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Title: Cardiovascular event rates and mortality according to achieved systolic and diastolic blood pressure in patients with stable coronary artery disease: an international cohort study

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Abstract: Background. The optimal blood pressure (BP) target in hypertension remains debated, especially in coronary artery disease (CAD), given concerns for reduced myocardial perfusion if diastolic BP is too low. We studied the relationship between achieved BP and cardiovascular outcomes in CAD patients with hypertension.
Methods. We analysed data from 22,672 patients with stable CAD enrolled (November 2009-June 2010) in the CLARIFY registry (45 countries) and treated for hypertension. Systolic and diastolic BPs before each event were averaged and categorised into 10-mmHg increments. The primary outcome was the composite of cardiovascular death, myocardial infarction, or stroke. Secondary outcomes were each component of the primary outcome, all-cause death, and hospitalisation for heart failure. Hazard ratios (HRs) were estimated with multivariable adjusted Cox proportional hazards models, using the 120-129 systolic BP and 70-79 mmHg diastolic BP subgroups as reference.
Findings. After a median follow-up of 5.0 years, elevated systolic BP ≥140 mm Hg and diastolic BP ≥80 mmHg were each associated with increased risk of cardiovascular events. Systolic BP <120 mmHg was also associated with increased risk for the primary outcome (adjusted HR 1·56 [95% CI 1·36-1·81]) and all secondary outcomes except stroke. Likewise, diastolic BP <70 mmHg was associated with an increase in the primary outcome (adjusted HR 1·41 [1·24-1·61] for diastolic BP 60-69 mmHg and 2·01 [1·50-2·70] for <60 mmHg) and in all secondary outcomes except stroke.
Interpretation. In hypertensive patients with CAD from routine clinical practice, systolic BP <120 mmHg and diastolic BP <70 mmHg were each associated with adverse cardiovascular outcomes, including mortality, supporting the existence of a J-curve phenomenon. This finding suggests caution in the use of BP-lowering treatment in CAD patients
Funding. The CLARIFY registry was supported by Servier.

Cardiovascular event rates and mortality according to achieved systolic and diastolic blood pressure in patients with stable coronary artery disease: an international cohort study

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SUMMARY 298 words

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Methods. We analysed data from 22,672 patients with stable CAD enrolled (November 2009–June 2010) in the CLARIFY registry (45 countries) and treated for hypertension. Systolic and diastolic BPs before each event were averaged and categorised into 10-mmHg increments. The primary outcome was the composite of cardiovascular death, myocardial infarction, or stroke. Secondary outcomes were each component of the primary outcome, all-cause death, and hospitalisation for heart failure. Hazard ratios (HRs) were estimated with multivariable adjusted Cox proportional hazards models, using the 120–129 systolic BP and 70–79 mmHg diastolic BP subgroups as reference.

Findings. After a median follow-up of 5.0 years, elevated systolic BP ≥140 mm Hg and diastolic BP ≥80 mmHg were each associated with increased risk of cardiovascular events. Systolic BP <120 mmHg was also associated with increased risk for the primary outcome (adjusted HR 1·56 [95% CI 1·36–1·81]) and all secondary outcomes except stroke. Likewise, diastolic BP <70 mmHg was associated with an increase in the primary outcome (adjusted HR 1·41 [1·24–1·61] for diastolic BP 60–69 mmHg and 2·01 [1·50–2·70] for <60 mmHg) and in all secondary outcomes except stroke.

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Introduction

Lowering blood pressure (BP) in patients with hypertension reduces the risk of cardiovascular events and death,[1,2] but the optimal target BP remains unresolved.[3-6] Randomised trials failed to demonstrate a benefit of targets <140/90 mmHg,[7,8] and post hoc analyses have suggested that the benefit of BP-lowering treatment might even be reversed below a certain threshold,[5,9-15] the so-called "J-curve phenomenon" reported in the Lancet in the 1980's. [9] Conversely, a large meta-analysis of trials that randomly assigned participants to intensive versus less intensive BP-lowering treatment showed that intensive BP lowering was associated with decreased cardiovascular events[16], and the recent SPRINT trial[17] demonstrated that targeting a systolic BP <120 mmHg in high-risk patients was associated with a reduction in BP-related adverse outcomes, rather favouring a "lower is better" approach.

These contradictory results leave clinicians with uncertainty as to the optimal BP target in patients treated for hypertension. The concern for a J-curve phenomenon is particularly relevant for cardiac events,[10] as the heart is perfused during diastole, and its perfusion may be compromised at low diastolic BP values, especially in patients with coronary artery disease (CAD), both because a coronary stenosis will lower perfusion pressure in the downstream territory and because autoregulation is altered in these patients.[18] Our aim was to study the association between achieved BP levels and cardiovascular outcomes in a large cohort of patients with stable CAD treated for hypertension from the CLARIFY registry.

Methods

CLARIFY (www.clarify-registry.com) was an international prospective observational longitudinal registry of 32,706 outpatients with stable CAD receiving standard medical care. The registry was observational, did not interfere with clinical management, and did not mandate any specific test, procedure, or treatment.[19] In brief, patients were enrolled in 45 countries (excluding the United States) and treated according to local standard medical care. Eligible patients had stable CAD, defined as at least one of the following: documented myocardial infarction >3 months before enrolment; angiographic demonstration of coronary stenosis >50%; chest pain with evidence of myocardial ischaemia (at least a stress electrocardiogram or preferably imaging); or coronary artery bypass graft or percutaneous coronary intervention >3 months before enrolment. These criteria were not mutually exclusive. Exclusion criteria were hospital admission for cardiovascular reasons (including

revascularisation) in the past 3 months, planned revascularisation, or conditions compromising the participation or 5-year follow-up (including severe other cardiovascular disease such as advanced heart failure, severe valve disease, or history of valve repair/replacement).[19] In each practice, enrolment was restricted over a brief period to achieve near consecutive patient recruitment. The first patient was included on 26 November 2009 and recruitment was completed on 30 June 2010. The present analysis was restricted to hypertensive patients (flow chart of study population is shown in Figure S1 in the Supplementary Appendix). Hypertension was defined as the combination of "history of hypertension" at baseline (with the usual 140/90mmHg threshold) and the use of at least one antihypertensive agent at baseline. The study was conducted in accordance with the principles in the Declaration of Helsinki and local ethical approval was obtained in all countries before recruitment. All patients gave written informed consent. The study is registered (ISRCTN43070564).

Data collection

The investigators completed standardised electronic case report forms at baseline and at a patient visit every year±3 months for up to 5 years. For patients missing the yearly visit, telephone contact with the patient, a designated relative or contact, or his/her physician was attempted. Where applicable, registries could be used to retrieve the vital status. A number of measures were implemented to ensure data quality, including onsite monitoring visits of 100% of the data in 5% of centres selected at random; regular telephone contact with investigators to limit missing data and loss to follow-up; and centralised verification of the electronic case report forms for completeness, consistency, and accuracy. At each yearly visit, symptoms, clinical examination, results of the main clinical and biological tests, treatment and clinical outcomes were recorded. The registry was purely observational, with no specific recommendation regarding BP management, and therefore reflects routine practice.

BP analysis

Office BP was measured yearly in patients, after a rest of 5 minutes in the sitting position. The main analysis was performed using the arithmetic mean of all BP values measured throughout the follow-up period, from the baseline visit to the visit before an event or, in patients without an event, up to the last visit. Outcomes were also analysed according to the baseline BP value (BP at enrolment) and to the

last measured BP before an event during follow-up. All analyses were performed for systolic BP and diastolic BP separately. Patients were categorised into 5 groups: systolic BP <120, 120–129 (reference), 130–139, 140–149, and ≥150 mmHg; diastolic BP <60, 60–69, 70–79 (reference), 80–89, and ≥90 mmHg.

Outcomes

The primary outcome was the composite of cardiovascular death, myocardial infarction, or stroke. Secondary outcomes were each component of the primary endpoint, all-cause death, and hospitalisation for heart failure. For all composite outcomes, we analysed the number of patients with at least one event from the composite outcome. Patients experiencing more than one contributing event were counted only once. Events were accepted as reported by physicians and were not adjudicated. However, all events were source-verified during audits.

Statistical analysis

A Cox proportional hazards model was used to evaluate the relationship between BP and cardiovascular outcomes. In addition to crude HRs, adjusted HRs were estimated after adjustment for potential confounding factors, selected using stepwise methods in the Cox proportional hazards models, namely age, geographic region, smoking status, myocardial infarction, percutaneous coronary intervention, diabetes, body mass index, glomerular filtration rate estimated with the chronic kidney disease Epidemiology Collaboration (CKD-EPI) equation, peripheral artery disease, hospitalisation for or symptoms of heart failure, left ventricular ejection fraction, stroke, transient ischaemic attack, angiotensin-receptor blockers, diuretics, and aspirin (model 1). In a separate model, we also adjusted for sex, coronary artery bypass grafting, low- and high-density lipoprotein cholesterol levels, ethnicity, statins, angiotensin-converting enzyme inhibitors, beta-blockers, calcium channel blockers, and other antihypertensive medications (model 2). Unless specified, all results are given for the fully adjusted model. Data were analysed as recorded without any imputation for missing data. Adjustment variables with a large amount of missing data were categorised including a category for missing data to minimise the loss of data in the analysis.

A restricted cubic spline smoothing technique was used to interpolate the overall trend of risks through the range of BP values. A sensitivity analysis excluding all patients with heart failure, defined

as previous hospitalisation for or symptoms of heart failure or a left ventricular ejection fraction <45%, was also performed to ensure that results were not due to reverse causality.

Interactions between average systolic or diastolic BP and the covariates age (>75 *vs* ≤75 years), diabetes, history of stroke or transient ischaemic attack, heart failure, previous coronary revascularisation, and chronic kidney disease (defined by an estimated glomerular filtration rate [eGFR] <60 mL/min/1·73 m^2) at baseline were tested. Subgroup analyses were performed when interactions were significant even after adjustment on the same variables as for the Cox proportional hazards model (model 2).

The statistical analysis was performed using SAS (version 9.2, Cary, NC, USA), and the restricted cubic splines were obtained using a SAS macro.[20]

Role of the funding source

The CLARIFY registry is supported by Servier. The study was designed and conducted by the investigators. All data were collected and analysed by NG and IF at the independent academic statistics centre (Robertson Centre for Biostatistics, University of Glasgow, UK), and were interpreted by the investigators. The sponsor had no role in the study design or in data analysis, and interpretation; or in the decision to submit the manuscript for publication, but assisted with the set-up, data collection and management of the study in each country. The sponsor funded editorial support for editing and revision of the manuscript and received the manuscript for review before submission. Sophie Rushton-Smith, PhD, provided editorial assistance, limited to editing, checking content and language, formatting, referencing, and preparing tables and figures, and was compensated by the sponsor. The CLARIFY registry enforces a no ghost-writing policy. This manuscript was written by the authors, who take full responsibility for its content.

Results

A total of 22,672 adult patients with CAD and hypertension were included in the analysis. Demographic data and baseline characteristics of the patients from the total population and each 10-mmHg-increment BP subgroup are given in Tables 1 and 2. Mean age at baseline was 65·2 years (SD 10.0), 75% were men, and 67% were white. Mean average systolic BP was 133·7 mmHg (SD 16·7) and mean average diastolic BP was 78·2 mmHg (SD 10·1). Compared with patients with high systolic

BP, those with a lower systolic BP tended to be younger, leaner, more likely to be men, without diabetes, and current smokers, with a higher baseline incidence of myocardial infarction and percutaneous coronary intervention, a lower prevalence of stroke, and lower baseline high-density and low-density lipoprotein cholesterol levels. Patients with lower diastolic BP tended to be older, leaner, more likely to be women, diabetic, and non-smokers, with lower baseline levels of low-density lipoprotein cholesterol.

After a median follow-up of 5·0 years (interquartile range 4·5–5·1), 2101 patients (9·3%) met the primary composite outcome. Cardiovascular death, all-cause death, myocardial infarction (fatal or not), stroke (fatal or not), and hospitalisation for heart failure occurred in 1209 (5·3%), 1890 (8·3%), 827 (3·6%), 526 (2·3%), and 1306 (5·8%) patients, respectively.

Crude and adjusted HRs for average systolic and diastolic BP subgroups are given in Table 3. Even after multiple adjustments for baseline cardiovascular disease, risk factors, and medication, a steep J-shaped curve was evidenced for the occurrence of the primary outcome, with increased risk at low and high BP values, both for systolic and diastolic BP (Figures 1 and 2). Compared with the reference group (systolic BP 120–129), the adjusted HR for the primary outcome was 1·51 (95% CI 1·32–1·73) for systolic BP 140–149 mmHg, and 2·48 (95% CI 2·14–2·87) for systolic BP ≥150 mmHg. Systolic BP <120 mmHg was also associated with an increased risk for the primary outcome (adjusted HR 1·56 [95% CI 1·36–1·81]). Likewise, in comparison with a reference group of patients with diastolic BP 70–79 mmHg, diastolic BP ≥80 mmHg was associated with an increased risk for the primary outcome, with adjusted HRs 1·41 (1·27–1·57) for diastolic BP 80–89 mmHg and 3·72 (3·15–4·38) for diastolic BP ≥90 mmHg; diastolic BP <70 mmHg was associated with an increase in the primary outcome (adjusted HR 1·41 [1·24–1·61] and 2·01 [1·50–2·70] for diastolic BP 60–69 and <60 mmHg respectively). A similar steep J-curve, for both systolic and diastolic BP, was seen for cardiovascular death, all-cause death, myocardial infarction, and hospitalisation for heart failure, but not for stroke (Figure 1 and Figure S2 in the Supplementary Appendix). Elevated systolic and diastolic BPs were associated with a marked increase in the risk of stroke. Adjusted HRs were 1·51 (95% CI 1·16–1·97) and 2·57 (1·94–3·41) for systolic BP 140–149 and ≥150 mmHg, respectively. Adjusted HRs were 1·46 (1·18–1·79) and 4·33 (3·15–5·94) for diastolic BP 80–89 and ≥90 mmHg, respectively. In contrast, there was no increased risk of stroke after the same adjustments for the lowest systolic and diastolic BP subgroups (adjusted HRs 1·06 [0·77–1·46] for systolic BP <120 mmHg and 1·23 [0·94–1·61] and

1·31 (0·64-2·69) for diastolic BP 60–69 and <60 mmHg, respectively). Similar results were observed in a sensitivity analysis excluding patients with heart failure at baseline (Table 3), and similar trends were obtained when using baseline BP and last BP before an event or during follow-up (Table S1 in the Supplementary Appendix).

Interaction analyses are presented in Table S2 in the Supplementary Appendix. No significant effect-modification of diabetes, previous stroke or transient ischaemic attack, heart failure, previous revascularisation, or chronic kidney disease at baseline was detected on the relationship between systolic or diastolic BP and the primary outcome. However, a significant interaction with age was seen for both systolic (p=0·02) and diastolic BP (p=0·02). Patients >75 years had an increased risk of the primary outcome for systolic BP ≥150 mmHg (adjusted HR, 1.84 [CI 1.40–2.43]) and systolic BP <120 mmHg (adjusted HR 1.47 [1.12–1.94]), but not for systolic BP 140–149 mmHg (adjusted HR 1.19 [0.92–1.56]), whereas patients ≤75 years had an increased risk for the primary outcome in these three BP subgroups (Table 3 and Figure S3 in the Supplementary Appendix) in comparison with the 120–129-mmHg systolic BP subgroup. For diastolic BP, the increased risk at low BP was only significant for diastolic BP <60 mmHg in patients >75 years, whereas it was significant as early as 70 mmHg in the younger patients (Table 3 and Figure S3 in the Supplementary Appendix).

Discussion

This observational study, conducted in "real-life" stable CAD patients with hypertension, shows that low systolic (<120 mmHg) and low diastolic (<70 mmHg) BPs are associated with an increased risk of cardiovascular events, with a steep J-curve not only for the composite of cardiovascular death, myocardial infarction, or stroke, but also separately for cardiovascular death, all-cause death, myocardial infarction, or hospitalisation for heart failure.

Our results are consistent with previous post hoc analyses from randomised trials in patients with hypertension and CAD.[10,12,18] Likewise, a J-curve (i.e. an increase in risk of cardiovascular events below a certain BP level) has also been described in other high-risk populations, such as patients with a previous cardiovascular event, or diabetes with target organ damage.[14] However, our study was based on a large cohort from routine clinical practice with no predefined BP intervention which may confound the analysis: any retrospective analysis of a BP intervention trial will carry the bias of baseline BP, which will differ between the groups defined by BP achieved during the trial. Additionally,

the J-curve phenomenon was robust and persisted after multiple adjustment procedures for potential confounding factors.

Previous observational studies have yielded conflicting results regarding the risk of stroke, which was J-shaped with systolic BP in the post hoc analysis of patients with previous stroke from the PRoFESS trial,[21] but did not increase at low values of either diastolic or systolic BP in other trials.[10-12] In our study, neither a low diastolic nor a low systolic BP was associated with increased risk of stroke, in contrast with high systolic or diastolic BP, and no interaction between BP and previous stroke was evidenced. The number of patients with a stroke was however smaller than that of other endpoints.

In the debate around the J-curve concept, there is a concern for "reverse causality" (i.e. a low systolic or diastolic BP may only be a marker of poor health rather than the cause of worse clinical outcomes).[5,6,22] However, several lines of evidence argue against this explanation for our findings. First, serious non-cardiovascular disease, conditions interfering with life expectancy (e.g. cancer, drug abuse) and other severe cardiovascular disease (e.g. advanced heart failure, severe valve disease, or history of valve repair/replacement) were exclusion criteria in CLARIFY. Furthermore, the association between low systolic and diastolic BP and increased risk was robust and persisted throughout multiple adjustments, including peripheral artery disease, heart failure, and left ventricular ejection fraction, and also in a sensitivity analysis excluding patients with heart failure. Finally, there was no association between low BP and stroke. Altogether, this strongly argues against reverse causality, but rather is in favour of a direct deleterious effect of low BP on cardiovascular events.

A particular strength of our study is that it includes a large international cohort of patients, and treated in "real-life" conditions. Results from this broad representative cohort may be more externally valid than those from the highly selected populations from randomised trials.[23] There is a concern that low BP goals from randomised trials, when translated into routine practice, may be associated with higher adverse effects or worse outcomes, especially in older patients.[3,24]

In light of discrepant results of tight BP control trials in patients with diabetes[7] or stroke[8] versus neither of these conditions,[17] we examined interactions between BP lowering and these conditions and found none, which is consistent with previous observations.[10,12] However, we found an interaction between both systolic and diastolic BP and age. Interestingly, the J-curve for systolic BP was shifted to the right in patients >75 years, which is in agreement with international guidelines, which advocate for a higher target systolic BP of 150 mmHg in older patients.[25]

The SPRINT trial and a recent meta-analysis appeared to argue against a J-curve phenomenon.[4,16] However, on closer examination, our observations are not inconsistent with their findings. In the recent meta-analysis of more versus less intensive BP treatment, which included relatively old studies,[16] the BP level reached in the more intensive BP-lowering treatment group was 133/76 mmHg *vs* 140/81 mmHg in the less intensive treatment group, so that the "strict control" BP arm remains clearly above the potentially harmful thresholds we observed. Our results are also consistent with the SPRINT trial, even though the BP reached in the intensive treatment group was fairly low (121·4/68·7 vs 136·2/76·3 mmHg in the standard treatment group), as unlike other BP intervention trials, the BP values in SPRINT were measured under unattended conditions to minimise any white coat effect,[7] but may underestimate casual BP values by at least 5–10 mmHg,[24] or up to 16 mmHg.[26] This actually led hypertension experts to warn that the SPRINT target translated into community practice may have deleterious effects[3,24] because the same targets obtained in routine clinical practice would potentially lie within the left part of the J-curve. Our results, which demonstrate a J-curve in patients with casual BP measurements with harmful thresholds very close to the achieved BP obtained in the intensive arm of SPRINT, indeed support this word of caution.

Our observations are in agreement with the fact that after decades of hypertension trials,[1,2] the benefit of lowering BP <140 mmHg remains unquestionable, whereas the benefit of lowering BP to <130 mmHg is uncertain.[7,8,13] These findings are in keeping with the HOPE-3 trial results in which lowering BP was only beneficial when baseline BP was >140/90,[27] and with a meta-analysis of randomised trials showing benefit of BP lowering only when systolic BP was >140 mmHg.[28] For diastolic BP, a target <90 mmHg is undoubtedly beneficial,[1,29] but there is more uncertainty below this threshold. Our study shows that a diastolic BP of 70–79 mmHg is associated with a better outcome than a diastolic BP ≥80 mmHg, in line with results from the SPRINT trial,[17] but also strongly argues against further lowering BP <70 mmHg.

Our results only apply to hypertensive patients with CAD and should not be extrapolated to hypertensive patients with other conditions. Also, these observations derive from an observational study and are prone to confounding. Only dedicated randomised controlled trials comparing BP targets can provide definitive evidence of the risk associated with each BP threshold. In particular, our results call for specific trials to address whether patients with a SBP >140 mmHg and a high pulse pressure should be treated with the goal of a systolic BP <140 mmHg, even at the cost of a diastolic BP <70

mmHg, and whether the answer to that question is different depending on the presence of CAD, a previous history of stroke, diabetes, or advanced age.

In conclusion, this large observational international study shows that high but also low systolic BP and diastolic BP levels are associated with an increased risk of cardiovascular events in CAD patients with hypertension. The increased risk appears under a threshold of 120 mmHg for systolic BP and 70 mmHg for diastolic BP. However, these observations should not slow down the constant effort that is still necessary to improve patient care, as even with the conventional BP goal of <140/90 mmHg, only about half of the hypertensive population is controlled.[30]

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Research in context

Evidence before this study

We searched PubMed without date restriction with the terms “J-curve”, “BP target”, “tight BP control”, ”SPRINT”, and synonyms or various combinations of those words to identify systematic reviews, observational studies, randomised controlled trials, and meta-analysis describing the relationship between achieved BP and cardiovascular events and/or mortality. We screened papers by title and abstract and title and full text in editorials to identify articles relevant for the study aim. We also screened cited papers from the full-texts of these articles for other relevant research. The papers cited in this article were selected to be representative of the existing evidence, and reviews from before and after the publication of the SPRINT trial are referenced.

Overall, although the benefits of blood pressure lowering treatment for the prevention of cardiovascular disease and death in hypertensive patients are well established, whether there is a threshold of achieved systolic and diastolic BP targets within the physiological range under which antihypertensive treatment may be harmful remains a matter of intense debate.

Added value of the study

This study provides important new information of the J-curve phenomenon in hypertensive patients with CAD. Achieved systolic BP <120 mmHg and achieved diastolic BP <70 mmHg are both associated with an increased risk of cardiovascular events and mortality, independently of potential confounding factors.

Implications of all the available evidence

Together with previous observational studies, randomised BP lowering trials, and meta-analyses, our study suggests caution when treating CAD patients with antihypertensive drugs. Future randomised controlled trials will be necessary to confirm the cut-off BP value below which harm outweighs benefit in this population.

Figure legends

Figure 1: Forest plots of adjusted hazard ratio (95% CI) of the primary outcome (cardiovascular death, myocardial infarction, or stroke), A), cardiovascular death (B), all-cause death (C), myocardial infarction (D), or stroke (E), and hospitalisation for heart failure (F) by systolic blood pressure (SBP) and diastolic blood pressure (DBP) increments

The analysis were adjusted for all the variables in the fully adjusted model (model 2), including age, sex, geographic region, smoking status, myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, diabetes, low and high density lipoprotein cholesterol levels, body mass index, glomerular filtration rate, peripheral artery disease, hospitalisation for or symptoms of heart failure, left ventricular ejection fraction, ethnicity, stroke, transient ischaemic attack, and baseline medications (aspirin, statins, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, beta-blockers, calcium channel blockers, diuretics and other antihypertensive medications).

Figure 2: Restricted cubic splines of the primary outcome versus average systolic (upper panel) and diastolic (lower panel) blood pressure (BP)

Restricted cubic splines are represented for the association between average BP level and primary composite outcome of cardiovascular death, myocardial infarction, or stroke. The analyses were adjusted for a variables selected using stepwise methods in the Cox proportional hazards models, namely age, geographic region, smoking status, myocardial infarction, percutaneous coronary Intervention, diabetes, body mass index, glomerular filtration rate, peripheral artery disease, hospitalisation for or symptoms of heart failure, left ventricular ejection fraction, stroke, transient ischaemic attack, angiotensin-receptor blockers, diuretics, and aspirin.

***Table 1*: Demographic and baseline characteristics of the patients, for the total population and each average on-treatment systolic blood-pressure subgroup**

		Mean systolic BP categories						
Parameter	**Number of patients**	**Total population (n=22,672)**	**<120 mmHg (n=2693)**	**120–129 mmHg (n=6946)**	**130–139 mmHg (n=7586)**	**140–149 mmHg (n=3584)**	**≥150 mmHg (n=1863)**	**p value**
Age (years)	22,666	65·2 (10·0)	63·9 (10·4)	64·3 (10·2)	65·4 (9·8)	66·2 (9·6)	67·21 (9·8)	<0·0001
Men	22,672	17,019 (75%)	2104 (78%)	5399 (78%)	5677 (75%)	2578 (72%)	1261 (68%)	<0·0001
Body mass index (kg/m²)	22,654	27·7 (25·2–30·9)	26·7 (24·2–29·7)	27·5 (25·1–30·5)	27·9 (25·3–31·1)	28·4 (25·6–31·5)	28·4 (25·5–31·9)	<0·0001
Diabetes	22,670	7591 (33%)	835 (31%)	2160 (31%)	2545 (34%)	1306 (36%)	745 (40%)	<0·0001
Smoking status	22,672							
Current		2569 (11%)	352 (13%)	780 (11%)	861 (11%)	383 (11%)	193 (10%)	<0·0001
Former		10,158 (45%)	1254 (47%)	3222 (46%)	3325 (44%)	1553 (43%)	804 (43%)	
Never		9945 (44%)	1087 (40%)	2944 (42%)	3400 (45%)	1648 (46%)	866 (46%)	
Systolic BP (mmHg)	22,659	133·7 (16·7)	114·3 (10·7)	125·9 (10·3)	135·8 (11·3)	145·5 (13·4)	159·3 (16·4)	–
Diastolic BP (mmHg)	22,659	78·2 (10·1)	71·0 (8·8)	76·0 (8·4)	79·2 (9·2)	82·2 (10·3)	85·5 (11·7)	–
Heart rate (beats/minute)	22,660	68·5 (10·6)	67·4 (10·2)	67·9 (10·2)	68·7 (10·6)	69·4 (11·1)	69·6 (11·7)	<0·0001
Myocardial Infarction	22,670	13,258 (58%)	1789 (66%)	4165 (60%)	4298 (57%)	2017 (56%)	989 (53%)	<0·0001
Percutaneous coronary intervention	22,670	12,962 (57%)	1632 (61%)	4106 (59%)	4282 (56%)	1962 (55%)	980 (53%)	<0·0001
Coronary artery bypass graft surgery	22,670	5691 (25%)	676 (25%)	1658 (24%)	1894 (25%)	939 (26%)	524 (28%)	0·0019
Transient ischaemic attack	22,670	801 (4%)	74 (3%)	235 (3%)	277 (4%)	137 (4%)	78 (4%)	0·065
Stroke	22,670	1089 (5%)	125 (5%)	327 (5%)	341 (4%)	181 (5%)	115 (6%)	0·041
Hospitalisation for heart failure	22,670	1211 (5%)	219 (8%)	317 (5%)	364 (5%)	193 (5%)	118 (6%)	<0·0001
Symptoms of heart failure								
None	22,671	18,787 (83%)	2201 (82%)	5813 (84%)	6318 (83%)	2923 (82%)	1532 (82%)	0·0033
NYHA Class II		3229 (14%)	396 (15%)	976 (14%)	1044 (14%)	545 (15%)	268 (14%)	
NYHA Class III		655 (3%)	96 (4%)	157 (2%)	223 (3%)	116 (3%)	63 (3%)	
Left ventricular ejection fraction (%)	15,969	56·1 (11·0)	52·7 (13·2)	56·2 (10·9)	56·6 (10·3)	56·7 (10·5)	57·0 (10·7)	<0·0001

Parameter	Number of patients	Mean systolic BP categories						p value
		Total population (n=22,672)	<120 mmHg (n=2693)	120–129 mmHg (n=6946)	130–139 mmHg (n=7586)	140–149 mmHg (n=3584)	≥150 mmHg (n=1863)	
HbA_{1C} (%)	6173	6·9 (1·8)	6·8 (1·4)	6·8 (1·8)	6·9 (1·4)	7·1 (2·8)	7·1 (1·5)	<0·0001
Creatinine (mmol/L)	17,165	0·088 (0·076–0·104)	0·088 (0·078–0·106)	0·088 (0·076–0·102)	0·088 (0·076–0·103)	0·088 (0·075–0·103)	0·088 (0·076–0·106)	0·0005
Total cholesterol (mmol/L)	18,265	4·3 (3·7–5·1)	4·1 (3·5–4·8)	4·2 (3·6–5·0)	4·4 (3·7–5·1)	4·5 (3·8–5·3)	4·6 (3·9–5·4)	<0·0001
HDL-cholesterol (mmol/L)	16,054	1·14 (0·96–1·36)	1·10 (0·94–1·32)	1·12 (0·96–1·35)	1·14 (0·99–1·38)	1·16 (0·97–1·40)	1·14 (0·99–1·39)	<0·0001
LDL-cholesterol (mmol/L)	15,257	2·37 (1·89–2·96)	2·26 (1·80–2·73)	2·30 (1·84–2·86)	2·39 (1·90–3·00)	2·42 (1·92–3·09)	2·55 (1·98–3·20)	<0·0001
Fasting triglycerides (mmol/L)	16,806	1·4 (1·0–2·0)	1·3 (1·0–1·9)	1·4 (1·0–1·9)	1·4 (1·0–2·0)	1·5 (1·1–2·1)	1·5 (1·1–2·0)	<0·0001

Data are n (%) for categorical data and mean (SD) or median (IQR) for continuous data, depending on the distribution of the data.

Some percentages do not add up to 100 because of rounding·

BP=blood pressure. NYHA=New York Heart Association Functional Classification. HDL-cholesterol=high-density lipoprotein cholesterol. LDL-cholesterol= low-density lipoprotein cholesterol.

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Table 2: **Demographic and baseline characteristics of the patients, for the total population and each average on-treatment diastolic blood-pressure subgroup**

		Mean DBP categories					
Parameter	**Number of patients**	**<60 mmHg (n=214)**	**60–69 mmHg (n=2838)**	**70–79 mmHg (n=10,816)**	**80–89mmHg (n=7681)**	**≥90 mmHg (n=1123)**	**p value**
Age (years)	22,666	71·9 (8·9)	69·2 (9·3)	65·9 (9·8)	63·1 (9·9)	60·3 (9·9)	<0·0001
Men	22,672	144 (67%)	2009 (71%)	8154 (75%)	5850 (76%)	862 (77%)	<0·0001
Body mass index (kg/m²)	22,654	25·6 (23·4–29·0)	26·8 (24·2–30·0)	27·5 (25·0–30·5)	28·4 (25·7–31·4)	29·1 (26·2–32·4)	<0·0001
Diabetes	22,670	91 (43%)	1144 (40%)	3634 (34%)	2373 (31%)	349 (31%)	<0·0001
Smoking status	22,672						<0·0001
Current		11 (5%)	257 (9%)	1094 (10%)	1033 (13%)	174 (15%)	
Former		103 (48%)	1252 (44%)	4994 (46%)	3333 (43%)	476 (42%)	
Never		100 (47%)	1329 (47%)	4728 (44%)	3315 (43%)	473 (42%)	
Systolic BP (mmHg)	22,659	120·5 (18·3)	125·9 (16·3)	130·7 (15·0)	138·4 (15·6)	152·6 (17·8)	-
Diastolic BP (mmHg)	22,659	57·7 (7·1)	66·9 (7·5)	75·8 (7·2)	84·0 (7·4)	94·7 (8·0)	-
Heart rate (beats/minute)	22,660	64·9 (10·4)	66·6 (10·6)	67·7 (10·3)	69·7 (10·6)	72·8 (11·9)	<0·0001
Myocardial infarction	22,670	123 (57%)	1582 (56%)	6241 (58%)	4560 (59%)	752 (67%)	<0·0001
Percutaneous coronary intervention	22,670	101 (47%)	1645 (58%)	6402 (59%)	4260 (55%)	554 (49%)	<0·0001
Coronary artery bypass graft surgery	22,670	80 (37%)	823 (29%)	2772 (26%)	1780 (23%)	236 (21%)	<0·0001
Transient ischaemic attack	22,670	9 (4%)	116 (4%)	361 (3%)	272 (4%)	43 (4%)	0·36
Stroke	22,670	22 (10%)	138 (5%)	523 (5%)	344 (4%)	62 (6%)	0·0018
Hospitalisation for heart failure	22,670	27 (13%)	170 (6%)	546 (5%)	400 (5%)	68 (6%)	<0·0001
Symptoms of heart failure							
None	22,671	187 (87%)	2515 (89%)	9321 (86%)	5991 (78%)	773 (69%)	<0·0001
NYHA Class II		22 (10%)	260 (9%)	1264 (12%)	1400 (18%)	283 (25%)	
NYHA Class III		5 (2%)	63 (2%)	231 (2%)	289 (4%)	67 (6%)	
Left ventricular ejection fraction (%)	15,969	51·4 (15·1)	54·5 (12·8)	56·4 (10·9)	56·4 (10·4)	55·1 (10·5)	<0·0001

Parameter	Number of patients	Mean DBP categories					
		<60 mmHg (n=214)	60–69 mmHg (n=2838)	70–79 mmHg (n=10,816)	80–89mmHg (n=7681)	≥90 mmHg (n=1123)	p value
HbA_{1C} (%)	6173	8·0 (8·4)	7·0 (1·6)	6·8 (1·6)	6·8 (1·3)	7·1 (1·7)	<0·0001
Creatinine (mmol/L)	17,165	0·103 (0·085–0·124)	0·088 (0·076–0·107)	0·088 (0·076–0·103)	0·088 (0·076–0·101)	0·088 (0·078–0·102)	<0·0001
Total cholesterol (mmol/L)	18,265	3·8 (3·4–4·6)	4·0 (3·5–4·7)	4·2 (3·6–4·9)	4·5 (3·8–5·3)	4·9 (4·1–5·8)	<0·0001
HDL-cholesterol (mmol/L)	16,054	1·11 (0·92–1·35)	1·14 (0·96–1·35)	1·14 (0·96–1·38)	1·13 (0·96–1·36)	1·10 (0·95–1·35)	0·28
LDL-cholesterol (mmol/L)	15,257	2·09 (1·66–2·62)	2·16 (1·73–2·68)	2·31 (1·87–2·86)	2·50 (1·98–3·12)	2·83 (2·20–3·60)	<0·0001
Fasting triglycerides (mmol/L)	16,806	1·2 (0·9–1·7)	1·3 (1·0–1·9)	1·4 (1·0–1·9)	1·5 (1·1–2·1)	1·7 (1·2–2·3)	<0·0001

Data are n (%) for categorical data and mean (SD) or median (IQR) for continuous data, depending on the distribution of the data.

Some percentages do not add up to 100 because of rounding·

BP=blood pressure. NYHA=New York Heart Association Functional Classification. HDL-cholesterol=high-density lipoprotein cholesterol. LDL-cholesterol= low-density lipoprotein cholesterol.

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Table 3: **Crude and adjusted hazard ratios for average systolic and diastolic blood pressure subgroups**

Outcome	Model	HR (95% CI) for average systolic BP subgroups						HR (95% CI) for average diastolic BP subgroups					
		<120 mmHg	120–129 mmHg	130–139 mmHg	140–149 mmHg	≥150 mmHg	p value	<60 mmHg	60–69 mmHg	70–79 mmHg	80–89 mmHg	≥90 mmHg	p value
Cardiovascular death, myocardial infarction, or stroke	Unadjusted	1·80 (1·57–2·07)	1·00 (–)	1·11 (0·99–1·25)	1·62 (1·42–1·85)	2·86 (2·48–3·29)	<0·0001	3·47 (2·61–4·62)	1·74 (1·53–1·97)	1·00 (–)	1·24 (1·12–1·37)	2·98 (2·55–3·48)	<0·0001
	Model 1	1·56 (1·35–1·80)	1·00 (–)	1·08 (0·96–1·22)	1·51 (1·32–1·73)	2·51 (2·17–2·89)	<0·0001	1·99 (1·49–2·67)	1·41 (1·24–1·60)	1·00 (–)	1·41 (1·27–1·57)	3·74 (3·18–4·39)	<0·0001
	Model 2	1·56 (1·36–1·81)	1·00 (–)	1·08 (0·95–1·21)	1·51 (1·32–1·73)	2·48 (2·14–2·87)	<0·0001	2·01 (1·50–2·70)	1·41 (1·24–1·61)	1·00 (–)	1·41 (1·27–1·57)	3·72 (3·15–4·38)	<0·0001
	Excluding heart failure	1·54 (1·27–1·87)	1·00 (–)	1·05 (0·90–1·22)	1·49 (1·25–1·76)	2·40 (2·00–2·88)	<0·0001	1·67 (1·09–2·55)	1·30 (1·11–1·53)	1·00 (–)	1·46 (1·28–1·67)	4·11 (3·30–5·12)	<0·0001
	≤75 years	1·56 (1·32–1·85)	1·00 (–)	1·07 (0·93–1·24)	1·66 (1·41–1·94)	2·80 (2·36–3·33)	<0·0001	2·36 (1·57–3·56)	1·70 (1·45–2·00)	1·00 (–)	1·37 (1·22–1·55)	3·15 (2·64–3·77)	<0·0001
	>75 years	1·47 (1·12–1·94)	1·00 (–)	1·12 (0·89–1·41)	1·19 (0·92–1·56)	1·84 (1·40–2·43)	0·0001	1·64 (1·07–2·53)	1·10 (0·88–1·37)	1·00 (–)	1·37 (1·11–1·70)	4·66 (3·08–7·05)	<0·0001
All-cause death	Unadjusted	1·89 (1·65–2·18)	1·00 (–)	1·02 (0·90–1·16)	1·34 (1·16–1·55)	2·25 (1·93–2·63)	<0·0001	3·96 (2·99–5·22)	1·93 (1·70–2·19)	1·00 (–)	1·11 (1·00–1·24)	2·21 (1·84–2·66)	<0·0001
	Model 1	1·61 (1·39–1·85)	1·00 (–)	0·98 (0·87–1·11)	1·22 (1·05–1·40)	1·88 (1·61–2·20)	<0·0001	2·13 (1·60–2·83)	1·47 (1·30–1·68)	1·00 (–)	1·37 (1·23–1·53)	3·19 (2·64–3·86)	<0·0001
	Model 2	1·60 (1·38–1·84)	1·00 (–)	0·98 (0·87–1·11)	1·22 (1·05–1·40)	1·86 (1·59–2·18)	<0·0001	2·13 (1·60–2·83)	1·48 (1·30–1·68)	1·00 (–)	1·37 (1·22–1·53)	3·19 (2·63–3·87)	<0·0001
	Excluding heart failure	1·51 (1·24–1·84)	1·00 (–)	0·97 (0·83–1·14)	1·22 (1·01–1·46)	1·75 (1·43–2·14)	<0·0001	1·89 (1·23–2·89)	1·51 (1·28–1·78)	1·00 (–)	1·55 (1·34–1·79)	3·19 (2·42–4·21)	<0·0001
Cardiovascular death	Unadjusted	2·30 (1·93–2·75)	1·00 (–)	1·11 (0·94–1·30)	1·65 (1·38–1·97)	2·84 (2·35–3·44)	<0·0001	4·05 (2·86–5·74)	1·88 (1·60–2·20)	1·00 (–)	1·16 (1·01–1·33)	2·69 (2·17–3·33)	<0·0001
	Model 1	1·83 (1·53–2·19)	1·00 (–)	1·07 (0·91–1·25)	1·50 (1·26–1·80)	2·39 (1·97–2·90)	<0·0001	2·05 (1·43–2·93)	1·43 (1·21–1·68)	1·00 (–)	1·42 (1·24–1·64)	3·81 (3·05–4·77)	<0·0001
	Model 2	1·83 (1·53–2·19)	1·00 (–)	1·07 (0·91–1·25)	1·50 (1·25–1·80)	2·35 (1·93–2·86)	<0·0001	2·06 (1·44–2·96)	1·44 (1·22–1·70)	1·00 (–)	1·42 (1·24–1·63)	3·81 (3·04–4·77)	<0·0001
	Excluding heart failure	1·71 (1·32–2·22)	1·00 (–)	1·04 (0·84–1·28)	1·62 (1·29–2·05)	2·19 (1·69–2·84)	<0·0001	1·68 (0·95–2·96)	1·30 (1·04–1·63)	1·00 (–)	1·57 (1·31–1·88)	3·97 (2·88–5·49)	<0·0001
Myocardial infarction	Unadjusted	1·65 (1·31–2·08)	1·00 (–)	1·17 (0·97–1·41)	1·60 (1·29–1·98)	3·01 (2·41–3·76)	<0·0001	3·42 (2·16–5·44)	1·66 (1·35–2·04)	1·00 (–)	1·32 (1·12–1·55)	3·35 (2·64–4·24)	<0·0001
	Model 1	1·48 (1·17–1·86)	1·00 (–)	1·17 (0·97–1·42)	1·57 (1·26–1·95)	2·85 (2·28–3·57)	<0·0001	2·31 (1·44–3·71)	1·42 (1·15–1·75)	1·00 (–)	1·43 (1·21–1·69)	3·61 (2·81–4·63)	<0·0001
	Model 2	1·48 (1·17–1·87)	1·00 (–)	1·18 (0·97–1·43)	1·60 (1·29–1·99)	2·92 (2·32–3·67)	<0·0001	2·38 (1·48–3·83)	1·43 (1·16–1·76)	1·00 (–)	1·44 (1·22–1·70)	3·68 (2·86–4·73)	<0·0001
	Excluding heart failure	1·46 (1·09–1·96)	1·00 (–)	1·15 (0·91–1·45)	1·53 (1·17–1·99)	2·88 (2·19–3·80)	<0·0001	1·49 (0·73–3·05)	1·23 (0·95–1·59)	1·00 (–)	1·43 (1·17–1·75)	3·77 (2·71–5·25)	<0·0001
Stroke	Unadjusted	1·11 (0·81–1·53)	1·00 (–)	1·12 (0·89–1·41)	1·63 (1·26–2·12)	2·90 (2·21–3·82)	<0·0001	2·18 (1·08–4·42)	1·49 (1·15–1·94)	1·00 (–)	1·27 (1·04–1·56)	3·28 (2·44–4·42)	<0·0001
	Model 1	1·05 (0·76–1·45)	1·00 (–)	1·08 (0·85–1·36)	1·54 (1·19–2·00)	2·64 (2·00–3·49)	<0·0001	1·34 (0·65–2·73)	1·22 (0·94–1·60)	1·00 (–)	1·44 (1·17–1·77)	4·29 (3·14–5·87)	<0·0001
	Model 2	1·06 (0·77–1·46)	1·00 (–)	1·06 (0·84–1·34)	1·51 (1·16–1·97)	2·57 (1·94–3·41)	<0·0001	1·31 (0·64–2·69)	1·23 (0·94–1·61)	1·00 (–)	1·46 (1·18–1·79)	4·33 (3·15–5·94)	<0·0001

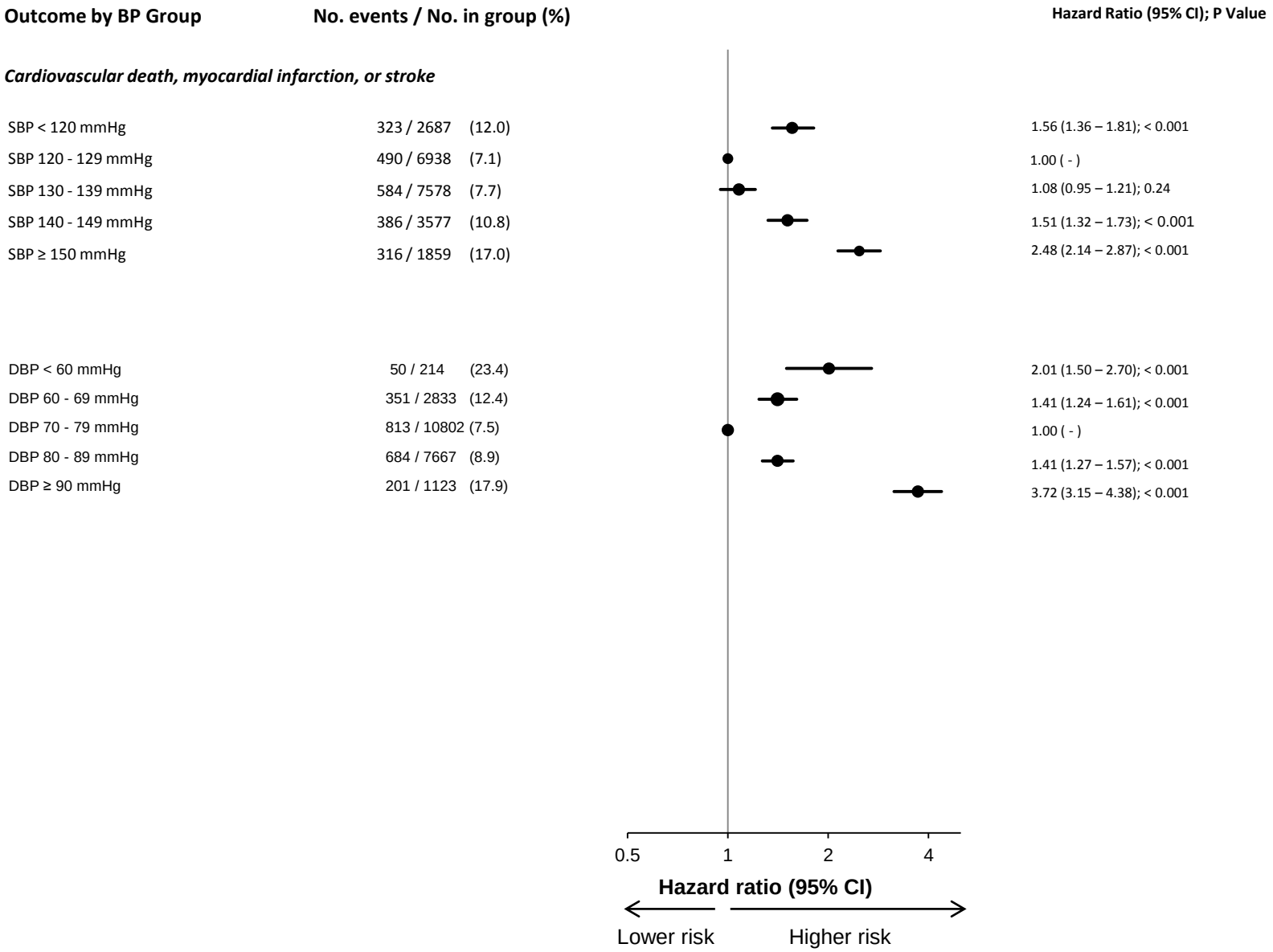
Outcome	Model	HR (95% CI) for average systolic BP subgroups						HR (95% CI) for average diastolic BP subgroups					
		<120 mmHg	120–129 mmHg	130–139 mmHg	140–149 mmHg	≥150 mmHg	p value	<60 mmHg	60–69 mmHg	70–79 mmHg	80–89 mmHg	≥90 mmHg	p value
	Excluding heart failure	1·25 (0·85–1·84)	1·00 (–)	1·04 (0·79–1·38)	1·32 (0·95–1·83)	2·09 (1·46–2·97)	0·0004	1·46 (0·64–3·34)	1·17 (0·85–1·60)	1·00 (–)	1·42 (1·10–1·83)	4·88 (3·26–7·31)	<0·0001
Hospitalisation for heart failure	Unadjusted	1·59 (1·33–1·90)	1·00 (–)	0·94 (0·81–1·10)	1·62 (1·37–1·91)	2·83 (2·38–3·37)	<0·0001	3·32 (2·22–4·97)	1·56 (1·31–1·87)	1·00 (–)	1·61 (1·41–1·83)	6·32 (5·37–7·44)	<0·0001
	Model 1	1·38 (1·15–1·66)	1·00 (–)	0·89 (0·76–1·04)	1·45 (1·23–1·70)	2·40 (2·01–2·86)	<0·0001	2·22 (1·47–3·36)	1·53 (1·28–1·84)	1·00 (–)	1·38 (1·21–1·58)	4·60 (3·86–5·48)	<0·0001
	Model 2	1·39 (1·16–1·67)	1·00 (–)	0·88 (0·75–1·03)	1·42 (1·20–1·68)	2·36 (1·98–2·83)	<0·0001	2·36 (1·55–3·58)	1·55 (1·29–1·86)	1·00 (–)	1·38 (1·21–1·59)	4·58 (3·83–5·48)	<0·0001
	Excluding heart failure	1·15 (0·83–1·60)	1·00 (–)	0·75 (0·58–0·95)	1·12 (0·85–1·48)	1·49 (1·09–2·04)	0·0003	2·32 (1·12–4·78)	1·67 (1·26–2·22)	1·00 (–)	1·53 (1·22–1·91)	4·58 (3·21–6·54)	<0·0001

Data are indicated for the whole population and for the sensitivity analysis excluding patients with heart failure for all outcomes. Data are also given by age subgroup (≤75 years or >75 years) for the primary outcome. BP=blood pressure

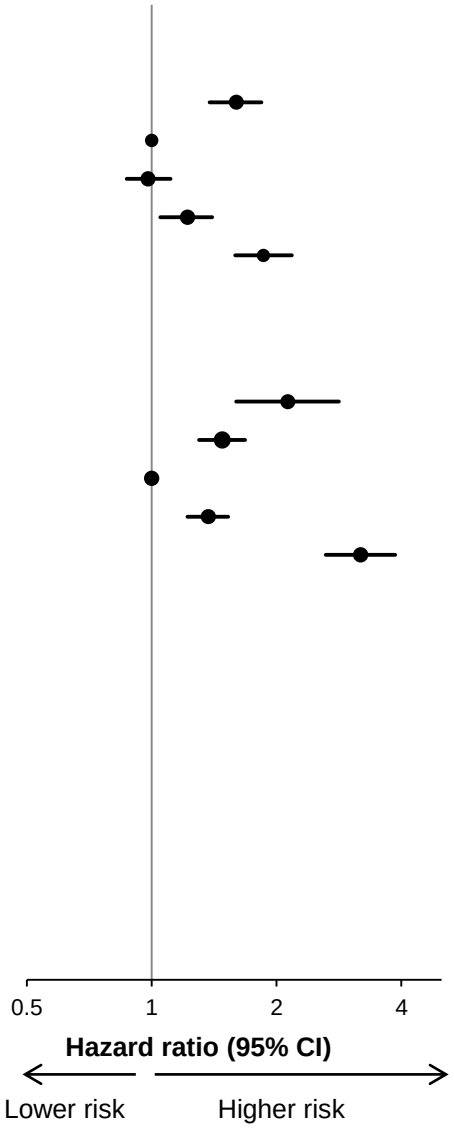
Model 1: adjusted for age, geographical region, smoking status, myocardial infarction, percutaneous coronary Intervention, diabetes, body mass index, glomerular filtration rate, peripheral artery disease, hospitalisation for or symptoms of heart failure, left ventricular ejection fraction, stroke, transient ischaemic attack, angiotensin-receptor blockers, diuretics and aspirin.

Model 2: adjusted for age, sex, geographical region, smoking status, myocardial infarction, percutaneous coronary Intervention, coronary artery bypass graft, diabetes, low- and high-density lipoprotein cholesterol levels, body mass index, glomerular filtration rate, peripheral artery disease, hospitalisation for or symptoms of heart failure, left ventricular ejection fraction, ethnicity, stroke, transient ischaemic attack and baseline medications, namely aspirin, statins, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, beta-blockers, calcium channel blockers, diuretics and other antihypertensive medications.

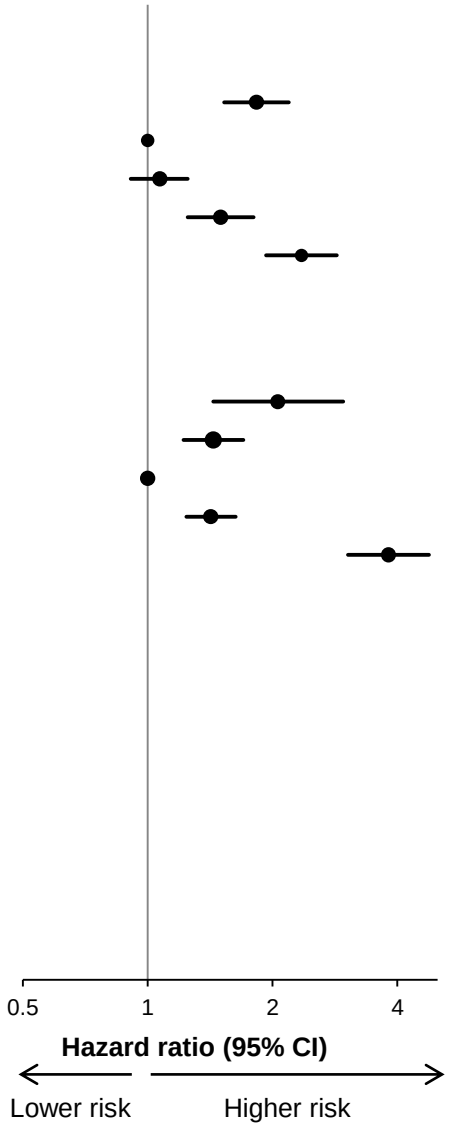
Figure 1


Outcome by BP Group
No. events / No. in group (%)
Hazard Ratio (95% CI); P Value
Cardiovascular death, myocardial infarction, or stroke
SBP < 120 mmHg 323 / 2687 (12.0) 1.56 (1.36 – 1.81); < 0.001
SBP 120 - 129 mmHg 490 / 6938 (7.1) 1.00 (-)
SBP 130 - 139 mmHg 584 / 7578 (7.7) 1.08 (0.95 – 1.21); 0.24
SBP 140 - 149 mmHg 386 / 3577 (10.8) 1.51 (1.32 – 1.73); < 0.001
SBP ≥ 150 mmHg 316 / 1859 (17.0) 2.48 (2.14 – 2.87); < 0.001
DBP < 60 mmHg 50 / 214 (23.4) 2.01 (1.50 – 2.70); < 0.001
DBP 60 - 69 mmHg 351 / 2833 (12.4) 1.41 (1.24 – 1.61); < 0.001
DBP 70 - 79 mmHg 813 / 10802 (7.5) 1.00 (-)
DBP 80 - 89 mmHg 684 / 7667 (8.9) 1.41 (1.27 – 1.57); < 0.001
DBP ≥ 90 mmHg 201 / 1123 (17.9) 3.72 (3.15 – 4.38); < 0.001
0.5
1
2
4
Hazard ratio (95% CI)
Lower risk
Higher risk

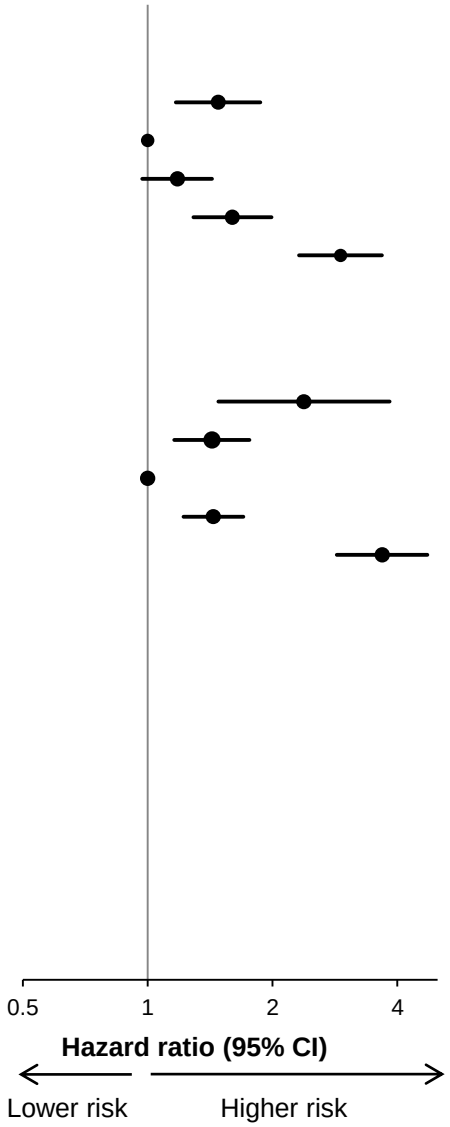
Outcome by BP Group	No. events / No. in group (%)	Hazard Ratio (95% CI); P Value
All cause death		
SBP < 120 mmHg	330 / 2693 (12.3)	1.60 (1.38 – 1.84); < 0.001
SBP 120 - 129 mmHg	479 / 6987 (6.9)	1.00 (-)
SBP 130 - 139 mmHg	526 / 7611 (6.9)	0.98 (0.87 – 1.11); 0.77
SBP 140 - 149 mmHg	312 / 3555 (8.8)	1.22 (1.05 – 1.40); 0.0081
SBP ≥ 150 mmHg	239 / 1793 (13.3)	1.86 (1.59 – 2.18); < 0.001
DBP < 60 mmHg	53 / 210 (25.2)	2.13 (1.60 – 2.83); < 0.001
DBP 60 - 69 mmHg	365 / 2842 (12.8)	1.48 (1.30 – 1.68); < 0.001
DBP 70 - 79 mmHg	759 / 10891 (7.0)	1.00 (-)
DBP 80 - 89 mmHg	574 / 7633 (7.5)	1.37 (1.22 – 1.53); < 0.001
DBP ≥ 90 mmHg	135 / 1063 (12.7)	3.19 (2.63 – 3.87); < 0.001



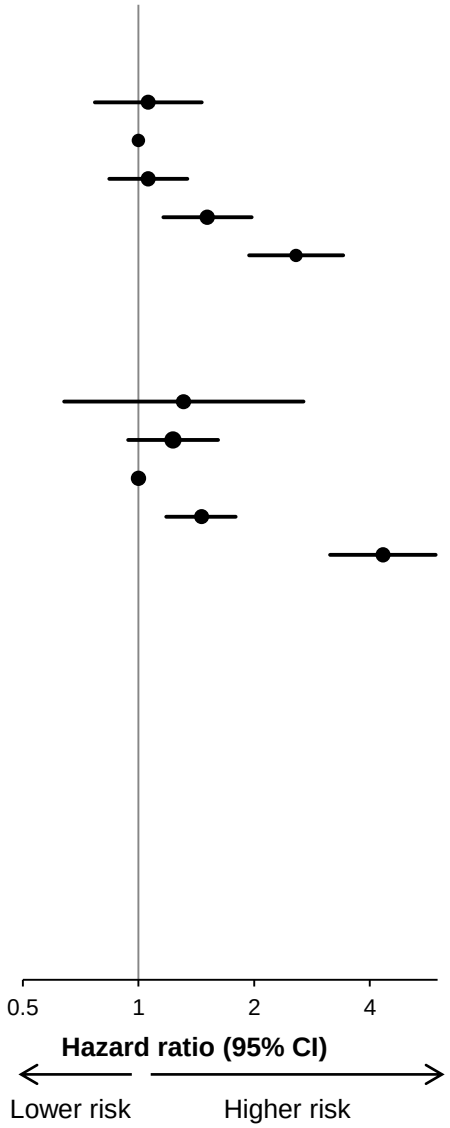
Outcome by BP Group	No. events / No. in group (%)	Hazard Ratio (95% CI); P Value
Cardiovascular death		
SBP < 120 mmHg	227 / 2693 (8.4)	1.83 (1.53 – 2.19); < 0.001
SBP 120 - 129 mmHg	271 / 6992 (3.9)	1.00 (-)
SBP 130 - 139 mmHg	322 / 7606 (4.2)	1.07 (0.91 – 1.25); 0.45
SBP 140 - 149 mmHg	217 / 3555 (6.1)	1.50 (1.25 – 1.80); < 0.001
SBP ≥ 150 mmHg	171 / 1793 (9.5)	2.35 (1.93 – 2.86); < 0.001
DBP < 60 mmHg	34 / 210 (16.2)	2.06 (1.44 – 2.96); < 0.001
DBP 60 - 69 mmHg	223 / 2842 (7.8)	1.44 (1.22 – 1.70); < 0.001
DBP 70 - 79 mmHg	475 / 10895 (4.4)	1.00 (-)
DBP 80 - 89 mmHg	373 / 7630 (4.9)	1.42 (1.24 – 1.63); < 0.001
DBP ≥ 90 mmHg	103 / 1062 (9.7)	3.81 (3.04 – 4.77); < 0.001



Outcome by BP Group	No. events / No. in group (%)	Hazard Ratio (95% CI); P Value
Myocardial infarction (fatal or non-fatal)		
SBP < 120 mmHg	115 / 2688 (4.3)	1.48 (1.17 – 1.87); 0.001
SBP 120 - 129 mmHg	191 / 6956 (2.7)	1.00 (-)
SBP 130 - 139 mmHg	240 / 7600 (3.2)	1.18 (0.97 – 1.43); 0.093
SBP 140 - 149 mmHg	149 / 3559 (4.2)	1.60 (1.29 – 1.99); < 0.001
SBP ≥ 150 mmHg	131 / 1836 (7.1)	2.92 (2.32 – 3.67); < 0.001
DBP < 60 mmHg	19 / 211 (9.0)	2.38 (1.48 – 3.83); < 0.001
DBP 60 - 69 mmHg	129 / 2835 (4.6)	1.43 (1.16 – 1.76); < 0.001
DBP 70 - 79 mmHg	311 / 10836 (2.9)	1.00 (-)
DBP 80 - 89 mmHg	280 / 7654 (3.7)	1.44 (1.22 – 1.70); < 0.001
DBP ≥ 90 mmHg	87 / 1103 (7.9)	3.68 (2.86 – 4.73); < 0.001



Outcome by BP Group	No. events / No. in group (%)	Hazard Ratio (95% CI); P Value
Stroke (fatal or non-fatal)		
SBP < 120 mmHg	53 / 2692 (2.0)	1.06 (0.77 – 1.46); 0.73
SBP 120 - 129 mmHg	130 / 6978 (1.9)	1.00 (-)
SBP 130 - 139 mmHg	155 / 7589 (2.0)	1.06 (0.84 – 1.34); 0.61
SBP 140 - 149 mmHg	103 / 3564 (2.9)	1.51 (1.16 – 1.97); 0.002
SBP ≥ 150 mmHg	84 / 1816 (4.6)	2.57 (1.94 – 3.41); < 0.001
DBP < 60 mmHg	8 / 213 (3.8)	1.31 (0.64 – 2.69); 0.46
DBP 60 - 69 mmHg	77 / 2842 (2.7)	1.23 (0.94 – 1.61); 0.12
DBP 70 - 79 mmHg	207 / 10857 (1.9)	1.00 (-)
DBP 80 - 89 mmHg	178 / 7646 (2.3)	1.46 (1.18 – 1.79); < 0.001
DBP ≥ 90 mmHg	55 / 1081 (5.1)	4.33 (3.15 – 5.94); < 0.001



Outcome by BP Group	No. events / No. in group (%)	Hazard Ratio (95% CI); P Value
Heart failure hospitalisation		
SBP < 120 mmHg	187 / 2559 (7.3)	1.39 (1.16 – 1.67); < 0.001
SBP 120 - 129 mmHg	325 / 6784 (4.8)	1.00 (-)
SBP 130 - 139 mmHg	328 / 7339 (4.5)	0.88 (0.75 – 1.03); 0.10
SBP 140 - 149 mmHg	257 / 3473 (7.4)	1.42 (1.20 – 1.68); < 0.001
SBP ≥ 150 mmHg	208 / 1756 (11.8)	2.36 (1.98 – 2.83); < 0.001
DBP < 60 mmHg	25 / 206 (12.1)	2.36 (1.55 – 3.58); < 0.001
DBP 60 - 69 mmHg	167 / 2721 (6.1)	1.55 (1.29 – 1.86); < 0.001
DBP 70 - 79 mmHg	430 / 10559 (4.1)	1.00 (-)
DBP 80 - 89 mmHg	463 / 7347 (6.3)	1.38 (1.21 – 1.59); < 0.001
DBP ≥ 90 mmHg	220 / 1078 (20.4)	4.58 (3.83 – 5.48); < 0.001

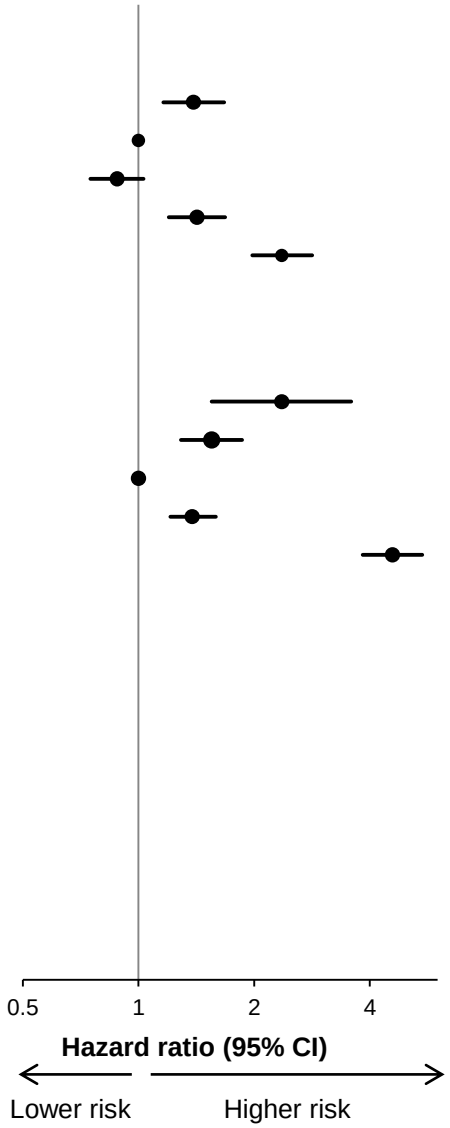
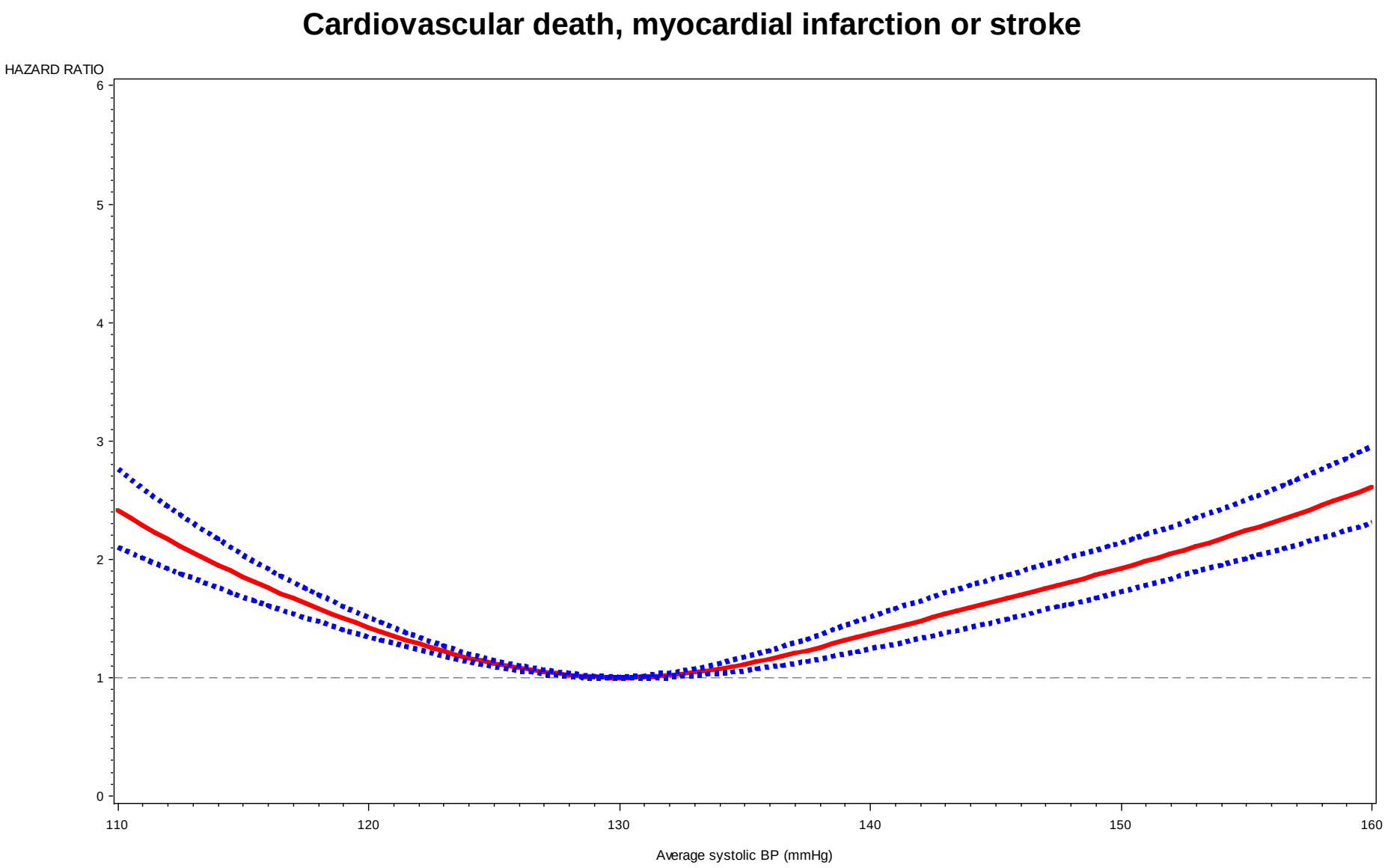
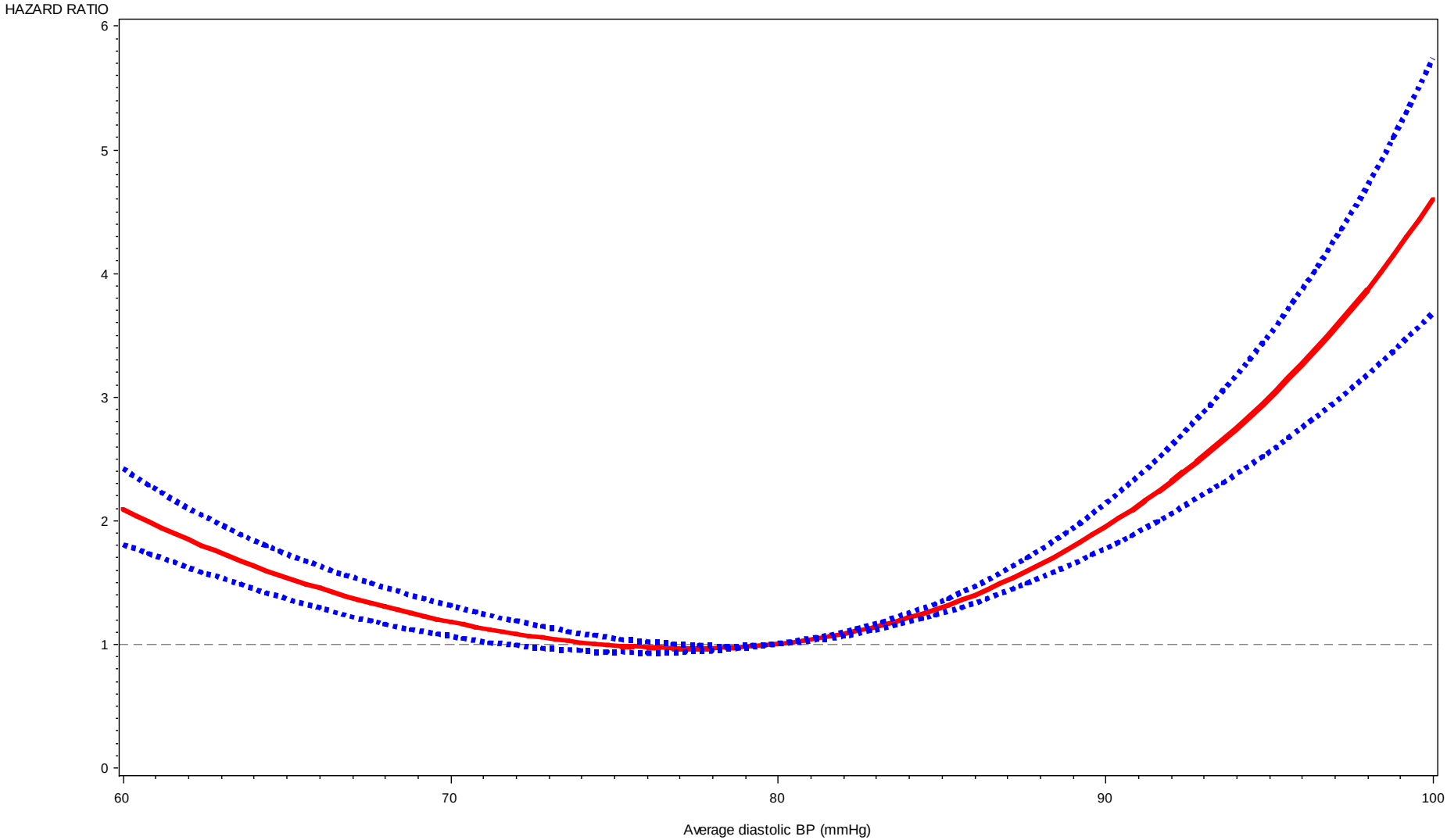


Figure 2


Cardiovascular death, myocardial infarction or stroke
HAZARD RATIO
6
5
4
3
2
1
0
110
120
130
140
150
160
Average systolic BP (mmHg)

Cardiovascular death, myocardial infarction or stroke



Appendix

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STROBE checklist

Click here to download Supplementary Material: STROBE-checklist-CLARIFY-11july-final.doc