The impact of blood pressure and treatment on long-term survival in hypertensive patients with high risk for cardiovascular disease using data from the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)

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Abstract

The ASCOT randomised factorial trial compared calcium channel blocker (CCB) based-therapy versus beta blocker (BB) based-therapy and statin versus placebo. 19,342 hypertensive patients were recruited between 1998 and 2001 and followed for a median of 5.5 years. Primary results were published in 2003 and 2005. A total of 8,580 British ASCOT patients were followed-up for a median of 17.4 years to the end of January 2018, by which time 4040 deaths had occurred, 1,402 from cardiovascular (CV) causes. This thesis analysed the impact of randomised treatment and blood pressure on long-term mortality in this subset of patients and consists of three main sections.

The effect of randomised treatment on long-term survival was assessed, taking into consideration potentially non-proportional treatment effects over time and competing risks from different causes of death. Results showed that statin-therapy reduced coronary heart disease (CHD) mortality compared to placebo (hazard ratio [HR]=0.76, p=0.018) and CCB-based treatment reduced stroke mortality compared to BB-based treatment (HR=0.73, p=0.011).

Several alternative components of blood pressure recorded at baseline were compared for their ability to predict long-term CV mortality. Each was strongly associated with CV mortality and their relative association attenuated with age. While systolic and pulse pressure (PP) were the strongest single predictors, PP had the clearest continuous monotonic relationship with risk, and was the stronger predictor in older subjects.

Repeated blood pressure measurements collected during the trial were used to investigate how features of blood pressure profiles relate to and predict CV-related mortality, e.g. within-subject mean blood pressure, variability and rate of change over time. Factors influencing blood pressure level and variation were investigated. Landmark survival analyses showed again that PP was the most useful summary measure, and both its mean and its variability were independently associated with risk of CV mortality. A clinically useful risk score model was developed containing mean PP and the coefficient of variation (COV) for PP, along with key risk factors.

Overall, this thesis provides useful insights into the impact of treatments on CV mortality risk in the long-term and how blood pressure relates to CV mortality risk in the long-term.

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Abbreviations

ACEi	Angiotensin-converting enzyme inhibitor
ARV	Average real variability
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial
BLUP	Best linear unbiased prediction
BMI	Body mass index
BP	Blood pressure
BPLA	Blood pressure-lowering arm
CHD	Coronary heart disease
CI	Confidence interval
CIF	Cumulative incidence function
CV	Cardiovascular
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DSMB	Data safety monitoring board
HDL	High-density lipoprotein
HR	Hazard ratio
ITT	Intention to treat intension
KM	Kaplan-Meier
LDL	Low-density lipoprotein
LLA	Lipid-lowering arm
LR test	Likelihood ratio test
MAP	Mean arterial pressure
MI	Myocardial infarction
PH	Proportional hazard
PP	Pulse pressure
RCS	Restricted cubic spline
RMSE	Root mean square error
SBP	Systolic blood pressure
SD	Standard deviation
SES	Socio-economic status
sHR	Sub-distribution hazard ratio
VIM	Variability independent of the mean
WHO	World Health Organisation

Chapter 1: Introduction and background to the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) and Legacy study

1.1 Background

1.1.1 Introduction

The collective group of disorders relating to the heart and vascular system is known as cardiovascular disease (CVD). CVD is responsible for the largest global mortality burden. The World Health Organisation (WHO) estimates that currently around 17.9 million people lose their lives to CV-related causes each year [1].

This research degree centres around blood pressure (BP) and treatment for hypertension and hyperlipidaemia, two of the most well-established risk factors for CVD. This thesis presents analyses which utilise long-term mortality follow-up data relating to a hypertensive UK cohort of subjects at high risk of CVD who took part in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), to address meaningful scientific questions with practical applications.

Subjects were eligible to be enrolled and randomised into the ASCOT trial if they presented with hypertension and had an additional three risk factors for CV disease. The factorial trial randomised all patients to one of two blood pressure lowering treatment regimens. This factor of the trial is referred to as the blood pressure-lowering arm (BPLA). The trial further randomised a subset of those patients who were eligible to either lipid-lowering statin-therapy or placebo. This factor of the trial, made up of a subset of the BPLA is referred to as the lipid-lowering arm (LLA).

A cohort of subjects from England, Wales, and Scotland were targeted for long-term post-trial follow-up for mortality outcomes.

This thesis presents research which focuses on three main topics that are covered across the next three chapters. The first investigates the long-term legacy effect on survival of originally allocated trial treatments. The second compares the predictive ability of different components of blood pressure as measured at baseline in relation to long-term CV-related mortality, with a particular focus on comparing systolic blood pressure (SBP) and pulse pressure (PP). The final topic focuses on assessing the impact of blood pressure level and variability on long-term CV-related mortality.

1.1.2 Blood pressure

Blood pressure is a well-established important risk factor for CV morbidity and mortality [2-4]. When blood pressure levels are too high (hypertension), excess strain is exerted in the arteries which can cause damage, leading to increased risk of CV disease. Hypertension is highly prevalent and recognised to be a leading preventable risk factor for cardiovascular disease and mortality.

Examination of the pulse goes back centuries, but it was not until the beginning of the 20th century that a non-invasive, clinically applicable way of measuring blood pressure was developed. After that time, a greater understanding of the link

between blood pressure was developed and CVD was developed. The first study to provide real evidence of the connection was the Framingham Heart Study [2].

Blood pressure is measured at two points: the maximum arterial pressure reached during the contraction of the left ventricle (SBP); and the lowest arterial pressure reached during cardiac relaxation (DBP). Other aspects of these measurements are often also of interest, such as pulse pressure (PP) which is the magnitude in change in blood pressure between systolic and diastolic states.

Only since the 1940s has hypertension been considered a treatable condition. The introduction of thiazide diuretics in the late 1950s were among the first to gain evidence of hypotensive effects. The Veterans Administration Medical Centres in the US conducted large multi-centre studies which led to the first multi-centre randomised placebo-controlled antihypertensive treatment trial, providing evidence that antihypertensive treatment exerted a beneficial effect in reducing CVD risk in high-risk patients [5].

Researchers have studied many new anti-hypertensive treatments over the years. The beta blocker (BB) were considered the leading anti-hypertensive treatment in the 1960s. Thereafter the converting-enzyme blockers and Calcium channel blocker (CCB) rose up as important treatments. Many studies have demonstrated the effectiveness of anti-hypertensive treatments [6]. The ASCOT trial is among a

number of studies that have compared active treatments and helped provide evidence that can help improve treatment strategies.

1.1.3 Lipids

Lipids play a variety of important roles in the body, such as acting as energy stores and contributing to tissue structures. Triglycerides and cholesterol are two types of lipids that circulate in the bloodstream.

Lipoproteins are compounds that serve to transport cholesterol around the body via the bloodstream. They are mainly differentiated by their density: low- and high-density lipoproteins (LDL and HDL, respectively). LDL transports cholesterol to bodily cells while HDL is involved in excess cholesterol removal and transportation to be broken down in the liver. High levels of LDL cholesterol greatly increase the risk of atherosclerosis in blood vessels because LDL molecules contribute to atherosclerotic plaque formation [7]. Conversely, low levels of HDL increase the risk of atherosclerosis because HDL molecules work to prevent plaque formation, and can even cause existing build-ups to reduce [8,9].

Atherosclerotic plaque is one of the main causes of CV dysfunction. As plaque builds up, walls of blood vessels thicken and vessel aperture narrows at the build-up sites. This can lead to restricted blood flow, vascular inflammation, remodelling, and vessel dysfunction, all of which can eventually lead to reduced blood flow to

target organs. In addition, the formation of blood clots (thrombosis) could occur at the plaque build-up sites which could break loose and cause blockages elsewhere.

High levels of triglycerides can also increase the risk of atherosclerosis, although the mechanism behind this is not exactly known.

The Framingham Heart Study was the first major study to link cholesterol to risk of CVD in the 1960s. The study identified the positive relationship between LDL level and risk and the negative relationship between HDL level and risk [2,9].

There are a variety of differently functioning lipid-lowering treatments available, but the most commonly prescribed are drugs from the statin family. Statins work by inhibiting the rate of cholesterol synthesis resulting in blood LDL cholesterol decline.

There is now a wealth of evidence for the efficacy of statins in reducing CVD morbidity and mortality. The West of Scotland Coronary Prevention Study (WOSCOPS) was the first primary prevention study to show that statins were associated with reducing coronary heart disease (CHD) events and CV mortality, compared to placebo [10].

Many other studies followed, such as the MRC/BHF Heart Protection Study (HPS) of simvastatin which showed a significant reduction in all-cause mortality associated with statin use compared to placebo [11]. More recently the Justification for the Use

of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) showed statin benefit in a population with elevated C-reactive protein levels [12]. The ASCOT trial is among those influential studies that demonstrated the cardio-protective effects of statin-use, contributing to their well-established efficacy and safety profile [13].

1.2 The ASCOT Trial

The ASCOT trial enrolled 19,342 hypertensive subjects between 1998 and 2001 who were over 40 years of age, had no history of CHD, but with at least three additional risk factors for CV disease. The trial had a two-by-two factorial design, with a blood pressure-lowering arm (BPLA) and a lipid lowering arm (LLA).

All eligible, consenting participants were randomised with a ratio of 1:1 to one of two blood pressure-lowering treatment regimen in the BPLA: either BB-based or CCB-based treatment. The BB-based regimen consisted of atenolol with additional thiazide diuretic, bendroflumethiazide (BFZ), if necessary, and the "newer" CCB-based regimen consisted of amlodipine with additional angiotensin-converting enzyme inhibitor (ACEi), perindopril, if necessary.

A subset of 10,305 patients with non-fasting total cholesterol concentrations of 6.5 mmol/L or less and no history of statin use were further randomised with a ratio of 1:1 to either anti-hyperlipidaemia statin therapy with atorvastatin or placebo.

The BPLA was stopped early, after a median of 5.5 years following the recommendation from the data safety and monitoring board (DSMB) in October 2004, on grounds of excess mortality and other secondary outcomes in the atenolol-based group. Results, published in the Lancet in 2005, provided evidence that amlodipine-based treatment is associated with reduced risk of CV-related and all-cause mortality, stroke, and heart failure, compared to atenolol-based treatment [14]. The primary endpoint of non-fatal MI plus fatal CHD did not quite reach statistical significance at the 5% level (HR=0.90, p=0.105), likely a consequence of reduced power from early trial termination.

Prior to the early termination of the BPLA, the LLA was also stopped early after a median of 3.3 years following the recommendation from the DSMB in September 2002, on grounds of reduced CHD and stroke events associated with the atorvastatin arm. Results, published in the Lancet in 2003, provided evidence that atorvastatin is associated with a reduction in the primary endpoint (HR=0.64, p=0.001), and also with reductions in CV events and procedures, and coronary events, compared to placebo [13].

1.3 The ASCOT Legacy Cohort

A subset of ASCOT patients from England and Scotland were targeted for long-term follow-up at the end of the trial. 718 (8.4%) of these patients had died within the trial period, and out of the remaining 7862 patients who were alive at the end of the

trial, 7300 (92.9%) consented to long-term follow-up for morbidity and mortality outcomes. The complete subset of 8580 patients are referred to as the ASCOT legacy cohort. Those who were alive at the end of the trial but did not give consent for further follow-up were included in relevant analyses but were censored at the trial end.

Mortality data has been acquired from NHS Digital for the consenting ASCOT legacy patients up to the end of 2015, a median follow-up time of 15.7 years (maximum 17.9 years). We used this data to analyse the long-term effects of the originally randomised trial treatment, results published in the Lancet in 2018 [15]. Subsequently, additional data has been received from NHS Digital containing mortality data up to the end of January 2019, a median follow-up time of 17.4 years (maximum 20.9 years). Hence, the analysis conducted in Chapter 2 of this thesis, which reflects the work done for the 2018 Lancet paper, has been updated to utilise the more recently updated follow-up data.

The mortality data includes date of death as well as detailed causes of death. Two clinicians independently adjudicated the causes of deaths, and classified them as being either CV-related or not CV-related. The CV-related deaths were further categorised as being related to either stroke, CHD, or "other" CV causes. Deaths that were classified as not being related to CVD were further categorised as being related to either cancer, infection or respiratory, or "other".

Over long-term follow-up after trial end, a further 3322 subjects had died, a total of 4040 subjects, 47.1% of the total 8580 ASCOT legacy cohort. This overall number of deaths is, of course, likely to be slightly less than the true number, due to the number of censored subjects for whom we have no post-trial follow-up data.

1.4 Aims and objectives of this research degree

This research degree uses long-term follow-up mortality data relating to participants who took part in the ASCOT trial, and who form the ASCOT legacy Cohort, to address three main aims.

1.4.1 Aim 1: Measure the impact of trial treatments on mortality over long-term follow-up

The first aim was to assess the impact of randomised trial treatments on long-term survival. This aim is addressed in Chapter 2, where the objective was to use survival analysis to measure the relationship between the trial treatment groups that subjects were randomised to on an intention to treat (ITT) basis, and mortality. Specifically, the objectives included assessing the effect of statin use as compared to placebo, and the effect of amlodipine-based treatment use as compared to atenolol-based, on long-term mortality. In addition to effects on all-cause mortality, effects on cause-specific mortality was also analysed.

1.4.2 Aim 2: Assess and compare the relationship that different components of blood pressure have with long-term mortality

The second aim was to assess how different components of blood pressure relate to mortality, and to compare their predictive ability. This aim is addressed in Chapter 3, with the objective to relate different components of blood pressure, using blood pressure recorded at baseline, to mortality using survival analysis, and to make direct comparisons between components' predictive ability. The influence of subject age on such relationships and strength of predictive ability was also considered. The focus for this aim was on CV-mortality, but in addition all-cause mortality, as well as the more specific stroke- and CHD-related causes of death were analysed.

1.4.3 Aim 3: Evaluate the relationship between blood pressure level and long-term CV-related mortality, and the independent importance of variability in blood pressure over time

The third aim was to evaluate how blood pressure level and variability predict CV-related mortality, and in the process identify the best representations of these characteristics of blood pressure profiles. This aim is addressed in Chapter 4, with the objective to use repeated measurements of blood pressure collected during the ASCOT trial period, to estimate blood pressure level and the amount of variability in blood pressure for each subject, to investigate factors that influence these characteristics of BP profile, and describe and quantify the relationship of these blood pressure characteristics with CV-related mortality.

Building upon the work in Chapter 3, those components of blood pressure: SBP and PP, that demonstrated the strongest predictive ability (both in this research and in wider research), became the focus to address this aim.

The final objective to conclude this thesis was to build a clinically useful and appropriate predictive survival model for CV-related mortality containing both a representation of blood pressure level and blood pressure variability, modelled appropriately together with other important risk factors. This model contained the single representation of both blood pressure level and blood pressure variability that demonstrated the strongest predictive ability in this dataset. The purpose of the model was to investigate and illustrate how both the level and viability of blood pressure can fit together appropriately within a useful clinical risk prediction model alongside other key risk factors.

Chapter 2: Impact of originally randomised trial treatment on long-term survival

2.1 Background

2.1.1 Legacy studies in cardiovascular medicine

The term "legacy study" is often used to describe a study which is birthed out of an existing interventional study. A legacy study uses longer-term follow-up of subjects beyond the original designed study period to assess potential treatment effects beyond that seen during the trial. "Legacy effect" refers to interventional effect that are sustained or even emerge beyond the original study period. Legacy effects have been described as "a memory of a treatment which produces benefits long after the cessation of the intervention" [16]. In many legacy studies, the assumption behind legacy effects is that the intervention was responsible for making pathological changes that have some permanency and in turn impact on disease in the long-term. However, in these settings, causal effects, whether direct or indirect, are often hard or impossible to prove.

There have been a number of legacy studies that have been born out of clinical trials in cardiovascular medicine, including placebo controlled statin and blood pressure-lowering trials that have shown long-term survival benefits to those originally randomised to active treatments [17-19].

2.1.2 Blood pressure lowering legacy studies

Evidence for long-term, post-trial, persistent effects of decreased all-cause mortality associated with randomisation to active antihypertensive medication has

been presented from placebo-controlled trials. A meta-analysis involving 18 anti-hypertensive studies was conducted by Kostis et al. which produced evidence of a reduction in all-cause mortality both within the trial periods as well as in the post-trial periods, and was observed in all drug classes included in the analysis (ACEis, BBs, diuretics) [20]. Overall reduction in mortality was similar out of trial (open-label period) as it was within the trial period, despite subjects in both active and placebo randomised arms being advised to go on to the same active treatments post-trial.

Many individual studies have reported a "carry-over" of effect on mortality reduction associated with active anti-hypertensive interventions in post-trial periods [21]. However, there is sparse long-term data available from studies comparing active treatments [22].

Evidence for sustained benefits of CCB therapy coupled with an ACEi as compared to placebo over longer post-trial follow-up have been presented [23]. Although there is good evidence of the benefits of randomisation to a CCB-based regimen compared to another active treatment within trial periods, there are few long-term follow-up studies that have investigated whether randomisation to a CCB-based therapy boasts longer-term benefits on survival beyond the end of a trial [24].

Another study to randomise subjects both to lipid-lowering and blood pressure-lowering treatment arms was the Antihypertensive Lipid-Lowering to prevent Heart Attack Trial (ALLHAT). They randomised hypertensive patients to one of four anti-

hypertensive treatments, either the diuretic: chlorthalidone, the ACEi: lisinopril, the CCB: amlodipine, or the alpha blocker: doxazosin (although the doxazosin arm was discontinued due to safety concerns). The trial duration varied from four to eight years, after which patients were followed-up up through electronic health records for morbidity and mortality outcomes for a total follow-up varying from eight to 13 years. At the end of follow-up results were varied, but the in-trial benefits associated with the diuretic chlorthalidone over Lisinopril and amlodipine were no longer evident over longer follow-up [25–27].

2.1.3 Lipid lowering legacy studies

There has been a lot of interest in the long-term benefits of statins and there has been evidence from a number of large placebo controlled trials for the longer-term benefits of statin use [18,28]. Such studies have presented evidence of sustained survival advantages beyond the trial period to subjects randomised to statins.

It has been suggested that legacy effects from statins could be due to plaque stabilisation, that statin treatment can slow down the development of atherosclerotic plaque build-ups in arteries which alters the progression of the disease even after cessation of treatment [29,30]. As a result it has been argued that treatment of high cholesterol in younger people with statins early on should be considered, and further, some have even argued that statins should be offered to all young people regardless of their cholesterol level [31–34].

The results from the 20-year follow-up of the West of Scotland Coronary Prevention Study (WOSCOPS) in high-risk men with elevated LDL cholesterol but no history of myocardial infarction (MI), concluded that a 5-year period of statin treatment was associated with a legacy benefit of statin use compared to placebo over the 20-year follow-up period [35]. They reported lower mortality from any cause in the statin arm over the whole of follow-up with a hazard ratio (HR) of 0.87 (95% CI: 0.80-0.94, p=0.0007), a larger reduction in CV-related mortality with a HR of 0.79 (95% CI: 0.69-0.90, p=0.0004), and an even stronger effect for mortality attributed to CHD with a HR of 0.73 (95% CI: 0.62-0.86, p=0.0002), estimated from adjusted Cox proportional hazards (PHs) models. They commented that although the greatest relative risk reduction was seen during the trial-treatment period, the continued long-lasting effect that was observed, questioned the need for life-long treatment. They concluded that life-long exposure to the drug may not be required if such legacy effects from shorter therapy duration yield clinically acceptable benefit, and that a study comparing outcomes from varying durations of statin-use could add value to this question.

The long-term follow-up of ASCOT legacy patients provided a great opportunity to investigate the long-term impact of being randomised to CCB-based treatment compared to BB-based treatment, as well as to potentially strengthen existing

evidence of the long-term benefits associated with statin therapy compared to placebo [36,37].

2.2 Aims

The aim of this chapter was to evaluate the impact of having been randomised to a particular blood-pressure lowering treatment regimen, and the impact of being randomised to statin-therapy compared with placebo, on long-term survival using post-trial follow-up data from the ASCOT legacy cohort. The focus was to assess the legacy impact of treatment on CV-related mortality, and more specifically from stroke-related and CHD-related mortality.

Furthermore, the aim was to assess whether treatment effects change over time, and describe such patterns of change should they exist. Paying particular focus to the comparison of within-trial and post-trial periods, the aim was to assess the extent to which effects are sustained and whether some effects are later to emerge over time.

Lastly, the aim was to assess the impact of competing causes of mortality (competing risks) when estimating effects on specific causes of death.

2.3 Measuring the effects of treatments on survival over time

The statistical analysis of time-to-event data is often referred to as survival analysis, although the event need not be mortality.

Survival analysis is distinct from other types of statistical analysis due to the presence of right or left censoring of observation time. Censoring refers to periods in time during which we are unable to observe subject outcomes. One of the most common types of censoring, and relevant in this context, is right censoring which occurs from the point when a subject is no longer being observed at a certain time-point. This could be due to the death of the subject, when a subject is lost-to-follow-up, or when a subject experiences an alternative event (also known as a competing event) which subsequently precludes the subject from experiencing the event of interest.

Censoring can be seen as either informative (i.e. the reason behind censoring is related to risk in some way) or non-informative (i.e. given observed co-variates, censoring can be considered to occur at random, unrelated to risk). Common approaches to survival analysis assume that censoring (not due to the event of interest) is not informative. This can lead to biased estimates if untrue.

There are many approaches to analysing survival data. There are non-parametric approaches such as life tables, Kaplan Meier or Nelson-Aalen methods [38]. There are parametric approaches relating a set of covariates to survival time assuming an appropriate distributional form of the underlying risk over time, for example Poisson, exponential, or Weibull models. There are also alternative parametric approaches, for example, the flexible parametric model proposed by Royston &

Parmar which involves the use of restricted cubic splines to model the underlying hazard rate over time rather than assuming a more specific distribution [39].

An alternative to a fully parametric approach was proposed by Sir David Cox in 1972, known as the Cox Proportional-Hazards (PH) model. While this semi-parametric model assumes that relative hazards (for unit increases in covariates present in a model) are proportional over time, it makes no parametric assumptions about the underlying "baseline" hazard, which is data-driven and free to vary over time. This approach has become the most commonly used model for analysing survival data, possibly due to its robust nature making it simple to use as one does not have to consider the distributional shape of the underlying risk over time. Still, as with other parametric approaches, care must be taken in assessing whether the assumption of proportional hazards is appropriate, otherwise estimates of hazard ratios can be misleading [40].

2.4 Challenges in estimating long-term impact of randomisation to trial treatment

There are many factors that make any long-term differences between randomised treatment groups difficult to interpret and form direct causal inferences. Any long-term differences in mortality observed between originally randomised groups must be interpreted within the context they are in, acknowledging existing limitations.

One of the main challenges in interpreting long-term effects beyond the end of the trial was that information about post-trial treatment was not available. It may be the case that treatment choices beyond the end of the trial were completely independent of which trial arms subjects were randomised to. However, there may be some association between post-trial treatment and randomised trial treatment.

If post-trial treatment choices were independent of the original treatment randomised to, then we might expect that any within-trial survival effect seen between groups would diminish post-trial over time as groups become more similar with regard to treatment received. It might be that some treatment effects could be sustained beyond the end of the trial if the effect of a treatment during the trial period actually was to have a fundamental impact that was able to continue to outwork, or possibly even emerge later.

However, it might be that post-trial treatment choices were impacted by which randomised treatment group a subject was assigned to, at least in some way. For example, subjects may be more likely to remain on the same treatment they were allocated to during the trial due to familiarity. Conversely, perhaps subjects in a treatment arm associated with worse outcomes would be more likely to go on to a more favourable therapy after the trial than those in the comparator group.

Depending on the mechanisms at play, differences in ongoing treatment choices between the originally allocated groups could have an effect on survival, but as

post-trial treatment choices were unknown, strong causal interpretations of effect that link directly to the randomised treatments are hard to make.

In addition to the problem of unknown confounding due to unknown post-trial treatment choices, the emergence of other confounders over time is an additional problem when analysing long-term survival differences between originally randomised groups. While treatment groups were similar at baseline as a result of the randomisation process, over time fundamental differences between groups could have emerged as a direct result of differences associated with allocation to specific trial group. When we analyse survival over time, at each time-point survival is conditional on subjects having survived at least up to that time-point. If differences between groups emerge over time, including in survival, prior to a certain time-point then the surviving populations in each group will no longer be completely random as a direct result of differences in interventions. Hence, randomised comparisons may become increasingly less similar over time.

While faced with such limitations, this research opportunity was rare and powerful, giving the opportunity to investigate treatment effects in a large cohort of subjects over an extensive time-span. Evidence for the benefits of statins over longer time-frames, and whether usage over a period can have long-lasting favourable effects on cardiovascular health is needed. The optimal therapy for hypertension is still uncertain, and while there are recommended strategies, evidence for the long-term

impacts of strategies is lacking. This research, while needing to be interpreted in the context of existing limitations, can contribute greatly and provide substantial insight into long-term benefit of these treatments.

2.5 Changes in effect over time

In the context of clinical trials and observational studies, a common approach to survival analysis is to estimate a measure of effect comparing different interventions that assumes that the effect is constant over time. For example, a common approach is to use the Cox PH model to estimate a hazard ratio, under the assumption that the relative hazards are the same across all of time. A single HR will represent an average effect over the whole of follow-up time, and the validity of this single measure depends on the assumption that the relative hazard has truly remained constant over time.

However, the assumption of proportional hazards over time may not always be valid. Treatment effects may change over time, even when use of treatment is consistent. For example, there may be delayed effects or early effects that reduce over time. In settings where the hazard ratio is not truly constant over follow-up time, estimating a single hazard ratio for the duration may no longer be meaningful or appropriate. In such settings there are many alternative approaches to describing and comparing treatment effects over time that have been proposed. Alternative approaches include the treatment effect expressed as a ratio of failure

time (accelerated failure time model), comparing mean survival times between interventions (restricted mean survival times), and milestone analyses whereby one compares the proportion of events that have occurred by a specified "milestone" time-point.

In settings where relative hazards do change with time, the choice of alternative approach should be appropriate to the scenario, e.g. early effect or delayed effect. The approach should be considered in the context of the research questions being asked, making sure that it is appropriate and ultimately meaningful.

2.5.1 Milestone analysis

Milestone analysis refers to the comparison of the difference in proportion of events between study groups that have occurred by a certain fixed milestone time-point. In this approach there is no assumption placed on whether the effect is constant over time, but purely the overall effect by the fixed time-point. Therefore, this approach is dependent on the choice of milestone time, and hence the choice of milestone time is important and should be meaningful.

2.5.2 Restricted mean survival time analysis

Restricted mean survival time (RMST) refers to the mean time spent free of an event of interest up to a defined time-point (milestone time). It is the integral of the survival function up to a specified time, i.e. area under the survival curve from time of origin to the defined time-point. This analysis is concerned with the comparison

of RMSTs between study groups. As with milestone analysis, this approach makes no assumption about the consistency of effect over time, but is dependent on the choice of milestone time.

2.5.3 Accelerated failure time analysis

Rather than considering the hazard of failure at a given time, the accelerated failure time approach considers the time until failure, and assumes that the effect of study group on failure time can be represented by a fixed constant. The accelerated failure time models used are predominantly fully parametric, with a distributional assumption placed on the underlying failure time, most commonly a log-logistic or Weibull distribution.

2.6 Competing risks

In time to event analysis, competing risk refers to the risk of the occurrence of an alternative event to that of interest, and the occurrence of such would preclude the event of interest from occurring. For example, a subject may be at risk of both CHD-related and stroke-related mortality, if they should die from one cause, they can no longer die from the other, and hence risk of either of these causes of death are competing risks for the other.

Standard approaches to survival analysis often ignore the issue of competing risk, and censor exposure time from the time a competing event occurs under the assumption that the competing event was not informative. However, if this

assumption was not true and the occurrence of a competing event was informative about subjects' risk for the event of interest, then to ignore this in the analysis could lead to biased estimation of underlying risk, and also relative risks between covariate levels [41].

In this context where we are studying specific causes of death, it is possible and indeed likely that to some extent certain classifications of death may be informative of the risk subjects were also at for death from an alternative cause.

If we censor time at the point of a death from a competing cause, then we may end up with an over-estimate of the overall risk of death from the cause of interest if both causes of death are in some way correlated. For example, if we study the time to stroke-related death but ignore the possibility of dying from something other than stroke and censor subjects at the time of death from an alternative cause, then eventually all cumulative incidence curves for stroke-related mortality would be one, i.e. everyone either leaves the study (censored prior to stroke event) or goes on to die from stroke. Hence this approach may increasingly overestimate the risk of stroke as time goes on and as an increasing number of subjects are censored from competing events. As mentioned above, this approach can also lead to biased estimates for relative effects between levels of covariates, if there are differences in risk of alternative events between groups, and correlation between the risk of alternative events and the risk of the event of interest. For example, consider

comparing the effect on stroke-related death of one treatment (treatment group A) to another (treatment group B). If there was an excess of CHD-related deaths in treatment group A, and if those who are at higher risk of CHD-related death are also at higher risk of stroke-related death, this would result in a higher number of subjects at high risk from stroke-related death being censored in treatment group A compared to treatment group B. Hence, a bias would be emerging over time as risk of mortality from stroke is being reduced in treatment group A at a higher rate than in treatment group B, and would falsely give the impression that there was lower risk of stroke-related death in relation to treatment B group. In such a scenario, it would be important to consider the effect on the event of interest in the context of the effect on correlated completing events.

There are a number of approaches to survival analysis which consider the issue of competing risks in some form. Each method carries some value along with its own limitations. While there is no single universally correct approach, it is important that competing risks are not simply ignored but should be taken into consideration as part of the analysis.

There are two main approaches in the literature, each describing the hazard function differently. The first approach is concerned with estimating cause-specific relative hazard, and the second with estimating sub-distribution relative hazard.

Each type of relative hazard has value but represents something different, and hence should be interpreted appropriately.

2.6.1 Cause-specific hazard model

The cause-specific approach refers to the most commonly used Cox PH model approach, and considers the hazard function for the cause of interest in the presence of competing causes of failure. The probability of each type of event is estimated, while treating other competing events as censored in addition to those who are censored from loss-to-follow-up or withdrawal etc.

The cause-specific hazard function $h_k(t)$ is defined as the probability, at a given time t, of a subject experiencing the event of interest k in the next infinitesimal space of time, given that the subject has survived until time t. The cause-specific hazard function for cause k is expressed below:

$$h_k(t) = lim_{dt \to 0} \frac{P(t \leq T < t + dt, K = k | T \geq t)}{dt}$$

A proportional cause-specific hazards model is as follows:

$$h_k(t|X) = h_{0k}(t) \exp\left(\sum_{i=1}^{P} \beta_{ik} X_i\right) \qquad k = 1, \ldots, N$$

Where h_{0k} is the baseline hazard and β_{ik} are the corresponding regression coefficients (log HRs) for cause k, for parameters i=1 to P.

The cause-specific modelling approach can be carried out by modelling a single cause of interest, or by jointly modelling all types of events together, using a stacked data approach [42,43].

In the cause-specific setting, one can only assume that the relative hazard is an actual true measure of effect if the assumption of independence of alternative risks is valid, otherwise the hazard ratio would represent an apparent effect given that individuals have survived all competing events up to time t. Obviously, there is no way to formally test this assumption directly from a dataset because subjects will never experience more than one such competing event.

As discussed above, the cause-specific hazard model might overestimate true cumulative hazard of an event over time when competing risks are present.

If the assumption of independence of competing risks was valid then this approach would lead to the interpretation of a relative hazard that represents a more conceptual difference, in a world where subjects can only experience the event of interest.

2.6.2 Sub-distribution hazard model

Due to the strong assumption of independence in the censoring of time following a competing risk in the cause specific approach, competing risk literature has also focused on alternative approaches, the most popular being based on the sub-

distribution of the cumulative incidence function (CIF) for each competing event. In this approach, the CIF for the event of interest would be equivalent to the 1-[Kaplan-Meier (KM)] estimator in the cause-specific setting when there are no competing events. When there are competing events, the CIF differs in that it represents an overall survival function that includes failures from all competing events in addition to the event of interest. Therefore, there is no assumption being made about independent censoring in relation to competing events, because subjects are not being censored upon the occurrence of a competing event, rather, they remain in the risk set thereafter.

Unlike in the cause-specific approach, with this approach, the cumulative incidence will have an interpretation that represents the proportion of subjects that experience the event of interest, recognising that those who have a competing event will never have that event of interest. Retaining subjects in the risk set following a competing event places a constraint on this hazard function definition. Under this structure, the hazard function is defined as the probability of the event of interest given a subject has survived up to time t either event-free or having experienced a competing event prior to time t.

Fine & Gray proposed a proportional hazards model, similar to the Cox PH model, except that it models the sub-distribution hazard which is derived from the CIF,

and uses inverse probability of censoring weighting with a time-dependent weight function [44].

The sub-distribution hazard function for cause k is expressed below:

$$h_k(t) = lim_{dt \to 0} \frac{P(t < T \leq t + dt, K = k | T < t \cup (T < t \cap K \neq k))}{dt}$$

A proportional sub-distribution hazard model is as follows:

$$h_k(t|X) = h_{0k}(t) \exp\left(\sum_{i=1}^{P} \gamma_{ik} X_i\right) \qquad k = 1, \ldots, N$$

Where h_{0k} is the baseline sub-distribution hazard for cause k, and γ_{ik} are the corresponding regression coefficients (log sub-distribution hazard ratios [log sHRs]) for cause k, for parameters i=1 to P. As with the Cox PH model, this model also carries the assumption of proportional hazards.

The estimated coefficients from the sub-distribution hazard model can be interpreted in a similar way to those from a Cox PH model, except that these coefficients are estimated in the presence of competing events. Therefore, this approach leads to more pragmatic, less theoretical estimates of underlying hazard and covariate effect. This approach may be more of interest when wanting to estimate the actual incidence, or predicting an individual's risk of an event truly occurring. This would be helpful in a clinical setting, or for the allocation of medical resources, for example.

2.7 Methods

Cumulative incidence curves were plotted for death from any cause, as well as from overall CV-related causes, and more specifically mortality from stroke and from CHD, showing the cumulative proportions of death for each randomised trial arm. Subjects who did not give consent for follow-up beyond the end of the trial period will be included in analyses, censored at their end of trial date if they were still alive. Those consenting to long-term post-trial follow-up will be censored at the time of a competing event, at the time when they are lost-to-follow-up or at the end of the follow-up period.

The impact of both the BPLA and the LLA randomised group allocations on long-term mortality were analysed using Cox PH models. The outcome of death from all causes was assessed, as well as death from a more specific cause, with a focus on overall CV-related mortality, and more specifically mortality from CHD and from stroke. Cause-specific HRs were estimated for each cause of death.

For each cause-specific Cox PH model, the proportional hazards assumption was tested for the randomised treatment effect for each treatment comparison using scaled Schoenfeld residuals (on the Cox models). The residuals when plotted against [functions of] time should have a zero gradient if hazards are proportional. The null hypothesis that the gradient is equal to zero for each model was be tested using a global test proposed by Grambsch and Therneau (1994) [45].

An alternative approach was also undertaken where sub-distribution hazard ratios were estimated from sub-distribution proportional hazards models in the analysis of each specific cause of death, using the approach proposed by Fine and Gray.

Cumulative hazard plots from both cause-specific and sub-distribution proportional hazards models were produced by randomised treatment arm.

Three alternative approaches to the analysis of treatment effect were undertaken using methods that do not make the assumption of proportional effects over time. Firstly, accelerated failure-time models were used to estimate failure time ratios, using a Weibull distribution to model failure times. Secondly, milestone analyses were used to compare the difference in the proportion of subjects experiencing the event of interest at the milestone time of 18 years. The proportion of patients experiencing the event at the milestone time was estimated using the Kaplan Meier method and the Greenwood formula was used to calculate the standard errors [46–48]. The milestone time was chosen as 18 years since randomisation, because this was close to the median subject follow-up of 17.4 years.

Lastly, RMST was calculated for each randomised treatment arm up to the same fixed milestone time of 18 years from randomisation. RMSTs were modelled using flexible parametric models with 3 degrees of freedom, as suggested by Royston and Parmar, and the difference in RMST between randomised treatment arms was estimated [49].

Piecewise proportional hazards models were used to estimate hazards ratios within each defined time segments since baseline. Two approaches were used to define time-segments. Firstly, time was split into within-trial and post-trial periods. The within-trial periods differed for BPLA and LLA parts of the trial, and were different in length for each subject. Secondly, time since randomisation was split into 3-year time-bands. Hazard ratios were calculated for each time band, and tests for linear trend between intervals were performed to investigate whether the hazard ratios differed between time-bands.

Subgroup analyses were undertaken to investigate whether treatment effects differed between: age-groups, sexes, diabetes status at baseline, SBP groups at baseline, and total cholesterol groups at baseline. In addition, a treatment interaction was investigated between the randomised BPLA group and the randomised LLA group, as well as assessing a difference in BPLA treatment effect between those randomised or not to an LLA treatment (LLA vs. non-LLA).

All adjusted models were adjusted for the pre-specified baseline risk factors: age; sex; BMI; SBP; total cholesterol; smoking status; diabetes status; the age at which the subject left full-time education; and ethnicity.

2.8 Results

2.8.1 Population

This analysis included all 8580 subjects who took part in the ASCOT trial from England and Scotland. However, 562 subjects who were alive at the end of the trial did not give consent to long-term follow-up. These subjects were kept in the analyses, but censored at the time they ceased trial participation. Other subjects were censored if they were lost to follow-up, died, or at the end of January 2018 if they were still alive and in follow-up at that time. Over the whole long-term period of observation including the trial period and beyond, the median follow-up time was 17.4 years (IQR: 9.1 to 19.3) with a maximum follow-up of 20.9 years.

The mean age of this ASCOT legacy cohort was 64 years at randomisation (with a SD of 8 years), ranging from 40 to 80 years. Over 80% were male, and almost 90% were of white ethnic background. On average trial participants were overweight based on WHO criteria with mean BMI just over 28 kg/m^2. 35% of subjects were in the obese category with a BMI over 30 kg/m^2, and 9% had a BMI over 35 kg/m^2. Over 28% of subjects were classed as diabetic at baseline.

Just over 11% of subjects had suffered a stroke or TIA in the past, and over 17% had a history of coronary artery disease. Over 90% of subjects were on some anti-hypertensive treatment within the month prior to randomisation.

Those who had a baseline total cholesterol of 6.5 mmol/L or higher, or who were currently already on statin or fibrate therapy were not further randomised to an LLA group. As a result, those not in the LLA part of the trial were a slightly higher risk group for CVD compared to those randomised to a LLA treatment. Mean total cholesterol and LDL cholesterol at baseline were slightly higher in those not eligible for the LLA compared to the LLA sub-cohort. Those who were not further randomised to an LLA group had mean total cholesterol at baseline of 6.5 mmol/L and over 23% had been on lipid-lowering therapy in the past. While the LLA cohort had mean total cholesterol of 5.5 mmol/L, with a small proportion (1.3%) having ever been on lipid-lowering therapy in the past.

Characteristics between both LLA and BPLA randomised groups were very well balanced as was expected from the randomisation process and the large number of study participants randomised. Baseline characteristics are presented in Table 1, split by both randomised treatment comparisons.

Table 1: Baseline characteristics of the ASCOT legacy cohort by randomised treatment group

		BPLA (N=8580)		LLA (N=4605)	
Characteristic		n (%), mean (SD) or median (IQR)			
		Amlodipine (n=4305)	Atenolol (n=4275)	Atorvastatin (n=2317)	Placebo (n=2288)
Age (years)		64 (8)	64 (8)	64 (8)	64 (8)
Sex	Female	813 (18.9%)	807 (18.9%)	301 (13.0%)	284 (12.4%)
	Male	3492 (81.1%)	3468 (81.1%)	2016 (87.0%)	2004 (87.6%)
Ethnicity	African/Caribbean	222 (5.2%)	237 (5.5%)	162 (7.0%)	154 (6.7%)
	Asian (East)	7 (0.2%)	3 (0.1%)	2 (0.1%)	2 (0.1%)
	Asian (South)	130 (3.0%)	109 (2.5%)	72 (3.1%)	80 (3.5%)
	Mixed/other	85 (2.0%)	86 (2.0%)	36 (1.6%)	33 (1.4%)
	White/European	3861 (89.7%)	3840 (89.8%)	2045 (88.3%)	2019 (88.2%)
Height (cm)		170 (9)	170 (9)	171 (8)	171 (9)
Weight (kg)		84 (16)	84 (15)	85 (15)	84 (15)
Body mass index (kg/m2)		28.9 (4.7)	28.9 (4.6)	28.8 (4.9)	28.8 (4.6)
Smoking status	Current smoker	1035 (24.0%)	1006 (23.5%)	547 (23.6%)	541 (23.6%)
	Ex-smoker <12 months	1882 (43.7%)	1874 (43.8%)	995 (42.9%)	984 (43.0%)
	Non or ex-smoker >12 months	1388 (32.2%)	1395 (32.6%)	775 (33.4%)	763 (33.3%)
Alcohol status	Non-drinker	1088 (25.3%)	1089 (25.5%)	574 (24.8%)	571 (25.0%)
	1-13 units per week	1816 (42.2%)	1831 (42.8%)	1010 (43.6%)	983 (43.0%)
	14+ units per week	1401 (32.5%)	1355 (31.7%)	733 (31.6%)	734 (32.1%)
Units of alcohol consumed per week		6 (0 to 17)	6 (0 to 16)	6 (1 to 16)	6 (1 to 16)
Systolic blood pressure (mmHg)		162 (18)	162 (17)	162 (17)	162 (18)
Diastolic blood pressure (mmHg)		92 (10)	92 (10)	92 (10)	93 (10)
Heart rate (bmp)		71 (13)	71 (12)	70 (12)	71 (13)
Total cholesterol (mmol/L)		5.9 (1.1)	5.9 (1.1)	5.5 (0.8)	5.5 (0.8)
HDL-cholesterol (mmol/L)		1.3 (0.4)	1.3 (0.4)	1.3 (0.3)	1.3 (0.3)
LDL-cholesterol (mmol/L)		3.8 (1.0)	3.8 (1.0)	3.5 (0.7)	3.5 (0.8)
Triglycerides (mmol/L)		1.6 (1.2 to 2.3)	1.6 (1.2 to 2.3)	1.4 (1.0 to 2.0)	1.4 (1.1 to 2.0)
Glucose (mmol/L)		5.6 (5.1 to 6.6)	5.6 (5.1 to 6.6)	5.6 (5.1 to 6.5)	5.6 (5.1 to 6.6)
Creatinine (umol/L)		99 (89 to 109)	98 (89 to 109)	99 (90 to 109)	99 (90 to 109)

		BPLA (N=8580)		LLA (N=4605)	
Characteristic		n (%), mean (SD) or median (IQR)			
Diabetes mellitus		1139 (26.5%)	1145 (26.8%)	621 (26.8%)	630 (27.5%)
Renal dysfunction		2803 (65.1%)	2813 (65.8%)	1544 (66.6%)	1538 (67.2%)
Metabolic syndrome		1914 (44.5%)	1880 (44.0%)	906 (39.1%)	937 (41.0%)
Number of	2	19 (0.4%)	18 (0.4%)	15 (0.6%)	8 (0.3%)
cardiovascular	3	2036 (47.3%)	2026 (47.4%)	1186 (51.2%)	1133 (49.5%)
risk factors	4	1416 (32.9%)	1417 (33.1%)	716 (30.9%)	746 (32.6%)
	5+	834 (19.4%)	814 (19.0%)	400 (17.3%)	401 (17.5%)
Prior stroke / transient ischemic attach		507 (11.8%)	492 (11.5%)	233 (10.1%)	239 (10.4%)
History of coronary artery disease		734 (17.0%)	745 (17.4%)	346 (14.9%)	388 (17.0%)
Peripheral vascular disease		359 (8.3%)	383 (9.0%)	160 (6.9%)	150 (6.6%)
Left ventricular hypertrophy		602 (14.0%)	584 (13.7%)	357 (15.4%)	341 (14.9%)
ECG abnormalities other than LVH		746 (17.3%)	742 (17.4%)	387 (16.7%)	391 (17.1%)
Atrial fibrillation		60 (1.4%)	60 (1.4%)	36 (1.6%)	32 (1.4%)
Antihypertensive treatment within last month		3961 (92.0%)	3924 (91.8%)	2118 (91.4%)	2106 (92.0%)
Prior lipid-lowering therapy		490 (11.4%)	478 (11.2%)	29 (1.3%)	22 (1.0%)
Prior aspirin use		1083 (25.2%)	1040 (24.3%)	533 (23.0%)	519 (22.7%)

2.8.2 Changes in blood pressure and lipid level during the ASCOT trial

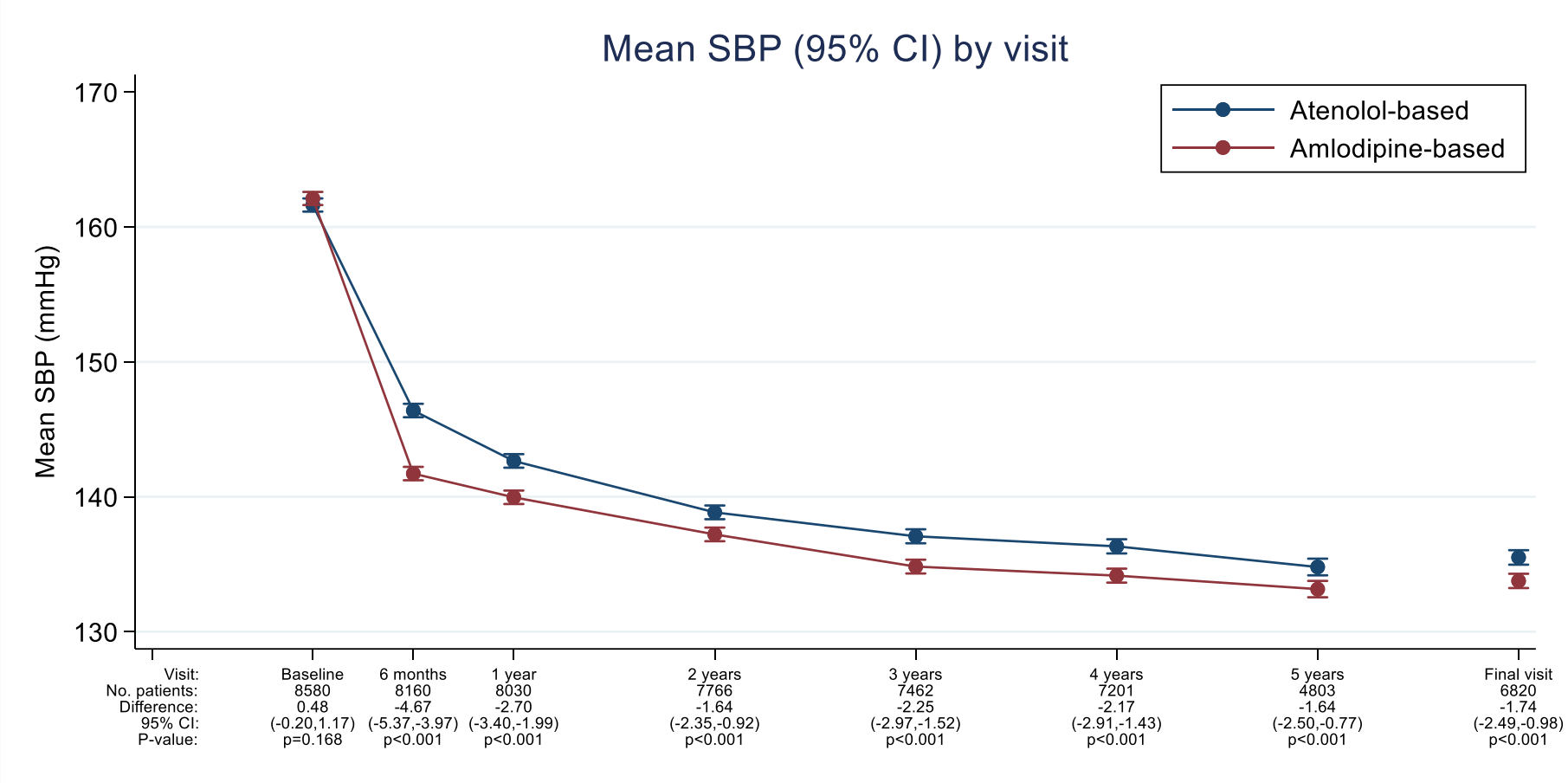
Mean blood pressure was very similar between BPLA treatment groups at baseline. SBP was 162 mmHg and DBP was 92 mmHg in both BPLA groups. Blood pressure levels dropped most dramatically during the first six months of blood pressure-lowering treatment initiation, and by the six-month trial visit, mean SBP had dropped in both groups to below 150 mmHg, but dropped 4.67 mmHg lower in the amlodipine-based arm compared to the atenolol-based arm. Over the course of the trial SBP continued to fall but to a lesser extent, as is evident from Figure 1.

There remained a small difference in SBP over the course of the trial, with SBP in the amlodipine-based group maintaining around a mean difference of 2 mmHg lower than the atenolol-based group.

A similar pattern was observed with DBP over the course of the trial. Mean DBP dropped from 92 mmHg to below 85 mmHg in both blood pressure-lowering groups by the six-month visit, but the drop was lower in the amlodipine-based group, about 82 mmHg compared to 84 mmHg in the atenolol-based group. As with SBP the difference of about 2 mmHg was maintained for DBP over the remainder of the trial period.

Blood pressure changes over the course of the trial are covered in more detail in Chapter 4 (Section 4.2).

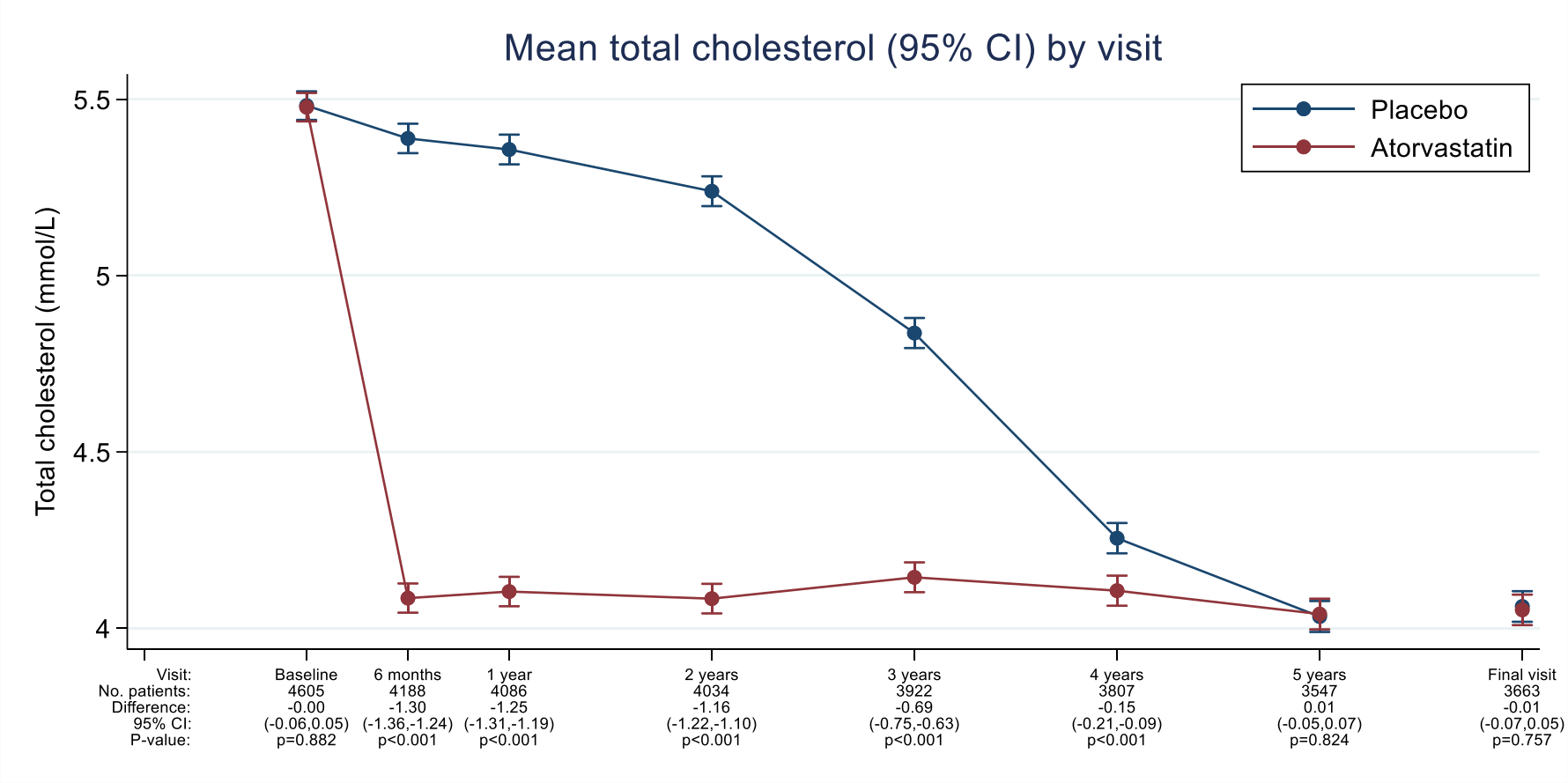
Figure 1: SBP profile graph by BPLA randomised groups during the trial



Note: Mean SBP is estimated using blood pressure taken at scheduled trial visits from a linear mixed model with a random subject effect and an interaction between visit and BPLA treatment groups.

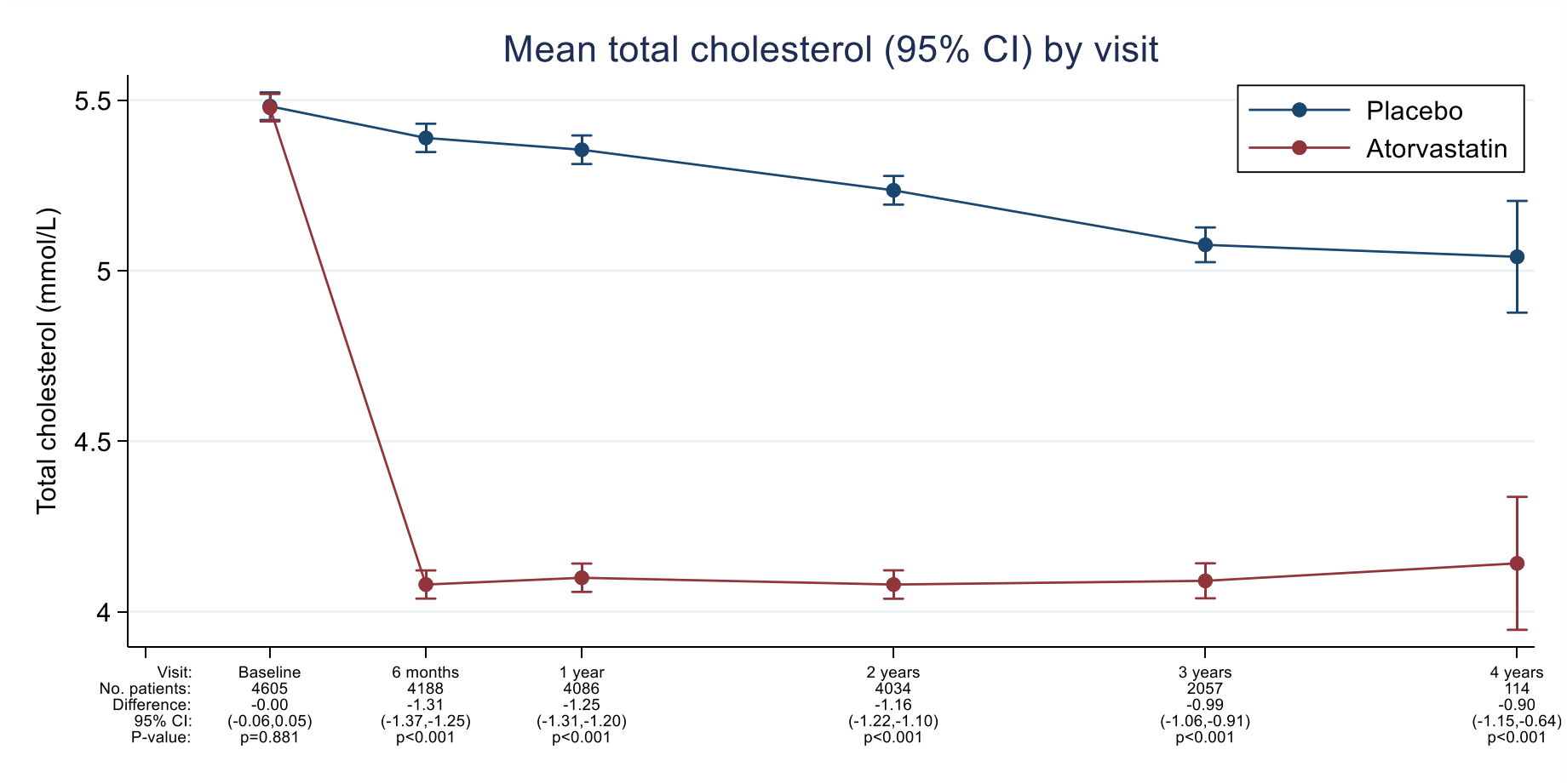
At baseline, mean total cholesterol was 5.5 mmol/L in both randomised LLA groups, but by the six-month trial visit it was down to just above 4 mmol/L in the statin arm, 1.31 mmol/L less than in the placebo arm. Figure 2 shows mean total cholesterol over the course of the whole BPLA trial and Figure 3 shows mean total cholesterol only during the blinded LLA period of the trial, split by randomised LLA group. When looking at the whole BPLA trial period, by the final trial visit total cholesterol ends up very similar in both LLA groups, just above 4 mmol/L. This is likely a result of those on placebo during the blinded LLA period switching to statin therapy following the end of the LLA trial, and hence catching up with observed reductions in lipids similar to that in the randomised statin group. When looking only at the blinded LLA period in Figure 3, we see a large sustained difference between groups. After six months, total cholesterol dropped to just over 4 mmol/L in the statin group, with only a small drop to 5.4 mmol/L in the placebo arm. Over the course of the LLA trial period, cholesterol levels in the statin group remained quite stable at just over 4 mmol/L, and in the placebo group levels fell slightly further but remained over 5 mmol/L for the duration of the blinded LLA trial.

Figure 2: Total cholesterol profile graph by LLA group during the whole trial (both blinded LLA period and beyond)



Note: Mean total cholesterol is estimated from a linear mixed model with subject random intercepts and an interaction between visit and LLA treatment groups.

Figure 3: Total cholesterol profile graph by LLA group during the trial – only including measurements taken during the blinded LLA phase



Note: Mean total cholesterol is estimated from a linear mixed model with subject random intercepts and an interaction between visit and LLA treatment groups.

2.8.3 Differences in mortality between those allocated to amlodipine-based treatment and those allocated to atenolol-based treatment in the blood pressure-lowering arm of the trial

2.8.3.1 Overall and cause-specific mortality

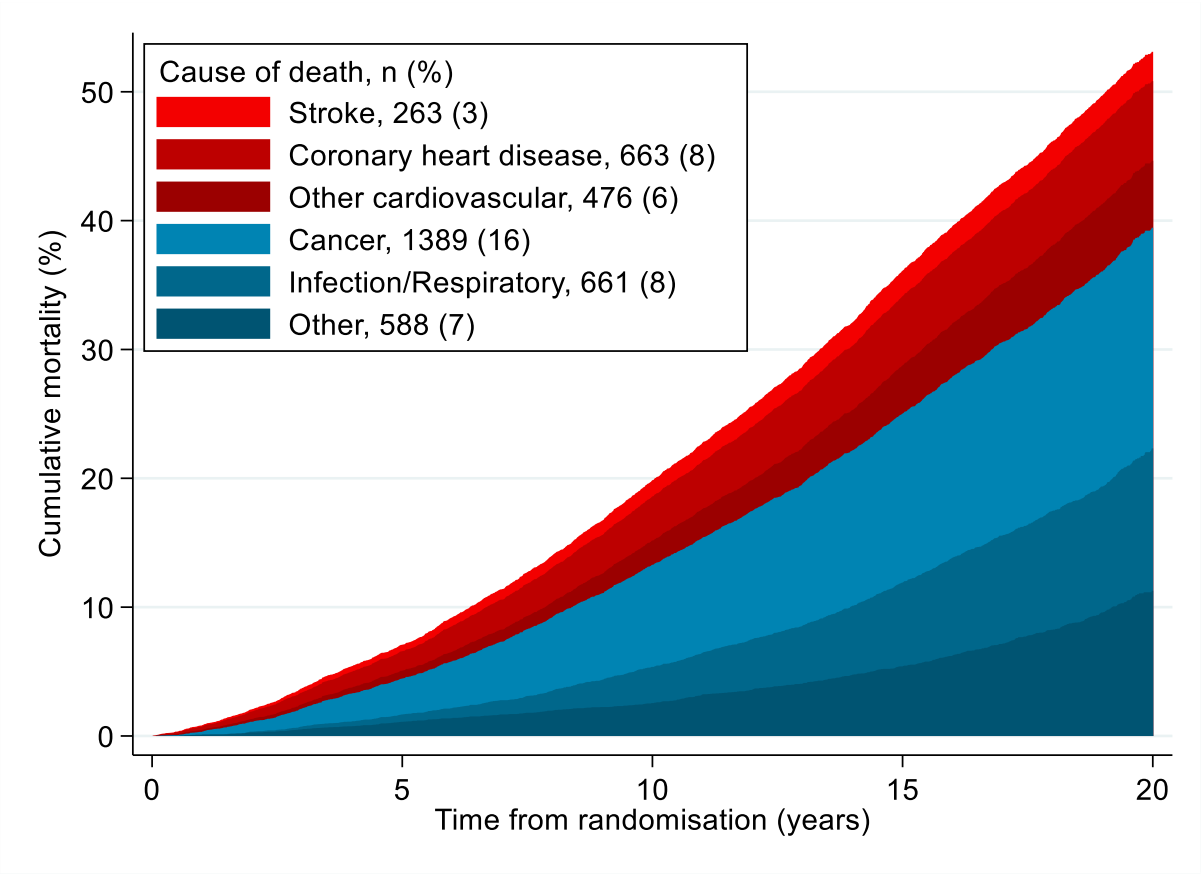
A total of 718 (8.4%) subjects died out of 8580 subjects in the ASCOT legacy cohort by the end of the BPLA trial period, 370 (8.7%) assigned to atenolol-based treatment and 348 (8.1%) assigned to amlodipine-based treatment.

Over the long-term, median 17.4-year observational period from randomisation until the end of January 2019, a total of 4040 (47.0%) deaths had occurred: 2015 (47.1%) in the atenolol-based group and 2025 (47.0%) in the amlodipine-based group. 1402 (34.7%) of the total deaths were classified as having resulted from CV-related causes (through independent cause of death adjudication), 725 (17.0%) in the atenolol-based group and 677 (15.7%) in the amlodipine-based group (see Table 2).

Figure 4 presents cause-specific cumulative incidence curves that have been stacked to give the overall cumulative incidence death from all causes, using the KM method. The cumulative incidence of mortality from any cause reaches 50% after 19.06 years from baseline. Median survival time for all-cause mortality was similar

in the amlodipine-based group to that in the atenolol-based group, 19.11 (p25: 11.91) and 19.01 (p25: 11.67), respectively.

Figure 4: Stacked cumulative incidence plot of cause-specific mortality



During the BPLA trial period, amlodipine-based treatment was associated with a reduction in CV-related mortality compared to atenolol-based treatment (HR=0.75, p=0.018). Somewhat weak evidence for an estimated 26% reduction in hazard of CHD-related death associated with the amlodipine-based group was observed (adjusted HR=0.74, p=0.066), and although there was a large estimated relative effect for stroke-related mortality (adjusted HR = 0.69), statistical evidence for the estimated effect was lacking (p=0.186). Overall, for all-cause mortality, there was

a lack of evidence of a treatment effect during the BPLA trial period (adjusted HR: 0.91, p=0.197). See Table 6 for within BPLA treatment effect estimates.

By the end of follow-up, evidence of a treatment effect for stroke-related mortality had strengthened, with amlodipine-based treatment being associated with an estimated decrease in hazard of stroke death by 27% (adjusted HR=0.73, p=0.011). There was no treatment effect observed for CHD-related mortality after the BPLA trial phase, and hence overall a lack of evidence for a sustained treatment effect over all follow-up (adjusted HR=0.92, p=0.283). For overall CV-related mortality there was evidence for a reduction in hazard associated with the amlodipine-based group, although the estimated effect size had reduced quite substantially compared to that seen during the trial period (adjusted HR=0.90, p=0.039).

There was no evidence of interactions with any of the baseline characteristics, having tested those pre-specified in the methods section.

For all models, there was no formal statistical evidence of a violation of the proportional hazards assumption, from tests based on scaled Schoenfeld residuals.

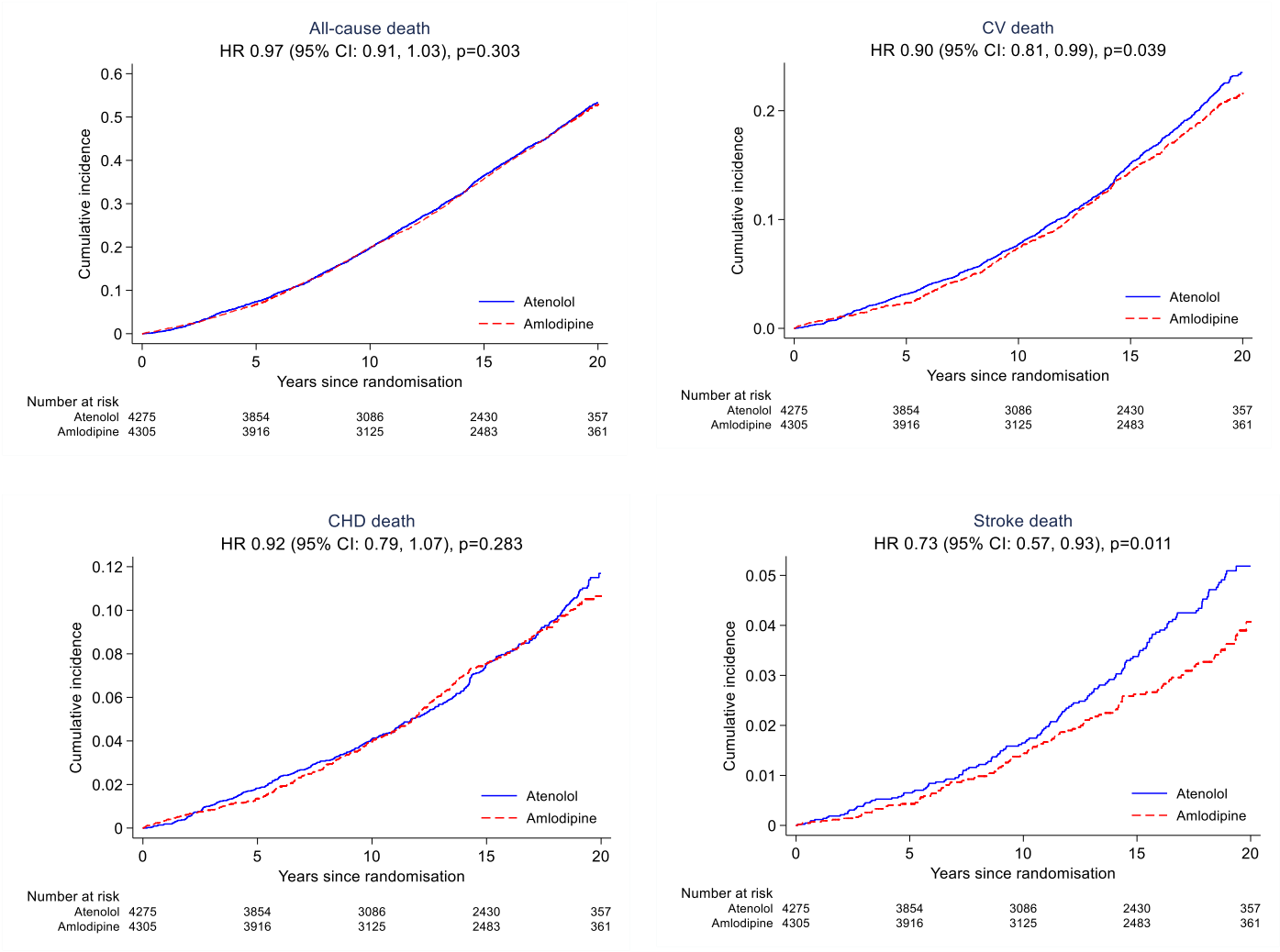
Table 2: Number and rate of deaths by BPLA treatment allocation, HRs (95% CI) from Cox PH models

	Total follow-up							
	Atenolol (N=4275)		Amlodipine (N=4305)					
Cause of death	n (%)	Rate*	n (%)	Rate*	Crude HR (95% CI)	p-value	Adjusted HR (95% CI)**	p-value
All-cause	2015 (47.13)	3.30	2025 (47.04)	3.27	0.99 (0.93, 1.05)	p=0.729	0.97 (0.91, 1.03)	p=0.303
CV	725 (16.96)	1.19	677 (15.73)	1.09	0.92 (0.83, 1.02)	p=0.115	0.90 (0.81, 0.99)	p=0.039
CHD	338 (7.91)	0.55	325 (7.55)	0.52	0.95 (0.81, 1.10)	p=0.480	0.92 (0.79, 1.07)	p=0.283
Stroke	150 (3.51)	0.25	113 (2.62)	0.18	0.74 (0.58, 0.95)	p=0.017	0.73 (0.57, 0.93)	p=0.011
Other CV	237 (5.54)	0.39	239 (5.55)	0.39	0.99 (0.83, 1.19)	p=0.935	0.97 (0.81, 1.16)	p=0.718
Non-CV	1290 (30.18)	2.11	1348 (31.31)	2.18	1.03 (0.95, 1.11)	p=0.472	1.01 (0.93, 1.09)	p=0.813
Cancer	687 (16.07)	1.12	702 (16.31)	1.13	1.01 (0.91, 1.12)	p=0.915	0.99 (0.90, 1.11)	p=0.923
Infection/respiratory	328 (7.67)	0.54	333 (7.74)	0.54	1.00 (0.86, 1.16)	p=0.993	0.96 (0.82, 1.12)	p=0.593
Other	275 (6.43)	0.45	313 (7.27)	0.51	1.12 (0.95, 1.32)	p=0.172	1.10 (0.93, 1.29)	p=0.259

*Rate per 100PY

**Adjusted for baseline age, sex, ethnicity, systolic blood pressure, total cholesterol, body mass index, diabetes, smoking status, years of education (socio-economic status), and lipid lowering arm randomisation

Figure 5: Kaplan Meier cumulative incidence plots for mortality by BPLA treatment group

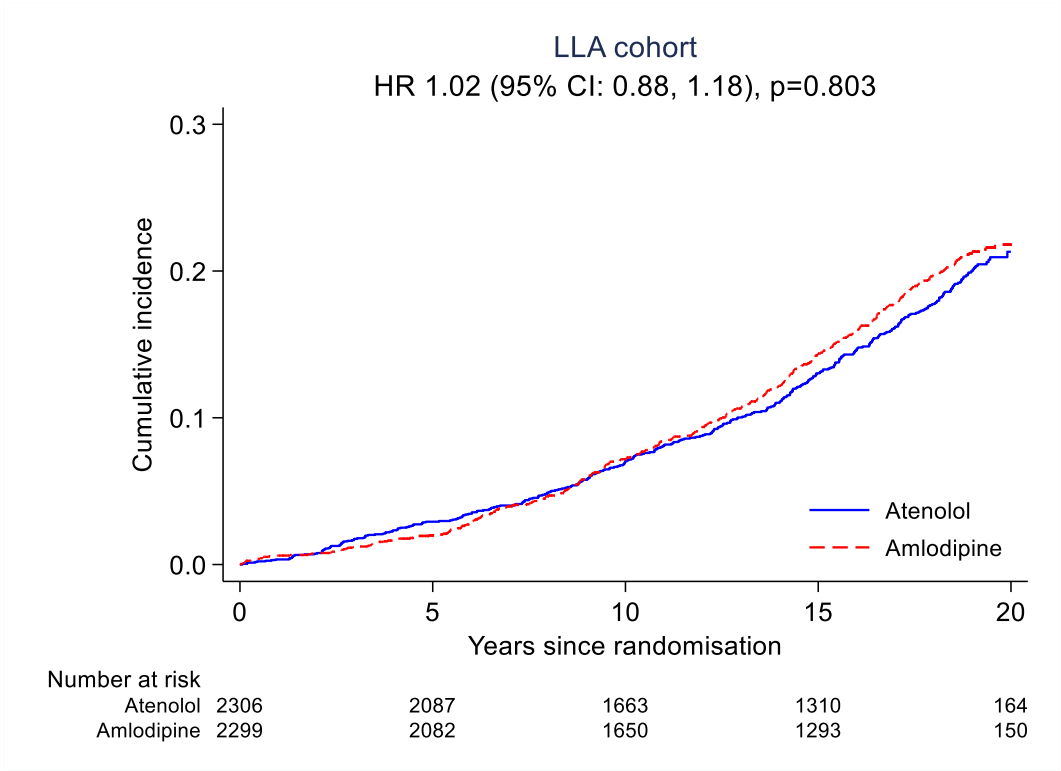


There was no evidence for an interaction between randomised treatment groups within the subgroup of subjects who were further randomised to either statin-therapy or placebo as part of the LLA factor of the trial, for any mortality outcome. In other words, the treatment effects in one factor of the trial did not depend on the group to which patients were randomised to in the other factor of the trial. However, the effect of BPLA treatment was assessed within the subgroup of 3975 subjects who were not part of the LLA factor of the trial, i.e. the higher-risk group of patients who had elevated cholesterol or were already on lipid-lowering therapy at baseline, and hence were not randomised to statin-therapy or placebo. In this subgroup there was strong evidence for a reduction in CV-related mortality associated with the amlodipine-based treatment (adjusted HR=0.79, p=0.002). In fact, the estimated HR in the subgroup of 4605 subjects who were included in the LLA part of the trial was very close to the null of 1 (adjusted HR=1.02, p=0.803), so it appeared that the overall effect on CV-related mortality was solely being driven by the effect seen only within the non-LLA subgroup. A test for heterogeneity in BPLA effect on CV-related mortality between those who were randomised to an LLA treatment group and those who were not provided evidence of heterogeneity (interaction p=0.015). CHD seemed to be the main cause of death that seemed to be driving this observed interaction for CV-related mortality. While there was a lack of evidence for an overall BPLA group effect over the whole population, there was evidence for a differing effect on CHD-related mortality between non-LLA and LLA

groups (interaction p=0.048), with some evidence of a reduction in CHD-related mortality associated with amlodipine-based therapy, with an estimated HR of 0.80 (p=0.036) in the non-LLA group, while the HR was 1.09 (p=0.447) in the LLA group. While there was a lack of evidence for such an interaction for stroke-related mortality, the estimated effect (in favour of amlodipine-based treatment) was stronger in the non-LLA group (HR=0.63, p=0.011) compared to the LLA group (HR=0.83, p=0.288). This combination of reduced mortality from both CHD and stroke gave rise to the overall stronger evidence for the interaction for overall CV-related mortality. Estimated effects from amlodipine-based treatment compared to atenolol-based in the non-LLA and LLA subgroups are presented in Table 3 along with interaction p-values. Figure 6 presents cumulative incidence plots for these 2 subgroups for CV-related mortality by BPLA group.

The percentage and rate of CV-related mortality was similar in the amlodipine-based group in both LLA and non-LLA subgroups. In the amlodipine-based group, 15.70% of subjects died in the non-LLA group, at a rate of 1.08 CV-related deaths per 100py, compared to 15.75% in the LLA group at a rate of 1.11 per 100py. In the atenolol-based group, while the percentage that died from CV-related causes and rate was very similar to that in the amlodipine-based group at 15.00% and at a rate of 1.05 per 100py, the percentage and rate was higher in those in the non-LLA subgroup at 19.25% and at a rate of 1.35 per 100py.

Figure 6: Kaplan Meier cumulative incidence plots for CV-related mortality by BPLA treatment group, by subgroups of those part of the LLA trial and those not



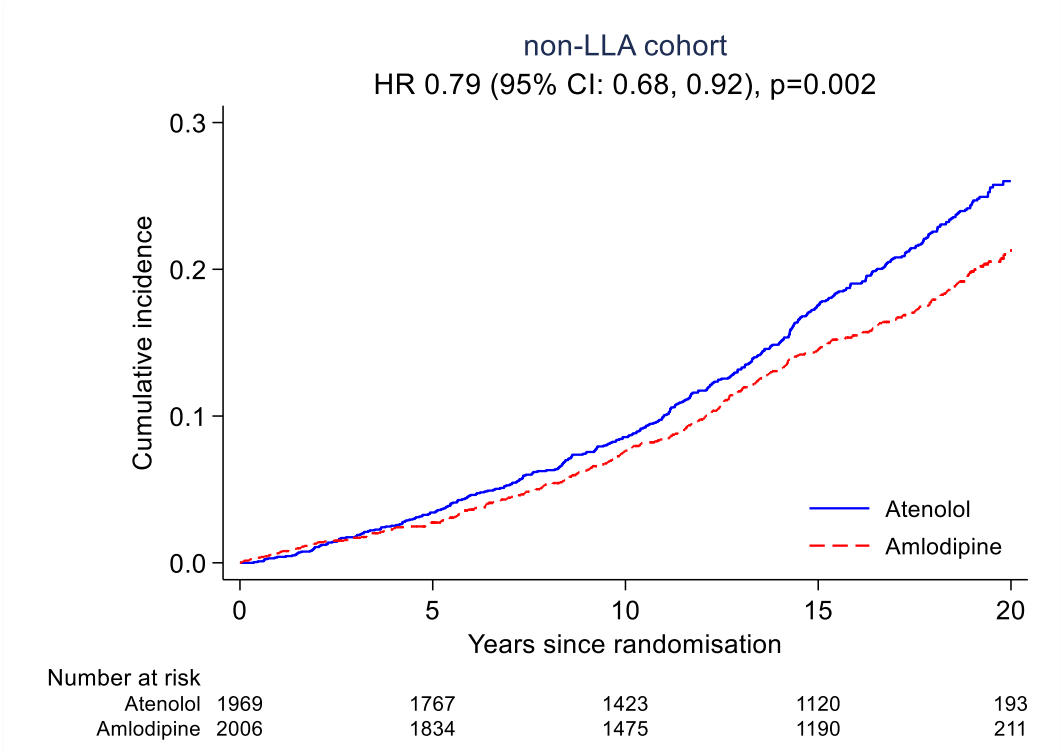


Table 3: Number and rate of deaths by BPLA treatment allocation, HRs (95% CI) from Cox PH models, in non-LLA and LLA subgroups with p-values from interaction tests

	Total follow-up								
	Atenolol (N=4275)		Amlodipine (N=4305)						
Cause of death	n (%)	Rate*	n (%)	Rate*	Crude HR (95% CI)	p-value	Adjusted HR (95% CI)**	p-value	Interaction p-value***
All-cause									
Non-LLA	933 (47.38)	3.31	933 (46.51)	3.19	0.96 (0.87, 1.05)	p=0.353	0.95 (0.86, 1.04)	p=0.237	
LLA	1082 (46.92)	3.29	1092 (47.50)	3.34	1.02 (0.94, 1.11)	p=0.686	0.99 (0.91, 1.08)	p=0.787	p=0.494
CV									
Non-LLA	379 (19.25)	1.35	315 (15.70)	1.08	0.80 (0.69, 0.93)	p=0.003	0.79 (0.68, 0.92)	p=0.002	
LLA	346 (15.00)	1.05	362 (15.75)	1.11	1.05 (0.91, 1.22)	p=0.481	1.02 (0.88, 1.18)	p=0.803	p=0.015
CHD									
Non-LLA	195 (9.90)	0.69	165 (8.23)	0.56	0.81 (0.66, 1.00)	p=0.049	0.80 (0.65, 0.99)	p=0.036	
LLA	143 (6.20)	0.43	160 (6.96)	0.49	1.13 (0.90, 1.41)	p=0.300	1.09 (0.87, 1.37)	p=0.447	p=0.048
Stroke									
Non-LLA	76 (3.86)	0.27	50 (2.49)	0.17	0.63 (0.44, 0.90)	p=0.012	0.63 (0.44, 0.90)	p=0.011	
LLA	74 (3.21)	0.22	63 (2.74)	0.19	0.86 (0.61, 1.20)	p=0.370	0.83 (0.60, 1.17)	p=0.288	p=0.262

*Rate per 100PY

**Adjusted for baseline age, sex, ethnicity, systolic blood pressure, total cholesterol, body mass index, diabetes, smoking status, years of education (socio-economic status), and lipid lowering arm randomisation

***Interaction test between BPLA randomised groups and non-LLA/LLA groups, from adjusted models.

2.8.3.2 Sub-distribution hazard approach to comparison of mortality from specific causes

The sub-distribution hazard ratios from Fine and Gray proportional hazards models for each cause of death were largely very similar to the cause-specific HR estimates from Cox PH models. There was evidence of a reduction in the sub-distribution hazard of stroke-related deaths associated with randomisation to the amlodipine-based group (adjusted sHR=0.74, p=0.015). In most cases the estimated sHRs and the level of statistical evidence for effects were very slightly reduced in Fine and Gray models in comparison to the estimated HRs. For the outcome of death from any CV-related cause, the estimated sHR was the same as the HR, 0.90, but the p-value was slightly larger (p=0.060) than for the HR in from the cause-specific approach. Results are presented from Fine and Gray models alongside estimates from Cox PH models in Table 4.

Figure 7 presents cumulative hazard curves by randomised BPLA treatment group for both the Cox cause-specific PH model approach and the Fine & Gray sub-distribution PH model. The cause-specific approach has higher cumulative hazards for both groups due to complete censorship, and hence removal from risk set of subjects who experience a competing event, inflating the estimated hazards in comparison to the sub-distribution hazards method.

This slight reduction in effect using Fine & Gray methods was likely because with this approach higher risk patients were being retained in the risk set after experiencing a competing event, but thereafter they had zero risk of experiencing the event of interest, e.g. stroke-related death. If there were more subjects experiencing a competing event in the atenolol-based treatment arm, it would reduce the appearance of the risk of death from stroke in that arm compared to analyses where these subjects were removed from the risk-set thereafter. Hence, this would result in the amlodipine-based arm appearing to have lower risk from stroke in Fine and Gray analyses and hence cause the estimated treatment effect to be reduced compared to the cause-specific approach.

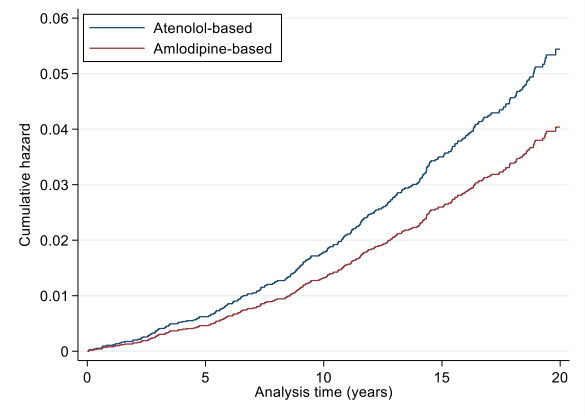
Table 4: BPLA cause-specific and sub-distribution adjusted hazard ratios for mortality from specific causes

Cause of death			Cause-specific		Sub-distribution	
			Adjusted HR (95%CI)*	p-value	Adjusted sHR (95% CI)*	p-value
	CV		0.90 (0.81, 0.99)	0.039	0.90 (0.81-1.00)	0.060
		CHD	0.92 (0.79, 1.07)	0.283	0.93 (0.80-1.09)	0.379
		Stroke	0.73 (0.57, 0.93)	0.011	0.74 (0.58-0.94)	0.015
		Other CV	0.97 (0.81, 1.16)	0.718	0.98 (0.82-1.17)	0.825
	Non-CV		1.01 (0.93, 1.09)	0.813	1.02 (0.95-1.11)	0.526
		Cancer	0.99 (0.90, 1.11)	0.923	1.01 (0.91-1.12)	0.890
		Respiratory/infection	0.96 (0.82, 1.12)	0.593	0.97 (0.83-1.13)	0.705
		Other non-CV	1.10 (0.93, 1.29)	0.259	1.13 (0.96-1.33)	0.146

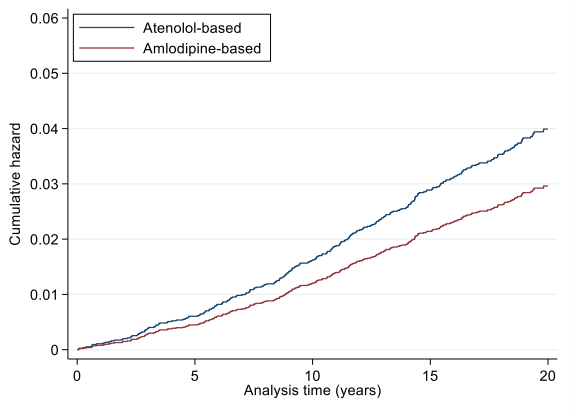
**Adjusted for baseline age, sex, ethnicity, systolic blood pressure, total cholesterol, body mass index, diabetes, smoking status, years of education (socio-economic status), and lipid lowering arm randomisation

Figure 7: Cumulative hazard plots by BPLA group for stroke death for each method

Cumulative hazard from Cox PH model



Cumulative hazard from sub-distribution PH model (Fine & Gray)



2.8.3.3 Alternative measures to the hazard ratio for describing randomised BPLA treatment differences

Three alternative approaches to the Cox PH model were used to quantify survival and estimate differences between treatment groups. As seen in previous analyses, with each different approach to survival analysis there was evidence of a beneficial effect on stroke related mortality associated with being in the amlodipine-based group compared to the atenolol-based group. In milestone analysis the stroke-related mortality cumulative incidence at 18-years post-randomisation was 4.53% in the atenolol-based group and 3.27% in the amlodipine-based group, an estimated reduction of 1.25% associated with randomisation to the amlodipine-based arm (p=0.013). For overall mortality from any CV-related cause, there was also a decrease in cumulative incidence associated with the amlodipine-based group, an estimated decrease of 1.15%, but there was weak evidence for this difference (p=0.250).

In restricted mean survival time analysis, there was an estimated increase in mean survival time for stroke-related mortality over 18 years by close to a month (26.48 days) in the amlodipine-based arm (p=0.045). Similarly, for death from any CV-related cause, there was also an increase in survival time by an estimated 31.61 days in the amlodipine-based group, but there was weak evidence for this (p=0.250).

The amlodipine-based group was associated with a relative decrease in hazard of stroke-related mortality by an estimated 27%, and in this analysis the group was associated with increased stroke-related mortality failure time, by an estimated 21% (p=0.012).

The accelerated failure time approach also gave evidence of an overall CV-related mortality effect, with an estimated relative increase in failure time of 7% associated with the amlodipine-based group (p=0.042, see Table 5).

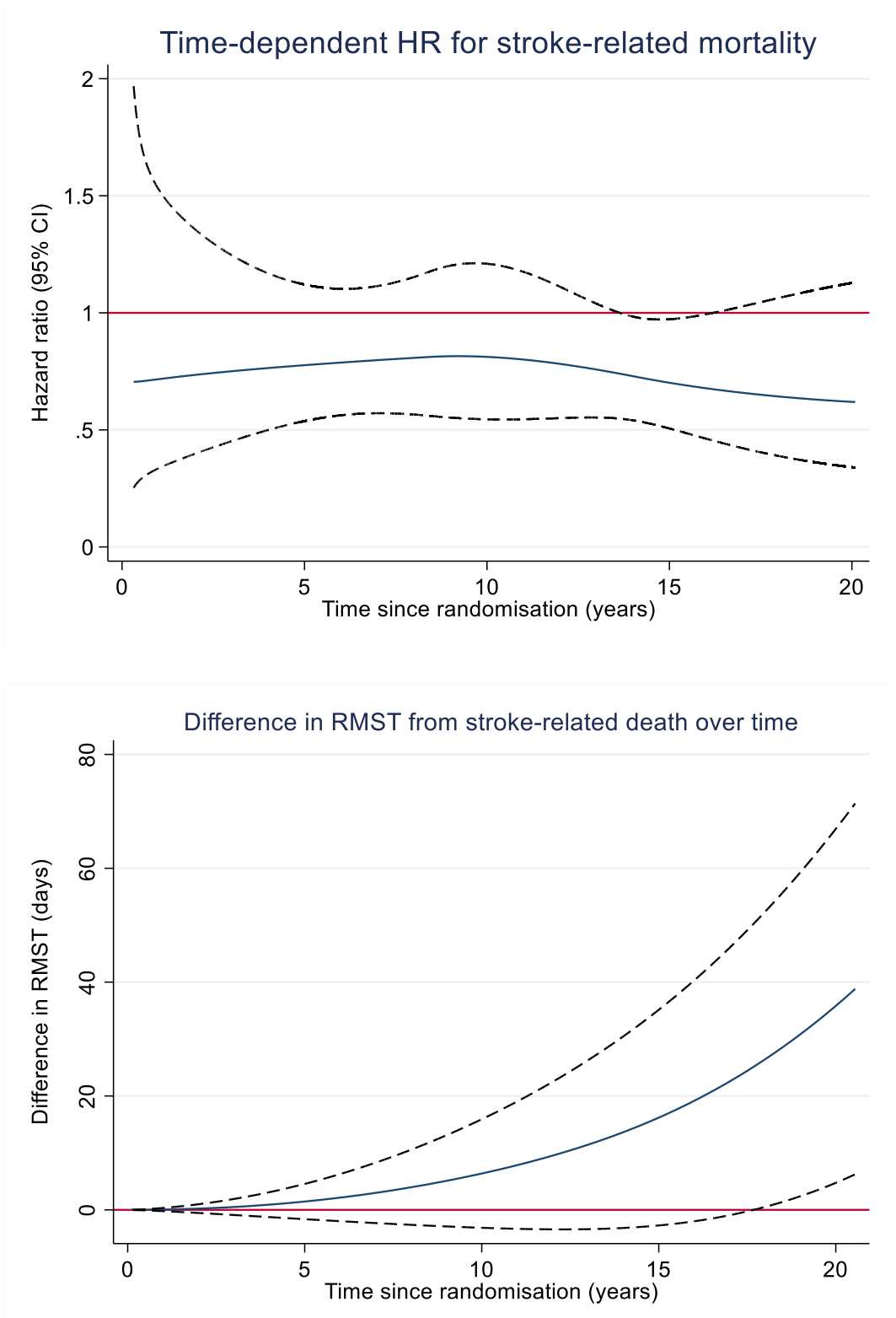
Table 5: Alternative measures of randomised treatment effect on survival

	Milestone at 18 years		Mean survival time (days), restricted to 18 years		Accelerated failure time (Weibull Distribution)	
Cause of death	Percentage difference (95%CI)	p-value	Mean event-free survival time difference (95%CI)	p-value	Failure time ratio (95%CI)	p-value
All-cause	-0.12 (-2.33, 2.10)	0.916	19.68 (-55.97, 95.33)	0.610	1.02 (0.98, 1.05)	0.317
CV	-1.15 (-3.10, 0.81)	0.250	31.61 (-22.44, 86.05)	0.250	1.07 (1.00, 1.13)	0.042
CHD	-0.08 (-1.55, 1.39)	0.916	2.09 (-39.24, 43.43)	0.921	1.06 (0.95, 1.17)	0.295
Stroke	-1.25 (-2.24, -0.27)	0.013	26.48 (0.54, 52.42)	0.045	1.21 (1.04, 1.41)	0.012
Other CV	-0.03 (-1.39, 1.33)	0.967	5.90 (-24.28, 36.08)	0.702	1.02 (0.93, 1.11)	0.727
Non-CV	0.80 (-1.42, 3.02)	0.478	-8.82 (-74.47, 56.84)	0.792	0.99 (0.96, 1.04)	0.803
Cancer	-0.38 (-2.30, 1.54)	0.701	-16.04 (-71.07, 38.99)	0.568	1.00 (0.94, 1.07)	0.925
Respiratory/infection	0.03 (-1.53, 1.59)	0.970	24.81 (-7.77, 57.40)	0.136	1.02 (0.96, 1.08)	0.586
Other non-CV	1.50 (0.08, 2.92)	0.039	-20.40 (-54.26, 13.46)	0.238	0.95 (0.88, 1.03)	0.240

Figure 8 presents two graphs from an analysis conducted on stroke-related mortality using a flexible parametric model. In this model, each BPLA group had their own baseline hazard, each modelled using a restricted cubic spline function with 3 knots (knot positions at the 25th, 50th, and 75th percentiles). Hence, the relative hazard was not constrained to be proportionate, but was dependent on time. The top plot presents the HR over time, which does not appear to vary to a huge extent over the 20-year follow-up, with the estimated HR ranging from about 0.80 to around to 0.60, with the effect consistently remaining in favour of the amlodipine arm throughout. There even appears to be a slight indication of an increased effect in the later years. The solid line in the plots represents the adjusted HR over time and the dashed lines are the 95% CI boundaries.

The bottom plot shows how the difference in RMST between groups varies over time. With a sustained effect over time, the difference in mean survival time is expected to continue to increase, but it appears that there may be some slight acceleration in effect in later years, the difference growing somewhat exponentially in favour of the amlodipine group over time. Indeed, these remains fairly weak evidence of a difference in RMST between groups over most of follow-up until it becomes stronger at about 17 to 18-years post-randomisation.

Figure 8: Plots of time-dependent HR and difference in RMST over all follow-up time, estimated from a flexible parametric model



2.8.3.4 Quantifying treatment-time interactions

While there was some evidence within the BPLA trial period of a reduction in CV-related mortality risk associated with randomisation to the amlodipine-based arm (adjusted HR=0.75, p=0.018), in the post-trial period there was no such evidence (adjusted HR=0.93, p=0.249), with test for interaction between periods p=0.102. This pattern appeared to be largely driven by CHD-related mortality, which showed weak evidence for a reduction in hazard associated with randomisation to the amlodipine-based group during the BPLA trial period, with an estimated decrease in Hazard of 25% (HR=0.74, p=0.066), but no evidence of an effect in the post-trial follow-up period (HR=0.98, p=0.829).

For the outcome of mortality from stroke, the HRs were very consistent between BPLA within-trial and post-trial periods: 0.69 and 0.74 respectively, with weak evidence for the within-trial period and stronger statistical evidence emerging with a higher number of events thereafter (p=0.186 and 0.030, respectively, see Table 6).

Figure 9 presents KM plots of cumulative incidence by BPLA treatment group, separated out by BPLA trial period, and post-trial period. For CHD-related mortality, the plot suggests that the reduction in events associated with the amlodipine-based group that occurred during the trial period, initially reverses at the beginning of the post-trial period, ultimately causing the incidence of CHD-

related deaths in the amlodipine-based group to catch-up with the atenolol-group. The separation between stroke-related mortality cumulative incidence lines appears fairly consistent in both periods, but there does appear to be very little difference in the first six-years post-trial, after which the treatment effect in favour of the amlodipine-based group emerges.

Splitting follow-up time into smaller sections based on three-year intervals provided no evidence of a trend in effect over time between the three-year time-period post randomisation (see Table 7).

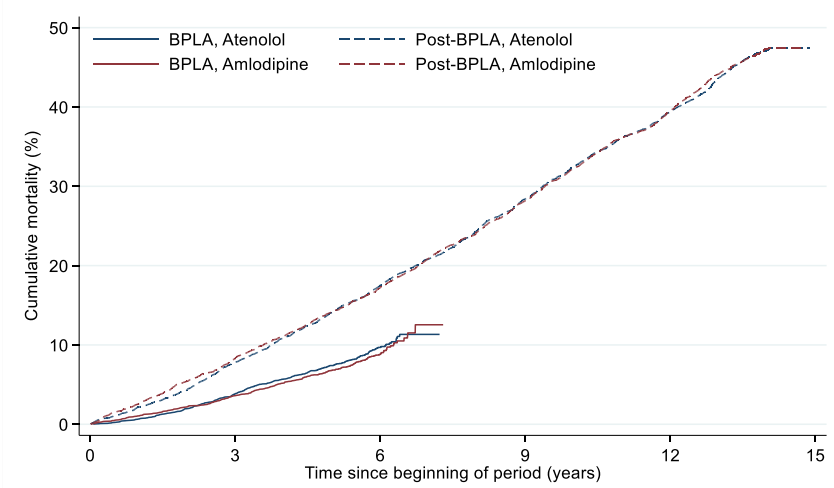
Table 6: Hazard ratios from piecewise proportional hazard models within and post- BPLA trial periods

		Time period (years)		
Cause of death		BPLA trial period	Post-BPLA trial period	P-value for difference in HRs between periods
All	Deaths in atenolol arm (%), rate	370 (8.65), 1.62	1645 (45.53), 4.30	
	Deaths in amlodipine arm (%), rate	348 (8.08), 1.51	1677 (45.48), 4.32	
	HR (95% CI)*	0.91 (0.78, 1.05)	0.98 (0.92, 1.05)	
	p-value	0.197	0.589	0.346
Cardiovascular	Deaths in atenolol arm (%), rate	149 (3.49), 0.65	576 (15.94), 1.51	
	Deaths in amlodipine arm (%), rate	115 (2.67), 0.50	562 (15.24), 1.45	
	HR (95% CI)*	0.75 (0.58, 0.95)	0.93 (0.83, 1.05)	
	p-value	0.018	0.249	0.102
CHD	Deaths in atenolol arm (%), rate	86 (2.01), 0.38	252 (6.97)	
	Deaths in amlodipine arm (%), rate	66 (1.53), 0.29	259 (7.02)	
	HR (95% CI)*	0.74 (0.54, 1.02)	0.98 (0.82, 1.17)	
	p-value	0.066	0.829	0.130
Stroke	Deaths in atenolol arm (%), rate	30 (0.70), 0.14	120 (3.32)	
	Deaths in amlodipine arm (%), rate	21 (0.49), 0.09	92 (2.50)	
	HR (95% CI)*	0.69 (0.39, 1.20)	0.74 (0.56, 0.97)	
	p-value	0.186	0.030	0.814

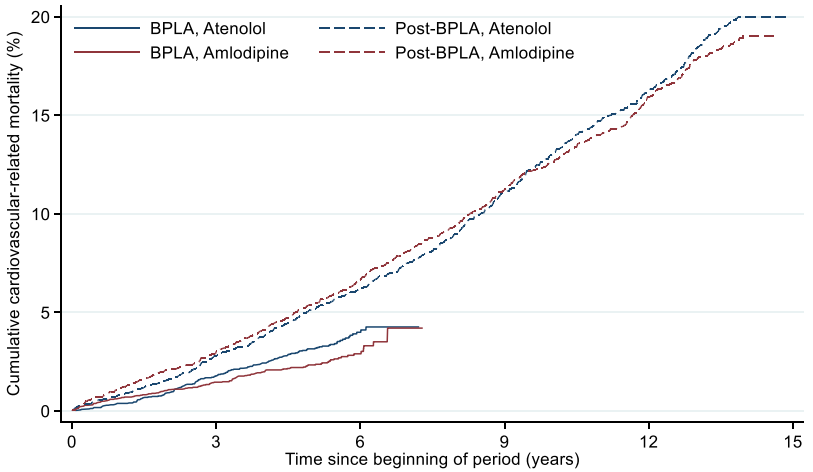
*Adjusted for baseline age, sex, ethnicity, systolic blood pressure, total cholesterol, body mass index, diabetes, smoking status, years of education (socio-economic status), and lipid lowering arm randomisation.
Note, percentages calculated using the denominators of number of subjects alive at the beginning of the time-period.

Figure 9: Cumulative mortality plots by BPLA treatment and follow-up period

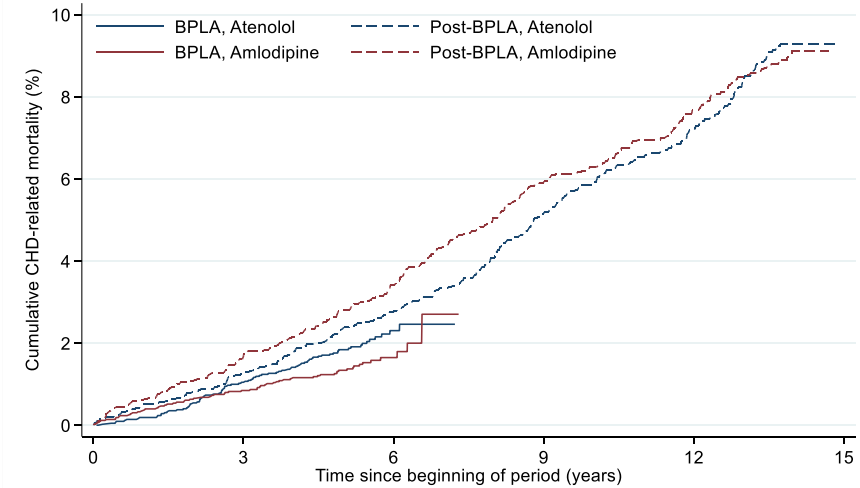
All-causes



Cardiovascular



CHD



Stroke

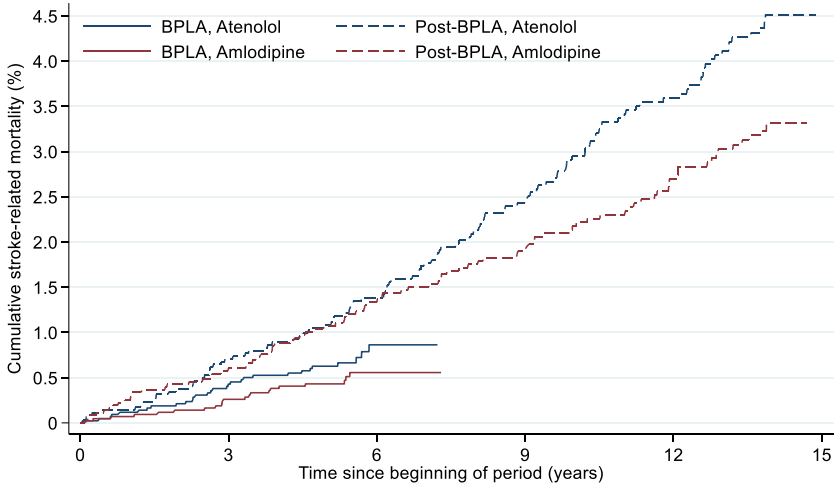


Table 7: Hazard ratios from piecewise proportional hazard models over follow-up for BPLA randomised comparison

		Time period (years)						
Cause of death		Within 3	3-6	6-9	9-12	12-15	15+	P-value for linear trend between periods
		N=8580	N=8256	N=7177	N=6460	N=5747	N=4913	
All	Deaths in atenolol arm	165 (3.7%)	234 (5.7%)	275 (7.8%)	361 (11.2%)	401 (14.1%)	579 (23.8%)	
	Deaths in amlodipine arm	154 (3.6%)	224 (5.4%)	310 (8.5%)	329 (10.1%)	407 (14.0%)	601 (24.2%)	
	HR (95% CI)*	0.91 (0.73, 1.14)	0.92 (0.77, 1.11)	1.09 (0.93, 1.29)	0.88 (0.76, 1.02)	0.97 (0.85, 1.11)	1.00 (0.89, 1.12)	
	p-value	0.421	0.393	0.282	0.089	0.678	0.947	0.636
Cardiovascular	Deaths in atenolol arm	75 (1.8%)	89 (2.2%)	92 (2.6%)	118 (3.7%)	149 (5.2%)	202 (8.3%)	
	Deaths in amlodipine arm	62 (1.4%)	71 (1.7%)	102 (2.8%)	116 (3.6%)	150 (5.2%)	176 (7.1%)	
	HR (95% CI)*	0.81 (0.58-1.13)	0.77 (0.56-1.05)	1.07 (0.81-1.42)	0.95 (0.73-1.22)	0.96 (0.76-1.20)	0.83 (0.68-1.01)	
	p-value	0.210	0.095	0.621	0.668	0.715	0.676	0.884
CHD	Deaths in atenolol arm	44 (1.0%)	52 (1.3%)	39 (1.1%)	51 (1.6%)	67 (2.4%)	85 (3.5%)	
	Deaths in amlodipine arm	36 (0.8%)	42 (1.0%)	52 (1.4%)	57 (1.8%)	70 (2.4%)	68 (2.7%)	
	HR (95% CI)*	0.80 (0.51-1.24)	0.77 (0.52-1.16)	1.29 (0.85-1.95)	1.07 (0.73-1.56)	0.99 (0.71-1.39)	0.76 (0.55-1.04)	
	p-value	0.309	0.217	0.234	0.722	0.976	0.085	0.886
Stroke	Deaths in atenolol arm	18 (0.4%)	16 (0.4%)	22 (0.6%)	27 (0.8%)	27 (1.0%)	40 (1.7%)	
	Deaths in amlodipine arm	11 (0.3%)	15 (0.4%)	18 (0.5%)	23 (0.7%)	20 (0.7%)	26 (1.1%)	
	HR (95% CI)*	0.60 (0.28-1.28)	0.91 (0.45-1.84)	0.80 (0.43-1.49)	0.82 (0.47-1.44)	0.71 (0.40-1.26)	0.62 (0.38-1.02)	
	p-value	0.187	0.798	0.487	0.492	0.242	0.061	0.989

*Adjusted for baseline age, sex, ethnicity, systolic blood pressure, total cholesterol, body mass index, diabetes, smoking status, years of education (socio-economic status), and lipid lowering arm randomisation.

Note, percentages calculated using the denominators of the number of subjects alive at the beginning of the time-period.

2.8.4 Differences in mortality between those allocated to atorvastatin and those allocated to placebo in the lipid-lowering arm of the trial

2.8.4.1 Overall and cause-specific mortality

Within the LLA trial period, ending for all trial sites in October 2002, a total of 173 (3.8%) out of the 4605 patients assigned to a lipid-lowering treatment arm died: 90 (3.9%) randomised to placebo and 83 (3.6%) randomised to atorvastatin. By the end of follow-up, a total of 2174 (46.8%) patients had died: 1096 (47.9%) in the placebo group and 1078 (46.5%) in the atorvastatin group. 708 (32.6%) of the total deaths were from CV-related causes, 373 (16.3%) in the placebo group and 335 (14.5%) in the atorvastatin group (see Table 8).

There was insufficient evidence for a treatment effect on all-cause mortality by the end of the LLA trial period (HR=0.93, p=0.642). The treatment difference was estimated to be similar by the end of follow-up, with, although stronger, still weak evidence of a difference associated with statin treatment compared to placebo (HR=0.94, p=0.133). There was evidence that statin treatment was associated with a reduction in CV-related mortality, an estimated 14% reduction in hazard over the whole of follow-up (HR=0.86, p=0.044).

There was no evidence of a treatment effect for death from CHD within the LLA trial period with the estimated HR very close to the null (HR=1.02, p=0.950). However, evidence of a randomised treatment group effect emerged by the end of follow-up,

with statin treatment associated with a reduction in CHD deaths, an estimated reduction in hazards of 24% over the whole of follow-up (HR=0.76, p=0.018). There was no evidence of a treatment effect on stroke-related mortality by the end of follow-up (HR=0.97, p=0.868). Figure 10 presents KM cumulative incidence plots by LLA treatment group.

In subgroup analyses, there was some evidence of an interaction with ethnicity for death due to CV-related causes (p=0.011). In those of black ethnic background, the HR was 2.86 (95% CI: 1.27-6.47, p=0.011), i.e. those in the statin group had increased risk of death from CHD with 8 (5.2%) CV-related deaths occurring in the placebo arm versus 21 (13.0%) in the statin arm. There was 1 (0.6%) death from stroke in the placebo group and 7 (4.3%) in the statin group. There was no evidence of any other interactions with baseline characteristics, having tested a total of 10 pre-specified baseline risk factors: age; sex; BMI; SBP; total cholesterol; smoking status; diabetes status; the age at which the subject left full-time education; and ethnicity.

For all models, there was no formal evidence of a violation of the proportional hazards assumption, from statistical tests based on scaled Schoenfeld residuals.

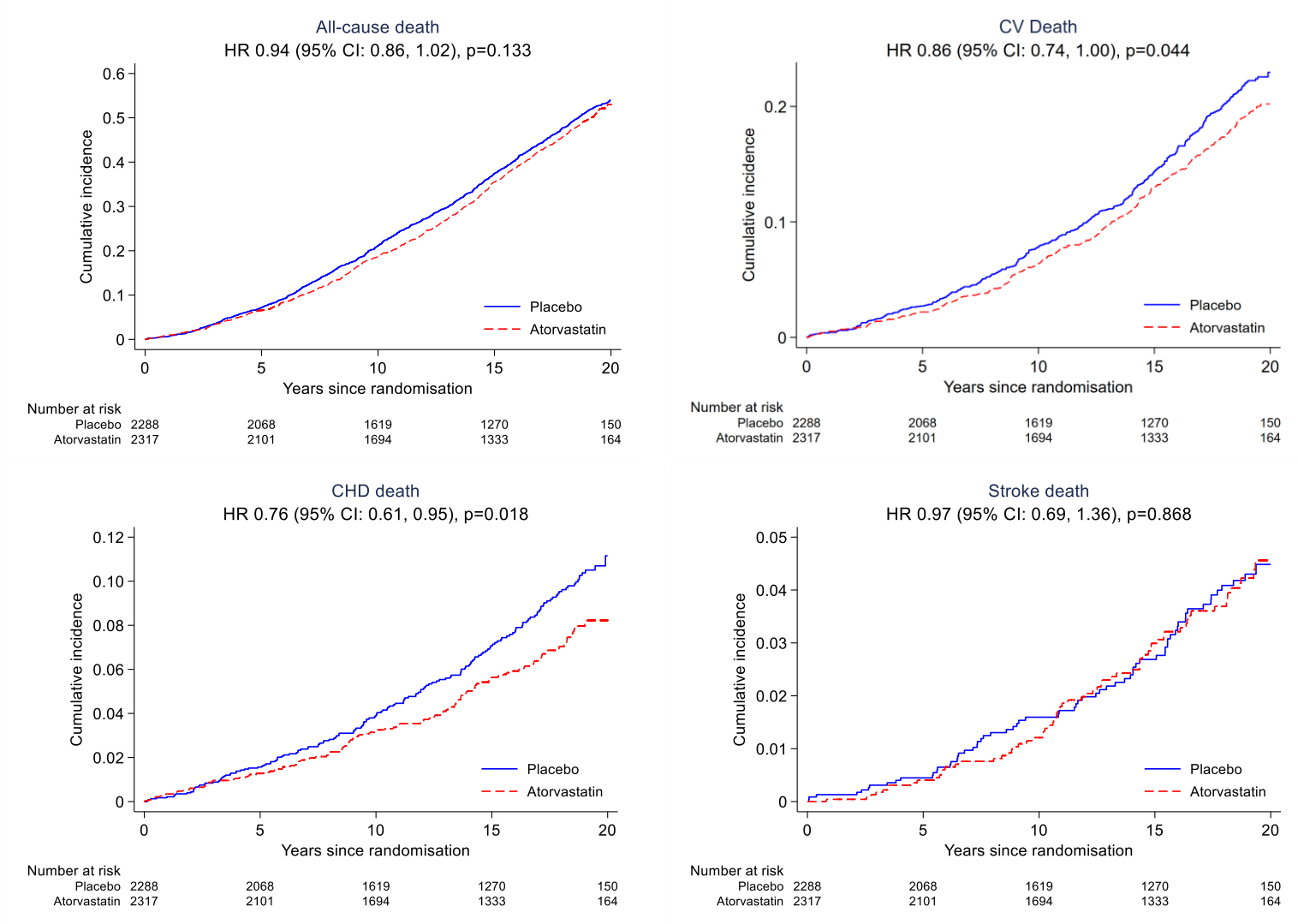
Table 8: Number and rate of deaths by LLA treatment allocation, HRs (95% CI) from Cox PH models

	Total follow-up							
	Placebo (N=2288)		Atorvastatin (N=2317)					
Cause of death	n (%)	Rate*	n (%)	Rate*	Crude HR (95% CI)	p-value	Adjusted HR (95% CI)**	p-value
All-cause	1096 (47.90)	3.40	1078 (46.53)	3.23	0.94 (0.87, 1.03)	p=0.176	0.94 (0.86, 1.02)	p=0.133
CV	373 (16.30)	1.16	335 (14.46)	1.00	0.86 (0.74, 1.00)	p=0.048	0.86 (0.74, 1.00)	p=0.044
CHD	169 (7.39)	0.52	134 (5.78)	0.40	0.76 (0.61, 0.96)	p=0.019	0.76 (0.61, 0.95)	p=0.018
Stroke	68 (2.97)	0.21	69 (2.98)	0.21	0.98 (0.70, 1.36)	p=0.882	0.97 (0.69, 1.36)	p=0.868
Other CV	136 (5.94)	0.42	132 (5.70)	0.40	0.93 (0.73, 1.18)	p=0.545	0.93 (0.73, 1.18)	p=0.526
Non-CV	723 (31.60)	2.24	743 (32.07)	2.23	0.99 (0.89, 1.09)	p=0.784	0.98 (0.88, 1.08)	p=0.664
Cancer	390 (17.05)	1.21	393 (16.96)	1.18	0.97 (0.84, 1.11)	p=0.650	0.96 (0.84, 1.11)	p=0.577
Infection/respiratory	180 (7.87)	0.56	195 (8.42)	0.58	1.04 (0.85, 1.27)	p=0.731	1.02 (0.84, 1.25)	p=0.817
Other	153 (6.69)	0.47	155 (6.69)	0.46	0.97 (0.78, 1.21)	p=0.801	0.97 (0.77, 1.21)	p=0.766

*Rate per 100PY

**Adjusted for baseline age, sex, ethnicity, systolic blood pressure, total cholesterol, body mass index, diabetes, smoking status, years of education (socio-economic status), and blood pressure lowering arm randomisation.

Figure 10: Kaplan Meier cumulative incidence of mortality plots by LLA treatment group



2.8.4.2 Sub-distribution hazard approach for specific causes of mortality

Consistent with results from the cause-specific analysis approach, there was evidence for a reduction in CHD-related mortality associated with randomisation to the atorvastatin group compared to placebo from a Fine and Gray sub-hazards model. The statin group was associated with an estimated reduction in sub-distribution hazard of 21% (sHR=0.079, p=0.038). Similarly, for overall CV-related mortality the estimated sHR of 0.88 (p=0.094) was fairly similar to the cause-specific HR or 0.86 (p=0.044).

As with the BPLA analysis, the sub-distribution hazard ratios tended to be slightly reduced in effect size and level of statistical evidence compared to the cause-specific HRs from Cox Proportional Hazards models (see Table 9 for all cause-specific and sub-distribution HR estimates, and Figure 11 for cumulative hazard plots for CHD-related mortality for the cause-specific HR approach and the sub-distribution HR approach by treatment group).

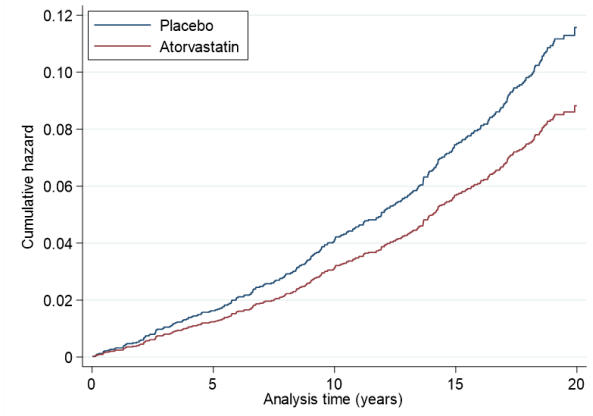
Table 9: LLA cause-specific and sub-distribution adjusted hazard ratios for mortality from specific causes

	Cause-specific		Sub-distribution	
Cause of death	Adjusted HR (95%CI)*	p-value	Adjusted sHR (95% CI)*	p-value
All-cause	0.94 (0.86-1.02)	0.133		
CV	0.86 (0.74-1.00)	0.044	0.88 (0.76-1.02)	0.094
CHD	0.76 (0.61-0.95)	0.018	0.79 (0.63-0.99)	0.038
Stroke	0.97 (0.69-1.36)	0.868	1.01 (0.72-1.41)	0.955
Other CV	0.93 (0.73-1.18)	0.526	0.96 (0.75-1.22)	0.728
Non-CV	0.98 (0.88-1.08)	0.664	1.00 (0.90-1.11)	0.968
Cancer	0.96 (0.82-1.11)	0.577	1.00 (0.87-1.15)	0.964
Respiratory/infection	1.02 (0.84-1.25)	0.817	1.06 (0.86-1.30)	0.601
Other non-CV	0.97 (0.77-1.21)	0.766	1.00 (0.80-1.25)	0.978

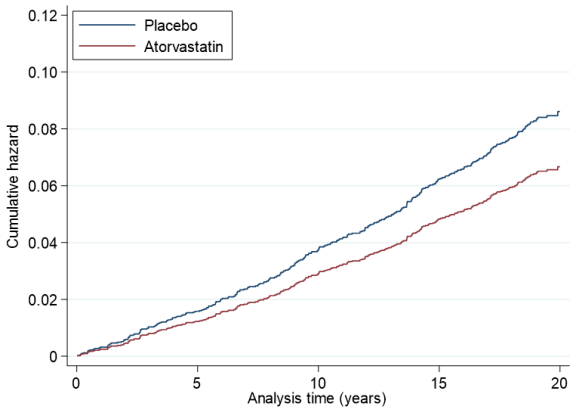
**Adjusted for baseline age, sex, ethnicity, systolic blood pressure, total cholesterol, body mass index, diabetes, smoking status, years of education (socio-economic status), and lipid lowering arm randomisation

Figure 11: Cumulative hazard plots by LLA group for CHD death for each method

Cumulative hazard from Cox PH model



Cumulative hazard from sub-distribution PH model (Fine & Gray)



2.8.4.3 Alternative measures to the hazard ratio for describing randomised LLA treatment differences

From each alternative approach to survival analysis comparing mortality between placebo and statin randomised groups, there was evidence for a difference in CHD-related death in favour of the statin group.

In the placebo group, the cumulative incidence of CHD-related death at the 18-year milestone time-point was 9.53%. The cumulative incidence was estimated to be 2.50% lower in the statin group at the milestone time-point (p=0.010).

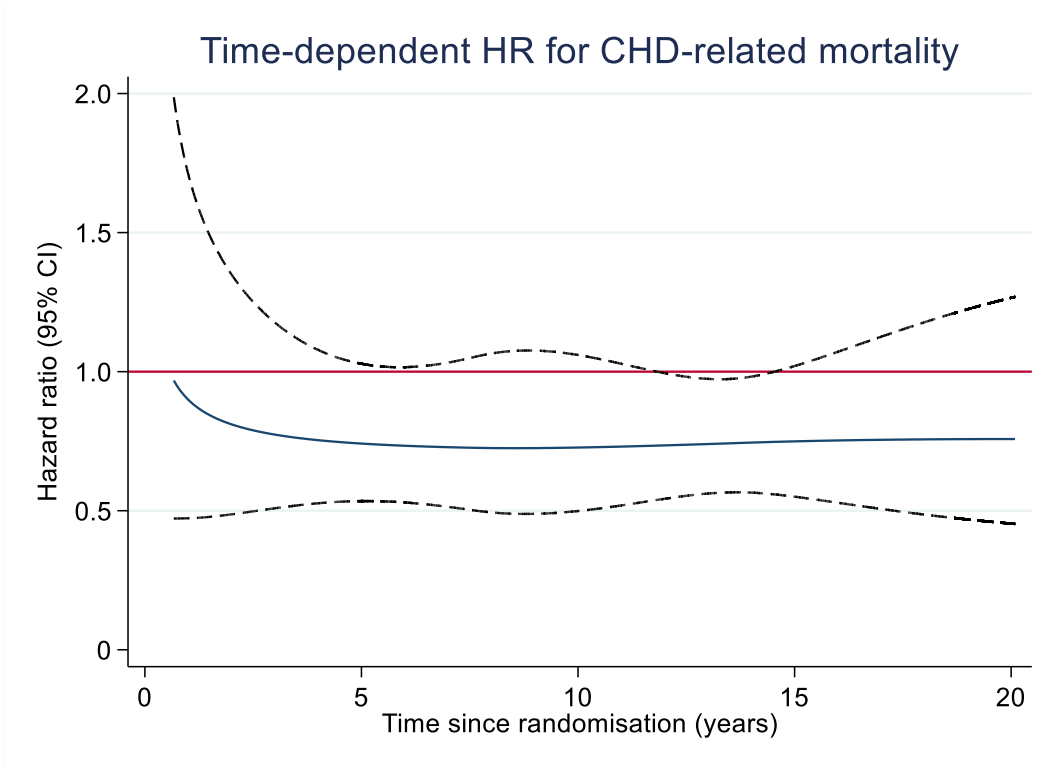
Figure 12 presents two plots from an analysis conducted on CHD-related mortality using a flexible parametric survival model to assess survival differences between LLA groups (methods as previously described). The bottom plot of Figure 12 shows how the difference in RMST between groups varied over time. The difference in survival time appears to have grown somewhat exponentially in favour of the statin group, such that, by 18-years post-randomisation the survival time is estimated to be 54.59 days longer in the statin group compared to those randomised to placebo (95% CI: 1.87, 107.32, p=0.042). The top plot of Figure 12 shows relative hazard over time, giving the impression that relative hazards appeared to remain quite consistent over time, in favour of the statin group. In addition, the relative failure time was estimated to be 20% higher in the statin group to the placebo group (p=0.020).

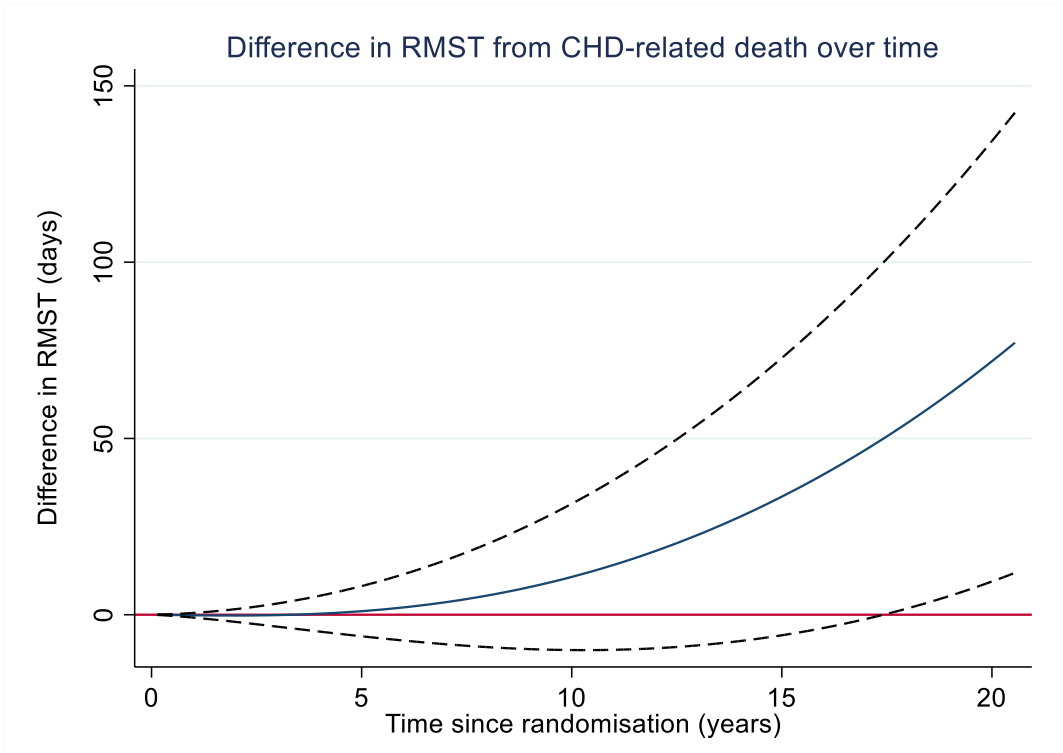
Overall CV-related mortality was reduced in the statin group for each different measure of survival, with somewhat borderline evidence at the 5% level. There was also evidence of a difference in all-cause mortality in RMST at 18 years, with the statin arm associated with an increase in survival time of over 3 months (104.66 days, p=0.046). Table 10 presents estimates from each of the three alternative survival analysis approaches.

Table 10: Alternative measures of randomised treatment effect on survival

	Milestone at 18 years		Mean survival time (days), restricted to 18 years		Accelerated failure time (Weibull Distribution)	
Cause of death	Percentage difference (95%CI)	p-value	Mean event-free survival time difference (95%CI)	p-value	Failure time ratio (95%CI)	p-value
All-cause	-1.93 (-4.96, 1.11)	0.214	104.66 (2.05, 207.28)	0.046	1.04 (0.99, 1.08)	0.129
CV	-2.81 (-5.47, -0.15)	0.038	69.40 (-1.74, 140.54)	0.056	1.09 (1.00, 1.19)	0.044
CHD	-2.50 (-4.41, -0.59)	0.010	54.59 (1.87, 107.32)	0.042	1.20 (1.03, 1.41)	0.020
Stroke	-0.40 (-1.76, 0.97)	0.568	5.57 (-28.17, 39.31)	0.746	1.02 (0.84, 1.23)	0.858
Other CV	-0.29 (-2.22, 1.64)	0.765	14.39 (-26.93, 55.71)	0.495	1.04 (0.93, 1.16)	0.517
Non-CV	-0.11 (-3.17, 2.95)	0.945	54.74 (-35.89, 145.37)	0.236	1.01 (0.96, 1.07)	0.667
Cancer	-0.55 (-3.22, 2.12)	0.684	24.84 (-52.63, 102.31)	0.530	1.02 (0.94, 1.12)	0.574
Respiratory/infection	0.27 (-1.94, 2.48)	0.814	15.87 (-28.87, 60.60)	0.487	0.99 (0.92, 1.07)	0.823
Other non-CV	0.21 (-1.76, 2.18)	0.834	20.27 (-24.95, 65.49)	0.380	1.02 (0.92, 1.13)	0.741

Figure 12: Plots of time-dependent hazard ratio and difference in RMST over all follow-up time, estimated from a flexible parametric model





2.8.4.4 Quantifying LLA treatment-time interactions

The estimated effect (adjusted HRs) comparing LLA groups was similar for CV-related mortality during the LLA trial period (HR: 0.85) to that in the post-trial period (HR: 0.87), but statistical evidence for the treatment effect was a lot stronger in the post-trial period due to the larger number of events. There was no evidence of an interaction in effect between within-trial and post-trial periods (p=0.939).

There was no evidence of a CHD-related mortality difference between randomised LLA groups during the LLA trial period, with an adjusted HR of 1.02 (p=0.950). The effect on CHD-related mortality emerged during the post-trial period with the reduction associated with the randomised atorvastatin group, with an estimated adjusted HR of 0.75 (p=0.023). From Figure 13 this post-trial effect can be visualised in the KM plot split by LLA trial period and post-trial period, showing little difference between cumulative incidence curves during the LLA trial period, but clear separation in the post-LLA period. Despite this, there was no evidence of an interaction between within and post-LLA periods for CHD-related mortality (interaction p=0.380), nor was there evidence of a trend over time when splitting time into 3-year periods (test for trend p=0.457, see Table 12).

Table 11: Hazard ratios from piecewise proportional hazard models within and post- LLA trial periods

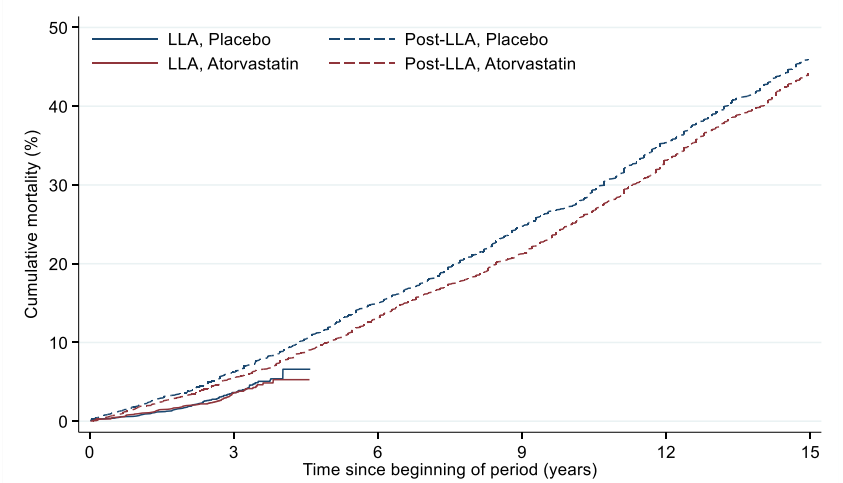
		Time period (years)		
Cause of death		LLA trial period	Post-LLA trial period	P-value for difference in HRs between periods
All	Deaths in placebo arm, rate	90 (3.93), 1.28	1006 (45.77), 3.98	
	Deaths in atorvastatin arm, rate	83 (3.58), 1.18	995 (44.54), 3.78	
	HR (95% CI)*	0.93 (0.69-1.26)	0.94 (0.86-1.02)	
	p-value	0.642	0.154	0.966
Any Cardiovascular	Deaths in placebo arm, rate	36 (1.57), 0.51	337 (15.33), 1.33	
	Deaths in atorvastatin arm, rate	30 (1.29), 0.43	305 (13.65), 1.16	
	HR (95% CI)*	0.85 (0.52-1.38)	0.87 (0.74-1.01)	
	p-value	0.509	0.073	0.939
CHD	Deaths in placebo arm, rate	19 (0.83), 0.27	150 (6.82), 0.59	
	Deaths in atorvastatin arm, rate	19 (0.82), 0.27	115 (5.15), 0.44	
	HR (95% CI)*	1.02 (0.54-1.93)	0.75 (0.59-0.96)	
	p-value	0.950	0.023	0.380
Stroke	Deaths in placebo arm, rate	8 (0.35), 0.11	60 (2.73), 0.24	
	Deaths in atorvastatin arm, rate	6 (0.26), 0.09	63 (2.82), 0.24	
	HR (95% CI)*	0.78 (0.27-2.25)	1.00 (0.70-1.42)	
	p-value	0.644	0.993	0.663

*Adjusted for baseline age, sex, ethnicity, systolic blood pressure, total cholesterol, body mass index, diabetes, smoking status, years of education (socio-economic status), and lipid lowering arm randomization

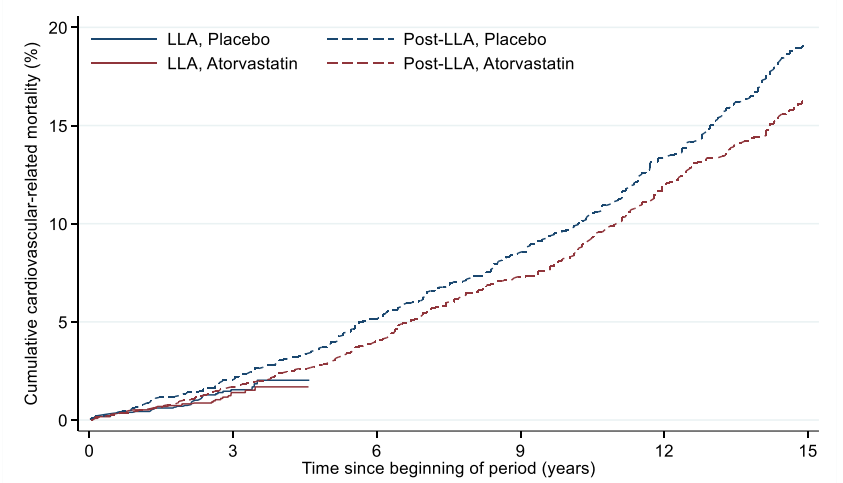
Note, percentages calculated using the denominators of how many subjects alive at the beginning of the time-period. CHD: coronary heart disease.

Figure 13: Cumulative mortality plots by LLA treatment and follow-up period

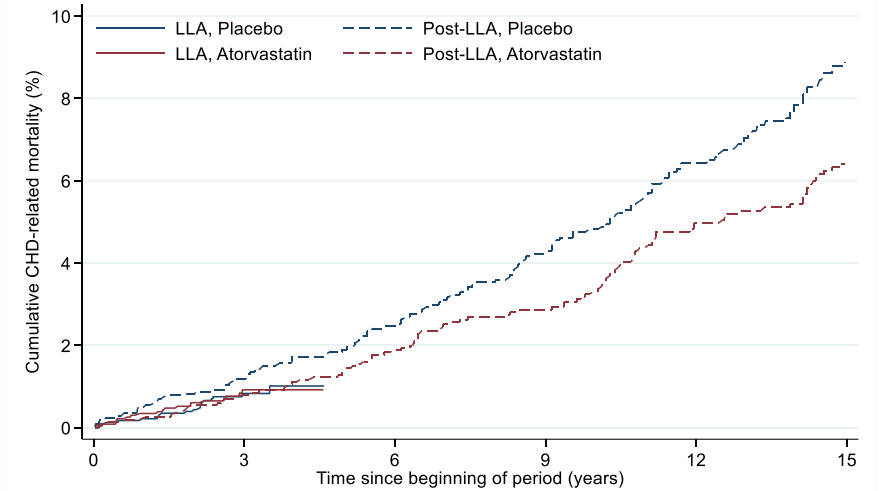
All-causes



Cardiovascular



CHD



Stroke

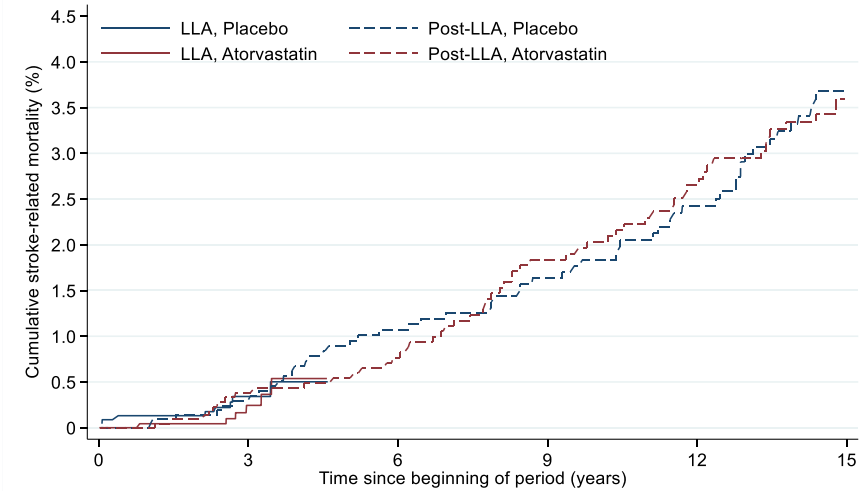


Table 12: Hazard ratios from piecewise proportional hazard models over follow-up for LLA randomised comparison

		Time period (years)						
Cause of death		Within 3	3-6	6-9	9-12	12-15	15+	P-value for linear trend between periods
		N=4605	N=4442	N=3844	N=3447	N=3068	N=2603	
All	Deaths in Placebo arm	81 (3.5%)	127 (5.8%)	174 (9.1%)	196 (11.6%)	209 (14.0%)	309 (24.3%)	
	Deaths in Atorvastatin arm	80 (3.5%)	115 (5.1%)	156 (8.1%)	167 (9.5%)	238 (15.1%)	322 (24.2%)	
	HR (95% CI)*	0.99 (0.73-1.34)	0.90 (0.70-1.16)	0.85 (0.69-1.06)	0.80 (0.65-0.98)	1.07 (0.89-1.29)	0.99 (0.85-1.15)	
	p-value	0.944	0.408	0.152	0.030	0.474	0.872	0.320
Cardiovascular	Deaths in Placebo arm	36 (1.6%)	40 (1.8%)	52 (2.7%)	64 (3.8%)	70 (4.7%)	111 (8.7%)	
	Deaths in Atorvastatin arm	32 (1.4%)	32 (1.4%)	49 (2.5%)	51 (2.9%)	77 (4.9%)	94 (7.1%)	
	HR (95% CI)*	0.90 (0.56-1.45)	0.80 (0.50-1.27)	0.91 (0.61-1.34)	0.75 (0.52-1.08)	1.03 (0.74-1.42)	0.80 (0.61-1.05)	
	p-value	0.664	0.347	0.626	0.125	0.860	0.108	0.931
CHD	Deaths in Placebo arm	20 (0.9%)	25 (1.1%)	19 (1.0%)	33 (2.0%)	29 (2.0%)	43 (3.4%)	
	Deaths in Atorvastatin arm	22 (1.0%)	13 (0.6%)	24 (1.2%)	14 (0.8%)	30 (1.9%)	31 (2.3%)	
	HR (95% CI)*	1.12 (0.61-2.05)	0.52 (0.27-1.02)	1.22 (0.67-2.22)	0.40 (0.21-0.75)	0.96 (0.58-1.61)	0.67 (0.43-1.07)	
	p-value	0.719	0.057	0.521	0.004	0.891	0.092	0.457
Stroke	Deaths in Placebo arm	7 (0.3%)	7 (0.3%)	14 (0.7%)	9 (0.5%)	10 (0.7%)	21 (1.7%)	
	Deaths in Atorvastatin arm	4 (0.2%)	10 (0.5%)	7 (0.4%)	17 (1.0%)	14 (0.9%)	17 (1.3%)	
	HR (95% CI)*	0.58 (0.17-1.99)	1.44 (0.5-3.77	0.49 (0.20-1.20)	1.76 (0.79-3.95)	1.31 (0.58-2.4)	0.77 (0.41-1.45)	
	p-value	0.386	0.462	0.119	0.168	0.512	0.412	0.865

*Adjusted for baseline age, sex, ethnicity, systolic blood pressure, total cholesterol, body mass index, diabetes, smoking status, years of education (socio-economic status), and lipid lowering arm randomisation.

Note, percentages calculated using the denominators of how many subjects alive at the beginning of the time-period. CHD: coronary heart disease.

2.9 Discussion

2.9.1 Summary of findings

This study provided evidence of the long-term benefits on cardiovascular mortality of lipid-lowering statin-therapy and of antihypertensive treatment based on the CCB amlodipine with the addition of the ACEi perindopril in patients with hypertension, with no previous coronary-related events, but considered high risk for CVD.

Randomisation to atorvastatin led to a decrease in mortality from CHD compared to those randomised to placebo and there were fewer deaths from stroke in those randomised to amlodipine-based treatment compared to those randomised to atenolol-based treatment. These effects extended beyond the end of the trial periods over the median 17.4 years of follow-up, suggesting that benefits can be long-lasting.

2.9.2 Long-term impact of blood pressure lowering treatment

The BPLA period of the ASCOT trial was ceased early after a median 5.5-years follow-up due to an excess in deaths associated with the atenolol-based group as well as worse outcomes on a number of other secondary endpoints [14]. The trial reported an estimated 24% reduction in hazard of CV-related mortality at the end of

the trial (p=0.001) and an 11% reduction in hazard of all-cause mortality (p=0.025) associated with the amlodipine-based treatment arm.

In the ASCOT legacy sub-population cohort of 8580 subjects from England and Scotland, while there was also evidence of a reduction in CV-related mortality during the BPLA trial period, while this effect seemed to diminish a little after the trial, overall there was a sustained effect of a reduction in CV-related mortality over the long-term follow-up.

More specifically, there was evidence of a reduction in the risk of stroke-related mortality over the whole of follow-up associated with randomisation to amlodipine-based treatment. The estimated adjusted HRs were similar within-trial to that post-trial (0.70 and 0.73, respectively), suggesting a continued and consistent beneficial effect on stroke-related mortality even after the trial. There was no evidence that hazards were not proportionate over time.

The beneficial effect on CV-related mortality seen with amlodipine-based therapy compared to atenolol-based therapy was only evident in the higher risk group that were not randomised into the LLA part of the trial. There was evidence for this interaction between LLA and non-LLA groups, with no effect seen at all in those who took part in the LLA factor of the trial. However, the underlying rate of CV-

related mortality was very similar between non-LLA and LLA subgroups for those randomised to amlodipine-based therapy, indicating that amlodipine had a similar effect in both groups. Within the atenolol-based group however, those not in the LLA factor of the trial had higher rates of CV-related mortality, while those in the LLA factor had similar rates of CV-related mortality to rates seen in those randomised to amlodipine-based therapy. Hence, it appeared the effect of atenolol-based treatment seemed inconsistent across subgroups, with poorer outcomes in the non-LLA group compared to the LLA group. The effect of amlodipine-based therapy appeared consistent in both subgroups, and while the effect of atenolol-based treatment was also similar in the LLA cohort, this implies that atenolol-based therapy was less effective in those at a higher CVD risk with a higher lipid profile at baseline.

Although there was no evidence of a BPLA effect on CHD-related mortality across the whole population, this pattern of differing effect on CV-related mortality between non-LLA and LLA subgroups was largely being driven by the differing effects on CHD-related mortality between subgroups. Rates of CHD-related mortality were similar in both BPLA treatment groups in the LLA group, and as expected higher overall and in both treatment groups in the higher risk non-LLA subgroup. However, the rate of CHD-related death was higher in the atenolol-

based group compared to amlodipine-based, within that higher risk non-LLA subgroup. Again this implies that while atenolol-based therapy may be as effective as amlodipine-based in the lower risk LLA subgroup, it was less effective in reducing CHD mortality in the higher non-LLA risk group. Other studies have shown beta blockers to be less effective in older subjects at reducing stroke and other CV events compared to other anti-hypertensive treatments, while at younger ages found similar efficacy between anti-hypertensive treatments [50-52]. Although there was no difference in age between non-LLA and LLA subgroups, the differences observed in other studies related to the increase CV-risk, which of course is associated with increased age. Other studies have found that atenolol demonstrated no reduction effect on mortality in those with coronary syndrome or heart failure, while alternative beta-blockers were found to reduce mortality in such patients [53,54].

Biological mechanisms behind the observed differences between BPLA trial groups are not entirely understood. While blood pressure control was slightly better in the amlodipine-based group, by about one-year post-baseline this difference was small, at around 2 mmHg for the duration of the trial. This small difference in blood pressure does not represent a large difference from a clinically important perspective, and cannot explain the differences in mortality between trial groups.

Another possibility is that the difference in visit-to-visit blood pressure variability between the treatment arms plays a role. Blood pressure variability was much lower in the amlodipine-based group compared to the atenolol-based group. Blood pressure variability is explored in depth in Chapter 4 of this thesis.

2.9.3 Long-term impact of lipid lowering treatment

The LLA part of the ASCOT trial also ceased early after a median 3.3-years follow-up due to the large reduction in the primary outcome of non-fatal myocardial infarction or fatal CHD that emerged in the atorvastatin arm, a final HR of 0.64 ($p<0.001$). The trial also reported reductions associated with statins for other outcomes including all coronary events and stroke events [13]. Although fewer deaths from any cause occurred in the statin arm compared to the placebo arm (185 vs. 212, respectively), statistical evidence was weak ($p=0.16$).

A difference in CHD-related mortality did not emerge between BPLA trial groups during the LLA trial period. However, over long-term follow-up there was evidence for a reduction in risk of CHD-related deaths in the statin arm, an estimated adjusted relative reduction in hazard of 24%. The LLA period was short with a median of 3.3 years and had relatively few events so it was hard to assess whether there might have been a delayed effect on CHD mortality or whether this apparent

delay in materialisation of effect was merely by chance. There was no statistical evidence of a change in effect on CHD-related mortality over time.

There was evidence for a reduction in overall CV-related deaths associated with the statin group, with an adjusted HR of 0.86 (p=0.044), but this was entirely a result of the effect on death from CHD, with no evidence for a difference in other CV-related causes of death.

Evidence for an interaction was found between ethnic background and LLA treatment group for CV-related mortality. There were more deaths due to CV-related causes in the statin group than in the placebo group for those of black ethnic background, while there were fewer deaths in the statin group in those of non-black background. This could not be explained by a difference in lipid profile, since those of black origin had a very similar cholesterol profile in both placebo and statin groups to those of non-black origin. Other studies have presented conflicting evidence. The ALLHAT researchers conducted a study to see if the apparent differences between ethnicities in the effect of assignment to statins on CHD compared to the standard of care could be explained by differences in baseline characteristics, adherence to medication or achieved blood pressure or lipid lowering. Results suggested that statin therapy was effective in preventing CHD in those of black origin but not in those of non-black origin [55]. On the other hand,

some studies have reported smaller effects of statins in black subjects compared to non-black. Often this seems to be because subjects of black ethnicity had higher baseline cholesterol and were associated with poorer adherence to statins compared to non-black subjects [56]. Then a number of other trials that have conducted subgroup analyses have found little difference in the effects of statins on lipid control [57-59]. However, there seems to be a lack of data on the effects of statins on those of black ethnicity, as most of the large clinical trials contain predominantly white subjects. Some studies have suggested that there is a lower prevalence of statin use among those of black ethnicity compared to those of non-black origin. Reasons for this seem to still be unclear [60].

There was a marked and sustained difference in lipid control during the blinded LLA trial period between statin and placebo arms. While mean total cholesterol had plummeted by the 6-month visit and remained consistently around 4 mmol/L throughout the blinded LLA trial phase in those assigned to statin therapy, the mean level remained over 5 mmol/L in the placebo arm throughout the LLA trial period. A slight reduction in total cholesterol in the placebo arm was likely due to changes in related factors over the trial as well as possibly some regression to the mean. If this sustained difference in lipid levels was responsible in part for sustained benefit in reduction in deaths from CHD, then it may indicate that even

relatively short periods of lipid control can have much longer-lasting clinically important benefits on coronary health. By the end of the BPLA trial, the difference in total cholesterol between statin and placebo arms had gone due to placebo patients being permitted to cross-over to atorvastatin. Mechanisms behind the long-lasting benefits associated from statins are somewhat unclear. Statin therapy is known to induce plaque stabilisation and even regression. Perhaps the occurrence of plaque stabilisation during the trial period is somewhat responsible for these long-term benefits to CV outcomes [61,62].

There have been consistent findings from other clinical trials of a relationship between statin use and reduction in CV mortality over long-term follow-up [35-37,63,64]. The WOSCOPS study concluded that their observation of long-term legacy benefit (20-year follow-up) after 5 years of LDL lowering by statin therapy could suggest that treatment might not need to be lifelong. However, the long-term effect they witnessed reduced slightly in the post-trial period compared to within-trial, suggesting that subjects might not have fully experienced the maximum long-term benefits. What is unknown is whether there could be a limited period of statin exposure that could give optimal sustained long-term benefits without the need for lifelong therapy, or whether continued statin therapy would always result in greater benefits. It is difficult to see how this could be studied.

2.9.4 Strengths & Limitations

The ASCOT legacy study provides a unique and valuable opportunity to study the effects of allocated treatment over a long follow-up time in subjects presenting with hypertension and at high risk for CVD. The long follow-up combined with the benefit from of the randomisation process in the allocation of treatment, gives this study an advantage over similar non-randomised observational studies. The greatest strength of this legacy study is its large cohort consisting of hypertensive patients with the opportunity to investigate the long-term impact of both lipid-lowering and blood pressure-lowering treatments on mortality, giving sizeable power to estimate effects between treatments.

As mentioned, the ASCOT legacy study, as with other studies born out of randomised trials, benefits from the randomisation process balancing known and unknown risk factors between trial groups. If the randomisation process is conducted well, then groups should differ only by chance. This allows for an unbiased comparison of effect between randomised groups. While in a randomised trial setting one can reasonably interpret associations as being causal, beyond the randomised trial it is more difficult to make such causal claims. One of the biggest limitations of the study is that there was no access to data on treatments that subjects went on to after the trial. As well as post-trial lipid-lowering and blood

pressure-lowering treatments, and any other treatments being unknown, risk factors, behavioural and lifestyle factors were also not known. This meant that there was the potential for a degree of unidentified and unmeasured confounding which may have emerged more and more as time passed from randomisation if individual subject choices were related to their original treatment allocation in some way. The only way one could make the assumption that randomised groups stayed balanced over time is if treatment groups were not influenced or affected in different ways to each other. In that case, one might expect changes in each group over time to vary in a similar way, and continue to only differ only by chance.

However, by the very nature of the interventions, randomised groups have different experiences as a result of their treatment. Therefore, randomised groups are likely to systematically become increasingly different as time passes. If the groups differ in terms of attributes that are on the causal pathway towards the outcomes, that won't bias estimation of treatment effects as the modification of these attributes are the mechanisms through which the treatments take effect. Some might be known mechanisms, such as the lowering of blood pressure or cholesterol levels, and others might be unknown biological or behavioural changes. These changes matter if we wish to understand the mechanisms involved in treatment effects, but won't stop us from being able to conclude that the treatment effect exists.

Problems arise when we face fundamental differences between groups that have arisen from the study design that may not be reflective of real-life.

As mentioned, a key limitation was that post-trial treatments were not available for these analyses. If post-trial treatment choices were balanced across originally randomised trial treatment groups, then estimated effects would be easier to interpret as we could be more confident of less bias from unknown future treatment differences between groups. However, as data on post-trial treatment choices was not available, the extent to which post-trial treatments and other potential unknown confounding factors impact the estimated effects over time were unknown and hence could not be analysed or taken into account in analyses. Interpretation of results must therefore be kept within the context of these limitations.

One could argue that if taking allocation to a specific treatment was related to future treatment choices and behaviours as well as the biological changes that take place, then these mechanisms could be seen as valid components of causal effects. However, this setting is not representative of a usual patient journey outside of this randomised blinded trial setting, and these mechanisms are unknown so we are not able to fully understand them.

Analyses were conducted on an intention-to-treat (ITT) basis, i.e. subjects were analysed according to the original treatment groups to which they were randomly assigned, regardless of the treatments they actually received during the trial. If some patients were to cease taking assigned treatment or to switch treatments, then groups could become more similar in terms of the actual treatment taken and estimated effects could have been diluted. Bias could arise if treatment adherence was systematically different between treatment groups. Although, if differences in adherence or likeliness to change treatments was a consequence of the treatment allocation, then this might reflect behaviours in a real-life setting out of the trial context, keeping treatment comparisons pragmatic.

Indeed, the ITT analysis approach is pragmatic, which is one of the reasons why it is a popular approach to analysis for many randomised clinical trials. The treatments in the two BPLA groups were drug-led regimens: one a CCB-led regimen with the option of an ACE-i as needed; and the other a BB-led regimen with the option of a diuretic as needed. Hence, the BPLA comparison was not a single drug comparison, but a treatment regimen strategy comparison. An ITT population was fitting for analysis in that it was reflective of how a treatment strategy might be conducted in real life clinical practice, where modifications to treatments occur as required.

Conducting a per protocol analysis can pose problems when those who are removed from the analysis due to protocol violations are systematically different to those who are not excluded from analyses. This can introduce bias.

In the ASCOT trial in general if a subject ceased trial medication or switched treatment, they would be withdrawn from the trial at that point. For the LLA factor of the trial, statin therapy was compared to placebo, so the interpretation of effect during the trial could be a fairly pure comparison if patients were able to remain fully unaware of which treatment they were taking, active or placebo. In the ALLHAT trial this wasn't the case, pravastatin was compared to the usual standard of care. As a result, many subjects in the usual care group received statins during the trial, and hence a smaller difference in cholesterol levels between the groups was detected. Total cholesterol dropped by 17.2% in the pravastatin group and by 7.6% in the usual care group at year 4 in the ALLHAT trial, with no significant difference [65]. While in the ASCOT trial total cholesterol dropped by 25.3% in the atorvastatin group and by 7.4% in the placebo group by the end of year 3 (24.5% and 8.1%, respectively by the end of year 4, although there were few subjects remaining in the LLA part of the trial for 4 years or more, n=389). Total cholesterol was 0.99 mmol/L less in the atorvastatin arm compared to placebo at the end of year 3 ($p<0.001$), and 0.90 mmol/L less at the end of year 4 ($p<0.001$) in the

ASCOT trial. In addition, baseline total cholesterol was slightly higher in ALLHAT subjects (5.82 & 5.81 mmol/L in the statin and usual care groups, respectively) compared to ASCOT (5.48 mmol/L in both groups). Hence, the ALLHAT trial may have been underpowered to detect effects in CV endpoints, and evidence for a difference in all-cause mortality and CV-related mortality over long-term follow-up was non-significant [65-67].

The main analysis approach used the Cox Proportional Hazards model. This model can be used in the context where competing risks are present and the cause-specific hazards are estimated. When a subject has a competing event, the subject is censored and hence removed from the risk-set thereafter, in the same way that a subject would be censored if they were lost to follow-up or did not give consent for follow-up beyond the end of the trial. The assumption in this approach is that censoring is not informative, given the other covariates in the model. If censorship is informative then estimated effects can be biased in one way or another.

It might be that a subject dying from a competing cause of death was informative about the level or risk that subject was also at for death from the cause of interest. For example, patients who died from a cause other than stroke may have been at increased risk of dying from stroke. We know that death from CHD has some common risk factors with death due to stroke, for example. Also, death from non-

CV causes, such as cancer, share some common risk factors with stroke-related death. Hence, if subjects who die from CHD were also at higher risk of dying from stroke, then to ignore this would mean that the hazard of stroke may be underestimated when CHD-related deaths are occurring, and vice-versa. If a higher rate of CHD-related death was occurring in one treatment group than another, then this could mean the estimated hazard of stroke-related death in that group was lower than it truly theoretically would be in relation to the alternative group, had we been able to observe a future stroke event if the competing event of CHD had not occurred.

Although there was weak statistical evidence, there was a slightly higher rate of CHD-related death in the atenolol-based group compared to the amlodipine-based group. If those censored at death by this competing cause were actually also at higher risk of stroke-related death, then this would mean the risk of stroke-related death in the atenolol-based arm was underestimated since those subjects who died from CHD were also at higher risk of dying from stroke.

Fine & Gray introduced sub-distribution hazard regression as a way to model the influence of covariates on the cumulative incidence function. The cumulative incidence function is preferable over Kaplan Meier estimates of the survival function in contexts where the desire is to estimate the empirical distribution of events

instead of the hypothetical distribution that is applicable in the context where no competing risks exist [68]. The sub-distribution proportional hazards model has become a popular alternative to the Cox PH model, and in some fields has become the standard approach when competing risks are present. This is because the Fine & Gray approach does not make the explicit assumption of non-informative censoring when a competing event occurs. Instead, when a competing event occurs, the subject is not censored but remains in the risk-set. While this does bypass the assumption of non-informative censoring, it poses a different problem in the context of causal analysis because whenever a competing event occurs this eliminates the possibility of any other competing event occurring in those subjects from that point on. For example, if there was a higher rate of death from CHD in the atenolol-based group, then this would reduce the estimate of the sub-distribution hazard of stroke-related death or any other competing cause of death. Hence, if competing events of death from CHD and stroke are both occurring more in the atenolol-based group, then the estimated effect will be reduced for each cause because of the higher occurrence of death from the competing cause.

There was little difference in HRs between the cause-specific and sub-distribution approaches. The effect was slightly reduced with the Fine & Gray method for stroke-related mortality for the BPLA comparison (cause-specific HR was 0.72 and

the sHR was 0.73). This could be a consequence of there also being a higher occurrence of CHD events in the atenolol-based arm (although no statistical evidence). There was also a slightly reduced effect with the Fine & Gray method for CHD-related mortality for the LLA comparison (cause-specific HR was 0.76 and the sHR was 0.79). These differences are small, likely because in each case there were no strong effects observed from competing causes of death.

While the Fine & Gray approach estimates the true cumulative incidence of events, it can lead to bias in causal analysis [69]. This is because the theoretical underlying risk will be underestimated. Hence, the Kaplan Meier cumulative incidence cause-specific approach would be more appropriate when trying to estimate a causal effect as long as censoring due to a competing event is non-informative. Ultimately, we cannot test this assumption [70], but since the assumption of competing event censoring being non-informative is conditional on covariates in the model, the most important way to increase the plausibility of the assumption is to include common risk factors for all causes of death. In this study, all adjusted analyses adjust for pre-specified known baseline risk factors.

Although many researchers see the Fine and Gray approach as the appropriate method when faced with competing risks, currently there is no perfect solution. Estimates from different methods represent slightly different things, and so need to

be interpreted differently. There are many other methods that have been proposed for analysis in the presence of competing risks, such as the use of multiple imputation to impute theoretical failure times for those subjects that experience a competing event [71].

In addition to competing risks causing bias, the specific cause of death of interest can itself cause bias over time. Miguel describes the hazard ratio as having a built-in selection bias [72]. If a favourable treatment group has a reduced rate for an outcome compared to an unfavourable group, then one way to look at it is that more subjects would be being preferentially removed from follow-up from the unfavourable group, leaving a higher risk population in the favourable group as a result. As a consequence, over time the favourable group would end up with a population that was increasingly higher risk of the outcome compared to the unfavourable group. Eventually this would lead to an increase in events in the, once favourable arm, relative to the unfavourable. The clearest example of this occurrence is with the outcome of death from any cause. If one treatment is able to deliver longer survival time compared to another, eventually this favourable treatment group would catch-up simply because everyone would die at some point in time. Therefore, what was a reduction in death rate in one group initially would eventually reduce and reverse in some form until the proportion of deaths was

equal between arms, i.e. everyone. The impact of this problem would be to reduce the overall effect when considering a fixed effect over all of follow-up time, or when considering how the effect changes over time. It would cause the effect to change (reduce) due to this evolving selection bias, rather than for the reason of a genuine change in treatment effect over time. Hence, an overall measure of effect might become more and more misleading or meaningless with time, and even time-updated effects could be biased.

Although there was no formal evidence against proportional hazards for each outcome, comparing treatment groups, conceptually one could argue that the assumption of proportional hazards may not be completely appropriate in this setting. It is likely that to some extent treatment groups became more similar to each other after the trial in terms on ongoing treatment, compared to within-trial. It seems logical that effects of trial treatment over long-term follow-up post-trial would be somewhat different to that during the trial. The treatment effects that were observed in this study came with fairly borderline evidence at the 5% significance level, so it may just be that there was a lack of power to detect any subtle changes in effect over time. However, there were no large deviations from proportional hazards observed for the outcomes for each treatment comparisons. The estimated treatment effect between antihypertensive groups on stroke-related

death and the estimated reduction in CHD-related death associated with statins compared to placebo, both appeared reasonably consistent and sustained over the whole of the long follow-up period. There may have been a hint of a delayed effect on CHD-related mortality associated with the statin therapy in the first few years from randomisation. This may have been a legitimate initial delay in effect, but few events early on makes it difficult to draw that conclusion.

Largely, results from alternative approaches to quantifying differences in survival between treatment groups were consistent with the findings from Cox PH models.

Within this analysis, multiple statistical tests were performed. No adjustment for multiple testing was applied, and hence p-values do not represent the true probability of observing an effect purely by chance, i.e. a false positive. In this analysis, a significant effect was not defined in a dichotomous way, but instead p-values represented a continuous scale of evidence that each need to be taken in the context of multiple testing. In this study, despite having a relatively large cohort of subjects, overall treatment effects, when observed for certain causes of mortality, do not come with extremely high levels of statistical evidence (i.e. very low p-values). Hence, discussion and conclusions from this analysis have remained in the context of what is plausible and alongside consideration of previous published

studies, recognising that this research serves to strengthen existing evidence and act as hypothesis generating.

In conclusion, this study provides evidence of both the long-term sustained beneficial effect of statins on CHD-related mortality and reduction in stroke-related mortality associated with amlodipine-based treatment compared to atenolol-based treatment. The study benefits from the large sample size of the ASCOT legacy cohort, and the long length of follow-up. While interpretation of results from this study come with the limitation of unknown treatments that subjects were taking post-trial, effects have appeared to be sustained over time, and results have shown to be robust to alternative analysis approaches. Hence, this study delivers strong and robust messages and there is tremendous value in these findings. This study presents important evidence to help strengthen and build upon existing evidence of long-term impacts of these treatments.

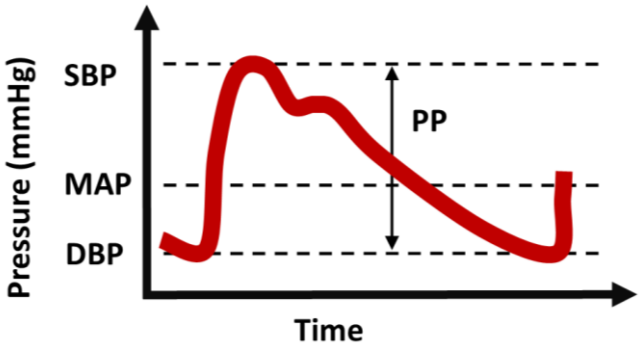
Chapter 3: Comparison of prognostic performance between components of blood pressure for cardiovascular mortality using baseline measurements

3.1 Background

Blood pressure is considered one of the most important risk factors for CVD. Both diastolic and systolic components of blood pressure are known important biological markers for CVD and mortality. Present guidelines focus on both of these components for the management of blood pressure and treatment of hypertension [73,74]. However, there is growing evidence to suggest that PP is also an important component of blood pressure, and that perhaps the focus should be on SBP and PP, since there is much evidence to suggest that both are stronger predictors of CVD than DBP [75–78].

PP is the difference in pressure between the maximum and the minimum pressure exerted on the walls of the arteries during a cardiac cycle. It is the increase in blood pressure when the cardiac cycle moves from its diastolic state to its systolic (see Figure 14).

Figure 14: Schematic of a blood pressure wave over a cardiac cycle



While DBP was once the main focus in blood pressure management due to its less variable nature compared to SBP, it is now widely accepted that SBP is the stronger predictor of CVD risk. Kannel et al. compared the contribution of SBP versus DBP to risk of CHD and found that as age increased there was a trend of declining importance of DBP with corresponding increase in importance of SBP [79]. Some studies have found DBP to be of little prognostic value over that of SBP in relation to CVD risk in older populations [80–83].

While guidelines for the management of blood pressure focus on targeting hypertension, suggesting healthy limits under which SBP and DBP should be controlled, both SBP and DBP have often been observed having a U- or J-shape association with CVD risk, with both low and high values associated with increased risk, particularly for DBP [84,85].

The pulsatile component of blood pressure has more recently been identified as an important risk factor for CVD [75,86–88]. It first gained interest as a potentially important risk factor for CVD when a link was found between the combination of both high SBP and low DBP with elevated CVD risk. Darne et al. were among the first to report PP as an independent risk factor for CVD [89]. Gasowski et al. describe the arterial pressure wave being better represented as a mean pressure and

pulsatile component. From their meta-analysis combining control-group data from 7 randomised clinical trials in patients with systolic-diastolic or isolated systolic hypertension, they conclude that PP and not mean pressure was independently associated with the increased risk of fatal events [90]. Other studies have suggested that PP is superior to both SBP and DBP individually as a predictor for CV disease risk, particularly in older subjects [76]. Glynn et al. analysed data from a population-based study in elderly subjects, aged 65 years and above, and concluded that PP appeared the best single measure of blood pressure in predicting mortality in older people [91]. PP is strongly correlated with SBP, and it may be that PP has the benefit of both being able to indicate risk associated with high SBP as well as picking up on risk associated with lower DBP. Glynn et al. also concluded that PP helped to explain the apparent J-shape relationship between DBP with risk, as those with low DBP most commonly had higher PP.

Some studies have highlighted the importance of mean arterial pressure (MAP), as a risk factor for CVD [92,93]. MAP represents the mean blood pressure over a complete cardiac cycle. MAP is most commonly estimated as [94]:

$$MAP = \frac{(2 \times DBP) + SBP}{3}$$

Studies have shown that SBP increases while DBP decreases with age, and hence, PP increases with age [95]. In addition, there is evidence that the relationship between both SBP and DBP with CVD alters with age [4]. It may be that this differing in relationship between components of blood pressure and risk with age might result in PP being the better predictor in older people, which has been shown to be as good as or better than other blood pressure components in the middle-aged and older [75–78]. However, in the face of this emerging evidence, there still remains some controversy as to which component of blood pressure is the superior predictor of CVD and mortality, SBP or PP, with some conflicting research. Some studies have found that while PP is important, it is inferior to SBP in the prediction of CVD risk [92,96]. Evidence for the importance of MAP is also somewhat conflicting, with some studies reporting associations with CVD [93,97], and others not [92,98].

Components of blood pressure in combination have been shown to be stronger in predicting CVD risk compared to single measures. Some evidence suggests that combining SBP with DBP, and PP with MBP leads to superior CVD prediction compared to single blood pressure components alone [99]. However, other studies suggest that there is no additional gain over adding DBP once SBP is considered, and adding MAP once PP is considered [90]. Hence, there is still uncertainty as to

which components of blood pressure, alone or in combination, are best at predicting the risk of CV-related morbidity and mortality.

The ASCOT legacy population spans a wide age range from 40 to 80 years, providing a good opportunity to study relationships between distinct components of blood pressure across a wide age-range in this hypertensive cohort from England and Scotland. The long-term follow-up provides a strong basis to assess the predictive ability of baseline measures of blood pressure in the prediction on long-term CV-related mortality.

3.2 Aims

Through the use of blood pressure measures collected at baseline (ASCOT trial randomisation visit), the aim in this chapter was to evaluate how components of blood pressure (SBP, DBP, PP, & MAP) relate to mortality, with a focus on mortality from CV-related causes, while considering the influence of age. The aim was to compare the predictive ability of each component to assess which might be the most powerful predictive marker, comparing single components alone and also pairs of components as to their joint predictive ability, and to assess whether prognostic ability varies with age.

As SBP and PP are already widely believed to be the strongest individual predictors of CV-related mortality, the main focus was to make the comparison between these two single components of blood pressure. In addition, the aim was to assess whether combinations of blood pressure components could improve prediction by evaluating the predictive gain when pairing DBP with SBP, and MAP with PP, to see if one coupling showed stronger prognostic ability than the other.

Analyses were repeated using blood pressure measures collected at the 1-year trial visit in order to assess whether conclusions change following the initial decline in SBP and DBP levels as a result of blood pressure-lowering therapy during trial participation. However, the main approach was on the analysis of baseline measurements, in order to assess how predictive measurements were at the point at which patients present with uncontrolled hypertension prior to trial treatment initiation, so as to reflect a patient presenting with hypertension at a clinical visit.

3.3 Methods

3.3.1 The collection of blood pressure during the ASCOT trial

As well as other characteristics, SBP and DBP were recorded at baseline for all 8580 ASCOT legacy subjects. In addition, blood pressure was routinely measured at scheduled visits (and unscheduled visits) throughout the trial, initially at the six-

week, three-month and six-month visits, thereafter at scheduled visits every six months until the end of the trial or until a subject left the trial early.

At baseline and subsequent visits, the procedure was to take three blood pressure measurements (although on some occasions less than three were recorded). In this analysis, the mean of the second and third blood pressure readings was used to represent an estimate of the blood pressure level at a trial visit, discarding the first. If only two measurements were available for at a single trial visit then the mean of those two was used, and if only a single measurement was recorded then the single value alone was used to represent blood pressure level at that visit.

PP was calculated as the difference between SBP and DBP, and MAP was calculated as the addition of DBP and one third PP.

3.3.2 Statistical methods

3.3.2.1 Relationship between components of blood pressure and other risk factors

Before conducting prognostic analyses, an assessment was made as to the relationship between blood pressure measures collected at baseline with other baseline characteristics. Summary statistics were produced and adjusted linear regression models used to estimate the adjusted associations between other risk

factors and blood pressure. This analysis was repeated for each of the four components of blood pressure.

The correlation between components of blood pressure was assessed by calculating the correlation coefficients between all pair-wise blood pressure components.

3.3.2.2 Relationship of components of blood pressure with mortality

Survival analyses were undertaken in order to assess the relationship of each of the four blood pressure components with mortality risk. The main focus was on the outcome of cause-specific mortality from any type CVD, however, the CV sub-categories of stroke-related and CHD-related mortality were also analysed, as well as mortality from any cause.

Cox proportional hazards (PH) models were used to model this survival data. Baseline blood pressure measurements were initially split into quintiles by number of subjects. These quintile groups were not completely even in number as some measures on quintile boundaries had the same values, and therefore, groups were split to be as even in number as possible while keeping all those with the same blood pressure values were in the same group.

Relationships between blood pressure quintiles and mortality was first explored in models containing only single components of blood pressure, and then modelled as

pairs of blood pressure components. SBP was jointly modelled with DBP, and PP with MAP, in order to gauge whether relationships changed when modelled with others, and whether there was evidence of independent associations once adjusted for another component.

Each model was adjusted for the pre-specified known baseline risk factors: age, sex, ethnicity, age subject left full-time education, body mass index, total cholesterol, presence of type II diabetes, and smoking history.

3.3.2.3 Relating components of blood pressure to CV-mortality, modelled continuously

Each component of blood pressure was then modelled as a continuous variable. In order to explore the shape of the relationship between each component of blood pressure with risk, each component was modelled continuously using restricted cubic spline transformations to allow for possible non-linear relationships with CV-related mortality. A spline is a function made up of piecewise polynomials that connect-up at knots (locations of connecting intervals). Restricted cubic splines are a transformation of the blood pressure measures, such that they are split up at the knot points and one obtains a continuous and smooth function that is linear below the lowest knot, linear above the highest knot, and a piecewise cubic polynomial

between adjacent knots. In each case, for each blood pressure component, three knots were used at locations of the 10th, 50th, and 90th percentile of the data. Hence the functions were linear in the lowest decile of the data, piecewise cubic polynomials between the 2nd decile and the 9th decile, and linear again in the highest decile. The overall function is smooth since the 1st and 2nd derivatives (the slope gradient and rate of change in slope gradient) are continuous at the knots. Restricting the functions to be linear at the tails helps to avoid poorly fitting and unrealistic extremities, which could arise if using polynomial functions that are not restricted. Three knots were used because this allowed relationships to be non-linear, while limiting the potential for overfitting the data with a higher number of knots, as suggested by Harrell [100].

For this stage of analysis, CV-related mortality was the focus and results for all-cause mortality and other specific causes of death are not presented. As before, Cox PH models were used to model the relationship between components of blood pressure with CV-related mortality, both as single-components, and also as paired components as previous described. Adjusted models were adjusted for the pre-specified risk factors as mentioned above.

Interaction tests were conducted in paired component models to see whether the relationship between one blood pressure component with risk was dependent on the other.

3.3.2.4 The influence of age on the association between components of blood pressure and CV-related mortality

ASCOT legacy subjects were split into three age-groups: 40 to 59, 60 to 69, and 70 to 80 years at baseline. The relationship between each blood pressure component and CV-related mortality was assessed in these subgroups in models containing single, and then pairs of blood pressure components with an interaction with age group, hence allowing effects to differ between age groups. Cox PH models were used, and components of blood pressure were modelled as continuous variables with restricted cubic spline transformations, as described above. Models were adjusted for the aforementioned pre-specified baseline risk factors.

3.3.2.5 Blood pressure model comparison

The fit and discrimination of models containing blood pressure components modelled continuously with RCS transformations (as described above), were compared.

The goodness-of-fit was compared between models using Akaike information criterion (AIC) [101,102]. In addition, R^2 (the variability explained by the model) was calculated for each model, using the approach proposed by Royston and Sauerbrei for survival analysis settings [39,103]. R^2 is the proportion of variation in the dependent variable (survival time) that is accounted for by the predictor variables in the model.

In addition, the discriminative ability of each model was assessed by calculating the concordance statistic (C-statistic). The C-statistic is a measure of model discrimination that is based on ranked correlations between the predicted and observed values, and is the probability of concordance between predicted and observed survival. Hence, the C-statistic ranges from 0 to 1, where c= 0.5 would represent completely random predictions, and c= 1 would represent a perfect correctly discriminating model. In this survival analysis context, the C-statistic is the proportion of all pairs of subjects whose survival time can be ordered such that the subject with the higher predicted survival is the one who survived longer.

All models being compared were adjusted for pre-specified risk factors.

3.3.2.6 Analysis of blood pressure at 1-year post randomisation

All analyses were repeated using blood pressure measurements taken at the 1-year visit. This gave the opportunity to assess whether patterns in relationships

observed with baseline measurements were evident in measurements taken once patients had initiated blood pressure-lowering therapy and average blood pressure levels had reduced and were more controlled. This also allowed the assessment of relationships between blood pressure components and mortality at slightly different ranges, since the baseline blood pressure measurements were elevated and restricted, as a consequence of the trial selection process and inclusion criteria into the trial.

3.4 Results

3.4.1 Relationships between baseline blood pressure measures with other baseline characteristics

Mean (SD) baseline SBP and DBP were 161.9 (17.5) mmHg and 92.1 (9.9) mmHg, respectively, and hence mean PP was 69.8 (16.4) mmHg and mean MAP was 115.4 (10.4) mmHg. As patients were recruited to the ASCOT trial based on being hypertensive, patients had an SBP of 140 mmHg or higher or a DBP of 90 mmHg or higher (except for three subjects that had SBP $<$ 140 mmHg and DBP $<$ 90 mmHg).

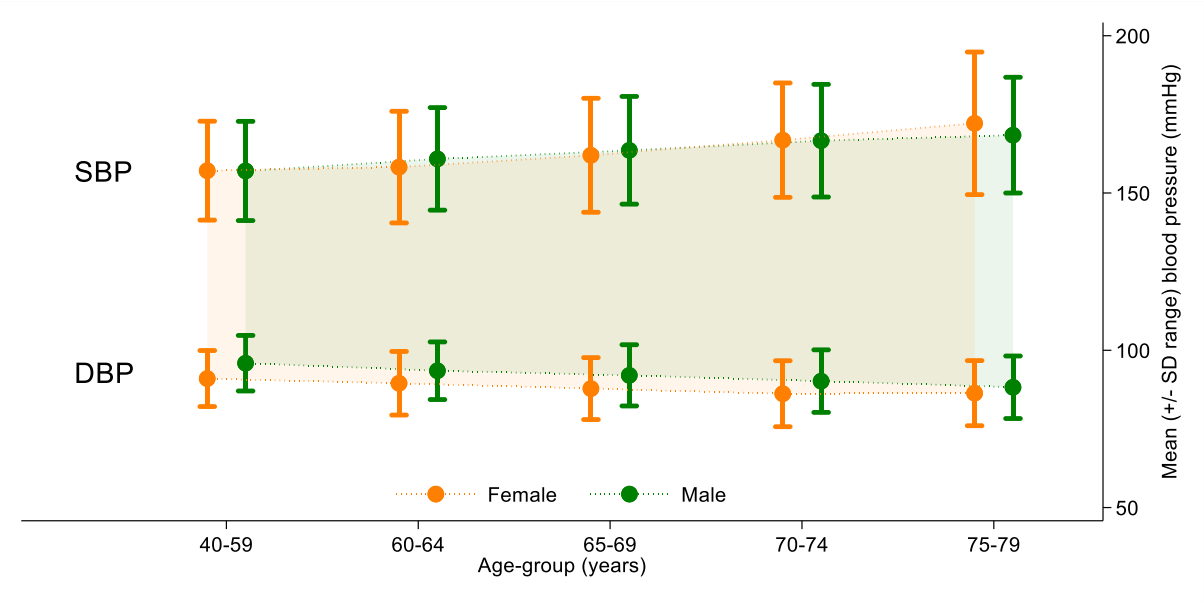
The mean of each blood pressure component at baseline is presented in Table 13 and Table 14, by categories of other baseline risk factors. In addition, mean

differences (95% CIs) in blood pressure components and p-values from tests of overall effect are presented from adjusted multivariable linear regression models.

SBP was markedly higher with increasing age of subjects while DBP was lower (see Figure 15). Those aged 75 years and over had mean SBP of almost 170 mmHg, an adjusted difference of 11.8 mmHg higher than those under 60 years ($p<0.001$). Mean DBP was just over 95 mmHg in those younger than 60 years, and was an estimated 6.5 mmHg lower in those 75 years and over ($p<0.001$, from adjusted analysis). As a result of these changes in SBP and DBP with age being in opposite directions, mean PP was even more strikingly different between age-groups: 18.3 mmHg higher in those aged 75 years and over compared to those between 40 and 59 years ($p<0.001$, from adjusted analysis).

While SBP was similar for both sexes, females had lower DBP (88.5 versus 92.9 mmHg), an adjusted difference of 3.7 mmHg ($p<0.001$), and hence females had higher baseline PP (73.5 versus 68.9 mmHg).

Figure 15: Mean (SD) baseline blood pressure by age category and sex



Those of White ethnic origin had the highest SBP (mean: 162.4 mmHg) compared to those of Asian, Black, or mixed/other ethnicity ($p<0.001$, from adjusted analysis). Those of Asian ethnicity had the lowest SBP (mean: 155.5 mmHg), an adjusted difference of 3.9 mmHg compared to those of White Ethnicity. Those of Black or mixed/other ethnic background had mean SBP just over 158 mmHg. There was less of a difference in DBP between the ethnicities ($p=0.035$, from adjusted analysis), although those of Asian ethnicity also had a lower DBP than those of alternative ethnicity. From adjusted analysis the difference in DBP appeared to come only from Asian subjects having slightly lower DBP compared to all other ethnic backgrounds, an estimated mean DBP 1.8 mmHg less than White subjects.

There seemed to be a trend with lower SBP associated with increasing age at which subjects left full-time education ($p=0.057$), however, there was a slight increase in DBP ($p=0.002$) and hence a reduction in PP ($p<0.001$) with increased age at which subjects left education. Mean PP was 75.5 mmHg in the group that left full-time education by age 14 and was over 10 mmHg less in those who left at 19+ years at 65.3 mmHg, although the adjusted difference was a lot less: 2.9 mmHg less in those who left at 19+ years ($p<0.001$).

There was no evidence of a difference in SBP over the categories of BMI ($p=0.226$), but there was evidence of differing DBP between BMI categories ($p<0.001$), with DBP higher in those with higher BMIs. There was also evidence of lower PP in those with higher BMI ($p<0.001$, see Figure 16). Those who were diabetic at baseline had a slightly higher SBP compared to those who were non-diabetic ($p=0.009$) and notably lower DBP ($p<0.001$), hence a larger mean PP (3.5 mmHg larger adjusted difference, $p<0.001$).

SBP was associated with level of alcohol intake, with increased SBP in those with higher alcohol intake compared to those with lower intake. There was less evidence of an association with alcohol intake for DBP. There was no evidence for a

difference in blood pressure levels between smokers and non-smokers for any of the blood pressure components.

Those with higher total cholesterol at baseline also had higher SBP and DBP (p=0.025 and p=0.001, respectively). Those with total cholesterol of 8 mmol/L or higher had nearly 4 mmHg higher SBP and 2.5 mmHg higher DBP compared to those with total cholesterol below 4 mmol/L.

Overall, risk factors that showed the strongest association with PP were age, sex, BMI and diabetes. Age was clearly the dominant factor of PP variation, with SBP increasing and DBP decreasing with increasing age, there was a striking difference in PP across the ages.

Figure 16: Mean (SD) baseline blood pressure by BMI category and diabetes status

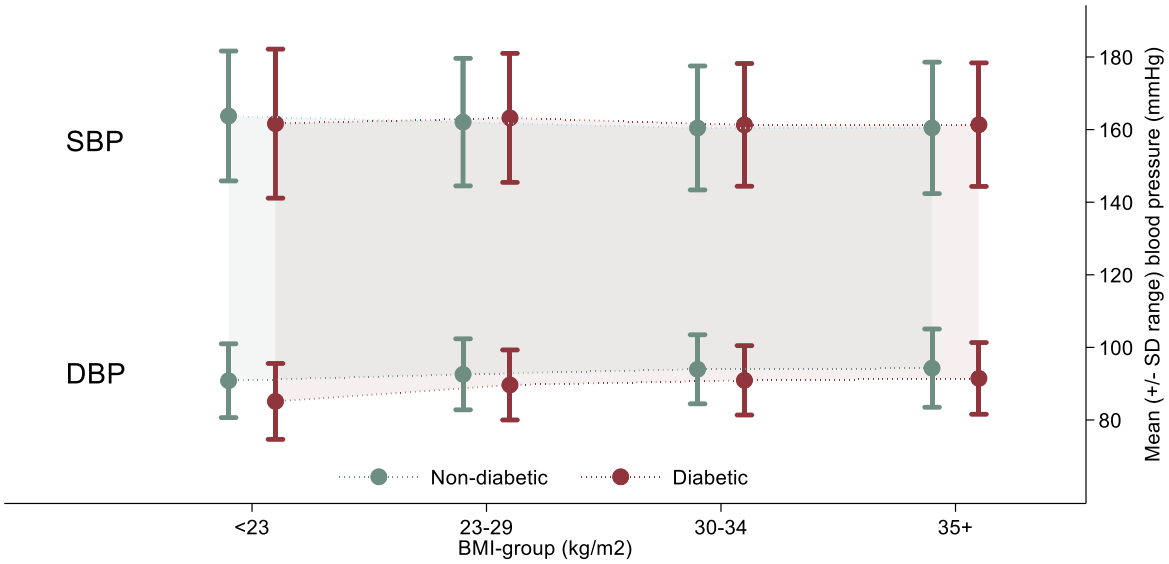


Table 13: Mean difference in systolic and diastolic blood pressure by categories of other baseline risk factors

			Systolic blood pressure			Diastolic blood pressure		
Risk factor	Risk factor group	No. subjects (N=8580)	Mean (SD)	Adjusted difference (95% CI)*	P-value**	Mean (SD)	Adjusted difference (95% CI)*	P-value**
Age (years)	40-59	2605	157.0 (15.8)	ref		95.1 (9.0)	ref	
	60-64	1856	160.3 (16.6)	3.3 (2.3, 4.3)		92.7 (9.5)	-2.0 (-2.6, -1.5)	
	65-69	1881	163.3 (17.3)	6.0 (4.9, 7.1)		91.2 (9.9)	-3.4 (-4.0, -2.8)	
	70-74	1437	166.7 (18.0)	9.2 (7.9, 10.4)		89.4 (10.2)	-5.2 (-5.8, -4.5)	
	75+	801	169.3 (19.5)	11.8 (10.3, 13.3)	p<0.001	87.8 (10.1)	-6.5 (-7.3, -5.7)	p<0.001
Sex	Female	1620	162.0 (18.8)	ref		88.5 (10.0)	ref	
	Male	6960	161.8 (17.2)	0.4 (-0.6, 1.4)	p=0.464	92.9 (9.7)	3.7 (3.2, 4.3)	p<0.001
Ethnic background	White	7701	162.4 (17.6)	ref		92.1 (10.0)	ref	
	Black	459	158.4 (17.3)	-2.2 (-3.9, -0.6)		92.4 (9.5)	0.0 (-0.9, 1.0)	
	Asian (east/south)	249	155.5 (16.2)	-3.9 (-6.1, -1.6)		91.5 (8.5)	-1.8 (-3.1, -0.6)	
	Mixed/other	171	158.1 (15.3)	-2.8 (-5.4, -0.2)	p<0.001	91.8 (10.3)	0.3 (-1.2, 1.7)	p=0.035
Age left full-time education (years) (5 missing)	12-14	2554	165.5 (18.5)	ref		90.0 (10.2)	ref	
	15-16	4256	160.6 (17.0)	-0.6 (-1.6, 0.4)		92.8 (9.6)	0.1 (-0.4, 0.7)	
	17-18	949	160.0 (16.6)	-1.7 (-3.1, -0.4)		93.1 (9.7)	0.8 (0.0, 1.5)	
	19+	816	159.3 (16.6)	-1.5 (-3.0, -0.1)	p=0.057	94.0 (9.7)	1.3 (0.5, 2.1)	p=0.002
BMI (kgm-2)	<25	579	163.4 (18.4)	ref		89.8 (10.4)	ref	
	25- <30	4986	162.4 (17.6)	-0.6 (-2.1, 0.9)		91.9 (9.8)	1.4 (0.6, 2.2)	
	30- <35	2208	160.7 (17.0)	-1.3 (-2.9, 0.3)		92.9 (9.6)	2.2 (1.3, 3.1)	
	≥35	807	160.9 (17.6)	-0.2 (-2.1, 1.6)	p=0.226	93.0 (10.5)	2.6 (1.6, 3.6)	p<0.001
Smoking status within 1 year	Non-smoker	6539	162.1 (17.5)	ref		92.0 (9.8)	ref	
	Current/ex	2041	161.0 (17.7)	0.0 (-0.9, 0.9)	p=0.950	92.5 (10.2)	-0.2 (-0.7, 0.3)	p=0.403
Average weekly units of alcohol consumed	No intake	2177	161.6 (18.2)	ref		90.6 (10.0)	ref	
	Intake 1 - <14	4054	161.7 (17.4)	0.1 (-0.8, 1.0)		92.0 (9.9)	0.3 (-0.2, 0.8)	
	Intake 14 - < 28	1448	162.2 (17.2)	1.4 (0.2, 2.6)		93.1 (9.6)	0.4 (-0.3, 1.1)	
	Intake 28+	901	162.8 (17.1)	2.8 (1.4, 4.2)	p<0.001	94.4 (9.8)	1.0 (0.2, 1.8)	p=0.094
Diabetes mellitus	No	6125	161.7 (17.5)	ref		92.9 (9.9)	ref	
	Yes	2455	162.3 (17.5)	1.1 (0.3, 1.9)	p=0.009	90.1 (9.8)	-2.5 (-2.9, -2.0)	p<0.001
Total cholesterol (mmol/L)	< 4	219	160.8 (16.0)	ref		90.8 (9.3)	ref	
	4 - <8	8025	161.8 (17.5)	1.4 (-0.9, 3.7)		92.1 (9.9)	0.6 (-0.7, 1.9)	
	≥8	336	164.3 (19.2)	3.7 (0.8, 6.7)	p=0.025	92.7 (11.1)	2.5 (0.8, 4.1)	p=0.001

* Adjusted for all other baseline risk factors shown in the table as well as baseline total cholesterol in multivariable linear regression models. Subjects with missing values for "age left education" were included in multivariable models, grouped into a missing category when missing.

** P-values from likelihood ratio tests.

Table 14: Mean difference in pulse pressure and mean arterial pressure by categories of other baseline risk factors

			Pulse pressure			Mean arterial pressure		
Risk factor	Risk factor group	No. subjects (N=8580)	Mean (SD)	Adjusted difference (95% CI)*	P-value**	Mean (SD)	Adjusted difference (95% CI)*	P-value**
Age (years)	40-59	2605	61.9 (13.8)	ref		115.8 (9.7)	ref	
	60-64	1856	67.6 (14.6)	5.3 (4.4, 6.2)		115.3 (10.2)	-0.2 (-0.9, 0.4)	
	65-69	1881	72.1 (15.1)	9.4 (8.5, 10.4)		115.2 (10.7)	-0.3 (-1.0, 0.4)	
	70-74	1437	77.3 (16.1)	14.3 (13.3, 15.4)		115.1 (10.9)	-0.4 (-1.1, 0.4)	
	75+	801	81.5 (17.7)	18.3 (17.0, 19.6)	p<0.001	115.0 (11.2)	-0.4 (-1.3, 0.5)	p=0.839
Sex	Female	1620	73.5 (17.5)	ref		113.0 (10.8)	ref	
	Male	6960	68.9 (16.0)	-3.4 (-4.2, -2.5)	p<0.001	115.9 (10.2)	2.6 (2.0, 3.2)	p<0.001
Ethnic background	White	7701	70.3 (16.5)	ref		115.5 (10.4)	ref	
	Black	459	65.9 (15.7)	-2.3 (-3.7, -0.8)		114.4 (10.3)	-0.7 (-1.7, 0.3)	
	Asian (east/south)	249	64.0 (15.7)	-2.1 (-4.0, -0.1)		112.8 (9.0)	-2.5 (-3.9, -1.1)	
	Mixed/other	171	66.3 (14.7)	-3.0 (-5.3, -0.7)	p<0.001	113.9 (10.0)	-0.8 (-2.3, 0.8)	p=0.002
Age left full-time education (years) (5 missing)	12-14	2554	75.5 (17.1)	ref		115.2 (10.9)	ref	
	15-16	4256	67.8 (15.6)	-0.7 (-1.6, 0.1)		115.4 (10.2)	-0.1 (-0.7, 0.5)	
	17-18	949	66.9 (15.2)	-2.5 (-3.7, -1.3)		115.4 (10.2)	-0.1 (-0.9, 0.8)	
	19+	816	65.3 (15.1)	-2.9 (-4.2, -1.6)	p<0.001	115.8 (10.2)	0.4 (-0.5, 1.3)	p=0.480
BMI (kgm-2)	<25	579	73.6 (17.1)	ref		114.3 (11.0)	ref	
	25- <30	4986	70.5 (16.6)	-2.0 (-3.3, -0.7)		115.4 (10.3)	0.7 (-0.2, 1.6)	
	30- <35	2208	67.8 (16.0)	-3.5 (-4.9, -2.1)		115.5 (10.1)	1.0 (0.1, 2.0)	
	≥35	807	67.9 (15.5)	-2.8 (-4.5, -1.2)	p<0.001	115.6 (11.1)	1.6 (0.5, 2.8)	p=0.023
Smoking status within 1 year	Non-smoker	6539	70.2 (16.3)	ref		115.4 (10.3)	ref	
	Current/ex	2041	68.5 (16.7)	0.2 (-0.5, 1.0)	p=0.548	115.3 (10.6)	-0.1 (-0.7, 0.4)	p=0.636
Average weekly units of alcohol consumed	No intake	2177	71.0 (17.3)	ref		114.3 (10.5)	ref	
	Intake 1 - <14	4054	69.7 (16.3)	-0.2 (-1.0, 0.6)		115.2 (10.3)	0.2 (-0.3, 0.8)	
	Intake 14 - < 28	1448	69.1 (15.7)	1.0 (-0.0, 2.0)		116.1 (10.2)	0.7 (0.0, 1.5)	
	Intake 28+	901	68.4 (15.5)	1.8 (0.6, 3.0)	p<0.001	117.2 (10.4)	1.6 (0.7, 2.4)	p=0.001
Diabetes mellitus	No	6125	68.8 (16.3)	ref		115.8 (10.4)	ref	
	Yes	2455	72.2 (16.5)	3.6 (2.8, 4.3)	p<0.001	114.2 (10.3)	-1.3 (-1.8, -0.8)	p<0.001
Total cholesterol (mmol/L)	< 4	219	70.0 (14.7)	ref		114.1 (9.7)	ref	
	4- <8	8025	69.7 (16.5)	0.8 (-1.2, 2.8)		115.3 (10.3)	0.9 (-0.5, 2.3)	
	≥8	336	71.6 (16.9)	1.3 (-1.3, 3.8)	p=0.619	116.6 (11.9)	2.9 (1.1, 4.7)	p=0.001

* Adjusted for all other baseline risk factors shown in the table as well as baseline total cholesterol in multivariable linear regression models. Subjects with missing values for "age left education" were included in multivariable models, grouped into a missing category when missing.

** P-values from likelihood ratio tests.

3.4.2 Relationships between baseline blood pressure measures

Patients with higher SBP at baseline tended to have higher DBP (overall correlation coefficient r=0.391, p<0.001). In the youngest age group, those between 40 and 49 years of age, the correlation between SBP and DBP was the strongest (r=0.609), and was weaker in those over 50.

PP was highly positively correlated with SBP (overall r=0.831, p<0.001), which was fairly consistent in magnitude over all age groups. PP had a slight negative correlation with DBP at baseline (overall r=-0.186, p<0.001). In subjects between 40 and 49 years of age there was no evidence of a correlation between PP and DBP at all, but in those 50 years and older the slight negative correlation was observed. PP was positively correlated with MAP, but to a much lesser degree than the correlation between SBP and PP, which is expected given its formation and how PP correlates with both DBP and SBP (see Table 15).

Table 15: Pair-wise correlations between blood pressure component measurements collected at baseline, by subgroups of age

	Correlation coefficient (p-value) between pairs of blood pressure measurements			
Age group (years)	SBP & DBP	SBP & PP	PP & DBP	PP & MAP
40 - <50 (n=443)	0.609 (p<0.001)	0.820 (p<0.001)	0.044 (p=0.355)	0.452 (p<0.001)
50 - <60 (n=2162)	0.478 (p<0.001)	0.824 (p<0.001)	-0.103 (p<0.001)	0.384 (p<0.001)
60 - <70 (n=3737)	0.482 (p<0.001)	0.823 (p<0.001)	-0.101 (p<0.001)	0.384 (p<0.001)
70 – 80 (n=2238)	0.440 (p<0.001)	0.840 (p<0.001)	-0.118 (p<0.001)	0.399 (p<0.001)

3.4.3 Relationship between single baseline blood pressure components with mortality

When modelled as single components of blood pressure, there was strong evidence that each component was associated with all-cause mortality, using this long-term ASCOT legacy data with median 17.4-years follow-up. Figure 17 presents plots of relative hazard comparing quintiles of the data for each blood pressure component. HRs for both SBP and PP are in relation to the lowest level quintile group, and DBP and MAP have their reference group as the middle (3rd) quintile group.

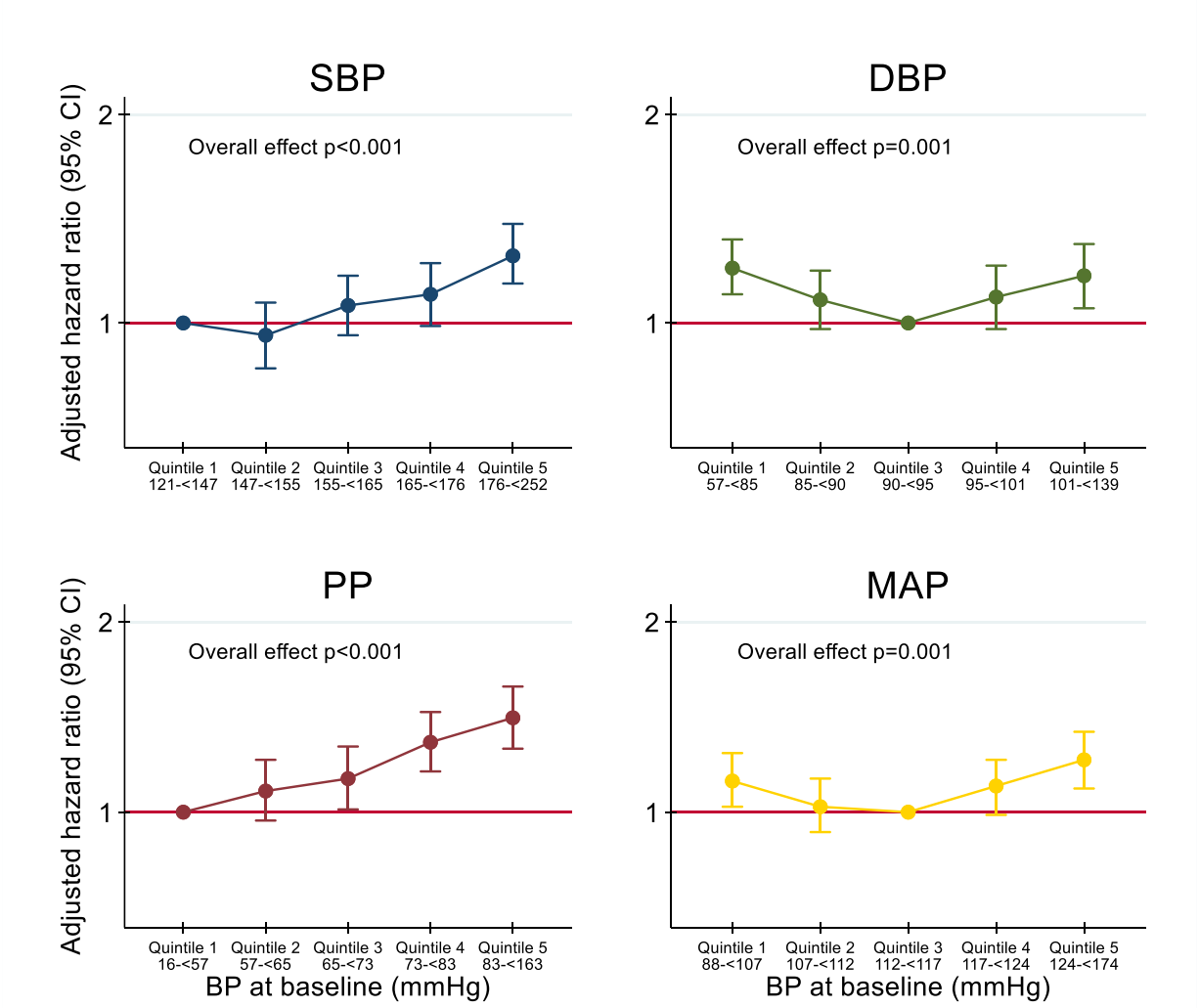
The relationship between SBP and all-cause mortality appeared to hint at a slight J-shape type relationship, with little difference in risk between the first 3 quintiles, with increased risk emerging in the highest 2 quintiles. The hazard of death was an estimated 25% higher (95% CI: 14%-39%) in the top quintile of SBP, those with SBP over 175 mmHg compared to those with SBP less than 147 mmHg.

While the highest quintile of SBP had the highest proportion of deaths (59.39%), for DBP it was the lowest quintile (those with less than 85 mmHg) that had the highest proportion of deaths (60.50%). For DBP the adjusted HRs compared to the middle quintile group (those with 90 to less than 95 mmHg) showed increased mortality hazard for both the lowest quintile and the highest, HRs of 1.20 (95% CI: 1.10-1.32) and 1.17 (95% CI: 1.05-1.30), respectively, suggesting this U-shape association.

The relationship between PP and mortality risk was rather more monotonically linear compared to that for SBP. There appeared a steady increase in mortality risk with increasing PP. There was also a notably larger range of proportions of deaths between the most extreme quintiles of PP compared to any other component. The proportion of deaths over follow-up ranged from 30.60% in those with PP lower than 57 at baseline (the lowest quintile group) to almost 65% in those with a baseline PP of 83 or higher (the highest quintile group). From adjusted analysis, those in the highest quintile had an estimated 41% increased hazard of death (95% CI: 26%-58%) compared to the lowest quintile group of PP.

The relationship between MAP and all-cause mortality appeared to be somewhere between that for SBP and DBP, showing slightly more curvature than SBP, but not as much as with DBP. Being a mixture of both DBP and SBP, MAP showed a similar J-shaped relationship with risk to DBP, but, diluted by the SBP, there was only a slightly raised risk associated with low MAP, but a more markedly raised risk with higher MAP levels. MAP showed the least variation in proportion of deaths across its quintile categories compared to other components.

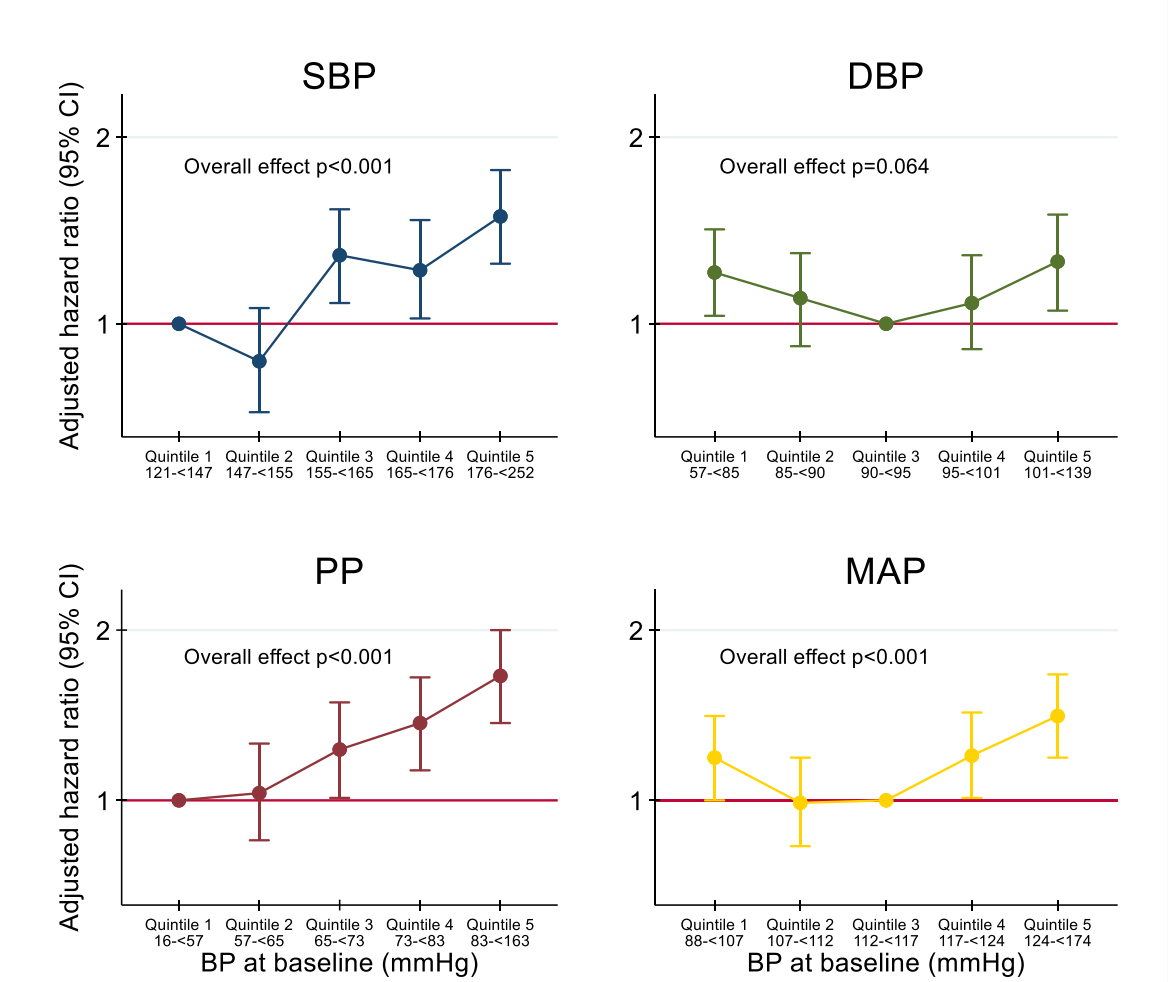
Figure 17: Adjusted relative hazard of all-cause mortality by quintiles of baseline blood pressure components



Note, p-values are from global likelihood ratio tests across quintile groups. Estimates are from models adjusted for pre-specified baseline risk factors.

For CV-related mortality, relationships between components of blood pressure with risk were a similar shape as for all-cause mortality, but as expected were more pronounced (see Figure 18). The proportion of subjects dying from CV-related causes ranged from just over 12% to over 22% comparing the lowest SBP quintile group to the highest, respectively, with an estimated adjusted HR of 1.49 (95% CI: 1.25-1.77) comparing highest to lowest quintile groups. As with all-cause death, PP quintiles showed the largest difference in the proportion of deaths from CV-related causes, with just over 10% in the lowest quintile compared to close to 25% of subjects in the highest quintile, an estimated adjusted HR of 1.66 (95% CI: 1.37-2.00) comparing the highest to the lowest quintiles. Although DBP showed a similar trend with its association with CV-related mortality as with all-cause mortality, there was only weak statistical evidence for an overall association between DBP and CV-related mortality ($p=0.064$, from a likelihood ratio test).

Figure 18: Adjusted relative hazard of CV-related mortality by quintiles of baseline blood pressure components

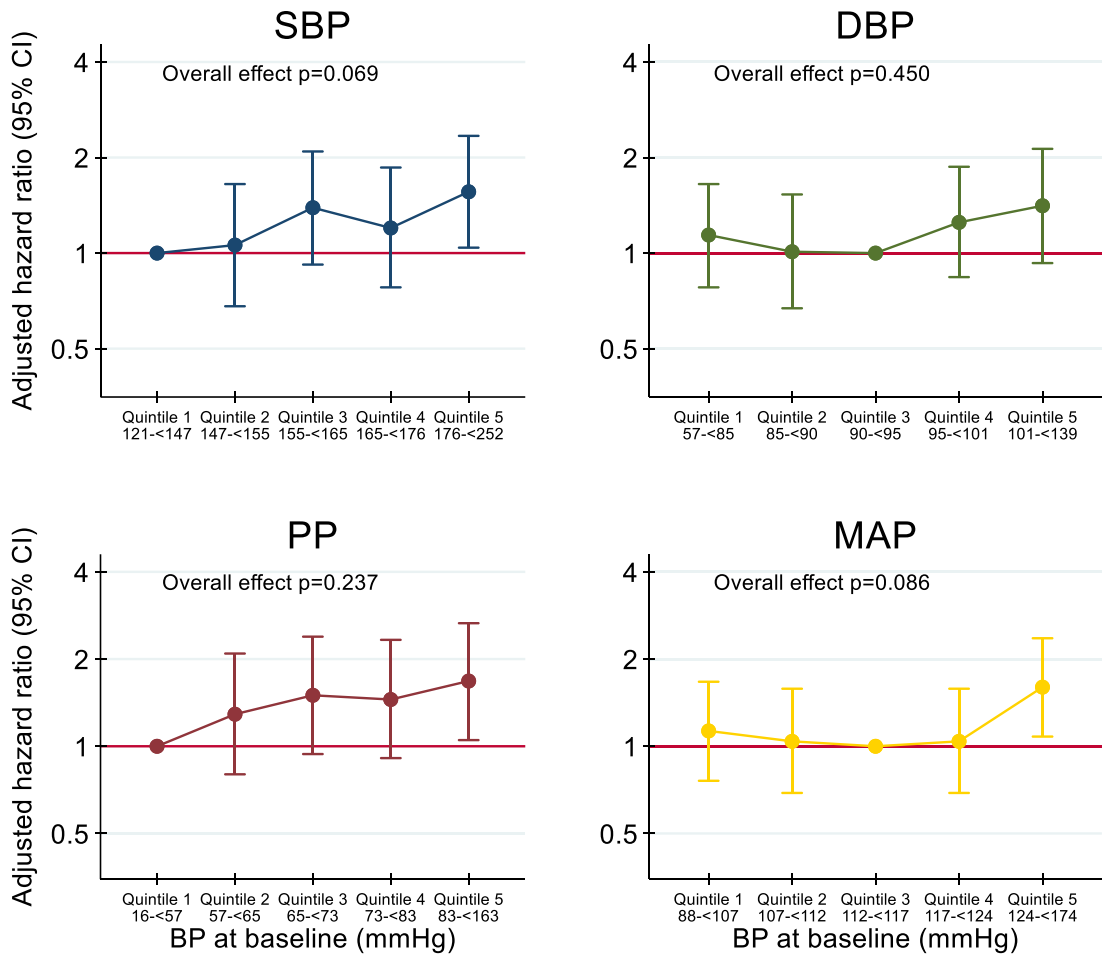


Note, p-values are from global likelihood ratio tests across quintile groups. Estimates are from models adjusted for pre-specified baseline risk factors.

Although patterns of relative hazard of stroke-related mortality across quintile groups of blood pressure components appeared to follow a similar pattern to that with CV-related mortality, there was weak evidence of an association for each component of blood pressure (see Figure 19). This is likely a result of the relatively low number of stroke deaths, a total of 263. While estimated adjusted HRs between quintile groups were not too dissimilar to those estimated for CV-related mortality,

overall statistical evidence for associations between each blood pressure component and stroke-related mortality was lacking.

Figure 19: Adjusted relative hazard of stroke-related mortality by quintiles of baseline blood pressure components



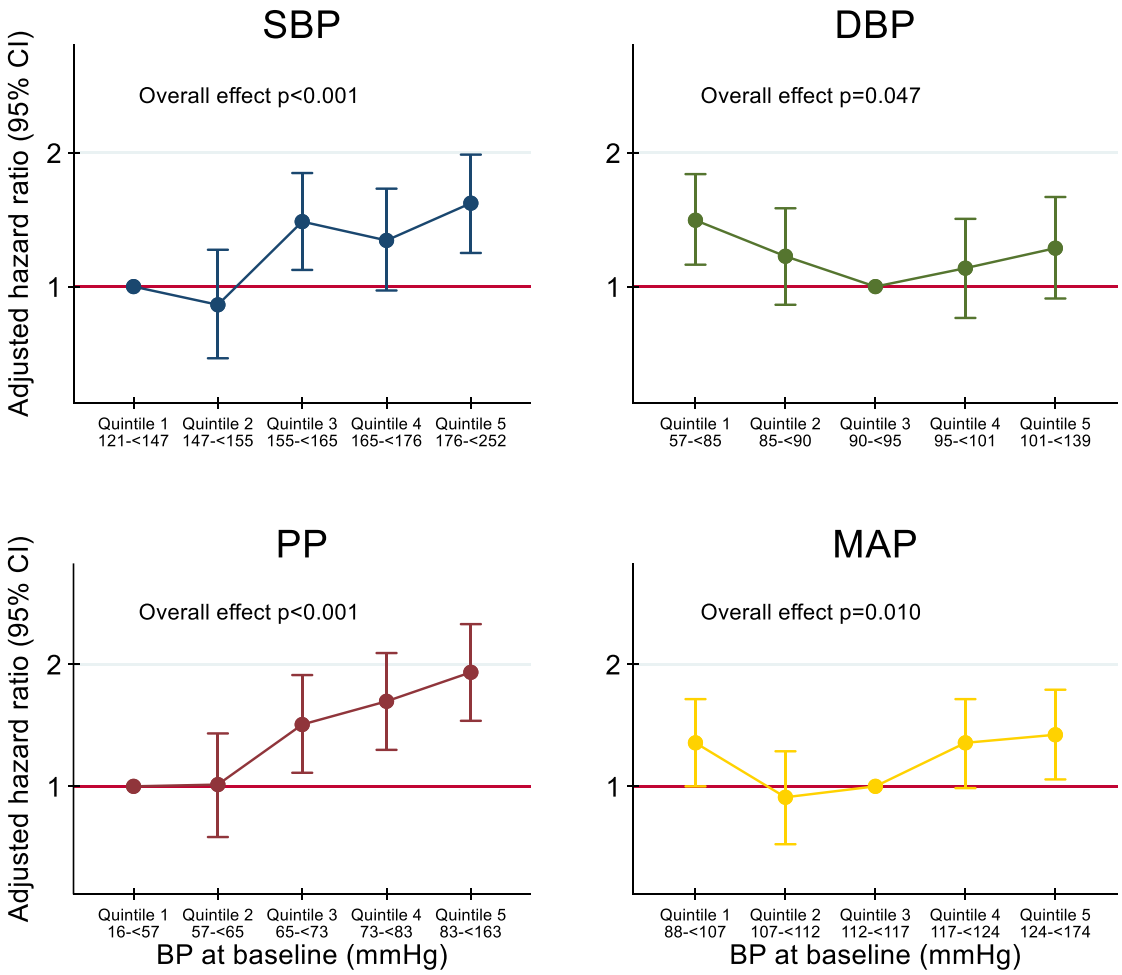
Note, p-values are from global likelihood ratio tests across quintile groups. Estimates are from models adjusted for pre-specified baseline risk factors.

There was strong evidence that both SBP and PP were associated with CHD-related mortality ($p<0.001$ and $p<0.001$, respectively, see Figure 20). The proportion of deaths from CHD ranged from under 5% in the lowest PP quintile group to over 11%

in the highest quintile group, an estimated adjusted HR of 1.91 (95% CI: 1.45-2.51). DBP and MAP showed somewhat weak evidence of a relationship with CHD-related mortality (p=0.047 and p=0.010, respectively, see Figure 20).

The number and percentage of deaths across quintile groups for each component of blood pressure are presented in Table 16, along with adjusted HR estimates from single-component models.

Figure 20: Adjusted relative hazard of CHD-related mortality by quintiles of baseline blood pressure components



Note, p-values are from global likelihood ratio tests across quintile groups. Estimates are from models adjusted for pre-specified baseline risk factors.

Table 16: Adjusted HRs (95% CI) for baseline blood pressure component quintile groups from single component models

				All deaths			CV deaths			CHD deaths			Stroke deaths		
	Quintile group	BP group range (mmHg)	Patients, N	Events, n (%)	Adjusted HR (95% CI)*	P-value	Events, n (%)	Adjusted HR (95% CI)*	P-value	Events, n (%)	Adjusted HR (95% CI)*	P-value	Events, n (%)	Adjusted HR (95% CI)*	P-value
SBP															
	1 (ref)	121-<147	1789	680 (38.01)	-	p<0.001	216 (12.07)	-	p<0.001	101 (5.65)	-	p<0.001	37 (2.07)	-	p=0.069
	2	147-<155	1662	693 (41.70)	0.96 (0.86-1.07)		201 (12.09)	0.87 (0.72-1.06)		96 (5.78)	0.91 (0.69-1.21)		42 (2.53)	1.06 (0.68-1.65)	
	3	155-<165	1874	879 (46.91)	1.06 (0.96-1.17)		336 (17.93)	1.29 (1.08-1.53)		167 (8.91)	1.40 (1.09-1.80)		63 (3.36)	1.39 (0.92-2.09)	
	4	165-<176	1541	770 (49.97)	1.10 (0.99-1.22)		269 (17.46)	1.22 (1.02-1.47)		126 (8.18)	1.27 (0.98-1.66)		47 (3.05)	1.20 (0.78-1.86)	
	5	176-<252	1714	1018 (59.39)	1.25 (1.14-1.39)		380 (22.17)	1.49 (1.25-1.77)		173 (10.09)	1.54 (1.19-1.98)		74 (4.32)	1.56 (1.04-2.34)	
DBP															
	1	57-<85	1929	1167 (60.50)	1.20 (1.10-1.32)		405 (21.00)	1.21 (1.03-1.42)		200 (10.37)	1.41 (1.12-1.79)		78 (4.04)	1.14 (0.78-1.65)	
	2	85-<90	1554	764 (49.16)	1.08 (0.98-1.19)		266 (17.12)	1.10 (0.92-1.30)		126 (8.11)	1.17 (0.91-1.50)		46 (2.96)	1.01 (0.67-1.53)	
	3 (ref)	90-<95	1913	765 (39.99)	-	p=0.001	260 (13.59)	-	p=0.064	119 (6.22)	-	p=0.047	46 (2.40)	-	p=0.450
	4	95-<101	1653	722 (43.68)	1.09 (0.98-1.21)		243 (14.70)	1.08 (0.91-1.29)		114 (6.90)	1.10 (0.85-1.42)		49 (2.96)	1.25 (0.84-1.87)	
	5	101-<139	1531	622 (40.63)	1.17 (1.05-1.30)		228 (14.89)	1.26 (1.05-1.50)		104 (6.79)	1.22 (0.94-1.59)		44 (2.87)	1.41 (0.93-2.13)	
PP															
	1 (ref)	16-<57	1791	548 (30.60)	-	p<0.001	180 (10.05)	-	p<0.001	84 (4.69)	-	p<0.001	27 (1.51)	-	p=0.237
	2	57-<65	1773	703 (39.65)	1.08 (0.97-1.21)		220 (12.41)	1.03 (0.85-1.26)		96 (5.41)	1.01 (0.75-1.35)		43 (2.43)	1.29 (0.80-2.09)	
	3	65-<73	1686	773 (45.85)	1.13 (1.01-1.27)		272 (16.13)	1.23 (1.01-1.49)		135 (8.01)	1.42 (1.08-1.88)		56 (3.32)	1.50 (0.94-2.39)	
	4	73-<83	1651	925 (56.03)	1.29 (1.16-1.44)		316 (19.14)	1.37 (1.13-1.65)		156 (9.45)	1.62 (1.23-2.13)		59 (3.57)	1.45 (0.91-2.33)	
	5	83-<163	1679	1091 (64.98)	1.41 (1.26-1.58)		414 (24.66)	1.66 (1.37-2.00)		192 (11.44)	1.91 (1.45-2.51)		78 (4.65)	1.68 (1.05-2.66)	
MAP															
	1	88-<107	1822	936 (51.37)	1.12 (1.02-1.24)		327 (17.95)	1.19 (1.00-1.41)		161 (8.84)	1.28 (1.00-1.64)		62 (3.40)	1.13 (0.76-1.67)	
	2	107-<112	1777	784 (44.12)	1.02 (0.93-1.13)		250 (14.07)	0.99 (0.83-1.19)		112 (6.30)	0.94 (0.72-1.22)		48 (2.70)	1.04 (0.69-1.58)	
	3 (ref)	112-<117	1601	702 (43.85)	-	p=0.001	229 (14.30)	-	p<0.001	108 (6.75)	-	p=0.010	42 (2.62)	-	p=0.086
	4	117-<124	1767	807 (45.67)	1.10 (0.99-1.21)		287 (16.24)	1.20 (1.01-1.43)		144 (8.15)	1.28 (0.99-1.64)		46 (2.60)	1.04 (0.69-1.58)	
	5	124-<175	1613	811 (50.28)	1.21 (1.09-1.34)		309 (19.16)	1.41 (1.19-1.67)		138 (8.56)	1.34 (1.04-1.73)		65 (4.03)	1.60 (1.08-2.36)	

* adjusted for pre-specified baseline risk factors: age, sex, ethnicity, age subject left full-time education, body mass index, total cholesterol, presence of type II diabetes, and smoking history.

3.4.4 Relationship between combinations of baseline blood pressure components with CV-related mortality

Two models were fitted, each containing a pair of blood pressure components, the first SBP and DBP, and the second PP and MAP, with both models also adjusted for pre-specified baseline risk factors. From the model containing SBP and DBP together, the highest quintile group of SBP (176 mmHg and over) and lowest quintile group of DBP (<85 mmHg) were associated with increased CV-related mortality risk. From the model with PP and MAP, the highest 3 quintile groups of PP (65 mmHg and over) were associated with increased CV-related mortality, and weaker evidence for increased risk associated with both low and high MAP.

There was strong evidence that both SBP and DBP were independently associated with CV-related mortality, from the model containing both components ($p<0.001$ and $p=0.004$, respectively, see Figure 21).

When SBP was modelled together with DBP, the relationship between SBP and CV-related mortality was more extreme compared to the singular component model. In other words, at a fixed level of DBP the increase in CV-related mortality risk associated with increasing SBP, which implies increasing PP, was higher in magnitude compared to when SBP was modelled alone. Compared to the lowest quintile of SBP, the hazard ratio for the highest quintile group of SBP increased from

1.49 (95% CI: 1.25, 1.77, p<0.001) when modelled without DBP adjustment to 1.64 (95% CI: 1.36, 1.98, p<0.001) with DBP adjustment. From the same dual-component model, once adjusted for SBP, the increased risk associated with high DBP was lessened compared to when unadjusted for SBP, while the relative risk associated with low DBP was more marked. Relative to the middle quintile, the HR in the highest quintile group of DBP reduced from 1.26 (95% CI: 1.05, 1.50, p=0.012) when unadjusted for SBP to 1.05 (95% CI: 0.87, 1.26, p=0.617 when adjusted. Conversely, the HR in the lowest quintile group of DBP increased from 1.21 (95% CI: 1.03, 1.42, p=0.021) to 1.33 (95% CI: 1.13, 1.56, p=0.001). It seemed that, once adjusted for SBP the increased risk associated with higher DBP levels was captured by SBP, and so higher DBP levels were no longer very predictive of increased risk, while lower levels of DBP were more strongly associated with increased risk. Once adjusted for SBP, lower DBP at baseline could be capturing both increased risk associated with diastolic hypotension, as well as increased risk associated with a wide PP, particularly in this context where a low DBP implies a high SBP at baseline due to the trial inclusion criteria.

There was strong evidence that PP was independently associated with CV-related mortality, from a model containing both PP and MAP (p<0.001), but the estimated HR comparing the highest quintile to the lowest slightly reduced slightly from 1.66

(95% CI: 1.37, 2.00, p<0.001) when unadjusted for MAP to 1.58 (95% CI: 1.29, 1.92, p<0.001) once adjusted (see Figure 21).

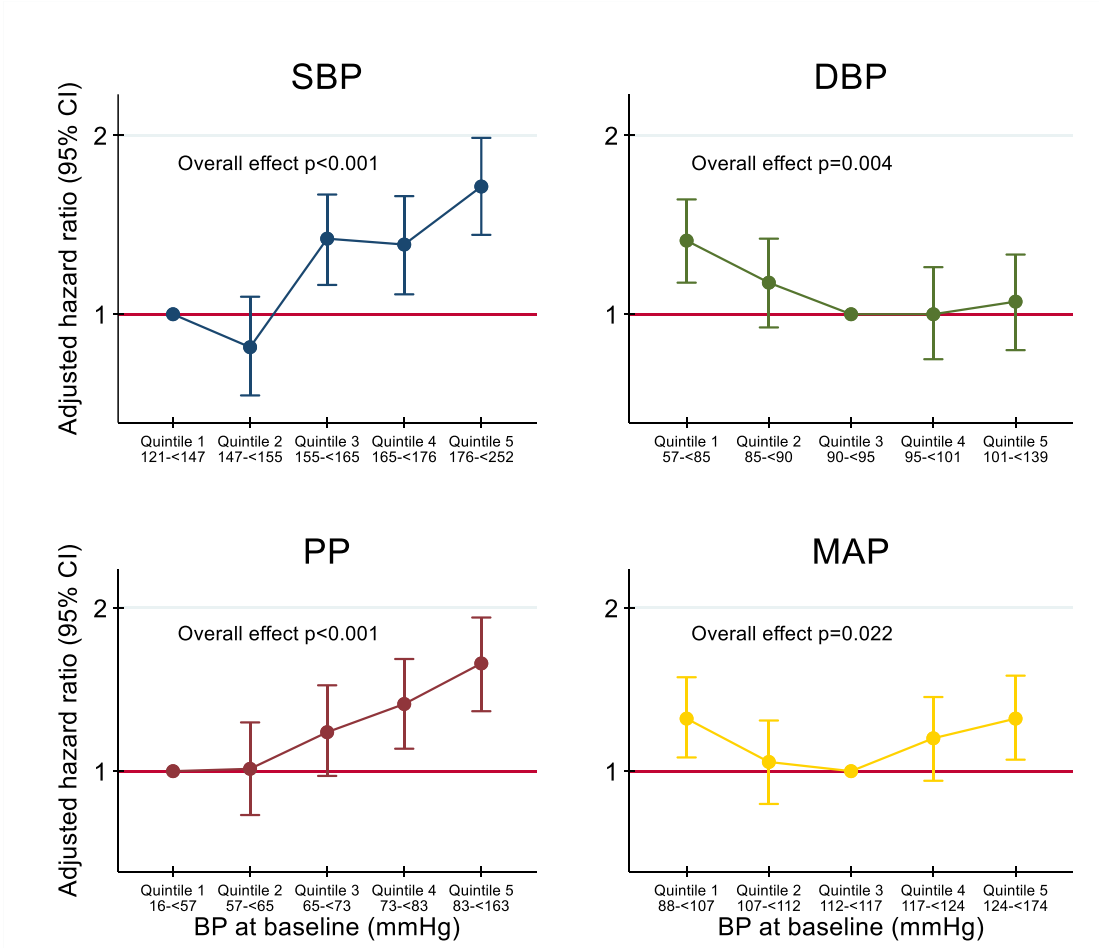
Once adjusted for PP, the overall relationship between MAP and CV-related mortality had diminished to leave only borderline evidence (p=0.022) of an overall association. Relative to the middle quintile, the HR in the highest quintile group of MAP reduced from 1.41 (95% CI: 1.19, 1.67, p<0.001) when unadjusted for PP to 1.25 (95% CI: 1.06, 1.23, p=0.010) when adjusted, however the HR in the lowest quintile group of MAP slightly increased after adjustment for PP from 1.19 (95% CI: 1.00, 1.41, p=0.049) to 1.25 (95% CI: 1.05, 1.50, p=0.012), after adjustment.

PP might be partially capturing increased risk as a result of elevated blood pressure levels, as well as that associated with wider PP. However, it is likely PP is not capturing it all, and MAP was still giving a hint of the increased risk associated with low blood pressure levels, probably coming specifically from low DBP levels.

Estimates from paired-component models are presented in Table 17.Table 16: Adjusted HRs (95% CI) for baseline blood pressure component quintile groups

Figure 21: Adjusted relative hazard plots of CV-related mortality by blood pressure quintile groups when adjusted for a second blood pressure component

Note: SBP and DBP are modelled together, and PP and MAP are modelled together.



Note, p-values are from global likelihood ratio tests across quintile groups. Estimates are from models adjusted for pre-specified baseline risk factors.

Table 17: Adjusted HRs (95% CI) for baseline blood pressure component quintile groups from paired component models

				All deaths			CV deaths			CHD deaths			Stroke deaths		
	Quintile group	BP group range (mmHg)	Patients, N	Events, n (%)	Adjusted HR (95% CI)*	P-value	Events, n (%)	Adjusted HR (95% CI)*	P-value	Events, n (%)	Adjusted HR (95% CI)*	P-value	Events, n (%)	Adjusted HR (95% CI)*	P-value
SBP															
	1 (ref)	121-<147	1789	680 (38.01)	-	p<0.001	216 (12.07)	-	p<0.001	101 (5.65)	-	p<0.001	37 (2.07)	-	p=0.252
	2	147-<155	1662	693 (41.70)	0.97 (0.87-1.07)		201 (12.09)	0.88 (0.73-1.07)		96 (5.78)	0.93 (0.71-1.24)		42 (2.53)	1.05 (0.67-1.64)	
	3	155-<165	1874	879 (46.91)	1.09 (0.99-1.21)		336 (17.93)	1.34 (1.12-1.59)		167 (8.91)	1.50 (1.17-1.93)		63 (3.36)	1.38 (0.92-2.09)	
	4	165-<176	1541	770 (49.97)	1.16 (1.04-1.29)		269 (17.46)	1.31 (1.08-1.58)		126 (8.18)	1.43 (1.09-1.88)		47 (3.05)	1.19 (0.76-1.86)	
	5	176-<252	1714	1018 (59.39)	1.36 (1.21-1.51)		380 (22.17)	1.64 (1.36-1.98)		173 (10.09)	1.86 (1.41-2.44)		74 (4.32)	1.52 (0.98-2.36)	
DBP															
	1	57-<85	1929	1167 (60.50)	1.27 (1.16-1.40)		405 (21.00)	1.33 (1.13-1.56)		200 (10.37)	1.58 (1.24-2.00)		78 (4.04)	1.21 (0.83-1.77)	
	2	85-<90	1554	764 (49.16)	1.10 (1.00-1.22)		266 (17.12)	1.13 (0.95-1.34)		126 (8.11)	1.21 (0.94-1.55)		46 (2.96)	1.03 (0.68-1.56)	
	3 (ref)	90-<95	1913	765 (39.99)	-	p<0.001	260 (13.59)	-	p=0.004	119 (6.22)	-	p<0.001	46 (2.40)	-	p=0.743
	4	95-<101	1653	722 (43.68)	1.04 (0.94-1.15)		243 (14.70)	1.00 (0.84-1.20)		114 (6.90)	1.01 (0.78-1.31)		49 (2.96)	1.19 (0.79-1.78)	
	5	101-<139	1531	622 (40.63)	1.04 (0.93-1.17)		228 (14.89)	1.05 (0.87-1.26)		104 (6.79)	0.99 (0.75-1.30)		44 (2.87)	1.25 (0.81-1.92)	
PP															
	1 (ref)	16-<57	1791	548 (30.60)	-	p<0.001	180 (10.05)	-	p<0.001	84 (4.69)	-	p<0.001	27 (1.51)	-	p=0.670
	2	57-<65	1773	703 (39.65)	1.07 (0.95-1.20)		220 (12.41)	1.01 (0.83-1.23)		96 (5.41)	0.98 (0.73-1.31)		43 (2.43)	1.27 (0.78-2.06)	
	3	65-<73	1686	773 (45.85)	1.12 (1.00-1.25)		272 (16.13)	1.18 (0.98-1.44)		135 (8.01)	1.37 (1.03-1.81)		56 (3.32)	1.46 (0.91-2.33)	
	4	73-<83	1651	925 (56.03)	1.28 (1.15-1.43)		316 (19.14)	1.33 (1.10-1.61)		156 (9.45)	1.60 (1.21-2.12)		59 (3.57)	1.37 (0.85-2.21)	
	5	83-<163	1679	1091 (64.98)	1.40 (1.25-1.58)		414 (24.66)	1.58 (1.29-1.92)		192 (11.44)	1.90 (1.42-2.55)		78 (4.65)	1.48 (0.91-2.40)	
MAP															
	1	88-<107	1822	936 (51.37)	1.16 (1.05-1.28)		327 (17.95)	1.25 (1.06-1.49)		161 (8.84)	1.38 (1.08-1.77)		62 (3.40)	1.13 (0.76-1.69)	
	2	107-<112	1777	784 (44.12)	1.06 (0.95-1.17)		250 (14.07)	1.04 (0.87-1.24)		112 (6.30)	1.00 (0.77-1.31)		48 (2.70)	1.07 (0.71-1.63)	
	3 (ref)	112-<117	1601	702 (43.85)	-	p=0.036	229 (14.30)	-	p=0.022	108 (6.75)	-	p=0.049	42 (2.62)	-	p=0.213
	4	117-<124	1767	807 (45.67)	1.06 (0.96-1.18)		287 (16.24)	1.15 (0.96-1.37)		144 (8.15)	1.20 (0.93-1.54)		46 (2.60)	1.01 (0.66-1.54)	
	5	124-<175	1613	811 (50.28)	1.11 (1.00-1.23)		309 (19.16)	1.25 (1.05-1.50)		138 (8.56)	1.14 (0.88-1.48)		65 (4.03)	1.51 (1.01-2.26)	

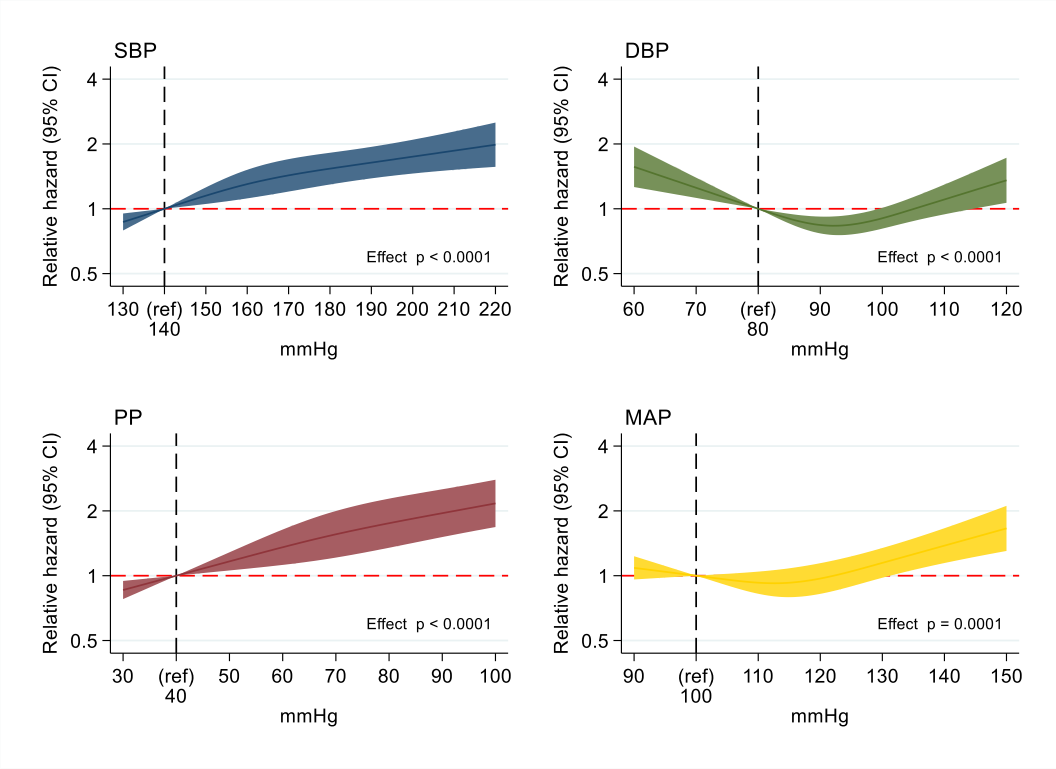
* adjusted for pre-specified known baseline risk factors: age, sex, ethnicity, age subject left full-time education, body mass index, total cholesterol, presence of type II diabetes, and smoking history.

Note, estimates for SBP and DBP are from a model containing both components, and estimates for PP and MAP are from a model containing both components.

3.4.5 Relationship between baseline blood pressure components with CV-related mortality with components modelled as continuous variables

Components of blood pressure were modelled continuously, each with restricted cubic spline transformations with 3 knots (at the 10th, 50th, and 90th percentiles) in order to allow curvature in their association with CV-related mortality. For each of the four blood pressure components, there was strong evidence of an association with risk in models containing only single components ($p<0.001$ for each). For DBP and MAP, there was evidence of a non-monotonic relationship with risk ($p<0.001$ & $p=0.005$, respectively), but no evidence against linearity for SBP or PP. Figure 22 presents plots of relative hazard, showing the relationships between each component of blood pressure with CV-related mortality. The relative hazards and 95% CIs for each blood pressure component shown on the plots are in relation to the reference levels indicated on each plot.

Figure 22: Adjusted relative hazard plots of CV-related mortality from models containing single components of baseline blood pressure



Note, for each blood pressure component, HRs and 95% CIs are shown in relation to reference level, labelled as "(ref)" on the plots. Blood pressure components are modelled with restricted cubic spline transformations. P-values are from global likelihood ratio tests comparing models with and without the blood pressure component present.

3.4.6 Relationship between baseline blood pressure components with CV-related mortality in subgroups of age

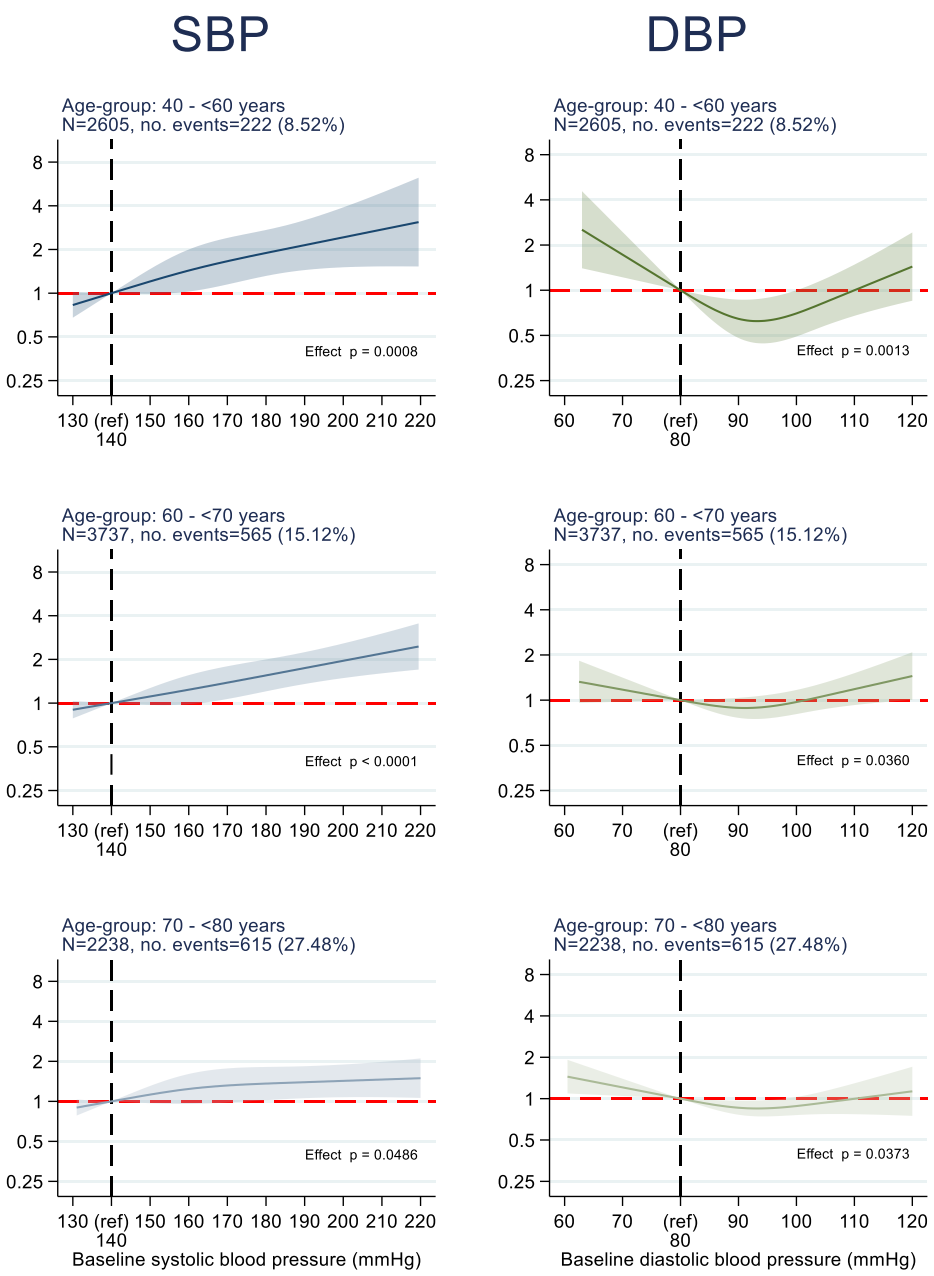
Relationships between components of blood pressure with CV-related mortality were stronger in younger subjects, and attenuated with increasing age for all components of blood pressure (see Figure 23 & Figure 24).

There was still some evidence for a relationship between both SBP and DBP with risk in the oldest age-group, those 70 years and older (p=0.049 & p=0.037, respectively, from global likelihood ratio tests).

In those 70 years and over, the increased risk associated with lower levels of DBP appeared more extreme than the increased risk associated with higher levels of DBP (see Figure 23).

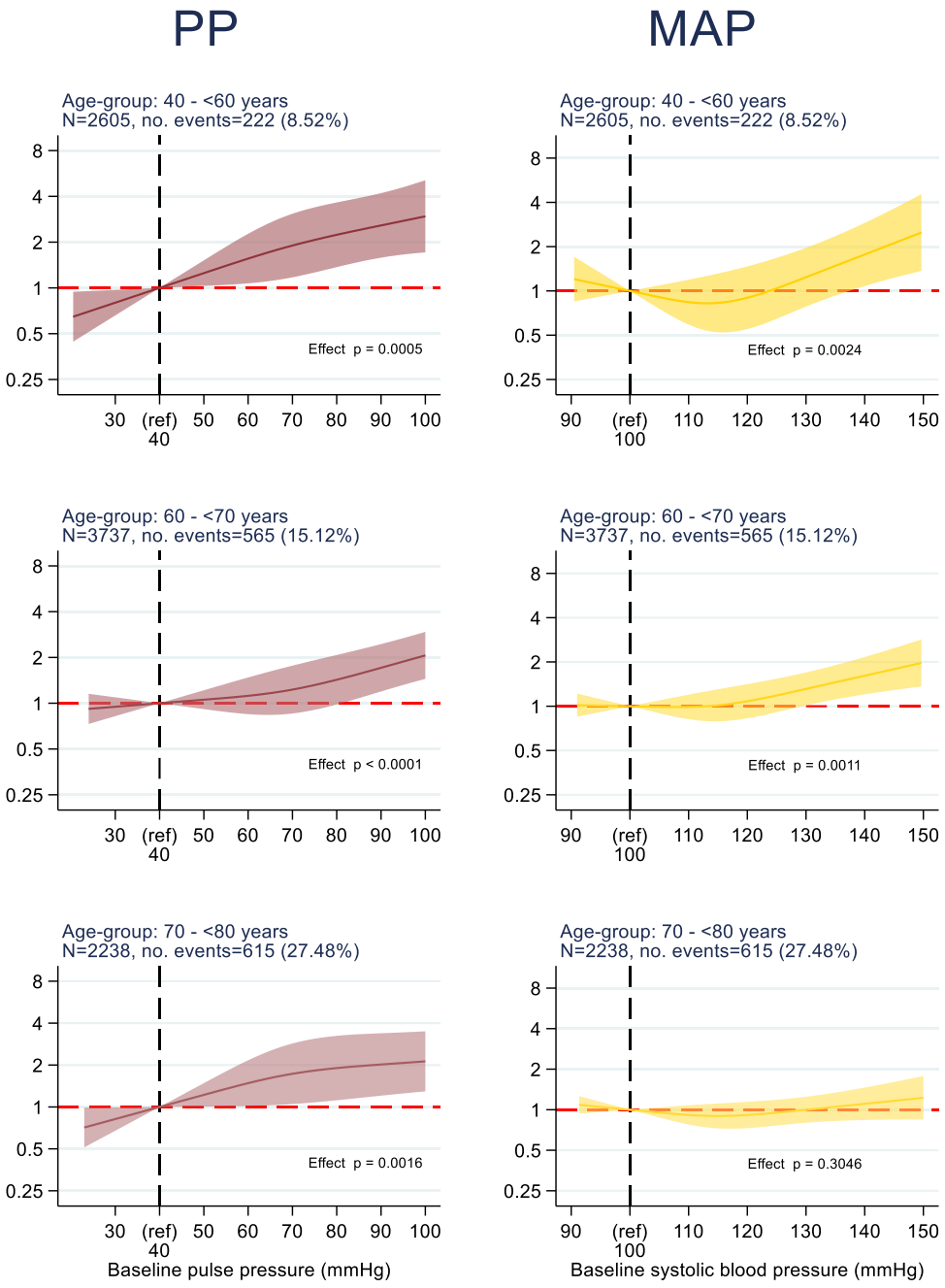
There was still strong evidence of a relationship between PP and CV-related mortality at all ages including those 70 years and over (p=0.002). While for MAP, there was very little evidence of a relationship with risk in those 70-80 years (p=0.305, see Figure 24).

Figure 23: Adjusted relative hazard plots of CV-related mortality from models containing SBP and DBP as single components of baseline blood pressure over 3 age categories



Note, for each blood pressure component, HRs and 95% CIs are shown in relation to reference level, labelled as "(ref)" on the plots. Blood pressure components are modelled with restricted cubic spline transformations, with interactions with age group. P-values are from global likelihood ratio tests comparing models with and without the blood pressure component present.

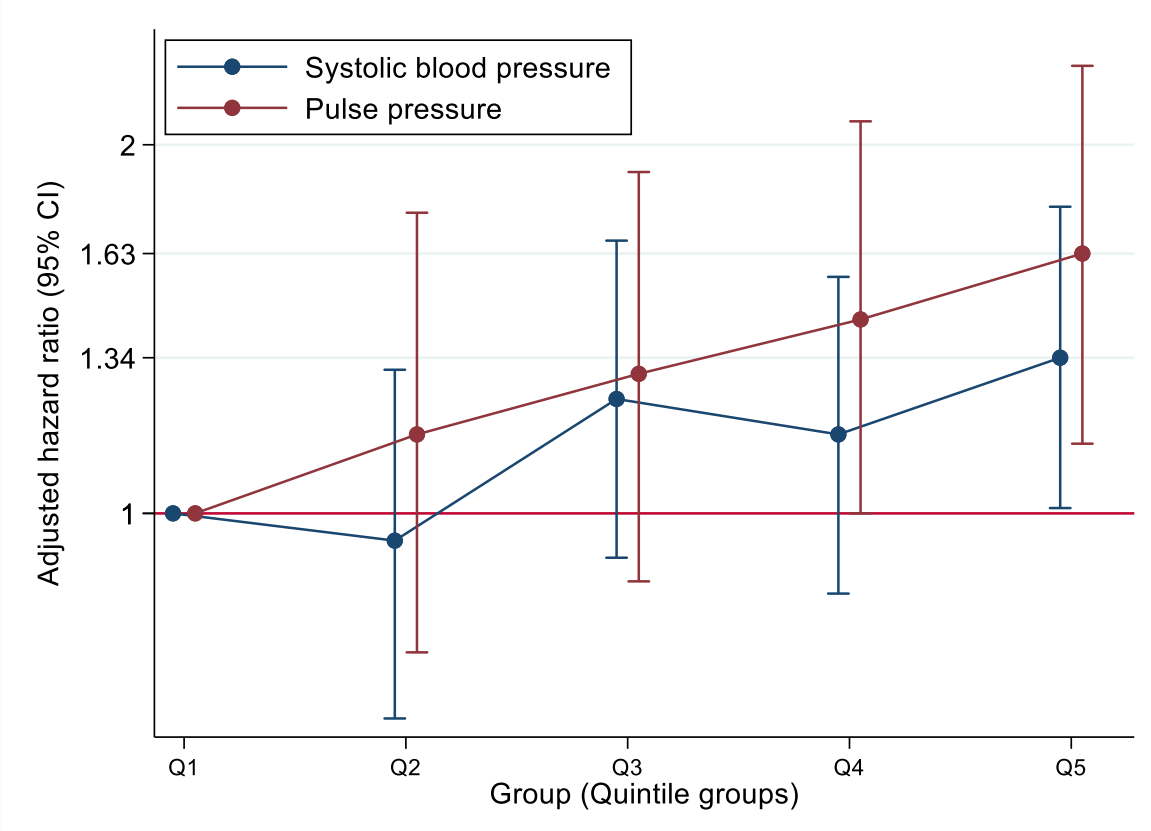
Figure 24: Adjusted relative hazard plots of CV-related mortality from models containing PP and MAP as single components of baseline blood pressure over 3 age categories



Note, for each blood pressure component, HRs and 95% CIs are shown in relation to reference level, labelled as "(ref)" on the plots. Blood pressure components are modelled with restricted cubic spline transformations, with interactions with age group. P-values are from global likelihood ratio tests comparing models with and without the blood pressure component present.

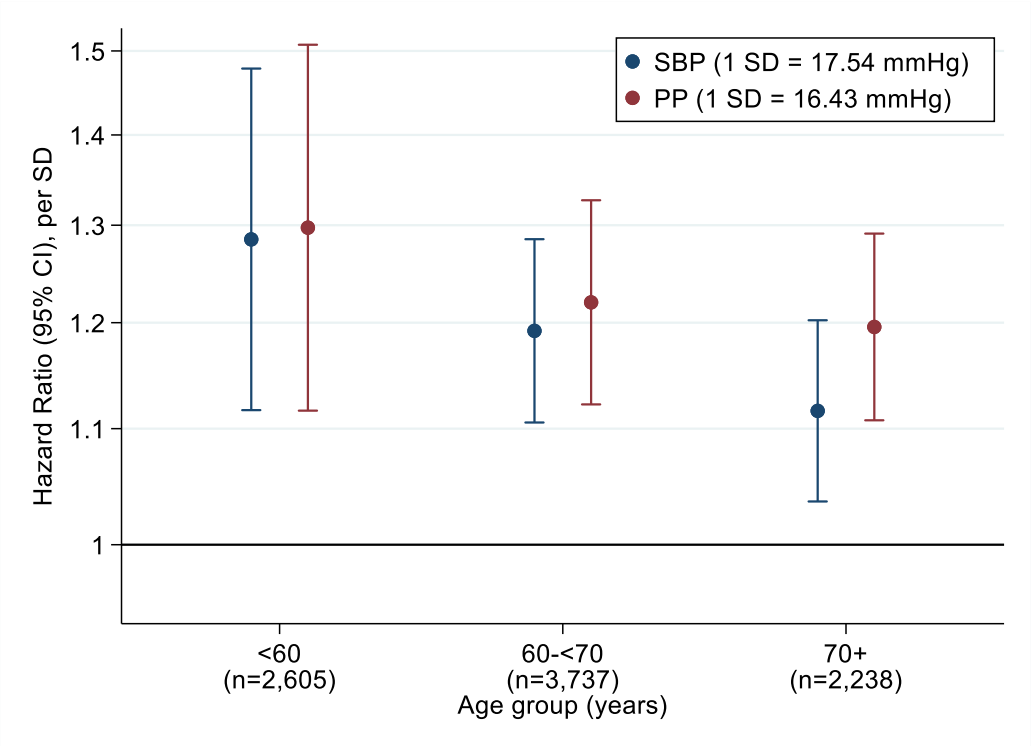
It appeared that PP was the strongest predictor of CV-related mortality in older subjects. To help visualise this, Figure 25 presents a plot of adjusted HRs comparing quintiles of SBP and PP, in the subgroup of those 70 years and older. In comparison with the lowest quintile, the adjusted HR for the highest quintile for PP was substantially higher, almost double the relative increase in hazard, than for SBP (HR=1.63 [95% CI: 1.14-2.32], p=0.007, & HR=1.34 [1.01-1.78], p=0.041, respectively).

Figure 25: Plot of adjusted HRs (95% CI) comparing quintiles of SBP and PP, in those 70 years and older



Since there was no evidence against linearity for both baseline SBP and PP relating to risk, modelling each component in a linear fashion the HR for a one SD increase in PP was, again, substantially higher than for SBP in those 70 years and older. There was a relative increase in hazard of 20% per SD increase for PP (95% CI: 11%–29%, p<0.001) and 12% for SBP (95% CI: 4%–20%, p=0.004). At lower ages, there was less of a difference between SBP and PP (see Figure 26).

Figure 26: Plot of adjusted HRs (95% CI) comparing CV-related mortality per SD increase in SBP and PP modelled as continues linear variables, by subgroups of age



Although relationships between blood pressure components and CV-related mortality risk attenuate with age when hazard rate is compared on the relative

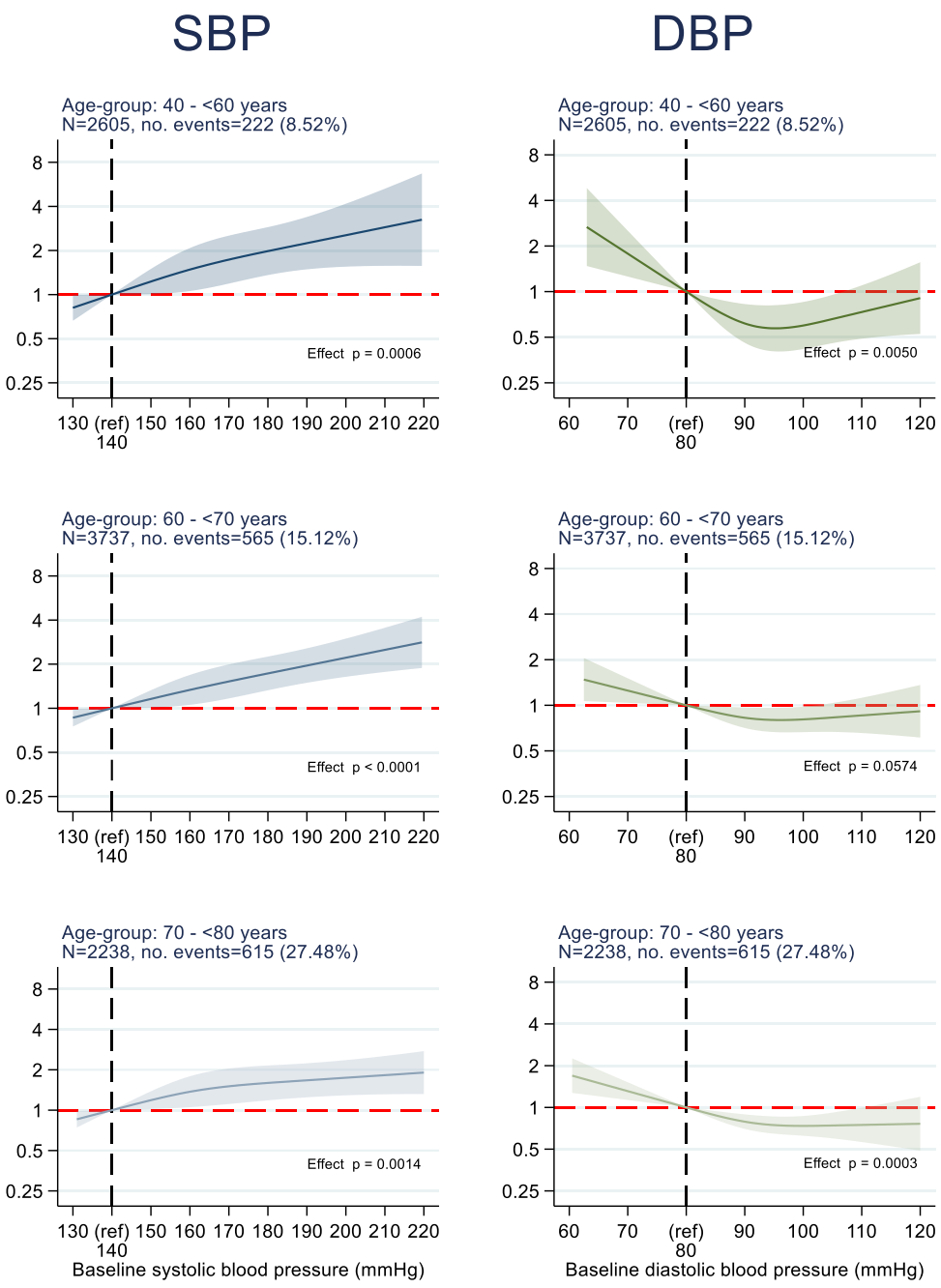
scale, this was not the case on the absolute scale. Absolute differences in CV-mortality rates were very similar over different ages, for each of the components of blood pressure. Analysis of CV-mortality rate was undertaken using Poisson survival models containing single blood pressure components modelled as quintile categories with an interaction with age and adjusted for other pre-specified baseline risk factors. From these models, the estimated adjusted absolute differences between blood pressure component quintile groups were calculated for those < 70 years of age and for those 70 years and older. For SBP, the absolute increase in rate between the lowest and highest quintile groups was estimated as 5.62 events per 1000 person-years (95% CI: 3.52-7.72) in those under 70 years, and 6.58 events per 1000 person-years (95% CI: 0.67-12.49) in those 70+ years. For PP the absolute increase in rate between the lowest and highest quintile groups was also similar between age-groups, an estimated: 7.52 events per 1000 person-years (95% CI: 5.20-9.83) in those under 70 years, and 9.65 events per 1000 person-years (95% CI: 3.20-16.10) in those 70+ years. For both SBP and PP, the estimated absolute differences were marginally higher in those 70 years and over, but with no statistical evidence for the differences.

Figure 27 and Figure 28 present plots of adjusted relative hazard over the same three age groups, from models containing pairs of blood pressure components (SBP with DBP, and PP with MAP) each modelled continuously with restricted cubic spline

transformations. As seen in the previous section when modelling components in quintile groups, the relationship of SBP with CV-related mortality risk, when adjusted for DBP, becomes more extreme. Also, the relationship between DBP and risk, once adjusted for SBP, becomes more extreme for the lower values of DBP but less so for higher DBP values. In the oldest age category, 70-80 years, there seems to no longer be any independent increase of risk associated with higher values of DBP at all. Once again, the relationships with risk were stronger in those younger (on a relative scale), and attenuate with increasing age, however, for both SBP and DBP there was stronger evidence of an association in each age group, including the oldest group, 70-80 years ($p=0.001$ & $p<0.001$, respectively).

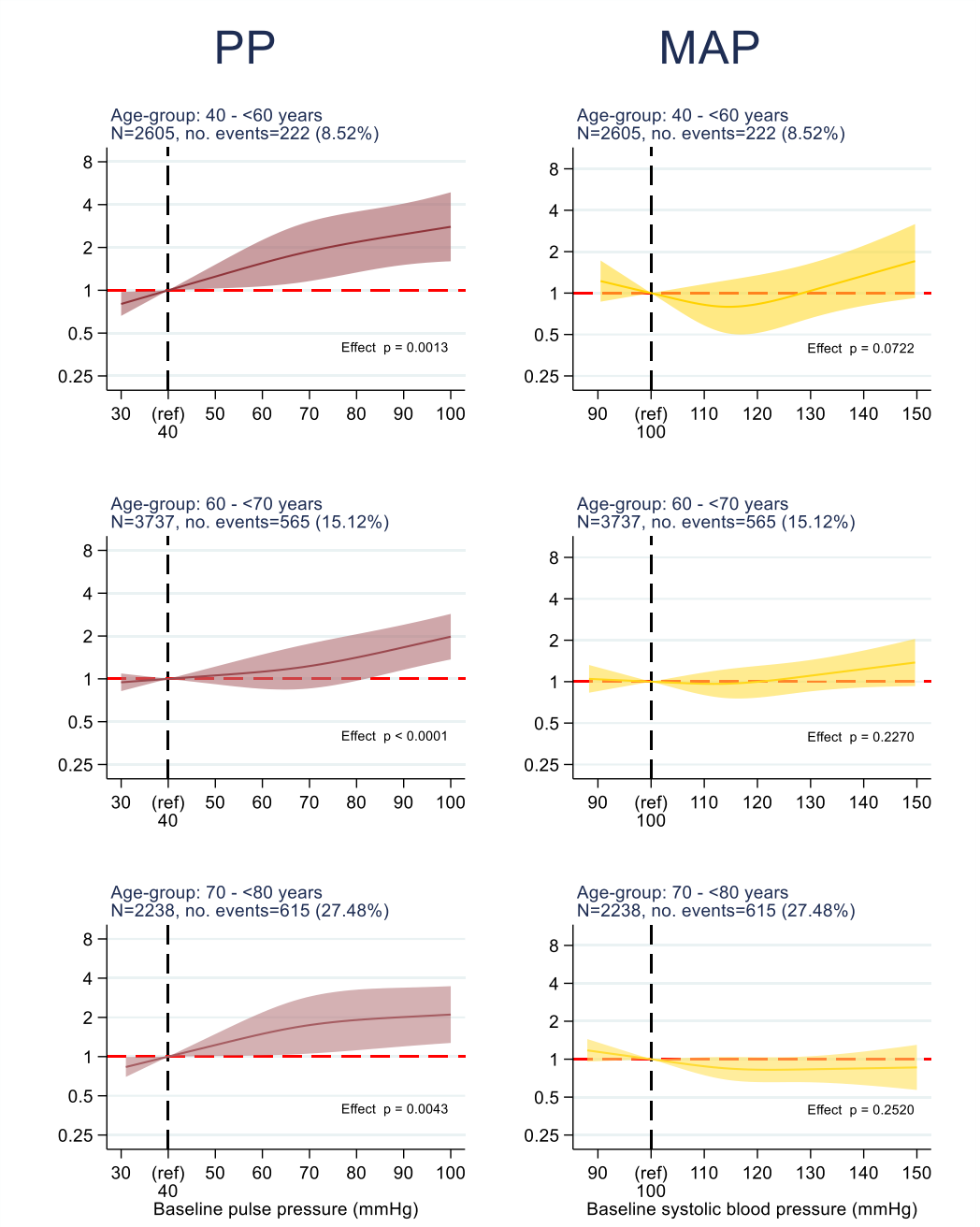
When adjusted for MAP, there remained strong evidence of an association between PP and CV-related mortality risk in each age group, although again the relationship become weaker with increasing age. Once adjusted for PP, there was poor evidence of an association between MAP and risk, in each age category (see Figure 28).

Figure 27: Adjusted relative hazard plots of CV-related mortality from models containing pairs of baseline blood pressure components, SBP adjusted for DBP and DBP adjusted for SBP over 3 age groups



Note, for each blood pressure component, HRs and 95% CIs are shown in relation to reference level, labelled as "(ref)" on the plots. Blood pressure components are modelled with restricted cubic spline transformations, with interactions with age group. P-values are from global likelihood ratio tests comparing models with and without the blood pressure component present.

Figure 28: Adjusted relative hazard plots of CV-related mortality from models containing pairs of baseline blood pressure components, PP adjusted for MAP and MAP adjusted for PP over 3 age groups



Note, for each blood pressure component, HRs and 95% CIs are shown in relation to reference level, labelled as "(ref)" on the plots. Blood pressure components are modelled with restricted cubic spline transformations, with interactions with age group. P-values are from global likelihood ratio tests comparing models with and without the blood pressure component present.

3.4.7 Comparing models containing different components of blood pressure modelled as continuous variables

A number of models were constructed containing difference single components of blood pressure, pairs of components, with and without allowing interactions between components with age. These models contain blood pressure components modelled continuously with restricted cubic splines as previously described, as well as being adjusted for pre-specified baseline risk factors. Age is also modelled continuously with the same spline transformations. A comparison of models is presented in Table 18.

For models containing single blood pressure components, goodness-of-fit was best in models containing SBP or PP, with slightly better fit statistics for PP models based on log likelihood and R^2, and slightly better discrimination based on C-statistic. The model with MAP alone showed the poorest fit and had the lowest discrimination compared to other single blood pressure component models. This was the case comparing single blood pressure component models both with and without an interaction with age.

For each component of blood pressure modelled singularly, there was somewhat borderline evidence of an interaction with age.

The best models with pairs of blood pressure components contained SBP and DBP, or PP and DBP. Whether allowing interactions with age or not, in both cases each

component of blood pressure in the paired models showed strong evidence of association with CV-related mortality while adjusted for the other component in the model. When MAP was modelled with PP, there was poor evidence for an independent association between MAP and risk, whether allowing interactions with age or not ($p=0.234$ & $p=0.088$, respectively).

Paired component models that contained both PP and SBP performed the worst, very closely to models with both PP and MAP. Once adjusted for PP, there was no longer evidence that SBP was independently associated with CV-related mortality whether allowing interactions with age or not ($p=0.525$ & $p=0.788$, respectively), however, evidence for the relationship between PP and risk was still strong ($p=0.008$ & $p=0.003$, respectively).

There was no evidence for an interaction between SBP and DBP ($p=0.441$). However, there was evidence of an interaction between PP and MAP ($p=0.005$). When MAP was lower, the relationship between PP and risk was stronger.

Table 18: Comparison of models containing different components of baseline blood pressure (N=8580)

Blood pressure in model			BP Effect p-value		Linearity p-value		Interaction p-value		Goodness-of-fit (calibration) Discrimination			
1st	2nd	Interaction with BP measures in model	1st	2nd	1st	2nd	1st	2nd	-2 x Log-likelihood	AIC	R2	C-statistic
No BP									-11730.43	23488.85	0.2725	0.7038
SBP			< 0.001		0.175				-11712.52	23457.05	0.2818	0.7101
DBP			< 0.001		< 0.001				-11720.90	23473.79	0.2765	0.7081
PP			< 0.001		0.251				-11706.80	23445.60	0.2868	0.7113
MAP			< 0.001		0.005				-11721.40	23474.79	0.2762	0.7074
SBP	DBP		< 0.001	< 0.001	0.087	< 0.001			-11699.86	23435.72	0.2872	0.7145
PP	DBP		< 0.001	0.002	0.292	< 0.001			-11700.77	23437.53	0.2873	0.7141
PP	MAP		< 0.001	0.088	0.196	0.030			-11704.37	23444.75	0.2867	0.7123
PP	SBP		0.003	0.788	0.610	0.572			-11706.56	23449.12	0.2868	0.7115
SBP		Age	< 0.001		0.906		0.055		-11707.89	23455.78	0.2821	0.7111
DBP		Age	< 0.001		< 0.001		0.072		-11716.60	23473.20	0.2777	0.7087
PP		Age	< 0.001		0.673		0.040		-11701.79	23443.57	0.2860	0.7127
MAP		Age	< 0.001		0.017		0.073		-11717.11	23474.22	0.2773	0.7085
SBP	DBP	Age	< 0.001	< 0.001	0.738	0.001	0.224	0.159	-11693.65	23439.31	0.2886	0.7155
PP	DBP	Age	< 0.001	0.010	0.625	0.002	0.088	0.279	-11693.41	23438.82	0.2878	0.7158
PP	MAP	Age	< 0.001	0.234	0.579	0.110	0.243	0.385	-11697.76	23447.52	0.2869	0.7141
PP	SBP	Age	0.008	0.525	0.231	0.373	0.306	0.345	-11699.21	23450.42	0.2871	0.7135

Note: each model is adjusted for a-priori covariates. Each blood pressure component, and age, is modelled as continuous using restricted cubic splines with 3 knots (knot positions at the 10th, 50th, and 90th percentiles).

Note: R2 measure is based on Royston & Sauerbrei (2004)'s D measure of discrimination.

3.4.8 Blood pressure measures collected at the 1-year ASCOT trial visit

Analyses were repeated using measurements of blood pressure components captured at the 1-year ASCOT trial visit, when mean blood pressure levels had fallen following the initiation of antihypertensive trial treatments.

In this approach, follow-up began from the time of the 1-year visit for each subject. 8030 (93.6%) out of the 8580 ASCOT legacy subjects had a 1-year scheduled visit at which blood pressure measurements were recorded. Out of the 550 patients without a 1-year visit, 70 had died prior to the visit, one had been withdrawn from the study, and the remaining 479 subjects missed the 1-year visit.

Mean age of subjects at the 1-year visit was 65.1 years (SD: 8.1), and 6541 (81.5%) subjects were male.

Mean SBP and DBP at 1-year were 141.18 mmHg (SD: 16.30) and 81.66 mmHg (SD: 9.31), a mean decrease from baseline of 20.53 mmHg (SD: 19.31) and 10.49 mmHg (SD: 10.32), respectively. Hence mean PP was 59.52 mmHg (SD: 14.19) at 1-year, a decrease of 10.04 mmHg (SD: 14.07) from baseline.

The correlation between SBP and DBP was slightly higher than with the baseline readings (overall r=0.497), likely due to truncated blood pressure measures at baseline as a result of the exclusion criteria. PP was again highly positively

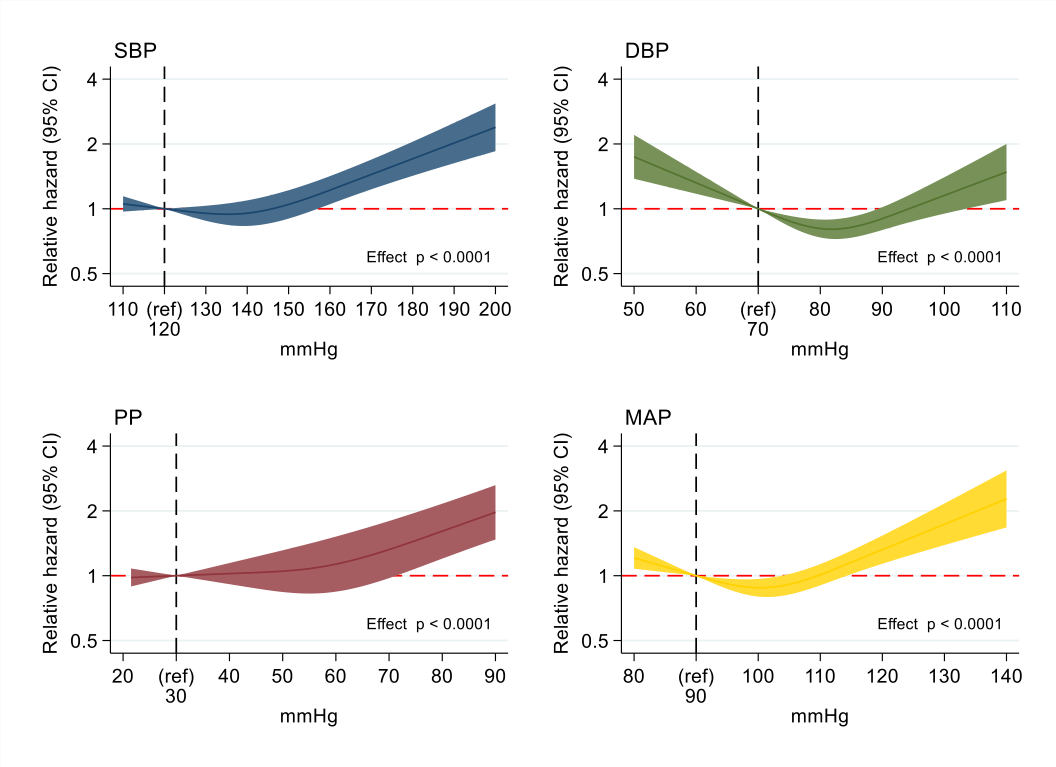
correlated with SBP (overall r=0.822), while the negative correlation between PP and DBP was less than that at baseline (overall r=-0.085).

Table 19: Pair-wise correlations between blood pressure component measurements collected at the 1-year ASCOT trial visit, by subgroups of age

	Correlation (p-value) between pairs of BP measurements			
Age group (years)	SBP & DBP	SBP & PP	PP & DBP	PP & MAP
40 - <50 (n=443)	0.728 (p<0.001)	0.787 (p<0.001)	0.150 (p=0.002)	0.118 (p=0.015)
50 - <60 (n=2162)	0.603 (p<0.001)	0.827 (p<0.001)	0.051 (p=0.022)	0.141 (p<0.001)
60 - <70 (n=3737)	0.574 (p<0.001)	0.842 (p<0.001)	0.041 (p=0.015)	0.119 (p<0.001)
70 - 80 (n=2238)	0.531 (p<0.001)	0.838 (p<0.001)	-0.018 (p=0.406)	0.083 (p<0.001)

As with baseline measures, there was strong evidence that each component of blood pressure was associated with CV-related mortality, and relationships were stronger with CV-related mortality than for all-cause (see Figure 29).

Figure 29: Adjusted relative hazard plots of CV-related mortality from models containing single components of blood pressure measured at 1 year



Note, for each blood pressure component, HRs and 95% CIs are shown in relation to reference level, labelled as "(ref)" on the plots. Blood pressure components are modelled with restricted cubic spline transformations. P-values are from global likelihood ratio tests comparing models with and without the blood pressure component present.

There was stronger evidence for a lack in linearity between SBP measured at 1-year with CV-related mortality ($p<0.001$) from single component models. SBP showed a slight J-shape association which began to look slightly more similar to the shape of relationship that DBP had with risk, although to a lesser extent. There also appeared to be a slight suggestion of curvature in the relationship between PP and risk, with there being less association at lower levels of PP, and an increase in risk when PP is higher than around 70 mmHg.

Relationships between all components of blood pressure taken at 1-year with risk became attenuated with increasing age. PP seemed to have the strongest relationship with risk in the oldest age group, as with the baseline blood pressure measures.

Table 20 presents details from a variety of models using components of blood pressure collected at the 1-year visit modelled as continuous variables with restricted cubic spline transformations as previously described. In general, the best models were consistent with those using baseline blood pressure measurements. Model goodness-of-fit was best in single blood pressure component models containing SBP or PP, and models with MAP alone showed the poorest performance. The best performing models containing pairs of blood pressure components contained SBP and DBP, or PP and DBP.

Table 20: Comparison of models containing difference single BP measures at 1-year visit (N=8030)

Blood pressure in model			BP Effect p-value		Linearity p-value		Interaction p-value		Goodness-of-fit (calibration) Discrimination			
1st	2nd	Interaction with BP measures in model	1st	2nd	1st	2nd	1st	2nd	-2 x Log-likelihood	AIC	R2	Somers' D (Dxy)
No BP									-10345.32	20718.63	0.2764	0.4143
SBP			< 0.001		< 0.001				-10324.86	20681.72	0.2851	0.4280
DBP			< 0.001		< 0.001				-10334.36	20700.72	0.2863	0.4226
PP			< 0.001		0.043				-10318.85	20669.71	0.2922	0.4320
MAP			0.002		0.013				-10339.22	20710.45	0.2789	0.4202
SBP	DBP		< 0.001	< 0.001	0.014	0.003			-10309.82	20655.65	0.2990	0.4370
PP	DBP		< 0.001	< 0.001	0.044	< 0.001			-10310.82	20657.63	0.2998	0.4375
PP	MAP		< 0.001	0.047	0.054	0.043			-10315.80	20667.59	0.2934	0.4347
PP	SBP		< 0.001	0.007	0.681	0.005			-10314.11	20664.22	0.2947	0.4337
SBP		Age	< 0.001		< 0.001		0.004		-10317.31	20674.61	0.2915	0.4304
DBP		Age	< 0.001		< 0.001		0.320		-10332.01	20704.03	0.2851	0.4235
PP		Age	< 0.001		0.004		< 0.001		-10307.15	20654.30	0.2990	0.4350
MAP		Age	0.007		0.066		0.247		-10336.52	20713.04	0.2798	0.4218
SBP	DBP	Age	< 0.001	< 0.001	0.073	0.036	0.004	0.121	-10300.60	20653.20	0.3037	0.4388
PP	DBP	Age	< 0.001	0.005	0.006	< 0.001	< 0.001	0.516	-10297.80	20647.60	0.3063	0.4406
PP	MAP	Age	< 0.001	0.182	0.006	0.203	< 0.001	0.466	-10302.73	20657.45	0.3011	0.4384
PP	SBP	Age	< 0.001	0.410	0.666	0.292	0.380	0.968	-10304.09	20660.18	0.3016	0.4366

Note: each model is adjusted for a-priori covariates. Each blood pressure component, and age, is modelled as continuous using restricted cubic splines with 3 knots (knot positions at the 10th, 50th, and 90th percentiles).

Note: R2 measure is based on Royston & Sauerbrei (2004)'s D measure of discrimination.

3.5 Discussion

This trial-based cohort study of 8580 hypertensive subjects aimed to compare the ability of components of blood pressure collected at baseline to predict mortality, with a focus on mortality from CV-related causes specifically, and to assess how associations depend on age. The main focus was the comparison between SBP and PP in their predictive value, while also considering the importance of DBP and MAP. The single components of blood pressure that undoubtedly had the strongest prognostic power for mortality, and specifically CV-related mortality were SBP and PP, but PP was the stronger predictor in older subjects.

It has long been accepted that blood pressure increases with age. Blood vessel function deteriorates with age, and vessels can become stiffer and less compliant leading to hypertension. However, the understanding of how to define hypertension, particularly in the elderly, has changed over time. Specifically, isolated systolic hypertension is known to be the most prevalent type of hypertension in older people [104-106]. Previous studies, such as the Framingham study, have demonstrated that SBP shows a continued steady increase over the age of 30, and that DBP begins to decrease after the age of 60. The Framingham study found a mixed pattern for DBP, showing an increase with age below the age of 60, followed by a steady decline thereafter [107]. In this study there was both a vastly higher SBP as well as a strikingly lower DBP in older subjects. As a result, there was

a steep gradient of increase in PP with increasing age as a result in part of isolated elevated SBP, but also due to this vastly lower DBP in older subjects.

SBP was found to be similar between the sexes across all age-groups, while females had a slightly lower DBP and hence wider PP compared to males. Many studies have shown that healthy males tend to have higher blood pressure, both systolic and diastolic, compared to healthy females [108–110]. The lack of difference in SBP between the sexes seen at baseline may be a consequence of the restriction of the trial entry criteria.

The age at which subjects left full-time education was used to attempt to act as a proxy for level of socio-economic status (SES). While SBP decreased with the assumed higher education level, perhaps rather unexpectedly DBP increased, and hence PP was lower in those with higher education levels. SES has been shown to be associated with blood pressure, and this has been demonstrated through the level of education, with lower levels of education, more socio-economically deprived areas being associated with higher blood pressure [111].

It is well-known that increased BMI is associated with increased blood pressure. In this cohort, due to the lack of increased SBP while DBP was increased in those with higher BMI, there was evidence of lower PP in those at higher BMIs. There have been other studies that have also seen this negative correlation with PP and BMI, with wider PP being reported in in the lean [112,113]. It has been suggested that this

backs up findings from reports that suggest an increased risk among lean compared to obese subjects who have isolated hypertension.

As is expected, those with higher lipid levels tended to have higher DBP and SBP. There is good evidence in the literature of the interrelation between blood pressure and blood lipid levels [114].

Each of the four components of blood pressure, diastolic, systolic, pulsatile and mean pressure, were strongly associated with all-cause mortality, and to a greater extent with CV-related mortality. For each component there was some evidence that their association had a dependence on age. SBP and PP were the strongest predictors of CV-related mortality, and MAP was the weakest. PP appeared to be the slightly better predictor of CV-related mortality compared to SBP, particularly in older subjects.

Having a high PP is known to be predominantly a consequence of increased stiffness of the artery walls, particularly in older people. Arterial stiffness is closely associated with biological aging and the build-up of atherosclerotic plaques in the arterial walls. This can lead to reduced arterial compliance (volume of blood increase per amount of pressure increase)[115]. As well as acting as a marker for arterial stiffness as a result of atherosclerosis and deterioration of the blood vessel walls, raised PP itself is said to be a cause of vascular damage, which in turn can

increase the risk of atherosclerosis, and other vascular and cardiac damage [116]. In young people, high PP is often more related to an increase in stroke volume [117].

While there was a lack of evidence against linearity for baseline measures of SBP and PP, DBP had a J-shape relationship with CV-related mortality with high levels, and more acutely at low levels, being associated with increased risk, as is very well documented [118,119]. It followed that MAP also had a somewhat lessened J-shape relationship with risk as a result be being formed from a combination of DBP and SBP. However, as subjects were hypertensive at baseline, one might not expect to see increased risk associated with lower DBP levels as these lower levels are still considered higher than ranges normally associated with hypotension in the general population. Research usually points to increased risk when DBP levels are around 70 mmHg or lower [120], whereas, risk seemed to be elevated in those with baseline DBP from around 90 mmHg and lower. A possible reason for this observed increase risk at lower baseline DBP values could be that having lower DBP at baseline was associated with having even lower DBP after treatment and hence a result of subsequent hypotension. Alternatively, it may be because lower levels of DBP at baseline indicate a higher baseline SBP and hence higher PP, due to the inclusion criteria constraints. Subjects recruited to the ASCOT trial needed to have baseline SBP $\geq$160 or DBP $\geq$100 if not currently being treated for hypertension, or an SBP $\geq$140 or DBP $\geq$90 if currently being treated. As a result, the distribution of baseline

blood pressure was restricted, and subjects with lower DBP, i.e. lower than 100 mmHg if untreated or 90 mmHg if treated, would have had a high SBP of ≥160 or ≥140, respectively. This constraint could be the cause of the negative correlation between baseline DBP and PP, which was not apparent in the 1-year blood pressure measures.

In addition, correlations between SBP and DBP were substantially lower than have been found in some other studies. For example, Kannel et al. found correlation coefficients to be over 0.60 in all age categories, and as much as 0.79 in those below 50 years in their study of 6539 individuals between 20 and 79 years from the Framingham study [83]. The reason for the weaker correlation between baseline SBP and DBP in the ASCOT legacy cohort, could also be a result of the inclusion criteria.

Baseline PP appeared to have the clearest monotonic relationship with CV-related mortality risk. However, there was slight evidence of a lack of linearity between both SBP and PP with CV-mortality risk when using the blood pressure measures collected at the 1-year visit. This is likely due to blood pressure measures being elevated at baseline, with SBP having to be 140 mmHg or above, and hence those low SBP levels associated with increased risk were not observed, this of course being a hypertensive patient group. At 1-year when mean blood pressure had decreased, low levels of SBP could well be representing subject frailty or other morbidities associated with low blood pressures, particularly in older subjects.

There was evidence that the relationship between each blood pressure component with CV-related mortality (on a relative scale) was dependent on age. As the age of subjects increased, relationships between components of blood pressure and risk attenuated.

As single components, baseline SBP and DBP presented weak, borderline evidence of a relationship with CV-related mortality in the oldest age group 70-80 years. Previous research suggests that with increasing age, SBP becomes more important and DBP becomes less so [80,83]. It appeared that associations weakened with age for both components in a similar way in this population. For DBP, this association seemed to come mostly from the increased risk associated with lower levels rather than higher levels in the older age group.

While associations attenuated with increasing age on the relative scale, this was not the case on the absolute scale. Absolute differences in rates of CV-related mortality over levels of blood pressure components were similar across age groups. Hence, as risk increased with age but absolute risk differences associated with blood pressure remained similar, this resulted in a reduction of relative effect with increasing age of subjects.

Both SBP and DBP were independently associated with CV-related mortality. Once adjusted for each other both SBP and DBP remained fairly strongly associated with risk in older subjects. In fact, across all age-groups, when adjusting DBP, the

relationship between SBP and CV-related mortality become slightly stronger than when unadjusted for DBP. When adjusting for SBP, the relationship between DBP and CV-related mortality also changed slightly in that elevated risk was only seen in those with low DBP and to a slightly greater degree compared to analysis not adjusted for SBP, and no increased risk associated with higher DBP.

Consistent with previous studies, in general, models containing SBP performed better than models with DBP [81]. However, the fact that DBP remained important in joint models with SBP conflicted with some studies that found DBP to not be an independent risk factor once adjusted for SBP, particularly in older patients. Kannel et al. found that when both SBP and DBP were in the same model, that DBP become less important with age and SBP more important in relation to CHD risk, with DBP being more important in under 50s and SBP more important in over 60s. This was not observed in this study, although there were few patients under 50, and none under 40, while in the Kannel study the age ranged from 28 to 62 [79]. This was perhaps also due again to the restricted ranges of SBP and DBP at baseline as a result of inclusion criteria (as previously discussed).

In many previous studies that compared the predictive abilities of blood pressure components, comparisons were made between models with components modelled as linear variables. Hence, relationships with risk were assumed linear and comparisons between their ability to predict were often made on the basis of

comparing their estimated change in risk per unit increases in blood pressure component, or per standardised increase such as SD or SE [79,83,92,96]. However, in many cases the relationships with risk are not linear, especially with DBP, and hence this approach is often inappropriate. By allowing relationships between blood pressure components with risk to be non-linear through the use of restricted cubic spline transformations, non-linear relationships could be captured and models containing different blood pressure components could be compared without the, often invalid, assumption linearity. In previous research, perhaps this is why the independent association between DBP and risk seemed to diminish once adjusted for SBP.

Baseline PP maintained a strong relationship with CV-related mortality, even in the oldest age group when modelled as a single blood pressure component. This supports other studies that have found PP to be a better predictor of CV events in older subjects compared to SBP [76]. While both elevated SBP and PP have been shown to be more powerful than DBP in predicting risk in older people, it is thought that this increased risk is predominantly coming from the increased PP due to the increase in SBP and decrease in DBP with age. Staessen et al. conducted a meta-analysis combining results from a number of large clinical trials which showed the increased risk of CV complications associated with a wider PP [121].

There was strong evidence of a relationship between MAP and risk in younger subjects, but not in those 70 years and older. Once PP and MAP were modelled together, there was a slight decrease in magnitude of independent association between PP and risk, but more so between MAP and risk. After adjustment for MAP there remained strong evidence of an association between PP and risk in all age groups, but after adjustment for PP, there was little evidence for an independent association between MAP and risk in any age group.

MAP was the poorest predictor of CV-related mortality risk out of all of the blood pressure components. This is in-keeping with much of the previous research, for example with the conclusions from the meta-analysis conducted by Gasowski et al. which found, after adjustment for PP and other known risk factors, that mean pressure was not associated with the risk of fatal events [90]. MAP may not be well capturing the important elements of DBP or SBP. However, there is conflicting research, for example, Palaniappan et al. found that SBP and MAP were the strongest predictors of CV-related mortality risk in both in men and women who were over 60 years old from the Dubbo study, compared to PP and DBP [92]. Dyer et al also found MAP more strongly associated with CVD risk compared to PP [97].

When modelled as single blood pressure components, models containing PP seemed to perform slightly better in terms of discrimination and model goodness-of-fit compared to models with SBP. The addition of DBP to either SBP or PP in

dual-component models seemed to add value beyond the single predicator. A model with the combination of SBP and DBP was slightly stronger in prediction compared to PP alone. A reason for this could be that when SBP and DBP are modelled together, they can collectively give insightful information about increased risk associated with both high and low levels of blood pressure as well as the increased risk associated with a wider PP. PP alone might be capturing part of the increased risk associated with high and also low blood pressure, but not as completely as SBP and DBP.

One might expect the relationship between SBP and risk to be dependent on DBP, and vice-versa. For example, it might be expected that the increased risk associated with low DBP might be more extreme at higher levels of SBP, as we might expect additional risk captured from a wider PP in that scenario. However, there was no evidence for such an interaction. However, there was evidence for an interaction between MAP and PP. The increased risk associated with a wider PP was greater when MAP was lower. Further, when adjusting for baseline PP, evidence for the increased risk associated with lower levels of DBP remained (although slightly attenuated). This might suggest that the increased risk associated with low DBP levels was not entirely indicating the increased risk associated with wider PP, but might also be representing increased risk associated with diastolic hypotension. Hence, while PP might be capturing slightly more of the risk than SBP alone, i.e.

increased risk from elevated blood pressure as well as from wider PP, PP alone may not be completely capturing the increased risk from lower DBP.

In dual component models, there was little difference between models containing SBP and DBP to models containing PP and DBP. This is expected as once a model contains both SBP and DBP, it has equivalent information to a model containing PP and DBP, with slight differences depending on how the blood pressure components are modelled. The combination of PP with MAP was inferior to SBP and DBP. This might be because MAP does not fully capture all of the informative information from either DBP or SBP.

Overall, results from the analysis of the 1-year blood pressure data analysis were consistent with the baseline data. Similar relationship patterns were observed for both. However, in general each blood pressure component seemed to have a slightly stronger association with CV-related mortality, when using the blood pressure measurements from the 1-year visit compared to baseline measurements. This slight increase in strength of association might be because baseline values are not representing the true underlying blood pressure for these patients as well as the 1-year measures. This might also be due to the inclusion criteria for the trial in the recruitment of hypertensive subjects resulting in a more constrained distribution of baseline blood pressure. After treatment initiation blood pressure measures had a wider and more unconstrained distribution and hence may be able

to predict risk and discriminate between those at higher and lower risk better. Differences in post-baseline blood pressure measures might be highlighting how well subjects are able to have their blood pressure controlled, emphasising those with resistant hypertension, those with chronic hypertension, and identifying those with more fundamental vascular damage, for example.

This research supports existing evidence that PP is as good as or better than other blood pressure components in the prediction of CV-related mortality, especially at older ages. There is evidence from clinical trials that some agents, particularly ACE-inhibitors, can directly affect arterial stiffness and other elements of vascular dysfunction that may be best identified by PP [122]. While most clinical trials in hypertension have outcomes that target the reduction of SBP and DBP, in some cases a reduction in PP may be a better marker of success in order to be able to assess the impact of therapies in targeting vascular dysfunction that directly affect PP. Although there is now much evidence to support the important role of PP as a marker for CV events, more investigation is needed through clinical studies to evaluate optimum PP targets to help with the formation of clinical guidelines for PP for the management of blood pressure and treatment of hypertension.

Chapter 4: Impact of blood pressure level and variability on cardiovascular-related mortality

4.1 Background & aims

4.1.1 Background

Blood pressure is a naturally highly variable parameter. A single blood pressure measurement or even a collection of measurements from a single occasion can be very limited in what they convey about some someone's underlying blood pressure. Blood pressure can vary both in the short-term from moment-to-moment as a direct result of daily activities and environmental factors and it can change more fundamentally over the long-term. Biological variations in blood pressure are known to be the result of complex interactions between external environmental and behavioural factors with internal CV-related mechanisms [123]. Many mechanisms behind variation in blood pressure are known but there are still many that are not fully understood.

As well as being naturally highly variable, the measurement of blood pressure is highly prone to measurement error [124]. The high degree of true natural variability in blood pressure from moment to moment throughout the day as well as more fundamental changes over time makes blood pressure a complex factor to understand and to clinically monitor. The addition of the high degree of measurement error that blood pressure is subject to creates a challenge in the assessment of risk and blood pressure management. Hence, a single measurement in time is of limited use when trying to understand an individual's long-term risk.

Utilisation of multiple blood pressure readings over time can greatly improve accuracy in the estimation of a true underlying blood pressure level.

The concept of a "true underlying" blood pressure represents a level at which someone is considered to have when at rest at a particular time. It is most often represented by some kind of mean value over several measurements in time, e.g. across multiple clinical visits. A common approach to help reduce blood pressure measurement error at a particular clinical visit is to take repeat measurements. Clinicians also use various techniques to relax a patient as much as possible in order to help a patient's blood pressure fall as close to resting as possible. Patients will often be asked to sit and relax for a number of minutes before blood pressure measures are taken. Often initial blood pressure measurements are discarded and subsequent readings used in an attempt to remove early potentially elevated measures before the subject is closer to being at a state of complete rest.

Measurement error can cause a reduction in estimated association between the object being measured and the outcome, a phenomenon known as regression dilution bias [125,126]. Methods for correcting for such a bias have been proposed when it is not possible to collect multiple measurements from all participants within a study [127]. Through the averaging of a set of multiple measurements, each carrying some uncertainty, overall uncertainty can be reduced. As the number of measurements increases, the level of precision can increase. By relating repeated

blood pressure measurements to risk of CV mortality, rather than using a single measurement, the increased precision gained can reduce regression dilution bias [128]. This works for multiple measurements that are taken on the same occasion, as well as for measurements taken on separate occasions over a longer period of time. Repeated measures over longer periods of time can help build a more accurate picture of true underlying blood pressure over that period [129].

The importance of blood pressure level as a risk factor for CVD and mortality has long been established and accepted. In the past blood pressure variability was often dismissed and simply seen as a challenging factor in the measurement of blood pressure level. There has more recently been increasing evidence that greater measurement-to-measurement short-term and clinical visit-to-visit long-term variability in blood pressure is associated with increased risk of CVD outcomes and mortality, over that of mean level [130–133]. There has been other evidence to suggest that blood pressure variability is also a risk factor for other morbidities such as dementia and chronic kidney disease [134,135]. A systematic review and meta-analysis conducted by Stevens et al. and published in 2016 concluded that long-term blood pressure variability was found to be associated with CV and mortality outcomes, over and above the effect of mean blood pressure [136]. Since 2018, variability in SBP was included in the QRISK risk model (version 3), an algorithm that calculates a person's risk of developing CHD or stroke within 10 years [137]. The

QRISK3 model uses the standard deviation (SD) of SBP (from at least 2 measurements) to represent blood pressure variability, along-side SBP mean level and other important risk factors in the model. Blood pressure variability is being seen not just as a nuisance to overcome in the measurement of blood pressure level, but an important part of a blood pressure profile that needs to be considered. If the variability in blood pressure can improve CVD prediction and indeed mortality prediction over that of usual level alone, it should be incorporated in patient care.

There may also be other aspects of a blood pressure profile that might be informative of individuals' risk and useful in the management of blood pressure. For example, it may be important to understand how blood pressure is fundamentally changing over time, or to understand periodic peaks in blood pressure.

Some guidelines for the management of hypertension do focus on what is considered a patient's "usual" blood pressure, most commonly defined as the mean over multiple visits. But despite the importance of repeated blood pressure measurements, the most common approaches to blood pressure management and the treatment of hypertension remain based on responses to measurements taken on one occasion. Modern approaches to blood pressure management should include considering current blood pressure levels in the context of historic blood pressure profiles.

Using repeated blood pressure measurements recorded for patients during the course of the ASCOT trial, this study enabled the assessment of blood pressure profiles and how they relate to CV-related mortality in this hypertensive ASCOT legacy cohort.

4.1.2 Aims

The aim of this chapter was to use blood pressure data collected repeatedly during the ASCOT trial to investigate relationships between visit-to-visit recurrent blood pressure measurements with CV-related mortality risk.

The first focus in this chapter was on exploring factors that influence blood pressure level and the variability in blood pressure measures from visit-to-visit.

The chapter begins by describing how blood pressure level and variability change over time in this ASCOT legacy cohort. An assessment of how subject characteristics relate to blood pressure level and variability was then undertaken. Furthermore, blood pressure variation over the calendar year was explored and an assessment of which factors influence seasonal variation in blood pressure was carried out.

The second main aim was to investigate the relationship between usual blood pressure levels and risk of CV-related mortality, and assess the independent

association of visit-to-visit blood pressure variability over that of blood pressure level.

The association between blood pressure level and CV-related mortality was initially assessed using the arithmetic mean of historic blood pressure measures to represent blood pressure level. The association between blood pressure variability and risk over and above that of mean level was then assessed using the standard deviation (SD) of historic blood pressure measures to represent blood pressure variability.

An investigation into how the number of historical blood pressure measures used in the estimation of blood pressure level and variability impacted the prediction of risk was undertaken. In addition, as assessment as to whether there was a difference in predictive ability between earlier or later blood pressure measures (older or more recent) was made.

Following analyses with the mean and SD used to represent blood pressure level and variability, respectively, alternative approaches of representation of blood pressure level and blood pressure variability were assessed as to their relationship with risk, in order to investigate how other expressions of these factors of repeated blood pressure measures relate to risk. In addition, other attributes of blood pressure profiles were assessed.

Building upon the findings in Chapter 3, the emphasis in this chapter was on the systolic and pulsatile components of blood pressure, since these were shown to be the strongest predictors of CV-related mortality. The objective to compare the predictive ability of PP and SBP was extended in this chapter with the use of repeated visit-to-visit blood pressure measurements following antihypertensive trial treatment initiation. The comparison between SBP and PP was made in relation to both blood pressure level and the variability in measurement of each blood pressure component, as well as other attributes of the blood pressure profiles.

The final part of this chapter aimed to develop a clinically useful predictive risk model for CV-related mortality, incorporating a representation of both blood pressure level and blood pressure variability, along with other key risk factors for the prediction of CV-related mortality.

4.2 Blood pressure during the trial in ASCOT legacy subjects

4.2.1 Blood pressure measurements collected over the trial

During the trial period which spanned a median of 5.5 years, blood pressure measurements were recorded at both scheduled and unscheduled visits. The intended visit schedule was at baseline (screening), 6 weeks, 3 months, 6 months, and then at 6 monthly intervals thereafter until trial end.

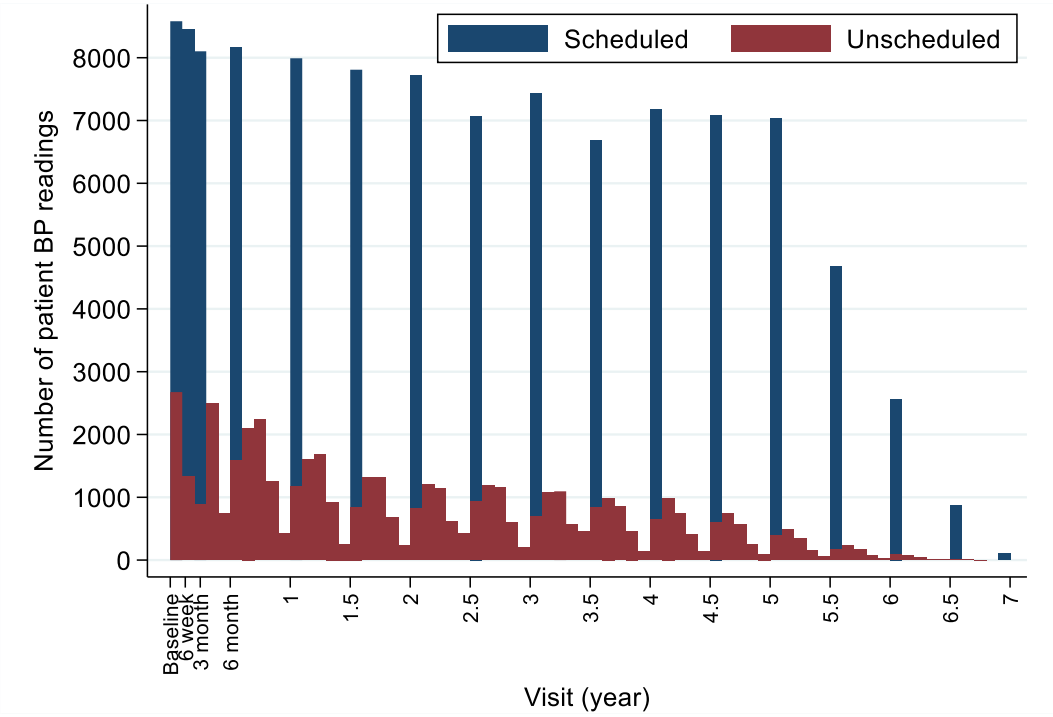
All ASCOT legacy patients had blood pressure measured at baseline. 150 patients (1%) had no post-baseline measurement, leaving 8470 with at least one post-baseline. The median time of last blood pressure visit out of those who had at least one measurement post-baseline was 5.3 years (IQR: 4.9-5.9, max: 7.1).

The distribution of visit times over the trial for ASCOT legacy patients is shown in the histogram below (Figure 30), split by those scheduled and unscheduled. 69% of all visits were scheduled. The unscheduled visits occurred for a variety of reasons: sometimes due to a patient having missed a scheduled visit; or because of a clinical visit for an unrelated reason, routine or otherwise.

The overall mean SBP at scheduled visits was lower than at unscheduled visits (when excluding blood pressure collected at randomisation), 139.42 vs. 141.60 mmHg, respectively. However, since average blood pressure was declining over time and a higher proportion of unscheduled visits occurred earlier on compared to scheduled,

once adjusted for time from randomisation to reduce confounding by time, the difference reduced substantially and scheduled visits were associated with only a slightly lower SBP of 0.39 mmHg compared to unscheduled visits (95% CI: 0.24, 0.55, $p<0.001$, from a linear mixed model with random components for time of visit and subject).

Figure 30: Distribution of patient visits at which a blood pressure reading was recorded



4.2.2 Changes in blood pressure during the ASCOT trial

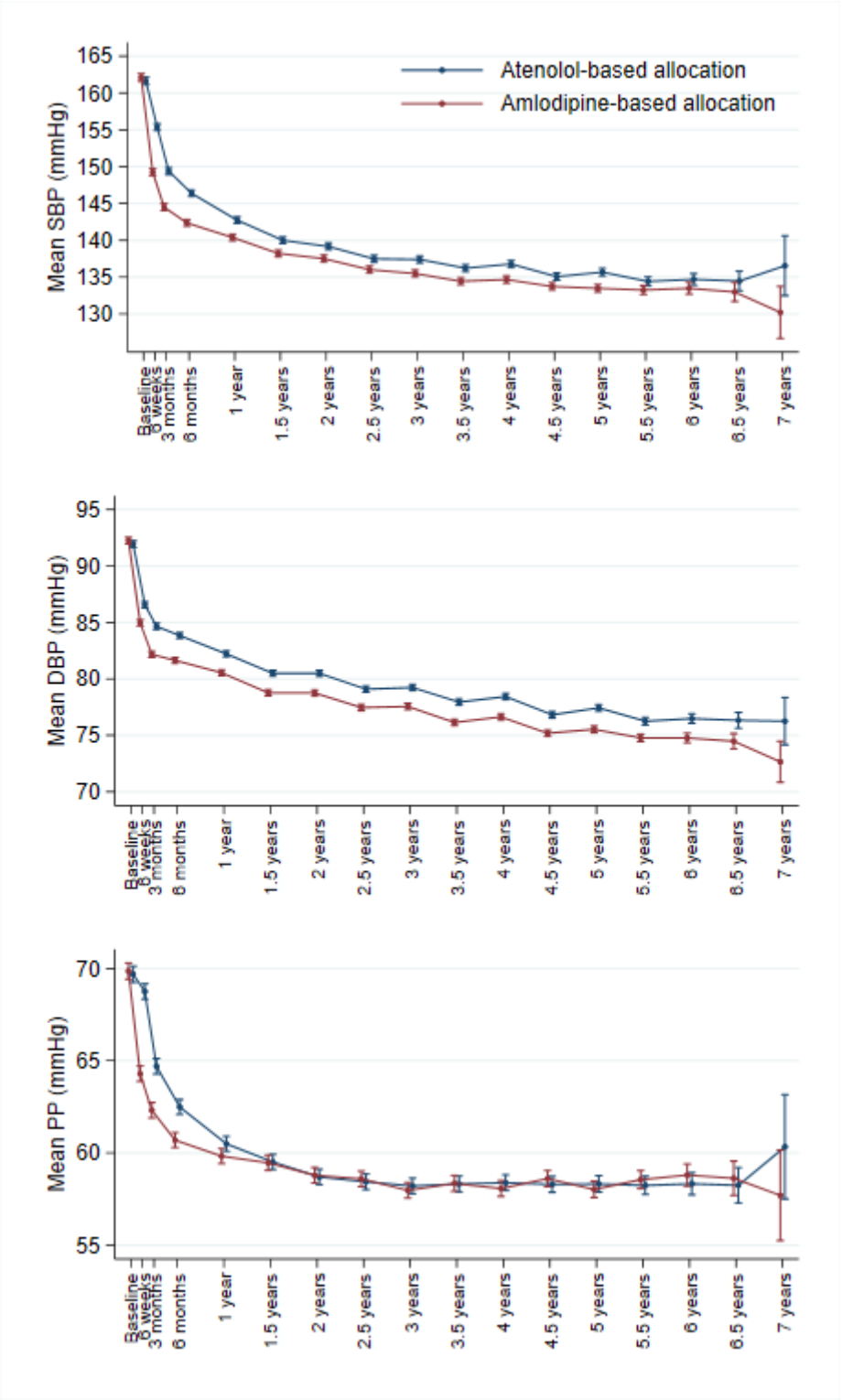
For the 8580 ASCOT legacy subjects, there was an initial steep decrease in blood pressure in the first 6 months after randomisation, following initiation of blood pressure-lowering trial treatment. As well as being a response to anti-hypertensive trial treatment, this initial decrease is also likely to be in part a consequence of being in a clinical trial context, as well as some regression to the mean as ASCOT

patients were recruited on the basis of having high blood pressure when measured at screening. After the first 6-month period, the steep decline in blood pressure reduced, but there remained a slight continued decrease in blood pressure over the remainder of the trial (see Figure 31). This pattern was similar for both SBP and DBP. For PP, following a similar steep early decline, there did not appear to be further decline PP after about year 3, while SBP and DBP continues to decline thereafter slightly.

Those allocated to amlodipine-based treatment had lower SBP and DBP following the baseline visit, compared to those allocated to atenolol-based treatment. There remained approximately a 2mmHg difference between treatment groups in both SBP and DBP throughout the whole of trial follow-up.

There appeared to be an initial difference in PP within the first year following baseline measurements, with those in the amlodipine-based group having lower PP. In the atenolol-based group, the initial decrease in SBP was proportionately less than the amlodipine-based group in relation to the initial decrease in DBP. This led to the initial difference in PP between groups, which later diminished once the difference in SBP and DBP between groups became similar after 1 year.

Figure 31: Mean profiles (with 95% CI bars) of blood pressure components across trial visits (scheduled only), by BPLA treatment allocation



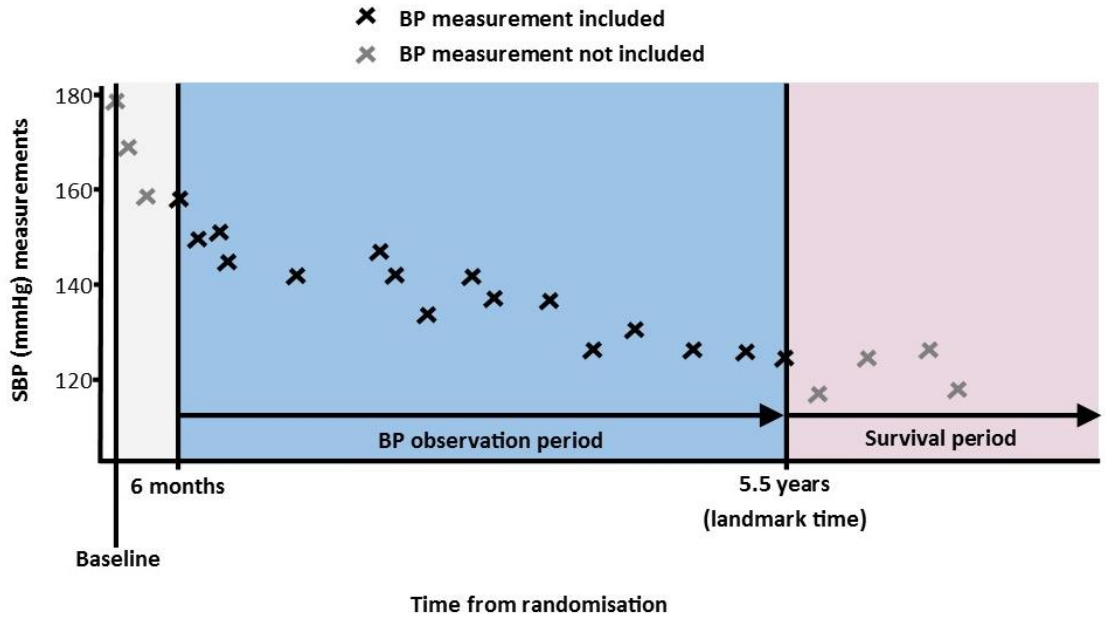
Number of patients with blood pressure measurement	8580	8188	8018	7855	7739	7577	7469	7299	7192	6996	6755	4434	2432	827	104

4.3 Broad analysis approach and descriptive statistics

4.3.1 General approach to analysis

A 5-year period defined from 6-months post-randomisation to the ASCOT trial until 5.5-years was used as the observation period from which repeated blood pressure measurements were utilised for analysis. 5.5 years was the median within-trial time for this population and so was thought an acceptable length in which to make use of the majority of measures, while maximising the survival follow-up time thereafter. The time of 5.5-years post randomisation represented a landmark time-point, which defined the origin for exposure time in survival analyses. Blood pressure measurements from the 6-month period after randomisation were excluded in order to remove the initial steep decline in blood pressure following initiation of trial treatment (see Figure 32).

Figure 32: Fictional SBP profile collected during the trial, blood pressure observation period and landmark time



Measurements of blood pressure from both scheduled and unscheduled visits were used in this analysis, and patients were included if they had at least 3 visits at which blood pressure was measured.

An initial exploration into how subject characteristics relate to blood pressure level and blood pressure variability was conducted. In addition, the change in blood pressure over seasons of the year and the influence of factors on seasonal variability were assessed.

The next step was to assess the relationship between both blood pressure level and blood pressure variability with the risk of CV-related mortality. The general approach to this analysis was to adopt a 2-stage method: the first stage consisting of estimation of blood pressure level and variability for each subject; and the

second stage involving relating these estimated within-subject measures to the survival process. This was a landmark analysis where repeated blood pressure measurements were utilised during the defined time period to estimate blood pressure level and variability. These estimates were then related to the survival process, beginning from the defined landmark time. Hence this analysis was conditional on subjects still being at risk at the landmark time, i.e. conditional on surviving until the landmark time and still being in follow-up.

4.3.2 Blood pressure during the 5-year observation period

By the specified landmark time, 5.5-years post-baseline, 7407 (86.3%) patients were alive and in observation. 681 patients had died prior and 492 patients had either been lost to follow-up or left the trial without giving consent for further follow-up.

Out of those 7407 patients still in follow-up, 7092 had at least three blood pressure measurements within the 5-year observation period and hence were included in analyses.

The median (IQR) number of visits at which blood pressure measures were taken was 13 (11-17), that's 9 (9-10) scheduled and 4 (2-7) unscheduled visits. 93.1% of subjects had at least one unscheduled visit during the observation period.

The overall mean across subjects for SBP and PP was 137.11 mmHg and 58.34 mmHg, respectively. Distributions of individuals' mean blood pressures are presented as histograms in Figure 33. The spread of PP mean relative to overall mean was larger than for SBP. The SD was 18.6% of the mean value (10.86 mmHg) for PP and 9.0% of the mean value (10.39 mmHg) for SBP. The wider distribution of PP mean values compared to SBP (and also DBP) seems logical as a consequence of its calculation from both DBP and SBP.

Distributions of the within-subject SD for PP and SBP are presented as histograms in Figure 34. The mean of the SDs was slightly higher for SBP at 11.77 mmHg than PP at 8.06 mmHg. For each component of blood pressure, the SD appeared slightly right-skewed from a normal distribution, expected to a degree as SDs are bound on the left-side by zero. SDs equal to zero can occur when all blood pressure measurements for a subject are the same. This was the case for one subject in relation to PP, but no subject had zero SD for SBP.

Within-subject SD was highly correlated with within-subject mean level for both PP and SBP. Figure 35 shows a plot of the relationship between the SD and mean level for each component of blood pressure. As mean blood pressure increases the SD increases. While this relationship appears to be fairly linear for PP, this relationship appears to have some curvature for SBP (test for linearity gives $p<0.001$), with the

gradient becoming steeper at higher SBP mean levels. The increase in variability in SBP measurements was not quite growing proportionately to the overall mean level.

Figure 33: Distributions of mean blood pressure presented as histograms for each component of blood pressure

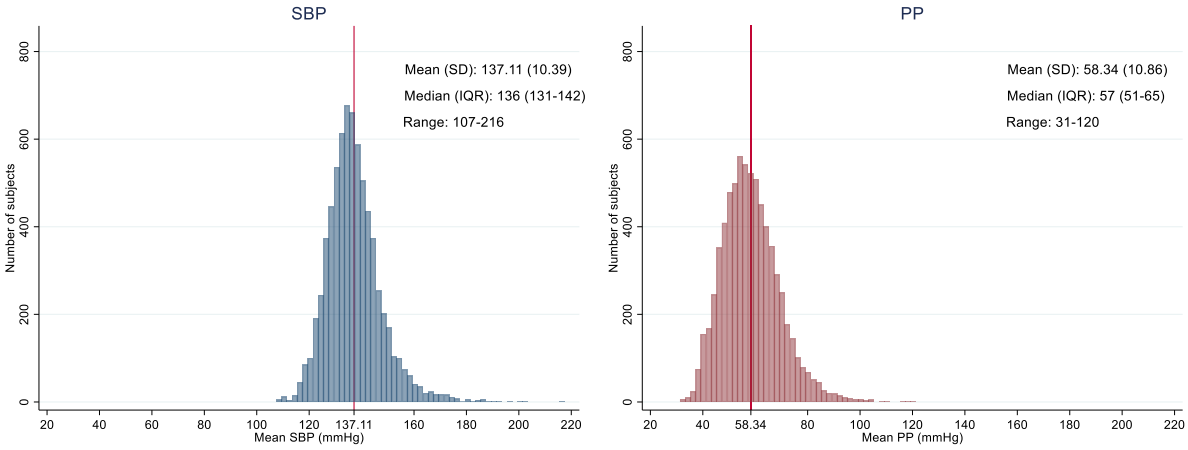


Figure 34: Distributions of blood pressure standard deviation presented as histograms for each component of blood pressure

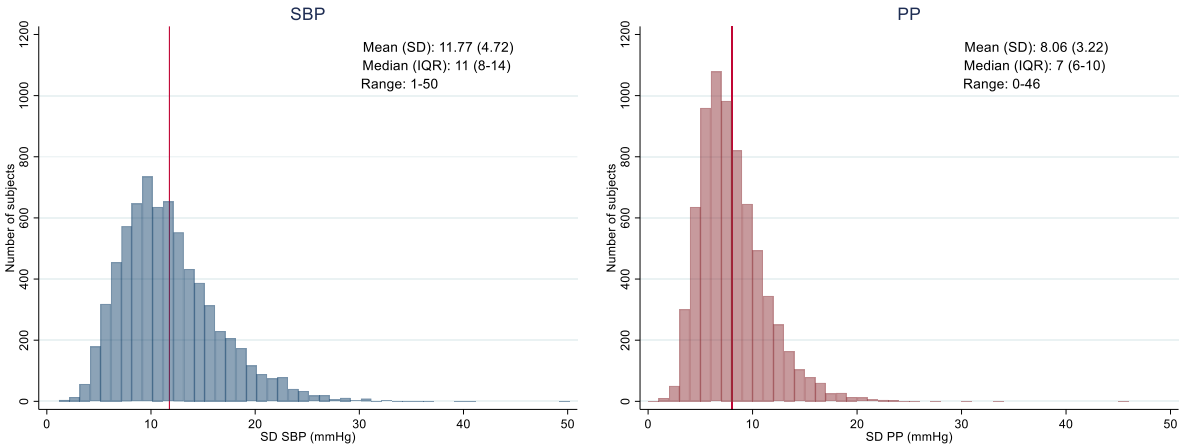
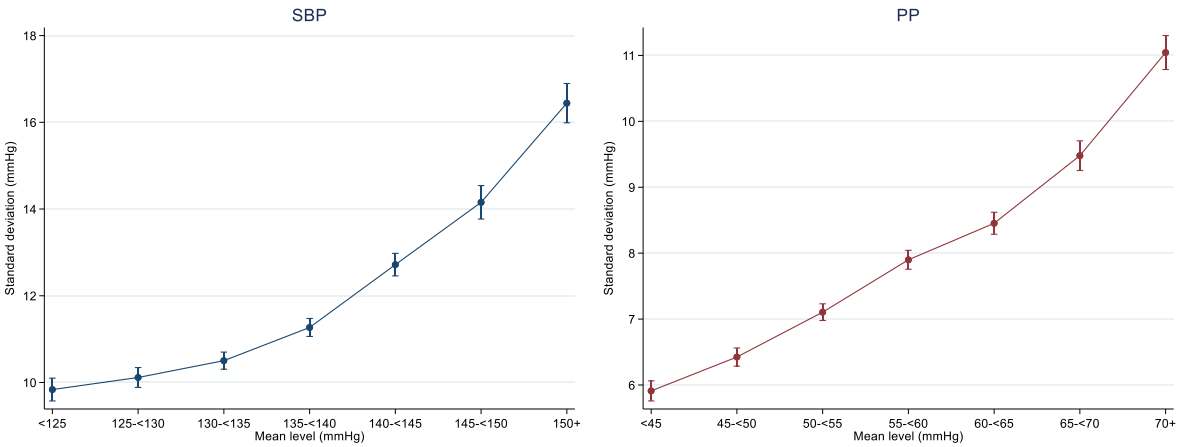


Figure 35: Relationship between standard deviation (95% CI) and mean blood pressure level



In the 7092 subjects included in analysis, mean SBP over the defined 5-year period of observation was lower in the amlodipine-based group (136.27 mmHg, SD=9.90) compared to the atenolol-based group (137.98 mmHg, SD=10.80), a difference of 1.71 mmHg (95% CI: 1.23-2.19, p<0.001). This difference was considered small from a clinically important perspective, and one that trial investigators suspected was not enough alone to account for the differences in outcomes between the treatment arms [138]. There was no difference in mean PP between the anti-hypertensive treatment arms (0.03 mmHg lower in the amlodipine-based arm, p=0.903).

There was a more striking difference between BPLA treatment groups in relation to blood pressure variability. The variability of both PP and SBP was substantially less in the amlodipine-based arm compared to that in the atenolol-based arm. The SD for SBP was 10.79 mmHg (SD=4.40) in the amlodipine-based arm and 12.78 mmHg

(SD=4.83) in the atenolol-based arm. Once adjusted for the mean level, the difference in SD was estimated at 1.69 mmHg lower in the amlodipine-based group (95% CI: 1.49-1.88, p<0.001). For PP the SD was estimated to be 1.06 mmHg lower in the amlodipine-based group (95% CI: 0.94-1.19, p<0.001) after adjustment for mean level.

4.4 Factors that influence blood pressure level and its variability following antihypertension treatment initiation

4.4.1 Background

Hypertension has long been understood to be both a disease and an important risk factor for other morbidities and death. It has been well established that there are many risk factors that increase the probability of developing hypertension. Genetic studies have suggested that certain individuals can have a susceptibility for hypertension, and when coupled with environmental risk factors can lead to increased risk of development. Certain risk factors have long been identified for high blood pressure, including age, obesity, having an inactive lifestyle, as well as dietary factors like high alcohol intake, smoking, and a high sodium intake [139-141]. Much research has focused on identifying genetic risk factors separate to environmental influences on blood pressure in order to improve the prediction of hypertension and improve patient care and assist with early intervention to help

reduce risk of hypertension-related morbidity and mortality in those identified as high risk [142].

Factors that influence variability in blood pressure have been explored and documented to a lesser extent than blood pressure level. With the growing realisation that variability as well as blood pressure level is an important risk factor for CV diseases, it is important to understand which factors influence variability, and which influences are associated with worse outcomes.

Clinical visit-to-visit variability in blood pressure in hypertensive subjects may be a result of poor blood pressure management as well as non-adherence to antihypertensive medication. Efforts to improve patient adherence have been an important research focus in recent years [143-147].

Blood pressure is known to vary in response to environmental changes, such as when there are changes in climate across the seasons [148-151]. This can occur for a number of reasons which include both direct effects from environmental changes such as changes in temperature, exposure to ultra-violet radiation, and other changes that people might be exposed to across the seasons, as well as indirect effects through comorbidities associated with different seasons [152].

The variation in blood pressure over the seasons has large implications for the management of blood pressure and hypertension. Some research has highlighted

factors that influence seasonal changes in blood pressure, such as age [153]. However, there has been relatively little research conducted to identify the extent to which patient-related characteristics influence seasonal variations in blood pressure.

4.4.2 Predictors of blood pressure level

4.4.2.1 Methods

Within-subject blood pressure level was represented by the arithmetic mean of each subject's blood pressure profile during the defined 5-year observation period (from 6 months to 5.5-years post-randomisation). Between-subject mean blood pressure was calculated across different categories of baseline characteristics. Multivariable linear regression was conducted in order to assess the relationship between baseline characteristics and within-subject blood pressure level. Mean differences in blood pressure level between categories, both unadjusted and adjusted, were estimated. These analyses were conducted for both SBP and PP.

4.4.2.2 Results

Mean within-subject SBP and PP mean levels during the defined 5-year observation period over categories of baseline characteristics are presented in Table 21.

Mean level of SBP was markedly higher with increasing age of subjects: an estimated 4.1 mmHg higher in those 75 years and over compared to those under

60, from an adjusted model ($p<0.001$). An even more striking difference was observed for PP between age-groups: an estimated 12.5 mmHg higher in those 75 years and over compared to those under 60 years ($p<0.001$). A similar pattern was seen with baseline measurements of blood pressure shown in Chapter 3, although differences were larger for baseline measurements with those 75 or more years of age having 11.8 mmHg and 18.3 mmHg higher baseline SBP and PP compared to those under 60 years, respectively.

While there was little difference in SBP between the sexes, males had a lower PP than women, with an adjusted estimated 1.6 mmHg lower ($p<0.001$), a smaller difference compared to baseline blood pressure with males having an adjusted 3.4 mmHg lower baseline PP compared to women ($p<0.001$).

Those of Asian ethnicity had the lowest mean SBP and PP compared to other ethnicities. After adjustment mean SBP was estimated to be 1.9 mmHg lower in those of Asian ethnicity compared to those of White ethnicity ($p=0.009$). Those of Black ethnicity had an estimated 1.3 mmHg higher SBP compared to those of White ethnicity ($p=0.023$). Those of White ethnicity had the highest mean PP, but after adjustment there was little difference between the different ethnic groups.

While there was no evidence of a difference in SBP between BMI groups, there was a trend towards decreased PP with higher BMI ($p<0.001$), as seen with baseline PP measurements. Those with diabetes mellitus at baseline had an estimated 3.3

mmHg higher PP compared to those without ($p<0.001$), while there was no difference in SBP in adjusted models.

There was strong evidence of a trend of decreasing blood pressure with increasing age at which subjects left full-time education, both for SBP and PP ($p<0.001$ for both). There was no evidence of a difference in blood pressure between non-smokers compared to ex- or current smokers. There was a trend of increasing blood pressure with increasing average weekly units of alcohol consumed for both SBP and PP. Those who reported drinking 28 units or more per week had estimated adjusted increased SBP and PP of 1.9 mmHg and 1.4 mmHg, respectively, compared to those who reported no intake ($p<0.001$ for both).

Table 21: Level of blood pressure based on within-subject arithmetic mean during 5-year observation period, by categories of baseline characteristics, with unadjusted and adjusted mean differences

			Systolic blood pressure					Pulse pressure				
Risk factor	Risk factor group	No. subjects (N=7092)	Mean (SD)	Crude difference (95% CI)	P-value**	Adjusted difference (95% CI)*	P-value**	Mean (SD)	Crude difference (95% CI)	P-value**	Adjusted difference (95% CI)*	P-value**
Age (years)	40-59	2255	135.7 (9.8)	ref		ref		53.2 (9.4)	ref		ref	
	60-64	1576	136.3 (9.7)	0.6 (-0.1, 1.2)		0.6 (-0.1, 1.2)		56.9 (9.6)	3.7 (3.0, 4.3)		3.4 (2.7, 4.0)	
	65-69	1568	137.6 (10.8)	1.9 (1.2, 2.6)		1.8 (1.1, 2.6)		60.4 (10.1)	7.2 (6.6, 7.8)		6.7 (6.0, 7.3)	
	70-74	1111	138.9 (11.1)	3.2 (2.4, 3.9)		3.0 (2.2, 3.9)		63.6 (10.8)	10.4 (9.7, 11.2)		9.6 (8.8, 10.4)	
	75+	582	139.9 (10.9)	4.2 (3.2, 5.1)	p<0.001	4.1 (3.0, 5.1)	p<0.001	66.6 (10.6)	13.4 (12.5, 14.3)	p<0.001	12.5 (11.5, 13.5)	p<0.001
Sex	Female	1335	136.7 (11.7)	ref		ref		60.6 (11.6)	ref		ref	
	Male	5757	137.2 (10.1)	0.5 (-0.1, 1.1)	p=0.096	0.6 (-0.1, 1.3)	p=0.075	57.8 (10.6)	-2.7 (-3.4, -2.1)	p<0.001	-1.6 (-2.3, -0.9)	p<0.001
Ethnic background	White	6328	137.2 (10.3)	ref		ref		58.6 (10.8)	ref		ref	
	Asian (east/south)	218	133.6 (12.4)	-3.6 (-5.0, -2.2)		-1.9 (-3.4, -0.5)		55.1 (11.8)	-3.5 (-4.9, -2.0)		-0.7 (-2.0, 0.7)	
	Black	397	137.5 (10.8)	0.2 (-0.8, 1.3)		1.3 (0.2, 2.3)		56.7 (10.6)	-1.8 (-2.9, -0.7)		-0.4 (-1.4, 0.7)	
	Mixed/other	149	136.2 (10.4)	-1.0 (-2.7, 0.7)	p<0.001	0.1 (-1.6, 1.8)	p=0.004	57.0 (10.6)	-1.6 (-3.3, 0.2)	p<0.001	-0.7 (-2.3, 0.9)	p=0.615
Age left full-time education (years) (4 missing)	12-14	1999	138.6 (11.0)	ref		ref		62.6 (11.0)	ref		ref	
	15-16	3562	136.9 (10.1)	-1.6 (-2.2, -1.0)		-0.1 (-0.8, 0.5)		57.2 (10.4)	-5.4 (-6.0, -4.8)		-0.6 (-1.3, -0.0)	
	17-18	811	135.5 (10.2)	-3.0 (-3.8, -2.2)		-1.8 (-2.7, -0.9)		55.7 (10.2)	-6.9 (-7.7, -6.0)		-2.8 (-3.7, -2.0)	
	19+	716	135.7 (9.6)	-2.8 (-3.7, -1.9)	p<0.001	-1.4 (-2.4, -0.5)	p<0.001	55.0 (9.9)	-7.6 (-8.5, -6.7)	p<0.001	-2.7 (-3.6, -1.8)	p<0.001
BMI (kgm-2)	<25	1283	136.9 (10.5)	ref		ref		59.5 (11.0)	ref		ref	
	25- <30	3325	137.4 (10.3)	0.5 (-0.1, 1.2)		0.6 (-0.1, 1.2)		58.7 (11.1)	-0.7 (-1.4, -0.0)		-0.5 (-1.1, 0.1)	
	30- <35	1819	136.7 (10.3)	-0.2 (-0.9, 0.6)		0.2 (-0.5, 0.9)		57.1 (10.4)	-2.4 (-3.2, -1.6)		-1.4 (-2.1, -0.7)	
	≥35	665	137.0 (10.9)	0.1 (-0.9, 1.1)	p=0.089	0.9 (-0.0, 1.9)	p=0.158	57.5 (10.4)	-2.0 (-3.0, -0.9)	p<0.001	-0.7 (-1.7, 0.2)	p<0.001
Smoking status within 1 year	Non-smoker	2346	137.1 (10.6)	ref		ref		58.1 (10.6)	ref		ref	
	Current/ex	4746	137.1 (10.3)	0.0 (-0.5, 0.5)	p=0.987	-0.4 (-0.9, 0.1)	p=0.116	58.4 (11.0)	0.3 (-0.2, 0.9)	p=0.215	0.4 (-0.1, 0.9)	p=0.118
Average weekly units of alcohol consumed	No intake	1773	136.9 (11.2)	ref		ref		59.3 (11.3)	ref		ref	
	Intake 1 - <14	3021	136.7 (10.2)	-0.2 (-0.8, 0.4)		-0.1 (-0.8, 0.5)		58.1 (10.8)	-1.2 (-1.9, -0.6)		-0.4 (-1.0, 0.2)	
	Intake 14 - < 28	1378	137.5 (9.7)	0.6 (-0.1, 1.3)		0.8 (0.1, 1.6)		57.8 (10.6)	-1.5 (-2.3, -0.8)		0.1 (-0.6, 0.9)	
	Intake 28+	920	138.3 (10.0)	1.4 (0.6, 2.2)	p<0.001	1.9 (1.0, 2.8)	p<0.001	58.0 (10.5)	-1.3 (-2.2, -0.4)	p<0.001	1.4 (0.6, 2.2)	p<0.001
Diabetes mellitus	No	5119	137.2 (10.0)	ref		ref		57.4 (10.6)	ref		ref	
	Yes	1973	136.8 (11.3)	-0.5 (-1.0, 0.1)	p=0.100	-0.3 (-0.8, 0.3)	p=0.359	60.6 (11.3)	3.2 (2.6, 3.8)	p<0.001	3.3 (2.7, 3.8)	p<0.001

* adjusted for all other baseline risk factors in the table in multivariable linear regression models. Subjects with missing values for "age left education" were included in multivariable models, grouped into missing categories when missing.

** P-values from likelihood ratio tests.

4.4.3 Predictors of blood pressure variability

4.4.3.1 Methods

The variability in blood pressure was expressed on a subject-by-subject basis as the standard deviation which was calculated on measures collected during the defined 5-year observation period (from 6 months to 5.5-years post-randomisation). Mean variability (mean of within-subject SD) was calculated across different categories of baseline characteristics. Crude and adjusted mean differences between categories were estimated using linear regression models. These analyses were conducted for both SBP and PP.

Adjusted models controlled for other important baseline risk factors. When estimating adjusted differences in blood pressure level (as presented in the previous section), models were not adjusted for blood pressure variability. This is because on average blood pressure variability increases with increasing mean level. Hence to adjust for variability when interested in blood pressure level would attribute some of the effect of blood pressure level to the corresponding level of variability, and reduce the estimated association between blood pressure level and risk in a way that we do not want. Conversely, when studying blood pressure variability, the part of increased blood pressure variability that is purely a consequence of increased blood pressure level is not of interest and the part of variability that is independent of the mean is of interest. Hence, when estimating

adjusted differences in blood pressure variability, blood pressure level was adjusted for in models.

4.4.3.2 Results

Mean within-subject SDs of SBP and PP during the defined 5-year observation period over categories of baseline characteristics are presented in Table 22.

The SD in SBP was strikingly different across categories of age, getting progressively larger with increasing age of subjects, even after adjustment for mean level. Those 75 years and over had 1.8 mmHg greater SD compared to those under 60 ($p<0.001$). While there was strong evidence of increasing PP SD with increasing age, in adjusted models the differences were reduced, with those 75 years and older having 0.5 mmHg higher PP SD compared to those under 60 years ($p<0.001$).

There was also a difference in the SD of SBP and PP between males and females, which remained after adjustment with males having 1.5 mmHg lower SBP SD ($p<0.001$) and 0.9 mmHg lower PP SD ($p<0.001$).

From adjusted models, those of White ethnicity had slightly lower SBP SD compared to other ethnic backgrounds, but there was no evidence of a difference in PP SD.

Although the SD of SBP seemed to decline as age the subject left full-time education increased, after adjustment there was no evidence of a difference, and neither was there for PP SD.

Although there was little difference in PP SD between BMI groups, after adjustment strong evidence for a small trend in increasing SD with increasing BMI level was revealed ($p<0.001$). There was no evidence of a difference in SBP SD across BMI groups.

Those who were diabetic at baseline had higher SBP SD compared to non-diabetics ($p<0.001$), as well as marginally higher PP SD ($p=0.009$). As obesity can contribute to the onset of diabetes and hence may be on the causal pathway, an adjusted model was built without adjustment for BMI. However, there was little change and the adjusted estimated differences in the SD of both SBP and PP were consistent with or without adjustment for BMI.

Those who were current smokers or ex-smokers within a year from randomisation had slightly higher SD for both SBP and PP compared to non-smokers ($p<0.001$ for both) after adjustment.

There were small differences in blood pressure variability across different levels of alcohol consumption. The group that had the lowest variability in both SBP and PP was those who reported alcohol consumption of between1 and 14 units per week. It appeared that there was a trend of increasing variability with increasing alcohol intake, but the group with no intake did not have the lowest variability. This pattern was the same for both SBP and PP.

Table 22: Variability of blood pressure based on within-subject standard deviation during 5-year observation period, by categories of baseline characteristics, with unadjusted and adjusted mean differences

			Systolic blood pressure					Pulse pressure				
Risk factor	Risk factor group	No. subjects (N=7092)	Mean (SD)	Crude difference (95% CI)	P-value**	Adjusted difference (95% CI)*	P-value**	Mean (SD)	Crude difference (95% CI)	P-value**	Adjusted difference (95% CI)*	P-value**
Age (years)	40-59	2255	10.8 (4.3)	ref		ref		7.1 (2.7)	ref		ref	
	60-64	1576	11.5 (4.5)	0.7 (0.4, 1.0)		0.5 (0.2, 0.8)		7.8 (2.9)	0.7 (0.5, 0.9)		0.2 (-0.0, 0.4)	
	65-69	1568	12.1 (4.8)	1.3 (1.0, 1.6)		0.9 (0.6, 1.2)		8.4 (3.3)	1.3 (1.1, 1.5)		0.3 (0.1, 0.5)	
	70-74	1111	12.8 (5.0)	1.9 (1.6, 2.3)		1.3 (1.0, 1.7)		9.0 (3.6)	1.9 (1.7, 2.1)		0.5 (0.2, 0.7)	
	75+	582	13.4 (5.2)	2.5 (2.1, 3.0)	p<0.001	1.8 (1.3, 2.2)	p<0.001	9.4 (3.5)	2.3 (2.0, 2.6)	p<0.001	0.5 (0.2, 0.8)	p<0.001
Sex	Female	1335	12.9 (5.2)	ref		ref		9.1 (3.7)	ref		ref	
	Male	5757	11.5 (4.6)	-1.4 (-1.7, -1.2)	p<0.001	-1.5 (-1.8, -1.2)	p<0.001	7.8 (3.1)	-1.3 (-1.5, -1.1)	p<0.001	-0.9 (-1.1, -0.8)	p<0.001
Ethnic background	White	6328	11.7 (4.7)	ref		ref		8.1 (3.2)	ref		ref	
	Asian (east/south)	218	11.2 (4.3)	-0.5 (-1.1, 0.1)		0.6 (-0.0, 1.2)		7.4 (3.0)	-0.6 (-1.1, -0.2)		-0.0 (-0.4, 0.4)	
	Black	397	12.3 (4.9)	0.6 (0.1, 1.1)		0.6 (0.1, 1.0)		8.0 (3.6)	-0.1 (-0.4, 0.3)		0.2 (-0.1, 0.5)	
	Mixed/other	149	12.5 (4.4)	0.8 (0.0, 1.6)	p=0.006	0.8 (0.1, 1.5)	p=0.005	8.1 (2.9)	0.0 (-0.5, 0.5)	p=0.036	0.1 (-0.4, 0.5)	p=0.681
Age left full-time education (years) (4 missing)	12-14	1999	12.5 (5.0)	ref		ref		8.8 (3.4)	ref		ref	
	15-16	3562	11.6 (4.6)	-1.0 (-1.2, -0.7)		-0.0 (-0.3, 0.3)		7.8 (3.1)	-1.0 (-1.2, -0.8)		0.0 (-0.2, 0.2)	
	17-18	811	11.2 (4.6)	-1.3 (-1.7, -0.9)		-0.2 (-0.6, 0.2)		7.7 (3.2)	-1.1 (-1.4, -0.9)		0.1 (-0.2, 0.3)	
	19+	716	11.3 (4.3)	-1.2 (-1.7, -0.8)	p<0.001	-0.1 (-0.4, 0.3)	p=0.091	7.5 (2.8)	-1.3 (-1.5, -1.0)	p<0.001	0.1 (-0.2, 0.4)	p=0.173
BMI (kgm-2)	<25	1283	11.9 (4.9)	ref		ref		8.1 (3.3)	ref		ref	
	25- <30	3325	11.7 (4.7)	-0.2 (-0.5, 0.1)		-0.2 (-0.4, 0.1)		8.0 (3.3)	-0.1 (-0.3, 0.1)		0.1 (-0.1, 0.2)	
	30- <35	1819	11.8 (4.6)	-0.1 (-0.4, 0.3)		0.1 (-0.2, 0.4)		8.1 (3.0)	-0.1 (-0.3, 0.2)		0.3 (0.1, 0.5)	
	≥35	665	11.8 (4.7)	-0.0 (-0.5, 0.4)	p=0.676	0.0 (-0.4, 0.4)	p=0.148	8.2 (3.1)	0.1 (-0.2, 0.4)	p=0.322	0.4 (0.1, 0.7)	p<0.001
Smoking status within 1 year	Non-smoker	2346	11.6 (4.7)	ref		ref		8.0 (3.2)	ref		ref	
	Current/ex	4746	11.8 (4.7)	0.2 (-0.0, 0.4)	p=0.108	0.4 (0.2, 0.6)	p<0.001	8.1 (3.2)	0.2 (-0.0, 0.3)	p=0.064	0.2 (0.1, 0.4)	p=0.001
Average weekly units of alcohol consumed	No intake	1773	12.3 (4.9)	ref		ref		8.5 (3.3)	ref		ref	
	Intake 1 - <14	3021	11.5 (4.7)	-0.7 (-1.0, -0.5)		-0.3 (-0.6, -0.1)		7.9 (3.2)	-0.5 (-0.7, -0.4)		-0.2 (-0.3, 0.0)	
	Intake 14 - < 28	1378	11.6 (4.5)	-0.7 (-1.0, -0.4)		-0.2 (-0.5, 0.2)		7.9 (3.0)	-0.6 (-0.8, -0.4)		0.0 (-0.2, 0.2)	
	Intake 28+	920	11.9 (4.6)	-0.4 (-0.8, -0.0)	p<0.001	0.2 (-0.2, 0.6)	p=0.005	7.9 (3.1)	-0.5 (-0.8, -0.3)	p<0.001	0.1 (-0.2, 0.3)	p=0.056
Diabetes mellitus	No	5119	11.6 (4.7)	ref		ref		7.8 (3.1)	ref		ref	
	Yes	1973	12.3 (4.8)	0.8 (0.5, 1.0)	p<0.001	0.7 (0.4, 0.9)	p<0.001	8.6 (3.4)	0.8 (0.6, 0.9)	p<0.001	0.2 (0.0, 0.4)	p=0.009

* adjusted for all other baseline risk factors in the table, as well as for mean level, in multivariable linear regression models. Subjects with missing values for "age left education" were included in multivariable models, grouped into missing categories when missing.

** P-values from likelihood ratio tests.

4.4.4 Seasonal variability in blood pressure

4.4.4.1 Methods

Using blood pressure measurements from subjects that had at least three blood pressure measurements within the defined 5-year observation period, the variation in blood pressure over seasons of the year was investigated. Linear mixed models with random components for time and subject were used to estimate mean blood pressure level in each month of the calendar year, allowing correlation between within-subject measures to differ from between-subject correlation. Mean blood pressure was estimated in each month of the year overall, and then in subgroups of baseline age, sex, and BPLA trial treatment allocation by adding interaction terms to the model.

Adjusted models were developed to estimate mean blood pressure differences between summer time and winter time. Summer was defined from 21 June to 22 September, and Winter time was defined from 21 December to 19 March, to reflect the seasons in the northern hemisphere. The models were adjusted for predefined baseline risk factors, and the time since randomisation (since blood pressure was on average also declining slightly over time year-to-year post baseline).

Adjusted mean differences between the coldest and warmest months were also calculated in each subgroup, from inclusion of an interaction term between a factor and time of year. Interactions were tested statistically.

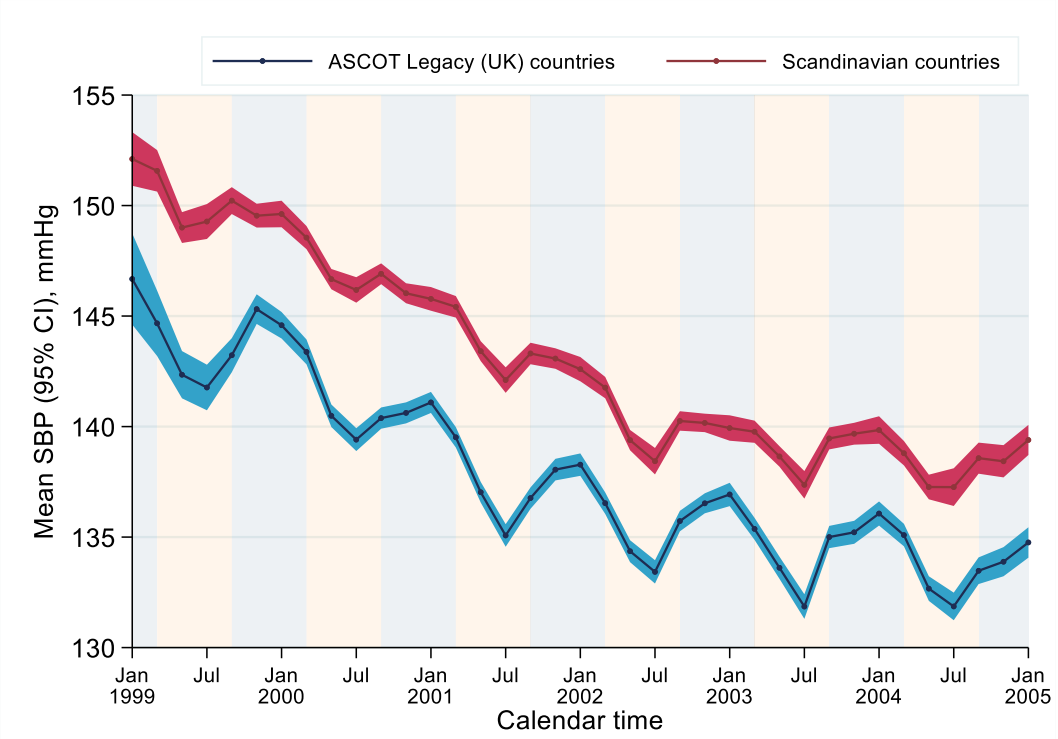
Baseline blood pressure measurements were excluded in these analyses. This was because baseline measures were substantially higher, on average, compared to the usual level over the course of the trial, and the time of year that patients were randomised was not spread out equally and likely to not be at random. In addition, the first 6 months of blood pressure measures were excluded from analysis as the mean blood pressure decreased rapidly at first following initiation into the trial and beginning trial treatment. After 6 months, mean blood pressure levels continued to decline but to a lesser extent and in more of a linear fashion. Hence, making an adjustment for time since randomisation when using post 6-month measurement was considered acceptable.

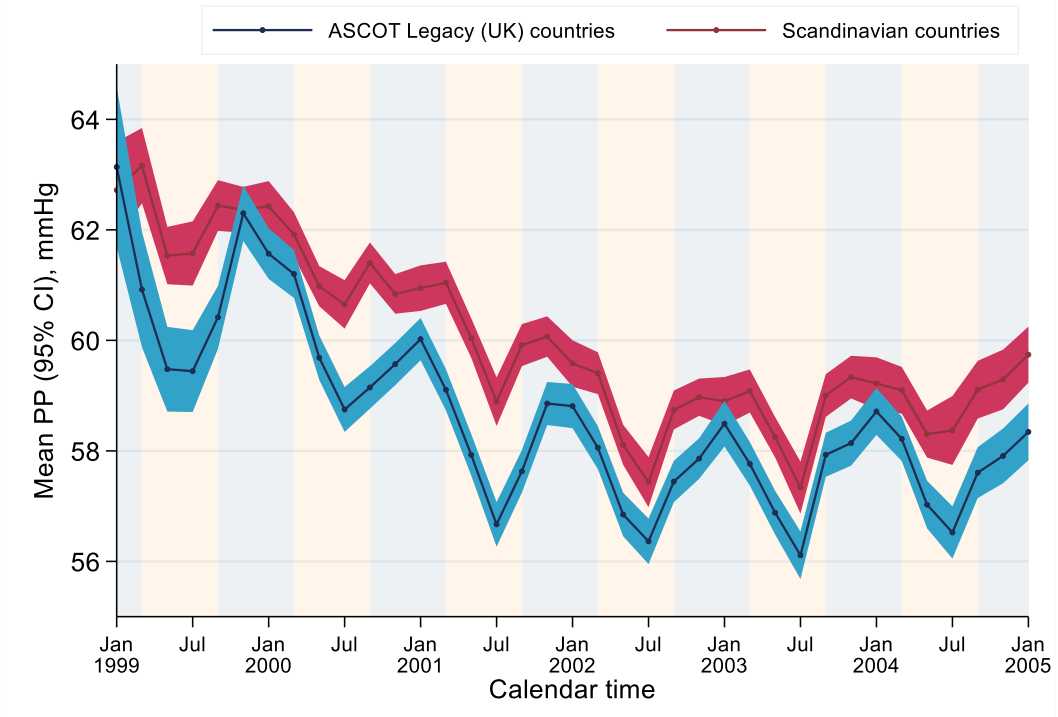
In order to explore geographical differences in seasonal variability, analyses were conducted on repeated blood pressure measures from the Scandinavian countries that participated in the ASCOT trial and compared to the ASCOT legacy UK subjects. Blood pressure measurements as recorded at scheduled and unscheduled visits from the same 5-year observation time-period as defined for UK subjects were used. Models were run with both UK patients and Scandinavian patients in the same model with an interaction between the two geographical regions.

4.4.4.2 Results

The 7092 UK ASCOT legacy subjects and a further 9795 subjects from Scandinavian counties were included in these analyses. Figure 36 presents mean SBP and PP levels over calendar time between 1999 and 2005, separately for the two geographical regions. The varying levels of SBP clearly follow a seasonal pattern with highs during the colder winter months and lows during the warmer summer months. Blood pressure levels were consistently higher in Scandinavian countries compared to the UK for both SBP and PP. However, the pattern in seasonal blood pressure change appears visually to be slightly less pronounced in Scandinavian countries compared the UK. Behind changes in blood pressure level over the seasons, there is a general overall decline which is steeper between 1999 and about 2002, before further overall reduction slows thereafter. The patterns for PP were similar to that of SBP.

Figure 36: Plots of mean SBP & PP (95% CI) over calendar time from 1999 to beginning of 2005





Note: estimates are from a linear mixed model with random components for calendar time and subject. Months are grouped into pairs, starting with January & February 1999, and so on.

Overall, the estimated adjusted mean difference in SBP and PP between the winter and summer periods was 2.63 mmHg and 1.58 mmHg, respectively.

There was strong evidence for a seasonal effect at all ages, with both SBP and PP being lower in summer months compared to winter in each age group. However, the difference was markedly larger in older subjects compared to younger, with strong evidence for this interaction for both SBP and PP ($p<0.001$ in both cases). Figure 38 illustrates the difference in magnitude of change in blood pressure over the months of the year between the age groups. For those <55 years of age, the estimated mean SBP was 1.74 mmHg lower in summer than in winter ($p<0.001$), and PP was 1.12 mmHg lower ($p<0.001$). Whilst in the oldest age group, those 75 years and older, SBP was 3.67 mmHg lower in summer compared to winter ($p<0.001$), and PP was 2.34 mmHg lower ($p<0.001$).

The change in mean blood pressure between seasons was similar for females and males, with females having a very slightly higher mean increase in both SBP and PP in summer compared to men (interaction p-values 0.204 & 0.014, respectively).

Figure 37 shows mean blood pressure levels by individual months of the year, separately for UK and Scandinavian countries. Overall, mean SBP was a lot higher in Scandinavian countries compared to the UK: 142.85 mmHg compared to 137.13

mmHg, respectively. Mean PP was also higher in Scandinavian countries compared to the UK, but the difference was not as striking: 59.89 mmHg compared to 58.35 mmHg, respectively. Trial entry criteria was the same for both geographical regions, but baseline SBP was higher in those from Scandinavia compared to the UK: mean SBP was 165.68 mmHg and 161.36 mmHg, respectively. However, there was little difference in PP at baseline: mean PP was 68.94 mmHg for Scandinavian subjects and 69.18 mmHg in UK subjects. These differences in blood pressure between geographical regions could not be explained by differences in ethnic background. For both regions, SBP and PP was lowest in the 3 summer months: June to August. The magnitude in change blood pressure was larger in UK subjects compared to Scandinavian subjects.

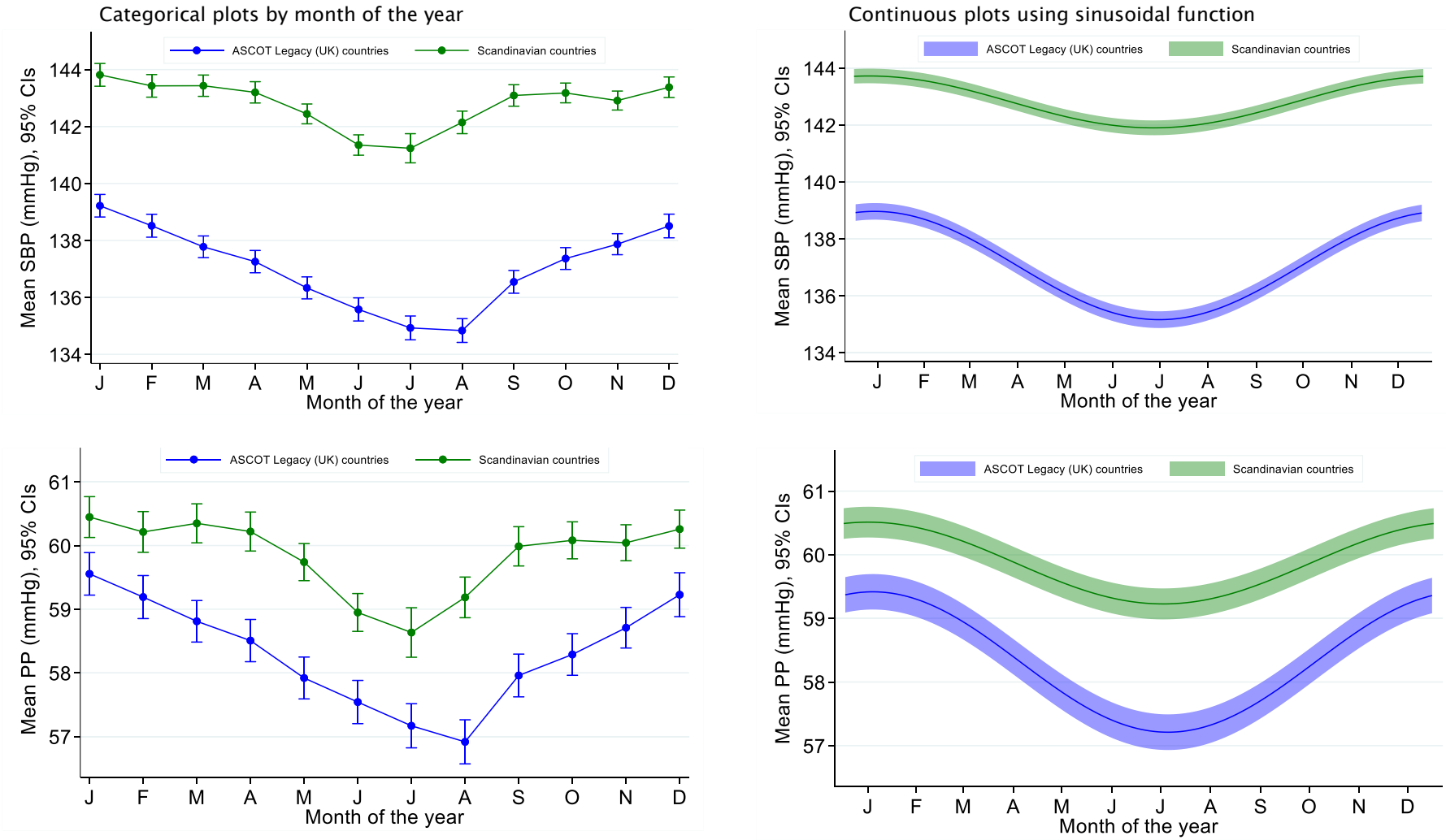
From adjusted models there was a fairly striking difference in the magnitude of change in SBP and PP between geographical regions, with strong evidence of interactions ($p<0.001$ in for both components of blood pressure). Mean SBP was estimated to have risen by 3.43 mmHg in the UK and 1.76 mmHg in Scandinavian countries in the summer compared to winter, and PP by 1.96 mmHg in the UK and 1.17 mmHg in Scandinavian countries.

There was some evidence for interactions between blood pressure levels and which allocated BPLA trial treatment group subjects were assigned to, although the actual differences were small. Those assigned to amlodipine-based treatment had a

slightly larger estimated adjusted increase in both SBP and PP in the summer season (interaction p-values 0.022 & 0.008, respectively).

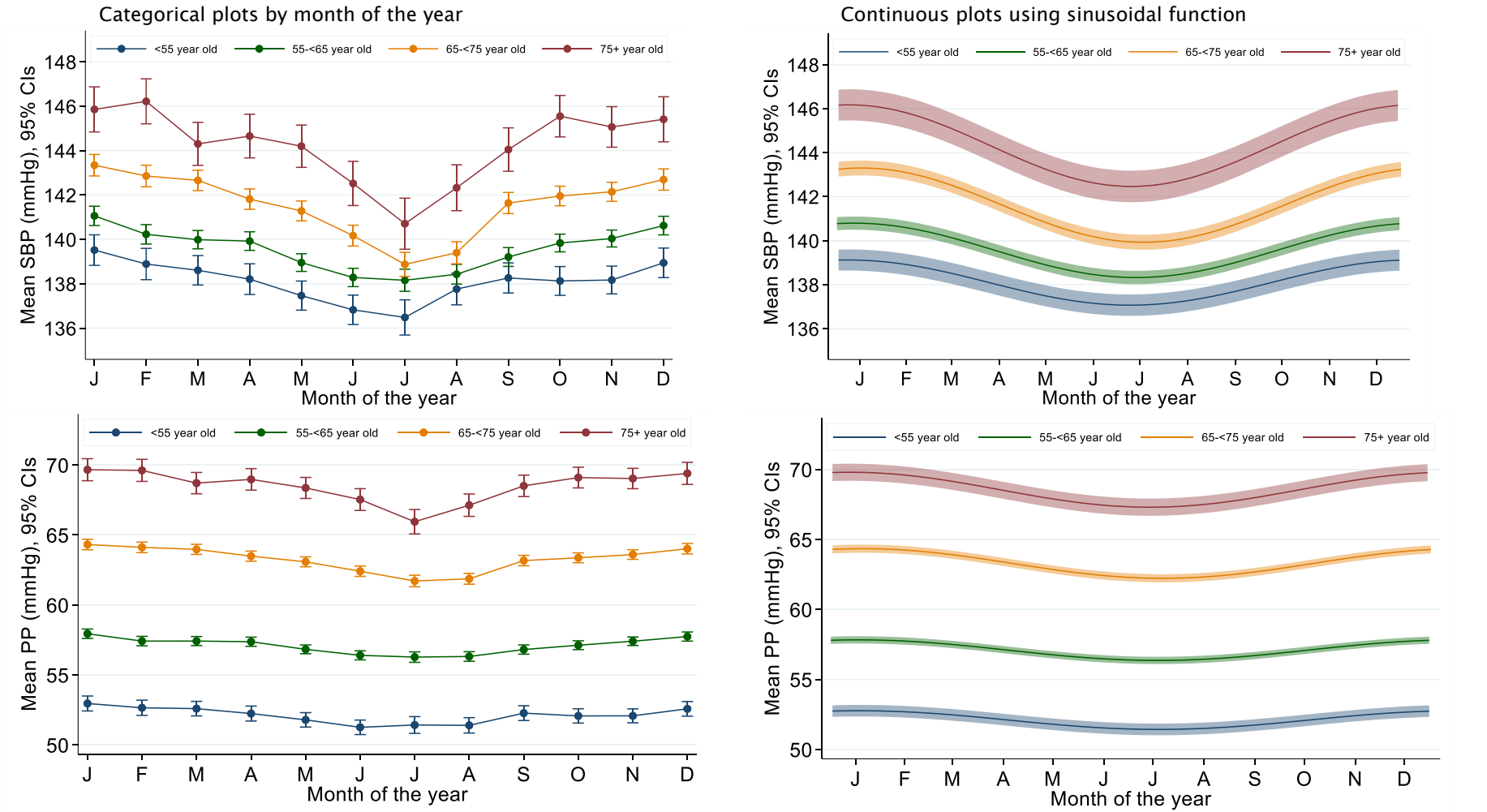
Table 23 presents adjusted blood pressure differences between summer and winter time by subgroups, and Figure 39 presents a forest plot of differences by subgroup.

Figure 37: Mean SBP (95% CI) by month of the year, by age at baseline and geographical region



Note: estimates are from a linear mixed model with random components for time of the year and subject, with a fixed component interaction between time of the year and geographical region

Figure 38: Mean SBP (95% CI) by month of the year, by age at baseline



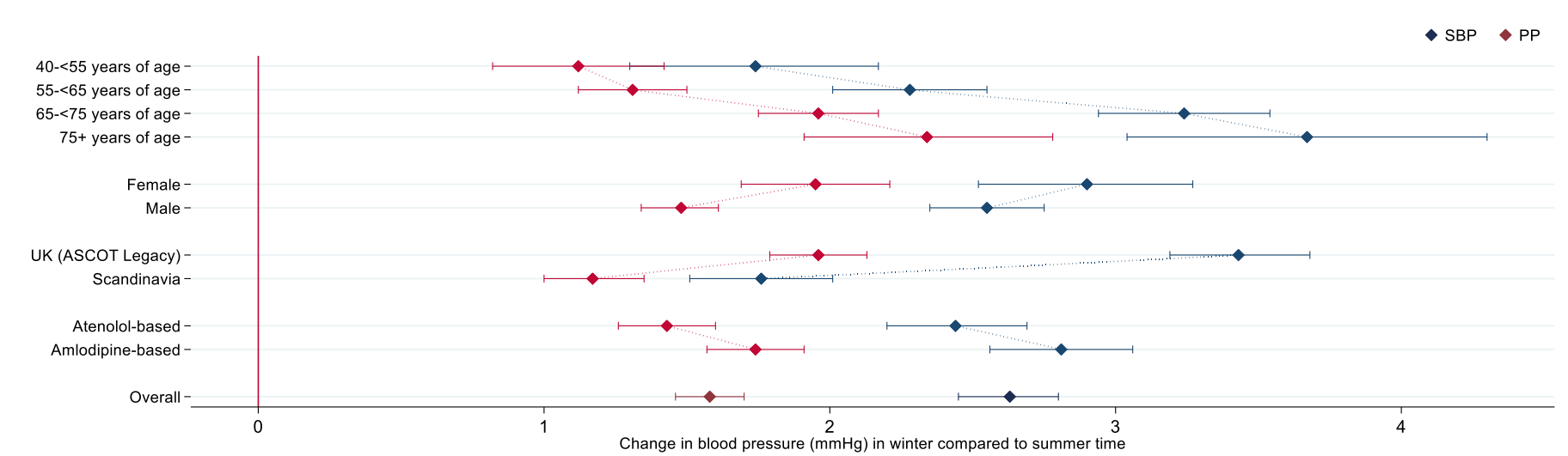
Note: estimates are from a linear mixed model with random components for time of the year and subject, with a fixed component interaction between time of the year and age-group)

Table 23: Mean difference in blood pressure (95% CI, mmHg) between Summer and Winter time, overall and by subgroups

			Systolic blood pressure			Pulse pressure		
Subgroup		Number of subjects	Adjusted mean difference (95% CI)	P-value	Interaction p-value	Adjusted mean difference (95% CI)	P-value	Interaction p-value
Age (years)	40-<55	2783	1.74 (1.30-2.17)		<0.001	1.12 (0.82-1.42)		<0.001
	55-<65	7171	2.28 (2.01-2.55)			1.31 (1.12-1.50)		
	65-<75	5649	3.24 (2.94-3.54)			1.96 (1.75-2.17)		
	75+	1284	3.67 (3.04-4.30)			2.34 (1.91-2.78)		
Sex	Female	3965	2.90 (2.52-3.27)		0.204	1.95 (1.69-2.21)		0.014
	Male	12922	2.55 (2.35-2.75)			1.48 (1.34-1.61)		
Region	UK (ASCOT Legacy)	7092	3.43 (3.19-3.68)		<0.001	1.96 (1.79-2.13)		<0.001
	Scandinavia	9795	1.76 (1.51-2.01)			1.17 (1.00-1.35)		
BPLA treatment allocation	Atenolol-based	8384	2.44 (2.20-2.69)		0.022	1.43 (1.26-1.60)		0.008
	Amlodipine-based	8503	2.81 (2.56-3.06)			1.74 (1.57-1.91)		
Overall		16887	2.63 (2.45-2.80)	<0.001		1.58 (1.46-1.70)	<0.001	

Note: estimates are from linear mixed models with random components for time of year group and subject, adjusted for pre-specified baseline risk factors. Interaction p-value for age groups is from a test for trend (linear).

Figure 39: Forest plot of mean change in blood pressure (95% CI, mmHg) in summer compared to winter time



4.4.5 Conclusions and Discussion

It is well documented that SBP increases with age, and that DBP decreases with age and hence a resultant large increase in pulsatile pressure with increasing age [95,104]. The mechanism behind a wider PP with increasing age is thought to be largely a consequence of arterial stiffness that increases with age, as mentioned in the previous chapter. In these data there was a striking increase in PP mean with increasing age, an average increase of over 12 mmHg in PP for those 75 years or older compared to those under 60 years.

The largest differences in blood pressure variability were seen across age-groups and between the sexes. The SD of SBP was higher in older subjects and to a lesser extent the trend was similar with PP variability. This was independent of the mean values. This may be in part due to the increased seasonal variation over the year that we see in older subjects, highlighting an increased frailty and vulnerability in those more elderly. Some studies have found visit-to-visit variability in blood pressure to attenuate with increasing age, particularly the variability of DBP [154,155], while others have found no association between SBP variability and age [156].

While there was only a very slight increase in SBP in males compared to females, males had a much larger increased DBP compared to females. Hence males had lower mean PP than females. This was also the case comparing baseline PP measurements (see Chapter 3) where males had a higher baseline DBP compared to

females, but with little difference in SBP men had a lower baseline PP compared to females. The majority of studies that compared males to females reported both higher SBP and PP in men compared to women of the same age [109]. Some studies, however, have found that although pulse pressure tends to be higher in males compared to females in younger people, females may have a steeper increase in PP with increasing age compared to men which may explain why PP may be higher in older women compared to men of the same age [157].

Males had lower variability in both SBP and PP compared to females. This was somewhat evident in the seasonal changes in blood pressure, with females having a slightly larger increase in SBP and PP in winter compared to summer. This is contrary to some other studies where males have often been shown to have a higher variability for both SBP and DBP [158].

Those who left full-time education at a younger age, a possible proxy for socio-economic status, had higher SBP and PP level, compared to those who left full-time education later on in life. This trend may be indicating poorer health for those who left education at a younger age, possibly resulting from higher levels of deprivation. Many other studies have reported higher blood pressure in those from lower socio-economic backgrounds, particularly in women [159]. It is thought that wealthier communities have lower blood pressures as a result of benefitting from improved health awareness, better diet and better access to anti-hypertensive medications.

After adjustment, there was no independent association between blood pressure variability and the age that subjects left full-time education.

There was a suggestion of a slight decrease in mean PP with increasing BMI. While SBP was higher in those with larger BMI, there was a relatively larger difference in DBP. There is clear evidence in the literature of the increased risk of hypertension associated with obesity [160-163]. However, studies have also shown that PP appeared to be higher in the lean compared to the overweight, increasing again in the obese [112,164,165]. In this study we also see the highest PP in the lean, those with a BMI less than 25 kg/m2, while the lowest PP was seen in those with BMI from 30 to <35 kg/m2. PP was then lower in those 35 kg/m2 or higher. It has been suggested that this higher PP seen in leaner subjects might help explain some of the increase in CV risk that has been seen in many studies in those who are lean compared to those overweight.

There was a very slight increase in the variability of PP with increasing BMI. BMI has been identified as a risk factor for increased variability in blood pressure in other studies [166-169].

While smoking is a well-known high-risk factor for CVD, it is not completely clear how it relates to blood pressure levels in the long-term. It is known that blood pressure can increase at the point of smoking as a result of acute vasoconstriction due to the nicotine content. However, there is some conflicting evidence from

different studies about the longer-term effects, with some studies reporting lower blood pressure in smokers compared to non-smokers [170-172]. While in this study, there was no difference observed in SBP or PP mean level between those reported to be non-smokers and those reporting to be current or ex-smokers within one year prior to randomisation, there was a slight increase in the variability of both SBP and PP in those who were either current or ex-smokers. This increased variability could potentially be due to the acute spikes in blood pressure at the point of smoking in those who continued to smoke during the trial. Studies have suggested that continuous smoking does not lead to increased short-term variability in blood pressure, but it is the temporary cessation of smoking that can lead to immediate short-term variability, particularly affecting morning blood pressure levels following overnight cessation [173].

As has been shown in other studies, in general those reporting increased alcohol consumption had higher SBP and PP. What is often unclear is the make-up of the group who report no alcohol consumption, as this group may represent a mixture of those who have always consumed little or no alcohol as well as those who have given up alcohol as a consequence of a morbidity, being at high risk of morbidities, or even because of excessive alcohol consumption in the past. The largest difference in blood pressure level was seen in those who reported consuming 28 units of alcohol or more per week. It is well known that drinking high levels of

alcohol in one sitting can cause an acute increase in blood pressure, and sustained high levels of alcohol consumption over time can cause longer-term increases in blood pressure. There was some weak evidence of a light increase in the SD of both SBP and PP as the amount of alcohol consumed increased [159,174-176]. The highest variability in both SBP and PP was seen in those who reported no alcohol intake, with little difference between other categories. After adjustment it appeared that those reporting no intake or the highest intake had the highest variability in blood pressure. An increase in blood pressure variability with increasing amount of alcohol consumed is plausible, considering the acute effects of alcohol on blood pressure. However, increased blood pressure variability in those who reported no alcohol intake could be a result of the potential mixed group making up this group.

Diabetes and blood pressure share some underlying causes and have been shown to be linked in a number of ways. It has been shown that over time, diabetes can damage the walls of small vessels and lead to endothelial dysfunction [177-179]. There was no difference in mean SBP between those with or without diabetes at baseline, but a fairly large mean difference in PP, with diabetic subjects having an adjusted mean PP 3.3 mmHg higher than non-diabetic subjects. This is consistent with many findings that PP may be the better predictor of new-onset diabetes and morbidities associated with diabetes as a result of increased arterial stiffness associated with diabetes [180-182].

Blood pressure level was strongly correlated with the time of the year. Blood pressure is known to vary over the seasons of the year, particularly in response to changes in temperature, exposure to UV light, and due to comorbidities associated with different seasons [183]. Some have speculated that changes in blood pressure in response to the seasons reflects seasonal variations in other risk factors [152]. In addition, studies have suggested a direct effect from environmental temperature, giving rise to evidence that it is was a strong risk factor for daily blood pressure, particularly in older subjects [184]. Cold temperatures can cause vessels to narrow and hence increase blood pressure.

Other studies have also shown that the change in blood pressure level over the seasons is greater in older subjects [153].

There are other changes in behaviours and habits that occur between seasons which may also contribute to blood pressure changes, such as reduced physical activity in the colder months.

The number of daylight hours has been shown to positively correlate with blood pressure level, independently of environmental temperature [148]. Differences between geographical regions might be explained by differing weather conditions. Overall, blood pressure was higher in Scandinavian countries compared to the UK. Scandinavian countries have a colder climate than the UK and have more extreme changes in their daylight hours across the year. Scandinavian countries tend to

have a slightly earlier summer compared to the UK, in that the warmer weather tends to be shifted a little earlier. It appears this is somewhat reflected in the blood pressure levels as there is a hint of this with a slightly earlier drop in blood pressure in Scandinavian countries.

Despite having higher blood pressures in general, quite strikingly Scandinavian countries had less variability over the seasons compared to the UK. This is despite countries further north having more extreme variation in number of daylight hours over the year compared to countries further south in the northern hemisphere. For example, Sweden's daylight hours vary from close to 6 in the winter, to over 17 in the summer, while the UK varies between around 8 to 16.5 daylight hours. It is plausible that the variation in vasodilation and hence blood pressure due to exposure to colder temperature depends on the underlying temperate. For example, it could be that when overall annual temperatures are colder, such as in Scandinavian countries as compared to the UK, the same level of temperature variation may have less impact on blood pressure change. Reduced variability in blood pressure in Scandinavian countries could also be a result of differing medical care, possible improvements in blood pressure control or better compliance to medication compared to the UK.

Blood pressure levels seemed to vary slightly more between summer and winter in those allocated to amlodipine-based treatment, compared to those allocated to

atenolol-based treatment. This might be a little surprising since overall the variability in blood pressure was lower in the amlodipine-based arm. However, these differences in blood pressure change between treatment arms were relatively small. This suggests that the lower variability observed in the amlodipine-based arm was not linked to impacts on variability associated with seasonality.

4.5 Relating blood pressure level and variability to cardiovascular-related mortality

4.5.1 Background

Following investigation into factors that influence blood pressure level and variability, an exploration of how these elements relate to CV-related mortality was undertaken.

Firstly, using the arithmetic mean to represent average blood pressure level and the SD to represent variability in blood pressure, the relationship between both these characteristics of blood pressure were assessed as to their relationship with risk.

Next, an assessment was made to see how the number of blood pressure measures used in the calculation of within-person blood pressure mean and SD impacts on the estimate of association that these measures had with risk. Single blood pressure measurements are prone to measurement error both from the equipment used to measure and in the inaccuracy in capturing resting blood pressure level. In addition, natural biological fluctuations in blood pressure levels both in the short-term and over longer periods means that capturing a "usual level" is improved with the inclusion of a higher number of measures. So, the inclusion of a higher number of measures would likely help to reduce measurement error, and better represent

usual underlying blood pressure for a subject, hence potentially strengthening the estimated relationship with risk.

It might seem somewhat intuitive to think that more recent measures may be more predictive of future risk compared to more historic measurements, that measures further in the past might not be as correlated with future risk as more current readings. For the clinical management of blood pressure, the focus of course would be mainly on recent and current blood pressure measurement in order to target keeping blood pressure controlled at the current time. However, there may be important insight into being aware of more historic blood pressure when assessing patient risk which may also impact patient treatment and care. It is uncertain which blood pressure measurements historically can be most predictive of long-term outcomes. It may be that blood pressure is more predictive when considered in relation to specific situations or events. For example, how much blood pressure varies when under stress of changing seasons, or how responsive blood pressure levels are to antihypertensive treatment.

Blood pressure data from the ASCOT legacy cohort allowed the investigation into which measurements might be the strongest predictors of risk, assessing baseline measurements prior to antihypertensive treatment initiation, assessing early blood pressure measurements once subjects had begun treatment and were first

responding to treatment, and assessing later measurements when subjects' blood pressure had more time to be controlled.

The next research question considered was whether risk prediction could be improved with alternative representations of blood pressure level and variability beyond the representation of these characteristics by the arithmetic mean and SD. While the mean and SD are the most commonly used measures to represent these characteristics, there may be other measures that could provide better discrimination in risk prediction. In this section a number of alternative measures were explored.

The majority of previous research analysing blood pressure variability has focused on the spread around a mean value (e.g. the standard deviation [SD] or coefficient of variation [SD/mean]) [136,185]. However, if blood pressure is systematically changing with time (for example with increasing age) then this trend won't be captured by the simple measurement of spread around the mean. Some patterns or trends in blood pressure over time might be useful to describe as they may be informative in the prediction of risk, over their influence when caught up in a single measure of variability around a mean value. Some researchers have studied variability in the context of the residual spread around a linear gradient over time, but little seems to be known about how more complex elements of a BP profile might help inform on CV mortality-related risk.

In the final part of this chapter, the measures of blood pressure level and variability that are considered the best are used to create a simple useful clinical model, in which both blood pressure level and variability are represented most appropriately, alongside other important risk factors.

4.5.2 Mean blood pressure and standard deviation

4.5.2.1 Methods

Using the 5-year time-period as previously defined, from 6 months to 5.5-years post randomisation, blood pressure measurements were used to calculate the arithmetic mean and SD for each subject, used to represent the blood pressure level and variability, respectively. The relationship between both blood pressure mean and SD with CV-related morbidity was explored using adjusted Cox Proportional Hazards models in conditional survival analyses beginning from the landmark time-point of 5.5 years.

In order to make HRs comparable between different components of blood pressure, each component was standardised, i.e. divided by the between subject SD of the component, before being modelled. Hence, the units of the standardised components were no longer mmHg but standardised z-scores. Therefore, estimated HRs represented the relative change in hazard per z-score increase. HRs per z-score increase for both within subject mean level and SD were estimated. This was done for both SBP and PP.

The assumption of linearity in the relationship between risk factor and outcome was assessed for blood pressure mean and SD by comparing a model assuming linearity to a model where the characteristics of blood pressure were transformed using restricted cubic spline transformations, with 3 knots at the 10th, 50th and 90th percentiles, where the assumption of linearity was relaxed allowing curvature. An adjusted model containing the blood pressure characteristic of interest modelled as a linear variable was compared to an adjusted model containing the blood pressure characteristic of interest modelled with a restricted cubic spline transformation using a likelihood ratio test, in order to assess the validity of linearity.

Model fit and discrimination were compared using AIC and the C-statistic from the models where the linearity assumption was relaxed.

All adjusted models were adjusted for the pre-specified baseline risk factors: age; sex; BMI; SBP; total cholesterol; smoking status; diabetes status; the age at which the subject left full-time education; and ethnicity.

4.5.2.2 Results

There was strong evidence that both within-subject SBP mean and PP mean were associated with CV-related mortality. A z-score increase in SBP mean (representing a 10.39mmHg increase) was associated with an estimated increase in relative hazard of 23% after adjustment ($p<0.001$, see Table 24). The effect was stronger

for PP, with a z-score increase in PP mean (representing 10.86mmHg) associated with an increase in relative hazard estimated at 33% after adjustment ($p<0.001$).

Furthermore, as with baseline blood pressure measures explored in Chapter 3, there was some, although weak evidence for an interaction between mean blood pressure and age ($p=0.072$ for SBP and $p=0.045$ for PP). The relative hazard for a z-score increase in mean blood pressure was larger in younger subjects and diminished with age for both mean SBP and PP. For those under the age of 60, the HR for a z-score increase in PP was 1.51 (95% CI: 1.31-1.76), while the HR was 1.34 (95% CI: 1.18-1.52) for SBP. In the oldest age group, those 70 years and older, the HR for a z-score increase in PP was 1.27 (95% CI: 1.15-1.39), while the HR was again lower at 1.16 (95% CI: 1.06-1.26) for SBP.

For both SBP and PP there was weak evidence for a lack of linearity in the relationship between mean level and risk ($p=0.022$ for SBP and $p=0.130$ for PP). When comparing the highest mean blood pressure decile group to the lowest quintile group for both SBP and PP, the relative hazard was larger for mean PP at 2.36 (95% CI: 1.85-3.02) compared to SBP at 1.85 (95% CI: 1.50-2.28, see Figure 41). When modelling both means continuously with restricted cubic spline transformations to relax the assumption of linearity and allow for curvature, discrimination was slightly better from the adjusted model involving PP compared

to the adjusted model containing SBP, a C-statistic of 0.732 compared to 0.729, respectively (see Table 25).

There was strong evidence of an association between the SD and risk for both SBP and PP, independent of the mean value. For SD there was also only weak evidence for a lack of linearity for both SBP and PP (p=0.175 and p=0.055, respectively). The estimated adjusted HRs for a z-score increase in SD for SBP (representing 4.72mmHg) and PP (representing 3.22mmHg) was very similar: 1.26 (95% CI: 1.18-1.34) for SBP; and 1.25 (95% CI: 1.17-1.33) for PP. In addition, comparing the highest decile of SD to the lowest quintile, the HR was slightly larger for SBP compared to PP: 2.53 (95% CI: 1.96-3.26) for SBP; and 2.33 (1.82-3.00) for PP. Models containing both SD and mean level (along with other pre-specified risk factors) discriminated slightly better when using PP (C-statistic 0.741) compared to using SBP (C-statistic 0.737). Relative hazards for each characterisation of blood pressure, and for both SBP and PP are plotted in order to visualise the shape of the relationships where restricted cubic spline transformations have been used, see Figure 40.

There was fairly strong evidence for interactions between blood pressure SD and age (p=0.002 for SBP and p=0.002 for PP). As was the case with mean level, the relative hazard for a z-score increase in the SD of BP was larger in younger subjects and attenuated with age for both the SD of SBP and PP. For those under the age of

60, the HR for a z-score increase in the SD of SBP was 1.56 (95% CI: 1.36-1.80), slightly larger than for the SD of PP at 1.49 (95% CI: 1.32-1.67). For the oldest age group, those 70 years and older, the HR for a z-score increase in the SD of SBP was 1.21 (95% CI: 1.11-1.31), slightly smaller than for the SD of PP at 1.23 (95% CI: 1.14-1.33, see Figure 42).

While there was no evidence for an interaction between blood pressure mean and SD when using SBP (p-value for interaction p=0.303), there was evidence that the relationship between the SD of PP with risk was dependent on mean level (p-value for interaction p=0.008). In particular, the relationship (on the relative scale) between the SD of PP and risk attenuated with higher PP mean level (see Figure 43).

Table 24: Hazard ratios (95% CIs) of CV-related mortality per z-score increase in components of blood pressure level, from Cox proportional hazards models

Characteristic of BP, mmHg	From Cox models assuming linear association					
	Mean	Z-score	Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)*	p-value
Systolic						
Arithmetic mean	137.11	10.39	1.33 (1.26-1.40)	<0.001	1.23 (1.16-1.30)	<0.001
Standard deviation	11.77	4.72	1.45 (1.38-1.53)	<0.001	1.26 (1.18-1.34)	<0.001
Pulse Pressure						
Arithmetic mean	58.34	10.86	1.68 (1.59-1.77)	<0.001	1.33 (1.25-1.42)	<0.001
Standard deviation	8.06	3.22	1.49 (1.43-1.56)	<0.001	1.25 (1.18-1.33)	<0.001

*Adjusted for pre-specified baseline risk factors. For SD, mean level was additionally adjusted for.

Table 25: Comparison of models containing estimates of blood pressure mean and SD with restricted cubic spline transformations, from Cox proportional hazards models with CV-related mortality outcome

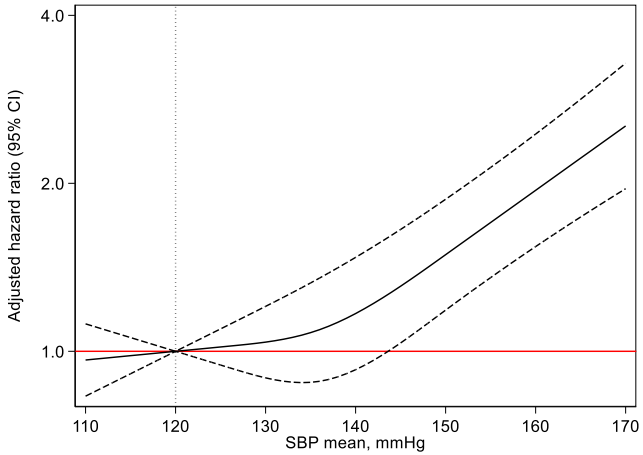
Characteristic of BP, mmHg	From Cox models with restricted cubic splines			
	Effect p-value	Linearity p-value	AIC	C-statistic
Systolic				
Arithmetic mean	<0.001	0.022	17374.71	0.729
Standard deviation of the mean	<0.001	0.175	17327.90	0.737
Pulse Pressure				
Arithmetic mean	<0.001	0.130	17351.37	0.732
Standard deviation of the mean	<0.001	0.055	17303.43	0.741

Each characteristic of BP was modelled using restricted cubic spline transformations with 3 knots (at 10th, 50th, and 90th percentiles), and adjusted for pre-specified baseline risk factors. For SD, mean level was additionally adjusted for.

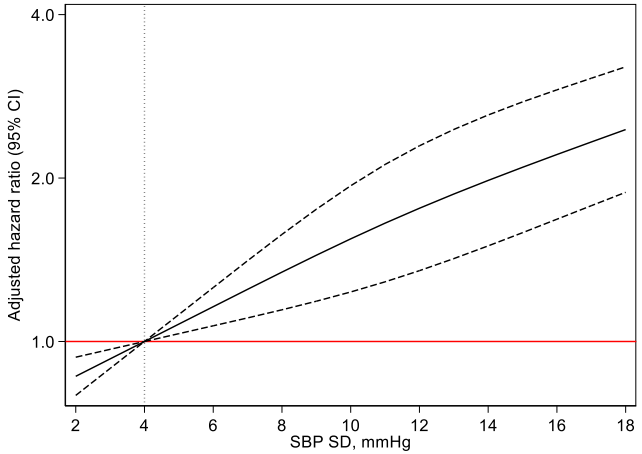
Figure 40: Plots of adjusted HRs (95% CI) for CV-related mortality for mean and SD modelled with restricted cubic spline transformations for SBP and PP, from Cox Proportional Hazards models

Systolic blood pressure

Mean level

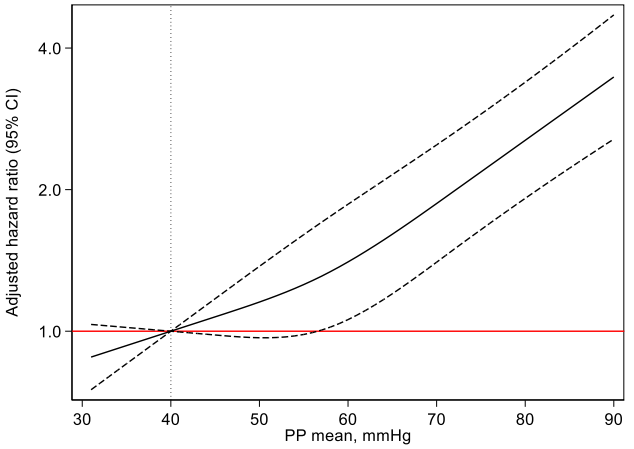


SD



Pulse Pressure

Mean level



SD

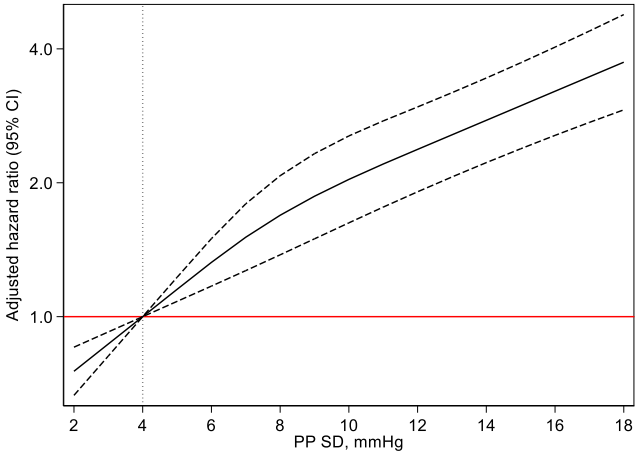
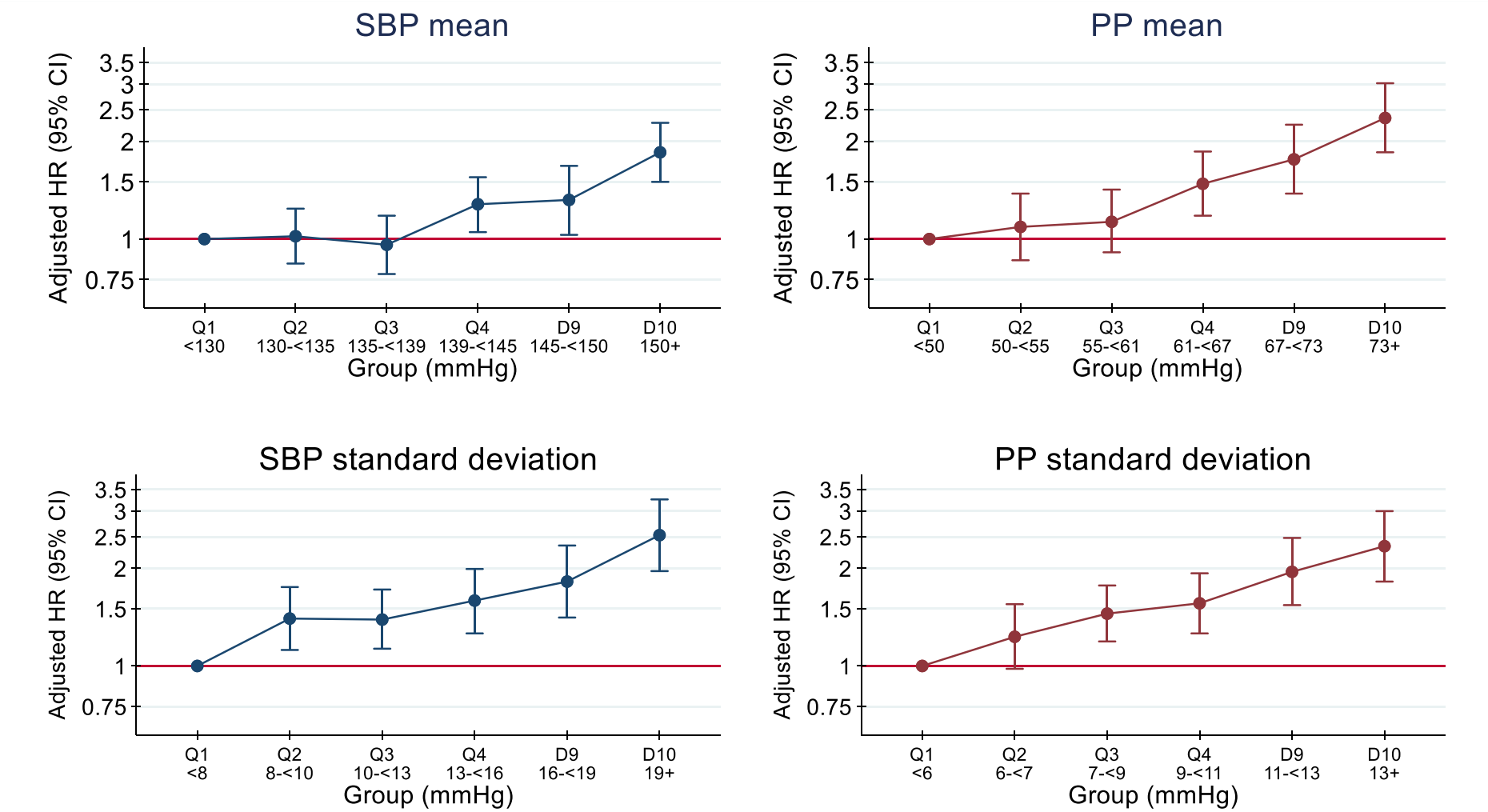


Figure 41: Plots of adjusted HRs (95% CI) for CV-related mortality for mean and SD, over intervals of SBP & PP



Note: Q1-Q4 represent quintiles of the data from the lowest quintile to the 4th quintile, respectively. D9 and D10 represent the top 2 deciles of the data. Adjusted HRs for each interval are in relation to the lowest quintile of the data, adjusted for pre-specified risk factors.

Figure 42: Adjusted HRs (95% CIs) for mean blood pressure and the SD, by subgroups of age

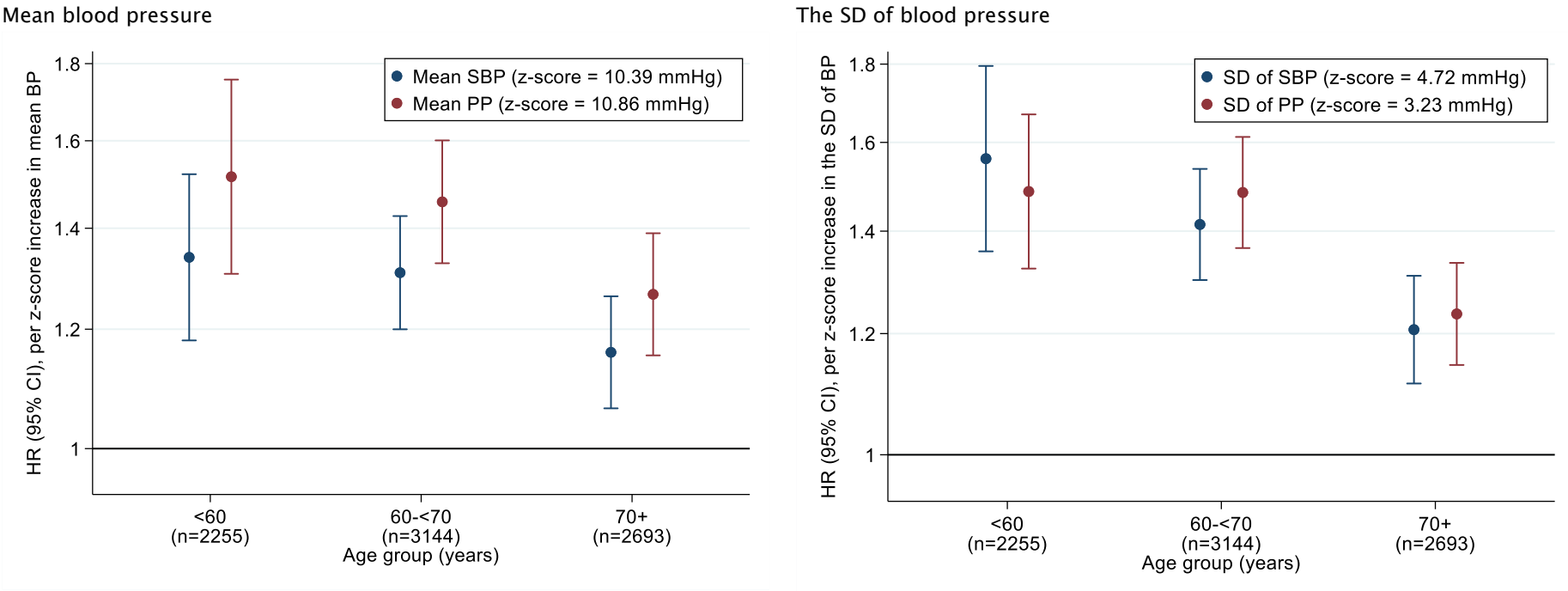
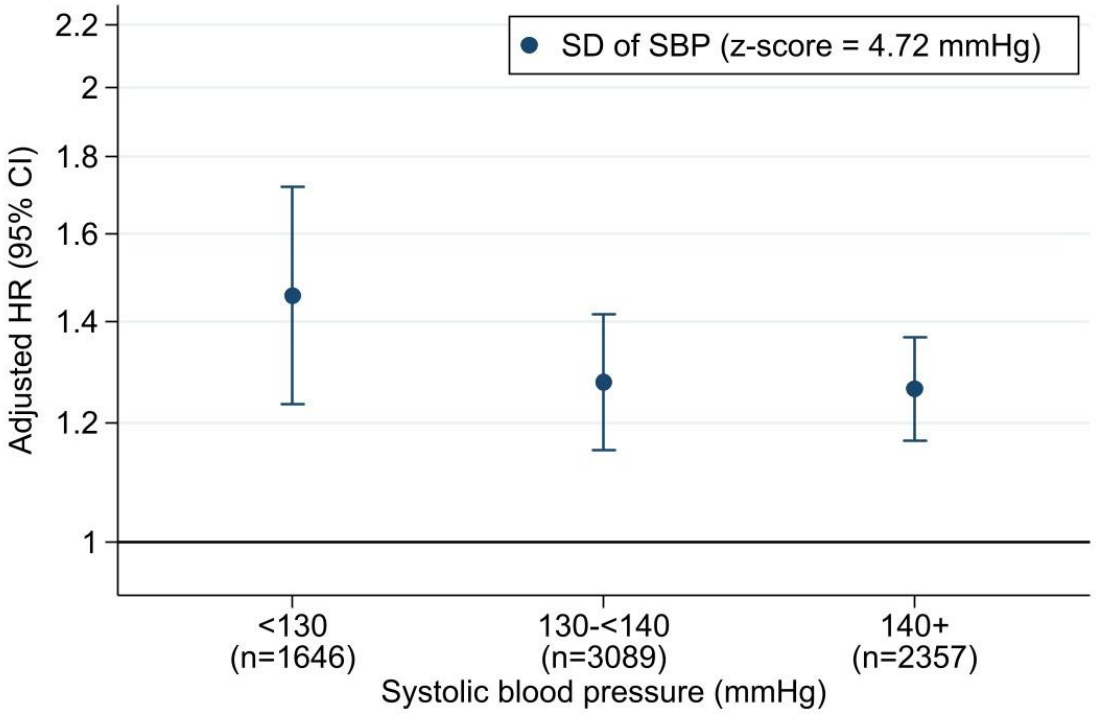
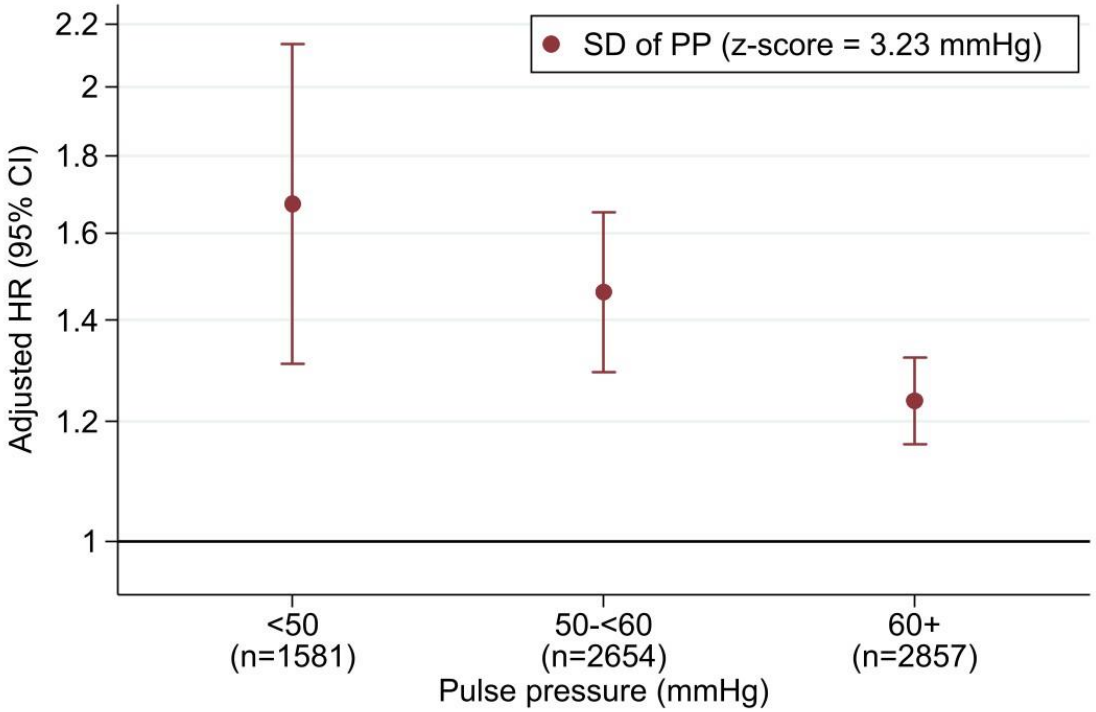


Figure 43: Adjusted HRs (95% CIs) for the SD of blood pressure, by subgroups of blood pressure mean level





4.5.3 Assessing how the number of measurements used in the calculation of blood pressure level and variability impacts their association with cardiovascular-related mortality

4.5.3.1 Methods

An investigation was undertaken into how the number of visits that were used in the calculation of blood pressure level and variability impacts the association between these risk characteristics of blood pressure with CV-related mortality. The purpose was to assess the incremental gain in strength of association with increasing numbers of visits used.

Using only scheduled 6-monthly trial visits spanning 5 years from the 6-month visit to the 5.5-year visit (i.e. excluding unscheduled visits), blood pressure level and variability were calculated for each individual using blood pressure from a varying number of visits. The arithmetic mean was used to represent blood pressure levels and the number of visits used ranged from a single visit to 11 scheduled visits. The SD was used to represent the variability in blood pressure measures across visits, and the number of visits used ranged from a minimum of two up to 11. These scheduled visits were all approximately 6 months apart (although there was some slight variation).

A landmark time was defined as the date of the last visit (i.e. date of the 5.5-year visit), which formed the beginning of exposure time for the conditional survival

analyses. Subjects were included in this analysis if they had data at all 11 scheduled visits within this period. The approach was to consider the landmark time as a representation of a clinical visit, with the aim to assess the incremental benefit of looking back further and further at previous blood pressure visits, on the strength of relationship between both blood pressure level and variability with risk.

For blood pressure level a single measure was considered as the blood pressure level at that final visit at 5.5 years. As mentioned previously, blood pressure from a single visit usually represents the mean of the last two of three repeated measurements. Using two blood pressure visits then took the mean of the last two consecutive visits, and so on, until all scheduled visits were included going back in time to the 6-month visit. The same approach was used for calculating the variability, but starting with a minimum of the last two visits on which to calculate the standard deviation. Further to this, for both mean level and the SD of blood pressure, after all 11 visits were utilised, all other unscheduled visits between the 6-month and 5.5-year visits were also included along with the 11 scheduled visits in the calculations, to see if these additional measures would have any further impact.

Cox PH models were used to estimate HRs per increase in z-score of blood pressure mean and SD, using subject-by-subject means and SDs calculated using blood pressure measures from the varying numbers of visits.

Adjusted models each model adjusted for pre-specified risk factors. In addition, when modelling the exposure of variability, models were adjusted for blood pressure level in order to control for the increased risk associated with increased blood pressure level, while models were not adjusted for SD when blood pressure level was exposure, as previously discussed.

4.5.3.2 Results

Out of the 8580 subjects in the ASCOT legacy cohort, there were 3814 subjects included in analyses who had blood pressure measurements recorded at all 11 scheduled trial visits from 6 months to 5.5 years. The median number of additional unscheduled visits within the time-period of observation for this sub-cohort was four, ranging from one to 34.

There was a striking increase in strength of association between blood pressure level and CV-related mortality with increasing numbers of visits used. The estimated increased risk per z-score of SBP level went from 9.31% when using blood pressure from only the last blood pressure visit, to 16.82% when using mean blood pressure across all 11 scheduled visits. It did not appear that the increase in strength of association had reached a peak with the use of all 11 visits, with additional increase to 19.62% when all available unscheduled visits were also included.

A similar pattern was observed with PP level, however, the association between PP level and CV-related mortality was stronger at every incremental number of visits used. The estimated increased risk per z-score of PP level went from 16.74% when using blood pressure only from the last blood pressure visit, to 23.90% when using mean blood pressure from all 11 visits. Again, the increase in strength of association did not seem to have hit a limit, and there was a slightly further increase to 25.56% when also using unscheduled visits.

A different pattern was observed with the variability of SBP as there seemed to be a peak in magnitude of association with risk from the use of the last six visits. Thereafter, the amplification in magnitude of association with further incorporation of additional blood pressure data diminished (see Figure 44). The estimated increase in risk per z-score of SBP variability went from 11.35% when using only the last two blood pressure visits, to 27.82% when using the last six visits, and did not increase any higher thereafter.

For the variability in PP, there was some additional increase in magnitude of association past the use of the last 6 visits, but the incremental gain was decelerating. The estimated increased risk per z-score of PP variability went from 4.74% when using only the last two blood pressure visits, to 30.93% when using all 11 visits, but did not increase with inclusion of the unscheduled visits (see Table 26).

Table 26: Model coefficients (SEs) and percentage increase in risk per Z-score increase in blood pressure mean and SD using differing numbers of visits, for the outcome of CV mortality

		Level (mean)				Variability (standard deviation)			
Number of scheduled visits included	Time-span	Mean	SD used in Z-score	Adjusted log HR coefficient (SE)	% increased risk per z-score increase	Mean	SD used in Z-score	Adjusted log HR coefficient (SE)	% increased risk per z-score increase
Systolic blood pressure									
1	Single visit	132.43	14.59	0.089 (0.043)	9.31				
2	6 months	132.74	12.29	0.095 (0.043)	9.95	8.28	7.46	0.107 (0.040)	11.35
3	1 year	132.66	11.25	0.089 (0.044)	9.30	9.14	6.23	0.151 (0.041)	16.28
4	1.5 years	132.93	10.75	0.102 (0.043)	10.69	9.65	5.73	0.196 (0.040)	21.62
5	2 years	133.02	10.34	0.120 (0.043)	12.73	9.89	5.28	0.226 (0.041)	25.30
6	2.5 years	133.26	10.00	0.124 (0.043)	13.16	10.16	5.12	0.245 (0.041)	27.82
7	3 years	133.46	9.70	0.131 (0.042)	13.98	10.36	4.91	0.228 (0.042)	25.59
8	3.5 years	133.92	9.60	0.133 (0.042)	14.19	10.63	4.85	0.220 (0.043)	24.60
9	4 years	134.36	9.42	0.145 (0.042)	15.57	10.90	4.76	0.239 (0.043)	26.95
10	4.5 years	134.95	9.31	0.143 (0.042)	15.35	11.26	4.75	0.224 (0.043)	25.13
11	5 years	135.73	9.29	0.155 (0.042)	16.82	11.73	4.81	0.241 (0.043)	27.19
11 plus	5 years	136.37	9.29	0.179 (0.043)	19.62	11.85	4.52	0.231 (0.046)	25.94
Pulse pressure									
1	Single visit	57.05	12.90	0.152 (0.045)	16.47				
2	6 months	56.78	11.72	0.180 (0.047)	19.74	5.84	5.17	0.047 (0.041)	4.76
3	1 year	56.78	11.14	0.175 (0.047)	19.15	6.49	4.26	0.131 (0.040)	13.96
4	1.5 years	56.63	10.89	0.176 (0.047)	19.28	6.83	3.94	0.184 (0.041)	20.19
5	2 years	56.65	10.67	0.189 (0.047)	20.80	7.00	3.60	0.193 (0.042)	21.30
6	2.5 years	56.58	10.50	0.188 (0.047)	20.67	7.17	3.47	0.225 (0.042)	25.26
7	3 years	56.63	10.37	0.195 (0.047)	21.50	7.27	3.33	0.229 (0.043)	25.72
8	3.5 years	56.72	10.36	0.197 (0.047)	21.78	7.42	3.27	0.233 (0.043)	26.18
9	4 years	56.90	10.30	0.205 (0.047)	22.79	7.57	3.22	0.255 (0.043)	28.99
10	4.5 years	57.08	10.29	0.204 (0.047)	22.68	7.74	3.22	0.248 (0.043)	28.14
11	5 years	57.37	10.35	0.214 (0.047)	23.90	7.93	3.22	0.270 (0.043)	30.93
11 plus	5 years	57.82	10.46	0.228 (0.047)	25.56	8.02	2.98	0.263 (0.046)	30.13

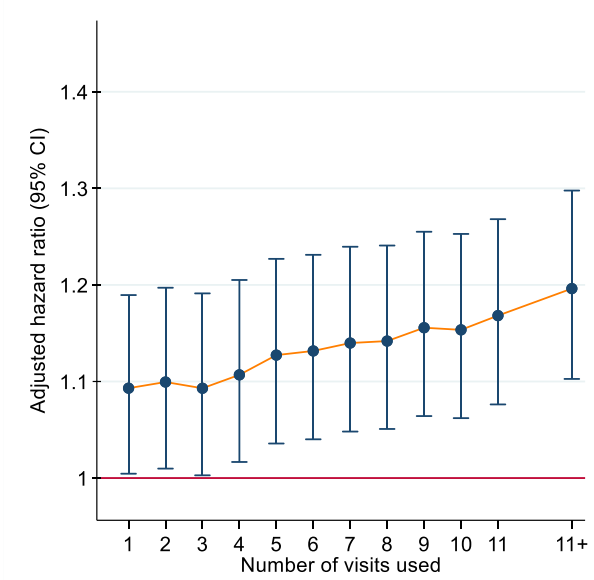
*Adjusted for pre-specified baseline risk factors. For SD of the mean, mean level was additionally adjusted for.

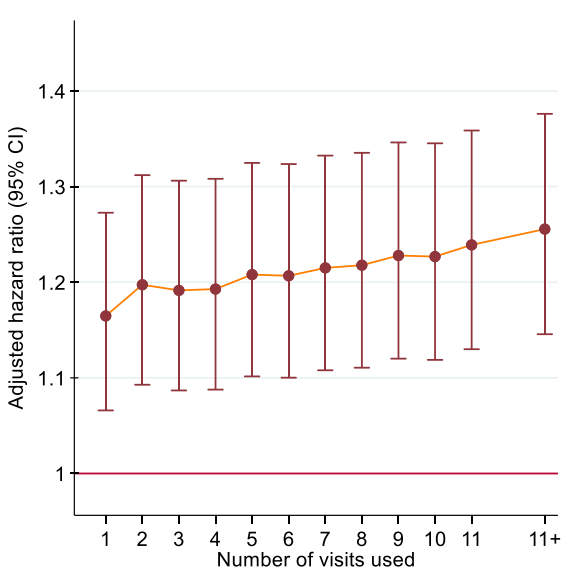
Figure 44: Hazard ratios (95% CI) for CV-related mortality per z-score increase in blood pressure level and variability using differing numbers of scheduled BP visits

Systolic blood pressure

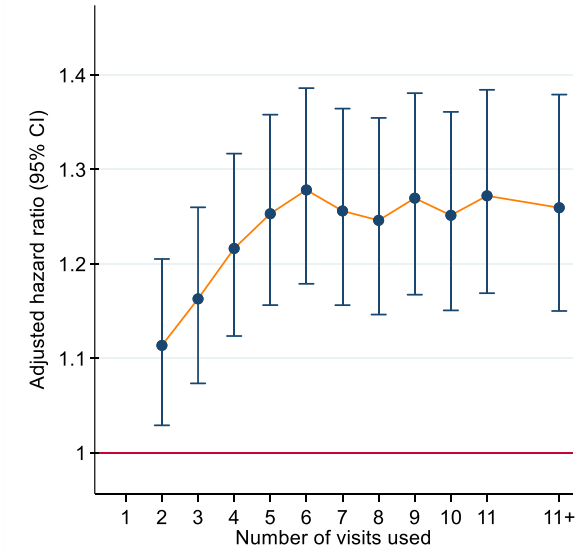
Pulse pressure

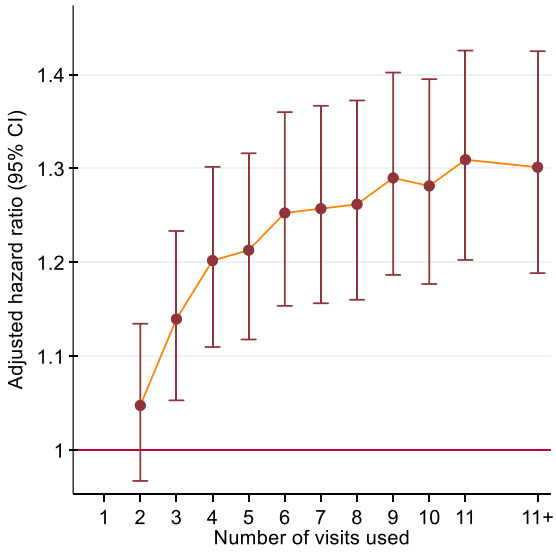
Mean





Standard deviation





4.5.4 Comparing the association of recent blood pressure measures to historic measures with cardiovascular-related mortality

4.5.4.1 Methods

As in the previous section, ASCOT legacy subjects who had blood pressure measures taken at all 11 scheduled visits from the 6-month visit to the 5.5-year visit were included in this analysis.

Firstly, blood pressure from each of the 11 single scheduled visits was used to separately estimate the relationship between blood pressure level and CV-related mortality. In addition to the 11 post-treatment visits, the blood pressure from baseline (pre-treatment) was also assessed for comparison to individual post-treatment initiation visits (note that baseline, pre-treatment blood pressure measures are not used in any other analyses in this chapter). Blood pressure from each visit was used in separate adjusted Cox proportional hazards models, adjusted for pre-specified baseline risk factors. Estimated adjusted HRs per SD increase (z-score) in blood pressure when using measures from each of the 11 visits and the baseline visit were compared as to their magnitude, and presented graphically.

Secondly, each individual's blood pressure mean and SD was calculated only on blood pressure from the first 5 visits (i.e. from the 6-month visit to the 2.5-year visit), and then separately only on blood pressure measured from the last 5 visits (i.e. the 3.5-year visit to the 5.5-year visit, baseline). Both calculated blood

pressure means were put into the same adjusted Cox proportional hazards model, and both calculations of the SD of blood pressure were put into another adjusted Cox proportional hazards model. Each model was again adjusted for pre-specified baseline risk factors, and when estimating the effect of the SD of blood pressure, both blood pressure means were adjusted for in those models. These analyses were repeated for SBP and PP.

4.5.4.2 Results

Using individual scheduled visits from 3814 subjects that had blood pressure from each scheduled visit from the 6-month to the 5.5-year visit, HRs per z-score increase in SBP ranged from around 1.05 to 1.16. There were a number of single visits from which the association between SBP measures with risk was fairly week at the 5% level. There appeared to be a suggestion that SBP from earlier visits tended to have a slightly stronger relationship with risk (see Figure 45). Overall, the associations between PP levels with risk were higher than for SBP, with HRs ranging from around 1.13 to 1.21 per z-score increase in PP. For PP from each individual visit, there was strong evidence of an association with risk. As with SBP, there appeared to be a slight hint that PP level from earlier visits tended to have a slightly stronger relationship with risk, in these conditional survival analyses.

It is worth noting that the pre-treatment (baseline) measurements were not the strongest predictors of risk in this sub-cohort surviving until 5.5 years post randomisation, compared to blood pressure from other single clinical visits.

When blood pressure mean from early and late sets of visits were modelled together, for both SBP and PP, the mean calculated from the earlier visits had a stronger association with risk compared to mean calculated from the later visits when both means were present in one model. For SBP, the adjusted HR was 1.15 (95% CI: 1.04-1.27) for the mean from earlier visits and 1.03 (95% CI:0.93-1.15) for the mean from later visits. For PP, the adjusted HR was 1.20 (1.05-1.38) for the mean from earlier visits and 1.05 (0.91-1.21) for the mean from later visits.

The opposite was found for the SD, with SD calculated on the later five visits being more strongly associated with risk compared to SD calculated on the earlier five visits when both calculated SDs were present in one model. This was the case for both SBP and PP (see Table 27 and Figure 46Figure 44).

Figure 45: Hazard ratios (95% CI) for CV-related mortality per z-score increase in blood pressure from single scheduled visits

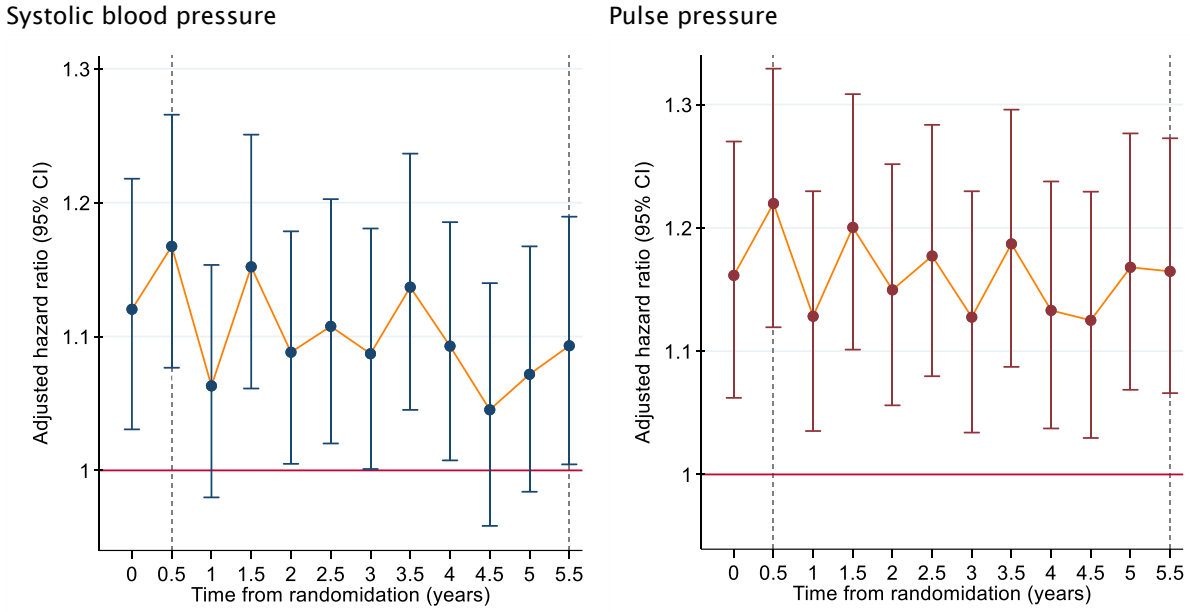
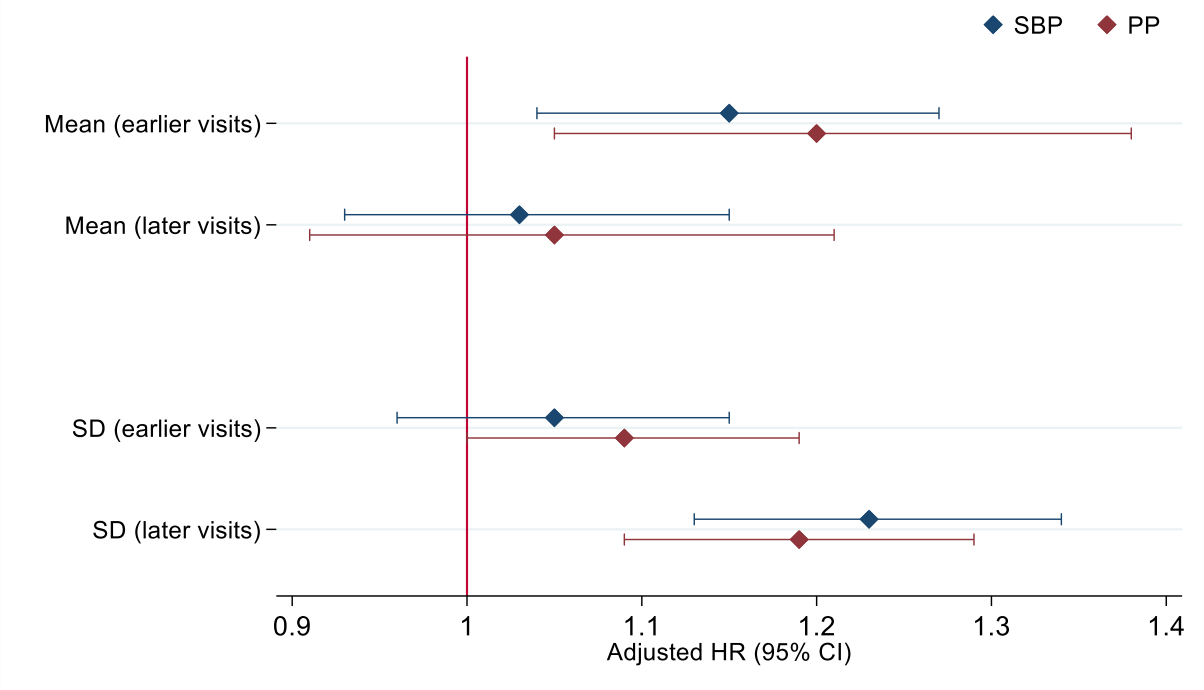


Table 27: Adjusted HRs (95% CI) per z-score increase in mean blood pressure and SD from early and late visits, for SBP and PP

	Level (mean)			Variability (standard deviation)		
Visits included	Mean (SD)	Adjusted HR (95% CI)*	p-value	Mean (SD)	Adjusted HR (95% CI)*	p-value
SBP						
First 5	137.56 (10.96)	1.15 (1.04–1.27)	0.005	10.73 (5.57)	1.05 (0.96–1.15)	0.251
Last 5	133.02 (10.34)	1.03 (0.93–1.15)	0.519	9.89 (5.28)	1.23 (1.13–1.34)	<0.001
PP						
First 5	57.99 (11.22)	1.20 (1.05–1.38)	0.009	7.40 (3.80)	1.09 (1.00–1.19)	0.052
Last 5	56.65 (10.67)	1.05 (0.91–1.21)	0.530	7.00 (3.60)	1.19 (1.09–1.29)	<0.001

*Adjusted for pre-specified baseline risk factors. For SD of the mean, mean level (from both periods) was additionally adjusted for.

Figure 46: Forest plot of adjusted HRs (95% CI) per z-score increase in mean blood pressure and SD from early and late visits, for SBP and PP



4.5.5 Consideration of alternative representation of blood pressure level and variability

4.5.5.1 Introduction

While the arithmetic mean and SD are the most commonly used representations of usual blood pressure level and variability, there are many other possible measures that might be of prognostic value. In this section alterative measures of blood pressure level and variability are considered. Assessments are made as to their relationship with CV-related mortality and their predictive ability. The purpose of this analysis is to investigate whether alternative measures to represent blood pressure level and variability can improve prediction over that of the arithmetic mean and SD.

Alternative representations of variability were considered, those that are less correlated with mean level than SD, variation independent of linear trend, and other representations of variation in blood pressure.

In addition, other aspects that characterise blood pressure profiles such as maximum (peak) blood pressure and rate of change in blood pressure over time were investigated.

4.5.5.2 Methods

Using the 5-year time-period previously defined, blood pressure measurements collected at scheduled and unscheduled visits were used to estimate various representations of subjects' blood pressure level and variability. These estimates for each subject were then each explored as to their relationship with CV-related morbidity, in survival analyses beginning from the landmark time-point of 5.5-years post-randomisation. Cox PH models were used, and adjusted models included pre-specified risk factors.

4.5.5.2.1 Estimating characteristics of blood pressure level on a subject-by-subject basis

In most research, blood pressure levels and variability have been estimated on a subject-by-subject basis, i.e. an estimate is calculated on individuals' data alone.

While usual blood pressure is most often taken to be the arithmetic mean, there are alternative approaches to characterising blood pressure level. The arithmetic mean does not account for the timings that each blood pressure measurement was taken. Hence, a "time-dependent mean" uses the area under a blood pressure-time graph to estimate a level which accounts for the timing of measurements (assuming linearity of blood pressure level between any 2 consecutive visits). The time-dependent mean was calculated using the trapezoidal rule with the formula:

$$\sum_{i=2}^{N} \frac{\left(x_i + x_{i-1}/2\right)(t_i - t_{i-1})}{t}$$

In addition to an estimate of usual blood pressure level, the overall rate of change was considered. Ordinary least squares regression was used on each individual's set of blood pressure measurements in order to calculate the gradient over time as well as an estimate of the blood pressure level at the mid-point over the 5-year observation period.

Blood pressure level from the single visit where the highest blood pressure level was recorded in the observation period was also investigated, representing the maximum or peak blood pressure. In order to try to capture a slightly more stable maximum blood pressure, the mean of the two visits at which blood pressure was highest was also evaluated.

4.5.5.2.2 Estimating characteristics of blood pressure level involving all individuals using random effects

Measures that are estimated on a person-by-person basis are prone to considerable measurement error, which can lead to regression dilution bias between the estimated association between blood pressure measures and mortality risk. As previously discussed and investigated in this chapter, the use of repeated blood pressure measures can improve accuracy in estimating attributes of blood pressure and hence reduce regression dilution bias.

In addition to utilising repeated individual blood pressure measurements, to help reduce regression dilution bias, mixed effects models have been proposed, which allow the borrowing of information across individuals [186]. This in turn can lead to less error in the estimation of the true value of the blood pressure characteristic for a particular individual, and hence can lead to reduced bias in the estimation of association with CV-related mortality risk.

A linear mixed effects model with a random component for each subject was used to estimate within-individual mean level over the observation period. A second mixed effects model with a random component for each subject and a random component for time (in order to allow each subject to have their own level and gradient over time) and a fixed effect of time was used to model the trajectory of slope (gradient) for each individual, along with predicted blood pressure level at the mid-point during the 5-year observation period. These estimates from mixed effects models are referred to as best linear unbiased predictions (BLUPs).

4.5.5.2.3 Estimating characteristics of blood pressure variability

The first alternative representation of blood pressure variability to be assessed was the coefficient of variation (COV). The COV is defined as the SD divided by the mean value. Hence, as this measure of variability has been scaled by the magnitude of the mean the strength of correlation with mean level is reduced. The COV is a proportion, the magnitude of the SD compared to the mean.

Because the COV can still be slightly correlated with mean level, the variation independent of the mean (VIM) was also calculated for each subject. The VIM is estimated as the SD ($\hat{s}$) divided by the mean level ($\bar{x}$) to some power p:

$$VIM = {\hat{s}}/{\bar{x}^p}$$

The value of p for SBP and PP was determined through curve fitting, i.e. an iterative process to find the value of p at which the correlation between mean level and VIM is closest to zero (to 3 DPs).

The variability independent of linear trend was next considered. This was calculated by fitting a linear relationship between blood pressure measurements and time using OLS regression on each individual's blood pressure profile over the 5-year observation period. The root mean square error (RMSE) was calculated as the square root of the sum of squared differences from each observed blood pressure measure (y_i) and the predicted ($\hat{y}_i$), divided by the number of blood pressure measures used in the calculation minus two:

$$RMSE = \sqrt{{(\hat{y}_i - y_i)^2}/{(n-2)}}$$

Next, the mean absolute difference in blood pressure between all chronologically consecutive blood pressure visits was investigated. This is known as the average real variability (ARV). This measure of variability considers the order in which the blood pressure measurements across visits were taken.

Lastly, the range was considered, i.e. the difference between the highest blood pressure from a single visit and the lowest blood pressure from a single visit. This approach utilised only the maximum and minimum blood pressure visits only and discarded all other data.

4.5.5.2.4 Relating blood pressure level, variability, and other attributes to cardiovascular-related mortality

Each type of representation of subjects' blood pressure level, variability, or other attribute was related to CV-related mortality using Cox PH survival models. Exposure time began from the landmark time of 5.5-years post-randomisation. Estimates of each individual's blood pressure level, variability, and other attributes were standardised (converted to a z-score by subtracting the overall between-subject mean and dividing by the between-subject SD of that particular measure). Crude and adjusted HRs for CV-related mortality were estimated representing the relative difference in hazard per z-score increase in each representation of blood pressure level, variability, and other attributes, assuming linearity.

Adjusted models were adjusted for the aforementioned pre-specified risk factors. As with SD and mean level, models assessing blood pressure level were not adjusted for a component of variability. However, models assessing blood pressure variability were adjusted for a measure of blood pressure level in order to estimate the effect of blood pressure variability independent of blood pressure level.

Analyses involving rate of change in blood pressure over time were always executed in conjunction with blood pressure level, represented as the predicted blood pressure level at the mid-point of the 5-year observation period. The mid-point was chosen in an attempt to have a level of blood pressure which was likely to be the least correlated with the slope, as opposed to the predicted blood pressure level at either the beginning or end of the period.

The assumption of linearity was assessed for each measure of blood pressure level, variability, and other attributes by comparing a model assuming linearity to a model with a restricted cubic spline transformation where the assumption of linearity was relaxed (as described in previous sections). Model fit and discrimination were compared between models using AIC and the C-statistic from the models where the linearity assumption was relaxed.

Once again, these analyses were repeated both for SBP and PP.

4.5.5.3 Results

4.5.5.3.1 Relating alternative representations of blood pressure level to cardiovascular-related mortality

In order to visualise some subject blood pressure profiles, Figure 47 presents the SBP readings over the 5-year observation period for three ASCOT legacy subjects, illustrating how measures of blood pressure level can vary depending on the shape of the profile. Subject A has an arithmetic mean SBP, SD, and gradient, all very close to the overall cohort between subject mean values (138.65 mmHg, 11.96 mmHg, and -1.62 mmHg, respectively). For this subject both the arithmetic and time-dependent mean were similar. The measures have lot of variability early on, for example the first three measurements within 6-months of each other vary from 125 mmHg to 173 mmHg. The maximum value of 173 mmHg seems to be a bit of an extreme outlier in this case.

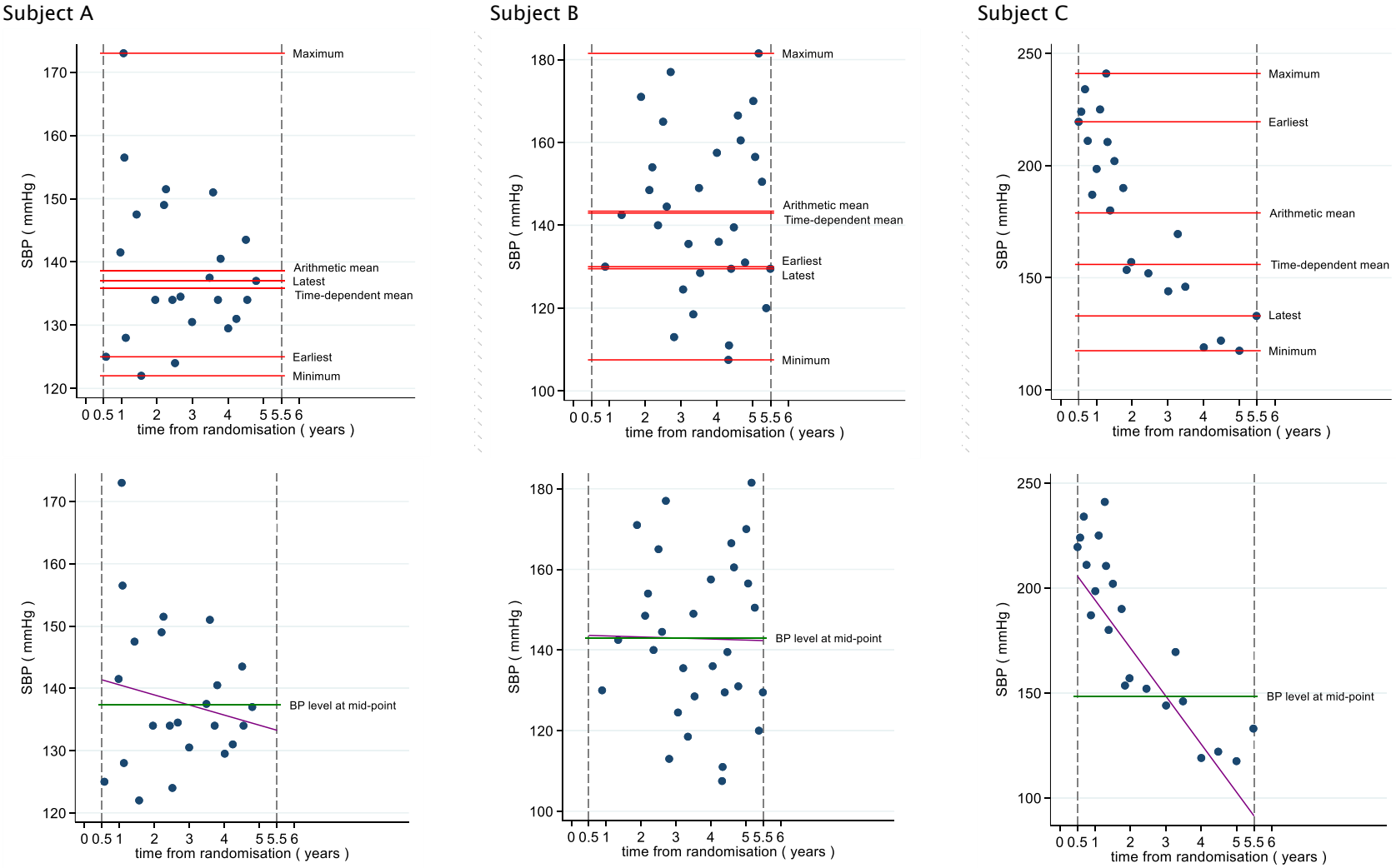
Subject B has a gradient which is very close to zero (-0.26 mmHg per year), but has fairly high variability in SBP with a SD of 20.17 mmHg. The arithmetic and time-dependent mean were also very similar for this subject.

Subject C has a very steep decreasing gradient over time (-22.85 mmHg per year). This extreme downward trend has a fairly convincing tight set of blood pressure measurements around it. For this subject the earlier values were close to the maximum level, and similarly the latest values were close to the minimum value.

The time-dependent mean was lower than the arithmetic mean for this subject as it appeared the decline in SBP was slightly steeper initially before becoming less steep towards the end of the period and hence the time-dependent mean was pulled lower than the arithmetic mean.

In each scenario it might be that the most important indicator of CV-mortality risk could be different. In some cases, the means may be most important, for Subject A and Subject B for example. While for Subject C, because they have such a steep decreasing SBP, possibly the maximum or first value might be important as they may more closely represent how high the subject's blood pressure levels were early on. For subject A, the maximum value looks to be quite an extreme outlier, and so might may not represent the true peak, but might be a result of measurement error or indeed an important true fluctuation in blood pressure. Hence in that case, the mean of the two highest blood pressure measures may represent a truer maximum value.

Figure 47: Plots of SBP profiles over time in 3 selected ASCOT Trial subjects, highlighting different characteristics of BP level and gradient



The arithmetic mean was highly correlated with the time-dependent mean (r=0.979 and r=0.991, for SBP and PP, respectively). The time-dependent mean had a very similar distribution to the arithmetic, but with slightly lower overall between-subject mean for both SBP and PP. The magnitude of the HRs per z-score were slightly lower with the time-dependent mean compared to the arithmetic (for SBP: HR=1.23 for arithmetic and 1.20 for time-dependent; and for PP: HR=1.33 for arithmetic and 1.31 for time-dependent, see Table 28).

Similarly, to the arithmetic mean, for SBP there was some evidence of a non-linear relationship between the time-dependent mean and hazard of CV-related mortality (p=0.022). There was less evidence of non-linearity for the PP time-dependent mean (p=0.068).

From models with RCS transformations, model fit and discrimination were very similar between the time-dependent and arithmetic means, but marginally better for the arithmetic mean for both SBP and PP (see Table 29).

The BLUP estimates for mean level were highly correlated with the arithmetic mean calculated on a subject-by-subject basis: r=0.996 and r=0.999, for SBP and PP, respectively, and had almost identical mean values. However, BLUP mean distributions were narrower than the arithmetic mean distributions for both SBP and PP. The SDs were 8.89 mmHg vs. 10.39 and 10.25 mmHg vs. 10.86 mmHg, comparing the BLUP mean to subject-by-subject arithmetic means for SBP and PP,

respectively. When calculating a mean on a subject-by-subject basis, there is more possibility for error and for extreme mean values to be estimated, particularly if a subject has few blood pressure measurements, while this is reduced in the estimates of BLUP means since they are estimated considering the distribution of means over all subjects assuming means are normally distributed between subjects. The range for the SBP arithmetic means was 107.45-216.00 mmHg and 111.16-190.58 mmHg for the BLUP means. The subject with the high arithmetic mean of 216 mmHg had blood pressure measurements from only four visits over the 5 years which were all within a 3-month period. Therefore, it is likely that this high estimate of SBP level might be somewhat inflated.

While estimates from mixed models led to BLUP blood pressure means that were more normally distributed compared to the subject-by-subject arithmetic means, ultimately there appeared to be no gain in predictive ability, the strength of relationship with CV-related mortality was no stronger.

Blood pressure from a single visit when blood pressure was highest over the 5-year period of observation (maximum blood pressure) had a slightly stronger association with CV-related mortality than each of the estimated mean level characteristics, for both SBP and PP. The HR was 1.26 for SBP and 1.37 for PP per z-score increase in maximum blood pressure value. The mean of the highest blood pressure measures from two visits during the observation period was also as strong a predictor as

maximum level, but made little improvement over the maximum single measure. There was no evidence against linearity for maximum blood pressure level for SBP or PP. Using maximum blood pressure, the fit and discrimination of models was slightly better than for any other representation of blood pressure level.

The patterns of magnitude of relationship between the different representations of blood pressure level with risk were consistent between SBP and PP. However, for each representation of blood pressure level the estimated HR was consistently larger for PP than it was for SBP, per z-score increase in the component measure. For each representation of blood pressure level, model fit and discrimination were also superior with PP when modelled with RCS transformation to relax the assumption of linearity (see Table 29).

Table 28: Hazard ratios (95% CI) of CV-related mortality per z-score increase in components of blood pressure level, from Cox proportional hazards models

Characteristic of blood pressure profile, mmHg	Mean	SD used in Z-score	Correlation coefficient (with arithmetic mean)	Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)*	p-value
Systolic blood pressure							
Arithmetic mean	137.11	10.39	1	1.33 (1.26-1.40)	<0.001	1.23 (1.16-1.30)	<0.001
Time-dependent mean	135.68	10.21	0.979	1.28 (1.22-1.35)	<0.001	1.20 (1.14-1.27)	<0.001
Maximum value	158.98	17.25	0.807	1.42 (1.34-1.50)	<0.001	1.26 (1.19-1.33)	<0.001
Mean of max 2 values	155.38	15.84	0.850	1.43 (1.36-1.51)	<0.001	1.27 (1.20-1.35)	<0.001
Mean level (BLUP)	137.13	8.89	0.996	1.33 (1.26-1.40)	<0.001	1.23 (1.16-1.30)	<0.001
Pulse pressure							
Arithmetic mean	58.34	10.86	1	1.68 (1.59-1.77)	<0.001	1.33 (1.25-1.42)	<0.001
Time-dependent mean	57.53	10.64	0.991	1.64 (1.56-1.73)	<0.001	1.31 (1.23-1.40)	<0.001
Maximum value	73.28	15.36	0.899	1.70 (1.62-1.80)	<0.001	1.37 (1.29-1.46)	<0.001
Mean of max 2 values	70.79	14.45	0.928	1.72 (1.63-1.81)	<0.001	1.37 (1.29-1.46)	<0.001
Mean level (BLUP)	58.35	10.25	0.999	1.68 (1.60-1.78)	<0.001	1.33 (1.25-1.42)	<0.001

* Adjusted for pre-specified baseline risk factors

BLUP: best linear unbiased prediction (estimated from mixed effects model).

Table 29: Comparison of models containing different representations of blood pressure level with restricted cubic spline transformations, from Cox proportional hazards models with CV-related mortality outcome

Characteristic of blood pressure profile, mmHg	From Cox models with restricted cubic splines			
	Effect p-value	Linearity p-value	AIC	C-statistic
Systolic blood pressure				
Arithmetic mean	<0.001	0.022	17374.71	0.729
Time-dependent mean	<0.001	0.022	17383.92	0.727
Maximum value	<0.001	0.524	17365.28	0.731
Mean of max 2 values	<0.001	0.244	17361.22	0.732
Mean level (BLUP)	<0.001	0.022	17376.26	0.729
Pulse pressure				
Arithmetic mean	<0.001	0.130	17351.37	0.732
Time-dependent mean	<0.001	0.068	17357.48	0.731
Maximum value	<0.001	0.573	17335.49	0.735
Mean of max 2 values	<0.001	0.735	17336.99	0.735
Mean level (BLUP)	<0.001	0.150	17353.01	0.731

Each characteristic of blood pressure profile was modelled using restricted cubic spline transformations with 3 knots (at 10th, 50th, and 90th percentiles), and adjusted for pre-specified baseline risk factors.

BLUP: Best linear unbiased prediction (estimated from mixed effects model).

The mean rate of change in SBP per year was -1.70 mmHg and in PP was -0.47 mmHg. After adjustment for blood pressure at the mid-point in the 5-year observation period and pre-specified baseline risk factors, the HR per increase in z-score in gradient was similar for SBP and PP: 0.79 ($p<0.001$) and 0.78 ($p<0.001$), respectively. This means that risk was estimated to be lower when the gradient was higher, after adjustment. In this context, when denoting to an "higher" gradient, this refers to the numeric value of the gradient being higher, not necessarily the steepness of the slope.

Once adjusted for the gradient (and other pre-specified risk factors), the blood pressure level estimated at the mid-point in the 5-year observation period had a HR per increase in z-score of 1.32 ($p<0.001$) and 1.41 ($p<0.001$) for SBP and PP, respectively. As was seen with other measures of blood pressure level, PP had the stronger relationship with risk (see Table 30). For both SBP and PP, after adjustment, the blood pressure level at the mid-point calculated from OLS regression on a subject-by-subject basis had a larger HR per z-score than any other representation of blood pressure level, for both SBP and PP.

Blood pressure level at the mid-point and gradient were highly correlated. A higher blood pressure level was associated with a higher gradient ($r=0.707$ for SBP and $r=0.625$ for PP). Gradient had a weak relationship with CV-related mortality when unadjusted, but was confounded by blood pressure level since lower gradient

indicated a lower blood pressure level on average. Once adjusted for blood pressure level, there was evidence for a relationship between the gradient and CV mortality, with no evidence against linearity for the measures calculated by OLS on a subject-by-subject basis. There was no evidence of an interaction between blood pressure level and gradient estimated by OLS regression for either SBP or PP (interaction tests p=0.976 for SBP and p=0.823 for PP).

Calculating gradients on a subject-by-subject basis was problematic, however, because this led to many very extreme gradient values calculated. The distribution of gradients had extremely long tails and ranged from -87.47 to 214.11 mmHg per year for SBP, with a kurtosis of 420.60. Hence, the z-score that was calculated for the gradient was very large and as a result the estimated HR for an increase in gradient per z-score is hard to interpret and compare to other characteristics of blood pressure since the distributions were so widely spread. Similarly, the distribution of blood pressure level at the mid-point was heavily kurtosed and ranged from, the impossible, -46.77 mmHg to, the implausible, 780.82 mmHg for SBP (kurtosis was 539.98). Extreme estimates of blood pressure gradient and blood pressure level are also highly influential, and so these results are likely unreliable and misleading.

As expected, BLUP blood pressure level at mid-point and blood pressure gradient were much more normally distributed than those calculated from OLS on a subject-

by-subject basis, since that is the assumption made about these characteristics in the random effects models with random components for subject and time. Estimates were less extreme and more realistic. For SBP the level at the mid-point ranged from 95.36 mmHg to 215.73 mmHg, with a kurtosis of 5.60, still a little wider than a perfect normal distribution of 3, but much closer. For BLUP gradient the distribution ranged from -11.38 to 5.43 mmHg per year (kurtosis was 5.58) for SBP.

After adjustment for BLUP blood pressure level at the mid-point in the 5-year observation period and pre-specified baseline risk factors, the HR per increase in z-score in BLUP gradient was similar when using SBP and PP, and for both the estimated effect was reduced compared to using these characteristics calculated on a subject-by-subject basis: 0.93 ($p<0.001$) and 0.95 ($p=0.091$), respectively. Still a hint of an association between gradient and risk estimated, with higher risk in those with lower value gradient.

Once adjusted for BLUP blood pressure gradient (and other pre-specified risk factors), the BLUP blood pressure at the mid-point in the 5-year observation period had a HR per increase in z-score of 1.24 ($p<0.001$) and 1.34 ($p<0.001$) for SBP and PP, respectively. These HRs were very similar in magnitude to those estimated when using the arithmetic mean.

There was, however, more evidence for lack of linearity of gradient with the BLUP measures (see Table 31). For both SBP and PP, the lack of linearity was such that at higher value gradients, the relationship between gradient and risk attenuated. When assessing only gradients that were above zero (positive increasing blood pressure trend), there was no evidence of an effect for both SBP and PP. It seemed that the relationship of decreased risk per increase in blood pressure gradient was stronger the more negative the blood pressure gradients.

There was also some evidence for interactions between BLUP estimates of blood pressure gradient and blood pressure level, when modelled with RCS transformations to allow for curvature (interaction test $p=0.043$ for SBP, and $p=0.038$ for PP). For example, to illustrate, for higher blood pressure levels the association of decreased risk with increasing blood pressure gradient became weaker. At higher blood pressure levels, for example above 140 mmHg for SBP and, there was no longer evidence for a relationship between gradient and risk.

For both SBP and PP, there was some slight improvement in discrimination and model fit when using the BLUP blood pressure level and gradient compared to the models containing the arithmetic mean calculated on a subject-by-subject basis, and to the models containing the BLUP mean estimates (see Table 31).

Table 30: Hazard ratios (95% CI) of CV-related mortality per z-score increase in component of blood pressure level & gradient, from Cox proportional hazards models

Characteristic of BP profile, mmHg	Mean	SD used in z-score	From Cox models assuming linear association					
			Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)*	p-value	Adjusted HR (95% CI)**	p-value
Systolic blood pressure (mmHg)								
BP level at mid-point	135.57	17.04	1.07 (1.04-1.10)	<0.001	1.46 (1.36-1.56)	<0.001	1.32 (1.22-1.42)	<0.001
Gradient (change per year)	-1.70	6.22	0.92 (0.86-0.99)	0.018	0.70 (0.65-0.76)	<0.001	0.79 (0.73-0.85)	<0.001
BLUP BP level at mid-point	136.59	9.09	1.31 (1.24-1.39)	<0.001	1.37 (1.29-1.45)	<0.001	1.24 (1.17-1.32)	<0.001
BLUP gradient (change per year)	-1.90	1.26	0.97 (0.91-1.03)	0.337	0.87 (0.82-0.93)	<0.001	0.93 (0.88-0.99)	<0.001
Pulse pressure (mmHg)								
BP level at mid-point	57.80	15.08	1.22 (1.10-1.14)	<0.001	1.84 (1.73-1.96)	<0.001	1.41 (1.30-1.52)	<0.001
Gradient (change per year)	-0.47	4.64	0.96 (0.89-1.03)	0.275	0.62 (0.59-0.66)	<0.001	0.78 (0.73-0.84)	<0.001
BLUP BP level at mid-point	58.14	10.31	1.68 (1.59-1.77)	<0.001	1.70 (1.61-1.80)	<0.001	1.34 (1.26-1.43)	<0.001
BLUP gradient (change per year)	-0.57	1.00	1.01 (0.95-1.08)	0.743	0.92 (0.87-0.97)	0.003	0.95 (0.90-1.01)	0.091

* Adjusted for the other blood pressure profile characteristic.

** Adjusted for pre-specified baseline risk factors, and the other blood pressure profile characteristic.

BLUP: best linear unbiased prediction (estimated from mixed effects model).

Table 31: Comparison of models containing estimates of blood pressure level and rate of change with restricted cubic spline transformations, from Cox proportional hazards models with CV-related mortality outcome

Characteristic of blood pressure profile, mmHg	From Cox models with restricted cubic splines			
	Effect p-value	Linearity p-value	AIC	C-statistic
Systolic blood pressure (mmHg)				
BP level at mid-point	<0.001	0.764	17380.36	0.728
Gradient (change per year)	<0.001	0.430		
BLUP BP level at mid-point	<0.001	0.044	17368.35	0.731
BLUP gradient (change per year)	<0.001	0.002		
Pulse pressure (mmHg)				
BP level at mid-point	<0.001	0.979	17354.22	0.732
Gradient (change per year)	<0.001	0.151		
BLUP BP level at mid-point	<0.001	0.156	17342.01	0.734
BLUP gradient (change per year)	<0.001	<0.001		

Each characteristic of blood pressure profile was modelled using restricted cubic spline transformations with 3 knots (at 10th, 50th, and 90th percentiles), and adjusted for pre-specified baseline risk factors and the other blood pressure profile characteristic.

BLUP: best linear unbiased prediction (estimated from mixed effects model).

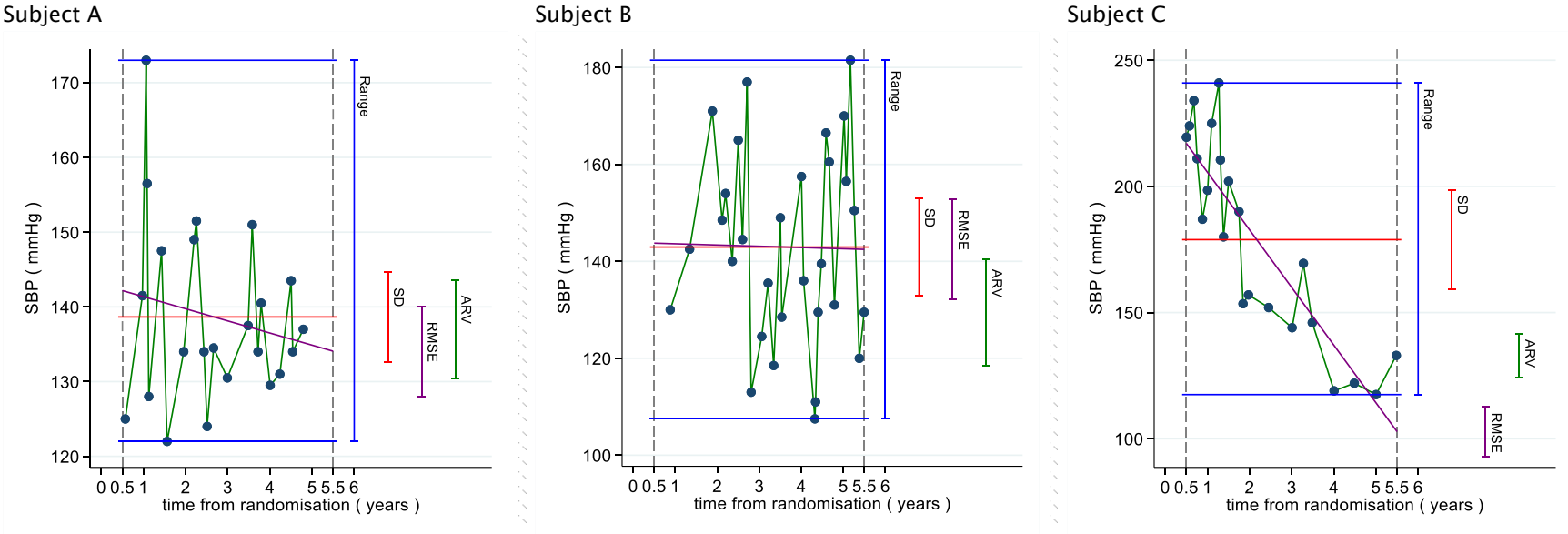
4.5.5.3.2 Relating alternative representations of blood pressure variability to cardiovascular-related mortality

Figure 48 presents SBP profiles for the same three subjects presented previously in Figure 47. The plots illustrate how these measures of blood pressure variability can differ depending on the shape of the profile. Subject A had an SD and RMSE fairly close to the overall mean values (11.96 mmHg, and 12.04 mmHg, respectively).

In comparison to Subject B and Subject C, the range for Subject A was wider in comparison to the other measures, as the range for Subject A was influenced by the maximum point which appeared to be somewhat of an outlier. The SD and RMSE are less influenced by single outliers as the number of observations increases.

Because of the steep negative gradient for Subject C (-22.85 mmHg per year) the SD was close to double that of RMSE (39.51 mmHg and 19.56 mmHg, respectively). In addition, the ARV was small for Subject C since the changes in blood pressure from one visit to the next were not so extreme because they followed an overall decline over time, as opposed Subject B who had large fluctuations with little overall trend. In contrast, Subject B had almost identical SD and RMSE, since their slope was close to zero.

Figure 48: Plots of SBP profiles over time in 3 selected ASCOT Trial subjects, highlighting different characteristics of blood pressure variability



As with SD, which showed strong evidence of an association with CV-related mortality independent of the mean, each alternative representation of blood pressure variability also had strong evidence of an association independent of mean level (or independent of blood pressure level at mid-point and slope for RMSE). While each alternative representation of variability of SBP had a similar strength of association with CV-related mortality (a similar magnitude of HR per z-score increase), none had higher than with SD. This pattern was similar for PP, except that the COV and VIM of PP had very slightly larger HRs compared to the SD (both had HR=1.26 compared to HR=1.25, respectively, see Table 32).

As expected the COV was less correlated with the mean compared to SD for both SBP and PP, however, while the correlation went from 0.407 for the SD of SBP down to 0.216 for the COV of SBP with mean SBP level, for PP the correlation went from 0.498 for the SD down to almost zero, r=0.025, for the COV of PP with mean PP level. Hence, the VIM for PP was very similar to the COV, with the power p estimated at 1.046 (to three DPs). While the power p for SBP was estimated to be 2.025 (to three DPs).

The ARV had the weakest association with CV-related mortality risk, with the smallest HRs of 1.18 for SBP and 1.17 for PP. There was little evidence against linearity for any representations of blood pressure variability except for ARV

(p=0.016 for both SBP and PP), as well as some weak evidence against linearity for the SD of PP (as previously mentioned, p=0.055).

For both SBP and PP, model fit and discrimination were very slightly better for adjusted models containing SD, COV, or VIM compared to other representations of blood pressure variability, all of which were adjusted for mean level except for RMSE which was adjusted for blood pressure level at the mid-point and gradient (from models where linearity assumption was relaxed, see Table 33). Even an adjusted model including RMSE, blood pressure level at mid-point, and gradient, did not improve prediction over that of an adjusted model with mean level and SD (or COV/VIM), all adjusted for the same pre-specified risk factors.

While PP was the stronger predictor of CV-related mortality compared to SBP when it came to each representation of blood pressure level, maximum blood pressure, or slope, there was little difference between SBP and PP in the magnitude of relationship between each representation of blood pressure variability and CV-related mortality. However, adjusted models with both a representation of blood pressure level and blood pressure variability (and slope in the case of RMSE) had better goodness-of-fit and discrimination when using the PP component of blood pressure compared to SBP (see Table 33).

Table 32: HR (95% CI) for CV-related mortality per z-score increase of variability measure, from Cox PH models

Characteristic of blood pressure variability	Mean	SD used in z-score	Correlation coefficient (with SD)	Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)*	p-value	Adjusted HR (95% CI)**	p-value
Systolic									
SD (mmHg)	11.77	4.72	1	1.45 (1.38–1.53)	<0.001	1.36 (1.28–1.44)	<0.001	1.26 (1.18–1.34)	<0.001
COV (x10²)	8.53	3.17	0.977	1.42 (1.35–1.50)	<0.001	1.35 (1.28–1.43)	<0.001	1.25 (1.18–1.33)	<0.001
VIM (x10⁴)	5.50	2.00	0.901	1.36 (1.28–1.43)	<0.001	1.36 (1.28–1.44)	<0.001	1.26 (1.19–1.33)	<0.001
RMSE (mmHg)	11.03	4.44	0.923	1.41 (1.34–1.48)	<0.001	1.32 (1.25–1.40)	<0.001	1.23 (1.16–1.31)	<0.001
ARV (mmHg)	11.81	4.93	0.826	1.35 (1.29–1.41)	<0.001	1.26 (1.20–1.33)	<0.001	1.18 (1.12–1.25)	<0.001
Range (mmHg)	40.90	17.66	0.926	1.42 (1.35–1.50)	<0.001	1.33 (1.25–1.41)	<0.001	1.21 (1.14–1.29)	<0.001
Pulse Pressure									
SD (mmHg)	8.06	3.22	1	1.49 (1.43–1.56)	<0.001	1.26 (1.19–1.33)	<0.001	1.25 (1.18–1.33)	<0.001
COV (x10²)	13.80	4.66	0.862	1.29 (1.22–1.36)	<0.001	1.27 (1.21–1.34)	<0.001	1.26 (1.19–1.33)	<0.001
VIM (x10²)	11.45	3.86	0.849	1.28 (1.21–1.35)	<0.001	1.27 (1.21–1.34)	<0.001	1.26 (1.19–1.34)	<0.001
RMSE (mmHg)	7.70	3.09	0.934	1.36 (1.31–1.41)	<0.001	1.21 (1.15–1.27)	<0.001	1.21 (1.14–1.27)	<0.001
ARV (mmHg)	8.39	3.46	0.847	1.31 (1.27–1.35)	<0.001	1.17 (1.11–1.22)	<0.001	1.17 (1.11–1.24)	<0.001
Range (mmHg)	28.04	12.06	0.921	1.51 (1.44–1.59)	<0.001	1.25 (1.43–1.61)	<0.001	1.21 (1.14–1.28)	<0.001

* Adjusted for: mean level for SD, COV, VIM, ARV, and range; and for gradient and intercept for RMSE.

** Adjusted for pre-specified baseline risk factors, and for: mean level for SD, COV, VIM, ARV, and range; and for gradient and level at mid-point for RMSE.

Table 33: Comparison of models containing characteristics of blood pressure variability modelled with RCS, from Cox PH models

Characteristic of blood pressure variability	Spline models			
	Effect p-value	Linearity p-value	AIC	C-statistic
Systolic blood pressure				
SD (mmHg)	<0.001	0.175	17327.90	0.737
COV (x10²)	<0.001	0.538	17326.01	0.737
VIM (x10⁴)	<0.001	0.901	17323.88	0.737
RMSE (mmHg)	<0.001	0.813	17338.53	0.736
ARV (mmHg)	<0.001	0.016	17343.75	0.734
Range (mmHg)	<0.001	0.682	17340.57	0.736
Pulse pressure				
SD (mmHg)	<0.001	0.055	17303.43	0.741
COV (x10²)	<0.001	0.483	17295.55	0.742
VIM (x10⁴)	<0.001	0.438	17295.01	0.742
RMSE (mmHg)	<0.001	0.288	17318.23	0.739
ARV (mmHg)	<0.001	0.016	17320.03	0.738
Range (mmHg)	<0.001	0.164	17318.29	0.740

Each characteristic of blood pressure variability was modelled using restricted cubic spline transformations with 3 knots (at 10th, 50th, and 90th percentiles), and adjusted for pre-specified baseline risk factors, and adjusted for: mean level for SD, COV, VIM, ARV, and range; for gradient and level at mid-point for RMSE.

4.5.6 The joint impact of blood pressure level and variability on CV-related mortality and development of a clinically useful risk prediction model

4.5.6.1 Introduction

The approach so far has been to assess the relationship between blood pressure level and CV-related mortality over a 5-year period of observation, and to assess the relationship between blood pressure variability and CV-related mortality that is independent of blood pressure level. The next stage in this section was to evaluate how blood pressure level and variability could best be used together to predict CV-related mortality, and hence, how they could be used practically for patient assessment of risk in a clinical setting, aiding patient management and risk reduction.

Since there was no other representation of underlying blood pressure level that seemed to improve the prediction of CV-related mortality over that of the arithmetic mean, this became the focal point in the representation of blood pressure level for this section. Blood pressure variability represented as the SD, COV, or VIM showed the strongest predictive ability. Since VIM is the measure of variability independent of the mean, this was initially the focal point in the representation of blood pressure variability for this section.

4.5.6.2 Methods

Both blood pressure mean and VIM were split into quartiles of the data, and their interaction with each other was investigated in an adjusted Cox PH model (adjusted for other pre-specified risk factors) for CV-related mortality. With an interaction between the two quartile blood pressure variables, 16 subgroups were hence created, and (15) HRs were estimated representing the relative change in hazard compared to the subgroup representing the lowest quartile of blood pressure mean and the lowest quartile of blood pressure VIM. Three-dimensional bar plots were created to visualise the relative change in hazard between each subgroup compared to the reference group. These analyses were performed with a focus on PP, but were repeated using SBP.

The modification of effect between both blood pressure mean and VIM with age was explored by further allowing an interaction between the subgroups of blood pressure mean and VIM with age. Age was split initially into four groups: those <65 years, 65-<70 years, 70-<75 years, and those 75 years and older at the landmark time-point (i.e. 5.5-years post-baseline). This analysis was also repeated with only two age groups, those below 70 and those 70 years and older at the landmark time. Again, adjusted HRs were estimated and three-dimensional bar plots were presented to show the relative hazard in each blood pressure mean and VIM

subgroup compared to a reference group within each category of age. These analyses were also performed using PP, but were repeated for SBP for comparison.

Having seen that PP had been the component of blood pressure that most strongly predicted CV-related mortality in terms of blood pressure level, and that PP had a similar level of predictive ability to SBP in terms of blood pressure variability, PP became the ultimate focus in the final analyses presented in this chapter.

The last part of this analysis involved the development of a clinically useful predictive model, consisting of blood pressure level and variability, along with key risk factors. The focus for this final objective was on PP, and results were not presented for SBP. Since the COV for PP was only very slightly different from the VIM ($COV = VIM \times \bar{x}^{0.046}$) and had very low correlation with mean PP level (r=0.025), for simplicity and ease of interpretation the COV of PP became the focal point in the representation of blood pressure variability in the development of the predictive model.

A series of models containing PP mean, PP COV, and age as continuous variables were produced which built upon each other to allow a higher degree of complexity, before being simplified in order to arrive at a final, more parsimonious model containing only the most important factors. The first model included PP mean, PP COV, and age, with no interactions, adjusted for other pre-specified risk factors (as previously described). Linearity of each variable in the model was assessed, which

led to the second model containing any variable which showed evidence against linearity modelled in a more suitable way. The next model added an interaction between PP mean and PP COV. Then an interaction between PP mean and age was added, followed by an interaction between PP COV and age. This became the fullest model from which backward stepwise elimination of parameters was undertaken.

Finally, the full model was then simplified, by removing any interactions for which there was a lack of evidence, and removing any other pre-specified risk factors that had so far been automatically adjusted for but did not show strong evidence of an association with the outcome in the final model. In order to demonstrate a convincing level of evidence, a threshold of $p<0.01$ was used as the level of evidence required for a risk factor, interaction, or non-linear relationship to be retained in the final model. The model was simplified where possible in order to produce an appropriate but simple risk model for CV-related mortality.

The C-statistic was calculated for the final clinically useful risk prediction model, as described by Harrell et al., in the context of Cox proportional hazards survival models [187]. The model was then validated internally using bootstrap resampling with 1000 resamples, in order to estimate the bias or "optimism" in the C-statistic calculated on the whole dataset, and hence estimate an unbiased C-statistic, as an estimate of external concordance (external discrimination) of the model.

4.5.6.3 Results

4.5.6.3.1 Exploring CV-related mortality across subgroups of blood pressure mean and VIM over age groups

The analysis of quartile groups of both blood pressure mean and VIM showed a clear pattern of similarly increasing risk with increasing level of mean and VIM, for both PP and SBP. The largest HR (as compared to the lowest quartile of blood pressure mean and VIM) was in the subgroup of those in the highest quartile of blood pressure mean and VIM for both PP and SBP, with a HR of 3.94 (95% CI: 2.51-6.17) for PP and 2.38 (95% CI: 1.64-3.46) for SBP. Table 34 presents the adjusted HRs, and Figure 49 visualises the relative differences in hazards between groups. Overall there was a similar increase in magnitude of relative hazard when moving up the quartile groups of one characteristic while keeping the other constant, for both SBP and PP, indicating that both blood pressure level and variability were of similar importance. Those in the lowest quartile of blood pressure mean level but the highest quartile of blood pressure VIM had a similar magnitude of increased hazard as those in the highest quartile group of blood pressure mean level but lowest quartile of blood pressure VIM (compared to the reference groups).

When further split into age groups, there was quite a striking difference in the magnitude of effect of blood pressure mean and VIM on CV-related mortality across ages. A similar pattern of increasing risk with increasing blood pressure mean and

also with increasing blood pressure VIM was evident in each age group, but to quite a severely attenuated degree in older subjects. For PP, there was not so much difference between those in the two youngest age groups (<70 years), and between those in the two eldest age groups (70+ years, see Figure 50). For SBP the largest difference in magnitude of effect was seen in those under 65, and a less striking difference between ages 65 years and above.

Splitting age into only two age-groups, for those <70 years, the HR comparing the group in the top quartiles of blood pressure mean and VIM to those in the bottom was 9.57 (95% CI: 5.39-16.99) for PP and 4.83 (95% CI: 2.86-8.13) for SBP (see Table 36 & Figure 51). The effects were attenuated in older subjects with HRs comparing the same groups of 3.26 (95% CI: 1.98-5.36) for PP and 2.16 (95% CI: 1.44-3.25) for SBP.

While the relative differences in hazard were different between age groups, the absolute differences were very similar. The absolute increase in rate of CV-related mortality from the lowest quartile groups of both mean and VIM to the highest was 22.09 events per 1000 person-years (95% CI: 14.54-29.63) in those under 70 years, and 25.32 events per 1000 person-years (95% CI: 16.04-34.59) in those 70+ years, for PP, from a Poisson survival model adjusted for other pre-specified risk factors. For SBP the absolute increase in rate was also similar between age-groups,

13.76 events per 1000 person-years (95% CI: 8.31-19.20) in those under 70 years, and 16.96 events per 1000 person-years (95% CI: 8.00-25.92) in those 70+ years.

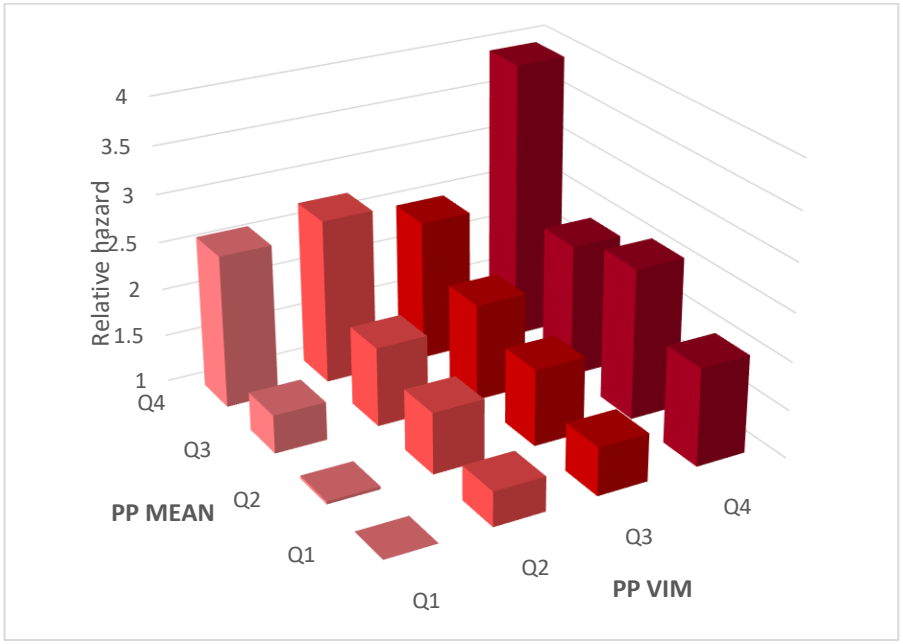
In all of these analyses, on average the effect sizes were quite markedly larger when using PP compared to SBP, across the ages.

Table 34: Adjusted HRs for sub-groups of blood pressure mean and VIM (each split into quartiles), from a Cox PH model

Mean quartile group	Pulse pressure				Systolic blood pressure				
Q4	2.60 (1.63–4.12)	2.73 (1.72–4.34)	2.48 (1.55–3.97)	3.94 (2.51–6.17)	1.63 (1.07–2.49)	1.57 (1.05–2.34)	2.14 (1.46–3.13)	2.38 (1.64–3.46)	
Q3	1.40 (0.85–2.31)	1.83 (1.14–2.95)	2.02 (1.26–3.25)	2.40 (1.50–3.85)	1.17 (0.77–1.79)	1.53 (1.02–2.28)	1.43 (0.95–2.14)	2.18 (1.48–3.21)	
Q2	1.03 (0.60–1.75)	1.64 (1.00–2.69)	1.80 (1.10–2.94)	2.58 (1.61–4.13)	0.95 (0.62–1.47)	1.19 (0.79–1.79)	1.17 (0.77–1.79)	1.79 (1.19–2.69)	
Q1	Reference group	1.36 (0.79–2.32)	1.50 (0.90–2.51)	2.02 (1.23–3.32)	Reference group	1.16 (0.75–1.80)	1.27 (0.84–1.93)	1.68 (1.13–2.48)	
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	VIM quartile group

Figure 49: 3-D bar plot of adjusted HRs for sub-groups of blood pressure mean and VIM (each split into quartiles), from a Cox PH model

Pulse pressure



Systolic blood pressure

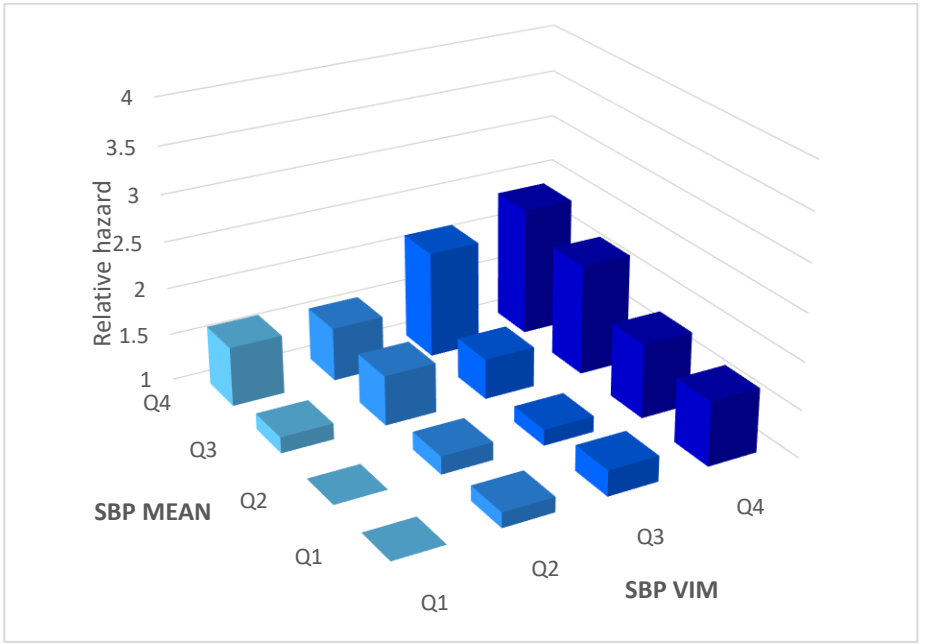
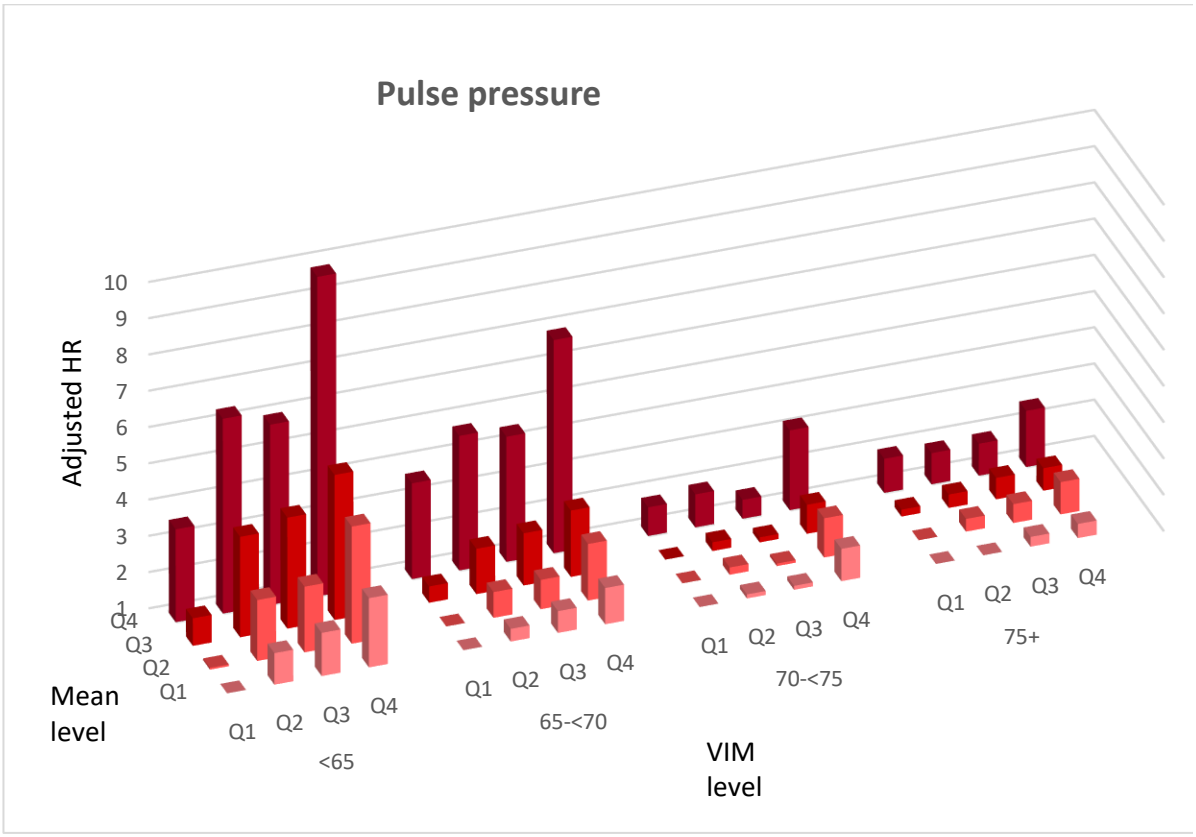


Table 35: Adjusted HRs for sub-groups of mean and VIM blood pressure (each split into quartiles), further split into four age groups, from a Cox PH model

Age group (years)	Mean quartile group	VIM quartile group			
		Q1	Q2	Q3	Q4
		Pulse pressure			
<65	Q4	3.56 (1.87–6.81)	6.37 (2.90–13.98)	5.97 (2.65–13.42)	9.81 (4.54–21.21)
	Q3	1.76 (0.91–3.89)	3.77 (1.71–8.28)	4.06 (1.88–8.75)	5.00 (2.31–10.82)
	Q2	1.05 (0.53–2.05)	2.68 (1.27–5.67)	2.81 (1.32–5.98)	4.23 (2.03–8.83)
	Q1	Reference group	1.87 (0.95–3.68)	2.19 (1.13–4.25)	2.91 (1.52–5.57)
65–<70	Q4	3.64 (1.94–6.84)	4.71 (2.21–10.04)	4.45 (2.03–9.74)	6.88 (3.26–14.54)
	Q3	1.45 (0.75–2.83)	2.25 (1.03–4.91)	2.44 (1.10–5.42)	2.83 (1.30–6.17)
	Q2	0.92 (0.46–1.86)	1.71 (0.77–3.77)	1.81 (0.80–4.08)	2.56 (1.17–5.59)
	Q1	Reference group	1.35 (0.67–2.72)	1.60 (0.81–3.15)	2.00 (1.04–3.82)
70–<75	Q4	1.79 (1.01–3.17)	1.91 (1.00–3.65)	1.52 (0.78–2.95)	3.20 (1.70–6.03)
	Q3	0.98 (0.53–1.78)	1.24 (0.65–2.40)	1.14 (0.58–2.24)	1.80 (0.94–3.45)
	Q2	0.79 (0.42–1.50)	1.20 (0.61–2.37)	1.07 (0.53–2.16)	2.08 (1.08–4.01)
	Q1	Reference group	1.11 (0.59–2.11)	1.11 (0.60–2.06)	1.89 (1.06–3.38)
75+	Q4	1.94 (1.11–3.38)	1.86 (1.02–3.40)	1.88 (1.03–3.43)	2.55 (1.42–4.57)
	Q3	1.19 (0.66–2.15)	1.37 (0.74–2.56)	1.59 (0.86–2.94)	1.62 (0.87–3.01)
	Q2	0.98 (0.52–1.85)	1.35 (0.68–2.66)	1.52 (0.79–2.92)	1.89 (1.01–3.55)
	Q1	Reference group	1.00 (0.54–1.86)	1.27 (0.70–2.30)	1.39 (0.78–2.46)
		Systolic blood pressure			
<65	Q4	2.55 (1.36–4.78)	3.64 (1.64–8.05)	5.05 (2.35–10.84)	7.70 (3.60–16.51)
	Q3	1.90 (1.01–3.56)	3.69 (1.71–7.98)	3.53 (1.62–7.72)	6.90 (3.23–14.71)
	Q2	1.78 (0.94–3.35)	3.23 (1.49–7.01)	3.25 (1.48–7.10)	6.53 (3.04–14.00)
	Q1	Reference group	1.69 (0.88–3.23)	1.82 (0.96–3.46)	3.14 (1.72–5.74)
65–<70	Q4	1.74 (0.99–3.03)	1.41 (0.71–2.78)	2.26 (1.18–4.30)	2.76 (1.47–5.18)
	Q3	1.09 (0.62–1.92)	1.21 (0.60–2.42)	1.33 (0.67–2.66)	2.09 (1.07–4.05)
	Q2	0.80 (0.44–1.46)	0.83 (0.40–1.71)	0.95 (0.47–1.94)	1.54 (0.77–3.09)
	Q1	Reference group	0.96 (0.53–1.75)	1.20 (0.67–2.13)	1.66 (0.97–2.84)
70–<75	Q4	1.48 (0.89–2.45)	1.35 (0.75–2.41)	2.02 (1.15–3.54)	2.55 (1.47–4.42)
	Q3	0.95 (0.57–1.60)	1.19 (0.65–2.17)	1.22 (0.68–2.22)	1.97 (1.12–3.49)
	Q2	0.66 (0.38–1.15)	0.77 (0.41–1.45)	0.83 (0.44–1.58)	1.39 (0.75–2.56)
	Q1	Reference group	1.08 (0.63–1.86)	1.26 (0.75–1.11)	1.79 (1.10–2.93)
75+	Q4	1.38 (0.86–2.22)	1.31 (0.79–2.18)	1.62 (0.99–2.64)	1.66 (1.03–2.67)
	Q3	1.08 (0.67–1.74)	1.39 (0.84–2.31)	1.18 (0.71–1.97)	1.55 (0.94–2.57)
	Q2	0.94 (0.57–1.53)	1.13 (0.68–1.90)	1.01 (0.59–1.72)	1.37 (0.81–2.31)
	Q1	Reference group	1.12 (0.68–1.85)	1.08 (0.66–1.75)	1.25 (0.80–1.96)

Figure 50: 3-D bar plots of adjusted HRs for sub-groups of mean and VIM BP (each split into quartiles), further split into four age groups, from a Cox PH model



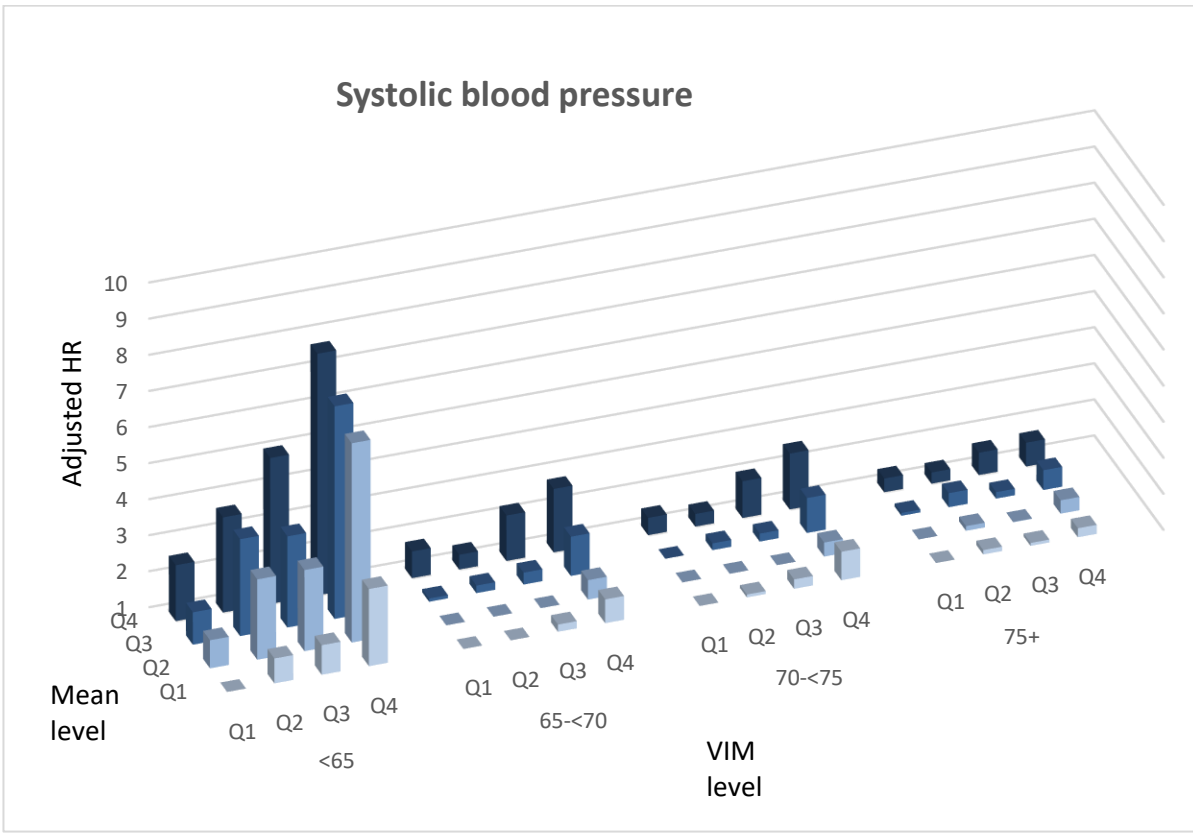
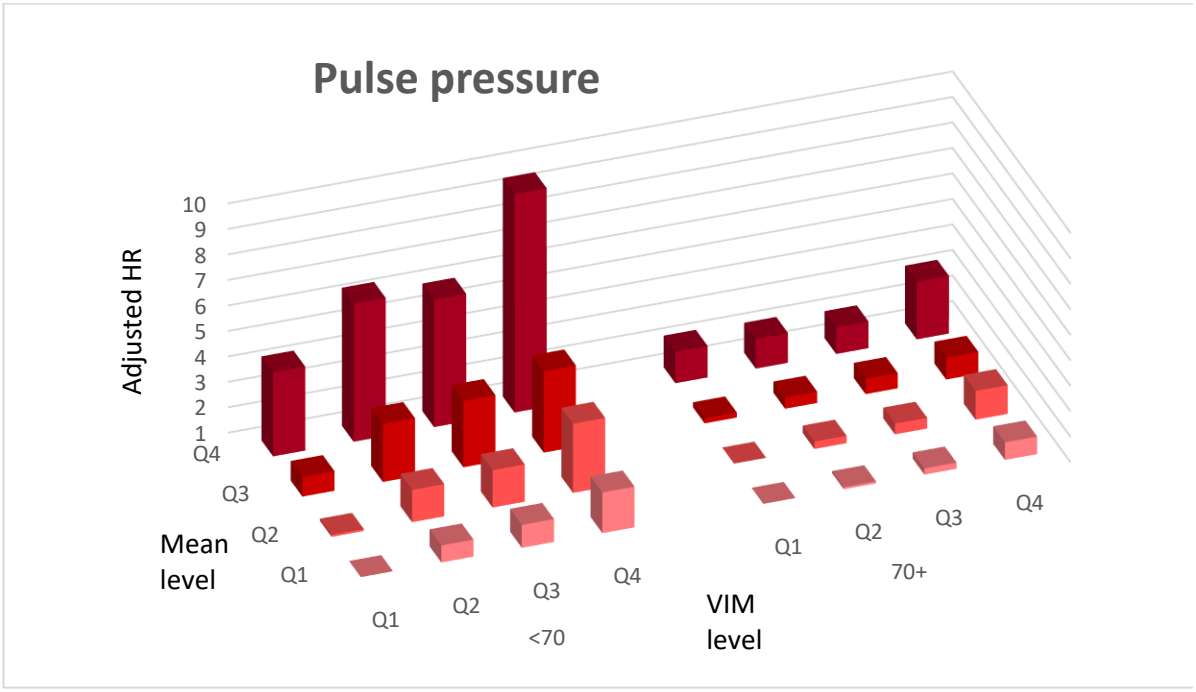
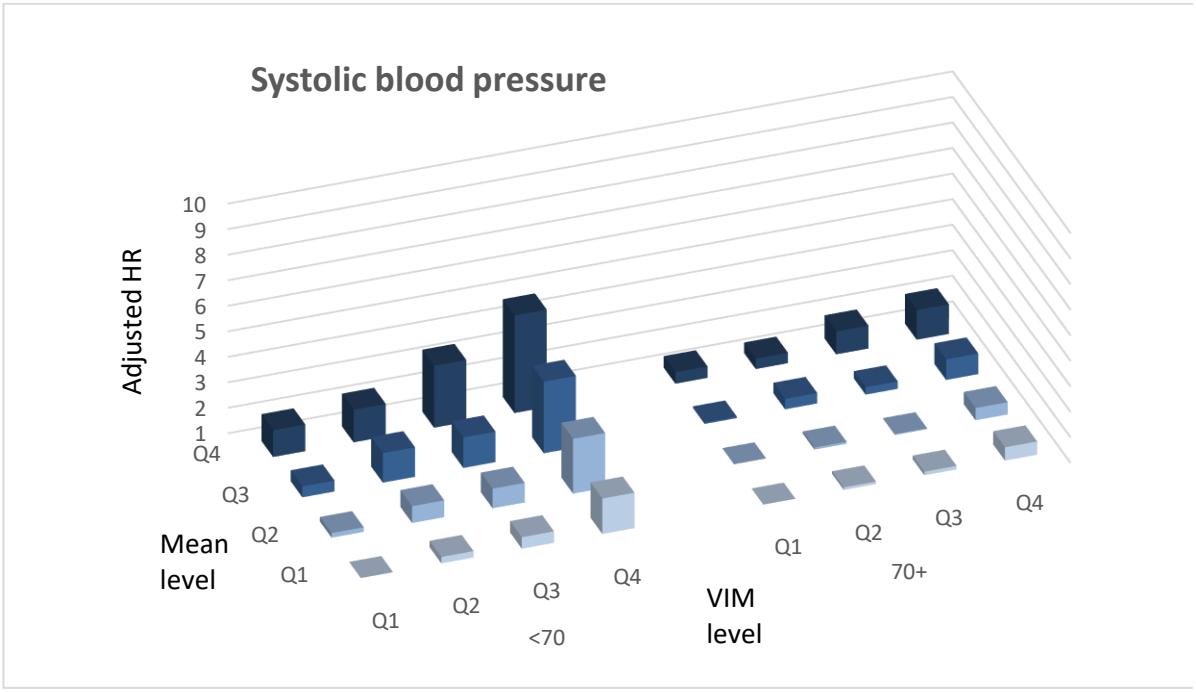


Table 36: Adjusted HRs for sub-groups of mean and VIM blood pressure (each split into quartiles), further split into two age groups, from a Cox PH model

Age group (years)	Mean quartile group	VIM quartile group			
		Q1	Q2	Q3	Q4
		Pulse pressure			
<70	Q4	4.30 (2.52–7.35)	6.42 (3.58–11.53)	6.01 (3.28–11.01)	9.57 (5.39–16.99)
	Q3	1.77 (1.00–3.12)	3.28 (1.80–5.98)	3.61 (1.99–6.53)	4.20 (2.32–7.60)
	Q2	1.08 (0.59–1.96)	2.27 (1.25–4.13)	2.47 (1.35–4.52)	3.72 (2.08–6.65)
	Q1	Ref group	1.67 (0.94–2.98)	1.90 (1.09–3.33)	2.60 (1.52–4.46)
70+	Q4	2.24 (1.37–3.67)	2.17 (1.30–3.62)	2.05 (1.22–3.43)	3.26 (1.98–5.36)
	Q3	1.20 (0.71–2.03)	1.44 (0.85–2.44)	1.60 (0.94–2.71)	1.86 (1.10–3.14)
	Q2	0.95 (0.54–1.66)	1.29 (0.73–2.27)	1.42 (0.81–2.48)	2.13 (0.25–4.63)
	Q1	Ref group	1.08 (0.61–1.93)	1.24 (0.71–2.17)	1.69 (1.00–2.89)
		Systolic blood pressure			
<70	Q4	2.05 (1.25–3.37)	2.28 (1.30–3.99)	3.43 (2.02–5.82)	4.83 (2.86–8.13)
	Q3	1.43 (0.87–2.35)	2.16 (1.24–3.75)	2.20 (1.26–3.85)	3.81 (2.23–6.52)
	Q2	1.18 (0.71–1.96)	1.66 (0.94–2.93)	1.77 (1.00–3.12)	3.15 (1.81–5.46)
	Q1	Ref group	1.25 (0.75–2.10)	1.45 (0.88–2.39)	2.39 (1.50–3.80)
70+	Q4	1.45 (0.93–2.25)	1.41 (0.91–2.18)	1.90 (1.25–2.89)	2.16 (1.44–3.25)
	Q3	1.06 (0.68–1.66)	1.41 (0.91–2.19)	1.29 (0.83–2.01)	1.81 (1.18–2.77)
	Q2	0.87 (0.55–1.37)	1.08 (0.69–1.69)	1.03 (0.65–1.64)	1.48 (0.94–2.33)
	Q1	Ref group	1.10 (0.70–1.74)	1.14 (0.73–1.77)	1.52 (1.01–2.29)

Figure 51: 3-D bar plots of adjusted HRs for sub-groups of mean and VIM blood pressure (each split into quartiles), further split into two age groups, from a Cox PH model





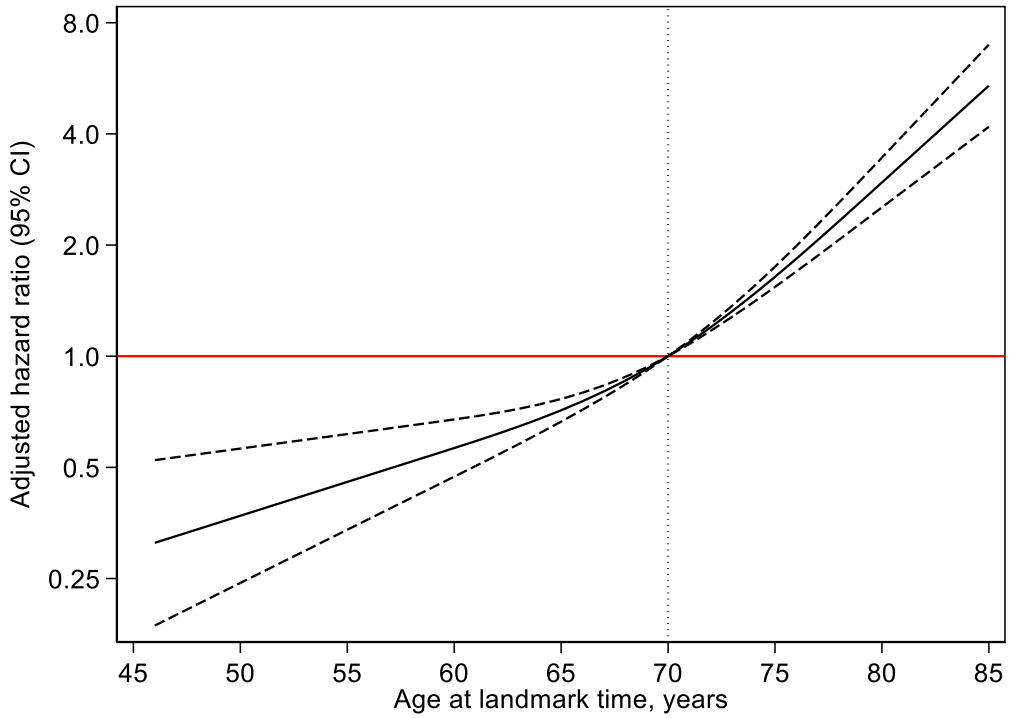
4.5.6.3.2 Developing a clinical useful CV-related mortality risk prediction model containing PP mean and COV

From a series of stages of model development focusing on the pulsatile component of blood pressure only, a clinically useful risk prediction model was developed including mean level and COV, along with age and other available risk factors (as previously identified as pre-specified risk factors for adjustment). Table 37 presents five models each increasing in complexity in some way from the previous.

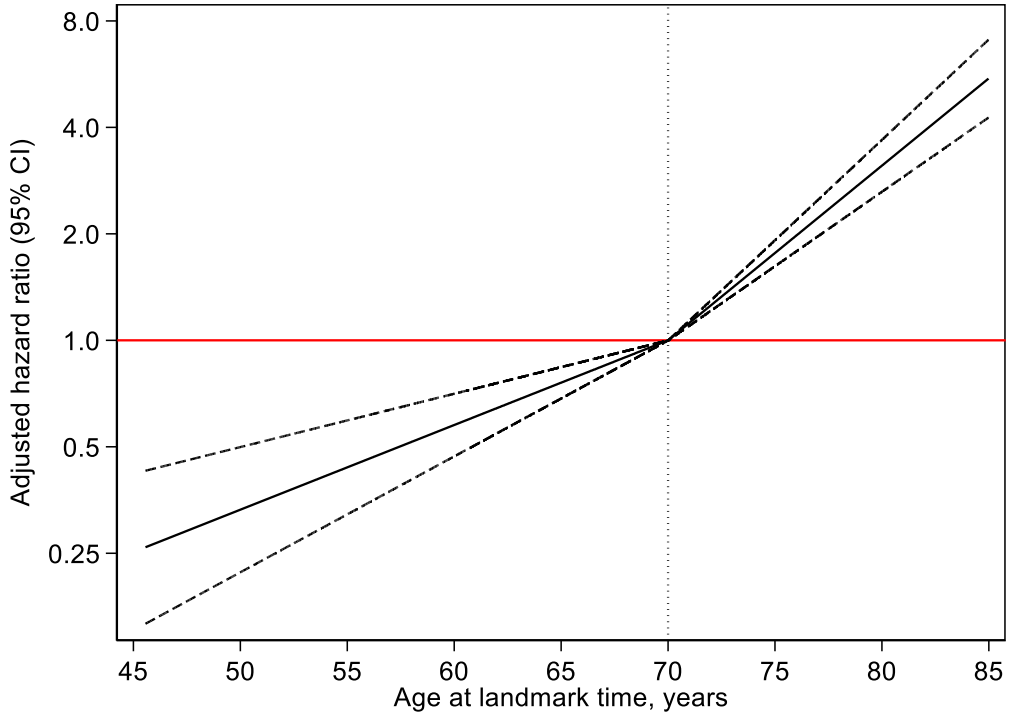
The simplest model presented in Table 37, Model 1, contained PP mean level, PP COV, and age modelled linearly, adjusted for other pre-specified risk factors. The characteristic of variability had a slightly weaker association with CV-related mortality than mean level, with HRs of 1.26 and 1.33 per z-score increase, respectively. There was no evidence against linearity for mean or COV, but evidence against linearity for age. Investigations revealed that the effect of age on CV-related mortality was larger when over around 70 years of age. A RCS transformation was considered for the modelling of age, however, a linear spline transformation with a single knot at 70 years of age, allowing the HRs to differ between ages <70 and 70+ years, was considered sufficient while still easily interpretable (see Figure 52 below for plots of adjusted relative hazard over age, with age modelled both with a RCS transformation and a linear spline transformation).

Figure 52: Plot of adjusted relative hazard (95% CIs) of age, modelled with spline transformations, with reference 70 years of age

Restricted cubic spline transformation with 3 knots at 10th, 50th, and 90th percentile



Linear spline transformation with a single knot at 70 years (as in final model)



Estimates from the final derived model, when PP mean is at mean level (i.e. z-score is zero), and adjusted for PP COV, sex, and diabetic status.

In Model 2, with the addition of the linear spline transformation with knot at 70 years for age, the estimated increase in hazard per 10-year increase in age was over double in those 70 years of age and over compared to those under 70 years. There was an estimated increase in hazard of 75% per 10-year increase in age (95% CI: 42%-117%) when under 70 years and 169% per 10-year increase in age (95% CI: 130%-214%) in those 70 years and older.

Model 3 introduced an interaction term between PP mean and PP COV. The interaction term was estimated at 0.93 (p=0.002), meaning that for every z-score increase in one of the variables (either PP mean or PP COV), the HR for the other variable was modified, estimated to decrease by 7%, and vice versa.

Model 4 introduced an interaction between PP mean and age, which produced 2 interaction terms, one for ages less than 70 years, and the other for ages 70 years and older. The overall p-value from a joint test of these two interaction components was 0.023. There was much stronger evidence for an interaction in those 70 years and older (HR=0.85, p=0.030) compared to those under 70 years (HR=0.98, p=0.852).

Finally, in Model 5, an interaction between PP COV and age was introduced, involving two interactions terms again. While there was fairly weak evidence overall from a joint test of the two interaction terms (0.068), as with PP mean, the evidence for an interaction was stronger between PP COV and age in those 70 years and older

(HR=0.85, p=0.021). All of these progressive models in Table 37 were adjusted for the additional aforementioned pre-specified risk factors.

Table 37: Progression of model complexity involving PP mean and COV, age, and other pre-specified risk factors

		<70 or 70+	Adjusted HR (95% CI)*	p-value	p-value for improvement of model vs. the last (LR test)
Model 1: • **All modelled linearly** • **No interactions**	PP arithmetic mean (per z-score)	-	1.33 (1.25-1.42)	<0.001	-
	PP COV (per z-score)	-	1.26 (1.19-1.33)	<0.001	
	Age (per 10 years)	-	2.29 (2.06-2.55)	<0.001	
Model 2: • **Mean & COV modelled linearly** • **Age modelled with linear spline transformation with 1 knot at 70 years** • **No interactions**	PP arithmetic mean (per z-score)	-	1.33 (1.25-1.42)	<0.001	0.007
	PP COV (per z-score)	-	1.26 (1.19-1.33)	<0.001	
	Age (per 10 years)	<70	1.75 (1.42-2.17)	<0.001	
	Age (per 10 years)	70+	2.69 (2.30-3.14)	<0.001	
Model 3: • **Mean & COV modelled linearly** • **Age modelled with linear spline transformation with 1 knot at 70 years** • **Interaction between mean and COV**	PP arithmetic mean (per z-score)	-	1.35 (1.27-1.44)	<0.001	0.004
	PP COV (per z-score)	-	1.29 (1.22-1.37)	<0.001	
	Interaction term (mean with COV)	-	0.93 (0.89-0.98)	0.002	
	Age (per 10 years)	<70	1.75 (1.41-2.17)	<0.001	
	Age (per 10 years)	70+	2.69 (2.30-3.14)	<0.001	
Model 4: • **Mean & COV modelled linearly** • **Age modelled with linear spline transformation with 1 knot at 70 years** • **Interaction between mean & COV** • **Interaction between age & mean**	PP arithmetic mean (per z-score)	-	1.48 (1.32-1.66)	<0.001	0.023
	PP COV (per z-score)	-	1.29 (1.22-1.37)	<0.001	
	Interaction term (mean with COV)	-	0.94 (0.90-0.98)	0.006	
	Age (per 10 years)	<70	1.63 (1.31-2.03)	<0.001	
	Age (per 10 years)	70+	2.97 (2.51-3.53)	<0.001	
	Interaction terms (age with mean)	<70	0.98 (0.80-1.20)	0.852	
	Interaction terms (age with mean)	70+	0.85 (0.74-0.98)	0.030	
Model 5: • **Mean & COV modelled linearly** • **Age modelled with linear spline transformation with 1 knot at 70 years** • **Interaction between mean & COV** • **Interaction between age & mean** • **Interaction between age & COV**	PP arithmetic mean (per z-score)	-	1.49 (1.33-1.67)	<0.001	0.068
	PP COV (per z-score)	-	1.44 (1.29-1.60)	<0.001	
	Interaction term (mean with COV)	-	0.94 (0.90-0.99)	0.012	
	Age (per 10 years)	<70	1.59 (1.28-1.99)	<0.001	
	Age (per 10 years)	70+	3.11 (2.61-3.81)	<0.001	
	Interaction terms (age with mean)	<70	0.99 (0.81-1.22)	0.951	
	Interaction terms (age with mean)	70+	0.84 (0.73-0.96)	0.013	
	Interaction terms (age with COV)	<70	1.15 (0.94-1.41)	0.173	
	Interaction terms (age with COV)	70+	0.85 (0.74-0.98)	0.021	

* Adjusted for other pre-defined baseline risk factors

After refining Model 5 to create the final simplified model, leaving only risk factors and interaction terms that had a convincing level of evidence ($p<0.01$), a total of five risk factors remained. The final model is presented in Table 38, containing PP mean ($p<0.001$), PP COV ($p<0.001$), an interaction between PP mean and PP COV ($p=0.004$), age ($p<0.001$), an interaction between age and PP mean when age is 70 years and above ($p=0.005$), sex ($p=0.004$), and diabetes diagnosis at the landmark time ($p<0.001$).

Both PP mean and PP COV were centred around their mean values (58.34 mmHg and 0.138, respectively), and age was centred around 70 years (which was very close to the mean age of 69.29 years). Therefore, the HRs in the model can be interpreted in that context.

An increase in z-score of PP mean (representing a 10.86 mmHg increase) was associated with a 50% increase in hazard for those with mean PP COV (0.138) and of age 70 years or younger, adjusted for sex and diabetes status. An increase in z-score of PP COV (representing a 0.047 increase) was associated with a 29% increase in hazard for those with mean PP mean (58.34 mmHg), adjusted for age, sex, and diabetes status. The interaction between PP mean and PP COV can be interpreted as the effect of a z-score increase in one risk factor decreases with the increase per z-score of another risk factor by an estimated factor of 0.94, and vice versa.

An increase in age of 10 years was associated with a 74% increase in hazard for those under 70 years of age adjusted for the other risk factors in the model. An increase in age of 10 years was associated with a 269% increase in hazard for those 70 years and older who had mean PP mean, adjusted for the other risk factors in the model. The interaction between age (for values of age 70 and older only) and PP mean can be interpreted as, for every additional 10-year increase in age, the estimated effect per z-score increase in PP mean decreases by an estimated factor of 0.83, and vice versa.

To help illustrate the changes in relative hazard in the context of the interactions present in the final model, Figure 53 presents two plots. The first (A) presents relative hazard across age, at different levels of PP mean (with the reference at 70 years of age and mean PP mean). The plot shows how, in general, the gradients get steeper after from 70 years of age and older (HRs get larger in magnitude) but to a lesser degree the larger the PP mean level was. The second plot (B) presents relative hazard across PP mean, at different levels of PP COV (with the reference at mean PP mean and mean PP COV). The gradient of the slope gets gentler (HR is smaller in magnitude) with increasing PP COV level. The plots allow us to compare relative hazard levels, for example: with all other variables in the model held constant, someone of 70 years of age and mean PP mean of 58.34 mmHg (z=0) had a similar hazard to someone aged 55 years but with a higher PP mean of 80.06

mmHg (z=2); and someone with mean PP of 58.34 mmHg (z=0) and mean PP COV of 0.138 (z=0) had a similar hazard as someone with low PP at around 40 mmHg but high PP COV of 0.231 (z=2).

Upon removal of each risk factor from the final model individually (with everything else remaining), the change in C-statistic was highest for age (0.058), and was the same for PP mean and PP COV (both 0.011).

Being diabetic at the landmark time was associated with a 47% increase in hazard compared to non-diabetics (95% CI: 1.30-1.66). Males had a 25% increased hazard compared to females (95% CI: 1.07-1.46).

Table 38: Final clinically useful risk prediction model containing PP mean, PP COV, and other important risk factors

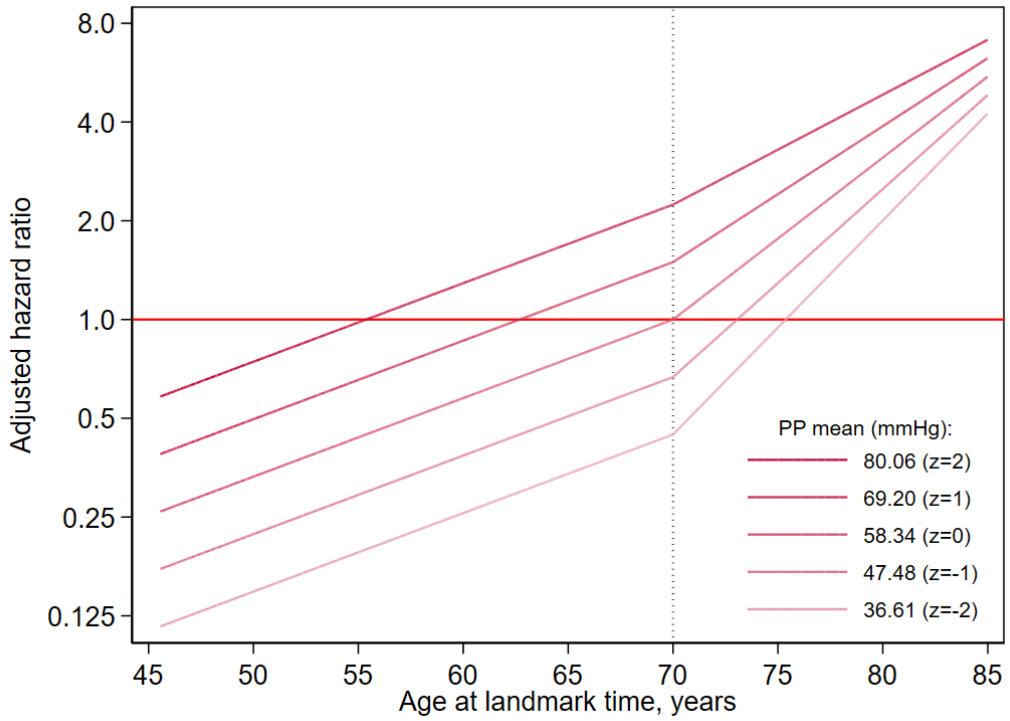
		Age (years) <70 or 70+	Adjusted HR (95% CI)*	p-value	C-statistic decrease when excluded from full model
PP arithmetic mean (per z-score)		-	1.50 (1.37-1.63)	<0.001	0.011
PP COV (per z-score)		-	1.29 (1.22-1.36)	<0.001	0.011
Interaction term (mean with COV)		-	0.94 (0.90-0.98)	0.004	-
Age (per 10 years)		<70 70+	1.74 (1.42-2.13) 3.12 (2.63-3.69)	<0.001 <0.001	0.058
Interaction term (age with mean)		70+	0.83 (0.73-0.95)	0.005	-
Sex	Female	-	-		
	Male	-	1.25 (1.07-1.46)	0.004	0.002
Diabetes Mellitus	No	-	-		
	Yes	-	1.47 (1.30-1.66)	<0.001	0.006

* adjusted for all other variables in the table.

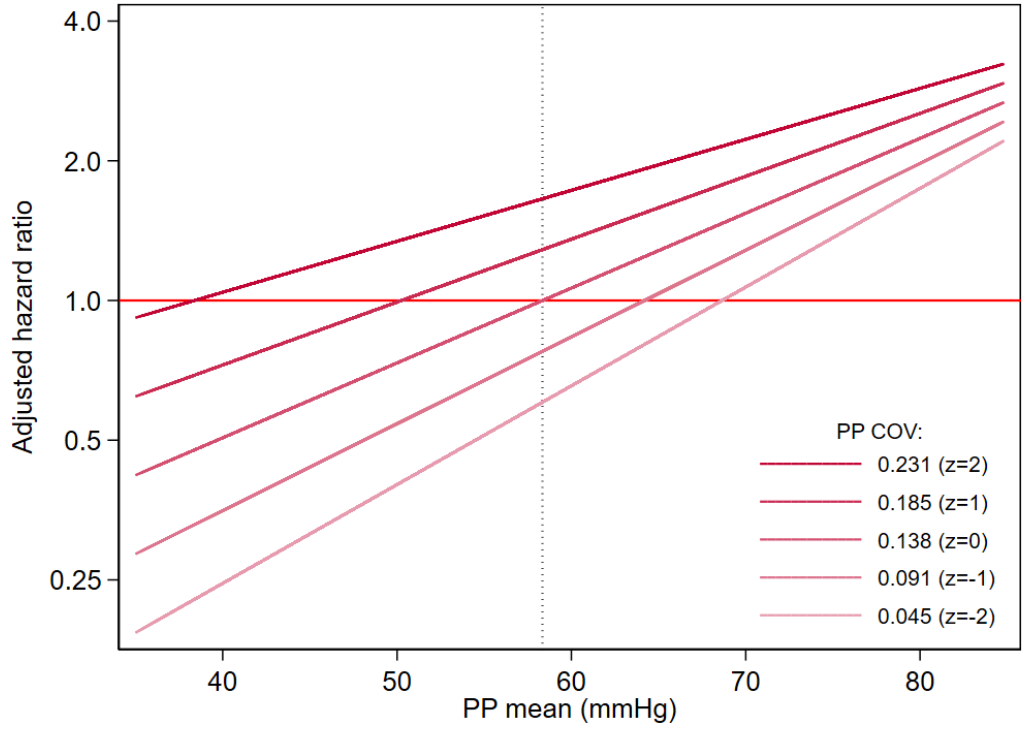
Note: the model C-statistic is 0.740

Figure 53: Plots of risk factors in final clinically useful risk prediction model against adjusted relative hazard, by levels of other risk factors where interactions are present

(A) Plot of age against adjusted relative hazard at different levels of PP mean
(reference point is 70 years of age, and when PP mean is mean level of 58.34 mmHg)

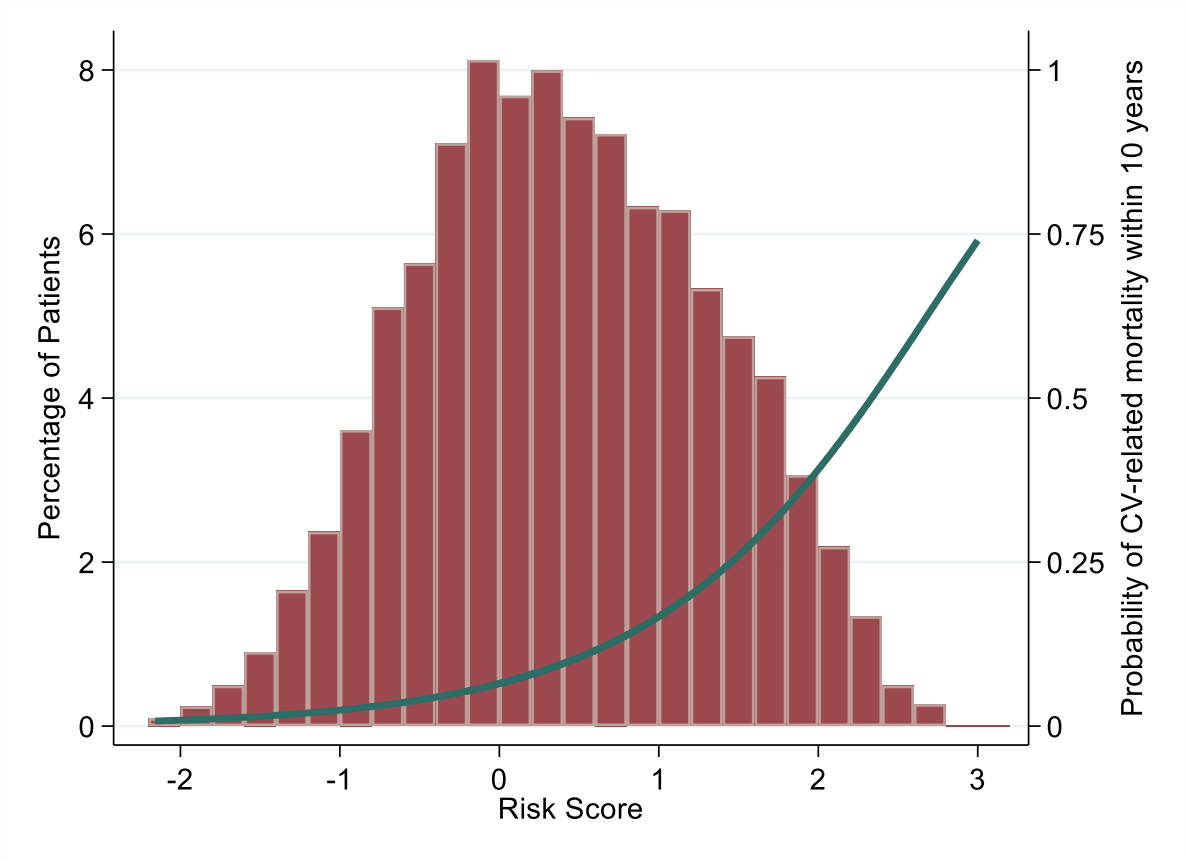


(B) Plot of PP mean against adjusted relative hazard at different levels of PP COV
(reference point is when PP mean is at mean level of 58.34 mmHg, and PP COV is at mean level of 0.138)



A risk score for 10-year CV-related mortality risk was calculated for each subject from the risk coefficients of the linear predictor from the final model, and 10-year CV-related mortality risk for each subject was calculated as $1 - baserisk^{\exp(score)} = 1 - 0.9350876^{\exp(score)}$. The distribution of risk scores is presented in Figure 54, along with the relationship between risk score and predicted probability of CV-related mortality within 10-years. 47.3% of subjects had a predicted probability of death from CV-related causes within 10 years of over 10%, 14.9% of subjects had a risk over 25%, and 1.0% had higher than 50% risk of mortality within 10 years.

Figure 54: Risk score distribution and predicted CV-related mortality risk



Subjects were stratified into groups based on their risk scores. Six groups were formed consisting of five quintiles of risk score, with the highest quintile further split (i.e. into two top deciles). Figure 55 presents a Kaplan Meier cumulative incidence plot of CV-related mortality, stratified by the 6 risk score groups. There appears to be good discrimination between the risk groups, with a clear separation between cumulative incidence curves, even between the lower risk groups. 10-year CV-related mortality risk varied from 2.7% (95% CI: 2.0%-3.8%) in the lowest quintile group to 38.0% (95% CI: 33.7%-42.7%) in the highest decile group.

Overall, the discrimination of the final model was good, with a C-statistic of 0.740 (95% CI: 0.726-0.754). Internal validation was conducted using a bootstrap resampling method to estimate the bias due to model overfitting, and hence estimate the magnitude of discrimination of the model if used on external data. Using 1000 bootstrap samples, the estimated bias in C-statistic was 0.005 (95% CI: 0.001-0.015). This implies that if this model was used on external data, the C-statistic would be 0.734 (95% CI: 0.725-0.740).

The model also showed good calibration (goodness-of-fit), with model-predicted CV-related mortality risk showing strong similarities within each risk group to the observed. This can be seen visually in Figure 56, a bar-chart of predicted and observed CV-related mortality risk in each risk score group where there appears to be good agreement across the groups, and formally from a Nam-D'Agostino test

assessing the difference between predicted and observed risk there was no evidence for a difference (p=0.543).

Figure 55: Cumulative CV-related mortality, by risk subgroups

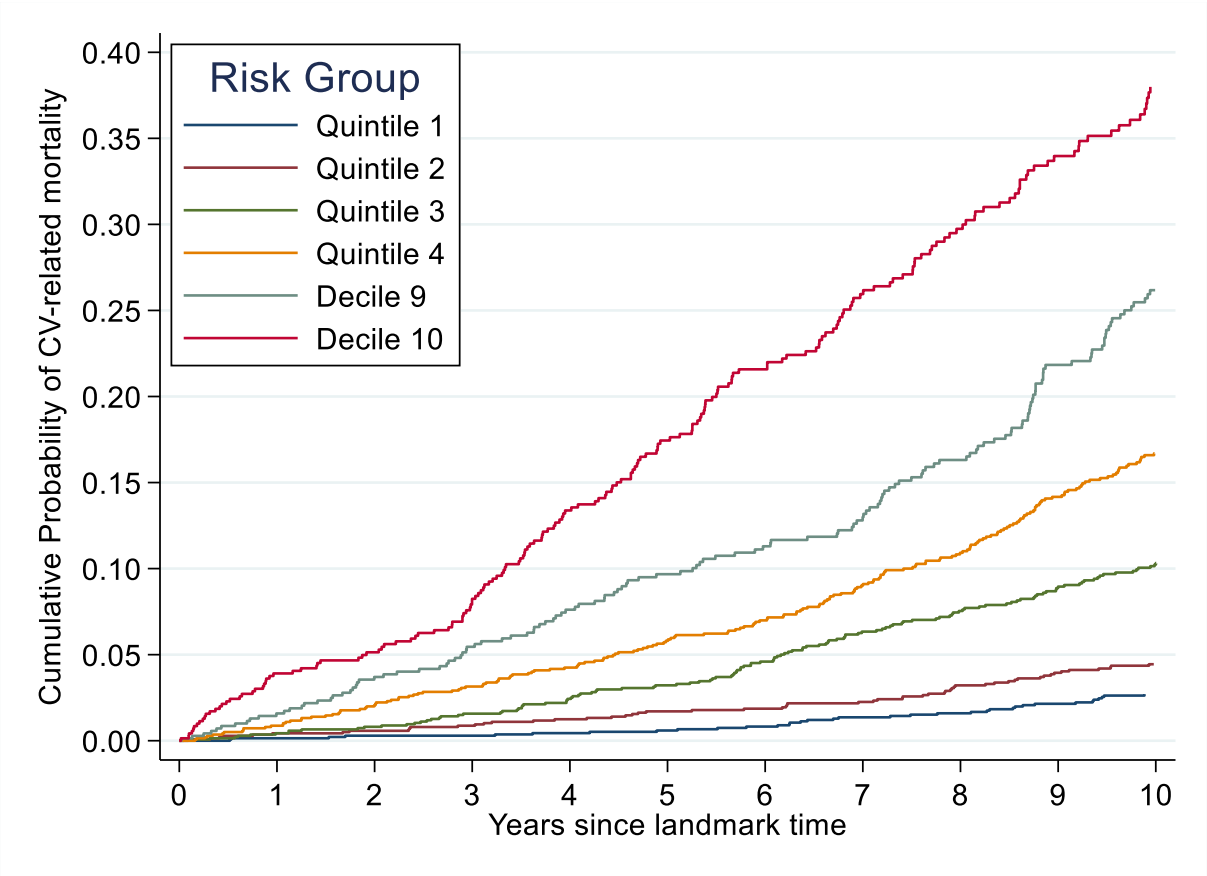
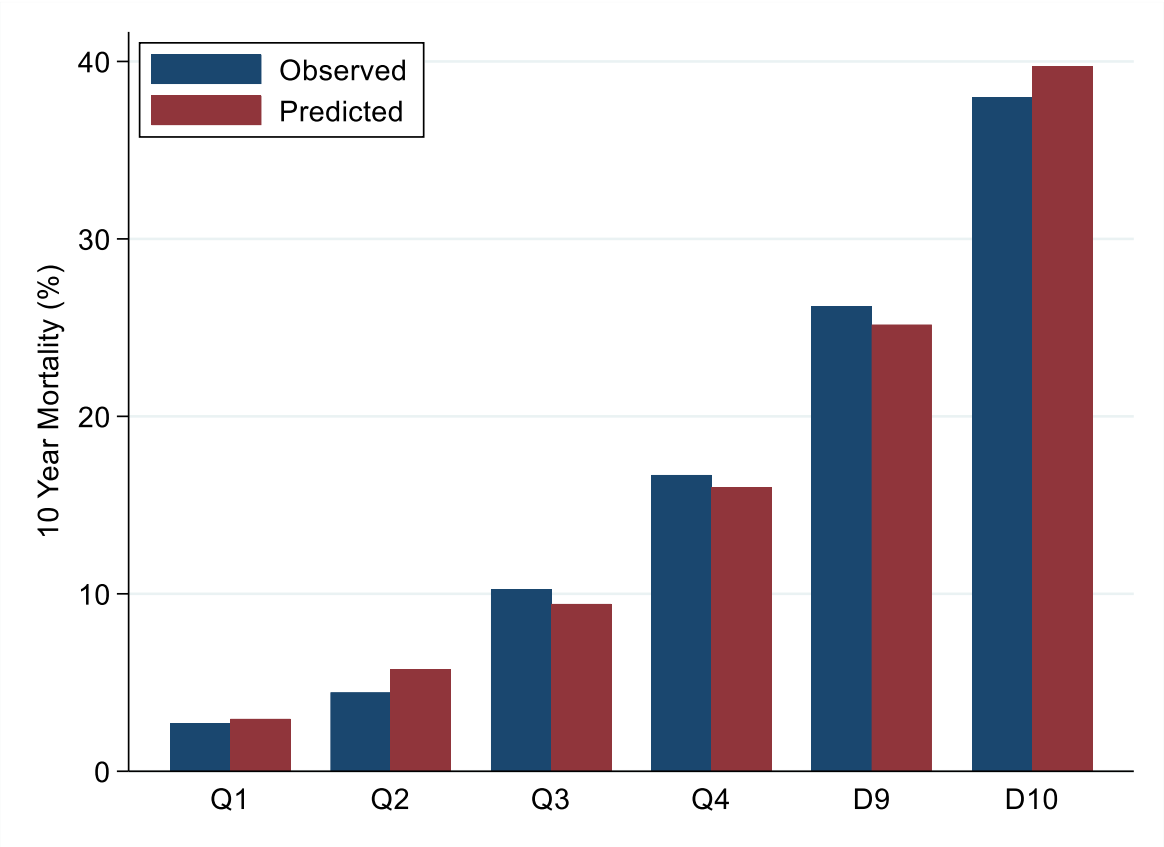


Figure 56: Risk discrimination and model goodness-of-fit



Note: Q1–Q4 represent the first four quintiles, and D9 and D10 represent the top two deciles of estimated risk from the final model.

Model risk factors were distributed over the six risk groups as shown in Table 39. Although SD was not the measure of PP variability in the model, it is also presented in the table (greyed out) to show a more easily interpretable distribution of variability across the risk groups. In the lowest risk group, mean age was 54 years and 15.5% were diabetic, compared to the highest decile risk group where mean age was 75 years and over 50% were diabetic. There was not a large difference in the distribution of sex across risk groups.

There was a striking difference in mean PP mean and mean PP COV across risk groups. Mean PP mean was 48 mmHg in the lowest risk group and nearly 72 mmHg in the highest. Mean PP COV was 0.115 in the lowest risk group and 0.167 in the highest. There was a very striking trend of increasing PP SD across risk groups, mean PP SD varying from 5.49 mmHg to 11.74 mmHg from lowest to highest risk groups, respectively, but of course the SD is not independent of the mean.

Table 39: Model risk factors across risk groups for the final model

	Quintile 1 N=1418	Quintile 2 N=1418	Quintile 3 N=1419	Quintile 4 N=1418	Decile 9 N=710	Decile 10 N=709
Age, years mean (SD)	54.01 (5.70)	60.05 (4.41)	63.55 (4.42)	67.82 (4.26)	71.84 (3.78)	75.16 (3.31)
Male n, (%)	1196 (84.34)	1144 (80.68)	1122 (79.07)	1167 (82.30)	561 (79.01)	567 (79.97)
Diabetes n, (%)	220 (15.51)	393 (27.72)	541 (38.13)	571 (40.27)	286 (40.28)	380 (53.60)
PP mean, mmHg mean (SD)	48.09 (5.91)	53.81 (6.45)	58.44 (7.56)	62.14 (8.57)	66.73 (9.57)	71.66 (12.10)
PP COV mean (SD)	0.115 (0.033)	0.132 (0.039)	0.139 (0.045)	0.147 (0.047)	0.148 (0.048)	0.167 (0.059)
PP SD mean (SD)	5.49 (1.57)	6.98 (1.88)	8.03 (2.49)	9.02 (2.90)	9.81 (3.36)	11.74 (4.14)

Note, PP SD does not feature in the final clinically useful risk prediction model.

4.5.7 Conclusions and Discussion

This long-term follow-up data of UK patients from the ASCOT trial provided solid evidence of the importance of visit-to-visit variability of blood pressure as a strong predictor of CV-related mortality, independent of mean level, in subjects with hypertension and at high risk of CVD. This supports and builds upon existing evidence of the prognostic importance of blood pressure variability [188-191]. In addition, this research provides evidence that the PP component of blood pressure is at least as strong a predictor as SBP, and in these data perhaps even stronger.

There have now been several studies that have provided evidence of the prognostic importance of blood pressure variability [132,192]. Despite growing evidence of the importance of blood pressure variability, it has been controversial as to how to use measures of variability in blood pressure in clinical practice. Clinical guidance has remained almost entirely on measures of blood pressure level as the focus for assessing CV risk and managing hypertension [193]. This is understandable since blood pressure level remains the most relevant risk factor and one that is known to be susceptible to change through lifestyle/behavioural modifications and anti-hypertensive pharmacological interventions.

While there have been many substantial developments in anti-hypertensive drug research, including many large-scale Phase III trials, there have been no trials to date that have focused on the reduction of blood pressure variability. This study

provides evidence that blood pressure variability may of similar importance as blood pressure level at identifying CV risk, and supports the concept that variability can be used to assess patient risk, and should be incorporated within the management of blood pressure.

Some treatments have been identified as having beneficial effects on reducing variability. It has been argued that some of the beneficent effects seen in the ASCOT trial from the CCB-based treatment regimen might be more through the mechanism which resulted in a reduction in blood pressure variability, as seen compared to the BB-based regimen, rather than due to differences in achieved blood pressure level [15,188]. The differences seen in achieved SBP were considered small from a clinically meaningful point of view [14,138]. Further, there was no difference in achieved PP level between BPLA groups of the ASCOT trial, while the differences seen in the variability of both SBP and PP between anti-hypertensive treatment arms were substantial. Blood pressure variability was considerably lower in those allocated to amlodipine-based compared to atenolol-based treatment.

The use of increasing numbers of blood pressure measures in the calculation of both blood pressure mean level and variability (SD), vastly increased their association with CV-related mortality. For mean level, this increase in association had not reached an obvious peak with inclusion of all available blood pressure measures, both for SBP and PP. It makes intuitive sense that the more measures

used, the more accurate the estimate of "usual level" can be. Given how naturally variable blood pressure is, and how prone to measurement error, more blood pressure measurements will increase the accuracy of estimating the underlying level and reduce regression dilution bias as measurement error decreases when more blood pressure measurements are used. For the variability in blood pressure, as measured by the SD, there seemed a threshold number of blood pressure measures used in its calculation of about six, after which there was little or no increase in the association between the SD and CV-related mortality with the addition of more blood pressure readings.

The mean of earlier blood pressure measures (post treatment initiation) were more strongly associated with CV-mortality compared to later (more recent) measures. This result might be surprising since it might seem more intuitive that more recent blood pressure would correlate more with future risk. It might be that in this context the blood pressure level soon after initiation of anti-hypertensive treatment could be an indication of how well subjects initially respond to treatment. The higher the blood pressure early on following treatment initiation could be an indication of resistant hypertension or worse underlying condition, possibly highlighting those for whom it was more difficult to blood pressure control. Later blood pressure measures were less informative, possibly because towards the of the trial there was less difference in blood pressure between patients, after sicker

patients had gone through more aggressive antihypertensive treatment and with longer treatment had slightly caught up those less ill who had had a more rapid decline in blood pressure earlier on. The opposite was seen with the SD, and later measures seemed more informative than earlier. It could be that earlier on a lot of the variability was coming from the decline in blood pressure level, while later on when blood pressure levels were more stable, the variability became more informative of underlying risk.

In addition to blood pressure variability being shown to be important, the maximum blood pressure from a single clinical visit over the period of observation was shown to have a very strong relationship with CV-related mortality. In fact, the association was stronger than for mean level, both for SBP and PP. While maximum blood pressure is the measure of blood pressure from only a single clinical visit, it is selected in the context of all other measurements that fall beneath it, so is not independent of the other blood pressure measures. Therefore, it doesn't fall under the same limitations as other single measurements that show weaker associations with risk compared to the use of multiple measurements. A potential reason for the strong prognostic value of maximum blood pressure could be that, in part, it may be capturing information about both underlying blood pressure level as well as some information about the magnitude of variability. It could be that peaks in blood pressure are simply more important than blood pressure level itself, if peaks

in blood pressure are the cause the severe CV damage or an indirect indication of other factors responsive for increasing risk. Also, the strong prognostic value of blood pressure variability could be, if only in part, because it will be capturing some information about damaging peaks in blood pressure. Although some studies have recently identified the prognostic value of maximum blood pressure as a predictor of CV events, research in this area is still limited and would benefit from further investigation in order to better understand the relationship and how maximum blood pressure might be used in risk prediction and clinical management of risk [188,194,195].

Calculating both blood pressure gradient and blood pressure level by fitting a linear regression line using OLS on a subject-by-subject basis was problematic, leading to very wide, extreme, and unrealistic distributions. Assuming these characteristics of blood pressure were normally distributed, using mixed effects models produced BLUP estimates of blood pressure gradient and blood pressure level that were more realistic. There was a hint of an overall association between blood pressure gradient and risk of CV-related mortality. Lower value gradients were associated with higher risk, both for SBP and PP, after adjustment for blood pressure level and other pre-specified risk factors, although evidence was weak in the case of PP. However, the relationships appeared more complex, with strong evidence against linearity for blood pressure gradient, and some evidence for interactions between

blood pressure gradient and blood pressure level, for both SBP and PP. In summary, it appeared that lower value blood pressure gradients were associated with increased risk, but this was only the case for negative gradients, and the association become stronger at lower overall blood pressure levels. These findings are hard to interpret and difficult to account for, and require further investigation. In general, one might expect the opposite, that the lower the blood pressure gradient, the lower the risk. However, in this context it is hard to know what is underlying in such patients who have more rapidly decreasing blood pressure levels.

Building upon evidence in Chapter 3 of this thesis, comparing the predictive power of different components of blood pressure as measured at baseline, this research has highlighted the importance of PP level, and has suggested it may be superior to SBP in the prediction of CV-related mortality. This further builds on the increasing evidence for the importance of PP, found to be more important in many studies than other components of blood pressure in predicting CVD-related events [196]. PP was quite strikingly the stronger predictor compared to SBP when looking at a number of different characteristics of blood pressure level, including the arithmetic mean, maximum, linear gradient and level at the mid-point over the period of observation. The differences seen between the two components of blood pressure appeared more striking than seen in the previous chapter when comparing these components using baseline blood pressure measures. A possible reason for a less

marked difference in association when using baseline measures could be because PP might suffer more from regression dilution bias than SBP. As a consequence of being calculated based on both SBP and DBP, PP combines measurement error from both. Hence, when this potential regression dilution bias is reduced when using a higher number of measurements to calculate blood pressure level, this could be causing the effect of PP to emerge stronger in comparison to SBP.

The final clinically useful risk prediction model presented both PP mean and PP COV, both carrying a similar level of importance in the model, as well as age, sex and diabetes status at the landmark time. The relative effect of PP variability was dependent on mean level, and vice versa, each seeming to have reduced relative association with CV-related mortality at higher levels of the other. These two attributes of PP might share in informing about some of the biological mechanisms linked to increased risk, and if so the interaction could be plausible, since, if one is already high and giving information about a particular biological risk factor, then the increase in the other attribute of blood pressure might no longer be as informative.

PP mean level increased with age (as did PP COV) but the relative effect of mean level reduced in magnitude with increasing age, with evidence for an interaction between those below 70 years and 70 years of age and older. A possible reason for this interaction with age could be because of fewer competing causes of mortality in

younger subjects. However, the absolute differences in rates of CV-related mortality were very similar for PP mean across the ages, so this interaction on the relative scale may simply be a result of the increased underlying risk that older subjects were at that reduced the relative risk while the absolute difference was maintained across the ages.

The final clinical useful model showed good discrimination and calibration. Appropriate external validation of the model is needed, however, internal validation using bootstrap resampling estimated only a slight reduction in discrimination, suggesting only a small amount of bias from model overfitting in this dataset. Internal validation using the bootstrap method as described by Harrell et. al. has been shown to be comparable to external validation [187,197]. In addition, this method of internal validation allows development of the model using all valid data-points, avoiding the need to develop the model on a reduced dataset in order to reserve some data for validation thereafter. This good level of discrimination was demonstrated by the model despite the fact that the model contained relatively few risk factors. Were it to be developed to include other known important risk factors for CV-related mortality, it could show greater discriminatory power [198].

While this research cannot explain the root biological causes of increased risk, and cannot prove a causal link between blood pressure variability and CV-related mortality, the strong association between blood pressure variability and CV-related

mortality make it a highly important characteristic of blood pressure for the monitoring of patient health. Possible mechanisms through which blood pressure variability may have a plausible causal impact on CV health are not entirely clear. Estimates of blood pressure variability will represent many things all contributing to its size. Some aspects, such as seasonal variability which differ depending on frailty of the subject and variability linked to lifestyle factors such as the consumption of alcohol or smoking will be caught up in the measure of variability of blood pressure to a degree. In addition, adherence to medication will also contribute to visit-to-visit variability in blood pressure. Beyond these external factors contributing to blood pressure variability, while there is still uncertainty, there have been suggestions of causal mechanisms through which the variability in blood pressure might have a direct causal impact on vascular health [130]. Higher variability in blood pressure has been found to be associated with vascular function such as arterial stiffness and endothelial dysfunction of other kinds [199-201].

While hypertension is diagnosed based on elevated levels of SBP and DBP, this evidence alongside existing suggests it might be as important to consider visit-to-visit variability alongside blood pressure level when monitoring blood pressure and treating hypertension. To focus solely on blood pressure level, as in current medical practice, may be missing important information that could aid patient management and treatment.

It would be beneficial to approach blood pressure monitoring, management and patient treatment with a more dynamic and broader approach, which could improve cardiovascular outcomes in high-risk patients. Through new technologies such as digital blood pressure diaries that enable patients themselves to record their blood pressures at repeated occasions, it might be more possible in future to utilise repeated measurements of blood pressure in the calculation of subjects individual risks for CVD, and aid better, more personally tailored therapy.

Chapter 5: Overall discussion, conclusions, limitations, strengths, and beyond

5.1 Overall conclusions and discussion

Long-term follow-up data from the ASCOT trial legacy cohort has enabled investigation of important scientific questions relating to the long-term effects of anti-hypertensive treatments and lipid-lowering statin therapy, and the prognostic value of different aspects of blood pressure in relation to mortality in subjects with hypertension and at high risk of CVD. The opportunity to utilise rich data from this large cohort of patients across a long follow-up has provided evidence that strengthens existing research, and aids in generating hypotheses for future research.

The focus of this research began with the assessment of the long-term impact of allocated ASCOT trial treatments on mortality over this long, 17.4-year median follow-up. A sustained beneficial effect of allocation to statin-therapy as compared to placebo was observed with a reduction in CV-related mortality, which appeared to be largely driven by a reduction in deaths from CHD. This finding supports existing evidence of the long-term benefits of statins, and begs the question as to whether limited periods of statin use could deliver sufficient sustained long-term CV-health benefits, implying a reduced need for a continued, life-long dependency and exposure to statins.

The difference in lipid levels between placebo and statin groups during the LLA blinded trial period was substantial. This difference disappeared completely as

soon as the blinded LLA trial was ceased early after a median 3.3 years. This might suggest that even a relatively short period of prolonged elevated lipid levels, as seen in the placebo group, could lead to worse outcomes in the long-term, and that the benefits associated with statin use over a small number of years can lead to long-term benefits in CV health and a longer life-span.

While evidence exists for the long-term benefits of CCB-led treatment over placebo, this study provides evidence that amlodipine-based blood pressure -lowering treatment delivers long-term benefits as compared to alternative active BB-led treatment. A sustained reduction in CV-related mortality was observed associated with amlodipine-based treatment compared to atenolol-based treatment, and more specifically a larger effect seen in the reduction of stroke-related deaths.

There was a different effect on CV-related mortality observed between anti-hypertensive treatment regimens between those involved in the LLA factor of the trial and those at higher risk, with higher lipid levels at baseline, who were not part of the LLA factor of the trial. The atenolol-based group appeared to have similar rates of CV-related mortality to the amlodipine-based group in the LLA subgroup of ASCOT participants, while atenolol-based treatment was less effective than amlodipine-based treatment in the higher risk non-LLA subgroup.

It was noted in the original trial results that it was unlikely that blood pressure control alone would have been responsible for the benefits observed with the

amlodipine-based allocation, as average within-trial blood pressure levels were not considered significantly different between blood pressure-lowering groups of the trial, from a clinically important perspective [15,138]. There may have been a number of other biological changes resulting from amlodipine-based treatment that account more for these observed improved health outcomes. The more clinically significant difference in blood pressure variability seen between treatment groups may explain some of the benefit. The reasons why a larger variability in one's blood pressure over time is associated with poorer prognosis is not entirely understood, but the observed reduction in blood pressure variability associated with amlodipine-based treatment compared to atenolol-based treatment suggests that amlodipine-based treatment may in some way be responsible for impacting the biological mechanisms that manifest in a larger variability. It could be that such a beneficial biological impact from a period of amlodipine-based treatment explains the sustained long-term effect on CV-related mortality, as compared to atenolol-based treatment.

The next part of this research compared components of blood pressure collected at baseline in their ability to predict mortality. While there is vast historical knowledge of the importance of diastolic and systolic blood pressure as risk factors for CVD, MAP and PP have more recently increasingly been identified as possessing important predictive value. SBP has more recently become known as the stronger

predictor of CVD compared to DBP, but the prognostic value of PP in comparison is still contentious. PP is not commonly used in clinical practice or common in risk prediction. Clinical guidelines for the management of hypertension give goals for DBP and SBP, but not PP. Although PP is being used more frequently in clinical research due to the increasing evidence as to its predictive ability for arterial stillness and blood vessel deterioration, it is most often not the component of blood pressure that is of primary focus in observational studies and interventional trials.

From the analysis of blood pressure as collected at baseline, there was evidence that PP was as strong a predictor of mortality as SBP, and perhaps stronger, particularly in older subjects. When using repeated clinical visit-to-visit measurements, the strength of association of PP with mortality from CV-related causes was strikingly higher than that of SBP, when looking at both blood pressure level, and PP seemed to have a similar strength of association to SBP when looking at blood pressure variability. The observed differences in magnitude of the relationships between the level of these two components and risk was more striking when using repeated measures compared to baseline measures alone. This could be a result of the regression dilution bias phenomenon being more present with PP compared to SBP when using baseline measurements alone. Since PP is calculated from two sources of uncertainly both from SBP and DBP, PP has the potential to possess more random variability and measurement uncertainly compared to the

other blood pressure components, and hence PP may be more exposed to regression dilution bias when using single measures in risk prediction.

This evidence that PP may be a stronger predictor for CV-related mortality risk suggests that perhaps there would be value in setting clinical guidelines and healthy targets for PP in the management of hypertension. In addition, PP as a single component representative of blood pressure may improve risk prediction over SBP in predictive models.

The final part of this research demonstrated the importance of blood pressure variability alongside and in addition to blood pressure level as a risk factor for CV-related mortality. This builds upon recent emerging evidence of the importance of blood pressure variability as a risk factor for CVD. When independent of the mean, visit-to-visit variability in blood pressure appeared to have a similar strength of relationship with CV-related mortality risk and a similar predictive value as blood pressure level. In the final clinically useful risk prediction model, both mean level and COV of PP appeared to be contributing equally to the discriminative ability of the model.

Currently, variability in blood pressure is most often represented as the variability in SBP. The QRISK3 predictive model for developing a heart attack or stroke over the next 10 years in those who do not already have a diagnosis of CHD, includes SBP mean and SBP SD. This model is the 3rd edition of the QRISK model updated to

include variability in SBP, amongst some other additional risk factors, in 2018 [137]. However, perhaps there is added prognostic value in substituting SBP for PP. In this study, models containing both PP level and variability in PP performed better than models containing SBP level and variability in SBP.

The final product in this thesis was the development of a clinically useful 10-year CV-related mortality risk prediction model containing PP mean and PP COV, alongside age, sex, and diabetes status. The model showed good discrimination, despite only containing a small number of risk factors.

5.2 Limitations

The research presented in this thesis comes with both strengths and limitations and it is important to interpret findings in the context of these strengths and limitations. Like any clinical study, certain assumptions were made when conducting analyses. In this study some assumptions could be tested, but others could not be.

Within the context of a randomised, controlled trial, it is easier to make causal statements about observed differences between treatment arms. This is because a randomised controlled trial benefits from the randomisation process, which, if carried out well, should lead to subjects being similar between groups except by chance. Therefore, if treatment differences emerge within the trial context, the assumption that the effect observed is due to the interventions and not due to other

unknown confounding factors is more plausible compared to a non-randomised study. Following the end of the ASCOT trial, as time went on over follow-up, differences between randomised groups may have before systematically more dissimilar as a direct consequence of the interventions. Hence, over time, the cohort may to some degree have become exposed to unknown confounding factors that made the originally balanced groups, more and more dissimilar. One of the main limitations in this study was that post-trial treatments were unknown. It was known that after the early cessation of the LLA factors of the trial, the balance in statin use recorded during the remainder of the trial until the BPLA factor ceased, was balanced between originally randomised statin and placebo groups. It might be reasonable to assume that both lipid-lowering and blood pressure-lowering treatment use were balanced between originally randomised groups if trial interventions had no impact, either biologically or psychologically, but given that this study presents evidence of treatment effects it is likely that some differences in future treatments emerged over time.

As could already have been occurring during the trial period, groups may also have differed biologically after the trial as a direct result of the treatments received during the trial. If the trial interventions led to differing health states, then the requirement for and impact of future treatments could surely be different between groups as a result. Also, knowledge of having been randomised to a particular

group could also have had an impact on subjects' future choices and attitudes. In addition to future treatment differences, it could be possible that originally randomised groups might differ over time in terms of behavioural habits and lifestyle choices as a consequence of the group to which they were originally randomised. As a result of all of these unknown factors, groups may have become slightly different over long-term follow-up.

It may be acceptable to assume that a lot of the balance in characteristics between groups would be partially maintained, but it is likely that over time this would become less and less true. The more different the groups become over follow-up time, the more the comparison of outcomes between groups could be biased, subject to potential unknown confounding factors. This makes the estimand that is being used to compare originally randomised trial groups more complex to define as time goes on, and in some respects slightly unknown.

Evidence for the treatment effects that emerged over follow-up, both from statin intervention and between the BPLA treatments, carried with them somewhat borderline statistical evidence at the 5% level. As a consequence of not having larger effect estimates which carried stronger statistical evidence, the study possibly lacked power to detect changes in effect over time, and possibly lacked power to identify if and how effects differ between some subgroups. The lack of identifying evidence of non-proportional hazards over time could be due to true

sustained and consistent effects over time except for random fluctuation, or it simply could be due to a lack of statistical power, given the borderline evidence for overall effects. It has been discussed already that the concept of the HR not changing at all is probably not entirely convincing as subjects go from within-trial conditions, to post-trial life. It is likely that any sustained effect from treatment, any late emerging effect, or any diminishing effect over time will in some way be muddied by unknown influences and confounding factors. Hence, the results need to be interpreted within the context of these unknowns.

In some places within this thesis, the 5% [significance] level was referred to, in reference to the most commonly used statistical significance level in clinical research. However, the intension throughout this thesis was to consider p-values on their continuous scale rather than constructing an arbitrary level at which to dichotomise evidence for estimates as being either statistically significant or non-significant (unless it was helpful to do so for variable selection when model building). No adjustments were made to account for multiple statistical testing in this study, hence p-values do not represent the true probability of a chance finding and interpretation of p-values should be made with that in mind. Having said that, the approach in this study was not to blindly conduct multiple tests to see which showed a statistical significance, often termed data dredging, but analyses were

considered in the context of what is clinically understood in light of existing evidence.

The comparison of prognostic ability between different components of blood pressure began with the use of baseline office measurements. This time-point was important, as it represented the point at which a patient might present at a clinical visit with uncontrolled hypertension in need of clinical intervention. Hence, understanding the importance of baseline blood pressure and which components can best help guide clinical discussions for patients from that time-point is highly valuable. A weakness in this study was that baseline blood pressure was measured from a single clinical visit. Pragmatically, this may mirror real life in that a clinician may only have access to blood pressure measurements from one occasion taken at a single clinical visit from which to make decisions. However, from an analysis perspective, having access to a larger number of blood pressure measurements from multiple clinical visits could lead to more accurate estimates of subjects' true underlying baseline blood pressure levels, and hence have stronger predictive ability. More recently conducted clinical trials and studies have optimised repeat blood pressure measurement collection through the use of ambulatory blood pressure machines which capture blood pressure continuously over the period during which they are used, or through the use of repeated blood pressure measurements taken at home by the patients themselves over a number of days

leading up to a clinical consultation. The utilisation of multiple clinical (office), home, or ambulatory measurements of blood pressure, would help to give a more accurate estimate of a patient's underlying blood pressure level at that particular time, reducing measurement error leading to less uncertainty.

This limitation was somewhat overcome when using repeated blood pressure measures taken at different trial visits, both scheduled and unscheduled in the analysis presented in Chapter 4. But of course, the analysis of repeated within-trial, post antihypertension treatment initiation represents a very different patient stage to that of baseline.

For the assessment of blood pressure variability, this study assessed the clinical visit-to-visit variation in blood pressure. The addition of the availability of repeated patient-recorded home blood pressure measurements and ambulatory blood pressure monitoring data, would have been highly valuable as the blood pressure variability in both of these methods of blood pressure measurement have been shown to possess stronger predictive ability for CV events than variability in clinic blood pressure measurements [202].

It is important to acknowledge limitations to the study and interpret results within the context of the study design, and in the context of the study population. These findings also need to be revaluated in different populations. Despite these limitations, this study possesses many strengths, and findings from these analyses

are an important contribution to continuously emerging CV health and treatment research and serve to provide evidence to inform hypotheses for future research.

5.3 Strengths

This study benefits from the wealth of data that it utilises to address these important CV health questions. The cohort of subjects included in these analyses was large and the follow-up time for this high-risk cohort was long during which a large number of events occurred. The study provided a considerable number of repeated blood pressure measurements that were collected routinely and frequently as part of the trial schedule, with the addition of extra unscheduled measurements. Finally, the context from which this study cohort came from was a large-scale, high quality, high profile randomised, controlled clinical trial.

The ASCOT trial was a very influential trial that impacted clinical practice. Although evidence for the benefits of statins existed at the time of the ASCOT trial, statins had a controversial and slightly uncertain clinical and public perception. The ASCOT trial played an important role, alongside other major trials, in helping to provide the much-needed strong and robust evidence for the good safety and efficacy profile of statin-therapy. Alongside other research, the ASCOT trial helped to increase clinical and public confidence in statins. Having said this, statins do remain a source of ongoing debate and controversy to some extent today. These

debates are mainly over the issue of who should and who shouldn't receive statins, with some claiming statins are overprescribed in people at low risk of CVD.

The results from the ASCOT trial also helped shape antihypertensive treatment, with amlodipine now one of the most commonly prescribed antihypertensive drugs along with ACE inhibitors such as Lisinopril. Atenolol therapy was once one of the most commonly prescribed treatments for hypertension. While it remains a highly prescribed drug to aid with the treatment of hypertension, beta blockers are not usually prescribed as first-line treatment for hypertension, with ACEi, calcium channel blockers and thiazide-type diuretics being the most common first-line treatments. In addition, while atenolol was once the beta blocker most used, it is no longer the most commonly prescribed in its class.

Having the opportunity to follow-up the ASCOT legacy cohort for future post-trial outcomes was a great opportunity. The quality of clinical data collection captured as part of the trial was able to be utilised in this long-term follow-up analysis, which despite its limitations as discussed, provided many strengths over an observational cohort study not born out of a trial context. Indeed, observational studies looking at treatment effects out of a randomised study context are at high risk of bias due to potential unknown and unmeasured confounding factors. There have been many great developments in statistical methods for analysing observational data which help to reduce biases as much as possible and there is

great value and insight gained from such observational studies. However, this study benefits from having a randomised comparison providing an unbiased foundation to this study. Even in light of the limitation that group differences could have emerged over time, the context that this legacy cohort study was born out of, is one of its major strengths.

This legacy cohort study richly benefits from data collected as part of a defined trial protocol, where patients would be treated more similarly to each other and their measurements recorded in a more equal and similarly frequent, routine fashion then would be the case in a non-trial observational setting. Hence collection of repeated blood pressure measurements over the trial period would likely be more regular, abundant, and reliable across the cohort subjects than it would using health record data etc.

The results from this study support, enrich and build upon previous research. It has supported and strengthened the evidence for the long-term benefits of statin-therapy in high risk patients, and provided evidence of the long-term superior benefits of an antihypertensive treatment strategy made up of a CCB and ACEi, as compared to BB and diuretic. The study has provided strong evidence as to the important prognostic strength of blood pressure variability alongside blood pressure level. Finally, the study has given rise to strong evidence as to the prognostic value of PP as the component of blood pressure that may be a superior

marker compared to SBP for the prediction of CV-related mortality in high risk patients. The strength of the study is that the findings are consistent with previous research, build upon existing knowledge and strengthen existing evidence, particularly where some uncertainty exists.

5.4 Future research

Since conducting this analysis, access to electronic health records through registry linkages for consenting ASCOT legacy cohort subjects has provided data on morbidity outcomes, to add to the mortality data. The availability of this data will allow for further development of the work presented within this thesis, for further and comprehensive evaluation of long-term treatment effects on morbidity, as well as, further assessment as to the relationship between blood pressure and clinical events.

While there has been a growing amount of research conducted looking at the prognostic role of blood pressure variability, there is still a lack of understanding as to the biological mechanisms behind the association with CVD risk. Future work should focus on trying to better understand underlying causal mechanisms at play. Blood pressure will vary over time due to a number of different factors: fundamental biological changes over time; lifestyle & behavioural factors; as a result of changes in antihypertensive medications possibly a consequence of poor blood pressure control; adherence to medications, even the type of antihypertensive medication,

for example. A better understanding of which specific factors are causing increased blood pressure variability and in which way they contribute to risk is needed. Developing a better understanding of why an increased variability in blood pressure is associated with poorer outcomes would help with the treatment of patients at high risk by being able to directly target and treat the source of elevated variability.

Work should also focus on the clinical implications of blood pressure variability, and the practical aspects of how best to measure, assess and use the assessment of blood pressure variability as part of patient care. For example, it would be good to assess how the use of patient electronic health records could be used to gain insight into patients' blood pressure variability, to be used by clinicians alongside blood pressure level and other risk factors in the management of cardiovascular health and the assessment of CVD risk.

Further investigation into the classes of antihypertensive drugs that help to reduce blood pressure variability is required. While historically clinical trials have aimed at the reduction of blood pressure as their primary objective, robust clinical trials with the focus on identifying those classes of antihypertensive drug that best control blood pressure variability are needed.

Isolated systolic hypertension is recognised to be the most common type of high blood pressure in older people. There is extensive evidence as to the increased risks associated with isolated systolic hypertension, and studies have shown the

benefit and importance of treating elderly patients with isolated systolic hypertension [203–206]. Despite this, and this growing evidence that PP may be the stronger marker of CV risk in older people than any other single component of blood pressure, PP still does not form part of guidelines for the management of high blood pressure. Further research should be conducted into identifying the best PP target, to be used alongside existing targets in the management and treatment of hypertension. In addition, the identification of the best existing therapies, and the development of new therapies that directly target the mechanisms behind the decline in vascular function that leads to increased arterial stiffness, the main cause of increased PP, is much needed.

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