

Effects of blood pressure lowering on clinical outcomes according to baseline blood pressure and cardiovascular risk in patients with type 2 diabetes: The ADVANCE trial

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Abstract:

Background: The optimal blood pressure (BP) goal in patients with diabetes remains controversial. We examined whether benefits and risks of intensified antihypertensive therapy in diabetes are influenced by either baseline BP or cardiovascular disease (CVD) risk.

Methods: We studied 10,948 people with diabetes, at moderate to high risk, in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial. Cox models were used to determine if baseline blood pressure category or CVD risk modified the outcomes of combination perindopril-indapamide treatment, compared with placebo.

Results: During 4.3-years follow-up, treatment with perindopril-indapamide versus placebo reduced mortality and major vascular (macrovascular or microvascular) events. There was no evidence of differences in these effects, regardless of baseline systolic BP (evaluated down to <120 mm Hg) (p for heterogeneity=0.85), diastolic BP (evaluated down to <70 mm Hg) ($p=0.49$) or whether 10-year CVD risk was $\geq 20\%$ or $< 20\%$ ($p = 0.08$). The effects of randomized treatment on discontinuation of treatment due to cough or hypotension/dizziness were also statistically consistent across subgroups defined by baseline BP and CVD risk (all $p \geq 0.08$).

Conclusion: Adults with diabetes appear to benefit from more intensive BP treatment even at levels of BP and CVD risk that some guidelines do not currently recommend for intervention.

Clinical Trial Registration: <http://www.clinicaltrials.gov>. Unique identifier: NCT00751972.

Key words: blood pressure; diabetes mellitus; cardiovascular disease; risk; mortality

Abbreviations: DBP = diastolic blood pressure; SBP = systolic blood pressure; atherosclerotic cardiovascular disease = ASCVD; Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE);

Introduction

The blood pressure (BP) threshold for initiation of anti-hypertensive treatment among patients with diabetes remains controversial.¹⁻³ This uncertainty complicates the care of these patients, as the risk of future cardiovascular events associated with the presence of diabetes is considered equivalent to that of people who have previously had a myocardial infarction.⁴ In addition, the prevalence of hypertension in patients with diabetes is high.^{5,6}

In adults without diabetes, there is persuasive recent trial evidence to support BP targets that are lower than were previously advised. In the Systolic Blood Pressure Intervention Trial (SPRINT), which included individuals with a high risk of cardiovascular disease (CVD), those randomized to a SBP target of < 120 mm Hg had a lower rate of death and cardiovascular events compared with their counterparts randomized to a SBP target of < 140 mm Hg.⁷ Also, in the Heart Outcomes Prevention Evaluation-3 (HOPE-3) study there was a reduction in cardiovascular events among patients with intermediate risk randomized to more intensive BP reduction who were in the upper third of the distribution of baseline SBP (> 143 mm Hg).⁸

However, none of those in SPRINT, and only 6% of HOPE-3 participants, had diabetes. Trial results in diabetes are inconsistent. The United Kingdom Prospective Diabetes Study (UKPDS) trial supports the use of intensive BP reduction in adults with diabetes, since the incidence of cardiovascular complications was 12% lower for each 10 mm Hg decrease in SBP, down to SBP levels < 120 mm Hg.⁹ It should be noted that this trial, initiated more than 25

years ago, was associated with initial and achieved blood pressures well above what would be considered clinically safe today (making it less applicable to contemporary practice considerations). By contrast, in the more contemporary Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, participants randomized to intensive therapy to a SBP target of < 120 mm Hg did not show a significant reduction in the primary combined cardiovascular outcome compared to those randomized to a SBP target of < 140 mm Hg.¹⁰

It is unclear why individuals with diabetes would not benefit from an SBP goal lower than < 140 mm Hg as much as do non-diabetics. Possible explanations for a lack of benefit of intensive therapy may be medication side-effects, such as renal impairment, adverse effects due to more hypotensive effects, such as falls, or electrolyte disturbances and reduction in diastolic BP, resulting in particular worsening coronary perfusion.¹¹ Guidelines do not have a consistent SBP and DBP goal for adults with diabetes and hypertension, although there is consensus that risk should be individualized. The American Diabetes Association (ADA) recommends a SBP/DBP goal of 140/90 mm Hg with an SBP/DBP goal of 130/80 mm Hg for high-risk individuals if it can be achieved without undue burden.³ In contrast, the 2017 American College of Cardiology/American Heart Association blood pressure guideline recommends a SBP/DBP goal of 130/80 mm Hg for all adults with diabetes.¹ Similarly, the European Society of Cardiology recently updated their guidelines to recommend a SBP target

< 130 mmHg for patients < 65 years of age and < 140 mmHg for > 65 years of age, and a DBP target of < 80 mmHg.²

Some additional support for intensive blood pressure treatment among diabetics came from The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial. In this randomized control trial, participants were randomized to intensive therapy with fixed combination of perindopril-indapamide or placebo with an average reduction of blood pressure of 5.6/2.2 mmHg in the active treatment arm. There was 9% reduction in major macrovascular or microvascular events and a 18% reduction in cardiovascular mortality with more intensive therapy.¹² Given these results and recent guidelines, we set out to examine whether the effects of intensification of BP therapy among people with diabetes in the ADVANCE trial,¹² differed by baseline SBP, DBP and/or estimated cardiovascular risk.

Methods

Details of the ADVANCE trial appear elsewhere.¹²⁻¹⁴ Briefly, the study was a multicenter, randomized controlled trial of 11,140 patients who had type 2 diabetes with a history of CVD or at least one other CVD risk factor. The study had a 2-by-2 factorial design with participants randomized to intensive or standard glucose control and to fixed-dose perindopril 4mg with indapamide 1.25mg or placebo. In this study, we focus on BP management and, therefore,

randomization to perindopril-indapamide versus placebo. All participants provided written informed consent. The ADVANCE trial data, analytic methods and study materials are not available to other researchers.

Participants' details were obtained at baseline, including demographics, medical history and medications. Weight was measured in kilograms and height in meters. Body mass index was calculated as weight in kilograms divided by height in meters squared. After the individual rested for 5 minutes, systolic and diastolic BP were taken as the mean of two attended measurements made while seated using an automated sphygmomanometer (Omron HEM-705CP, Tokyo, Japan). Current smoking, current alcohol drinking, fasting lipids, hemoglobin A1c, and serum creatinine (and estimated glomerular filtration rate using the modified diet in renal disease [MDRD] equation) were also recorded.

Outcomes

The primary outcome in ADVANCE was the composite of major macrovascular and microvascular events (hereafter referred to as a major vascular event). Major macrovascular events were cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. Major microvascular events were new or worsening nephropathy (defined as macroalbuminuria, doubling of serum creatinine to $\geq 200 \mu\text{mol/L}$, need for renal replacement therapy, or death due to renal disease), or retinopathy (defined as proliferative retinopathy, macular edema,

diabetes-related blindness, or retinal photocoagulation therapy). In the current study, we considered this and all-cause mortality as twin primary efficacy outcomes. Secondary outcomes were the individual components of the major vascular disease endpoints. These outcomes were adjudicated by an independent End Point Adjudication Committee and coded using the 10th revision of the *International Classification of Diseases*. We also analyzed serious adverse events, leading to discontinuation of study treatment (active or placebo), as recorded at local clinics in study visits during the trial. Cough and hypotension or dizziness were key adverse events recorded in ADVANCE.

Statistical Analyses

Participants were divided into six categories using baseline SBP: < 120, 120 to 129, 130 to 139, 140 to 149, 150 to 159 and $\geq$ 160 mmHg. Results were also generated according to a binary split at 140 mmHg baseline SBP. Baseline DBP was similarly split into four groups, with thresholds at 70, 80 and 90 mmHg, and also using a binary split at 90 mm Hg. In secondary analyses of components of major vascular events, in which numbers in subgroups were relatively small, only the binary strata were analyzed.

The 10-year risk of atherosclerotic CVD (ASCVD) was estimated using the Pooled Cohort risk equations, as described by the American College of Cardiology/American Heart Association guidelines,^{15,16} and was analyzed in two groups, < 20% and $\geq$ 20%, chosen to allow

a sufficient number of events in the lower risk category, bearing in mind the relatively high-risk nature of the ADVANCE population. Roughly one third of ADVANCE participants had a history of CVD at baseline; these were included in the $\geq 20\%$ group. People for whom it was not possible to compute the ASCVD risk were excluded from all analyses.

We modeled the association between randomized treatment (perindopril plus indapamide versus placebo) and major vascular events and death, stratified by baseline SBP, DBP, ASCVD categories and combinations of SBP and DBP categories and of SBP and ASCVD categories, using Cox proportional hazard models. Tests for interaction between the stratification variable and treatment were performed by adding interaction terms to the relevant model with the main effects only. Adverse events leading to discontinuation were analyzed using risk ratios and interaction tests came from logistic regression models. *A priori*, no adjustment was made for covariates (as in the pre-specified analysis plan for ADVANCE) or for multiple statistical testing. Analyses were carried out using SAS Enterprise Guide, version 7.11, and Stata version 13.1. We considered a 2-sided $p < 0.05$ as statistically significant.

Results

After excluding 14 patients due to missing lipid results, and 178 patients aged ≥ 80 years, 10,948 participants were included in the final analyses. Participants with SBP ≥ 140 mm Hg were more likely to be female, have higher body mass index and urinary albumin:creatinine

ratio, and taking BP-lowering medication prior to randomization, whereas they were less likely to live in Asia and be currently smoking, compared to those with SBP <140 mm Hg, irrespective of whether ASCVD risk was <20% or ≥20%. Participants with ASCVD risk ≥20% were more likely to be male, be current smokers or be on BP-lowering treatment compared to participants with ASCVD risk < 20% (**Table 1**). The baseline characteristics of participants stratified by DBP groups are shown in **Supplemental Table 1** and baseline characteristics by randomized treatment, after first stratifying by baseline SBP and 10-year ASCVD risk, are shown in **Supplemental Table 2**.

Compared with the placebo arm, the mean on-treatment BP was lower in the intervention arm regardless of baseline 10-year ASCVD risk or baseline SBP category (**Figure 1**). In the SBP < 140 mmHg group, the on-treatment BP was < 130/80. Although no reduction in BP is noted in the run-in period in the SBP < 140 mmHg group, there is a difference in SBP between the placebo and intervention groups on follow-up after randomization in all groups.

Over a mean follow-up of 4.3 years, there were 837 deaths, and 966 major vascular events. The fixed dose combination of perindopril-indapamide reduced major vascular events (hazard ratio [HR] 0.91; 95% confidence interval [CI] 0.83 to 0.997) and all-cause mortality (0.86; 0.75 to 0.99) (**Figure 2**). There was no evidence of heterogeneity in the treatment effects across SBP subgroups for all-cause mortality (p=0.36) or major vascular events (p=0.83). Similar findings were present within subgroups defined by baseline DBP levels or combination

of SBP and DBP (**Figure 3, and Figure 4A**, p for heterogeneity ≥ 0.20). Overall findings were broadly the same for the individual components of major vascular events (**Supplemental Figures 1-3**, p for heterogeneity ≥ 0.19).

There was no evidence of heterogeneity in the effect of randomized treatment across subgroups defined by ASCVD risk (**Figure 4B** and **Supplemental Figure 4**), although the p value for heterogeneity for major vascular events was borderline at $p=0.08$. When results for the broad subgroups of baseline SBP (split at 140 mm Hg) or DBP (split at 90 mm Hg) levels were compared within levels of ASCVD risk ($<20\%$ or $\geq 20\%$), there was, again, no evidence of heterogeneity for the primary outcomes ($p \geq 0.17$) or for the secondary outcomes ($p \geq 0.08$) (**Supplemental Figures 5 and 6**).

Although adverse events leading to permanent discontinuation were more frequently present in the perindopril-indapamide group, compared with placebo, there was no statistically significant heterogeneity in the effects across subgroups defined by baseline SBP, DBP or 10-year ASCVD risk (**Figure 5, Supplemental Figures 7 and 8**; all p for heterogeneity ≥ 0.08).

Discussion

This study builds on previous reports of BP lowering treatment in patients with diabetes. First, we found that more intense antihypertensive treatment, using a fixed regimen consisting of perindopril-indapamide, reduced all-cause mortality and major vascular events in patients with

diabetes, irrespective of baseline BP or 10-year ASCVD risk. Regardless of the baseline SBP or ASCVD group, the intervention arm had lower on-treatment SBP compared with the placebo arm. For those with baseline SBP <140 mm Hg, most of the benefit for more intensive therapy was driven by the group with baseline SBP 130-139 mm Hg; a finding that supports current ACC/AHA guidelines.¹ There was also no evidence of heterogeneity in the effects of randomized treatment, comparing whether SBP was below 140 mm Hg or not, or DBP was below 90 mm Hg or not, amongst both those with <20% 10-year ASCVD risk and amongst those with higher ASCVD risk. Second, we found no evidence that cough and in particular hypotension/dizziness, both side effects common to antihypertensive therapy, were more likely to lead to permanent drug discontinuation in those with baseline SBP <140 mm Hg versus baseline SBP $\geq$ 140 mm Hg, compared to placebo.

Previous studies have demonstrated the relative benefit of SBP below < 140 mm Hg in the general population. In a meta-analysis of 1 million individuals in prospective observational studies, the risk of ASCVD death increased above SBP > 115 mm Hg in untreated adults.¹⁷ Another meta-analysis of randomized control trials reported that, compared to participants who had a baseline SBP < 130, those with baseline SBP $\geq$ 130 mm Hg were at increased stroke and all-cause mortality risk.¹⁸ These findings were corroborated by the SPRINT trial findings among adults without diabetes but with a mean 10-year ASCVD risk of 20.1%. Participants were randomized to intensive therapy with a target SBP < 120 mmHg or standard therapy with

target < 140 mmHg. The intensive therapy arm had a lower rate of the primary composite outcome of myocardial infarction, other acute coronary syndromes, stroke, heart failure or CVD death.⁷ Although individuals with diabetes were not included in SPRINT, post-hoc analyses of participants with prediabetes or normoglycemia also demonstrated a significant reduction in the primary outcome with intensive therapy in both groups.¹⁹

Nonetheless, arguments against an intensive BP goal in patients with diabetes are somewhat supported by the ACCORD trial. In this trial, there was no reduction in the primary combined outcome of nonfatal myocardial infarction, stroke or cardiovascular death with intensive SBP therapy to target < 120 mmHg compared with standard therapy target of < 140 mmHg among diabetics.¹⁰ However, ACCORD does not rule out benefit to a target < 130 mmHg and, indeed, showed a trend towards benefit of intensive BP control to < 120 mmHg with a significant reduction in stroke and a point estimate for the primary composite outcome that was in favor of intensive therapy. In addition, the actual number of events was significantly lower than expected reducing the power of the ACCORD analysis.

Further support for a potential benefit for lower BP targets, irrespective of diabetes status, comes from an analysis combining results from both ACCORD and SPRINT, which showed that intensive BP management was associated with a reduction in stroke, heart failure and each study's primary outcome, without evidence of heterogeneity in effect across both studies.²⁰ In addition, a recent post-hoc analysis from ACCORD suggests that the benefit of intensive BP

control may potentially be related to an interaction with the intensity of glycemic control in the factorial design of the study, with patients randomized to standard glycemic treatment (HbA1c goal of 7% to 7.9%) demonstrating statistically significant benefit from more aggressive BP treatment, whereas those receiving more intensive glycemic control did not.^{21,22}

In terms of baseline CVD risk, the benefits of intensive BP treatment seen in ADVANCE are consistent with the SPRINT study results, which also included moderate-to-high risk adults. This finding contrasts with the lower risk patient population in the HOPE-3 study where no reduction in CVD events was found with more intense antihypertensive treatment in the overall sample.^{7,8} In addition, our results are also supported by a meta-analysis demonstrating that lowering of SBP with intensive BP treatment regimens is associated with a greater reduction in the 5-year risk of cardiovascular events in groups stratified as having a high predicted ASCVD risk, compared to lower ASCVD risk groups.²³ Further, this finding matches well with a recent subgroup analysis of diabetic patients in ACCORD who had elevated 10-year ASCVD risk (mean ~ 15%) and were shown to have a reduction in the composite primary outcome of cardiovascular death, non-fatal myocardial infarction, nonfatal stroke, revascularization and heart failure with more intensive BP lowering.²⁴ The current study also adds to the findings of a meta-analyses of randomized trials showing a reduction in ASCVD events of intensive BP lowering treatment in patients with diabetes and a mean SBP of <140 mm Hg.^{25,26} Furthermore, a recent study indicates that over 95% of US adults with

diabetes and SBP/DBP $\geq 130/80$ mm Hg have a 10-year ASCVD risk $\geq 10\%$ or a history of CVD.²⁷ Taken together with the results from the current study, this suggests that most adults with type 2 diabetes taking antihypertensive medication would benefit from a BP goal of $< 130/80$ mmHg, thus raising the possibility that the current ADA guidelines³ may be too conservative.

There was no evidence to suggest that the effects of BP-lowering treatment on the risk of adverse side effects leading to discontinuation would differ according to baseline BP or ASCVD risk. Importantly, such adverse events were negligible, compared to clinical events, in the intervention group, although the disadvantage in statistical terms is that the small number of adverse events recorded increases the uncertainty in these analyses. Furthermore, we did not evaluate all possible adverse events, such as electrolyte abnormalities and renal dysfunction.

The current analysis has several strengths. We included a large number of individuals with diabetes and high ASCVD risk, with a comprehensive ascertainment of demographics and clinical history, and regular follow-up for adverse events. In addition, participants were drawn from 215 sites from 20 countries. However, this study is a *post-hoc* analysis of a randomized control trial, which was not originally designed, or powered, to study the distinct baseline SBP groups included in this study. The most recent guidelines¹ recommend pharmacological therapy for 10-year ASCVD risk of $\geq 10\%$. However, due to the small number of individuals with a 10-year ASCVD risk of $< 10\%$ in our study, which would therefore result in inadequate

power for analysis, we chose a cut-off of 20%. This limits our ability to comment if there would be any difference with intensive BP therapy between individuals with $< 10\%$ and $\geq 10\%$ ASCVD risk. While we found no evidence for statistical heterogeneity and while the confidence intervals include evidence for benefit with more intensive BP therapy, our results also cannot rule out the possibility that persons at lower ASCVD risk may not benefit from more intensive treatment. Further, the ADVANCE trial used a specific antihypertensive regimen and the benefit seen may be drug specific and may not be more widely applicable to other antihypertensive medications. In addition, in our study population the majority of individuals were already on antihypertensives at baseline and therefore the active arm represents an intensification of BP treatment rather than initiation of treatment of BP.

In conclusion, in the current study, ADVANCE participants with diabetes benefitted from more intensive BP treatment regardless of baseline BP and of 10-year estimated ASCVD risk. This is consistent with recent guidelines recommending a lower BP target than the previous target of 140/90 mmHg.^{1,2} Nonetheless, a future randomized control trial which evaluates whether adults with diabetes benefit from intensive therapy to a SBP goal < 130 mm Hg, compared to SBP < 140 mm Hg, is warranted. It also remains unclear how intensive glycemic control interacts with intensive BP management, especially with the incorporation of newer medications such as SGLT2 inhibitors.

Perspectives

There has been significant debate regarding the threshold for initiation of anti-hypertensive treatment among individuals with diabetes. The results of our study support intense blood pressure treatment not only among individuals without diabetes as supported by the SPRINT study, but also among individuals with diabetes. This is consistent with recent recommendations from the 2017 AHA/ACC blood pressure guidelines, which recommend a BP target of <130/80 mmHg.

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Conflicts of Interest

Dr. Muntner was a member of the writing group for the 2017 ADA position statement on diabetes and hypertension. Dr. Williams was the European Society of Cardiology Chairman of the ESC-ESH 2018 guidelines on arterial hypertension task force. Dr. Hamet received consulting fees from Servier. Dr. Harrap received lecture fees from Servier, Takeda, and Novartis. Dr. Chalmers received research grants from the National Health and Medical Research Council of Australia and from Servier for the ADVANCE trial and ADVANCE-ON post-trial follow-up, and honoraria for speaking about these studies at scientific meetings. Dr. Woodward reports consultancy fees from Amgen. Dr. Williams has received honoraria for lectures from Servier.

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Novelty and Significance

What is new?

- This study showed that more intense antihypertensive treatment reduced all-cause mortality and major vascular events in patients with diabetes, irrespective of 10-year estimated risk of atherosclerotic cardiovascular disease.
- We also demonstrated that more intense antihypertensive treatment reduced all-cause mortality in patients with diabetes, regardless of baseline systolic or diastolic blood pressure category.

What is relevant?

- While further randomized trials would be prudent to conduct for confirmation, this study results supports the 2017 American College of Cardiology/American Heart Association blood pressure guidelines, which recommends a target BP for diabetics of 130/90 mmHg.

Summary

- Individuals with diabetes benefit from intense blood pressure treatment regardless of baseline blood pressure or cardiovascular risk.

Figure Legends

Figure 1: Mean blood pressure levels during active run-in period and after randomization to perindopril-indapamide or placebo. The mean SBP and DBP in the **a)** 10-year ASCVD risk < 20%, **b)** 10-year ASCVD risk $\geq$ 20%, **c)** SBP < 140 mmHg, and **d)** SBP $\geq$ 140 mmHg groups.

Abbreviations: w, week; m, month; SBP, systolic blood pressure; DBP, diastolic blood pressure; ASCVD, atherosclerotic cardiovascular disease

Figure 2. Treatment effects of blood pressure lowering intervention in ADVANCE on the risk of major clinical outcomes according to baseline systolic blood pressure levels.

White diamonds indicate the hazard ratios for those with SBP <140 mmHg and for those with $\geq$ 140 mmHg. Black diamonds indicate the hazard ratios of overall for the current study.

Abbreviations: CI, confidence interval; SBP, systolic blood pressure.

Figure 3. Treatment effects of blood pressure lowering intervention in ADVANCE on the risk of major clinical outcomes according to baseline diastolic blood pressure levels.

White diamonds indicate the hazard ratios for those with DBP <90 mmHg and for those with $\geq$ 90 mmHg. Black diamonds indicate the hazard ratios of overall for the current study.

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure.

Figure 4. Treatment effects of blood pressure lowering intervention in ADVANCE on the risk of major clinical outcomes according to A) baseline systolic and diastolic blood pressure levels, and B) categories of 10-year risk for atherosclerotic cardiovascular disease and baseline systolic blood pressure levels. White diamonds in B) indicate the hazard ratios for those with ASCVD risk <20% and for those with ASCVD risk $\geq$ 20%. Black diamonds indicate the hazard ratios of overall for the current study. Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Figure 5. Adverse drug reactions leading to permanent discontinuation according to baseline systolic blood pressure levels. White diamonds indicate the risk ratios for those with SBP <140 mmHg and for those with $\geq$ 140 mmHg. Black diamonds indicate the risk ratios of overall for the current study. Abbreviations: CI, confidence interval; SBP, systolic blood pressure;

Table 1. Baseline characteristics of study participants according to categories of 10-year risk for incident atherosclerotic cardiovascular disease and baseline systolic blood pressure levels

Variable	ASCVD risk <20%		ASCVD risk $\geq$ 20%	
	SBP<140	SBP $\geq$ 140	SBP<140	SBP $\geq$ 140
	mmHg	mmHg	mmHg	mmHg
Number of participants	1509	824	3133	5482
Demographic factors				
Age (years)	62 (5)	60 (4)	66 (6)	67 (6)
Female (%)	72	84	28	36
Residence in Asia (%)	53	46	40	30
Medical and Lifestyle history				
Duration of diabetes mellitus (years)	8.0 (6.0)	8.1 (6.0)	7.6 (6.4)	8.0 (6.4)
History of macrovascular disease (%)	0	0	49	36
History of microvascular disease (%)	10	11	9	11
Current smoking (%)	11	4	20	16
Current alcohol drinking (%)	19	17	32	35
Risk factors				
Systolic BP (mmHg)	124 (10)	153 (12)	127 (10)	160 (17)
Diastolic BP (mmHg)	74 (8)	85 (10)	75 (9)	85 (10)
Heart rate (bpm)	76 (11)	77 (12)	73 (12)	74 (12)
Hemoglobin A _{1c} (%)	7.6 (1.7)	7.8 (1.7)	7.5 (1.5)	7.5 (1.5)
Total cholesterol (mmol/l)	5.3 (1.2)	5.5 (1.1)	5.0 (1.1)	5.2 (1.2)
HDL cholesterol (mmol/l)	1.4 (0.4)	1.4 (0.4)	1.2 (0.3)	1.2 (0.3)

Triglycerides (mmol/l) *	1.5 (1.1-2.1)	1.7 (1.2-2.5)	1.6 (1.2-2.3)	1.7 (1.2-2.4)
Body mass index (kg/m ²)	27.5 (5.4)	28.9 (6.0)	27.8 (5.1)	28.7 (5.0)
eGFR (ml/min/1.73m ²)	80 (17)	80 (17)	74 (17)	73 (17)
UACR (µg/mg) *	13 (7-30)	17 (8-44)	12 (6-32)	17 (8-46)
Randomized treatments				
Perindopril-indapamide	50	49	50	50
Intensive blood glucose control	49	50	50	50
Blood glucose-lowering treatments				
Oral hypoglycemic agents† (%)	93	90	91	91
Insulin (%)	2	2	1	1
BP-lowering treatments				
β-blocker (%)	13	19	26	27
Calcium-channel blocker (%)	19	28	29	36
Diuretics† (%)	15	22	22	26
Angiotensin-converting enzyme inhibitors† (%)	27	36	41	49
Angiotensin II receptor blockers (%)	4	4	5	6
Other antihypertensive agents (%)	8	15	11	14
Any BP-lowering agents† (%)	53	71	73	83

Variables presented as mean (standard deviation) or percentage.

* Median (interquartile interval).

† Randomized treatment with perindopril-indapamide was not included.

The ASCVD Pooled Cohort Risk Equation¹⁶ was used to estimate 10-year risk of ASCVD.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure, eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; UACR, urine albumin to creatinine ratio.

Figure 1.

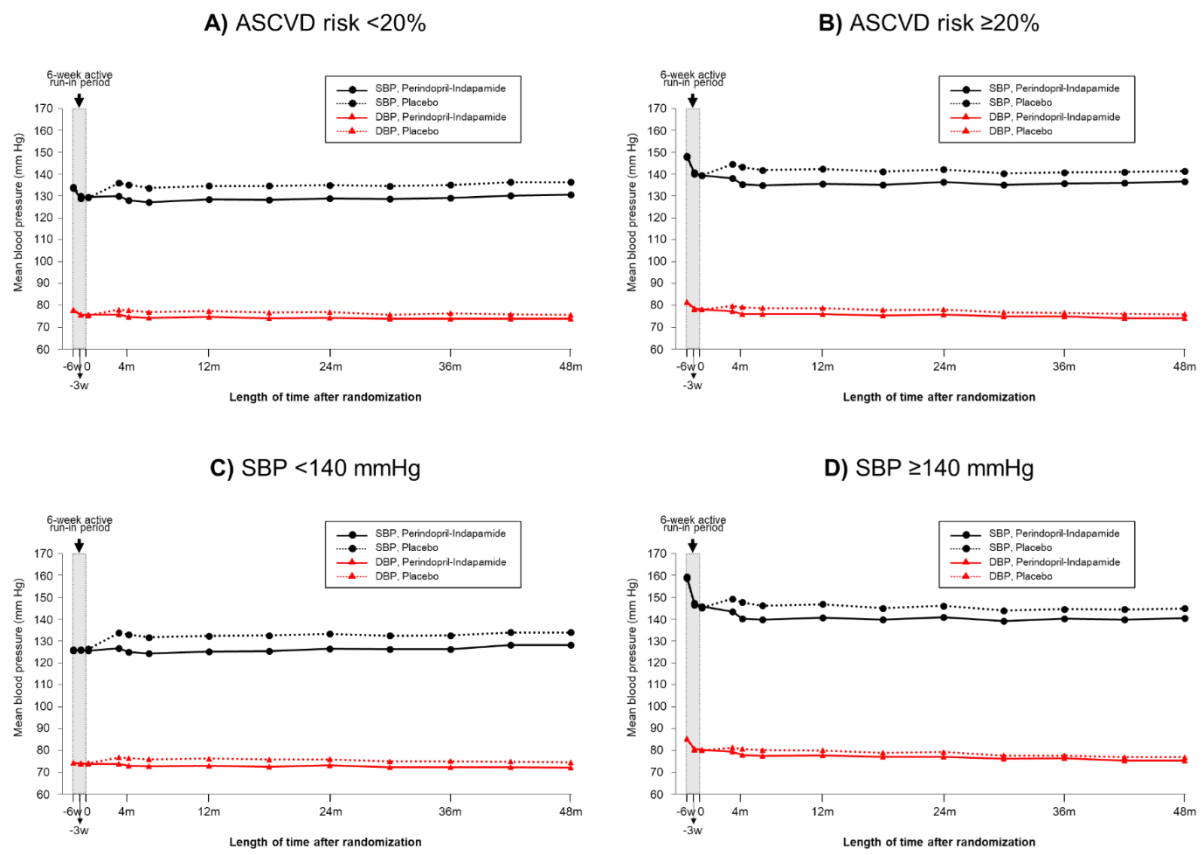


Figure 2.

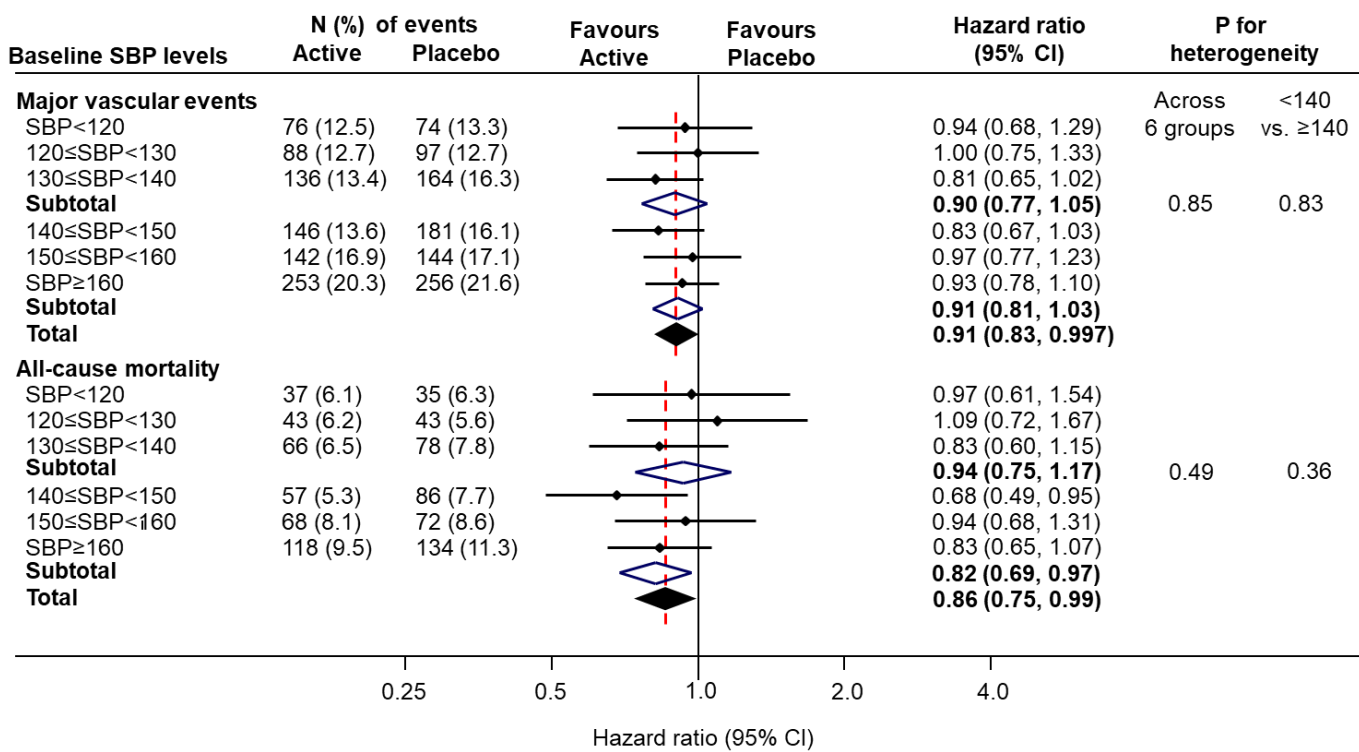


Figure 3.

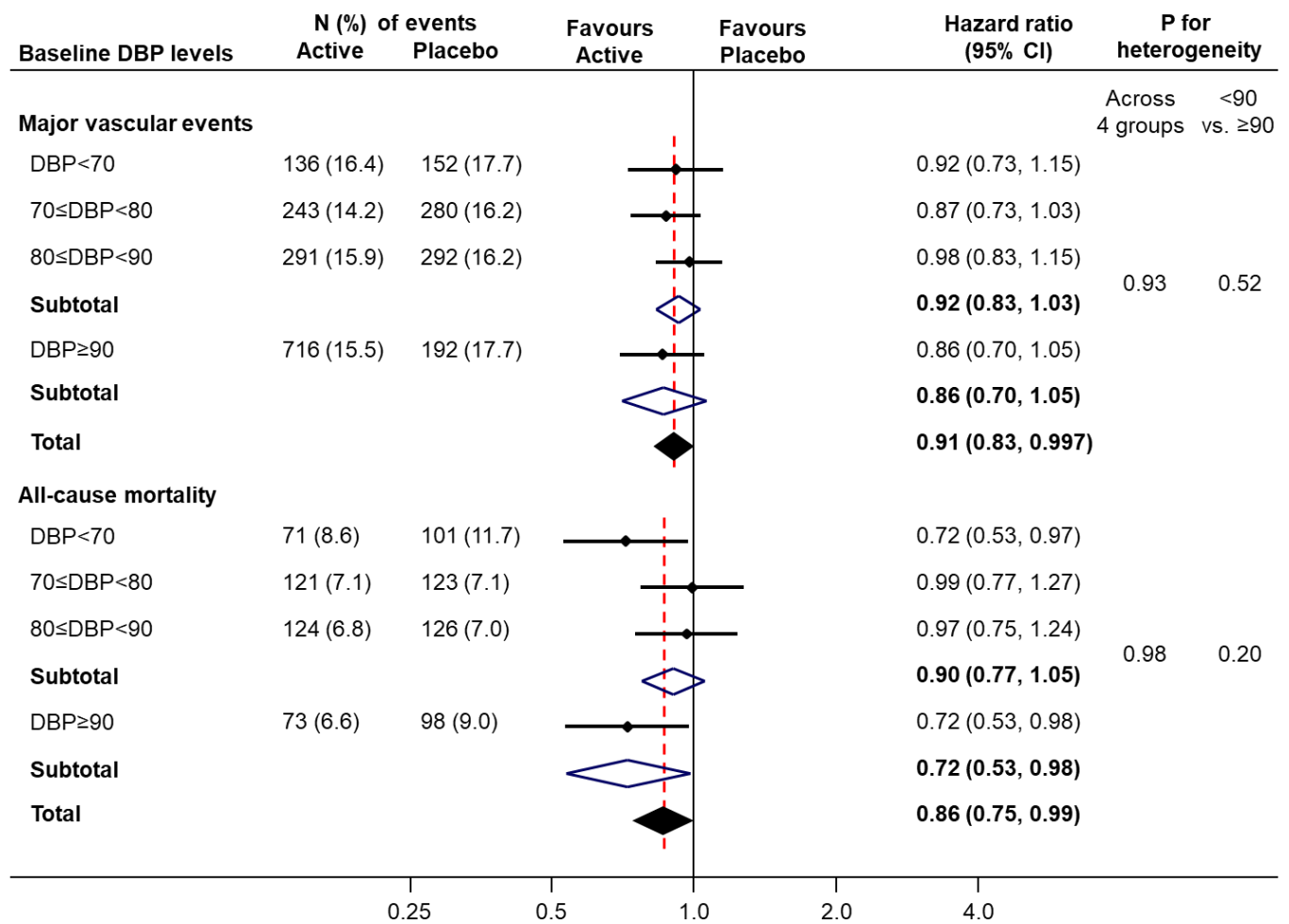


Figure 4.

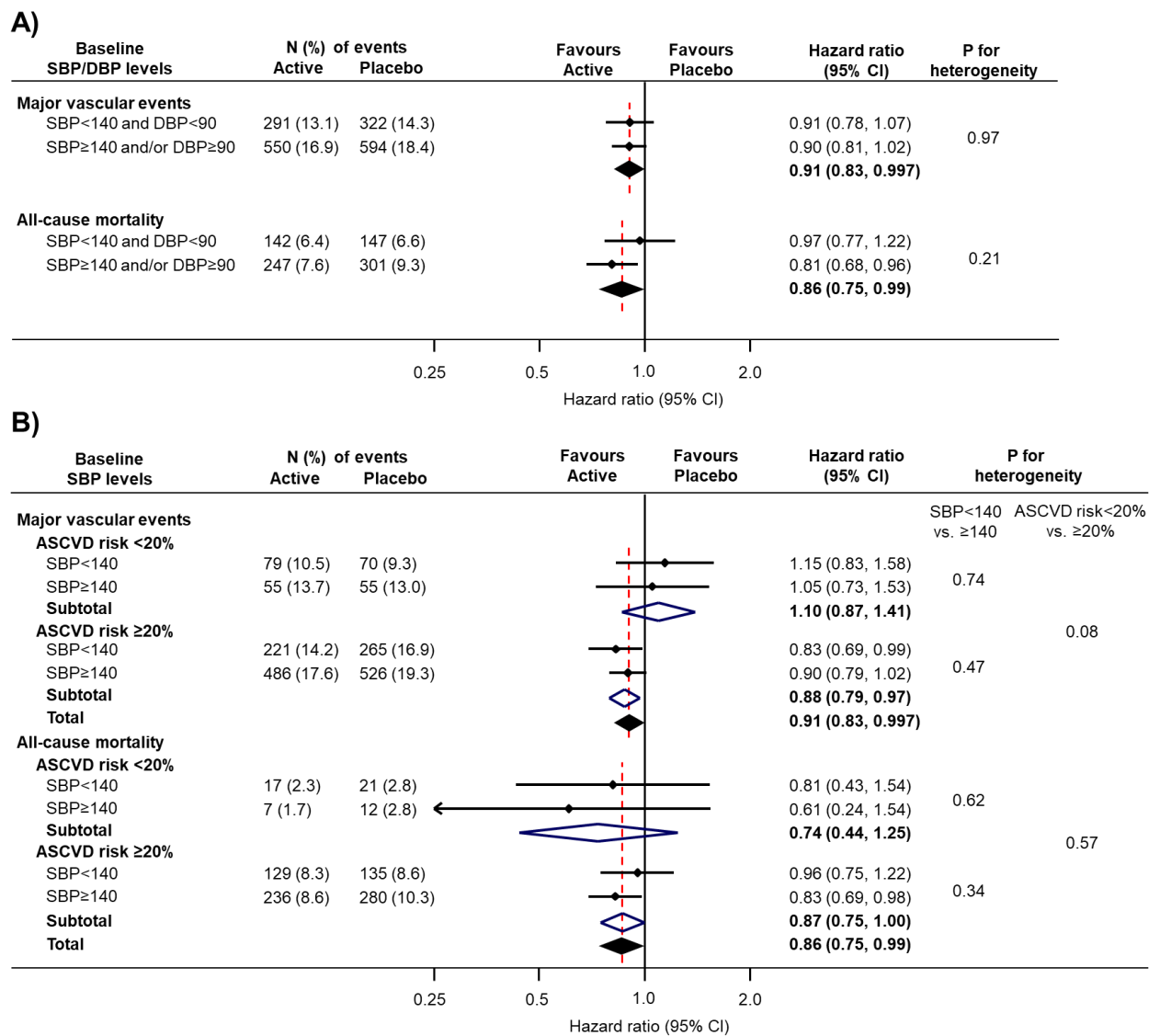


Figure 5.

