ESC European Society of Cardiology

European Heart Journal (2019) **0**, 1–12
doi:10.1093/eurheartj/ehz149

CLINICAL RESEARCH
Hypertension

Cardiovascular outcomes and achieved blood pressure in patients with and without diabetes at high cardiovascular risk

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Received 19 June 2018; revised 27 November 2018; editorial decision 7 February 2019; accepted 20 March 2019

Aims

Studies have shown a non-linear relationship between systolic blood pressure (SBP) and diastolic blood pressure (DBP) and outcomes, with increased risk observed at both low and high blood pressure (BP) levels. We hypothesized that the BP-risk association is different in individuals with and without diabetes at high cardiovascular risk.

Methods and results

We identified patients with ($N = 11\,487$) or without diabetes ($N = 19\,450$), from 30 937 patients, from 133 centres in 44 countries with a median follow-up of 56 months in the ONTARGET/TRANSCEND studies. Patients had a prior history of stroke, myocardial infarction (MI), peripheral artery disease, or were high-risk diabetics. Patients in ONTARGET had been randomized to ramipril 10 mg daily, telmisartan 80 mg daily, or the combination of both. Patients in TRANSCEND were ACE intolerant and randomized to telmisartan 80 mg daily or matching placebo. We analysed the association of mean achieved in-trial SBP and DBP with the composite outcome of cardiovascular death, MI, stroke and hospitalization for congestive heart failure (CHF), the components of the composite, and all-cause death. Data were analysed by Cox regression and restricted cubic splines, adjusting for risk markers including treatment allocation and accompanying cardiovascular treatments. In patients with diabetes, event rates were higher across the whole spectrum of SBP and DBP compared with those without diabetes ($P < 0.0001$ for the primary composite outcome, $P < 0.01$ for all other endpoints). Mean achieved in-trial SBP ≥160 mmHg was associated with increased risk for the primary outcome [diabetes/no diabetes: adjusted hazard ratio (HR) 2.31 (1.93–2.76)/1.66 (1.36–2.02) compared with non-diabetics with SBP 120 to <140 mmHg], with similar findings for all other endpoints in patients with diabetes, and for MI and stroke in patients without diabetes. In-trial SBP <120 mmHg was associated with increased risk for the combined outcome in patients with diabetes [HR 1.53 (1.27–1.85)], and for cardiovascular death and all-cause death in all patients. In-trial DBP ≥90 mmHg was associated with increased risk for the primary outcome [diabetes/no diabetes: HR 2.32 (1.91–2.82)/1.61 (1.35–1.93) compared with non-diabetics with DBP 70 to <80 mmHg], with similar findings for all other endpoints, but not for CHF hospitalizations in patients without diabetes. In-trial DBP <70 mmHg was associated with increased risk for the combined outcome in all patients [diabetes/no diabetes: HR 1.77 (1.51–2.06)/1.30 (1.16–1.46)], and also for all other endpoints except stroke.

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Conclusion High on treatment BP levels (≥160 or ≥90 mmHg) are associated with increased risk of cardiovascular outcomes and death. Also low levels (<120 or <70 mmHg) are associated with increased cardiovascular outcomes (except stroke) and death. Patients with diabetes have consistently higher risks over the whole BP range, indicating that achieving optimal BP goals is most impactful in this group. These data favour guidelines taking lower BP boundaries into consideration, in particular in diabetes.

Clinical trial registration http://clinicaltrials.gov.Unique identifier: NCT00153101.

Keywords Blood pressure • Hypertension • High cardiovascular risk • Diabetes • Stroke • Myocardial infarction

Introduction

Guidelines recommend systolic blood pressure (SBP) targets of <140 mmHg and <90 mmHg for diastolic blood pressure (DBP)[1–3] and the recent guidelines of the American Heart Association (AHA) suggest even lower goals,[4,5] which is in agreement with the European Society of Cardiology (ESC) guideline.[6] Association between SBP and risk varies for different outcomes, such as stroke and myocardial infarction (MI).[7,8] In turn, a reduction of SBP and DBP on treatment below 120 mmHg and below 70 mmHg, respectively, has been shown to be associated with increased risk for cardiovascular death, total death, and coronary death in patients with stable coronary artery disease[9] and patients with high cardiovascular risk.[10] Diabetes mellitus and hypertension are frequently co-existent and metabolic disease is more common in hypertensives than in non-hypertensives[11–13] enhancing the risk for subsequent microvascular and macrovascular complications.[13,14] If guidelines recommend stricter blood pressure (BP) levels,[4–6] the number of patients exhibiting BP levels below 120–130 mmHg SBP or below 70 mmHg DBP might increase in low BP classes associated with higher risk.[7–10] In patients with diabetes, J-curves reflecting an increase of risk at low BP levels have been demonstrated[15–17] and BP targets remain a matter of debate in this population.[18,19] The ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET)[20] and the Telmisartan Randomised AssessmeNt Study in ACE intolerant subjects with cardiovascular Disease (TRANSCEND)[21] randomized patients after MI, stroke, peripheral artery disease, or at high cardiovascular risk to receive ramipril, telmisartan, or both of these drugs. Of 31 546 patients randomized, 11 730 patients had diabetes and 19 806 patients exhibited no diabetes with no differences on outcomes between patients receiving ramipril, telmisartan, or both drugs after 56 months allowing a direct comparison of these two groups. Therefore, the objective of this secondary analysis was to assess the risk in patients with or without diabetes over the whole spectrum of achieved SBP and DBP in a broad spectrum of patients after stroke, MI with proven peripheral artery disease, and high cardiovascular risk.

Methods

In ONTARGET/TRANSCEND patients without symptomatic heart failure at entry but with a history of coronary artery disease or peripheral artery disease or transient ischaemic attack or stroke or diabetes mellitus complicated by end-organ damage were included. Since high-risk patients were randomized and the history of diabetes was a criterion for randomization for a subset of patients, this has the power to compare no diabetes with diabetes, the prevalence of which is higher than in the general population. Recruitment took place for the whole study programme in the same 733 centres in 40 countries with a follow-up of a median of 56 months. Both twin trials shared the same committees, inclusion and exclusion criteria (except ACE intolerance in TRANSCEND). A detailed description of design, treatment allocations, algorithms, and results of these trials were reported previously.[20,21] Inclusion and exclusion criteria are summarized in Supplementary material online, *Table S1*. The study protocols were approved by the local ethic committees of the participating centres. All patients gave written informed consent. In brief, in ONTARGET patients tolerant to angiotensin-converting enzyme (ACE)-inhibitors were randomly assigned to ramipril 10 mg daily, telmisartan 80 mg daily, or the combination of both after a run-in period in a double dummy design. In TRANSCEND, patients intolerant to ACE-inhibitors were assigned to either telmisartan 80 mg daily or matching placebo. Standard treatment was provided by the treating physicians according to best clinical practice and study medication was given on top. Investigators were specifically advised to adjust the existing BP medication according to their clinical practice. Visits were scheduled at 6 weeks and 6 months after randomization and every 6 months thereafter. Different treatment arms of ONTARGET showed similar results of the composite outcome of cardiovascular death, MI, stroke and hospitalization for heart failure, as well as the individual components of the composites (time to first event) on ramipril, telmisartan, or the combination of both drugs.

Procedures

The primary composite outcome and the individual components between the treatment groups allowed to pool data of all patients in order to perform an adequately powered comprehensive *post hoc* analysis of patients with or without diabetes according to mean achieved in-trial SBP and DBP. Attended BP was taken after resting for 3 min in a sitting position using an automated validated device (Omron model HEM 757, Omron Corporation, Kyoto, Japan) in the presence of the study nurse or investigator. Only patients with complete data were allowed to enter the analysis. The flow of the study, the treatment allocations and the exclusion of patients at every step of the analysis is depicted in *Figure 1*. A total of 31 546 patients were randomized into ONTARGET/TRANSCEND with 19 806 patients without and 11 730 patients with diabetes mellitus. Information on diabetes was lacking in 10 patients. Thirty-one patients did not have available baseline BP measurements. In 242 patients, there was no follow-up of BP before the first event. Of the remaining 31 263 patients, there were missing values of important covariates in 226 patients. Finally, 30 937 patients were analysed (19 450 without diabetes and 11 487 with diabetes). Patients were randomly assigned to the

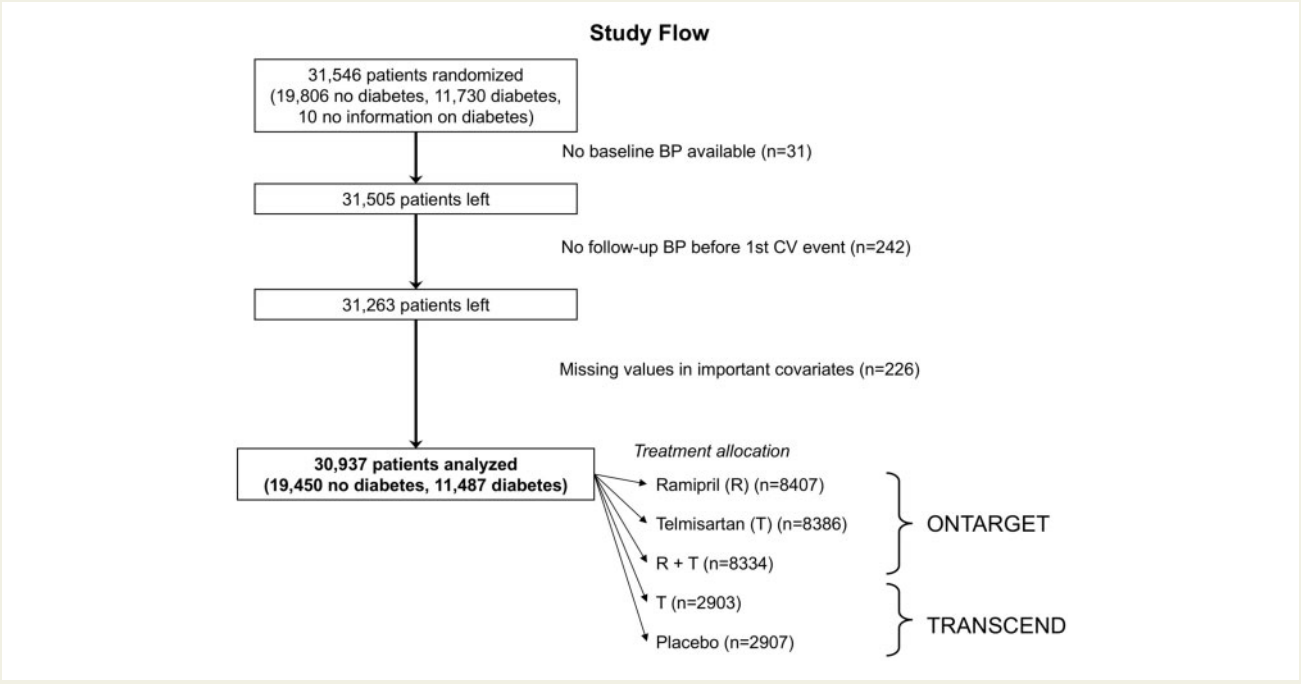


Figure 1 Diagram showing analysis flow of patient selection and treatment allocation of ONTARGET/TRANSCEND.

treatment groups ONTARGET/TRANSCEND (*Figure 1*). An average of 8.4 ± 2.5 BP measurements taken over 55.3 ± 10.2 months was available in patients without diabetes. In patients with diabetes an average of 8.2 ± 2.6 BP measurements taken over 54.3 ± 11.8 months was available. If diabetes was the only inclusion criterion that was met, evidence of end-organ damage such as retinopathy, left ventricular hypertrophy, macro- or micro-albuminuria had to be present. This group of high-risk diabetes consisted of 4133 patients.

Outcomes

The primary outcome was the composite of cardiovascular death, MI, stroke, and hospital admission for heart failure. The composite and the individual components of the composite as well as all-cause death were explored in this secondary analysis. All primary and secondary outcomes events were evaluated by a blinded central committee according to standard criteria.[20,21] Patients with non-fatal events were not censored for other outcomes; e.g. patients with an MI were still on risk for stroke.

Statistical analysis

All outcome events were combined for this analysis as outcomes in the different arms did not show significant differences in ONTARGET/TRANSCEND. Patients with diabetes or without diabetes were divided into subgroups according to their mean achieved in-trial seated clinic SBP and DBP. For SBP, the following cut-offs were chosen: <120 mmHg, 120 to <140 mmHg, 140 to <160 mmHg, and >160 mmHg. For DBP, the cut-offs were: <70 mmHg, 70 to <80 mmHg, 80 to <90 mmHg, and >90 mmHg. Baseline characteristics are displayed for baseline SBP and DBP (Supplementary material online, *Tables S2* and *S3*) as well as for mean achieved in-trial SBP and DBP (Supplementary material online, *Tables S4* and *S5*). Continuous data are presented as means ± standard deviation and categorical data as percentages. Groups were tested for differences using an analysis of variance (ANOVA) for continuous data and the χ^2 test for categorical data. Yearly events rates and cumulative incidence curves for the composite and the individual components of the outcomes as well as all-cause death were presented according to the diabetes and non-diabetes groups separated by the SBP and DBP criteria as described above. Cumulative incidence curves were adjusted for competing risk of death or non-cardiovascular death whatever appropriate. Relative differences between BP categories for patients with or without diabetes were analysed using Cox regression including the interaction between prevalence of diabetes and BP categories. The analysis was adjusted for all variables in Supplementary material online, *Tables S2–S5* and the competing risk of death was also considered. The results were presented as hazard ratios (HRs) with 95% confidence intervals (CIs) using SBP of 120 to <140 mmHg and DBP of 70 to <80 mmHg as references. The association between hazard and mean achieved BP as continuous variables was analysed non-parametrically using restricted cubic splines allowing for non-linear relationships.[22] Four knots (5th, 35th, 65th, and 95th percentile of in-trial SBP and DBP) were chosen for the analysis. Prevalence of diabetes and the interaction of diabetes with mean achieved SBP and DBP were included. Hazard ratios and 95% confidence bands depending on mean achieved SBP/DBP and prevalence of diabetes were presented, using non-diabetics with 140/80 mmHg as references (HR = 1). Also in this analysis the competing risk of death was taken into account. All analyses were done with the SAS version 9.4 (SAS Institute, NC, USA).

Results

From ONTARGET/TRANSCEND, 30 937 patients were stratified according to the presence (11 487) or absence of diabetes (19 450). Supplementary material online, *Table S2* shows the demographic and clinical characteristics of the ONTARGET/TRANSCEND patients grouped by SBP at baseline in patients with or without diabetes. Patients with a higher BP were older, had a higher body mass index

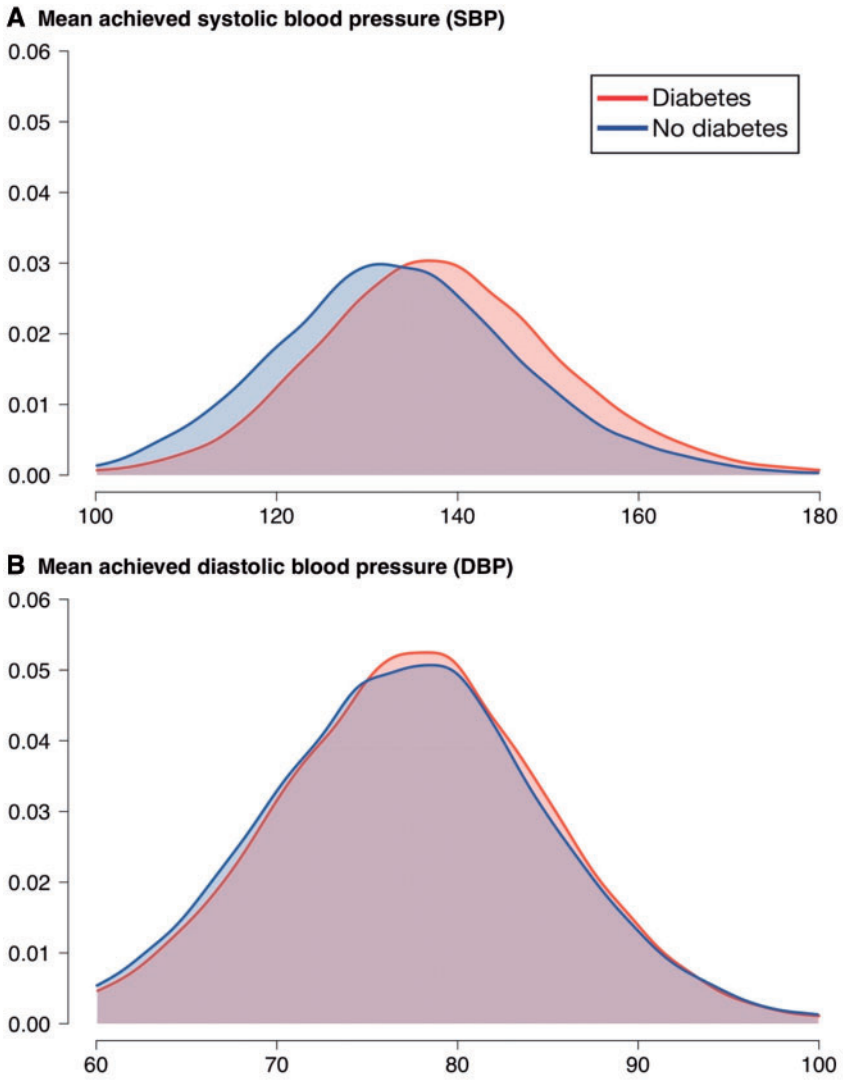


Figure 2 Distribution of mean achieved systolic blood pressure (*A*) and mean achieved diastolic blood pressure (*B*) in patients with diabetes (red) or no diabetes (blue).

and lower glomerular filtration rate, a higher incidence of pre-existing diabetes, and a history of stroke. Patients in the different treatment allocations were similarly distributed between the two groups. Supplementary material online, *Tables S3–S5* show that baseline DBP as well as achieved SBP and DBP followed a similar distribution. *Figure 2* shows the distribution of mean achieved in-trial SBP (*A*) and mean achieved in-trial DBP (*B*) in patients with diabetes (red) and non-diabetes (blue). Patients with diabetes had a slightly higher SBP achieved on treatment (diabetes: 137.9 ± 13.6 mmHg; no diabetes: 133.5 ± 13.8 mmHg, $P < 0.0001$), while the distribution of DBP in the two groups was superimposable.

Supplementary material online, *Figures S1* and *S2* show the cumulative incidence curves [adjusted for competing risk of (non-cardiovascular) death] for baseline SBP and DBP categories in patients with diabetes and no diabetes. The cumulative incidence for patients with diabetes was higher compared with those without diabetes for all outcomes. The lowest risk in diabetes and no diabetes was observed at baseline SBP between 120 and <140 mmHg and a baseline DBP of 70–80 mmHg in both groups. Mean achieved in-trial SBP showed more incident outcomes in diabetes than no diabetes (*Figure 3A–F*). Similar findings were observed with in-trial DBP (Supplementary material online, *Figure S3*).

Figure 4 summarizes the HRs of achieved SBP (left) and DBP (right) in diabetes (red) and no diabetes (blue) taking patients without diabetes and SBP 120 to <140 mmHg or DBP 70 to <80 mmHg as references. For the primary outcome, the main effects of diabetes, in-trial SBP and DBP were significant (all $P < 0.0001$), but there was no interaction between diabetes and SBP as well as DBP, meaning that the detrimental effects of diabetes and high or low BP were additive. Patients with an in-trial SBP ≥140 mmHg or DBP ≥80 mmHg had an increased hazard compared with the references [diabetes: HR 1.67 95% CI (1.48–1.89) at SBP 140 to <160 mmHg, 2.31 (1.93–2.76) at

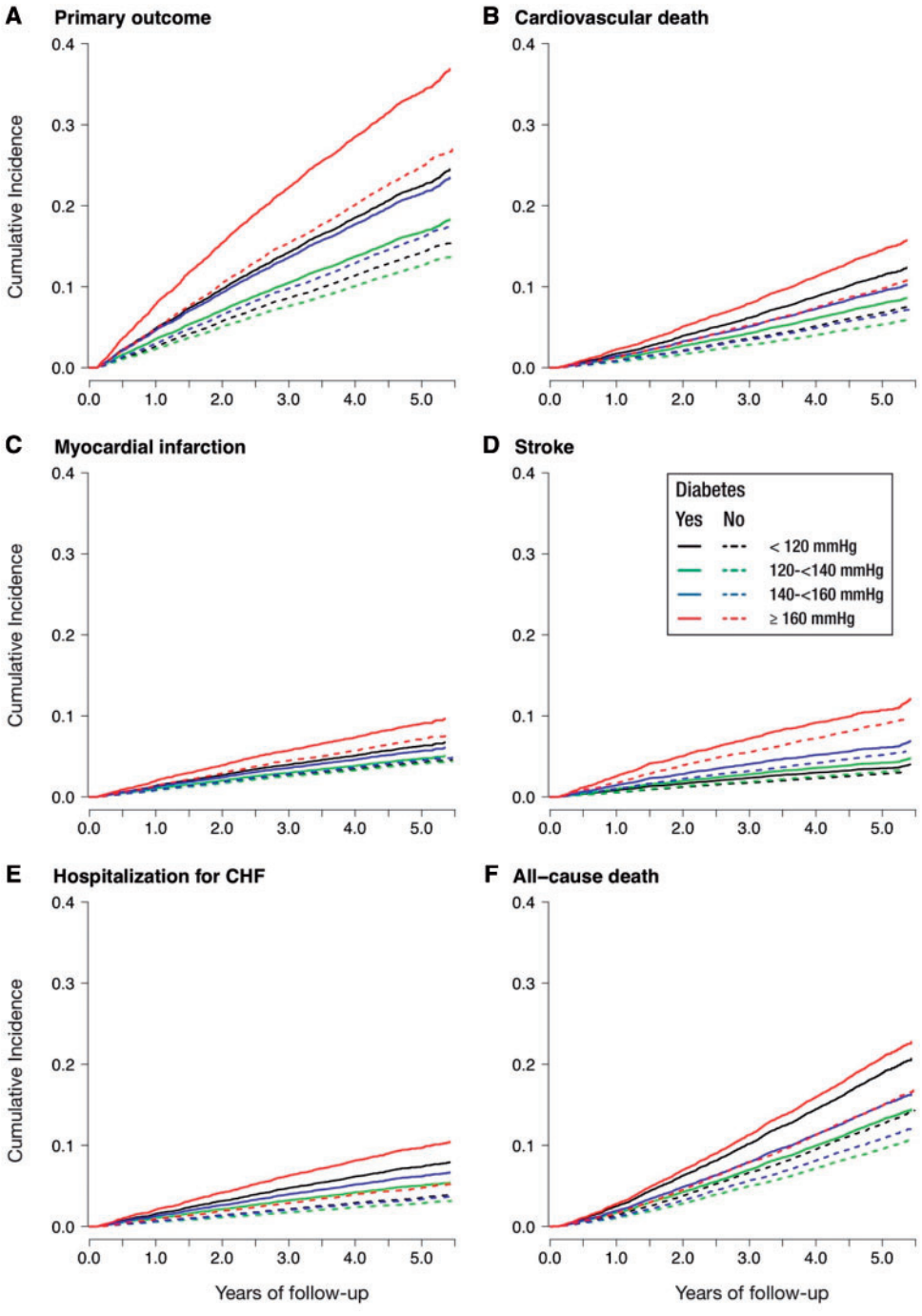


Figure 3 Cumulative incidence curves for the primary outcome (*A*), cardiovascular death (*B*), myocardial infarction (*C*), stroke (*D*), hospitalization for congestive heart failure (*E*), and all-cause death (*F*) according to mean achieved systolic blood pressure groups (<120 mmHg, 120 to <140 mmHg, 140 to <160 mmHg, and ≥160 mmHg). The primary outcome includes cardiovascular death, myocardial infarction, stroke, and hospitalization for heart failure. Solid lines depict diabetes and dotted lines no diabetes.

SBP ≥160 mmHg, 1.61 (1.40–1.85) at DBP 80 to <90 mmHg, 2.32 (1.91–2.82) at DBP ≥90 mmHg; no diabetes: 1.14 (1.03–1.26) at SBP 140 to <160 mmHg, 1.66 (1.36–2.02) at SBP ≥160 mmHg, 1.16 (1.05–1.28) at DBP 80 to <90 mmHg, 1.61 (1.35–1.93) at DBP ≥90 mmHg]. Also patients with diabetes and in-trial SBP <120 mmHg and all patients with in-trial DBP <70 mmHg had increased hazards [diabetes: 1.53 (1.27–1.85) at SBP <120 mmHg, 1.77 (1.52–2.06) at DBP <70 mmHg; no diabetes: 1.30 (1.16–1.46) at DBP <70 mmHg].

Also for the other outcomes significant effects of diabetes and SBP as well as DBP categories were detected, without any interaction

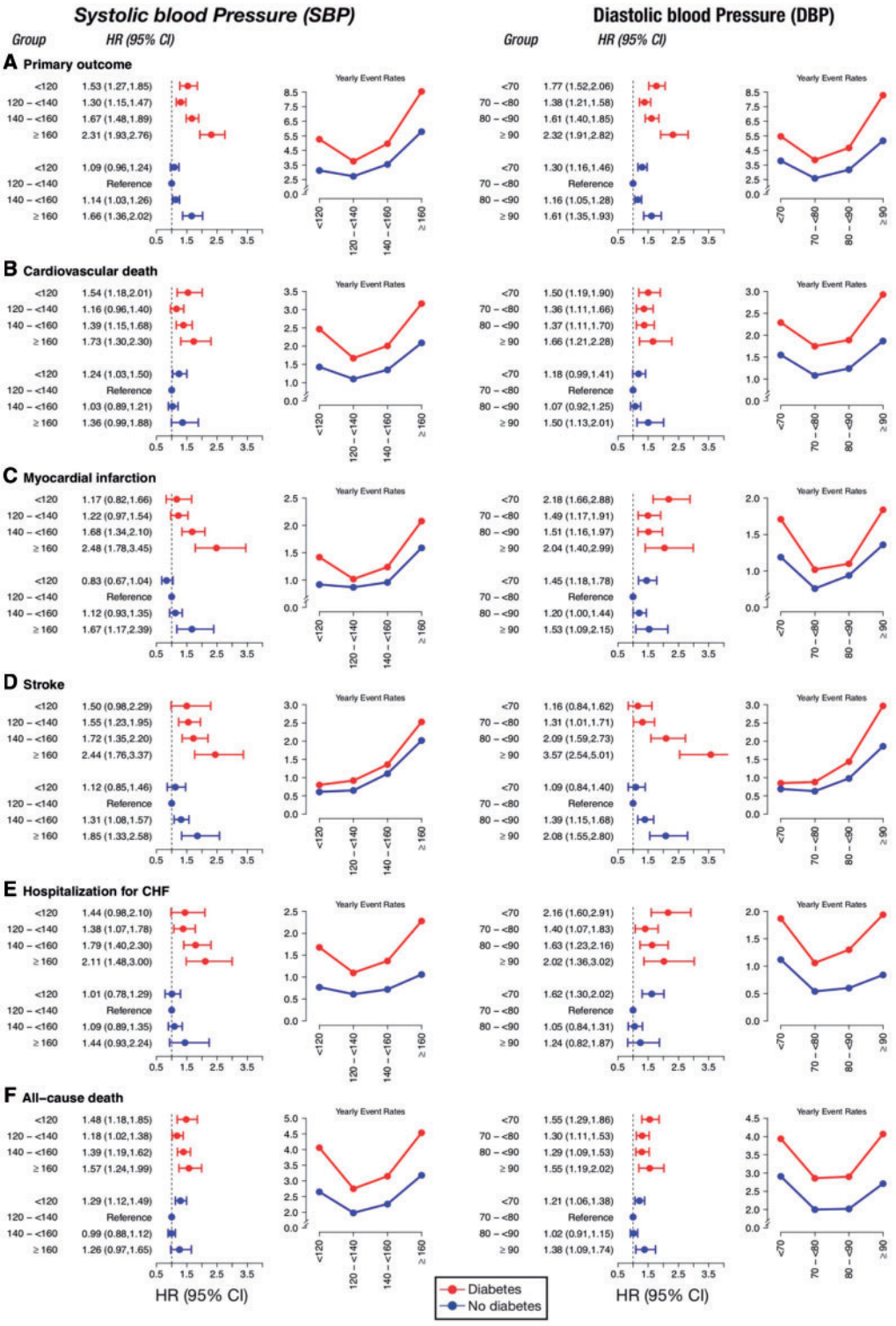


Figure 4 Hazard ratios (left) and yearly event rates (right) for mean achieved systolic (SBP) (left) and mean achieved diastolic (DBP) (right) blood pressure in diabetes (red, above) and no diabetes (blue, below) for the primary outcome (*A*), cardiovascular death (*B*), myocardial infarction (*C*), stroke (*D*), hospitalization for congestive heart failure (*E*), and all-cause death (*F*). The primary outcome includes cardiovascular death, myocardial infarction, stroke, and hospitalization for heart failure. The hazard ratios (Cox regression) were adjusted for the variables diastolic blood pressure (for systolic blood pressure), systolic blood pressure (for achieved diastolic blood pressure), heart rate, age, sex, body mass index, renal function, geographical region, physical activity, formal education, alcohol consumption, tobacco use, history of hypertension, myocardial infarction, stroke/transient ischaemic attack, heart rhythm, co-medications, study and study medications.

between diabetes status and in-trial BP category. For all outcomes patients with diabetes and in-trial SBP 140 to <160 mmHg had increased hazards. For patients without diabetes an increase with in-trial SBP 140 to <160 mmHg was only seen for stroke. Achieved SBP ≥160 mmHg was associated with increased hazards for all outcomes in patients with diabetes, and for MI and stroke in patients without diabetes. A mean achieved SBP <120 mmHg was associated with an increased risk of cardiovascular death and all-cause death in all patients. When SBP categories were compared solely within diabetic patients, it was seen that in-trial SBP ≥140 mmHg was associated with increased risk for all outcomes and SBP <120 mmHg for cardiovascular death and all-cause death, when compared with an SBP 120 to <140 mmHg.

Achieved DBP ≥80 mmHg was associated with higher incidents of all outcomes in patients with diabetes, and for stroke and MI in patients without diabetes. In patients without diabetes the risk of death (cardiovascular and all-cause) was also increased when the achieved DBP was ≥90 mmHg. A low achieved DBP (<70 mmHg) was associated with an increase of MI, congestive heart failure (CHF) hospitalizations, and all-cause death in all patients, and for cardiovascular death in patients with diabetes. When DBP categories were compared solely within diabetic patients, it was seen that in-trial DBP ≥80 mmHg was associated with increased risk for stroke, and DBP <70 mmHg for MI, CHF hospitalizations, and all-cause death, when compared with DBP 70 to <80 mmHg.

At low SBP (<120 mmHg) (Supplementary material online, *Table S4*) and low (<70 mmHg) DBP (Supplementary material online, *Table S5*) more patients were on double renin-angiotensin system (RAS) blockade but less accompanying antihypertensive drugs with no differences between patients with or without diabetes.

In order to account for non-linear relationships, mean achieved SBP and mean achieved DBP was analysed as continuous variable and related to primary composite outcome and its components as well as all-cause death using restricted cubic splines. Hazard ratios and 95% confidence bands depending on mean achieved in-trial SBP (*Figure 5*) or mean achieved in-trial DBP (*Figure 6*) are presented using SBP of 140 mmHg or DBP of 80 mmHg in patients without diabetes as reference. Over the whole spectrum of SBP and DBP, hazards were increased in patients with diabetes compared with those without diabetes. Most of the curves were J- or U-shaped with minima in the area of SBP values between 120 and 140 mmHg and DBP values between 70 and 80 mmHg. This confirms the analysis results when BP categories are used, and highlights the clearly increased cardiovascular risk at SBP values above 150 mmHg or DBP values above 90 mmHg, but also the increased risk at low SBP or DBP values for most of the endpoints.

To add further plausibility, we separated the patients with diabetes into those without further complications ($N = 6588$) and those with retinopathy, cardiac hypertrophy, micro- or macro-albuminuria ($N = 4899$). In the latter group with high-risk diabetes, the yearly event rates were further increased with no different association to high or low SBP or DBP (Supplementary material online, *Figure S3*). Since new guidelines recommend a SBP target of 120 to <130 mmHg in high-risk patients,[4,6] we separated the 120 to <140 mmHg group into 120 to <130 mmHg and 130 to <140 mmHg. Risk was significantly higher for MI in patients without diabetes and for the primary outcome and stroke in patients with diabetes at 130 to <140 mmHg compared with 120 to <130 mmHg (Supplementary material online, *Figure S5*).

Discussion

This secondary analysis of the large ONTARGET/TRANSCEND trials in patients at high cardiovascular risk with high prevalence of hypertension, most of them taking anti-hypertensive drugs, showed that the association between mean achieved SBP and mean achieved DBP is non-linear with the lowest risk occurring at 120 to <140 mmHg SBP and 70 to <80 mmHg DBP. The association of cardiovascular outcomes to diabetic status and BP demonstrated similar relative risks of achieved in-trial SBP and DBP, but with higher outcome rates in patients with diabetes over the entire spectrum of achieved BP. These findings extend previous studies demonstrating lower boundaries of BP are associated with increased risk in the high risk group of patients with diabetes and diabetes with end-organ damage.

Hypertension and diabetes are two of the most prevalent and powerful risk factors for adverse cardiovascular events.[23] Blood pressure reduction reduces cardiovascular outcomes in hypertensives with or without diabetes.[24] The recently published SPRINT trial[25] suggested lower BP targets in patients with hypertension and high cardiovascular risk. This study excluded patients with diabetes mellitus. The ACCORD study on intensive BP control in Type 2 diabetes found, except for a reduction of incident strokes, no reduction of cardiovascular outcomes. Therefore, the BP goals in patients with diabetes remain a matter of debate. A recent meta-analysis on 191 353 patients without and 61 772 patients with diabetes showed that BP reduction to standard goals recommended by previous guidelines[1–3] reduced outcomes in diabetic patients according to BP levels at baseline.[26] A significant difference between diabetes and no diabetes according to BP lowering on outcomes was not observed.[26] A somewhat smaller risk reduction of major cardiovascular events in diabetes compared with no diabetes was recently reported,[27] however, these differences were small. Nevertheless, the new guidelines of the AHA[4] and of the ESC[6] recommended SBP targets in cardiovascular high risk patients to 120–130 mmHg.[6] Transferring this message into clinical practice would potentially render more patients at particular low BP levels. In patients with stable coronary artery disease[9] and patients with high cardiovascular risk,[10] SBP below 120 mmHg and DBP below 70 mmHg were associated with higher outcome rates including cardiovascular death. Applying lower treatment targets in hypertensives with high cardiovascular risk, more patients might cross a lower boundary associated with higher cardiovascular risk. Since patients with diabetes have higher rates of macrovascular and microvascular complications, it has been speculated that this J-curve might be more expressed in diabetics.[13,14] Herein, we showed that the relative risks for events at particularly low SBP and DBP are not different between diabetes and no diabetes. However, given the higher absolute event rates over the entire spectrum of in-trial SBP and DBP, these data suggest that crossing the lower boundary would be associated with higher absolute numbers of events in patients with diabetes than without diabetes. When ramipril plus telmisartan-treated patients, discouraged by guidelines,[4–6] were excluded from the analysis, the results were not changed.

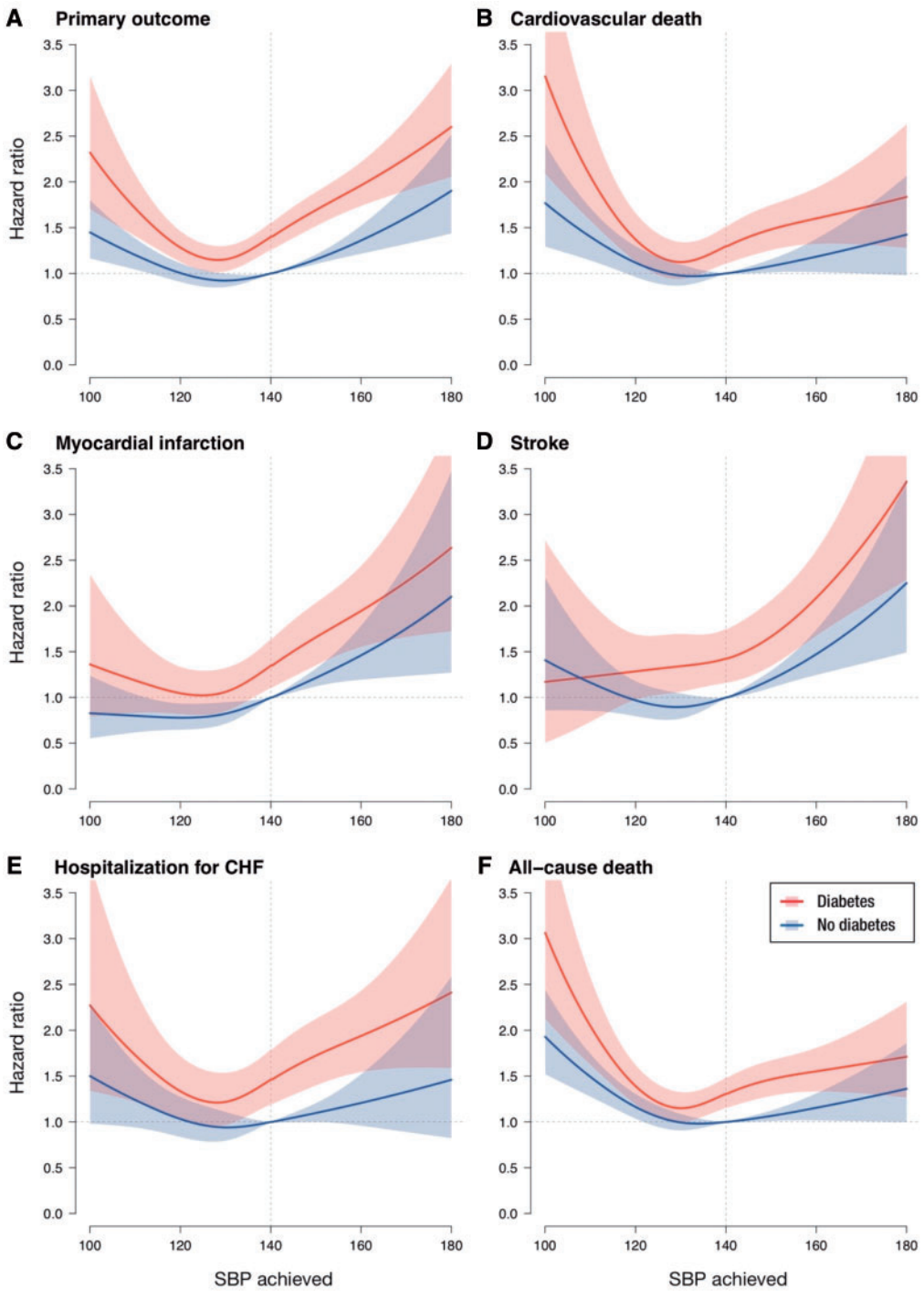


Figure 5 Hazard ratio according to mean achieved systolic blood pressure for the adjusted hazard ratios for primary outcome (*A*), cardiovascular death (*B*), myocardial infarction (*C*), stroke (*D*), hospitalization for congestive heart failure (*E*), and all-cause death (*F*). The analyses were adjusted for the same variables as described in *Figure 4*. The reference (hazard ratio = 1) is mean in-trial systolic blood pressure of 140 mmHg in patients without diabetes.

The hypertension guideline of the AHA/>American College of Cardiology (ACC) suggesting lower BP targets[4] is principally based on the data of the SPRINT study.[25] It needs to be pointed out that SPRINT[25] excluded patients with diabetes. The ACCORD study[28] on diabetic patients found no benefit of strict BP control. Recent *post hoc* analyses of SPRINT and ACCORD were showing that the lower BP goals were more strictly achieved in the SPRINT trial than in the ACCORD trial with a greater variation in the ACCORD trial.[26,27]

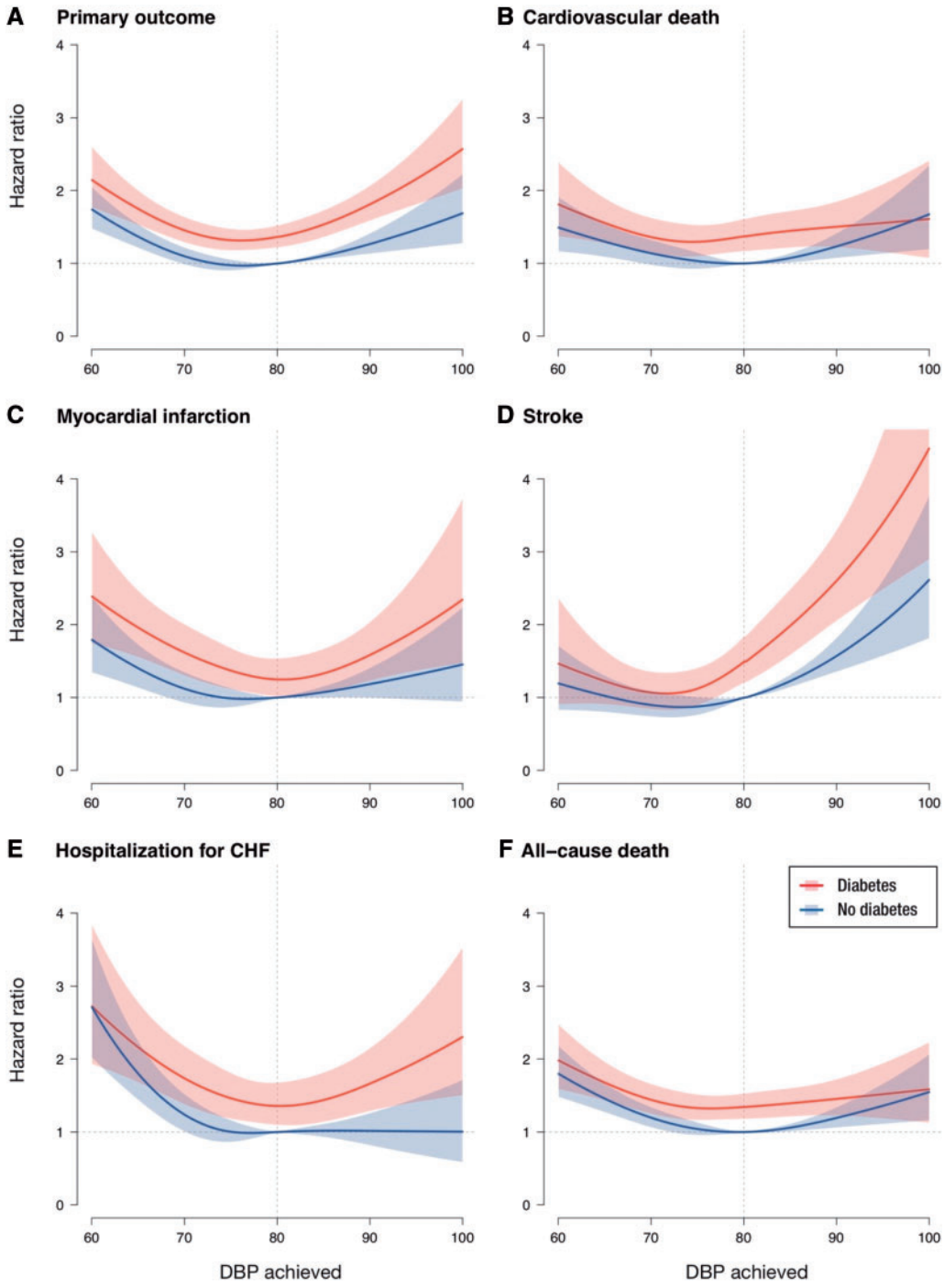
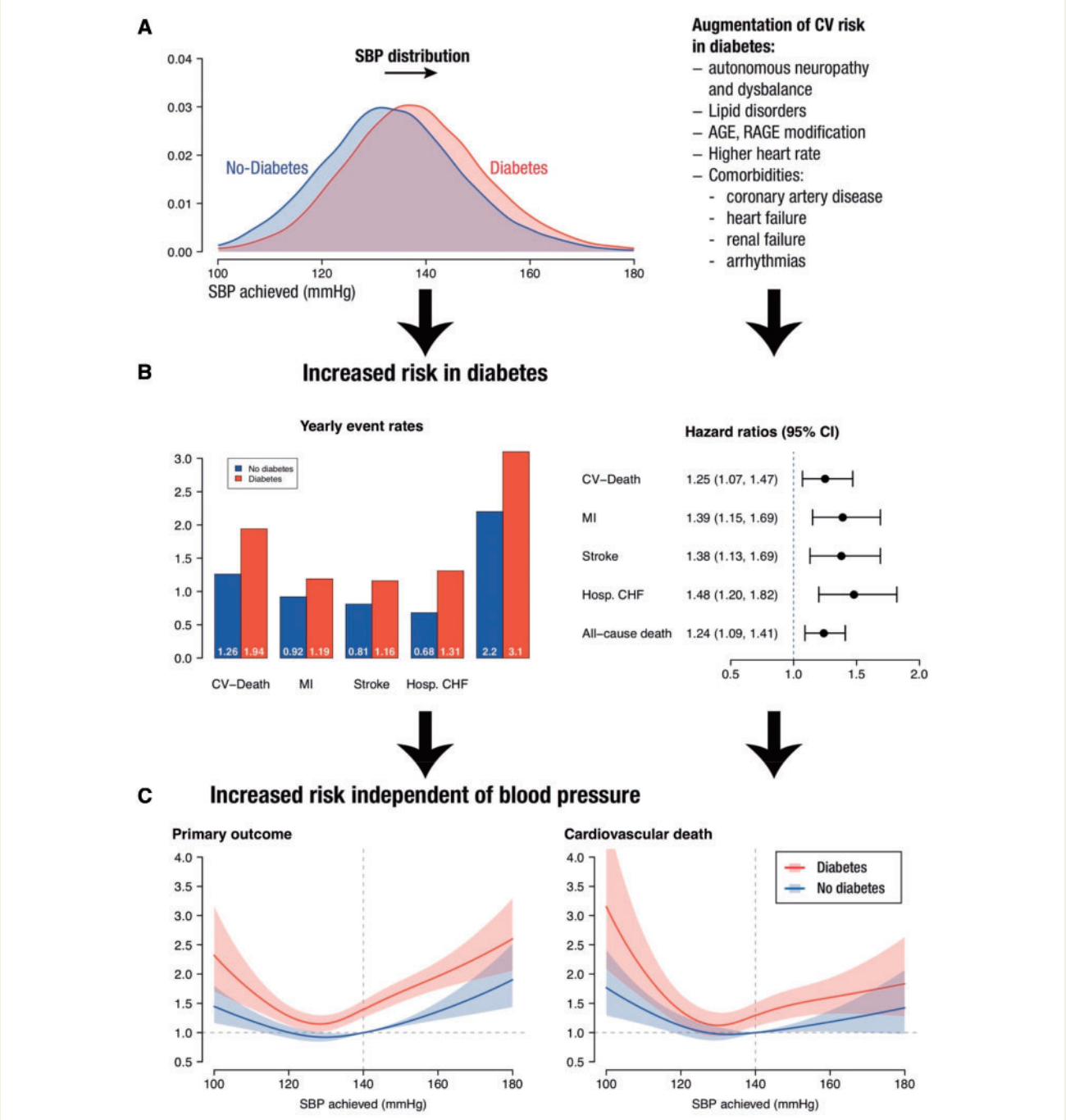


Figure 6 Hazard ratio according to mean achieved diastolic blood pressure for the adjusted hazard ratios for primary outcome (*A*), cardiovascular death (*B*), myocardial infarction (*C*), stroke (*D*), hospitalization for congestive heart failure (*E*), and all-cause death (*F*). The analyses were adjusted for the same variables as described in *Figure 4*. The reference (hazard ratio = 1) is mean in-trial diastolic blood pressure of 80 mmHg in patients without diabetes.

Matching the patients in ACCORD and SPRINT according to in-trial BP achieved provided evidence that the outcome data in both trials indeed were similar.[27] In another *post hoc* analysis, it was shown that despite diabetes the ACCORD patients had a lower risk profile. By adjusting for these risk differences the authors showed that most likely similar results would have been achieved when both trials would have incorporated patients at the same level of baseline risk.[29] In agreement with these suggestions the relative risk-benefit association



Take home figure Systolic blood pressure is shifted to a higher average level in patients with diabetes (*A*, left). Cardiovascular risk in diabetic patients is further augmented by autonomic neuropathy and dysbalance, lipid disorder, RAGE and AGE modifications, higher heart rates, comorbidities such as coronary artery disease, heart failure, renal failure, arrhythmias, and others (*A*, right). This leads to higher event rates and increased hazards for cardiovascular death, myocardial infarction, stroke, hospitalized congestive heart failure, and all-cause death (*B*), which is independent of levels of in-trial blood pressure for all outcomes (*C*).

herein was similar between patients with diabetes and without diabetes, however, the risk in patients with was higher than those without diabetes.

The risk association at low SBP might be related to morbidities occurring during follow-up of these patients. In a previous analysis,[9] we could not detect any potential of inverse causality causing this effect. Low achieved DBP was even stronger associated with negative outcomes. Low DBP might be associated with increased pulse pressure and worse outcomes in the general population and high risk patients[30,31] as well as in elderly individuals[32] which might then

increase incident coronary artery disease[33] and vascular disease.[34] Interestingly, in parallel to elevated risk at low DBP, high sensitivity troponin T (hs-TnT) was increased as were MIs in diabetic patients[31] or subclinical myocardial injury in the general population.[35] Interestingly, the J-curve is maintained at controlled SBP of 120–130 mmHg as well as 130–140 mmHg,[36] however, in the total population without separation in diabetes and non-diabetes.

This study has some limitations but also strengths. This analysis showed that the possibility of inverse causality exists. However, we have in the total population actually addressed in all patients of ONTARGET/TRANSCEND inverse causality, but have previously found no evidence or proof of inverse causality.[9] This is a retrospective observational analysis which is not subject to randomization creating a source of confounding and is therefore, hypothesis generating by nature. Nevertheless, the large number of patients at risk (>30 000) and the standardized measurement of BP and follow-up procedures suggest that these data are highly solid and relevant. It is important to note that ONTARGET/TRANSCEND were not hypertension trials. Nevertheless, 70% of the patients had a history of hypertension and were also treated with a high prevalence with anti-hypertensive drugs in addition to study medication at the discretion of the investigators. Therefore, the database appears to be robust for investigating the BP risk association in patients with and without diabetes.

In conclusion, in patients with and without diabetes at high cardiovascular risk extreme lowering of SBP or DBP was associated with increased risk. The J- and U-shaped curves were similar between individuals with or without diabetes. However, giving the higher absolute number of events in diabetics and especially in diabetics with end-organ damage (*Take home figure*), these data show that those findings by crossing lower boundaries of BP associated with increased risk can expose diabetic individuals to even higher absolute event rates. These data support the appreciation of lower SBP and DBP boundaries in the presence of high cardiovascular risk, in particular in patients with diabetes. Future recommendations should take lower boundaries into consideration.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Acknowledgements

M.B., N.M., and F.M. are supported by the Deutsche Forschungsgemeinschaft (DFG, TTR 219, S-01). We are grateful to Armin Schweitzer for technical and editorial help as well as artwork.

Funding

The funding organizations of the trials had no role in the design and interpretation of this analysis. The trial was designed and conducted by the Steering Committees of ONTARGET and TRANSCEND. The authors had full access to all data of the study with final responsibility to submit this manuscript for publication. Boehringer Ingelheim (ONTARGET/TRANSCEND trials).

Conflict of interest: M.B. reports personal fees from Amgen, Bayer, Servier, Medtronic, Boehringer Ingelheim, Vifor and Bristol Myers Squibb, outside the submitted work. F.M. reports grants and personal fees from Medtronic and Recor, outside the submitted work. R.S. reports grants and personal fees from Boehringer Ingelheim, during the conduct of the study. S.Y. reports other from Boehringer Ingelheim, during the conduct of the study. M.W. reports personal fees from Medtronic, Boston Scientific, ReCor, Omron, Ablative Solutions and Menarini, outside the submitted work. B.W. reports personal fees from Servier, Novartis, Pfizer and Boehringer Ingelheim, outside the submitted work. J.M. reports personal fees from NovoNordisk, during the conduct of the study; personal fees from AstraZeneca, Amgen, Braun, ACI, Fresenius, Gambro, Lanthio, ZS Pharma, Sanifit, Medice and Relypsa; grants and personal fees from NovoNordisk, Roche, Sandoz, Celgene, Abbvie; grants from Europe Union and McMaster University Canada outside the submitted work. G.M. reports personal fees from Boehringer Ingelheim, Ferrer, Medtronic, Menarini, Merck Serono, Novartis, Recordati and Servier, outside the submitted work. H.S., K.T., E.L., J.R., N.M., K.S. have nothing to disclose.

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