	0.001
Other ethnic group	0.93 (0.61 - 1.44)	0.753	0.90 (0.58 - 1.40)	0.652
Unknown	0.80 (0.56 - 1.15)	0.227	0.89 (0.56 - 1.39)	0.62
Referent White				
Being prescribed any antihypertensive drug	0.81 (0.63 - 1.04)	0.096	0.74 (0.47 - 1.16)	0.186
Referent group				
Not being prescribed				

*CI confidence interval

†Patients with at least one of the follow disease: coronary heart disease, heart failure, atrial fibrillation, stroke or renal failure.

7.4 Discussion

In 28 general practices with 15761 hypertensive patients differences in the proportion of PCHs were quantified when different targets were used. The use of the 150/90 mm Hg QOF target produced a higher proportion of PCHs, overall 79.5%. In comparison, the proportion of patients with controlled hypertension was 60.7% using the NICE target. There were 26 (93%) of practices with more than 70% of their patients with controlled hypertension by using the QOF. In contrast when the NICE target is used, only 4 (14.2%) of practices had more than 70% patients with controlled hypertension.

The difference in the proportions of patients with controlled hypertension between both blood pressure targets can be explained by variations in systolic blood pressure levels among hypertensive patients because the diastolic blood pressure threshold was the same for both targets. Then the lower proportions of PCHs observed by using the NICE target may be attributed to patients having systolic blood pressure levels above the NICE threshold. Reductions in systolic blood pressure levels have been less well achieved than reductions in diastolic blood pressure levels even in controlled clinical trials (214, 667). Therefore despite improvements in blood pressure control, it seems that higher systolic blood pressure levels still account for most cases of uncontrolled hypertensive patients (668). That occurring particularly in adults over 50 year because systolic blood pressure continually increased with age and the opposite trend is observed in diastolic blood pressure (73).

On overall women had mean systolic blood pressure 137.4 mmHg (sd 16.2). Women aged 17 to 44 years had the lowest systolic blood pressure levels, mean systolic blood pressure 131.5 (sd 16.2) mmHg. Of note, mean systolic blood pressure 139.5 mmHg (sd16.4) observed in those aged 65 years and over was comparable to that observed in some clinical trials. For instance, results from individual trials such as JATOS and VALISH illustrated that hypertensive patients aged over 70 years were able to achieve mean systolic blood pressure of 135.9 mmHg and 135.6 mmHg respectively without excess in side effects

(198, 200). It appears that blood pressure reductions are correlated with baseline blood pressure so that more intensive approach may be required to those with higher blood levels (173). Then the current results suggested that high reduction in systolic blood pressure is possible to achieve in the daily clinical practice.

Systolic blood pressure was similar in men at different age groups; overall mean systolic blood 138.2 (16.4) mmHg. There were no differences in systolic blood pressure between age groups. Similar to what observed in women, there seems that these levels were in the range of what observed in clinical trials (139) and in the last Health survey for England. The survey revealed that men had a mean systolic blood pressure of 130.8/74.2 mmHg (284). The current results showed that men aged 65 years and over had lower blood pressure levels than that those observed in women at same age. Early reports suggested a differential lowering blood pressure effect of antihypertensive drugs in women (669). However, Turnbull et al. in a meta-analysis of 31 clinical trials did not find differences in blood pressure reductions between men and women neither in the hypertension-related cardiovascular risk reduction across clinical trials (670). The analysis used individual clinical data and the follow up period was comparable between studies (670). Hence the observed differences in blood pressure levels between men and women could be explained by other factors different from sex, age and antihypertensive drug therapy effect.

Comparisons of blood pressure between ethnic groups revealed that for men and women blood pressure levels were lower in patients of South Asian origin. In an analysis of 12 studies, Agyemang et al reported that population of South Asian origin living in England had lower blood pressure levels than those observed in the general population (90). Women had lower blood pressure levels than men (90). Similarly, In analysis of 99683 patients from 148 practices in east London, Mathur et al found that hypertensive patients of South Asian origin had lower blood pressure levels compared to that observed in patients of white and black origin (535). They also had a higher prevalence of other cardiovascular comorbidities such diabetes. Hence it seems that the observed lower blood pressure levels may be due to both the biological conditions presented in this population and the interventions they received.

Patients of black origin had similar blood pressure levels to those observed in the white population. Thus 78.2% and 60% of black patients were classified as a PCH using the QOF target and the NICE target respectively. In a study conducted among 16613 hypertensive patients from general practice located in South London, Ashworth et al reported that 77.0% of black patients had controlled hypertension with a mean systolic blood pressure of 138.2 mmHg (497). Similarly in an analysis of data from the 2004 Health Survey for England, Nazroo et al did not find differences in the risk of having controlled blood pressure between whites and other ethnic groups (495). By contrast, people of African origin living in other countries have been found to have higher blood pressure levels than those of white origin. In the NHANES surveys carried out between 1988 and 2008, Egan et al found that African American people had a higher prevalence of hypertension with lower blood pressure control rates than the white people (283). Similarly, in a survey conducted in Netherlands, Agyemang reported that people of African origin were less likely to have controlled blood pressure than the white population (671).

The reasons for these differences could be a lower baseline blood pressure levels in the African British population. In a review of population surveys carried out in the UK and the Netherlands, Agyemang et al found that Dutch African people had higher blood pressure levels than African British. Differences in access to treatment may account for these differences between countries. In that, the review showed that African British people were more likely to receive treatment and to have controlled blood pressure (671). The hypertensive patients of the current study came from those who had periodically been treated by health services. Those patients have been found to have better blood pressure control than hypertensive individuals included in national surveys. Being treated by a multidisciplinary team and access to treatment are factors which may contribute to the high proportion of black patients with controlled hypertension (672). Moreover reductions in the discrepancies of blood pressure control rates between patients of different ethnic origin have been reported in patients exposed to health care over a long follow-up period (672). Then black patients under appropriate treatment are able to attain similar reductions in blood pressure levels to those observed in patients of other ethnic origin (143, 673). Differences in life

style such as exercise and diet between black populations living in different countries could also explain the differences in blood pressure control rates (674). Globally, it seems that people of African origin living in the UK are more physically active than those living in Netherlands (674-675).

For men and women systolic and diastolic blood pressure levels were lower in hypertensive patients with an additional cardiovascular than those observed in hypertensive patients without an additional cardiovascular comorbidity. The most frequently associated comorbidity was diabetes. The lower blood pressure targets for these patients established in the hypertension guidelines may contribute to this finding (174). Early clinical studies showing the benefit of lowering blood pressure below 140/90 mmHg in hypertensive patients with additional comorbidity such as diabetes also may influence the use of lower blood pressure targets (201). In English primary care, Meran et al also documented improvements in blood pressure control in patients with kidney chronic disease associated with the implementation of the NICE guidelines for the management of chronic kidney disease (569). Similarly in the analysis of diabetic patients from the US 1999 -2010 NHANES Wong et al reported improvements in the management of blood pressure in this patient group over the period (676). Hence, it seems that the lower blood pressure threshold established in the guidelines has influenced the management of hypertensive patients in primary care.

The higher blood pressure levels observed in patients without cardiovascular comorbidity could be related to the lack of evidence supporting the benefit of using lower targets for this patient group. The recommended targets are mainly based on blood pressure levels achieved by patients included in clinical trials. However these patients have been mainly at high cardiovascular risk (677-678). Analysis from subgroups of patients included in clinical trials have shown that using lower targets in hypertensive patients at low cardiovascular risk could result in higher reductions in the hypertension-related cardiovascular risk (210, 262, 679). Moreover an excess of cardiovascular risk is still present at the level of the current blood pressure target as the hypertension-related cardiovascular risk has been observed at levels up to 115/75 mmHg blood pressure (7, 680). People with these blood

pressure levels could also account for the major burden of hypertension at population level (681). Hence, despite not having a clinical trial supporting a defined lower blood pressure target for patients at low or middle cardiovascular risk, there is no a clear reason for not attempting lower blood pressure levels in this patient group.

Blood pressure control

The percentage of patients with controlled blood pressure equal to or below 140/90 mmHg was 60.5%. Overall 50% of patients without cardiovascular disease had blood pressure levels below 140/90 mm Hg. Data from the Health Survey for England showed that blood pressure rates have been improved in England since 2002 (284, 682). The 2006 Health Survey for England showed that on overall 28% of hypertensive patients have blood pressure levels below 140/90 mm HG. Similarly to my results, the percentage of women with controlled hypertension tended to decreased with age. For men there were not significant variations across age categories (284). The fact that the population included in the current study were managing in primary care settings could be explained the higher percentage of PCHs compared to that reported by the national survey. The survey sampled civil population having or not having care in primary care settings.

The percentage of hypertensive patients with blood pressure levels equal to or below 150/90 mmHg was 79.5%. The percentage tended to increase with age in both sexes. This may be because diastolic blood pressure levels were higher in those at younger age than in those at older age. Systolic blood pressure had less variation across age groups, particular in men. In a cohort of 470725 hypertensive patients, Serumaga et al reported that nearly 70% achieved blood pressure levels $\leq 150/90$ mmHg during a seven years follow up period (683). This target was established as the audit threshold for the management of hypertensive patients in a clinical practice in the 2004 BHS hypertension guidelines (174). However using this target may leave patients classified as patients with controlled hypertension but with an excess of cardiovascular risk potentially intervened. That is because reductions in systolic blood pressure below 150 mmHg are feasible attained with a subsequent reduction in hypertension-related risk (7, 140). Therefore, The classification of hypertensive patients as those with controlled or uncontrolled hypertension based on this

target could fail to provide accurate information on the long-term blood pressure control needed to achieve the maximal cardiovascular risk reduction for each patient (171, 684).

Regardless of the target used higher proportions of blood pressure control were identified in those of South Asian origin, overall 82.2% with the QOF target and 68.8% with the NICE target. That may be expected due to the lower blood pressure levels observed in these population (90). In study carried out in South east London, Ashworth et al found that patients of South Asian origin had higher rates of blood pressure control and also had more additional cardiovascular comorbidity (497). The percentage of black PCHs was similar to what observed in white population. Thus 78.2% and 60.6% of patients of black origin were classified as a HCP using the QOF target and NICE target respectively. Similarly Ashworth P et al reported that by using the QOF target 77.8% of Black patients had controlled blood pressure with a mean systolic blood pressure of 137.8 mmHg. In the analysis of data from the 2004 Health Survey for England, Nazroo et al also did not find differences in blood pressure control rates between patients of different race/ethnic origin (495). However, they acknowledged that this finding may be due to the small sample size in some ethnic groups.

In both target distributions the percentage of hypertensive patients with controlled blood pressure was higher in those with an additional cardiovascular comorbidity compared to that in those without additional cardiovascular comorbidity. In an analysis of 148 practices located in east London, Mathur et al found that patients with multicomorbidity were more likely to achieve blood pressure targets than those with only one comorbidity (535). Similarly Laverty et al reported better improvement in blood pressure control in patients with cardiovascular comorbidity compared to those without cardiovascular comorbidity over a period of 10 years (609). Reassuring the management of hypertensive patients at high cardiovascular risk such those with an additional cardiovascular comorbidity has been improved in England.

The probability of achieving either the QOF target or the NICE target was lower for men. However the probability varied between sexes across age groups. Thus women aged 17

to 44 years and men over 65 years had the highest probability of being with controlled hypertension. Differences in blood pressure control between men and women have been inconsistent between different studies. Falascheti et al did not report significant differences in blood pressure control between men and women on hypertensive treatment in the Health survey for England (284). In the analysis of NHANES 1999-2004, Ong et al reported that men and women had similar blood pressure control rates (685). However in a cross sectional analysis of the NHANES 1999 – 2004, Gu et al revealed that women were less likely to achieve blood pressure control than men (320). In a cohort of 288916 patients with incident hypertension Daugherty et al analysed gender differences in blood pressure control (274). They found that hypertensive younger men with or without cardiovascular comorbidity had lower blood pressure rates than women but older men had higher blood pressure control rates than women (274). The reasons for those differences have not been clarified. The well-known differences in age-related blood pressure levels between sexes could play a role in the probability of achieving a specific target (38, 73, 686). Other explanations may be related to differences in blood pressure response to therapy between males and females. However evidence from two meta-analyses on differences in the effect of antihypertensive drug therapy between sexes did not revealed significant variations in blood pressure reductions between women and men (670, 687). Also, differences in life-style and behaviour could account for this effect (688). Therefore more exploration on the contribution of sex and age in the probability of having controlled hypertension may be needed.

The assessment of blood pressure control in practices

Using the QOF target produced slight differences in the proportion of PCHs between practices. 95% of the practices had more than 70% of hypertensive patients with blood pressure equal or below 150/90 mmHg. In an analysis of more than 2000 practices in England, Ashworth et al found that slight differences in the percentages of patients with blood pressure equal to or below 150/90 mmHg after the introduction of the QOF (498). Similarly in sample of 303 patients, Hammouche et al reported that there were no differences in blood pressure control between patients in the least and most deprived areas using the QOF target (689). The 2008 and subsequently reports of the QOF indicators revealed that more than 90% of the registered practices had nearly 90% of hypertensive patients with blood pressure levels below 150/90 mm Hg. The report also showed a reduction in inequalities of blood pressure control between practices located at different socio-economic strata (529).

Using the NICE target, practices located in the least deprived areas had a lower percentage of patients with controlled blood pressure than those located at the most deprived areas. This finding may differ from others reports shown that practices working at the most deprived areas had lower quality of care (608). However reductions in inequalities of care between socio-economic strata have been observed in England and also in Wandsworth (690-693). Therefore other factors different from socio-economic status may explain this finding. Population characteristics could account for that difference because patients registered with these practices were more likely to be younger, of other ethnic origin different from white and without cardiovascular comorbidity. Patients of black origin may have low adherence to antihypertensive interventions (464). Differences in dietary habits have been found between ethnic groups (466). South Asian people have been found to experience more psychosocial adversity than whites in the UK (694). That may result in additional cardiovascular risk (648, 694). They also tended to have lower physical activity (695). Consequently, the care provided by the practices may need a complementary approach taking into account the cultural background of its population.

The QOF indicators used for the assessment of blood pressure control in primary care may need revision. The small variations in blood pressure control rates between practices using the QOF target suggest that the QOF target may not be able to capture differences in blood pressure control rates between general practices. That could be attributed to the higher blood pressure threshold used as a target. A reduction in blood pressure levels has been observed in the UK according to the Health Survey for England. In 2006, overall mean blood pressures were 127.3/73.3 mmHg suggesting that most of the population have blood pressure levels below the QOF target (284). Hence the threshold may need a revision and in fact a consultation is ongoing to replace the current blood pressure level of 150/90 mmHg with 140/90 mmHg (605).

Lester H and Campbell S propose that one of the characteristics of QOF indicators is the capability of detecting variations in quality of care (279). Additionally, it has been argued that the QOF indicator may detract attention from improving reductions in hypertension cardiovascular risk for all hypertensive patients (696). Then the QOF indicator may be suitable as a proxy measure of the blood pressure control but more stringent measures may be needed. Moreover, Millet et al have proposed to develop targets regarding local and populations' characteristics. The development of local operational definitions of blood pressure control could improve the monitoring of the hypertension-related cardiovascular risk for all hypertensive patients at community level (697).

7.5 Strengths and weaknesses of the study

I have illustrated the utility of medical registers to assess the implications of two definitions of blood pressure control. As the conditions and patients included in clinical trials usually differ from those in routine clinical practice, information collected in that routine practice is an important resource to explain the discrepancies between both contexts. Moreover, the register included a large proportion of patients from ethnic minorities and women groups who are often under-represented in clinical trials (670, 698).

The study does however have several limitations. In line with observational studies, findings from this analysis may not always be generalised to patients with hypertension in other settings. The associations explored are only limited to the variables available in routine clinical data. The proportions of patients who achieved the blood pressure targets were derived from one blood pressure measurement. They could be overestimated or underestimated the number of PCH due to the variability of blood pressure levels (699-700). However, our findings such as the proportion of patients classified as PCH was consistent with other studies analysing QOF data (498).

7.6 Conclusion

I illustrated to what extent using targets can modify the concept of blood pressure control. The QOF target of 150/90 mm Hg produced higher blood pressure control rates than the NICE target of 140/90 mm Hg. Regardless of the target men over 65 years and over were more likely to be classified as a patient with controlled hypertension. Hypertensive patients with an additional cardiovascular comorbidity also were more likely to be classified as a patient with controlled hypertension. That may be due to the lower blood targets established in the national guidelines for the management of these patients. The observed differences in blood pressure levels between age, sex and ethnic origin may suggest the need for age, gender and ethnic orientation for the management of hypertensive patients in primary care.

The use of a target of 150/90 mm Hg may not accurately reveal differences in blood pressure control between general practices. In England there has been a constant reduction in blood pressure levels since 2000 so that a more stringent target may be needed. An approach using local blood pressure targets for geographical areas may contribute to improve blood pressure control in primary care.

Key points

- ✓ In England the 2004, 2006 and 2011 hypertension NICE recommend a blood pressure target equal or below 140/90 mmHg for hypertensive patients without cardiovascular comorbidity.
- ✓ In England the assessment of blood pressure control in primary care is based on the QOF indicators.
- ✓ The percentage of hypertensive patients with blood pressure equal to or below 150/90 mmHg is the QOF indicator for the assessment of blood pressure control in primary care.
- ✓ In 2007 among 15761 hypertensive patients registered with 28 practices located at Wandsworth, on overall 60.5% and 79.5% of patients were classified as patients with controlled hypertension by using the NICE target of 140/90 mmHg and the QOF target of 150/90 mmHg respectively.
- ✓ Regardless of the target used, men aged 65 years and over with additional cardiovascular comorbidity were more likely to have controlled hypertension.
- ✓ On overall, younger women were more likely to have controlled hypertension but the probability of having controlled hypertension decreased with age.
- ✓ Patients of South Asian origin had lower blood pressure levels than patients of other race/ethnic origin.
- ✓ Younger black patients had the highest levels of blood pressure
- ✓ By using the 150/90 mmHg target there were no differences in the percentage of patients with controlled hypertension between general practices.
- ✓ By using the 140/90 mmHg target the percentage of patients with controlled hypertension varied between practices.

Chapter 8 Impact of ethnic-specific guidelines for antihypertensive prescribing in primary care in England: longitudinal study

Providing hypertensive patients with appropriate drug therapy is essential for achieving blood pressure control. The reductions in blood pressure obtained from taking antihypertensive drugs lead to a lower risk of stroke and coronary events (139, 701). However, inappropriate management of hypertensive patients is recognized as one of the most important causes of poor blood pressure control (45, 702). The percentage of clinical visits in which physicians have not intensified the antihypertensive treatment for hypertensive patients with high blood pressure levels may vary between 20% and 45% (402, 404-406). Guidelines have been produced to summarize information on the management of hypertensive patients and help physicians to choose therapeutic treatment (13, 144, 703-705). This chapter explores the impact of the England national hypertension guidelines on drug therapy prescription.

8.1 Guidelines for the management of hypertension

The definition of clinical practice guidelines promulgated by the Institute of Medicine in 1992 was recently updated as "Clinical practice guidelines are statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options" (706-707). Thus clinical recommendations established in these guidelines should be evidence-based, prepared by a multidisciplinary team and taken into account the patient's preferences on treatment (706-708). The guidelines for the management of hypertension establish recommendations on the definition of hypertension, the use of antihypertensive drugs, the targets for blood pressure control and the non-pharmacological aspects on the management of hypertension (13, 144, 703-705). Since 1978, when the first WHO hyper-

tension report was launched (709) hypertension guidelines have proliferated worldwide. The current guidelines diverge in topics such as blood pressure thresholds to initiate therapy, the first line drug therapy recommendations and/or blood pressure targets for hypertensive patients on treatment (710-711).

Impact of hypertension guidelines

Evidence from interventional studies had shed light on the positive impact of implementing hypertension guidelines on the management of hypertension. In a longitudinal study conducted in an Italian primary care, Grandi et al tested the effect of training 588 general practitioners on the use hypertension guidelines. After nine months follow-up period, the rate of blood pressure control increased from 33.4% to 52.7% (712). This improvement was attributed to the use of guidelines because there were no others interventions occurring in the settings. Similar findings were revealed by Avanzini et al in a cohort study. They showed that whereas there was an increase in antihypertensive prescribing and lower blood pressure levels among hypertensive patients being treated in the intervened clinical settings, there were no significant variations in these outcomes among hypertensive patients being managed in clinical settings where hypertension guidelines were not implemented (713). The additional input of this study relied on the participation of general practitioners in the preparation of the guidelines. In a case-control study among patients being managed in private and public primary care, Allaire et al found that a continuing medical education program on using hypertension guidelines were associated with higher reductions in blood pressure levels (714).

The impact of hypertension guidelines on the management of hypertension has however been variable (473, 715-716). On the one hand, using hypertension guidelines has not always produced improvements on the management of hypertensive patients (451, 455, 473, 717-718). In Finland, there was no a significant increase in the percentage of patients with controlled hypertension after the introduction of the national guidelines (473), although the hypertension guidelines have been highly adopted (719). Also changes in prescribing patterns were not found after the introduction of the Finish guidelines (716). That observa-

tion may have been due to differences in the implementation of the Finnish hypertension guidelines across general practices (720). On the other hand, structured programs introducing hypertension guidelines have produced improvements on blood pressure control (280, 721-722). The implementation of the Canadian Hypertension Education Program, incorporating evidence-based hypertension guidelines, has produced an increase in both the percentage of patients with controlled hypertension and the percentage of hypertensive patients under hypertensive treatment (723-724). Similarly experiences from China, Japan and Catalonia also documented the positive impact of introducing national guidelines (451, 721, 725). Reductions in the number of patients without treatment also account for the positive results derived from the introduction of the guidelines. Additionally, physicians aware of hypertension guidelines are more likely to use lower thresholds of blood pressure for the management of hypertensive patients (409). By contrast lower adherence to guideline recommendations could lead to poor pressure control (726).

The inconsistencies in the impact of hypertension guidelines on blood pressure control have been attributed to different causes. The mentioned physician-related factors, patient-related conditions and the guideline implementation procedures may determine the effectiveness of the guidelines in clinical practice. Patient-related conditions are those which are impediments to the use of the recommendations established in the guidelines, for instance, having a terminal disease or intolerance to medications (727). The failures of the diffusion process may detract health workers from being aware of the local hypertension guidelines (715). Then poor adherence to established recommendations could be observed. In contrast providing physicians with continual education may improve the use of the guidelines (728-731). Similarly the use of computer-based clinical guidelines reminder systems has resulted in higher levels of adherence to the guideline-based recommendations (732). Hence, it seems that the effectiveness of guidelines is highly dependent on the methods used to implement and disseminate them among the potential users (451, 733-734). Additionally, a multidisciplinary approach including strategies targeting patient's behaviors may be needed to improve blood pressure control (735).

Guidelines are also tools to standardize the care of hypertensive patients at the primary care level (736-737). Observational studies have shown differences in the management of hypertension between localities in one geographical area (413). The percentage of hypertensive patients on drug therapy prescriptions varies even though they are managed under similar organizational health conditions. Hence, recommendations established in the guidelines have been used as criteria to measure the quality of care offered to hypertensive patients in primary care settings (738).

8.2 England guidelines for the management of hypertension in primary care

This section describes a summary of the antihypertensive drug treatments established in the English hypertensive guidelines. The topics related to hypertension definitions and blood pressure targets were described in chapter 3. Since 1993, when the first guidelines were published, modifications in drug therapy prescription have been produced (739). The British Hypertension Society (BHS) produced guidelines for the management of hypertension as an independent institution until 2004 afterwards the BHS has been part of the committee working with NICE to elaborate the national guidelines. The summary of changes is presented below (Table 32).

Table 32 Variations in antihypertensive therapy recommendations established in England hypertension guidelines

	1993 BHS	1999 BHS	2004 BHS	2004 NICE	2006 NICE	2011 NICE
First line monotherapy	For all patients: Beta-blocker or Diuretics	For all patients: Thiazide-type diuretic	For patients younger<55 years and non-black: A or B For patients Older>=55 years or Black: C or D	For all patients: Thiazide-type diuretic Consider beta-blocker for patients under 55 years	For patients younger<55 years and non-black: A For Older>=55 years or Black: C or D	For patients younger<55 years: A For patients aged over 55 years or black person of African or Caribbean family origin of any age: C
Addition of second line monotherapy	For all patients*: Calcium channel blockers ACE inhibitors Alfa-blockers	For all patients*: Alpha-blockers ACE inhibitors Alphall-antagonists Beta-blockers Calcium channels blockers	For all patients: A (or B) + C or D	For all patients: B or A	For all patients: A** + C or A** + D	For all patients: A + C
<p>* The list of the second line monotherapy does not imply any particular order for prescribing.</p> <p>A: ACE inhibitor or angiotensin receptor blocker (ARB) ; B: Beta-blocker; C: Calcium channel blocker; D: Diuretic</p> <p>** Considering ARB if ACE inhibitor intolerant</p>						

In essence the evolution of the guidelines has been towards providing hypertensive patients with treatment based on their characteristics. Since 2004 three patient groups have been considered by the national guidelines in England: patients under 55 years, patients aged 55 years and over and black patients of any age (740). The 2011 NICE guidelines called the latter group as Black person of African or Caribbean family origin of any age (144). The groups were based on the varying role of the renin-angiotensin system in the genesis of hypertension. Younger patients exhibit higher plasma renin activity (PRA) associated with high blood pressure but black patients and older patients have lower PRA (741-742). Patients with low PRA also have volume excess and those with high PRA exhibit high arteriolar vasoconstriction (743). Some studies revealed that ACEI and angiotensin receptor blockers (ARB) are associated with attaining lower blood pressure levels in patients with high PRA (744-746). In comparison, diuretics such as hydrochlorothiazide produce lower blood pressure levels in those with low PRA (747-748). However the cut-off age defining the variation in the role of PRA has been less well-established. Whereas a meta-analysis of 35 trials did not find differences in blood pressure reductions between antihypertensive drug class for patients aged 65 years and over compared with those below 55 years (142, 749-750), other clinical trials showed that in comparison with calcium channels blockers and diuretics, beta-blockers and ACEI produce significantly higher blood pressure reductions in younger patients of Caucasian origin (751-752).

The recommendations on the use of beta blockers and diuretics have also changed over time. Beta blockers were recommended as a first line treatment in the 1993, 1999 and 2004 BHS guidelines (500, 739, 753) but were downgraded in the 2006 NICE guidelines. The reported association between a long-term use of beta blockers and increases in the risk of diabetes may explain the change in the recommendation (754). Additionally some meta-analyses reported that comparing with other blood pressure lowering drugs beta blockers may have less efficacy in preventing stroke and other adverse cardiovascular outcomes (755-757). However, this observation has been questioned as the results may have varied including clinical trials with patients with different characteristics (139, 142). Diuretics were discouraged as a first line therapy for patients aged 55 years and older and black patients in the 2011 NICE guidelines (NICE). The decision was based on the assumption that diuretics are less effective in reducing cardiovascular events than calcium

channels blockers (240). This result has not always been replicated by other clinical studies comparing diuretics against calcium channel blocker (228, 504).

8.2.1 Impact of hypertension guidelines on the management of hypertension in England

The Health Survey for England reported that the proportion of hypertensive patients on treatment has increased from 48% in 2003 to 54% in 2006 (284). The surveys suggested that the guidelines may have had an impact on that change. I searched for studies assessing the impact of the England guidelines on drug therapy prescribing between 1999 and 2012 using MEDLINE and PUBMED sources (Table 33).

Table 33 Studies conducted in England showing the use of therapeutic recommendations established in the time-related hypertension guidelines between 1999 and 2012

Year	Type study	Results related to drug therapy prescription
2003 (531)	Longitudinal study	55% of patients were prescribed with diuretic or beta-blocker monotherapy. The recommendation established in the guideline.
2007 (758)	Cross sectional survey	62% of GPs reported not choosing the recommend drug despite being aware of the guideline. Between 12% and 25% of GPs considered that there are differences in the lowering pressure effect between antihypertensive drugs though the guideline postulated the opposite statement.
2011 (759)	Cohort study hypertensive patients with stroke	Between 1997 and 2006 the proportion of patients prescribed with guideline drug recommendations increased from 24% to 37%. Overall 31%. Using the recommended treatment was associated with lower recurrence of stroke.
2010 (760)	Analysis of the electronic Prescribing Analysis Cost Tool system	After the 2006 NICE hypertension guidelines there has been an increase in the number of younger<55 years prescribed with ACEI. The usage of calcium channels blockers also increased. There was a reduction in beta-blocker use.
2012(761)	Cross sectional study	44% of hypertensive patients were prescribed with the guideline recommended treatment.

In England there have been few studies assessing the impact of the guidelines on drug therapy prescribing. The studies mainly assessed adherence to the time-related guidelines (531, 758, 761). None of the studies reported a level of adherence higher than 60% to the recommendation established in the time-related guidelines. One study described the prescribing patterns over the period but it did not quantify the impact of the guidelines in the reported trend (759). This study also found that less than 50% of hypertensive patients were prescribed the recommended treatment (759).

To sum up, hypertension guidelines aim to improve blood control. The association between the introduction of the guidelines and blood pressure control varied across different studies. Because drug therapy prescribing is more likely to be influenced by the recommendations established in time-related guidelines, it has been used as indicator to measure the impact of the guidelines on the management of blood pressure. Generally low rates of physician adherence to drug therapy recommendations have been reported worldwide.

8.3 Study

Background

In England few studies have explored the association between antihypertensive drug prescribing and the implementation of the hypertension guidelines. I conducted a longitudinal study to explore the variations in antihypertensive drug prescribing in a cohort of hypertensive patients from the Wandsworth database. The cohort is formed of hypertensive patients who were registered with 28 general practices in Wandsworth from 1998 to 2007. Because the recommendations established in the guidelines are based on studies already published, I also aimed to assess the impact of the ethnic-specific recommendations introduced by the 2004 BHS guidelines and incorporated in the 2006 NICE guidelines on the first line recommended treatment prescribe by general practitioners over this period.

Secondary objectives

1. To describe variation in drug therapy prescribing between 1998 and 2007 among hypertensive patients managed in primary care
2. To determine variations in drug class monotherapy prescribing over the study period.
3. To describe variations in the recommended monotherapy drug prescribing across NICE patient groups over the study period.

8.3.1 Methods

I performed a retrospective longitudinal study to assess variations in antihypertensive prescribing among hypertensive patients treated in primary care between 1998 and 2007. For this analysis all hypertensive patients aged 17 years and over forming the retrospective cohort were included. The data contained information on the prescription of the following antihypertensive drug class: angiotensin converting enzyme inhibitors (ACEI), beta-blockers (BB), calcium channel blockers (CCB), and diuretics (DD). The drug prescription was recorded once each year for each patient as 0 for not prescribed and 1 for prescribed. Patients who had other additional cardiovascular comorbidity such as diabetes mellitus, coronary heart disease, stroke, atrial fibrillation, renal failure and heart failure were classified as a patient with an additional cardiovascular comorbidity.

I used the 2006 NICE first line antihypertensive recommendation as the reference to assess the use of the recommendations established in the guidelines (499) (Box 10). I quantified variations in drug prescription across the 3 main groups established in the 2006 NICE guidelines such as *black* for patients at all ages with black ethnicity, *younger non-black* for patients below 55 years with other ethnic origin different from black and *older non-black* for patients over 55 years with other ethnic origin different from black.

To examine variations in antihypertensive prescribing over the study period, I measured the following annual percentages a) the percentage of patients on antihypertensive treatment as the number of patients being prescribed no antihypertensive drug, one antihypertensive drug and two or more antihypertensive drugs over the total number of patients in each NICE patient group; b) the percentage of patients on ACEI, BB, CCB and DD monotherapy as number of patients prescribed each class drug over the number of patients on monotherapy in each NICE patient group; c) the annual percentage of patients on the recommended monotherapy as the number of patients prescribed the recommended monotherapy over the total number of patients on monotherapy in each NICE patient group. Because the recommendations established in the 2006 NICE guidelines applied to hyper-

tensive patients aged 18 years and over without other cardiovascular comorbidity, I included only this hypertensive patient category to calculate the last two percentages (Box 11).

Box 10 First line monotherapy treatment established in the 2006 NICE hypertension guidelines

NICE group	Younger than 55 years	55 years or older or Black at any age
First line monotherapy treatment	Angiotensin converting enzyme inhibitors (ACEI)	Calcium antagonist blockers (CCB) or diuretics (DD)

Box 11 Definition of the outcomes

Outcome	Description
Annual percentage of patients on antihypertensive treatment	Number of patients being prescribed no drug, one drug, two or more drugs by the total number of patients in each NICE group*100
Annual percentage of patients without other cardiovascular comorbidity on ACEI, BB, CCB and DD monotherapy	Number of patients prescribed each drug class as monotherapy by the number of patients on monotherapy in each NICE group*100.
Annual percentage of patients without other cardiovascular comorbidity on the first line NICE recommended monotherapy	Number of patients prescribed the first line recommended monotherapy by the total number of patients on monotherapy in each NICE group*100

Statistical methods

The characteristics of patients were presented as mean values or percentages where appropriate. The analysis of the outcomes was separately conducted for all registered patients and newly registered patients.

Unadjusted trend analysis for the percentage of hypertensive patients being prescribed antihypertensive treatment, the percentage of those on antihypertensive drug class and the percentage of those on the first line NICE recommended monotherapy between 1998 and 2007 was performed using the chi-Squared Stata test for trend assessment. The analysis was separately conducted for newly registered patients and all registered patients (762).

Models for all included patients

Variations in drug class monotherapy prescribing were assessed using generalized estimating equation (GEE) regression models. The models were selected to take into account the potential correlation among drug prescriptions for each individual over the time (763-764). Because the GEE models estimate variations in the outcomes at group level, they allow to measure the impact of interventions on subgroups exposed to an intervention over time (765). Models were performed separately for all registered patients in each NICE patient group. Only patients without cardiovascular comorbidity were included in this analysis as the NICE recommendations applied to this patient group.

The GEE models were run using logit function to measure variation in the odds of being prescribing each antihypertensive drug class as a monotherapy over the period. The models were adjusted for the introduction of the BHS and NICE guidelines. The effect of the NICE guideline was measured by including a dummy variable with levels 0 and 1 representing the before (1998-2005 years) and after (2006-2007 years) periods respectively. Similarly, for the introduction of BHS guideline in 2004 a value of 0 was assigned for years between 1998 and 2003 and 1 for 2004 and afterwards.

A logistic regression (population-average logistic regression GEE) was performed to assess the variation in the odds ratio of being prescribed the first line NICE recommended

treatment over the study period. The models take into account the correlation occurring in repeated measurements over time (766-768). For this model, the binary outcome variable was the prescription of the first line recommended monotherapy for each hypertensive patient regarding the NICE guideline recommendation. I adjusted the model for the inclusion of NICE and BHS guidelines as I did in the GEE models. The variation of the recommended prescription in time was assessed by including year as a continuous variable. The model was adjusted for sex using a dummy variable. An interaction term between the NICE introduction and each NICE patient group was also included.

Models for newly registered patients

Data from the newly registered hypertensive patients is independent because the patient is registered with the data only once over the period. For these patients a logistic regression was run to test variation in the odds of being prescribing each antihypertensive drug class as monotherapy. The analysis was performed without divided patients into NICE patient groups because the small number of individuals in some groups. The models were adjusted for the inclusion of BHS and NICE guidelines as I did for the GEE models.

A logistic regression model with standard errors adjusted for practice clustering was performed to assess the variation in the odds ratio of being prescribed the first line recommended treatment over the period (768). The model included the explanatory variables as I did in the logistic model for all included patients

The statistical model

The mathematical formulation was

$$Y = \beta * t + \beta_1 * BHS + \beta_2 * NICE$$

The $\beta * t$ was the term used to adjust for the baseline trend of Odds ratio prescribing so that the other variations in the trend prescribing could be attributed to the introduction of whichever guidelines.

β_1 represents the coefficient for the introduction of the BHS guidelines

β_2 represents the coefficient for the introduction of the NICE guidelines

The data was analyzed using STATA version 11 (Stata Corporation, College Station, TX, USA).

8.3.2 Results

17245 hypertensive patients registered in 2007 formed the retrospective cohort. Among them 9510 (55.4%) were female, 9085 (68.29%) White, and 10179 (50.2%) were 55 years and over. The frequency of associated cardiovascular comorbidities was diabetes in 3519 (20.4%), coronary heart disease in 1889 (10.9%), stroke in 1212 (7.0%), atrial fibrillation in 793 (4.6%), renal failure in 707 (4.1%) and heart failure in 412 (2.4%). The presence of other cardiovascular comorbidity was higher in older non-black patients than in others NICE patient groups (Table 34).

Table 34 Patients characteristics by NICE patient groups, 2007

	Black patients	<55 years*	>= 55years*	Total
Number of Patients number (%)	3926	3140	10179	17245
Mean age (sd)	60.4 (13.2)	44.7 (7.7)	70.9 (9.9)	14.4)
Male no. (%)	1588 (40.5)	1685 (53.7)	4462 (43.8)	7735 (44.9)
Ethnicity different from Black number (%)				
White		1936 (61.7)	7149 (70.2)	9085 (68.2)
South Asian		403 (12.8)	1153 (11.3)	1556 (11.7)
Other Asian		160 (5.1)	434 (4.3)	594 (4.5)
Other Ethnicity		247 (7.9)	525 (5.2)	772 (5.8)
Unknwon		394 (12.6)	918 (9.0)	1312 (9.9)
Presence of cardiovascular comorbidity				
No	2517 (64.1)	2549 (81.2)	5892 (57.9)	10958 (63.5)
Yes	1409 (35.9)	591 (18.8)	4287 (42.1)	6287 (36.5)

% Indicate proportion

sd Standard deviation

** Patients with one or more than of the follow diseases: coronary heart disease, diabetes mellitus, heart failure, atrial fibrillation or stroke

*Included those of white, Asian Other Asian origin, Other ethnic origin and unknown origin

Intensity of treatment

All hypertensive patients

Between 1998 and 2007, there was an increase in the percentage of patients who were prescribed antihypertensive medication. Thus the percentage of patients not being prescribed antihypertensive medication decreased from 49.0% in 1998 to 14.8% in 2007 ($p < 0.0001$ for annual trend). By contrast, the percentage of patients being prescribed two or more antihypertensive medication increased from 21.2% in 1998 to 54.7 in 2007 ($p < 0.0001$ for annual trend). The percentage of patients on antihypertensive monotherapy slightly changed though significantly over the period (Table 35 Figure 17).

Figure 17 Variation in the proportion of all include patients on antihypertensive treatment, between 1998 and 2007

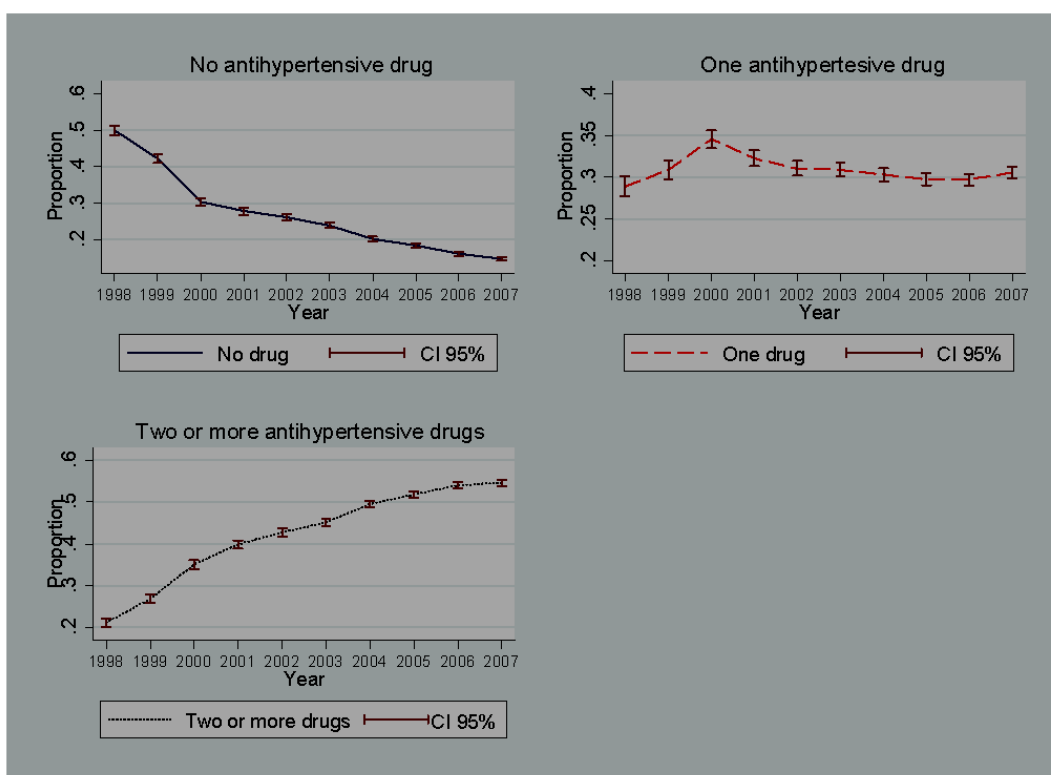


Table 35 Variation in percentages of all hypertensive patients on antihypertensive treatment between 1998 and 2007

	1998	2007	
	% (Number)‡	% (Number)	p value *
Younger non black patients**			
No drug therapy	60.8 (798)	31.7 (994)	<0.0001
One antihypertensive drug	25.9 (341)	32.5 (1020)	0.0003
Two or more antihypertensive drugs	13.2 (173)	35.9 (1126)	<0.0001
Total	1312	3140	
Black patients			
No drug therapy	48.6 (678)	13.5 (531)	<0.0001
One antihypertensive drug	25.7 (358)	28.5 (1115)	0.804
Two or more antihypertensive drugs	25.7 (359)	58.1 (2280)	<0.0001
Total	1395	3926	
Older non black patients**			
No drug therapy	45.8 (1390)	10.0 (1019)	<0.0001
One antihypertensive drug	31.7 (962)	30.9 (3140)	<0.0001
Two or more antihypertensive drugs	22.5 (684)	59.2 (6020)	<0.0001
Total	3036	10179	
All included			
No drug therapy	49.0 (2866)	14.8 (2544)	<0.0001
One antihypertensive drug	28.9 (1661)	30.6 (5275)	0.0001
Two or more antihypertensive drugs	21.2 (1216)	54.7 (9426)	<0.0001
Total	5743	17245	

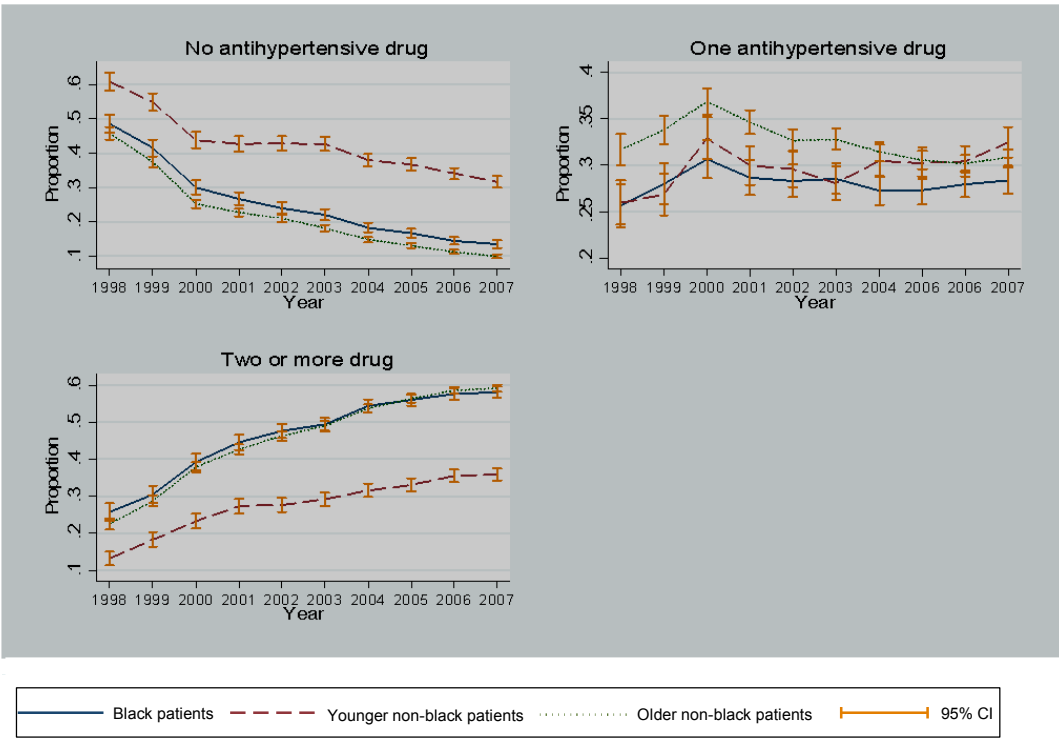
**Included those of White, Asian, Other Asian and other and unknown ethnicity origin

‡ Percentage = number of patients in each prescribing category/ total patient-group in each year*100

*p value for annual variation

Over the study period the percentage of black patients on antihypertensive treatment also increased. The percentage of black patients without antihypertensive medication decreased from 48.6% in 1998 to 13.5% in 2007 ($p < 0.0001$ for annual trend). A constant increase in the percentage of black patients being prescribed two or more antihypertensive drugs was observed from 25.7% in 1998 to 58.1% in 2007 ($p < 0.0001$ for annual trend). There was no a significant variation in the percentage of black patients on antihypertensive monotherapy (Table 35, Figure 18).

Figure 18 Variation in the proportion of all patients on antihypertensive treatment by NICE groups between 1998 and 2007



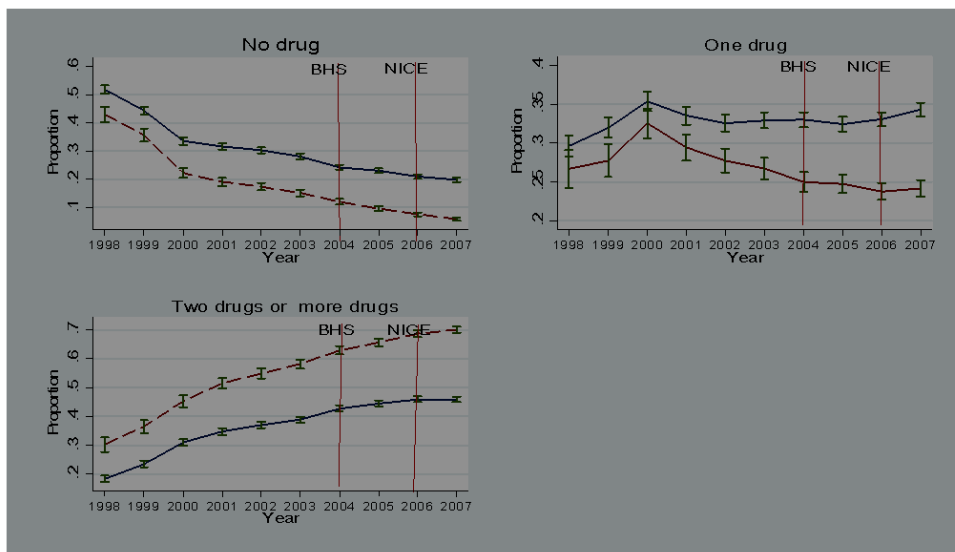
Percentage: number of patients on monotherapy /total of patients on monotherapy in each patient group by drug classes
Vertical line indicated the introduction year of the BHS and NICE guidelines
*Patients without one of the follow diseases coronary heart disease, diabetes mellitus, heart failure, atrial fibrillation, stroke or renal failure

Similarly, the percentage of younger non-black patients on antihypertensive medication increased between 1997 and 2008. Thus, the percentage of younger non-black patients without antihypertensive medication decreased from 60.8% in 1998 to 31.7% in 2007 ($p<0.0001$ for annual trend). By comparison, there were an increase in the percentages of younger non-black patients being prescribed one antihypertensive drug and two drugs, from 25.9% to 32.5% and from 13.2% to 35.9% ($p=0.003$ and $p<0.0001$ for annual trend) respectively. (Table 35 Figure 18)

From 1998 to 2007 for older non-black patients the variation in antihypertensive prescribing changed as follows: the percentage of those not being prescribed antihypertensive medication decreased from 45.8% in 1998 to 10.0% in 2007 ($p<0.0001$ for annual trend), the percentage of patients on two or more antihypertensive drugs increased from 22.5% in 1998 to 59.2% in 2007 ($p<0.0001$). The percentage of patients being prescribed one antihypertensive varied from 31.7% in 1997 to 30.9% in 2008 ($p<0.0001$). Although the percentages were similar, a trend tend to reduce the percentage of patients on monotherapy prescribing was observed (Table 35 Figure 18).

Over the period hypertensive patients with another cardiovascular comorbidity were more likely to receive more antihypertensive medication in comparison with those without other cardiovascular comorbidity. However there was an increase in the percentage of patients being prescribed antihypertensive medication for both groups. For patients registered as having cardiovascular comorbidities the percentage of those without antihypertensive medication decreased from 43.0% in 1998 to 5.9% in 2007 ($p<0.0001$ for annual trend) and the percentage of those being prescribed two or more medication increased from 30.3% in 1998 to 69.9% in 2007 ($p<0.0001$ for annual trend). There was small but statistical significant reduction in the percentage of patient on antihypertensive monotherapy prescription from 26.7% 1998 to 24.2% in 2007 ($p<0.0001$ for annual trend) (Table 36 Figure 19).

Figure 19 Variation in the proportion of all patients on antihypertensive treatment by presence of cardiovascular comorbidity between 1998 an 2007



— No comorbidity - - - With comorbidity — 95% CI

Table 36 Variation in percentages of all hypertensive patients on antihypertensive treatment by presence of cardiovascular comorbidity between 1998 and 2007

	1998	2007	
	% (Number)‡	% (Number)	p value
Patients without comorbidity*			
No drug	51.9 (2306)	2175 (19.8)	<0.0001
One antihypertensive drug	1314 (29.6)	3757 (34.3)	0.0066
Two or more antihypertensive drugs	821(18.5)	5026 (45.9)	<0.0001
Total	4441	10958	
Patients with comorbidity			
No drug	560 (43.0)	369 (5.9)	<0.0001
One antihypertensive drug	347 (26.7)	1518 (24.2)	<0.0001
Two or more antihypertensive drugs	395 (30.3)	4400 (69.9)	<0.001
Total	1302	6287	
Total	5743	17245	

* Patients with at least one of the follow disease: coronary heart disease, diabetes mellitus, heart failure, atrial fibrillation, stroke or renal

‡ Percentage = number of patients in each prescribing category/ total patient-group in each year*100

*p value for annual variation

Newly hypertensive registered patients

As for all registered patients, the percentages of newly registered patients being prescribed antihypertensive medication increased over the study period. Thus, an overall the percentage of newly registered patients without antihypertensive medication decreased from 49.6% to 18.4% ($p < 0.0001$ for annual variation). Both the percentage of newly registered patient on one antihypertensive drug and on two or more medication increased from 30.8% to 47.8% and from 19.7% to 33.8% respectively over the study period ($p < 0.0001$ annual trend for both). (Table 37 Figure 20)

From 1998 to 2007 the variation in antihypertensive prescribing for black patients changed; the percentage of those not being prescribed antihypertensive drug dropped from 46.5% to 17.9% ($p < 0.0001$ annual trend), the percentage of those on one antihypertensive increased from 29.7% to 45.2% ($p = 0.0001$ for annual trend) and the percentage of those on two or more antihypertensive medication increased from 23.9% to 36.9% ($p = 0.0087$ for annual trend).

Over the study period the prescribing patterns significantly changed for newly registered younger non-black patients. A significant reduction in the percentage of those not being prescribed medication was present from 62.1% in 1998 to 27.0% in 2007 ($p < 0.0001$ for annual trend). The percentage of patients prescribed two or more antihypertensive drugs increased from 10.9% to 24.8% ($p < 0.0001$ for annual trend).

Similar variations were observed in newly registered older non-black patients. In 1998, 42.8% of them were not prescribed any antihypertensive drugs, with 33.7% were prescribed only one antihypertensive, and 23.5% prescribed two or more antihypertensive medications. In 2007 by contrast, only 11.2% of newly registered older non-black hypertensive patients were not prescribed any antihypertensive medications, 48.6% were prescribed one antihypertensive and 40.2% were prescribed two or more antihypertensive medications. These variations were statistically significant over the period ($p < 0.0001$ for annual trend for all).

Table 37 Variation in percentages of newly* registered hypertensive patients on antihypertensive treatment between 1998 and 2007

		1998	2007	
		% (Number)‡	% (Number)	p value
Younger non black**				
	number (%)‡			
No drug therapy		62.1 (143)	27.0 (108)	<0.0001
One antihypertensive drug		26.9 (62)	48.3 (193)	<0.0001
Two or more antihypertensive drugs		10.9 (25)	24.8 (99)	<0.0001
Total		230	400	
Black				
	number (%)			
No drug therapy		46.5 (72)	17.9 (41)	<0.0001
One antihypertensive drug		29.7 (46)	45.2 (103)	0.0001
Two or more antihypertensive drugs		23.9 (37)	36.9 (84)	0.0087
Total		155	228	
Older non-black **				
	number (%)			
No drug therapy		42.8 (151)	11.2 (53)	<0.0001
One antihypertensive drug		33.7 (119)	48.6 (225)	<0.0001
Two or more antihypertensive drugs		23.5 (83)	40.2 (186)	<0.0001
Total		353	463	
All newly registered				
No drug therapy		49.6 (366)	18.4 (201)	<0.0001
One antihypertensive drug		30.8 (227)	47.8 (521)	<0.0001
Two or more antihypertensive drugs		19.7 (145)	33.8 (369)	<0.0001
Total		738	1091	

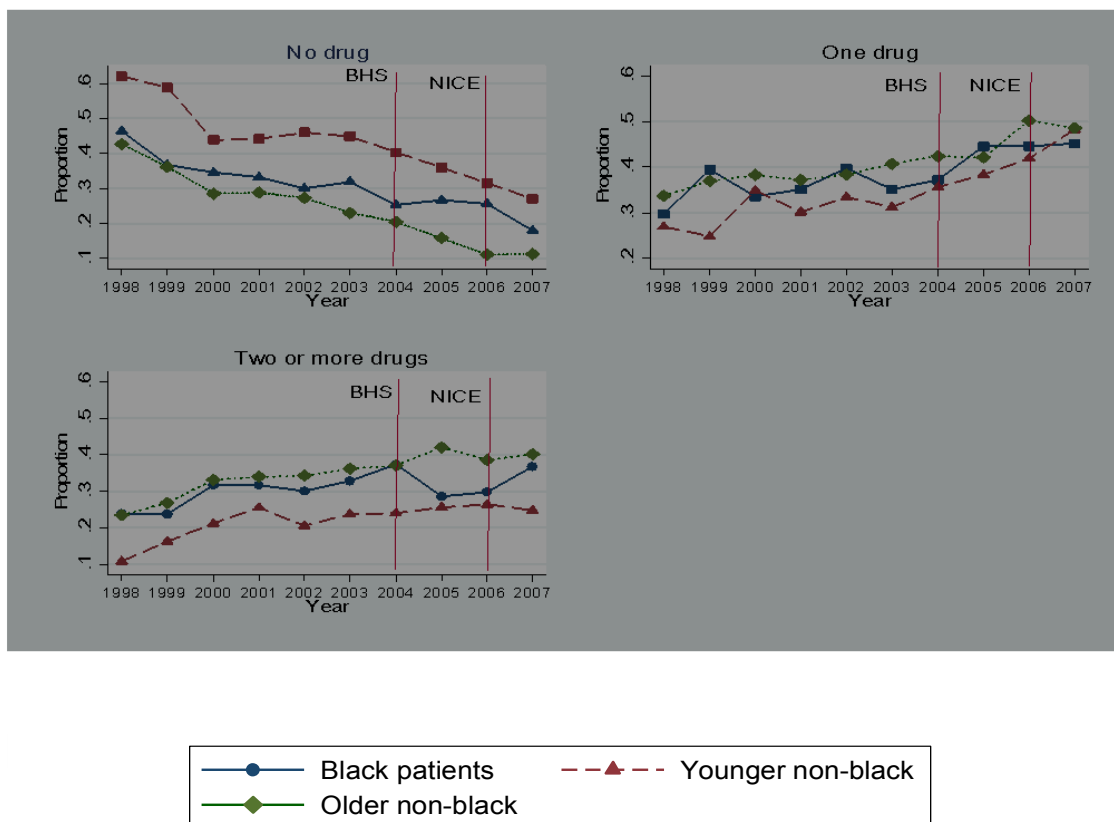
*Patients first time registered with hypertension diagnosis over the referred year

**Included those with White, Asian, Other Asian and other ethnicity origin

‡ Percentage = number of patients in each prescribing category/ total patient-group in each year*100

*p value for annual variation

Figure 20 Variations in the percentage on antihypertensive treatment in newly registered patients between 1998 and 2007



Newly hypertensive patients with additional cardiovascular comorbidity were more likely to be on antihypertensive treatment over the period. For this group, there was a decrease in the percentage of those not having antihypertensive drug from 36.2% in 1998 to 6.4% in 2007 ($p<0.0001$). Consequently the percentage of those on two or more drugs significantly increased from 29.5% to 55.9% ($p<0.0001$) over the period. However there was no a significant variation in the percentage of those prescribed one antihypertensive medication. In comparison, the percentage of hypertensive patients without cardiovascular comorbidity prescribed with one antihypertensive treatment significantly increased from 29.8 in 1998 to 50.1% in 2007 ($p<0.0001$ for annual trend) (Table 38 Figure 5).

Table 38 Variation in the percentage of newly* hypertensive patients on anti-hypertensive treatment by comorbidity between 1998 and 2007

	1998	2007	
	% (Number)‡	% (Number)	p value***
Patients without comorbidity**			
No drug	52.8 (312)	21.2 (188)	<0.0001
One antihypertensive drug	29.8 (176)	50.1 (445)	<0.0001
Two or more antihypertensive drugs	17.2 (101)	28.8 (256)	<0.0001
Total	589	889	
Patients with comorbidity			
No drug	36.2 (54)	6.4 (13)	<0.0001
One antihypertensive drug	34.2 (51)	37.6 (76)	0.2067
Two or more antihypertensive drugs	29.5 (44)	55.9 (113)	<0.0001
Total	149	202	
Total	738	1091	

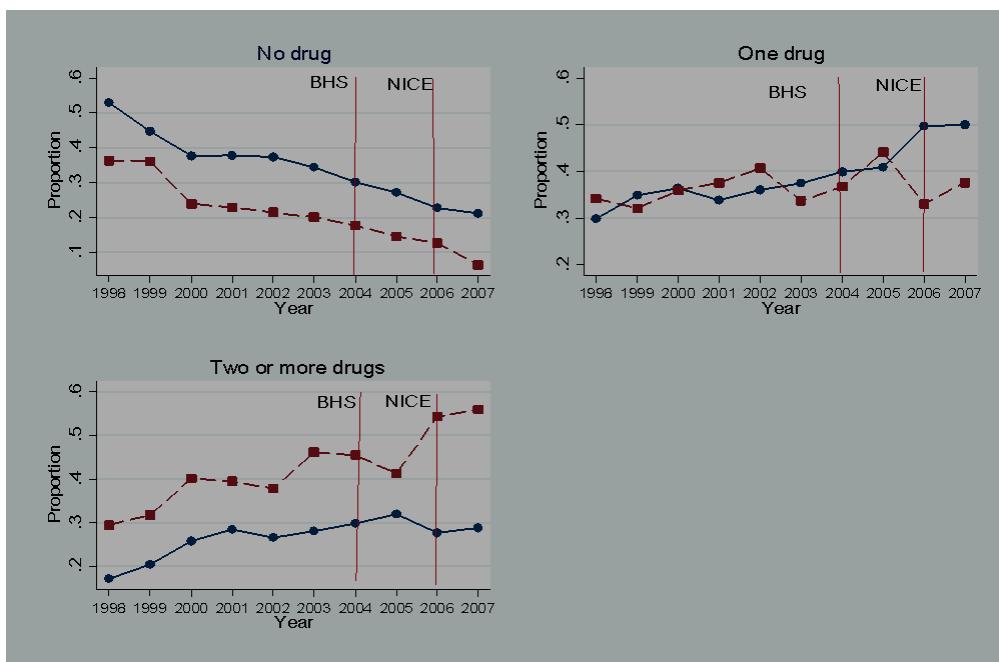
** Patients with at least one of the follow disease: coronary heart disease, diabetes mellitus, heart failure, atrial fibrillation, stroke or renal failure

‡ Percentage = number of patients in each prescribing category/ total patient-group in each year*100

***p value for annual variation

*Patients first time registered with hypertension diagnosis over the referred year

Figure 21 Variation in the percentage of newly registered patients on anti-hypertensive treatment by comorbidity



—●— No comorbidity - - ■ - - With comorbidity

Summary intensity of treatment

To sum up from 1997 to 2008 there was an increase in the percentage of patients on anti-hypertensive treatment. The increase was observed in both newly and all hypertensive patients registered with general practices. The greatest increase was observed in younger non-black patients. Patients with additional cardiovascular comorbidity were more likely to receive more than one hypertensive medication.

Variations in antihypertensive drug class monotherapy prescribing among patients without cardiovascular comorbidity

All patients

ACEI

Between 1998 and 2007, the use of ACEI monotherapy varied as follows: in younger non-black patients from 25.3% to 52.3% ($p < 0.0001$ for annual trend), in older non-black patients from 16.9% in 1998 to 32.6% ($p < 0.0001$ for annual trend) and in black patients from 9.6% to 11.7% ($p = 0.2106$ for annual trend). The GEE models revealed that for younger non-black patients and older non-black patients, the introduction of the NICE guidelines was associated with an additional increase in ACEI prescribing odds ratio 1.2 (95% CI 1.07 – 1.34) ($p < 0.0001$) and odds ratio 1.07 (95% CI 1.01 – 1.14) ($p < 0.0001$) respectively. For black patients, there was no significant change odds ratio 1.06 (95% CI 0.93-1.22) ($p = 0.370$). Over the period, younger non-black patients were more likely to be on ACEI monotherapy and an additional increase in its prescription for this NICE patient group was observed after the introduction of the NICE guidelines (Figure 22 Table 39-40).

Beta blockers

During 1998-2007, there has been a reduction in the use of beta blockers as monotherapy for all NICE patient groups. The percentage of younger non-black patients on beta blocker monotherapy decreased from 33.9% to 12.3%, ($p < 0.0001$ for annual trend); from 25.8% to 11.1% in older non-black patients, ($p < 0.0001$ for annual trend) and from 22.4% to 5.6%, ($p < 0.0001$ for annual trend) in black patients. The GEE models also showed that the introduction of NICE guidelines was associated with an additional reduction in the beta-blockers prescribing, with odds ratio 0.56 (95% CI 0.44 – 0.70) ($p = 0.003$), 0.52 (95% CI 0.42 – 0.65) ($p < 0.0001$) and 0.88 (95% CI 0.81 – 0.94) ($p < 0.001$) for black patients, younger non-black patients and older non-black patients respectively.

Calcium channel blockers

There was a significant increase in the percentage of black patients on CCB monotherapy from 46.6% in 1998 to 58.3% in 2007 ($p = 0.0001$ for annual trend). The percentage slightly changed from 22.5% in 1998 and 23.4% in 2007 in younger non-black ($p = 0.096$ for annual trend) and from 22.7% to 30.5% ($p = 0.0144$) for annual trend) in older non-black patients. There was a significant contribution of the NICE guidelines to the use of CCB as obtained from the GEE models. Thus, the odds ratio associated with the introduction of the NICE guidelines was 1.20 (95% CI 1.08 – 1.32) ($p < 0.0001$), 1.17 (95% CI 1.02 – 1.35) ($p = 0.023$) and 1.07 (1.01 – 1.13) ($p = 0.001$) for black patients, younger non-black patients and older non-black patients respectively.

Diuretics

The percentage of black patients on DD monotherapy was 21.4% in 1998 and 24.4% in 2007 ($p = 0.0124$ for annual trend). There were fluctuations in the trend over period with a slightly increase in the percentage in 2005. The percentage changed from 18.3% to 11.9% ($p = 0.010$ for annual trend) in younger non-black patients and from 29.6% to 25.9% ($p = 0.0419$ for annual trend) in older non-black patients. The GEE models showed that the introduction of the NICE guidelines led to an additional reduction in the use of diuretics,

odds ratio 0.74 (95% CI 0.62 – 0.87) ($p=0.001$), 0.70 (95% CI 0.62 – 0.80) ($p<0.001$) and 0.92 (95% CI 0.87 – 0.97) ($p=0.007$) for black patients, younger non-black patients, and older non-black patients respectively.

Table 39 Variation in percentages of all antihypertensive patients on anti-hypertensive drug monotherapy between 1998 and 2007

	1997	2008	
	% (Number)	% (Number)	p value*
Younger non black**			
ACEI	25.3 (73)	52.3 (441)	<0.0001
BB	33.9 (98)	12.3 (104)	<0.0001
CCB	22.5 (65)	23.5 (198)	0.0096
DD	18.3 (53)	11.9 (101)	0.0095
Total	289	844	
Black number (%)			
ACEI	9.6 (27)	11.8 (97)	0.2106
BB	22.4 (63)	5.6 (46)	<0.0001
CCB	46.6 (131)	58.3 (480)	0.0001
DD	21.4 (60)	24.4 (201)	0.0124
Total	281	824	
Older non-black ** number (%)			
ACEI	126 (16.9)	32.6 (681)	<0.0001
BB	192 (25.8)	11.1 (232)	<0.0001
CCB	206 (27.8)	30.5 (636)	0.0144
DD	220 (29.6)	25.8 (540)	0.0419
Total	744	2089	
Total number (%)			
ACEI	17.2 (226)	32.5 (1219)	<0.0001
BB	26.9 (353)	10.7 (382)	<0.0001
CCB	30.6(402)	34.9 (1314)	0.0055
DD	25.3 (333)	22.4 (842)	0.1158
Total	1314	3757	

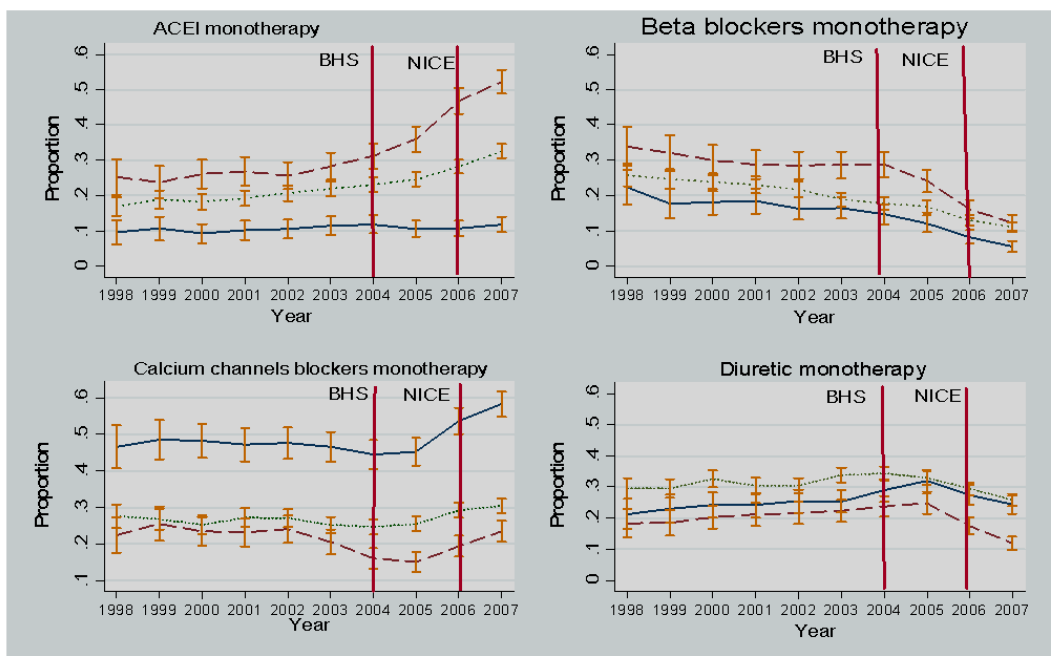
**Included those of White, Asian, Other Asian and other ethnicity origin

‡ Percentage = number of patients in each drug category/ total patient-group in each year*100

ACEI : Angiotensin-converting enzyme inhibitor BB Beta blockers CCB Calcium channel blockers DD Diuretic

* p value for trend

Figure 22 Variation in the percentage hypertensive patients on drug monotherapy class from 1998 to 2007



— Black patients — Younger non-black patients Older non-black patients — 95% CI
 Percentage: number of patients on monotherapy/total patients on monotherapy in each group drug category
 Vertical line indicated the introduction year of the BHS and NICE guidelines

Table 40 Variation in the odds of being prescribed antihypertensive drug class in each NICE patient group between 1998 and 2007

ACEI monotherapy												
	Black patients				Younger non-black<55				Older non-black>=55			
	Odds ratio	CI 95%	p value		Odds ratio	CI 95%	p value		Odds ratio	CI 95%	p value	
Year ‡	1.00	0.98	1.03	0.557	1.11	1.08	1.13	<0.0001	1.06	1.05	1.08	<0.0001
	Odds ratio	CI 95%	p value		Odds ratio	CI 95%	p value		Odds ratio	CI 95%	p value	
Year	1.00	0.95	1.04	0.920	1.08	1.04	1.12	<0.0001	1.06	1.04	1.08	<0.0001
NICE**	1.06	0.93	1.22	0.370	1.20	1.07	1.34	<0.0001	1.07	1.01	1.14	0.029
Reference												
Period before introduction 1998-2005												
BHS***	0.98	0.84	1.14	0.804	0.98	0.88	1.09	0.795	0.97	0.91	1.03	0.306
Reference												
Period before introduction 1998-2003												
Beta blockers monotherapy												
	Black patients				Younger non-black<55				Older non-black>=55			
	Odds ratio	CI 95%	p value		Odds ratio	CI 95%	p value		Odds ratio	CI 95%	p value	
Year ‡	0.87	0.84 - 0.89	<0.0001		0.88	0.86	0.91	<0.0001	0.94	0.93	0.96	<0.0001
	Odds ratio	CI 95%	p value		Odds ratio	CI 95%	p value		Odds ratio	CI 95%	p value	
Year	0.93	0.88 - 0.98	0.014		0.94	0.89	0.9800	0.017	0.96	0.93	0.98	0.001
NICE	0.56	0.44 - 0.70	0.003		0.52	0.42	0.65	<0.0001	0.88	0.81	0.94	<0.0001
Reference												
Period before introduction 1998-2005												
BHS	0.92	0.73 - 1.15	0.488		1.06	0.86	1.30	0.555	1.00	0.93	1.06	0.99
Reference												
Period before introduction 1998-2003												
Calcium channel blockers monotherapy												
	Black patients				Younger non-black<55				Older non-black>=55			
	Odds ratio	CI 95%	p value		Odds ratio	CI 95%	p value		Odds ratio	CI 95%	p value	
Year ‡	1.06	1.04 - 1.08	<0.0001		1.01	0.98	1.03	0.303	1.02	1.00	1.03	0.001
	Odds ratio	CI 95%	p value		Odds ratio	CI 95%	p value		Odds ratio	CI 95%	p value	
Year	1.04	1.00 - 1.07	0.010		1.01	0.97	1.06	0.505	1.01	0.99	1.03	0.191
NICE	1.20	1.08 - 1.32	<0.0001		1.17	1.02	1.35	0.023	1.07	1.01	1.13	0.018
Reference												
Period before introduction 1998-2005												
BHS	0.97	0.88 - 1.07	0.564		0.86	0.76	0.98	0.320	1.00	0.94	1.06	0.914
Reference												
Period before introduction 1998-2003												
Diuretic monotherapy												
	Black patients				Younger non-black<55				Older non-black>=55			
	Odds ratio	CI 95%	p value		Odds ratio	CI 95%	p value		Odds ratio	CI 95%	p value	
Year ‡	1.03	0.99 - 1.06	0.067		0.95	0.93	0.97	<0.0001	0.96	0.95	0.97	<0.0001
	Odds ratio	CI 95%	p value		Odds ratio	CI 95%	p value		Odds ratio	CI 95%	p value	
Year	1.03	0.98 - 1.09	0.208		0.99	0.96	1.02	0.729	0.97	0.95	0.99	0.007
NICE	0.74	0.62 - 0.87	0.001		0.70	0.62	0.80	<0.0001	0.92	0.87	0.97	0.007
Reference												
Period before introduction 1998-2005												
BHS	1.21	0.99 - 1.47	0.054		0.99	0.87	1.12	0.913	1.01	0.96	1.07	0.576
Reference												
Period before introduction 1998-2003												

*Patients without cardiovascular comorbidity such as diabetes mellitus, stroke, atrial fibrillation, heart failure, renal failure or coronary heart disease

**NICE variable for the introduction of 2006 NICE guideline

***BHS variable for the introduction of 2004 BHS guideline

‡Overall trend without adjustment

Newly registered patients

ACEI

Over the period ACEI was the most common antihypertensive prescribed as monotherapy among the newly registered hypertensive patients. The use increased from 14.7% to 37.5% ($p < 0.0001$ for annual variation). The percentage in use started changing after the introduction of the 2004 BHS guideline. The logistic model showed an additional increase in the use of was observed after the introduction of NICE guidelines, odds ratio 1.61 (95% CI 1.29 – 2.01) ($p < 0.0001$). The observed increase in use was mainly due variations occurring at the end of the 10 year period (Figure 23, Table 41-42).

Beta blockers

Between 1998 and 2007 the usage of beta blockers as monotherapy has significantly dropped from 27.3% to 5.2% ($p < 0.0001$) among newly registered hypertensive patients. An additional decrease was observed in the period after the introduction of the NICE guidelines, odds ratio 0.36 (95% CI 0.26 – 0.52) ($p < 0.0001$) (Figure 23, Table 41-42).

Calcium channels blockers

From 1998 to 2007 the percentage of newly registered patients on CCB monotherapy increased from 25.0% to 45.2% ($p < 0.0001$ for annual trend). Between 1998 and 2003 the use remained stable. Then a sharply rise in use was observed coincident with the introduction of the 2004 BHS guidelines. Finally after the introduction of the NICE guidelines, there was an additional increase in the prescribing of CCB as monotherapy, odds ratio 2.93 (95% CI 2.36 – 3.65) ($p < 0.0001$). The overall increase in CCB use was mainly produced by the growth observed at the end of the period (Figure 23, Table 41-42)

Diuretics

The prescribing of diuretics as monotherapy declined from 32.9% to 12.1% ($p < 0.0001$) annual trend). The percentage of newly registered on DD monotherapy remained nearly stable from 1998 to 2004. Afterwards the percentage steeply declined which as associated with the introduction of the NICE guidelines. Thus, the odds ratio of being prescribed DD was OR 0.27 (95% CI 0.22 – 0.34) ($p < 0.001$) after the introduction of the NICE guidelines. The decline in the use of diuretics was mainly marked at the end of the period.

Summary monotherapy drug class prescribing

To summarize from 1998 to 2007 the most noticeable variation in drug class prescribing has been the decline in the use of the beta blocker as monotherapy in all NICE patient groups. ACEI has been the most frequently antihypertensive prescribed as monotherapy mainly for younger non-black and older non-black. CCB has been the most common monotherapy used for black patients. After the introduction of the NICE guidelines the following variations in drug class monotherapy were quantified: a significant increase in the ACE use in younger non-black and older, an additional decrease in the usage of BB in all NICE groups, a higher use in CCB in all NICE groups and additional decrease in the use of DD.

Table 41 Variation in the percentage of newly* registered patients on drug monotherapy class between 1998 and 2007

		1998	2007	
		% (Number)‡	% (Number)	p value
Younger non black**				
	number (%)‡			
ACEI		19.2 (10)	57.4 (101)	<0.0001
BB		42.3 (22)	7.4 (13)	<0.0001
CCB		17.3 (9)	31.2 (55)	0.0663
DD		21.2 (11)	3.9 (7)	0.0001
Total		52	176	
Black				
	number (%)			
ACEI		10.5 (4)	8.1 (7)	0.764
BB		15.8 (6)	5.8 (5)	0.0082
CCB		42.1 (16)	67.4 (58)	0.0019
DD		31.6 (12)	18.6 (16)	0.0902
Total		38	86	
Older non-black **				
	number (%)			
ACEI		13.9 (12)	32.2 (59)	<0.0001
BB		23.3 (20)	2.7 (5)	<0.0001
CCB		22.1 (19)	48.1 (88)	<0.0001
DD		40.7 (30)	16.9 (31)	0.0005
Total		86	183	
Total				
	number (%)			
ACEI		14.7 (26)	37.5 (167)	<0.0001
BB		27.3 (48)	5.2 (23)	<0.0001
CCB		25.0 (44)	45.2 (201)	<0.0001
DD		32.9 (58)	12.1 (54)	<0.0001
Total		176	445	

*Patients first time registered with hypertension diagnosis over the referred year

**Included those with White, Asian, Other Asian and other ethnicity origin

‡ Percentage = number of patients in each drug category/ total patient-group in each year*100

ACEI : Angiotensin-converting enzyme inhibitor BB Beta blockers CCB Calcium channel blockers DD Diuretic

Figure 23 Variation in the percentage of newly registered hypertensive patients on drug monotherapy class between 1998 and 2007

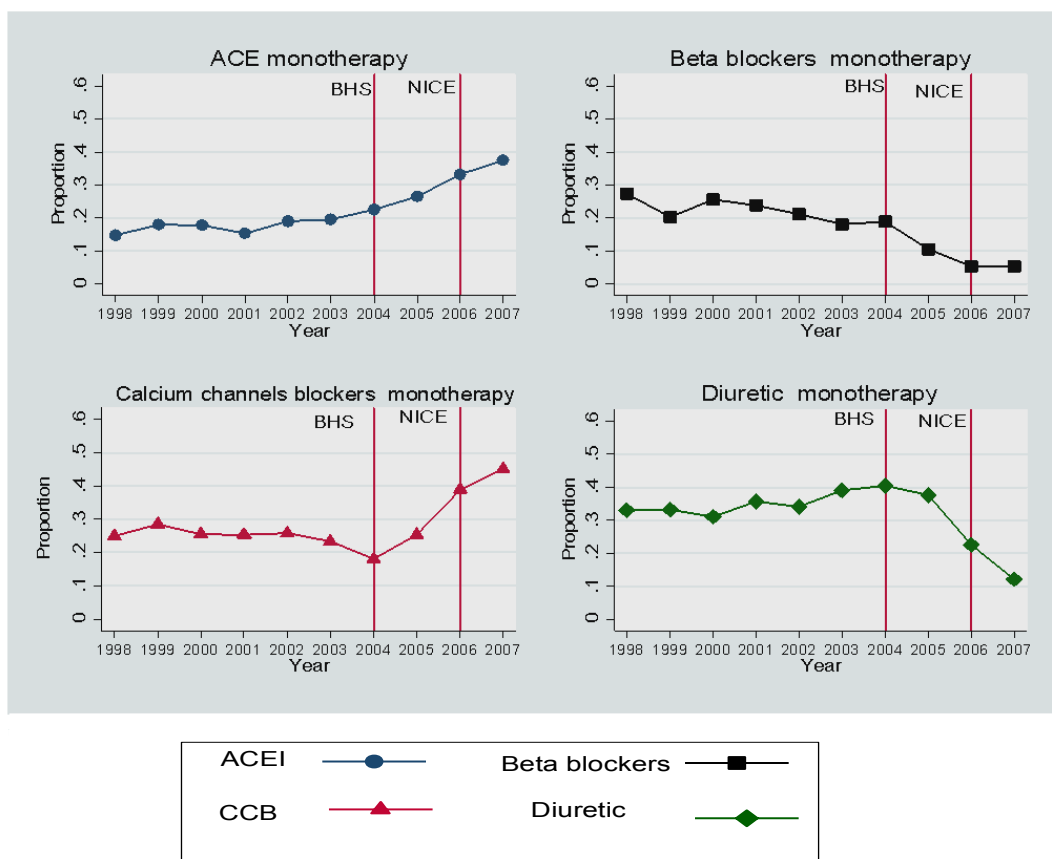


Table 42 Variations in the odds ratio of being prescribed antihypertensive drug monotherapy class for newly registered hypertensive patients between 1998 and 2007

	ACEI			Beta blockers			Calcium channels blockers			Diuretic		
	Odds ratio	CI 95%	p value	Odds ratio	CI 95%	p value	Odds ratio	CI 95%	p value	Odds ratio	CI 95%	p value
Year ‡	1.10	1.08 - 1.12	<0.0001	0.87	0.85 - 0.88	<0.0001	1.02	1.00 - 1.004	0.013	0.99	0.98 - 1.01	0.787
Year	1.02	0.98 - 1.06	0.239	0.92	0.89 - 0.96	<0.0001	0.94	0.92 - 0.98	0.003	1.09	1.06 - 1.13	<0.0001
NICE**	1.61	1.29 - 2.01	<0.0001	0.36	0.26 - 0.52	<0.0001	2.93	2.36 - 3.69	<0.0001	0.27	0.22 - 0.34	<0.0001
Reference												
Period before introduction 1998-2005												
BHS***	1.33	1.02 - 1.73	0.032	0.82	0.62 - 1.08	0.165	0.92	0.72 - 1.18	0.548	0.92	0.72 - 1.15	0.439
Reference												
Period before introduction 1998-2003												

*Newly registered patients without cardiovascular comorbidity such as diabetes mellitus, stroke, atrial fibrillation, heart failure , renal failure

**NICE variable for the introduction of 2006 NICE guideline

***BHS variable for the introduction of the 2004 BHS guidelines

Variations in the odds ratio of being prescribed with the first line NICE recommended monotherapy

All patients without cardiovascular comorbidity

Between 1998 and 2007, the percentage of patients prescribed with recommended monotherapy changed from 52.1% to 61.2% ($p < 0.0001$ for annual trend). For black patients the increase was from 67.9% to 82.6% ($p < 0.0001$ for annual trend). Between 1998 and 2004 the percentage of black on first recommended monotherapy stayed at nearly same level. After 2004 a constant increased was observed.

The percentage of younger non black patients on recommended treatment increased from 25.3% to 52.3% ($p < 0.0001$ for annual trend) over the study period. From 1998 to 2004 the percentage leveled off and then constantly increased. This has been the highest increase in the first line monotherapy among all NICE patient groups over the period (Figure 24 Table 43).

For older non-black patients the percentage of hypertensive patients on recommended treatment varied from 57.3% to 56.3% ($p = 0.7645$ for annual trend). The percentage almost remained stable over the period and it has not been influenced by the introduction of the guidelines.

The logistic model revealed that after the introduction the NICE guidelines (2006- 2007) there was an increase in the use of the first line NICE recommended monotherapy (OR 1.19, 95% CI 1.08 – 1.32) compared with the period before (2000 – 2005). An increase in the use of first line recommended monotherapy in younger non-black patients was also observed (OR 1.23, 95% CI 1.07 – 1.41) compared to the first line monotherapy offered to black patients. In contrast, older non-black patients were less likely to be

prescribed the first line recommended monotherapy in comparison with black patients, (OR 0.76, 95% CI 0.68 – 0.84). On overall black patients were significantly more likely to be prescribed the first line recommended monotherapy than younger non-black (OR 0.21, 95% CI 0.17 – 0.25) and older non-black patients (OR 0.45, 95% CI 0.39 – 0.52) respectively over the study period. (Table 44 Figure 24)

Newly registered patients without cardiovascular comorbidity

Overall the percentage of newly registered patients being prescribed the first line recommended treatment increased from 52.3% in 1998 to 66.1% in 2007 ($p < 0.0001$ for annual trend). The percentage remained nearly stable up to 2004 and afterwards sharply increased and leveled off at the end of the period (Table 43).

For newly registered black patients the percentage of patients on the recommended treatment increased from 73.6% in 1998 to 86.1% in 2007 ($p = 0.0812$ for annual trend). Although there was an increase in the percentage, the variations over the period prevented from configuring a defined trend over the period. Between 1998 and 2003 the percentage remained constant and plummeted in 2004. The fallen coincided with a decrease in the use of CCB monotherapy at the same year. After that a continual increase was observed (Table 43, Figure 23).

The greatest increase in the percentage of patients on the first line recommended treatment was observed in younger non-black patients. Thus in 1998 the percentage was 19.2% following with a period of fluctuations up to 2004. After 2004, the percentage sharply increased reaching a peak of 57.4% by 2007 ($p < 0.0001$ for annual trend) (Table 43).

There was a slight variation of older non-black patients on the first recommended treatment over the study period. The percentage changed from 62.8% in 1998 to 65.0% ($p = 0.0366$). The percentage fluctuated over the period without demarking a constant pattern.

The logistic model showed that there was a significant variation in the use of the first line recommended treatment after the introduction of the 2006 NICE guidelines, overall (OR 1.74 95% CI 1.31- 2.34). Younger non-black patients were more likely to be on the first line recommended treatment (OR 1.83 95% CI 1.15 – 2.93) in comparison with black patients.

By contrast, after the introduction of NICE guidelines older non-black patients were less likely to be prescribed with the recommended first line treatment (OR 0.59 CI 95% 0.38 – 0.92) in relation to black patients. Over the period younger non-black patients and older non-black patients were less likely to have the first line recommended treatment compared to black patients, (OR 0.11 95% CI 0.07 – 0.18) and (OR 0.54 95% CI 0.36 – 0.94) respectively (Table 44).

Table 43 Variation in the percentage of hypertensive on first line monotherapy recommended treatment between 1998 and 2007

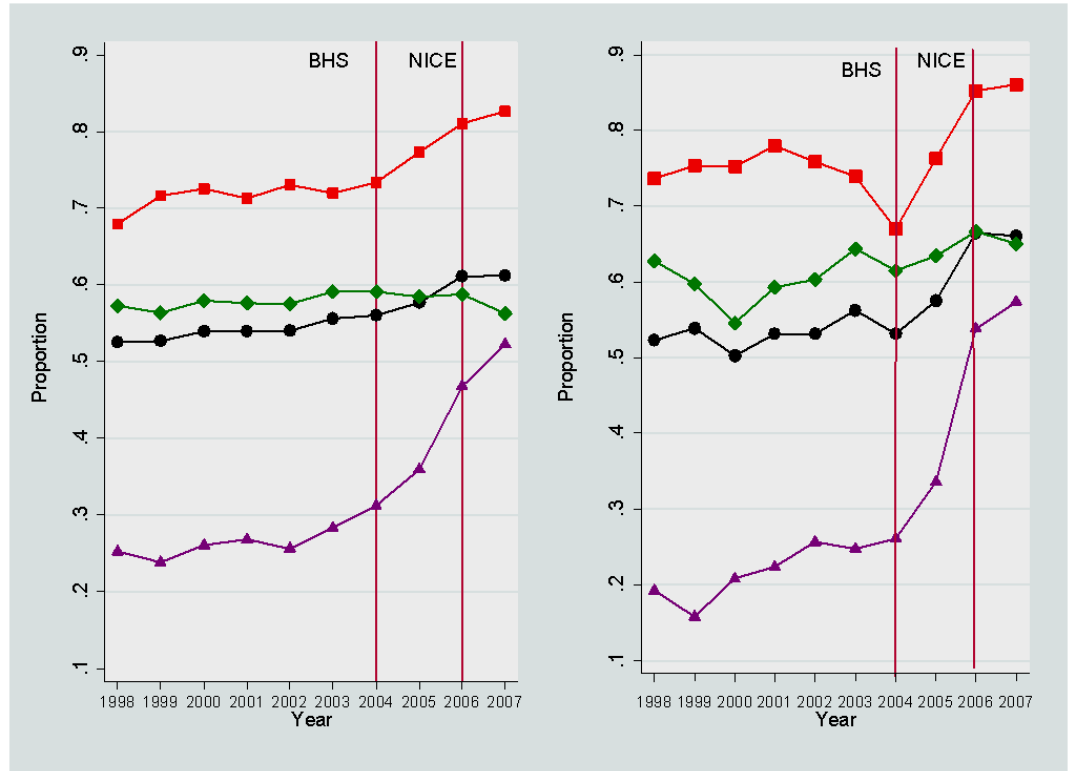
	1998		2007		p value for trend	
	Newly registered *(N=176) % (number)‡	All Patients (N=1314) % (number)	Newly registered (N=445) % (number)	All patients (N=3757) % (number)	Newly registered	All patients
Younger non black** number (%)‡	19.2 (10)	25.3 (73)	57.4 (101)	52.3 (441)	<0.0001	<0.0001
Black number (%)	73.7 (28)	67.9 (197)	86.1 (74)	82.6 (681)	0.0812	<0.0001
Older non-black ** number (%)	62.8 (54)	57.3 (426)	65.0 (119)	56.3 (913)	0.0366	0.7645
Total patients on recommended treatment	52.3 (92)	52.1 (690)	66.1 (294)	61.2 (2298)	<0.0001	<0.0001
Total						

*Patients first time registered with hypertension diagnosis over the referred year

**Included those of White, Asian, Other Asian and other ethnicity origin

‡ Percentage = number of patients in each drug category/ total patient-group in each year*100

Figure 24 Variation in the percentage of hypertensive patients on the first line monotherapy recommended treatment between 1998 and 2007



The graphs included only hypertensive patients without other cardiovascular comorbidity

Percentage: patients on monotherapy/total patients on monotherapy by each NICE patients group*100

Table 44 Variation in the odds of being prescribed the first line NICE recommended monotherapy between 1997 and 2008

Variable	All hypertensive patients*			Newly registered patients*		
	Odds ratio	95% CI ‡	p value	Odds ratio	95% CI	p value
NICE ²	1.19	1.08 - 1.32	<0.001	1.74	1.31 - 2.34	<0.0001
Reference						
Period before introduction 1998-2005						
Interaction term NICE*Guidelines groups						
Younger non-black patients*NICE	1.23	1.07 - 1.41	0.002	1.83	1.15 - 2.93	0.011
Older non-black patients *NICE	0.76	0.68 - 0.84	<0.001	0.59	0.38 - 0.92	0.021
Reference						
Black patients* period previous NICE introduction						
Patients group						
Younger non-black patients	0.21	0.17 - 0.25	<0.001	0.11	0.07 - 0.18	<0.0001
Older non-black patients	0.45	0.39 - 0.52	<0.001	0.54	0.36 - 0.94	0.028
Reference						
Black patients						
Year	1.00	0.98 - 1.02	0.477	1.05	0.99 - 1.10	0.059
Sex	0.91	0.84 - 1.00	0.062	1.02	0.87 - 1.18	0.753
Reference						
Female						
BHS ³	1.02	0.97 - 1.08	0.301	0.92	0.71 - 1.22	0.595
Reference						
Period before introduction 1998-2003						

‡CI confidence interval

* Patients without one of the follow disease: coronary heart disease, diabetes mellitus, heart failure, atrial fibrillation, stroke or renal failure

²NICE variable for the introduction of 2006 NICE guideline

³BHS variable for the introduction of 2004 BHS guideline

⁴Reference 10

8.3.3 Discussion

For the hypertensive patients registered with 28 general practices in Wandsworth, there have been major changes in antihypertensive prescribing between 1998 and 2007. Over this period, an annual decrease in the percentage of all hypertensive patients with no medication was observed. Hypertensive patients having an additional cardiovascular comorbidity were more likely to receive more antihypertensive drugs. Overall the percentage of hypertensive patients without additional cardiovascular comorbidity being prescribed the first line NICE recommended treatment slightly increased over the period. Black patients without any cardiovascular comorbidity were more likely to receive the first line NICE recommended treatment than younger non-black patients and older non-black patients. The percentage of black patients being prescribed the first line treatment also increased over time. Similarly the percentage of younger non-black patients without a cardiovascular comorbidity being prescribed the first line NICE recommended treatment significantly increased over the period. For all NICE patient groups there has been a reduction in the use of beta-blockers and diuretics as monotherapy. These prescribing patterns suggested that some recommendations established in the 2004 BHS guidelines and the 2006 NICE guidelines were already in use by general practitioners. However, the introduction of the 2006 NICE guidelines significantly increased the use of the first line recommended monotherapy in younger non-black patients. The 2006 NICE guidelines also significantly contribute to the observed reduction in the use of beta-blockers use as monotherapy.

Intensity of treatment

Globally the use of antihypertensive medication increased over the period. Thus the percentage of patients not being prescribed antihypertensive medication decreased from 49.0% in 1998 to 14.8% in 2007. Increases in the number of hypertensive patients on treatment have been reported by the Health survey for England over same period (284, 492). These trends were observed for all NICE patient groups but patients with an additional cardiovascular comorbidity were more likely to receive more than one antihypertensive drug. Hypertension guidelines advised that hypertensive patients may need more than one hypertensive drugs to lower blood pressure (13, 144, 184, 501). A sub-analysis from the Health survey for England found a similar trend in prescribing for hypertensive patients with additional comorbidity

(494). These observations may also be related to the lower recommended blood pressure targets recommended for these patients (225-226). Then these results provide evidence that general practitioners have continuously intensified the treatment offered to hypertensive patients over the study period in Wandsworth.

Patterns of each class drug as monotherapy

For all NICE patient groups the use of beta-blockers decreased over the period. This reduction may be due to the growing evidence that beta blockers might be less effective at reducing both blood pressure and some cardiovascular outcomes (755), as well as being associated with new onset diabetes (769). Additionally, there have been differences in the percentage of hypertensive patients on beta-blockers monotherapy between the three NICE patient groups, with the lowest percentage amongst black patients. These differences may be due to the effect of the recommendations established in the national guidelines published before 2004 (265). A decline in the use of BB has also been observed elsewhere. In analysis of the Taiwan National Health Insurance, Chou et al documented that between 1997 and 2004 the ratio of BB prescribing per patient significantly dropped from 0.408 to 0.303 (770). The introduction of the NICE guidelines intensified the drop of beta-blocker usage in all NICE patient groups. A similar pattern was documented by the national report of antihypertensive prescribing published by NICE (760).

A reduction in the use of diuretics was observed over the study period. For all NICE patient groups diuretics were less frequently prescribed as monotherapy than other antihypertensive drugs. The low rates of prescribing were not completely in concordance with the former guidelines available over the period. Whereas the 1999 BHS guidelines and the 2004 NICE guidelines recommended diuretics as the first line antihypertensive treatment for all patients, the 2004 BHS guidelines and the 2006 NICE guidelines established diuretics as first line for black patients and older non-black patients (223, 265, 501). A lower use of diuretics has also been reported by Fumaga et al in the USA (771). Although it has not been consistently demonstrated (228, 504, 772), the observed underuse may be due to the reports that have shown that diuretics may be inferior to amlodipine in reducing hypertension-related cardiovascular events (240). The potential side effects associated with diuretics such as new-onset diabetes and renal toxicity may also explain the lower usage (504, 773-775).

A rise in the ACEI use was observed in younger non-black patients and older-non black patients. For both groups the percentage of patients on ACEI monotherapy has increased annually over the period. Since, the early 2000s ACEI have been promoted as first line monotherapy particularly for those patients with higher activity PAR renin (231, 776-777). However, only in 2004 ACEIs were introduced as the first line recommendation for younger non-black patient (223). Even though there may be differences upon hypertension-related morbidity and mortality between the drug class categories (139), other long term benefits have been associated with ACEI use such as preventing from developing type 2 diabetes mellitus (238, 778-779). A similar pattern in ACEI was also found in the Health Survey for England (284). An additional increase in the ACEI use for younger non-black patients was observed after the introduction of the NICE guidelines. These observations provided additional evidence of the influence of the guidelines in the prescribing of antihypertensive drug class in primary care.

Calcium channels blockers were mainly used in black patients over the entire period. Thus the percentage of black patients on CCB monotherapy was nearly three times higher than that observed in younger non-black patient and older non-black patients. Although the BHS guidelines only introduced distinct prescribing advice for black patients in 2004 (223), previous evidence showing that antihypertensive drugs differ in their effect upon the lowering of blood pressure in black patients may account for this trend (746, 780). Additionally, a significant impact of the 2006 NICE guidelines was quantified as imposing an additional increase upon the percentage of black patients on CCB monotherapy. By contrary the percentage of older non-black on CCB monotherapy did not significantly vary over the period. Neither the 2004 BHS guidelines nor the 2006 NICE guidelines significantly modified the observed prescribing pattern of this group.

Impact of the guidelines

The major impact of the guidelines was observed in the use of some antihypertensive drug class. Thus, the guidelines result in an increased use of ACEI for younger non-black and decreased use of BB for all NICE patient groups. The contribution of the guidelines to the improvements in the management of hypertension has been less explored. Toschke et al reported an increase of 31% in use of antihypertensive prescribing after the introduction of the former BHS guidelines (759). An increase in antihypertensive prescribing has been reported by the Health Survey for England though the impact of the guideline has not been well measured (284). Others authors reported adherence to the recommendations established in the guidelines (761). However, the current results have also consistent with improvements in the management of stroke in the UK (781). Although this evidence may support the value of the guidelines in the management of hypertension, there seems that the increase in antihypertensive usage may also occur as a result of the continuity of care in primary care settings.

Black patients had already been prescribed the first line monotherapy established in the 2004 BHS guidelines and the 2006 NICE guidelines even before they were launched. Thus nearly 67.9% of them received calcium channels blockers or diuretics as monotherapy in 1998. Moreover the use of CCB was higher than the use of diuretics. That prescribing pattern has not been in concordance with the recommendations established before 2004 as initiating diuretic or beta-blockers had been advised for all hypertensive patients. Then, this prescribing pattern may be mainly due to general practitioner's criteria on drug selection. As mentioned, reports on black hypertensive patients reacting differently to antihypertensive drugs have been produced before the introduction of guidelines (746). Hence, general practitioners could have been aware of the benefits of providing black patients with a different first line treatment. The results also showed that general practitioners are more in favor of using CCB than diuretic as monotherapy for black patients. Moreover the introduction of the ethnic algorithm in the 2006 NICE guidelines significantly increased the risk of having being prescribed CCB in black patients. This did not happen when the same algorithm was published in the 2004 BHS guidelines.

Younger non-black patients had the highest variation in the monotherapy prescription. Thus, this group experienced the greatest reduction in the number of patients without medication and the highest variation in the type of antihypertensive monotherapy being prescribed. From 1998 to 2004 there was not a specific age-drug recommendation in the national hypertension guidelines (265). However the data showed that younger non-black patients were more likely to receive ACEI and beta-blockers in the years before 2004. Afterwards the percentage of younger non-black patients on ACEI monotherapy increased. Thus, it seems that general practitioners' preference towards the use of ACEI for this patient group may have been adopted a long time ago. Two clinical trials carried on a Caucasian population may support this selection (751-752). However this observation has not been replicated by others authors (142). The potential lower side effects associated with long term ACEI use, in comparison to those on diuretics and beta-blockers could influence this criteria selection in younger non-black patients (779, 782). The 2006 NICE guidelines positively impact the ACEI prescribing trend though only around 50% of this NICE patient group received ACEI as monotherapy at the end of the study period.

Older non-black patients had the lowest variation in the monotherapy prescription over the period. The prescription offered to them was mainly CCB, diuretics and ACEI. At the end of the period there has been a reduction in diuretic use with an increase in ACEI use. Neither CCB nor ACEI were the first line recommendation established in the guidelines published before 2004 (502, 739). Subsequently, the 2004 BHS guidelines and the 2006 NICE guidelines recommended CCB or diuretic as the first line monotherapy for this patient group (174, 499). The prescription for older non-black patients may be affected by other considerations that could not be accounted for by the guidelines. Side effects, taking other medications or the presence of other non-cardiovascular comorbidities may explain the gap between the registered prescribing patterns and the recommendations established in the guidelines.

I found that in 2007 on average 61.2% of hypertensive patients were on the monotherapy prescription standard established in the 2006 NICE guidelines. The percentage was similar to what reported in other studies carried out in the UK general practices (761). The level of adherence has been variable in the international context (414, 783). It seems that the introduction of the hypertension guidelines in a national program has the potential of changing antihypertensive prescribing patterns among physicians (414, 784-785). On average, there was an increase in the use of the recommended monotherapy after the introduction of the 2006 NICE guidelines. However this mainly affected younger non-black patients. Physicians seem to adhere less to hypertension guidelines when prescribing antihypertensives to older patients (786-787). The presence of other comorbidities, the use of other medications and the potential higher prevalence of side effects may detract physicians using medications recommended in the guidelines (411).

Heneghan et al carried out a survey aimed at evaluating awareness, agreement, adoption and adherence to the 2004 BHS and 2006 NICE hypertension guidelines among 800 GPs in the UK (758). They found that 62% of GPs did not adhere to the guideline recommendations. The survey was sent by the doctors.net.uk website on 10-14 May in 2006. The rate of response was only 50.1% (401 GPs) and their geographic location was not mentioned. The authors stated that this GP population was similar to the all English GP population but with a lower representation of GP partner status. However some considerations should be taken into account about the generalization of these results. The sample seems small as 32111 full time-equivalent GPs were reported in the UK in 2009 (586). It might not represent all GPs

because the method of calculating the sample size was not mentioned in the study. Additionally the results may be biased because the participation was voluntary with 50% response rate. There was no description of non-responders (788). Therefore the use of the recommendations may be underestimated.

Globally, the observed drug class patterns were more influenced by the 2006 NICE guidelines rather than by the 2004 BHS guidelines. There may be some potential explanations for this finding. The BHS provides recommendations as an academic institution but it does not have a regulatory basis. By contrast NICE, an official NHS organization and health care, demands health providers following its guidance. Moreover the recommendations established in the NICE guidelines have been integrated into the standards of care promulgated by QOF (279). The NICE guidelines aim not only to improve quality of care but also to reduce the variation in care across general practices. Hence it seems that integrating clinical guidelines into health policy improves the effectiveness of the established recommendations.

8.3.4 Strength and Limitations

The most important strength of this study is the comparison of trends in the management of hypertension across patient groups established since 2004 in the BHS guidelines. The report estimated the impact of national guidelines in antihypertensive drug prescribing in a cohort of patients registered with 28 general practices in England. Therefore I can estimate the temporal variations in antihypertensive prescribing patterns and how long prescribing patterns remain over a long term period. Other reports have also quantified the percentage of hypertensive patients on the NICE recommended treatment (761). But they did neither quantify how much variation there was before and after the introduction of the guidelines (531, 761) nor they could assess variations across ethnic groups (759). Hence the current analyses provide new evidence on how antihypertensive prescribing varied with patient characteristics and quantify the impact of the guidelines on these variations

I was only able to examine the impact of the 2006 NICE guidelines over an 18 months period because the guidelines were launched between April and June 2006. Therefore the observed impact may only reflect a short term effect. However the observed prescribing pattern is consistent to the prescribing trend reported in the National implementation uptake report

for the management of hypertension (760). The validity of the association also could be enhanced by the GEE models as they allow making comparison between short time periods (764, 789). The study was based on hypertensive patients registered with general practices in a specific area of London.

Other limitations of the present study are the lack of information on the criteria used by the general practitioner to choose the antihypertensive medication for an individual patient. Therefore I cannot provide reasons for the differences between the guideline recommendations and some of the reported trends. Additionally, the patients included in the register may be different from all hypertensive patients as the data came from general practices located in a specific area in London. Hence our results may not be generalized to other population but the findings are in the line with the current trend in antihypertensive drug prescription reported by other authors (284, 761).

8.3.5 Conclusion

The introduction of a treatment algorithm incorporating patient age and ethnicity established in the 2006 NICE hypertension guidance was associated with significant changes in the antihypertensive prescribing pattern observed in the general practices in Wandsworth. The findings suggest that the guidelines had the greatest impact on prescribing for younger non-black patients. The smaller change in the recommended prescribing among black patients may be due to higher levels of appropriate prescribing in this group at baseline. Similarly a weaker influence of the guidelines upon the treatment offered to older non-black patients was observed. The use of beta-blockers as a monotherapy decreased over the period but an additional use reduction was associated with the introduction of the guidelines. The findings therefore suggest that the ethnic specific recommendations established in the national clinical guidelines influence antihypertensive prescribing in primary care but that the impact of these guidelines can vary in the different patient groups

Implications

The use of national hypertension guidelines has the potential of influencing antihypertensive prescribing patterns in general practice. However general practitioner criteria on antihypertensive choice selection may be beyond the criteria established in the guidelines. Therapeutic recommendations from well evidenced based studies may be more likely to influence a general practitioner's practice than those based on less evidence-graded studies. Therefore the impact of the recommendations established in the guidelines unevenly affect drugs prescribing across different age-ethnic patient groups.

The findings of the study revealed that around 50% of patients received the recommended treatment at the end of the period. In particular older non black patients were less likely to be on their first line recommended treatment. Additional exploration may be needed to assess the implications of this discrepancy. The recommendations established in the guidelines could consider data not only from clinical trials but also data from current clinical practice.

Key points

- ✓ To provide hypertensive patients with appropriate antihypertensive medication is essential for the management of hypertension.
- ✓ Guidelines on the management of hypertension guidelines have been proliferated to help physicians with antihypertensive drug choices.
- ✓ Poor physician adherence to drug prescribing recommendations established in the guidelines has been reported worldwide.
- ✓ In 2006 the NICE hypertension guidelines incorporated the ethnic algorithm proposed by the 2004 BHS guidelines to guide the first line treatment.
- ✓ In 28 general practices located in Wandsworth, London, there have been major changes in antihypertensive prescribing between 1998 and 2007.
- ✓ Over this period there was a reduction in the percentage of all hypertensive patients without antihypertensive medication.
- ✓ Black patients without a cardiovascular comorbidity were more likely to receive the first line NICE recommended treatment.
- ✓ For younger non-black patients without a cardiovascular comorbidity the risk of being prescribed the first line NICE recommendation significantly increased after the introduction of the 2006 NICE guidelines.
- ✓ Older non-black patients without a cardiovascular comorbidity were less likely to receive the first line recommended treatment over the period.
- ✓ The use of beta-blockers as a monotherapy significantly decreased over the period
- ✓ The introduction of 2006 NICE guidelines was associated with an additional reduction in the prescription of BB.
- ✓ On average, at the end of the period, nearly 50% of patients received the first line recommended treatment.
- ✓ General practitioners' choices in selecting antihypertensive medication may not always be based on the criteria established in the guidelines, particularly in older non-black patients.

Chapter 9 A Bayesian model for the assessment of factors affecting blood pressure control in a retrospective cohort of hypertensive patients

Background

From the review presented in the chapter five I considered the following statements. The studies assessing factors affecting blood pressure control showed that achieving a blood pressure target is a complex health outcome. It depends upon the interaction between patient-factors, physician factors and the performance of health services essentially within primary care. The relationship between these factors and blood pressure control varied across the studies and sometimes was contradictory.

Studies conducted in primary care services risk overestimating or underestimating the associations as sampling may result in choice of those patients more recurrent visitors or more adherent to recommendations. The scope for generalizing the associations outside the study context may be limited due to differences in patient characteristics, physician's performance and the conditions of the health system across the referred populations. Therefore, the reported associations may be context-dependent.

The studies reported associations between factors and blood pressure control mainly from cross sectional studies using a logistic regression models in a Frequentist framework. These associations are highly dependent on the frequency of variable presented in each population. They also cannot assess into account the variation on the outcome over time as the outcome is measured once at time point. These studies can neither assess the potential lag time effect of some variables on blood pressure control. Although some studies took samples including patients nested into practices, the effect of general practices in a multilevel analysis has not regularly been taken into account. To consider the mentioned aspects on blood pressure control, I assessed factors affecting blood control in a retrospective cohort of

hypertensive patients being treated in 28 general practices from 1998 to 2007. The contribution of individual factors, physician factors and health service factors on having controlled blood pressure was assessed using a survival model in a Bayesian Framework. The rationale for using this approach is explained below.

Secondary objectives

1. To describe variations in blood pressure control among patient cohort between 1998 and 2007
2. To compare the contribution of study factors in different subpopulations of hypertensive patients.

9.1 The Bayesian framework

The Bayesian statistical approach relies on the fact that the probability of an event depends on i) its historical tendency, called the prior belief and ii) the information about the event occurrence obtained from the current data (790). Combining both sources under Bayes theorem gives the final probability of the event, called posterior probability (790). (Figure 25)

Bayes theorem

Bayes theorem established the probability of an event occurrence conditioned on other event occurrence (790)

Mathematical formulation:

Given two events A and B, the probability (p) of A conditioned on B is

$$p(A \cap B) = p(A|B) p(B)$$

$$p(A|B) = \frac{p(A \cap B)}{p(B)}$$

Given the standard probability rules for mutually and exclusive events

$$p(U_i A_i) = \sum_i p(A_i) = 1$$

Then based on the above, Bayes theorem establishes that

$$p(A|B) = \frac{p(B|A)p(A)}{\sum_j p(B|A_j)p(A_j)}$$

For example: If we are interested in estimating the distribution of β (parameter of interest of a binomial outcome) from a dataset (D), we calculated it based on the following

$P(\beta)$: The prior probability

D: information from data

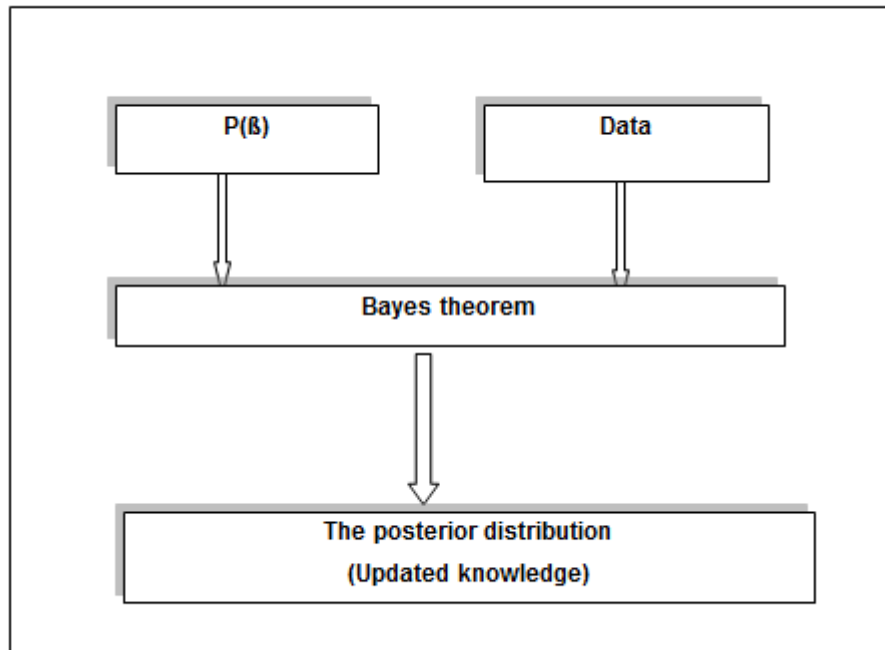
$$p(\beta|D) = \frac{P(D|\beta) \times p(\beta)}{\sum P(D|\beta) \times P(\beta)}$$

Or

$$Posterior(\beta|D) = \frac{likelihood(D|\beta) \times prior(\beta)}{\sum likelihood(D|\beta) * prior(\beta)}$$

Where the posterior is the posterior distribution of the parameter conditioned on data. It gives the updated information of the parameter.

Figure 25 The Bayesian framework



9.1.1 Bayesian statistical inference

Statistical analyses are frequently used to make inferences on unknown parameters. The estimated parameters allow us to assess hypotheses, to generalize results outside the data or to uncover process occurring in the data (791). In a Bayesian framework the unknown parameters are estimated using the data collected, the prior distribution and the model. The final result is the posterior distribution of the parameter.

The prior distribution

In a Bayesian framework all the parameters have a probability distribution. They are a random variable rather than a fixed quantity, as seen in the frequentist framework. This distribution should be defined before conducting a study analysis therefore it is called the prior distribution. The selection of the prior distributions could be based on previous studies, personal opinion, expert's opinion or other data (791).

The prior distributions represent the knowledge or our beliefs about the parameters before conducting the current experiment and they can be non-informative or informative (792). The former are used when little or no information is known: one of the most common non-informative prior distributions is a uniform prior which gives equal probability to any potential value of the parameter. The latter are used when there is information available on the parameters from previous studies, personal or expert opinion: normal, gamma or binomial distribution are typically used (790).

The posterior distribution

After combining the data and the model, the Bayesian analysis produces a posterior distribution of the parameters. Thus the mean, median, percentiles, standard deviation and standard error of the distribution are provided. Based on boundaries of percentiles for the parameter, a credible interval is calculated. 95% credible interval is based on the 2.5% and 97.5% percentile value of the posterior distribution. The credible interval corresponds loosely to the frequentist confidence interval but with a different interpretation. It tells that there is a 95% probability that the value of the parameter occurs within the estimated 95% boundaries (790).

9.2 The rationale of using a Bayesian approach in the current analysis

The present study used a retrospective cohort of hypertensive patients managed in primary care services. The data was collected by registering information on clinical evaluations of hypertensive patients taking during routine clinical visits. The data has a natural hierarchical structure with patients nested within practices and also with multiple outcomes for each patient. I selected the Bayesian approach to analyse the data based on the following reasons:

- 1) Clinical trials and random-sample observational studies have been the traditional source of evidence in health research (793). As these studies produce inferences based on the calculation of sample size, the use of the Frequentist framework has rendered acceptable results (794). However, nowadays observational studies from

data collected in clinical settings have been shown to be a tool to provide evidence about interventions and quality of care taking in daily clinical practice (601). The analysis of that data may require a different approach because its origin is not sample size based-collected and the exposure to interventions is not usually randomly allocated (794). Therefore using a Frequentist framework in the analysis of that observational data has been questioned (790). A Bayesian approach, which is not highly dependent on sample size, could be a more suitable method to understand the relationships between variables present in the data (790, 795).

- 2) The data from health services is periodically collected regarding patient's attendance. Consequently, there may be some variables with low frequency of observations. By using the Frequentist approach, information from sparse data is commonly discarded because it may result in non-significant associations(796). That is due to the frequency of the variable being one of the conditions affecting the significance of the associations. Therefore the analysis may be biased towards highly represented variables even though they may not be clinical or social determinants of the outcome. By comparison in the Bayesian approach, those variables with lower frequency are integrated into the analysis equally to those with higher frequencies (797).
- 3) The data has patients nested within general practices. This data is also called hierarchical data (798). The analysis of this data structure should require some considerations. Firstly, patients within each practice are supposed to receive similar health care so that they would have a similar probability of achieving an expected outcome (799). In other words, the health outcome for individuals clustered within practices is considered to be correlated. A statistical analysis which ignores this correlation could produce inaccurate results. Secondly, there is variability in the outcome between practices. For multivariate models, the number of groups needed to estimate this variability is an area of controversy (800-801). Thirdly, the practice's characteristics may contribute differently to the outcome. Using dummy variables for grouping practices without including practice's variables could limit the assessment of this contribution (799).

The data also has patients from whom multiples observations of the outcome have been collected. For each patient, the measurements of the outcome recorded at various times are dependent (791). Particularly, the measurement of blood pressure levels would be considered correlated over the time (8, 802). Therefore the data is a complex structure with two sources of random effects: one comes from the repeated measurement of the outcome for each patient and the other comes from the patients clustered into practices.

In the Frequentist approach, the probability of the estimators is one that can be replicated in a long run of estimations (790). Thus if a study is repeated one hundred times under similar conditions, 95% of these new studies should produce a confidence interval containing the true value of the parameter (790). However when data is routinely collected health services, the replication of the conditions occurring in these services may be unlikely. Because these conditions may be unique, the assessment of the probability presented in the data could be of more interest rather than the assessment based on multiple replications. Using the Bayesian framework we can directly determine the probability of the estimated parameter. Thus the 95% credible interval expresses the distribution of the values for the parameter. Therefore, it expresses the amount of uncertainty presents in the data given some priors and a selected model (790).

9.2.1 Potential limitations on using a Bayesian framework

The definition of the prior distributions has been one of the most questionable aspects of the Bayesian analysis (803). The prior distributions reflect information other than that presented in the data (794). They should be as close as possible to the knowledge available on the parameter of interest (790). That knowledge is not always achievable so the selection of the priors may rely on the researcher's expertise. Therefore, a Bayesian analysis has been considered a subjective method (803). However strategies such as the use of previous reported priors, the use of broad priors, the comparison of different priors and the analysis of different levels of adjustment in the models allow the credibility of selected priors to be assessed (794).

Later, Bayesian analysis has been categorized as objective and subjective (792). The objective uses non informative priors and the subjective uses informative priors (792). The use of informative priors introduces information for the parameter which could influence the posterior distribution and the statistical inference. Some authors argued that the use of these priors may modify the information contained in the data and the results would mainly reflect the research's opinions. However, the choice of the priors should not be arbitrary and based on the expected relationship between variables and outcome (794). By comparison, using non-informative priors the results are typically data driven and similar to the ones obtained using the Frequentist framework (804).

As occurred in the Frequentist framework, in the Bayesian framework the estimation of the probability depends on the model used (790). These models are intended to explain the information contained in the data. Their configuration should be based on the following aspects: the focus of the study, the aim of the model (prediction, classification or exploratory models), the parsimony of the model and a balance between bias and variance (805). Regardless of the statistical framework, the use of these criteria relies on the researcher. Consequently, the model selection afflicts Frequentist and Bayesian methods in a similar way. The variable selection may rely not only on its statistical significance but also on its clinical or contextual significance. Because of these conditions, the statistical models may be approximations to the real world.

9.2 Methods

Patient characteristics were described as mean or percentage for continuous or binomial variables respectively. Comparisons of blood pressure means were performed using ANOVA test.

9.2.1 The Data

For each hypertensive patient I identified the annual measurement of blood pressure over from 1998 to 2007. Hypertensive patients with a blood pressure equal to or below 140/90 mm Hg were classified as those with controlled hypertension; those with blood pressures above this level were considered as having uncontrolled hypertension. The data had patients who entered the register at different times over the study period. For the majority of patients having a controlled blood pressure was a recurrent event (see descriptive results). Because patients with variations in their blood pressure control status were the most frequent group, a cohort with this group was used for the assessment of factors affecting blood pressure control over the study period.

9.2.2 The model

9.2.2.1 General considerations

The assessment of blood control required some considerations. Repeated measurements of blood pressure are known to be correlated (8). The probability of having controlled blood pressure is depending on the basal blood pressure levels at starting therapy (210). Blood pressure has an intrinsic variability so that one blood pressure measurement may not reflect the true blood pressure value (8). Blood pressure measurement taking close to periods after initiating therapy could not reflect real variations in blood pressure levels (806). Hypertensive patients could change their blood pressure control status even in short time periods of three months (807).

Currently, the aim of the management of blood pressure is to achieve a target. Then, for a hypertensive patient having controlled pressure is a binary outcome. It can be interpreted as having or not an event over a defined period of time. Because of the variability in blood pressure control status, it can be considered as a recurrent event. Time periods in which patients have a recurrent outcome are related to each other over a follow-up period (791). Additionally, hypertensive patients being treated within the same practice are more likely to have a similar outcome. Hence I selected a survival parametric model for recurrent events to assess factors affecting blood pressure control in the hypertensive patient cohort over a ten year period. In the model, the outcome is the event time (time periods) of having controlled blood pressure as function of set covariates.

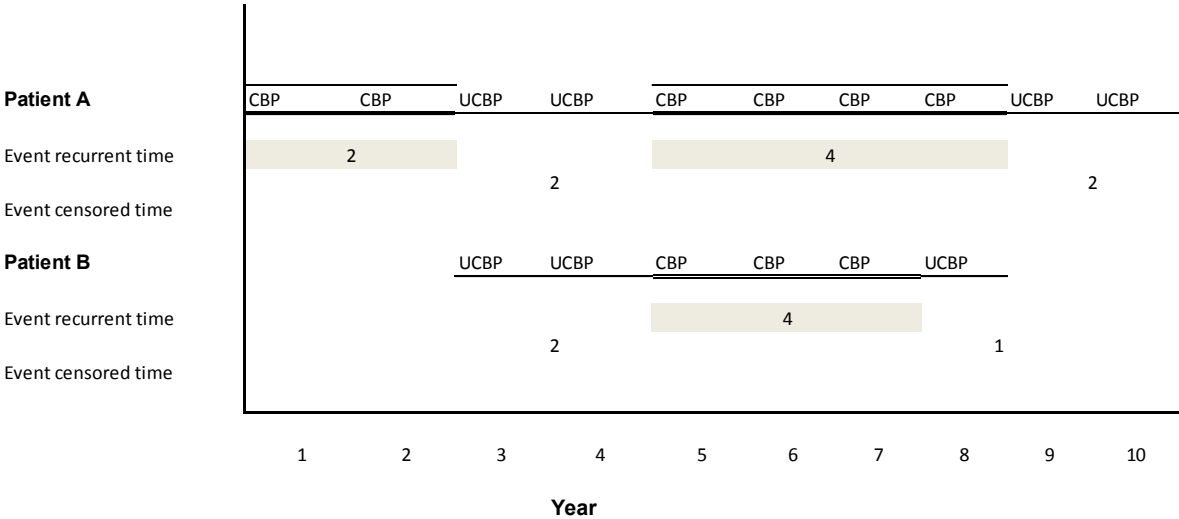
Factors affected blood pressure control are classified into individual factors, physician-related factors and health system factors (289). As mentioned in chapter 2, the contribution of these factors varied across studies. I developed a model which included all the potential factors related to blood pressure control presented in the data. The outcome was measured at patient level and the factors were classified as follows: 1) Individual factors included age, sex, race/ethnicity, presence of cardiovascular comorbidity, presence of non-cardiovascular comorbidity and smoking. 2) Factors related of physician performance included being prescribed antihypertensive medication in one of the models. I also assessed the use of the recommended antihypertensive treatment established in the 2006 NICE guidelines (499). A variable indicated whether or not a patient has been prescribed antihypertensive medication based on the algorithm established in the 2006 NICE guidelines was used in the model. The variable described the use of the first, second or third line antihypertensive prescription as it was established in the guideline. I used this treatment recommendation because the recommended algorithm was promoted in the 2004 British Hypertension Society guidelines (174). Also some recommendations were already published before 2004, for instance the differential hypertensive treatment for patients of black origin (504). 3) Factors related to practice services included the number of hypertensive patients registered in each practice. Because socio economic status was based on deprivation index of the area at which each practice was located, this factor was assessed as a practice characteristic. The performance of service was indirectly measured as the individual characteristic of being registered before or after the introduction of QOF.

9.2.2.2 Statistical formulation for the model

Definition of period times

The time periods started from the year in which the patient was registered. The calculation of the time period in which each patient had controlled blood pressure was based on the gap time formulation (808) Thus, for each patient, all time periods with equal blood pressure status were added when they appeared consecutively over year calendar. But, when a variation in the blood pressure control status appeared, a new time sequence was performed (see Figure 26).

Figure 26 Illustration of the time calculation



CBP Controlled blood pressure

UCBP Uncontrolled blood pressure

The frailty survival hierarchical model

The descriptive analysis showed that blood pressure levels decreased over the period. Then it seems that the risk of having controlled pressure increased over the period. Therefore I selected a Weibull distribution to model the hazard risk of having controlled blood pressure. The Weibull distribution allows modelling time events whose probability tends to monotonically increase over a period of time (809).

The Weibull distribution for the event recurrent times is formulated as follows

$$f(t) = \mu \gamma t^{\gamma-1} e^{-\mu t} \quad (1.1)$$

The hazard function is

$$h(t) = \gamma \mu t^{\mu-1} \quad (1.2)$$

The correlation between time periods was measured using a frailty term in the model. The frailty term allows for taking into account random effects due to the multiple recurrence times of the same event in one individual (809). The term also accounts for other sources of variability due to differences in experiencing the outcome between individuals (809).

Using a Bayesian framework a parametric hierarchical survival frailty model for the hazard risk of having controlled blood pressure was formulated. The model is hierarchical with two levels. The first level is given by patients having repeated event times. The second level was formed by patients clustered with general practices. The model was formulated as follows:

General formulation:

$$h(t)_{ij} = (\text{shape} * \text{scale} * t)^{\text{scale}-1} \quad (1.3)$$

Level one individual

$$\log(\text{scale}_{ij}) = \beta * \text{age}_i + \beta * \text{sex}_i + \beta * \text{ethnicity}_i + \beta * \text{treatment}_i +$$

$$\beta * \text{comorbidity}_i +$$

$$\beta * \text{nocomorbidity}_i + \beta * \text{bmi}_i + \beta * \text{cholesterol}_i + \beta * \text{smoke}_i + \beta * \text{qof}_i + \rho_{ij}$$

Level two individual nested within practices

$$\rho_i \sim N(\mu_i, \delta_{zi}^2)$$

$$\mu_i = a_{zi}$$

$$a_z \sim N(\mu_z, \delta^2)$$

$$u_z = \beta * z + \beta * practicelist_z + \beta * deprivation_z$$

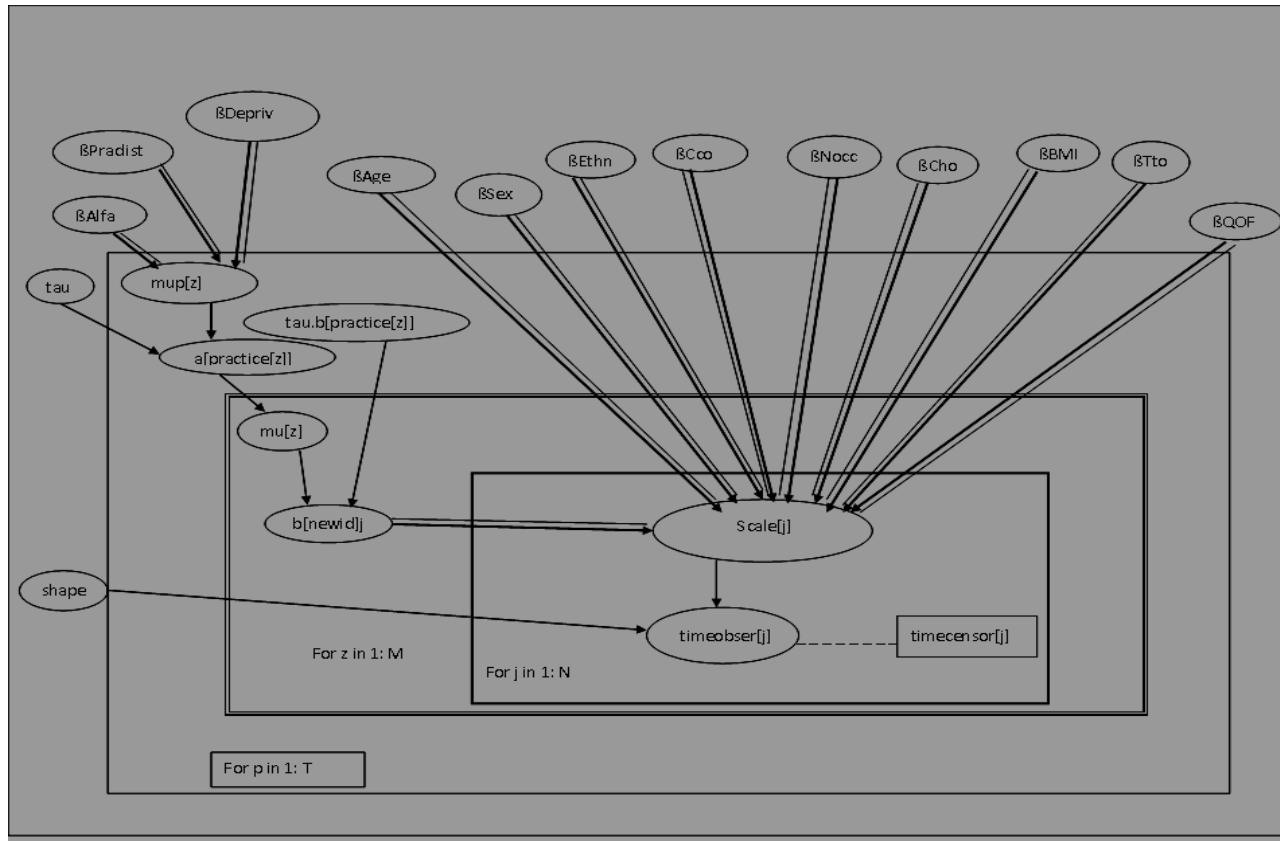
Where $i = 1, \dots, N$ patients; $j =$ each individual measurement of outcome; $z = 1 \dots 28$ practices

β is the regression coefficient for each variable included in the model. The variables were labelled as described in the chapter 6. The value of the variables was the first measurement registered in the dataset. For this model an additional variable (QOF) was included to take into account the potential effect of QOF on the outcome. It was a binomial variable named as 0 for those individuals with a first record registered before 2004 and 1 otherwise. The deprivation index was categorized into tertiles of the distribution. The number of individuals registered with practice was taken from that registered in 1998 and it was categorized in tertiles of the distribution.

ρ_i is the frailty term which accounts for random effects derived from individuals with multiple measurements and nested within practices. The random effects are assumed to have a normal distribution with a mean u_i and δ_{ij}^2 variance depending on the effect of patients nested within practices. u_i depends on the effects on individuals nested within practices. a_j is the coefficient for practice effect with a mean μ_j depending on practice characteristics and δ^2 common variance for all practices. β_j is the intercept for practice effect. The code for the model is in the appendix.

The representation of the model is shown below using the directed acyclic graph (DAG) (810). The graph illustrates the relationship between all quantities or nodes included in the model (variables and outcomes) which are in rectangular or elliptical shape. The rectangular nodes represent those nodes which are constants and the elliptical nodes those which represent either stochastic quantities or functional relationship. The single-edged arrows indicate a stochastic relational and the double edged arrows the functional relationship between two nodes respectively. The repeated structures such as j , for individuals, and nested structures such as z , for practices, are represented by plates. The DAG shows the contribution of the coefficients to the outcome. It also illustrates how the frailty term ρ_i was formed (Figure 27). The code for the model is presented in appendix C.

Figure 27 Directed acyclic graph (DAG) for describing the frailty survival Bayesian model



Where:

Alfa = intercept for practices

Praclist: Number of individuals registered with each practice

Depriv: deprivation index

Eth: race/ethnicity

Cco: cardiovascular comorbidity

Nocc: no cardiovascular comorbidity

Cho: cholesterol

BMI Body mass index

Tto: Antihypertensive treatment

QOF Quality and Outcome Framework

The prior distributions

Prior specification on the shape parameter (S)

The prior distribution for the shape parameter was defined as a Gamma (1, 0.01). This distribution was chosen considering that the hazard risk follows a positive distribution and may increase over the time (809).

Prior specification on coefficients

The regression coefficients were given a normal distribution with zero mean and variance 0.001. This is non-informative prior but with a large variance to reduce the influence of the prior distribution on the data (811).

The frailty term

The frailty term was the random effects of the model. The random effects are assumed to have a normal distribution with mean and variance for individuals nested within practices. A gamma distribution with mean 0.5 and 0.5 variance was used for the precision of the individuals nested into practices. A gamma distribution with mean 1 and variance 0.5 was given for the overall precision of practices. Comparisons of gamma distributions for variance were performed. The gamma distribution with these informative priors was selected because the number of units in each hierarchical level is variable. For instance one individual can have only two measurements of blood pressure. Similarly the number of individuals within each practice is below ten in some models. Under these conditions the use of non informative priors may led to a miscalibration of the posterior distribution (811-812). I also observed that the models did not convergence using gamma distributions with mean 0.0001 and variance 0.0001 for variance of individuals nested within practices.

Censored data

The data has right censored, left censored and interval censored observations. For instance a patient could be registered with blood pressure control (outcome) but the time period before the outcome is unknown. Also, a patient could have uncontrolled blood pressure in the first observation and have controlled pressure in the second observation but the second observation could be taken there years after. The parametric model deals with both of these censored observations (809).

9.2.3 Data Processing

Formatting the data for WinBUGS

The data was analysed using WinBUGS software. WinBUGS is a program for carrying out Bayesian analysis developed between Medical Research Council Biostatistics Unit, Cambridge and Imperial College School of Medicine at St Mary's, London (810). WinBUGS performs the statistical analysis using Markov chain Monte Carlo (MCMC). Thus from each iteration, a new value for each unobserved stochastic node is taken. The value came from the conditional distribution formed by models parameters and data (810).

The data was originally recorded en excel files linked by the patient's code. Then it was transferred into STATA format. I converted the data from STATA format to WinBUGS format using the commands provided by Thompson et al (813). In WlinBUGS, the data was set up a rectangular format. Three data sets were configured as one set for variables related to individuals, one for practice code and one for variables related to practices. The individuals were nested into practices.

Convergence of the parameters and model choice

The assessment of the model was carried out for the parameters and the model. For the parameters looked at the convergence based on the patterns of time series, the autocorrelation and the Gelman Rubin test (814). All of them are graphic test provided by the assessment tool. The Gelman Rubin test assesses convergence for the parameters. For the model choice, the assessment of the models was based on the Deviance Information Criterion (DIC) (810, 815).

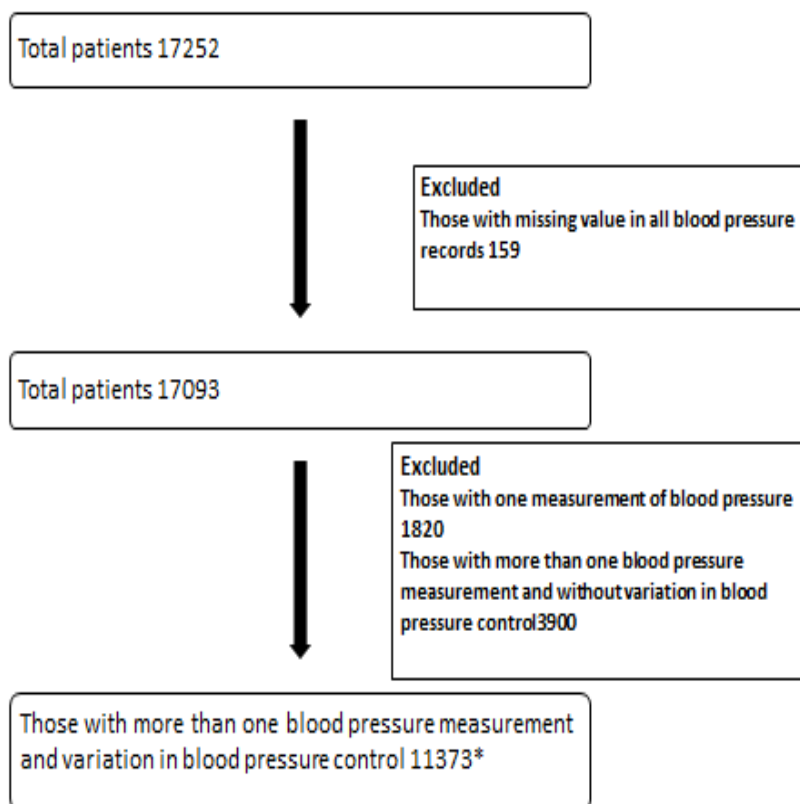
9.3 Results

Baseline patient characteristics

Of 17242 patients registered in the dataset, 11373 were selected for the survival analysis. (Figure 28) These patients had more than one blood pressure measurement and variation in the blood control status. The mean age of selected group was 60.5 (12.8 sd) years. 6459 (56.8%) were female and 6610 (53.7%) were white. 3044 (26.7) had an additional cardiovascular comorbidity. Of them, 1635 (14.4%) had diabetes, 919 (8%) had coronary heart disease, 11 (0.9%) had heart failure, 226 (2.3%) had atrial fibrillation, 211 (1.9%) had chronic renal disease and 558 (4.9%) had stroke. Among those with other non-cardiovascular comorbidity, 947 (45.9%) had asthma, 1109 (9.8%) had depression, 1093 (9.6%) had chronic obstructive pulmonary disease (COPD). BMI, cholesterol levels and smoking status were recorded at different times over the follow-up period. The first record of these variables was used. Patients without variation in the blood pressure status and those with only one blood pressure measurement tend to be younger and with less cardiovascular comorbidity than those included in the cohort group (Table 45).

Among those included in the survival analysis, the median of blood pressure records was 6 ranging from 2 to 10. The median follow up period was seven years ranging from 1 to 10. For those without variation in the blood pressure status, the median was 2 ranging from 2 to 10 (Figure 29-30).

Figure 28 Cohort profile



*Patients configuring the cohort group

Figure 29 Distribution of patients include in the survival cohort by number of blood pressure records over the 10 years period

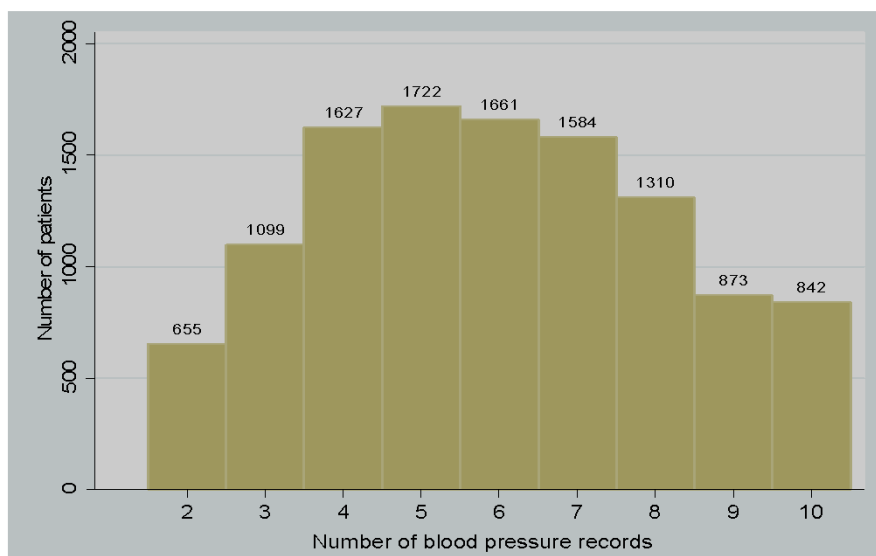


Figure 30 Distribution of patients by number of blood pressure records for those without variation in blood pressure control

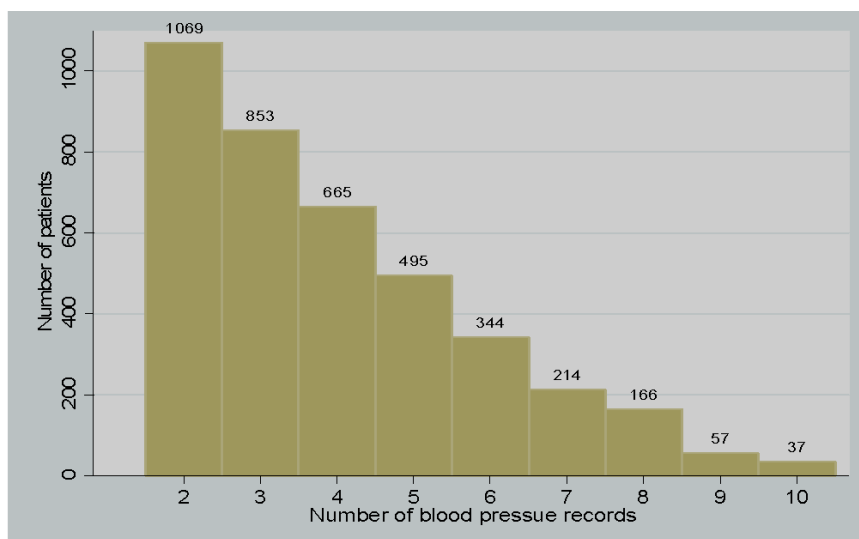


Table 45 Baseline patient characteristics

Patient characteristics	Those with more than one blood pressure measurement and variation in blood pressure control (N=11373)	Those with more than one blood pressure measurement and without variation in blood pressure control (N=3900)	Those with one blood pressure measurement (N=1820)
Age mean (sd)	60.5 (12.8)	57.6 (14.6)	55.1 (15.9)
Male number (%)	4919 (43.2)	1816 (46.6)	931 (51.5)
Body index mass mean weight/cm ² (sd)	28.5 (5.6)§§	28.6 (6.1) ¥¥	28.5 (5.8) **
Cholesterol mmol mean (sd)	5.5 (1.01) §	5.4 (1.0)¥	5.5 (1.02) ***

Patient characteristics	(N=11373)	(N=3900)	(N=1820)
Ethnicity number (%)			
White	6610 (53.7)	2006 (51.4)	910 (50.0)
Black	2679 (23.6)	827 (21.2)	399 (21.9)
South Asian	988 (8.7)	401 (10.3)	157 (8.6)
Other Asian	355 (3.1)	161 (4.1)	75 (4.1)
Other ethnicity	471 (4.1)	193 (4.9)	97 (5.3)
Unknown	770 (6.8)	312 (8.0)	182 (10.0)
Presence of cardiovascular comorbidity number‡ (%)	3044 (26.7)	985 (25.3)	385 (21.2)
Presence of other cardiovascular co-morbidity number ‡‡ (%)	2060 (18.1)	753 (19.3)	318 (17.5)

Patient characteristics	(N=11373)	(N=3900)	(N=1820)
Patients on antihypertensive treatment number (%)	9215 (81.0)	2998 (76.8)	1350 (74.2)
Systolic blood pressure mm Hg mean (sd)	146.8 (17.3)	140.7 (21.1)	142.4 (19.1)
Diastolic blood pressure mm Hg mean (sd)	85.9 (10.7)	83.5 (11.2)	84.8 (11.7)

*Baseline patient characteristics referred to those characteristics recorded with the first record of each patient

**Recorded for 1262 (69.4%) patients

***Recorded for 1004 (55.1%) patients

¥ Recorded for 3224 (82.7%) patients

¥¥ Recorded for 3380 (86.7%) patients

§Recorded for 10482 (92.2%) patients

§§ Recorded for 10407 (91.5%) patients

‡Patients with at least one of the follow disease: coronary heart disease, diabetes mellitus, heart failure, atrial fibrillation, stroke or renal failure

‡‡Patients with at least one of the follow disease: depression, asthma or chronic pulmonary disease (COPD)

Sd standard deviation

Blood pressure levels

On overall, mean systolic blood pressure was 146.8 (sd17.3) at first entry. Mean systolic blood pressure levels at the first record was lower for those patients registered after 2002 ($p<0.0001$). Mean diastolic blood pressure at first entry was 85.9 (sd 10.7). Although there were differences in mean diastolic blood pressure at first entry over the years, the differences were less significant than those observed for systolic blood pressure. ($p=0.006$). By comparison there was a significant reduction in systolic and diastolic blood pressure levels over the study period. Mean systolic blood pressure was 148.5 mm Hg (sd) in the first year observation and 137.4 mg (sd 14.8) in the last year (10th) ($p<0.0001$). Similarly, mean diastolic blood pressure was 85.9 (10.3) mm Hg at first year registration and 78.9 mm Hg (10.1) in the last year observation ($p<0.0001$). The percentage of hypertensive patients with controlled blood pressure increased from 37% in 1998 to 62.4% in 2007 over ten years period (Figure 31-34).

Figure 31 Mean systolic blood pressure at first record in the cohort group (N11373)

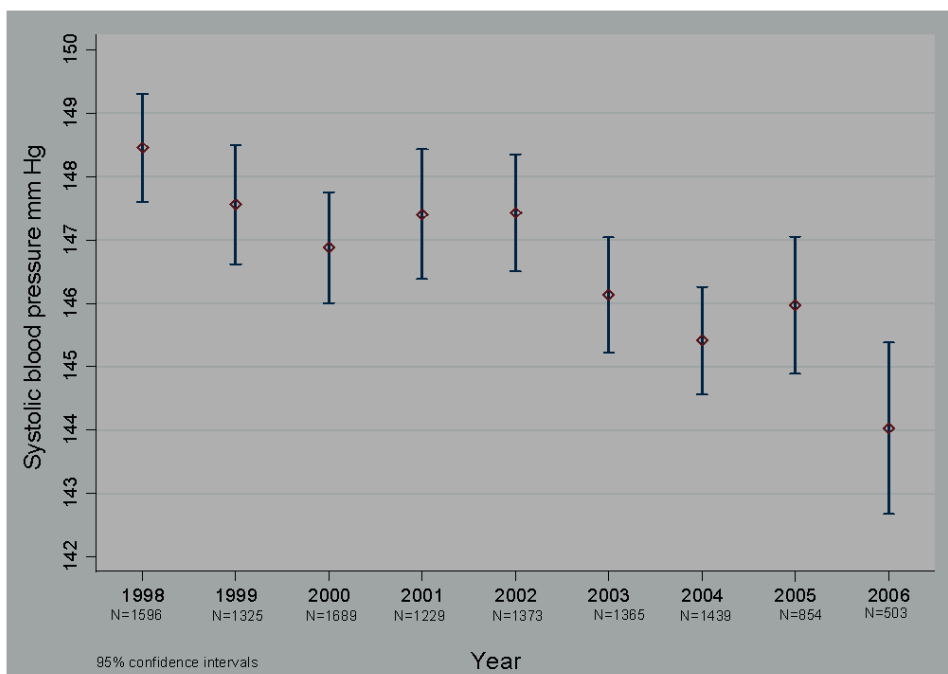


Figure 32 Mean diastolic blood pressure at first record in the cohort group (N=11373)

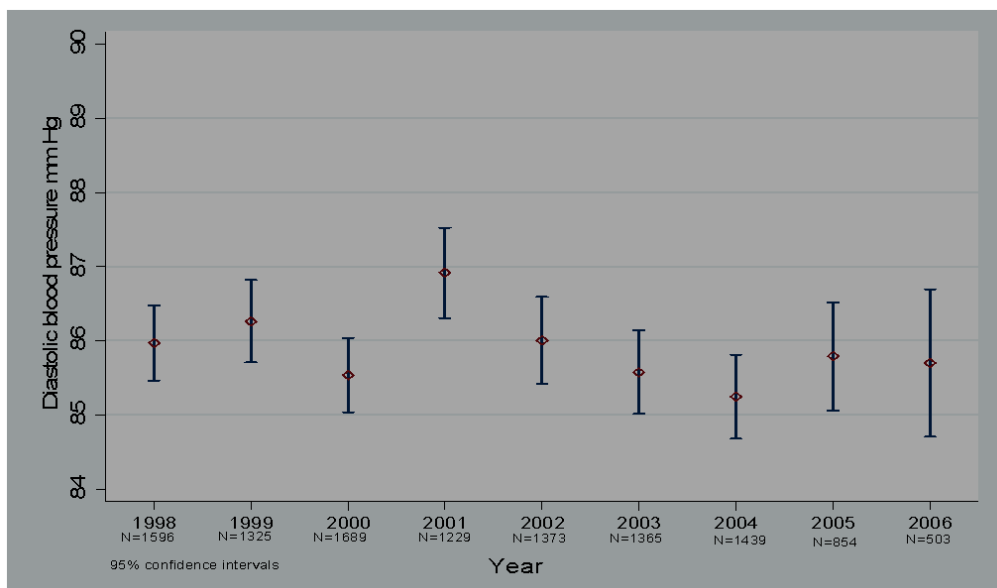


Figure 33 Annual mean systolic blood pressure in the cohort group (N=11373)

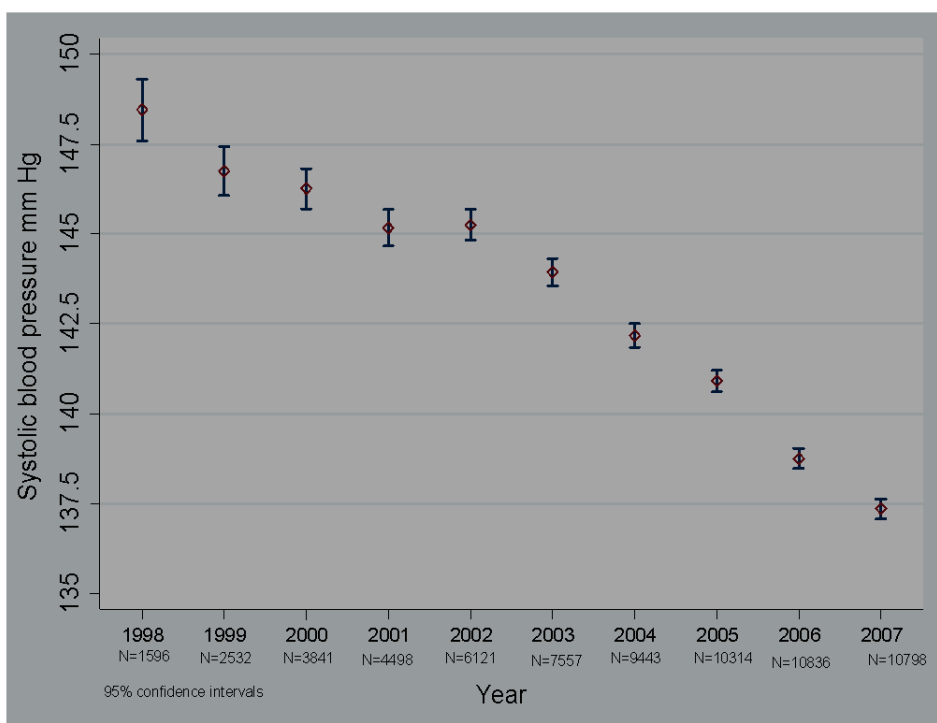
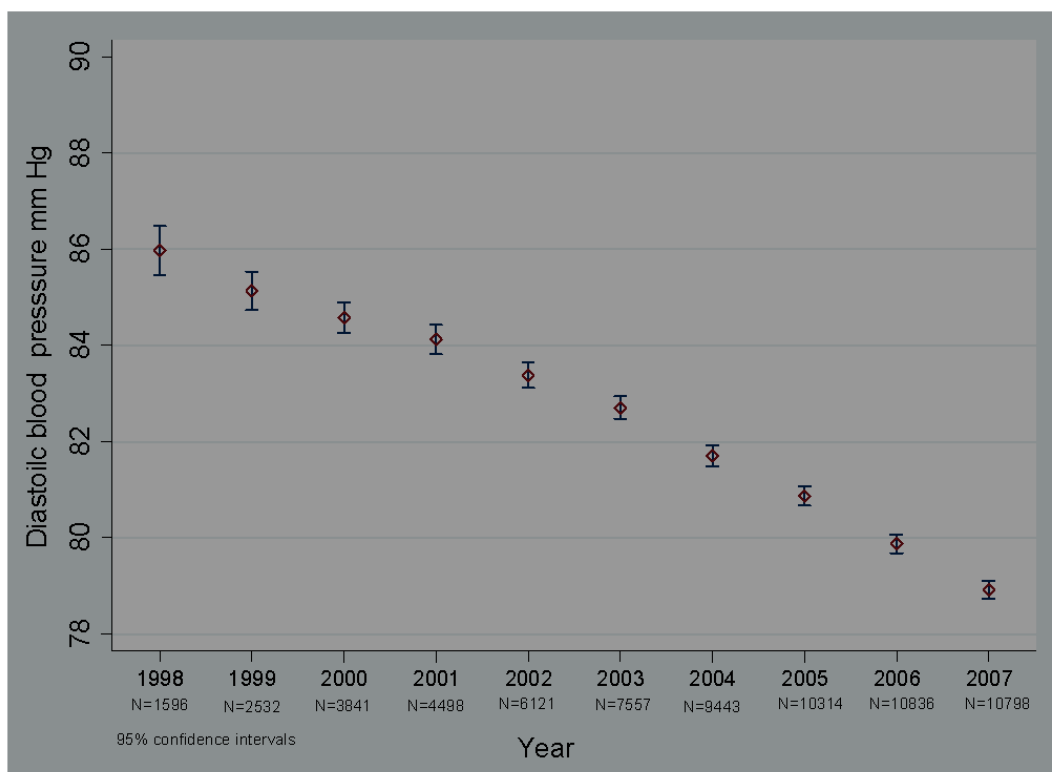


Figure 34 Annual mean diastolic blood pressure in the cohort group (N=11373)



Hierarchical survival frailty model

Five models are presented including different sample size from the data.

Models 1 and 2

Model 1 was performed using the total of included patients, 11373. BMI, cholesterol levels and smoking variables were excluded. The model was running up to 8350 iterations and the first 1330 were discharged. The total time was 27 hours. Model 2 included those patients who had no missing data in the variables used in the analysis. The posterior estimators were taken after running 17000 iterations. The first 1000 chains were discharged. The total time for running this model was 56 hours. For both models a high correlation was observed for the beta parameter of treatment. The correlation was corrected after using a lag of ten iterations.

The models produced similar results. For one year increase in age, there was a reduction in the risk of having controlled pressure over the study period. One year increase in age was associated with a reduction in the risk of having controlled blood pressure, posterior hazard ratio 0.99, (95% credible interval 0.99 - 0.99). There was no significant association between sex and the risk of having controlled blood pressure. Compared to patients of white origin, those of other ethnic origin were more likely to have controlled pressure over the period, hazard ratio 1.09 (95% credible interval 1.0 - 1.19). Although there were no significant differences, patients of black origin tended to have uncontrolled blood pressure over the period (Figure 35). Neither having an additional non cardiovascular comorbidity, nor having an additional cardiovascular comorbidity had a significant effect on the risk of having controlled hypertension. Increases in BMI tended to reduce the risk of having controlled pressure even though the estimators did not achieve significance. For those with overweight blood pressure control seems to improve but the credible interval has a long distribution. Then, this observation may change including a higher number of patients in this category (Figure 36). Higher levels in cholesterol were significantly associated with a reduction in the risk of having controlled blood pressure. For those patients with very high levels of cholesterol (over 6.1 mmol/L), the hazard risk was 0.94 (95% credible interval 0.91 – 0.98). The risk of having controlled blood pressure did not vary by smoking status. In model 1 being prescribed antihypertensive medication was negatively associated with having controlled blood pressure. However in model 2 this association disappeared after adjustment for BMI, cholesterol levels and smoking status (Table 46-47).

The risk of having controlled blood pressure was higher for patients registered after the introduction of QOF, hazard ratio 1.87 (95% credible interval 1.74- 2.00) and hazard ratio 2.05 (95% credible interval 1.94 – 2.16) in model 1 and model 1 respectively. That association was observed in both models. There was no variation in the individual hazard risk of having controlled pressure among practices with different number of registered patients or located in areas with different deprivation index. The distribution of random effects was similar across the practices (Figure 37).

Table 46 Posterior hazard ratio associated with associated with variables included in the model 1 (N=11373)

Variable	sd	Median	95 % CrI‡
Age *	0.676	0.99	0.99 - 0.99
Sex Reference Female	0.016	0.99	0.96 - 1.03
Ethnicity			
Black	0.021	0.97	0.96 - 1.03
South Asian	0.035	1.06	0.99 - 1.13
Other Asian	0.050	1.07	0.98 - 1.17
Other ethnicity	0.045	1.08	0.99 - 1.17
Unknown Referent White	0.041	1.09	1.02 - 1.17
Being prescribed antihypertensive medication at first entry Reference Not being prescribed antihypertensive medication	0.020	0.94	0.91 - 0.96
Presence of an additional cardiovascular comorbidity¶ Reference Those without additional cardiovascular comorbidity	0.018	0.94	0.98 - 1.02
Presence of an additional no cardiovascular Reference Referent those without additional non cardiovascular comorbidity	0.022	1.04	0.99 - 1.08
Smoking Reference no smoking	0.018	0.98	0.94 - 1.02
Deprivation index			
Category Intermediate	0.122	1.03	0.82 - 1.29
Category 2 most deprived Reference least deprived	0.123	1.00	0.79 - 1.27
Practice list			
Practices with 2836 to 4123 patients	0.142	1.07	0.83 - 1.38
Practices with 4124 to 5808 patients Reference practices with 806 to 2835 patients	0.140	1.018	0.78 - 1.32
Being registered after the introduction of QOF Reference Being registered before the introduction of QOF	0.024	1.87	1.74 - 2.00

sd standard deviation

‡Credible interval

*Age variable was age minus mean population age in the model

¶ Patients with at least one of the follow disease: coronary heart disease, diabetes mellitus, heart failure, atrial fibrillation, stroke or renal failure

¶¶ Patients with at least one of the follow disease: depression, asthma or chronic pulmonary disease (COPD)

Table 47 Posterior hazard ratio associated with variables included in the model 2 (N=9679)

Variable	sd	Median	95 % CrI‡
Age *	0.781	0.99	0.99 - 0.99
Sex Reference Female	0.018	0.95	0.98 - 1.02
Ethnicity			
Black	0.022	0.97	0.94 - 1.02
South Asian	0.038	1.07	0.99 - 1.15
Other Asian	0.053	1.07	0.97 - 1.18
Other ethnicity	0.048	1.09	1.00 - 1.19
Unknown Reference White	0.049	1.09	0.99 - 1.19
Being prescribed antihypertensive medication at first entry Reference Not being prescribed antihypertensive medication	0.022	0.96	0.92 - 1.00
Body mass index			
Overweight	0.021	0.97	0.93 - 1.01
Obesity I	0.024	0.95	0.91 - 1.00
Obesity II	0.033	0.96	0.89 - 1.03
Obesity III Reference BMI 20-24.9Kg/m²	0.045	0.97	0.88 - 1.06
Cholesterol			
High cholesterol 5.1 to 6.1 mm/L	0.019	0.98	0.94 - 1.02
Very high cholesterol >6.2 mm/L Reference Cholesterol<5.1 mmol/L	0.021	0.95	0.91 - 0.98
Presence of an additional cardiovascular comorbidity¶ Reference Patients without an additional cardiovascular comorbidity	0.020	0.98	0.94 - 1.02
Presence of an additional non- cardiovascular comorbidity ¶¶ Referent Patients without non-cardiovascular comorbidity	0.023	1.04	0.99 - 1.09
Smoking Reference no smoking	0.023	0.99	0.96 - 1.05
Deprivation index			
Category Intermediate	0.118	1.023	0.82 - 1.28
Category most deprived Reference least deprived	0.119	0.9984	0.79 - 1.26
Practice list			
Practices with 2836 to 4123 patients	0.142	1.07	0.82 - 1.38
Practices with 4124 to 5808 patients Reference Practices with 806 to 2835 patients	0.141	1.02	0.78 - 1.34
Being registered after the introduction of QOF Reference Being registered before the introduction of QOF	0.055	2.05	1.94 - 2.16

‡Credible interval; sd standard deviation

*Age variable was age minus mean population age in the model

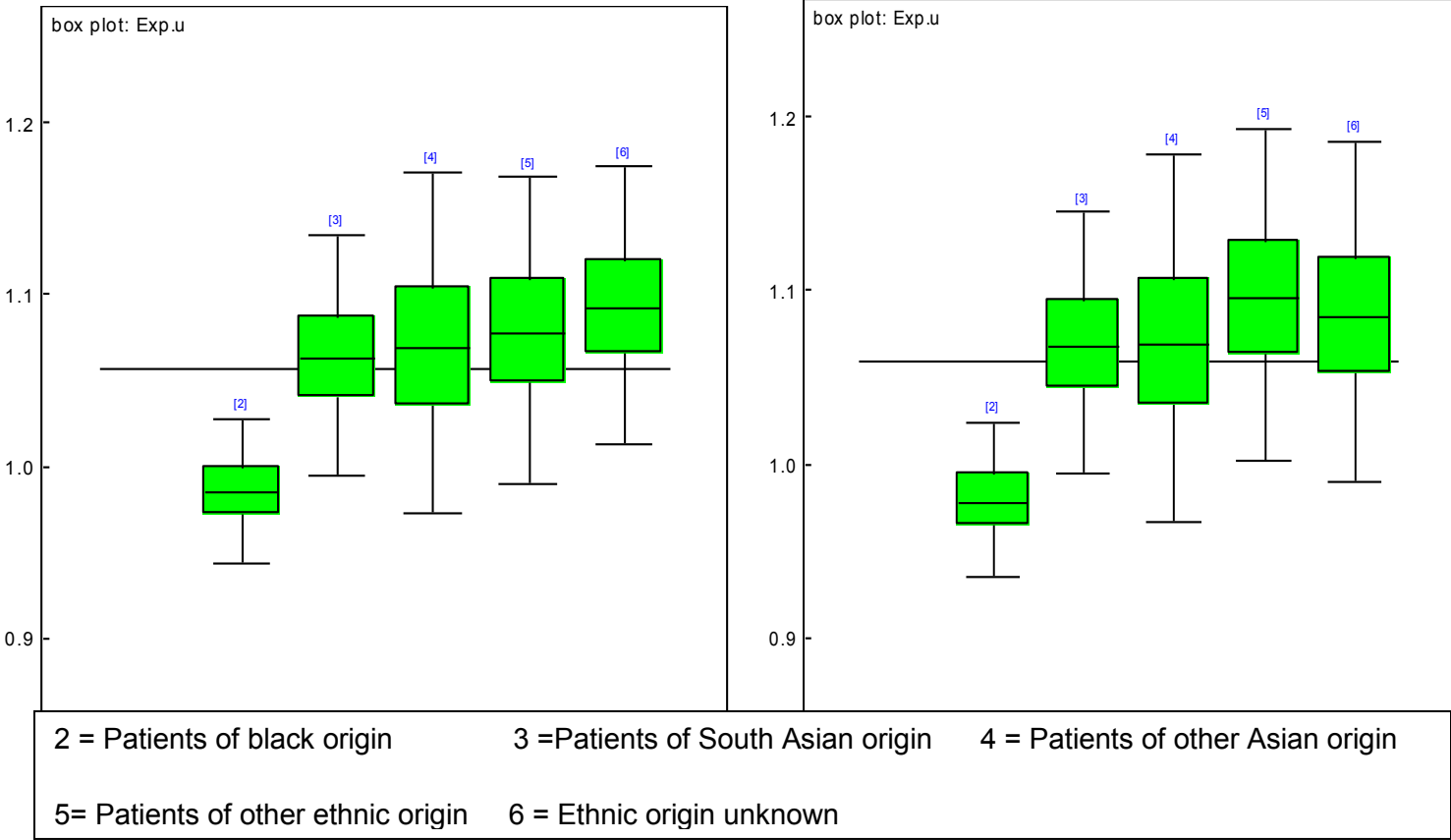
¶ Patients with at least one of the follow disease: coronary heart disease, diabetes mellitus, heart failure, atrial fibrillation, stroke or renal failure

¶¶ Patients with at least one of the follow disease: depression, asthma or chronic pulmonary disease (COPD)

Figure 35 Box plot of the hazard ratio for having controlled blood pressure by race/ethnic Models 1 and 2

Population Model 1

Population Model 2



Model 3

For this model I included only patients without cardiovascular comorbidity to test the effect of being prescribed the 2006 NICE treatment at first entry on having controlled blood pressure over the period. The model was running using a lag of ten iterations to reduce the autocorrelation in the parameter for the intercept. The model was run up to 11000 iterations. The first 1000 iterations were discharged. The total time for running this model was 22 hours. (Table 48)

Similar to what observed in models 1 and 2, a year increase in age was associated with a reduction in the risk of having controlled blood pressure, 0.99 hazard risk (95% credible interval 0.99 – 0.99). The association between sex and having controlled blood pressure was no significant. Compared to patients of white origin, those of South Asian origin were more likely to have controlled blood pressure, 1.05 hazard ratio (95% credible interval 1.003 – 1.09) (Figure 38). Although the association was no statistical significant, patients of black origin tended to have uncontrolled blood pressure over the period. The presence of other non-cardiovascular comorbidity and smoking did not significantly modify the risk of having controlled blood pressure. There was a negative association between increases in body index mass and having controlled blood pressure. This association was significant for those in the category obesity I, 0.93 hazard ratio (95% credible interval 0.88 – 0.99). The association between cholesterol levels and having controlled blood pressure was not significant. Similarly there was no significant association between smoking and having controlled blood pressure. Being prescribed the 2006 NICE recommended treatment was not significantly associated with having controlled blood pressure. However there was a trend showing a positive association between being on NICE treatment and having controlled blood pressure.

Patients registered with the practices after the introduction of QOF were more likely to have controlled blood pressure, 2.06 hazard ratio (95% credible interval 1.93 – 2.19). As occurred in models 1 and 2, the distribution of random effects was similar between practices (Figure 37).

Table 48 Posterior hazard ratio associated with variables include the model 3 (N = 6947)

Variable	sd	Median	95 % CrI
Age *	0.001	0.99	0.99 - 0.99
Sex	0.021	0.97	0.93 - 1.01
Reference female			
Ethnicity			
Black	0.014	0.99	0.97 - 1.02
South Asian	0.024	1.05	1.00 - 1.09
Other Asian	0.033	1.02	0.96 - 1.08
Other ethnicity	0.028	1.05	0.99 - 1.11
Unknown	0.027	1.05	0.99 - 1.09
Referent white			
Being prescribed antihypertensive medication at first entry			
NICE treatment**	0.150	1.07	0.93 - 1.39
Other treatment	0.149	1.04	0.79 - 1.38
Reference not being prescribed antihypertensive medication			
Body mass index			
Overweight	0.026	0.97	0.93 - 1.03
Obesity I	0.028	0.93	0.88 - 0.99
Obesity II	0.040	0.97	0.89 - 1.05
Obesity III	0.054	0.99	0.89 - 1.10
Reference BMI 20, 24.9 Kg/m ²			
Cholesterol			
High cholesterol >5.1 mmol/L	0.025	1.01	0.96 - 1.06
Very high cholesterol >6.1 mmol/L	0.026	0.97	0.92 - 1.02
Reference Cholesterol <5.1 mmol/L			
Presence of an additional non- cardiovascular comorbidity ††			
Reference			
Those without non-cardiovascular comorbidity			
Smoking	0.027	1.01	0.96-1.06
Reference no smoking			
Deprivation index			
Category Intermediate	0.120	1.02	0.81 - 1.28
Category 2 most deprived	0.125	1.02	0.79 - 1.29
Reference least deprived			
Practice list			
Practices with 2386 to 4123 patients	0.150	1.07	0.82 - 1.39
Practices with 4124 to 5808 patients	0.149	1.04	0.79 - 1.38
Reference			
Practices with 806 to 2835 patients			
Being registered after the introduction of QOF	0.065	2.06	1.93 - 2.19
Reference			
Being registered before the introduction of QOF			

†Credible interval; sd standard deviation

*Age variable was age minus mean population age in the model

† Patients with at least one of the follow disease: coronary heart disease, diabetes mellitus, heart failure, atrial fibrillation, stroke or renal failure

†† Patients with at least one of the follow disease: depression, asthma or chronic pulmonary disease (COPD)

**Those being prescribed first monotherapy recommended treated as established in 2006 NICE guideline

Figure 36 Distribution of hazard ratio associated with BMI in population from models 2 and 3

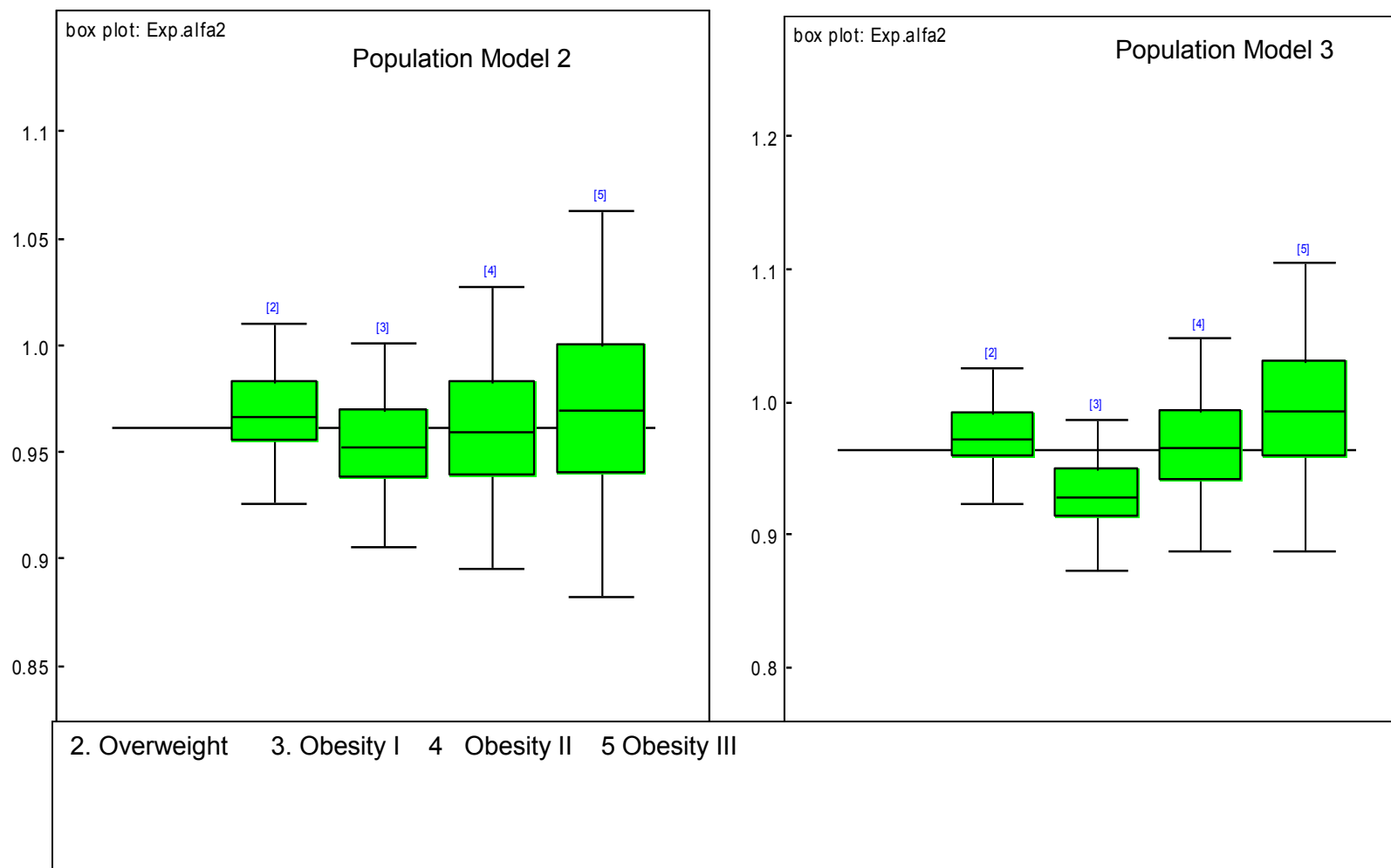


Figure 37 Box plot of mean for random effects in 28 practices Models 2 and 3

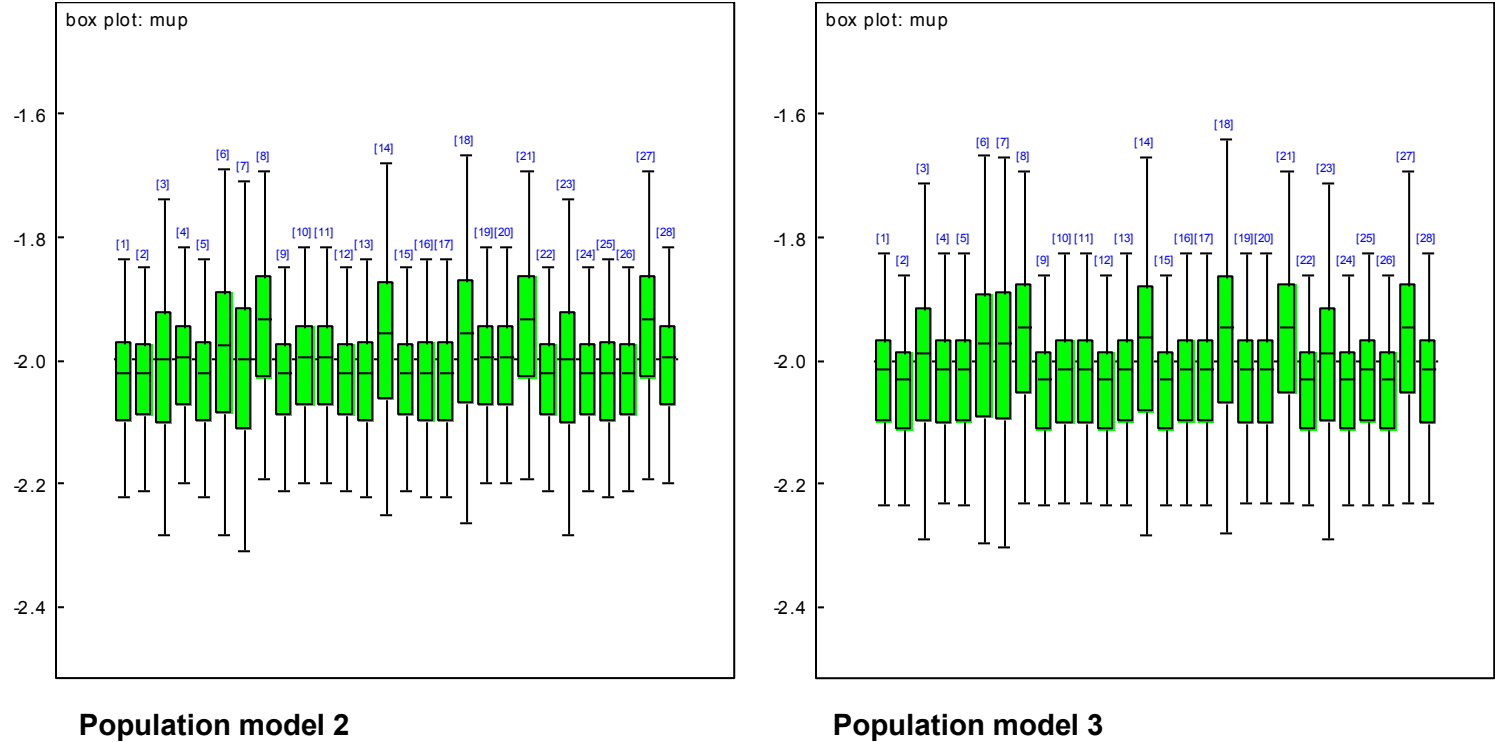
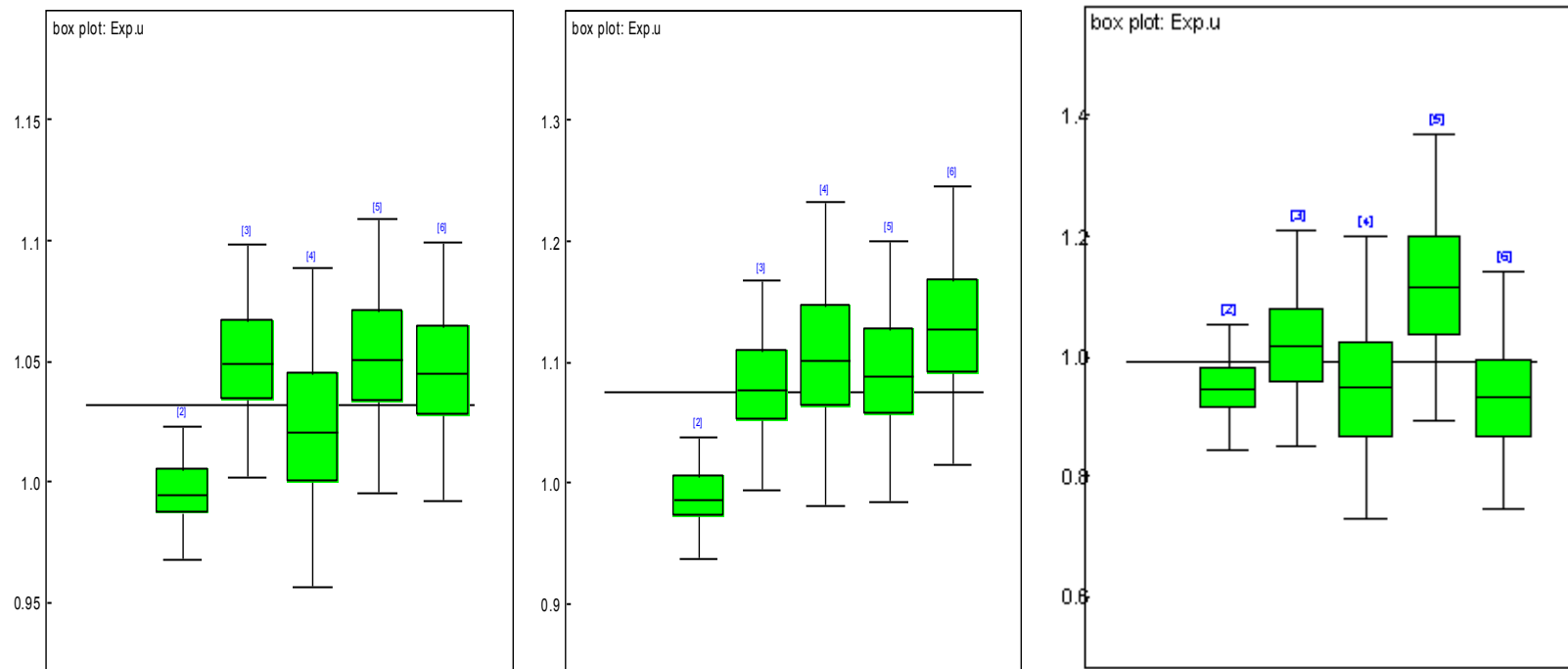


Figure 38 Box plot of hazard ratio for having controlled blood pressure by race/ethnic. Models 3, 4 and 5



2=Patients of black origin 3 = Patients of South Asian origin 4= Patients of other Asian origin

5= Patients of other origin 6 = Unknown

Model 4

For this model, I included only those who received antihypertensive treatment at first entry. The model was run use a lag of ten iterations to reduce the autocorrelation in the parameter for the intercept. The model was run up to 8700 iterations and the first 1000 were discharged. The total time was 29 hours.

Similar to the previous models, age was negatively associated with the risk of having controlled blood pressure, 0.99 hazard ratio (95% credible interval 0.99 – 0.99). There was not significant association between sex, the presence of other cardiovascular and non-cardiovascular comorbidities and having controlled blood pressure. Being registered after the introduction of QOF was positively associated with having controlled blood pressure 2.09 hazard ratio (95% credible interval 1.97 – 2.21). Compared to white, the risk of having controlled blood pressure was higher in those patients with unknown race/ethnic origin, 1.23 hazard risk (95% credible interval 1.02 – 1.25). None of the included practice characteristics were significantly associated with variation in the individual risk. (Table 49, Figure 38-40)

Table 49 Posterior hazard ratio of patient characteristics included in the model 4(N=7885)

Variable	sd	Median	95 % CrI‡
Age *	0.001	0.99	0.99 - 0.99
Sex	0.020	0.99	0.95 - 1.03
Reference female			
Ethnicity			
Black	0.025	0.99	0.95 - 1.03
South Asian	0.043	1.08	0.99 - 1.17
Other Asian	0.062	1.1	0.99 - 1.23
Other ethnicity	0.054	1.09	0.99 - 1.20
Unknown	0.058	1.13	1.02 - 1.25
Reference white			
Body index mass			
Overweight	0.024	0.97	0.93 - 1.02
Obesity I	0.027	0.96	0.91 - 1.02
Obesity II	0.037	0.96	0.89 - 1.04
Obesity III	0.053	1.02	0.92 - 1.13
Reference BMI 20-24.9 Kg/m²			
Cholesterol			
High cholesterol >5.1mmol/L	0.022	0.98	0.94 - 1.03
Very high cholesterol >6.1mmol/L	0.024	0.96	0.91 - 1.00
Reference Cholesterol <5.1 mmol/L			
Presence of an additional cardiovascular comorbidity¶	0.021	0.98	0.94 - 1.03
Reference			
No additional cardiovascular comorbidity			
Presence of an additional no cardiovascular comorbidity¶¶	0.026	1.03	0.98 - 1.08
Reference			
Referent those without additional non cardiovascular comorbidity			
Smoking	0.026	1	0.95 - 1.05
Reference no smoking			
Deprivation index			
Category intermediate	0.121	1.02	0.81 - 1.28
Category Most deprived	0.118	0.98	0.78 - 1.24
Reference least deprived			
Practice list			
Practices with 2836 to 4123 patients	0.142	1.04	0.79 - 1.36
Practices with 4124 to 5808 patients	0.141	1.01	0.77 - 1.32
Reference practices with 806 to 2835 patients			
Being registered after the introduction of QOF	0.062	2.08	1.97 - 2.21
Reference			
Being registered before the introduction of QOF			

‡Credible interval; sd standard deviation

*Age variable was age minus mean population age in the model

¶ Patients with at least one of the follow disease: coronary heart disease, diabetes mellitus, heart failure, atrial fibrillation, stroke or renal failure

¶¶ Patients with at least one of the follow disease: depression, asthma or chronic pulmonary disease (COPD)

Figure 39 Distribution of posterior hazard ratio by body mass index. Models 4 and 5

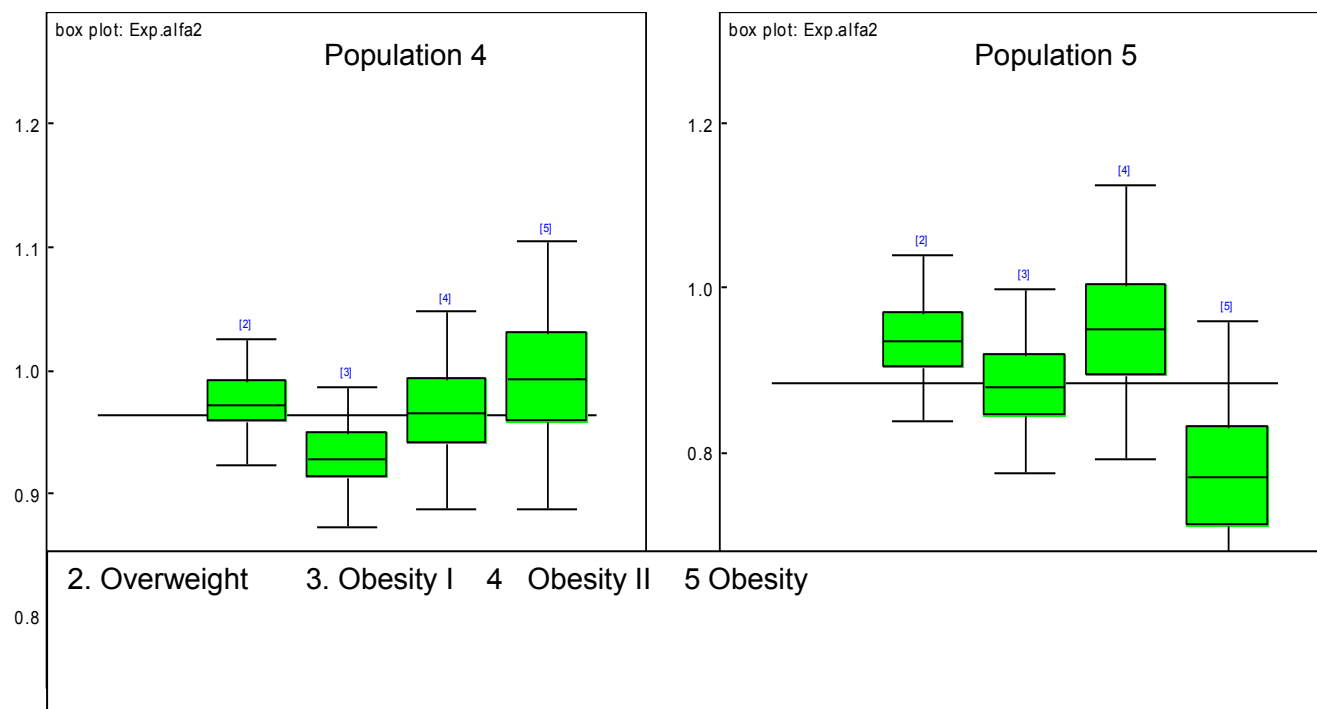
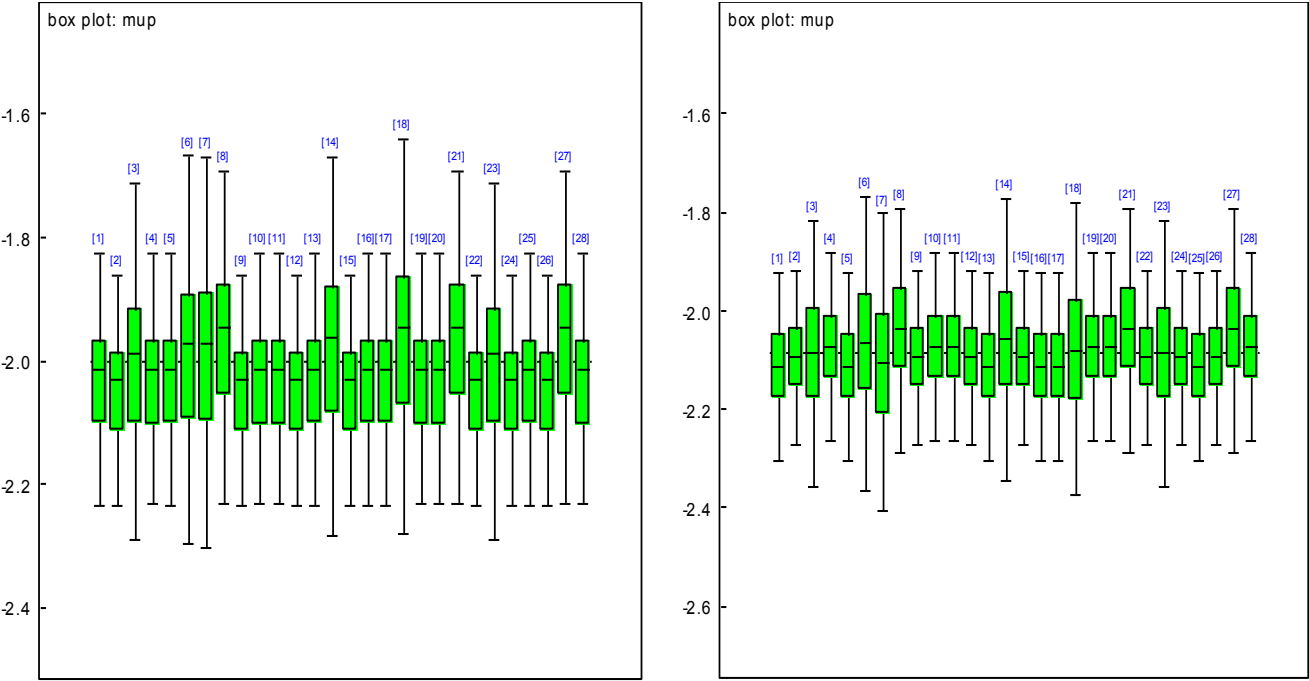


Figure 40 Box plot of mean for the random effects in 28 practices. Models 4 and 5



Model 5

For this model I included only those who were not prescribed antihypertensive treatment at first entry. The posterior estimators were taken after running 11000 iterations. The first 1000 were discharged. The model was run used a lag of 10 iterations. A high autocorrelation in the parameter for the intercept was observed. The total time was 15 hours.

The findings were similar to those described above. Age was negatively associated with having controlled blood pressure 0.99 hazard ratio (95% credible interval 0.99 – 0.99). There were no significant association between sex, having other cardiovascular or no cardiovascular comorbidity or smoking and having controlled blood pressure. There was a negative association between body index mass and having controlled pressure. The association was significant for those with obesity grade III 0.77 hazard ratio (95% credible interval 0.61 – 0.97) respectively. There was also a negative association between cholesterol and having controlled blood pressure. Those with very high cholesterol had a lower risk of having controlled blood pressure 0.89 hazard ratio (credible interval 95% 0.79-0.99). The risk of having controlled pressure was similar between patients of different ethnic groups. (Table 50, Figures 38-40)

Patients registered after the introduction of QOF were more likely to have controlled blood pressure with a 1.99 hazard ratio (95% credible interval 1.72 – 2.28). As it was observed in the previous models, the distribution of the random effects was similar across the practices.

Table 50 Posterior hazard ratio associated with variables included in the model 5 (N=1794)

Variable	sd	Median	95 % CrI‡
Age *	0.002	0.99	0.99 - 0.99
Sex	0.045	0.99	0.91 – 1.09
Reference female			
Ethnicity			
Black	0.053	0.95	0.84 -1.06
South Asian	0.092	1.02	0.85 -1.21
Other Asian	0.119	0.94	0.74 -1.19
Other ethnicity	0.123	1.11	0.89 -1.37
Unknown	0.099	0.93	0.75 -1.14
Referent white			
Body mass index			
Overweight	0.051	0.94	0.84 -1.04
Obesity I	0.057	0.88	0.78 -1.00
Obesity II	0.084	0.95	0.79 -1.12
Obesity III	0.091	0.77	0.61 – 0.96
Reference			
BMI 20-24.9 Kg/m ²			
Cholesterol			
High cholesterol >5.1 mmol/L	0.048	0.94	0.85 – 1.04
Very high cholesterol >6.1 mmol/L	0.051	0.89	0.79 – 0.99
Reference			
Cholesterol <5.1 mmol/L			
Presence of an additional cardiovascular comorbidity¶	0.055	0.97	0.87 – 1.08
Referent			
Those without additional cardiovascular comorbidity			
Presence of an additional non cardiovascular comorbidity ¶¶	0.060	1.09	0.98 – 1.22
Referent those without additional non cardiovascular comorbidity			
Smoking	0.053	0.98	0.88-1.09
Reference no smoking			
Deprivation index			
Category intermediate	0.159	1.03	0.76 -1.38
Category Most deprived	0.161	1.06	0.79 -1.43
Reference least deprived			
Practice list			
Practices with 2836 to 4123 patients	0.220	1.17	0.81 -1.68
Practices with 4124 to 5808 patients	0.185	1.08	0.78 -1.51
Reference practices with 806 to 2835 patients			
Being registered after the introduction of QOF	0.144	1.99	1.72 -2.28
Reference			
Being registered before the introduction of QOF			

‡Credible interval; sd standard deviation

*Age variable was age minus mean population age in the model

¶ Patients with at least one of the follow disease: coronary heart disease, diabetes mellitus, heart failure, atrial fibrillation, stroke or renal failure

¶¶ Patients with at least one of the follow disease: depression, asthma or chronic pulmonary disease (COPD)

Sensitivity analysis for hierarchical priors

I compared the posteriors estimators of the age coefficient produced by a gamma distribution (0.0001, 0.0001) and gamma distribution (1, 0.5) for the precision of the practices. The analysis was performed using the population included in the model 2.

Figure 41 Beta coefficient of age for a gamma (0.0001, 0.0001) prior distribution

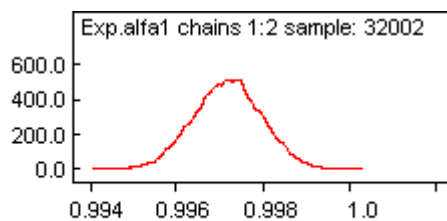
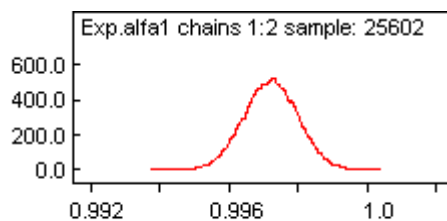


Figure 42 Beta coefficient of age for a gamma (1, 05) prior distribution



As it can be seen in figure 41 and figure 42 the posterior distribution of the beta coefficient for age is similar regardless of the prior distribution used for the precision. In other words, the result has not markedly been affected by the variation in the priors used for the precision.

9.4 The Frequentist model

To compare the results from the Bayesian framework, a parametric frailty shared survival model was also performed in a Frequentist framework. The comparison was based on the model 2. This model used a population that had no missing values in all variables included in the analysis. The model was run using the `streg` function provided by the STATA Corporation v. 11 statistical program.

The model

In this frequentist framework, the model was formed by two components. The first one was based on the individual's characteristics and aimed to model the potential heterogeneity occurring among individuals with multiples measurements of the outcome. This is the frailty component for the heterogeneity among individuals. The second one represented the variability between patients nested into practices. This component was setting using the practice code which is called the shared frailty model (816). The shared frailty was assumed to have a gamma distribution. The time calculation was performed using the Anderson and Gill model for STATA (817-818). Thus, sequentially from the year of the registration to one event a one period time was counted and from this one event to next one another time event until completing all follow-up periods. An example is shown below (Table 5):

Table 51 Time calculation for the Frequentist model

Patient	Initial time	Time	Event
A	0	3	1
A	3	5	0
A	4	6	1
A	6	10	0
B	0	7	0
B	7	9	1

Explanation

Patient A had the event 1 in his three initial follow-up periods, then two periods with event 0, the following two with event 1 and the final four periods with event 0.

Patient B had the event 0 in his seven initial periods and then two periods with event 1.

A Weibull distribution was used for the model with the following mathematical formulation

$$h_{ij}(t | \alpha_i) = \alpha_i \exp(x_{ij} \beta) p t^{p-1}$$

Where h is the hazard ratio for each j individual into the each practice i . The hazard ratio is multiplied by the shared frailty α_i . β is the coefficient of x_{ij} variables and p is the shape of the model.

Results

The results are shown in the table 6. Increase in age was associated with a reduction in the risk of having controlled blood pressure, hazard ratio (HR) 0.98 (95% CI 0.98 – 0.99). Women were less likely to have controlled blood pressure over the period HR 0.89 (95% CI 0.84 – 0.96). Compared with white patients, those of other Asian origin, other ethnic origin and those of unknown origin were more likely to have controlled pressure with HR 1.33 (95% CI 1.11 – 1.59), 1.23 (95% CI 1.05 – 1.44) and 1.26 (95% CI 1.06 – 1.49) respectively. There were no significant differences in the risk of having controlled pressure between whites and those of black origin or South Asian origin. Those having an additional cardiovascular comorbidity were more likely to have controlled pressure HR 1.13 (95% CI 1.05 – 1.21). Similarly those with an additional no cardiovascular comorbidity were less likely to have controlled blood pressure 1.09 (95% CI 1.01 – 1.19). Obesity grade I and Obesity grade III reduced the risk of having controlled blood pressure HR 0.88 (95% CI 0.80 – 0.97) and HR 0.75 (95% CI 0.63 - 0.91) respectively. Patients registered after the introduction of QOF were more likely to have controlled blood pressure related to those who were registered in the previous period HR 1.90 (95% CI 1.73 – 2.09) (Table 52).

Table 52 Hazard ratio associated with factors affecting blood pressure control in the Frequentist model 2 (N=9679)

Variable	HR	standard error	95 % CrI‡	p value
Age	0.99	0.0015	0.98 - 0.99	<0.0001
Sex Reference female	0.89	0.0313	0.84 - 0.96	0.002
Ethnicity				
Black	0.99	0.0444	0.91 - 1.08	0.946
South Asian	1.12	0.0742	0.98 - 1.27	0.099
Other Asian	1.33	0.1209	1.11 - 1.59	0.002
Other ethnicity	1.23	0.101	1.05 - 1.45	0.010
Unknown Reference white	1.26	0.107	1.06 - 1.49	0.007
Body index mass				
Overweight	0.97	0.0377	0.90 - 1.05	0.471
Obesity I	0.88	0.0432	0.80 - 0.97	0.012
Obesity II	0.92	0.0622	0.81 - 1.06	0.246
Obesity III Reference BMI 20-24.9 Kg/m²	0.75	0.072	0.63 - 0.91	0.003
Cholesterol				
High cholesterol >5.1mmol/L	0.97	0.377	0.90 - 1.05	0.471
Very high cholesterol >6.1mmol/L Reference Cholesterol <5.1 mmol/L	0.93	0.0408	0.86 - 1.02	0.120
Presence of an additional cardiovascular comorbidity¶ Reference No additional cardiovascular comorbidity	1.13	0.428	1.05 - 1.21	0.002
Presence of an additional no cardiovascular comorbidity¶¶ Reference Referent those without additional non cardiovascular comorbidity	1.09	0.474	1.00 - 1.19	0.033
Being prescribed antihypertensive medication at first entry Reference not being prescribed antihypertensive medication	0.99	0.461	0.91 - 1.09	0.963
Smoking Reference no smoking	0.98	0.435	0.90 - 1.07	0.702
Deprivation Index				
Category intermediate	0.97	0.1124	0.78 - 1.23	0.853
Category Most deprived Reference least deprived	0.82	0.0923	0.66 - 1.01	0.085
Practice list				
Practices with 2836 to 4123 patients	0.78	0.0974	0.62 - 1.00	0.052
Practices with 4124 to 5808 patients Reference practices with 806 to 2835 patients	0.91	0.1167	0.71 - 1.17	483
Being registered after the introduction of QOF Reference Being registered before the introduction of QOF	1.9	0.0907	1.73 - 2.09	<0.0001

‡Confidence interval; sd standard error

¶ Patients with at least one of the follow disease: coronary heart disease, diabetes mellitus, heart failure, atrial fibrillation, stroke or renal failure

¶¶ Patients with at least one of the follow disease: depression, asthma or chronic pulmonary disease (COPD)

9.5 Discussion

In the included cohort of hypertensive patients managed in 28 general practices, the control of blood pressure was improved over the 10 years study period. Thus there has been a reduction in both diastolic and systolic blood pressure over the period. The individual baseline characteristics negatively associated with controlled blood pressure were one year increase in age, BMI and high levels of cholesterol. Compared to patients of white origin, patients of black origin tended to have uncontrolled blood pressure and those of South Asian origin tended to have controlled blood pressure over the period. Those registered after the introduction of QOF were more likely to have controlled blood pressure.

Over the study period there have been improvements in blood pressure control, the percentage of patients with controlled hypertension increased from 37.0% to 62.4%. Patients included in this cohort had four median visits over the study period. In an analysis of blood pressure records from 236467 hypertensive patients, Carey et al observed a decrease in the number of blood pressure records below 150/90 mm Hg from 2000 to 2005 (699). The observed reductions in blood pressure may reflect the impact of continuity of care in blood pressure control. Hypertensive patients included in the analysis were benefit from continuity in their health care. The available information over 10 year period and being contact with the same health provider are essential features of continuity of care in primary care (819). Watson et al reported the benefit of the continuity of care in a clinical trial. Patients randomized to the group managed by same health provider over the study period had fewer hospitalizations and patients referred being more satisfactory with the services (820). Howard et al showed that hypertensive patients with access to same health provider had better blood pressure control than those who did not have the same health provider over the study period (821). In a cross-sectional study, He et al also identified that those who refereed have been treated by the same health provider were more likely to have controlled blood pressure than those who have received treatment for a different provider (317). Bolen et al also found that hypertensive patients were more likely to receive an additional therapy when they regular visit the same health provider (822). Although there have been other national initiatives such as salt reduction to improve blood pressure control, its impact could have been modest (612). Since the current variations in blood pressure control may reflect the impact of having periodical contacts with the same provider.

The blood pressure status varied across the period. Thus, 65% of the total patients registered with dataset had periods controlled blood pressure and periods without controlled blood pressure. It is known that blood pressure levels had both random variability and systematic variability (8, 823). For hypertensive patients on hypertensive treatment the variability increases over the period. Keenan et al demonstrated that increases in blood pressure identified in periods closer to initiating therapy could be false positive increases (806). Mabotuwana et al also documented this variability in an analysis of records from hypertensive patients being treated in general practices (807). They found that 31% of the included hypertensive patients did not have controlled blood pressure over three months period (807). The variations in blood control status observed in the current cohort also concur with these findings.

Patients registered after the introduction of QOF were more likely to have controlled pressure. The association was significant accounting for all individual variables contained in the register and the number of patients registered at the beginning of the period in each practice and the deprivation index. The association between the introduction of QOF and blood pressure control has been controversial. In an analysis of 470725 hypertensive patients, Serumaga et al did not find differences in blood pressure rates after the introduction of QOF in a study using interrupted time series. They used a target of 150/90 mm Hg blood pressure to assess variations in blood pressure control. Although this target is the one established in the QOF guidance for the assessment of the performance of general practices, it could have low sensitivity to capture differences in blood pressure control (683). However, Ashworth et al reported that improvements in blood pressure control and monitoring have been observed after the introduction of QOF. This analysis was performed using aggregated data at practice level (498). In a longitudinal analysis using data from 35 practices located in Northern California, Lester et al documented that the rate of blood pressure control continually improved in periods in which financial incentives were attached to the achievement of targets. They could not associate the variation in the rate of blood pressure control with the introduction of the payment system (824).

In the studies mentioned above the impact of QOF on blood pressure control was based on aggregated indicators taking from practice records. By comparison, the current analysis was

done using the individual records. The assessment of the QOF introduction was performed by using a variable identifying whether or not the patient was registered before or after the introduction of QOF. The variable intended to compare those who were exposed to the intervention with those who were not at first entry. The positive effect associated with being registered after the introduction of QOF means that those patients had more periods with control blood pressure. The association is not explained by having lower blood pressure at first entry as the model account for the individual basal risk. The association could be considered due to an effect of the longer observation time for those registered before the introduction of QOF. However patients were registered consecutively over the study period and the median observation time was four years. The association also seems to be strength as it was based on the total available blood pressure measurement rather than one estimation point in time.

This patient cohort was also exposed to the use of national guidelines for the management of hypertension. I did not find a significant association between being prescribed antihypertensive treatment at first entry and having controlled blood pressure over the period. However the use of 2006 NICE recommended treatment at first entry seems to have a positive association with having controlled blood pressure. The posterior distribution of the associated hazard ratio associated with the variable of using the recommended treatment tended to be towards positive values. Moreover those who were prescribed a different medication tended to have uncontrolled blood pressure. The assessment of the recommended therapy was done for all included patients regardless of the year entry because the recommended treatment was already known before the introduction of the guidance (223). In primary care settings, others authors have also observed that patients prescribed antihypertensive medication did not always achieve blood pressure targets (314, 397). That could be due to fact that hypertensive patients frequently stopped using antihypertensive medication even in clinical trials (296-297). Therefore the described association could change if information about adherence is considered in the analysis. Although the efficacy of antihypertensive therapy for the management of high blood pressure control is unquestionable (142), these observations give light on the fact in primary care settings improvements in blood pressure control go beyond prescribing antihypertensive drug. They also suggested a possible positive impact of using age-ethnic oriented prescribing on blood pressure control.

I found that for each year increase in age, there has been a reduction of 0.01% in the hazard risk of having controlled blood pressure. In primary care settings the association between age and poor blood pressure control has been recognized (205, 287, 289). This association has been independent from social, education or other health service conditions. The reasons for that association have not been completely elucidated. The well-established increase in systolic blood pressure with age may account for some the association (73). This increase has been attributed to reductions in elasticity and compliance of the central and peripheral vessel with age (825). This variation occurs regardless of sex and race/ethnic origin (826). Even under controlled conditions, reductions in systolic blood pressure are less achievable than reductions in diastolic blood pressure (214). Therefore the achievability of lower systolic blood pressure levels in elderly hypertensive patients has been a matter of controversy. However, results from the JATOS study revealed that blood pressure levels below 140/90 mm Hg are possible to obtain in patients aged 65 years and over. In the study 65% of hypertensive patients achieved his target among those to who the target was applied (198). Reassuring aging is a significant factor for having uncontrolled pressure. The limitations in modifying the established changes in vascular vessel could account for this association.

A negative association between increases in BMI and having controlled blood pressure was observed. The association was significant particularly in those who were not prescribed medication at first entry. Obesity have been recognised as a risk factor for having uncontrolled blood pressure (287, 827). The association relies on the positive relationship between increases in weight and blood pressure levels (118, 120, 828). Lowering weight leads to reductions in blood pressure (154, 156). However for hypertensive patients undertaken in primary care, reductions in body index mass have not been well attained (156). Low adherence to lowering weight interventions account for the most frequently reason (158). The impact of obesity on blood pressure control has not been quantified but it is known that body index mass over 22.5 kg/m² is risk for vascular mortality (829). There is a potential for improving blood pressure control by lowering BMI

Compared to hypertensive patients of white origin, patients of other ethnic group were more likely to have controlled blood pressure adjusted for BMI, cholesterol, smoking, age, sex, the presence of other cardiovascular comorbidity and non cardiovascular comorbidity and practice characteristics. Patients of black origin tended to have uncontrolled blood pressure and

those of Asian origin tended to have controlled blood pressure over the period. Hence there seems that under similar conditions of care, the differences in blood pressure control between ethnic groups tended to disappear. Howard et al revealed that there were not differences in blood pressures control rates among patient of different ethnic origins when they have been attending by the same provider under similar conditions (821). Rehman et al also revealed that hypertensive patients of black origin being treated in the Department of Veterans Affairs (VA) services had better blood pressure control than those in non-VA services (360). In the analysis of Health Survey for England, Nazroo et al revealed that differences in blood pressure control between patients of white origin and those of other ethnic origin are minimal (495). However, patients of black origin have been found less likely to achieve the target of 140/90 mm Hg in reports from some general practices in London (496-497). There seems that despite biological, social or behaviour conditions present among patients of different ethnic origin, primary care services have the potential to reduce differences in blood pressure control between ethnic groups.

There were not significant associations between the presence of other cardiovascular and non-cardiovascular comorbidities and blood pressure control over the period. However I did not disintegrate the effect of any particular disease due to the small numbers in each group to make comparisons across the period. However the impact of other comorbidities such as depression on blood pressure control has varied across different studies (377).

Comparison between the Frequentist and Bayesian models

The results of the Frequentist model 2 look similar for all variables to those produced by the Bayesian model 2. The only differences were for the coefficients associated with patients of other Asian group, unknown ethnicity, having an additional cardiovascular comorbidity and having an additional no cardiovascular comorbidity. All of them were significant and positively associated with having controlled blood pressure. By contrast, in the Bayesian model 2 these coefficients were not significantly associated with the probability of having controlled blood pressure. However the directionality of the association was similar except for the coefficient of having an additional cardiovascular comorbidity variable. An explanation for these differences will be addressed below.

I aimed to develop a Frequentist model as comparable as possible to the Bayesian model. However some considerations are addressed to explain the reasons for the mentioned discrepancies and support the potential benefit of using a Bayesian approach in the analysis of the current data.

Firstly the Frequentist formulation does not completely account for the hierarchical structure of the data. The formulation included a dummy variable indicating to which practice each patient belonged. However this formulation did not allow for including the practice variables in the practice level model. And the practice-level variables such as deprivation index and practice list were assigned as a dummy variable for each individual. Therefore the variability of the practices due to practice level characteristics is not taken into account by the model. In other words, the random effects due to between practice variability due to practice characteristics are not measured in the model. As a consequence the standard errors of the model may be inaccurate (798-799).

The frequentist model did not provide the estimations of the parameters associated with practice level. Although it accounted for the heterogeneity of the practices, the model was unable to estimate the effects of each practice. By contrast, the Bayesian model incorporates both the variability within practices and between practices. This allows us to estimate regression parameters for practices and practice variables. Hence, the Bayesian model can provide the uncertainty at both levels.

The frequentist model did not fit the data completely according to the pattern of the observed residuals. In the frequentist approach, the analysis of hierarchical data is affected by the sample size. The hierarchical structure makes some categories with small numbers lead to limitations in fitting the data to the model. The standard errors also become bigger. Consequently, more information is needed to estimate the parameters (798, 830). By contrast, the Bayesian approach can use information from sparse data as it is joined with previous information. The model is more flexible producing more accurate estimators (830). For instance, the standard errors of ethnic groups with small size (South Asian, other Asian and other ethnicity) are bigger in the Frequentist model than those in the Bayesian model. In the Bayesian model the standard deviation is the equivalent of the standard error produced by the Frequentist model.

In the Bayesian framework, the credible interval describes the distribution of the estimator in the study population. This distribution also gives the probability of obtaining each value. For instance, the figure 35 shows the HR of having controlled blood pressure for black patients compared with white patients. One can observe that the probability of having a HR between 0.95 and 1.0 is around 30% for black patients. Similarly the probability of having a HR below 1.02 is 97.5%. One can infer the following statements. The probability of having controlled pressure was similar between black and white patients as for some black patients the HR could lay at the value of 1.00. However, for most of the black patients the HR of having controlled pressure lay in the values below 1.00. In other words, although there was no a significant statistical difference in the risk of having controlled blood pressure between black and white patients, black patients clinically may require more intensive blood pressure control. In conclusion, the lack of statistically significant difference may not detract attention from attempting improvements in blood pressure control for black patients. This is one of the most important benefits from using a Bayesian statistical framework, particularly in clinical areas. Knowing the distribution of the probability of the outcome in a population allows us taking decisions beyond the interpretation of p values or significant differences (831).

9.6 Strengths and limitations

The model

The innovation of this analysis is the use of a Bayesian framework. Not also the hierarchical frailty survival model allows analysing recurrent events but also takes into account the heterogeneity between individuals due to factors not to measure in the dataset (809). The inclusion of the initial blood pressure status also account for the individual basal risk of achieving the blood pressure targets. Additionally, using the Bayesian framework allows using data from variables with low frequencies in the dataset. The assessment of blood pressure control as an event recurrent over a period of time is in line with the natural variation of blood pressure.(8) Then the inclusion of different measurements of blood pressure over long time has

been recommended to obtain a more accurate representation of the blood pressure control occurring in clinical settings.

The model also accounts for the correlation observed among individuals nested into practices. The need for taking into account this correlation into the analysis of dataset from health services has been recognised. It improves the accuracy of the estimations and also the possibility to find differences between groups (832). The omission of this condition could result in underestimating the possible impact of some associations or interventions.

The current analysis illustrated the use of a Bayesian approach in the analysis of data collecting daily in clinical settings. The clinical registers have mainly been analysed using a Frequentist framework. However, using this framework has led to some concerns when the data is not sample based collected (794). Then, the Bayesian framework emerges as an alternative which provides a closer estimation of the uncertainty contained in the data.

The limitations may rely on the prior distributions selection. I used informative priors for both hierarchical variances. The informative priors could be used cases of groups of low frequencies (811). This is the case for the first hierarchical level as some individuals have only two repeated measurements of blood pressure. Additionally, it has been observed that the variance of blood pressure increase over the time after starting antihypertensive therapy. (806) However the results were consistent by using different samples from the data set and also using vague distributions for the hierarchical variance for practices.

Some limitations are related to data. The blood pressure measurement was performed in clinical visits using sphygmomanometer or an Omron device. Although these are the standard of blood pressure measurement, some authors are reported digital preference in the register of blood pressure levels (699). However I used all the measurements available which can correct for this measurement bias. The data contained missing valuables in some variables such as cholesterol levels and body index mass. I did not replace it to reduce the influence of external parameters into the analysis. I compared instead of different populations from the data set to assess the associations. Finally, nor I did have information on adherence to therapy neither information on the use of non-pharmacological interventions on the management of these patients. However this information reflects what is currently happening in primary care. In these contexts the use of non-pharmacological interventions is not

recorded as well as pharmacological interventions. Nevertheless, the adjustment for deprivation index could be a proxy for conditions related to non-pharmacological interventions such as individual behaviour. It has been observed a direct association between behaviour and socio economic status (833).

9.7 Conclusion

Over a ten year period, the analysis of 11373 hypertensive patients revealed that individual factors such age and BMI are negatively associated with having controlled blood pressure. Compared to white, other ethnic groups were equally or more likely to have controlled pressure but those of black origin tended to have uncontrolled blood pressure. None of the variables at practice level were significantly associated with the risk of having controlled blood pressure. Patients registered after the introduction to QOF were more likely to have controlled blood pressure. Finally, the analysis adds evidence on the impact of continuity of care. Thus, these hypertensive patients continually managed by the same provider had reductions in blood pressure levels over the study period.

I illustrated the use of a Bayesian framework in the analysis of clinical records taking in current clinical settings. This could be an alternative in the analysis of this data with regard to its hierarchical structure. The use of this framework allows assessing the uncertainty present in the data.

Key points

- ✓ A Bayesian analysis to assess factors affecting blood pressure control was performed using a data set of hypertensive patients being managed in 28 practices located in Wandsworth, London.
- ✓ A Bayesian survival Weibull frailty hierarchical model was developed using event recurrent times as an outcome. The model fit the data.
- ✓ A cohort of 11373 hypertensive patients was used for the analysis

- ✓ Over the period the period there has been an improvement in blood pressure control. The percentage of patients with controlled hypertension increased from 37% to 62.4%.
- ✓ Increases in age, BMI and cholesterol levels were found negatively associated with blood pressure control.
- ✓ Compared to white, patients of other ethnic origin have a similar risk of having blood pressure control. Those of other ethnic origin were more likely to have controlled blood pressure and those of black origin tended to have uncontrolled blood pressure.
- ✓ Patients registered after the introduction of QOF were more likely to have controlled blood pressure.
- ✓ The results add evidence on the benefit of continuity of care on the management of hypertensive patients in primary care.
- ✓ This study illustrated the use of the Bayesian approach in the analysis of clinical data.
- ✓ This approach is an alternative method particularly in cases when the data is not sample based collected.
- ✓ The Bayesian approach allows assessing the uncertainty presented in the data which could be more informative for health workers.

Chapter 10 General discussion, conclusion and future work

10.1 Summary of main findings

Study 1: Blood pressure control and blood pressure targets definition. Cross sectional study

In 2007, among 15761 hypertensive patients registered with 28 general practices, 79.5% of them were classified as patients with controlled hypertension by using the QOF target of 150/90 mmHg. By comparison, the percentage is 60.7% when the NICE target of 140/90 mmHg was used.

Overall, 59.4% of men had controlled hypertension by using the NICE target and 78.5% had controlled hypertension by using the QOF target. The percentage of women with controlled hypertension was 80.7% and 61.7% using the QOF and NICE target respectively. Regardless of the target, the percentage of men with controlled hypertension increased with age. By contrast, the percentage of women with controlled hypertension rose with age using the QOF target but decreased using the NICE target. The probability of achieving a blood pressure target varied between sex across age categories.

Between ethnic groups, the highest percentage of percentage of PCH's was in those of South Asian origin, 1184 (82.2%) and 990 (68.8%) using the QOF target and the NICE target respectively. For men mean systolic blood pressure was 138.2 mmHg (sd 16.30 and mean diastolic blood pressure was 80.3 mmHg (sd 11.8). For women was 137.4 mmHg (16.7) and mean diastolic blood pressure was 79.3 mmHg (sd 10.3). Patients of south Asian had lower blood pressure levels and patients of black origin had higher blood pressure levels.

Study 2: Impact of ethnic-specific guidelines in antihypertensive prescribing. Longitudinal analysis

Between 1998 and 2007, there was an increase in the percentage of patients who were prescribed antihypertensive medication for 17245 hypertensive patients with race/ethnic record. Thus, the percentage of patients not being prescribed antihypertensive medication decreased from 49.0% in 1998 to 14.8% in 2007. By contrast, the percentage of patients being prescribed two or more antihypertensive medication increased from 21.2% in 1998 to 54.7% in 2007.

Over the study period, the most noticeable variation in drug class prescribing has been the decline in the use of the beta blocker as monotherapy in all NICE patient groups. ACEI has been the most frequently antihypertensive prescribed as monotherapy mainly for younger non-black and older non-black. CCB has been the most common monotherapy used for black patients. After the introduction of the guidelines there was an increase in first line NICE recommended monotherapy (OR 1.44, 95% CI 1.18 – 1.75) compared with the underlying trend. Compared to black patients, an increase in recommended monotherapy was observed in younger non-black patients (OR 1.49, 95% CI 1.17 – 1.90) but not in older non-black patients. Over the study period, black patients were more likely to be prescribed recommended monotherapy treatment than younger non-black (OR 0.16, 95% CI 0.12 – 0.21) and older non-black patients (OR 0.49, 95% CI 0.37 – 0.65).

Study 3 Factors affecting blood pressure control: a survival longitudinal study using a Bayesian framework

Among 11373 hypertensive patients included in the survival analysis, there was a significant reduction in systolic and diastolic blood pressure levels from 1998 to 2007. Mean systolic blood pressure was 148.5 mmHg (sd) in the first year observation and 137.4 mmHg (sd 14.8) in the last year (10th). Similarly, mean diastolic blood pressure was 85.9 (10.3) mmHg at first year registration and 78.9 mmHg (10.1) in the last year observation. The percentage

of hypertensive patients with controlled blood pressure increased from 37% to 62.4% over ten years period.

Over the period, increases in age were negatively associated with having controlled blood pressure. Compared to patients of white origin, those of other ethnic origin were more likely to have controlled pressure over the period, hazard ratio 1.09 (95% credible interval 1.0 - 1.19). Although there were no significant differences, patients of black origin tended to have uncontrolled blood pressure. Increases in body index mass tended to reduce the risk of having controlled pressure even though the estimators did not achieve significance (Figure 11). Higher levels in cholesterol were negatively associated with controlled blood pressure. For those patients with very high levels of cholesterol (over 6.1 mmol/L), the hazard risk was 0.94 (95% credible interval 0.91 – 0.98). Patients registered after the introduction of QOF were more likely to have controlled blood pressure. The risk of having controlled blood pressure was higher for patients registered after the introduction of QOF, hazard ratio 2.05 (95% credible interval 1.94 – 2.16). The use of NICE guidelines recommended treatment tended to improve blood pressure control.

10.2 Comparison with previous research

Blood pressure control rates

The control of blood pressure improved in Wandsworth, south west London between 1998 and 2007. A similar trend has been reported by the Health Survey for England (284). The percentage of hypertensive patients with controlled blood pressure is similar to what has been observed in others general practices-based studies in the UK. In a cross sectional study of 315 practices in Scotland, Simpson et al reported that nearly 50% of hypertensive patients achieved blood pressure levels equal to or below 140/90 mm Hg (834). Among 148 practices located in East London, Mathur et al found that almost 70% of patients with cardiovascular comorbidity had controlled blood pressure (535). By comparison, the percentage of hypertensive of controlled blood pressure has been reported between 25 and 50% among general practices from countries with well-developed primary care services (286-287, 474, 835).

Continuity of care may be a key aspect for the control of blood pressure in this patient cohort. It could be argued that I did not have a control group to establish this consideration. However the constant improvement of the outcome suggests that patients exposed to the health system could reduce blood pressure levels. Evidence from clinical trials conducted in primary care reported that access to service and periodical visits were the most significant factors associated with better blood pressure control (280, 447, 820, 836). Richard et al similarly illustrated the impact of primary care on the control of chronic kidney disease. They found that a reduction in the fall of glomerular filtration rate and reduction in blood pressure levels associated with interventions that were part of a primary care based program (495). Visiting the same health provider, maintaining clinical records and having regular clinical visits are features present in the current primary care settings which have been associated with a better control of chronic diseases (837), for instance hypertension (820). By contrast, a lack of continuity care has led to poor blood pressure control (474).

Factors affecting blood pressure control

Individual factors

Become older was negatively associated with achieving blood pressure levels equal to or below 140/90 mmHg. The association was observed in both the cross sectional analysis and the longitudinal analysis. Increases in age have consistently and negatively associated with poor blood pressure control among hypertensive patients treated in primary care services. In a study conducted in ten primary care services from Sweden, Hedblad et al found that the percentage of hypertensive patients with blood pressure levels over 140/90 mmHg were higher in those aged 75 years and over (84%) than in those aged below 65 years (68%) (314). Among a representative sample of hypertensive patients being treated in German primary care services, Labeit et al reported that increases in age reduce the risk of having controlled blood pressure by 43% in patients aged 75 years and over compared to those aged between 18 and 24 years (287). The association has also been observed in different health care contexts. Meng et al identified a significant trend of declining blood pressure control with increases in age among hypertensive patients sampled from general population in China (838). Similar to the current findings, uncontrolled blood pressure has been mainly due to high systolic blood pressure levels (314). Although the constant increase in blood pressure with age can explain limitations in lowering blood pressure among older patient (73), other factors may account for the high blood pressure levels in these patients. Among

hypertensive patients aged 75 years and older, Krousel-Wood et al found lower blood pressure was associated with decline in the use of antihypertensive treatment (839). The decrease in use was attributed to depression symptoms (839).

The result showed that physicians switch to a new antihypertensive treatment less frequently in older patients than in younger patients. In a survey of ambulatory hypertensive patients, De Giusti et al reported that older hypertensive patients were less likely to receive antihypertensive treatment than younger (840). In primary care services from Spain, Gil-Gillen et al reported that older hypertensive patients have been given less antihypertensive treatments than younger patients (841). Treatment resistant hypertension has also been found as a potential cause for poor blood pressure control in older patients. In the analysis of the NHANES 1998 to 1994 and 1999 to 2008, Egan et al found that older age was a risk factor for having apparent treatment resistant to hypertension (842). In other words, older patients did not achieve blood pressure targets though they receive more than two antihypertensive medications.

I found that those with high scores of BMI had uncontrolled blood pressure over the study period. Among those without antihypertensive treatment, the association was significant for overweight hypertensive patients. BMI has been consistently reported as a risk factor for poor blood pressure control. In a cohort of hypertensive patients being treated in primary care services, Suarez et al found that hypertensive patients who gained weight could not remain with controlled blood pressure over one year follow up period (374). In a cohort analysis of 150000 patients registered with 35 family practices in Ontario, Petrella et al found that hypertensive overweight patients were less likely to achieve controlled blood pressure compared to those with normal weight (373). Data from cross sectional studies also has reported this association. In a survey of hypertensive patients treated in French primary care services, Roux et al documented that for each 14 kg increase in weight, there has been a reduction of 10% in the risk of having controlled blood pressure, odds ratio (0.90 95% CI 0.81 – 0.99) (372). The observation has been documented in different populations. In sample of hypertensive patient from Chilean primary care services, Sandoval et al reported that having a BMI equal to or higher than 30 kg/m² is a risk factor for having blood pressure over 140/90 mm Hg (292).

The relationship between BMI and poor blood pressure control may be expected. Increases in BMI are found a risk factor for having hypertension. In the Framingham study, Kannel et al found that the incidence of hypertension rise with increases in body mass index regardless of age and sex (828). In a study a population with a diverse ethnic origin, Foulds et al found that both BMI and in waist circumference are factors predisposing to hypertension. But the strength of association varied across ethnic groups. Among aboriginal people the incidence of hypertension is higher than that observed in those of Caucasian or East Asian origin at same levels of BMI (120). In a UK population of 12090 participants, Dexter et al identified that blood pressure levels increases with increases in both waist hip ratio and in BMI. The association between waist hip ratio and blood pressure levels was independent of body mass index levels and consistent in both men and women (118). This association may result in a need for using more antihypertensive drugs in overweight hypertensive individuals. Saito et al showed that hypertensive patients with higher levels of body mass index achieve similar blood pressure control rates than those with lower levels of body mass index but using more antihypertensive medication (843).

Patients with very high cholesterol levels (≥ 6.1 mmol/L) were less likely to have controlled pressure over the period. In a cross sectional study of hypertensive patients managed in primary care services in Pakistan, Saleheen et al reported that those with cholesterol higher than 200 mg/dL were associated with poor blood pressure control (327). In 4235 hypertensive patients treated in Spanish primary care services, Llisterri et al documented that those with low density lipoprotein cholesterol higher than 115 mg/dL were less likely to have blood pressure below 140/90 mmHg (381). Similar observations have reported by Sandoval et al (292) and Suarez et al (374). The positive association between high cholesterol levels and developing hypertension could make it difficult to achieve lower blood pressure levels in these patients. Among 4953 women with a ten years follow-up period, Sesso et al demonstrated that the incidence of hypertension increased with increases in cholesterol levels. Although there was a significant trend across blood pressure levels, the associated relative risk was particular significant for those with high cholesterol levels (cholesterol total ≥ 240 mg/dL) (844). The association becomes less strong after adjustment for BMI but remain significant. Similar observations have reported in men (845). The impact of high cholesterol levels on the incidence of hypertension has been more notorious in those with high normal blood pressure (846). In an analysis of 2864 hypertensive with hypercholesterolemia from the 2001-2002 NHANES survey, Wong et al found that only 9% of those achieve targets for both clinical conditions. Individuals aged 80 years and over had the worst control rates for both comorbidities (847). However, among hypertensive patients aged 80 years and over

from New Zealand primary care, Senior et al those with hypercholesterolemia were more likely to have controlled pressure (386). Hence it seems that high cholesterol levels at baseline may be a negative factor for achieving blood pressure targets but this association may change with regard to cholesterol treatment.

Having an additional cardiovascular comorbidity such as diabetes, stroke, heart failure, atrial fibrillation or chronic renal disease, was not associated with variations in the risk of having controlled blood pressure in the survival analysis. However those with an additional comorbidity were more likely to deep in the category of those with controlled blood pressure in the cross sectional study. As expected, differences between cross sectional studies and longitudinal studies may reflect the time lag effect of the variable on the outcome. In other words, in a long time the probability of achieving a blood pressure target may not depend on the presence of an additional comorbidity. In a cross sectional analysis of patients registered with 148 general practices in East London, Mathur et al found that there were no significant differences in the achievement blood pressure targets between those with one and more than one associated comorbidity. Differences in the probability of having controlled pressure were attributed to race/ethnicity background (535). In contrast, in a cross sectional study of hypertensive patients from primary care services among 16 practices from Wandsworth, London, Millet et al reported that hypertensive patients with and additional cardiovascular comorbidity were more likely to have blood pressure below 140/90 mm Hg than those without cardiovascular comorbidity (496).

Evidence from a diverse of observational studies showed that among hypertensive patients treated in primary care, those with an additional comorbidity have been found to have worse blood pressure control (323, 325, 332, 344, 379, 381) or better blood pressure control (373, 385-386). Some surveys particularly reported that hypertensive patients with diabetes are less likely to have controlled blood pressure (286, 325, 332). These discrepancies may reflect differences in quality of care. Peterson et al compared the quality of care among hypertensive patients treated in eight Veteran Affairs primary care services. They found hypertensive patients with an additional cardiovascular comorbidity were more likely to have blood pressure below 140/90 mmHg than those without cardiovascular comorbidity at first entry. Over the a six months follow up period, they also received better health care resulted in higher probability of having controlled blood pressure compared to those without comorbidity

(OR 2.25 95% CI 2.13 to 2.36) (387). In a follow up study including 6083 elderly hypertensive patients, Chowdhury et al found that those with comorbidity such as increased plasma creatinine were more likely to achieve blood pressure targets (397). Of note, in clinical trials hypertensive patients with diabetes have been able to achieve blood pressure targets below 135/85 mm Hg though the clinical impact of achieving these targets is unclear (199). Hence, the discrepancies between studies may reflect differences in health care offered to hypertensive patients with an additional comorbidity.

Compared to white, lower blood pressure control rates in race/ethnic minorities were not observed in the current analysis. In fact, in the cross sectional study patients of South Asian origin and those of other Asian origin were more likely to be classified as hypertensive patients with controlled blood pressure. And among hypertensive patients without additional cardiovascular comorbidity, the survival analysis showed that those of South Asian origin were more likely to have controlled blood pressure over the period. Those of other race/ethnicity were more likely to have controlled in the model included only those on hypertensive treatment. There were not significant differences in the risk of having controlled blood pressure between ethnic groups in the results from the survival model adjusted for all include variables. Reductions in blood pressure control inequalities between ethnicity groups have been observed in the UK. In the 1998-2005 Health Survey for England there were no differences in the probability of having controlled blood pressure between race/ethnic groups. They compared those of Irish, Caribbean, Indian, Pakistani, Bangladeshi or Chinese origin to whites (495). Similarly Mathur et al reported that patients of South Asian origin were more likely to have controlled blood pressure compared to those of white origin (535).

Particularly, I did not find a significant difference in the risk of having control blood pressure between hypertensive black patients and white patients. Other studies conducted in primary care settings have shown that patients of black origin were less likely to achieve blood pressure targets (496-497). These studies were a cross sectional analysis and without adjustment for other factors such as body mass index or smoking status. The current results rely on a longitudinal analysis including a range of individual factors and using a hierarchical model. Kressin et al conducted a retrospective study of hypertensive patients aged 21 years and over managed in primary care settings to assess factors explaining differences in blood pressure control between white and black patients. They found that after adjustment for phy-

sician care, clinic care, patient income, patient education, patient health insurance, patient adherence to medical interventions, perception of discrimination and personal beliefs black origin was no longer associated with poor blood pressure control (352).

However the survival analysis revealed that black patients tended to have uncontrolled blood pressure as the distribution of hazard ratios show lower values for black patients than those observed in other race/ethnic over the study period. Other factors different from being prescribed on antihypertensive treatment may account for low blood pressure control rates in black patients. In a study of hypertensive patients treated in 30 primary Durham Veterans Affairs Medical Center Primary Care Clinics, Bosworth et al found that compared to white black patients had lower adherence to antihypertensive medication (OR 1.47 95% CI 1.02 – 2.01) compared to white (848). Similarly, Gerber et al reported lower adherence to physician instructions on antihypertensive medication among elderly black patients compared to white, (OR 2.49 95% CI 1.07 – 5.80). (849). Misbelieves about hypertension such as the need of taking pill only under perceiving symptoms may account for their lower blood pressure control rates among patients of black origin (352, 400).

Smoking was not associated with lower blood pressure control. The relation between smoking and blood pressure control has varied across the studies. For instance, among 631 hypertensive patients managed in primary care, Majernick et al did not find a significant difference in the risk of having controlled pressure between smokers and non smokers (332). By contrast, among hypertensive patients on treatment recruited from 33 communities in China, Tian et al found that current smokers were less likely to have controlled blood pressure, (OR 0.49 95% CI 0.26 – 0.91) (295). Differences in sample size and prevalence of smoking between studies could account for these discrepancies.

Physician factors

I assessed physician factors by means of analyzing prescribing patterns of antihypertensive medication over the study. Additionally, I quantified the use of recommended treatment established in the 2006 NICE guidelines. Both the number of hypertensive patients on antihypertensive treatment and the number of antihypertensive medications prescribed for each patient increased over the period. It seems that inertia clinical may not be a relevant factor associated with poor blood pressure control in this patient cohort. In England, improvements in antihypertensive prescribing have been observed (284). From the Health survey for England, Falaschetti et al reported that the percentage of hypertensive patients on antihypertensive treatment increased from 48% to 57% between 2003 and 2006 (284). This is consistent with improvements in the management of stroke. In a cohort analysis of 32151 patients with stroke, Lee et al found that the percentage of patients on antihypertensive treatment continually increased from 1999 to 2008 (781). Comparing data from NHANES 1998 to 1994 and 1999 to 2008, Egan et al observed that the percentage of hypertensive patients without antihypertensive medication decreased from 42% in 1998 to 28% in 2008 (842).

I found that after the introduction of the 2006 NICE guideline, there was an additional increase in the use of recommended NICE monotherapy treatment. Toshke, et al also have documented increases in antihypertensive prescribing may related to the implementation of BHS guidelines (759). In an analysis of 28320 hypertensive patients managed in general practices from Lamberth, London, Schofield et al have reported nearly 50% of hypertensive patients were prescribed with 2006 recommended treatment (761). The impact of clinical guidelines on the management of hypertension has been observed elsewhere (451, 721, 725). Campbell et al showed the use of antihypertensive medication increased by 58% between 1998 and 2003 among hypertensive citizens from Ontario (Canada) (723). This increase was associated with the Canadian Hypertension Education Program because the prescribing trends were in the line with the recommendations establish in these guidelines (723).

The national guidelines could also have an impact on improvements in blood pressure control. The results showed that patients being prescribed the recommended treatment at first entry tended to have better controlled blood pressure compared to those without antihypertensive medication. By contrast, those not being prescribed other antihypertensive medica-

tion were less likely to have controlled blood pressure. Toschke et al also found that patients being prescribed the NICE recommended treatment had lower recurrence of stroke compared to those prescribed a different treatment (759). In an intervention taken in community services from China, Wang et al found the group which used hypertension guidelines achieved higher reductions in systolic blood pressure (21.4 mmHg) compared to those under standard care (16.0 mmHg) (850). In a implementation of a quality improvement including the use of hypertension guidelines, Vallez-Fernandez et al revealed that hypertensive patients under intervention had an 92% increase in the odds of having controlled blood pressure compare to control group (451).

Health services factors

Pay for performance has been advocated as strategy for improvement blood pressure control (824). The analysis reported that those hypertensive patients who were registered after the introduction of QOF were more likely to have controlled hypertension. The association was consistent after adjustment for all included variables. The association was also present in all models and by using different priors. That could be interpreted as a possible cohort effect related to the introduction of QOF (851). Then, patients at same age exposed to variations in care observed after the introduction of QOF were more likely to have controlled blood pressure. Other studies assessing the effect of QOF on hypertension control have contradictory results. After the introduction of QOF, Millet et al found that ethnic differences in blood pressure control remained with black patients less likely to have controlled blood pressure (496). Similar findings was reported by Lee et al (852). Serumaga et al did not find variation in blood pressure control rates comparing before and after periods of the introduction of QOF (683). Simpson et al neither found differences in blood pressure control rates after the introduction of QOF among patients being treated in Scottish general practices (834). By contrast, a reduction in the percentage of patients with blood pressure above 150/90 mmHg was reported in an analysis of blood pressure measurements from 236467 patients taken between 2000 and 2005 (699). Also improvements in blood pressure control particularly in practices located in the most deprived areas has been associated with the introduction of QOF (498).

The referred studies used aggregated data to make comparisons. The studies also commonly used the target of 150/90 mmHg which may prevent from identifying differences be-

tween periods. The discordant results may also be due to the fact that hypertension control is a complex health outcome (288). The lack of including other explanatory variables, the presence spatial and temporal correlation of the outcome, the insufficiency time periods and the comparability of the populations are of the most common limitations compromising the ability of before and after studies to find differences (853-854). The current analysis used the individual data with a model allowing taking into account the individual heterogeneity (809). In addition to, the analysis included all individual measurements of the outcome rather using a point estimation of the blood pressure.

I did not find significant differences in the individual hazard risk of having controlled blood pressure between practices located at least deprived area and those located at the most affluent areas. Then there seems that there were no differences in health care between general practices. In a cross sectional study of 13330 patients with heart failure registered with GPRD, Hawkins et al did not find differences in treatment or case fatality across socio economic strata. The treatment offered to patients with heart failure improved over two years regardless of socioeconomic circumstances (616). In a model to assess the decline of coronary heart disease in England, Bajekal et al demonstrated that one of the major contributors to this decline was the fell in blood pressure at population level. A reduction of nearly 2.5 mm Hg in systolic blood pressure for men and 5.5 mm Hg in systolic blood pressure for women were observed across all socio economic areas between 2000 and 2007 (613). Ashworth et al reported a reduction in differences between quality of blood pressure monitoring after the introduction of QOF across general practices after the introduction of QOF (498). Similarly, McLean et al did not find differences in the QOF blood pressure indicators between practices located in the most and least deprived areas in Scotland (628). Using information from 2003 and 2006 Health Survey for England, Crawley et al documented that blood control rates (target<150/90 mm Hg) were similar between manual and non manual worker before and after the introduction of QOF (855). The participation of nurses and pharmacists in the delivery of care has been associated with reduction in inequalities between practices (856-857) .

The differences between the percentages of patients with controlled blood pressure between practices located at different socio-economic strata and the individual hazard risk of having controlled blood pressure over the period may be explained by the following reasons. Firstly

the included populations differ between both analyses. The study presented in chapter seven is a cross-sectional study including all patients without missing blood pressure values in 2007. They could have only one measure of blood pressure as they could be registered in 2007. By comparison, in the survival study those who had only one measure were excluded. The sample included those with at least two blood pressure measurements. Secondly, the survival analysis used more than one measure of blood pressure to assess the control of blood pressure over the period (471, 858). The cross-sectional analysis used only one measured which may not completely capture the effect of primary care interventions over a long time follow-up. Thirdly whereas the percentage of patients with controlled blood pressure measurement in each practice is a group outcome, the hazard risk is an outcome measured individual level. The socioeconomic status was also a variable measures at practice level. This discrepancy could illustrate the fallacy concept. In essence, factors associated with an outcome at population or group level, may not always be associated with the outcome at individual level (859-860).

10.3 The implications of current model

A diversity of factors affecting blood pressure control are identified in cross sectional studies which have been useful to establish national strategies to improve blood pressure control. One can count more than twenty conditions influencing the likelihood of blood pressure control. However the impact of some factors may vary between population and individuals. The principle that factors associated with the incidence of disease at population level may not explain the presence of disease at individual level (861) could also happen in the analysis of factors affecting blood pressure control. For instance, a gradient of blood pressure control across individual income categories have been frequently reported in cross sectional studies conducted at population level. However, these associations have less frequently identified among patients being treated in primary care settings and also contradictories. For instance, whereas Ostchega et al reported that those with low income were less likely to have controlled blood pressure (313), Majernick et al did not find differences in the likelihood of having controlled blood pressure between those currently employed and those not working (332).. Therefore, among hypertensive patients undertaken in primary care, the improvement of blood pressure control could be benefit from the analysis of local data from these patients.

The current analysis was done among hypertensive patients treated in primary care conditions over a long follow up period. This analysis not only estimate associations between some factors and blood pressure control but also could provide information to predict the achievement of a blood pressure target. In primary care the prediction of an outcome is an essential part of the management. In other words, physician may need going beyond the diagnosis of the disease to improve a long term outcome (862). The current model offers a ground for constructing a prediction rule of blood pressure control. Firstly, the model has internal validity as the associations have demonstrated across different subpopulations from the dataset. Altman et al have pointed out that analysing different samples from a dataset is a strategy for assessing the internal validity of the results (863). Secondly, the risk of having controlled blood pressure was evaluated over a long follow up period using at least two measurements of blood pressure. Additionally, the baseline individual characteristics were used to assess the outcome. Thirdly, the model was based on multiple factors which allow us take into account for the variability among the included patients (864)

The Bayesian model gives the posterior distribution of the estimators. Consequently, it is possible to know the spectrum of the response. This information could better inform physicians on what would be expected from the estimated associations. In other words, it allows for knowing the uncertainty of the result. For instance, the results revealed that there were no significant differences in the hazard risk of having controlled blood pressure between women and men. It was observed that the posterior probability of the hazard risk was 1.0 (95% credible interval 0.96 – 1.03) so that there may be cases in which women be less likely to have controlled blood pressure and other in which they may more likely to have controlled blood pressure compare to men.

10.3 Strengths and Limitations

The strength and innovations of the studies I have undertaken are as follows: the large number of patients and the long term follow period, the number of blood pressure control measurements having for each patient and the availability of information about the most frequent variables affecting blood pressure control. Additionally, the use of a longitudinal analysis allows assessing the long term relationship between factor and blood pressure control. That assessment is relevant when an outcome is attained progressively over the time.

The assessment of factors affecting blood pressure control has been mainly reported from cross-sectional studies (283, 285, 319, 349) or prevalence studies (284, 344, 865). Despite the important information provided, they could not properly assess the temporal relationship between variables and outcomes (866). That is relevant when the outcome is a chronic condition which may be affected by long term exposures (866). Hence, a key aspect of understanding the control of blood pressure at individual level is to identify long term modifiable factors. Then, an important aspect of the present study is the use of all available factors having by the patient at first entry. It provides a potential profile of the hypertensive patient who is less or more likely to have controlled pressure over the time.

The use of a hierarchical model is a relevant characteristic of the model. The model included two levels the individual level and practice level. It is known that individuals being treated at

the same practice are likely to have similar outcome. There is a high correlation of the outcome between individuals nested with each practice (799). Blood pressure control is a complex outcome which depends on the interaction between patient factors, physician factors and health system factors (317). The Bayesian framework could deal with hierarchical structures better than the Frequentist framework. Not only the Bayesian framework models the random effects present among all hierarchical levels, but also it takes into account the uncertainty in all parameters' estimations (867).

The use of a Bayesian framework gives strength to the described associations. The Bayesian framework has been proposed as an alternative to analyse observational studies with data not sample based collected (794). Integration of prior information in the analysis of observational data has been considered as strategy to assess the validity of information contained in the data (471). Additionally, the frailty survival model allows taking into account heterogeneity due to unobserved confounders (809). The model fit to data producing results coherent to what has been observed. Moreover, the results reflect the true probability of the expected associations.

The Bayesian framework has been postulated as an option in the analysis of the observational studies. Trend estimations of the cardiovascular risk factors have been performed by using this framework (34, 868). The benefits of using the Bayesian framework in the analysis of administrative datasets have been reported (869-870). The Bayesian framework also allows for assessing multiple bias analyses. I illustrated the consistency of relevant associations across the different samples from the dataset and by using different prior distributions for the precision of the random effects.

There are two important limitations of the study. Firstly, there was a lack of information on patient adherence to pharmacological and non-pharmacological interventions. It is known that hypertensive patients often fail to follow these recommendations over long term periods (300). However, I expected this unmeasured information to be randomly distributed among included patients. Second, there was a lack of information on why the general practitioner chose the antihypertensive medication used. Therefore, I cannot provide reasons for the

differences between the guideline recommendations and some of the reported trends of antihypertensive use.

Other limitations are related to observational studies in general. Firstly I may have measurement error in blood pressure measurements. There has been observed that blood pressure measurements taking clinical settings may be subject to error due to inadequate measurement technique or the white coat effect (871-872). However those conditions might equally affect to all hypertensive patients so that it may not be biased the results. Secondly, the use of a year period meaning the blood pressure control status over the year could also be considered as a measurement error. That due to the fact that one annual measurement could not assess the blood pressure status having by the patient over the mentioned period (807) That situation again compromised all patient in a same way so that I can consider the this was a non-differential error. Thirdly, there could be a bias selection in the sample population using for the assessment of factors affecting blood pressure control. Both hypertensive patients without variation in the outcome and those with only one measurement had less follow up over the study period. Then, these groups were less exposed to interventions over the period so that the assessment of interventions could be less attainable. Additionally, the group, that did not have variation in the outcome, was already included in the analysis performed in the cross sectional study.

10.4 Future research

The control of blood pressure is defined by the achievement of a blood pressure target. The definition of a target is a matter of uncertainty without supportive evidence for any of the recommended targets. Current guidelines differ in the recommended blood pressure target. For instance for all hypertensive patients the 2011 NICE hypertension guidelines (144) and the 2003 US hypertension guideline recommend a target of below 140/90 mm Hg for all hypertensive patients aged below 85 years but the lowest threshold needed is undefined (13). In comparison, the 2009 European hypertension guidelines recommend a target of 30-139/80-85 mm Hg (243). These discrepancies have led to confusion in the management of hypertensive patients among physicians and may account for some of the differences in blood pressure control rates. Of note individuals with blood pressure levels below 140/90 mm Hg

markedly contribute to the morbidity and mortality associated with hypertension (47). Evidence clarifying the target for the management of hypertensive patients particularly younger is needed. That may result in a better blood pressure control rates and lower hypertension-related comorbidity rates.

To further improve blood pressure control in primary care, the concept of a universal target may need to be reevaluated. Evidence supports that the probability of achieving a blood pressure target highly depends on patient age (274). I observed that an increase in one year age reduces the probability of having controlled blood pressure. I also found that the probability of achieving a target varies across age between sexes (interaction effect). Blood pressure levels varied between race/ethnicity as individuals of black origin tend to have higher blood pressure levels and those of South Asian origin tend to have lower blood pressure levels compared to whites (81, 90). Considering this variations, a universal target for all hypertensive patients may be questionable. Research on age and race/ethnic approach in the management of hypertension could contribute to clarify the current differences in blood pressure control between race/ethnicity and age-groups.

Hypertensive patients commonly have other cardiovascular comorbidities. For instance, diabetes and hypertension are closely linked (873). The results from this research added evidence on the negative association between poor blood pressure control and obesity. However, the current guidelines are disease-related guidelines (144, 225). Moreover the concept of control highly relies on the achievement of a specific-disease blood pressure target. But it may distract physician from intensively intervening other risk factors and also analysing the reasons for not having controlled blood pressure. It has been reported that physician did not intensify treatment when the level of blood pressure is slightly above the target (434). For example, a hypertensive patient may have controlled blood pressure but simultaneously is overweight. The hypertension guidelines commonly advice on weight loss but a standardised approach is not sufficiently provided. That information usually is available in an independent guideline. It could be useful to explore the benefit of using a guideline incorporating a wider approach for the management of hypertension. That guideline could also integrate a monitoring of reductions in cardiovascular risk.

The lack of information on adherence highlighted the loss of information for improving blood pressure control. It is known that regardless of the method used, patient adherence to phar-

macological and non-pharmacological interventions is not satisfactory (306). Monitoring adherence to clinical recommendations in primary care is needed. Interventions on how to cope with poor adherence could provide light on reasons for not having controlled blood pressure. This certainly is an area which has not been well explored yet.

My findings show the impact of the guidelines on the management of hypertension. National hypertension guidelines have been proved to be a useful resource for improving blood pressure control (723). However, the observed differences between the guidelines and some prescribing patterns need to be clarified. Studies evaluating the use of the guidelines to determine the effectiveness of the guidelines on blood pressure control are needed. The results from these studies could provide a useful for including modifications in the guidelines. This is an area for conducting research in primary care.

The analysis of blood pressure control may need to incorporate long term follow up periods to identify risk factors for achieving blood pressure targets. The analysis may use previous information with regard to the available information about blood pressure control. This study used a Bayesian framework in the analysis of data. It provides the true probability of the estimators given the data. The models presented could be an input to be used in posterior studies. The Bayesian framework has become a useful method particularly in the analysis of data which is not based sample collected.

10.5 Implications for policy and practice

10.5.1 The assessment of blood pressure control in primary care

The first consideration is the definition of a blood pressure target. The study revealed that the QOF target of 150/90 mm Hg could not identify differences in blood pressure control between practices. Similarly, Calvert et al found that the QOF targets for diabetes did not properly capture variations in diabetes control comparing periods before and after the introduction of QOF (874). Additionally, blood pressure control rates have improved in England (284). It is expected that most hypertensive patients have blood pressure levels below the QOF target levels. Hence the blood pressure targets established in the NICE hypertension

guidelines could be more suitable for the assessment of blood pressure control in England primary care. For adults, the 140/90 mmHg blood pressure target, as established in the last updated NICE guideline (144), could be the more appropriate blood pressure target. It is also the international blood pressure target and there is currently no evidence supporting a lower blood pressure target for those at middle or low cardiovascular risk (17).

The use of two different targets could mislead the control of blood pressure in primary care. Physicians may not achieve further lower reductions in blood pressure after achieving the higher target because it is the measurement of quality of care. Then the achievement of that target also pushes health workers meeting a target regardless of hypertension population needs. Also practices achieving higher blood pressure control rates with lower targets may be rewarded similarly to those achieving higher blood pressures control rates with higher blood pressure targets. That may discourage health workers to attempt improvements in blood pressure control.

The assessment of blood pressure control in general practices could benefit from using additional indicators. The percentage of patients with controlled blood pressure does not provide information on where is a problem needed to intervene. I suggest four potential indicators to assess the quality of blood pressure control in primary care services. One is related to the use of antihypertensive medication. A measurement of the percentage of patients who have not received intensification of treatment despite visiting periodically a general practitioner has been proposed (402). The inclusion of other indicators such as percentage of patients on therapy or percentage of patients being prescribed recommended treatments could provide a complementary assessment of the management of hypertensive patients in primary care settings. Assessment of antihypertensive prescribing may provide additional information on the quality of care provided by general practices. This indicator also allows for identifying factors potentially modifiable and carrying out more appropriate comparisons of performance between practices (402).

My findings confirmed that hypertensive patients had variability in their blood pressure control status. Therefore, other potential indicator of the blood pressure control at practice level may be the analysis of individual records over a period of time (807). The periods may be

longer than three months. An assessment of the number of clinical visits in which the patient had controlled or uncontrolled blood pressure by the total of clinical visits by year could be useful to monitor the sustainability of the control. This evaluation might reflect more accurately the quality of care provided by the practices. Another indicator may be the registration of non-pharmacological interventions and advice measured as a numbers of people given advices by the number of attending a practice or clinic. An assessment of the number of clinical visits in which the patient had controlled or uncontrolled blood pressure by the total of clinical visits by year could be useful to monitor the sustainability of the control.

The indicators might be analysed by age, sex, race/ethnicity and socio-economic strata with regard to population characteristics. Consistently older patients have been found less likely to have controlled blood pressure (205, 287). Then, general practices with older patients could report lower achievement of blood pressure targets than those practices with younger patients.

10.5.2 The orientation of blood pressure control in primary care

The identification of factors affecting blood pressure control could need more information from local services. Although national surveys are an essential tool of monitoring blood pressure control rates, they reported associations between some factors and blood pressure control may not be replicated at individual level. It may reflect ecological fallacy (859). Thus factors affecting health population outcomes not always explained the achievement of health outcome at individual level. Hence, the control of blood pressure could further improve with strategies to tackle individuals with risk factors for uncontrolled blood pressure in local settings

The assessment of factor affecting blood pressure in local level could help to identify patients at higher risk of not having controlled blood pressure. For instance, the current analysis shows that hypertensive patients with high body mass index and older patients were less likely to have controlled blood pressure over the period. These patients may need a particular approach to reduce blood pressure levels. The current approach based on general recommendation establish in the guidelines could fail to improve blood pressure control in these

patients. They may need complex interventions with regard to their particular conditions to low their blood pressure.

There was a lack of information about adherence to pharmacological and non pharmacological interventions. Hypertensive patients have been known to fail the recommendations given by physicians (296-297). This led to low blood pressure control rates among hypertensive patients. Hence health providers may consider establishing surveillance strategies to monitoring adherence to these interventions. These systems could contribute to monitor factors influencing adherence to medications. Because a diversity of factors has been associated with patient adherence to medications, the interventions of improving adherence should be based on the assessment of local data. This information may drive future interventions to tackle local conditions affecting blood pressure control among hypertensive patients with uncontrolled blood pressure. It is expected that higher blood pressure control rates could be achieved after introducing strategies led to improve adherence to pharmacological and non-pharmacological interventions.

The control of blood pressure generally takes place in primary care. This study showed improvements in blood pressure control among hypertensive patients being managed in primary care settings. Then, it reinforces the key role of primary care in the management of hypertensive patients. Periodical visits, medical register and patient continuity with the same provider seems to be effective in the control of blood pressure (317, 340, 836). Hence, there seems a consistent evidence supporting that primary care service may be grounded on these characteristics. Policy planners may take into account the observed conditions when planning care for hypertensive in primary care.

10.6 Conclusion

This is one of the largest analyses of hypertensive patients assessing factors affecting blood pressure control over a long follow up period. Being older and increases in BMI and cholesterol were negatively associated with having controlled blood pressure. Compare to white, patients of race/ethnicity different origin did not significantly differ in the risk of having controlled blood pressure. Patients of black origin tended to have uncontrolled blood pressure over the period.

The percentage of hypertensive patients with controlled blood pressure increased over the period. Some possible reasons for this change may include aspects related to health system factors. There was a decrease in the percentage of hypertensive patients not being prescribed antihypertensive medication. The implementation of the NICE guidelines was associated with an increase in the use of the NICE recommended monotherapy treatment. Patients registered after the introduction of QOF were more likely to have controlled blood pressure. The improvement may reflect the effect of continuity of care on blood pressure control.

Blood pressure control in primary care could be improved by using information about adherence to pharmacological and non-pharmacological interventions. Currently, there is neither a standard to monitor adherence nor guidelines to deal with situations in which poor adherence is identified as a cause of poor blood pressure control.

The assessment of blood pressure control in primary care may use a lower blood pressure than that established in the QOF guidelines. The 150/90 mmHg may not capture the differences in blood pressure control rates between general practices. The inclusion of other indicators such adherence to medication, and the number of visits with controlled blood pressure could give information on what interventions could be needed to improve blood pressure control.

Finally, the study added evidence on the positive impact of primary care on blood pressure control. The continuity of care resulted in a significant reduction in blood pressure levels for patients include in the cohort.

11 References

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Appendix A Publications and outputs from this thesis

Journal articles

Lena Barrera, Christopher Millett, Marta Blangiardo, Utz J Pape and Azeem Majeed Differences in the classification of hypertensive controlled patient in primary care: Cross sectional study. JRSM Short Reports 2012 3:72

Lena Barrera, Craig Laeper, , Marta Blangiardo, Utz J Pape Azeem Majeed and Christopher Millett. 'Impact of ethnic-specific guidelines for antihypertensive prescribing in primary care in England: longitudinal study' on submission

Presentation in conferences

Lena Barrera, Christopher Millett, and Azeem Majeed Inequalities in blood pressure control in patients with hypertension in Wandsworth, south London 2007. Annual conference of The Society for Academic Primary Care taking in Norwich from July 2010 Oral presentation

Lena Barrera, Craig Laeper, , Marta Blangiardo, Utz J Pape Azeem Majeed and Christopher Millett. Trends in antihypertensive prescribing in primary care 2000-2007 observational study. Annual Primary Care Conference in Liverpool, October,. 2011. Poster presentation

Appendix B Characteristics of the studies included in the systematic reviews described in chapter one

Study	Year	Design	Population characteristics	Intervention comparison	
				Treatment	Blood pressure targets Standard vs Intensive
MDRD	1994	Randomised open label controlled Intention to treat	840 patients Patients with chronic renal disease Age range 18 - 70 years Mean 52 years Men 60% Ethnicity White 85% African American 7.9%	Diet Usual protein intake vs Low protein intake Antihypertensive treatment First choice : ACEI or ACEI and DD Second choice : CCB or CCB and DD	Targets for patients aged<60 years Mean blood pressure<=107 vs <=92 mm Hg Targets for patients aged>60 years MeanBP<=113mmHg vs <= 98 mm Hg
Toto RD et al	1995	Randomised double blind placebo control 2x2 Factorial	77 patients Patients with hypertensive nephrosclerosis Age range 25 - 73 years Mean 55.8 years Male 57.1% Black 75%	Antihypertensive treatment Placebo vs enalapril	Diastolic blood pressure 85 to 95 mmHg vs 65 to 80 mm Hg
UKPDS	1998	Randomised clinical trial Intention to treat	1148 patients Hypertensive patients with diabetes type 2 Age range 25-65 years mean 56.4 years Men 55% Ethnicity White 84% Afro-Caribbean 8% Asian Indian 5% Other 1%	Antihypertensive treatment ACEI (Captopril) or Betablocker	Blood pressure <180/105 mm Hg vs <150/85 mm Hg
HOT	1998	Randomised clinical trial	18790 patients Hypertensive patients at high cardiovascular risk Smokers 15.8% Previous MI 1.6% Other CHD 6.0% Previous stroke 1.2% Diabetes mellitus 8.0% Age range 50 -80 years mean 61.5 +-7.5 years Men 47% Ethnicity no report	Antihypertensive treatment First line Felodipine Other treatments ACEI, BB, DD Other interventions Placebo vs Acetylsalicylic acid	Diastolic blood pressure <=90 mmHg, vs<=85 mmHg vs 80 mm Hg

Appendix B Characteristics of the studies included in the systematic reviews described in chapter one

Study	Year	Design	Population characteristics	Intervention comparison	
				Treatment	Blood pressure targets Standard vs Intensive
ABCD (H)	2000	Randomised clinical trial	470 patients Patients with diabetes and hypertension Age range 40 - 74 years mean 58 years Men 67% Ethnicity Not reported	Antihypertensive treatment Nisoldipine vs Enalapril	Diastolic blood pressure 80-89 mm Hg vs <75 mm Hg
ABCD (N)	2002	Randomised clinical trial	480 patients Patients with diabetes without hypertension Age range 40-74 years mean 58.6 years Men 55% Ethnicity Not reported	Antihypertensive treatment Nisoldipine vs Enalapril	Diastolic blood pressure 80-89 mm Hg vs 10 mm Hg reduction in DPB
Scherier R	2002	Randomised clinical trial	79 patients Autosomal Dominant Polycystic Kidney disease patients with hypertension Age range 27 - 59 years mean 41 years Men 52% Ethnicity NA	Antihypertensive treatment Enalapril vs Amlodipine	Blood pressure 135-145/85-90 mm Hg vs < 120/80 mm Hg
AASK	2002	Randomised clinical trial 3x2 Factorial	1094 Hypertensive patients with renal insufficiency Age range 18 - 90 years mean 54.5 years Male 61% African Americans 100%	Antihypertensive treatment Ramipril Metoprolol Amlodipine	Mean blood pressure 102-107 mm Hg vs <92 mm Hg

Appendix B Characteristics of the studies included in the systematic reviews described in chapter one

Study	Year	Design	Population characteristics	Intervention comparison	
				Treatment	Blood pressure targets Standard vs Intensive
REIN -2	2005	Randomised clinical trial	338 Patients with non-diabetic proteinuric nephropaties With or without hypertension Age range 18 -70 years mean 53 years Men (76%) Ethnicity NR	Antihypertensive treatment Ramipril Felodipine	Diastolic blood pressure <90mm Hg vs <130/80 mm Hg B
ABCD 2V	2006	Randomised clinical trial	129 Patients with diabetes type 2 without hypertension Age range 40 - 81 years mean 56.7 Men 67% Ethnicity White 71.2% Hispanic 19.7% African American 9.1%	Antihypertensive treatment Valsartan vs placebo Open labeled additional treatment	Diastolic blood pressure 80 - 90mm Hg vs < 75 mm Hg
JATOS	2008	Randomised clinical trial	4418 Hypertensive patients with systolic blood pressure > 160 mm Hg Age range 65- 85 years Men 39% Ethnicity NR	Antihypertensive treatment Efonidipine Other calcium CCB	Systolic blood pressure 140-160 mm Hg vs <140 mm Hg
Cardio-Sis	2009	Randomised clinical trial	1111 Hypertensive patients with other cardiovascular risk factor Age 55 years and older Men 41% Ethnicity NR	Antihypertensive treatment Open labeled treatment	Systolic blood pressure <140 mm Hg vs <130 mm Hg
ACCORD	2010	Randomised clinical trial	4733 Diabetic patients with or without hypertension Age range 40-79 years mean 62.2years Male 53% Ethnicity White 60.5% Black 24.1% Hispanic 7.1%	Antihypertensive treatment Open labeled treatment	Systolic blood pressure <140 mm Hg vs <120 mm Hg
VALISH	2010	Randomised clinical trial	3079 Hypertensive patients with isolated systolic hypertension Age range 70 - 85 years mean 76.1 years Male 37.7% Ethnicity NA	Antihypertensive treatment First line valsartan	Systolic blood pressure 140 - 150 mm Hg vs <140 mm Hg

Appendix B Characteristics of the studies included in the systematic reviews described in chapter one

Study	Year	Participants completing follow up period	Baseline blood pressure		Achieved blood pressure		Blood pressure comparison between standard and intensive groups	Percentage of patients achieved Blood pressure targets		Primary outcome results		
			SBP /DBP (mean, sd mm Hg)	Standard target	Intensive target	Standard target		Intensive target	Difference in mean blood pressure		Standard target	Intensive target
MDRD	1994	N1	132 (17)/80 (10)	131 (19)/81(10)	Study 1 Mean BP 90 mm Hg	Study 1 80 mm Hg	Study 1 4.7 mm Hg (p<0.001)	95,1%	61,1%	There were no differences in the in the rate of decline in the glomerular filtration rate between standard and intensive blood pressure control groups		
					Study 2 Mean BP 96 mm Hg	Study 2 94 mm Hg	Study 2 2.0 mm Hg					
Toto RD et al	1995	69%	122 (3)/77 (1)	124 (2)/76 (1)	Mean systolic blood pressure 138 (2)	Mean systolic blood pressure 133 (3)	Mean difference in systolic blood pressure NS	NA	NA	There wer no difference in the rate of decline in the glomerular filtration rate between standard and intensive blood pressure control groups		
					Mean diastolic blood pressure 87 (1)	Mean diastolic blood pressure 81 (1)	Mean difference in diastolic blood pressure 5.7 mm Hg (p<0.0001)					
					Mean arterial blood pressure 104 (1)	Mean arterial blood pressure 98 (1)	Mean difference in mean arterial blood pressure 5.5 mm Hg (p<0.0001)					
UKPDS	1998	96%*	160 (18)/94 (9)	159 (20)/94 (10)	Mean systolic blood pressure 154 (16)	Mean systolic blood pressure 144 (14)	Mean difference in systolic blood pressure 10 (95% CI 9 to 12) mm Hg	91%	56%	In comparison with less tight group, the tight blood pressure group have: 24% reduction in risk of total diabetes related outcomes 32% reduction in risk of total mortality from diseases with increased risk 34% reduction in risk of total macrovascular diabetes diseases 37% reduction in risk of total microvascular diabetes diseases		
					Mean diastolic blood pressure 87 (7)	Mean diastolic blood pressure 82 (7)	Mean difference in diastolic blood pressure 5 (95% CI 4 to 6) mm Hg					
					N2							
HOT	1998	97%	Standard target	Diastolic BP<=85 mm Hg	Standard target	Diastolic BP<=85 mm Hg	NR	Peretage of patients with diastolic > 90 mm Hg		There were no differences in all major cardiovascular evens between all blood pressure target groups		
			170 (14.4) / 105 (3.4)	170 (14.0)/89 (23)	143.7 (11.3)/85.2 (5.1)	141.4 (11.7)/83.2 (4.8)		Standard target	Diastolic BP<=85 mm Hg			
				Diastolic BP<=80 mm Hg	Mean diastolic blood pressure 65.2 (5.1)	Mean diastolic presssure 63.2 (4.8)		12%	7%			
				170 (14.1)/89 (23)		Diastolic BP<=80 mm Hg			Diastolic BP<=80 mm Hg	Patients with DM achieved the lower BP target had less risk of total cardiovascular mortality		
						139.7 (11.7)/81.1 (5.3)			6%			
						Mean diastolic presssure 61.1 (5.3)						

N2 Blood pressure data from 297 patients in the intensive group and 154 patients in the standard group

N1 Blood pressure data available for 178 patients at the end of the study

*Patients with known vital status at the end of the study

Appendix B Characteristics of the studies included in the systematic reviews described in chapter one

Study	Year	Participants completing follow up period	Baseline blood pressure SBP /DBP (mean, sd mm Hg)		Achieved blood pressure SBP /DBP (mean, sd mm Hg)		Blood pressure comparison between standard and intensive groups	Percentage of patients achieved Blood pressure targets		Primary outcome results
ABCD (H)	2000	70% ^{xx}	154 (16.9)/98 (6.4)	156 (16.1)/98 (6.4)	138/86	132/78 mm Hg	p<0.001 for comparison of mean systolic blood pressure and mean diastolic blood pressure between groups	NA	NA	There was no significant difference in creatinine clearance between standard and intensive blood pressure control groups The rate of all cause mortality was significant lower in the intensive control group than in the standard control group
ABCD (N)	2002	83%	137.2 (0.9)/84.4 (0.2)	135.6 (0.8)/84.4 (0.2)	137 (0.7)/81 (0.3)	128(0.8)/75 (0.3)	p<0.0001 for comparison of mean systolic blood pressure and mean diastolic blood pressure between groups	NA	NA	There was no significant difference in creatinine clearance between standard and intensive blood pressure control groups The incidence of cerebral vascular accidents was significant lower in the intensive blood pressure control group than in standar blood pressure control group
Scherier R	2002	94%	142(17)/96 (11) Mean BP 111 (12)	143 (15)/95 (11) Mean BP 111 (12)	Mean BP 101 (4)	Mean BP BP 90(5)	p<0.0001 for comparison of mean systolic blood pressure and mean diastolic blood pressure between groups			The percentage of patients achieve lower left ventricular hipertrophy was significant higher in the intensive blood pressure control group than in the standard control aroud There was no significant difference in creatinine clearance between standard and intensive blood pressure control groups
AASK	2002	69%	149 (23)/95(14) Mean BP 113 (15)	152(25)/96(15) Mean BP 115 (17)	141 (12)/85 (7) Mean BP 104 (7)	128 (12)/78 (8) Mean BP 95 (8)	Mean difference in the mean blood pressure between both groups over the period 10 mm Hg There is no level of significance reported	NA	NA	There was no significant difference in mean GFR decline between standard and intensive blood pressure control groups over the period
REIN-2	2005	53%	136.4 (17)/83.9 (10.4) Mean BP 101.4 (11.4)	137.0 (16.7)/84.3 (9.0) Mean BP 101.9 (10.4)	133.7 (12.6)/82.3 (7.1)	129.6 (10.9)/ 79.5 (5.3)	p<0.0001 for comparison of mean systolic blood pressure and mean diastolic blood pressure between groups Mean difference in the mean blood pressure between both groups over the period 3.0 mm Hg	NA	NA	There was no significant difference in mean GFR decline between usual in mean GFR decline between usual and intensive target groups over the study period

^{xx}Patients with known vital status at the end of the study

NA Not applied

Appendix B Characteristics of the studies included in the systematics reviews described in chapter one

Study	Year	Participants completing follow up period	Baseline blood pressure SBP /DBP (mean, sd mm Hg)		Achieved blood pressure SBP /DBP (mean, sd mm Hg)		Blood pressure comparison between standard and intensive groups	Percentage of patients achieved Blood pressure targets		Primary outcome results
ABCD 2V	2006	NA	126 (9)/84(2)	126(9)/84(2)	124(10.9)/80(6.5)	118(10.9)/73(5.7)	p<0.001 for comparison of mean systolic blood pressure and mean diastolic blood pressure between groups	NA	NA	The progression of urinary albumin excretion was significant lower in the intensive blood pressure target group than in the standard blood pressure target group
JATOS	2008	81%	171.5 (9.8)/89.1(9.5)	171.6 (9.7)/89.1(9.5)	145.6 (11.1)/78.1(8.9)	135.9 (11.7)/74.8 (9.1)	p<0.001 for comparison of mean systolic blood pressure and mean diastolic blood pressure between groups	64%		There was no significant difference in the rate of the primary outcome (cerebrovascular disease, cardiac disease , vascular disease and renal failure) and strict target groups between standard
Cardio-Sis	2009	87%	163.3 (11.1)/88.7(8.8)	163.3(11.3)/88.6(8.8)	Mean reduction in blood pressure 23.5(10.6)/8.9(7.0) 27.3(11.0)/10.4(7.5)		Mean difference in systolic BP between both groups 3.8 mm Hg (95% CI 2.5 - 5.2) Mean difference in diastolic BP between both groups 1.5 mm Hg (0.6 - 2.4)	66.9%	72.2%	The prevalence of electrocardiographic left ventricular hypertrophy was significant lower in the intensive blood pressure target than in the standard blood pressure target group
ACCORD	2010	98,40%	139.4 (15.5)/76.0 (10.2)	139.0 (16.1)/75.9(10.6)	Mean systolic blood pressure 133.5 (95% CI 133.1 - 133.8) Mean diastolic blood pressure 70.5 (95% CI 70.2 - 70.8)	Mean systolic blood pressure 119.3 (95% CI 118.9 - 119.7) Mean diastolic blood pressure 64.5 (95% CI 64.1 - 64.7)	Mean difference in systolic BP between both groups 14.2 mm Hg (95% CI 13.7 - 14.7) Mean difference in diastolic BP between both groups 6.1 mm Hg (95% CI 5.7 - 6.5)	NA	NA	There was no significant differences in the rate of total outcome (myocardial infarction, nonfatal stroke, or death from cardiovascular causes) between both groups There was a significant lower rate of stroke in those in intensive group than in the standard group
VALISH	2010	945%	169.6 (7.9)/81.2(6.8)	169.5(7.9)/81.7(6.6)	142 (12.5)/76.5 (8.9)	136.6 (13.3)/74.8(8.8)	Difference in systolic BP between both groups 5.6 mm Hg (p<0.001) Difference in diastolic BP between both groups 1.7 mm Hg (p<0.001)	NA	NA	There was no significant difference in the rate of the primary outcome (sudden death, fatal or non fatal stroke, fatal or non fatal myocardial infarction, death due to heart failure or other cardiovascular death, unplanned hospitalization for cardiovascular disease and renal dysfunction) between moderate and strict blood

NA Not applied

Appendix C Model code

```

Model {
  for (j in 1:N) {

    timeobserv[j] ~ dweib(shape, Scale[j]) l(timecensor[j],)

    HRx[j]<-Scale[j]*shape*pow(timeobserv[j], shape-1)

    S[j]<-exp(-Scale[j]*pow(timeobserv[j], shape))

    log(Scale[j])<-alfa1*(firststage[j]-mean(firststage[])) + beta[1]*firstsex[j] + u[Lastethnic[j]] +
    beta[2]*FirsTTO[j] + beta[3]*FirsCom[j] + beta[4]*FirstNOCCOM[j] + beta[5]*firstsmoker2[j]+
    beta[6]*QOF[j] + alfa3[Firstcatecholesterol[j]] + alfa2[catefirstBMI[j]] + b[newid4[j]]

  }
  # Random effects on individuals into practice

  or (z in 1:M) {b[z] ~ dnorm(mu[z], tau.b[practice4[z]])

    mu[z]<-a[practice4[z]] }

#Random effects on practices

  for (p in 1:T) {a[p] ~dnorm(mup[p], tau)
    mup[p]<-alfa0 + alfa[practicelistfirst[p]] + d[deprivation[p]]
  }

# Priors distribution for variance parameter of each practice

  for (p in 1: T) {
    tau.b[p] ~ dgamma (0.5, 0.5)
    sigmap[p]<-1/tau.b[p]
    sigmap2[p]<-sqrt(sigmap[p]) }

#Priors distribution for overall variance parameter of the practices

    tau ~ dgamma (1, 0.5)
    sigma <-1/tau
    sigmab<-sqrt(sigma)

#Prior distribution of baseline hazard function
    shape ~dgamma(1, 0.01)

#Prior on betas
    for (k in 1: 6) {
      beta[k] ~ dnorm (0, 0.01) }

```

```

#Prior on u
u[1]<-0
for (e in 2:6) {u[e] ~dnorm (0, 0.001)}

#Prior on deprivation
d[1]<-0
for (t in 2:3) {d[t] ~ dnorm(0, 0.001) }

#Prior on practice list
alfa[1]<-0
for (l in 2:3) {alfa[l] ~ dnorm (0, 0.001)}

#Prior on intercept
alfa0 ~ dnorm (0, 0.01)
#Prior on alfa age
alfa1 ~ dnorm (0, 0.01)

#Prior on alfa2(BMI)
alfa2[1]<-0
for (o in 2:5) {alfa2[o]~dnorm(0, 0.001)}

#Prior on alfa3(CHOL)
alfa3[1]<-0
for (c in 2:3) {alfa3[c]~dnorm(0, 0.001)}

#Exponential coefficients

Exp.alfa0<-exp(alfa0)
Exp.alfa1<-exp(alfa1)
for (l in 2:3) {Exp.alfa[l]<-exp(alfa[l])}
for (k in 1:6) {Exp.beta[k]<-exp(beta[k])}
for (e in 2: 6) {Exp.u[e]<-exp(u[e])}
for (t in 2:3) {Exp.d[t]<-exp(d[t])}
for (o in 2:5) {Exp.alfa2[o]<-exp(alfa2[o])}
for (c in 2:3) {Exp.alfa3[c]<-exp(alfa3[c])}

}

```

Model parameters

alfa	Coefficient for the categories of the number of patients registered with each practice.
alfa0	Overall intercept for practices
alfa1	Coefficient for age
alfa2	Coefficient for BMI categories
alfa 3	Coefficient for cholesterol categories
beta[1]	Coefficient for sex
beta[2]	Coefficient for being prescribed any antihypertensive
beta[3]	Coefficient for having an additional cardiovascular
beta[4]	Coefficient for having an additional no cardiovascular comorbidity
beta[5]	Coefficient for being current smoker
beta[6]	Coefficient for being registered before the introduction of QOF
d	Coefficient for deprivation index in tertiles
mup[p]	overall effect of the practices
u	Coefficient for race/ethnicity

