Prognostic value of variability in systolic blood pressure related to vascular events and premature death in type 2 diabetes: ADVANCE-ON

Short title: Prognostic value of blood pressure variability

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Abstract

Visit-to-visit variability (VVV) in systolic blood pressure (SBP) is a risk factor for cardiovascular events. However, whether it provides additional predictive information beyond traditional risk factors, including mean SBP, in the long term is unclear.

The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial was a randomized controlled trial in patients with type 2 diabetes; ADVANCE-ON followed up patients subsequently. In these analyses, 9,114 patients without major macrovascular or renal events or death during the first 24 months were included. Data on SBP from six visits during the first 24 months after randomization were used to estimate VVV in several ways: the primary measure was the standard deviation (SD). Events accrued during the following 7.6 years. The primary outcome was a composite of major macrovascular and renal events and all-cause mortality.

SD of SBP was log-linearly associated with an increased risk of the primary outcome (P<0.001) after adjustment for mean SBP and other cardiovascular risk factors. The hazard ratio (95% confidence interval) in the highest, compared with the lowest, tenth of the SD was 1.39 (1.15-1.69). Results were similar for major macrovascular events alone and all-cause mortality alone (both P<0.01). Addition of SD of SBP significantly improved 8-year risk classification (continuous net reclassification improvement, 5.3%). Results were similar for other measures of VVV, except maximum SBP.

VVV in SBP is an independent predictor of vascular complications and death, which improves risk prediction beyond that provided by traditional risk factors, including mean SBP.

Key words: Blood pressure variability, cardiovascular disease, diabetes mellitus, mortality, myocardial infarction, stroke

Every cardiovascular disease (CVD) risk score, from the earliest[1] to the present day,[2] across the world, has included a measure of blood pressure (BP). For men and women, systolic blood pressure (SBP) is likely to be the next most important CVD factor to age. However, unlike age, SBP is prone to both short- and long-term variation, so that the inclusion of a single value of SBP in a risk score will underestimate its true effect due to regression dilution bias.[3] Multiple measurements are therefore recommended to calculate 'usual' BP, but visit-to-visit variability (VVV) in SBP has also been identified as an independent risk factor for CVD, with greater VVV leading to greater risk.[4-6] Whether this means that VVV in SBP should be included in CVD risk scores is unknown. Furthermore, few studies of VVV in SBP have been conducted in patients with diabetes, who may be particularly susceptible to increased BP variability given the high prevalence of arterial stiffness and autonomic dysfunction in this high-risk group.

SBP is also a major risk factor for renal disease,[7, 8] and premature death (henceforth referred to as death).[7, 8] Hence, the same question of the additional predictive worth of VVV in SBP also arises for these outcomes.

We previously reported that increased VVV in SBP was a risk factor for macrovascular and microvascular events and death, independent of mean SBP and other cardiovascular risk factors, in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial.[9] However, the short-term follow-up period (median 2.4 years) did not allow us to assess the suitability of including VVV in SBP in a CVD risk score beyond traditional risk factors, including mean SBP.

The objective of the present study was, thus, to examine the long-term impact of SBP variability and its predictive ability for vascular complications and mortality in patients with type 2 diabetes.

Methods

Study design

ADVANCE was a factorial randomized controlled trial (RCT) evaluating the effects of BP lowering and intensive blood glucose lowering treatment on vascular outcomes in patients with type 2 diabetes. A detailed description of the design has been published previously.[10-12] In brief, a total of 11,140 individuals with type 2 diabetes at high risk of cardiovascular events were enrolled from 215 centres in 20 countries. Participants were randomly assigned to either a fixed-dose combination of perindopril (4 mg) and indapamide (1.25 mg) or matching placebo and to either a gliclazide (modified release)-based intensive glucose control regimen aiming to achieve a hemoglobin A_{1c} $\leq$6.5 %, or standard glucose control based on local guidelines of participating countries, after a 6-week active run-in period. The ADVANCE-Observational (ADVANCE-ON) study was a post-trial follow-up study of the ADVANCE trial. Post-trial follow-up was obtained from 8,494 patients out of a total of 10,082 patients alive when the randomized treatment phase of the ADVANCE trial was completed.[13] Participants were followed up for an overall median duration of 9.9 years. The median durations of follow-up for the blood pressure and glucose lowering trial interventions were 4.4 and 5.0 years, respectively. Patients with major macrovascular or renal events or death during the first 24 months, those with missing SBP values at any of 6 occasions (3, 4, 6, 12, 18 and 24 months after randomization), and those with missing values in covariates were excluded from the present analysis. Approval for the study was obtained from the institutional review board of each centre and all participants provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and the procedures followed were in accordance with the institutional guidelines.

BP measurements and visit-to-visit variability

BP was measured in duplicate, with an interval of at least 1 minute, after 5 minutes of rest in the seated position, by using a standardized automated sphygmomanometer (Omron HEM-705CP, Tokyo, Japan), and then averaged. BP recordings were taken at registration, randomization, 3, 4, and 6 months after randomization, and at every 6 months thereafter. Standard deviation (SD), coefficient of variation (CV), variation independent of mean (VIM), average successive variability (ASV), residual standard deviation (RSD), and range of SBP were determined using values measured on 6 occasions (3, 4, 6, 12, 18 and 24 months after randomization) and maximum value were used as VVV parameters.[4, 9, 14] Mean of SBP during the 24-month measurement period, averaged over the 6 occasions, was taken as a covariate.

Follow-Up and Study Outcomes

Participants were followed up from their 24-month visit until the first event or the end of follow-up (Figure 1). The primary outcome was a composite of major macrovascular events, major renal events and all-cause mortality. Major macrovascular events were defined as myocardial infarction (nonfatal and fatal), stroke (nonfatal and fatal), or cardiovascular death. Major renal events were defined as requirement for chronic renal-replacement therapy and death from renal disease. Secondary outcomes were components of primary outcome. Through to the end of randomized treatment, an independent endpoint advisory committee adjudicated all the outcomes. Outcomes occurring during post-trial follow-up were reported by the study centers using the standardized definitions adopted during the trial, without central adjudication.[13]

Statistical analysis

Pearson's correlation coefficients were estimated between measures of VVV of SBP

and mean SBP during the first 24 months, and between measures of VVV of SBP adjusted for mean SBP. VVV of SBP was compared between the active treatment group and the placebo group by the analysis of covariance after adjustment for mean SBP during the first 24 months. The effect of SBP parameters on outcomes were estimated by Cox proportional hazards model using groups defined by the tenths and for an increase of 1 SD for each SBP parameter. The proportional hazards assumption was verified through cumulative hazard plots. Adjustments were made for age, sex, region of residence, duration of diabetes mellitus, current smoking, current alcohol drinking, heart rate, total cholesterol, log of triglycerides, body mass index, use of β-blockers, use of calcium-channel blockers, randomized blood pressure-lowering intervention, and randomized glucose control intervention (model 1), or variables in model 1 plus mean SBP (model 2). Unless invariant over time, these covariates were as measured at the 24-month visit. When data at the 24-month visit were missing, the latest data before the 24-month visit were used. A linear trend across tenths was tested taking the tenths as a continuous variable ranging from 1 to 10.

We repeated all analyses using after imputing missing values of BP and the covariates among 1,375 patients using multiple imputation by Monte Carlo Markov Chains (n = 10,489), with ten imputations.[3] We also performed sensitivity analyses which added pulse pressure or estimated glomerular filtration rate (eGFR, using CKD-EPI equation[15]) as covariates. We also conducted subgroup analysis stratified by randomized blood pressure-lowering intervention, by mean SBP during the measurement period (<140 mmHg or ≥140 mmHg), and by sex.

For the primary outcome and its three major components, discrimination was evaluated using c-statistics for 8-year risk, accounting for censoring,[16] and compared between model 2 and when adding each SBP parameter individually. In addition, the ability to reclassify the 8-year risk was assessed by the integrated discrimination index (IDI) and the net

reclassification improvement (NRI), using methods suitable for survival data.[3]

All analyses were performed using SAS Enterprise Guide 7.11 (SAS Institute Inc., Cary, NC) or Stata software (release 13; StataCorp, College Station, TX, USA). A two-sided P <0.05 was considered to be statistically significant in all analyses.

Results

Baseline Characteristics

Of the 11,140 patients who participated in the ADVANCE trial, 9,114 patients were included in the primary analyses (Figure 1, Table 1, and Figure S1). For those in the current study, the mean age at the 24-month visit was 68 years, 42% were female, and 37% were recruited in Asia. BP at 24-month visit was 137/77 mmHg. Mean ten-year predicted risk of major vascular events in the present study estimated by the AD-ON score[17] was 23.3%.

Blood Pressure Variability

All the measures of VVV of SBP, except the maximum value, were strongly correlated (*r* between 0.78 and 0.99) with each other (Table S1). After controlling for mean SBP all measures of VVV of SBP, including the maximum value, were highly correlated (*r* between 0.71 and 1) with each other, and the correlations between our primary measure, SD, and the other measures of VVV were all very strong (*r* between 0.83 and 0.99) (Table S2). There was no statistically significant difference in VVV of SBP between the active treatment group and the placebo group, after adjustment for mean SBP (Table S3).

Effect of VVV in SBP on outcomes

During a median of 7.6 years of follow-up, 1,476 patients developed a major macrovascular event, 122 experienced a major renal event, and there were 1,550 deaths.

Higher mean SBP during the measurement period was associated with increased risk of the primary outcome and its components after adjusting for cardiovascular risk factors (Figure S2).

The risk of the primary outcome increased log-linearly with increasing SBP SD after adjustment for mean SBP and other cardiovascular risk factors (*P* for trend <0.001), with the highest tenth associated with a 39% greater risk of the primary outcome compared with the lowest tenth (HR 1.39, 95% CI: 1.15-1.69; Figure 2). Similar statistically significant adjusted trends were observed for all-cause mortality (*P* for trend <0.001) and major macrovascular events (*P* for trend = 0.007); the corresponding HRs (95% CIs) for the highest tenth compared with the lowest tenth of SBP SD were 1.67 (1.31-2.14) and 1.17 (0.92-1.49), respectively. After controlling for mean SBP and other cardiovascular risk factors, there was no statistically significant trend in the risk of either cardiovascular death or major renal events (Figure 2 and 3) (*P* values were 0.07 and 0.11, respectively). However, in both cases there was a statistically significant difference between the extreme tenths: the HRs (95% CIs) for the highest tenth compared with the lowest tenth were 1.53 (1.001-2.33) and 2.97 (1.10-8.01), respectively. For myocardial infarction and stroke there was no evidence of either a trend (*P* values were 0.13 and 0.33, respectively) or a difference in risk between those in the top and bottom 10% of the distribution of SDs (HRs (95%CIs: 1.08 (0.72-1.63) and 1.08 (0.77-1.53), respectively) (Figure 3). Similar results were present for all but one other measures of VVV in SBP: CV, VIM, ASV, RSD, and range of SBP (Figure S3-7). For maximum of SBP, similar statistically significant trends for all seven outcomes were seen using model 1, but were attenuated and became non-significant after additional adjustment for mean SBP in model 2 (Figure S8). The analyses for mean SBP and a variety of indices of VVV in SBP as continuous variables, instead of tenths, showed similar results (Table 2 and Table S4).

Results remained unchanged when 1) missing values were imputed (Figure S9) and 2) models were adjusted for pulse pressure (Figure S10) or eGFR (Figure S11) as covariates, and the pattern of association between SD of SBP and each of the outcomes analyzed was also very similar whether or not adjustment was made for the mean of SBP (Figure S12). Subgroup analyses, stratified by randomized blood pressure-lowering intervention or mean SBP levels during the measurement period, showed no significant heterogeneity in the associations between SD of SBP and the risks of each outcome considered (Figures S13 and S14). Similar associations were also observed by sex (Figure S15).

Discrimination and Reclassification

For the primary outcome, addition of SBP SD to the model with established cardiovascular risk factors, including mean SBP, significantly improved the c-statistic (0.6459 to 0.6499, P = 0.003), IDI (Relative IDI: 4.18 [95% CI 2.94-5.47], P <0.001), continuous NRI (0.053 [95% CI 0.003-0.107], P = 0.03), and categorical NRI (0.017 [95% CI 0.006-0.029], P = 0.002) (Table 3). CV, VIM, ASV, RSD, range, and maximum of SBP showed broadly similar improvements in the prediction metrics (Table S5). For macrovascular disease and death, discrimination of events was significantly improved by adding SBP SD to the prediction model; for major renal disease the change in c-statistic was similar but not statistically significant. IDI was significantly positive in all three cases, with relative IDI highest for major renal disease. For NRI, results were mainly positive but not significant.

Discussion

This study showed that increased VVV in SBP was linearly associated with the increased risk of a composite of major macrovascular events, major renal events and all-cause

mortality in patients with type 2 diabetes over an 8-year period. This association remained statistically significant after multivariate-adjustment for mean SBP and other cardiovascular risk factors. A similar trend was observed when macrovascular events and all-cause mortality were analysed separately. Addition of VVV in SBP significantly improved the prediction of major outcomes beyond that obtained from mean SBP and traditional risk factors.

A number of studies have examined the association between VVV in BP and the risk of cardiovascular diseases. A recent systematic review and meta-analysis of prospective studies has demonstrated that increased long term variability in SBP (such as monitoring of BP in clinics) was significantly associated with increased risk of all-cause mortality, cardiovascular disease mortality, cardiovascular disease events, coronary heart disease, and stroke.[18] However, most of these studies were conducted in general populations, patients with hypertension, or those with cardiovascular disease, whereas few studies have investigated the associations with vascular complications in patients with diabetes. While we have previously reported that VVV was positively associated with vascular outcomes in patients with type 2 diabetes,[9] the present study confirms and extends that evidence from a relatively short median 2.4 years of follow-up to a much longer period of median 7.6 years.

Regarding the components of macrovascular disease, neither myocardial infarction nor stroke showed a linear association with VVV in SBP. In contrast, a recent meta-analysis found a significant positive association between increases in VVV in SBP and coronary heart disease and stroke, although with significant heterogeneity in the magnitude of the association across studies.[18] Although we cannot be certain of the reasons for the lack of significant association in our study, it seems likely that sample size and the small number of events (only 478 myocardial infarction events and 668 stroke events) in our cohort might explain the discrepancy versus the positive association seen in our study for the primary

outcome (2,345 events), all-cause mortality (1,550 events) and major macrovascular events (1,476 events) (Figure 2 and 3). Sample size consideration may also explain the difference between our findings and the report from the meta-analysis.[18] Further studies, such as individual participant data meta-analyses, are needed to elucidate this issue.

Here we detected only a marginally significant association between VVV in SBP and major renal events, although our prior analysis of the ADVANCE trial only showed a significant association with renal events when defined as new or worsening nephropathy.[9] However, these endpoints are quite different, as "new or worsening nephropathy" included doubling of serum creatinine and development of macroalbuminuria, which were only recorded in a limited subgroup in the ADVANCE-ON post-trial follow-up and could not be included in the present analyses, which were thus restricted to major renal events.

Although a significant association between VVV in BP and vascular events has been reported several times, only one previous study is known to have examined whether VVV in BP provides additional predictive information for future vascular events beyond the traditional risk factors, including mean BP. This study conducted among 2,501 patients with a history of cardiovascular disease showed that addition of CV of SBP significantly improved IDI (0.0048, $P = 0.03$) for CVD, but did not improve the area under the receiver operating characteristic curve.[19] Our study, of primary prevention of CVD and other outcomes, amongst patients with diabetes, provides evidence that addition of measures of VVV in SBP also improved the NRI, as well as the c-statistic and IDI. Although the improvements in statistics were modest, even a small improvement in risk prediction could be important, especially in the management of high risk patients.

The potential pathophysiologic mechanisms underlying the association between VVV in SBP and vascular events and death have not been fully clarified. Higher variability of BP may reflect reductions in large elastic artery compliance. An increase in BP variability has

shown to be associated with arterial stiffness,[20, 21] which may explain the increased incidence of vascular events. In addition, fluctuation of BP may reflect abnormal autonomic regulation. However, adjustment for heart rate, a marker of sympathetic activity, did not change the significant association between VVV in SBP and outcomes in this study, which suggests other underlying mechanisms. End-organ damage resulting from BP variability has been reported in animal models.[22] BP variability-induced endothelial damage, renin-angiotensin system activation, inflammation initiation, and cardiomyocyte apoptosis augmentation may lead to cardiovascular remodeling, and consequently lead to end-organ damage.[22] BP variability showed significant association with endothelial dysfunction and markers of inflammation in humans.[23, 24] Although VVV in BP was associated with CVD independent of medication adherence,[25] poor adherence to medication may partly explain the association.[26] Further studies are needed to clarify the mechanisms responsible.

The strengths of the present study are the large sample size, the long-term follow-up, and the rigorous evaluation of VVV in SBP by using a variety of measures, in particular the VIM which is not correlated with mean SBP. In addition, to the best of our knowledge, this is the first study to use a comprehensive set of discrimination and reclassification statistics to show the additional impact of VVV in SBP beyond mean SBP and other risk factors on the risk prediction of cardiovascular diseases. However, limitations of our study should be noted. First, the endpoints during the post-trial follow-up were not adjudicated by central adjudication committee. However, we have previously shown that the endpoint adjudication process in the ADVANCE trial had no discernible effect on the observed HRs for any outcomes.[27] Second, selection bias might have arisen by excluding patients with missing BP value at any of 6 measurement occasions. However, the sensitivity analyses using imputation of missing values of BP did not materially change the results. Third, our study population was enrolled in a clinical trial, which may limit the generalizability of the results to

unselected populations. Fourth, this is a post-hoc observational study and there may be residual confounding factors other than those included in the present analysis. Fifth, we were only able to follow-up 84% of the patients alive when the original trial period was completed, but it is unlikely that selective drop-out could have resulted in any major bias, whilst baseline characteristics of patients included in the post-trial follow-up were similar to those of the entire trial population.[13] Sixth, previous reports[28,29] have found heterogeneity in the effects of VVV in SBP on stroke across drug classes. ADVANCE lacks reliable data regarding the effectiveness of the various drug classes in reducing VVV in SBP, but our on-going research programme includes looking at this issue using data from the Blood Pressure Lowering Treatment Trialists' Collaboration. Seventh, it is possible that treatment exposure varied during the observational post-trial follow-up period, which may have affected the association between VVV in SBP and study outcomes. Finally, event numbers were likely insufficient to provide reliable, consistent information on the additional prognostic value of VVV in SBP for the major components of the primary outcome, particularly, major renal disease. Nevertheless, there was sufficient information to conclude that VVV in SBP does seem to be a prime candidate for addition to CVD, and possibly renal, risk scores, at least in the context of diabetes.

Perspectives

VVV in SBP was significantly associated with increased 8-year risk of vascular events and all-cause mortality, independent of mean SBP and other traditional risk factors in patients with type 2 diabetes. In addition, VVV in SBP provided additional predictive information beyond that obtained from mean SBP and the traditional risk factors.

With the advent of linked clinical records, and home monitoring of BP, it is becoming practical to use VVV in SBP to improve individual risk stratification, beyond using mean

SBP and other factors. Our findings suggest that reduced VVV in SBP may be an important therapeutic target in patients with type 2 diabetes.

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Novelty and Significance

What Is New?

- This is the first study to show that visit-to-visit variability (VVV) in systolic blood pressure (SBP) provides additional predictive information on vascular events beyond that from mean blood pressure (BP) and traditional risk factors, using a variety of measures of VVV and discrimination and reclassification statistics.

What Is Relevant?

- VVV in BP is associated with increased risk of cardiovascular events, but the additional utility of VVV in BP for the risk prediction of events in diabetes has not previously been clarified.

Summary

VVV in SBP was significantly associated with an increased risk of vascular events and all-cause mortality independent of mean SBP and other traditional risk factors in patients with type 2 diabetes over an 8-year period, and improved risk prediction beyond that provided by traditional risk factors over the next 8 years. Assessment of VVV in BP can be incorporated into clinical practice.

Figure legends

Figure 1: Flow diagram for study participants.
Blood pressure (BP), measured at 6 occasions (3, 4, 6, 12, 18, and 24 months after randomization), was used to determine the mean, visit-to-visit variability, and maximum of systolic BP. After excluding 651 patients who had experienced major macrovascular or renal events or death within 24 months, 1,373 patients with missing BP values at any of 6 occasions, and 2 patients with missing values of covariates, 9,114 patients were eligible for the present study.

Figure 2: Hazard ratios and 95% confidence intervals (CIs) for major macrovascular and renal events and all-cause mortality according to tenths of standard deviation (SD) of systolic blood pressure (SBP).
SBP SD was categorized according to the tenths. The ranges of SBP SD were 0.49-5.15, 5.16-6.79, 6.80-7.99, 8.00-9.13, 9.14-10.26, 10.27-11.47, 11.48-12.90, 12.91-14.79, 14.80-17.61, and 17.62-47.20 mmHg. Hazard ratios were adjusted for age, sex, region of residence, duration of diabetes mellitus, current smoking, current alcohol drinking, heart rate, total cholesterol, log of triglycerides, body mass index, use of β-blockers, use of calcium-channel blockers, randomized blood pressure-lowering intervention, randomized glucose control intervention, and mean SBP during the measurement period (the same covariates as model 2 in Table 2).

Figure 3: Hazard ratios and 95% confidence intervals (CIs) for components of major macrovascular events according to tenths of standard deviation (SD) of systolic blood pressure (SBP).
SBP SD was categorized according to the tenths, same as in Figure 2. Hazard ratios were adjusted for the same covariates as in Figure 2.

Table 1. Characteristics of ADVANCE-ON participants overall and those included in the present study

Variable	Overall	Included in the present study	
	Baseline (n=11,140)	Baseline (n=9,114)	24-month visit (n=9,114)
Demographic factors			
Age (years)	66 (6)	66 (6)	68 (6)
Female (%)	4735 (43)	3849 (42)	
Resident in Asia (%)	4136 (37)	3392 (37)	
Asian (%)	4242 (38)	3476 (38)	
Non-Asian (%)	6898 (62)	5638 (62)	
Medical and Lifestyle history			
Duration of diabetes mellitus (years)	7.9 (6.4)	7.8 (6.3)	9.8 (6.3)
Current smoking (%)	1682 (15)	1356 (15)	919 (10)*****
Current alcohol drinking (%)	3396 (30)	2812 (31)	2541 (28)*****
Clinical measurements			
Systolic blood pressure (mmHg)	145 (22)	145 (21)	137 (19)
Diastolic blood pressure (mmHg)	81 (11)	81 (11)	77 (10)
Pulse pressure (mmHg)	64 (17)	64 (17)	61 (15)
Heart rate (bpm)	74 (12)	74 (12)	73 (12)*****
Hemoglobin A_{1c} (%)	7.5 (1.6)	7.5 (1.5)	7.0 (1.2)*****
Total cholesterol (mmol/l)	5.2 (1.2)	5.2 (1.2)	4.9 (1.1)*****
Triglycerides (mmol/l)	1.6 (1.2-2.3)	1.6 (1.2-2.3)	1.6 (1.1-2.2)*****
Body mass index (kg/m^2)	28.3 (5.2)	28.4 (5.2)	28.3 (5.2)*****
eGFR ($ml/min/1.73m^2$)	73 (17)	74 (17)	70 (18)*****
Oral hypoglycemic agents (%)	10129 (91)	8281 (91)	8629 (95)*****
Insulin (%)	159 (1)	133 (1)	1605 (18)*****
10-year risk of major vascular events (%)	21.9 (12.6)	21.4 (12.0)	23.3 (12.6)*****
Randomized treatments			
Perindopril-indapamide	5569 (50)	4567 (50)	
Intensive blood glucose control	5571 (50)	4547 (50)	
Additional BP-lowering treatments			
β-blocker (%)	2729 (25)	2242 (25)	2713 (30)*****
Calcium-channel blocker (%)	3427 (31)	2758 (30)	3116 (34)*****
Diuretics† (%)	2640 (24)	2138 (23)	1312 (14)*****
Angiotensin-converting enzyme inhibitors† (%)	4790 (43)	3963 (43)	4698 (52)*****
Angiotensin II receptor blockers (%)	609 (5)	469 (5)	635 (7)*****
Other antihypertensive agents (%)	1383 (12)	1102 (12)	946 (10)*****
Any BP-lowering agents† (%)	8366 (75)	6822 (75)	6976 (77)*****
Visit-to-visit variability in systolic blood pressure‡			
Mean (mmHg)			137 (15)

SD (mmHg)	11.0 (5.0)
CV (%)	8.0 (3.4)
VIM (mmHg)	11.0 (4.7)
ASV (mmHg)	12.0 (6.1)
RSD (mmHg)	10.2 (5.0)
Range (mmHg)	29 (14)
Maximum (mmHg)	152 (19)

Values are mean (SD) for continuous variables (except for triglycerides), median (interquartile range) for triglycerides, and number (%) for categorical variables. Abbreviations: eGFR, estimated glomerular filtration rate; SD, standard deviation; CV, coefficient of variation; VIM, variation independent of the mean ASV, average successive variability; RSD, residual standard deviation.

* When data at the 24-month visit were missing, the latest data before the 24-month visit were used.

† Randomized treatment with perindopril-indapamide was not included.

‡ Defined using SBP values at 3, 4, 6, 12, 18, and 24 months after randomization.

Table 2. Effects of 1-SD increment in mean and SD of SBP on primary outcome (combination of major macrovascular events, renal events and all-cause mortality) and its components

	No. of events	Model 1*			Model 2†		
		HR	95% CI	P	HR	95% CI	P
Combined macrovascular, renal events and all-cause mortality							
	2,345						
Mean SBP		1.11	(1.06-1.16)	<0.001			
SD SBP		1.14	(1.09-1.18)	<0.001	1.11	(1.07-1.16)	<0.001
All-cause mortality							
	1,550						
Mean SBP		1.09	(1.04-1.15)	0.001			
SD SBP		1.14	(1.09-1.20)	<0.001	1.13	(1.07-1.19)	<0.001
Major macrovascular events							
	1,476						
Mean SBP		1.13	(1.07-1.20)	<0.001			
SD SBP		1.11	(1.06-1.17)	<0.001	1.08	(1.03-1.14)	0.004
Major renal events							
	122						
Mean SBP		1.52	(1.27-1.81)	<0.001			
SD SBP		1.27	(1.08-1.50)	0.005	1.15	(0.97-1.37)	0.11
Myocardial infarction							
	478						
Mean SBP		1.21	(1.10-1.33)	<0.001			
SD SBP		1.15	(1.05-1.26)	0.002	1.11	(1.01-1.21)	0.03
Stroke							
	668						
Mean SBP		1.14	(1.05-1.23)	0.002			
SD SBP		1.08	(1.00-1.17)	0.04	1.05	(0.97-1.14)	0.20
Cardiovascular death							
	614						
Mean SBP		1.16	(1.06-1.26)	<0.001			
SD SBP		1.12	(1.03-1.21)	0.006	1.08	(0.998-1.18)	0.06

HR (95% CI) per increase of 1 SD for each parameter was shown. SD values were 15.2 mmHg for mean SBP, and 5.0 mmHg for SD SBP.

Abbreviations: ASV, average successive variability; CI, confidence intervals; HR, hazard ratio; SBP, systolic blood pressure; SD, standard deviation.

* Model 1 was adjusted for age, sex, region of residence, duration of diabetes mellitus, current smoking, current alcohol drinking, heart rate, total cholesterol, log of triglycerides, body mass index, use of β-blockers, use of calcium-channel blockers, randomized blood pressure-lowering intervention, and randomized glucose control intervention. † Model 2 was adjusted for all variables in model 1 and mean SBP.

Table 3. Discrimination and reclassification statistics (95% confidence intervals) for standard deviation of systolic blood pressure and primary outcome (combination of major macrovascular events, renal events and all-cause mortality) and its major components

				NRI	
	c-statistic	IDI	Relative IDI (%)	Continuous	Categorical†
Combined macrovascular, renal events and all-cause mortality					
Base model*	0.6459 (0.6339, 0.6580)				
plus SD SBP	0.6499 (0.6379, 0.6619)	0.0029 (0.0021, 0.0038)	4.18 (2.94, 5.47)	0.053 (0.003, 0.107)	0.017 (0.006, 0.029)
	P = 0.003	*P* <0.001		*P* = 0.03	*P* = 0.002
All-cause mortality					
Base model*	0.6976 (0.6836, 0.7117)				
plus SD SBP	0.7009 (0.6870, 0.7149)	0.0026 (0.0014, 0.0039)	2.68 (1.40, 3.98)	0.074 (0.017, 0.134)	-0.0024 (-0.019, 0.015)
	P = 0.01	*P* <0.001		*P* = 0.02	*P* = 0.75
Major macrovascular events					
Base model*	0.6280 (0.6125, 0.6435)				
plus SD SBP	0.6312 (0.6158, 0.6466)	0.0014 (0.0010, 0.0019)	4.11 (2.84, 5.33)	0.010 (-0.051, 0.070)	0.002 (-0.014, 0.017)
	P = 0.02	*P* <0.001		*P* = 0.47	*P* = 0.42
Major renal events					
Base model*	0.7079 (0.6590, 0.7568)				
plus SD SBP	0.7175 (0.6708, 0.7642)	0.0018 (0.0010, 0.0030)	11.54 (6.31, 17.24)	0.150 (-0.023, 0.342)	-0.029 (-0.073, 0.007)
	P = 0.11	*P* <0.001		*P* = 0.09	*P* = 0.10

* Base model included age, sex, region of residence, duration of diabetes mellitus, current smoking, current alcohol drinking, heart rate, total cholesterol, log of triglycerides, body mass index, use of β-blockers, use of calcium-channel blockers, randomized blood pressure-lowering intervention, randomized glucose control intervention, and mean SBP. † Using cutoff points of 10% and 20% 8-year risk.

Abbreviations: IDI, integrated discrimination index; NRI, net reclassification improvement; SBP, systolic blood pressure; SD, standard deviation.

Figure 1

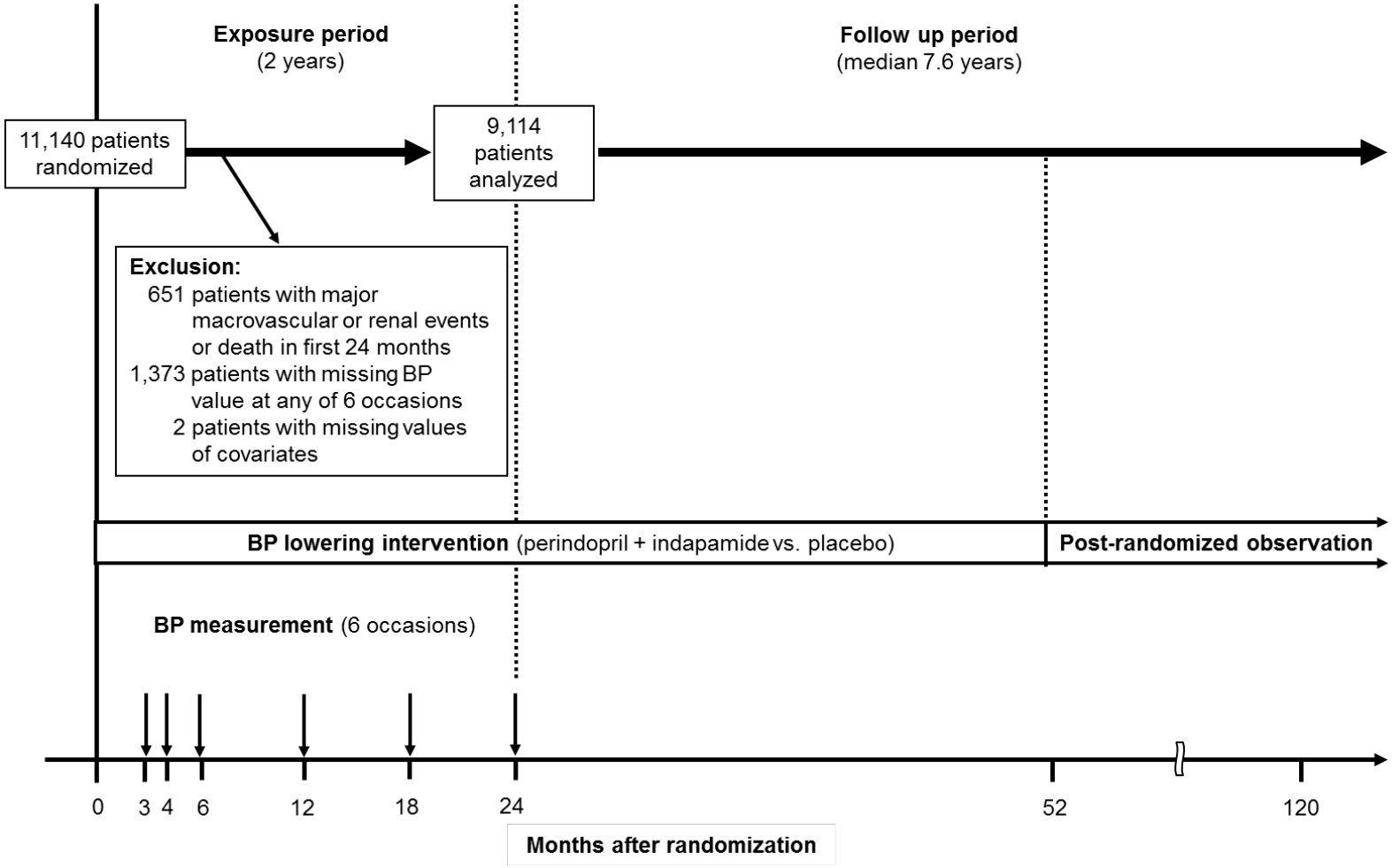

Exposure period
(2 years)
Follow up period
(median 7.6 years)
11,140 patients randomized
9,114 patients analyzed
Exclusion:
651 patients with major macrovascular or renal events or death in first 24 months
1,373 patients with missing BP value at any of 6 occasions
2 patients with missing values of covariates
BP lowering intervention (perindopril + indapamide vs. placebo)
Post-randomized observation
BP measurement (6 occasions)
0 3 4 6 12 18 24 52 120
Months after randomization

Figure 2

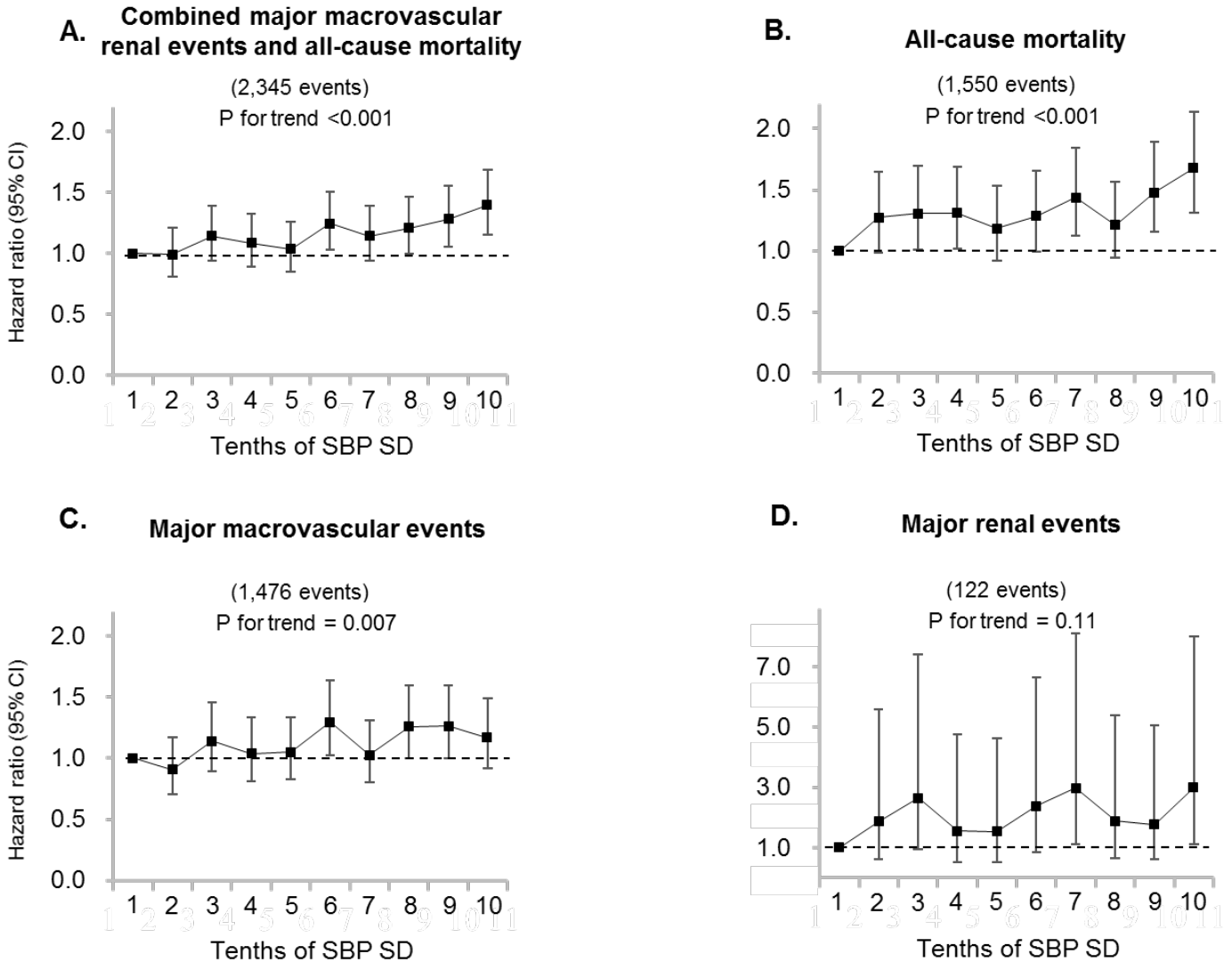
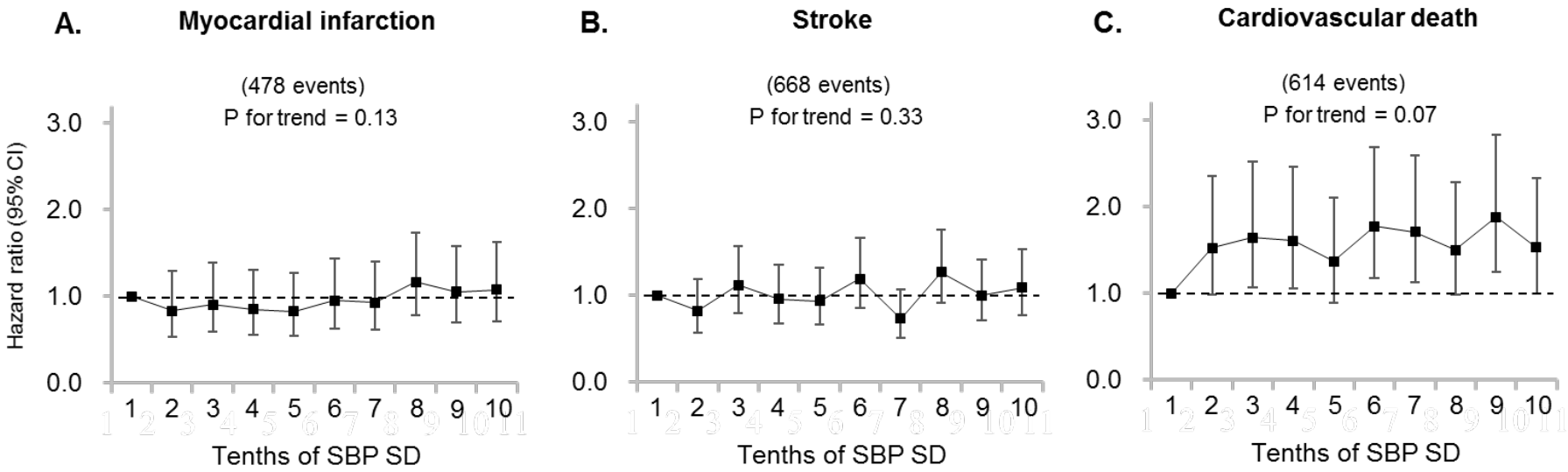

A.
Combined major macrovascular renal events and all-cause mortality
(2,345 events)
P for trend <0.001
Hazard ratio (95% CI)
2.0
1.5
1.0
0.5
0.0
1 2 3 4 5 6 7 8 9 10
Tenths of SBP SD
B.
All-cause mortality
(1,550 events)
P for trend <0.001
2.0
1.5
1.0
0.5
0.0
1 2 3 4 5 6 7 8 9 10
Tenths of SBP SD
C.
Major macrovascular events
(1,476 events)
P for trend = 0.007
Hazard ratio (95% CI)
2.0
1.5
1.0
0.5
0.0
1 2 3 4 5 6 7 8 9 10
Tenths of SBP SD
D.
Major renal events
(122 events)
P for trend = 0.11
7.0
5.0
3.0
1.0
1 2 3 4 5 6 7 8 9 10
Tenths of SBP SD

Figure 3


A.
Myocardial infarction
(478 events)
P for trend = 0.13
B.
Stroke
(668 events)
P for trend = 0.33
C.
Cardiovascular death
(614 events)
P for trend = 0.07
Hazard ratio (95% CI)
3.0
2.0
1.0
0.0
1 2 3 4 5 6 7 8 9 10
Tenths of SBP SD

Online Supplement

Prognostic value of variability in systolic blood pressure related to vascular events and premature death in type 2 diabetes: ADVANCE-ON

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Table S1. Pearson's correlation coefficients for parameters of systolic blood pressure

	Mean	SD	CV	VIM	ASV	RSD	Range
SD	0.32						
CV	0.08	0.96					
VIM	-0.03	0.93	0.99				
ASV	0.27	0.84	0.81	0.78			
RSD	0.28	0.88	0.85	0.82	0.92		
Range	0.32	0.98	0.94	0.91	0.84	0.87	
Maximum	0.92	0.63	0.42	0.33	0.52	0.55	0.64

Abbreviations: ASV, average successive variability; CV, coefficient of variation; RSD, residual standard deviation; SBP, systolic blood pressure; SD, standard deviation; VIM, variation independent of the mean.

Table S2. Pearson's partial correlation coefficients for parameters of systolic blood pressure after controlling for mean systolic blood pressure

	SD	CV	VIM	ASV	RSD	Range
CV	0.99					
VIM	0.99	1.00				
ASV	0.83	0.82	0.82			
RSD	0.87	0.86	0.86	0.92		
Range	0.98	0.97	0.97	0.82	0.86	
Maximum	0.88	0.88	0.87	0.71	0.77	0.90

Abbreviations: ASV, average successive variability; CV, coefficient of variation; RSD, residual standard deviation; SBP, systolic blood pressure; SD, standard deviation; VIM, variation independent of the mean.

Table S3. Parameters of systolic blood pressure after controlling for mean systolic blood pressure according to randomized blood pressure-lowering intervention

	Perindopril-indapamide (n=4,567)	Placebo (n=4,547)	*P* value
SD (mmHg)	11.0 (0.07)	10.9 (0.07)	0.58
CV (%)	8.0 (0.05)	7.9 (0.05)	0.53
VIM (mmHg)	11.0 (0.07)	10.9 (0.07)	0.47
ASV (mmHg)	12.1 (0.09)	11.9 (0.09)	0.19
RSD (mmHg)	10.3 (0.07)	10.1 (0.07)	0.20
Range (mmHg)	29.2 (0.2)	29.1 (0.2)	0.73
Maximum (mmHg)	152.4 (0.1)	152.4 (0.1)	0.93

Abbreviations: ASV, average successive variability; CV, coefficient of variation; RSD, residual standard deviation; SBP, systolic blood pressure; SD, standard deviation; VIM, variation independent of the mean. The numbers in parentheses represent the standard errors.

Table S4. Effects of 1-SD increment in mean, SD, CV, VIM, ASV, RSD, range, and maximum of SBP on primary outcome (combination of major macrovascular events, renal events and all-cause mortality) and its components

	No. of events	Model 1*			Model 2†		
		HR	95% CI	P	HR	95% CI	P
Combined macrovascular, renal events and all-cause mortality							
	2,345						
Mean SBP		1.11	(1.06-1.16)	<0.001			
SD SBP		1.14	(1.09-1.18)	<0.001	1.11	(1.07-1.16)	<0.001
CV SBP		1.11	(1.07-1.16)	<0.001	1.11	(1.06-1.15)	<0.001
VIM SBP		1.10	(1.06-1.15)	<0.001	1.11	(1.06-1.15)	<0.001
ASV SBP		1.10	(1.06-1.14)	<0.001	1.08	(1.04-1.12)	<0.001
RSD SBP		1.11	(1.07-1.16)	<0.001	1.10	(1.05-1.14)	<0.001
Range SBP		1.12	(1.08-1.17)	<0.001	1.10	(1.06-1.15)	<0.001
Maximum SBP		1.13	(1.09-1.18)	<0.001	1.18	(1.07-1.31)	<0.001
All-cause mortality							
	1,550						
Mean SBP		1.09	(1.04-1.15)	0.001			
SD SBP		1.14	(1.09-1.20)	<0.001	1.13	(1.07-1.19)	<0.001
CV SBP		1.12	(1.06-1.17)	<0.001	1.12	(1.06-1.17)	<0.001
VIM SBP		1.11	(1.05-1.16)	<0.001	1.12	(1.06-1.17)	<0.001
ASV SBP		1.10	(1.04-1.15)	<0.001	1.08	(1.03-1.14)	0.002
RSD SBP		1.11	(1.06-1.17)	<0.001	1.09	(1.04-1.15)	<0.001
Range SBP		1.13	(1.08-1.19)	<0.001	1.12	(1.06-1.18)	<0.001
Maximum SBP		1.12	(1.06-1.18)	<0.001	1.20	(1.06-1.35)	0.003
Major macrovascular events							
	1,476						
Mean SBP		1.13	(1.07-1.20)	<0.001			
SD SBP		1.11	(1.06-1.17)	<0.001	1.08	(1.03-1.14)	0.004
CV SBP		1.08	(1.03-1.14)	0.002	1.08	(1.03-1.14)	0.003
VIM SBP		1.07	(1.02-1.13)	0.007	1.08	(1.03-1.14)	0.003
ASV SBP		1.09	(1.03-1.14)	0.001	1.06	(1.01-1.12)	0.02
RSD SBP		1.10	(1.05-1.16)	<0.001	1.08	(1.02-1.14)	0.005
Range SBP		1.11	(1.05-1.16)	<0.001	1.08	(1.02-1.13)	0.007
Maximum SBP		1.14	(1.08-1.21)	<0.001	1.12	(0.99-1.27)	0.07
Major renal events							
	122						
Mean SBP		1.52	(1.27-1.81)	<0.001			
SD SBP		1.27	(1.08-1.50)	0.005	1.15	(0.97-1.37)	0.11
CV SBP		1.16	(0.98-1.38)	0.09	1.15	(0.97-1.36)	0.12
VIM SBP		1.11	(0.94-1.33)	0.22	1.14	(0.96-1.36)	0.13
ASV SBP		1.22	(1.03-1.43)	0.02	1.12	(0.94-1.32)	0.20
RSD SBP		1.21	(1.02-1.43)	0.03	1.10	(0.93-1.31)	0.26

Range SBP	1.27	(1.07-1.49)	0.005	1.15	(0.97-1.36)	0.12
Maximum SBP	1.52	(1.28-1.81)	<0.001	1.28	(0.85-1.91)	0.23
Myocardial infarction						
478						
Mean SBP	1.21	(1.10-1.33)	<0.001			
SD SBP	1.15	(1.05-1.26)	0.002	1.11	(1.01-1.21)	0.03
CV SBP	1.11	(1.01-1.21)	0.02	1.10	(1.01-1.21)	0.03
VIM SBP	1.09	(0.99-1.19)	0.06	1.10	(1.01-1.21)	0.03
ASV SBP	1.14	(1.05-1.24)	0.003	1.10	(1.01-1.20)	0.03
RSD SBP	1.14	(1.05-1.25)	0.003	1.10	(1.01-1.21)	0.04
Range SBP	1.14	(1.05-1.25)	0.003	1.10	(1.00-1.20)	0.05
Maximum SBP	1.23	(1.12-1.35)	<0.001	1.21	(0.98-1.50)	0.08
Stroke						
668						
Mean SBP	1.14	(1.05-1.23)	0.002			
SD SBP	1.08	(1.00-1.17)	0.04	1.05	(0.97-1.14)	0.20
CV SBP	1.05	(0.98-1.14)	0.18	1.05	(0.97-1.13)	0.21
VIM SBP	1.04	(0.97-1.12)	0.29	1.05	(0.97-1.13)	0.20
ASV SBP	1.05	(0.97-1.13)	0.23	1.02	(0.95-1.11)	0.58
RSD SBP	1.09	(1.01-1.18)	0.03	1.06	(0.98-1.15)	0.12
Range SBP	1.09	(1.01-1.17)	0.03	1.06	(0.98-1.14)	0.18
Maximum SBP	1.15	(1.06-1.24)	<0.001	1.12	(0.93-1.35)	0.24
Cardiovascular death						
614						
Mean SBP	1.16	(1.06-1.26)	<0.001			
SD SBP	1.12	(1.03-1.21)	0.006	1.08	(0.998-1.18)	0.06
CV SBP	1.08	(1.00-1.17)	0.047	1.08	(0.998-1.17)	0.06
VIM SBP	1.07	(0.99-1.16)	0.09	1.08	(0.998-1.17)	0.06
ASV SBP	1.09	(1.01-1.18)	0.03	1.06	(0.98-1.15)	0.13
RSD SBP	1.10	(1.02-1.19)	0.02	1.07	(0.99-1.16)	0.10
Range SBP	1.11	(1.03-1.20)	0.01	1.08	(0.99-1.17)	0.08
Maximum SBP	1.16	(1.06-1.26)	<0.001	1.08	(0.89-1.30)	0.46

HR (95% CI) per increase of 1 SD for each parameter was shown. SD values were 15.2 mmHg for mean SBP, 5.0 mmHg for SD SBP, 3.4% for SBP CV, 4.7 mmHg for SBP VIM, 6.1 mmHg for SBP ASV, 5.0 mmHg for SBP RSD, 13.6 mmHg for SBP range, and 19.0 mmHg for maximum SBP.

Abbreviations: ASV, average successive variability; CI, confidence intervals; HR, hazard ratio; CV, coefficient of variation; SBP, systolic blood pressure; SD, standard deviation; RSD, residual standard deviation; VIM, variation independent of the mean.

* Model 1 was adjusted for age, sex, region of residence, duration of diabetes mellitus, current smoking, current alcohol drinking, heart rate, total cholesterol, log of triglycerides, body mass index, use of β-blockers, use of calcium-channel blockers, randomized blood pressure-lowering intervention, and randomized glucose control intervention.

† Model 2 was adjusted for all variables in model 1 and mean SBP.

Table S5. Reclassification and discrimination statistics (95% confidence intervals) for systolic blood pressure parameters and primary outcome (combination of major macrovascular events, renal events and all-cause mortality) and its components

				NRI	
	c-statistic	IDI	Relative IDI (%)	Continuous	Categorical†
Base model*	0.6459 (0.6339, 0.6580)				
plus CV SBP	0.6499 (0.6379, 0.6620)	0.0028 (0.0020, 0.0036)	3.97 (2.83, 5.15)	0.062 (0.014, 0.118)	0.012 (0.0002, 0.024)
	P = 0.003	*P* <0.001		*P* = 0.01	*P* = 0.04
plus VIM SBP	0.6500 (0.6379, 0.6620)	0.0027 (0.0020, 0.0035)	3.94 (2.80, 5.07)	0.061 (0.013, 0.117)	0.011 (-0.0005, 0.023)
	P = 0.003	*P* <0.001		*P* = 0.01	*P* = 0.07
plus ASV SBP	0.6491 (0.6370, 0.6611)	0.0014 (0.0008 0.0020)	2.03 (1.13, 2.88)	0.056 (0.006, 0.106)	0.006 (-0.004, 0.017)
	P = 0.003	*P* <0.001		*P* = 0.02	*P* = 0.26
plus RSD SBP	0.6498 (0.6377, 0.6618)	0.0022 (0.0014, 0.0029)	3.11 (2.06, 4.13)	0.089 (0.044, 0.139)	0.010 (-0.0007, 0.021)
	P = 0.002	*P* <0.001		*P* <0.001	*P* = 0.06
plus range SBP	0.6497 (0.6377, 0.6617)	0.0023 (0.0016, 0.0032)	3.38 (2.31, 4.56)	0.060 (0.012, 0.111)	0.016 (0.005, 0.027)
	P = 0.003	*P* <0.001		*P* = 0.01	*P* <0.001
plus maximum SBP	0.6482 (0.6362, 0.6603)	0.0012 (0.0007, 0.0018)	1.73 (1.02, 2.51)	0.056 (0.008, 0.107)	0.011 (0.002, 0.020)
	P = 0.01	*P* <0.001		*P* = 0.03	*P* = 0.02

* Base model included age, sex, region of residence, duration of diabetes mellitus, current smoking, current alcohol drinking, heart rate, total cholesterol, log of triglycerides, body mass index, use of β-blockers, use of calcium-channel blockers, randomized blood pressure-lowering intervention, randomized glucose control intervention, and mean SBP.

† Using cutoff points of 10% and 20% 8-year risk.

Abbreviations: ASV, average successive variability; CV, coefficient of variation; IDI, integrated discrimination index; NRI, net reclassification improvement; SBP, systolic blood pressure; RSD, residual standard deviation; VIM, variation independent of the mean.

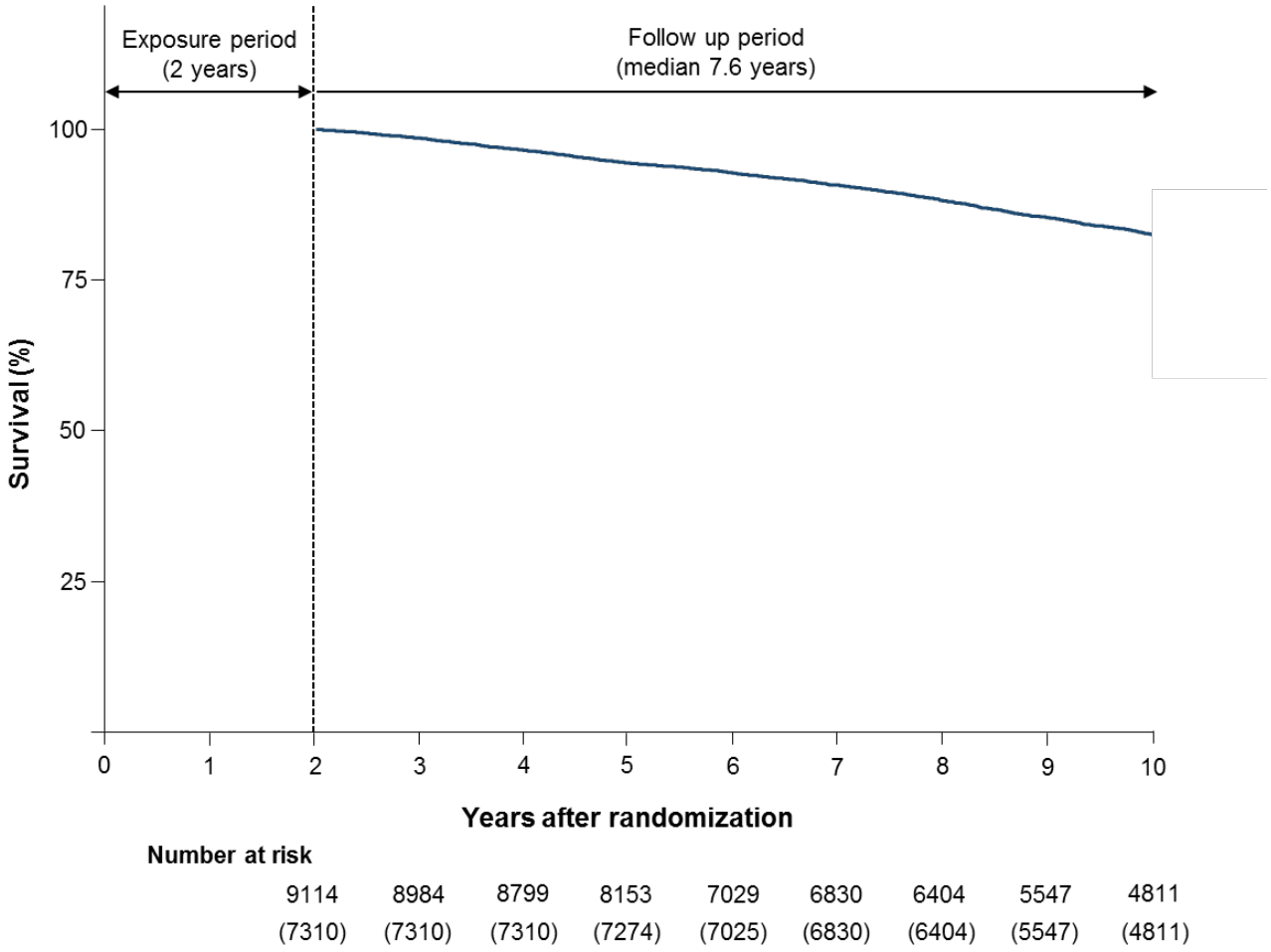

Figure S1. Kaplan-Meier curve of event-free survival for all-cause mortality.
Numbers in parentheses represent the number of patients included in the post-trial follow-up period.

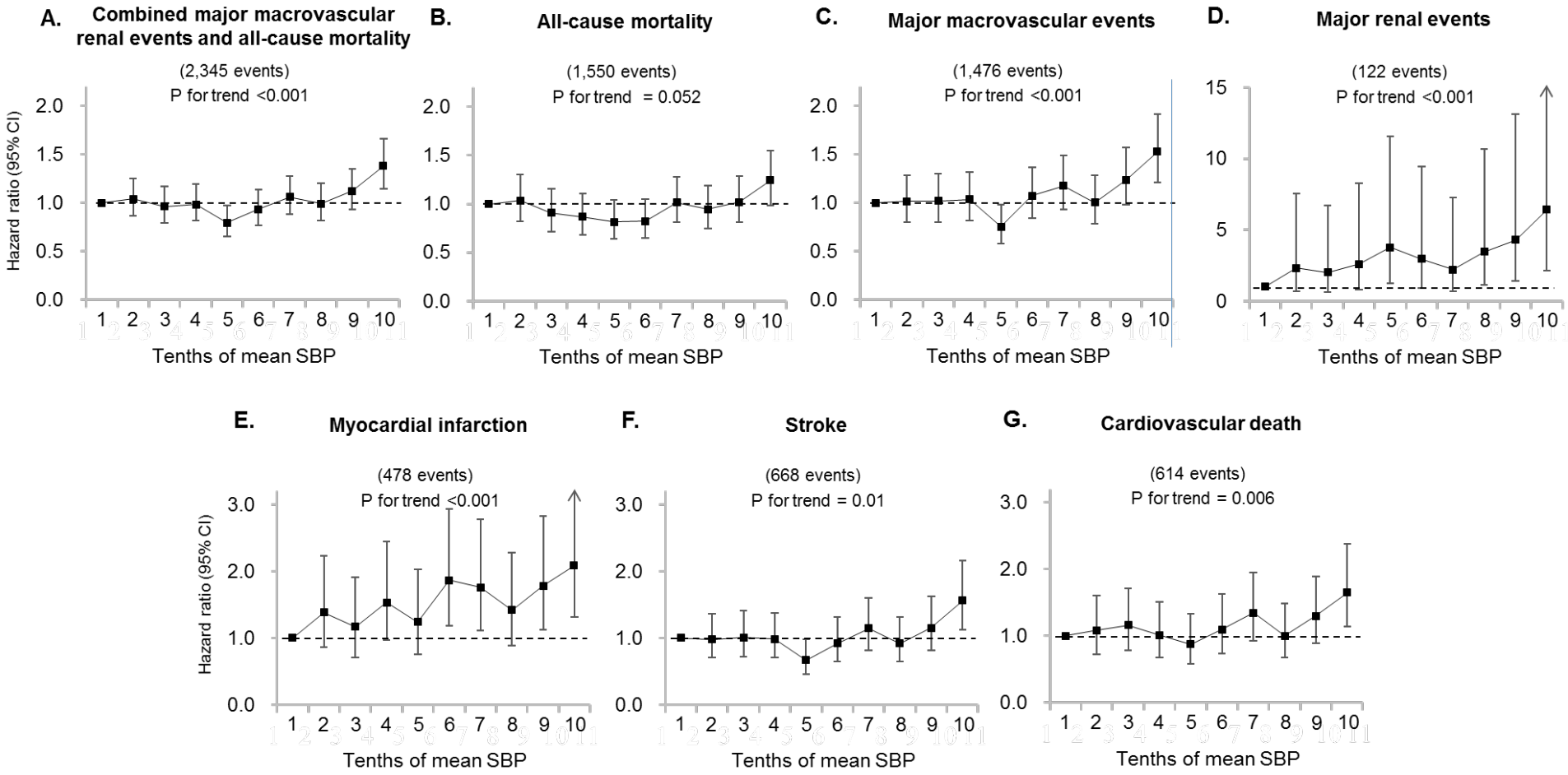

Figure S2. Hazard ratios and 95% confidence intervals (CIs) for outcomes according to tenths of mean systolic blood pressure (SBP) during the measurement period. Mean SBP was categorized according to the tenths. The ranges of mean SBP were 84.2-118.5, 118.6-124.8, 124.9-129.4, 129.5-133.3, 133.4-136.7, 136.8-140.2, 140.3-144.2, 144.3-149.4, 149.5-156.7, and 156.8-215.4 mmHg. Hazard ratios were adjusted for age, sex, region of residence, duration of diabetes mellitus, current smoking, current alcohol drinking, heart rate, total cholesterol, log of triglycerides, body mass index, use of b-blockers, use of calcium-channel blockers, randomized blood pressure-lowering intervention, and randomized glucose control intervention (the same covariates as model 1 in Table 2).

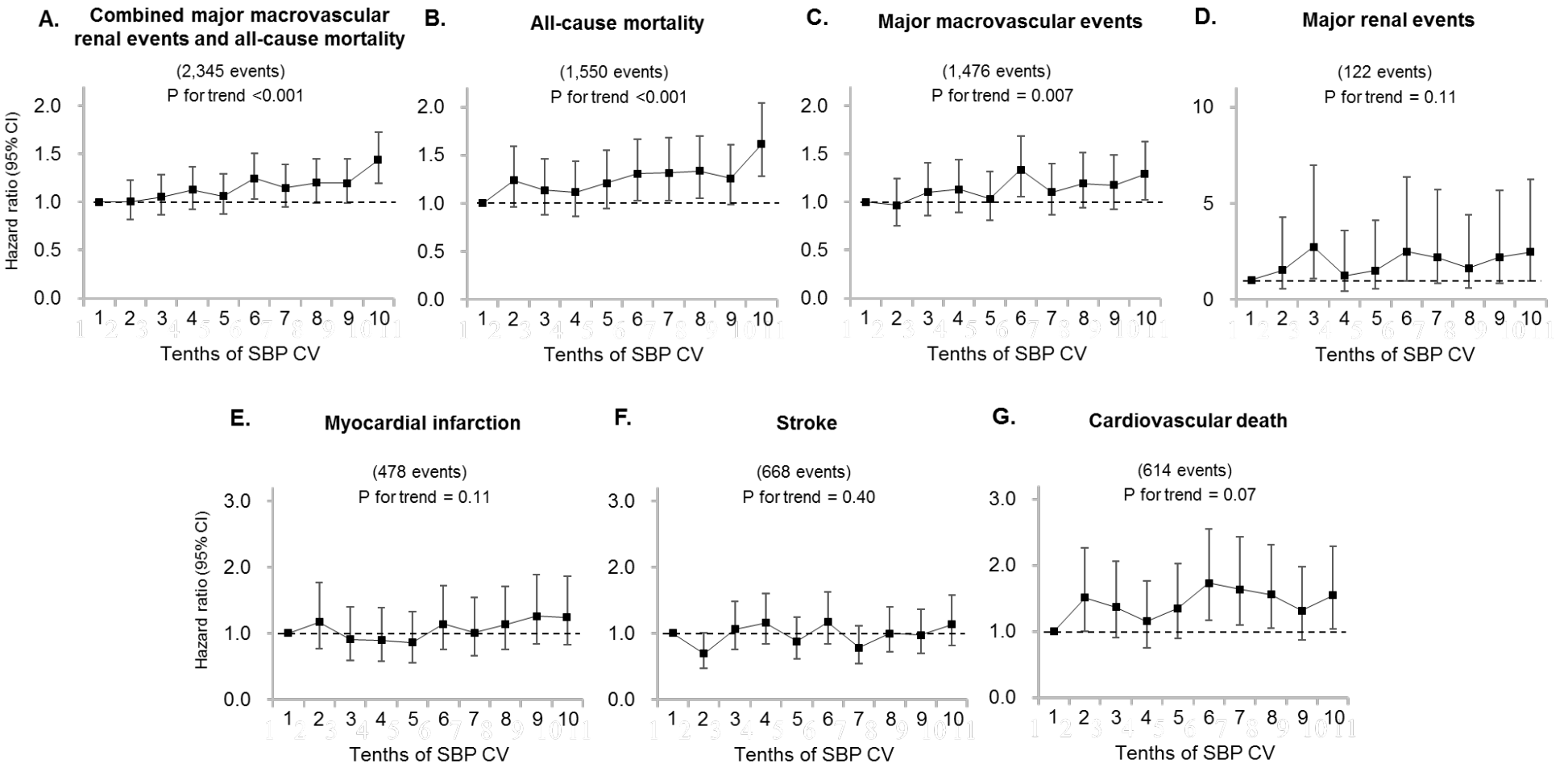

Figure S3: Hazard ratios and 95% confidence intervals (CIs) for outcomes according to tenths of coefficient of variation (CV) of systolic blood pressure (SBP). SBP CV was categorized according to the tenths. The ranges of SBP CV were 0.44-3.89, 3.90-5.07, 5.08-5.96, 5.97-6.77, 6.78-7.53, 7.54-8.37, 8.38-9.39, 9.40-10.64, 10.65-12.54, and 12.55-24.82%. Hazard ratios were adjusted for the same covariates as in Figure 2.

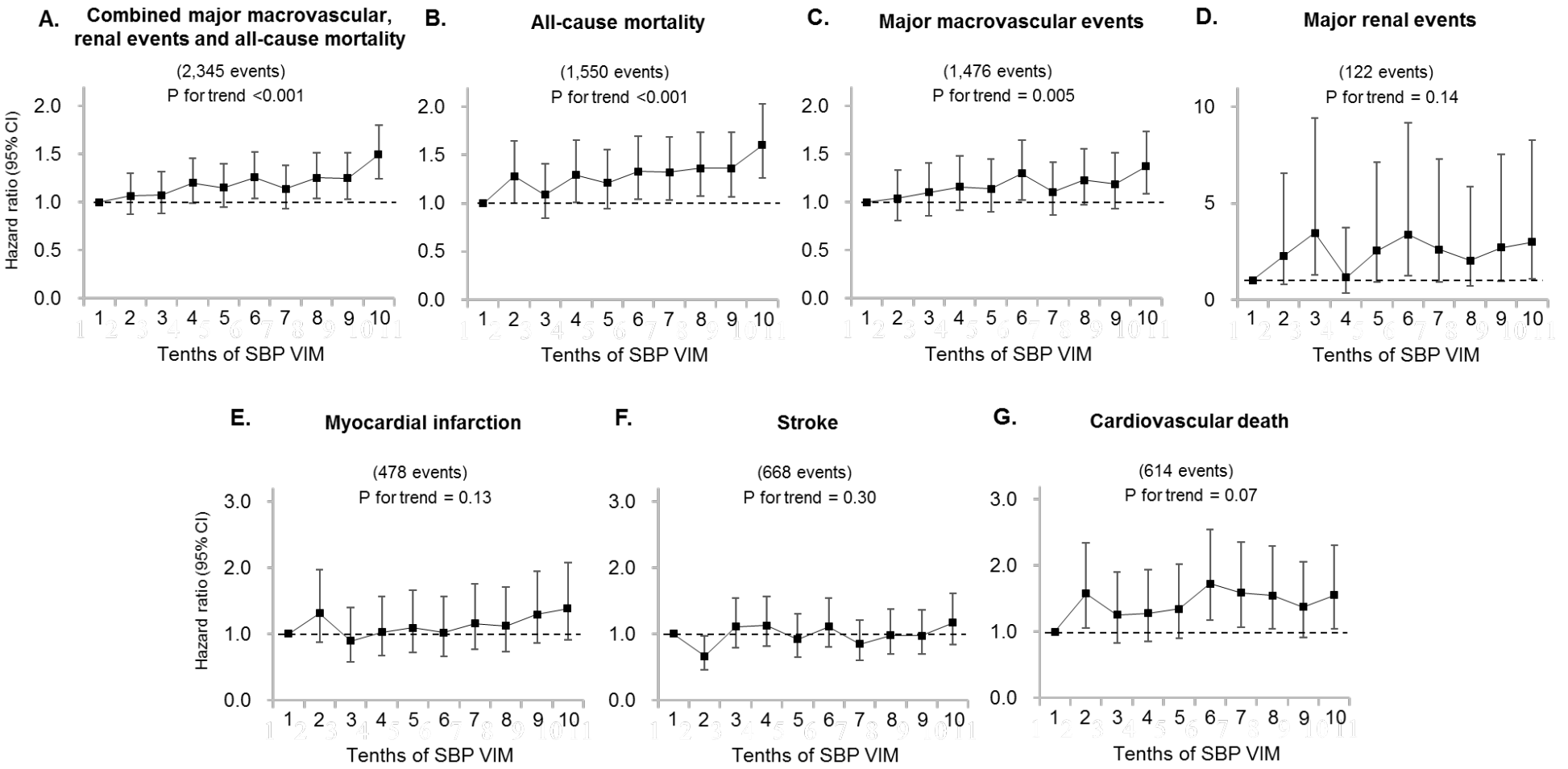

Figure S4: Hazard ratios and 95% confidence intervals (CIs) for outcomes according to tenths of variation independent of the mean (VIM) of systolic blood pressure (SBP). SBP VIM was categorized according to the tenths. The ranges of SBP VIM were 0.60-5.36, 5.37-6.98, 6.99-8.21, 8.22-9.30, 9.31-10.37, 10.38-11.56, 11.57-12.90, 12.91-14.64, 14.65-17.19, and 17.20-35.79 mmHg. Hazard ratios were adjusted for the same covariates as in Figure 2.

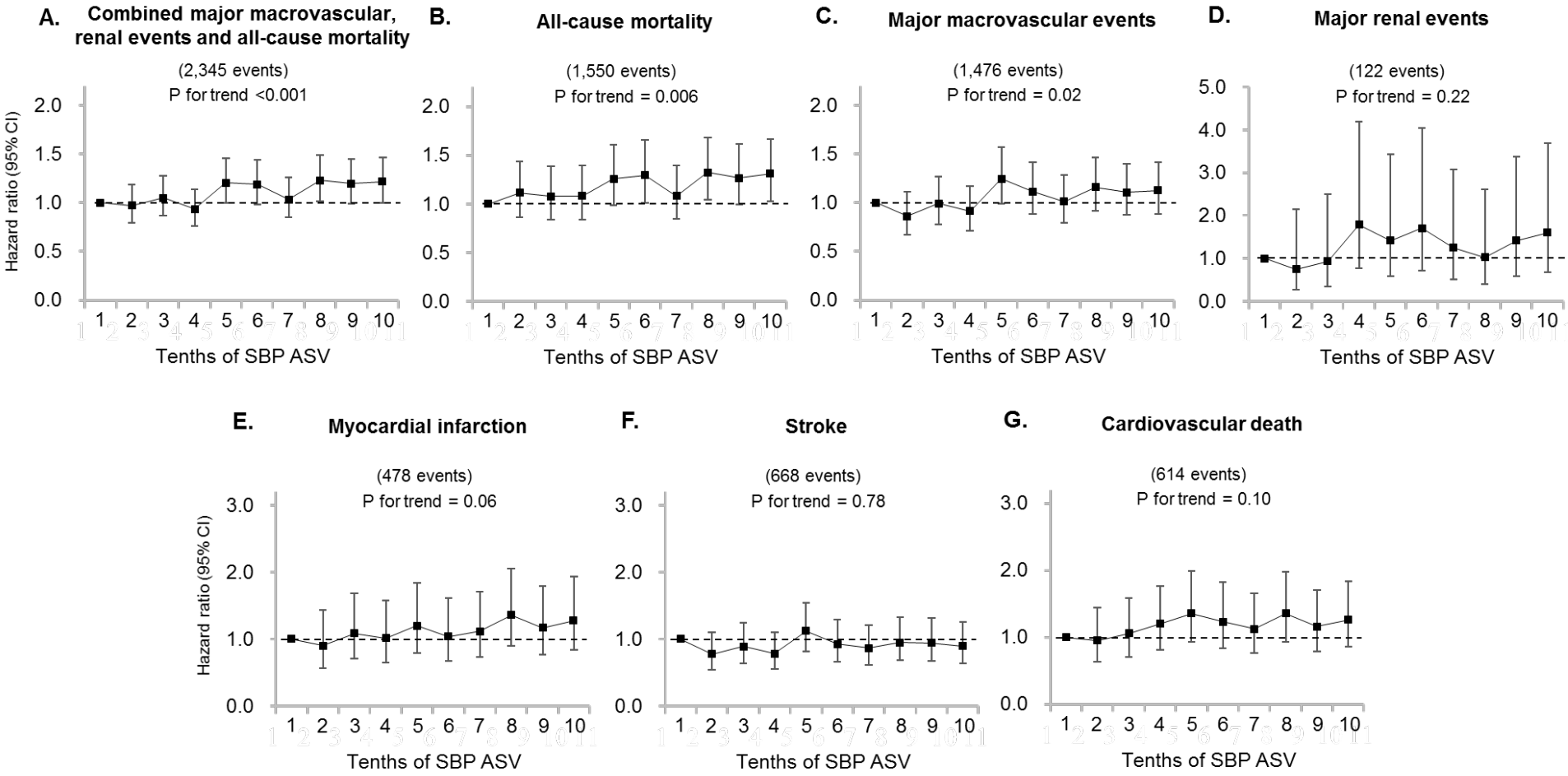

Figure S5: Hazard ratios and 95% confidence intervals (CIs) for outcomes according to tenths of average successive variability (ASV) of systolic blood pressure (SBP). SBP ASV was categorized according to the tenths. The ranges of SBP ASV were 0.4-5.1, 5.2-6.9, 7.0-8.4, 8.5-9.8, 9.9-11.1, 11.2-12.5, 12.6-14.2, 14.3-16.5, 16.6-20.0, and 20.1-57.8 mmHg. Hazard ratios were adjusted for the same covariates as in Figure 2.

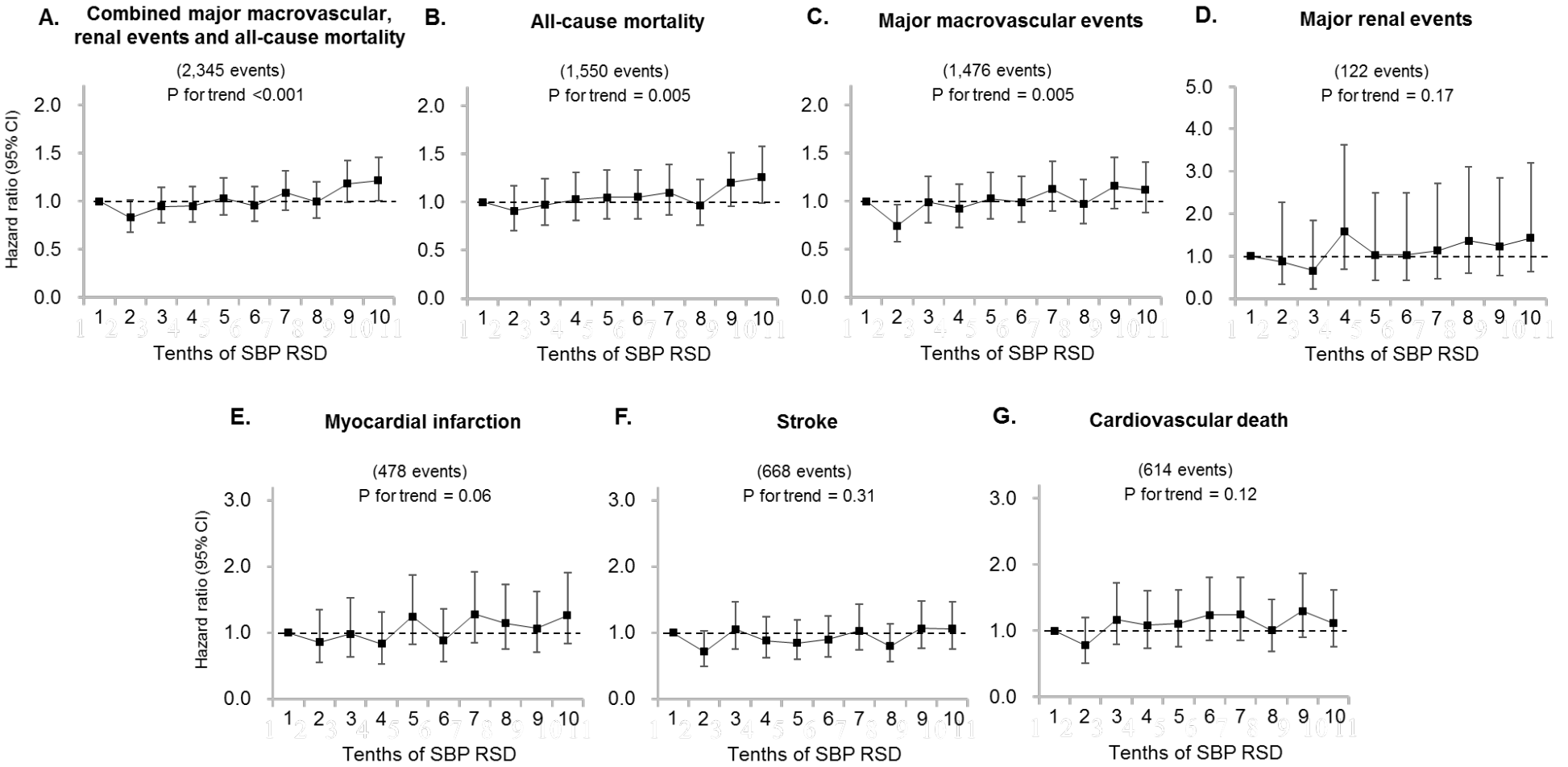

Figure S6: Hazard ratios and 95% confidence intervals (CIs) for outcomes according to tenths of residual standard deviation (RSD) of systolic blood pressure (SBP). SBP RSD was categorized according to the tenths. The ranges of SBP RSD were 0.37-4.43, 4.44-6.00, 6.01-7.29, 7.30-8.40, 8.41-9.50, 9.51-10.70, 10.71-12.11, 12.12-13.92, 13.93-16.62, and 16.63-50.43 mmHg. Hazard ratios were adjusted for the same covariates as in Figure 2.

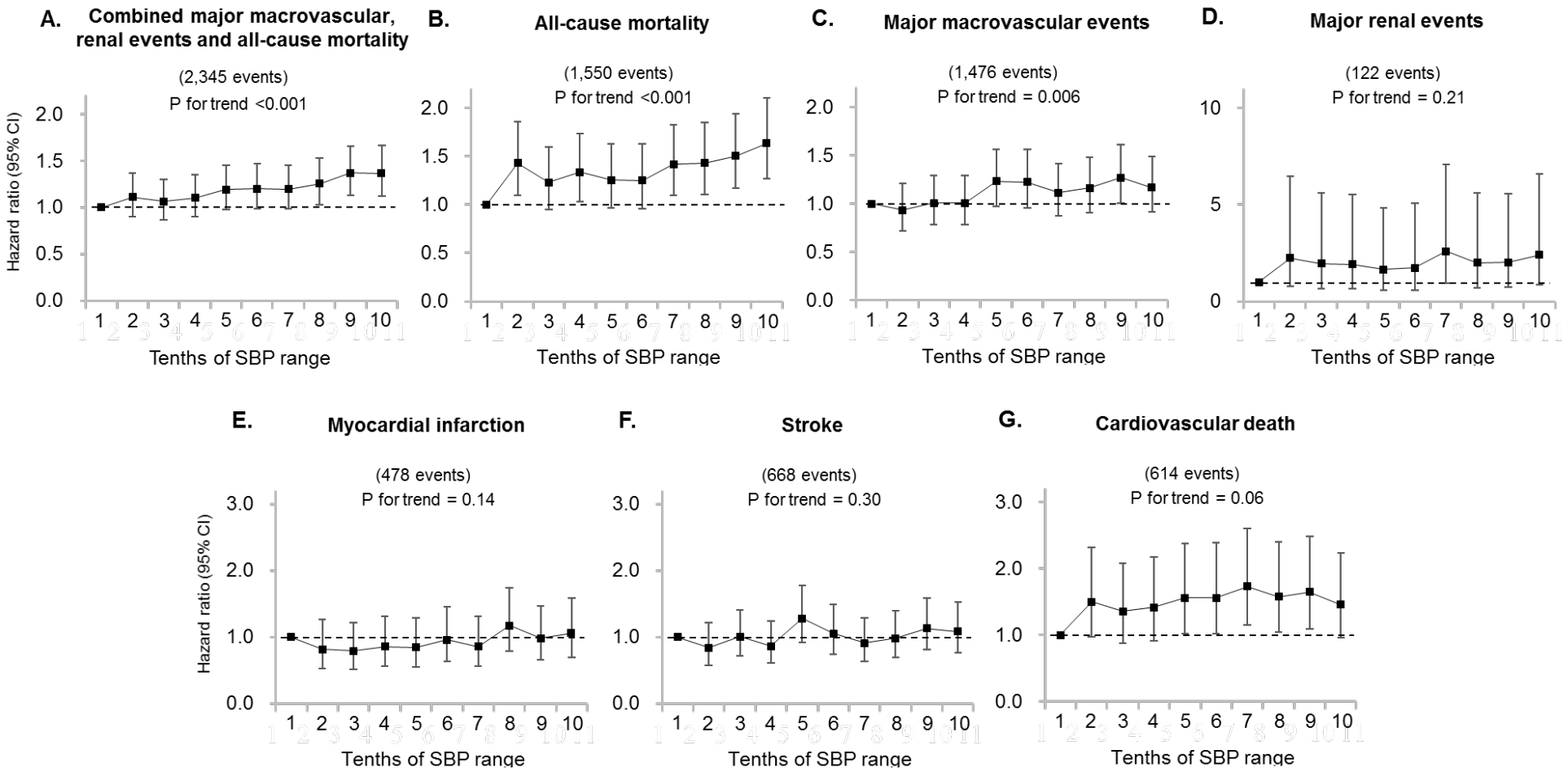

Figure S7: Hazard ratios and 95% confidence intervals (CIs) for outcomes according to tenths of range of systolic blood pressure (SBP).
SBP range was categorized according to the tenths. The ranges of SBP range were 1.5-13.0, 13.5-17.5, 18.0-21.0, 21.5-24.0, 24.5-27.0, 27.5-30.0, 30.5-34.0, 34.5-39.0, 39.5-47.0, and 47.5-121.0 mmHg. Hazard ratios were adjusted for the same covariates as in Figure 2.

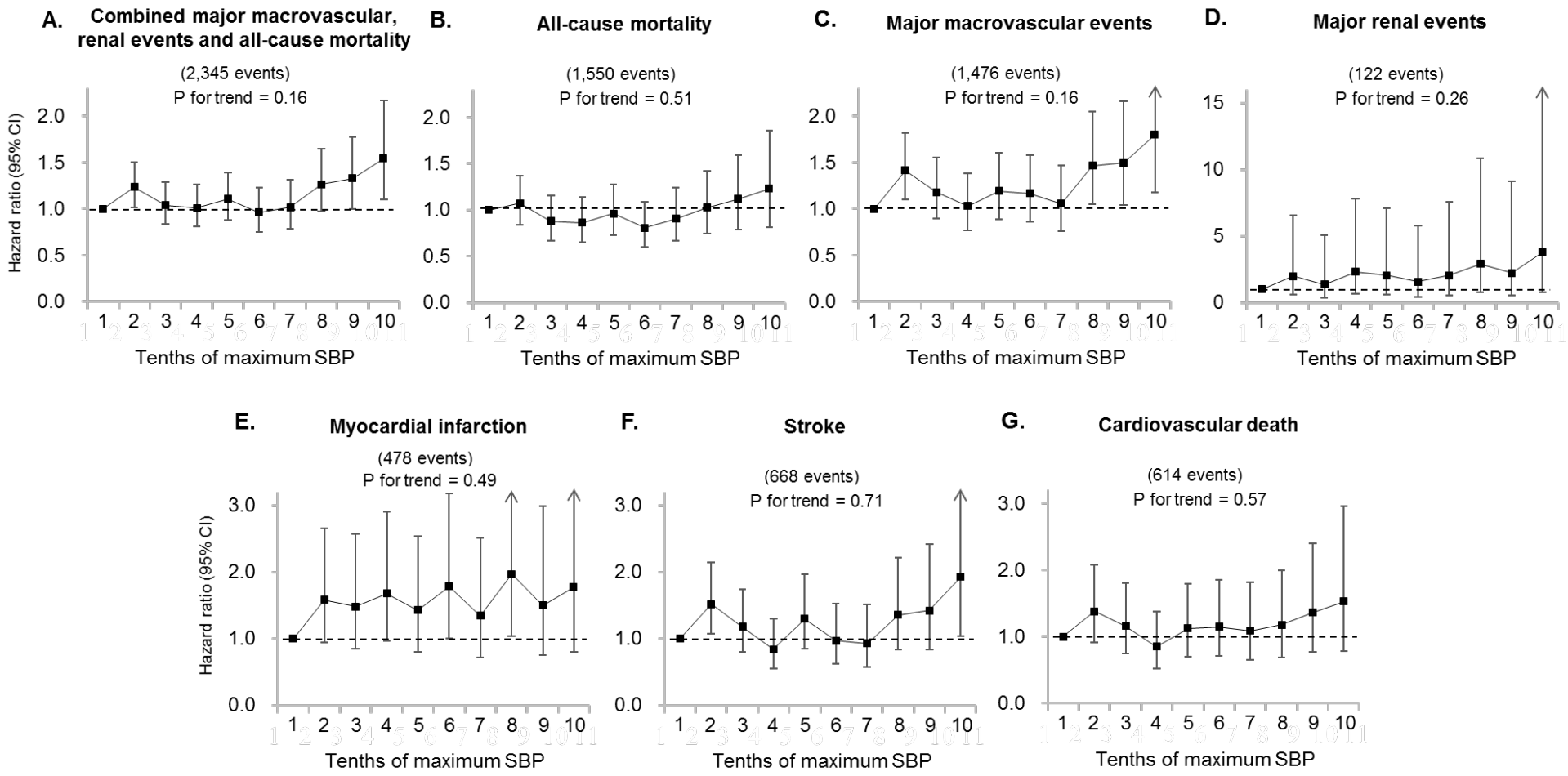

Figure S8: Hazard ratios and 95% confidence intervals (CIs) for outcomes according to tenths of maximum of systolic blood pressure (SBP).
Maximum SBP was categorized according to the tenths. The ranges of maximum SBP were 91.0-129.5, 130.0-136.5, 137.0-141.0, 141.5-145.5, 146.0-150.0, 150.5-155.0, 155.5-160.5, 161.0-167.5, 168.0-177.5, and 178.0-263.0 mmHg. Hazard ratios were adjusted for the same covariates as in Figure 2.

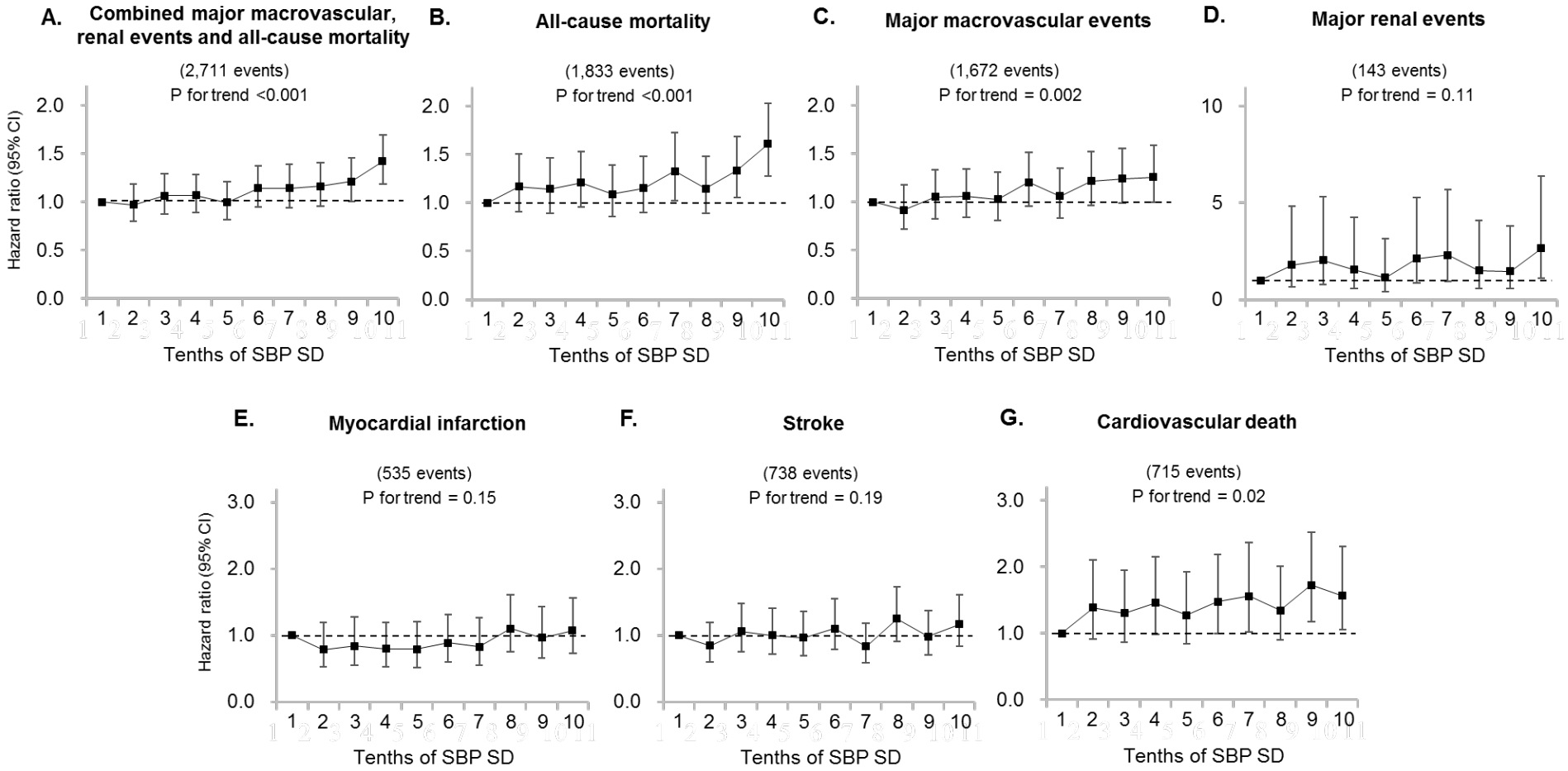

Figure S9: Sensitivity analysis; Hazard ratios and 95% confidence intervals (CIs) for outcomes according to tenths of standard deviation (SD) of systolic blood pressure (SBP) in the models including imputation of missing values.
Hazard ratios were adjusted for the same covariates as in Figure 2.

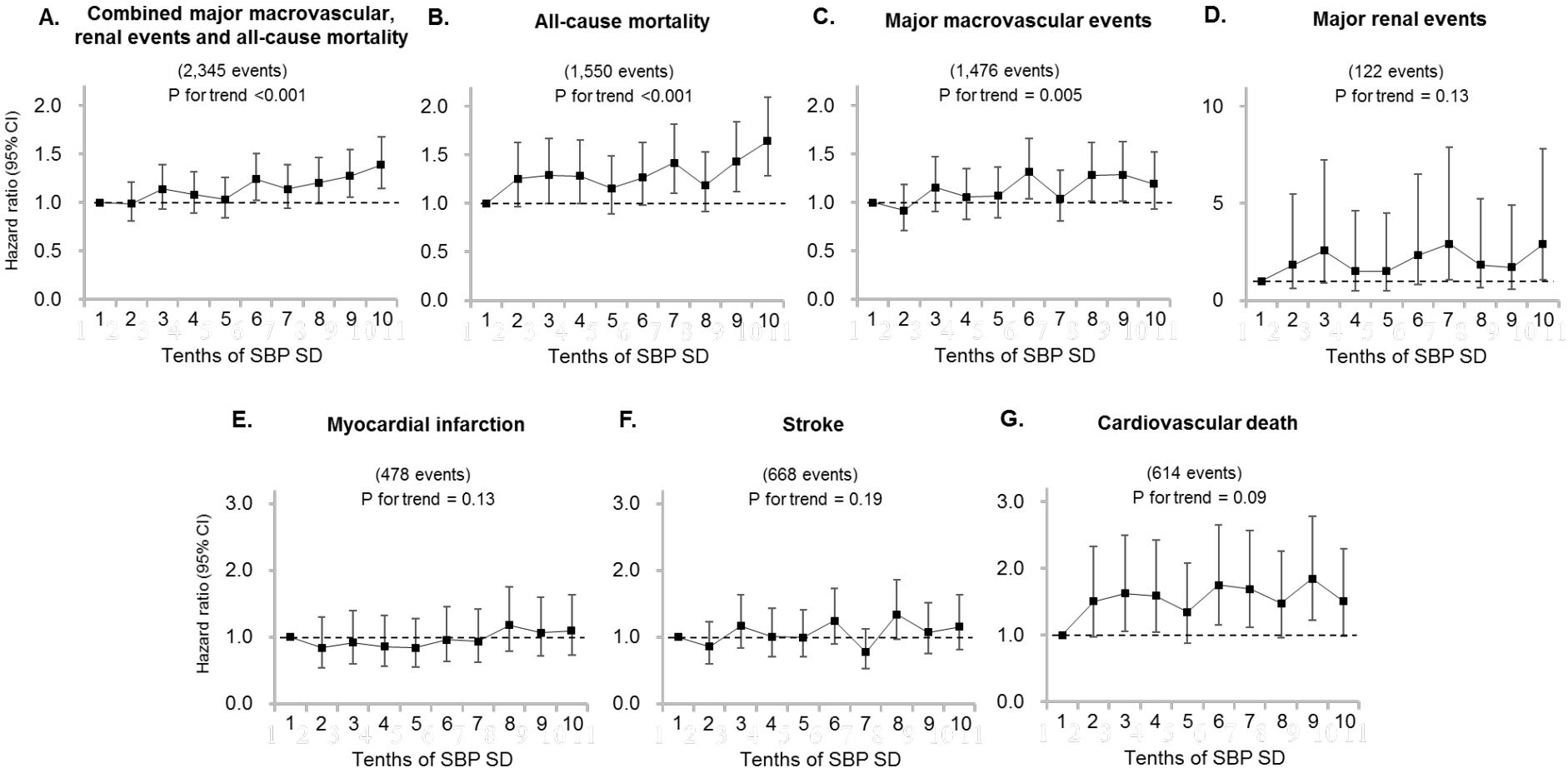

Figure S10: Sensitivity analysis; Hazard ratios and 95% confidence intervals (CIs) for outcomes according to tenths of standard deviation (SD) of systolic blood pressure (SBP) after addition of mean pulse pressure during measurement period as covariates.

SBP SD was categorized according to the tenths, same as in Figure 2. Hazard ratios were adjusted for the same covariates as in Figure 2. Hazard ratios were adjusted for the same covariates as in Figure 2 plus mean pulse pressure during the measurement period.

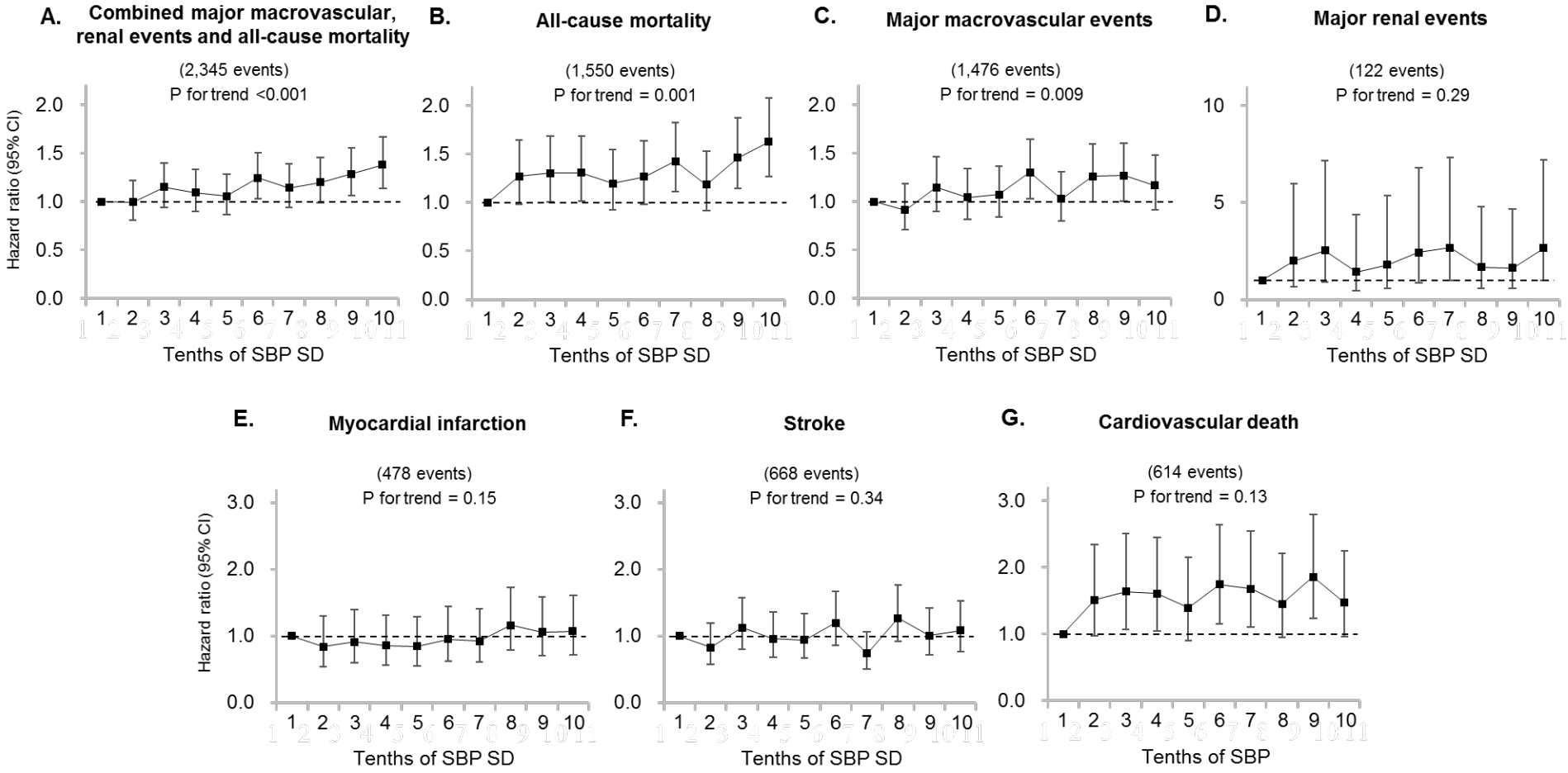

Figure S11: Sensitivity analysis; Hazard ratios and 95% confidence intervals (CIs) for outcomes according to tenths of standard deviation (SD) of systolic blood pressure (SBP) after addition of estimated glomerular filtration rate as covariates.

SBP SD was categorized according to the tenths, same as in Figure 2. Hazard ratios were adjusted for the same covariates as in Figure 2. Hazard ratios were adjusted for the same covariates as in Figure 2 plus estimated glomerular filtration rate.

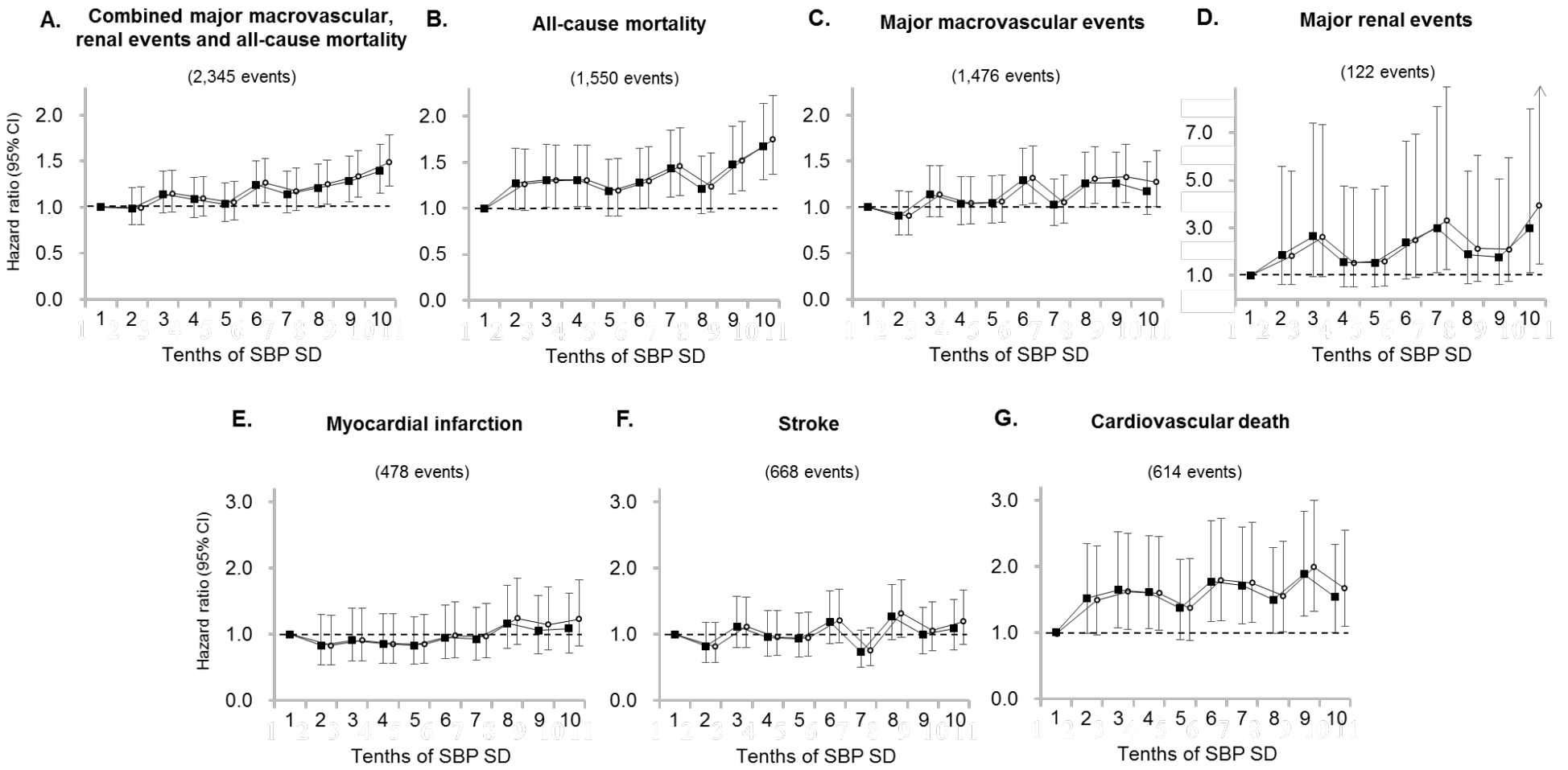

Figure S12: Hazard ratios and 95% confidence intervals (CIs) for outcomes according to tenths of standard deviation (SD) of systolic blood pressure (SBP) with and without adjustment for mean SBP.

SBP SD was categorized according to the tenths, same as in Figure 2. White circles indicate model 1. Black squares indicate model 2. Model 1 was adjusted for age, sex, region of residence, duration of diabetes mellitus, current smoking, current alcohol drinking, heart rate, total cholesterol, log of triglycerides, body mass index, use of b-blockers, use of calcium-channel blockers, randomized blood pressure-lowering intervention, and randomized glucose control intervention (the same covariates as model 1 in Table 2). Model 2 was additionally adjusted for mean SBP during the measurement period (the same covariates as model 2 in Table 2).

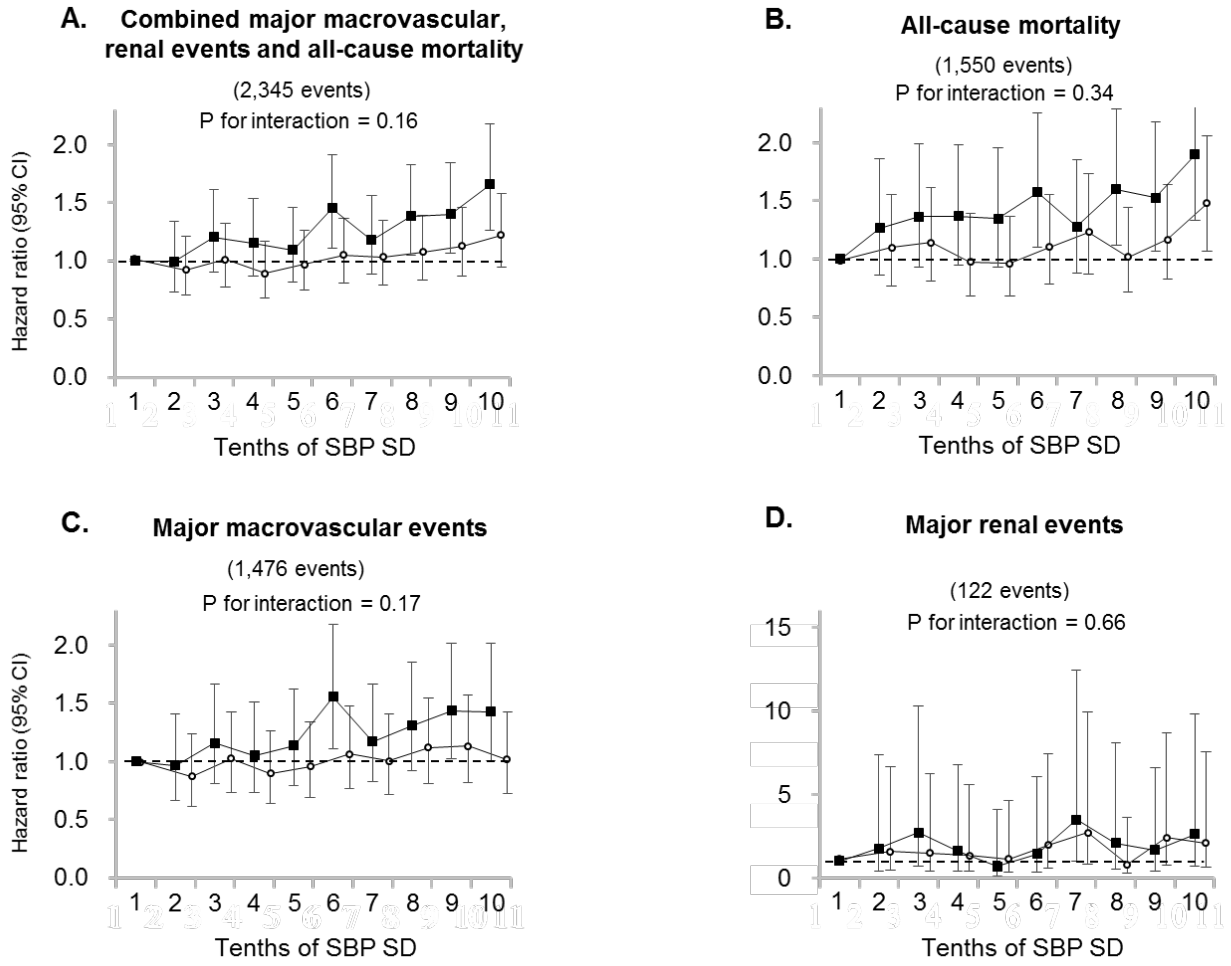

Figure S13: Subgroup analyses; Hazard ratios and 95% confidence intervals (CIs) for outcomes according to tenths of standard deviation (SD) of systolic blood pressure (SBP) stratified by randomized blood pressure-lowering intervention.

SBP SD was categorized according to the tenths. The ranges of SBP SD were 0.49-5.06, 5.07-6.67, 6.68-7.81, 7.82-8.88, 8.89-9.98, 9.99-11.20, 11.21-12.57, 12.58-14.33, 14.35-;16.88, and 16.90-33.45 mmHg in the active group, 0.61-5.24, 5.25-6.92, 6.93-8.18, 8.19-9.39, 9.40-10.55, 10.56-11.80, 11.81-13.23, 13.24-15.29, 15.30-18.06, and 18.07-47.20 mmHg in the placebo group. Black squares indicate the active group. White circles indicate the placebo group. Hazard ratios were adjusted for the same covariates as in Figure 2.

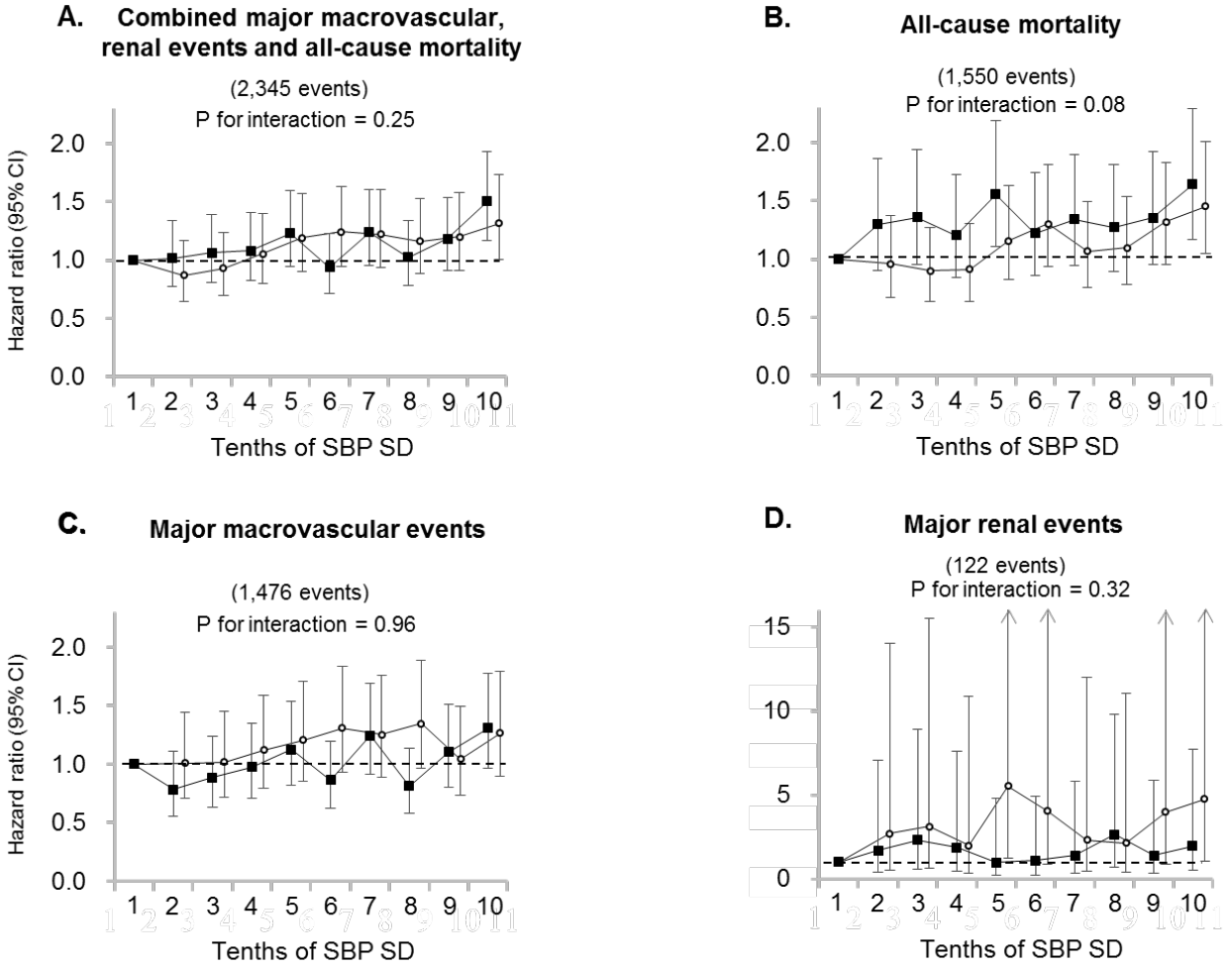

Figure S14: Subgroup analyses; Hazard ratios and 95% confidence intervals (CIs) for outcomes according to tenths of standard deviation (SD) of systolic blood pressure (SBP) stratified by mean SBP levels during measurement period.

SBP SD was categorized according to the tenths. The ranges of SBP SD were 0.49-4.79, 4.80-6.21, 6.22-7.31, 7.32-8.29, 8.30-9.28, 9.29-10.35, 10.36-11.58, 11.59-13.07, 13.08-15.50, and 15.51-30.53 mmHg in the patients with mean SBP <140 mmHg, 1.16-6.17, 6.18-7.93, 7.94-9.35, 9.36-10.65, 10.66-11.87, 11.88-13.30, 13.31-14.93, 14.97-16.85, 16.86-19.97, and 19.98-47.20 mmHg in the patients with mean SBP ≥140 mmHg. Black squares indicate the patients with mean SBP <140 mmHg. White circles indicate the patients with mean SBP ≥140 mmHg. Hazard ratios were adjusted for the same covariates as in Figure 2.

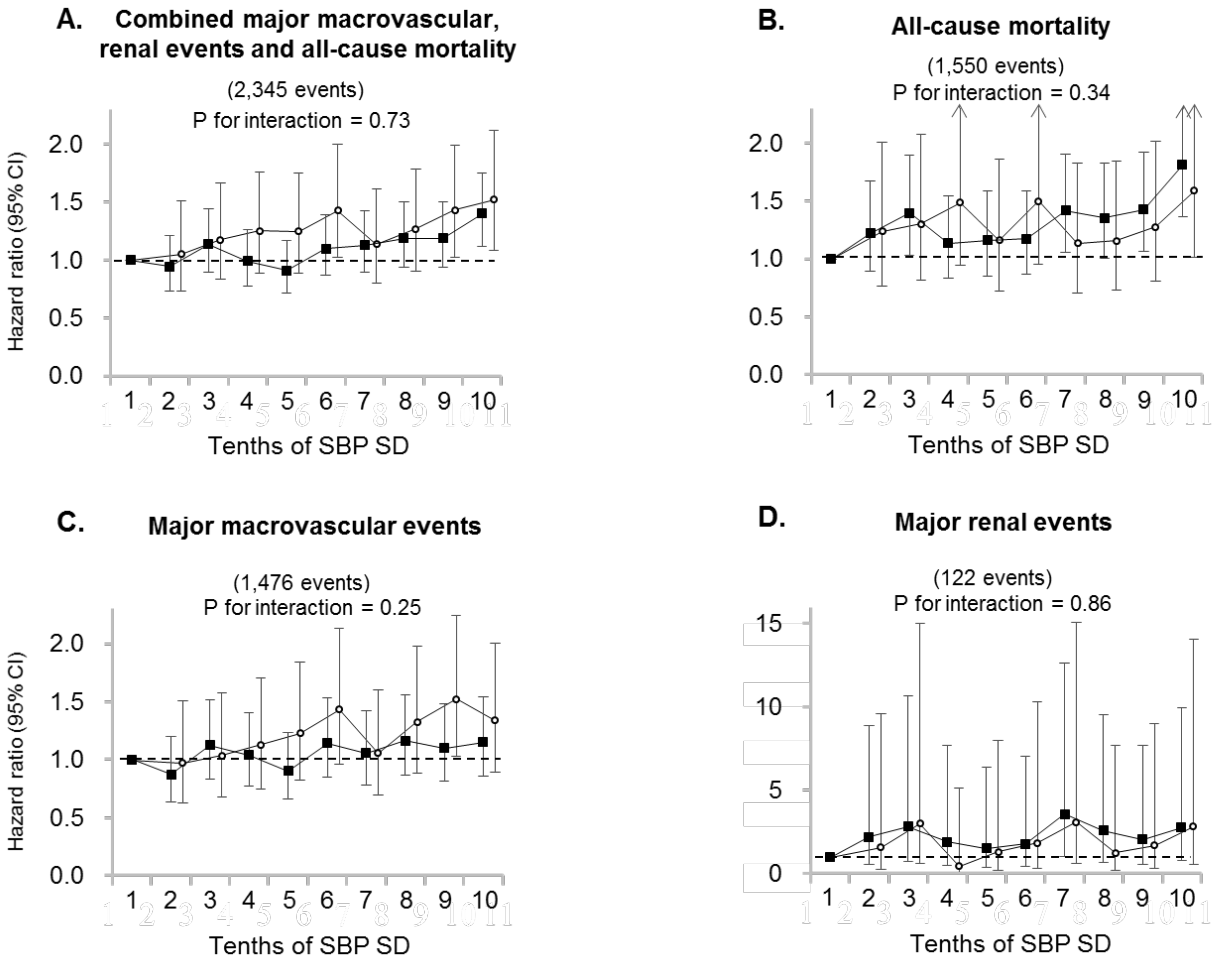

Figure S15: Subgroup analyses; Hazard ratios and 95% confidence intervals (CIs) for outcomes according to tenths of standard deviation (SD) of systolic blood pressure (SBP) stratified by sex.

SBP SD was categorized according to the tenths. The ranges of SBP SD were 0.66-5.20, 5.21-6.69, 6.70-7.82, 7.83-8.98, 8.99-10.03, 10.04-11.22, 11.23-12.59, 12.60-14.41, 14.42-17.04, and 17.05-34.43 mmHg in the male patients, 0.49-5.07, 5.08-6.95, 6.96-8.22, 8.23-9.36, 9.37-10.62, 10.63-11.88, 11.89-13.27, 13.28-15.24, 15.25-18.27, and 18.29-47.20 mmHg in the female patients. Black squares indicate the male patients. White circles indicate the female patients. Hazard ratios were adjusted for the same covariates as in Figure 2.