Improving cardiovascular risk prediction through more accurate and alternative methods of blood pressure measurement

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Abstract

Background

Cardiovascular risk scores are used to estimate absolute risk of disease and identify patients who will benefit most from treatments to lower risk. As a key risk factor for cardiovascular disease, blood pressure is accounted for in many risk scores, but is inherently variable and may be influenced by both biological and measurement factors. This thesis aims to determine how routinely collected blood pressure measurements should best be used for accurate estimation of cardiovascular risk.

Methods

This thesis describes four main studies. A patient survey and prospective study establish the current practice of blood pressure measurement. Secondary analyses of data from blood pressure monitoring trials determine how risk estimates may be affected by the use of different summary measures of blood pressure. A systematic review evaluates the evidence of an association between blood pressure variability and cardiovascular risk. Finally, a cohort study in the Clinical Practice Research Datalink determines if inclusion of blood pressure variability in cardiovascular risk scores may improve risk estimation.

Results

Current practice of blood pressure measurement may differ from that in risk score derivation studies. However, these differences have limited effects on cardiovascular risk estimates with few patients reclassified across risk thresholds. Increased long-term variability in blood pressure is in itself a risk factor for cardiovascular disease over and

above mean blood pressure but its inclusion in a cardiovascular risk score does not materially improve the accuracy of risk estimates.

Conclusions

Healthcare professionals should continue to estimate risk for primary prevention of cardiovascular disease using the blood pressure measurements available to them, whether measured at home or in the clinic. There is also no additional benefit of considering measures of long-term blood pressure variability in risk estimation.

Statement of originality

I can confirm that I wrote this thesis and carried out all of the research described within it myself between October 2014 and August 2017. This thesis has not previously been submitted for a degree at another university and to the best of my knowledge contains no previously published work, except where referenced.

Specifically, my contribution to each chapter and any relevant contributions by others were as follows:

Chapter 1: I carried out the literature review and wrote the chapter.

Chapter 2: I designed the survey, obtained ethical approval, piloted and tested the online survey system, managed the survey data collection process, carried out the statistical analysis and wrote the chapter. The programming to set up the online survey system was conducted by two clinical trials programmers working in the Nuffield Department of Primary Care Health Sciences Clinical Trials Unit (David Judge and Luis Castello).

Chapter 3: I determined the analysis plan, carried out the data cleaning and analysis and wrote the chapter. Data used in this chapter were collected prior to the start of this thesis by teams led by Professor Richard McManus and Professors Willem Verberk and Peter de Leeuw.

Chapter 4: I developed the systematic review protocol, screened eligible studies, extracted data, carried out the statistical analysis and wrote the chapter. The search strategy was developed by my supervisor, Professor Richard McManus and

colleagues Professor Paul Glasziou and Dr Sally Wood, prior to the beginning of this thesis. My involvement began after an initial search was completed and some data on included study characteristics had been extracted. However I subsequently modified the inclusion/ exclusion criteria and was responsible for re-screening studies based on the modified criteria and all subsequent work. Article screening and data extraction was carried out in duplicate with assistance from Professor Richard McManus, Professor Richard Stevens, Dr Sally Wood, Constantinos Koshiaris and Dr Kathryn Law.

Chapter 5: I designed the study, obtained ethical approval, carried out the data cleaning and statistical analysis and wrote the chapter.

Chapter 6: I carried out the literature review and wrote the chapter.

Abbreviations

ABPM	Ambulatory blood pressure monitoring
ARV	Average real variability
BMI	Body mass index
BP	Blood pressure
CHD	Coronary heart disease
CIMT	Carotid intima media thickness
CPRD	Clinical Practice Research Datalink
CV	Coefficient of variation
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
GP	General practitioner
HDL	High density lipoprotein
HES	Hospital Episodes Statistics
hsCRP	High sensitivity C-reactive protein
IDI	Integrated discrimination improvement
IMD	Index of multiple deprivation
LDL	Low density lipoprotein
LVH	Left ventricular hypertrophy
MI	Myocardial infarction
MINAP	Myocardial Infarction National Audit Project
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NRI	Net reclassification improvement
ONS	Office for National Statistics
QOF	Quality and Outcomes Framework
RMSE	Root mean squared error
SBP	Systolic blood pressure
SD	Standard deviation

TIA	Transient ischaemic attack
TC	Total cholesterol
VIM	Variation independent of mean

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Chapter 1 Introduction

This thesis aims to determine how blood pressure (BP) measurements obtained routinely in primary care should best be used for the accurate prediction of cardiovascular disease (CVD) risk in patients with no prior history. This is important to ensure that those at highest risk can be correctly identified and benefit from preventative treatment interventions. My interest in this topic began in part after joining the Nuffield Department of Primary Care Health Sciences in 2012 and working on a series of BP and CVD related projects. On a personal level, there is a history of premature CVD in my family, meaning that I never met either of my Grandfathers, and my Gran and Grandma lived for many more years than expected without them. I therefore have a keen personal interest in preventing CVD more widely, so that other families do not experience such premature losses.

This first chapter outlines the morbidity and mortality burden of high blood pressure and cardiovascular disease, the role of blood pressure as a risk factor for CVD and the calculators that have been developed to predict risk of future CVD in individual patients.

1.1. What is blood pressure?

Blood pressure (measured in mm of mercury, mm Hg) is the force exerted on the walls of the arteries as blood is pumped through them to different parts of the body by the heart. Systolic BP is the highest pressure the blood reaches when the heart contracts and diastolic pressure is the force exerted when the heart is at rest between beats.(1) Blood pressure is considered normal or optimal if systolic/ diastolic pressure is below 120/80 mm Hg respectively.(2) In the UK and internationally, high blood pressure (termed hypertension) is

typically defined as Stage 1 hypertension if systolic/ diastolic BP measured in a clinic setting exceeds 140/90 mm Hg. Stage 2 hypertension is defined as clinic BP is above 160/100 mm Hg.(1–3)

Systolic BP typically rises with increasing age, whereas diastolic BP rises until around age 60, before decreasing again.(4) Although increased systolic and diastolic BP are both associated with increased vascular resistance, increased systolic BP and *decreased* diastolic BP are associated with greater arterial stiffness.(5) Hence, as the relative contribution of arterial stiffness becomes greater in old-age, systolic BP continues to rise and diastolic BP falls.(5)

Globally, raised blood pressure is the leading risk factor for premature morbidity and mortality, estimated to be implicated in 7.5 million deaths (13% of the total) and 57 million disability-adjusted life-years (years of healthy life lost due to death, illness and disability; 3.7% of the total).(6) This is due to the link between increased BP and numerous adverse health outcomes, such as reduced kidney function,(7) and in particular, cardiovascular disease.(8)

1.2. Cardiovascular disease and blood pressure

Cardiovascular disease is a general term used to refer to conditions that adversely affect the circulatory system, encompassing heart disease (principally ischaemic) and cerebrovascular disease. Together, they are the leading cause of death and disease burden worldwide, annually accounting for 13 million global deaths (22% of the total) and 109 million disability-adjusted life-years (7.2% of the total).(9) In the UK in 2012, CVD was the primary cause of death for women and was second only to cancer for men.(10) Coronary heart disease (CHD) and stroke were the most common forms of CVD, accounting for 46% and 26% of overall CVD deaths respectively.

The additional cardiovascular risk attributable to increased BP is substantial, with a 20 mm Hg greater systolic BP associated with a doubling of stroke and CHD mortality risk.(8) This association is observed regardless of the initial BP level down to at least 110/70 mmHg systolic/ diastolic.(11) As such, the decision over which people should be targeted by therapeutic or lifestyle interventions to lower BP is driven primarily by healthcare system resources and priorities, with BP thresholds to define hypertension being relatively arbitrary.(11)

Current UK National Institute for Health and Care Excellence (NICE) guidance for the diagnosis and management of hypertension states that antihypertensive treatment should be initiated in all patients with Stage 2 hypertension. Treatment is only recommended in those with Stage 1 hypertension who additionally have a greater than 1 in 5 chance of developing CVD in the next 10 years or other significant cardiovascular risk factors (e.g. pre-existing CVD, diabetes or evidence of target organ damage).(1) Similar guidance, based on both BP level and absolute CVD risk, is implemented in several other international guidelines.(2,3,12)

Regular measurement of blood pressure and treatment of those with hypertension is incentivised in UK primary care through the National Health Service (NHS) Quality and Outcomes Framework (QOF).(13) In 2015/16, 7.9 million adults were included on the QOF hypertension register in England and Wales (13.8%; the highest prevalence rate across all conditions assessed).(14) Hence BP measurement and control are key activities of day-to-day general practice and high BP affects a significant proportion of patients.

1.3. Cardiovascular disease prevention

Despite the continued burden of CVD, significant reductions in CVD-related mortality have been achieved in the UK since the 1960s; for example the rate of CHD-related mortality has more than halved.(15) This decline can in part be attributed to improvements in population level risk factors for CVD/ CHD such as smoking and diet.(16) However in more recent years, increasing uptake of medical and surgical interventions may explain a larger proportion of the decline in CHD-related mortality than changes in population level risk factors, with some studies suggesting that 52% and 34% of the decline is due to medical interventions and population changes respectively.(17) Key treatments relevant to, and administered in the primary care setting include statins to lower cholesterol (accounting for an estimated 14% of the reduction in CHD-related mortality), and antihypertensive therapies (accounting for 5%).(17)

As mentioned briefly in Section 1.2, current UK and international hypertension guidance recommends that decisions to initiate antihypertensive treatment should be based on an individual's absolute level of CVD risk unless their BP readings are very high.(1–3,12) A similar approach is recommended with respect to lipid-lowering therapy,(18–21) with UK NICE guidance for the primary prevention of CVD stating that statin treatment should be initiated in patients with a greater than 1 in 10 chance of developing CVD.(18) This approach has been adopted because the relative effect of reducing mean BP or cholesterol is similar regardless of baseline risk: CVD risk is reduced by approximately 20% for each 10 mm Hg reduction in systolic BP(11,22,23) and each 1 mmol/ L reduction in low-density lipoprotein cholesterol.(24) Hence the recommendations aim to ensure that, given limited resources, treatment is given to those at the highest risk of future CVD who will benefit most (in terms of absolute risk reduction) from treatment.

1.4. Identifying high risk patients

A patient's risk of future CVD is dependent on many medical history and socio-economic characteristics. Known risk factors for CVD include increasing age and BP,(8) cholesterol,(25) kidney function,(26) deprivation,(27) and Black or South Asian ethnicity.(28,29) For some patients, their eligibility for treatment with antihypertensive or statin medication is predicated on the basis of very high BP or cholesterol values (as discussed in Section 1.3) or the presence of a single factor which substantially increases their risk, such as pre-existing diabetes,(30) or CVD.(31) For the remaining patients, however, UK and international guidelines for the prevention of CVD recommend that assessment of absolute cardiovascular risk should be carried out more formally, by combining information about multiple risk factors using risk prediction equations, often termed "risk scores" or "clinical prediction rules".

The definition of a risk score or clinical prediction rule varies considerably across the literature.(32–36) Keogh et al. define a clinical prediction rule as;

"a clinical tool that quantifies the individual contributions that various components of the history, physical examination and basic laboratory results make towards the diagnosis, prognosis or likely response to treatment in a patient."(36)

In the context of CVD prevention, established risk scores typically combine data regarding age, gender, systolic BP, cholesterol and smoking status to estimate the likelihood that a patient will develop CVD in the future (for example over the next 10 years). Systolic BP is typically included instead of diastolic BP due to its continuous rise with age,(4) and relatively stronger association with CVD outcomes in those over 60 where more morbidity and mortality occurs.(8)Well established risk scores that were derived in populations from

America, the UK and Europe include the Framingham risk scores,(37–40) the QRISK2 equation,(41) and the SCORE equation,(42) respectively.

1.5. Blood pressure measurement

As a key risk factor for CVD, a summary measure of mean or true underlying systolic BP (hereby termed "usual" systolic BP) is included in many risk scores. However, compared to other risk factors that can be measured accurately (e.g. age), blood pressure is subject to substantial biological variation,(43–45) making determination of an individual's "usual" BP difficult and subject to error. Many factors can affect the accuracy of BP measurement and estimates of BP control including the number of repeat measurements taken,(46,47) cuff size,(48) measurement setting,(49) measurement arm,(50,51) and clinical personnel.(52) As a result, BP measurement in clinical studies and trials is usually carried out according to a pre-specified measurement protocol. Published BP measurement recommendations detail several factors which should be considered in a measurement protocol,(53) including:

- the blood pressure measurement device used including details of its clinical validation,
- whether alternative cuff bladder sizes were available and used appropriately,
- the personnel taking the readings and their training,
- the arm on which measurements were taken,
- the position of the patient (standing, seated or supine),
- the length of any period of rest before measurement,
- the number of measurements taken,
- the time between multiple measurements and

- how the measurements were used and recorded (e.g. mean of 2nd and 3rd measurements)

Commonly, study protocols specify that multiple BP measurements should be taken at a single visit. This is due to concerns that initial clinic BP measurements may be systematically different from repeat measurements or those taken during usual activities,(49) and because BP measurements taken across several readings through home monitoring or ambulatory BP monitoring (ABPM) are more strongly associated with cardiovascular outcomes.(54,55) Current national,(1) European,(2) and North American(3,12) hypertension guidelines also make similar recommendations regarding repeat BP measurements in the clinic setting and measurement by a patient at home. This is especially true for the diagnosis of hypertension where ABPM by a patient over 24 hours is now the diagnostic gold standard.(1)

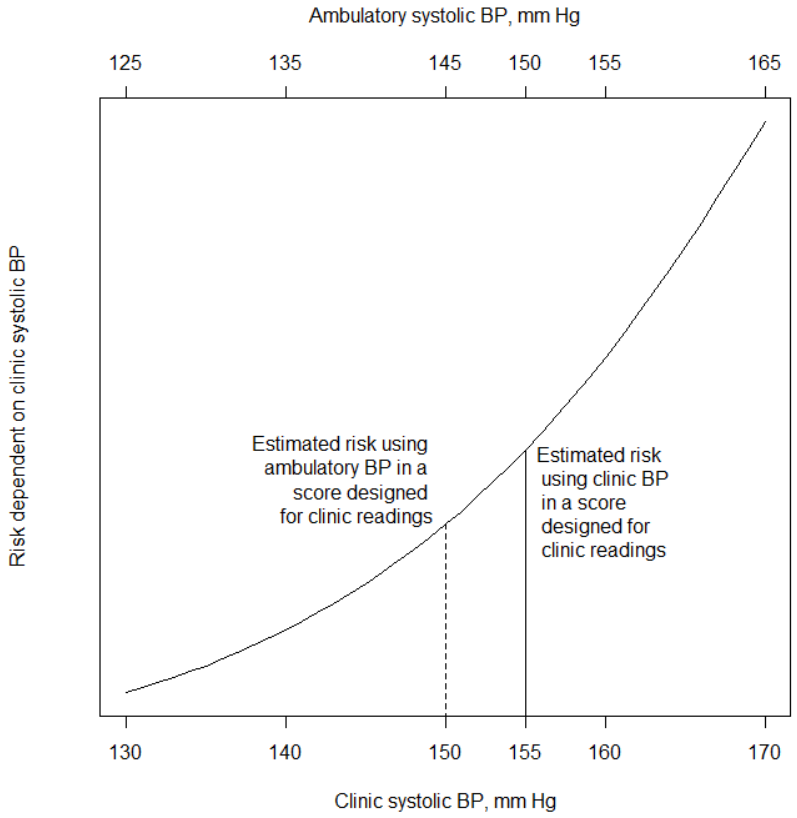
1.6. Mean blood pressure as a risk factor for CVD

Although current recommendations for BP measurement to determine an individual's "usual", mean or underlying BP may have improved the accuracy of hypertension diagnoses, they have additional implications for CVD risk estimation. Differing BP measurement techniques between risk score derivation studies and clinical practice will lead to estimates of mean BP with differing levels of bias (systematic over or underestimation) and noise (measurement error) which can subsequently impact risk estimation.

Figure 1.1 gives a hypothetical illustration of how differing levels of bias may affect risk estimation in practice. Clinic systolic BP is represented on the bottom horizontal axis and ambulatory BP is represented on the upper horizontal access (note that each ambulatory BP value is 5 mm Hg lower than the corresponding clinic BP reflecting the possible

difference in BP on average, as suggested in UK diagnostic guidelines for hypertension).(1) The solid line represents hypothetical risk of CVD in relation to clinic BP. As the graph indicates, an ambulatory BP reading of 145 or 150 mm Hg may correspond, on average, to a clinic reading of 150 or 155 mm Hg respectively. If an ambulatory BP reading of 150 mm Hg is used directly in a risk score derived using clinic BP measurements (as if it is a clinic reading), risk will be underestimated on average, compared to using the equivalent clinic BP measurement (155 mm Hg). The extent to which absolute risk is underestimated (or possibly overestimated) in a specific patient will depend on how much their clinic and ambulatory BP readings differ, the strength of the association between BP and risk in the derived risk score (represented by the gradient of the risk line in Figure 1.1), and also on the patients underlying risk level (note that the difference in risk would be smaller at the 140/135 clinic/ ambulatory BP point, where overall risk is lower).

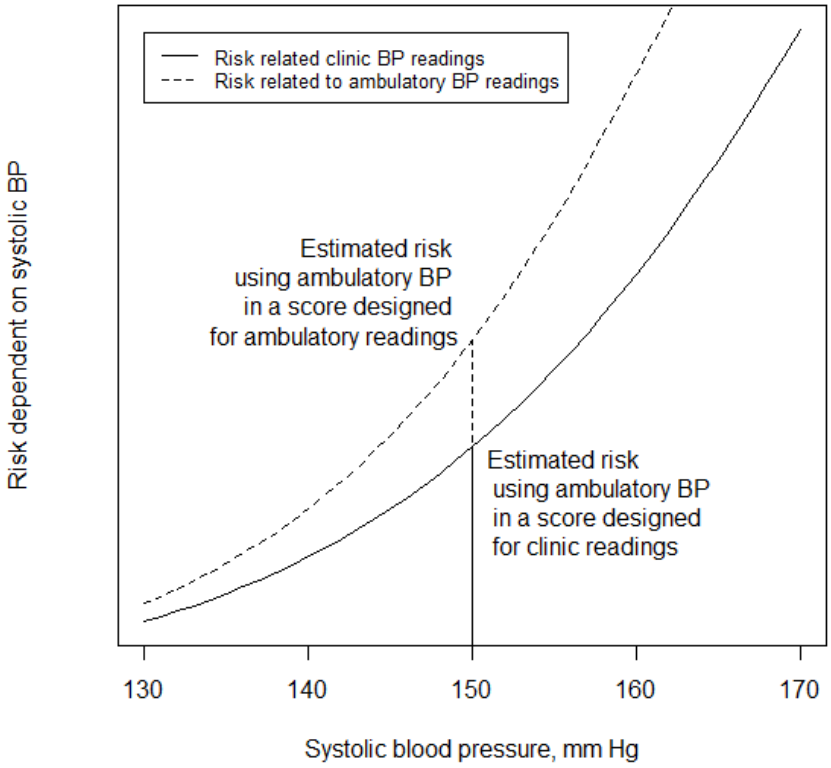
Figure 1.1: Illustration of possible differences in estimated risk when ambulatory or clinic BP measurements are used in a risk score developed using clinic BP measurements



The possible effect of measurement error on risk estimation is illustrated in Figure 1.2. Home and ambulatory BP monitoring estimate underlying, mean or "usual" BP with much less error as BP is averaged across many readings, and these average BP values are stronger predictors of cardiovascular risk than clinic readings.(54,55) This may reflect in part a phenomenon known as regression dilution, whereby observed associations between a risk factor and outcomes may be diluted (biased towards zero) when the risk factor is measured with increasing levels of error.(56–58) In Figure 1.2, the solid line represents CVD risk depending on clinic BP values and the dotted line represents CVD risk depending on ambulatory BP values (note that an ambulatory BP value of 150 mm Hg is much worse prognostically than a clinic reading of 150 mm Hg). If an ambulatory BP reading of 150 mm Hg is used in a risk score developed using clinic readings, risk will be underestimated

compared to using ambulatory BP in a risk score that was developed for use with such readings. As before, the magnitude and direction of the risk difference depends on the underlying risk level but also on the differential measurement error between the two types of BP measurement.

Figure 1.2: Illustration of possible differences in estimated risk due to the differing levels of measurement error between clinic and ambulatory BP measurements



In practice, both of the issues illustrated by Figures 1.1 and 1.2 will effect risk estimation simultaneously and hence, risk scores should ideally be used with BP measurements obtained in a similar manner to those in the risk score derivation studies to limit the impact of these errors.

1.7. Blood pressure variability as a novel risk factor

As already mentioned in Section 1.5, many factors can affect estimates of mean, "usual" or underlying BP, due to the inherent variability in blood pressure. Blood pressure shows marked oscillations from one reading to the next, over both the short and long term.(45) In addition to the measurement factors mentioned in Section 1.5, in the short term, blood pressure can be affected by behavioural and postural changes,(43,44,59) as well as medication use,(60) medication adherence,(61) and is known to be affected by temperature/seasonality in the longer term.(62) Such fluctuations in BP have been viewed historically as a "nuisance" phenomenon making the primary goal of estimating "usual" or mean BP difficult.(63) This is reflected in international measurement guidelines that seek to standardize measurement techniques and reduce measurement error by averaging across many readings (as discussed in Section 1.5).

However, in recent years many people have sought to investigate whether such fluctuation, or variability, in repeated BP measurements may be considered as a cardiovascular risk factor in its own right. Although the first studies relating BP variability to CVD outcomes were published as early as the 1990s,(64) the contemporary increase in investigations into the association of BP variability with CVD outcomes was prompted primarily by a series of papers published by Peter Rothwell and colleagues in 2010.(65–67) In particular, one study of patients with previous history of stroke or transient ischaemic attack (TIA), found that those in the highest decile of BP variability were up to four times more likely to have a stroke than those in the lowest decile, even after adjusting for mean BP.(66)

Many subsequent studies have since considered whether BP variability may be a novel risk factor for cardiovascular disease and mortality, considering clinic,(68) home,(69) or

ambulatory measurement.(70) Some studies have demonstrated a positive association of increased BP variability with CVD outcomes,(71–73) but others gave failed to show an effect.(74) Hence, consideration of BP variability in addition to mean BP may also be important when trying to determine cardiovascular risk.

1.8. Measurement of blood pressure in risk score derivation studies

To investigate to what extent there may be differences between the current practice of mean BP measurement and that in risk score derivation studies, I reviewed the derivation papers of cardiovascular risk scores that are available for use in clinical practice to establish how BP was measured in their respective derivation studies (and hence how BP should be ideally measured for use in the risk scores).

I identified cardiovascular risk scores from two key review studies. The first study reviewed clinical guidelines to identify risk scores in any disease area that are recommended for use in practice and asked GPs to report which risk scores they use routinely.(32) The second study reviewed risk scores published in journals relevant to primary care and grouped them according to clinical domain (including CVD).(36) I considered risk scores that could be used to estimate cardiovascular disease risk for primary prevention that combined three or more components of patient characteristics and demographics, medical history information, physical examination data and laboratory test results to estimate the absolute risk of future CVD over any time horizon.

I summarized details about the risk score derivation study characteristics (including, importantly, the BP measurement protocol), the analysis methods and the key risk score

characteristics, if the risk score was derived from primary studies collecting blood pressure data explicitly. Practically, this meant that risk tables developed as part of guidelines and based on literature review only or studies that sought to update/ utilise previous risk scores without re-estimation of effects, were not studied in detail. Although the specific definition of CVD varies across the literature, coronary/ ischaemic heart disease including angina and myocardial infarction and cerebrovascular disease including haemorrhagic or ischaemic stroke are common across the majority of definitions.(39,41,42,75,76) I therefore studied risk scores if the outcome of interest included one of these common outcomes.

A total of nineteen risk score derivation papers were identified,(38–42,76–89) and their key properties are given in Tables 1.1 and 1.2. Of these, seven used data from UK populations,(41,76,77,80–83) and seven used data from populations in the USA.(38–40,78,79,86,87) Only two risk scores could be used for both primary and secondary prevention.(85,89) Four risk scores were developed solely for use in men,(82,84,87,88) and one for use in women.(86) There were three risk scores that were developed by combining data from multiple different sources.(42,85,89)

Table 1.1: Risk score properties where blood pressure was measured according to a consistent pre-defined protocol in the derivation study

Paper	Risk score	Population	Outcome	BP measurement	Inclusion of BP	Adjustment variables
Blood pressure measured according to a consistent pre-defined protocol with a single reading recorded						
Assmann, 2002(84)	PROCAM	Men aged 35-65 recruited through companies and local government authorities in Munster 1979 to 1985. Primarily white.	CHD events.	Readings made on the left arm with the subject seated and arm at heart level. Two measurements were taken and the second measurement was recorded.(90)	As a continuous variable (per mmHg).	Age, LDL, HDL, family history of MI, diabetes and triglycerides.
Clarke, 2009(82)	Life expectancy in relation to cardiovascular risk factors	Men aged 40-69, working in the civil service in London 1967-1970. Primarily white.	CVD death.	Measured once in the left arm using the London school of hygiene sphygmomanometer.	As a dichotomous variable (>140 vs <140 mmHg), interacted with cholesterol and stratified by smoking status.	Cholesterol, smoking status, age and calendar period.
Zhang, 2005(88)	Framingham CHD in a Chinese cohort	Steelworkers from the Beijing Iron and Steel Complex aged 35+, recruited 1974, 1979 and 1980. Primarily Chinese.	CHD events and stroke events separately.	Measured in the right arm using a standard mercury sphygmomanometer on a single occasion after 5 minutes rest.(91)	As a continuous variable (per mmHg).	Age, cigarette smoking, BMI and TC.
Blood pressure measured according to a consistent pre-defined protocol with a summary measure from two or more readings recorded						
Anderson, 1991(40)	Framingham 1991	Framingham Original and Offspring cohort aged 30-74. Primarily white.	CHD events.	Three measurements taken after 5 minutes rest using a mercury sphygmomanometer (1 by a nurse, then 2 by a physician). Mean of 2nd and 3rd measurements recorded. All readings taken on the left arm with the subject seated and the arm at heart level.(92)	As a continuous variable (per 1 unit increase in log-SBP).	Age, female, TC/HDL, current smoker, diabetes and ECG-LVH.

Paper	Risk score	Population	Outcome	BP measurement	Inclusion of BP	Adjustment variables
D'Agostino, 2000(78)	Framingham coronary risk appraisal	Framingham Original and Offspring cohort, aged 35-74, examined at least once during the 1970s. Primarily white.	CHD events.	Three measurements taken after 5 minutes rest using a mercury sphygmomanometer (1 by a nurse, then 2 by a physician). Mean of 2nd and 3rd measurements recorded. All readings taken on the left arm with the subject seated and the arm at heart level.(92)	As a continuous variable (per unit increase in log-SBP) interacted with treatment and sex.	Age, sex, TC/HDL, diabetes, current smoker, ethyl alcohol, antihypertensive treatment, plus menopause and triglycerides for women.
D'Agostino, 2008(39)	General CVD Risk Profile for use in Primary Care	Framingham Original and Offspring cohort participants, aged 30-74, examined 1968 to 1971, 1971 to 1975 or 1984 to 1987. Primarily white.	CVD events.	Measurements made on left arm of seated participants with a mercury sphygmomanometer and appropriate cuff; the mean of 2 physician measures was recorded (mean of 2nd and 3rd as 1st measurement taken by a nurse.(92))	As a continuous variable (per unit increase in log-SBP) interacted with treatment and sex.	Age, sex, TC, HDL, smoking status, antihypertensive treatment and diabetes.
Kothari, 2002(81)	UKPDS 60	Patients aged 25-65 presenting with newly diagnosed diabetes at GP practices from 1977 to 1991. 82% white.	Stroke events.	Mean of clinic SBP at year 1 and 2 (mean of 3 measurements at each year).	As a continuous variable (per 10 mmHg).	Age, sex, current smoker, atrial fibrillation, TC/HDL and diabetes duration.
Pencina, 2009(79)	30-year risk of CVD	Framingham Offspring cohort, aged 20-59, 1971 to 1974. Primarily white.	CVD events.	Three measurements taken after 5 minutes rest using a mercury sphygmomanometer (1 by a nurse, then 2 by a physician). Mean of 2nd and 3rd measurements recorded. All readings taken on the left arm with the subject seated and the arm at heart level.(92)	As a continuous variable (per 1 SD increase in log-SBP).	Sex, age, smoking status, diabetes, TC, HDL, antihypertensive treatment.
Stevens, 2001(80)	UKPDS 56	Patients aged 25-65 presenting with newly diagnosed diabetes at GP practices 1977 to 1991. 83% white.	CHD events.	Mean of clinic SBP at year 1 and 2 (mean of 3 measurements at each year).	As a continuous variable (per 10 mm Hg).	Age at diagnosis, sex, Afro-Caribbean, current smoker, HbA1c, TC/HDL, diabetes duration.

Paper	Risk score	Population	Outcome	BP measurement	Inclusion of BP	Adjustment variables
Simmons, 2008(83)	Framingham CHD for the Cancer-Norfolk cohort	Patients aged 40-79 recruited from GPs in Norfolk March 1993 to February 1998. Primarily white.	CHD events.	Two clinic BP measurements taken using an Accutorr sphygmomanometer after 3 mins rest and appropriate cuff.(93)	Combined SBP and DBP as a categorical variable e.g. category 1: SBP<120, DBP<80.	Age, sex, TC, HDL, diabetes, current smoker and HbA1c.
Wilson, 1998(38)	Framingham CHD 1998	Framingham Original and Offspring cohort aged 30-74, 1971-74. Primarily white.	CHD events.	Three measurements taken after 5 minutes rest using a mercury sphygmomanometer (1 by a nurse, then 2 by a physician). Mean of 2nd and 3rd measurements recorded. All readings taken on the left arm with the subject seated and the arm at heart level.(92)	As a categorical variable (vs. reference category of normal blood pressure (SBP 120-9 mmHg or DBP 80-4 mmHg)).	Age, age squared, TC, HDL, diabetes, current smoker.
Woodward, 2007(76)	ASSIGN	Scottish Heart Health Study: participants aged 40-59 recruited 1984 to 1987 AND Scottish MONICA Project, Edinburgh and Glasgow, 1989, 1992, 1995. Primarily white.	CVD death or hospitalisation.	Mean of two clinic measures taken seated in clinic using random-zero sphygmomanometer.	As a continuous variable (per mmHg) stratified by sex.	Age, sex, Scottish IMD, family history of CVD, diabetes, cigarettes per day, TC and HDL.

Twelve risk scores were developed using data from seven distinct studies where BP measurements were taken according to a consistent predefined protocol (Table 1.1). Of these, three used only a single clinic BP reading and the other nine used a summary measure of mean BP based on two or more clinic readings (up to a maximum of six readings). The measurement arm was specified in four distinct studies but only the Framingham study specified the type of health professional taking the reading. Three studies specified the period of rest prior to measurement and five specified the type of sphygmomanometer.

Of the seven risk scores that were not developed using BP measurements taken according to a consistent pre-defined protocol, four used only a single clinic BP reading and the other three used a summary measure of mean BP calculated from multiple clinic readings (up to a maximum of three readings; Table 1.2). Two were developed using self-reported BP from questionnaire data and two were developed from routinely collected electronic health record data where BP measurement is likely to vary by practice, professional and/or over time. The remaining three risk scores were developed by pooling data from several cohorts, and although BP may have been measured according to a predefined protocol in each individual cohort, the pooling of patient data resulted in inconsistent methods of measurement across the pooled populations.

All risk scores included adjustments for age and cholesterol and all but one included adjustment for smoking status. Other common adjustment variables included ethnicity, diabetes, family history of the outcome and treatment for hypertension. Of the nineteen identified risk scores, ten included mean systolic BP as a continuous variable and six included log mean systolic BP as a continuous variable. The remaining three risk scores

included mean systolic BP as a categorical variable or included mean BP in a term combining both systolic and diastolic BP.

Note that I carried out this review at the beginning of the DPhil process and subsequently, in 2017, a new risk score, QRISK3, was published.(94) Its properties were similar to that of the previous QRISK2 score described in Table 1.2, except that a measure of both mean BP and BP variability (standard deviation) were included in the algorithm. I have chosen not to include the details of QRISK3 explicitly in Table 1.2, since it did not inform the subsequent work carried out, but I have discussed the implications of its publication and relevance to this thesis in particular in Sections 5.5 and 6.2.

Since the Framingham and QRISK2 equations are discussed and used in detail throughout this thesis, the explicit risk equations are given in Tables 1.3 and 1.4 respectively.

Table 1.2: Risk score properties where blood pressure was not measured according to a consistent pre-defined protocol in the derivation study

Paper	Risk score	Population	Outcome	BP measurement	Inclusion of BP	Adjustment variables
Blood pressure not measured according to a consistent pre-defined protocol with a single reading recorded						
Hippisley-Cox, 2008(41)	QRISK2	Patients aged 35-74 registered at UK GP practices January 1993 to March 2008. 97% white.	CVD events.	SBP in the clinical record closest to the index date.	As a continuous variable (per 20 mmHg) with interactions for age, stratified by sex.	Age, sex, smoking status, TC/HDL, BMI, family history of CHD, Townsend score, treated hypertension, rheumatoid arthritis, chronic renal disease, type 2 diabetes, atrial fibrillation, and ethnicity.
Hippisley-Cox, 2010(77)	QRISK lifetime	Patients aged 30-84 registered at GP practices in England and Wales January 1994 and April 2010. 95% white.	CVD events.	SBP in the clinical record closest to the index date.	As a continuous Variable (per 20mmHg), stratified by sex.	Age, sex, smoking status, TC/HDL, BMI, family history of CHD, Townsend score, treated hypertension, rheumatoid arthritis, chronic renal disease, type 2 diabetes, atrial fibrillation and ethnicity.
Ridker, 2007(86)	Reynolds Risk Score	Women's Health Study: Women health professionals aged 45 and over, recruited from 1992. 95% white.	CVD events.	Self-reported through questionnaires.(95)	As a continuous variable (per 1 unit increase in log-SBP).	Age, HbA1c with diabetes, current smoker, HDL, TC, hsCRP and parental history.
Ridker, 2008(87)	Reynolds Risk Score for men	Physicians Health Study II participants aged 50-80 with blood collection in 1995. Primarily white.	CVD events.	Self-reported through questionnaires.(96)	As a continuous variable (per 1 unit increase in log-SBP).	Age, TC, HDL, current smoker, hsCRP and parental history of MI.
Blood pressure not measured according to a consistent pre-defined protocol with summary measure from two or more readings recorded						
Conroy, 2003(42)	SCORE	Patients from 12 general population cohort studies, 19-80 overall, recruited 1967 to 1991. Primarily white.	CHD death and stroke death.	Differed across cohorts: single measure (23%), min of two (6%), mean of two (41%), mean of 2nd and 3rd clinic SBP measurements (2%) or unclear (28%).	As a continuous variable (per 1 mmHg).	Age, sex, TC and current smoker.

Paper	Risk score	Population	Outcome	BP measurement	Inclusion of BP	Adjustment variables
Pocock, 2001(85)	Predicting risk of death from CVD	Patients enrolled in one of 8 antihypertensive trials with raised BP. Primarily white.	CHD, stroke and CVD mortality separately.	Differed across trials: single measure (11%), mean of 2nd and 3rd (9%), mean of 2nd and 4th (22%), mean of two (58%) or mean of three clinic measures (2%).	As a continuous variable (per 10 mmHg) or as a categorical variable in simplified score,	Age, sex, TC, creatinine, height, smoking status, diabetes, history of stroke, history of MI, LVH and treatment group.
Thomsen, 2001(89)	Copenhagen Risk Score	Glostrup Population Studies: survey respondents aged 30-80, 1977 to 1991 AND Copenhagen City Heart Study: survey respondents aged 20+, 1976-78. Primarily white.	CHD events.	Glostrup: BP taken twice by a nurse (86%).(97) Copenhagen: Arterial BP measured once (14%).(98,99)	As a continuous variable (per 10 mmHg).	TC, HDL, BMI, gender, smoking status, diabetes, previous CHD and family history of CHD.

Table 1.3: Framingham (1991) risk equation

Variable	Coefficient*
Female gender	-1.2146
Log(age)	-1.8443
Log(age) x female gender	0.3668
Log(systolic blood pressure)	-1.4032
Smoker (yes/ no)	-0.3899
Log(Total cholesterol/ high-density lipoprotein cholesterol)	-0.5390
Diabetes	-0.3036
Diabetes x female gender	-0.1697
Left-ventricular hypertrophy on echocardiogram	-0.3362
θ_0	0.6536
θ_1	-0.2402
β_0	18.8144
* Note the equation is a non-proportional hazards Weibull accelerated failure time regression model, hence a negative coefficient implies higher risk.(37) Explicitly risk over time t is given as exp(-exp(u)), where $u = \frac{log(t)-\beta_0-\sum \beta_i x_i}{\exp(\theta_0+\theta_1(\beta_0+\sum \beta_i x_i))}$	

Table 1.4: QRISK2 risk equation (2015 update)

	Log-hazard ratio per unit increase	
Variable	**Men**	**Women**
Ethnic group (white=reference)		
Indian	0.3567	0.2672
Pakistani	0.5370	0.7148
Bangladeshi	0.5191	0.3703
Other Asian	0.2183	0.2074
Black Caribbean	-0.3474	-0.1744
Black African	-0.3675	-0.3272
Chinese	-0.3750	-0.2201
Other ethnicity	-0.1927	-0.2090
Smoking status (non-smoker = reference)		
Ex-smoker	0.2785	0.1947
Light smoker	0.6068	0.6229
Moderate smoker	0.7104	0.7406
Heavy smoker	0.8626	0.9134
Age term 1^1*	-17.6226	3.8735
Age term 2^2*	0.0242	0.1347
(Body mass index/10)$^{-2}$*	1.7320	-0.1558
(Body mass index/10)$^{-2}$ x log(body mass index/10)*	-7.2312	-3.7728
Townsend score (deprivation)*	0.0298	0.0644
Systolic blood pressure*	0.0102	0.0132
Total cholesterol/ high-density lipoprotein cholesterol*	0.1751	0.1526
Family history of coronary heart disease	0.5923	0.5134

	Log-hazard ratio per unit increase	
Variable	**Men**	**Women**
Treated hypertension	0.6229	0.5889
Type 1 diabetes	1.3330	1.6685
Type 2 diabetes	0.9373	1.1350
Rheumatoid arthritis	0.2542	0.3021
Atrial fibrillation	0.9891	1.4235
Renal disease	0.7850	0.8615
Interactions with age term 1		
Ex-smoker	0.9244	0.6891
Light smoker	1.9598	0.6943
Moderate smoker	2.9994	-1.6952
Heavy smoker	5.0371	-1.2150
(Body mass index/10)$^{-2}$*	33.5438	-5.5934
(Body mass index/10)-2 x log(body mass index/10)*	-129.9767	64.3636
Townsend score (deprivation)*	-0.1731	0.1519
Systolic blood pressure*	0.0523	-0.0509
Family history of coronary heart disease	1.9280	0.8605
Treated hypertension	7.8738	-4.0295
Type 1 diabetes	5.4239	-0.3344
Type 2 diabetes	5.0624	-3.3145
Atrial fibrillation	8.2354	-3.5855
Renal disease	-3.9747	-3.0767
Interactions with age term 2		
Ex-smoker	-0.0034	-0.1765
Light smoker	-0.0051	-0.2324
Moderate smoker	0.0003	0.2734
Heavy smoker	0.0031	0.1433
(Body mass index/10)$^{-2}$*	0.0812	1.5223
(Body mass index/10)-2 x log(body mass index/10)*	-0.2559	-12.7413
Townsend score (deprivation)*	-0.0011	-0.0487
Systolic blood pressure*	-0.00005	0.0074
Family history of coronary heart disease	-0.0057	-0.2757
Treated hypertension	0.0086	0.6904
Type 1 diabetes	0.0021	-0.1734
Type 2 diabetes	-0.0002	0.4865
Atrial fibrillation	0.0073	0.4987
Renal disease	-0.0262	0.4393
Baseline survival over 10 years	0.9777	0.9889

Age term 1 = $(age/10)^{-1}$ in men and $(age/10)^{0.5}$ in women
Age term 2 = $(age/10)^{2}$ in men and $(age/10)$ in women
* All continuous variables centred.
Risk calculated using a Cox model, as per the 2015 update version of QRISK2, available online.(100)

1.9. Evidence gaps regarding BP measurement for CVD risk prediction

My initial review work indicated that established cardiovascular risk scores that are likely to be used in clinical practice were developed using a limited number of clinic BP measurements obtained with varying levels of precision. This contrasts with current UK and international guidance for BP measurement which places increasing importance on repeat BP measurements and those taken outside the clinic setting. It is currently unclear how these potential differences in BP measurement may impact risk estimates for individual patients and their subsequent clinical management. Questions remain about whether potential differences are indeed true differences (depending on whether health professionals follow BP measurement guidance or not) and how much risk estimates may be changed in the presence of these differences.

Furthermore, I have shown that established risk scores incorporate information about blood pressure by including a single summary measure for mean, "usual" or underlying systolic or diastolic blood pressure. This approach ignores the inherent variability in blood pressure, which has been also been shown to be independently associated with CVD outcomes in some studies and could be assessed ever more straightforwardly as increasing numbers of repeat BP measurements are obtained routinely. Even if BP variability does predict CVD over and above traditional risk factors, it is unclear if its inclusion in a new cardiovascular risk score would materially improve the accuracy of risk estimates.

Hence, the overall aim of this thesis is to investigate how BP measurements recorded as part of routine practice in primary care should best be used for accurate estimation of CVD risk. Specific aims are as follows:

1. To determine the current practice of BP measurement during routine general practice appointments.
2. To quantify differences in CVD risk estimates obtained using different measures of "usual" BP.
3. To systematically review the evidence for BP variability as an independent risk factor for CVD.
4. To evaluate the potential for improvement in CVD risk estimation by using BP variability.

1.10. Outline of the thesis

Having introduced the key concepts regarding blood pressure as a risk factor, BP measurement, cardiovascular risk and risk prediction in primary care, the remainder of the thesis is comprised of four main project chapters and a final discussion chapter. The contents of the four project chapters are outlined as follows:

Chapter 2: Determining the current practice of "usual" blood pressure measurement

This chapter describes a patient survey and prospective study designed to establish the current practice of routine BP measurement and if this varies according to certain patient characteristics. Findings are discussed in particular comparison with existing NICE hypertension guidance and primary study protocols.

Chapter 3: Quantifying differences in CVD risk estimates obtained using different measures of "usual" BP

Data from two BP monitoring trials are analysed to describe differences in CVD risk estimates obtained when using BP measurements obtained as in the risk score derivation studies or according to current practice. The clinical implications, in terms of reclassification above or below treatment thresholds, are summarised.

Chapter 4: Reviewing the evidence for BP variability as an independent risk factor for CVD

The evidence of an independent association between BP variability and CVD is established through a systematic review and meta-analyses. Blood pressure variability is considered over the long, medium and short-term, as measured through visit-to-visit clinic, home or ambulatory BP monitoring. The pooled association of BP variability with CVD outcomes, independent of mean BP and other established risk factors, is estimated.

Chapter 5: Evaluating the potential for improvement in CVD risk estimation by using BP variability

This chapter describes a risk score derivation and validation study using cohort data from the Clinical Practice Research Datalink. A CVD risk prediction model incorporating long-term BP variability as a novel risk factor is developed in a derivation subsample of data. The accuracy of the CVD risk prediction model with and without BP variability is then evaluated in a separate validation subsample.

Chapter 2 Determining the current practice of "usual" blood pressure measurement

Blood pressures recorded as part of clinical trials and epidemiological studies are often taken in line with strict measurement protocols. These protocols can specify (for example); how many times blood pressure should be measured, the device to be used and the required periods of rest before or between readings. However, as review work in Chapter 1 demonstrated, these measurement protocols are not necessarily consistent between studies, making study comparisons difficult. More importantly, there is uncertainty as to whether such strict BP measurement practices reflect how BP is measured in routine clinical practice. This has implications for the generalisability and implementation of research findings, including the accurate implementation of cardiovascular risk scores. I therefore aimed to determine the current practice of BP measurement during routine clinical appointments in UK primary care, through a patient survey and prospective study.

2.1. Introduction

As discussed in Section 1.5, many factors can affect the accuracy of BP measurement and the number of measurements used can profoundly influence estimates of BP control.(47,48) As a result, blood pressure measurement in clinical studies and trials is usually carried out according to a pre-specified measurement protocol. For example, a research paper using data from the Women's Health Initiative study reported that:

"… blood pressure was measured in the right arm with a mercury sphygmomanometer after the participant was seated and had rested for 5 minutes; 2 measures, taken 30 seconds apart, were recorded."(101)

The paper additionally reported that measurements were taken by certified staff using an appropriate bladder cuff size. Such strict measurement protocols in trials and primary research studies are important to ensure study quality, including consistency of methods across participants and centres, and to enable study replication. As a consequence, however, study methods are less easily replicated in real-world scenarios e.g. in time-pressured general practice appointments (typically 10 minutes long).

Understanding if and how BP measurements taken routinely differ from those taken according to strict protocols is important for a number of reasons. Firstly, there are implications for how research findings are implemented in routine practice and their generalisability to different settings. For example, the recent Systolic Blood Pressure Intervention Trial (SPRINT) measured blood pressure 3 times at each study visit, using an automated device after a period of 5 minutes rest with the patient left alone during the measurement.(102) The trial concluded that treatment to a systolic BP target of less than 120 mm Hg was effective in reducing the rate of cardiovascular events compared with a target of less than 140 mm Hg.(102) An obvious question arising from this trial is, "should recommended BP treatment targets be lowered in the light of this new evidence?". Some have suggested that a lower target is not warranted citing research showing that carefully measured BP, obtained without a clinician present, is between 10-15 mm Hg systolic lower than routinely measured BP.(103,104) However, much of this evidence comes from studies in which patients were pre-selected with initially high clinic BP and studies in unselected patients have shown opposite patterns.(105) Even if routinely measured BP is significantly higher than BP measured more carefully, treatment to a routinely measured BP target of 120 mm Hg may still be worthwhile but this is unclear.

Secondly, implications for routine care extend to cardiovascular risk scores that have been developed using data from primary research studies. Section 1.6 discussed how differences in routine and derivation study BP readings may have a knock-on effect for risk estimation, affecting subsequent treatment or patient management decisions and this will be studied in Chapter 3.

Thirdly, data from electronic healthcare records databases are increasingly used for observational research; for example the recommended risk calculator in the UK, QRISK2, which was derived using the QRESEARCH primary care records database.(41) Although, results from these studies may be generalised to routine settings straightforwardly, consideration of routine data collection methods is required to compare the results to those from primary studies. For example, if BP is measured less carefully routinely, estimated associations of BP with outcomes may be biased towards the null.(56,57) Researchers can attempt to quantify this bias, however, by examining differences in how BP measurements were obtained routinely and for research purposes.

Current UK and international guidance for the diagnosis and management of hypertension recommends that multiple measurements of BP are taken in a clinic setting and that high clinic readings should be confirmed through home or ambulatory monitoring (introduced in Section 1.5).(1–3,12) However, little is known about whether this guidance is followed routinely. A previous survey of UK general practitioners (GPs) asked about adherence to some recommendations within the NICE hypertension guidelines, but did not ask about repeat measurements and relied on GP self-report.(106) Other European studies have reported rates of adherence to recommendations for lifestyle or treatment change once a BP reading is obtained,(107–109) or the reasons for non-adherence.(110,111) Hence these

studies have assumed that an accurate measure of BP is obtained initially and ignore the specifics of BP measurement.

In this chapter I aimed to determine the current practice of BP measurement during routine GP and nurse appointments in primary care. Specific aims were as follows:

1. To describe how BP is measured in the UK and determine if this in in accordance with NICE hypertension guidelines,
2. To determine if BP is measured differently in patients with certain clinical characteristics e.g. hypertension,
3. To determine if BP is measured differently depending on whether a GP or nurse takes the measurement.

2.2. Methods

2.2.1. Study design

Initial designs considered

To achieve the objectives outlined above, I considered several different study designs.

Initially I considered an updated survey of GPs to ask about their usual practice but this design was rejected because GPs and nurses may be inclined to give socially desirable responses, whereby they admit/ agree to things that are more socially acceptable or will be seen as more favourable (following guidelines in this case).(112) Health professionals choosing to respond to a survey about blood pressure might also be those that have a special interest in BP monitoring and/or hypertension and therefore might be more likely to be aware of and/or follow guidelines, biasing results.

Secondly I considered an observational (ethnographic-type) study in which I would directly observe appointments and note down the usual practice. This has disadvantages because the presence of an observer may bias results in itself. Firstly patients may be reluctant to take part in a study which involves having a researcher in a consultation with them, particularly as many other topics may be discussed during an appointment over and above that of BP. Secondly, having a researcher present in a consultation may alter the interaction between the patient and health professional. In particular, if health professionals are aware of the study objectives, this may lead them to adhere more closely to recommended standards, with the potential for similar biases to the GP survey design. I did consider whether filming the consultations would be a less intrusive option compared to direct observation, but the same biases could still apply.

A further study design option was to use the memory functions in automated BP devices as another alternative to direct observation since only the required information about BP would have been captured. This might have been more acceptable to patients and could have considered data after a run-in period during which healthcare professionals became accustomed to using the alternative devices. However, even with date and time stamped BP readings linked to patient records, it would have been difficult to match readings to patients, consultations and the health professional conducting the consultation in order to analyse the readings appropriately. All study designs involving direct or indirect observation would also have been small in scope, providing data from only a small number of GP practices around Oxford and results may not have been generalizable to the rest of the UK.

The final study design considered was a survey asking patients to recall whether and how BP was measured at their last appointment. Advantages of this approach are that patients should not feel pressured into giving socially desirable responses about their GPs and only

the relevant information about BP is collected. Disadvantages are that it would not allow tracking of individual GP or nurse behaviour since patients are not able to ethically provide information about their GP/ nurse without consent. Patients might also find it difficult to recall specific details about their last appointment and BP accurately. However, it seemed possible to overcome these problems by including a question about location in the survey (since patients who live in different postcode areas will likely have different GPs) and by including a prospective follow-up element to the survey. Patients could therefore enter their next appointment knowing that they would be asked about their BP in a follow-up questionnaire and this could help to reduce problems of recall bias. Hence of all the designs considered, such a survey design was selected as the most appropriate. The detailed survey design methods are explained below.

Recruitment

Respondents for the survey were initially recruited through two charities: the University of the Third Age (U3A, a charity for retired and semi-retired individuals) and Blood Pressure UK (BPUK, a charity providing specific advice and support on BP monitoring and hypertension). These charities were chosen since the members of U3A are likely to be older individuals who visit their GPs on a regular basis regarding a wide range of conditions. Similarly, members of BPUK are likely to have hypertension and regularly visit their GP for monitoring. I contacted both charities initially to determine their interest in and capability to advertise the survey and liaised with them during development of the survey to determine exactly how and when the adverts would be distributed.

The explicit methods of recruitment differed slightly between the two charities. Although it is a national charity, U3A is split into a 964 local groups representing 342,000 members in total and is organised at the local level. I designed an advert describing the study (see

Document A.1, Appendix A) and this was sent out in a mailing to the head of each local group, who was then responsible for redistributing the information to local members. Local group heads could choose how they distributed the information given to them, for example by using email lists or posting information on notice boards where local meetings are held. The advert was also distributed at the U3A's annual national conference and posted on the member pages of the U3A website.

The same advert was distributed by BPUK using email, to the 1190 people who are registered to receive their e-bulletins. In total, BPUK has 3400 members and the information was additionally posted on the home page of the public BPUK website. The study was prospectively approved by the University of Oxford's Medical Sciences Division Central University Research Ethics Committee, (reference MS-IDREC-C1-2015-095).

Following lower than anticipated response rates, an amendment to ethical approval was sought to additionally advertise the survey to patient research groups. The survey was then advertised online through Citizen Scientist, Patients Active in Research and Call for Participants. Although ethical approval was additionally given to advertise through NHS Choices, this was not pursued after more in-depth conversations with them about the feasibility and timescale for setting up an online advert. As a result of the advert on the Citizen Scientist website, a patient involvement group for diabetes, Research for the Future (Help BEAT Diabetes), asked if they could additionally advertise the survey to their members by email and this was agreed.

Sample size

The study was powered to estimate the proportion of people who have their BP measured according to NICE hypertension guidelines. Previous surveys have shown that GP

adherence to some specific recommendations within guidelines is low, with 13% of GPs adhering to guidelines to measure BP in both arms.(106) It was therefore expected that the proportion of patients who have their BP measured according to guidelines would be similarly low (approximately 10%). In order to estimate the proportion with an accuracy of +/- 5% at the 95% confidence level, a sample size of 139 respondents who had their BP measured was required.(113)

Data from the Health Survey for England(114) indicated that approximately 60% of people aged 55+ years have hypertension and are therefore be likely to have their BP measured regularly by their GP. To achieve a sample of 139 respondents with BP measured, the survey therefore needed to be returned by about 231 individuals. A summary of the different sample sizes required, given differing assumptions is given in Table 2.1.

Table 2.1: Sample sizes required to estimate a given proportion with differing margins of error, assuming 60% of people have their BP measured at any one appointment.

	Error (%)				
Proportion (%)	**2**	**3**	**4**	**5**	**6**
5	761	338	191	122	85
8	1179	524	295	189	131
10	1441	641	361	**231**	161
11	1691	752	423	271	188
12	2041	908	511	327	227

In order to determine the likely final sample size, I used information about recruitment rates from a study which recruited Multiple Sclerosis Society members through newsletters and on the society's website.(115) The society has approximately 38,000 members and the study achieved participation from 27 people who contacted researchers following the adverts. Assuming a similar response rate from U3A and BPUK I expected participation

from 245 individuals. As described above, the actual response rate in these two groups was lower than expected, and so advertising was extended to other charities and patient groups.

Survey design

The survey was designed to have two parts, both of which were conducted online using a survey system developed and hosted by the Clinical Trials Unit at the Nuffield Department of Primary Care Health Sciences, University of Oxford.

The first survey was designed to collect basic demographic and clinical history information and to ask simple questions about whether and how respondents had their blood pressure measured during their last general practice appointment. From the advert, respondents were directed to the webpage for the first survey, where further more detailed information was provided regarding the aims of the survey and how responses would be collected and used (see Document A.2, Appendix A).

Initially, respondents were asked to recall one BP reading from their previous appointment, although it was expected that this information might be sparsely/ poorly reported. Overall, the aim of the first survey was to instigate thoughts about BP and BP monitoring in the respondents, in the hope that they would be more likely to take notice of, and remember BP monitoring practices during their next appointment. The specific format of the first survey is detailed in Appendix A (Document A.3).

Respondents completing the first survey were then invited to take part in a prospective follow-up survey and, if willing to take part, asked to give formal consent and provide their email address. Respondents were told that they would be asked similar questions about their BP in the follow-up survey after their next appointment. The link to the second survey webpage was then emailed to participants, timed to follow their next appointment

based on the information provided in their responses to the first survey (see Document A.4, Appendix A). For those who had no appointment scheduled at the time of completing the first survey, an email was sent three months later. A month prior to closing the follow-up survey, further reminder emails were sent to all participants who had not yet completed it asking them to do so if they had had subsequent appointments.

The second survey contained similar questions to the first survey (see Document A.5, Appendix A). The major difference between the first and second surveys was that instead of being asked to recall only one blood pressure reading from their previous appointment, respondents were asked to recall up to three readings (if their BP was measured multiple times). Furthermore, a question about any previous measurement of BP in both arms was included in the first survey but not duplicated in the second. Demographic and clinical history information was obtained from the first survey by linking information through the email addresses provided.

Patient and Public Involvement

The initial drafts of the survey advert, information sheet and questionnaires were revised based on feedback from two patient representatives and following piloting with friends and family members. In general this included the addition and removal of certain questions and rewording. In particular, the patient representatives helped to decide how much information respondents should be given about the second part of the survey, to ensure that good quality data was collected at this stage. The aim was to ensure that enough information was given to respondents to instigate thought about their blood pressure and the survey during their next appointment, but so as not to unduly worry the patients or risk altering their interaction with the GP.

The patient representatives decided that asking patients to explicitly ask their GP/ nurse about their BP readings and to remember or write them down would likely make patients anxious or worried about their blood pressure even if they had no need to be. They thought that simply stating that the second survey would ask similar questions to the first would be enough to prompt the respondents without making them unduly worried. A further two patient representatives were asked to pilot the first survey using the online system, to test the functionality and to suggest any further changes.

2.2.2. Statistical Analysis

Patient demographic and clinical history data were summarised using means and standard deviations for continuous data or proportions for binary and categorical data. Blood pressure data were summarized by means and 95% confidence intervals.

Respondents who had their BP measured at their follow-up appointment were deemed to have had their BP measured according to NICE hypertension guidelines if BP was measured in the following way:

i. One BP reading was taken and the reading was below 140/90 mm Hg,
ii. Two BP readings were taken if the initial reading was above 140/90 mm Hg and the second systolic reading was within 5 mm Hg of the first, or
iii. Three BP readings were taken if the first two readings differed by more than 5 mm Hg systolic

The proportion of people having their BP measured multiple times, or being asked to monitor their BP at home was compared by hypertensive status and by the type of professional (GP or nurse) taking the BP reading. Proportions were compared using two-

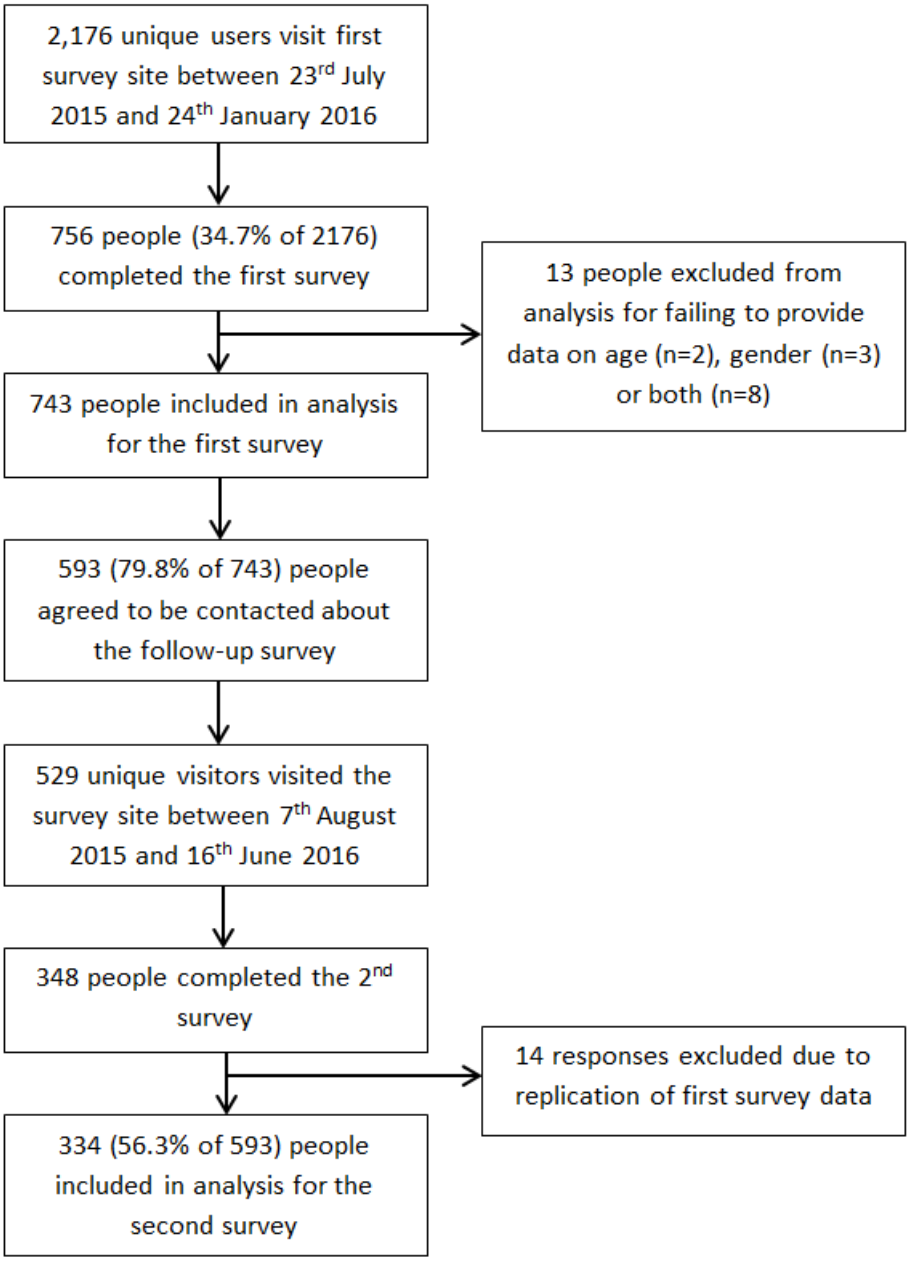
sided tests of proportions under the assumption of large samples (i.e. normally distributed test statistics), at the 5% level. Due to a large proportion of participants having diabetes, post-hoc subgroup analysis was performed by patient diabetes status.

Since behaviour amongst professionals from the same GP practice may be similar, sensitivity analysis was carried out restricting data to one randomly selected observation from each postcode district (assuming respondents from different districts will be registered to distinct practices). I also conducted sensitivity analyses excluding prospective responses that were suspected of being duplicate submissions of the same initial survey data. All analyses were conducted using Stata 14.(116) Graphs were produced using R 3.3.1.(117)

2.3. Results

In total 2176 unique users visited the first survey site, of which 756 completed the survey, with complete data (valid gender and age information) available in 743 individuals. Five hundred and ninety-three people gave consent to be contacted about the prospective study and of these, 334 people (56.3%) completed the follow-up questionnaire and did not obviously provide duplicate responses from the first to follow-up survey. Note that respondents could complete the follow-up survey whilst recruitment for the first survey was still ongoing; hence the overlap of date ranges in the study flowchart in Figure 2.1. Of those who gave consent to take part in the follow-up survey but did not complete it (n=245), 75 people were unlikely to have had a second eligible appointment because they a) did not have another appointment scheduled (n=52), b) did not know when their next appointment would be (n=20) or c) did not give any information.

Figure 2.1: Survey participation flow diagram



Those completing the prospective survey were broadly similar to those completing the initial survey (Table 2.2). A majority of respondents had diabetes or hypertension and could be considered at increased risk of cardiovascular disease, and over a third of patients were from the North West of England.

Table 2.2: Survey participant characteristics

		Completed 1st survey (N=743)	Completed prospective survey (N=334)
Characteristic		**Mean (SD) / N (%)**	**Mean (SD) / N (%)**
Male		377 (50.7)	172 (51.5)
Age		57.4 (13.28)	59.3 (12.14)
Current smoker		48 (6.5)	25 (7.5)
Hypertensive		413 (55.6)	200 (59.9)
	Antihypertensive medication	353 (85.5)	173 (86.5)
Diabetes		623 (83.9)	279 (83.5)
Previous CVD		62 (8.3)	31 (9.3)
Chronic kidney disease		25 (3.4)	12 (3.6)
Rheumatoid arthritis		23 (3.1)	13 (3.9)
Told at high risk of CVD		55 (7.4)	30 (9.0)
Region			
	North East	18 (2.4)	9 (2.7)
	North West	285 (38.4)	125 (37.4)
	Yorkshire & The Humber	55 (7.4)	20 (6.0)
	East Midlands	23 (3.1)	8 (2.4)
	West Midlands	38 (5.1)	16 (4.8)
	East of England	42 (5.7)	28 (8.4)
	South West	103 (13.9)	49 (14.7)
	South East	93 (12.5)	57 (17.1)
	London	50 (6.7)	15 (4.5)
	Other	8 (1.1)	2 (0.6)
	Unknown	28 (3.8)	5 (1.5)

2.3.1. Initial survey results

Of the 743 people contributing to the first survey, 489 (65.8%) had their BP measured at their last consultation: 156 (31.9% of 489) by a GP, 321 (65.6%) by a nurse and 12 (2.5%) in the waiting room. Four hundred and eighty (98.2% of 489) could recall how many BP readings were taken: 286 (59.6% of 480) one reading, 144 (30.0%) two readings and 50 (10.4%) three or more readings. The proportion of people who were able to remember and report a BP value increased with the number of measurements taken during the appointment (Table 2.3). Those who had their BP measured multiple times reported higher

systolic and diastolic BP readings and were more likely to be asked to monitor their BP at home. In total, only 88 patients (11.8%) recalled ever having their BP measured in both arms at any one previous appointment. Compared to normotensives (20/330, (6.7%)), respondents with a previous diagnosis of hypertension (68/413, (16.5%)) were more likely to report having had their BP measured in both arms at any appointment previously.

Table 2.3: Blood pressure measurements reported in the initial survey

Number of BP readings	N	Provided a BP reading	Systolic BP mean (95% CI), mm Hg	Diastolic BP mean (95% CI), mm Hg	Proportion asked to monitor their BP at home (95% CI)
1	286	100 (35.0%)	131.6 (128.4 to 134.8)	75.2 (73.2 to 77.1)	7.7% (4.6 to 10.8%)
2	144	69 (47.9%)	140.0 (135.7 to 144.2)	79.4 (76.7 to 82.2)	22.2% (15.4 to 29.0%)
3 or more	50	27 (54.0%)	147.3 (137.8 to 156.9)	85.2 (80.2 to 90.2)	29.5% (16.1 to 43.0%)

Comparing measurement practice by hypertensive status

Respondents with a previous diagnosis of hypertension were more likely to have their BP measured multiple times (143/281 (50.9%) vs. 51/199 (25.6%); difference = 25.3%, 95% CI [16.8 to 33.7%]) and were also more likely to be asked to monitor their BP at home (78/413 (18.9%) vs. 13/330 (3.9%); difference = 14.9%, 95% CI [10.6 to 19.3%]). Compared to treated hypertensives, hypertensives not yet on medication appeared more likely to have their BP measured multiple times (28/42 (66.7%) vs. 115/239 (48.1%); difference = 18.5%, 95% CI [2.9 to 34.2%]) and possibly more likely be asked to monitor their BP at home (17/60 (28.3%) vs. 61/353 (17.3%); difference=11.1%, 95% CI [-1.0% to 23.1%]).

Comparing measurement practice between GPs and nurses

There was little evidence of a difference in GP and nurse behaviour. When BP was measured by a GP compared to a nurse, more people had their BP measured multiple times (66/153 (43.1%) vs. 122/316 (38.6%); difference = 4.5%, 95% CI [-5.0 to 14.0%]) or were asked to monitor their BP at home (27/156 (17.3%) vs. 41/321 (12.8%); difference = 4.5%, 95% CI [-2.4 to 11.5%]) but these differences were not statistically significant. Similarly, GPs and nurses appeared to be equally likely to tell patients their BP or have a discussion about it (130/156 (83.3%) vs. 275/321 (85.7%); difference = -2.3%, 95% CI [-9.3 to 4.7]). In most cases (91.2%), measurement of BP was carried out by the professional conducting the appointment, so results were similar when comparing consultations with GPs and nurses.

2.3.2. Prospective survey results

Of the 334 people completing the follow-up questionnaire, 217 (65.0%) had their BP measured at the follow-up appointment: 59 (27.2% of 217) by a GP, 150 (69.1%) by a nurse and 8 (3.7%) by themselves in the waiting room. The majority were told their BP level or had a discussion about it (193 people, 88.9%). Blood pressure was measured once, twice or three or more times in 132 (60.8%), 56 (25.8%) and 29 (13.4%) people respectively. Compared to the first survey, similar proportions of people could recall and report at least one BP reading, regardless of how many times BP was measured (Table 2.4). Those who had their BP measured multiple times were more likely to be asked to monitor their BP at home.

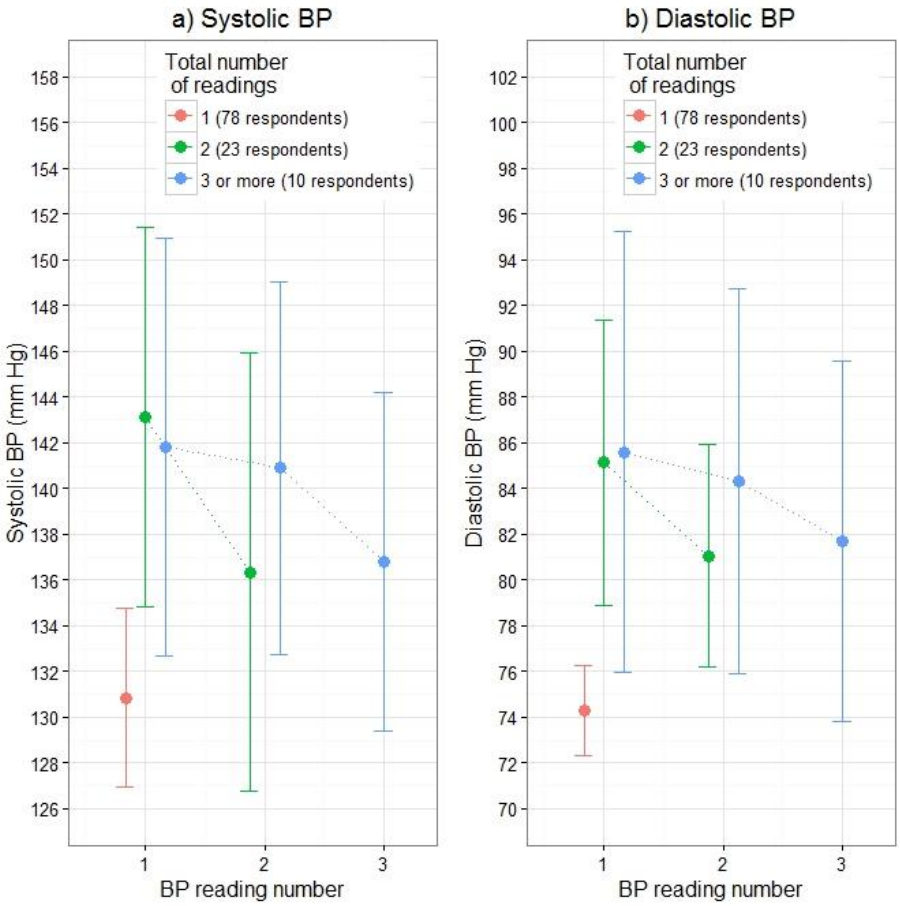
Table 2.4: Blood pressure measurements reported in the prospective survey

Number of BP readings	N	Provided at least one BP reading	Provided all BP readings	Proportion asked to monitor their BP at home (95% CI)
1	132	78 (59.1%)	78 (59.1%)	11.4% (5.9 to 16.8%)
2	56	32 (57.1%)	23 (50.0%)	25.0% (13.7 to 36.3%)
3 or more	29	16 (55.2%)	10 (34.5%)	32.5% (17.2 to 51.8%)

Blood pressure measurement according to guidelines

One hundred and eleven people (51.1% of 217) provided values for all of the BP readings taken during the appointment. In those reporting all readings, 70 people (63.1%; 95% CI [53.9 to 72.2]) had their BP measured in line with diagnostic guidelines as defined in Section 2.2.2. The remainder either had their BP measured too few times (n=23, 20.7%) or more than guidance recommends (n=18, 16.2%). The pattern of BP measurement by reading number is shown in Figure 2.2.

Figure 2.2: Blood pressure values (mean with 95% confidence intervals) by reading number in 111 respondents reporting a value for all blood pressure readings



Repeat BP measurements were taken when readings were initially high or remained so on average (Table 2.5 and Figure 2.2). Initial BP readings were significantly lower in those with only a single reading compared to those with two readings (Table 2.5, systolic p=0.004 and diastolic p<0.001) or those with three readings (Table 2.5, systolic p=0.06 and diastolic p<0.001). Second BP readings were not significantly different in those with two or three readings (systolic p=0.55 and diastolic p=0.46) although numbers in these groups were small. Visual inspection of the plots suggests that GPs and nurses may be more likely to continue measuring BP when presented with a further high reading.

Table 2.5: Blood pressure values by reading number and total number of readings in 111 respondents reporting a value for all blood pressure readings

	Total number of readings	Mean (95% CI) [Range]		
		Reading number		
		1	2	3
Systolic	**1 (n=78)**	130.8 (127.0 to 134.8)	-	-
		[100, 213]	-	-
	2 (n=23)	143.1 (134.8 to 151.4)	136.3 (126.8 to 145.9)	-
		[100, 181]	[80, 179]	-
	3 (n=10)	141.8 (132.7 to 150.9)	140.9 (130.8 to 144.6)	136.8 (129.4 to 144.2)
		[126, 166]	[126, 162]	[121, 155]
Diastolic	**1 (n=78)**	74.3 (72.3 to 76.2)	-	-
		[60, 100]	-	-
	2 (n=23)	85.1 (78.9 to 91.4)	81.0 (76.2 to 85.9)	-
		[65, 133]	[62, 112]	-
	3 (n=10)	85.6 (76.0 to 95.2)	84.3 (75.9 to 92.7)	81.7 (73.8 to 89.6)
		[66, 108]	[69, 101]	[65, 97]

Despite the overall observed patterns, there was considerable variability for individual patients. For example, in those with only one reading, systolic BP was as high as 213/100 mm Hg in one respondent when their BP was measured by a GP. Comparatively, one individual who had their BP measured three times by a nurse had an initial reading of 128/87 mm Hg (in those with three readings, the respondent with the lowest initial reading of 126/ 66 mm Hg measured their BP themselves). This suggests that for certain individuals, the BP reading alone does not dictate whether repeat readings are taken. This may be driven by the reason for the consultation or other patient factors. In this particular example, the respondent with only a single reading had no other cardiovascular risk factors or comorbidities, despite being older (71 years). The respondent who had their BP measured three times was younger (60 years) but had diabetes, rheumatoid arthritis, a history of heart attack and was taking both antihypertensive and statin medication.

Comparing measurement practice by hypertensive status

Respondents with a previous diagnosis of hypertension were more likely to be asked to monitor their BP at home (38/200 (19.0%) vs. 13/134 (9.7%); difference = 9.3%, 95% CI [1.9 to 16.7%]) compared to normotensives, in line with results from the initial survey. Hypertensive status was not significantly associated with having BP measured multiple times (55/131 (42.0%) vs. 30/86 (34.9%); difference = 7.1%, 95% CI [-6.0 to 20.2%]), although this result was directionally similar to that of the first survey. As in the first survey, there was some evidence that compared to treated hypertensives, those not yet on medication were more likely to have their BP measured multiple times (48/116 (41.4%) vs. 7/15 (46.7%); difference = -5.3%, 95% CI [-32.1 to 21.5%]) or be asked to monitor their BP at home (31/173 (17.9%) vs. 7/27 (25.9%); difference= -8.0%, 95% CI [-25.5 to 9.5%]) but numbers were too small to determine significance.

Comparing GP and nurse measurement practice

When BP was measured by a GP compared to a nurse, similar proportions of people had their BP measured multiple times (25/59 (42.4%) vs. 58/150 (38.7%); difference = 3.7%, 95% CI [-11.1 to 18.5%]). GPs and nurses were equally likely to discuss a patient's BP with them (54/59 (91.5%) vs. 135/150 (90.0%); difference = 1.5%, 95% CI [-7.1 to 10.1]). A greater proportion of people were asked to measure their BP at home when BP was measured by a GP compared to a nurse (18/59 (30.5%) vs. 19/150 (12.7%); difference = 17.8%, 95% CI [4.9 to 30.7%]), which is in line with findings from the first survey. In most cases (91.7%), BP measurement was carried out by the professional conducting the appointment, so results were similar when comparing consultations with GPs and nurses.

Results stratified by diabetes status

Similar results were observed when the analysis was stratified by diabetes status. Of the 55 (16.5%) people without diabetes contributing to the prospective survey, 34 (61.8%) had their BP measured at their last appointment: 21 (61.8%) by a GP, 11 (32.4%) by a nurse and 2 (5.9%) by themselves in the waiting room. Those who had their BP measured once, twice and three or more times, were asked to monitor their BP at home in 5/23 (21.7%, 95% CI [4.9 to 38.6%]), 3/5 (60.0%, 95% CI [17.1% to 100.0%]) and 3/6 (50.0%, 95% CI [10.0 to 90.0%]) cases respectively. Of the 34 who had their BP measured, 20 (58.8%) provided a value for all of the BP readings given and of these, 12 respondents (60.0%, 95% CI [36.1% to 80.9%]) had their BP measured according to guidelines. Mean BP values by reading number are given in Table 2.6. As in the main analysis, initial mean BP was lower in those with one reading, although there were too few observations to determine significant differences.

Table 2.6: Blood pressure values by reading number and total number of readings in 20 respondents without diabetes reporting a value for all blood pressure readings

	Total number of readings	**Mean (95% CI) [Range]**		
		Reading number		
		1	**2**	**3**
Systolic	**1 (n=12)**	135.8 (115.8 to 155.8) [110, 213]	- -	- -
	2 (n=4)	160.8 (124.9 to 196.6) [137,181]	158.5 (127.7 to 189.3) [137, 179]	- -
	3 (n=4)	154.5 (141.2 to 167.8) [147, 166]	152.3 (141.7 to 162.8) [147, 162]	144.3 (126.0 to 162.5) [128, 155]
Diastolic	**1 (n=12)**	75.3 (67.3 to 83.2) [60, 100]	- -	- -
	2 (n=4)	89.8 (75.6 to 103.9) [78, 98]	87.8 (70.5 to 105.0) [78, 99]	- -
	3 (n=4)	89.0 (63.1 to 114.9) [70, 108]	87.0 (64.5 to 109.5) [69, 101]	84.0 (61.9 to 106.1) [65, 97]

Of the remaining 279 (83.5%) people contributing to the prospective survey that did have diabetes, 183 (65.6%) had their BP measured at their last appointment: 38 (20.8%) by a GP, 139 (76.0%) by a nurse and 6 (3.3%) by themselves in the waiting room. Hence those with diabetes were more likely to have their BP measured by a nurse which reflects the fact their appointments were more generally with a nurse. Those who had their BP measured once, twice and three or more times, were asked to monitor their BP at home in 10/109 (9.2%, 95% CI [3.8 to 14.6%]), 11/51 (21.6%, 95% CI [10.3% to 32.9%]) and 7/23 (30.4%, 95% CI [11.6 to 49.2%]) cases respectively. Of the 183 who had their BP measured, 91 (49.7%) provided a value for all of the BP readings given and of these, 58 respondents (63.7%, 95% CI [53.0 to 73.6%]) had their BP measured according to guidelines. Mean BP values by reading number are given in Table 2.7. As in the main analysis and those without diabetes, initial mean BP was lower in those with one reading compared to those with two or three readings.

Table 2.7: Blood pressure values by reading number and total number of readings in 91 respondents with diabetes who reported a value for each blood pressure reading

	Total number of readings	Mean (95% CI) [Range]		
		Reading number		
		1	2	3
Systolic	**1 (n=66)**	130.0 (126.6 to 133.3) [110,176]	- -	- -
	2 (n=19)	139.4 (131.3 to 147.5) [100,173]	131.7 (122.0 to 141.4) [80, 173]	- -
	3 (n=6)	133.3 (127.0 to 139.7) [126, 140]	133.3 (127.0 to 139.6) [126, 140]	131.8 (125.3 to 138.4) [121, 139]
Diastolic	**1 (n=66)**	74.1 (72.2 to 76.1) [60, 95]	- -	- -
	2 (n=19)	84.2 (76.7 to 91.6) [65, 133]	79.6 (74.3 to 85.0) [62, 112]	- -
	3 (n=6)	83.3 (70.4 to 96.2) [66, 96]	82.5 (71.0 to 94.0) [69, 94]	80.2 (70.0 to 90.3) [68, 91]

In both those with and without diabetes, results regarding hypertensive status and treatment were similar to the main findings, as were results regarding the practitioner taking the BP measurement (Table 2.8). In both groups, all observed differences were in the same direction as those in the main analysis but some findings did not reach statistical significance due to the lower numbers in each group. An exception was that nurses were more likely to recommend home monitoring than GPs in those without diabetes, but confidence intervals were wide and overlapped those in the main analysis. GPs or nurses were equally likely to discuss a patient's BP with them if the patient did not have diabetes (20/21 (95.2%) vs. 10/11 (90.9%); difference = 4.3%, 95% CI [-14.9 to 23.6]) and similarly if the patient did have diabetes (34/38 (89.5%) vs. 125/139 (89.9%); difference = -0.5%, 95% CI [-11.4 to 10.5%]).

Table 2.8: Likelihood of having BP measured multiple times or being asked to monitor BP at home, according to patient and practitioner characteristics (stratified by diabetes status)

	Likelihood of multiple BP measurements (n (%) in each group) (difference [95% confidence interval])	**Likelihood of being asked to monitor BP at home (n (%) in each group) (difference [95% confidence interval])**
In patients without diabetes (n=34)		
If the patient is hypertensive vs. normotensive	2/6 (33.3%) vs. 9/28 (32.1%) difference = 1.2% [-40.3 to 42.7%]	14/41 (34.1%) vs. 0/14 (0.0%) difference = 34.1% [19.6 to 48.7%]
If the patient has treated hypertension vs. untreated hypertension	8/23 (34.8%) vs. 1/5 (20.0%) difference = 14.8% [-25.3 to 54.9%]	9/32 (28.1%) vs. 5/9 (55.6%) difference = -27.4% [-63.4% to 8.6%]
If BP was measured by a GP vs. a nurse (n=32)	9/21 (42.9%) vs. 2/11 (18.2%) difference = 24.7% [-6.4 to 55.8%]	7/21 (33.3%) vs. 4/11 (36.4%) difference = -3.0% [-37.9 to 31.8%]
In patients with diabetes (n=183)		
If the patient is hypertensive vs. normotensive	46/103 (44.7%) vs. 28/80 (35.0%) difference = 9.7% [-4.5 to 23.9%])	24/159 (15.1%) vs. 13/120 (10.8%) difference=4.3% [-3.6 to 12.1%]
If the patient has treated hypertension vs. untreated hypertension	40/93 (43.0%) vs. 6/10 (60.0%) difference = -17.0% [-49.0 to 15.0%]	22/141 (15.6%) vs. 2/18 (11.1%) difference = 4.5% [-11.2 to 20.2%]
If BP was measured by a GP vs. a nurse (n=177)	16/38 (42.1%) vs. 56/139 (40.3%) difference = 1.8% [-15.9 to 19.5%]	11/38 (28.9%) vs. 15/139 (10.8%) difference = 18.2% [2.8 to 33.5%]

Sensitivity analyses

Sensitivity analysis was carried out by removing observations (n=17) where there was suspicion that a participant had submitted the same information for both the initial survey and the prospective questionnaire, but where this could not be determined conclusively. Of the remaining 317 respondents, 205 (64.7%) had their BP measured at the follow-up appointment: 57 (27.8% of 205) by a GP, 140 (68.3%) by a nurse and 8 (3.9%) by themselves in the waiting room. Blood pressure was measured once, twice or three or more times in 122 (59.5%), 55 (26.8%) and 28 (13.7%) people respectively. The 111 people providing all BP readings in the main analysis were also included in this sensitivity analysis, so the pattern of BP readings is the same as that shown in Table 2.5. As in the main analysis, GPs and nurses were equally likely to discuss a patient's BP with them (52/57 (91.2%) vs. 125/140 (89.3%); difference = 1.9%, 95% CI [-7.0 to 10.9]). All other results were similar to those in the main analysis and conclusions remained unchanged (Table 2.9).

A further sensitivity analysis was carried out by taking a random sample of responses from unique postcode districts. Of the 743 responses to the first survey, 463 were randomly selected from each unique postcode district. Of these, 375 gave consent to take part in the follow-up survey and 207 completed the prospective questionnaire (compared to 343 in main analyses). Of those completing follow-up, 128 people (61.8%) had their BP measured at their last appointment; 40 (31.2%) by a GP, 83 (64.8%) by a nurse and 5 (3.9%) in the waiting room. Blood pressure was measured once, twice and three or more times in 76 (59.4%), 35 (27.3%) and 17 (13.3%) respondents respectively.

Table 2.9: Likelihood of having BP measured multiple times or being asked to monitor BP at home, according to patient and practitioner characteristics in each sensitivity analysis

	Likelihood of multiple BP measurements (n (%) in each group) (difference [95% confidence interval])	**Likelihood of being asked to monitor BP at home (n (%) in each group) (difference [95% confidence interval])**
Removing n=17 observations where duplicate submission suspected (n=205)		
If the patient is hypertensive vs. normotensive	54/125 (43.2%) vs. 29/80 (36.3%) difference = 7.0% [-6.7 to 20.6%]	38/193 (19.7%) vs. 11/124 (8.9%) difference = 10.8% [3.3 to 18.3%]
If the patient has treated hypertension vs. untreated hypertension	47/110 (42.7%) vs. 7/15 (46.7%) difference = -3.9% [-22.9 to 30.8%]	31/166 (18.7%) vs. 7/27 (25.9%) difference=-7.3% [-10.3 to 24.8%]
If BP was measured by a GP vs. a nurse (n=197)	25/57 (43.9%) vs. 56/140 (40.0%) difference = 3.9% [-11.4 to 19.1%]	18/57 (31.6%) vs. 19/140 (13.6%) difference = 18.0% [7.9 to 19.2%]
Random sample from unique postcode districts (n=128)		
If the patient is hypertensive vs. normotensive	33/75 (44.0%) vs. 19/53 (35.9%) difference = 8.2% [-9.0 to 25.3%]	26/118 (22.0%) vs. 12/89 (13.5%) difference= 8.6% [-1.8 to18.9%]
If the patient has treated hypertension vs. untreated hypertension	29/64 (45.3%) vs. 4/11 (36.4%) difference = 8.9% [-39.9 to 22.0%]	20/97 (20.6%) vs. 6/21 (28.6%) difference=-8.0 % [-28.9 to 13.0%]
If BP was measured by a GP vs. a nurse (n=123)	17/40 (42.5%) vs. 33/83 (39.8%) difference = 2.7% [-15.8 to 21.3%]	16/40 (40.0%) vs. 11/83 (13.3%) difference = 26.7% [9.9 to 43.6%]

In the sample of responses from unique postcode districts, 67 people provided a reading for all BP measurements taken and of these 43 (64.2%, 95% CI [51.5 to 75.5%]) had their BP measured according to guidelines. Those with hypertension were equally likely to be asked to monitor their BP at home compared to normotensives although the observed difference was in the same direction and of a similar magnitude as in the main analysis (Table 2.9). All other results were similar to those in the main analysis (Table 2.9). Similarly, GPs and nurses were equally likely to discuss a patient's BP with them (36/40 (90.0%) vs. 73/83 (88.0%); difference = 2.0%, 95% CI [-9.6 to 13.7]). BP was also lowest on average in those who had their BP measured once (Table 2.10).

Table 2.10: Blood pressure values by reading number and total number of readings in 67 respondents from unique postcode districts who reported a value for each blood pressure reading

	Total number of readings	**Mean (95% CI) [Range]**		
		Reading number		
		1	**2**	**3**
Systolic	**1 (n=47)**	129.5 (123.6 to 135.4)	-	-
		[100, 213]	-	-
	2 (n=13)	145.7 (134.6 to 156.7)	138.0 (123.3 to 152.7)	-
		[120, 181]	[80, 179]	-
	3 (n=7)	144.4 (131.1 to 157.8)	143.0 (130.8 to 155.2)	138.0 (126.5 to 149.5)
		[126, 166]	[126,162]	[121, 155]
Diastolic	**1 (n=47)**	75.7 (72.9 to 78.4)	-	-
		[60, 100]	-	-
	2 (n=13)	88.5 (78.4 to 98.6)	83.2 (75.1 to 91.2)	-
		[65,133]	[62, 112]	-
	3 (n=7)	85.7 (72.3 to 99.1)	85.0 (73.6 to 96.4)	82.4 (71.3 to 93.6)
		[66, 108]	[69, 101]	[65, 97]

2.4. Discussion

This study has examined how BP is measured during routine general practice appointments in the UK. Blood pressure was more likely to be measured multiple times in those with initially high clinic pressures and GPs and nurses were more likely to recommend home monitoring in these individuals or those with a previous diagnosis of hypertension. Patterns of repeat BP measurement in the same arm were in line with current NICE guidelines for the diagnosis of hypertension in the majority of patients, but very few patients could recall ever having BP measured in both arms. Although GPs were more likely to recommend home monitoring compared to nurses, they were equally likely to take multiple BP measurements during clinic appointments and to discuss them with their patients.

2.4.1. Strengths and limitations

The patient centred nature of this study has allowed me to examine differences in BP measurement practices according to certain patient characteristics, whereas previous studies have taken a healthcare professional view.(106) A limitation is the reliance on self-reported data from patients but I attempted to maximise the accuracy of the data collected by informing respondents that they would be asked about BP measurement practices in the follow-up survey. A greater proportion of patients provided a BP reading in the follow-up survey compared to the first survey, indicating that this approach was in part successful.

Despite this, blood pressure readings reported by patients were subject rounding error or digit preference. In the 111 patients reporting all BP readings, 47 systolic readings (30.5%) and 44 diastolic readings (28.6%) ended in a zero. We were not able to collect information on the type of sphygmomanometer used, but digital monitors report readings to the nearest 1 mm Hg and are the most common monitors used in UK primary care according to a

2009 study.(118) Research carried out after the introduction of electronic monitors showed that around 20% of readings still ended in a zero so it is possible that some of this digit preference was introduced when the GP or nurse read readings from the monitor and communicated them to the patient, or when the patient completed the survey. Errors in reporting by the patients may have been more likely in those reporting multiple readings and may also be linked to the ordering of the readings (e.g. the last reading may be remembered more accurately than the first). A previous study of the validity of self-reported home BP readings found that patients were more likely to report erroneous readings when actual BP readings were above 140 mm Hg.(119) If respondents to the survey behaved similarly and rounded down initially high readings, this would have diluted the observed trend of reducing BP with increasing numbers of measurement, but the overall conclusions would remain unchanged.

A further limitation of this study is the use of a convenience sample and the large proportion of respondents with diabetes. A much lower than expected response rate from members of the University of the Third Age charity meant that recruitment had to be extended to other charities and patient involvement groups, and the subsequent response rate from members of the Help BEAT Diabetes group was very strong.

The reason for such a poor response rate from U3A members is unclear. It may have been due to the disparate way in which study information is distributed amongst local groups or there may be many more registered members compared to those who actively participate. I have since obtained a copy of the monthly newsletter for the Stoke-On-Trent local group when the survey was advertised and there were two other adverts about external research projects in the same newsletter. If research projects are advertised regularly and in large numbers to U3A members, they may have become apathetic towards research studies and

reluctant to take part. The high response rate amongst those with diabetes may have impacted the results due to their known increase in cardiovascular risk,(30) and the potential for GPs and nurses to measure BP more (or less) carefully in these patients. However, post-hoc analyses stratified by diabetes status showed similar results so it is likely findings are robust to non-diabetes patient populations.

A further consequence of the high response rate from the Help BEAT Diabetes group is that because the group is based in Manchester, over a third of respondents to the survey were from the North West of England. This limits the generalisability of results to other areas which may have differing levels of provision for certain conditions (and specifically hypertension) in terms of location, funding and training. Overall spending on cardiovascular disease related activity does vary by region in England (for example £136 per head per year in the North West compared to £113 in the East Midlands)(10) but funding level will be confounded by burden of disease and it is not clear how funding is distributed between prevention activities (such as controlling BP) or immediate treatment following major cardiovascular events.

Generalisability of results may have also been affected by the use of an online recruitment and survey system, potentially under-representing groups with lower computer-literacy such as older patients.(120) Those who chose to take part in the survey and reported BP readings may have a vested interest in, and control over, their health and, as such, higher, uncontrolled BP values may be under-represented. Similarly, due to the inverse care law (whereby good healthcare provision is often inversely related to need), those responding may be more affluent and have fewer health problems than the general population,(121) and GPs and nurses may have measured BP more carefully in these patients. It is therefore

possible that the proportion of patients having their BP measured according to guidelines may have been over-estimated.

Although patients were the unit of analysis for the survey, the original aim of this chapter was to examine the usual practice of healthcare professionals. It is difficult to determine if the patients who responded had appointments with GPs or nurses who are representative of the overall workforce. Patients who responded were older (mean age of 57 years) and there is some evidence to suggest that older patients prefer to see older and therefore more experienced GPs.(122) A recent study of Danish GPs found that those who were older were less likely to seek information from guidelines,(123) and so in this respect the proportion of people who have their BP measured according to guidelines may be underestimated if appointments with older GPs were disproportionately represented. However given increasing workload pressures in UK primary care,(124) it is likely that respondents had appointments with whoever was available, regardless of the characteristics of the professional.

The number of participants in the follow-up survey who provided all BP readings (n=111) was smaller than our target sample size (n=139) and, a much larger proportion of patients had their BP measured in line with guidelines than anticipated. As a result I have only been able to estimate the proportion of people having their BP measured according to guidelines with an error of +/- 9% (compared to a target of +/-5%). However, data were obtained from more than 50% of prospective consultations and this study has demonstrated important differences (for example in first systolic BP readings) despite this lower than anticipated recruitment. Although BP measurement was in line with guidance in the majority of cases, this was primarily driven by a majority of participants with initially low BP who had their BP measured only once. Further, larger studies would be required to

examine adherence to NICE hypertension guidance after a second BP reading is taken and to confirm my initial findings, particularly in subgroups.

The survey did not ask respondents about the primary reason for their consultation, which may influence the time dedicated to BP measurement during an appointment. However, as many respondents had multiple different conditions, it is unlikely that any one condition was the sole purpose of the appointment and respondents may have found it difficult to "pigeon-hole" the purpose of the appointment. Furthermore, I did not collect ethnicity data despite its association with cardiovascular risk.(28,29) However, given the small sample size and since 86% of the UK population identify as "White",(125) it is unlikely that meaningful differences in BP measurement between ethnic groups could have been identified.

Many factors can affect the accuracy of BP measurement, as discussed in Section 1.5, but I chose to limit the focus of this study to factors that are easily assessed by patients in order to maximise response rates. The type and accuracy of devices used in UK general practice has been studied previously,(118) but further direct observation of clinician behaviour is warranted to assess whether other aspects of BP measurement are carried out correctly.

2.4.2. Comparison with existing literature

The study results suggest that healthcare professionals tend to take a second BP measurement if the initial reading is approximately above 140/85 mm Hg and this is in line with NICE guidelines for the diagnosis of hypertension.(1) It was not possible to draw conclusive results regarding third BP readings, but plots suggested that healthcare professionals may be more likely to continue measuring BP when presented with a second high reading, which would contradict guidance.(1) A previous review of physician barriers

to hypertension awareness and treatment found that professionals were concerned about the accuracy of individual clinic BP readings and white-coat effects.(111) My results support the idea that professionals are reluctant to believe initially high readings. This may be due to the fact that high readings require further action (e.g. in the form of treatment change) which professionals may wish to avoid given competing health interests of the patient, patient and clinician inertia,(126) performance related pay,(13) and lack of consultation time.(124) This hypothesis is supported by research showing that following the introduction of BP targets in the UK's Quality and Outcomes Framework, there was an increase in the recording of pressures just below the target BP level, despite the fact that recording of BPs far from the target remained similar.(127) Such selective recording of blood pressures may have implications for patient outcomes. Research regarding excess recording of diastolic blood pressures just below the 90 mm Hg threshold has shown that women with recorded diastolic pressure of 88 or 89 mm Hg have an excess mortality risk, compared to those with lower or higher pressures.(128)

The finding that patients are more likely to be monitored at home if they have high clinic pressures or have a diagnosis of hypertension is consistent with results from a recent practitioner survey in Canada. Although no practitioners reported using home or ambulatory BP monitoring for initial screening of high BP, 14% and 22% reported using ABPM and home measurement respectively for the diagnosis of hypertension if the initial screening BP was high. Similarly, 23% and 69% reported using ABPM and home measurement respectively for ongoing management of hypertension.(129) Although this data is from a non-UK setting, UK NICE guidelines and Canadian guidelines for the diagnosis and management of hypertension are similar so one would expect an overlap in practice.(12)

A recent survey of general practices in the South West of England found that only 1 in 10 GP practices were not following current guidelines for the use of home and ambulatory BP monitoring in the diagnosis of hypertension.(130) This is consistent with my findings that patterns of repeat BP measurement (in particular second readings) are in line with guidance in a majority of patients. This survey also indicated that healthcare assistants were primarily responsible for BP monitoring in hypertensive patients in the majority of practices. As I did not distinguish explicitly between nurses and healthcare assistants in the design of the survey, it is likely healthcare assistants were classified as nurses by respondents and this may explain why the majority of patients in this survey reported having appointments with a nurse.

2.4.3. Implications for practice

The current practice of BP measurement will identify those with white-coat effects but those with masked effects may be missed, potentially resulting in missed diagnoses and sub-optimal treatment. Although home monitoring is generally acceptable to patients,(131,132) and home and ambulatory BP measurements are more strongly linked with CVD outcomes,(54,55) it would be infeasible and costly to ask all patients to monitor their BP at home. However, several demographic and health factors are associated with masked effects including male sex and smoking status.(133) The PROOF-BP tool combines these factors with BP readings to identify which patients may exhibit masked or white coat effects and should therefore benefit most from out-of-office monitoring. It has been shown to accurately identify hypertension in 93% of cases and is more accurate than current NICE diagnostic guidelines for hypertension.(134) By using this tool, GPs could improve the detection of masked effects and avoid unnecessary out-of-office monitoring in patients who are truly hypertensive.

Only 16% of respondents with a diagnosis of hypertension reported having their BP measured in both arms at a single appointment previously, yet large differences between arms are associated with vascular disease and mortality.(50,51,135) Only 13% of GPs said they adhered to this recommendation for diagnosis a decade ago(106) and our results indicate that little progress has been made. In the previous study only 30% of GPs reported agreeing with this recommendation which may be a barrier to improvements and could be resolved through general practitioner education and training. Others have commented that, compared to the availability of single arm devices, there are comparatively few validated devices to measure BP in both arms simultaneously and this may be also be a barrier.(136) Other recent research in the South West of England at the practice level suggests that improvements have been made, with around half of practices measuring blood pressure in both arms as part of the diagnostic procedure.(130) Differing study designs may explain the discrepancy between my findings and those at the practice level, but in any case, there is still room for improvement in this respect.

A small number of respondents to the survey measured their BP themselves in the waiting room. This represents a halfway-house between clinic and home BP measurement which appears to be increasing in many GP practices. Research suggests that these are considered more reliable and easier to use by patients compared with home monitors(137) and that GPs believe that they are beneficial in reducing workload and helping to meet targets.(138) The potential utility of this in practice requires further investigation.

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2.4.4. Implications for research

This study indicates that routine BP measurement does not reflect the strict measurement protocols in primary research studies. This has implications for patient care unless routine practice can be brought in-line with study protocols or results from primary research studies can be appropriately translated into guidance for routine care (e.g. in the form of adjusted treatment targets). Recent analysis of the Australian Health Survey showed that 3% of patients under 50 years old and 5% of those over 50 would be reclassified across the diagnostic threshold for hypertension based on the mean of two readings instead of a single reading. However differences between the first and second readings were dependent on the level of BP (a regression to the mean effect) and age, with second systolic BP readings 25-30 mm Hg lower on average in those under 30 years old.(139) Hence greater proportions of people may be reclassified in certain groups.

Users of electronic health record databases should also be aware of the potential for recording biases. For example, it is likely that the last reading taken will be the only one recorded electronically and this study has demonstrated that this reading will be artificially low. Such biases will dilute the observed effect of BP on outcomes(56,57) and may, at least partly, explain differences in results between observational database and primary studies.

The results of this study provide a preliminary insight into how BP is measured on a day-to-day basis and indicate that initial repeat measurement of blood pressure is in line with NICE diagnostic guidelines for hypertension but not with strict study protocols. The impact of these differences on patient care, in particular when implementing new research findings, requires further investigation. Further consideration of methods to identify those with masked effects is also warranted. Finally, users of electronic healthcare databases

should be aware that observed effects of BP on outcomes may be biased towards the null compared to those in primary studies.

This chapter has presented results from a patient survey and prospective follow-up questionnaire, asking patients to report how their BP was measured during their last appointment. The findings inform work in Chapter 3 which explores how differences between routine BP measurement and that in risk score derivation studies may impact estimates of risk obtained in practice. The finding that multiple repeat BP measurements are being taken, in particular through recommendations for monitoring at home, also informs work in Chapter 4 which examines whether variability in these repeat measurements may in itself be predictive of CVD.

Chapter 3 Quantifying differences in CVD risk estimates obtained using different measures of "usual" BP

Chapter 2 established that measurement of blood pressure in UK primary care is broadly consistent with NICE hypertension guidelines but less consistent with BP measurement protocols for primary studies. Repeat BP measurements are more likely to be taken when initial readings are high and those with high clinic readings or hypertension are often asked to monitor their BP outside of the clinic setting. Hence, in any given patient, a GP may obtain several repeat BP measurements taken in a clinic and home setting, all of which may be slightly different from one another and any of which could be subsequently used to predict cardiovascular risk. In this chapter I quantify differences in CVD risk estimates obtained using different summary measures of "usual" BP in established risk scores and determine the clinical implications of these differences.

3.1. Introduction

In Chapter 1, I showed that existing cardiovascular risk scores used in clinical practice were all derived using clinic BP measurements obtained from clinical studies or routine records. Derivation studies differed, however, in terms of the measurement arm and how many BP readings were used to obtain a single summary measure of "usual" BP. This has implications for risk estimation in practice because mean BP measurements used in established risk scores may be obtained differently to those in the risk score derivation studies. For example, risk scores derived from the Framingham study cohorts were

developed using the mean of second and third BP measurements on the left arm in a clinic setting, but, as detailed in Chapter 2, only those patients with initially high clinic readings on average are likely to have two or three measurements taken in practice.

The effect of these differences on risk estimation is two-fold. Firstly, BP measurements obtained in different settings may be systematically different from each other. Secondly BP measurements obtained using different protocols may have differing levels of measurement error. The mechanism of these effects was described in detail in Section 1.6. As discussed, both of the issues illustrated by Figure 1.1 and Figure 1.2 can affect risk estimation and ideally risk scores should be used with BP measurements obtained in a similar manner to blood pressures in the risk score derivation studies in order to limit these errors. Little work has been carried out to date to describe the possible differences in risk when this does not happen. One previous study did examine differences in Framingham risk when clinic BP readings were subject to end digit preference,(140) but did not consider the use of out-of-office measurements and was limited in its generalisability to a single risk score. It also only simulated rounding of pressures and did not consider the extent to which this may actually occur in practice.

It would be feasible to use published information to estimate the possible risk differences on average. For example, in the scenario illustrated in Figure 1.1, if a 20 mm Hg difference in systolic BP equates to approximately a 20% relative difference in risk as in the QRISK2 equation,(41) then a 5 mm Hg difference in blood pressure equates to a 4.6% difference in estimated risk. However this approach ignores patient-level variation in BP differences across measurement settings (which may also be linked to underlying risk) and does not address the importance of these differences at specific treatment threshold levels. Hence in this chapter I aimed to describe the differences in estimated risk when using different

summary measures of "usual" or mean BP in established risk scores and to determine the clinical implications of these differences.

3.2. Methods

3.2.1. Data sources

Data from two sources were used for this analysis. Firstly, data from the Blood Pressure in different Ethnic groups (BP-Eth) study were used.(141) This study compared home, and ambulatory blood pressure measurement in 822 UK general practice patients aged between 40 and 74, with or without hypertension, belonging to one of four ethnic groups (white British, white Irish, South Asian, African-Caribbean).

The BP-Eth cohort has been described in full previously.(141,142) After an initial clinic visit participants were randomized to carry out ambulatory or home monitoring first. After a second clinic visit, participants were asked to carry out whichever type of monitoring (ambulatory or home) they had not yet performed before returning to the clinic on a third and final occasion. Clinic measurement during the study used the BpTRU sphygmomanometer. Measurements on both arms were taken at the first clinic visit and on the higher reading arm at subsequent visits. Ambulatory BP measurement over 24 hours used half hourly measurement from 0800 to 2300 and hourly measurement from 2300 to 0800. During home BP measurement, participants were asked to take two readings twice daily over seven days. The last BP measurement recorded in the patient's medical record prior to the study was also recorded, including the date on which the measurement was taken.

For this analysis, those with a history of CVD were excluded, as they would automatically be considered at high risk of subsequent events and are unlikely to undergo risk assessment. A limitation of the BP-Eth dataset is that it did not collect data on cholesterol, which is a key risk factor for cardiovascular disease. As described below in Section 3.2.6, this was overcome in the analysis by simulating cholesterol values for each individual. However, in order to verify that results would be similar when using actual cholesterol values, I decided to conduct the analysis in a second dataset which did have cholesterol measures.

Data was therefore additionally obtained from the Home versus Office blood pressure MEasurements: Reduction of Unnecessary treatment Study (HOMERUS).(143) This was a multi-centre, prospective randomized trial in essential hypertension patients aged 18 and over, recruited in primary and secondary care in the Netherlands. Patients were excluded if they had history of previous cardiovascular disease or other severe disease e.g. chronic kidney disease. Patients were randomized into an office or home monitoring group and anti-hypertensive treatment was adjusted according to the measurements made in clinic or at home respectively. Six office BP measurements were taken in the dominant arm at each visit, monthly for up to five visits and then every two months thereafter. Home BP measurements were made in the week preceding each study visit. Three BP measurements were taken in the morning and the evening over seven days, and the mean of all measurements was recorded. Ambulatory monitoring was carried out at the beginning and at the end of the study, with readings every 15 minutes from 0700 to 2300 and every 30 minutes overnight.

3.2.2. Objectives and definitions

The primary objective in this chapter was to determine the magnitude of within-person differences in 10-year cardiovascular disease risk estimates when using different methods of BP measurement and whether these differences are clinically important. Although there are several risk scores currently available for use by GPs/ nurses, analysis was limited to the Framingham (1991),(37) QRISK2,(41) and SCORE,(42) risk equations as these have been reported to be the most used risk scores by UK GPs.(32) For each risk score, within-person differences in risk estimates were calculated when using blood pressure measured as defined in the derivation study of the risk score, or using clinic measurements taken according to current practice and current NICE hypertension guidance,(1) home BP measurements or ambulatory BP measurements.

The primary analysis considered changes in Framingham risk estimates as the method of BP measurement in the Framingham study is well documented(92) and was summarised in Section 1.8. The derivation study for QRISK2 obtained blood pressures from electronic healthcare records and although results from Chapter 2 inform how blood pressure is currently measured routinely, QRISK2 was developed using historical data when routine practice may have been different. NICE guidance for the diagnosis and management of hypertension in 2004,(144) and 2006,(145) stated that clinic BP should be measured once and if >140/90mmHg, a second measurement should be taken at the end of the appointment "if practical". The 2014 version of QRISK2 used data from 1998 onward with around 1/3 of follow-up occurring pre-2004 (pre-guidance) and around 80% of the follow-up occurring before 2011 (current guidance date).(146) Therefore it is not clear how BP would have been measured and is likely to have been inconsistent across the cohort. Similarly, the SCORE equation was developed using data from several different cohorts

where BP measurement varied. Hence there is no clear and consistent protocol for BP measurement in the derivation study for either the QRISK2 or SCORE equations and these were studied in secondary analyses.

3.2.3. Blood pressure variables

In BP-Eth, I used clinic BP measurements from the first visit as this was when measurements in both arms were taken. In HOMERUS, I used clinic BP measurements from the final study visit as this was the only time during the study that ambulatory BP and lipid measurements were taken concurrently. Several different measures of "usual" BP were calculated as follows:

1. Clinic blood pressure:
    1. As defined by the risk scores (mm Hg)
        1. Framingham: mean of the 2nd and 3rd clinic measurements in the left arm
        2. QRISK2: first clinic measurement in a randomly selected arm
        3. SCORE: first clinic measurement in a randomly selected arm
    2. Defined according to current practice in clinic (determined from results in Chapter 2): This was defined as the first measurement if less than 140/90mm Hg. If ≥140/90 mm Hg, then the second measurement was considered. If the second measurement differed from the first by >5 mm Hg systolic then the third measurement was also considered. The minimum of the last two measurements was recorded and used in analyses. Measurements were taken from an arm selected at random in each patient. This was the primary clinic comparison.

3. Defined according to current NICE hypertension guidance in clinic: This was defined as above in (ii) except that BP readings were taken from the higher reading arm in patients who had a difference between arms of ≥20 mm Hg systolic which was sustained after two readings.
4. Defined according to current NICE hypertension guidance in clinic but with readings taken in the higher arm in all patients: This was defined as above (iii) except that BP readings were taken from the higher reading arm in all patients (based on the first reading for most patients or the second reading in patients who had a difference between arms of ≥20 mm Hg systolic on the first reading).
5. Mean of clinic measurements two to six in the higher reading arm in all patients.

2. Home blood pressure
    1. Mean of two readings in the morning and two readings in the evening over seven days, excluding the first days readings (provided a minimum of 12 readings excluding the first days readings were available). This was the primary home comparison.
    2. As above but including the first days readings.
3. Ambulatory blood pressure
    1. Daytime ambulatory BP providing at least 14 valid measurements were available. This was the primary ABPM comparison.
    2. Night-time ambulatory BP providing at least five valid measurements were available.
    3. 24-hour ambulatory BP providing at least 19 valid measurements were available.

In the HOMERUS study, BP measurements were taken in the dominant arm only and as a result, I simply used the available measurements (hence 1.2, 1.3 and 1.4 above were equivalent). Any individual clinic systolic BP measurements that fell outside the range of 70-210 mm Hg (clinic) , 70-250 mm Hg (home) and 70-260 mm Hg (ambulatory) were classified as outliers and set to missing.(147)

3.2.4. Risk factor variables

The risk factor variables required by each of the risk scores were defined in the following ways:

- Age (years, 30-84)
- Gender (male/ female)
- Smoking status (current smoker/ not for Framingham and SCORE or non-smoker, ex-smoker, light-smoker (<10 cigarettes per day), moderate smoker (10-19 cigarettes per day) and heavy smoker (20+ cigarettes par day) for QRISK2)
- Body mass index (kg/m^2). Values outside the range 20-40 kg/m^2 were rounded up/ down as the web calculator for QRISK2 does this for values outside the score's permitted range
- Ethnicity (White, Indian, Pakistani, Bangladeshi, Other Asian, Black Caribbean, Black African, Chinese, other as in QRISK2). All patients classified as South Asian in the BP-Eth data set were assumed Indian.
- Townsend deprivation score (range -6 to +11)
- Ratio of total cholesterol to high density lipoprotein cholesterol (mmol/L). Values outside the range of 1-12 mmol/L were rounded up/down (again due to limits imposed by the QRISK2 score)

- Diabetes (yes/ no for Framingham and None, Type 1, Type 2 for QRISK2)
- Rheumatoid Arthritis (yes/ no)
- Chronic kidney disease (yes/ no)
- Family history of CVD in a first degree relative <60 years of age (yes/ no)
- Diagnosis of hypertension (yes/no)
- Current prescription for antihypertensive medication (yes/ no)
- Atrial fibrillation (yes/ no)
- Left ventricular hypertrophy on electrocardiogram (yes/ no)

3.2.5. Statistical analysis

In both cohorts, those outside the 30-84 age range were excluded, as were those with previous CVD. In the HOMERUS study, only those in the intervention arm contributed to analysis as only the intervention arm underwent all forms of monitoring. For each of the three risk scores, estimates of an individual's 10-year risk of cardiovascular disease were calculated using BP measured as in the derivation study (measurements 1.1.1, 1.1.2 or 1.1.3 in Section 3.2.3 above). This was then compared with the risk calculated with BP measured in the following ways:

1. Current practice (measurement 1.2 in Section 3.2.3 above)
2. Current NICE hypertension guidance (measurement 1.3)
3. Current NICE hypertension guidance in the higher reading arm (measurement 1.4)
4. Mean of measurements two to six in the higher reading arm (measurement 1.5)
5. Home BP (measurement 2.1 or 2.2)
6. ABPM (measurement 3.1, 3.2 or 3.3)

On the basis of results in Chapter 2, and to examine the importance of considering the measurement arm, further comparisons were made between risk calculated using BP measured as in current practice (measurement 1.2) and risk calculated using BP measured as in current NICE hypertension guidance (measurement 1.3), or as in current NICE hypertension guidance in the higher reading arm (measurement 1.4).

Due to the skewed nature of absolute differences, these were summarized by medians and interquartile ranges, rather than means and 95% confidence intervals. Minimum and maximum differences were also summarized. Significant differences were determined using the non-parametric Wilcoxon signed-rank test.

To determine clinical significance, the proportion of people re-classified above or below the treatment threshold of risk was calculated. Since the SCORE risk equation deals with risk of cardiovascular death, the treatment threshold used was 5% absolute risk, in accordance with European guidelines for prevention of CVD.(148) These guidelines state that such a threshold is equivalent to a threshold of 10-25% for fatal and non-fatal CVD events combined based on the Framingham equations. Since current NICE(18) and American(149) guidelines for the primary prevention of CVD recommend a treatment threshold of 10% and 7.5% respectively, a 10% threshold was used for evaluation of Framingham and QRISK2 scores. Scatter plots were used to examine differences in risk and reclassification above or below treatment thresholds. Bland-Altman plots were used to examine patterns in risk differences by levels of average risk. Analyses were carried out using Stata 14.2.(116)

3.2.6. Missing data

Missing data were handled in a number of different ways, depending on the variable type. For all variables, the number of complete observations was reported along with descriptive statistics. For dichotomous variables such as diagnosis of diabetes, an absence of information was assumed to reflect absence of disease. Similarly, individuals with missing smoking information were defined as non-smokers and those with missing ethnicity information were assumed to be white.

It was possible to calculate Townsend scores in the BP-Eth dataset given each participants postcode, by mapping postcodes to the relevant ward area using the Postcode Directory produced by the ONS(150) and then mapping the ward area to the relevant 2001 Townsend score provided by the UK Data Service.(151)

In the two source datasets, there were two important variables that were entirely missing from each dataset; cholesterol in BP-Eth and Townsend score in the HOMERUS study. Cholesterol values were assigned to each individual in the BP-Eth data by simulating values in each age-sex strata from a normal distribution, with means obtained from the Health Survey for England 2011.(114) Non-risk-modifying values of the Townsend score were applied to all individuals in the HOMERUS study, since the Townsend score is a measure of deprivation specific to the UK and it would be difficult to specify other values that could be applied to a Danish population. Although the HOMERUS study did collect information on participants' profession, it was not clear how such information could be reliably translated into a measure of deprivation that accounts for many other socio-economic factors.

The analysis was conducted in complete case samples of the data (i.e. those with complete covariate data, at least the first 3 consecutive clinic readings, at least 12 home blood pressure readings and at least 14 daytime and 5 night-time ambulatory BP readings respectively). Imputed analysis was not performed since, ideally, the outcome variable should be included in the imputation model. However, because the outcome variable in this analysis is cardiovascular risk, which cannot be calculated for individuals with missing covariates, this was not possible.

3.2.7. Post-hoc analyses

Over the course of the analysis, a second important objective emerged; that of comparing risk estimates obtained using the same BP measurements but with different risk calculators. This was because initial results indicated that although the choice of BP measurement did affect the risk estimate obtained in some cases, the differences were arguably smaller than those observed when using different risk calculators. I therefore decided to address this comparison more formally by comparing within-person differences in risk estimates calculated using the QRISK2 or Framingham equations using the same BP measurement. No comparison was made with risk estimates obtained using the SCORE risk equations, as these equations estimate CVD mortality risk only and are not directly comparable.

3.3. Results

A total of 442 patients from the BP-Eth cohort were included in complete case analysis. The characteristics of these included individuals are given in Table 3.1. One hundred and sixty-five patients from the intervention arm of the HOMERUS cohort were included (see Table 3.2). Patients in the BP-Eth cohort were older than those in the HOMERUS cohort and were from a mix of ethnic backgrounds. As a result of the study inclusion criteria,

those in the HOMERUS cohort were less likely to have conditions such as diabetes and chronic kidney disease that are risk factors for cardiovascular disease, but had higher clinic BP values.

Table 3.1: Baseline characteristics of the BP-Eth cohort (N=442)

Variable	Mean (SD)/ N (%)
Age (years)	58.4 (9.4)
Female	222 (50.2)
BMI (kg/m^2)	29.1 (4.5)
Current smoker	66 (14.9)
Chronic kidney disease	3 (6.8)
Atrial fibrillation	16 (3.6)
Treated hypertension	249 (56.3)
Left ventricular hypertrophy	0 (0.0)
Type 1 diabetes	2 (0.5)
Type 2 diabetes	57 (12.9)
Townsend score	6.1 (4.1)
Total cholesterol (mmol/L) (simulated)	5.4 (1.1)
HDL cholesterol (mmol/L) (simulated)	1.5 (0.4)
Total/HDL cholesterol (mmol/L)	4.0 (1.7)
Ethnicity: White	203 (45.9)
Ethnicity: Indian	79 (17.9)
Ethnicity: Pakistani	24 (5.4)
Ethnicity: Bangladeshi	5 (1.1)
Ethnicity: Black Caribbean	115 (26.0)
Ethnicity: Black African	16 (3.6)
Systolic BP (mm Hg): single reading (random arm)	136.2 (18.3)
Systolic BP (mm Hg): mean of 2nd and 3rd readings in left arm	132.4 (17.1)
Systolic BP (mm Hg): according to current practice	132.8 (16.0)
Systolic BP (mm Hg): according to current guidance	132.8(15.9)
Systolic BP (mm Hg): mean of home readings excluding the first day	133.4 (12.4)
Systolic BP (mm Hg): mean of daytime ambulatory readings	133.0(14.2)
QRISK2 10-year CVD risk	16.0 (12.1)
Framingham 10-year CVD risk	15.6 (10.8)
SCORE 10-year CVD death risk	3.1 (3.3)

Table 3.2: Baseline characteristics of the HOMERUS cohort (N=165)

Variable	Mean (SD)/ N (%)
Age (years)	55.6 (9.7)
Female	75 (45.5)
BMI (kg/m2)	27.5 (4.2)
Current smoker	30 (18.2)
Chronic kidney disease	0 (0.0)
Atrial fibrillation	0 (0.0)
Treated hypertension	165 (100.0)
Type 1 diabetes	0 (0.0)
Type 2 diabetes	6 (3.6)
Left ventricular hypertrophy	37 (22.4)
Townsend score (fixed for men and women separately)	0.1 (0.06)
Total cholesterol (mmol/L)	5.5 (1.1)
HDL cholesterol (mmol/L)	1.4 (0.4)
Total/HDL cholesterol (mmol/L)	4.4 (1.4)
Ethnicity: White	165 (100.0)
Systolic BP (mm Hg): single measurement	146.5 (19.1)
Systolic BP (mm Hg): mean of 2nd and 3rd readings	142.3 (17.1)
Systolic BP (mm Hg): according to current practice	141.4 (16.2)
Systolic BP (mm Hg): mean of home readings excluding the first day	134.0 (10.5)
Systolic BP (mm Hg): mean of daytime ambulatory readings	131.3 (9.9)
QRISK2 10-year CVD risk	13.2 (8.8)
Framingham 10-year CVD risk	19.6 (13.5)
SCORE 10-year CVD death risk	3.3 (3.7)

3.3.1. Differences in Framingham risk using clinic, home or ambulatory BP measurements

In the BP-Eth cohort, comparing estimates of Framingham risk calculated using BP taken to be the mean of 2nd and 3rd measurements on the left arm or an alternative measure revealed that observed risk differences were generally small. Median absolute differences were less than 1% for all clinic BP measurement alternatives and less than 2% for all comparisons except night-time ambulatory BP measurement, although differences were much larger than this for some individuals (Table 3.3). There were no significant differences in Framingham risk when calculated using BP measurements taken according to

current practice compared to the mean of 2nd and 3rd BP readings in the left arm (p=0.25) The same was true when using home BP measurements excluding the first days readings (p=0.08) or daytime ambulatory BP measurements (p=0.67).

Table 3.3: Differences in Framingham risk estimates using alternative summary measures of "usual" blood pressure in the BP-Eth cohort

Alternative BP measurement used in risk score	Median absolute difference (%)	Inter-quartile range		Difference range (original – alternative)	
Clinic measurements					
Current practice	0.80	0.38	1.61	-15.22	10.46
Current guidance	0.78	0.35	1.62	-15.22	9.15
Mean of 2nd-6th measurements in higher reading arm	0.99	0.42	1.78	-14.20	8.45
Home measurements					
Excluding first days readings	1.66	0.61	3.12	-15.94	11.56
Including first days readings	1.69	0.58	3.09	-16.54	12.23
Ambulatory measurements					
Daytime ABPM	1.84	0.65	3.63	-18.04	12.59
Night-time ABPM	2.65	1.09	5.91	-17.96	19.61
24-hour ABPM	1.85	0.76	3.63	-17.61	13.45

Figure 3.1 compares Framingham risk calculated using BP as measured according to current practice compared to the ideal of measuring BP as in the derivation study. In this case a small proportion of people were re-classified; nine people moved from high to low risk (2.0%) and eight moved from low to high risk (1.8%). Figure 3.2 shows that the largest differences in risk were observed in those patients who were already at high risk. This is unsurprising given how risk is calculated through exponentiation of the linear predictor. Even small changes in blood pressure, resulting in small changes in the value of each patient's linear predictor, can be magnified by exponentiation when risk is already high. When risk is low, this does not happen to the same degree.

Figure 3.1: Framingham risk estimates in the BP-Eth cohort calculated using BP measurements obtained as in the Framingham study or as in current practice

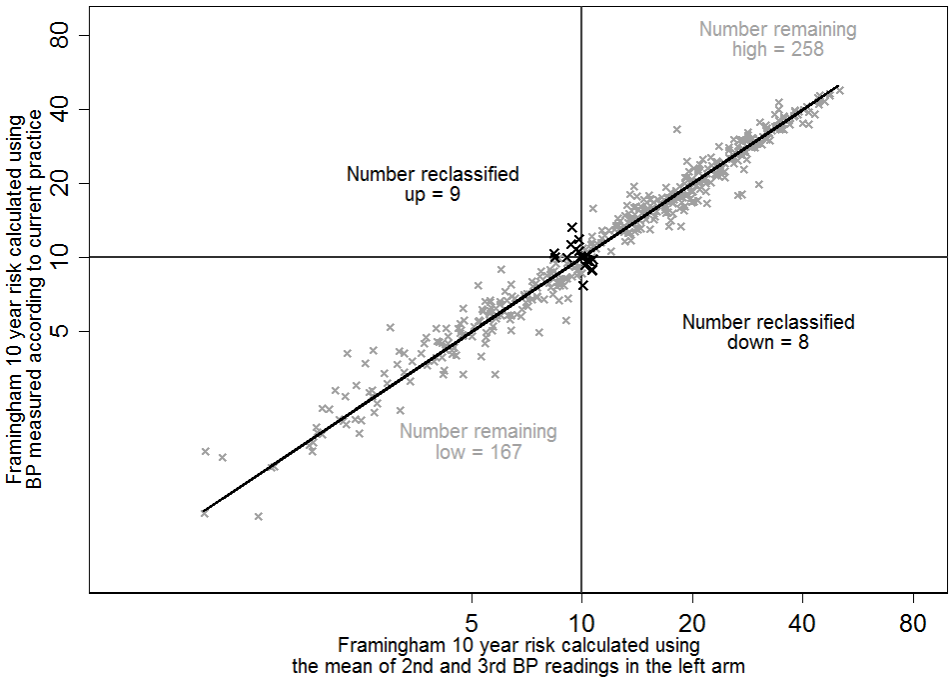
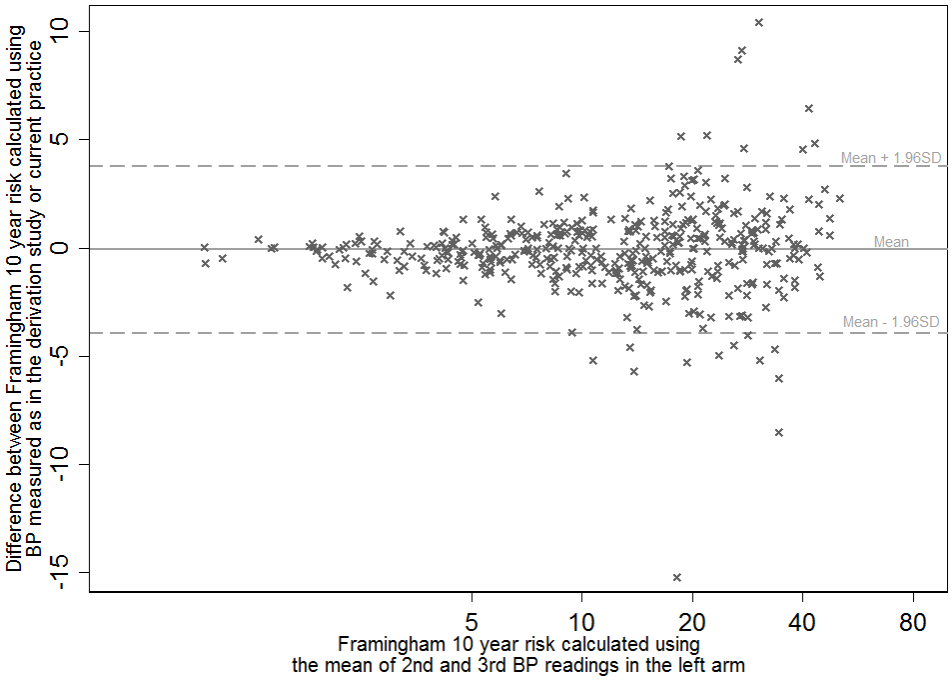


Figure 3.2: Bland-Altman plot for Framingham risk in the BP-Eth cohort calculated using BP measurements obtained as in the Framingham study or as in current practice



As would be expected given the larger absolute differences in risk given in Table 3.3, a larger proportion of people were reclassified across the risk threshold when using home BP measurements (Figure 3.3) or ambulatory BP measurements (Figure 3.4), but overall proportions remained small (7.5% and 7.0% respectively). Those who were reclassified tended to have risk estimates close to the threshold.

Figure 3.3: Framingham risk estimates in the BP-Eth cohort calculated using BP measurements obtained as in the Framingham study or through home monitoring

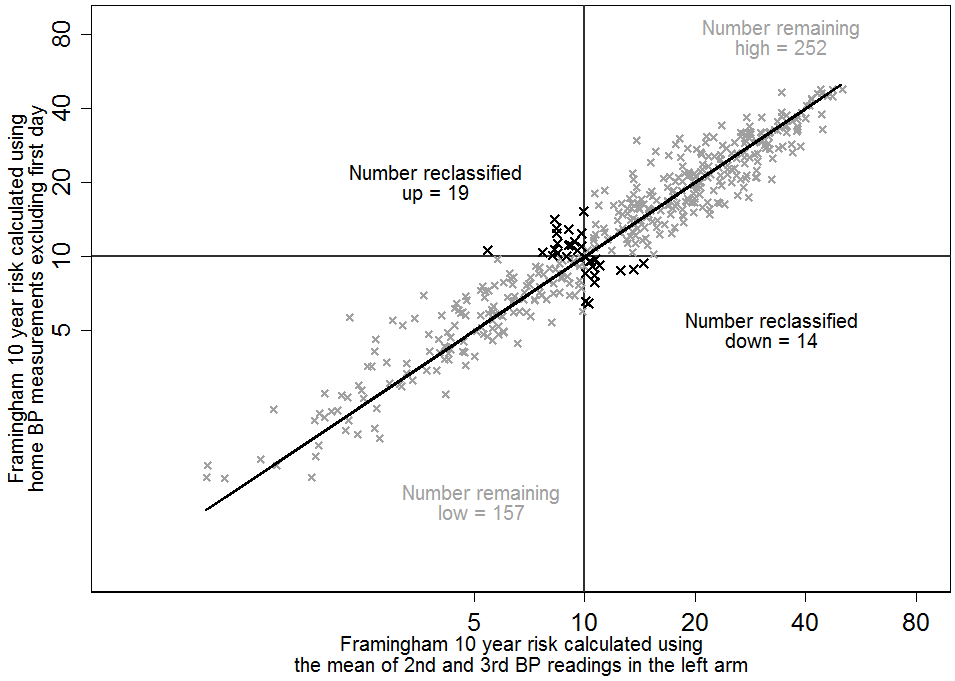
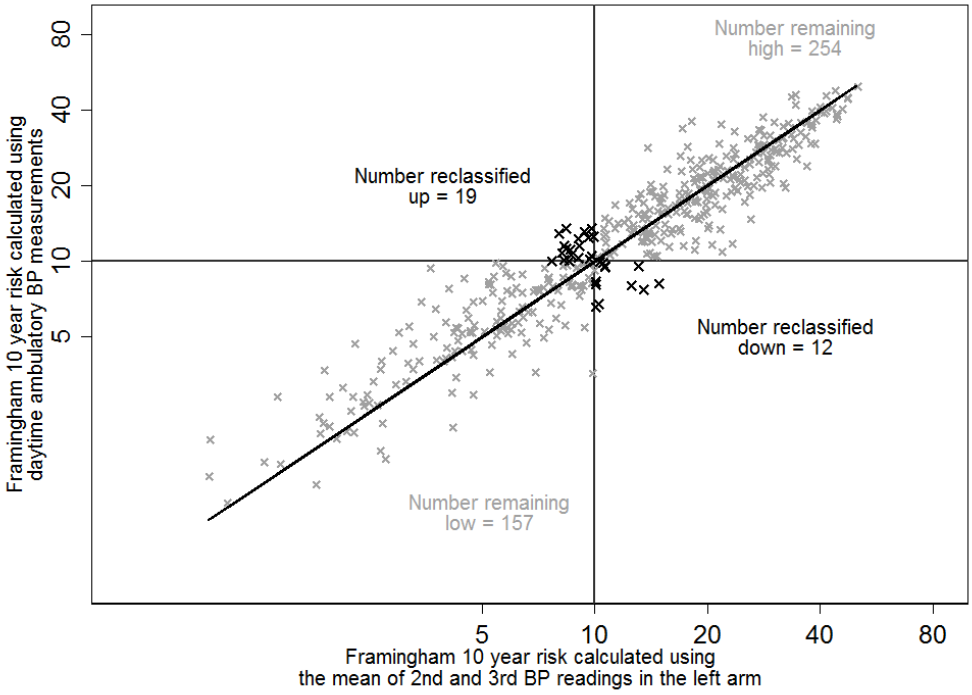
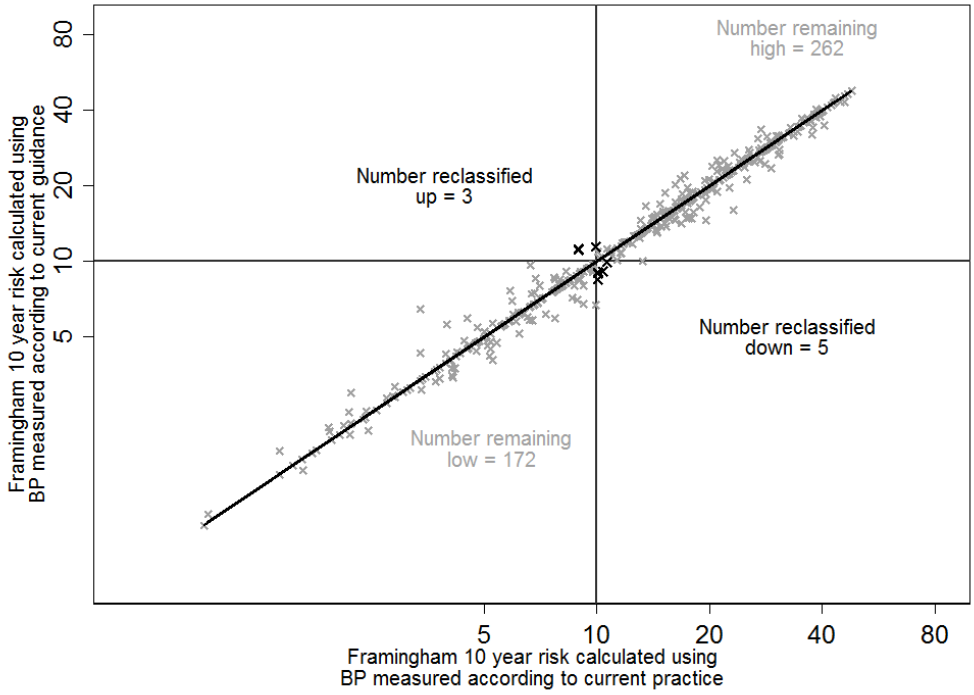


Figure 3.4: Framingham risk estimates in the BP-Eth cohort calculated using BP measurements obtained as in the Framingham study or through ABPM



The choice of measurement arm also had little effect on Framingham risk estimation in the BP-Eth cohort, whether taking measurements in the higher reading arm only in those with a sustained difference (as per guidance) or in all patients, compared to taking measurements in a random arm (as in current practice). When risk was calculated using BP measured according to guidance instead of current practice, the median absolute difference in risk was 0.00% (IQR 0.00 to 0.88) and differences ranged from -6.27% to 7.11%. Three people (0.7%) were reclassified from low to high risk and five people (1.1%) were reclassified from high to low risk (Figure 3.5). Differences were similarly small when risk was calculated using BP measured in the higher arm for all patients instead of according to current practice (median absolute difference = 0.07% (IQR 0.00 to 0.92), difference range -6.27% to 7.11%) and only ten patients (2.3%) were reclassified across the risk threshold (five moved from low to high risk).

Figure 3.5: Framingham risk estimates in the BP-Eth cohort calculated using BP measurements obtained according to current practice or current guidance



In the HOMERUS cohort, compared to the BP-Eth cohort, smaller median differences in risk were observed when using different combinations of clinic BP measurements, but larger median differences were observed when using home or ambulatory BP measurements (Table 3.4). This is likely due to the fact that differences between clinic BP measurements and home/ ambulatory measurements were larger on average in the HOMERUS cohort compared to the BP-Eth cohort. Differences in median risk were statistically significant when using BP measured according to current practice ($p=0.006$), through home monitoring excluding the first days readings ($p<0.001$) or through daytime ambulatory monitoring ($p<0.001$) but only a small proportion of people were reclassified across the 10% risk threshold; three (1.8%), ten (6.7%) and eight (4.8%) people were reclassified respectively. In most cases patients were reclassified from high to low risk (three, seven and five patients respectively).

Table 3.4: Differences in Framingham risk estimates using alternative summary measures of "usual" blood pressure in the HOMERUS cohort

Alternative BP measurement used in risk score	Median absolute difference (%)	Inter-quartile range		Difference range (original – alternative)	
Clinic measurements					
Current practice	0.51	0.21	1.32	-3.56	4.34
Mean of 2nd-6th measurements	0.16	0.07	0.35	-1.03	1.27
Home measurements					
Excluding first days readings	2.50	0.89	5.32	-8.52	16.33
Including first days readings	2.41	0.92	5.24	-9.03	16.05
Ambulatory measurements					
Daytime ABPM	2.76	1.19	6.39	-8.65	18.80
Night-time ABPM	5.35	2.04	11.42	-5.88	28.28
24-hour ABPM	3.05	1.10	7.40	-7.97	20.93

3.3.2. Differences in QRISK2 risk using clinic, home or ambulatory BP measurements

Median absolute differences in estimated QRISK2 risk were less than 1.5% in the BP-Eth cohort when using any alternative measures of BP (compared to a single clinic measure) and interquartile ranges were narrower than those observed for Framingham risk (Table 3.5). This suggests that the contribution of BP to overall risk is lower in the QRISK2 equation compared to the Framingham equation. Although differences in median risk were statistically significant when using BP measured as in current practice ($p<0.001$), through home monitoring excluding the first day ($p<0.001$) or through ambulatory monitoring ($p<0.001$), the differences were of little clinical significance. Fewer people were reclassified across the risk threshold compared to the reclassifications observed when using the Framingham equation; only four people (0.9%) were reclassified when BP was measured according to current practice (Figure 3.6), ten people (2.3%) were reclassified when home measurements were used (Figure 3.7) and eleven people were reclassified when daytime ambulatory BP was used (2.5%, Figure 3.8).

Table 3.5: Differences in QRISK2 risk estimates when using alternative summary measures of "usual" blood pressure in the BP-Eth cohort

Alternative BP measurement used in risk score	Median absolute difference (%)	Inter-quartile range		Difference range (original – alternative)	
Clinic measurements					
Current practice	0.00	0.00	0.38	-1.26	5.62
Current guidance	0.15	0.00	0.64	-3.27	5.69
Mean of 2nd-6th measurements in higher reading arm	0.45	0.18	0.93	-4.41	4.89
Home measurements					
Excluding first days readings	0.60	0.23	1.36	-20.54	12.27
Including first days readings	0.59	0.24	1.31	-21.66	12.38
Ambulatory measurements					
Daytime ABPM	0.63	0.26	1.39	-6.02	8.24
Night-time ABPM	1.02	0.40	2.46	-12.61	14.14
24-hour ABPM	0.69	0.28	1.55	-6.07	8.85

Figure 3.6: QRISK2 risk estimates in the BP-Eth cohort calculated using BP measurements obtained as in the derivation study or as in current practice

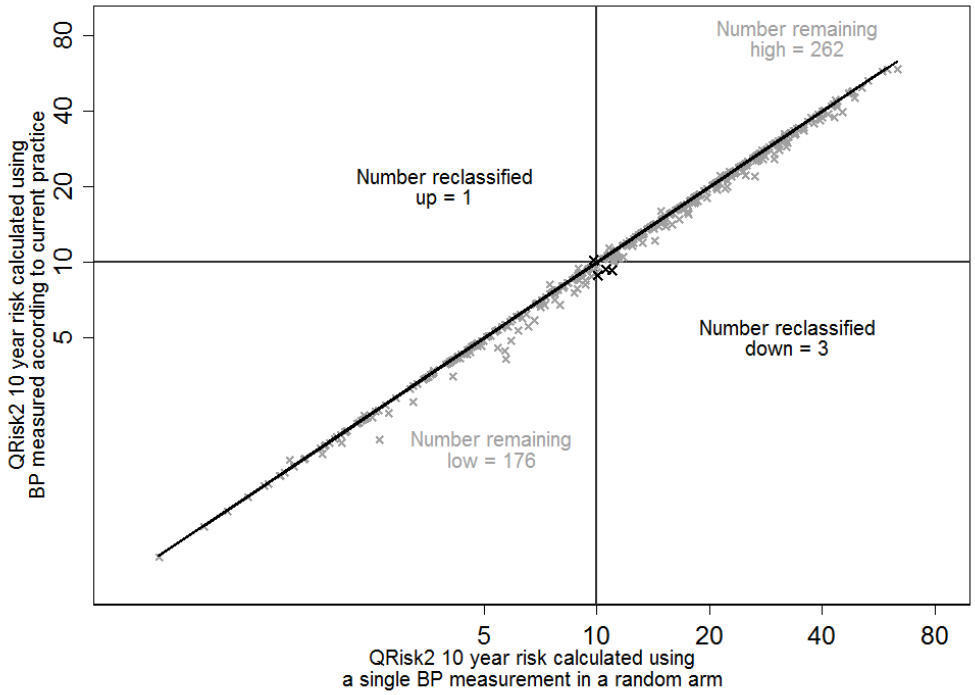


Figure 3.7: QRISK2 risk estimates in the BP-Eth cohort calculated using BP measurements obtained as in the derivation study or through home monitoring

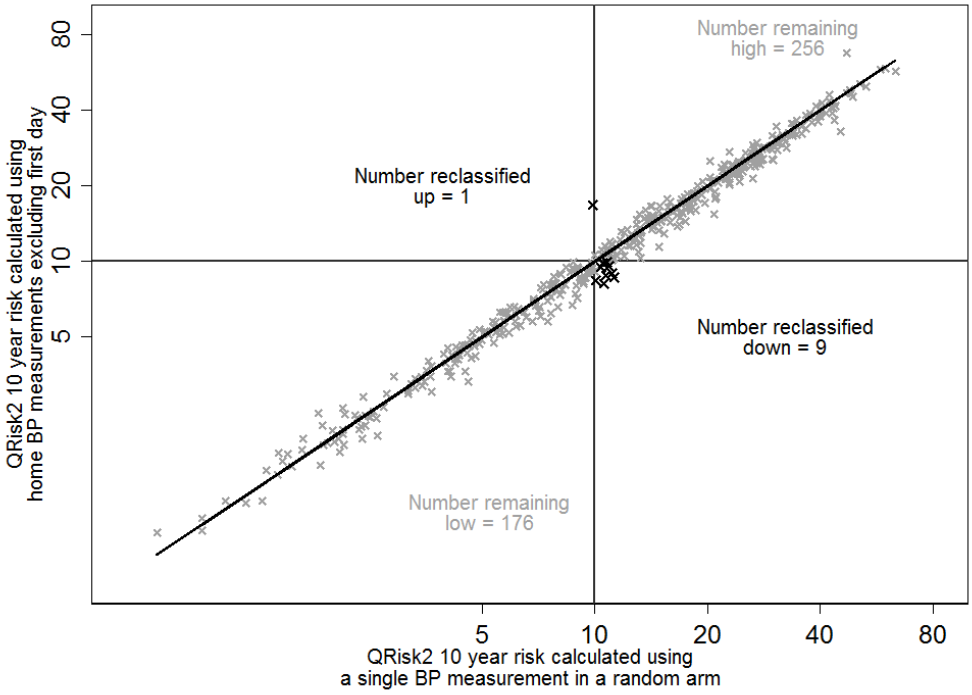
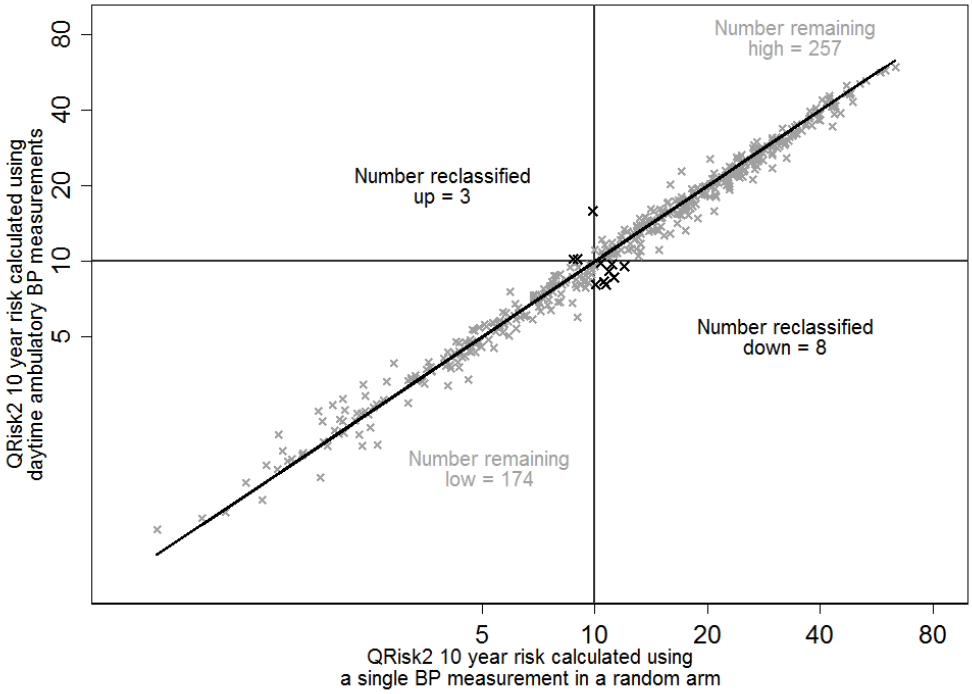
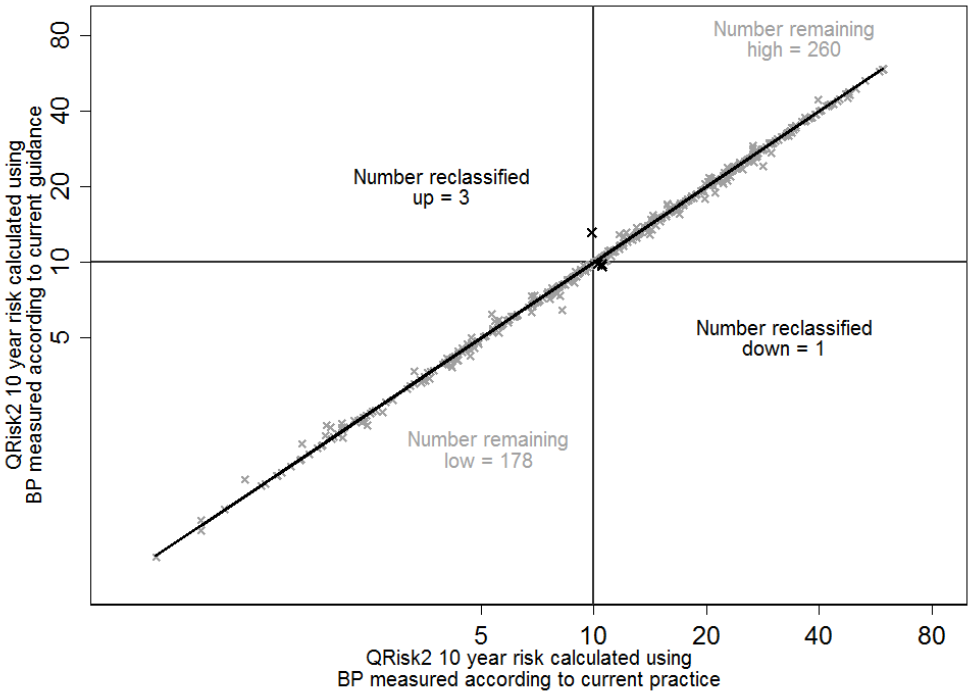


Figure 3.8: QRISK2 risk estimates in the BP-Eth cohort calculated using BP measurements obtained as in the derivation study or through ABPM



The choice of measurement arm had a smaller effect on QRISK2 risk estimates than that observed on Framingham risk estimates. When QRISK2 risk was calculated using BP measured according to guidance instead of current practice, the median absolute difference in risk was 0.00% (IQR 0.00 to 0.26) and differences ranged from -4.89% to 4.11%. Only four patients were reclassified across the 10% risk threshold (Figure 3.9). Differences remained small when risk was calculated using BP measured in the higher arm for all patients instead of according to current practice (median absolute difference = 0.03% [IQR 0.00 to 0.31]). Although risk differences ranged from -11.31% to 1.84%, only a single patient was reclassified from low to high risk.

Figure 3.9: QRISK2 risk estimates in the BP-Eth cohort calculated using BP measurements obtained according to current practice or current guidance



Similarly in the HOMERUS cohort, significant differences in median risk were observed when using BP measured as in current practice ($p<0.001$), through home monitoring excluding the first days reading ($p<0.001$) or through daytime ambulatory monitoring

(p<0.001), but median absolute differences were small (Table 3.6). As in the BP-Eth cohort, differences were smaller than those observed using the Framingham equation, reiterating the possibility that BP contributes comparatively less to overall risk in the QRISK2 equation. Three, six and seven people (1.8%, 3.6% and 4.2%) were reclassified across the 10% risk threshold when BP was measured as in current practice, through home monitoring excluding the first days reading, or through daytime ABPM respectively (three, five and seven people were reclassified from high to low risk).

Table 3.6: Differences in QRISK2 risk estimates when using alternative summary measures of "usual" blood pressure in the HOMERUS cohort

Alternative BP measurement used in risk score	Median absolute difference (%)	Inter-quartile range		Difference range (original – alternative)	
Clinic measurements					
Current practice	0.10	0.00	0.71	-1.30	4.27
Mean of 2nd-6th measurements	0.43	0.16	0.80	-2.20	3.26
Home measurements					
Excluding first days readings	0.93	0.31	2.08	-1.92	7.30
Including first days readings	0.91	0.32	2.04	-1.92	7.51
Ambulatory measurements					
Daytime ABPM	0.98	0.32	2.39	-2.00	7.66
Night-time ABPM	1.79	0.77	3.36	-1.28	10.53
24-hour ABPM	1.15	0.32	2.50	-1.82	8.18

3.3.3. Differences in SCORE risk using clinic, home or ambulatory BP measurements

Finally differences in risk estimates from the SCORE equation were examined. As previously in the BP-Eth cohort, the smallest differences in risk were observed using alternative clinic measurements (compared to a single clinic measure) but even when using ambulatory BP measurements, median absolute differences in risk were below 0.5% (Table 3.7). These differences are not directly comparable, however, to those from the Framingham or QRISK2 equations since the SCORE equation estimates risk of death

from CVD only and not risk of any cardiovascular event, hence absolute risk levels are lower.

Table 3.7: Differences in SCORE risk estimates when using alternative summary measures of "usual" blood pressure in the BP-Eth cohort

Alternative BP measurement used in risk score	Median absolute difference (%)	Inter-quartile range		Difference range (original – alternative)	
Clinic measurements					
Current practice	0.00	0.00	0.22	-1.88	8.03
Current guidance	0.05	0.00	0.41	-2.67	8.03
Mean of 2nd-6th measurements in higher reading arm	0.20	0.05	0.62	-2.63	8.11
Home measurements					
Excluding first days readings	0.30	0.07	0.86	-9.20	7.68
Including first days readings	0.29	0.07	0.83	-9.14	7.48
Ambulatory measurements					
Daytime ABPM	0.29	0.07	0.89	-11.58	8.60
Night-time ABPM	0.46	0.10	1.41	-12.92	13.40
24-hour ABPM	0.31	0.07	0.95	-12.47	8.98

Observed differences in median risk were statistically significant when risk was calculated using BP measured as in current practice, through home monitoring excluding the first days reading, or through daytime ABPM ($p<0.001$ in all cases). Despite this statistical significance, again, the differences did not affect many people in terms of reclassification above/ below the 5% CVD mortality risk threshold: eight (1.8%), thirty-three (7.5%) and thirty-four (7.7%) people were reclassified respectively (Figures 3.10, 3.11 and 3.12). The relative variation in risk observed when using different measures of "usual" BP is comparable to that observed for the Framingham equation and more than that observed for QRISK2, reinforcing the suggestion that BP contributes less to the risk estimate in the QRISK2 equation compared to other risk scores.

Figure 3.10: SCORE risk estimates in the BP-Eth cohort calculated using BP measurements obtained as in the derivation study or in current practice

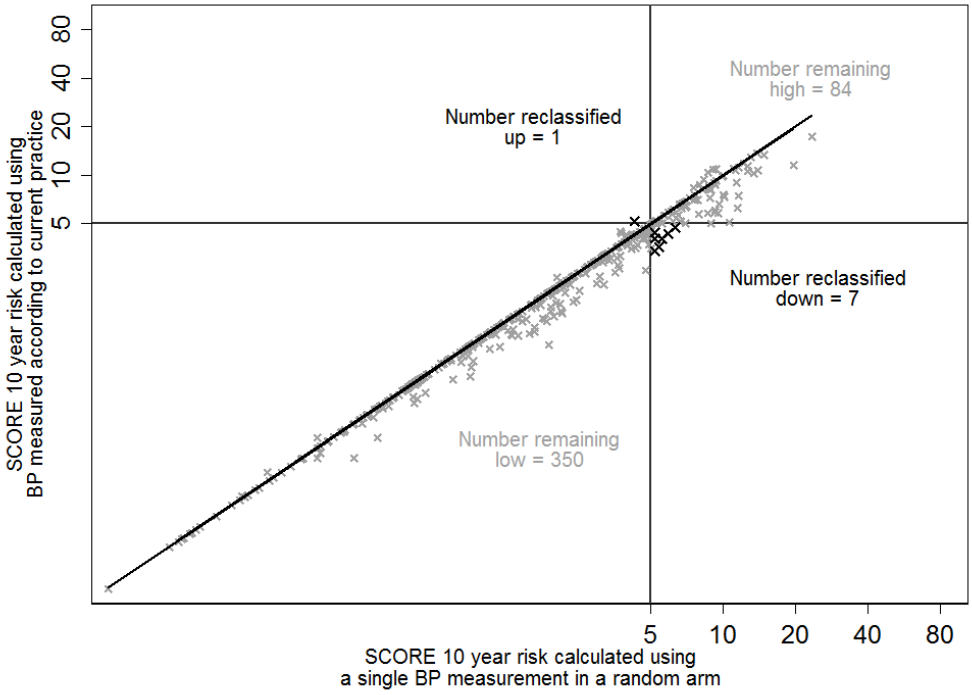


Figure 3.11: SCORE risk estimates in the BP-Eth cohort calculated using BP measurements obtained as in the derivation study or through home monitoring

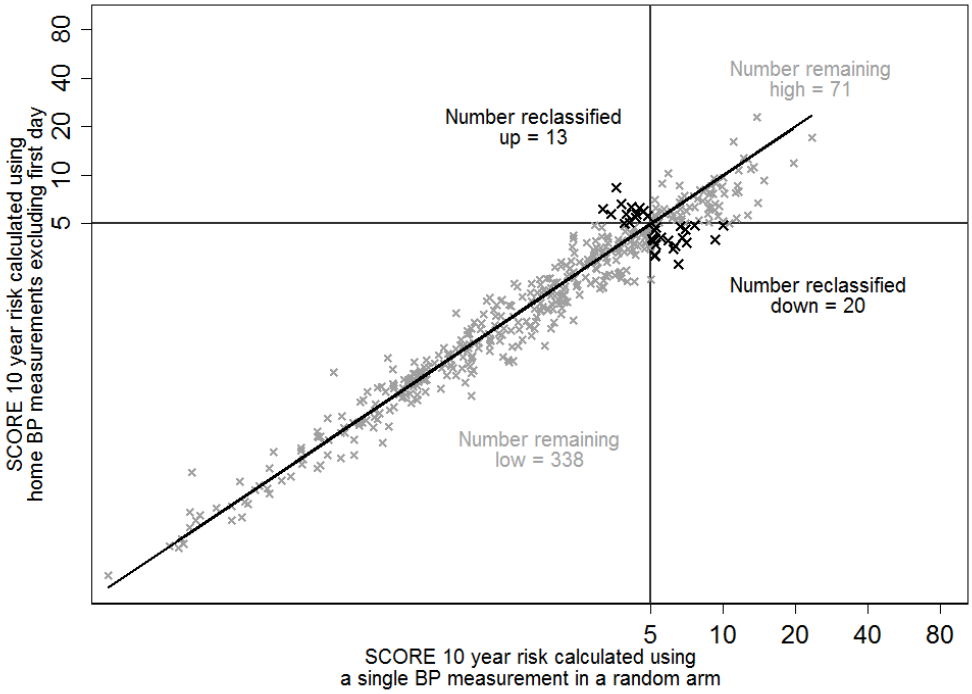
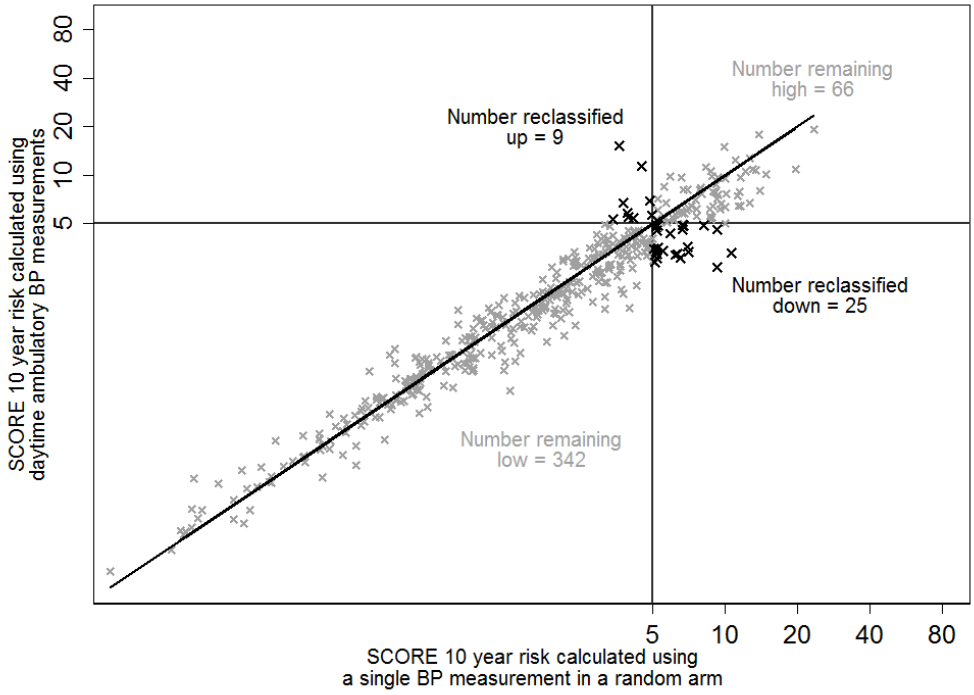
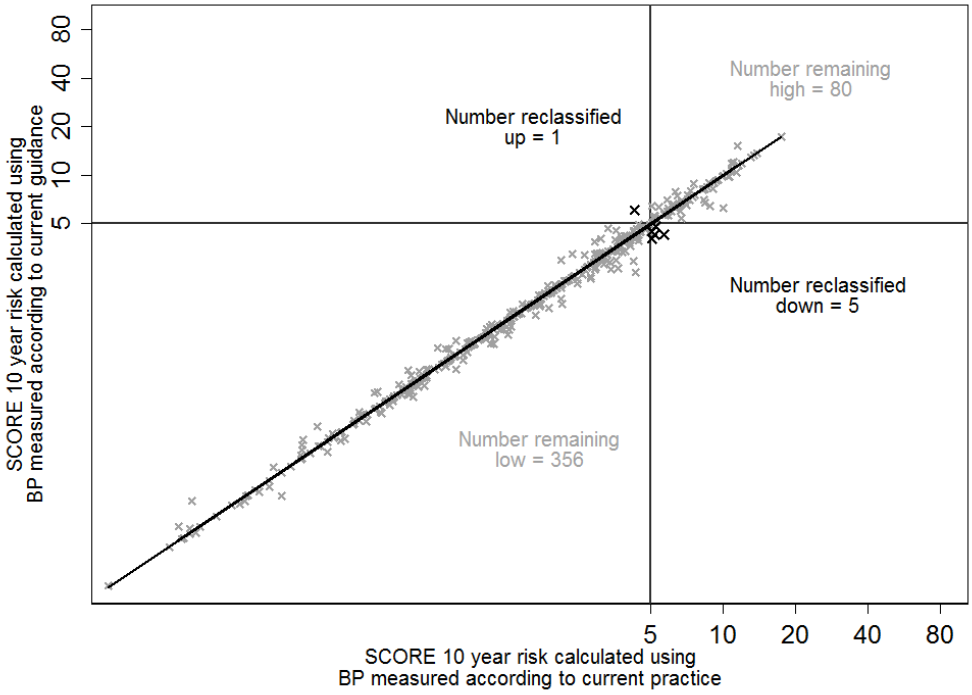


Figure 3.12: SCORE risk estimates in the BP-Eth cohort calculated using BP measurements obtained as in the derivation study or through ABPM



As in the Framingham and QRISK2 analyses, BP measurement arm did not materially affect risk estimates. When SCORE risk was calculated using BP measured according to guidance instead of current practice, the median absolute difference in risk was 0.00% (IQR 0.00 to 0.12) and differences ranged from -3.82% to 3.64%. Six patients were reclassified across the 5% risk threshold (Figure 3.13). Similar results were observed when risk was calculated using BP measured in the higher arm for all patients instead of according to current practice (median absolute difference = 0.00% (IQR 0.00 to 0.13), difference range= -5.28% to 2.75%), with three patients reclassified from low to high risk and four patients reclassified from high to low.

Figure 3.13: SCORE risk estimates in the BP-Eth cohort calculated using BP measurements obtained according to current practice or current guidance



In the HOMERUS cohort, observed differences in median risk were similarly small (Table 3.8). When risk was calculated using BP measured as in current practice, through home monitoring excluding the first days reading, or through daytime ABPM, significant differences were observed ($p<0.001$ for all) but only ten (6.1%), twenty-two (13.3%) and twenty-six (15.8%) people were reclassified across the 5% risk threshold respectively. In the majority of cases, patients were reclassified from high to low risk (ten, twenty and twenty-six cases respectively).

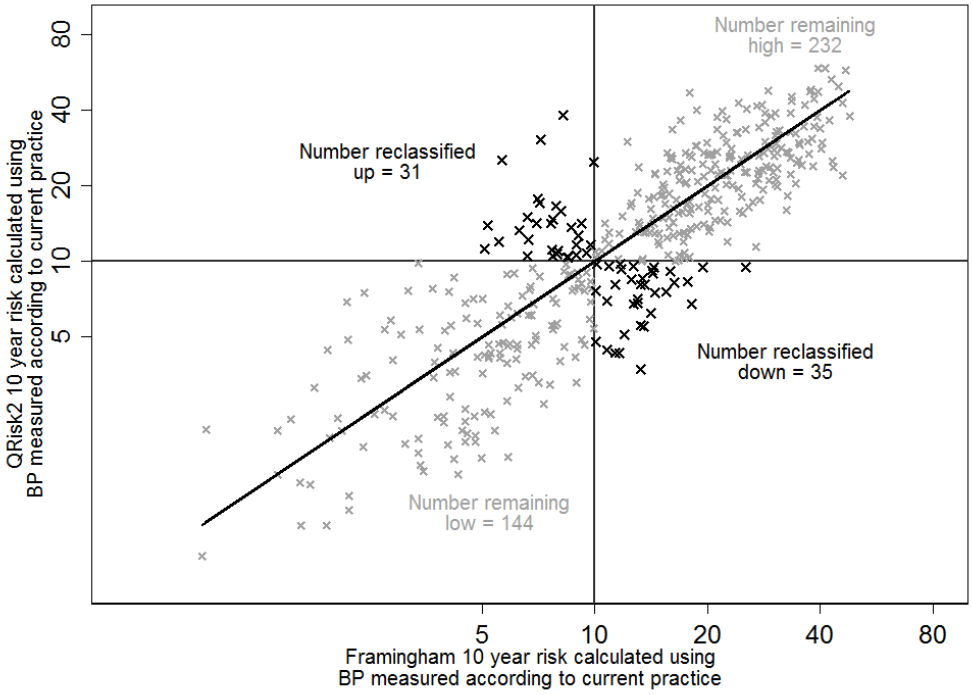
Table 3.8: Differences in SCORE risk estimates when using alternative summary measures of "usual" blood pressure in the HOMERUS cohort

Alternative BP measurement used in risk score	Median absolute difference (%)	Inter-quartile range		Difference range (original – alternative)	
Clinic measurements					
Current practice	0.04	0.00	0.47	-1.21	7.21
Mean of 2nd-6th measurements	0.21	0.04	0.71	-2.14	6.69
Home measurements					
Excluding first days readings	0.43	0.08	1.37	-2.00	11.54
Including first days readings	0.44	0.07	1.33	-1.73	11.60
Ambulatory measurements					
Daytime ABPM	0.39	0.07	1.44	-1.69	12.83
Night-time ABPM	0.81	0.16	2.23	-1.00	14.54
24-hour ABPM	0.48	0.07	1.52	-1.51	13.29

3.3.4. Estimated risk using different risk scores (post-hoc analysis)

In comparing results from Section 3.3.2 to those in Section 3.3.1, it appeared that the contribution of BP to the overall risk estimate was smaller for QRISK2 than that for the Framingham equation. Hence, when confronted with the option of calculating CVD risk with a number of different BP readings, the more important choice may be which risk score to use. In post-hoc analysis in the BP-Eth dataset, the median absolute difference in Framingham and QRISK2 estimated risk (both calculated using BP measured as in current practice) was 3.31% (IQR = [1.38, 6.92]) with a difference range of -29.85% to 23.67%. Thirty-one patents were reclassified upwards and thirty-five patients were reclassified downwards (14.9% reclassified in total, Figure 3.14) when using QRISK2 compared to Framingham.

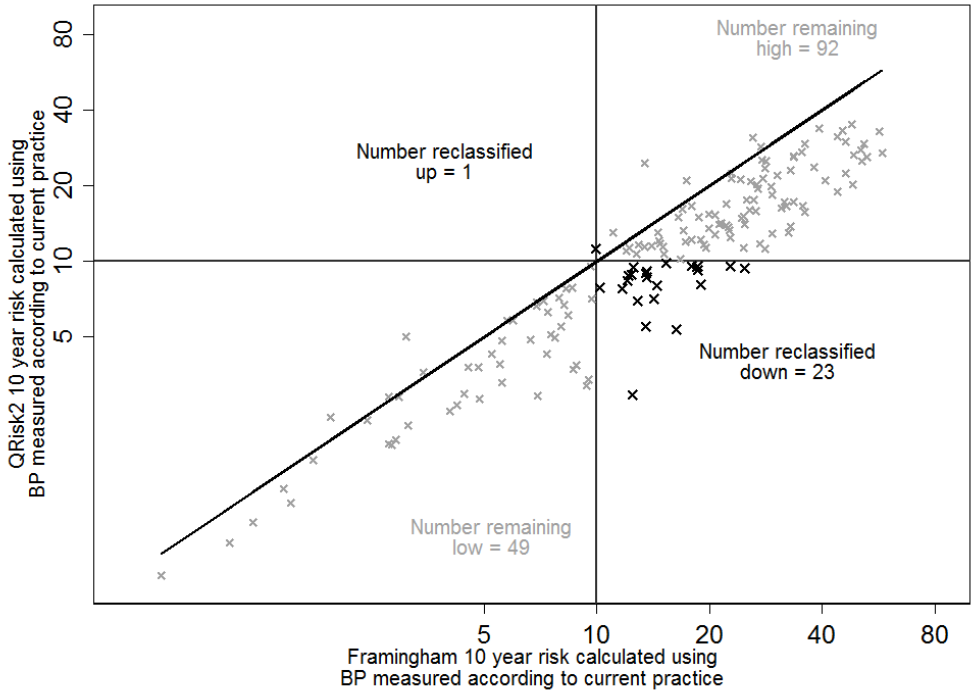
Figure 3.14: QRISK2 and Framingham risk calculated using BP measured according to current practice in the BP-Eth cohort



In the HOMERUS dataset the median absolute difference in risk was 4.94% (IQR = [1.52, 9.40]) with a difference range of -11.17% to 30.71%. Twenty-four patients (14.5%) were reclassified across the risk threshold, with all but one of these patients moving from high to low risk (Figure 3.15). The fact that very few people were reclassified upwards in the HOMERUS cohort compared to the BP-Eth cohort can be explained due to differences in the population characteristics and the characteristics of the risk scores. Those in the HOMERUS cohort had little comorbidity, whereas the BP-Eth cohort included people with a mix of comorbidities and those from at-risk ethnic groups. As the QRISK2 score accounts for a greater number of such comorbidities than the Framingham risk score, it is unsurprising that in the comparatively healthy HOMERUS cohort, estimated Framingham risk is higher on average than the estimated risk obtained from QRISK2. Regardless, it is clear from the results in both cohorts, that the choice of which risk score to use affected

the end risk estimate much more than the choice of which BP measurement to use which was described in previous sections.

Figure 3.15: QRISK2 and Framingham risk calculated using BP measured according to current practice in the HOMERUS cohort



3.4. Discussion

This analysis has shown that using alternative measures of "usual" or mean blood pressure in the Framingham, QRISK2 or SCORE risk equations has a relatively small effect on estimated CVD risk. Where differences did occur, less than 10% of people were reclassified across risk thresholds for treatment in most cases and those reclassified tended to be those with risk estimates close to the thresholds. Risk differences were largest in those at the highest risk, who tended to remain at high risk regardless. The contribution of BP to risk appeared to be lower in the QRISK2 compared to the Framingham equation. The choice

of which risk score to use may have a greater bearing on risk estimates than the choice of which BP measurement to use.

3.4.1. Strengths

The results of this study have been demonstrated in two populations from distinct countries with differing cardiovascular risk profiles and therefore have good face validity. It is likely that the findings will be generalizable to other populations, including ethnic minorities. A further strength is that this work was informed by initial review work in Chapter 1 and I chose to study the three most well-known and well-used risk scores relevant to UK primary care. Having considered the effects of BP measurement on three different risk scores with broadly similar results, and since the majority of risk scores were developed using similar methods and contain similar risk factors (as evidenced in Chapter 1), it is reasonable to assume that these results are generalizable to other risk scores.

This work was also informed by results from Chapter 2 from which I was able to form a definition of blood pressure measurement according to current practice. In particular, based on the patient survey results, I chose to explicitly make comparisons between measurement practices that specify the reading arm and those that do not, showing that this has little effect on obtained risk estimates.

3.4.2. Limitations

A limitation of this analysis was that outcomes data were not available to allow comparison between estimated and observed risks. Hence, although I demonstrated that differences in risk are small when using different measures of "usual" BP, I was not able to determine whether using one type of BP measurement over another results in more accurate risk assessment. The extent to which such covariate measurement error affects the accuracy of

risk estimation has been studied previously, but limited to the use of accurate/ error prone covariates in the derivation of risk scores rather than the use of error prone covariates in established scores.(152,153). It is not clear how issues of bias and measurement error in covariates will affect estimates of risk score accuracy in validation studies and this requires further study.

Further limitations of this analysis are that data for cholesterol had to be simulated in the BP-Eth dataset, deprivation data was fixed at non-risk modifying values in the HOMERUS dataset and only complete case analyses were carried out. Imputation methods derived for individual-patient data meta-analyses, whereby a variable is systematically missing in one dataset but not another, were considered. However, these methods were largely in their infancy and at the time, useable statistical software was only available for the case of one systematically missing continuous variable,(154) rather than two across different clusters, as was the case here. Missing data for other variables could have been imputed separately in each dataset, but this would have been limited by an inability to include the outcome in the imputation model. Furthermore this analysis primarily aimed to describe *possible* changes in risk estimates across a range of risk values and BP differences, rather than provide an accurate estimate of risk differences at a population level. Therefore, it is unlikely that an imputed analysis would have added value to the current results.

3.4.3. Comparisons with the literature

Previous research carried out in New Zealand examined the differences observed in Framingham risk estimates when BP measurements were subject to zero-end digit preference. This study found that the mean difference in risk was 0.16% and that 2.4% of individuals were reclassified across the 20% risk threshold.(140) This study can be viewed as a generalisation of the same problem: that of using BP measurements with differing

levels of bias/ measurement error than those used in risk score derivation. The differences and subsequent reclassifications observed in this study are of a similarly small magnitude, confirming the previous studies finding that risk estimates are not very susceptible to changes in BP accuracy.

The results of this analysis are in line with separate analysis conducted by myself and colleagues in the BP-Eth cohort, aiming to modify CVD risk scores for use with home BP measurements instead of clinic measurements.(155) Modifications to existing equations were modest and differences in risk between the modified equations and existing risk equations using clinic or home BP measurements were small. The results for home BP have been confirmed here in a further dataset, and those for ambulatory BP indicate that any changes to risk scores for use with ambulatory measurements would be similarly modest.

It has previously been shown that home and ambulatory BP is predictive of CVD risk over and above clinic BP.(54,55) Despite this, adding daytime ambulatory BP measurements to the Framingham risk score in a cohort of older men did not improve the accuracy of the Framingham risk score.(156) This suggests that when including a measure of BP in risk scores, the type of BP measurement may have little influence on risk score accuracy. The small differences in risk observed when using ambulatory instead of clinic BP measurements in this study support these previous findings. The small differences observed in particular for the QRISK2 equation may also be explained by the relatively small hazard ratio for BP in this risk score, compared to those from published reviews of clinical trials and other epidemiological studies. In QRISK2, the hazard ratio for CVD events per 20 mm Hg difference in systolic BP was 1.20.(41) This is much smaller than published hazard ratios of at least 1.49 for CHD and stroke mortality from observational

cohort studies,(8) and hazard ratios of 1.60 for CHD events and 3.43 for stroke events in primary prevention groups from BP lowering trials.(11)

3.4.4. Implications for research and practice

These results indicate that GPs and nurses need not be unduly worried about which BP measurements to use when calculating cardiovascular risk, particularly when using the recommended QRISK2 score where the overall contribution of BP is less. More careful BP measurement, in line with measurement in the risk score derivation studies may be warranted in those with estimated risk close to treatment thresholds who are most likely to be reclassified. However, it has been shown previously that statin medications were started in only 18% of men and 21% of women identified at high risk of CVD between 2010 and 2013.(157) Hence even if a small number of reclassifications across thresholds do occur, decisions to start treatment are clearly influenced by several other factors.

This study has indicated that risk estimates differ most between risk scores and so the decision of which risk score to use is an important one. A previous GP survey showed that the most popular of the CVD risk scores amongst GPs was the Framingham risk score,(32) but this was carried out before UK NICE guidance for the primary prevention of CVD recommended the use of the QRISK2 risk equation.(18) The QRISK2 equation has been shown to predict risk more accurately than the Framingham score in an independent database validation,(158) but was not shown to be superior in a tri-ethnic UK population,(159) raising questions of which risk score is "best" despite current guidance. A pragmatic approach may be for GPs to estimate risk using both equations and make a judgement regarding lifestyle or medication changes based on results from both.

A further finding in this analysis was that the contribution of blood pressure appeared to be less important in QRISK2, compared to SCORE or Framingham and the reason for this should be explored. Published hazard ratios for BP in each of the three risk scores are in line with those from other risk scores identified in the review work in Chapter 1. However the QRISK2 score includes many more risk factors than Framingham or SCORE, including a term for treated hypertension and this may explain the observed differences.

This chapter has examined how the use of summary measures of "usual" or mean blood pressure obtained in different settings or from a different number of readings may influence estimates of cardiovascular risk. It has shown that despite the inherent variability in BP and its subsequent effect on estimates of mean BP, estimates of cardiovascular risk are similar regardless of how mean blood pressure is measured. Chapter 4 extends this work to consider whether such variability in BP is a predictor of risk in its own right, rather than simply a "nuisance" factor which makes the assessment of mean BP difficult.

Chapter 4 Reviewing the evidence for BP variability as an independent risk factor for CVD

Survey results in Chapter 2 demonstrated that those with initially high clinic blood pressures are more likely to have multiple, repeat BP measurements taken over short periods of time such as during a single appointment or through out-of-office monitoring. Furthermore, repeat visit-to-visit BP readings may also be obtained as a result of long-term management of chronic conditions or through repeated screening for hypertension over several weeks and months.

Review work in Chapter 1 also found that many established risk scores were developed using repeated measurements of clinic blood pressure, but that these repeat measurements were combined by taking an average to produce a single overall mean summary measure. However, blood pressure is not a constant and shows marked oscillations from one reading to the next, over both the short and long term.(45) As discussed in Section 1.7, blood pressure can be affected by a number of factors and fluctuations in BP have been viewed historically as a "nuisance" phenomenon to be overcome by improved monitoring.(63) Yet more recent studies have indicated that BP variability may be a risk factor for CVD in its own right.(65–67). In this chapter I consider whether such fluctuations in BP may themselves be predictive of cardiovascular disease and mortality. Specifically, I systematically review the evidence for BP variability as a risk factor for CVD outcomes, independently of the established association with mean BP.

As discussed in the Statement of Originality, although several people were involved in conducting this review, I developed the systematic review protocol, screened eligible studies, extracted data and carried out the statistical analysis. The work described in this chapter was also published in a peer-reviewed journal article, for which I was the first author, during the course of the thesis (see Document B.1, Appendix B).(160)

4.1. Introduction and methodological challenges

Although several studies have demonstrated a positive association of increased BP variability with CVD outcomes,(71–73) some studies fail to show an effect.(74) The mix of results reflects not only heterogeneity of approach in terms of study design, but also in analysis. To date studies have differed in terms of the modality of measurement (clinic,(68) home,(69) or ambulatory measurement(70)) and the statistical measure of variability used for analysis (for example standard deviation(69) or standard deviation divided by the mean, known as coefficient of variation(68)). Within this, studies differ in terms of the definition of each measurement with which BP variability is calculated, for example using single BP readings,(66) or averages of two BP readings.(161) Studies also differ according to the time between measurements and the total number of measurements used to calculate variability in much the same way as the literature regarding mean BP. As in other research areas, studies have also been limited by small sample sizes,(162) short follow-up periods,(163) or the use of proxy measures instead of hard outcomes.(64) Such heterogeneity makes an "at-a-glance" review of the literature virtually impossible.

Furthermore, there are many confounding factors specific to the problem of variability which have not always been appropriately addressed. Firstly, some studies fail to define a consistent measurement protocol including details regarding the device used, the personnel

taking the measurements or the timing of measurements in relation to activity and medications.(72,164,165) Since different devices can have different degrees of error and the magnitude of the white-coat effect is known to differ according to the type of health professional taking a reading,(52) this leaves doubt as to the source of any perceived variability. Natural diurnal or seasonal variation must also be taken into account in the analysis. Some studies also fail to adjust for mean BP in the analysis and since those with higher mean BP also tend to have higher variability, this means variability becomes a surrogate for mean in the analysis.(166) In these cases it is unsurprising to find a positive association between the variability measure being studied and CVD outcomes.

Many of the previously published studies stem from secondary analyses of clinical trial data,(66,73) in which patients may have had their antihypertensive medications titrated, or had additional agents added, in order to achieve good control of mean BP. Blood pressure measurements taken during this period may therefore exhibit high variability but these individuals are also more likely to have good control over mean BP, thereby reducing their CVD risk. Hence failure to account for medication change may confound the relationship between BP variability and CVD events, and bias any estimate of an association towards the null.

Finally, the assessment of visit-to-visit BP variability in particular requires a long period of observation during which variability can be measured. Similarly, an adequate period of follow-up is required to ascertain CVD events in sufficient numbers, yet these observation and follow-up periods should be distinct from one another. Overlap between the observation period (during which BP variability is calculated) and the follow-up period (during which events are ascertained) may cause biases such as immortal time bias in the case of mortality outcomes.(167) In this case, if individuals are required to have a certain

number of repeat BP measurements in order to be included in any analysis, the time up until their qualifying measurement becomes "immortal time" since, by definition, these individuals could not have died prior to having the prerequisite number of BP readings. Informative censoring can also be a problem if patients were withdrawn from a study early due to safety concerns, for example due to erratic BP measurements, in secondary analysis of trial data. It is also important to distinguish the two time periods since the primary interest in this chapter was that of the association of BP variability with future CVD outcomes in the long term. If BP variability is measured up until CVD events occur, then any observed increases in BP variability may be an artefact of the events themselves, thereby inducing reverse causality.

For all of the reasons described, results from previous studies cannot necessarily be taken at face value and require critical appraisal. I therefore aimed to review the evidence for an independent association of BP variability with CVD outcomes and mortality in prospective cohort studies and clinical trials in adults, in consideration of the above challenges in the literature.

4.2. Methods

A protocol for the review was made available online during the course of the thesis and prior to data extraction and analysis (see PROSPERO International prospective register of systematic reviews, ID: CRD42014015695).

4.2.1. Search strategy

Electronic databases (Medline, Embase, Cinahl and Web of Science) were searched on 26th April 2013 for articles describing trials and prospective cohort studies, which quantified the

association of BP variability (measured in clinic, at home or by ambulatory monitoring) with cardiovascular outcomes in adults (see Table B.1, Appendix B, for full search strategy). The search was limited to full text articles published in English and studies in adult humans. Titles and abstracts were scrutinised independently by two reviewers (myself and one other) and potentially eligible studies reviewed in detail to assess eligibility. Where disagreement occurred, differences were adjudicated by a third reviewer. The search was further updated on 27th February 2014 and, following requests from peer reviewers, again on 15th February 2016. Over the course of this process, other reviews in the field were also published and the studies included in these reviews were also screened for eligibility and included where appropriate.(168–171)

4.2.2. Inclusion and exclusion criteria

Study designs, size and follow-up

Studies were eligible for inclusion if they were prospective, longitudinal, observational cohort studies or clinical trials in adults (aged 18 years or over) and had a minimum of 2500 person-years of follow-up. Initially, instead of requiring a minimum number of person-years of follow-up, two separate inclusion criteria were applied: one specifying a minimum of five years mean/ median follow-up and a second specifying that included studies had a minimum of 500 participants. However, this led to the exclusion of some relevant studies that failed to meet one of the inclusion criteria by only a small margin and therefore a more inclusive approach was taken by combining the inclusion criteria into one person-years based rule. This change was made before analysis and publication of the review protocol.

Study populations

Studies of hypertensive patients and those taking antihypertensive medications were included. Studies of patients in other specific disease groups such as stroke, chronic kidney disease, dementia and diabetes were originally excluded from the review so that results were applicable primarily to the general or healthy population. However, this exclusion criterion proved to be very strict and this was changed after the initial search in order to maximise data collected and increase statistical validity. An exception to this was studies specifically conducted in haemodialysis patients, which remained an exclusion criterion. This is due to the nature of haemodialysis treatment, where common changes in blood pressure (intradialysis hypo- and hypertension(172,173)) are associated with hospitalisation and mortality.(174,175) Hence any observed BP variability in these patients might reflect haemodynamic changes as a result of treatment rather than natural physiological variation, which was the primary concern of this review.

Blood pressure measurements

Participants were required to have undergone BP monitoring in clinics, at home or through ABPM. Studies of clinic monitoring had to consider visit-to-visit not within-visit variability, with measurements on at least five separate visits. For home monitoring, a minimum of twelve measurements over at least three days were required and for ABPM, at least fourteen daytime readings were required.(1)

The requirement for a minimum number of readings was assessed against the study protocol (i.e. the number of readings the study set out to achieve). Where there was no evidence of a specific intention via a protocol (e.g. the study was observational and based on usual practice), the number of readings was taken to be the minimum number of measurements required for a participants data to be included in the analysis (as specified by

the study authors). This criterion was applied according to the study authors' intention, rather than the data that was actually collected to make the rule easy to apply. As an illustrative example, one excluded study specified a minimum of three measurements for inclusion in the analysis but in some sub-analyses patients had an average of over seven repeat measurements (range four to ten). The paper did not report further statistics to determine whether the majority of patients in these sub-analyses had at least five readings or not (for example an average of seven readings could be obtained from a majority of patients having only four readings and a minority having ten or more readings). Applying the rule based on author intention reduced the risk of inconsistency in decision making arising from such ambiguous examples.

Outcomes

Studies had to quantify the association between BP variability with the risk of cardiovascular or mortality outcomes including: all-cause mortality, cardiovascular events (including stroke, myocardial infarction, coronary heart disease, heart failure), cardiovascular mortality (including sudden death) and combinations thereof. Studies of intermediate outcomes such as arterial intima-media thickness were excluded. No restriction was made in terms of the statistical measure of variability studied (e.g. standard deviation (SD), coefficient of variation (CV) etc.) except that studies concerning only "nocturnal dipping" or "day-night variation" in ABPM were excluded because another review specific to these measures had already been carried out.(176)

4.2.3. Data extraction

Basic study and patient characteristics data were extracted independently by two reviewers (myself and one other), as were statistical and results data (myself and one other) using pre-

specified coding forms. Details of the information extracted are given in Table 4.1.Where papers reported results for multiple modalities (clinic/ home/ ABPM), outcomes and variability measures, hazard ratios (HRs) for every variability measure, outcome and modality combination were extracted. Where there was evidence of unpublished data, or further information was required, this was requested from the corresponding authors by email. For studies reporting results from multiple statistical models, the HR from the model with the greatest adjustment for confounders but containing only a single variability measure was extracted.

Table 4.1: Information extracted from included articles

Patient characteristics

- Number of participants
- Age
- Proportion on anti-hypertensive medication
- Gender
- Source population

Study characteristics

- Type of monitoring
- Measurement device used*
- Person taking readings*
- Length of monitoring period
- Length of follow-up
- Authors overall conclusion
- Type of study (trial/ observational)
- Measurement arm*
- Cuff size used*
- Outcomes studied
- Variability measures studied

Statistical analysis

- Analysis strategy
- Variability measure
- Systolic or diastolic BP
- Reported hazard ratio/ 95% confidence interval
- Adjustment for equivalent mean BP*
- Regression to the mean considered*
- Medication change during measurement period limited/ adjusted for*
- Medication change during follow-up period limited/ adjusted for*
- Definition of a single measurement
- Outcome
- Units of reported hazard ratio
- Standard deviation of variability measure
- Diurnal/ Seasonal variation considered*

*considered as potential confounders of the effect of BP variability on outcomes.

4.2.4. Statistical analysis

Variability in systolic blood pressure was considered as the primary analysis, as mean systolic blood pressure is traditionally included in risk scores. For completeness, secondary analysis was also carried out for diastolic BP variability. In the case of ABPM, the primary

analysis was carried out for variability in daytime ABPM as daytime ABPM is recommended for the diagnoses of hypertension.(1) Night-time and 24-hour BP variability were studied in secondary analyses.

Extracted hazard ratios were converted to standardized hazard ratios, to allow comparisons of predictive power and pooling across different measures of variability. This was because it is common for hazard ratios to be reported in such a way that they convey the increase in risk associated with a 1 unit increase in a risk factor (e.g. per 1 mm Hg), but they may be standardized so that they convey the increase in risk associated with a one standard deviation increase in a risk factor (e.g. per 10 mm Hg if the observed standard deviation in blood pressure is 10 mm Hg). Such standardization is common in regression modelling and allows comparison of hazard ratios if risk factors are not measured on the same scale,(177) as was the case in this review in which several different measures of BP variability, on different scales, were considered.

As an illustrative example, Eguchi et al.,(178) reported that the standard deviation of standard deviation in clinic systolic BP was 4.6 mm Hg (i.e. the variability in blood pressure standard deviation between individuals was 4.6 mm Hg). The univariate HR per 5 mm Hg of systolic BP standard deviation (SD) was 1.158 (log-hazard ratio = 0.147 per 5 mm Hg). From this, the log-hazard ratio per 1 mm Hg of systolic BP SD is therefore 0.147/5 = 0.0294 and hence the log-hazard ratio per 4.6 mm Hg is given by 0.0294 x 4.6 = 0.135. Finally, through exponentiation, the hazard ratio per 4.6 mm Hg of systolic BP SD is 1.14. This represents the hazard ratio per standard deviation change in standard deviation of systolic BP and reflects the risk associated with a one standard deviation change in BP variability. Unfortunately, because this review deals with variability measured through standard deviation, the term hazard ratio per one SD of SD is difficult to comprehend

clearly. As a result, the term standardized hazard ratio rather than hazard ratio per one SD is used throughout the remaining methods and results section.

Standardized hazard ratios as defined above (with corresponding 95% confidence intervals) were pooled using DerSimonian-Laird random-effects meta-analysis using the "metan" command in Stata, which estimates heterogeneity using the Mantel-Haenszel model. Analyses were stratified by outcome and modality of measurement. Analysis of home monitoring data was further stratified according to measurements taken in the morning, evening or both the morning and evening, and analysis of ambulatory monitoring data was stratified according to daytime, night-time and 24-hour measurements. Heterogeneity was assessed using both the Chi-squared test and the I-squared statistic, with an I-squared value greater than 50% considered substantial. In cases of substantial heterogeneity caused by a single outlying study, analysis was repeated excluding the study in question.

Where studies reported results for multiple different variability measures, HRs were selected for inclusion according to the following pre-specified hierarchy (preferred to least preferred): standard deviation (SD), coefficient of variation (CV), variation independent of mean (VIM), average real variability (ARV), standardised residual (SR), root successive variance (RSV) and other. Note that variation independent of mean is a generalisation of both coefficient of variation and standard deviation, since it is proportional to the standard deviation divided by the mean, where the mean is also raised to some power (x, derived from curve fitting in the dataset: $SD/(mean^{x})$).(66,179) Average real variability is the mean absolute difference between successive readings.(180)

If equivalent hazard ratios were calculated using data from the same primary study or trial but reported in multiple different papers, we included the HR from the most recently published paper. Where papers reported results by subgroups (e.g. treated and untreated),

hazard ratios from each of the subgroups were combined to give an overall study measure, which was then included in the analysis. The impact of this approach on results was assessed by comparing the main analysis results to those where subgroup hazard ratios were entered into the model separately.

Risk of bias assessments

An important aim of this review was to ensure that, as far as possible, the pooled results would not be affected by confounding. Data were extracted regarding a large number of confounding factors, but restricting analysis, or performing subgroup analyses based on all of these confounders was impractical. I therefore selected, a-priori, the three most important confounding factors against which studies could be assessed for inclusion in main or sensitivity analyses. Studies were regarded as being at low risk of confounding if:

1. hazard ratios for BP variability were adjusted for the equivalent mean BP level (e.g. adjusted for mean daytime BP if variability was assessed over daytime ABPM readings),
2. outcome ascertainment took place after (and distinct from) the measurement period for BP variability,
3. for studies including patients randomized to treatment or placebo arms, at least 80% of patients in each group did not change their treatment or patients were censored at the point of treatment change.

Primary analyses were carried out for studies meeting the above pre-specified methodological criteria only. Additional data from studies not meeting pre-specified criteria were included as part of sensitivity analyses.

Furthermore, risk of bias was assessed using the QUIPS risk of bias tool for prognostic factor studies(181) by two independent reviewers (myself and one other), with adjudication by a third. The risk of bias assessment was not used to stratify analysis since the major potential for confounding and bias was captured by the alternative assessments described above. Although the QUIPS tool is adequate for most standard prognostic factor studies, the items in the tool did not capture many of the areas of concern which are specific to the problem of BP variability. I therefore decided to conduct the risk of bias assessment for completeness only.

Egger's test was used to assess possible small study effects.(182) Due to its low power in meta-analyses involving few studies, I also investigated how robust results were to the possibility of unpublished null effect studies using the "fail-safe N" approach (the number of null effect studies of mean weight that would need to be included in meta-analyses to result in a non-significant pooled effect).(183)

4.3. Results

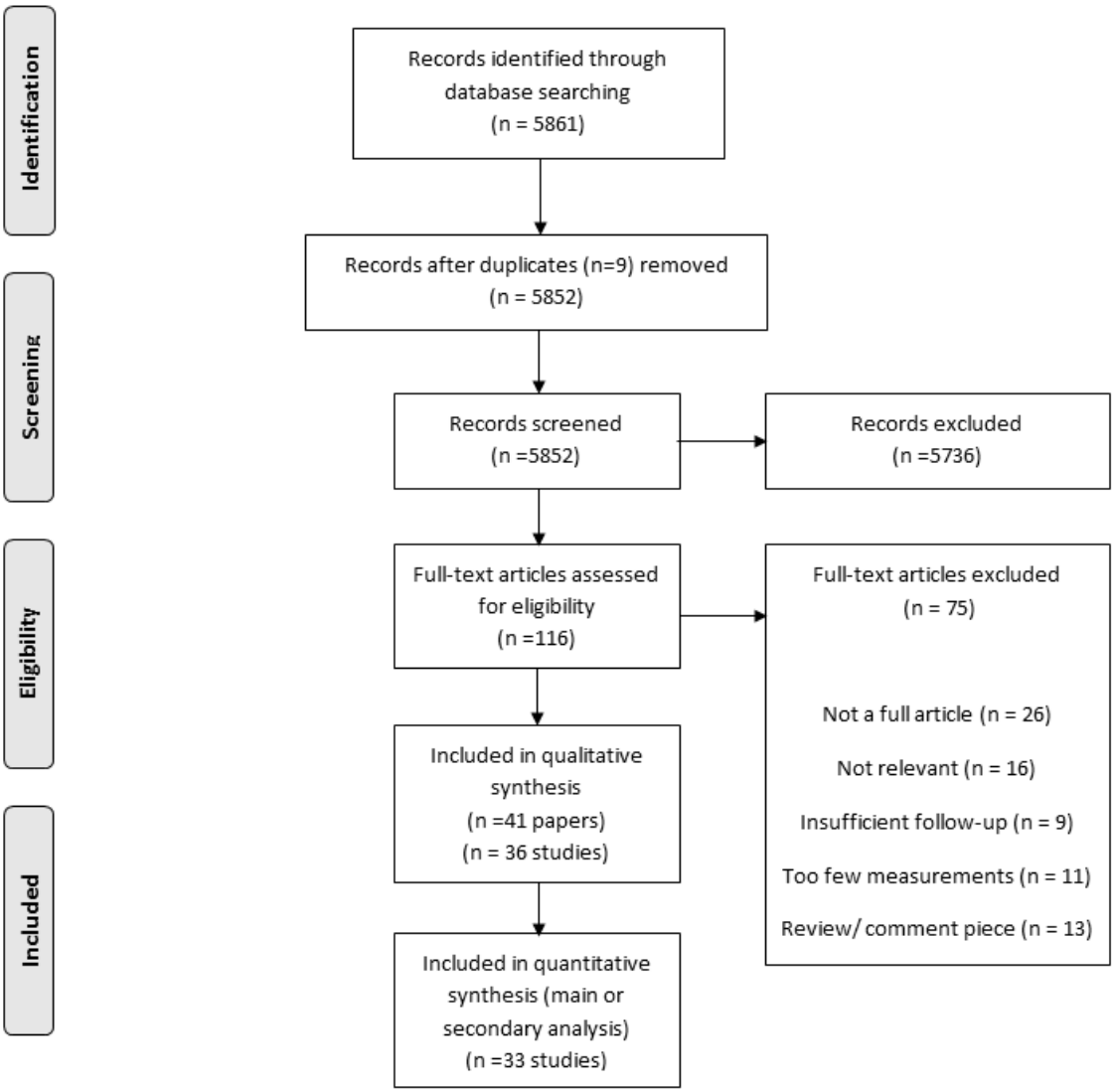
A total of 5861 references were identified through searches. Removal of duplicates and abstract screening yielded 116 articles for full text review (Figure 4.1). Of these, 41 articles were selected for inclusion. Some articles presented equivalent analyses of data from the same cohorts, whereas others analysed data from multiple cohorts. Overall, the 41 articles represented analysis of 19 distinct observational study cohorts and 17 clinical trial cohorts, and 46 separate analyses.

Four papers included results from the Ohasama study in Japan,(184–187) three papers included results from a study based in Abruzzo, Italy,(188–190) and two papers included results from the International Database of Ambulatory Blood Pressure in relation to

Cardiovascular Outcome (IDACO) cohort.(70,191) One paper presented results from four different trial cohorts.(66) There was also overlap of studies in many papers studying ABPM since the IDACO cohort(70,180) and the Ambulatory Blood Pressure International (ABP-International) cohort(192) combined data from several individual studies.

Fifteen papers (66,70,166,178,186,188–197) studied short-term variability in ABPM and four papers(69,184,185,187) studied mid-term variability in home monitoring. Twenty-four papers(66,68,71–74,101,161,164,165,178,198–210) studied long-term variability in clinic monitoring. The number of participants in each included study ranged from 457(178) to 122,636(209) and follow-up ranged from 2514(178) person years to 490,544(209) person years. Full details of the study and patient characteristics for each included paper are given in Table 4.2.

Figure 4.1: Study inclusion flowchart



4.3.1. Risk of bias and confounding

I chose to determine risk of bias for each analysis (paper and study combination) because in cases where multiple papers presented data from the same study, the same analysis techniques were not always used, leading to differing levels of bias in the different categories. Similarly, some papers presented results from multiple different studies which may have had different study designs and hence differing levels of bias.

In all studies, variability in blood pressure may have been introduced due to study design characteristics such as consistency of cuff size, measurement arm, device, and staff (e.g. mercury sphygmomanometers and changing staff) or these characteristics were unclear (Table 4.3). In the 46 distinct analyses of the 36 included studies, the analytical approach had the potential to introduce confounding in all 46 analyses and results from 23 analyses were excluded from the main analyses on the basis of the three pre-specified criteria. Eight analyses failed to correctly adjust for mean blood pressure, 15 did not account for major drug change during the measurement period, and 20 did not separate the measurement and follow-up periods. Results were not reported in sufficient detail to allow extraction of data from four analyses in three studies.(188,202,206,208)

Based on the QUIPS tool, moderate risk of bias was observed for the majority of studies in the study participation category (Table 4.4). This was because a large number of studies could have been affected by regression to the mean effects due to inclusion criteria based on high BP readings. Many studies were also at moderate risk of bias in the measurement of prognostic factors category because they did not use a consistent measurement protocol or device for the duration of the study or across participants. Information regarding cuff size, reading arm and the type of healthcare professional taking each reading was limited.

Eighteen analyses were at high risk of bias in at least one category, either because measurement of BP variability took place at the same time as follow-up (n=17) or because the papers did not report some non-significant findings (n=1). Results from these studies were all excluded from our main analysis according to our pre-specified methodological criteria.

Table 4.2: Characteristics of included studies

Paper, Year (Country)	Study	Population	N	Frequency of measurement	Measure of Variability	Follow-up	Antihypertensive medication	Outcome Measure
Short term BP variability measured through ambulatory BP monitoring (ABPM)								
Bjorklund, 2004(166) (Sweden)	ULSAM (observational)	70 year old men (Uppsala Longitudinal Study of Adult Men). Mean age 71. 100% male.	872	Every 20 mins	SD	9.5 years (max, mean 6.6 +/- 2.1 years)	30.0%	CVD events
Eguchi, 2012(178) (Japan)	Observational	Asymptomatic patients aged 33-88 attending general internal medicine clinics at three institutes in Japan, for the evaluation and management of hypertension. Mean age 67. 38% male.	457	Every 30 mins	SD	66 months (mean)	55.6%	Hard and all CVD events
Gavish, 2009(193) (Israel)	Observational	Non pregnant, greater than 16 years old, good quality ABPM. Mean age 56. 45% male	3433	Every 20 mins (day) or 30 mins (night)	SD, CV, day/night SD ratio	7.6 years (mean, max 16 years)	59.0%	All-cause mortality
Gavish, 2015(194) (Israel)	Observational	Hypertensive patients included in the ambulatory BP (ABP) measurement service database. Mean age 57. 46% male. (analysis of subset of Gavish, 2009)	1246	Every 20 mins (day) or 30 mins (night)	SD, ratio of systolic and diastolic SD	5 years	61.0%	All-cause mortality
Hansen, 2010(70) (Worldwide)	IDACO (observational)	Multiple different populations in ABPM database. Mean age 53. 53% male. [IDACO]	8939	Every 30 mins	SD, ARV, mean of day and night SD	11.3 years (median)	19.6%	All-cause mortality, CVD mortality, CVD events, cardiac and coronary events
Kikuya, 2000(186) (Japan)	Ohasama (observational)	Japanese general population > 40 years (mean age 61.7, men: women=40:60)	1542	Every 30 mins	SD	8.5 years (mean)	30.9%	CVD mortality
Mancia, 2007(195) (Italy)	PAMELA (observational)	Randomly selected individuals in Milan aged 25-74 years. Mean age 51. 50% male.	2012	Every 20 mins	SD	148 months (max follow-up)	Not stated	All-cause mortality and CVD mortality
Mena, 2014(191) (Worldwide)	IDACO (observational)	Discovery data: - subset of IDACO, Copenhagen cohort subjects equally distributed among the 2 sexes and among 4 age wit complete ABPM readings groups (41, 51, 61, and 71 years). Test data: IDACO subjects 18+, at least 10 daytime readings, 5 night-time readings, and 48 readings over 24 hours and were not included in the discovery dataset. Mean age54. 54% male.	1254 (discovery data), 5353 (test data)	Every 15 to 30 minutes (day) and 30 to 60 mins (night)	ARV	10.2 years (median, test data)	21.3% (test data)	All-cause mortality, CVD mortality, CHD mortality, CVD events, CHD events, stroke events
Palatini, 2014(192) (Worldwide)	ABP-International (observational)	Ambulatory BP International Study: combination of 8 prospective studies of random samples of patients referred to hospital for hypertension. Untreated patients with entry office BP >140/90 mmHg. Mean age 51. 56% male.	7112	Every 10 to 30 mins (day) and 15 to 30 mins (night)	SD, CV	5.5 years (median)	No - untreated population	CVD events and CVD mortality

Paper, Year (Country)	Study	Population	N	Frequency of measurement	Measure of Variability	Follow-up	Antihypertensive medication	Outcome Measure
Pierdomenico, 2005(188) (Italy)	Abruzzo, Italy (observational)	Uncomplicated mild clinic hypertensives. Mean age 49. 54% male.	1088	Every 15 mins (day) and 30 mins (night)	SD	4.74 years (mean)	87% at follow-up	CVD events
Pierdomenico, 2006(189) (Italy)	Abruzzo, Italy (observational)	Hypertensive patients undergoing ABPM in Italy. Mean age 59. 47% male.	1472	Every 15 mins (day) and 30 mins (night)	SD	4.88 years (mean)	100.0%	CVD events
Pierdomenico, 2009(190) (Italy)	Abruzzo, Italy (observational)	Hypertensive patients age 40+ years who were referred for an outpatient evaluation for hypertension in Italy. Mean age 58. 49% male.	1280	Every 15 mins (day) and 30 mins (night)	SD, ARV	4.75 +/- 1.8 years (mean, range 0.2-7.5)	57.0%	CVD events
Pringle, 2003(196) (Europe)	Syst-Eur trial	Syst-Eur study. Elderly patients (60+) with isolated systolic hypertension. Median age 69.5. 39% male.	744	Every 30 mins	SD	4.4 years (median)	100% (384 on active treatment in trial)	Stroke events, CHD events and CVD mortality
Rothwell, 2010(66) (UK/ Scandinavia)	ASCOT-BPLA trial ABPM substudy (subset of stroke/TIA patients)	Patients with previous TIA or stroke	1905	Every 30 mins	SD, CV, VIM	5 years (median)	100.0%	Stroke events
Verdecchia, 2007(197) (Italy)	PIUMA (observational)	Initially untreated subjects with essential hypertension. Mean age = 51 yrs. Prevalence of women 47%	2649	Every 15 mins	SD	6 years (mean, max 16 years)	Untreated initially - subsequent antihypertensive use recorded	CVD events
Long-term BP variability measured through clinic BP monitoring								
Arashi, 2015(198) (Japan)	HIJ-CREATE trial	Participants of the Heart Institute of Japan Candesartan Randomised Trial for Evaluation in Coronary Artery Disease. Hospitalized patients with coronary artery disease and hypertension aged 20-80, June 2001 to April 2004. Mean age 48.5. 80% male.	1734	Every 6 months for a year, then every 12 months	SD, CV, VIM	4.2 years (median)	100% (trial of antihypertensives)	CVD events
Blacher, 2015(199) (France)	SU.FOL.OM3 trial	Participants from the SU.FOL.OM3 trial with experience of a coronary or cerebral ischemic acute event 1–12 months before inclusion. 45-80 years. Mean age 61. 80% male.	2157	Baseline then annually for 5 years	SD, CV	4.2±1.0 years (mean, max 5 years)	Yes - between 5% on alpha blockers to 69% on beta blockers.	CVD events
Carr, 2012(73) (UK)	MRC Elderly Trial	Hypertensive patients with a mean systolic BP at 160-209mmHg and diastolic BP < 115mmHg at entry	4396	Fortnightly basis for first month then monthly basis for 3 months, then 3 monthly	SR and RSV (Root successive variance = SR divided by BP at baseline)	5.8 years (mean)	100% (trial of antihypertensives)	Stroke events and CHD events
Eguchi, 2012(178) (Japan)	Observational	Asymptomatic patients aged 33-88 attending general internal medicine clinics at three institutes in Japan, for the evaluation and management of hypertension. Mean age 67. 38% male.	457	Every month	SD	66 months (mean)	55.6%	Hard and all CVD events

Paper, Year (Country)	Study	Population	N	Frequency of measurement	Measure of Variability	Follow-up	Antihypertensive medication	Outcome Measure
Gao, 2014(74) (USA)	Observational	US Primary care patients aged 60+ years approached for a depression screening study 1991-1993. Mean age 68. 31% male.	2906	At routine outpatient visits	RMSE (root mean squared error)	12.9 years (median)	89.7%	All-cause mortality, CHD events and stroke events
Hara, 2014(200) (Europe)	Syst-Eur trial	Patients aged 60+ with isolated systolic hypertension (SBP <160, DBP<95). Mean age 70. 33% male.	4695	Every 3 months	SD, CV, VIM, ARV, MMD (min-max difference)	2 years (median)	50% (randomised to active treatment)	CVD events and mortality
Hata, 2013(201) (Worldwide)	ADVANCE trial	Patients aged 55+ with type 2 diabetes and history of major macro- or micro- vascular disease. Mean age 66. 58% male.	8811	Months 3, 4 and 6 then every 6 months up to 24 months	SD, CV	2.4 years (median)	69% (at baseline but trial of antihypertensives)	All-cause mortality, CVD mortality, CVD events, stroke events and MI events
Hsieh, 2012(202) (Taiwan)	Observational	Patients with type 2 diabetes visiting the diabetic clinic in the Metabolism Division at Changhua Christian hospital Sept 2003-Apr 2005. Mean age 63.5. 43% male.	2161	Every 2-6 months	SD, CV	66.7 months (mean)	80.0%	All-cause and CVD mortality
Kawai, 2013(164) (Japan)	NOAH (observational)	Non-Invasive Atherosclerotic Evaluation in Hypertension study. Outpatients diagnosed with essential hypertension recruited between January 1998 and June 2004 at Osaka University Medical Hospital. Mena age 62. 53% male.	485	Every 1-2 months (6 visits total)	SD	7.59 years (mean)	47.3%	CVD events
Kostis, 2014(203) (USA)	SHEP (trial)	Systolic hypertension in the elderly program. Average age 72, 57% women and 15% black. USA.	4736	Baseline, months 1, 2 and 3, then every 3 months	VIM, rSSR (sum of squared deviations between average and trend predicted BP), VABS2 (variance of absolute difference between successive daily BP (VABS2)	17 years (max)	100.0%	CVD mortality
Lau, 2014a(68) (China)	Observational	Ischaemic stroke patients without atrial fibrillation, Hong Kong. Average age 71 years. 53% male.	632	Every 3-4 months	CV	76+/- 18 months (mean)	80.0%	All-cause and CVD mortality, nonfatal recurrent stroke and nonfatal acute coronary syndrome
Lau, 2014b(204) (China)	Observational	Patients with known history of coronary artery disease, ischaemic stroke or diabetes. Mean age 66. 68% male.	656	Every 3-4 months	SD	81 +/- 12 months (mean)	Yes - from 8% on alpha-blockers to 51% on beta blocker	CVD events
Mallamaci, 2013(205) (Italy)	Observational	Italians aged 18-75 with CKD stages 3 and 4, recruited in renal clinics from Oct 2005 to Nov 2007. Mean age 64. 59% male.	1618	Two visits per year for 3 years	SD, CV	37 months (median)	94.0%	All-cause mortality and CVD events

Paper, Year (Country)	Study	Population	N	Frequency of measurement	Measure of Variability	Follow-up	Antihypertensive medication	Outcome Measure
Mancia, 2012(206) (Europe)	ELSA trial	European Lacidipine Study on Atherosclerosis which randomized antihypertensive treatment for 4 years to mildly or moderately hypertensive patients at relatively low cardiovascular risk Mean age 56. 56% male.	1521	Every 6 months	SD, CV	4 years (max)	Yes (trial of antihypertensives)	CVD events
McMullan, 2013(71) (USA)	AASK (trial)	African American Study of Kidney Disease. African Americans with hypertensive nephropathy. Mean age 55 years, 62% men.	908	Months 4, 6, 8, 10 and 12	SD	52 months (median, max 75 months)	Yes (trial of antihypertensives)	All-cause mortality, CVD mortality, CVD events
Muntner, 2015(161) (USA)	ALLHAT (trial)	Participants from the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial. Mean age 66. 52% male.	25,814	At 6, 9, 12, 16, 20, 24 and 28 months	SD, ARV, VIM	2.7 to 2.9 years (mean: outcome dependent, 5.7 years max)	100% (trial of antihypertensives)	Fatal CHD or non-fatal MI, all-cause mortality, stroke and heart failure.
Poortvliet, 2012(207) (Ireland/ Netherlands)	PROSPER trial	Men and women aged 70-82 years in Scotland, Ireland and the Netherlands with either pre-existing vascular disease (coronary, cerebral, or peripheral) or at high risk due to smoking, hypertension or diabetes. Long-term follow-up: mean age 75, 48.5% male.	4819 (short-term follow-up) 1808 (long-term follow-up)	Every 3 months	SD, CV	2.3 years (mean, max 3 years, Scottish sub-group: max of 9.3 years (mean 7.1))	62.6% (short term follow up), 59.6%(long term follow up)	All-cause mortality, CVD mortality, stroke events, CHD events
Rakugi, 2015(210) (Japan)	COLM trial(211)	Participants in the Combination of OLMesartan and a calcium channel blocker (CCB) or a diuretic in Japanese elderly hypertensive patients (COLM) trial. Hypertensive patients ages 65–84 years with a history of cardiovascular disease and/or cardiovascular risk factors and hypertensive. Mean age 74. 51% male.	4876	At , 3 and 6 months, then every 6 months to at least 3 years	SD, VIM, ARV	3.3. years (median)	100% (trial of antihypertensives)	CVD events
Rossignol, 2015(208) (Worldwide)	HEAAL trial	Patients from the Heart failure Endpoint evaluation of Angiotensin II Antagonist Losartan (HEAAL) study - patients with HF classes II-IV, LVEF<40% or intolerance to ACEi. Mean age 64. 70% male.	3732	Three times in the first year then semi-annually	SD, CV, ARV	6.8 years	100% (trial of antihypertensives)	All-cause mortality or hospitalisation for worsening heart failure
Rothwell, 2010(66) (UK/ Scandinavia)	ASCOT-BPLA trial (subset of stroke/TIA patients)	Patients with previous TIA or stroke	2011	At baseline, 6 weeks, 3 months, 6 months, then every 6 months	SD, CV, VIM	5 years (median)	100% (trial of antihypertensives)	Stroke events
Rothwell, 2010(66) (Netherlands)	Dutch-TIA trial(212) (subset of stroke/TIA patients)	Patients with recent TIA or stroke	3150	Every 4 months for 2.6 years	SD, CV, VIM	2.6 years. (mean)	42.0%	Stroke events
Rothwell, 2010(66) (Europe)	ESPS-1 trial(213) (subset of stroke/TIA patients)	Patients with recent cerebrovascular event	2500	Every 3 months for 2 years	SD, CV, VIM	2 years (max)	Not stated	Stroke events

Paper, Year (Country)	Study	Population	N	Frequency of measurement	Measure of Variability	Follow-up	Antihypertensive medication	Outcome Measure
Rothwell, 2010(66) (UK)	UK-TIA trial(214) (subset of stroke/TIA patients)	Patients with history of TIA, mean age 60.3 years.	2006	Every 4 months for 2.6 years	SD, CV, VIM	3.3 years (median, max 6.67 years)	27.0%	Stroke events
Shimbo, 2012(101) (USA)	Women's health initiative (observational)	Post-menopausal patients enrolled in the women's health initiative.	58228	Annually. (Mean visits = 7.9)	SD	5.4 years (median)	Not stated	Stroke events
Suchy-Dicey, 2013(72) (USA)	Cardiovascular health study (observational)	Subjects who either used no antihypertensives during a 5 year baseline period or who used the same anti-hypertensive regimen during that period. Mean age 71 yrs. 95% white	2548	5 annual clinic visits	SD	9.9 years (mean)	38.4%	All-cause mortality, MI events and stroke events
Wei, 2013(165) (China)	PROBE trial	Hypertensive Chinese patients aged 70+. Mean age 77. 66% male.	724	Every 6 months	SD	4 years (mean)	100.0%	CVD events
Yu, 2014(209) (China)	Observational	Hypertensive patients with records in an electronic database for Shanghai, China, Jan 2005 - July 2011. Aged 18+, without history of stroke, and with at least 6 database BP readings on average no more than 6 months apart. Mean age 64. 46% male.	122,636	Every 6 months	SD, CV	48 months (mean, range 36-60 months)	Not stated	Stroke events
Mid-term BP variability measured through home BP monitoring								
Asayama, 2013(185) (Japan)	Ohasama (observational)	>35 years old, at home during working hours, not hospitalised, not incapacitated. Mean age 59. 39% male.	2421	Every morning and evening for 28 days	VIM, ARV, MMD (min-max difference)	12 years (median)	27.1%	All-cause mortality, CVD mortality and stroke events
Hashimoto, 2012(184) (Japan)	Ohasama (observational)	Japanese Men. Mean age 58.6 years. 100% men.	902	28 morning readings over 28 days	SD	13.1 years (median)	26.1%	All-cause mortality, CVD mortality, stroke mortality, MI mortality, stroke events
Johanssen, 2012(69) (Finland)	Health 2000 study (observational)	Finnish adults aged 45-74 years. Mean age 56. 44% male.	1866	7 consecutive days - 2 in the morning and 2 in the evening	SD, ARV	7.8 years (mean)	30.6%	CVD events and all-cause mortality
Kikuya, 2008(187) (Japan)	Ohasama (observational)	Japanese. Baseline age 35-96 years (mean age = 59.3 +/- 12.3 years). 60.5% women	2455	One reading every day for 4 weeks	SD	11.9 years (median)	72.6%	All-cause mortality, CVD mortality, Non-CVD mortality, stoke mortality, CHD mortality, MI mortality

Table 4.3: Study design and analysis characteristics

Paper, Year	Study design characteristics				Potential confounders							
	Appropriate cuff size used	Consistent reading arm	Consistent device used	Same person taking readings	Appropriate adjustment for mean BP	Regression to mean considered (if relevant)	Diurnal/ seasonal variation considered	Medication change during measurement period limited	Medication change during follow-up limited	Measurement before follow-up	Definition of a single measurement given	Main analysis (yes or reason for exclusion)
Short-term BP variability measured through ambulatory BP monitoring (ABPM)												
Bjorklund, 2004	Unclear	Yes	Mercury sphyg	Yes (ABPM)	No	Not relevant	Yes	No but ABPM	No	Yes (ABPM)	Yes	No adjustment for mean BP
Eguchi, 2012: ABPM analyses	Unclear	Unclear	Yes	Yes (ABPM)	No –adjusted for clinic mean	Not relevant	No	No but ABPM	No	Yes (ABPM)	Yes	ABPM analyses adjusted for clinic mean
Gavish, 2009	Yes	Yes	No	Yes (ABPM)	No -adjusted for mean arterial pressure	No	No	No but ABPM	No	Yes (ABPM)	Yes	Incorrect adjustment for mean BP
Gavish, 2015	Yes	Yes	No	Yes	Yes	Not relevant	No	No but ABPM	No	Yes (ABPM)	Yes	Yes
Hansen, 2010	Unclear	Unclear	Unclear	Yes (ABPM)	Yes	Not relevant	Yes	No but ABPM	No	Yes (ABPM)	Yes	Yes
Kikuya, 2000	Unclear	Unclear	Yes	Yes (ABPM)	No -adjusted for 24-hour BP in day/night analysis	Not relevant	Yes	No but ABPM	No	Yes (ABPM)	Yes	Adjusted for 24-hour BP in day/night analysis
Mancia, 2007	Unclear	Unclear	Yes	Yes (ABPM)	No - adjusted for 24-hour mean in day/ night analysis	Not relevant	Yes	No but ABPM	No	Yes (ABPM)	Yes	Adjusted for 24-hour mean in day/ night analysis
Mena, 2014	Yes	Unclear	Unclear	Yes (ABPM)	Yes	Not relevant	No	No but ABPM	No	Yes	Yes	Yes
Palatini, 2014	Unclear	Unclear	Unclear	Yes (ABPM)	Yes	Not relevant	Yes	Yes - untreated patients	No	Yes (ABPM)	Yes	Yes

Paper, Year	Study design characteristics				Potential confounders							
	Appropriate cuff size used	Consistent reading arm	Consistent device used	Same person taking readings	Appropriate adjustment for mean BP	Regression to mean considered (if relevant)	Diurnal/ seasonal variation considered	Medication change during measurement period limited	Medication change during follow-up limited	Measurement before follow-up	Definition of a single measurement given	Main analysis (yes or reason for exclusion)
Pierdomenico, 2005	Unclear	Unclear	Yes	Yes (ABPM)	Yes	Not relevant	No	No but ABPM	No	Yes (ABPM)	Yes	No extractable data
Pierdomenico, 2006	Yes	Unclear	Yes	Yes (ABPM)	Yes	Not relevant	Yes	No but ABPM	No	Yes (ABPM)	Yes	Yes
Pierdomenico, 2009	Yes	Unclear	Yes	Yes (ABPM)	Yes	Not relevant	Yes	No but ABPM	No	Yes (ABPM)	Yes	Yes
Pringle, 2003	Yes	Yes	No	Yes (ABPM)	Yes	Not relevant	Yes	No but ABPM	No	Yes (ABPM)	Yes	Yes
Rothwell, 2010: ASCOT-BPLA ABPM substudy	Unclear	Unclear	Yes	Yes (ABPM)	Unclear	No	Yes	Yes (ABPM)	No	Yes (ABPM)	Yes	Adjustment for mean unclear
Verdecchia, 2007	Unclear	Unclear	No	Yes (ABPM)	Yes	Not relevant	Yes	No but ABPM	No	Yes (ABPM)	Yes	Yes
Long-term BP variability measured through clinic BP monitoring												
Arashi, 2015	Unclear	Unclear	Mercury sphyg	Unclear	No - diastolic analysis adjusted for systolic mean	Yes	No	No	No	No	Unclear	Follow-up and measurement confounded
Blacher, 2015	Unclear	Unclear	Yes	Unclear	Yes	Not relevant	No	No	No	Unclear	Yes	Follow-up and measurement confounded
Carr, 2012	Unclear	Unclear	Yes	No	Yes	Yes	Yes	No	No	No	Yes	Treatment adherence low
Eguchi, 2012: clinic analyses	Unclear	Unclear	Mercury sphyg	Unclear	Yes	Not relevant	No	No	No	Unclear	Yes	Measurement and follow-up confounded
Gao, 2014	Unclear	Unclear	Unclear	Unclear	Yes	Not relevant	No	No	No	No	Unclear	Follow-up and measurement confounded

Paper, Year	Study design characteristics				Potential confounders							
	Appropriate cuff size used	Consistent reading arm	Consistent device used	Same person taking readings	Appropriate adjustment for mean BP	Regression to mean considered (if relevant)	Diurnal/ seasonal variation considered	Medication change during measurement period limited	Medication change during follow-up limited	Measurement before follow-up	Definition of a single measurement given	Main analysis (yes or reason for exclusion)
Hara, 2014	Yes	Yes	Mercury sphyg	Unclear	Yes	Yes	No	No but adjusted for in secondary analysis	Yes	No	Yes	Follow-up and measurement confounded
Hata, 2013	Unclear	Unclear	Yes	Unclear	Yes	Not relevant	No	No but results similar in those who did not change	No	Yes	Yes	Yes
Hsieh, 2012	Yes	Unclear	Yes	Unclear	Yes	Not relevant	No	No	No	Unclear	Yes	No extractable data
Kawai, 2013	Unclear	Unclear	No	Unclear	Yes	Not relevant	No	Yes	No	Unclear	Yes	Follow-up and measurement confounded
Kostis, 2014	Unclear	Unclear	Yes	Unclear	Yes	No	No	No but adherence high, results in cross-over patients similar	No	No	Yes	Yes
Lau, 2014a	Unclear	Unclear	Yes	Unclear	Yes	Not relevant	No	No but adjusted for medication use	No	Unclear	Yes	Follow-up and measurement confounded
Lau, 2014b	Unclear	Unclear	Yes	Unclear	Yes	Not relevant	No	No - only adjusted for baseline medication	No	Unclear	Yes	Follow-up and measurement confounded
Mallamaci, 2013	Yes	Yes	Mercury sphyg	No	Yes	Not relevant	No	No	No	Unclear	Yes	Follow-up and measurement confounded
Mancia, 2012	Unclear	Unclear	Mercury sphyg	Unclear	Yes	No	No	Yes	Yes	No	Yes	No extractable data
McMullan, 2013	Unclear	Unclear	Yes	Unclear	Yes	Not relevant	No	No (adherence low)	No	Yes	Yes	Medication adherence low
Muntner, 2015	Unclear	Unclear	Unclear	Unclear	Yes	Yes	No	No but adjusted for medication use	No	Yes	Yes	Yes

Paper, Year	Study design characteristics				Potential confounders							
	Appropriate cuff size used	Consistent reading arm	Consistent device used	Same person taking readings	Appropriate adjustment for mean BP	Regression to mean considered (if relevant)	Diurnal/ seasonal variation considered	Medication change during measurement period limited	Medication change during follow-up limited	Measurement before follow-up	Definition of a single measurement given	Main analysis (yes or reason for exclusion)
Poortvliet, 2012	Unclear	Unclear	Yes	Unclear	Yes	Not relevant	No	No but trial of statins	No	Yes	Yes	Yes
Rakugi, 2015	Unclear	Unclear	Unclear	Unclear	Yes	No	No	Unclear (trial of antihypertensives, adherence unclear)	No	No	Unclear	Measurement and follow-up confounded
Rossignol, 2015	Unclear	Yes	No	Unclear	No	Not relevant	No	Unclear (trial of antihypertensives, adherence unclear)	Unclear	No	Unclear	No extractable data for review outcomes
Rothwell, 2010: ASCOT-BPLA	Unclear	Unclear	Yes	Unclear	Yes	No	No	No	No	Unclear	Yes	Follow-up and measurement confounded
Rothwell, 2010: Dutch TIA	Unclear	Unclear	Mercury sphyg	Unclear	Yes	Not relevant	No	No	No	Unclear	Yes	Follow-up and measurement confounded
Rothwell, 2010: ESPS-1	Unclear	Yes	Mercury sphyg	Unclear	Yes	Not relevant	No	Analysis of placebo group only	Yes	Unclear	Yes	Follow-up and measurement confounded
Rothwell, 2010: UK-TIA	Unclear	Unclear	Mercury sphyg	Unclear	Yes	Not relevant	No	RCT of aspirin only	No	Yes	Yes	Yes
Shimbo, 2012	Yes	Yes	Mercury sphyg	Unclear	Yes	Not relevant	No	No but medication adjusted for in analysis	Yes	Yes	Yes	Yes
Suchy-Dicey, 2013	Unclear	Yes	Mercury sphyg	Unclear	Yes	Not relevant	No	Yes (users of changing medication excluded)	No	Yes	Yes	Yes
Wei, 2013	Unclear	Yes	Manual sphyg	Unclear	Yes	Not relevant	No	No	No	Unclear	Yes	Follow-up and measurement confounded

Paper, Year	Study design characteristics				Potential confounders							
	Appropriate cuff size used	Consistent reading arm	Consistent device used	Same person taking readings	Appropriate adjustment for mean BP	Regression to mean considered (if relevant)	Diurnal/ seasonal variation considered	Medication change during measurement period limited	Medication change during follow-up limited	Measurement before follow-up	Definition of a single measurement given	Main analysis (yes or reason for exclusion)
Yu, 2014	Yes	Yes	Mercury sphyg	Unclear	Yes	No	No	No	No	No	Yes	Follow-up and measurement confounded
Mid-term BP variability measured through home BP monitoring												
Asayama, 2013	Unclear	Unclear	Yes	Yes (home)	Yes	Not relevant	Yes	Yes	No	Yes (home)	Yes	Yes
Hashimoto, 2012	Unclear	Unclear	Yes	Yes (home)	Yes	Not relevant	No	No but home	No	Yes (home)	Yes	Yes
Johanssen, 2012	Unclear	Unclear	Yes	Yes (home)	Yes	Not relevant	Yes	No but home	No	Yes (home)	Yes	Yes
Kikuya, 2008	Unclear	Unclear	Yes	Yes (home)	Yes	No	No	No but adjusted for medication use	No	Yes (home)	Yes	Yes

Table 4.4: QUIPS risk of bias assessment

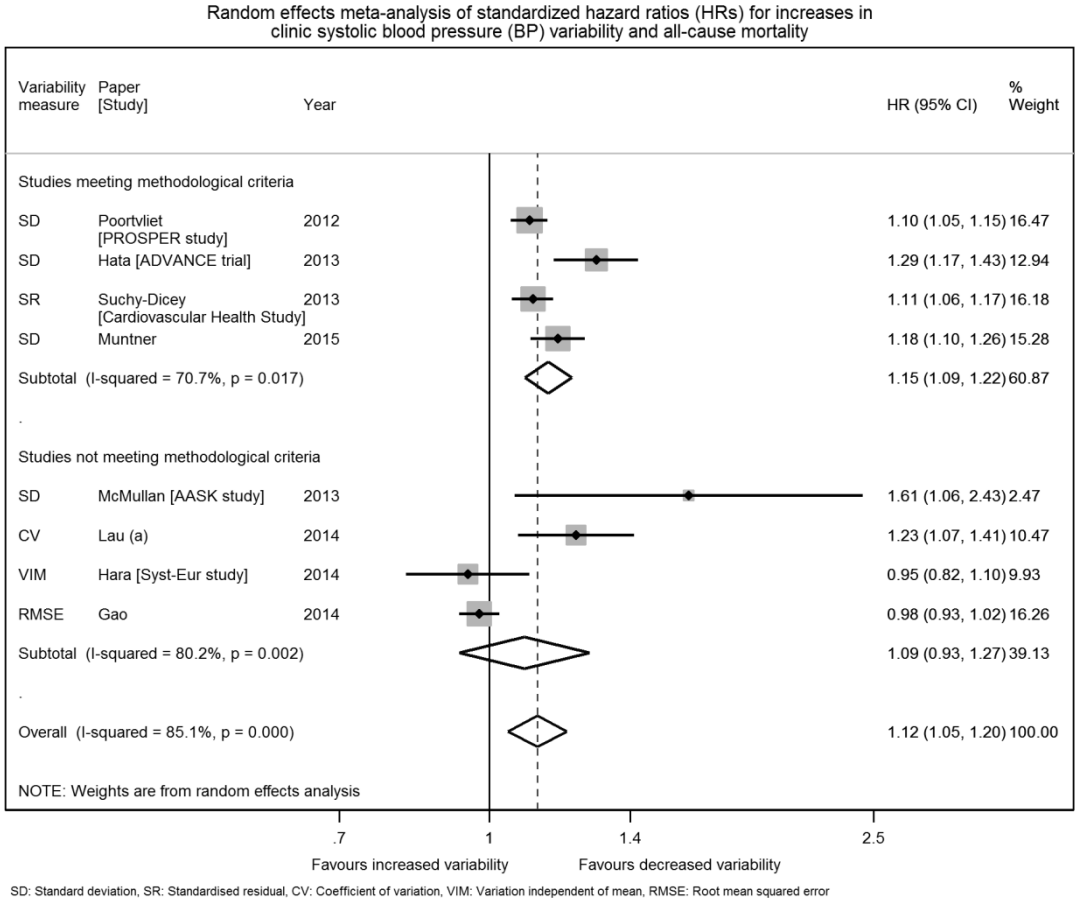
Paper, Year	Study	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Statistical Analysis and Reporting
Short-term BP variability measured through ABPM							
Bjorklund, 2004	ULSAM (observational)	low	moderate	low	low	moderate	low
Eguchi, 2012	Observational (ABPM)	moderate	low	low	low	moderate	low
Gavish, 2009	Observational	moderate	low	moderate	low	moderate	low
Gavish, 2015	Observational	moderate	low	moderate	low	low	low
Hansen, 2010	IDACO (observational)	moderate	low	low	low	low	low
Kikuya, 2000	Ohasama (observational)	moderate	low	low	low	moderate	low
Mancia, 2007	PAMELA (observational)	moderate	low	low	low	moderate	low
Mena, 2014	IDACO (observational)	moderate	low	low	low	low	low
Palatini, 2014	ABP-International (observational)	moderate	low	low	low	low	low
Pierdomenico, 2005	Abruzzo, Italy (observational)	moderate	moderate	low	moderate	low	high
Pierdomenico, 2006	Abruzzo, Italy (observational)	moderate	moderate	low	moderate	low	low
Pierdomenico, 2009	Abruzzo, Italy (observational)	moderate	moderate	low	moderate	low	low
Pringle, 2003	Syst-Eur trial	moderate	low	moderate	low	low	low
Rothwell, 2010	ASCOT-BPLA trial ABPM substudy (subset of stroke/TIA patients)	low	low	low	low	moderate	low
Verdecchia, 2007	PIUMA (observational)	moderate	low	low	moderate	low	moderate
Long-term BP variability measured through clinic BP monitoring							
Arashi, 2015	HIJ-CREATE trial	moderate	moderate	moderate	high	moderate	low
Blacher, 2015	SU.FOL.OM3 trial	low	low	low	high	low	high
Carr, 2012	MRC Elderly Trial	moderate	moderate	moderate	moderate	low	low
Eguchi, 2012	Observational (clinic)	moderate	low	low	high	low	low
Gao, 2014	Observational	low	low	moderate	high	high	low
Hara, 2014	Syst-Eur trial	moderate	low	low	high	low	low
Hata, 2013	ADVANCE trial	low	low	low	low	low	low
Hsieh, 2012	Observational	low	low	low	high	low	low

Paper, Year	Study	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Statistical Analysis and Reporting
Kawai, 2013	NOAH (observational)	low	moderate	moderate	moderate	low	low
Kostis, 2014	SHEP (trial)	moderate	low	moderate	low	low	low
Lau, 2014a	Observational	low	high	low	high	low	low
Lau, 2014b	Observational	low	low	low	high	low	low
Mallamaci, 2013	Observational	moderate	low	moderate	high	low	low
Mancia, 2012	ELSA trial	moderate	low	low	high	low	moderate
McMullan, 2013	AASK (trial)	moderate	low	moderate	moderate	low	low
Muntner, 2015	ALLHAT (trial)	low	low	low	low	low	low
Poortvliet, 2012	PROSPER trial	low	low	low	low	low	low
Rakugi, 2015	COLM trial(211)	low	low	high	high	low	moderate
Rossignol, 2015	HEAAL trial	moderate	low	high	high	high	moderate
Rothwell, 2010	ASCOT-BPLA trial (subset of stroke/TIA patients)	moderate	low	low	high	low	low
Rothwell, 2010	Dutch-TIA trial(212) (subset of stroke/TIA patients)	low	low	moderate	high	low	low
Rothwell, 2010	ESPS-1 trial(213) (subset of stroke/TIA patients)	low	low	moderate	high	low	low
Rothwell, 2010	UK-TIA trial(214) (subset of stroke/TIA patients)	low	low	moderate	low	low	low
Shimbo, 2012	Women's health initiative (observational)	low	moderate	moderate	low	low	low
Suchy-Dicey, 2013	Cardiovascular health study (observational)	moderate	low	moderate	low	low	low
Wei, 2013	PROBE trial	low	moderate	moderate	high	moderate	low
Yu, 2014	Observational	low	moderate	low	high	low	low
Mid-term BP variability measured through home BP monitoring							
Asayama, 2013	Ohasama (observational)	moderate	low	low	low	low	low
Hashimoto, 2012	Ohasama (observational)	moderate	low	low	low	low	low
Johanssen, 2012	Health 2000 study (observational)	low	low	low	low	low	low
Kikuya, 2008	Ohasama (observational)	moderate	moderate	low	low	low	low

4.3.2. Long term variability in clinic blood pressure

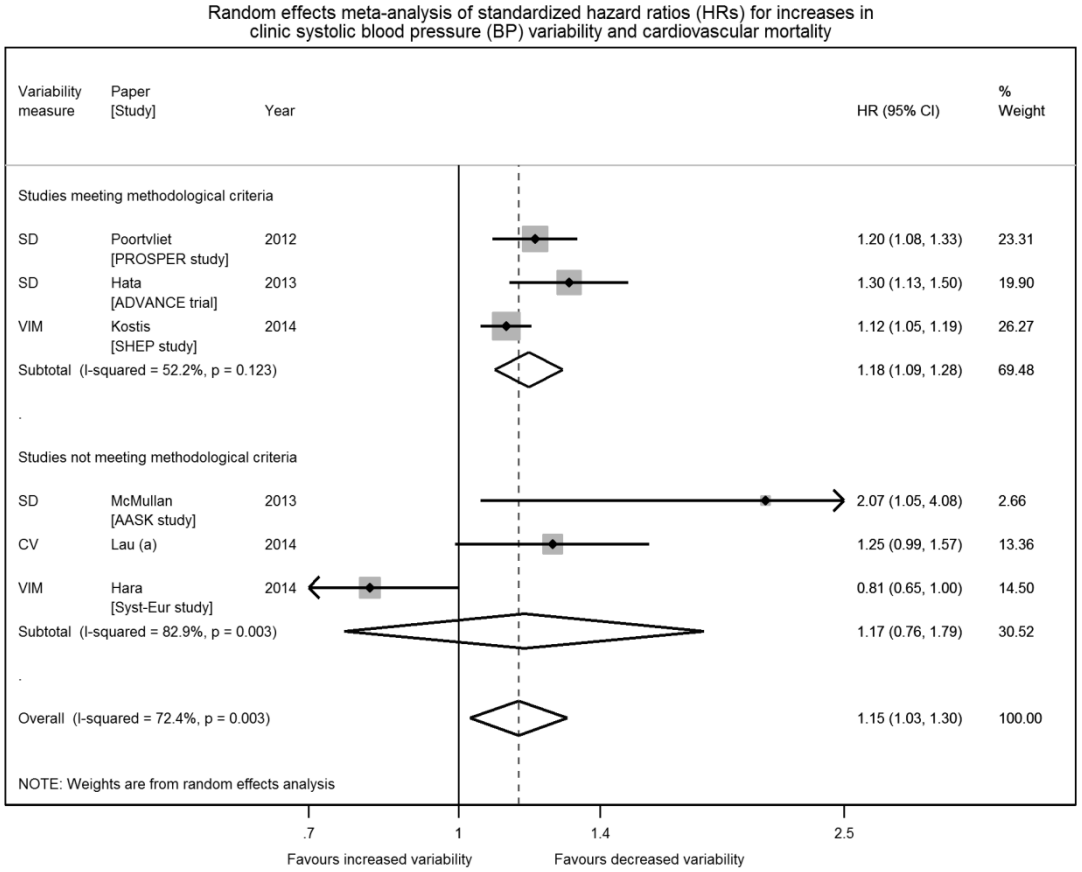
Twenty-four papers reported results from twenty-seven distinct studies in which clinic BP was measured and results were reported in sufficient detail for extraction in twenty-four studies. Meta-analyses of four studies meeting pre-specified methodological criteria showed that increased variability in systolic BP was significantly associated with an increased risk of death (Figure 4.2; HR per SD of variability measure/ standardized HR = 1.15, 95% CI [1.09 to 1.22]). A study in patients with previous stroke or vascular disease was responsible for significant heterogeneity (I-squared = 70.7%, p=0.017) which was reduced after removal of the study and did not significantly change the estimated hazard ratio (HR = 1.12, 95% CI [1.08 to 1.16], I-squared=34.9%, p=0.215). When a further four studies not meeting methodological criteria were included in sensitivity analyses, results were unchanged (HR = 1.12, 95% CI [1.05 to 1.20]).

Figure 4.2: Association of clinic systolic blood pressure variability with all-cause mortality



Blood pressure variability was also associated with cardiovascular mortality across three studies (Figure 4.3; HR = 1.18, 95% CI [1.09 to 1.28]), and was unchanged in sensitivity analysis (HR = 1.15, 95% CI [1.03 to 1.30]).

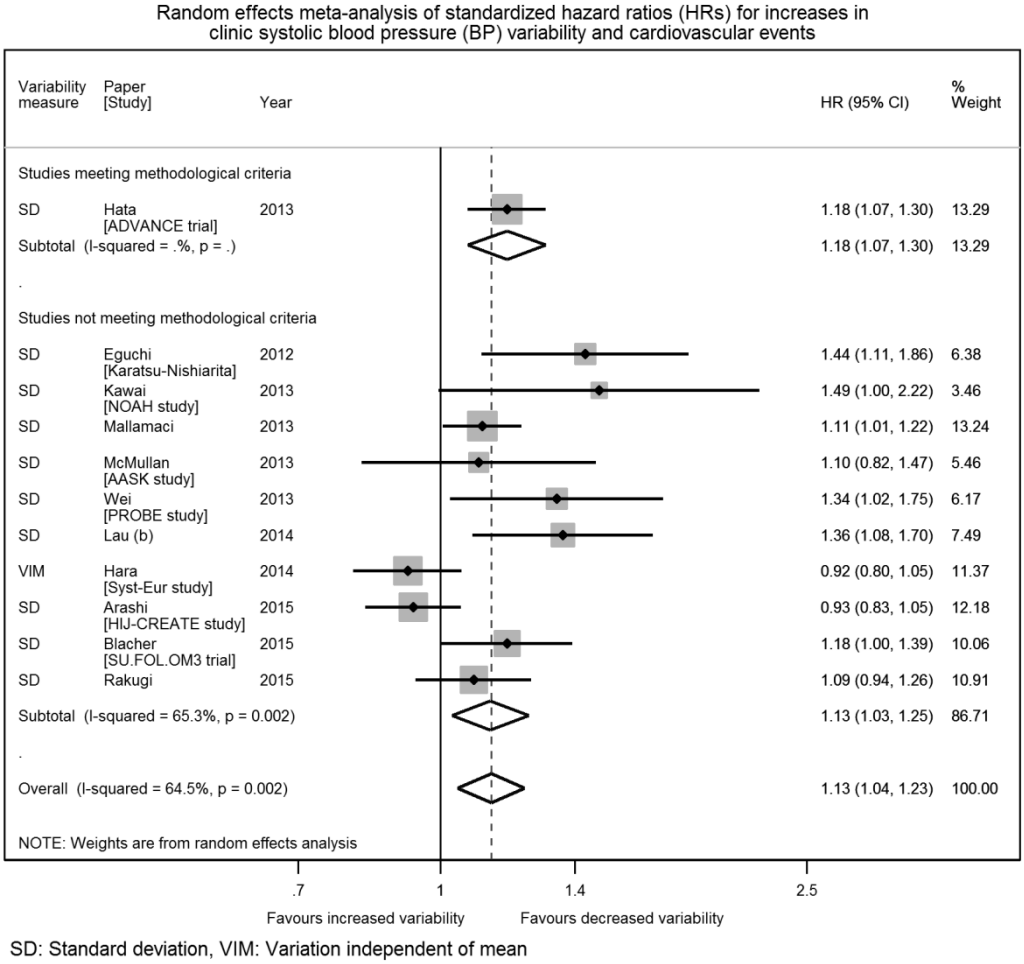
Figure 4.3: Association of clinic systolic blood pressure variability with cardiovascular mortality



SD: Standard deviation, VIM: Variation independent of mean, CV: Coefficient of variation

Eleven studies examined systolic BP variability and CVD events, but only one met methodological criteria. However, results from both the single study and analyses including all studies showed similarly significant associations (Figure 4.4; HR = 1.18, 95% CI [1.07 to 1.30] and HR = 1.13, 95% CI [1.04 to 1.23] respectively).

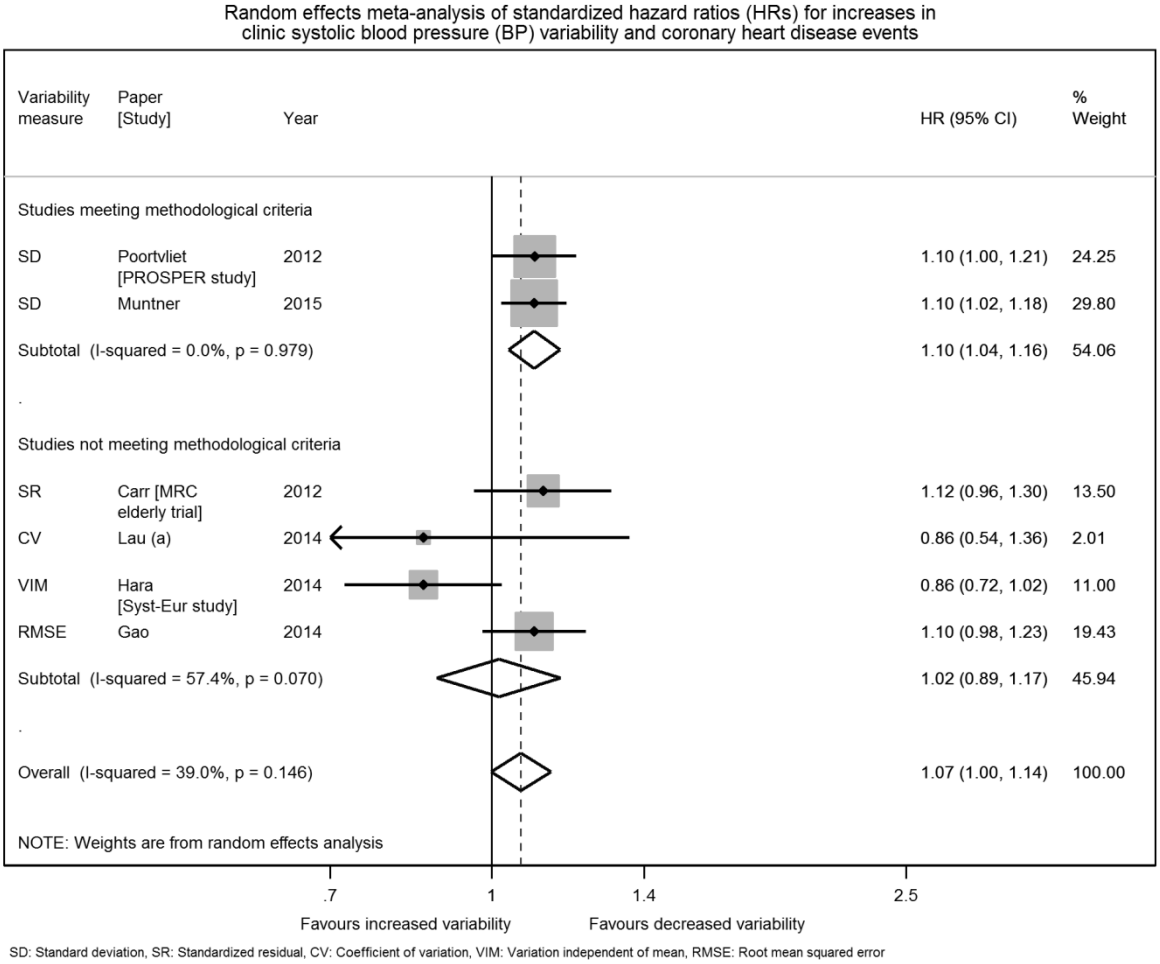
Figure 4.4: Association of clinic systolic blood pressure variability with cardiovascular events



SD: Standard deviation, VIM: Variation independent of mean

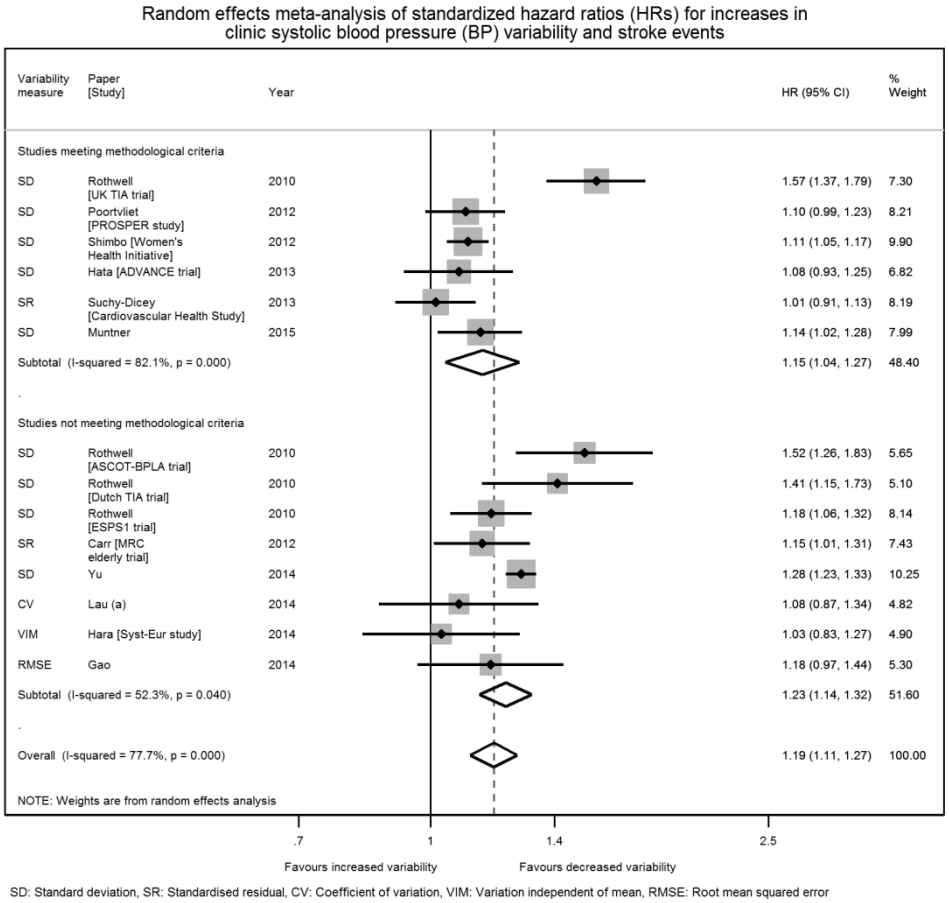
Two studies meeting methodological criteria examined systolic BP variability and coronary heart disease events, showing a significant relationship (Figure 4.5; HR = 1.10, 95% CI [1.04 to 1.16]) which was unchanged in sensitivity analyses including an additional four studies (HR=1.07, 95% CI [1.00 to 1.14]).

Figure 4.5: Association of clinic systolic blood pressure variability and coronary heart disease events



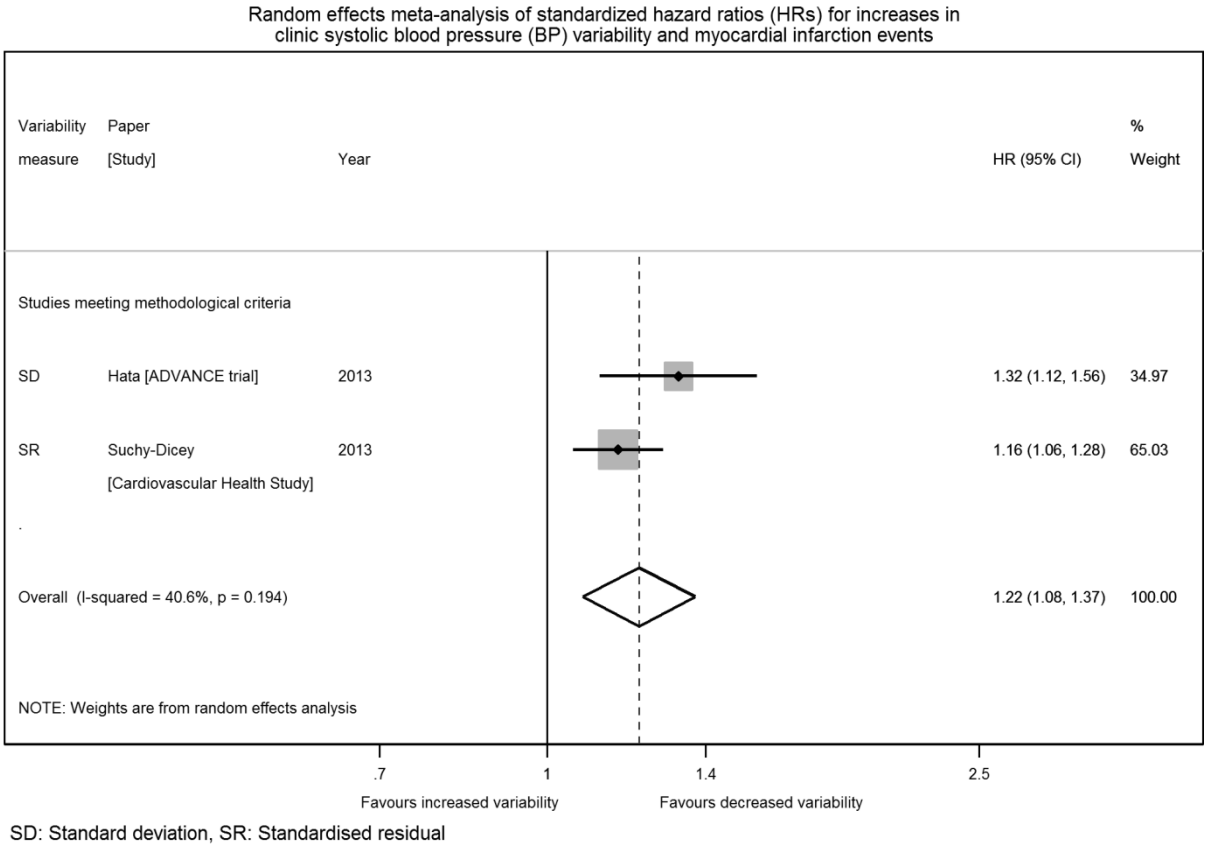
Fourteen studies reported results for stroke events, for which systolic BP variability was a significant predictor in main analysis of six studies (Figure 4.6; HR = 1.15, 95% CI [1.04 to 1.27]). The HR from the UK-TIA trial was significantly larger than the HRs reported by other studies and was responsible for the considerable heterogeneity between pooled studies (I-squared = 82.1%, p<0.001). Removing this study reduced heterogeneity and did not significantly alter the main results (HR = 1.10, 95% CI [1.04 to 1.14]; I-squared=0.0%, p=0.618). Results from sensitivity analysis including a further eight studies were also similar (HR = 1.19, 95% CI [1.11 to 1.27]).

Figure 4.6: Association of clinic systolic blood pressure variability with stroke events



Finally, meta-analysis of two studies showed that BP variability is significantly associated to risk of myocardial infarction events (Figure 4.7; HR = 1.22, 95% CI [1.08 to 1.37]).

Figure 4.7: Association of clinic systolic blood pressure variability with myocardial infarction events



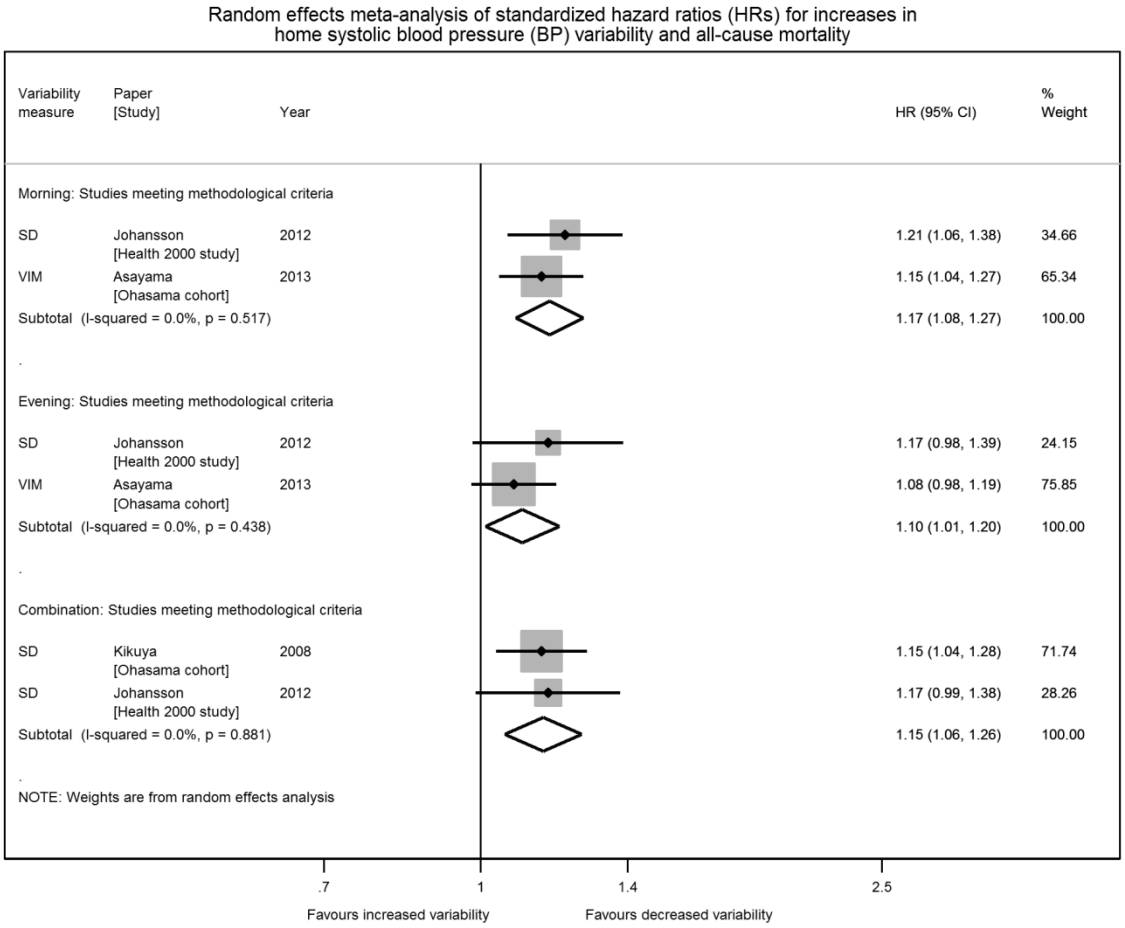
SD: Standard deviation, SR: Standardised residual

4.3.3. Mid-term variability in home blood pressure

Home blood pressure was measured in only two distinct studies, reported in four papers. Although results from all papers met the pre-specified methodological criteria, the outcomes studied were heterogeneous meaning I could only perform formal meta-analysis for all-cause mortality. However, systolic BP variability, when calculated from morning, evening or morning and evening BP measurements, was a significant predictor of death

(Figure 4.8). The extracted hazard ratios for other outcomes are given in Table 4.5 and supported an association of home systolic BP variability with the majority of outcomes.

Figure 4.8: Association of home systolic blood pressure variability with all-cause mortality



SD: Standard deviation, VIM: Variation independent of mean

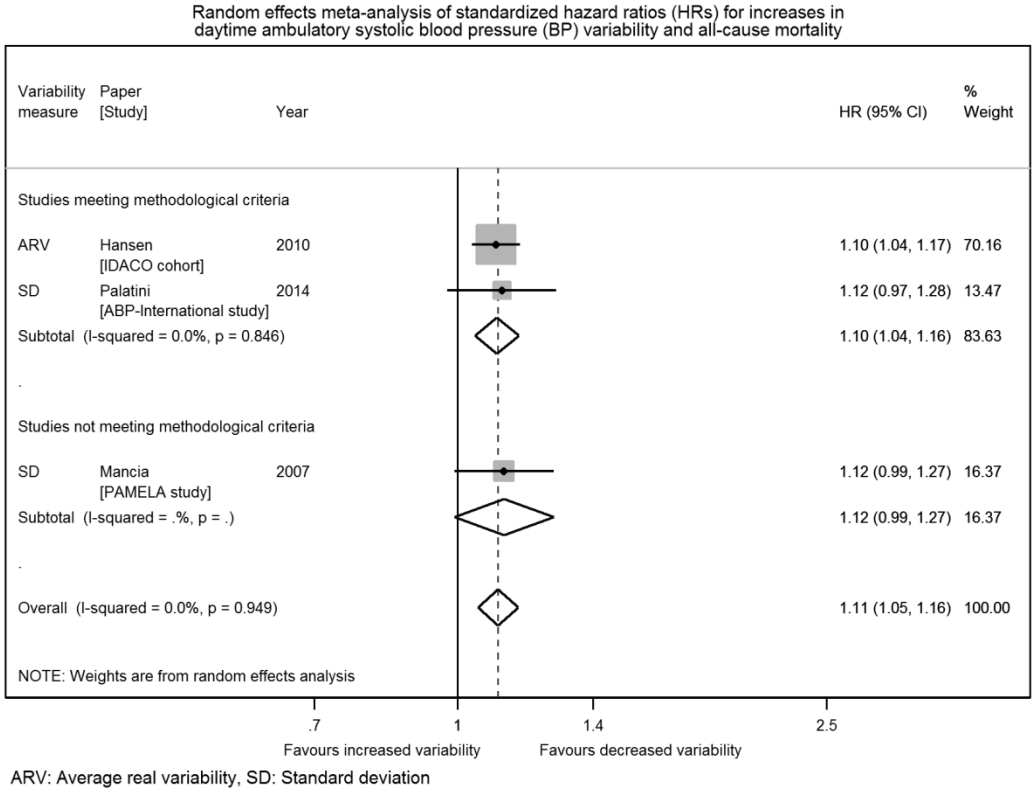
Table 4.5: Reported associations of home systolic blood pressure variability with review outcomes

	Morning measurements			Evening measurements			Morning and evening measurements		
Outcome	**Variability measure**	**Paper [Study], year**	**HR (95% CI)**	**Variability measure**	**Paper [Study], year**	**HR (95% CI)**	**Variability measure**	**Paper [Study], year**	**HR (95% CI)**
CVD mortality	VIM	Asayama [Ohasama], 2013	1.26 (1.07, 1.49)	VIM	Asayama [Ohasama], 2013	1.23 (1.05, 1.45)	SD	Kikuya [Ohasama], 2008	1.16 (0.99, 1.36)
CHD mortality	SD	Hashimoto [Ohasama], 2012	0.84 (0.59, 1.19)	SD	Kikuya [Ohasama], 2008	0.99 (0.79, 1.25)	SD	Kikuya [Ohasama], 2008	1.02 (0.81, 1.29)
Stroke mortality	SD	Hashimoto [Ohasama], 2012	1.47 (1.11, 1.95)	SD	Kikuya [Ohasama], 2008	1.38 (1.12, 1.70)	SD	Kikuya [Ohasama], 2008	1.31 (1.05, 1.64)
Non-CVD mortality	SD	Kikuya [Ohasama], 2008	1.18 (1.04, 1.34)	SD	Kikuya [Ohasama], 2008	1.07 (0.94, 1.22)	SD	Kikuya [Ohasama], 2008	1.15 (1.01, 1.31)
Cerebral infarction mortality	SD	Hashimoto [Ohasama], 2012	1.88 (1.31, 2.69)	SD	Kikuya [Ohasama], 2008	1.42 (1.08, 1.86)	SD	Kikuya [Ohasama], 2008	1.47 (1.11, 1.95)
CVD events	SD	Johansson [Health 2000], 2012	1.17 (1.02, 1.34)	SD	Johansson [Health 2000], 2012	1.08 (0.93, 1.26)	SD	Johansson [Health 2000], 2012	1.06 (0.93, 1.22)
Stroke events	VIM	Asayama [Ohasama], 2013	1.14 (1.00, 1.30)	VIM	Asayama [Ohasama], 2013	1.06 (0.93, 1.21)	-	-	-

4.3.4. Short term variability in ambulatory blood pressure

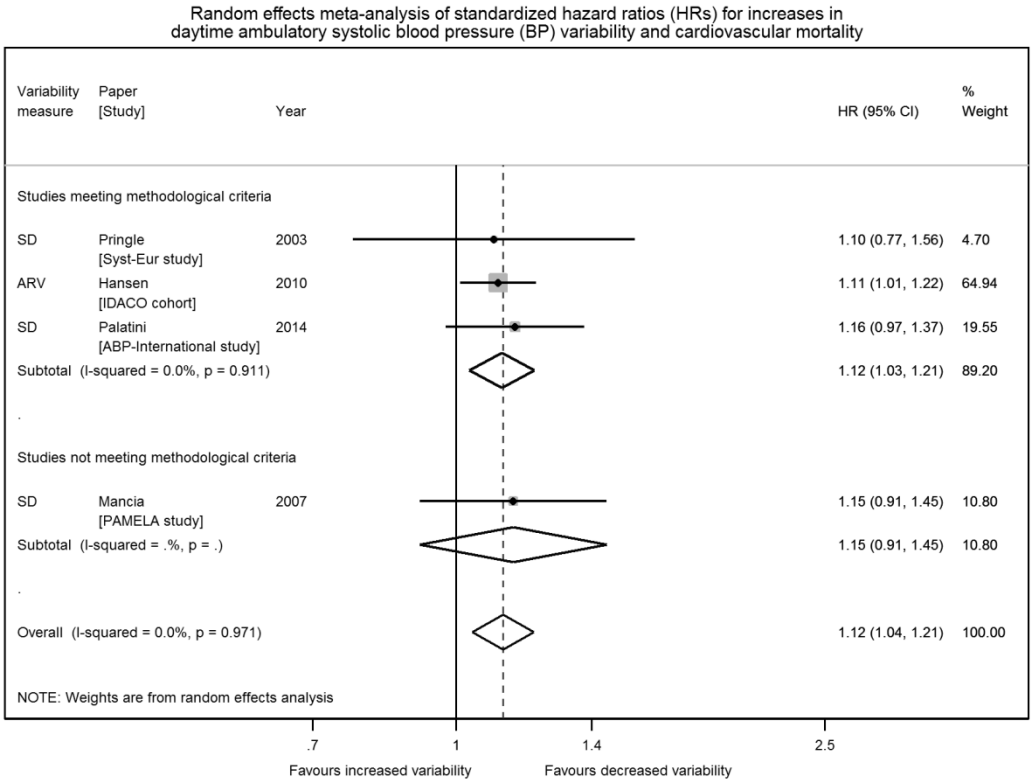
Ambulatory BP monitoring was carried out in eleven studies reported in fifteen papers, of which five studies did not meet pre-specified methodological criteria for main analyses. However, several studies were not included in the analyses due to overlap with two large studies that combined data from several different cohorts: the Ohasama(184–186) and ULSAM(166) studies were included in the IDACO cohort(70,180) and the Ohasama,(184–186) Eguchi et al.,(178) Verdecchia et al.,(197) and Pierdomenico at al.(188–190) studies were included in the ABP-International cohort(192). Three studies examined daytime systolic BP variability and all-cause mortality, of which two were eligible for inclusion in the main analysis and showed a significant association between increased daytime variability and risk of death (Figure 4.9; standardized HR = 1.12, 95% CI [1.04 to 1.16]). Including results from the third study did not significantly change the results (HR = 1.11, 95% CI [1.05 to 1.16]).

Figure 4.9: Association of daytime ambulatory systolic blood pressure variability with all-cause mortality



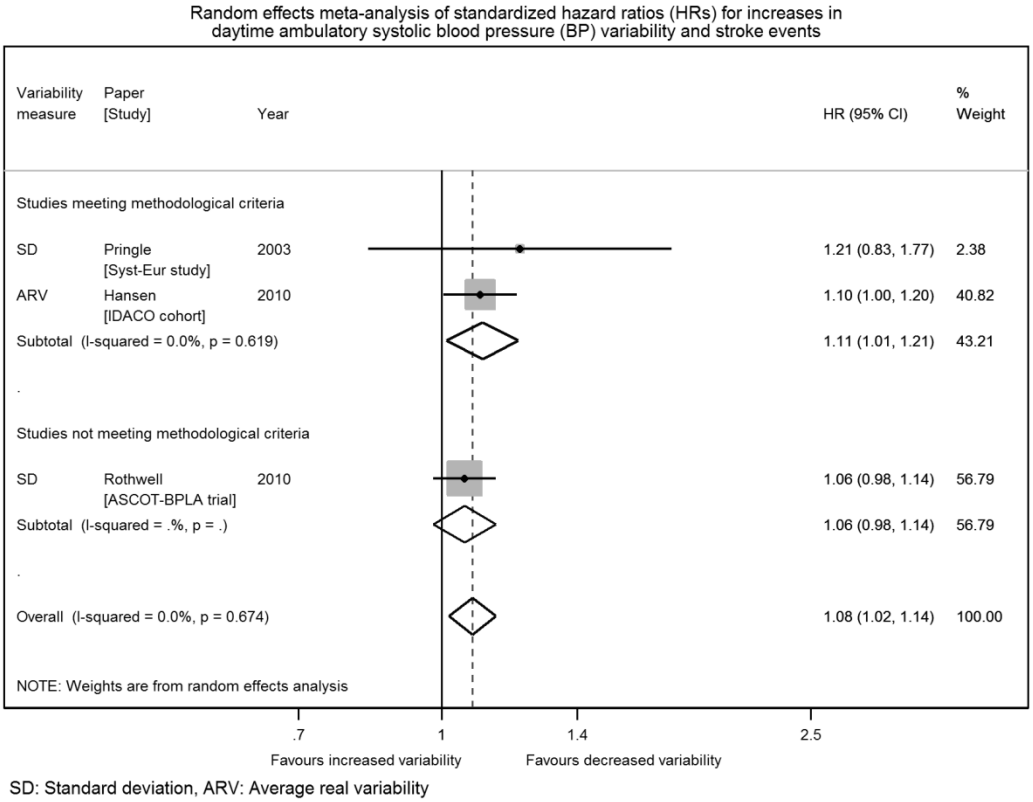
Daytime ambulatory BP variability was also associated with cardiovascular mortality in three studies with low risk of bias (Figure 4.10; HR=1.12, 95% CI [1.03 to 1.21]) which was unchanged when including an additional study in sensitivity analyses (HR=1.12, 95% CI [1.04 to 1.21]). Daytime BP variability was significantly associated with increased risk of stroke in main analysis (Figure 4.11; HR = 1.11, 95% CI [1.01 to 1.21]) and sensitivity analysis (HR = 1.08, 95% CI [1.02 to 1.14]).

Figure 4.10: Association of daytime systolic ambulatory blood pressure variability with cardiovascular mortality



SD: Standard deviation, ARV: Average real variability

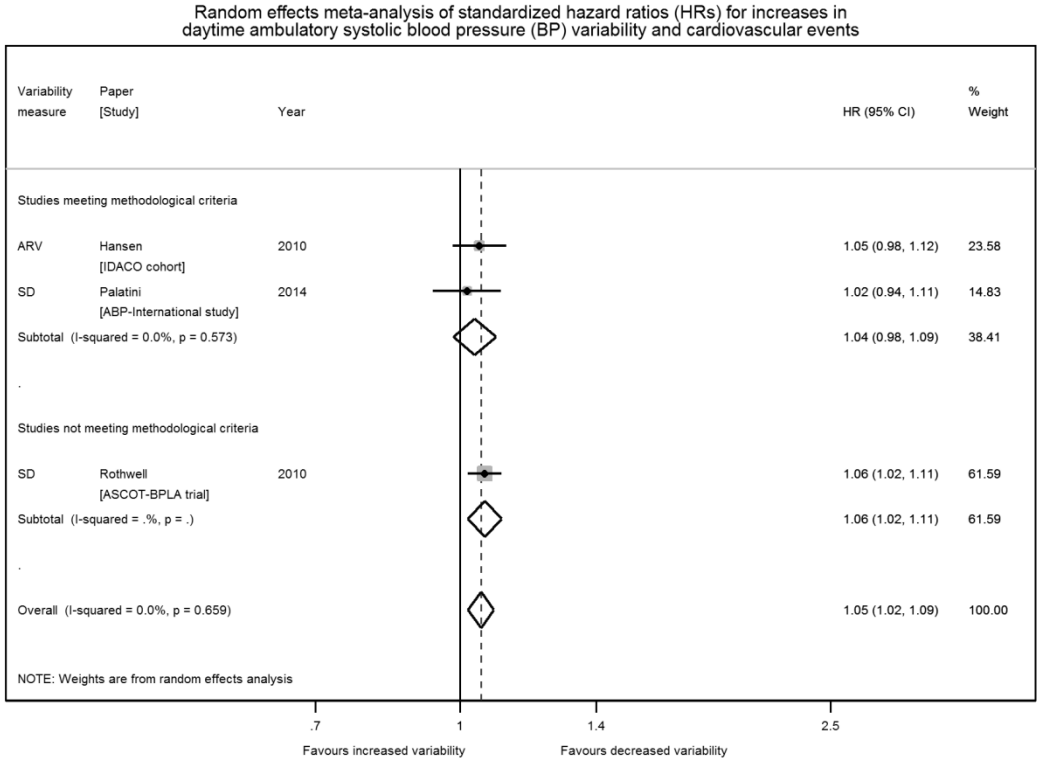
Figure 4.11: Association of daytime ambulatory systolic blood pressure variability with stroke events



SD: Standard deviation, ARV: Average real variability

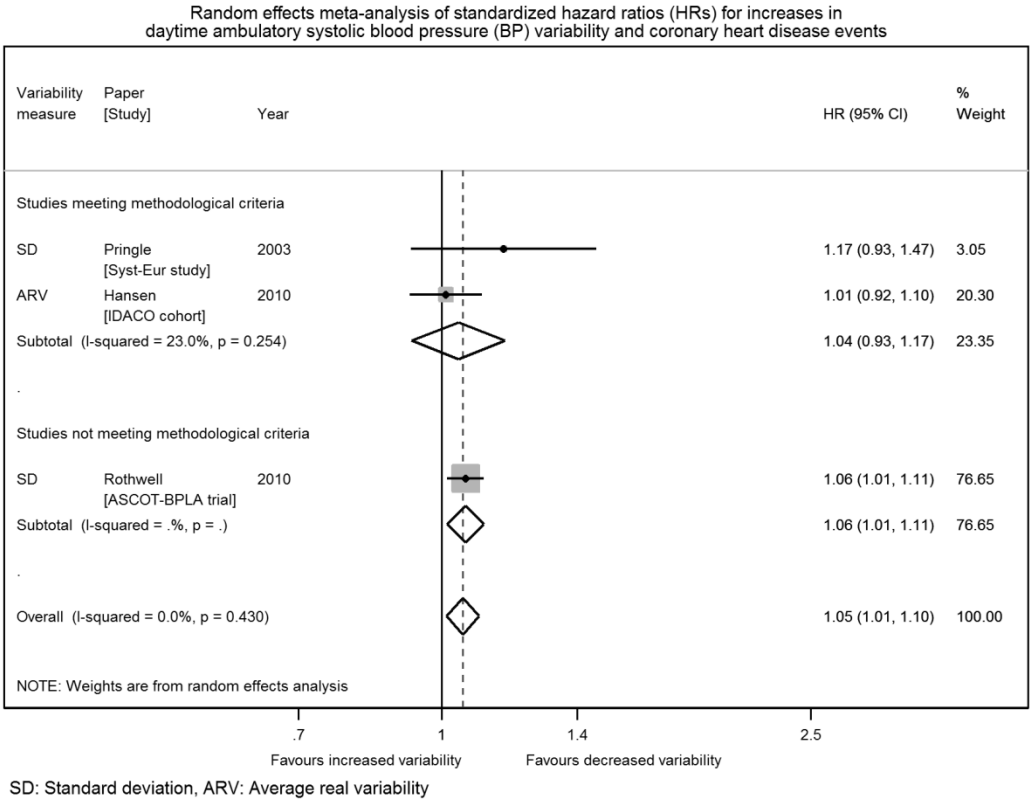
In studies with low risk of bias, there was no association between daytime BP variability and cardiovascular disease events (Figure 4.12; HR=1.04, 95% CI [0.98 to 1.09]), or coronary heart disease events (Figure 4.13; HR=1.01, 95% CI [0.93 to 1.09]). However, these associations did become significant in sensitivity analyses after the addition of results from a single study in both cases (HR=1.05, 95% CI [1.02 to 1.09] and HR=1.05, 95% CI [1.01 to 1.10] respectively).

Figure 4.12: Association of daytime ambulatory systolic blood pressure variability with cardiovascular events



SD: Standard deviation, ARV: Average real variability

Figure 4.13: Association of daytime ambulatory systolic blood pressure variability with coronary heart disease events



SD: Standard deviation, ARV: Average real variability

Across all outcomes, results were dominated by the two largest studies, with the addition of smaller studies having little impact. This was also the case when considering variability in night-time readings (Appendix B, Figures B.1 to B.5) or across 24-hours (Appendix B, Figures B.6 to B.10), where results were similar.

4.3.5. Publication bias and small study effects

Across long, mid and short-term variabilities and all outcomes, there was no evidence of small study effects according to Egger's test. Results for long term variability in clinic blood pressure are robust to the addition of more than 20 null effect studies, except for the myocardial infarction outcome, where only a single null effect study would nullify the results. The addition of a single null effect study would reduce the results for home BP

variability to non-significance. Results for ambulatory blood pressure are robust to the addition of between one and six null effect studies, depending on outcome and period of measurement.

4.4. Discussion

This systematic review has comprehensively assessed the literature for evidence of an independent association between long term (clinic), mid-term (home) and short term (ambulatory) blood pressure variability with cardiovascular outcomes and mortality. Long term variability in clinic BP measurements was shown to be significantly associated with all-cause and CVD mortality, CVD and CHD events, stroke and myocardial infarction, independently of mean BP. Data were limited for mid- and short term blood pressure variability (measured through home and ambulatory monitoring respectively), but broadly supported the associations found for long term variability.

In this review, across long, mid- and short term variabilities, the magnitude of the association of BP variability with coronary heart disease events was generally smaller than the association with stroke events. However in the case of long-term variability in particular, considerably more studies considered stroke outcomes and confidence intervals did overlap. It is possible that a large part of the observed association of BP variability with overall CVD events may be driven by cerebrovascular events, but this requires further investigation.

A recent review indicated that morning blood pressure surge was associated with stroke risk independently of mean BP,(215) suggesting that in some cases the onset of stroke may be caused by such short-term peaks in blood pressure. This may be true in particular for haemorrhagic stroke where BP readings taken shortly after the event have been shown to

be significantly higher than usual levels.(216) Although these surges would not be identified in their entirety through longer-term monitoring, less frequent monitoring may detect elements of a surge, subsequently inflating long-term BP variability. This would be consistent with the fact that, when unadjusted for BP variability, reductions in mean BP are more strongly associated with stroke compared to CHD risk.(11) This suggests that stroke risk may be affected more rapidly by BP changes whereas the link with BP and CHD risk may be mediated by chronic atherosclerotic damage which develops over time.(217)

4.4.1. Strengths

This review included data from over 250,000 people and was the first to compare the association of BP variability in the long, mid- and short term with cardiovascular and mortality outcomes. I paid particular attention to the study design and analysis factors which are specific to variability research and that may introduce confounding, showing that a majority of studies were of poor quality in this respect. Previous reviews did not assess study quality in this way and also included studies with few repeat BP measurements(218) or short follow-up.(179) By restricting the main analysis to studies which avoid potential confounding pitfalls, this review confirmed that the association of blood pressure variability with cardiovascular outcomes is apparent in good quality studies as well as in all relevant studies.

The results for long-term BP variability were comparable to those in previous reviews which is to be expected given the overlap of included studies.(168,169) However, the approach of using standardised hazard ratios allowed me to combine evidence regardless of the statistical measure of variability used in original analyses and the pooled results include information from a much greater number of studies than previously. For example, the meta-analysis for the association of long term systolic BP variability on stroke outcomes

included data from 14 separate studies, more than double the number in previous reviews.(168,169)

This review was also the first with sufficient data to enable meta-analysis for the association of mid- and short term BP variability with cardiovascular outcomes. A previous review of home BP variability could not perform formal meta-analysis despite including studies that considered target organ damage in addition to the hard outcomes considered here.(170) A previous review regarding day and night dipping and day-night variation in ABPM was also only able to review included studies narratively.(176) Although these results were less robust to the possibility of unpublished null effect studies; I have shown that the results for long-term variability may be considered conclusive.

4.4.2. Limitations

Participants in the included studies were primarily older adults at increased risk of cardiovascular disease from European or East Asian countries. The results of this review may not be applicable to younger, healthier individuals or those from other ethnic groups. Although results suggested that the association between BP variability and outcomes may be more pronounced in those with a history of cerebrovascular events, significant associations remained when such studies were removed in sensitivity analyses and our findings are applicable to those with and without previous events. Regression to the mean effects(219) and treatment changes may have confounded results from studies in hypertensive patients,(73,164,197) but this was accounted for in the quality assessments of each study. Furthermore, these effects would bias observed hazard ratios for variability towards the null, so the overall review conclusions would be unchanged.

I was unable to combine data in meta-analysis regarding the association of mid-term home BP variability with several outcomes. Results for short-term variability in ambulatory BP were also dominated by two large studies. Caution should be taken in interpreting these results, as more evidence from novel cohorts is required. The number of studies included in some main analyses for long-term variability was small, so the validity of these meta-analyses may also be questioned. However, a greater amount of data was included in secondary analyses and results remained similar.

It was not possible to extract results in a standardized format from all papers due to a lack of detailed reporting, despite contacting the corresponding authors of these studies to request the required data. However, we were able to include data from all but three studies so the impact of any unreported data is likely to be small. Paucity of data also prevented me from comparing the prognostic utility of different statistical measures of variability, or determining whether the magnitude of associations varied with number or timing of BP measurements.

There was considerable heterogeneity between studies in some analyses, which was due to differing study populations (e.g. those with previous vascular disease) in some cases. In other cases I had to convert the hazard ratios reported in the source papers from a categorical (e.g. from deciles(66) or tertiles(71)) to a continuous scale and this was reliant on assumptions of normality that may not necessarily hold exactly. Alternatively, using categorized variables in statistical models can inflate effect estimates and increase the chance of concluding an association exists when it does not, so it is possible these outlying studies were subject to such biases. However, not all converted hazard ratios were outliers,(161) so this is unlikely to explain all instances of substantial heterogeneity. Significant heterogeneity was reduced after removal of outlying studies in post-hoc

sensitivity analyses but results were not significantly altered. It may also be possible that studies using categories of BP variability were subject to reporting biases, whereby several different category cut-points were studied and only those found to have a significant relationship with outcomes were published. However, I demonstrated that many results for long-term BP variability were robust to the inclusion of unpublished null effect studies, and hence the impact of these issues on the overall conclusions is likely to be small.

Traditional methods for random-effects meta-analysis may produce confidence intervals that are too narrow, particularly when there are few studies and heterogeneity is large,(220) as was the case in this review. I did not use methods to correct confidence interval widths, and as such, results may be more uncertain than the presented confidence intervals suggest. However, many significant results relating to long-term BP variability are robust to a 50% increase in confidence interval width and hence the main findings are likely to have been similar had more complex adjustment methods been employed.

Data regarding confounding factors was generally poorly reported. Whilst main analyses were conducted in studies at low risk of confounding based on the three most important confounding factors, it was impractical to evaluate studies according to further criteria. Future studies of BP variability (and variability in other biological factors) should address these issues in more detail. As with all observational studies, residual confounding cannot be ruled out. This and the other limitations stated above could well be overcome using individual patient data, but such an analysis was beyond the scope of this review.

4.4.3. Implications for research and practice

The clinical mechanisms explaining the link between BP variability and cardiovascular outcomes are currently unclear. In the short term, BP is affected by behavioural and

postural changes and arterial stiffness is also thought to be important in short and long-term variability.(44,59) Poor BP control resulting in the up-titration or addition of antihypertensive medications will increase variability.(44) Evidence also suggests that different classes of antihypertensive medications have differential effects on variability,(60,67,221) with calcium channel blockers appearing to lower variability compared with other agents in stroke patients.(60) Furthermore low levels of medication adherence have been linked to increased variability,(61,222) even after adjusting for medication class, explaining approximately 0.6% of the between person variability in standard deviation of BP.(61)

It is important to place the importance of BP variability into context with that of mean BP. According to a recent meta-analyses, the standardised hazard ratio for the effect of mean BP on cardiovascular mortality was approximately 1.7 (assuming a between person standard deviation of 15 mm Hg).(8) This hazard ratio was not adjusted for BP variability and so cannot be directly compared with those estimated from this review. However, I found that increased visit-to-visit systolic BP variability was significantly associated with risk of cardiovascular related mortality (standardized HR= 1.18), independent of/ adjusting for mean BP. This indicates that although the relative associations of mean BP and BP variability with CVD mortality cannot be directly compared, BP variability is prognostically useful over and above mean BP.

Compared to other risk factors, the adjusted standardized hazard ratio for increases in cholesterol on CVD mortality is between 1.16 and 1.29 in primary prevention groups (depending on the measure of cholesterol used).(25) This suggests that BP variability may be of similar importance in determining prognosis as cholesterol measures. Considering results on a standardized scale, differences in BP variability between individuals are unlikely

to exceed three standard deviations in most cases. This would correspond to a relative increase in CVD mortality risk of $1.18^3 = 1.64$, which is relatively small compared to the effect of other key factors such as age, gender and mean BP (as discussed above). Furthermore, BP variability cannot be easily assessed by GPs in routine practice and despite some evidence that different classes of antihypertensive medication may affect BP variability differently; BP variability is not currently regarded as a modifiable risk factor.

Some measures of BP variability can be calculated easily by hand (e.g. average real variability) but calculators for other variability measures could be incorporated into electronic health records systems. This would allow GPs to consider BP variability as an additional risk factor in CVD risk assessment. This is likely to be most useful in patients whose usual risk estimate lies close to a risk threshold for treatment or for those individuals who have normal mean BP, with highly variable individual measures. The impact of such additional information on the accuracy of risk estimates and subsequent clinical management remains to be determined and is studied in detail in Chapter 5.

This chapter has established that blood pressure variability is a risk factor for cardiovascular disease even when adjusting for mean blood pressure and other traditional risk factors. As the majority of the review evidence related to long-term visit-to-visit variability in clinic BP, the utility of long-term BP variability for risk prediction is further explored in Chapter 5, where measures of long-term BP variability are incorporated into cardiovascular risk scores.

Chapter 5 Evaluating the potential for improvement in CVD risk estimation by using BP variability

In Chapter 4, I demonstrated that variability in BP is associated with CVD mortality and events, over and above mean blood pressure and other traditional risk factors. The weight of this evidence related to variability over the longer term (months and years) compared to day-by-day or hour-by-hour variability. In this chapter I build on these results by evaluating the potential for improvement in CVD risk estimation by including information about long-term BP variability in a new risk score, using data from the Clinical Practice Research Datalink (CPRD).

5.1. Introduction

The systematic review and meta-analysis described in Chapter 4 showed that the risk of cardiovascular disease was 15% higher for every standard deviation increase in blood pressure variability, independent of other traditional risk factors. This association was similar in magnitude to that of cholesterol measures with CVD.

However, a factor that is independently associated with risk in prospective studies and trials may not necessarily help to improve risk estimation when included in a risk prediction model. For example, a 2007 systematic review indicated that carotid intima media thickness (CIMT; a marker of subclinical vascular damage) was independently associated with cardiovascular disease after adjustment for age and sex.(223) When the same group of

researchers added a measure of CIMT to the Framingham risk score, the overall accuracy of estimated risk remained similar.(224)

The benefit of adding measures of BP variability into existing risk prediction scores has been little studied. A 2014 study showed that adding information about night-time ambulatory systolic BP standard deviation to models predicting cardiovascular disease did improve predictive accuracy when assessed through net reclassification improvement (NRI) or integrated discrimination improvement (IDI).(192) Such measures are more sensitive to improvement than other traditional measures of model performance e.g. c statistic, by design.(225) Whilst these newer measures may highlight small statistically significant differences in risk score accuracy, such differences are less likely to be clinically important. A similar study, which investigated the effect of adding long-term BP coefficient of variation to logistic models for cardiovascular disease, found an improvement in performance when measured by IDI, but not when measured by the c-statistic.(199) In both cases improvement statistics were potentially optimistic since model performance was compared in the same dataset as that used to develop the models, which leaves doubt over the added benefit of variability measures.(226)

The aim of this chapter was to evaluate the potential for improvement in CVD risk estimation by using BP variability in addition to traditional risk factors. Specific aims were:

1. To develop two risk scores for prediction of CVD in a derivation subsample of the data: one using traditional risk factors only, and a second additionally using BP variability information.
2. To compare the accuracy of the new risk scores with each other in both the derivation sample and a separate validation subsample.

5.2. Methods

5.2.1. Study design

I chose to undertake a cohort study using data from the Clinical Practice Research Datalink (CPRD). The CPRD is a database of electronic medical records drawn from over 600 general practices across the UK which can be linked to other health data including Office for National Statistics (ONS) mortality data, Hospital Episodes Statistics (HES) and deprivation data (linked data is available for English practices only).(227)

The study population was defined as men and women with acceptable patient records (as defined by CPRD), aged 40 to 74 on 1st January 2005, reflecting a suitable target population for primary prevention, as defined by the NHS health check scheme.(228) The study was designed as an open cohort so patients entered the study on the latest of the following dates: 1st January 2005, date of current registration with the practice plus two years, the practice up-to-standard date plus two years and coverage start date for linked data plus two years. Patients exited the study on the earliest of the following dates: date of death, transfer out date, last practice upload date, coverage end date for linked data or index date plus ten years.

Patients were excluded if they had a history of CVD prior to study entry since the intended use of the risk score is for primary prevention. Patients were also excluded if they were being treated with statins in the year prior to study entry, since these patients will generally have been identified as being at high risk of CVD previously, and again, do not reflect the target patient group for use of the risk score.

Patients were included only if their records were available for linkage to ONS/ HES data. Previous research has shown that ascertainment of myocardial infarction events is improved when using data from multiple sources(229) and it is important to capture these events accurately. It is also reasonable to assume that ascertainment of other outcomes of interest that tend to present similarly in secondary care (e.g. stroke) will also be improved by utilizing linked data. Data was additionally linked to patient-level index of multiple deprivation (IMD) data. The study protocol was approved by the CPRD's Independent Scientific Advisory Committee (protocol number 16_034).

Following protocol approval, but before data extraction, an amendment to the protocol was made to additionally exclude patients taking antihypertensive medication prior to study entry. This is because class of antihypertensive medication has been shown to be associated with BP variability(230) and subsequent stroke risk.(60,67,221) Changes in medication class and dose to control mean BP can also impact variability, as can varying levels of medication adherence,(61,222) both of which are also confounded with cardiovascular risk. It was unclear how these factors could be adequately incorporated into the analysis without over-complicating the risk score and limiting its real-word usability. Identifying medication changes in CPRD records can also be complex, particularly as those on medication are not prescribed all their medications at the same time, or at regular intervals. CPRD also only provides details of prescriptions issued, rather than those which are filled and/or the amount of medication that is subsequently taken, making measures of adherence liable to significant error. For these reasons, I decided that I could only be confident in limiting confounding due to medication change by excluding those prescribed antihypertensive medication prior to study entry, even though this would reduce the population to which the risk score could be applied.

5.2.2. Sample size calculation

I calculated the sample size required to estimate model accuracy using previously published estimates of accuracy and event rates. Estimates of the discrimination statistic (D) for the QRISK2 calculator have previously been published in a validation study (D=1.45 in men and D=1.66 in women).(231) Assuming similar discrimination of the developed risk score and a proportion censored of 95%, sample size calculations for prognostics models indicated that to estimate D with a 95% confidence interval half-width of 0.1, I required 1,368 and 1,533 CVD events in men and women respectively.(232) In the derivation study for QRISK2 (developed in a similar primary prevention population), the event rate for CVD was approximately 7 per 1000 person years,(41) hence I required approximately 2900 CVD events in total, or approximately 60,000 people in the validation dataset (and equivalent in the derivation dataset).To allow for more conservative estimates of accuracy and event rates, a total sample size of 200,000 was chosen.

5.2.3. Exposures, outcomes and covariates

Code lists used to identify outcomes and covariates are listed in Appendix C (Tables C.1 to C.12).

Exposures

The exposure in this study was blood pressure variability measured by standard deviation (SD), coefficient of variation (CV), variation independent of mean (VIM) or average real variability (ARV), as defined previously in Section 4.2.4. Blood pressure variability was calculated using the previous six BP measurements occurring at least one month apart prior to study entry, up to a maximum of 10 years. An interval of at least one month between measurements was chosen to exclude measurements taken in short succession that may

occur for reasons other than routine monitoring (e.g. for diagnosis of hypertension). Such measurements are less likely to reflect underlying long-term biological BP variability and may be influenced by other factors (e.g. monitoring of BP due to prescription of medications that may raise BP(233)). A longer interval between measurements would potentially discard large amounts of data, so a one month interval was chosen as a middle ground.

Outcomes

The primary outcome for this study was cardiovascular events, defined as a composite of myocardial infarction, coronary and ischaemic heart disease, angina, cerebrovascular and haemorrhagic stroke events and cause-specific mortality, similarly to the recommended CVD risk score in the UK, QRISK2.(41). Outcomes were identified in CPRD using READ codes and in ONS/ HES data using ICD-10 codes.

Covariates

Variables that have previously been identified as risk factors for cardiovascular disease and were included in the three primary risk scores considered in this thesis(37,41,42) were included as covariates in the analyses. Specifically, this included: age, gender, mean systolic blood pressure (mm Hg), history of hypertension, total cholesterol to high density lipoprotein cholesterol ratio (mmol/L), ethnicity, IMD score, family history of angina or myocardial infarction or stroke, smoking status (never, ex, current smoker), body mass index (kg/ m^2), history of diabetes (Type 1 or 2), history of chronic kidney disease (Stage 3-5), history of rheumatoid arthritis, history of atrial fibrillation and history of left ventricular hypertrophy.

In conjunction with the decision to exclude those on antihypertensive medication from the cohort, I also decided to remove hypertension as a covariate from the models. Those few remaining in the cohort with a code for the diagnosis of hypertension were likely to be patients with mild hypertension not requiring medication, those who have been misdiagnosed or those who refused treatment, which makes interpretation of this covariate difficult. Furthermore, any excess cardiovascular risk in these individuals should be explained by their untreated BP readings, negating the need to account for hypertension diagnoses. Post data extraction, a post-hoc decision was also made to exclude left ventricular hypertrophy from the developed risk scores because few people in the cohort had the condition.

Whilst it was theoretically possible to consider a larger number of covariates in the analyses (e.g. alcohol consumption) these may be disparately recorded in primary care(234) or may not be reliable and were likely to be associated with the other covariates considered.(235) It was also important that the newly developed risk score could be easily used in general practice and should therefore only consider risk factors that are routinely collected by GPs.

5.2.4. Statistical analyses

The full dataset was split into two subsamples according to region; broadly North (North, Midlands and East Anglia) and South (South West, South East and London). The Southern subsample was used as a derivation dataset for development of the two risk scores and the second (North) was used as a validation dataset. Splitting the data in this way is preferable to random splitting, as random splitting can yield two very similar datasets by chance.(236) I chose a North-South divide because the rate of cardiovascular disease is known to be higher in Northern regions of the England,(10) thus decreasing the likelihood of obtaining

two similar datasets. The decision to use data from the South / North for the derivation/validation dataset respectively was not based on any specific rationale.

The risk prediction models were derived in the derivation dataset using Weibull parametric survival models. This approach allows the underlying survival function to be modelled explicitly compared to Cox proportional hazard models where the underlying survival function must be interpolated from non-parametric measures (e.g. Kaplan-Meier curves).

An initial (reference) model was built including traditional risk factors for cardiovascular disease. Initially, I intended to model non-linear relationships using fractional polynomials. This approach would have allowed me to model more accurately any substantially non-linear relationships that may have resulted in confounding if otherwise ignored, or analysed using categorical variables.(237,238) However, after receiving the data I discovered that such an analysis is not yet automated in Stata for multiply imputed datasets with multiple covariates and methods for combining these methods are still being explored.(239) I therefore tested for fractional polynomial terms in complete case data and any non-linear terms identified were carried forward to the imputed analysis. In imputed data I also tested for interaction effects between covariates, e.g. between age,(41,240) using Wald tests. Interactions and non-linear terms were included in the model based on a significance level of 10%.

Each measure of BP variability (SD, CV, VIM, and ARV) was added to the initial model separately and their significance assessed by Wald tests. Of those measures with a significant association, the measure with the largest standardised hazard ratio was chosen for inclusion in the final variability model. The standardized hazard ratios for each variability measure were calculated by estimating the standard deviation of each variability measure using an empty mixed effects model and multiplying the average Weibull model

coefficient by the average SD estimate across imputed datasets. As a sensitivity analysis, standardized hazard ratios were also estimated by standardizing the variability measures in each imputed dataset before fitting the Weibull model and calculating the average standardized estimate.

Validation of the reference and variability models was carried out in the derivation and validation datasets. Predicted risk was calculated from the models and observed risk was calculated from Kaplan-Meier estimates. The following model validation statistics were calculated for both models: calibration slope, E/O calibration statistic (ratio of expected (E) to observed (O) number of events),(241) c statistic for discrimination (Harrell's version, to allow for censored survival data),(242) Royston's R-squared statistic (transformation of D statistic)(243) and net reclassification improvement/ integrated discrimination improvement statistics.(225,244) The threshold to define high-risk patients was set at 10%, in line with current NICE guidance for primary prevention of CVD.(18) Plots of the observed risk of events against predicted risk in each decile of predicted risk for men and women were also created.

The performance of the reference and variability models was tested in the derivation and validation datasets separately by applying the average model estimates across imputed derivation datasets to each individual imputed dataset. Estimates of performance from each imputed dataset were then combined using Rubin's rules. As a sensitivity analysis in the derivation dataset, within-imputation model estimates were also used in each imputed dataset to calculate risk and measures of performance, instead of using the average estimates across imputations.

I initially intended to carry out internal validation of the two models in the derivation dataset using bootstrap resampling methods, which were originally developed for use with

logistic models.(236,245) Using this method, the same model fitting procedure used to derive the models in the derivation dataset was carried out in bootstrap samples of the data. The models developed in the bootstrap samples were then validated in the bootstrap and derivation datasets and overall validation statistics obtained by averaging across the bootstrap samples. This method allowed an estimate of "optimism" to be obtained (apparent performance in bootstrap samples minus test performance of bootstrap models in the derivation data), reflecting the fact that a model built and validated on the same dataset will be subject to some overfitting. The originally derived model coefficients can then be adjusted using linear or uniform shrinkage factors to correct for any over/underestimation of risk.(246)

However, due to the size of the dataset and the multiple imputations required to deal with missing data, the bootstrap methods were computationally intensive, with each bootstrap taking several hours to complete. Even when using a 32-core PC with 64GB of random access memory, completing the minimally desired 1000 bootstrap would have taken at least 2 years which was clearly infeasible in the time-frame of this thesis. I considered creating bootstrap samples from the imputed dataset, (instead of bootstrapping the entire process including imputation) but current best practice indicates that this results in biased model performance estimates.(247) I also considered reducing the number of imputed datasets created, but since the majority of missing data was observed in the main variable of interest (BP variability), I decided that obtaining a reliable estimate of the association of BP variability with CVD outcomes was relatively more important. Hence, I demonstrated the process of adjusting for optimism in a small number of bootstrap samples but did not adjust the final risk score for optimism as I was unable to perform the large number of bootstraps recommended.(247)

5.2.5. Missing data

Missing data were handled differently depending on the variable in question. For diagnoses, absence of a relevant READ/ ICD-10 code was assumed to reflect absence of disease. Age and sex variables required to define the population were observed in all cases. Initially, the aim was to impute all other variables (including IMD) using multiple imputation by chained equations,(248,249) to create a total of 80 imputed datasets. The event indicator and Nelson-Aalen estimate of the cumulative hazard were included in the imputation model.(250,251) However, because IMD was provided as a categorical variable by CPRD, it was imputed using ordinal logistic regression. This was successful in the initial derivation and validation cohorts but problems were encountered when imputing data in bootstrap samples. In some bootstrap samples, imputing IMD led to problems of perfect prediction, where a certain combination of factors always result in only one outcome, leading to infinite parameter estimates in the imputation model. Although this could be overcome by using the "augment" option in Stata which adds a small number of observations with small weight so that prefect prediction cannot occur,(252) this then led to problems of model convergence. Hence, those with missing IMD (who represented less than 0.1% of the total cohort) were excluded from analyses.

Continuous variables were transformed prior to imputation to ensure that they were normally distributed. No attempt was made to ensure that the values of imputed variables were "plausible" (e.g. by imputing using truncated regression or by rounding after imputation) because there is no evidence that this improves model estimates in terms of bias and coverage of confidence intervals over and above normal regression.(253,254) Estimates from each imputed dataset were combined using Rubin's rules,(255) including transformations as recommended in the literature (e.g. complimentary log-log

transformation for survival probabilities).(256) Since Rubin's rules may not be appropriate for all estimates of model discrimination and calibration, except in large samples,(256) median and quartile values across imputations were also summarized for comparison. A total of 80 imputed datasets were created as this was the number required to reduce the Monte Carlo error of the reference model coefficients to approximately 10% of their standard errors and was also adequate for a loss of statistical efficiency in the estimates of <1%. (248)

Transformed/ interaction variables were imputed explicitly rather than passively from their components, as the latter has been shown to result in biased estimates of effects.(257,258) Where individuals had fewer than six BP measurements, mean and variability measures were calculated from the measurements available (e.g. mean and variability over two, three, four, up to five measurements) and included in the imputation model to impute mean and variability measures across six measurements. This utilised the available data as far as possible, whilst maintaining consistency of the BP variability definition included in the models across all individuals.

5.3. Challenges of using routinely collected data in variability research

The initial list of eligible individuals was identified from the CPRD data. In total 1,030,748 people met the eligibility criteria for study entry, from which a 210,000 sample could then be selected and sent to CPRD for linkage. However, on inspection of the BP data for these eligible patients, I found that less than half of patients had at least one BP measurement occurring before their study entry date and within their up-to-standard registration period

(Table 5.1). Those with more measurements tended to be older and were more likely to be female but had similar BP levels.

Such a high proportion of missing data is a problematic for a number of reasons. Firstly, it calls into question the clinical relevance of a risk score incorporating BP variability measures, if repeat measures of blood pressure are not collected routinely in patients in whom the risk score will be used.

Multiple imputation relies on the assumption that data are missing at random, meaning that the likelihood a patient has missing BP data is independent of their BP level (but may be related to other observed variables such as age, sex etc.). However, this assumption cannot be tested. When such a large proportion of data is missing, results may be more susceptible to deviations from this assumption or misspecification of the imputation model, making them (potentially) less valid. From a practical point of view, imputation of large amounts of data also requires a large number of imputed datasets to be created which can be computationally intensive. I therefore decided to investigate ways in which the study design could be changed in order to increase the number of available BP measurements.

Table 5.1: Characteristics of eligible individuals by number of blood pressure readings

Number of blood pressure readings	N (%)	Mean age at index date (SD)	% male	Mean systolic BP across all readings (SD)	Mean systolic BP closest to index date (SD)
0	262,801 (25.5)	51.9 (8.72)	65.8	-	-
1	328,691 (31.9)	52.8 (8.80)	56.0	129.3 (15.86)	129.3 (15.86)
2	187,929 (18.2)	53.9 (9.14)	48.1	129.7 (14.18)	130.2 (15.81)
3	96,936 (9.4)	54.6 (9.33)	40.0	130.5 (13.90)	130.8 (16.01)
4	53,195 (5.2)	54.9 (9.47)	33.0	130.8 (13.75)	131.2 (16.25)
5	31,515 (3.1)	54.9 (9.50)	27.3	130.9 (13.79)	131.2 (16.42)
6	69,681 (6.8)	54.3 (9.46)	16.8	130.6 (13.72)	130.9 (16.32)

5.3.1. Increased minimum prior registration period

Firstly, I investigated how the number of non-missing BP measurements was related to the minimum prior registration period. Although BP measurements were drawn from up to 10 years prior to study entry, included participants were only required to have a minimum of two years up-to-standard prior registration and therefore had potentially very few measurements.

Table 5.2 shows how the proportion of people with zero to six BP measurements changed in those with at least two to at least 10 years prior registration. As expected, the proportion of people with six BP measurements increased and the proportion with zero or one measurement decreased as minimum registration increased. In particular, by increasing the minimum registration period past 4 years, more than 50% of patients had the required minimum of two readings from which variability could be calculated. Increasing the minimum registration period beyond six years did not markedly improve the number of BP readings however, and significantly reduced the pool of eligible patients.

A large increase in the minimum prior registration period would have limited the representativeness of the included sample in comparison to the population in which the developed risk score was intended for use. Those who are geographically mobile, for example due to work or due to unstable living arrangements (such as the renting population or the elderly moving into care homes), would not be included in this sample. Those included would be expected to be more likely to be those who own their own home and/ or be parents with school age children.

Table 5.2: Proportion of people with zero to six blood pressure measurements by minimum prior registration period

Minimum prior registration (years)	Number of BP measurements 0	1	2	3	4	5	6	Total N
At least: 2	25.50	31.89	18.23	9.40	5.16	3.06	6.76	1,030,748
3	24.31	27.17	17.93	10.43	6.22	3.97	9.96	650,184
4	23.71	26.16	17.99	10.71	6.44	4.17	10.83	567,193
5	23.43	25.12	17.93	10.95	6.66	4.29	11.62	473,276
6	21.86	23.80	18.28	11.50	7.09	4.57	12.91	366,805
7	20.10	22.78	18.52	12.11	7.60	4.91	13.98	286,735
8	20.36	22.30	18.17	12.13	7.73	5.00	14.31	240,068
9	20.24	22.09	17.99	12.14	7.76	5.08	14.69	192,031
10	20.62	21.98	17.89	12.10	7.75	5.09	14.58	176,010

5.3.2. Moving study start date to 1st January 2010

The second option considered was that of moving the study start date forward by 5 years to 1st January 2010, and calculating risk over 5 years instead 10 years. This would mean that the period of baseline BP measurement would coincide with changes in the healthcare system that promoted increased monitoring and might lead to more BP measurements being taken, notably the Quality and Outcomes Framework.(13)

Changing the study start date resulted in a smaller pool of eligible people (928, 372), but increased the proportion of people with at least 2 blood pressure measurements (Table 5.3). This was primarily due to an increase in the proportion of people with a longer period of prior registration e.g. from 17% having >10 years registration in the original sample (Table 5.2) to 39% in Table 5.3.

Table 5.3: Proportion of people with zero to six blood pressure measurements by minimum prior registration period (study start date of 1st January 2010)

Minimum prior registration (years)	Number of BP measurements 0	1	2	3	4	5	6	Total N
At least: 2	17.15	24.45	18.77	12.22	7.90	5.19	14.31	928,372
3	14.31	20.08	18.61	13.42	9.18	6.25	18.14	717,969
4	14.01	19.29	18.48	13.56	9.37	6.41	18.88	679,516
5	13.78	18.69	18.36	13.65	9.50	6.53	19.50	642,193
6	13.70	18.19	18.20	13.68	9.58	6.61	20.04	599,090
7	13.85	17.87	17.98	13.63	9.62	6.65	20.40	563,781
8	14.17	17.59	17.75	13.53	9.58	6.67	20.71	503,545
9	14.58	17.48	17.53	13.43	9.51	6.63	20.83	438,968
10	15.01	17.75	17.55	13.30	9.40	6.50	20.49	361,814

Changing the study start date had disadvantages because the developed risk score would only calculate five year risk and hence would not be comparable with existing scores or current UK NICE guidelines for primary prevention of CVD. Given that the benefit of bringing the study start date forward to 2010 acts through minimum registration, which can be changed in isolation, this was a major disadvantage to this approach.

5.3.3. Including blood pressure measurements outside the up-to-standard current registration period

In the original analyses, measurements that occurred outside the practice up-to-standard date or prior to each patient's current registration date were excluded. The practice up-to-standard date is derived by CPRD to indicate the latest date that each practice meets quality standards relating to continuity and quality of data recording and CPRD recommends using this date to identify quality data.(227) Data recorded before a patient's current registration date may be from an earlier period of registration (which may/ may not be during the up-to-standard period for the practice) but may also be from a period of time when the patient was registered with a different (possibly non-CPRD) practice. The quality of this data is therefore open to question. However, I decided to investigate if the number of available

BP measurements could be significantly increased by including readings recorded outside of the up-to-standard current registration period and more than 10 years prior to index date in the interests of maximising the available data.

This approach increased the number of BP readings (49% had no extra readings, 28% had one extra reading, 12% had two extra readings and 11% had three or more extra readings). In total this yielded 973,296 extra readings (Table 5.4; 2,757,094 instead of 1,783,798). The majority of these additional measurements occurred during each patient's registration period but outside the practice up-to-standard period (Table 5.5), so the quality of this data could be questionable.

Table 5.4: Number of blood pressure measurements including measurements outside the up-to-standard current registration period and more than 10 years before index date

Number of BP measurements	N	%
0	117,442	11.39
1	252,897	24.54
2	202,516	19.65
3	135,819	13.18
4	89,866	8.72
5	61,004	5.92
6	171,204	16.61
Total	**1,030,748**	**100.00**

Table 5.5: Source of additional blood pressure measurements

	N	%
Within patients UTS registration period but more than 10 years before index date	109,652	11.3
Within current registration period but before practice UTS date	596,520	61.3
Between first and current registration dates and after practice UTS date	43,453	4.5
Between first and current registration dates and before practice UTS date	14,856	1.5
Before first registration date and after practice UTS date	117,854	12.1
Before first registration date and before practice UTS date	90,961	9.4
Total	**973,296**	**100.0**

5.3.4. Including patients taking antihypertensive medication

Finally, I considered the option of including patients on antihypertensive medication, since they should be having their blood pressure monitored on a regular basis, in spite of the fact that medication changes can affect variability and cardiovascular risk. To overcome this confounding problem, I decided to include only BP measurements occurring during a period of constant medication use.

After identifying up to six baseline BP measurements for each patient, the BP measurement period was split into treatment windows. The first window was defined as the time between each patient's index date and their first BP reading (closest to the index date). The second window was defined as the time between each patient's index date and their second BP reading (second closest to the index date) and so on. I determined treatment to be stable in each treatment window if each substance and dose combination was prescribed for at least 80% of the time. If treatment was stable in treatment window 1, I included the first BP reading; if treatment was stable in treatment window 2, I included the first and second BP readings etc.

In total, 274,895 people who had been on antihypertensive treatment at any time prior to their index date (and were previously excluded) were added back into the list of eligible patients. A small number of people were treated prior to their index date but had no BP measurements (N= 7,222). These people generally had stable treatment and had been on the same medication for a long time, so were still included.

Including those on antihypertensive medication did increase the number of available BP measurements initially, but not after excluding BP readings occurring during periods of medication change (Table 5.6). This negated any benefit of including those on antihypertensive medication.

Table 5.6: Proportion of people with zero to six blood pressure readings including patients on antihypertensive medication

Number of BP measurements	N prior to excluding readings during periods of medication change (%)	N after excluding readings during periods of medication change (%)
0	270,023 (20.7%)	374,052 (28.6%)
1	349,040 (26.7%)	374,979 (28.7%)
2	215,317 (16.5%)	219,488 (16.8%)
3	126,961 (9.7%)	121,082 (9.3%)
4	81,718 (6.3%)	70,724 (5.4%)
5	56,414 (4.3%)	43,928 (3.4%)
6	206,170 (15.8%)	101,390 (7.8%)

5.3.5. Determining the best approach to maximise the number of blood pressure measurements

Considering all of the approaches above to increase the number of blood pressure measurements, the two best options were to increase the minimum prior registration period for included patients or to include measurements occurring before the up-to-standard current registration period. The second of these was problematic however because the quality of the data was open to debate and including data from this period

would be in contradiction to CPRD's own advice. Data quality is a concern with any research of this kind making it difficult to justify a decision to include data occurring outside the up-to-standard period. Such a decision would also raise questions about whether to include other data e.g. cholesterol measures, from outside this period or not. For these reasons, I decided not to pursue this approach and took forward the idea of extending the minimum prior registration period.

How much should the minimum prior registration period be extended by? As shown in Table 5.2, extending the period to four years meant that more than 50% of people had at least two measurements, but extending the period by more than six years did not result in significant gains and markedly reduced the pool of eligible patients. Choosing a middle ground of five years (three years more than previously) therefore seemed to be a sensible approach.

5.3.6. Consideration of the "missing at random" assumption

Finally, having decided how to modify the study to increase the number of BP measurements in the dataset, it was important to consider if there was any evidence that the data was missing not at random. Although it is not possible to prove if data is missing at random (the assumption required for imputation to be valid), inspecting the relationship of BP variability with cardiovascular risk, by the number of BP readings, might have indicated if this assumption did not hold.

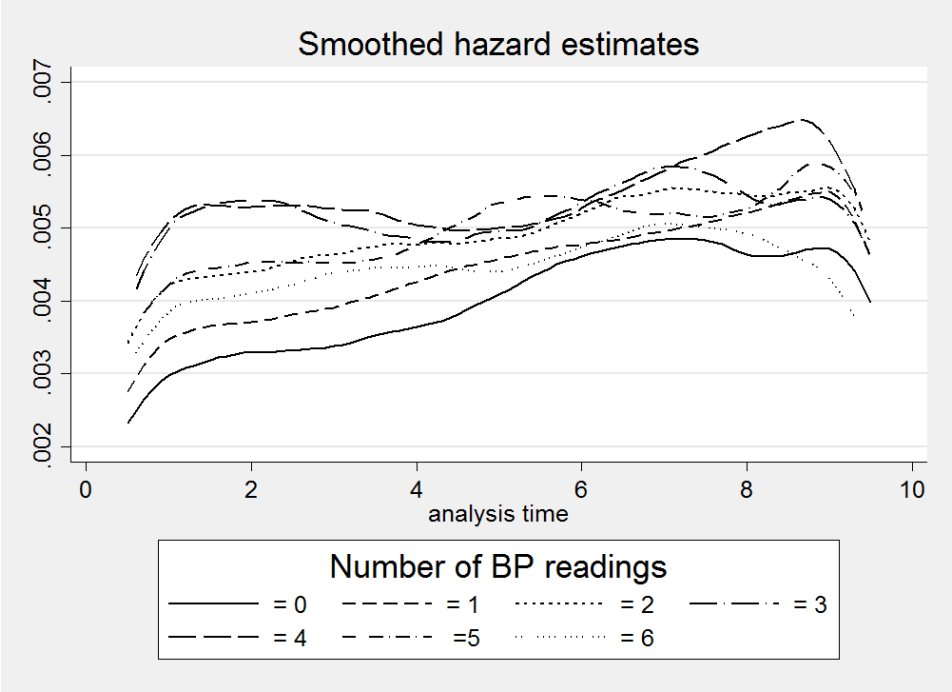
Table 5.7 shows that the standard deviation of BP and the hazard ratio (from log-rank test) for high vs. low variability did increase with the number of measurements, but that this relationship disappeared after adjustment for age and sex. Figure 5.1 also shows that the hazard rate over time was very similar across the different number of complete BP

measurements. From this data, I could be reasonably confident that, after adjustment for other measured variables, those with little or no blood pressure measurements were not materially different to those with fully observed measurements in terms of blood pressure variability and cardiovascular risk. There was little evidence that the assumption of missing at random would be violated, and therefore imputation of missing blood pressure variability values was likely to be valid, assuming a correctly specified imputation model.

Table 5.7: Relationship of blood pressure variability with cardiovascular risk, by number of measurements

Number of BP measurement	Median follow-up (years)	Event rate (per 1000 person-years)	SD of SBP (mean (SD))	Proportion SD>15	Hazard ratio (unadjusted): High (>15) vs. low SD	Hazard ratio (age-sex adjusted): High (>15) vs. low SD
0	6.88	3.78	-	-	-	-
1	7.08	4.24	-	-	-	-
2	7.48	4.83	8.55 (7.20)	15.1%	1.21 (1.14 to 1.30)	1.13 (1.05 to 1.20)
3	7.92	5.22	9.78 (5.90)	18.8%	1.37 (1.27 to 1.48)	1.23 (1.14 to 1.33)
4	8.20	5.44	10.30 (5.14)	16.3%	1.33 (1.20 to 1.49)	1.16 (1.04 to 1.29)
5	8.50	5.04	10.57 (4.65)	15.9%	1.40 (1.21 to 1.62)	1.20 (1.04 to 1.39)
6	9.21	4.42	10.34 (4.17)	12.6%	1.47 (1.32 to 1.63)	1.18 (1.06 to 1.31)

Figure 5.1: Hazard rate over time by the number of complete blood pressure readings

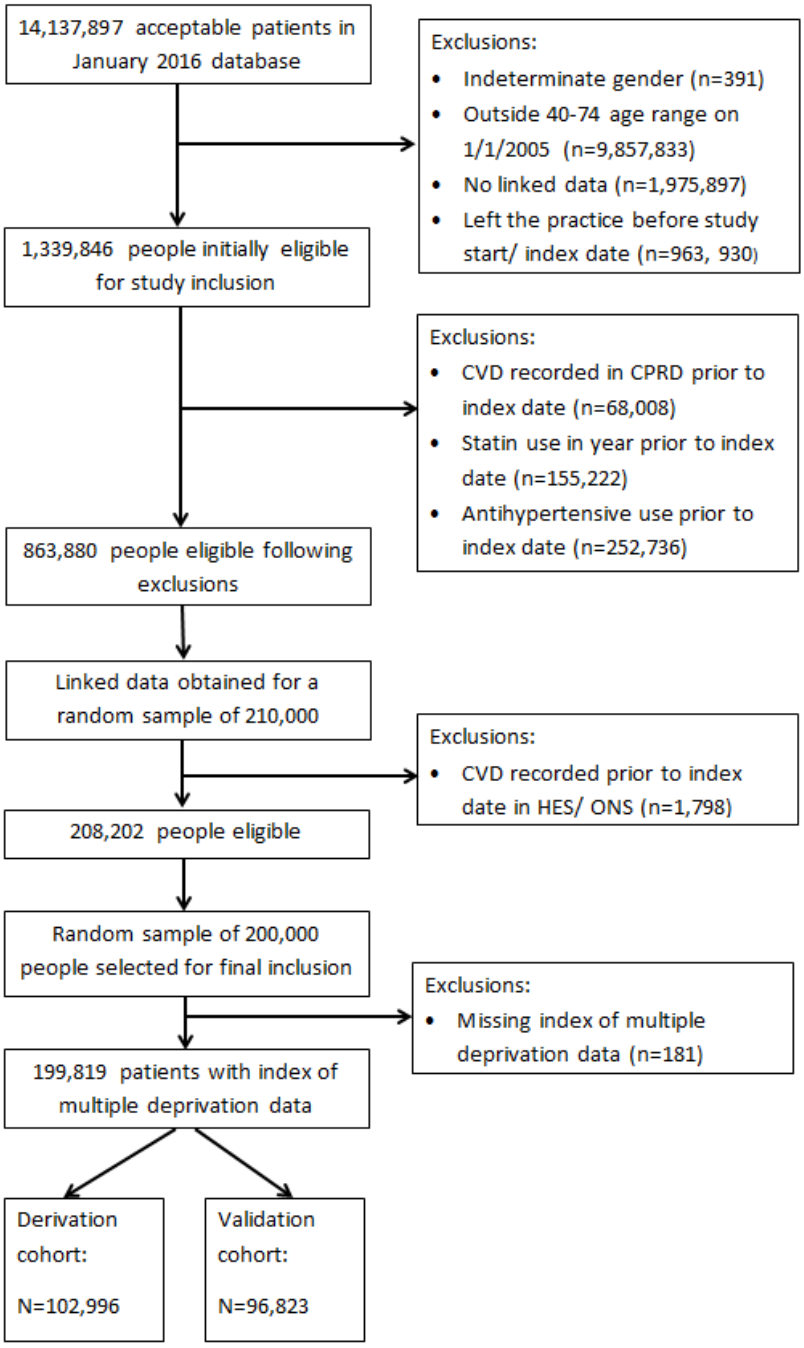


5.4. Results

5.4.1. Baseline characteristics

After making the described changes to the cohort definition, 863,880 eligible individuals were identified and linked data were obtained for a random sample of 210,000 patients (inflated from 200,000 to allow for further exclusions due to prior CVD events recorded in HES/ ONS data alone). A further 1,798 patients were excluded based on cardiovascular events identified in linked data and a final 200,000 person random sample was selected from the 208,202 people who remained eligible. Data were available on 199,819 patients after removal of 181 people with missing IMD data. The full study flowchart is given in Figure 5.2.

Figure 5.2: Study flowchart



The derivation dataset included 102,996 patients from London and the South and 663,492 person-years of follow-up. The remaining 96,823 patients from the North, Midlands and East Anglia formed the validation dataset with a total of 646,684 person-years of follow-up. The characteristics of the included individuals are given in Table 5.8. Mean age at entry to

the derivation and validation cohorts was 54 and 53 years respectively and a majority of patients were male. Both cohorts were similar in terms of baseline characteristics, except that those in the validation cohort were more likely to be in the most deprived quintiles of deprivation.

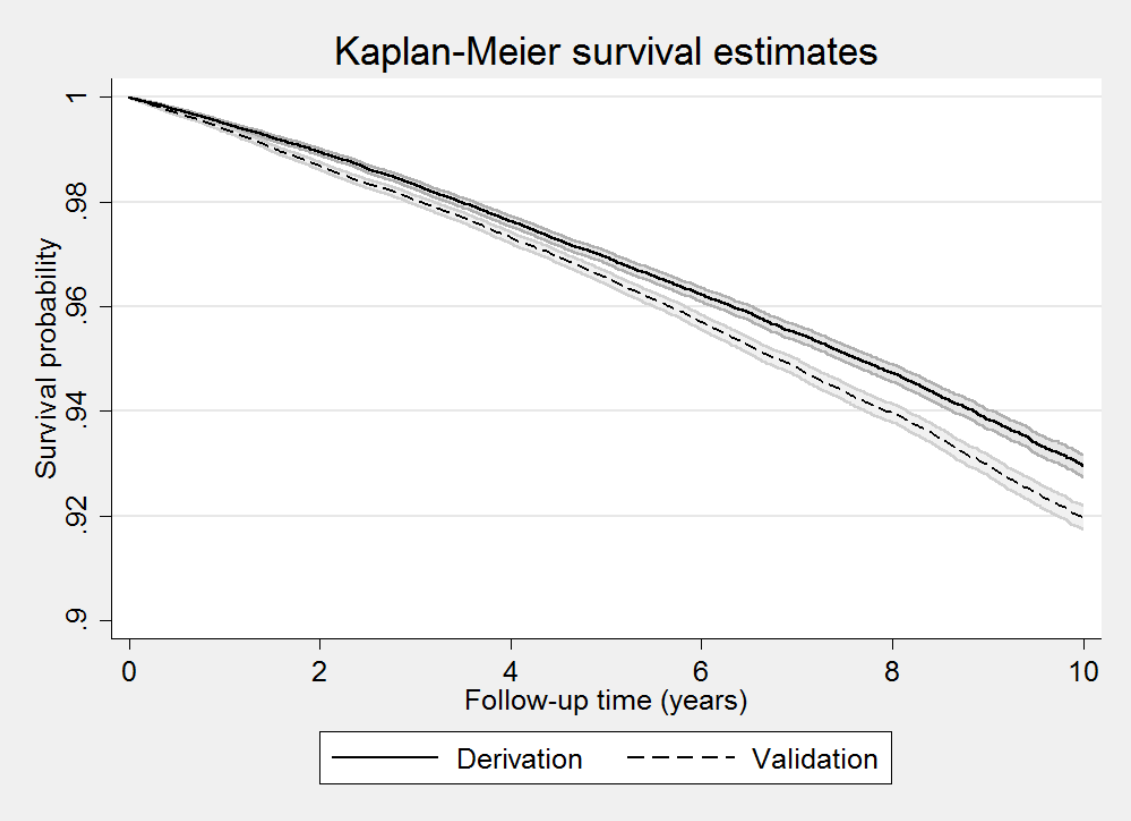
Table 5.8: Baseline characteristics of 199,819 patients in the derivation and validation cohorts

	Derivation cohort (N=102,996)	**Validation cohort (N=96,823)**
Variable	**Mean (SD)/ N (%)**	**Mean (SD)/ N (%)**
Female gender	51,150 (49.7)	47,332 (47.9)
Age	53.9 (9.08)	53.3 (9.00)
CVD event outcome	4,562 (4.4)	5,105 (5.3)
Hypertension	812 (0.8)	938 (1.0)
Atrial fibrillation	189 (0.2)	169 (0.2)
Family history of CHD	14,836 (14.4)	18,207 (18.8)
Family history of stroke	3,665 (3.56)	3,797 (3.8)
Chronic kidney disease (Stage 3 to 5)	279 (0.3)	165 (0.2)
Diabetes (Type 1 or 2)	849 (0.8)	802 (0.8)
Rheumatoid arthritis	553 (0.5)	590 (0.6)
Left ventricular hypertrophy	15 (0.0)	24 (0.0)
Body mass index (kg/ m^2)	26.7 (5.03) (N=51,649)	26.9 (5.06) (N=44,774)
Total cholesterol (mmol/L)	5.53 (0.99) (N=29,896)	5.59 (1.00) (N=25,467)
High density lipoprotein (mmol/L)	1.51 (0.46) (N=23,897)	1.50 (0.43) (N=18,539)
Mean blood pressure (across all readings, mm Hg)	129.3 (14.5) (N=82,007)	130.4 (14.4) (N=76,980)
Smoking status		
Non-smoker	40,311 (39.1)	37,923 (39.2)
Ex-smoker	16,582 (16.1)	14,323 (14.8)
Current smoker	20,506 (19.9)	21,138 (21.8)
Missing (assumed non-smoker)	25,597 (24.9)	23,439 (24.2)
Ethnicity		
White	42,992 (41.7)	43,006 (44.4)
Missing (assumed white)	43,989 (42.7)	38,000 (39.3)
Index of multiple deprivation		
Bottom quintile (least deprived)	33,992 (33.0)	22,569 (23.3)
2nd quintile	25,113 (24.4)	22,675 (23.4)
3rd quintile	21,134 (20.5)	19,506 (20.2)
4th quintile	17,029 (16.5)	17,013 (17.6)
Top quintile (most deprived)	5,728 (5.6)	15,060 (15.6)

Median follow-up time in the derivation and validation cohorts was 7.12 and 7.34 years with an event rate of 6.89 and 7.89 per 1000-person years respectively. As expected, the

event rate in the validation cohort was slightly higher than that in the derivation cohort and this difference was observed at all time points (Figure 5.3).

Figure 5.3: Kaplan-Meier survival estimates over time (with 95% confidence intervals) in the derivation and validation cohorts



Data on BMI, total and HDL cholesterol, smoking and ethnicity were missing in up to 81% of patients. As expected from the scoping work to increase the number of non-missing blood pressure measurements (Section 5.3), in both the derivation and validation cohorts approximately 20% of patients had no BP measurements at baseline and only 10% had the maximum of six measurements pre-index date (Table 5.9). Average within-person mean systolic BP was approximately 130 mm Hg regardless of the number of BP measurements patients had at baseline. When BP variability was measured according to standard deviation, coefficient of variation or variation independent of mean, those with

more BP measurements appeared to have more variable BP on average. Conversely average real variability did not exhibit this pattern.

Table 5.9: Systolic blood pressure (BP) characteristics of patients in the derivation and validation cohorts by number of BP readings (within person mean, standard deviation (SD), coefficient of variation (CV), variation independent of mean (VIM) and average real variability (ARV))

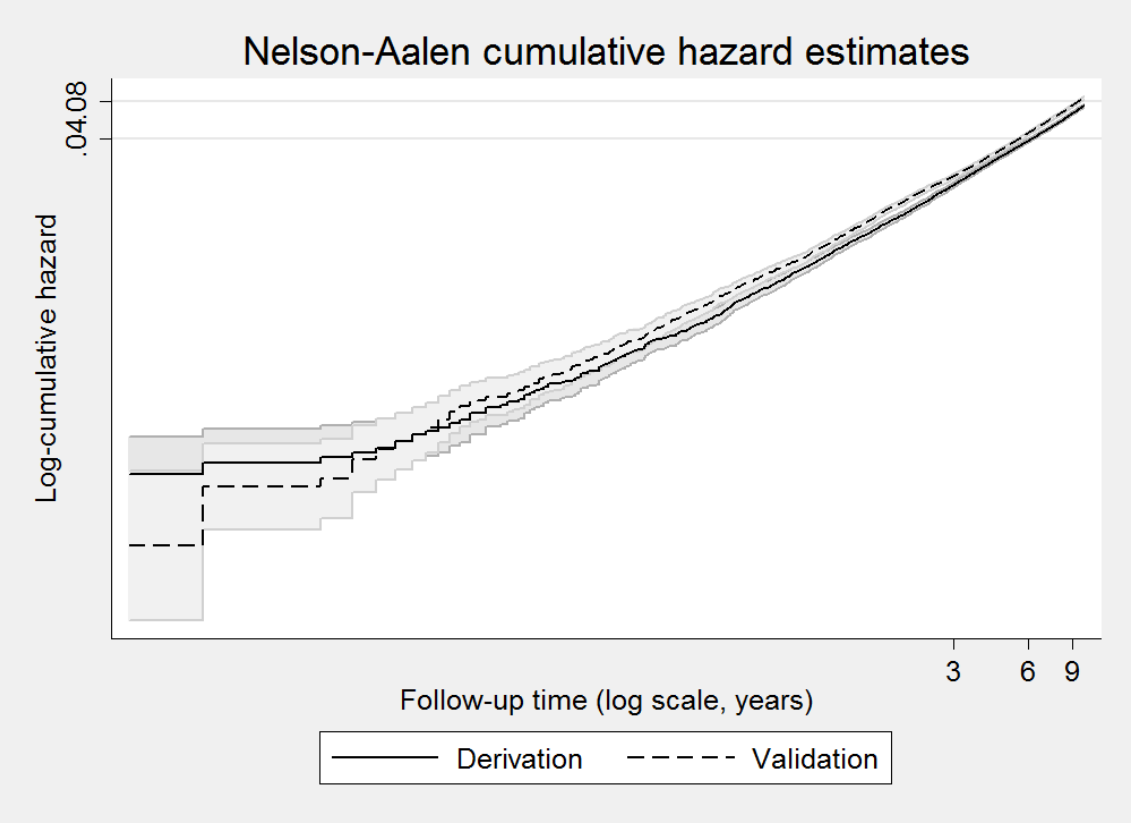
Derivation cohort (N=102,996)						
		Mean (SD) of within-person BP parameter (mm Hg)				
Number of BP readings	**Number of patients (%)**	**Mean**	**SD**	**CV**	**VIM**	**ARV**
0	20,989 (20.4)	-	-	-	-	-
1	28,277 (27.5)	129.1 (15.9)	-	-	-	-
2	20,079 (19.5)	129.0 (13.8)	8.42 (7.14)	6.55 (5.48)	8.45 (7.09)	11.91 (10.10)
3	11,942 (11.6)	129.5 (13.6)	9.54 (5.78)	7.38 (4.38)	9.57 (5.69)	11.80 (7.98)
4	7,140 (6.9)	130.0 (13.4)	10.25 (5.11)	7.89 (3.79)	10.26 (4.94)	11.98 (6.93)
5	4,393 (4.3)	129.9 (13.3)	10.48 (4.54)	8.07 (3.41)	10.49 (4.43)	11.89 (6.12)
6	10,176 (9.9)	130.0 (13.4)	10.21 (4.09)	7.87 (3.04)	10.21 (3.95)	11.34 (5.32)
Validation cohort (N=96,823)						
		Mean (SD) of within-person BP parameter (mm Hg)				
Number of BP readings	**Number of patients (%)**	**Mean**	**SD**	**CV**	**VIM**	**ARV**
0	19,843 (20.5)	-	-	-	-	-
1	25,181 (26.0)	130.2 (15.9)	-	-	-	-
2	18,291 (18.9)	130.0 (14.1)	8.66 (7.24)	6.66 (5.49)	8.68 (7.16)	12.25 (10.24)
3	11,328 (11.7)	130.5 (13.5)	9.80 (5.94)	7.50 (4.43)	9.82 (5.81)	12.09 (8.17)
4	6,985 (7.2)	130.9 (13.2)	10.24 (5.16)	7.83 (3.82)	10.25 (5.02)	12.02 (6.97)
5	4,484 (4.6)	130.9 (13.2)	10.58 (4.59)	8.07 (3.37)	10.58 (4.42)	11.96 (6.05)
6	10,711 (11.1)	130.9 (13.4)	10.34 (4.16)	7.91 (3.07)	10.34 (4.02)	11.39 (5.33)

5.4.2. Risk score development

The appropriateness of a Weibull model for the data was assessed graphically by plotting the log-cumulative hazard estimate against log-time. The approximate linear relationship observed (Figure 5.4) indicates that the assumption that survival times are distributed

according to a Weibull distribution is valid. The proportional hazards assumption was also assessed graphically for all variables and did not appear to be violated for any variable (data not shown).

Figure 5.4: Nelson-Aalen log-cumulative hazard estimates over time (log-scale) in the derivation and validation cohorts



In complete case analysis of the derivation cohort, there was no indication that fractional polynomial terms were required for continuous variables when considering BP measured over a minimum of two readings (N=15,146) or over the maximum six readings (N=3,678), so these were not included in imputed analysis. Three interaction terms were included in the reference model, namely an interaction between age and total/ HDL cholesterol ratio, age and mean BP and age and smoking status based on significance of <10%.

The results for the reference model, excluding any measures of BP variability are given in Table 5.10. In this model, the risk of CVD was 44% lower in women compared to men and was 13% higher with each increasing year of age. People with diabetes were 65% more likely to develop CVD, those with rheumatoid arthritis were at 70% higher risk and those with atrial fibrillation were nearly three times more likely to develop CVD. Risk was also 32% higher with each mmol/L increase in TC/HDL cholesterol ratio (although this association reduced by 0.3% for each year of age).

Table 5.10: Reference model for risk of cardiovascular disease

Variable	Adjusted hazard ratio	Standard error	p-value	95% confidence interval	
Female gender	0.564	0.036	0.000	0.526	0.605
Age (per year)	1.129	0.019	0.000	1.088	1.172
Atrial fibrillation	2.777	0.159	0.000	2.034	3.790
Family history of CVD	1.029	0.040	0.485	0.950	1.113
Chronic kidney disease (Stage 3 to 5)	1.010	0.270	0.970	0.595	1.714
Diabetes (Type 1 or 2)	1.653	0.111	0.000	1.330	2.053
Rheumatoid arthritis	1.699	0.144	0.000	1.282	2.252
Body mass index (per kg/ m^2)	1.008	0.004	0.059	1.000	1.017
TC/HDL cholesterol (per mmol/L)	1.315	0.081	0.001	1.121	1.543
Smoking status (reference = Non-smoker)					
Current smoker (n=20,506)	4.501	0.222	0.000	2.913	6.956
Ex-smoker (n=16,582)	1.987	0.277	0.013	1.153	3.422
Ethnic group (reference= White/ Unknown)					
Indian (n=973)	1.387	0.156	0.036	1.021	1.882
Bangladeshi (n=45)	1.812	0.711	0.403	0.450	7.301
Pakistani (n=180)	1.095	0.379	0.812	0.520	2.302
Chinese (n=214)	0.172	1.001	0.079	0.024	1.225
Black African (n=524)	1.014	0.290	0.961	0.574	1.792
Black Caribbean (n=494)	0.642	0.303	0.144	0.354	1.163
Other Black (n=210)	0.911	0.449	0.836	0.378	2.196
Other Asian (n=487)	1.338	0.231	0.208	0.850	2.105
Other (n=651)	0.911	0.215	0.665	0.598	1.388
Mixed (n=12,337)	0.970	0.045	0.493	0.888	1.059
Index of multiple deprivation (reference = 1st quintile (least deprived))					
2	1.149	0.041	0.001	1.060	1.246
3	1.196	0.043	0.000	1.099	1.300
4	1.365	0.044	0.000	1.251	1.489
5	1.406	0.067	0.000	1.233	1.603
Mean systolic BP over 6 readings (per mm Hg)	1.029	0.009	0.001	1.012	1.046
Age x smoking status					
Age (per year) in current smokers	0.986	0.004	0.000	0.979	0.993
Age (per year) in ex-smokers	0.991	0.004	0.053	0.983	1.000
Age x TC/HDL cholesterol ratio	0.997	0.001	0.067	0.995	1.000
Age x Mean systolic BP over 6 readings	1.000	0.000	0.064	0.999	1.000
Constant	-15.029	1.160	0.000	-17.304	-12.754
Log(scale)	0.195	0.013	0.000	0.169	0.221

There was a clear association between deprivation and CVD; risk was 15% higher in patients in the 2nd quintile of IMD compared to the first quintile and this increased to 41% higher in the 5th (most deprived) quintile. Current smokers were over four times more likely to develop CVD than non-smokers and the risk in ex-smokers was nearly twice as high as

that for non-smokers (although these associations were moderated with increasing age). Finally, risk of CVD increased by 3% for every mm Hg increase in mean systolic BP.

Although patients of Indian ethnicity appeared to be at 39% greater risk of CVD, there was no association observed for other ethnic groups, which may be due in part to the low numbers in these groups and adjustment for other risk factors. Similarly, there was no observed difference in risk in the few people with chronic kidney disease (n=279, 0.3%). Family history of CVD was also not significantly associated with CVD outcomes, although owing to the data available in CPRD, this variable was not specific to premature coronary heart disease and included any family history of CHD and/or stroke. Finally, the association between body mass index and CVD risk was borderline significant. When investigated further, this was found to be due to confounding between BMI and TC/HDL cholesterol; when cholesterol measures were removed from the model, BMI was found to be significant.

When each of the four BP variability measures was added to the model, the model estimates for the reference coefficients were similar (data not shown). The coefficient values for each of the variability parameters and their standardised equivalents are given in Table 5.11. When standardized hazard ratios were also estimated by standardizing the variability measures in each imputed dataset before fitting the Weibull model, similar results were observed (see Table C.13, Appendix C).

Table 5.11: Model coefficients for systolic blood pressure variability parameters

Variability measure	Adjusted hazard ratio* (per mm Hg)	Standard error	p-value	95% confidence interval		Standard deviation	Standardized hazard ratio
SD	1.0204	0.0071	0.0050	1.0062	1.0348	4.1480	1.0872
CV	1.0259	0.0100	0.0120	1.0058	1.0464	3.1256	1.0833
ARV	1.0158	0.0056	0.0060	1.0046	1.0271	5.3995	1.0883
VIM	1.0215	0.0075	0.0050	1.0065	1.0367	4.0575	1.0901

*Adjusted for variables listed in Table 5.10

The largest standardized hazard ratio was observed for variability independent of mean (VIM); higher systolic BP variability independent of mean was associated with a 2.15% increased CVD risk per mm Hg (95% CI 0.65 to 3.67%) equating to a difference in risk of 9% per standard deviation (4.06 mm Hg). All other measures of variability were also significantly associated with CVD risk but the associations were weaker compared to VIM on a standardized scale. Hence, the model including variability independent of mean was taken forward to internal and external validation procedures (see Table C.14, Appendix C for full variability model coefficients).

5.4.3. Internal validation

Estimates of the reference and variability model performance in the derivation dataset along with bootstrap estimates of optimism are summarized in Table 5.12. Model performance results were practically identical when using the within-imputation model estimates to estimate risk (see Table C.15, Appendix C).

Table 5.12: Internal model validation statistics

Statistic	Estimate	95% confidence interval		Apparent performance (bootstrap)	Test performance (derivation)	Optimism	Optimism corrected statistic
Reference model							
Calibration slope	1.0036	0.9704	1.0368	1.0035	0.9881	0.0154	0.9882
c-statistic	0.7514	0.7441	0.7588	0.7527	0.7503	0.0023	0.7491
R^2 (%)	33.89	32.38	35.39	34.22	33.62	0.61	33.28
E/O calibration	1.0312	1.0004	1.0621	1.0316	1.0308	0.0008	1.0304
Variability model							
Calibration slope	1.0036	0.9706	1.0366	1.0035	0.9863	0.0172	0.9864
c-statistic	0.7526	0.7451	0.7601	0.7538	0.7511	0.0027	0.7499
R^2 (%)	34.13	32.59	35.66	34.46	33.78	0.67	33.46
E/O calibration	1.0306	0.9998	1.0614	1.0309	1.0303	0.0007	1.0299
Across both models							
NRI	0.0020	-0.0059	0.0099	0.0027	0.0019	0.0008	0.0012
IDI	0.0010	-0.0002	0.0021	0.0010	0.0008	0.0001	0.0009

The internal validation statistics indicate that the addition of a term for variation independent of mean resulted in little, non-significant improvement in the performance of the risk score both in terms of calibration and discrimination. The net reclassification improvement indicates that classification across the 10% 10-year risk threshold was improved for a net 0.2% of individuals when using the variability model compared to the reference model, but this was also non-significant. Similarly, there was non-significant improvement as measured by the integrated discrimination improvement. The difference between apparent model performance in bootstrap samples and test performance in the derivation dataset indicates that optimism was low for both the reference and variability models. As with the uncorrected statistics, validation statistics corrected for optimism were similar in both the reference and variability models.

Figure 5.5 shows the observed and predicted risk in each decile of risk for men and women, when predicted risk is calculated from the reference model. This shows that the reference model performed well on average for men and women in the lower risk groups but tended to underestimate risk in the higher risk groups and the degree of error increased as risk increased. The graphs also indicate that the reference model estimated risk more accurately on average for women than men.

Figure 5.6 shows the equivalent information for risk predicted using the variability model and is almost identical to Figure 5.5 (on first glance they may be mistaken for the same graph). However, there are small differences, for example for women in the 9th decile of risk. These two graphs reinforce what is shown in the formal validation statistics; that the addition of a measure for variability did not materially improve risk estimates.

Figure 5.5: Observed and predicted 10-year risk of cardiovascular disease by decile of risk for males and females in the derivation cohort: reference model

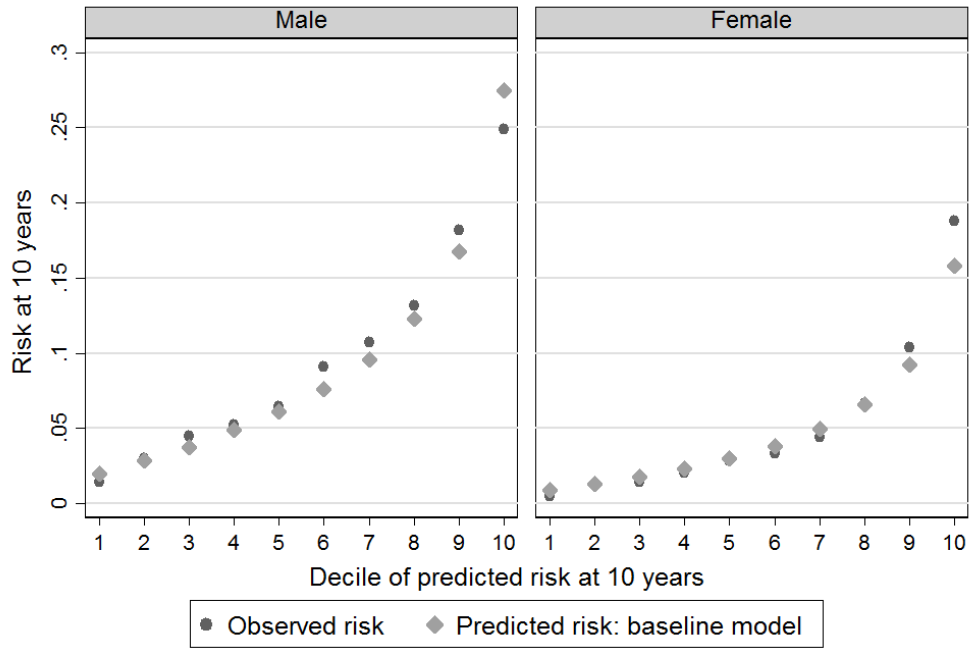
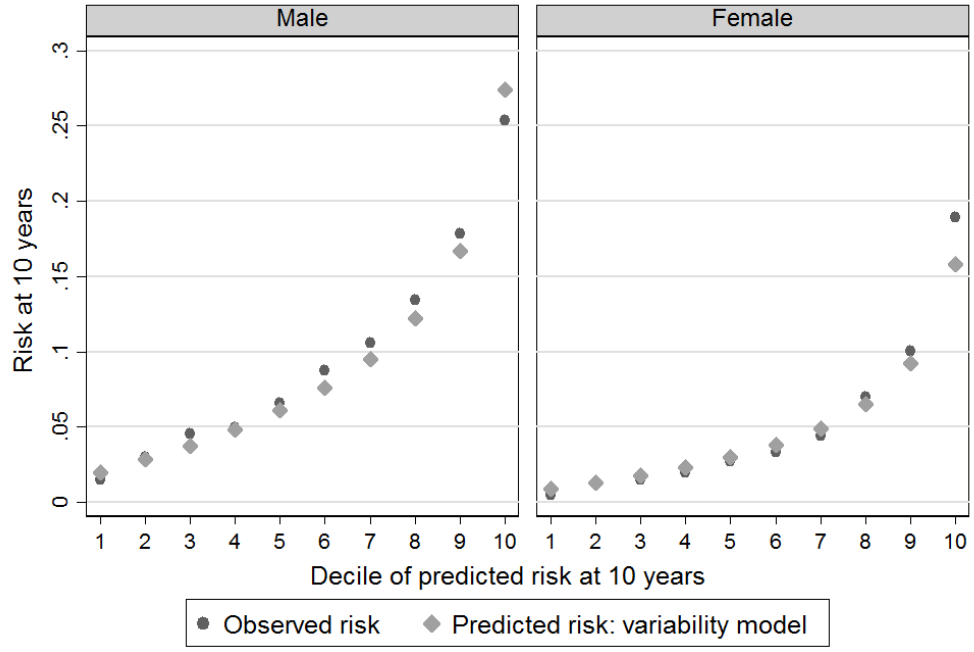


Figure 5.6: Observed and predicted 10-year risk of cardiovascular disease by decile of risk for males and females in the derivation cohort: variability model



5.4.4. External validation

Table 5.13 shows the validation statistics in the derivation dataset for both the reference and variability models. Both models had good discrimination with c-statistics >0.74. Calibration statistics indicated that both models explained approximately 32% of the variation in risk and underestimated risk slightly on average (expected divided by observed risk ratios were 0.94). However, across all measures, including a term for blood pressure variability independent of mean in the model did not significantly improve model performance.

The net reclassification improvement indicated that classification across the 10% risk threshold was non-significantly worse, with a net improvement of -0.02% (equivalent to 20 people in the validation cohort being incorrectly reclassified). The integrated discrimination

improvement index, which is an equivalent to NRI calculated across all risk thresholds, indicated a significant improvement but the improvement was very small.

Table 5.13: External model validation statistics

Statistic	Estimate	95% confidence interval		Median across imputed datasets	Interquartile range across imputed datasets	
Reference model						
Calibration slope	0.9659	0.9303	1.0016	0.9669	0.9597	0.9717
c-statistic	0.7415	0.7344	0.7485	0.7415	0.7406	0.7424
R^2 (%)	31.84	30.37	33.31	31.85	31.63	32.04
E/O calibration	0.9384	0.9113	0.9656	0.9385	0.9365	0.9401
Variability model						
Calibration slope	0.9622	0.9252	0.9992	0.9621	0.9561	0.9698
c-statistic	0.7419	0.7348	0.7491	0.7420	0.7412	0.7430
R^2 (%)	32.04	30.54	33.53	32.03	31.84	32.23
E/O calibration	0.9399	0.9126	0.9673	0.9398	0.9376	0.9417
Across both models						
NRI	-0.0002	-0.0071	0.0068	0.0000	-0.0020	0.0015
IDI	0.0010	0.0000	0.0021	0.0010	0.0007	0.0013

Figures 5.7 and 5.8 show the observed and predicted risks by decile of risk in the validation cohort, when risk was calculated using the reference and variability models respectively. The graphs indicate that both models performed well in women in the lowest risk deciles but poorly for women in the top three deciles. In men, both models underestimated risk except in the 1st and 5th deciles and in the 2nd decile for the variability model. As was observed in the internal validation, it would be easy to mistake Figure 5.7 and Figure 5.8 for the same graph, but small differences are visible on close inspection (e.g. for men in the 6th decile of risk). The graphs show that the addition of the term for variation independent of mean into the model did not materially improve the accuracy of the predicted risk estimate on average and in some groups actually resulted in a poorer estimate of risk on average (e.g. for women in the 5th decile of risk).

Figure 5.7: Observed and predicted risk by decile of risk for males and females in the validation cohort: reference model

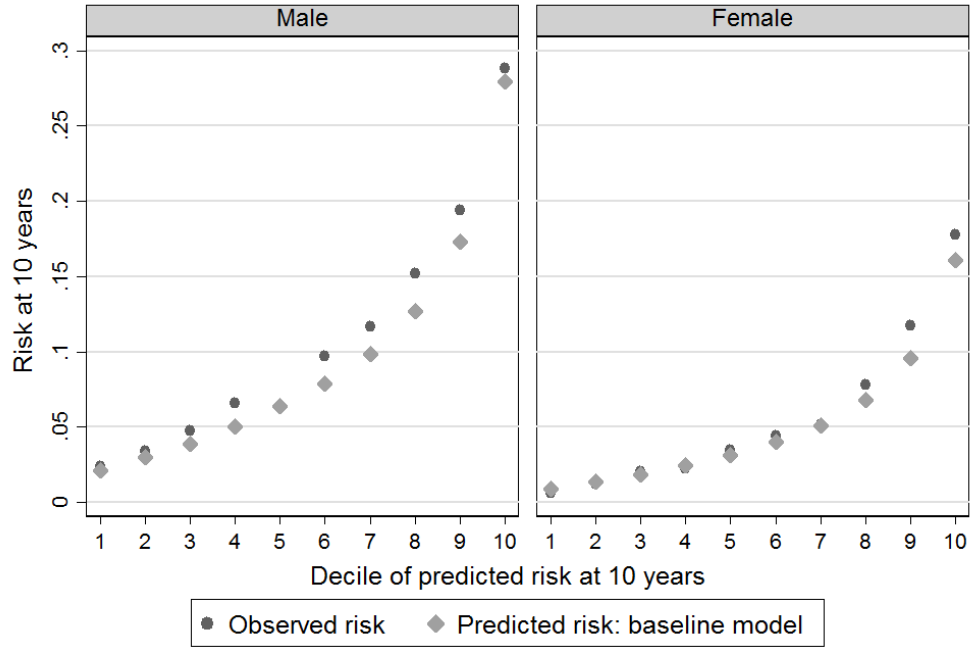
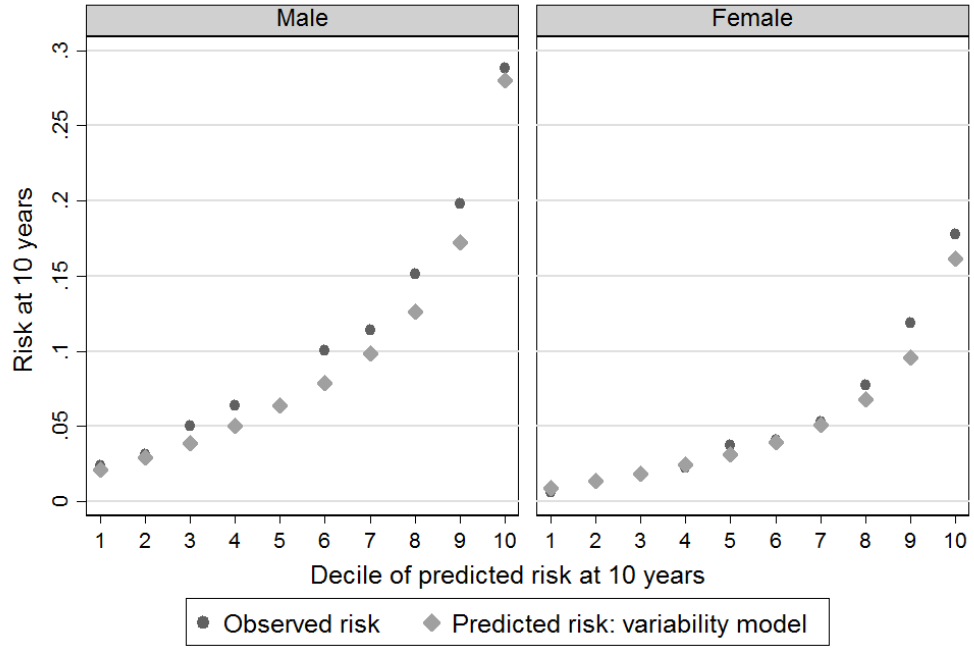


Figure 5.8: Observed and predicted risk by decile of risk for males and females in the validation cohort: variability model



5.5. Discussion

This chapter has shown that in routinely collected primary care data from England, blood pressure variability is a significantly associated with 10-year cardiovascular risk, over and above traditional risk factors. However, including a term for BP variability in a risk score for CVD did not improve the accuracy of the risk score in terms of discrimination, calibration or proportion of people correctly classified into risk groups.

5.5.1. Strengths

This analysis included data from nearly 200,000 individuals with over 9500 events and was large enough in size to detect meaningful differences in risk score performance. The estimated calibration and discrimination of the reference model were similar to published validation estimates for the recommended risk score in the UK (QRISK2) and the previously recommended NICE modified Framingham equation (Table 5.14).(231) This study demonstrated that BP variability has almost no added predictive value given a well performing initial model. It may be reasonable to assume there would be similarly no benefit in modifying other well established risk scores which have already demonstrated good performance, such as the QRISK2 equation, to further accommodate measures of variability.

Table 5.14: Comparison of model performance statistics in this study and published estimates for the QRISK2 and Framingham equations.

	Reference model in this study (ages 40-74)	**QRISK 2011 (ages 35-84)**(231)		**NICE Framingham equation (ages 35-74)**(231)	
	Men and women	Women	Men	Women	Men
c-statistic	0.742	0.802	0.771	0.776	0.750
R-squared	31.8	40.1	33.1	34.2	29.2

The use of routinely collected electronic health records data allowed me to examine the real-world utility of BP variability as a novel risk factor for CVD risk prediction. Previous work to assess the added predictive value of BP variability indices used trial(199) or prospective study data(192) which may not reflect how data is collected and recorded in primary care settings. Furthermore, the CPRD is broadly representative of the UK population,(227) so I am confident this study reflects the current utility of BP variability for CVD risk prediction in those undergoing risk assessments across England.

A previous study assessed the additional benefit of including long-term BP variability in risk algorithms but failed to exclude patients on treatment or to separate the measurement and follow-up periods.(199) The recently published QRISK3 algorithm also failed to account for treatment during the measurement period for BP variability,(94) and hence both these studies may be subject to confounding between BP variability, treatment and outcomes. This study population was carefully selected to limit the potential for confounding due to treatment-induced variability and separation of the measurement and follow-up periods ensures that the observed effects represent true prospective associations.

5.5.2. Limitations

The main limitation of the analyses in Section 5.4 was the large proportion of missing data, particularly with respect to blood pressure. Consequently, a large number of imputations were required to reduce the Monte Carlo error to acceptable levels in the derivation models,(248) and this made the bootstrap validation analysis computationally and practically infeasible. However, optimism is a particular problem in small samples where model over-fitting is more likely.(242) It may be reasonable to assume that optimism in the reference and variability models would be similar given they differ by only a single covariate, and relatively low given the large sample size relative to the number of included

variables. Hence any adjustment would likely have resulted in similar overall differences in model performance. In a sensitivity analysis using BP variability measured over only two readings, where the proportion of missing data was much less, BP variability had a similarly small effect on risk score accuracy in internal validation.

The large amount of missing data in this study may be surprising, as approximately 20% of included participants did not have any BP readings prior to index date. Currently, the Quality and Outcomes Framework (QOF) incentivises GPs to collect BP data at least every five years on all adults aged 45 years and over, and in 2015/16, this was achieved in 91% of patients across England.(14) However, this 91% will include those on antihypertensive medication who have their BP monitored regularly, and the prevalence of hypertension was approximately 13.8% in 2015/16 according to the same QOF report. Hence, in healthier individuals such as those included in this study, QOF data suggests that approximately 77% will have one BP reading in their primary care record in the last five years which is in line with the missing data figures in this study.

In sensitivity analyses using a simpler imputation model for both the derivation and validation datasets, there were slight differences in the reference and variability models; for example average real variability was included in the variability model (instead of variation independent of mean) due to marginal differences in the estimated standardized ratios (although across both analyses, the estimated effect of variability was similar regardless of the measure used and confidence intervals overlapped across all measures). However, in both internal and external validation, there was no significant difference between the performance of the reference and variability models, and so the overall conclusions from this chapter may be considered robust.

It is well documented that many risk scores, and especially those developed using routine databases, may underestimate true untreated risk due to "treatment drop-in" during follow-up.(259) Given the now widespread use of treatments to reduce CVD risk, such as statins, only historical cohorts (e.g. Framingham(260)) are free from this form of bias, despite the fact that most GPs and patients would like to know how risk will be affected by maintaining the status quo. However, methods to effectively limit this form of bias have not yet been developed so I was not able to account for this. Recent investigations into the scale of the problem in CVD risk scores indicate that treatment drop in may affect approximately 15% of people.(261) However, this bias would have affected the estimates of risk in both the reference and variability models so would to some extent cancel out when comparing the two models.

The risk scores I developed may not be generalizable to other populations, such as younger people under the age of 40, or those taking antihypertensive medications. Other risk scores, for example QRISK2 which was developed in patients aged 25 and over and explicitly includes a term for treated hypertension,(41) may be more applicable to such patients. Although I separated the derivation and validation cohorts by region, practices choosing to contribute to CPRD may still be similar to each other in several respects and are known to be larger than those throughout England.(262) Further validations in distinct cohorts would be required to confirm the performance of the derived risk scores.

I did not use data from the Myocardial Infarction National Audit Project (MINAP) to ascertain CVD outcomes and hence some, particularly non-fatal, myocardial infarctions may not have been captured (approximately 92% of myocardial infarction events will have been captured using CPRD and HES data without MINAP).(229) This may have resulted in underestimation of risk in some patients. However, myocardial infarction was only one

component of a composite CVD outcome and other outcomes in the same patient may have been captured. The observed incidence rate of CVD in this study was also similar to that from other database studies of CVD. For example the incidence rate per 1000 person-years in the derivation and validation cohorts was 6.89 and 7.89 respectively, compared to 7.89 in the THIN database,(231) and 8.85 in the QRESEARCH database(41), so the impact of any under-ascertainment of events is unlikely to have been large.

One of the measures of model performance studied, the net reclassification index (NRI), has been criticised because it cannot be interpreted in terms of the clinical benefit of using one model compared to another and can mislead by suggesting an improvement in prediction when there is none.(263) Measures of net-benefit and decision curve analysis have been suggested as more appropriate ways to jointly assess the benefit and harms of using one model over another in order to classify those at high risk and identify who should receive treatment.(264) All of these approaches rely on the assumption that treatment is always given when risk exceeds a certain threshold and is definitely not given when risk is below the threshold. However, this is may not be the case in the context of primary prevention of CVD, since some evidence suggests that fewer than 20% of high-risk patients are subsequently prescribed antihypertensive or statin medication.(157) Hence the risk threshold is, in itself, somewhat arbitrary and these methods are unlikely to exactly reflect the net-benefit of using one model over another in this setting.

5.5.3. Comparisons with existing literature

The estimated association of BP variability on CVD outcomes in this study is at the lower end of the 95% confidence interval for the estimated association calculated from the meta-analysis in Chapter 4 (Figure 4.4). This is to be expected given the use of routinely collected data and that blood pressure is likely to be measured only once unless initial readings are

high (as observed in Chapter 2). This introduces measurement error into the readings available in CPRD (in particular recorded BP may appear less variable and lower on average than true underlying BP if only the last measurement is recorded) and this may have attenuated the blood pressure model parameters. Such an effect may well be compounded if those with truly more variable blood pressure are also more likely to be asked to return for repeat readings, which will be similarly recorded in a biased manner.

Studies assessing the added predictive value of risk factors are common, yet traditional methods of model assessment can be conservative when estimating improvements in model performance.(225) It is therefore unsurprising, given the relatively good performance of the reference model in this study, that the variability model did not predict CVD more accurately according to traditional measures of discrimination and calibration. No improvement was observed even when using newer more sensitive measures of reclassification such as NRI or IDI, despite the observed significant relationship between BP variability and CVD risk in fitted models. This will be due in part to the relatively small association between BP variability and risk, in particular compared to more traditional risk factors, as discussed in Section 4.4.3 and observed in the models derived in this chapter.

Furthermore, such a result is not uncommon in the field of CVD risk prediction and has been observed when assessing the incremental value of many risk factors including: subclinical hyperthyroidism,(265) carotid intima-media thickness,(224) glycated haemoglobin,(266) job strain,(267) genetic variation at chromosome 9p21.3,(268) and combinations of multiple risk factors,(269) to name a few. Indeed, in a further sensitivity analysis in this study, removing gender from the variability model but retaining all other variables had a similarly small effect on internal model performance estimates to that of removing BP variability, despite the hazard ratio for gender being very strong. This study

therefore provides further evidence that there are limited gains to be had by adding new variables to existing risk scores and that possibly, a c-statistic of approximately 0.75 is the optimum achievable based on current methods.

In this study, BP variability independent of mean was found to be the strongest predictor of risk when compared with other measures of visit-to-visit BP variability in terms of the standardized hazard ratio, although differences were small. The literature review described in Chapter 4 was not able to formally compare measures of variability due to the large number of studies considering standard deviation alone and heterogeneity in the other variability measures studied. Of the papers included in the review, few formally compared the strength of the relationship of different measures in variability with CVD and simply used other measures of variability in sensitivity analyses to broadly confirm findings. One study that did, reported the same standardized hazard ratio for both visit-to-visit SD and CV on cardiovascular events(201) and this mirrors the findings here. Informally, in extracted data from five review studies that provided data on the association between at least two measures of visit-to-visit variability and CVD events, the standardized hazard ratio was highest for SD in three cases and highest for CV in the remaining two, but confidence intervals overlapped in all five studies. Future research could seek to more formally determine if certain measures of variability have greater predictive power over others as more data becomes available.

During the final stages of this thesis, an update to the QRISK2 algorithm (QRISK3) was published, including a measure of BP standard deviation in the risk algorithm.(94) There were several methodological differences between the QRISK3 study and this study which may have affected the overall QRISK3 study conclusions and I have raised these with the authors in a response to the study.(270) For example, the QRISK3 study included patients

on antihypertensive treatment and calculated BP variability from a minimum of only two repeat BP readings. Despite these differences, the authors similarly found little additional benefit of including a measure of BP standard deviation on overall risk score calibration and discrimination.

5.5.4. Implications for research and practice

This research shows that there is no benefit to updating existing cardiovascular risk scores used in primary care to include measures of long-term BP variability. Indeed, the large amount of missing data in this study indicates that, even if BP variability measures do have added predictive value in certain sub-populations, they would be of little practical use as the data required is simply not collected. Future research could focus on the added predictive ability of BP variability in the medium and short-term, as measured by home and ambulatory BP, but would be limited in generalisability since patients undergoing out-of-office measurement are likely to be those with suspected hypertension only. Even in these patients, it is unclear whether all measurements or a simple summary value from a 24-hour or week long period would be noted in the clinical record, and practice is likely to vary. Furthermore, despite mean ambulatory BP being a significant predictor of CVD independently of mean clinic BP,(55) its addition to the Framingham risk score did not materially improve discrimination and calibration in a sample of 780 men,(156) so the addition of ambulatory variability measures is likely be similarly disappointing.

The systematic review in Chapter 4 indicated that BP variability may well be more predictive of stroke events than coronary events. Future research could assess the added predictive ability of BP variability for stroke events specifically, but this may be of less use clinically since a larger proportion of deaths were attributable to coronary heart disease than to stroke in both men (16% vs. 6%) and women (10% vs 9%) in 2014.(10) Current

NICE guidelines for primary prevention of CVD also only advocate risk assessment for CVD as a composite end-point.(18)

The utility of BP variability as a predictor of outcomes may be more useful in other settings (e.g. hospitals) where BP monitoring is more systematic and routine, but this has yet to be explored. Research in these settings must give careful consideration to the effect of treatments on BP variability and on outcomes (for example in dialysis patients who may experience intra-dialysis hypo- and hypertension(172,173)) to ensure appropriate controls for confounding effects. In primary care, the assessment of BP variability may also become more feasible as repeat BP measurement becomes more common and the completeness of repeat BP measurement records improves over time, thus expanding the population in whom assessment of variability is feasible. However, additional BP measurement could place a further burden on healthcare professionals who are already facing high workloads(124) and is unlikely to occur unless patient driven self-measurement can be encouraged and recorded more routinely.

This study has raised many methodological questions about missing data methods and how to carry out multiple imputation in electronic healthcare records. Firstly, there is little evidence regarding how to impute summary measures that are calculated across multiple readings (such as means or variability measures) where some or all of the individual readings may be missing. Current evidence suggests that it is better to impute transformations and interactions explicitly,(258) for example by imputing age multiplied by cholesterol as one variable, rather than imputing the components separately (e.g. by imputing age on its own and cholesterol on its own and then creating the new variable from the imputed components). The former is the approach I adopted in this study as means and variability measures may be considered as a special case of such transformations

and interactions. An alternative approach would have been to impute individual BP readings and to calculate summary measures from these. This could have been done using traditional methods or using two-fold fully conditional approaches(271) which account for correlations between repeat measurements recorded in pre-defined time windows.

In imputing summary measures directly, it is unclear how much information from the available readings should be included in the imputation model and whether this should include the raw readings and/ or summary measures (e.g. mean across two, three, four etc. readings). Finally, there is the question of "how much missing data is too much"? Whilst in theory the number of imputed datasets can be increased to cover any given proportion of missing data, computational power becomes prohibitive and results may lack face validity. It is currently unclear where this tipping point lies.

In summary, this chapter has assessed the potential for an improvement in the accuracy of cardiovascular risk estimation by incorporating a measure of long-term visit-to-visit BP variability into a risk score. Adding BP variability to a risk score including several traditional risk factors did not improve either the calibration or discrimination of the score and in fact, the limited number of repeat BP measurements taken in primary care suggests that measurement of BP variability may only be possible in select groups of patients or in other settings in practice.

Chapter 6 Discussion

The research questions addressed in this thesis were borne out of the inherent variability in blood pressure, which makes assessment of an individual's "usual" BP difficult and may in itself be important in determining future CVD risk. In this thesis I have sought to determine how blood pressure readings are obtained during usual practice in primary care and how these readings should best be summarised for use in cardiovascular risk scores. I have considered the use of mean summary measures of BP, where BP variability may be considered as "noise" that inhibits the accurate assessment of "usual" BP levels; and the use of summary measures of BP variability in their own right.

6.1. Summary of findings

In Chapter 1 I reviewed the cardiovascular risk scores that are currently available for use for primary prevention of CVD in a primary care setting and summarized their key properties. This indicated that all established CVD risk scores were developed using a single summary measure of BP measurements taken in a clinic setting, but with considerable variation in accuracy. The risk scores were developed using data from studies that differed in terms of the device used, the period of rest given before or between readings and the total number of BP readings used to calculate a single summary measure of "usual" or mean BP.

On the basis of the initial review work, I undertook a patient survey and prospective study in Chapter 2 to examine how BP is measured in practice and to compare this with current NICE guidance, how BP is measured in risk score derivation studies and how BP is measured in other primary studies with strict measurement protocols. This showed that BP

measurement in practice is not consistent with the strict measurement practices in primary studies. Instead, a second BP reading was taken only if the initial blood pressure reading was high on average and those with sustained high clinic blood pressures were more likely to be asked to monitor their BP at home, potentially missing those with masked hypertension. However, results from Chapter 3 indicated that such differences in approach to BP measurement correspond to only small differences in estimated CVD risk in three popular risk scores. The few patients who were reclassified across treatment thresholds, tended to have risk estimates close to the threshold, so these are unlikely to represent clinically important reclassifications. In post-hoc analysis I demonstrated that larger differences were observed when comparing risk estimates from different risk scores, indicating that the choice of risk score may be the more important decision for GPs to make compared to the choice of which BP measurement to use.

Whereas the research described in Chapter 3 considered the use of different summary measures of mean BP in CVD risk scores and treated BP variability as a "nuisance" factor in the assessment of mean BP, subsequent work in Chapters 4 and 5 considered such variability in BP as a cardiovascular risk factor in its own right. The systematic review and meta-analyses in Chapter 4 showed that BP variability is associated with CVD and mortality outcomes in the short, medium and long-term even when restricting analyses to studies meeting strict methodological criteria. There was considerably more evidence regarding the association of long-term BP variability with outcomes and hence Chapter 5 built on this to determine if the inclusion of long-term BP variability information in risk scores may improve risk prediction, using data from the CPRD. The results in Chapter 5 confirmed that BP variability is predictive of CVD over and above traditional risk factors but this did not translate into a substantial improvement in the accuracy of risk prediction. This analysis also highlighted the difficulties of using routinely collected data to study BP

variability and raised questions about the feasibility of using BP variability information in practice, due to the lack of repeat measurement in most individuals.

6.2. Strengths

The strengths of each individual chapter have been described at length in the respective discussion sections. A key strength of Chapter 2 was the novelty of the survey design used to overcome possible biases that may have arisen due to more traditional direct observation of clinicians. To my knowledge the data collected are unique in this respect.

In Chapter 3; the definition of BP measured according to current practice was informed by the patient survey in Chapter 2, and the risk scores studied were also selected on the basis of the initial review work in Chapter 1. Results from Chapter 3 are therefore likely to accurately reflect the implications of the current practice of BP measurement on cardiovascular risk estimation (as far as current evidence/ knowledge allows) and are applicable to the most relevant and well-used risk scores in UK primary care.

A key strength of the systematic review in Chapter 4 was the inclusion of short, mid- and long term BP variability which had not been studied concurrently previously. The relevance of BP variability measured across several time periods was also confirmed by the survey results in Chapter 2, which indicated that repeat BP measurements are taken routinely in both the long and short term. Furthermore, study design and analysis characteristics which are specific to the problem of studying variability and may confound observed associations were critically assessed. Although this review was not the first in the field, it was the first to critically assess included studies in this way.

The availability of evidence for the association of long-term variability in clinic BP with CVD outcomes subsequently informed the CPRD study described in Chapter 5 and this study was able to build substantially on existing knowledge. In particular, the results from this chapter are likely to have broad generalisability due to the representativeness of CPRD for the UK population as a whole(227) and the risk score developed had similar performance properties to existing scores.(231) Findings were also consistent with those described in the derivation study of the new QRISK3 algorithm, which was published during the write-up of this thesis.(94) A further strength of this work, compared to the QRISK3 analysis, was the careful consideration of the population under study, the BP measurement period and how to define the BP variability measure.

6.3. Limitations

The limitations of each individual chapter have been discussed at length in the respective discussion sections. Limitations of particular relevance to subsequent chapters and to the overall conclusions are discussed below.

The initial review carried out to identify established CVD risk scores that may be used in practice was not a fully specific systematic review, and nor does it purport to provide a comprehensive list of CVD risk calculators that have ever been developed. Indeed, such a systematic review was completed by another research group during the course of this thesis and due to the wealth of research in this area, proved to be a hugely time consuming task; 125 articles concerning the development of one or more CVD risk prediction models and 136 articles describing external validations were identified and the review took nearly three years to complete.(272) Hence it would have been infeasible to conduct such a review as part of this thesis. Many of the risk scores identified by my pragmatic review had very

similar properties and had further risk scores been identified, it is likely they would have been similar. Hence, subsequent decisions taken on the basis of the review (for example to study clinic BP measurement in Chapter 2 or to include certain covariates in the risk score development in Chapter 5) are unlikely to have changed. Furthermore, the risk scores studied in this thesis were selected from those reportedly used by UK general practitioners.(32)

Despite the novelty of the survey described in Chapter 2, results may not be generalizable to all populations due to the use of convenience sampling, self-reported data and a large number of responses from those with diabetes. This may have resulted in the proportion of patients having their BP measured according to NICE guidelines being over-estimated if those responding to the survey were more involved with their healthcare, had fewer health problems and were more affluent, since such patients may receive better quality care due to the inverse care law.(121) The survey results directly influenced the definition of BP measured according to current practice in Chapter 3, and hence results from Chapter 3 may be overly optimistic or pessimistic if BP is measured less or more carefully than results in Chapter 2 suggest. I did, however, study the influence of both more and less careful BP measurement practices on risk estimates in Chapter 3, with similar results. Therefore, results are robust to the possibility of differing BP measurement practices across different populations.

Although results in Chapter 2 were consistent with other recent studies regarding the extent to which hypertension guidance is followed,(129,130) similar studies in other populations or confirmatory studies directly observing clinician behaviour are warranted. In particular, further research is required to establish when a third BP reading is likely to be obtained in practice as only a handful of survey participants had several repeat readings.

A key limitation of Chapter 3 was the lack of outcomes data to assess the accuracy of risk estimates calculated using different measures of "usual" or mean BP. However, because few patients were reclassified across risk thresholds, it is unlikely that using different measures of mean BP in risk scores will substantially affect their discriminative abilities, as a large majority of patients will remain at low or high risk regardless of the BP measurement used. There may be a greater effect on the calibration of risk scores since although median differences in risk were small, substantial differences were observed for some patients (particularly those at high risk) and this could be more formally investigated through validation-type studies using data with CVD outcomes. However, differences in risk were smallest for the recommended risk score in the UK, QRISK2, so the clinical implications of differences in discrimination and calibration are likely to be limited in current practice.

The systematic review evidence from Chapter 4 regarding mid and short-term variability was limited by a lack of data from distinct study populations. Few studies were therefore included in meta-analyses and I was unable to draw strong conclusions regarding the association of shorter term variability with CVD risk. Had this been possible, it is unlikely that the subsequent decision to study long-term BP variability in Chapter 5 would have changed, however, since monitoring over the shorter term is carried out most often in those with high clinic pressures only (as demonstrated in Chapter 2). Furthermore, had BP variability measured over shorter time periods been studied in Chapter 5, results are likely to have been similar since associations for mid- and short-term variability with CVD were similar to those for long-term variability in the review evidence.

Paucity of data prevented comparison of the prognostic significance of different measures of BP variability in Chapter 4. I subsequently studied four different measures of BP

variability in CPRD in Chapter 5. Had it been possible to identify a measure of variability with particular prognostic significance from the review evidence, a different measure of variability might have been included in the developed risk score. However, since the associations between the four BP variability measures studied and CVD risk were similar, this is unlikely to have altered the overall conclusions of Chapter 5.

Analysis of CPRD data encountered several difficulties and was limited by the large proportion of patients without several repeat BP readings. Despite this, findings regarding the relationship between BP variability and CVD outcomes were consistent with those from the systematic review and the difficulties surrounding missing data represent a finding in itself. Unless repeat long-term measurement of BP becomes commonplace, the utility of BP variability information in practice may be reserved to specific patient populations who are closely monitored or to variability measured over the shorter term. Researchers who want to use electronic healthcare records data to study variability or repeat measurements of any biological factors should also carefully consider the population to be studied, to ensure adequate numbers of measurements.

6.4. Methodological research implications

Work in Chapter 2 detailed how blood pressure measurements are obtained in practice and provides some insight into how blood pressure measurements recorded in research databases may be obtained. Despite the many advantages of using electronic healthcare records for research, there are still areas where data accuracy is unknown. Much of the early research in this area focussed on the validity of diagnostic coding in the CPRD database alone,(273,274) rather than the accuracy of measured clinical or demographic variables (with an exception being smoking).(275) Although more recent work has

considered data quality in several databases(229) and, for example, ethnicity,(276) an updated review of studies assessing data quality and validity in electronic healthcare databases is now needed given the expansion of database research in the last ten years.

A related issue is that of missing data in electronic healthcare records which has also been relatively little studied. It is possible that many patients with missing BP data in Chapter 5 had BP readings recorded in free text notes, which are unavailable to researchers. A 2007 study, of general practice notes in the Netherlands, indicated that up to 80% of the numeric data for clinical measurements relevant to diabetes (including BP) were recorded in free text notes alone.(277) Rates of structured data entry may be higher in the UK and may have improved over time (particularly in disease areas incentivised by the Quality and Outcomes Framework),(13) but an updated review as described above could be extended to investigate the rates of free text and structured data recording in UK primary care. If levels of structured data recording were shown to be poor, this may indicate a need for training of clinicians and/or removal of perverse incentives against recoding.

The findings from an updated review of database validity could help to identify knowledge gaps so that studies similar to the "mystery shopper" type study described in Chapter 2 can be carried out for other clinical variables. For example, a similar study could recruit parents of children who have had their capillary refill time assessed (a "red flag" indicator for serious illness in children). Capillary refill time measurement guidance states that the finger is the preferred measurement site and that pressure should be applied for 5 seconds.(278) Such measurement factors could be easily assessed and reported by members of the public with no training. Measurement practices for other clinical variables may be less easily assessed by lay-persons, but it may be possible to design future "mystery-shopper" studies to include an element of patient education and training to overcome this. For example, in

the context of BP measurement, it may be possible to train individuals to recognize when an inappropriately sized measurement cuff is used.

The findings in Chapter 3, that the choice of which risk score to use may be more important than which BP measurement to use in the risk scores, have consequences for research using estimates of cardiovascular risk. Additional sensitivity analyses using estimates of cardiovascular risk calculated using different risk scores may be warranted in other research studies, to ensure that research findings are consistent across risk scores. This would also increase the generalizability of research findings to populations which may have different recommended risk calculators.

As discussed, the assessment of BP variability may be more useful in those who are closely monitored (such as those taking antihypertensive medications) or other populations (such as secondary prevention groups). However, due to the potential confounding effects between treatment change, adherence and BP variability on outcomes (highlighted in the review work in Chapter 4), it will be first be necessary to establish whether there is any association of BP variability with outcomes, when accounting for these confounding factors. This could be done by establishing what level of BP variability may be considered "normal" in patients on treatment, given various treatment regimens/ adherence patterns, and considering the risk associated with variability above these levels, since such increased variability is more likely to be due to other underlying biological mechanisms. Alternatively, more complex statistical methods could be employed to separate BP variability due to treatment and adherence effects from that simply due to biological mechanisms. Joint modelling methods for longitudinal data and survival-type outcomes may be useful for this purpose(279) and this requires further investigation.

It is possible that results in Chapter 5 were confounded by "treatment drop-in" during the follow-up period which may be related to baseline characteristics and affect end outcomes. This problem has been identified previously in the area of cardiovascular risk(259) and is applicable to other clinical areas where treatments are routinely administered and data from historical cohorts (when treatment drop-in was less likely) are uncommon. The extent of this problem in CVD and other clinical areas remains unclear, for example in terms of the proportion of people starting preventive treatment during derivation study follow-up and if certain baseline characteristics are associated with a greater chance of treatment initiation.

Intuitively it seems sensible to assume that those with a greater number of or worse risk factors at baseline are more likely to receive treatment subsequently, and hence risk scores will underestimate risk in these groups in particular. If the extent and nature of the problem can be established then statistical methods to adjust for treatment drop-in, such as inflating risk estimates appropriately, can be developed. Alternatively, healthcare professionals could receive further training and education to increase their understanding and awareness of the issue, allowing them to make more flexible clinical judgements compared to adjusting the risk scores explicitly.

Results from Chapter 5 and other similar studies in the field show very limited gains from adding novel risk factors into CVD risk equations. Future research could investigate the relationship between the predictive ability of existing risk scores and the potential for improvement in risk score accuracy based on the strength of the association between a novel risk factor and outcomes. Such research could seek to determine a general "rule" to indicate when carrying out a formal derivation and validation study may be worthwhile, for example by providing an answer to the question "How big an association does a novel risk factor need to have with outcomes, in order to improve on the current risk score accuracy

of x?" This generic approach could guide researchers in any field and prevent research waste.

It has also previously been noted that cardiovascular risk scores may not accurately estimate high risks and that published estimates of population level accuracy may be driven by the majority of low risk patients.(280) Hence if substantial improvements in the accuracy of population level risk prediction cannot be made; future research could focus on how to improve risk score accuracy at the patient level. However, if the majority of the patient-level improvements in accuracy are to be made in those already considered at high risk, the clinical implications are likely to be negligible.

6.5. Clinical research implications

Findings from Chapter 2, that BP monitoring in routine practice is quite different from that in primary studies, have implications for how future research is conducted and implemented. Although I demonstrated in Chapter 3 that these differences may have a small effect on cardiovascular risk estimation on average, there may be certain groups in whom differences in risk are more marked e.g. those with large masked or white coat BP effects and this could be further studied. Furthermore, these findings have a more direct implication for the diagnosis and treatment of hypertension, since the majority of the evidence regarding BP treatment comes from controlled trials with strict BP measurement protocols.

Future research could address how existing evidence should be implemented, with appropriate consideration of BP measurement differences (e.g. in the form of adjusted treatment targets), or investigate how the benefits and harms of treatments may be altered in practice if BP measurement differences are ignored (including which patients would be

most affected). Alternatively, the barriers to more careful measurement of BP in practice could be explored (e.g. lack of dual cuff monitors) and interventions to encourage more careful BP measurement by healthcare professionals could be developed and tested. These two research areas could be prioritised initially to maintain the relevance of traditional trial evidence to routine care. However, going forward it may be more important to examine BP related interventions in more pragmatic trials, with BP measured as in routine care. Such trials could also seek to measure BP more carefully in parallel, as this would help to establish how findings from traditional trials may differ to what is observed routinely.

Despite the observed associations between visit-to-visit BP variability and outcomes in both Chapters 4 and 5, the mechanisms responsible for long-term BP variability are little understood. For example, there is currently no evidence that reducing BP variability will lead to reductions in cardiovascular risk in the same way as for mean BP,(22) or cholesterol.(24) Evidence from BP-lowering trials has suggested that certain drug classes may be more effective than others at stabilising BP (e.g. calcium channel blockers compared to beta-blockers),(67) but drugs have yet to be compared in a head-to-head manner with the explicit aim of reducing BP variability. Since I have established that BP variability is of minimal use in predicting CVD risk, future trials could address these issues to establish whether BP variability is something that can be monitored and intervened upon in primary care.

The confounding issues relevant to long-term BP variability (mentioned above) are less important in the short and mid-term. However, the lack of evidence from distinct studies in Chapter 4 means that further study in novel cohorts is required to draw conclusions about the utility of shorter term variability in practice. Questions over whether BP

variability can and should be monitored or altered, as discussed above regarding long-term BP variability, are just as applicable in the shorter term.

Compared to longer term BP variability, mid- and short-term variability may have an additional role to play in assessing medication adherence. It has previously been shown that monitoring mean clinic BP is a poor way of detecting non-adherence to medication,(281) and it has also been shown that poor adherence explains only a small proportion of visit-to-visit variability in BP,(61) and its subsequent relationship with outcomes,(282) so it is unlikely that long term variability will be useful in identifying non-adherent patients. However shorter-term home or ambulatory BP variability may well be more immediately influenced by medication adherence, and the potential for this to be exploited to identify non-adherence could be further explored.

Blood pressure is one of many biological variables that are subject to variability over time, such as lipids.(283) Future research could investigate the relationships between variability in such biological variables and outcomes, if a plausible mechanism exists, and this has indeed begun in the case of cholesterol,(284) and blood glucose.(285) It will be important. however, for future work to adequately address the common pitfalls of variability research (as identified in Chapter 4) to ensure that initial findings are not subject to the same confounding (e.g. due to treatment effects) and biases (e.g. immortal time bias) demonstrated in the BP variability literature.

6.6. Implications for practice

Overall, results from this thesis indicate that healthcare professionals should estimate risk for primary prevention of CVD using mean summary measures of the BP measurements available to them, regardless of whether they are measured in the clinic, at home or through

ABPM. However, GPs may wish to more carefully consider the choice of BP measurement in patients known to have substantial masked or white-coat effects or those with risk estimates close to treatment thresholds, where the use of alternative BP measurements may affect individual risk classifications. Calculating risk based on one or two alternative BP readings may be warranted in either of these cases. However, the choice of which risk score to use may be a more important decision and have greater implications for estimated patient risk and subsequent treatment decisions.

Due to the strong evidence linking long-term BP variability with outcomes demonstrated in Chapters 4 and 5, clinicians should perhaps interpret high BP variability cautiously until the mechanisms of BP variability can be more fully understood, particularly in those with treated hypertension where medication change and adherence play a role. Since interventions which may reduce BP variability also reduce mean blood pressure (e.g. calcium channel blockers),(60) data showing these are beneficial in reducing cardiovascular risk over and above their effect on mean blood pressure are required before monitoring of, and intervening on, BP variability is to become a priority.

Key areas of potential improvement in practice, identified by the survey work in Chapter 2, are the measurement of BP in both arms and consideration of potential masked hypertension effects in patients with apparently normotensive BP in clinic. The former could be implemented straightforwardly through the purchase of appropriate dual-cuff BP monitors, so that measurement in a second arm does not unnecessarily increase the length of a consultation, but would need additional funding. For the latter, the PROOF-BP algorithm(134) can be easily accessed online although it does require three repeat BP measurements to be taken and would likely increase the burden of BP measurement compared to current practice. However, a stricter routine measurement procedure across

all individuals, regardless of their initial BP level, would be more in line with procedures from primary research studies and may make it easier for clinicians to interpret and apply findings from clinical trials to their everyday practice.

6.7. Other relevant avenues of research

As part of this thesis I have highlighted the differences between BP measurement during routine appointments and primary research studies. Questions over how best to determine an individual's "usual" mean BP in a clinic setting are also applicable to BP measurements taken at home. Current NICE hypertension guidance is based on the prognostic utility and reproducibility of BP measurements obtained over different home monitoring schedules,(1) but specific aspects of the schedules have been differentially studied. Although several studies have considered whether to discard any home BP measurements,(147,286–288) few have considered the interval between measurements,(289) and these aspects should be studied in more detail. Related research could also consider to what extent patients are directed to follow the recommended schedules by GPs, and whether patients subsequently follow this advice in practice.

Although I have primarily considered home BP measurement due to its role in the diagnosis of hypertension and stronger association with CVD outcomes compared to clinic BP, patient self-monitoring of BP has been increasingly studied as an intervention in its own right. It has been shown to improve adherence to medication,(290) and, when coupled with self-management of medication, to improve BP control.(291,292) The role of self-monitoring and self-management of BP in new populations (e.g. pregnancy),(293) whilst far beyond the scope of this thesis, is likely to be a priority for future research.

Despite the large number of risk scores that have been developed for predicting cardiovascular disease, their recommended use in clinical guidelines,(18) and their use as part of national screening programs (such as the NHS Health Check in England),(228) few studies have assessed the impact of their use on patient health outcomes. A 2016 systematic review of studies assessing the impact of risk scores compared to usual care in several disease areas in primary care, found only six studies relevant to cardiovascular disease.(294) A further overview of impact studies specifically relevant to primary prevention of cardiovascular disease found that existing review evidence was of poor quality and there was no evidence that global cardiovascular risk assessment reduced cardiovascular morbidity and mortality.(295) Although risk assessment did have positive effects on intermediate outcomes, such as blood pressure, the authors noted that these may not translate into reductions in risk and events unless sustained in the long-term. A Cochrane review of trials assessing more general health check programs also found no effect on cardiovascular mortality and noted, importantly, that possible negative consequences of (e.g. hospital admissions, psychological distress or absence from work) were little studied.(296) Hence there is a need to assess the impact of cardiovascular risk assessment through high quality methods, with particular reference to hard outcomes and possible negative consequences.

Since the introduction of risk screening programs is relatively novel, the need for, and costs associated with, long-term follow-up to assess cardiovascular outcomes may have been a barrier to their evaluation historically. However, observational studies could now play a role in establishing the usefulness of screening for high risk patients. For example, a recent study examined the impact of the Scottish Keep Well initiative (a program in deprived areas that is analogous to the NHS health check in England) through interrupted time series and found that since its introduction in 2006, the initiative had had little effect on

prescribing or on coronary heart disease or stroke hospitalisations and mortality.(297) Although one study in England has similarly shown that there was no impact of NHS health checks on the prevalence of five conditions, including CVD, in practices that did/ did not provide health checks over a three year period, it was only conducted in 79 practices in the Midlands, did not randomize practices, and may have been subject to residual confounding.(298) Given that there is now more than eight years of follow-up since the introduction of NHS Health Checks in England, an interrupted time series analysis, similar to that conducted in Scotland, may now be feasible to assess the impact of NHS Health Checks on hard cardiovascular outcomes.

The possibly limited effect of cardiovascular risk assessment on health outcomes may be due to suboptimal uptake of such risk assessment programs. Only 30% of eligible individuals attended an NHS Health Check in 2012/13.(299) Furthermore, of those undergoing risk assessment and being identified as high risk, prescribing of statins in the subsequent 12 months occurred in only approximately 20% of patients and even less frequently for antihypertensive medication.(157) The reasons for this may be related to variation in the delivery of the program at the practice level(300) or variability in the individual patient experience and subsequent non-adherence with recommended treatment or lifestyle change.(301) Lack of understanding of risk and problems with risk communication for both the patient(302) and the healthcare professional(303,304) may also play a role.

Future research could seek to determine which of these factors (if any) explain the limited impact of risk assessment programs and ways in which to improve them. Practitioners should consider different risk presentations for their patients, for example the use of "heart age" as currently implemented by the Joint British Societies risk score,(19) or Cates plots

which convey both relative and absolute risks using coloured face diagrams.(305) Strategies that have been shown to have positive effects on medication adherence could also be recommended more widely, for example patient self-monitoring of blood pressure at home has been shown to improve adherence to antihypertensive medication(290) but may not be as widely practiced in the UK(306) compared to elsewhere.(307)

Given the lack of real-world evidence regarding the impact of risk assessment and subsequent treatment on outcomes, it is perhaps surprising that treating all patients with risk over certain thresholds has been shown to be cost-effective.(18,308) However, these analyses may have optimistic assumptions regarding uptake and adherence compared to what has been observed in practice. For example, analysis of the recommended US risk threshold assumed statin adherence rates of 67% initially, dropping to 50% after 3 years, based on published estimates from filled prescriptions.(308) However, much lower levels of adherence have been observed in the UK,(157) and real-world costs of implementing the recommended risk thresholds may be much higher than current evidence suggests.

6.8. Concluding remarks

In conclusion, this thesis has shown that despite the inherent variability in blood pressure, cardiovascular risk estimation for the primary prevention of CVD need not account for this variability, either through the choice of particular summary measures of mean BP for use in existing risk scores or through the specific inclusion of BP variability as a risk factor.

Priorities for future research stemming from this thesis include methodological research to establish how to estimate the association of BP variability with outcomes, with appropriate adjustment for medication change, adherence and other relevant confounders. Clinical research should focus on whether the additional cardiovascular risk associated with

increased BP variability can be altered through interventions to reduce variability. In practice, GPs should more carefully consider how their BP measurement practices may differ from that in primary studies and how this may affect the application of trial evidence to everyday practice. More generally, the future of cardiovascular risk prediction and screening will depend on research to demonstrate its benefit for hard patient outcomes and the maximisation of any potential benefits routinely.

Appendices

Appendix A Survey documents

Document A.1: Survey advert

NUFFIELD DEPARTMENT OF
PRIMARY CARE
HEALTH SCIENCES

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Sarah Stevens
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Sarah Stevens, a doctoral research student at the University of Oxford, is investigating how doctors and nurses measure blood pressure during routine general practice (GP) appointments. The study hopes to find out how people have their blood pressure measured in daily practice. This includes how many times blood pressure is measured during each appointment and if the number of measurements taken changes depending on the patient's health or the value of the blood pressure reading itself. It also hopes to discover how many patients are recommended to measure their blood pressure at home and how this is accomplished.

We are looking for volunteers to complete two short surveys about their experiences of having their blood pressure measured. In total, both questionnaires will take no more than 15 minutes to complete. To take part online please visit: https://ctu2.phc.ox.ac.uk/bp-survey1. For more information, please contact Sarah Stevens by email or phone: sarah.stevens@phc.ox.ac.uk; 01865 289449.

Document A.2: Survey information sheet

NUFFIELD DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES

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Survey of blood pressure measurement in primary care: Information
(CUREC ethics reference: MS-IDREC-C1-2015-095)

This survey aims to find out how individuals are having their blood pressure measured by their doctors (general practitioners (GPs)) or nurses as part of routine appointments. The research is being carried out by Sarah Stevens who is a doctoral research student in the Nuffield Department of Primary Care Health Sciences, University of Oxford (sarah.stevens@phc.ox.ac.uk, 01865 289449). This survey has two parts. You may participate in just the first part (below), or both parts. To participate in the second survey, the researcher will need to contact you by email and will need your consent to do this. You may choose to withdraw from the second survey at any time by advising the researchers of this decision.

All information provided and obtained will be treated with the strictest confidentiality. The data will be held on secure University of Oxford computers in accordance with the Data Protection Act. This research will be published in peer-reviewed journals and presented at research meetings. The University of Oxford is committed to the dissemination of its research for the benefit of society and the economy and, in support of this commitment, has established an online archive of research materials. This archive includes digital copies of student theses successfully submitted as part of a University of Oxford postgraduate degree programme. Holding the archive online gives easy access for researchers to the full text of freely available theses, thereby increasing the likely impact and use of that research. If you agree to participate in this project, the research will be written up as a thesis. On successful submission of the thesis, it will be deposited both in print and online in the University archives, to facilitate its use in future research. The thesis will be published with open access, meaning it will be available to every internet user.

This project has been reviewed by, and received ethics clearance through, the University of Oxford Central University Research Ethics Committee. If you have a concern about any aspect of this project, please speak to the relevant researcher (Sarah Stevens, 01865 289449) who will do her best to answer your query. The researcher should acknowledge your concern within 10 working days and give you an indication of how she intends to deal with it. If you remain unhappy or wish to make a formal complaint, please contact the chair of the Research Ethics Committee at the University of Oxford: Chair, **Medical Sciences Inter-Divisional Research Ethics Committee**; Email: ethics@medsci.ox.ac.uk; Address: Research Services, University of Oxford, Wellington Square, Oxford OX1 2JD.

Document A.3: Initial survey

NUFFIELD DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES

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Survey of blood pressure measurement in primary care (Survey 1)

Q1 Have you got high blood pressure or have you ever been told by your GP that you have high blood pressure?
- ☐ Yes. Go to Q2
- ☐ No. Go to Q3

Q2 Do you take any medication for your high blood pressure?
- ☐ Yes
- ☐ No

Q3 When was your last appointment with a GP or practice nurse at your general practice surgery?
- ☐ In the last week
- ☐ In the last month
- ☐ In the last 6 months
- ☐ In the last year
- ☐ More than a year ago
- ☐ Can't remember

Q4 Who was your last appointment at the surgery with?
- ☐ GP
- ☐ Nurse
- ☐ Can't remember

Q5 Was your blood pressure measured during your last appointment?
- ☐ Yes, by a GP. Go to Q6
- ☐ Yes, by a nurse. Go to Q6
- ☐ Yes, by yourself in the waiting room. Go to Q6.
- ☐ No. Go to Q9
- ☐ Can't remember

Q6 How many times was your blood pressure measured during the appointment? Count one measurement for each time the cuff on your arm went up.
- ☐ Once
- ☐ Twice
- ☐ Three times
- ☐ Four or more times
- ☐ Can't remember

Q7 Did your GP/ nurse tell you your blood pressure reading or discuss it with you?
- ☐ Yes
- ☐ No
- ☐ Can't remember

Q8 Do you know your blood pressure reading from the appointment?
- ☐ Yes. Go to Q9
- ☐ No. Go to Q10
- ☐ Wasn't told. Go to Q10
- ☐ Can't remember. Go to Q10

Q9 What was your blood pressure reading during the appointment?
(Your blood pressure consists of two numbers: systolic pressure and diastolic pressure. Systolic pressure is always the larger of the two numbers. For example if your blood pressure was 130/80 mmHg, 130 is the systolic reading and 80 is the diastolic reading.)

Systolic _____ Diastolic _____

Q10 During your last appointment, were you asked to measure your blood pressure yourself away from the practice e.g. at home?

- ☐ Yes
- ☐ No
- ☐ Can't remember

Q11 Have you ever had your blood pressure measured on both arms at the same appointment?

- ☐ Yes
- ☐ No
- ☐ Can't remember

Q12 Are you

- ☐ Male
- ☐ Female

Q13 How old are you? _____ years

Q14 Do you currently smoke?

- ☐ Yes
- ☐ No

Q15 Do you take any medication for high cholesterol e.g. statins?

- ☐ Yes
- ☐ No

Q16 Have you ever been told by your GP that you have had any of the following conditions or a chronic condition?
(Tick all that apply)

- ☐ Diabetes (Type 1 or Type 2)
- ☐ Chronic kidney disease
- ☐ Stroke
- ☐ Heart attack
- ☐ Irregular heart beat (atrial fibrillation)
- ☐ Rheumatoid arthritis
- ☐ At high risk of having a heart attack or stroke
- ☐ Other. Please specify _____
- ☐ None of the above

Q17 How did you hear about this survey?

- ☐ University of the Third Age
- ☐ Blood Pressure UK
- ☐ Other. Please specify _____

Q18 Please provide the first half of your postcode (e.g. ME19 4SH would be ME19. This will be used to analyse results by area only)

_____

Q19 When do you expect your next appointment with your GP or nurse at your general practice surgery to be (confirmed or possible)?

- ☐ In the next week
- ☐ In the next two weeks
- ☐ In the next month
- ☐ In the next 3 months
- ☐ Don't know
- ☐ None scheduled

Q20 Would you be prepared to take part in a short (5 minute) follow-on survey after your next appointment?
(The follow-on survey will ask further, similar questions about whether and how your blood pressure was measured at the appointment. This will include how many times your blood pressure was measured and what the level of your blood pressure was.)

- ☐ Yes (Go to Q21)
- ☐ No (END)

Q21 In order to take part in the follow-on survey, the researcher will need to contact you by email and needs your consent to do this. Please complete the following participant declaration:

a) I have read the study information above, had the opportunity to ask questions and have received satisfactory answers (Q1 of 8)
- ☐ Yes

b) I understand that this project has been reviewed by, and received ethics clearance through, the University of Oxford Central University Research Ethics Committee (Q2 of 8)
- ☐ Yes

c) I understand that my participation is voluntary and I am free to withdraw myself and my data at any time, without giving any reason, and without any adverse consequences (Q3 of 8)
- ☐ Yes

d) I understand who will have access to personal data provided (Q4 of 8)
- ☐ Yes

e) I understand that personal data will be stored according to the Data Protection Act and will only be accessed by researchers from the Nuffield Department of Primary Care Health Sciences, University of Oxford (Q5 of 8)
- ☐ Yes

f) I understand that the research will be written up and published peer-reviewed journals, presented at research meetings and published online as part of a student thesis, deposited both in print and online in the University of Oxford archives (Q6 of 8)
- ☐ Yes

g) I understand how to raise concerns or make a complaint (Q7 of 8)
- ☐ Yes

h) I agree to take part in the study (Q8 of 8)
- ☐ Yes

i) Please enter your email address (This will only be used to contact you via email)

_____

Thank you for taking the time to complete this survey.

Document A.4: Survey email

NUFFIELD DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES

Nuffield Department of Primary Care Health Sciences · University of Oxford · New Radcliffe House · Radcliffe Observatory Quarter · Woodstock Road · Oxford OX2 6GG · www.phc.ox.ac.uk

Sarah Stevens
+44 (0)1865 289449 · sarah.stevens@phc.ox.ac.uk

Subject: Patient survey of blood pressure measurement in primary care, University of Oxford

Dear participant,

You are receiving this email because you recently took part in an online survey about blood pressure measurement in primary care, run by the Nuffield Department of Primary Care Health Sciences, University of Oxford (CUREC ethics reference: MS-IDREC-C1-2015-095). In your responses, you indicated that you would be willing to take part in a follow-up survey after your next appointment at your general practice surgery. According to the information provided, you recently had another appointment and can now complete the follow-up survey.

If you are still happy to take part in the follow-up survey, please visit: https://ctu2.phc.ox.ac.uk/bp-survey2. If your appointment has changed, please only complete the follow-up survey after your next appointment.

If you have any questions, please feel free to contact me by email or on the phone (sarah.stevens@phc.ox.ac.uk, 01865 289449). If you no longer wish to take part, please disregard this email.

Thank you very much for your time.
Kind regards,

Document A.5: Follow-up survey

NUFFIELD DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES

Nuffield Department of Primary Care Health Sciences • University of Oxford • New Radcliffe House • Radcliffe Observatory Quarter • Woodstock Road • Oxford OX2 6GG • www.phc.ox.ac.uk

Sarah Stevens
+44 (0)1865 289449 • sarah.stevens@phc.ox.ac.uk

Survey of blood pressure measurement in primary care (Survey 2)

Q1 Please enter your email address (the email address given in survey 1. This will be used to match your responses from both surveys.)

Email address _____

Q3 When was your last appointment with a GP or practice nurse at your general practice surgery?

- ☐ In the last week
- ☐ In the last month
- ☐ In the last 6 months
- ☐ In the last year
- ☐ More than a year ago
- ☐ Can't remember

Q4 Who was your last appointment at the surgery with?

- ☐ GP
- ☐ Nurse
- ☐ Can't remember

Q5 Was your blood pressure measured during your last appointment?

- ☐ Yes, by a GP. Go to Q6
- ☐ Yes, by a nurse. Go to Q6
- ☐ Yes, by yourself in the waiting room. Go to Q6.
- ☐ No. Go to Q9
- ☐ Can't remember

Q6 How many times was your blood pressure measured during the appointment? Count one measurement for each time the cuff on your arm went up.

- ☐ Once
- ☐ Twice
- ☐ Three times
- ☐ Four or more times
- ☐ Can't remember

Q7 Did your GP/ nurse tell you your blood pressure level or discuss it with you?

- ☐ Yes
- ☐ No
- ☐ Can't remember

Q8 Do you know your blood pressure reading from the appointment?

- ☐ Yes. Go to Q9
- ☐ No. Go to Q10
- ☐ Wasn't told. Go to Q10
- ☐ Can't remember. Go to Q10

Q9 What was your blood pressure reading during the appointment?
(Your blood pressure consists of two numbers: systolic pressure and diastolic pressure. Systolic pressure is always the larger of the two numbers. For example if your blood pressure was 130/80 mmHg, 130 is the systolic reading and 80 is the diastolic reading.)

	Systolic	Diastolic
First measurement	_____	_____
Second measurement	_____	_____
Third measurement	_____	_____

Q10 During your last appointment, were you asked to measure your blood pressure yourself away from the practice e.g. at home?

- ☐ Yes
- ☐ No
- ☐ Can't remember

Thank you for taking the time to complete this survey.

Appendix B Systematic review

Document B.1: Systematic review publication

Blood pressure variability and cardiovascular disease: systematic review and meta-analysis

Sarah L Stevens,[1] Sally Wood,[1] Constantinos Koshiaris,[1] Kathryn Law,[1] Paul Glasziou,[2] Richard J Stevens,[1] Richard J McManus[1]

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Additional material is published online only. To view please visit the journal online.

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ABSTRACT

OBJECTIVE
To systematically review studies quantifying the associations of long term (clinic), mid-term (home), and short term (ambulatory) variability in blood pressure, independent of mean blood pressure, with cardiovascular disease events and mortality.

DATA SOURCES
Medline, Embase, Cinahl, and Web of Science, searched to 15 February 2016 for full text articles in English.

ELIGIBILITY CRITERIA FOR STUDY SELECTION
Prospective cohort studies or clinical trials in adults, except those in patients receiving haemodialysis, where the condition may directly impact blood pressure variability. Standardised hazard ratios were extracted and, if there was little risk of confounding, combined using random effects meta-analysis in main analyses. Outcomes included all cause and cardiovascular disease mortality and cardiovascular disease events. Measures of variability included standard deviation, coefficient of variation, variation independent of mean, and average real variability, but not night dipping or day-night variation.

RESULTS
41 papers representing 19 observational cohort studies and 17 clinical trial cohorts, comprising 46 separate analyses were identified. Long term variability in blood pressure was studied in 24 papers, mid-term in four, and short-term in 15 (two studied both long term and short term variability). Results from 23 analyses were excluded from main analyses owing to high risks of confounding. Increased long term variability in systolic blood pressure was associated with risk of all cause mortality (hazard ratio 1.15, 95% confidence interval 1.09 to 1.22), cardiovascular disease mortality (1.18, 1.09 to 1.28), cardiovascular disease events (1.18, 1.07 to 1.30), coronary heart disease (1.10, 1.04 to 1.16), and stroke (1.15, 1.04 to 1.27). Increased mid-term and short term variability in daytime systolic blood pressure were also associated with all cause mortality (1.15, 1.06 to 1.26 and 1.10, 1.04 to 1.16, respectively).

CONCLUSIONS
Long term variability in blood pressure is associated with cardiovascular and mortality outcomes, over and above the effect of mean blood pressure. Associations are similar in magnitude to those of cholesterol measures with cardiovascular disease. Limited data for mid-term and short term variability showed similar associations. Future work should focus on the clinical implications of assessment of variability in blood pressure and avoid the common confounding pitfalls observed to date.

SYSTEMATIC REVIEW REGISTRATION
PROSPERO CRD42014015695.

WHAT IS ALREADY KNOWN ON THIS TOPIC

It is well established that patients with high blood pressure are at higher risk of future cardiovascular disease

Some studies have also suggested that patients with higher variability in blood pressure over time are at higher risk compared with patients with the same mean blood pressure level

It is not clear whether this risk depends on the method of measurement of variability, and few have correctly accounted for mean blood pressure or changes in treatment

WHAT THIS STUDY ADDS

Methodological errors are present in approximately half of prospective studies of blood pressure variability, but the association of long term (clinic) variability in blood pressure with future cardiovascular disease is found even in studies that avoid errors

Mid-term and short term variability in blood pressure measured at home or by ambulatory monitoring, respectively, has been little studied comparatively, but shows similar associations with outcomes

Introduction

Blood pressure is a leading risk factor for cardiovascular disease.[1 2] Most studies have used mean blood pressure as the indicator of risk, measured in clinic or "out of office" settings.[3-5] However, blood pressure shows noticeable oscillations over the short and long term.[6] Historically, variability in blood pressure has been viewed as inhibiting accurate measurement of mean blood pressure and as a phenomenon to be overcome by improved monitoring.[7] For at least two decades, this variability has also been recognised as a potential risk factor in its own right.[8 9] In 2010 an analysis of three cohort studies and two randomised trials found that long term variability in blood pressure was a predictor of stroke and coronary events in high risk patients.[10]

However, understanding this variability has been hampered by statistical and clinical methodological problems. Some analyses of variability have not adjusted for mean blood pressure, potentially confounding high variability with high mean blood pressure,[11] or have adjusted for a mean that is not fully consistent with the variability measure.[12] Others, in using 24 hour mean to adjust for daytime variability, might have turned high daytime variability into a surrogate marker for nocturnal or 24 hour blood pressure.[13] Further studies have defined variability on the basis of measurements taken during follow-up, but analysed it as a baseline risk factor,[14-16] potentially introducing problems of informative censoring or immortal time bias.[17] Informative censoring occurs when reasons for loss to follow-up are confounded with the exposure

(eg, if individuals with extreme or erratic blood pressures are withdrawn from studies because of concerns about safety). Immortal time bias can occur if individuals are required to have a certain number of blood pressure measurements in order to be included in analysis for mortality outcomes. The time up until the qualifying measurement becomes "immortal time," because, by definition, death could not occur earlier.

Other studies failed to use consistent blood pressure monitoring equipment over time, to define a consistent measurement protocol, or to account for change in drugs, leaving doubt as to the source of any observed variability.[14 18 19] Measurement at different times of the day[20] or year,[21] in different arms,[22] or using inconsistent cuff sizes[23] can affect accurate measurement, thereby inducing variability. We reviewed prospective studies in adults that quantified the associations of blood pressure variability with cardiovascular events and mortality, independent of mean blood pressure. Our main analysis focused on studies meeting prespecified methodological criteria, so that any apparent effect of variability was likely to be a true independent effect.

Methods

Study selection

We searched Medline, Embase, Cinahl, and Web of Science to 15 February 2016 for full text articles in English describing trials and prospective cohort studies in adults that assessed the association of periods of variability in blood pressure with cardiovascular outcomes (see supplementary table e1). Long term variability was measured through clinic blood pressure monitoring, mid-term through home monitoring, and short term through ambulatory monitoring. Studies included in recent systematic reviews[24-27] were also screened. Two reviewers (SW/SS and KL/KC) scrutinised the titles and abstracts, with adjudication by a third reviewer (RM).

Inclusion and exclusion criteria

Studies had to consider at least one of the following outcomes: all cause mortality, cardiovascular events (including stroke, myocardial infarction, coronary heart disease, and heart failure), or cardiovascular mortality (including sudden death). We excluded studies only assessing intermediate outcomes (eg, arterial intima media thickness) or concerning nocturnal dipping or day-night variation, as these have been considered previously.[28]

Studies in disease specific populations (eg, people with diabetes) were included, except those in patients receiving haemodialysis where changes in blood pressure (intradialysis hypotension and hypertension[29 30]) are common and have been shown to be associated with hospital admission and mortality.[31 32]

Included studies had at least 2500 person years of follow-up. Blood pressure variability was assessed in the long term (in clinics), mid-term (at home), or short term (through ambulatory monitoring). Studies of clinic monitoring had to measure visit-to-visit variability over at least five clinic visits. Studies of home monitoring had to consider day-by-day variability over at least 12 measurements on at least three days.[33] Studies for ambulatory monitoring had to assess variability up to 24 hours, with at least 14 daytime readings.[33]

Data extraction

Using prespecified forms, two reviewers (SS/SW and KL/RM) independently extracted data on study and patient characteristics and two (SS and KC/RS) on statistical results (see supplementary table e2). Hazard ratios were extracted for every variability measure and outcome. The hazard ratio from the analysis with the greatest adjustment for confounders but containing only a single variability measure was extracted. Where required data were not available, we emailed the study authors.

Data analysis and statistical methods

Hazard ratios were converted to standardised hazard ratios, using a general method for regression models (see supplementary table e3).[34] Briefly, a standardised log-hazard ratio was calculated as the log-hazard ratio for each unit of standardised blood pressure variability (blood pressure variability divided by its sample standard deviation). These were pooled using a random effects meta-analysis, stratified by outcome. Separate analyses were performed for each period of variability (long term, mid-term, or short term). Heterogeneity was assessed using the χ^2 test and I^2 statistic.

Where studies used multiple measures of variability, we included hazard ratios in analysis according to the following hierarchy (preferred to least preferred): standard deviation, coefficient of variation, variation independent of mean, average real variability, standardised residual, root successive variance, and other. Where hazard ratios were calculated using data from the same primary study but reported in different papers, we included the most recently published hazard ratio. We combined the hazard ratios for study subgroups before inclusion.

Two reviewers (SS and RS) independently assessed the risk of bias using the QUIPS tool,[35] with adjudication by a third reviewer (RM). We also extracted information about other potential confounders, specific to studies of blood pressure variability (see supplementary table e2). Consistency of blood pressure measurement with respect to device, cuff size, staff, and measurement is important to prevent inducing the variability. The impact of other potential confounders may be adjusted for during analyses. We decided (a priori) to include in main analyses only hazard ratios that were correctly adjusted for the equivalent mean blood pressure level (eg, adjusted for mean daytime systolic blood pressure if variability was assessed for daytime systolic blood pressure), where outcome ascertainment took place after the blood pressure measurement period and, for studies involving antihypertensive treatment, where at least 80% of patients were adherent to treatment or did not change drugs during the measurement period, or where patients were censored at the point of change of treatment. We carried out secondary analyses including all studies.

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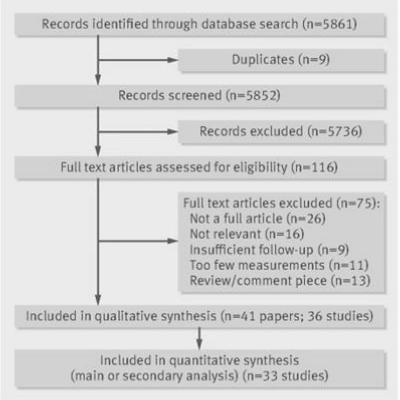

Fig 1 | Study screening flowchart

Publication bias was assessed by Egger's test.[36] However, since this has low power for small numbers of studies, we also calculated the number of null effect studies of mean weight that would need to be included in meta-analyses to result in a non-significant pooled effect (known as fail-safe N).[37]

Patient involvement

Two lay representatives contributed to the design and content of the National Institute for Health Research programme grant from which this work arose. Results from this work have been presented as part of the wider programme at regular steering group meetings.

Results

Searches identified 5861 references. Removal of duplicates and screening by two reviewers yielded 41 full text articles for inclusion (fig 1). These 41 papers represented 19 observational cohort studies and 17 clinical trial cohorts, and 46 separate analyses (see supplementary table e4). Twenty four papers[10 14-16 18 19 38-55] studied long term variability (ie, monitoring of blood pressure in clinics), four[56-59] studied mid-term variability (home monitoring), and 15[10 13 41 60-69] studied short term variability (ambulatory monitoring). The number of participants in each study ranged from 457[41] to 122 636[54] and follow-up ranged from 2514 person years[41] to 490 544 person years.[54]

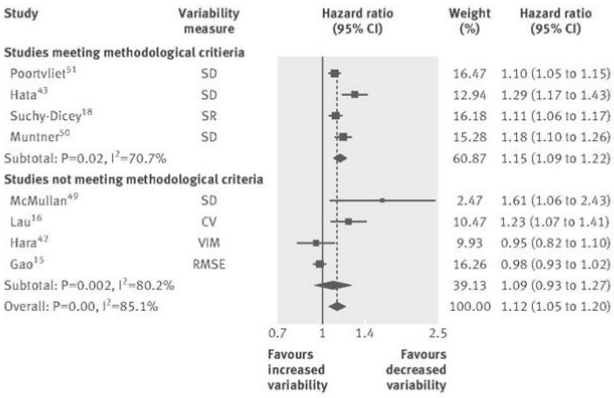

Fig 2 | Random effects meta-analysis of standardised hazard ratios for increases in clinic systolic blood pressure variability and all cause mortality. SD=standard deviation; SR=standardised residual; CV=coefficient of variation; VIM=variation independent of the mean; RMSE=root mean squared error

Study design and analysis characteristics

Consistency of blood pressure measurement with respect to cuff size, arm, device, and staff was unclear or had the potential to introduce variability (eg, mercury sphygmomanometers and changing staff) in all of the 36 included studies (see supplementary table e5). Similarly, the potential for confounding was introduced because of the analysis (or this was unclear) in all 46 separate analyses. Results from 23 analyses were excluded from our main analyses on the basis of the three prespecified criteria: eight analyses failed to correctly adjust for mean blood pressure, 15 did not account for major drug change during the measurement period, and 20 did not separate the measurement and follow-up periods. Results from four analyses (three studies) were not reported in sufficient detail to allow data extraction.

QUIPS risk of bias

Using QUIPS, most of the 46 analyses were rated at moderate risk of bias for study participation, often because of inclusion criteria based on blood pressure readings and a potential for regression to the mean effects (see supplementary table e6). Eighteen analyses were at high risk of bias because the measurement period for blood pressure variability was confounded by follow-up (n=17), and one analysis[67] failed to report non-significant results. All of the analyses rated at high risk of bias using QUIPS were excluded from our main analysis based on the assessments in supplementary table e5.

Long term variability measured by clinic monitoring

Twenty four papers reported results from 27 studies that measured blood pressure variability in clinics (long term). Results from three studies[44 48 52] were not presented in sufficient detail for extraction.

Eight studies examined long term variability in systolic blood pressure and all cause mortality, of which four had sufficiently low risk of bias to be included in the main analysis (fig 2, standardised hazard ratio 1.15, 95% confidence interval 1.09 to 1.22). Heterogeneity between studies (I^2=70.7%, P=0.02) was reduced after removal of a study in patients with previous stroke or vascular disease:[43] this did not significantly alter the results (hazard ratio 1.12, 95% confidence interval 1.08 to 1.16; I^2=34.9%, P=0.21).

Three studies assessing blood pressure variability and cardiovascular disease mortality showed a

significant relation (see supplementary figure e1, hazard ratio 1.18, 95% confidence interval 1.09 to 1.28) but only a single study examining cardiovascular disease events was suitable for inclusion (see supplementary figure e2, 1.18, 1.07 to 1.30).

Fourteen studies reported results for stroke events, of which six were included in the main analysis (fig 3; 1.15, 1.04 to 1.27; I^2=82.1%, P<0.001). Results were similar after omission of the hazard ratio from the UK-TIA trial,[70] which removed the heterogeneity (1.10, 1.05 to 1.14; I^2=0.0%, P=0.62).

Results for coronary heart disease events and myocardial infarction showed similar results (see supplementary figures e3 and e4). Across all outcomes, secondary analysis including results from all studies regardless of risk of bias did not alter results.

Mid-term variability measured by home monitoring

Four papers reported results from two studies that measured mid-term variability in home blood pressure monitoring. All four papers were of sufficient quality to be included in main analyses, but a lack of data from distinct studies meant it was only possible to perform formal meta-analysis for the all cause mortality outcome. Variability in systolic blood pressure was a significant predictor of death when blood pressure was measured in the morning or evening, or both (fig 4, eg, hazard ratio for increases in combined blood pressure variability 1.15, 95% confidence interval 1.06 to 1.26). Study level results for other outcomes are given in supplementary table e7).

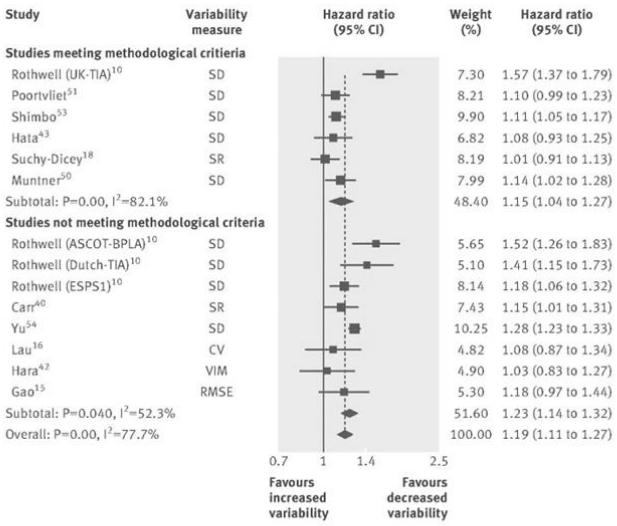

Fig 3 | Random effects meta-analysis of standardised hazard ratios for increases in clinic systolic blood pressure variability and stroke events. SD=standard deviation; SR=standardised residual; CV=coefficient of variation; VIM=variation independent of the mean; RMSE=root mean squared error

Short term variability measured by ambulatory monitoring

Fifteen papers examined short term variability in ambulatory blood pressure in 11 distinct studies. We were unable to include results from many studies,[11 13 41 56 57 65-67 69] owing to overlap with two large studies (IDACO[61] and ABP-International[64]), which combined results across cohorts.

Three studies examined daytime variability in systolic blood pressure and all cause mortality, of which two were included in the main analysis (fig 5; hazard ratio 1.10, 95% confidence interval 1.04 to 1.16). Four studies examined daytime variability in blood pressure and cardiovascular disease mortality, and analysis of three studies with low risk of bias showed a significant association (see supplementary figure e5, 1.12, 1.03 to 1.21). Daytime blood pressure variability was also significantly associated with increased risk of stroke (see supplementary figure e6; 1.11, 1.01 to 1.21). Results for all three outcomes were unchanged in secondary analysis including results from all studies.

No associations were found between variability in blood pressure and cardiovascular disease (see supplementary figure e7) or coronary heart disease events (see supplementary figure e8), although results became significant in secondary analyses. The supplementary file details the results for night-time and 24 hour systolic ambulatory blood pressure (see figures e9 to e18).

Publication bias

There was no evidence of publication bias for any outcome in relation to long term, mid-term, or short term variability in systolic blood pressure as judged by Egger's test. Significant findings for clinic monitoring would remain unchanged for all outcomes even if at least 20 null effect studies were included in meta-analyses, except for myocardial infarction where only a single null effect study would be required. Results for home monitoring would become non-significant after the addition of a single null effect study and those for variability in ambulatory blood pressure would become non-significant by the addition of between one and six null effect studies, depending on outcome and period of measurement.

Discussion

This review has systematically assessed the literature for the association of long term (clinic monitoring), mid-term (home monitoring), and short term (ambulatory) variability in blood pressure with cardiovascular outcomes and mortality. Long term variability in measurements is significantly associated with all cause and cardiovascular disease mortality, cardiovascular disease events, stroke, and myocardial infarction, independent of mean blood pressure. Mid-term and short term variability are also associated with mortality, and limited data for other outcomes also broadly support an association with cardiovascular outcomes. Across all analyses (long term, mid-term, and short term), the hazard ratios for coronary heart disease events were smaller than those for stroke, suggesting that the effect

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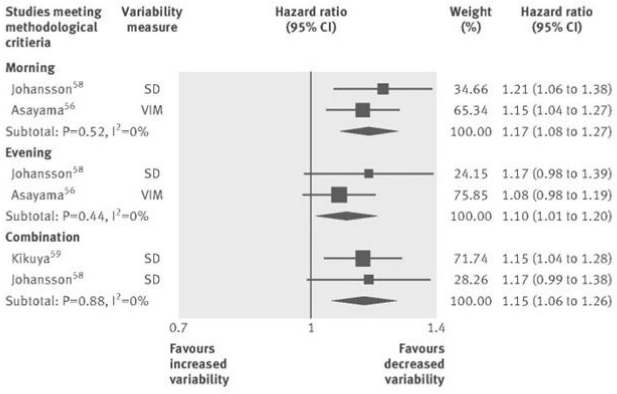

Fig 4 | Random effects meta-analysis of standardized hazard ratios for increases in home systolic blood pressure variability and all cause mortality. SD=standard deviation; VIM=variation independent of mean

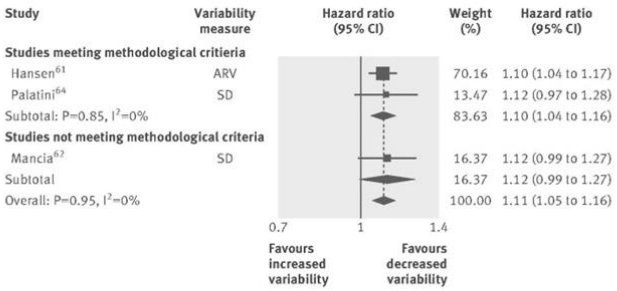

Fig 5 | Random effects meta-analysis of standardised hazard ratios for increases in variability of ambulatory systolic blood pressure and all cause mortality. SD=standard deviation; ARV=average real variability

observed for cardiovascular disease events—as with mean blood pressure—may be driven primarily by cerebrovascular events.

Strengths in relation to the literature

This review includes over one million person years of data and combines the results from long, mid-term, and short-term blood pressure measurement, allowing comparison. We have addressed the methodological issues that are particular to research on variability in blood pressure and have shown that although there is now considerable evidence on this topic, most studies are of poor quality or poorly reported. By limiting our main analysis to studies that avoid potential sources of confounding, this review confirms that the apparent prognostic value of blood pressure variability is a true prospective association and can be demonstrated even in studies with low risk of bias.

In this review we used standardised hazard ratios to overcome the diversity of measures for variability used in primary studies, and hence combined more data. For example, our meta-analysis for long term variability and stroke events includes 14 studies, more than double the number in previous analyses.[24 25] This review also had sufficient data for meta-analysis of the effect of short term variability of blood pressure on outcomes, which was a limitation of a previous work.[28]

Finally, we demonstrated the robustness of results to possible unpublished null effect studies across long term, mid-term, and short term variability in blood pressure. Although results for long term variability may be considered conclusive, results for mid-term and short term variability are more susceptible to publication bias and may warrant further investigation.

Limitations of this review

Included studies were primarily in older adults (mean age 48.5 to 77 years) and those at increased risk of cardiovascular disease (eg, due to hypertension) and conducted in European or East Asian populations. Hence the applicability of our findings to younger or healthier people and other ethnic groups is unknown. Studies in patients with a history of cerebrovascular events reported the largest hazard ratios, but significant associations remained after removal of these studies from analyses, and so findings remain applicable to people free from cerebrovascular disease. In studies in hypertensive patients,[14 40 69] blood pressure variability could be confounded by entry criteria (regression to the mean)[71] and treatment. However, such effects would diminish rather than exaggerate hazard ratios for variability, and so our overall conclusions are sound.

Lack of data from distinct cohorts prevented formal meta-analyses for many outcomes for to mid-term variability in blood pressure. A previous review was similarly limited by paucity of data,[26] despite broader inclusion criteria. Our meta-analyses for short term variability in blood pressure were also dominated by two large studies. Despite these caveats, results supported an effect of shorter term variability on cardiovascular outcomes, and pooled hazard ratios were similar to those observed for long term variability. We were unable to determine if findings varied with timing and frequency of measurement.

In several analyses, there was significant heterogeneity between studies, potentially due to outlying studies in specific populations (eg, previous vascular disease) or to approximations necessary during data extraction, such as conversion from categorical (eg, from 10ths[10] or thirds[49]) to continuous scale. However, not all converted hazard ratios were outliers,[50] and we verified our conversion method in simulated data (not shown). Significant heterogeneity was reduced by removal of outlier studies, but this did not significantly alter the results.

In some cases, few studies contributed to main analyses, and the validity of these meta-analyses is debateable. Secondary analysis utilising data from all studies regardless of quality greatly increased the amount of available data but did not materially change results. Only three otherwise eligible studies

failed to contribute any quantitative data, despite contact with authors.[44 48 52]

In general, there was poor reporting of study factors that may confound the relation between blood pressure variability and outcomes. Although studies were excluded from main analyses based on the three most important factors (prespecified), it was not feasible to do this for all factors. Further adjustment for confounders might be possible using individual patient data but was beyond the scope of this review. The importance of consideration and reporting of such confounding factors in future work on blood pressure variability (and variability in other biological measures) should be emphasised. Although our results indicate that these may be less important in the assessment of blood pressure variability, they may prove instrumental in other clinical areas.

Clinical implications

The mechanism linking blood pressure variability to cardiovascular events is not well understood. Short term variability in blood pressure is affected by behavioural, emotional, and postural influences on cardiovascular physiology and cardiac rhythm.[72 73] Arterial stiffness contributes to both short term[74 75] and long term variability in blood pressure.[73 76 77] Meanwhile, poor control of blood pressure resulting in changes to antihypertensive drugs also affects variability.[72] Use of certain classes of antihypertensive drugs has also been linked with increased visit-to-visit variability[78] and may not be entirely explained by adherence.[79]

The estimated standardised hazard ratio for the effect of long term variability in blood pressure on cardiovascular disease mortality was 1.18. For comparison, the effect of mean blood pressure on cardiovascular disease mortality reported in a previous meta-analysis[3] corresponds to a standardised hazard ratio of approximately 1.7 (assuming a between person standard deviation of 15 mm Hg). Note that the latter standardised hazard ratio for mean blood pressure is not adjusted for variability, whereas the former (for blood pressure variability) is adjusted for mean blood pressure, showing the additional prognostic value of variability over and above the mean. This supports the results of recent work showing the improved discrimination of models including short term night-time variability in blood pressure[64] or long term variability,[39] over and above traditional risk factors.

How does blood pressure variability compare with other risk factors for cardiovascular disease? A recent review[80] found that the adjusted standardised hazard ratio for increases in cholesterol on cardiovascular disease events varied between 1.16 and 1.29 in primary prevention groups, depending on the measure of cholesterol considered (eg, total cholesterol, triglycerides). Hence variability in blood pressure has similar prognostic value to cholesterol measures (standardised hazard ratio for long term variability on cardiovascular disease events=1.18).

Variability in blood pressure is not easily assessed clinically, and it is unclear if certain measures of variability should be preferred. Some measures could be calculated by hand (eg, average real variability), whereas others could be automatically calculated by electronic health records. This would enable doctors to account for both mean and variability in blood pressure concurrently when assessing cardiovascular risk. For example, assuming a standard deviation for variability (standard deviation) in systolic blood pressure of 5 mm Hg, an individual with variable blood pressure readings (139, 132, and 125 mm Hg, mean 132, SD 7) could be considered at 18% greater risk of cardiovascular disease events than a similar person with stable blood pressure (134, 130, and 132 mm Hg, mean 132, SD 2). This may be particularly important for patients with a highly variable but comparatively low mean blood pressure or for whom traditional cardiovascular risk estimates lie close to treatment thresholds. Further work is needed to determine the feasibility of obtaining such additional information, and the clinical impact on subsequent risk management.

Conclusion

Long term variability in blood pressure measured in adults at clinic visits is associated with cardiovascular and mortality outcomes, over and above the effect of mean blood pressure. Mid-term (home monitoring) and short term (ambulatory monitoring) variability in blood pressure is also associated with all cause mortality, but the association with cardiovascular disease outcomes requires further investigation in novel cohorts.

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Ethical approval: Not required.

Data sharing: Data extracted from the studies in this review are available on request from the corresponding author.

Transparency: The lead author (SS) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Supplementary information: supplementary tables e1-e7 and figures e1-e18

Table B.1: Search strategy

CINAHL (EBSCOHost)

S24	S22 OR S23 Limiters - Clinical Queries: Prognosis - Specificity
S23	S20 OR S21 Limiters - Clinical Queries: Prognosis - High Sensitivity
S22	S20 OR S21
S21	TI (((blood pressure or bp or sbp or dbp) N5 (variabilit* or variation*))) OR AB (((blood pressure or bp or sbp or dbp) N5 (variabilit* or variation*)))
S20	S3 AND S6 AND S19
S19	S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18
S18	TI within subject* OR AB within subject*
S17	TI ((dipping or dipper* or nondipping or nondipper* or non-dipping or non-dipper*)) OR AB ((dipping or dipper* or nondipping or nondipper* or non-dipping or non-dipper*))
S16	TI ((((daytime or day-time or diurnal) N5 (blood pressure or bp or sbp or sbp)) and ((night-time or nocturnal) N5 (blood pressure or bp or sbp or sbp)))) OR AB ((((daytime or day-time or diurnal) N5 (blood pressure or bp or sbp or sbp)) and ((night-time or nocturnal) N5 (blood pressure or bp or sbp or sbp))))
S15	TI (((daytime or day-time or diurnal) N5 (night-time or nocturnal))) OR AB (((daytime or day-time or diurnal) N5 (night-time or nocturnal)))
S14	TI repeat* measure* OR AB repeat* measure*
S13	TI "measure* to measure*" OR AB "measure* to measure*"
S12	TI (("day to day" or "day by day")) OR AB (("day to day" or "day by day"))
S11	TI ("between day" OR "within day") OR AB ("between day" OR "within day")
S10	TI "visit to visit" OR AB "visit to visit"
S9	TI (((between or within) N3 visit*)) OR AB (((between or within) N3 visit*))
S8	TI variation*
S7	TI (variability or variabilities) OR AB (variability or variabilities)
S6	S4 OR S5
S5	TI (blood pressure or bp or sbp or dbp) OR AB (blood pressure or bp or sbp or dbp)
S4	(MH "Blood Pressure") OR (MH "Blood Pressure Determination")
S3	S1 OR S2
S2	TI (hypertensive* or hypertension* or antihypertens* or anti-hypertens*) OR AB (hypertensive* or hypertension* or antihypertens* or anti-hypertens*)
S1	(MH "Hypertension+")

Embase (OvidSP)

1	*hypertension/
2	(hypertensive* or hypertension* or antihypertens* or anti-hypertens*).ti,ab.
3	1 or 2
4	*Blood Pressure/
5	exp *blood pressure measurement/
6	(blood pressure or bp or sbp or dbp).ti,ab.
7	4 or 5 or 6
8	(variability or variabilities).ti,ab.
9	variation?.ti.
10	((between or within) adj3 visit?).ti,ab.
11	"visit to visit".ti,ab.
12	((between or within) adj day?).ti,ab.
13	("day to day" or "day by day").ti,ab.
14	"measure* to measure*".ti,ab.
15	"reading? to reading?".ti,ab.
16	repeat* measure*.ti,ab.
17	((daytime or day-time or diurnal) adj5 (night-time or nocturnal)).ti,ab.
18	(((daytime or day-time or diurnal) adj5 (blood pressure or bp or sbp or sbp)) and ((night-time or nocturnal) adj5 (blood pressure or bp or sbp or sbp))).ti,ab.
19	(dipping or dipper? or nondipping or nondipper? or non-dipping or non-dipper?).ti,ab.
20	within subject?.ti,ab.
21	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22	3 and 7 and 21
23	blood pressure variability/
24	3 and 23
25	((blood pressure or bp or sbp or dbp) adj5 (variabilit* or variation?)).ti,ab.
26	22 or 24 or 25
27	((exp animal/ or exp vertebrate/ or exp invertebrate/) not human/) or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
28	26 not 27
29	follow up.mp. or ep.fs. or prognos*.tw.
30	28 and 29
31	(prognos* or survival).tw.
32	28 and 31
33	30 or 32

Medline (OvidSP)

1	exp Hypertension/
2	(hypertensive* or hypertension* or antihypertens* or anti-hypertens*).ti,ab.
3	1 or 2
4	*Blood Pressure/
5	*Blood Pressure Determination/
6	(blood pressure or bp or sbp or dbp).ti,ab.
7	4 or 5 or 6
8	(variability or variabilities).ti,ab.
9	variation?.ti.
10	((between or within) adj3 visit?).ti,ab.
11	"visit to visit".ti,ab.
12	((between or within) adj day?).ti,ab.
13	("day to day" or "day by day").ti,ab.
14	"measure* to measure*".ti,ab.
15	"reading? to reading?".ti,ab.
16	repeat* measure*.ti,ab.
17	((daytime or day-time or diurnal) adj5 (night-time or nocturnal)).ti,ab.
18	(((daytime or day-time or diurnal) adj5 (blood pressure or bp or sbp or sbp)) and ((night-time or nocturnal) adj5 (blood pressure or bp or sbp or sbp))).ti,ab.
19	(dipping or dipper? or nondipping or nondipper? or non-dipping or non-dipper?).ti,ab.
20	within subject?.ti,ab.
21	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22	3 and 7 and 21
23	((blood pressure or bp or sbp or dbp) adj5 (variabilit* or variation?)).ti,ab.
24	22 or 23
25	exp animal/ not human/
26	24 not 25
27	incidence.sh. or exp mortality/ or follow-up studies.sh. or prognos*.tw. or predict*.tw. or course*.tw.
28	26 and 27

29 (prognos* or first episode or cohort).tw.

30 26 and 29

31 28 or 30

17 #16 AND #15

16 Topic=(prognos* OR cohort* OR incidence OR mortality OR "follow-up" OR predict OR course)

15 #14 AND #13

14 Topic=(hypertens* OR antihypertens* OR anti-hypertens*)

13 #12 OR #2 OR #1

12 #11 AND #3

11 #10 OR #9 OR #8 OR #5 OR #4

10 Topic=("within subject*")

9 Topic=(dipping or dipper* or nondipping or nondipper* or non-dipping or non-dipper*)

8 #7 AND #6

7 Topic=(nightime NEAR/5 ("blood pressure" or bp or sbp or dbp)) OR Topic=(nocturnal NEAR/5 ("blood pressure" or bp or or dbp))

6 Topic=(daytime NEAR/5 ("blood pressure" or bp or sbp or dbp)) OR Topic=(day-time NEAR/5 ("blood pressure" or bp or s dbp)) OR Topic=(diurnal NEAR/5 ("blood pressure" or bp or sbp or dbp))

5 Topic=((daytime NEAR/5 (night-time or nocturnal))) OR Topic=((day-time NEAR/5 (night-time or nocturnal))) OR Topic=((diurnal NEAR/5 (night-time or nocturnal)))

4 Topic=(between NEAR/3 visit*) OR Topic=(within NEAR/3 visit*) OR Topic=("between day*" OR "within day*") OR Topic=("day to day" OR "day by day") OR Topic=("measure to measure") OR Topic=("measurement to measurement") OR Topic=("repeat measur*" OR "repeated measur*") OR Topic=("visit to visit") OR Topic=("reading to reading" OR "readings readings")

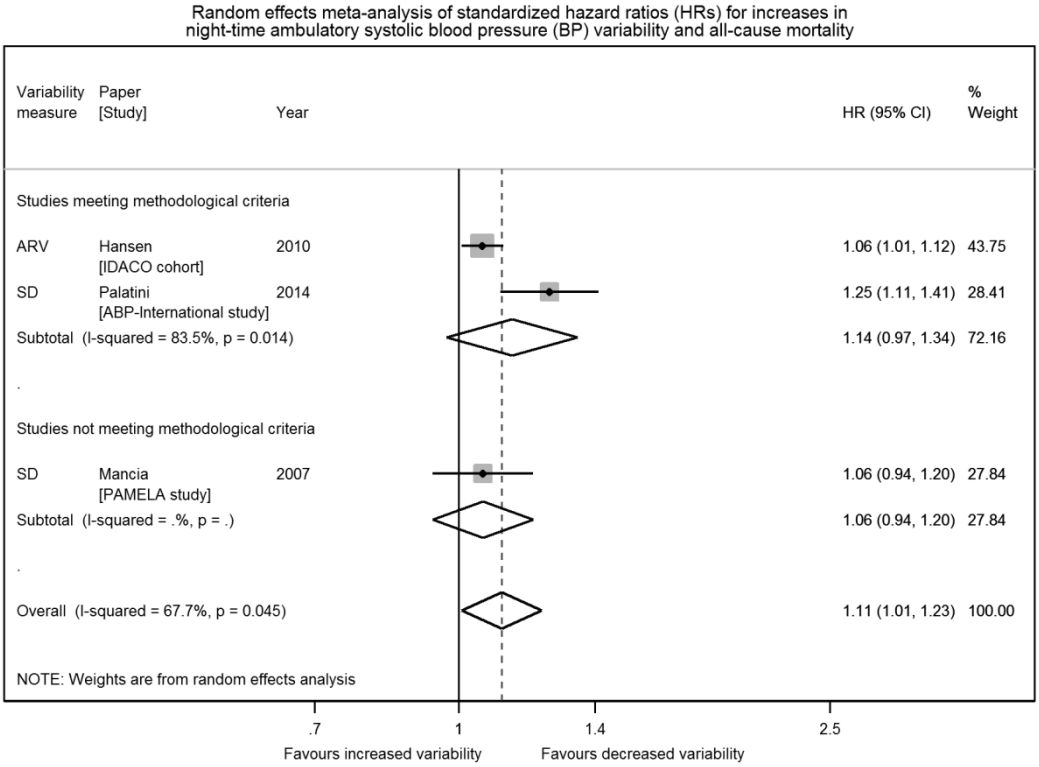
3 Topic=("blood pressure" OR bp OR sbp OR dbp)

2 Title=(variation* OR variability OR variabilities) AND Title=("blood pressure" OR bp OR sbp OR dbp)

1 Topic=("blood pressure" NEAR/5 (variability OR variabilities OR variation*)) OR Topic=(bp NEAR/5 (variability OR variabilities OR variation*)) OR Topic=(dbp NEAR/5 (variability OR variabilities OR variation*)) OR Topic=(sbp NEAR/5 (variability OR variabilities OR variation*))

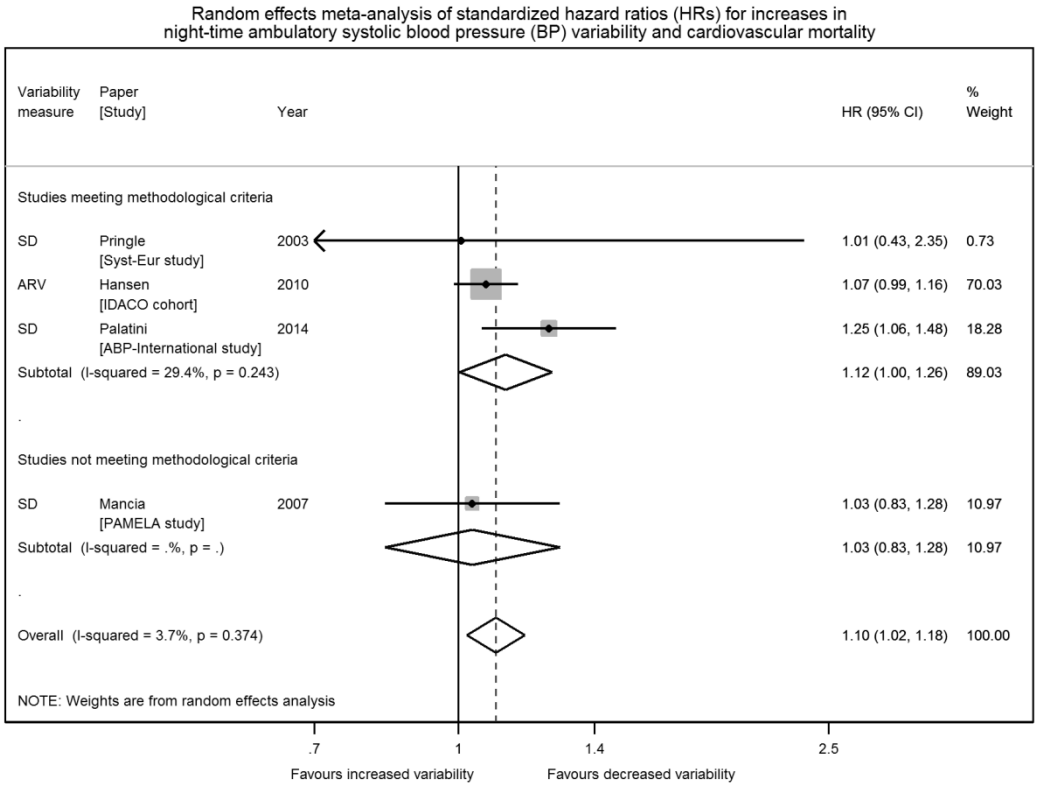
Web of Science:

Figure B.1: Association of night-time ambulatory systolic blood pressure variability with all-cause mortality



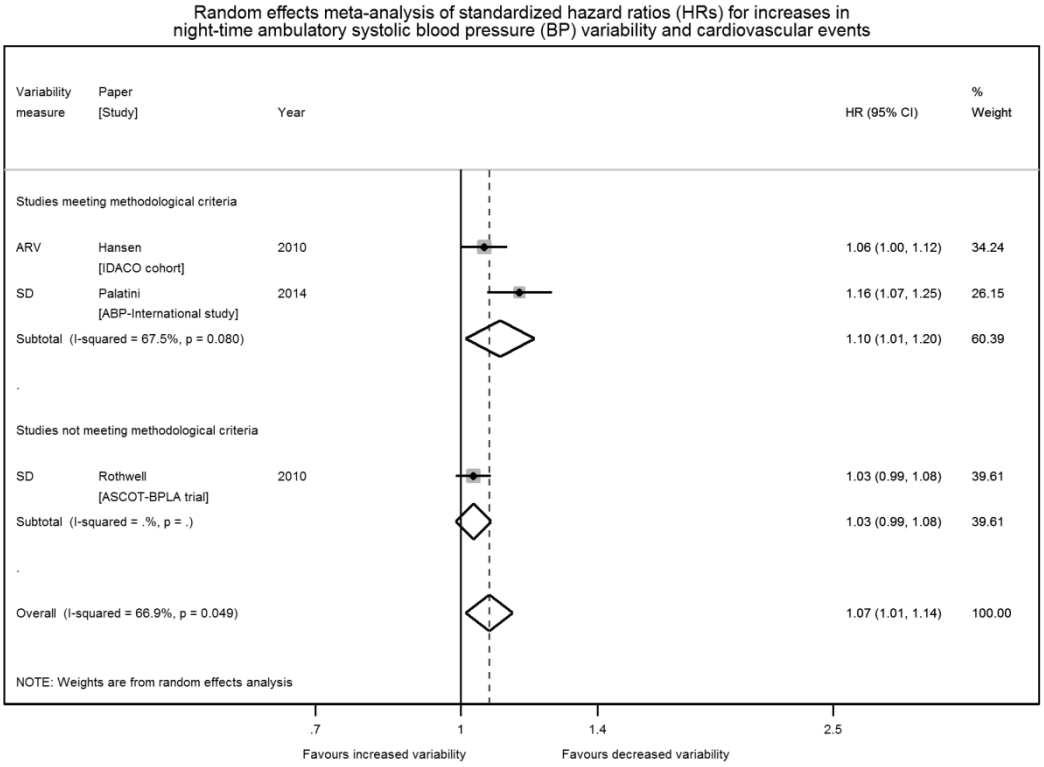
ARV: Average real variability, SD: Standard deviation

Figure B.2: Association of night-time ambulatory systolic blood pressure variability with cardiovascular mortality



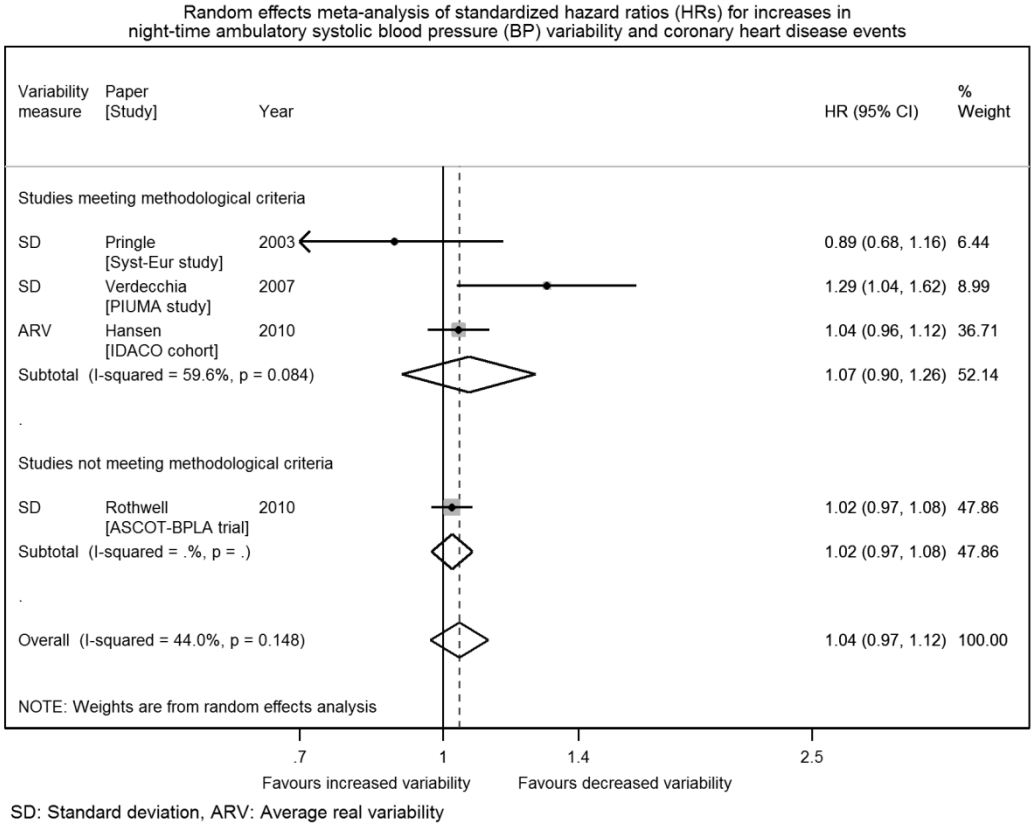
SD: Standard deviation, ARV: Average real variability

Figure B.3: Association of night-time ambulatory systolic blood pressure variability with cardiovascular events



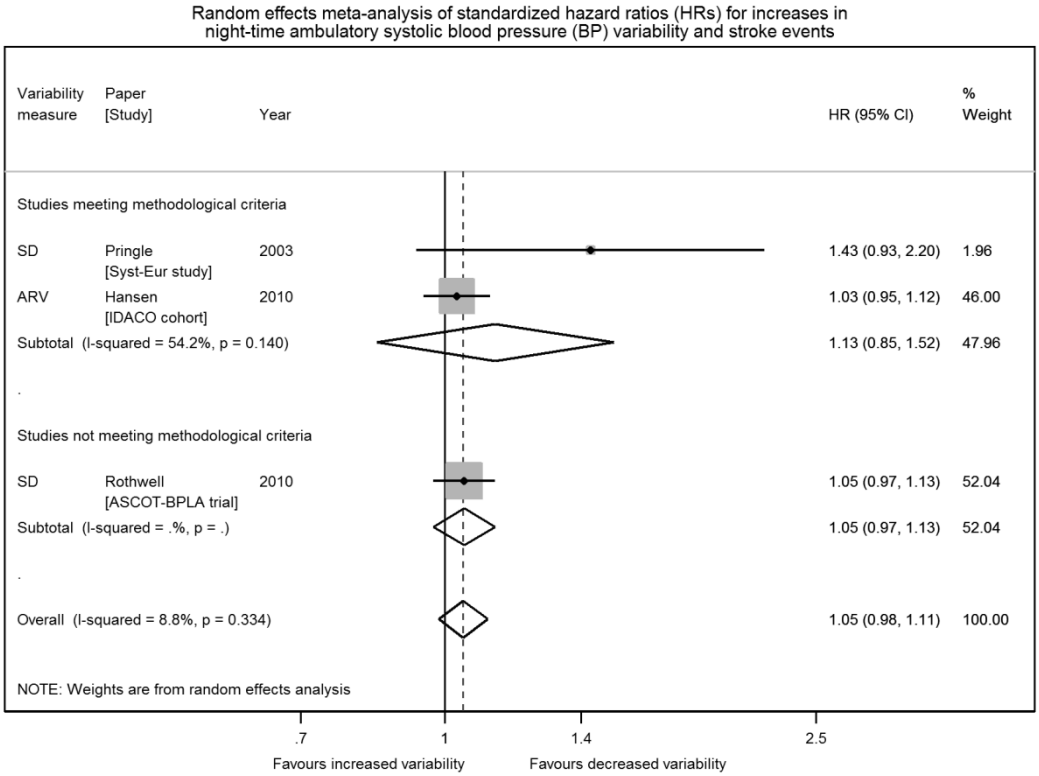
SD: Standard deviation, ARV: Average real variability

Figure B.4: Association of night-time ambulatory systolic blood pressure variability with coronary heart disease events



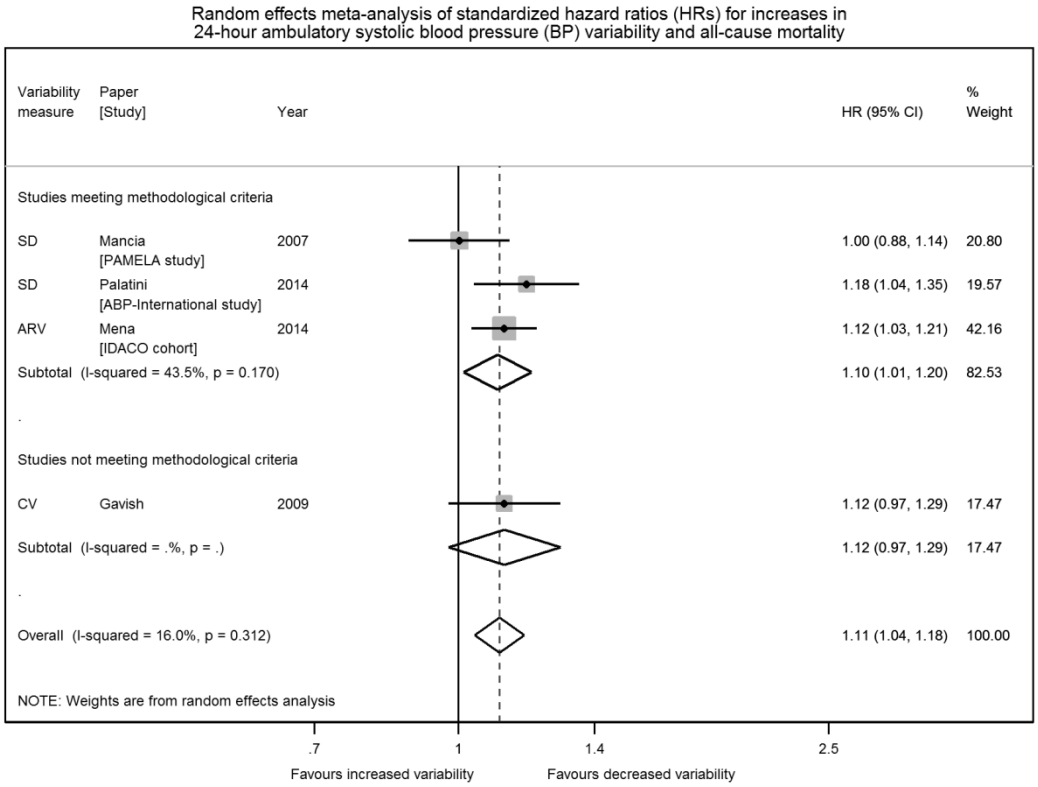
SD: Standard deviation, ARV: Average real variability

Figure B.5: Association of night-time ambulatory systolic blood pressure variability with stroke events



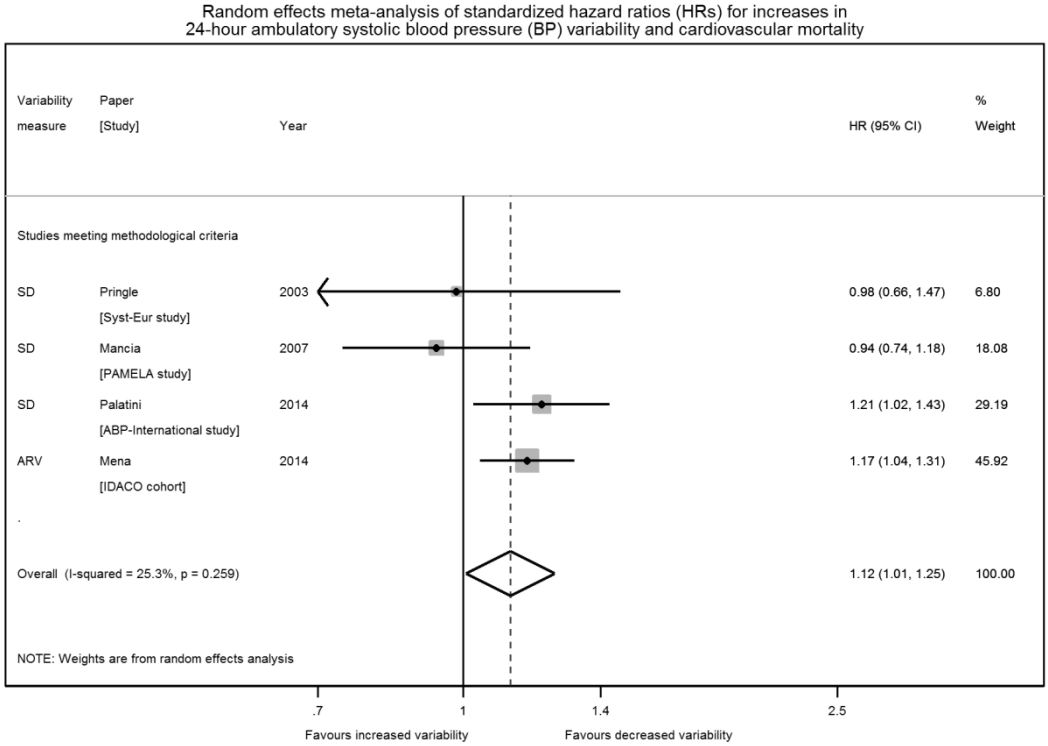
SD: Standard deviation, ARV: Average real variability

Figure B.6: Association of 24-hour ambulatory systolic blood pressure variability with all-cause mortality



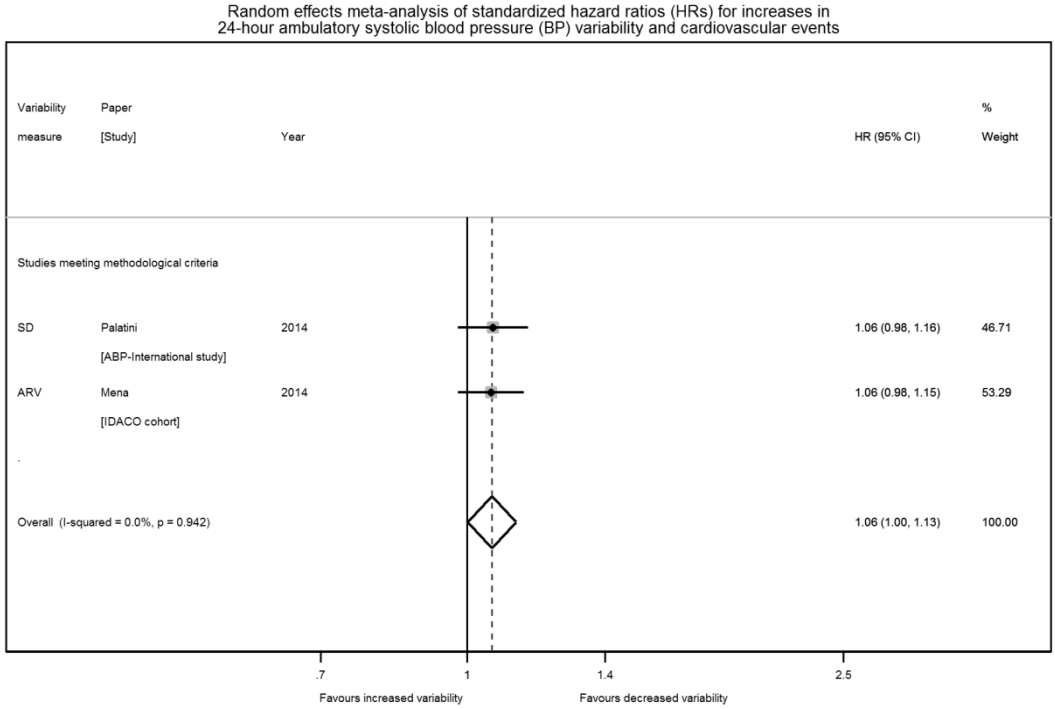
SD: Standard deviation, ARV: Average real variability, CV: Coefficient of variation

Figure B.7: Association of 24-hour ambulatory systolic blood pressure variability with cardiovascular mortality



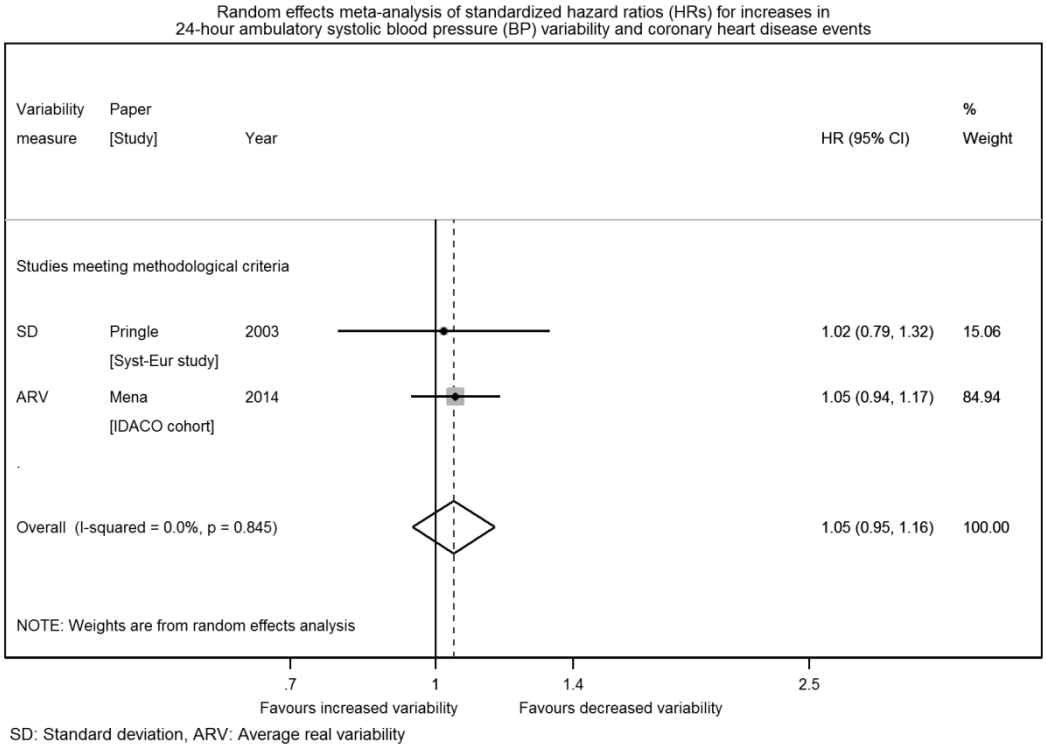
SD: Standard deviation, ARV: Average real variability

Figure B.8: Association of 24-hour ambulatory systolic blood pressure variability with cardiovascular events



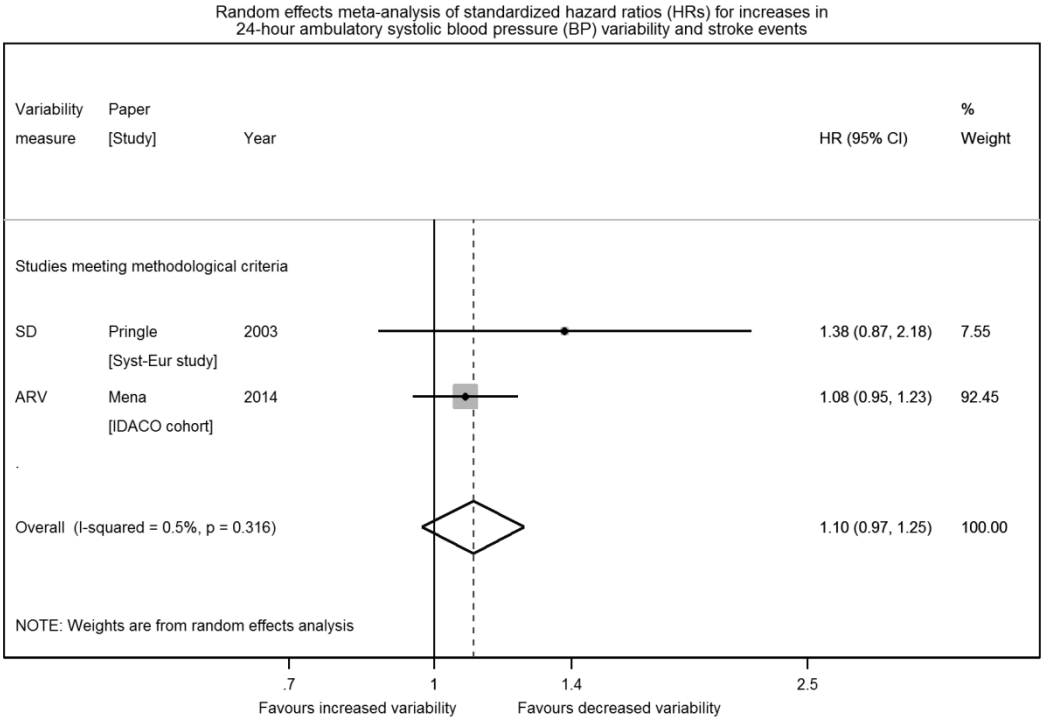
ARV: Average real variability

Figure B.9: Association of 24-hour ambulatory systolic blood pressure variability with coronary heart disease events



SD: Standard deviation, ARV: Average real variability

Figure B.10: Association of 24-hour ambulatory systolic blood pressure variability with stroke events



SD: Standard deviation, ARV: Average real variability

Appendix C Cohort study using CPRD

Table C.1: READ codes used to identify stroke in CPRD

READ code	READ term
G61..00	Intracerebral haemorrhage
G61..11	CVA - cerebrovascular accid due to intracerebral haemorrhage
G61..12	Stroke due to intracerebral haemorrhage
G610.00	Cortical haemorrhage
G611.00	Internal capsule haemorrhage
G612.00	Basal nucleus haemorrhage
G613.00	Cerebellar haemorrhage
G614.00	Pontine haemorrhage
G615.00	Bulbar haemorrhage
G616.00	External capsule haemorrhage
G618.00	Intracerebral haemorrhage, multiple localized
G619.00	Lobar cerebral haemorrhage
G61X.00	Intracerebral haemorrhage in hemisphere, unspecified
G61X000	Left sided intracerebral haemorrhage, unspecified
G61X100	Right sided intracerebral haemorrhage, unspecified
G61z.00	Intracerebral haemorrhage NOS
G63y000	Cerebral infarct due to thrombosis of precerebral arteries
G63y100	Cerebral infarction due to embolism of precerebral arteries
G64..00	Cerebral arterial occlusion
G64..11	CVA - cerebral artery occlusion
G64..12	Infarction - cerebral
G64..13	Stroke due to cerebral arterial occlusion
G640.00	Cerebral thrombosis
G640000	Cerebral infarction due to thrombosis of cerebral arteries
G641.00	Cerebral embolism
G641.11	Cerebral embolus
G641000	Cerebral infarction due to embolism of cerebral arteries
G64z.00	Cerebral infarction NOS
G64z.11	Brainstem infarction NOS
G64z.12	Cerebellar infarction
G64z000	Brainstem infarction
G64z100	Wallenberg syndrome
G64z111	Lateral medullary syndrome
G64z200	Left sided cerebral infarction
G64z300	Right sided cerebral infarction
G64z400	Infarction of basal ganglia
G66..00	Stroke and cerebrovascular accident unspecified
G66..11	CVA unspecified
G66..12	Stroke unspecified

G66..13	CVA - Cerebrovascular accident unspecified
G660.00	Middle cerebral artery syndrome
G661.00	Anterior cerebral artery syndrome
G662.00	Posterior cerebral artery syndrome
G664.00	Cerebellar stroke syndrome
G665.00	Pure motor lacunar syndrome
G666.00	Pure sensory lacunar syndrome
G667.00	Left sided CVA
G668.00	Right sided CVA
G676000	Cereb infarct due cerebral venous thrombosis, nonpyogenic
G6W..00	Cereb infarct due unsp occlus/stenos precerebr arteries
G6X..00	Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
Gyu6200	[X]Other intracerebral haemorrhage
Gyu6300	[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
Gyu6400	[X]Other cerebral infarction
Gyu6500	[X]Occlusion and stenosis of other precerebral arteries
Gyu6600	[X]Occlusion and stenosis of other cerebral arteries
Gyu6F00	[X]Intracerebral haemorrhage in hemisphere, unspecified
Gyu6G00	[X]Cereb infarct due unsp occlus/stenos precerebr arteries

Table C.2: READ codes used to identify CHD and myocardial infarction in CPRD

READ code	READ term
G3...00	Ischaemic heart disease
G3...11	Arteriosclerotic heart disease
G3...12	Atherosclerotic heart disease
G3...13	IHD - Ischaemic heart disease
G30..00	Acute myocardial infarction
G30..11	Attack - heart
G30..12	Coronary thrombosis
G30..13	Cardiac rupture following myocardial infarction (MI)
G30..14	Heart attack
G30..15	MI - acute myocardial infarction
G30..16	Thrombosis - coronary
G30..17	Silent myocardial infarction
G300.00	Acute anterolateral infarction
G301.00	Other specified anterior myocardial infarction
G301000	Acute anteroapical infarction
G301100	Acute anteroseptal infarction
G301z00	Anterior myocardial infarction NOS
G302.00	Acute inferolateral infarction
G303.00	Acute inferoposterior infarction
G304.00	Posterior myocardial infarction NOS
G305.00	Lateral myocardial infarction NOS

G306.00	True posterior myocardial infarction
G307.00	Acute subendocardial infarction
G307000	Acute non-Q wave infarction
G307100	Acute non-ST segment elevation myocardial infarction
G308.00	Inferior myocardial infarction NOS
G309.00	Acute Q-wave infarct
G30A.00	Mural thrombosis
G30B.00	Acute posterolateral myocardial infarction
G30X.00	Acute transmural myocardial infarction of unspecif site
G30X000	Acute ST segment elevation myocardial infarction
G30y.00	Other acute myocardial infarction
G30y000	Acute atrial infarction
G30y100	Acute papillary muscle infarction
G30y200	Acute septal infarction
G30yz00	Other acute myocardial infarction NOS
G30z.00	Acute myocardial infarction NOS
G31..00	Other acute and subacute ischaemic heart disease
G310.00	Postmyocardial infarction syndrome
G310.11	Dressler's syndrome
G311.00	Preinfarction syndrome
G311.11	Crescendo angina
G311.12	Impending infarction
G311.13	Unstable angina
G311.14	Angina at rest
G311000	Myocardial infarction aborted
G311011	MI - myocardial infarction aborted
G311100	Unstable angina
G311200	Angina at rest
G311300	Refractory angina
G311400	Worsening angina
G311500	Acute coronary syndrome
G311z00	Preinfarction syndrome NOS
G312.00	Coronary thrombosis not resulting in myocardial infarction
G31y.00	Other acute and subacute ischaemic heart disease
G31y000	Acute coronary insufficiency
G31y100	Microinfarction of heart
G31y200	Subendocardial ischaemia
G31y300	Transient myocardial ischaemia
G31yz00	Other acute and subacute ischaemic heart disease NOS
G32..00	Old myocardial infarction
G32..11	Healed myocardial infarction
G32..12	Personal history of myocardial infarction
G33..00	Angina pectoris
G330.00	Angina decubitus
G330000	Nocturnal angina

G330z00	Angina decubitus NOS
G331.00	Prinzmetal's angina
G331.11	Variant angina pectoris
G332.00	Coronary artery spasm
G33z.00	Angina pectoris NOS
G33z000	Status anginosus
G33z100	Stenocardia
G33z200	Syncope anginosa
G33z300	Angina on effort
G33z400	Ischaemic chest pain
G33z500	Post infarct angina
G33z600	New onset angina
G33z700	Stable angina
G33zz00	Angina pectoris NOS
G34..00	Other chronic ischaemic heart disease
G340.00	Coronary atherosclerosis
G340.11	Triple vessel disease of the heart
G340.12	Coronary artery disease
G340000	Single coronary vessel disease
G340100	Double coronary vessel disease
G342.00	Atherosclerotic cardiovascular disease
G343.00	Ischaemic cardiomyopathy
G344.00	Silent myocardial ischaemia
G34y.00	Other specified chronic ischaemic heart disease
G34y000	Chronic coronary insufficiency
G34y100	Chronic myocardial ischaemia
G34yz00	Other specified chronic ischaemic heart disease NOS
G34z.00	Other chronic ischaemic heart disease NOS
G34z000	Asymptomatic coronary heart disease
G35..00	Subsequent myocardial infarction
G350.00	Subsequent myocardial infarction of anterior wall
G351.00	Subsequent myocardial infarction of inferior wall
G353.00	Subsequent myocardial infarction of other sites
G35X.00	Subsequent myocardial infarction of unspecified site
G36..00	Certain current complication follow acute myocardial infarct
G360.00	Haemopericardium/current comp folow acut myocard infarct
G361.00	Atrial septal defect/curr comp folow acut myocardal infarct
G362.00	Ventric septal defect/curr comp fol acut myocardal infarctn
G363.00	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI
G364.00	Ruptur chordae tendinae/curr comp fol acute myocard infarct
G365.00	Rupture papillary muscle/curr comp fol acute myocard infarct
G366.00	Thrombosis atrium,auric append&vent/curr comp foll acute MI
G38..00	Postoperative myocardial infarction
G380.00	Postoperative transmural myocardial infarction anterior wall
G381.00	Postoperative transmural myocardial infarction inferior wall

G383.00	Postoperative transmural myocardial infarction unspec site
G384.00	Postoperative subendocardial myocardial infarction
G38z.00	Postoperative myocardial infarction, unspecified
G39..00	Coronary microvascular disease
G3y..00	Other specified ischaemic heart disease
G3z..00	Ischaemic heart disease NOS
Gyu3.00	[X]Ischaemic heart diseases
Gyu3000	[X]Other forms of angina pectoris
Gyu3200	[X]Other forms of acute ischaemic heart disease
Gyu3300	[X]Other forms of chronic ischaemic heart disease
Gyu3400	[X]Acute transmural myocardial infarction of unspecif site
Gyu3500	[X]Subsequent myocardial infarction of other sites
Gyu3600	[X]Subsequent myocardial infarction of unspecified site

Table C.3: ICD 10 codes used to identify CVD in ONS mortality and hospital episodes data

ICD 10 code	**Description**
I20	Angina pectoris
I21	Acute myocardial infarction
I22	Subsequent myocardial infarction
I23	Certain current complications following acute myocardial infarction
I24	Other acute ischaemic heart diseases
I25	Chronic ischaemic heart disease
I60	Subarachnoid haemorrhage
I61	Intracerebral haemorrhage
I62	Other nontraumatic intracranial haemorrhage
I63	Cerebral infarction
I64	Stroke, not specified as haemorrhage or infarction
I65	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
I66	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction
I67	Other cerebrovascular diseases

Table C.4: READ codes to identify family history of CVD in CPRD

READ code	READ term
12C..00	FH: Cardiovascular disease
12C2.00	FH: Ischaemic heart dis. <60
12C2.11	FH: Myocardial infarction < 60
12C2.12	FH: MI- Myocardial infarct <60

12C2.13	FH: Angina < 60yrs
12C3.00	FH: Ischaemic heart dis. >60
12C3.11	FH: Myocardial infarction > 60
12C3.12	FH: MI- myocardial infarct >60
12C3.13	FH: Angina > 60yrs
12C4.00	FH: CVA/stroke
12C4.11	FH: CVA
12C4.12	FH: Stroke
12C5.00	FH: Myocardial infarction
12C5.12	FH: Ischaemic heart disease
12C7.00	Family history of transient ischaemic attack
12CA.00	FH myocardial infarction male first degree age known
12CB.00	FH myocardial infarction male first degree age unknown
12CC.00	FH myocardial infarction female first degree age known
12CD.00	FH myocardial infarction female first degree age unknown
12CE.00	FH angina male first degree age known
12CF.00	FH angina male first degree age unknown
12CG.00	FH angina female first degree age known
12CH.00	FH angina female first degree age unknown
12CI.00	FH: premature coronary heart disease
12CL.00	FH: Angina in 1st degree female relative <65 years
12CM.00	FH: Angina in 1st degree male relative <55 years
12CN.00	FH: Myocardial infarct in 1st degree female relative <65 yrs
12CP.00	FH: Myocardial infarct in 1st degree male relative <55 years
12CV.00	FH: Cardiovascular disease 1st degree male relative < 55 yrs
12CW.00	FH: Cardiovascular disease 1st degree female reltve < 65 yrs
ZV17100	[V]Family history of stroke (cerebrovascular)
ZV17111	[V]Family history of cerebrovascular accident (CVA)
ZV17300	[V]Family history of ischaemic heart disease
ZV17311	[V]Family history of ischaemic heart disease (IHD)
ZV17312	[V]Family history of myocardial infarction
ZV17400	[V]Family history of other cardiovascular disease

Table C.5: READ codes to identify atrial fibrillation in CPRD

READ code	READ term
G573200	Paroxysmal atrial fibrillation
G573400	Permanent atrial fibrillation
G573300	Non-rheumatic atrial fibrillation
G573000	Atrial fibrillation
G573500	Persistent atrial fibrillation
G573.00	Atrial fibrillation and flutter
G573z00	Atrial fibrillation and flutter NOS

3272	ECG: atrial fibrillation

Table C.6: READ codes to identify chronic kidney disease stages 3 to 5 in CPRD

READ code	READ term
1Z12.00	Chronic kidney disease stage 3
1Z13.00	Chronic kidney disease stage 4
1Z14.00	Chronic kidney disease stage 5
1Z15.00	Chronic kidney disease stage 3A
1Z16.00	Chronic kidney disease stage 3B
1Z1B.00	Chronic kidney disease stage 3 with proteinuria
1Z1B.11	CKD stage 3 with proteinuria
1Z1C.00	Chronic kidney disease stage 3 without proteinuria
1Z1C.11	CKD stage 3 without proteinuria
1Z1D.00	Chronic kidney disease stage 3A with proteinuria
1Z1D.11	CKD stage 3A with proteinuria
1Z1E.00	Chronic kidney disease stage 3A without proteinuria
1Z1E.11	CKD stage 3A without proteinuria
1Z1F.00	Chronic kidney disease stage 3B with proteinuria
1Z1F.11	CKD stage 3B with proteinuria
1Z1G.00	Chronic kidney disease stage 3B without proteinuria
1Z1G.11	CKD stage 3B without proteinuria
1Z1H.00	Chronic kidney disease stage 4 with proteinuria
1Z1H.11	CKD stage 4 with proteinuria
1Z1J.00	Chronic kidney disease stage 4 without proteinuria
1Z1J.11	CKD stage 4 without proteinuria
1Z1K.00	Chronic kidney disease stage 5 with proteinuria
1Z1K.11	CKD stage 5 with proteinuria
1Z1L.00	Chronic kidney disease stage 5 without proteinuria
1Z1L.11	CKD stage 5 without proteinuria
K053.00	Chronic kidney disease stage 3
K054.00	Chronic kidney disease stage 4
K055.00	Chronic kidney disease stage 5

Table C.7: READ codes to identify diabetes mellitus in CPRD

READ code	READ term
C10..00	Diabetes mellitus
C100.00	Diabetes mellitus with no mention of complication
C100000	Diabetes mellitus, juvenile type, no mention of complication
C100011	Insulin dependent diabetes mellitus

C100100	Diabetes mellitus, adult onset, no mention of complication
C100111	Maturity onset diabetes
C100112	Non-insulin dependent diabetes mellitus
C100z00	Diabetes mellitus NOS with no mention of complication
C101.00	Diabetes mellitus with ketoacidosis
C101000	Diabetes mellitus, juvenile type, with ketoacidosis
C101100	Diabetes mellitus, adult onset, with ketoacidosis
C101y00	Other specified diabetes mellitus with ketoacidosis
C101z00	Diabetes mellitus NOS with ketoacidosis
C102.00	Diabetes mellitus with hyperosmolar coma
C102000	Diabetes mellitus, juvenile type, with hyperosmolar coma
C102100	Diabetes mellitus, adult onset, with hyperosmolar coma
C102z00	Diabetes mellitus NOS with hyperosmolar coma
C103.00	Diabetes mellitus with ketoacidotic coma
C103000	Diabetes mellitus, juvenile type, with ketoacidotic coma
C103100	Diabetes mellitus, adult onset, with ketoacidotic coma
C103y00	Other specified diabetes mellitus with coma
C103z00	Diabetes mellitus NOS with ketoacidotic coma
C104.00	Diabetes mellitus with renal manifestation
C104.11	Diabetic nephropathy
C104000	Diabetes mellitus, juvenile type, with renal manifestation
C104100	Diabetes mellitus, adult onset, with renal manifestation
C104y00	Other specified diabetes mellitus with renal complications
C104z00	Diabetes mellitus with nephropathy NOS
C105.00	Diabetes mellitus with ophthalmic manifestation
C105000	Diabetes mellitus, juvenile type, + ophthalmic manifestation
C105100	Diabetes mellitus, adult onset, + ophthalmic manifestation
C105y00	Other specified diabetes mellitus with ophthalmic complicatn
C105z00	Diabetes mellitus NOS with ophthalmic manifestation
C106.00	Diabetes mellitus with neurological manifestation
C106.11	Diabetic amyotrophy
C106.12	Diabetes mellitus with neuropathy
C106.13	Diabetes mellitus with polyneuropathy
C106000	Diabetes mellitus, juvenile, + neurological manifestation
C106100	Diabetes mellitus, adult onset, + neurological manifestation
C106y00	Other specified diabetes mellitus with neurological comps
C106z00	Diabetes mellitus NOS with neurological manifestation
C107.00	Diabetes mellitus with peripheral circulatory disorder
C107.11	Diabetes mellitus with gangrene
C107.12	Diabetes with gangrene
C107000	Diabetes mellitus, juvenile +peripheral circulatory disorder
C107100	Diabetes mellitus, adult, + peripheral circulatory disorder
C107200	Diabetes mellitus, adult with gangrene
C107300	IDDM with peripheral circulatory disorder
C107400	NIDDM with peripheral circulatory disorder

C107z00	Diabetes mellitus NOS with peripheral circulatory disorder
C108.00	Insulin dependent diabetes mellitus
C108.11	IDDM-Insulin dependent diabetes mellitus
C108.12	Type 1 diabetes mellitus
C108.13	Type I diabetes mellitus
C108000	Insulin-dependent diabetes mellitus with renal complications
C108011	Type I diabetes mellitus with renal complications
C108012	Type 1 diabetes mellitus with renal complications
C108100	Insulin-dependent diabetes mellitus with ophthalmic comps
C108112	Type 1 diabetes mellitus with ophthalmic complications
C108200	Insulin-dependent diabetes mellitus with neurological comps
C108211	Type I diabetes mellitus with neurological complications
C108212	Type 1 diabetes mellitus with neurological complications
C108300	Insulin dependent diabetes mellitus with multiple complicatn
C108311	Type I diabetes mellitus with multiple complications
C108400	Unstable insulin dependent diabetes mellitus
C108411	Unstable type I diabetes mellitus
C108412	Unstable type 1 diabetes mellitus
C108500	Insulin dependent diabetes mellitus with ulcer
C108511	Type I diabetes mellitus with ulcer
C108512	Type 1 diabetes mellitus with ulcer
C108600	Insulin dependent diabetes mellitus with gangrene
C108700	Insulin dependent diabetes mellitus with retinopathy
C108711	Type I diabetes mellitus with retinopathy
C108712	Type 1 diabetes mellitus with retinopathy
C108800	Insulin dependent diabetes mellitus - poor control
C108811	Type I diabetes mellitus - poor control
C108812	Type 1 diabetes mellitus - poor control
C108900	Insulin dependent diabetes maturity onset
C108911	Type I diabetes mellitus maturity onset
C108912	Type 1 diabetes mellitus maturity onset
C108A00	Insulin-dependent diabetes without complication
C108A11	Type I diabetes mellitus without complication
C108B00	Insulin dependent diabetes mellitus with mononeuropathy
C108B11	Type I diabetes mellitus with mononeuropathy
C108C00	Insulin dependent diabetes mellitus with polyneuropathy
C108D00	Insulin dependent diabetes mellitus with nephropathy
C108D11	Type I diabetes mellitus with nephropathy
C108E00	Insulin dependent diabetes mellitus with hypoglycaemic coma
C108E11	Type I diabetes mellitus with hypoglycaemic coma
C108E12	Type 1 diabetes mellitus with hypoglycaemic coma
C108F00	Insulin dependent diabetes mellitus with diabetic cataract
C108F11	Type I diabetes mellitus with diabetic cataract
C108G00	Insulin dependent diab mell with peripheral angiopathy
C108H00	Insulin dependent diabetes mellitus with arthropathy

C108H11	Type I diabetes mellitus with arthropathy
C108J00	Insulin dependent diab mell with neuropathic arthropathy
C108J11	Type I diabetes mellitus with neuropathic arthropathy
C108J12	Type 1 diabetes mellitus with neuropathic arthropathy
C108y00	Other specified diabetes mellitus with multiple comps
C108z00	Unspecified diabetes mellitus with multiple complications
C109.00	Non-insulin dependent diabetes mellitus
C109.11	NIDDM - Non-insulin dependent diabetes mellitus
C109.12	Type 2 diabetes mellitus
C109.13	Type II diabetes mellitus
C109000	Non-insulin-dependent diabetes mellitus with renal comps
C109011	Type II diabetes mellitus with renal complications
C109012	Type 2 diabetes mellitus with renal complications
C109100	Non-insulin-dependent diabetes mellitus with ophthalm comps
C109111	Type II diabetes mellitus with ophthalmic complications
C109112	Type 2 diabetes mellitus with ophthalmic complications
C109200	Non-insulin-dependent diabetes mellitus with neuro comps
C109211	Type II diabetes mellitus with neurological complications
C109212	Type 2 diabetes mellitus with neurological complications
C109300	Non-insulin-dependent diabetes mellitus with multiple comps
C109312	Type 2 diabetes mellitus with multiple complications
C109400	Non-insulin dependent diabetes mellitus with ulcer
C109411	Type II diabetes mellitus with ulcer
C109412	Type 2 diabetes mellitus with ulcer
C109500	Non-insulin dependent diabetes mellitus with gangrene
C109511	Type II diabetes mellitus with gangrene
C109512	Type 2 diabetes mellitus with gangrene
C109600	Non-insulin-dependent diabetes mellitus with retinopathy
C109611	Type II diabetes mellitus with retinopathy
C109612	Type 2 diabetes mellitus with retinopathy
C109700	Non-insulin dependent diabetes mellitus - poor control
C109711	Type II diabetes mellitus - poor control
C109712	Type 2 diabetes mellitus - poor control
C109800	Reaven's syndrome
C109900	Non-insulin-dependent diabetes mellitus without complication
C109911	Type II diabetes mellitus without complication
C109912	Type 2 diabetes mellitus without complication
C109A00	Non-insulin dependent diabetes mellitus with mononeuropathy
C109A11	Type II diabetes mellitus with mononeuropathy
C109B00	Non-insulin dependent diabetes mellitus with polyneuropathy
C109B11	Type II diabetes mellitus with polyneuropathy
C109C00	Non-insulin dependent diabetes mellitus with nephropathy
C109C11	Type II diabetes mellitus with nephropathy
C109C12	Type 2 diabetes mellitus with nephropathy
C109D00	Non-insulin dependent diabetes mellitus with hypoglyca coma

C109D11	Type II diabetes mellitus with hypoglycaemic coma
C109D12	Type 2 diabetes mellitus with hypoglycaemic coma
C109E00	Non-insulin depend diabetes mellitus with diabetic cataract
C109E11	Type II diabetes mellitus with diabetic cataract
C109E12	Type 2 diabetes mellitus with diabetic cataract
C109F00	Non-insulin-dependent d m with peripheral angiopath
C109F11	Type II diabetes mellitus with peripheral angiopathy
C109F12	Type 2 diabetes mellitus with peripheral angiopathy
C109G00	Non-insulin dependent diabetes mellitus with arthropathy
C109G11	Type II diabetes mellitus with arthropathy
C109G12	Type 2 diabetes mellitus with arthropathy
C109H00	Non-insulin dependent d m with neuropathic arthropathy
C109H11	Type II diabetes mellitus with neuropathic arthropathy
C109H12	Type 2 diabetes mellitus with neuropathic arthropathy
C109J00	Insulin treated Type 2 diabetes mellitus
C109J11	Insulin treated non-insulin dependent diabetes mellitus
C109J12	Insulin treated Type II diabetes mellitus
C109K00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C10A.00	Malnutrition-related diabetes mellitus
C10A000	Malnutrition-related diabetes mellitus with coma
C10A100	Malnutrition-related diabetes mellitus with ketoacidosis
C10A500	Malnutritn-relat diabetes melitus wth periph circul complctn
C10B.00	Diabetes mellitus induced by steroids
C10B000	Steroid induced diabetes mellitus without complication
C10C.00	Diabetes mellitus autosomal dominant
C10C.11	Maturity onset diabetes in youth
C10C.12	Maturity onset diabetes in youth type 1
C10D.00	Diabetes mellitus autosomal dominant type 2
C10D.11	Maturity onset diabetes in youth type 2
C10E.00	Type 1 diabetes mellitus
C10E.11	Type I diabetes mellitus
C10E.12	Insulin dependent diabetes mellitus
C10E000	Type 1 diabetes mellitus with renal complications
C10E012	Insulin-dependent diabetes mellitus with renal complications
C10E100	Type 1 diabetes mellitus with ophthalmic complications
C10E111	Type I diabetes mellitus with ophthalmic complications
C10E112	Insulin-dependent diabetes mellitus with ophthalmic comps
C10E200	Type 1 diabetes mellitus with neurological complications
C10E212	Insulin-dependent diabetes mellitus with neurological comps
C10E300	Type 1 diabetes mellitus with multiple complications
C10E311	Type I diabetes mellitus with multiple complications
C10E312	Insulin dependent diabetes mellitus with multiple complicat
C10E400	Unstable type 1 diabetes mellitus
C10E411	Unstable type I diabetes mellitus
C10E412	Unstable insulin dependent diabetes mellitus

C10E500	Type 1 diabetes mellitus with ulcer
C10E511	Type I diabetes mellitus with ulcer
C10E512	Insulin dependent diabetes mellitus with ulcer
C10E600	Type 1 diabetes mellitus with gangrene
C10E611	Type I diabetes mellitus with gangrene
C10E612	Insulin dependent diabetes mellitus with gangrene
C10E700	Type 1 diabetes mellitus with retinopathy
C10E711	Type I diabetes mellitus with retinopathy
C10E712	Insulin dependent diabetes mellitus with retinopathy
C10E800	Type 1 diabetes mellitus - poor control
C10E811	Type I diabetes mellitus - poor control
C10E812	Insulin dependent diabetes mellitus - poor control
C10E900	Type 1 diabetes mellitus maturity onset
C10E911	Type I diabetes mellitus maturity onset
C10E912	Insulin dependent diabetes maturity onset
C10EA00	Type 1 diabetes mellitus without complication
C10EA11	Type I diabetes mellitus without complication
C10EA12	Insulin-dependent diabetes without complication
C10EB00	Type 1 diabetes mellitus with mononeuropathy
C10EC00	Type 1 diabetes mellitus with polyneuropathy
C10EC11	Type I diabetes mellitus with polyneuropathy
C10EC12	Insulin dependent diabetes mellitus with polyneuropathy
C10ED00	Type 1 diabetes mellitus with nephropathy
C10ED12	Insulin dependent diabetes mellitus with nephropathy
C10EE00	Type 1 diabetes mellitus with hypoglycaemic coma
C10EE12	Insulin dependent diabetes mellitus with hypoglycaemic coma
C10EF00	Type 1 diabetes mellitus with diabetic cataract
C10EF12	Insulin dependent diabetes mellitus with diabetic cataract
C10EG00	Type 1 diabetes mellitus with peripheral angiopathy
C10EH00	Type 1 diabetes mellitus with arthropathy
C10EJ00	Type 1 diabetes mellitus with neuropathic arthropathy
C10EK00	Type 1 diabetes mellitus with persistent proteinuria
C10EL00	Type 1 diabetes mellitus with persistent microalbuminuria
C10EL11	Type I diabetes mellitus with persistent microalbuminuria
C10EM00	Type 1 diabetes mellitus with ketoacidosis
C10EM11	Type I diabetes mellitus with ketoacidosis
C10EN00	Type 1 diabetes mellitus with ketoacidotic coma
C10EN11	Type I diabetes mellitus with ketoacidotic coma
C10EP00	Type 1 diabetes mellitus with exudative maculopathy
C10EP11	Type I diabetes mellitus with exudative maculopathy
C10EQ00	Type 1 diabetes mellitus with gastroparesis
C10EQ11	Type I diabetes mellitus with gastroparesis
C10ER00	Latent autoimmune diabetes mellitus in adult
C10F.00	Type 2 diabetes mellitus
C10F.11	Type II diabetes mellitus

C10F000	Type 2 diabetes mellitus with renal complications
C10F011	Type II diabetes mellitus with renal complications
C10F100	Type 2 diabetes mellitus with ophthalmic complications
C10F111	Type II diabetes mellitus with ophthalmic complications
C10F200	Type 2 diabetes mellitus with neurological complications
C10F211	Type II diabetes mellitus with neurological complications
C10F300	Type 2 diabetes mellitus with multiple complications
C10F311	Type II diabetes mellitus with multiple complications
C10F400	Type 2 diabetes mellitus with ulcer
C10F411	Type II diabetes mellitus with ulcer
C10F500	Type 2 diabetes mellitus with gangrene
C10F511	Type II diabetes mellitus with gangrene
C10F600	Type 2 diabetes mellitus with retinopathy
C10F611	Type II diabetes mellitus with retinopathy
C10F700	Type 2 diabetes mellitus - poor control
C10F711	Type II diabetes mellitus - poor control
C10F900	Type 2 diabetes mellitus without complication
C10F911	Type II diabetes mellitus without complication
C10FA00	Type 2 diabetes mellitus with mononeuropathy
C10FA11	Type II diabetes mellitus with mononeuropathy
C10FB00	Type 2 diabetes mellitus with polyneuropathy
C10FB11	Type II diabetes mellitus with polyneuropathy
C10FC00	Type 2 diabetes mellitus with nephropathy
C10FC11	Type II diabetes mellitus with nephropathy
C10FD00	Type 2 diabetes mellitus with hypoglycaemic coma
C10FD11	Type II diabetes mellitus with hypoglycaemic coma
C10FE00	Type 2 diabetes mellitus with diabetic cataract
C10FE11	Type II diabetes mellitus with diabetic cataract
C10FF00	Type 2 diabetes mellitus with peripheral angiopathy
C10FF11	Type II diabetes mellitus with peripheral angiopathy
C10FG00	Type 2 diabetes mellitus with arthropathy
C10FG11	Type II diabetes mellitus with arthropathy
C10FH00	Type 2 diabetes mellitus with neuropathic arthropathy
C10FH11	Type II diabetes mellitus with neuropathic arthropathy
C10FJ00	Insulin treated Type 2 diabetes mellitus
C10FJ11	Insulin treated Type II diabetes mellitus
C10FK00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C10FK11	Hyperosmolar non-ketotic state in type II diabetes mellitus
C10FL00	Type 2 diabetes mellitus with persistent proteinuria
C10FL11	Type II diabetes mellitus with persistent proteinuria
C10FM00	Type 2 diabetes mellitus with persistent microalbuminuria
C10FM11	Type II diabetes mellitus with persistent microalbuminuria
C10FN00	Type 2 diabetes mellitus with ketoacidosis
C10FN11	Type II diabetes mellitus with ketoacidosis
C10FP00	Type 2 diabetes mellitus with ketoacidotic coma

C10FP11	Type II diabetes mellitus with ketoacidotic coma
C10FQ00	Type 2 diabetes mellitus with exudative maculopathy
C10FR00	Type 2 diabetes mellitus with gastroparesis
C10FS00	Maternally inherited diabetes mellitus
C10G.00	Secondary pancreatic diabetes mellitus
C10G000	Secondary pancreatic diabetes mellitus without complication
C10H000	DM induced by non-steroid drugs without complication
C10J.00	Insulin autoimmune syndrome
C10K.00	Type A insulin resistance
C10K000	Type A insulin resistance without complication
C10M.00	Lipoatrophic diabetes mellitus
C10N.00	Secondary diabetes mellitus
C10N000	Secondary diabetes mellitus without complication
C10N100	Cystic fibrosis related diabetes mellitus
C10P.00	Diabetes mellitus in remission
C10P000	Type I diabetes mellitus in remission
C10P100	Type II diabetes mellitus in remission
C10y.00	Diabetes mellitus with other specified manifestation
C10y100	Diabetes mellitus, adult, + other specified manifestation
C10yy00	Other specified diabetes mellitus with other spec comps
C10yz00	Diabetes mellitus NOS with other specified manifestation
C10z.00	Diabetes mellitus with unspecified complication
C10z000	Diabetes mellitus, juvenile type, + unspecified complication
C10z100	Diabetes mellitus, adult onset, + unspecified complication
C10zy00	Other specified diabetes mellitus with unspecified comps
C10zz00	Diabetes mellitus NOS with unspecified complication
PKyP.11	Wolfram syndrome
PKyP.00	Diab insipidus,diab mell,optic atrophy and deafness

Table C.8: READ codes to identify hypertension in CPRD

READ code	READ term
G20..00	Essential hypertension
G2...00	Hypertensive disease
G20..11	High blood pressure
G20z.00	Essential hypertension NOS
G20z.11	Hypertension NOS
G2z..00	Hypertensive disease NOS
G201.00	Benign essential hypertension
G2...11	BP - hypertensive disease
G202.00	Systolic hypertension
G200.00	Malignant essential hypertension
G24..00	Secondary hypertension
G25..11	Stage 1 hypertension

G28..00	Stage 2 hypertension (NICE - Nat Ins for Hth Clin Excl 2011)
G25..00	Stage 1 hypertension (NICE - Nat Ins for Hth Clin Excl 2011)
G2y..00	Other specified hypertensive disease
G203.00	Diastolic hypertension
G24z.00	Secondary hypertension NOS
G244.00	Hypertension secondary to endocrine disorders
G24z000	Secondary renovascular hypertension NOS
G24zz00	Secondary hypertension NOS
G26..11	Severe hypertension
G240.00	Secondary malignant hypertension
G241.00	Secondary benign hypertension
Gyu2.00	[X]Hypertensive diseases
G241z00	Secondary benign hypertension NOS
G250.00	N/A
G20..12	Primary hypertension
G26..00	Severe hypertension (Nat Inst for Health Clinical Ex 2011)
G240z00	Secondary malignant hypertension NOS
G251.00	N/A
Gyu2000	[X]Other secondary hypertension

Table C.9: READ codes to identify left ventricular hypertrophy in CPRD

READ code	READ term
G5y3411	Left ventricular hypertrophy
3242	ECG: shows LVH
324Z.00	ECG: LVH NOS

Table C.10: READ codes to identify rheumatoid arthritis in CPRD

READ code	READ term
G5y8.00	Rheumatoid myocarditis
G5yA.00	Rheumatoid carditis
N005.00	Adult Still's Disease
N040.00	Rheumatoid arthritis
N040000	Rheumatoid arthritis of cervical spine
N040100	Other rheumatoid arthritis of spine
N040200	Rheumatoid arthritis of shoulder
N040300	Rheumatoid arthritis of sternoclavicular joint
N040400	Rheumatoid arthritis of acromioclavicular joint
N040500	Rheumatoid arthritis of elbow
N040600	Rheumatoid arthritis of distal radio-ulnar joint

N040700	Rheumatoid arthritis of wrist
N040800	Rheumatoid arthritis of MCP joint
N040900	Rheumatoid arthritis of PIP joint of finger
N040A00	Rheumatoid arthritis of DIP joint of finger
N040B00	Rheumatoid arthritis of hip
N040C00	Rheumatoid arthritis of sacro-iliac joint
N040D00	Rheumatoid arthritis of knee
N040E00	Rheumatoid arthritis of tibio-fibular joint
N040F00	Rheumatoid arthritis of ankle
N040G00	Rheumatoid arthritis of subtalar joint
N040H00	Rheumatoid arthritis of talonavicular joint
N040J00	Rheumatoid arthritis of other tarsal joint
N040K00	Rheumatoid arthritis of 1st MTP joint
N040L00	Rheumatoid arthritis of lesser MTP joint
N040M00	Rheumatoid arthritis of IP joint of toe
N040N00	Rheumatoid vasculitis
N040P00	Seronegative rheumatoid arthritis
N040Q00	Rheumatoid bursitis
N040R00	Rheumatoid nodule
N040S00	Rheumatoid arthritis - multiple joint
N040T00	Flare of rheumatoid arthritis
N041.00	Felty's syndrome
N042.00	Other rheumatoid arthropathy + visceral/systemic involvement
N042100	Rheumatoid lung disease
N042200	Rheumatoid nodule
N042z00	Rheumatoid arthropathy + visceral/systemic involvement NOS
N047.00	Seropositive errosive rheumatoid arthritis
N04X.00	Seropositive rheumatoid arthritis, unspecified
N04y000	Rheumatoid lung
N04y011	Caplan's syndrome
N04y012	Fibrosing alveolitis associated with rheumatoid arthritis
N04y200	Adult-onset Still's disease
Nyu1000	[X]Rheumatoid arthritis+involvement/other organs or systems
Nyu1100	[X]Other seropositive rheumatoid arthritis
Nyu1200	[X]Other specified rheumatoid arthritis
Nyu1G00	[X]Seropositive rheumatoid arthritis, unspecified

Table C.11: READ codes to identify smoking status in CPRD

READ code	READ term
137..11	Smoker - amount smoked
1371	Never smoked tobacco
1371.11	Non-smoker

1372	Trivial smoker - < 1 cig/day
1372.11	Occasional smoker
1373	Light smoker - 1-9 cigs/day
1374	Moderate smoker - 10-19 cigs/d
1375	Heavy smoker - 20-39 cigs/day
1376	Very heavy smoker - 40+cigs/d
1377	Ex-trivial smoker (<1/day)
1378	Ex-light smoker (1-9/day)
1379	Ex-moderate smoker (10-19/day)
137A.00	Ex-heavy smoker (20-39/day)
137b.00	Ready to stop smoking
137B.00	Ex-very heavy smoker (40+/day)
137C.00	Keeps trying to stop smoking
137c.00	Thinking about stopping smoking
137d.00	Not interested in stopping smoking
137e.00	Smoking restarted
137F.00	Ex-smoker - amount unknown
137f.00	Reason for restarting smoking
137G.00	Trying to give up smoking
137H.00	Pipe smoker
137J.00	Cigar smoker
137j.00	Ex-cigarette smoker
137K.00	Stopped smoking
137K000	Recently stopped smoking
137l.00	Ex roll-up cigarette smoker
137L.00	Current non-smoker
137m.00	Failed attempt to stop smoking
137N.00	Ex pipe smoker
137O.00	Ex cigar smoker
137P.00	Cigarette smoker
137P.11	Smoker
137Q.00	Smoking started
137Q.11	Smoking restarted
137R.00	Current smoker
137S.00	Ex smoker
137T.00	Date ceased smoking
137V.00	Smoking reduced

Table C.12: READ codes to identify ethnicity in CPRD

READ code	READ term
1341	European origin
1342	African origin
1343	Asian origin

1344	North American origin
1345	South American origin
1346	Australian origin
1347	Indian origin
1348	Middle Eastern origin
1349	Far Eastern origin
134A.00	West Indian origin
134B.00	RACE: Caucasian
134C.00	RACE: Arab
134D.00	RACE: Chinese
134E.00	RACE: Japanese
134F.00	RACE: Korean
134G.00	RACE: Oriental
134H.00	RACE: Afro-caribbean
134I.00	RACE: Bangladeshi
134J.00	RACE: Mixed
134K.00	RACE: West indian
134L.00	RACE: Afro-caucasian
134M.00	RACE: Pakistani
134N.00	RACE: White
134P.11	RACE: Other
9i0..00	British or mixed British - ethnic category 2001 census
9i00.00	White British - ethnic category 2001 census
9i1..00	Irish - ethnic category 2001 census
9i10.00	White Irish - ethnic category 2001 census
9i2..00	Other White background - ethnic category 2001 census
9i20.00	English - ethnic category 2001 census
9i21.00	Scottish - ethnic category 2001 census
9i22.00	Welsh - ethnic category 2001 census
9i23.00	Cornish - ethnic category 2001 census
9i24.00	Northern Irish - ethnic category 2001 census
9i25.00	Ulster Scots - ethnic category 2001 census
9i2Q.00	Mixed Irish and other White - ethnic category 2001 census
9i2R.00	Oth White European/European unsp/Mixed European 2001 census
9i2S.00	Other mixed White - ethnic category 2001 census
9i2T.00	Other White or White unspecified ethnic category 2001 census
9i3..00	White and Black Caribbean - ethnic category 2001 census
9i4..00	White and Black African - ethnic category 2001 census
9i5..00	White and Asian - ethnic category 2001 census
9i6..00	Other Mixed background - ethnic category 2001 census
9i60.00	Black and Asian - ethnic category 2001 census
9i61.00	Black and Chinese - ethnic category 2001 census
9i62.00	Black and White - ethnic category 2001 census
9i63.00	Chinese and White - ethnic category 2001 census
9i64.00	Asian and Chinese - ethnic category 2001 census

9i65.00	Other Mixed or Mixed unspecified ethnic category 2001 census
9i7..00	Indian or British Indian - ethnic category 2001 census
9i8..00	Pakistani or British Pakistani - ethnic category 2001 census
9i9..00	Bangladeshi or British Bangladeshi - ethn categ 2001 census
9iA..00	Other Asian background - ethnic category 2001 census
9iA1.00	Punjabi - ethnic category 2001 census
9iA2.00	Kashmiri - ethnic category 2001 census
9iA3.00	East African Asian - ethnic category 2001 census
9iA4.00	Sri Lankan - ethnic category 2001 census
9iA5.00	Tamil - ethnic category 2001 census
9iA6.00	Sinhalese - ethnic category 2001 census
9iA7.00	Caribbean Asian - ethnic category 2001 census
9iA8.00	British Asian - ethnic category 2001 census
9iA9.00	Mixed Asian - ethnic category 2001 census
9iAA.00	Other Asian or Asian unspecified ethnic category 2001 census
9iB..00	Caribbean - ethnic category 2001 census
9iC..00	African - ethnic category 2001 census
9iD..00	Other Black background - ethnic category 2001 census
9iD0.00	Somali - ethnic category 2001 census
9iD1.00	Nigerian - ethnic category 2001 census
9iD2.00	Black British - ethnic category 2001 census
9iD3.00	Mixed Black - ethnic category 2001 census
9iD4.00	Other Black or Black unspecified ethnic category 2001 census
9iE..00	Chinese - ethnic category 2001 census
9iF..00	Other - ethnic category 2001 census
9iF0.00	Vietnamese - ethnic category 2001 census
9iF1.00	Japanese - ethnic category 2001 census
9iF2.00	Filipino - ethnic category 2001 census
9iF3.00	Malaysian - ethnic category 2001 census
9iF9.00	Arab - ethnic category 2001 census
9iFA.00	North African - ethnic category 2001 census
9iFB.00	Mid East (excl Israeli, Iranian & Arab) - eth cat 2001 cens
9iFC.00	Israeli - ethnic category 2001 census
9iFD.00	Iranian - ethnic category 2001 census
9iFE.00	Kurdish - ethnic category 2001 census
9iFF.00	Moroccan - ethnic category 2001 census
9iFG.00	Latin American - ethnic category 2001 census
9iFH.00	South and Central American - ethnic category 2001 census
9iFJ.00	Mauritian/Seychellois/Maldivian/St Helena eth cat 2001census
9iFK.00	Any other group - ethnic category 2001 census
9S1..00	White
9S10.00	White British
9S11.00	White Irish
9S12.00	Other white ethnic group
9S13.00	White Scottish

9S14.00	Other white British ethnic group
9S2..00	Black Caribbean
9S3..00	Black African
9S4..00	Black, other, non-mixed origin
9S41.00	Black British
9S42.00	Black Caribbean/W.I./Guyana
9S42.11	Black Caribbean
9S42.12	Black West Indian
9S42.13	Black Guyana
9S43.00	Black N African/Arab/Iranian
9S43.11	Black North African
9S43.12	Black Arab
9S43.13	Black Iranian
9S44.00	Black - other African country
9S45.00	Black E Afric Asia/Indo-Caribb
9S45.11	Black East African Asian
9S45.12	Black Indo-Caribbean
9S46.00	Black Indian sub-continent
9S47.00	Black - other Asian
9S48.00	Black Black - other
9S5..00	Black - other, mixed
9S51.00	Other Black - Black/White orig
9S52.00	Other Black - Black/Asian orig
9S6..00	Indian
9S7..00	Pakistani
9S8..00	Bangladeshi
9S9..00	Chinese
9SA..00	Other ethnic non-mixed (NMO)
9SA3.00	Caribbean I./W.I./Guyana (NMO)
9SA3.11	Caribbean Island (NMO)
9SA3.12	West Indian (NMO)
9SA3.13	Guyana (NMO)
9SA4.00	N African Arab/Iranian (NMO)
9SA4.11	North African Arab (NMO)
9SA4.12	Iranian (NMO)
9SA5.00	Other African countries (NMO)
9SA6.00	E Afric Asian/Indo-Carib (NMO)
9SA6.11	East African Asian (NMO)
9SA6.12	Indo-Caribbean (NMO)
9SA7.00	Indian sub-continent (NMO)
9SA8.00	Other Asian (NMO)
9SA9.00	Irish (NMO)
9SAC.00	Other European (NMO)
9SAD.00	Other ethnic NEC (NMO)
9SB..00	Other ethnic, mixed origin

9SB1.00	Other ethnic, Black/White orig
9SB2.00	Other ethnic, Asian/White orig
9SB3.00	Other ethnic, mixed white orig
9SB4.00	Other ethnic, other mixed orig
9SB5.00	Black Caribbean and White
9SB6.00	Black African and White
9SC..00	Vietnamese
9SG..00	Other black ethnic group
9SH..00	Other Asian ethnic group
9SI..00	Irish traveller
9SJ..00	Other ethnic group
9T1B.00	South East Asian
9T1C.00	Chinese
9T1D.00	Indian
9T1E.00	Other Asian

Table C.13: Standardized hazard ratios for variability measures when each variability measure is standardized in the imputed datasets before model fitting

Variability measure	Standardized hazard ratio (per mm Hg)	95% confidence interval	
SD	1.087	1.026	1.152
CV	1.083	1.018	1.153
ARV	1.088	1.025	1.155
VIM	1.090	1.027	1.158

Table C.14: Variability model for risk of cardiovascular disease

Variable	Adjusted hazard ratio	Standard error	p-value	95% confidence interval	
Female gender	0.560	0.036	0.000	0.522	0.601
Age (per year)	1.129	0.019	0.000	1.088	1.171
Atrial fibrillation	2.761	0.159	0.000	2.022	3.772
Family history of CVD	1.027	0.041	0.512	0.949	1.112
Chronic kidney disease (Stage 3 to 5)	1.013	0.270	0.963	0.597	1.718
Diabetes (Type 1 or 2)	1.654	0.111	0.000	1.332	2.055
Rheumatoid arthritis	1.709	0.144	0.000	1.289	2.265
Body mass index (per kg/ m^2)	1.009	0.004	0.047	1.000	1.018
TC/HDL cholesterol (per mmol/L)	1.315	0.081	0.001	1.121	1.543
Smoking status (reference = Non-smoker)					
Current smoker (n=20,506)	4.458	0.222	0.000	2.883	6.893
Ex-smoker (n=16,582)	1.959	0.278	0.015	1.137	3.374
Ethnic group (reference= White/ Unknown)					
Indian (n=973)	1.391	0.156	0.034	1.024	1.889
Bangladeshi (n=45)	1.800	0.711	0.409	0.446	7.255
Pakistani (n=180)	1.101	0.380	0.799	0.523	2.319
Chinese (n=214)	0.171	1.001	0.078	0.024	1.216
Black African (n=524)	1.015	0.290	0.959	0.574	1.794
Black Caribbean (n=494)	0.644	0.303	0.146	0.355	1.166
Other Black (n=210)	0.922	0.449	0.857	0.382	2.224
Other Asian (n=487)	1.350	0.231	0.195	0.857	2.124
Other (n=651)	0.929	0.215	0.731	0.609	1.415
Mixed (n=12,337)	0.970	0.045	0.493	0.888	1.059
Index of multiple deprivation (reference = 1st quintile (least deprived))					
2	1.146	0.041	0.001	1.057	1.243
3	1.192	0.043	0.000	1.096	1.297
4	1.357	0.044	0.000	1.243	1.480
5	1.401	0.067	0.000	1.228	1.598
Mean systolic BP over 6 readings (per mm Hg)	1.029	0.009	0.001	1.011	1.046
Age x smoking status					
Age (per year) in current smokers	0.986	0.004	0.000	0.979	0.993
Age (per year) in ex-smokers	0.992	0.004	0.060	0.983	1.000
Age x TC/HDL cholesterol ratio	0.997	0.001	0.066	0.995	1.000
Age x Mean systolic BP over 6 readings	1.000	0.000	0.064	0.999	1.000
Variation independent of mean (per mm Hg)	1.021	0.007	0.005	1.006	1.037
Constant	-15.213	1.163	0.000	-17.493	-12.933
Log(scale)	0.195	0.013	0.000	0.169	0.221

Table C.15: Internal model performance results when using within-imputation model estimates to estimate risk (derivation cohort)

Statistic	Estimate	95% confidence interval	
Reference model			
Calibration slope	1.0036	0.9704	1.0368
c-statistic	0.7514	0.7441	0.7588
R^2 (%)	33.89	32.38	35.39
E/O calibration	1.0312	1.0004	1.0621
Variability model			
Calibration slope	1.0036	0.9706	1.0366
c-statistic	0.7526	0.7451	0.7600
R^2 (%)	34.13	32.59	35.66
E/O calibration	1.0307	0.9998	1.0616
Across both models			
NRI	0.0024	-0.0056	0.0105
IDI	0.0010	-0.0002	0.0021

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