

# Achieved diastolic blood pressure and pulse pressure at target systolic blood pressure (120–140 mmHg) and cardiovascular outcomes in high-risk patients: results from ONTARGET and TRANSCEND trials

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## Aims

Current guidelines of hypertensive management recommend upper limits for systolic (SBP) and diastolic blood pressure (DBP). J-curve associations of BP with risk exist for some outcomes suggesting that lower limits of DBP goals may also apply. We examined the association between mean attained DBP and cardiovascular (CV) outcomes in patients who achieved an on-treatment SBP in the range of 120 to <140 mmHg in the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) and Telmisartan Randomized Assessment Study in ACE intolerant participants with cardiovascular Disease (TRANSCEND) trials on patients with high CV risk. This SBP range was associated with the lowest CV risk.

## Methods

We analysed the outcome data from patients age 55 years or older with CV disease from the ONTARGET and TRANSCEND trials that randomized high-risk patients to ramipril, telmisartan, and the combination. In patients with controlled SBP (on-treatment 120 to <140 mmHg), the composite outcome of CV death, myocardial infarction, stroke and hospital admission for heart failure, the components thereof, and all-cause mortality were analysed according to mean on-treatment DBP as categorical (<70, 70 to <80, 80 to <90, and ≥90 mmHg) and continuous variable as well as the change of DBP according to baseline DBP. Pulse pressure (PP) was related to outcomes as a continuous variable.

## Results

In 16 099 of 31 546 patients, mean achieved SBP was 120 to <140 mmHg. The nominally lowest risk for all outcomes was observed at an achieved DBP of 70 to <80 mmHg. A higher achieved DBP was associated with a higher risk for the outcomes of stroke and of hospitalization for heart failure (≥80 mmHg) and myocardial infarction (≥90 mmHg). A lower achieved DBP (<70 mmHg) was associated with a higher risk for the primary outcome [hazard ratio (HR) 1.29, 95% confidence interval (95% CI) 1.15–1.45;  $P < 0.0001$ ], myocardial infarction HR 1.54 (95% CI 1.26–1.88,  $P < 0.0001$ ) and hospitalization for heart failure HR 1.81 (95% CI 1.47–2.24,  $P < 0.0001$ ) and all-cause death (HR 1.19, 95% CI 1.04–1.35;  $P < 0.0001$ ) while there was no signal for stroke and CV death compared to DBP 70 to <80 mmHg. A decrease of DBP was associated with lower risk when baseline DBP was >80 mmHg. The

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associations to outcomes were similar when patients were divided to SBP 120 to <130 mmHg or 130 to <140 mmHg for DBP or PP.

## Conclusion

Compared to a DBP of 70 to <80 mmHg, lower and higher DBP was associated with a higher risk in patients achieving a SBP of 120 to <140 mmHg. Associations of DBP and PP to risk were similar notably at controlled SBP. These data suggest at optimal achieved SBP, risk is still defined by low or high DBP. These findings support guidelines which take DBP at optimal SBP control into consideration.

## Keywords

Hypertension • Cardiovascular risk • Stroke • Myocardial infarction • Heart failure • Blood pressure • Diastolic blood pressure • ONTARGET • TRANSCEND

## Introduction

Hypertension is highly prevalent and is recognized being the leading global preventable risk factor for cardiovascular (CV) disease, morbidity, and mortality.<sup>1,2</sup> Many guidelines recommend a target blood pressure (BP) of less than 140/90 mmHg to reduce CV outcomes.<sup>3–5</sup> Recently, the Systolic Blood Pressure Intervention Trial (SPRINT) included patients with BP values of 130/80 mmHg or higher and additional risk factors but without diabetes or previous stroke.<sup>6</sup> The results of SPRINT suggest that achieving lower BP targets <120 mmHg, measured by an automated BP device, may lead to a further reduction of outcomes.<sup>7</sup> However, other analyses have suggested that risk might increase for some CV outcomes at low systolic blood pressure (SBP) and diastolic blood pressure (DBP) resulting in a J-shape curve for BP–risk relationship.<sup>8,9</sup> Recently, data from an international cohort study on patients with stable coronary artery disease<sup>10</sup> and data from the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) and Telmisartan Randomized Assessment Study in ACE intolerant participants with cardiovascular Disease (TRANSCEND) trials in patients at high CV risk<sup>11</sup> have shown that mean achieved SBP between 120 and <140 mmHg provides the lowest CV event rate, but SBP of <120 mmHg was associated with an increased risk for CV death and all-cause death, but not for stroke. In the overall population, J-shaped curves were also observed for DBP <70 mmHg for the outcomes CV-death, myocardial infarction, all-cause death but again not for stroke.<sup>10,11</sup> It is not known whether in the presence of controlled SBP, low DBP, which might be frequently achieved when strict BP control is targeted, affects outcomes. Recently, a pooled analysis from observational studies in contemporary populations reported that the majority of incident CV events occurred at controlled SBP of <140 mmHg.<sup>12</sup> It is unknown whether within the optimal range of SBP (120 to <140 mmHg),<sup>10,11</sup> a DBP-risk association exists. If so, it might be reasonable to adjust antihypertensive therapy according to DBP.

The ONTARGET<sup>13</sup> and the TRANSCEND<sup>14</sup> randomly assigned 31 546 patients with high CV risk to ramipril, telmisartan, or the combination. In this secondary analysis, we report associations of DBP and pulse pressure (PP) at optimal SBP (120 to <140 mmHg) with the composite CV outcome and further outcomes of CV death, myocardial infarction, stroke, and hospital admission for heart failure. The key objective was to explore the possibility of further risk reduction by modifying DBP in the presence of optimal on-treatment SBP.

## Methods

The design and outcomes of ONTARGET and TRANSCEND have been published previously.<sup>13,14</sup> In brief, patients enrolled were aged 55 years or older with a history of coronary artery disease, peripheral artery disease, transient ischaemic attack, stroke, or with diabetes mellitus complicated by end-organ damage. Patients with symptomatic heart failure at entry were excluded. Patients were enrolled in 733 centres in 40 countries and followed-up for a median of 56 months. All patients gave written informed consent and the study protocols were approved by the local ethics committees of the participating centres. In ONTARGET, patients known to be tolerant to angiotensin-converting enzyme inhibitors (ACEi) were randomly assigned to oral ramipril 10 mg per day, telmisartan 80 mg per day or both at the same doses (double dummy design) after a run-in period (single-blind run-in period with oral ramipril 2.5 mg per day) for 3 days followed by oral telmisartan 40 mg per day and oral ramipril 2.5 mg per day for 7 days followed by 5 mg ramipril plus 40 mg telmisartan for 11–18 days. TRANSCEND had a single-blind run-in period with placebo for 7 days followed by oral telmisartan 80 mg per day. In TRANSCEND, patients intolerant to ACEi, were randomly assigned to telmisartan 80 mg per day or placebo. Study medication was given on top of standard treatment used by the treating physician according to best clinical practice. In both trials, investigators were mandated to use anti-hypertensive drugs to control BP in addition to study medication in order to control BP. Investigators were advised to maintain and (when necessary) to adjust existing BP medications. The results of ONTARGET showed no difference for any of the CV outcomes in the three treatment groups. In TRANSCEND, no significant differences between the two treatment arms were observed. Study visits were scheduled at 6 weeks and at 6 months after randomization and every 6 months thereafter.

## Study outcomes

The primary outcome was a composite of CV death, non-fatal myocardial infarction, stroke, or hospitalization for heart failure. Secondary outcomes included the individual components of the composite as well as all-cause death.

## Systolic blood pressure and diastolic blood pressure analysis

Systolic blood pressure and diastolic blood pressure were measured in a sitting position after resting for 3 min using an automated validated device (OMRON model HEM 757, OMRON Kyoto, Japan). Systolic blood pressure and diastolic blood pressure were taken attended by study nurse or investigator. Patients with complete data were included in this analysis. Patients with missing data of BP at baseline or before a first event or

missing covariates were excluded from our analysis. All outcome events were assessed by a blinded expert committee according to standard criteria.

## Statistical analysis

There were no differences in outcomes between randomized groups in ONTARGET and TRANSCEND. Therefore, the total population was combined for this analysis, and patients with optimal achieved SBP (120 to <140 mmHg) were divided into subgroups on the basis of their mean achieved DBP at the following cut-offs: <70 mmHg, 70 to <80 mmHg, 80 to <90 mmHg, and  $\geq$ 90 mmHg. Groups were tested for differences using ANOVA for continuous data and  $\chi^2$  test for categorical data. Yearly event rates for all outcomes were analysed by DBP categories and tested for differences using Cox regression, adjusting for baseline patient characteristics (heart rate, age, sex, body mass index, renal function, physical activity, education, alcohol consumption, tobacco use, history of hypertension, history of diabetes, myocardial infarction, stroke, transient ischemic attack, heart rhythm, concomitant medications, study and study medications). The association between the various on-treatment DBP and PP measures at SBP 120 to <140 mmHg expressed as continuous variables were also analysed non-parametrically with restricted cubic splines that allowed exploration of non-linear relationships.<sup>15</sup> The assessment whether the relationship was really non-linear was based on the likelihood-ratio test. We also analysed the effect on DBP change according to baseline DBP as continuous variables. In order to explore the possibility of reverse causality, we did several sensitivity analyses. We adjusted for physiological parameters, morbidities and comorbidities occurring before the event of interest. Furthermore, we adjusted for pre-existing morbidities. Finally, we excluded patients with SBP < 120 mmHg at baseline to eliminate individuals in whom comorbidities affecting BP could have been undetected and those individuals not on BP-lowering drugs.

All analyses were done using SAS version 9.4 (SAS Institute, NC, USA). A P-value of 0.05 was considered statistically significant.

## Results

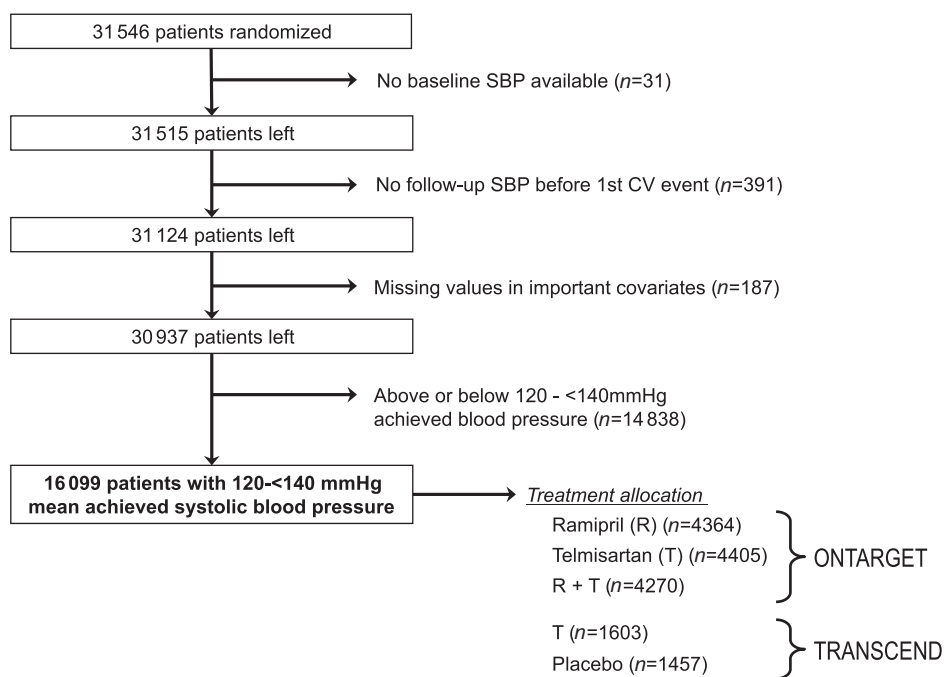
### Baseline data

In ONTARGET and TRANSCEND, 31 546 patients were randomized. After exclusion of patients without baseline SBP values ( $n = 31$ ), follow-up SBP values ( $n = 391$ ) or missing covariates ( $n = 187$ ), 30 937 patients were left, of those 16 099 with mean achieved SBP 120 to <140 mmHg entered this analysis. The patient flow and the allocation to the treatment arms are summarized in the Consolidated Standard of Reporting Trials diagram (Figure 1).

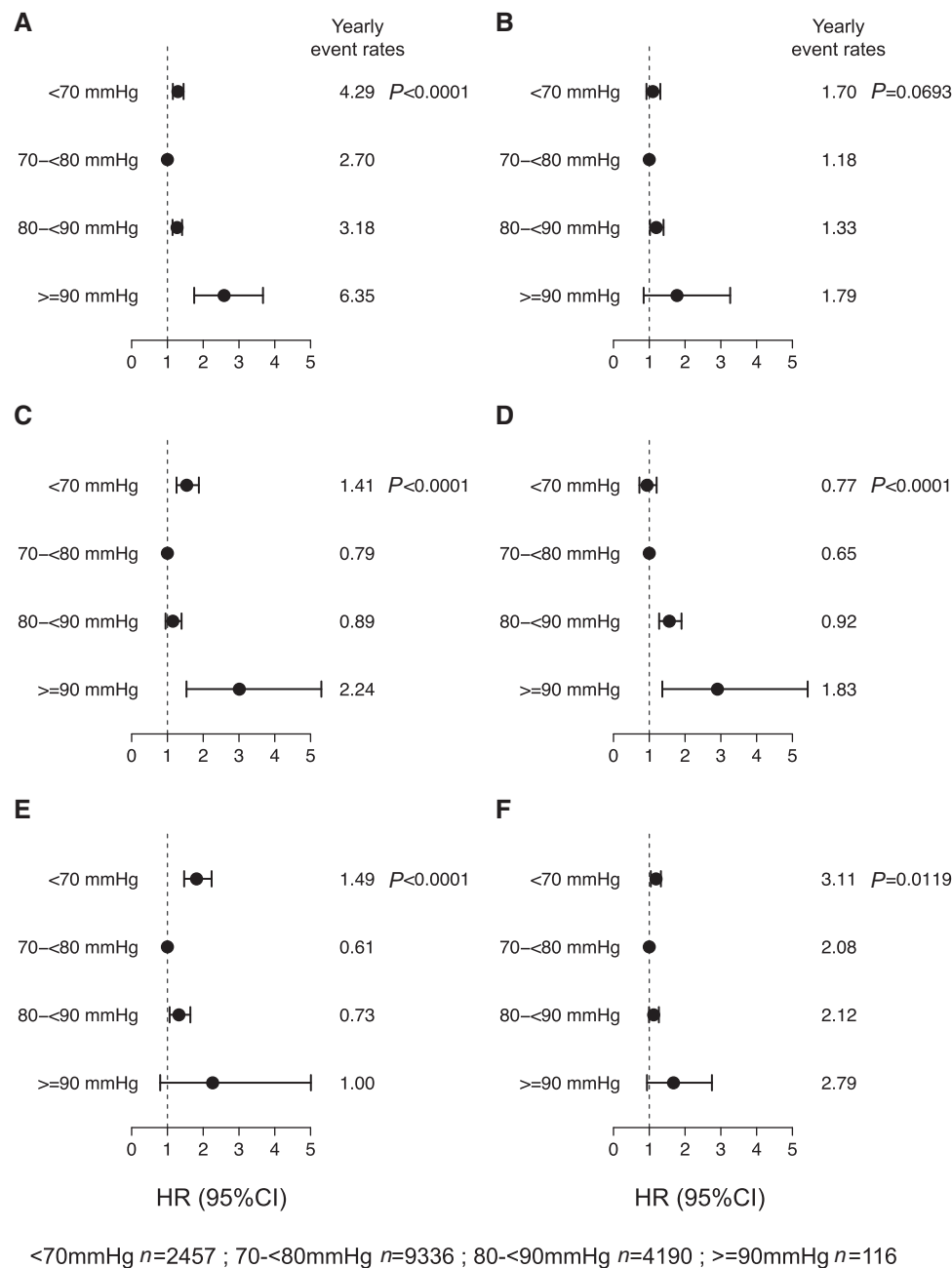
Supplementary material online, Table S1 shows the demographic and clinical characteristics of the study population grouped by mean achieved DBP. Patients with lower DBP tended to have lower SBP, pulse rate, body mass index, estimated glomerular filtration rate, and less hypertension or stroke more frequently a history of diabetes mellitus and were more likely to be older than  $\geq 65$  years (Supplementary material online, Table S1).

### On-treatment diastolic blood pressure and outcomes

Figure 2 shows forest plots of adjusted hazard ratios (HRs) and the calculated yearly event rates at different mean DBP achieved for the primary outcome and the secondary outcomes (Figure 2A–F). The nominally lowest risk for all CV outcomes was achieved at a DBP of 70 to <80 mmHg. At higher achieved DBP, risk increased



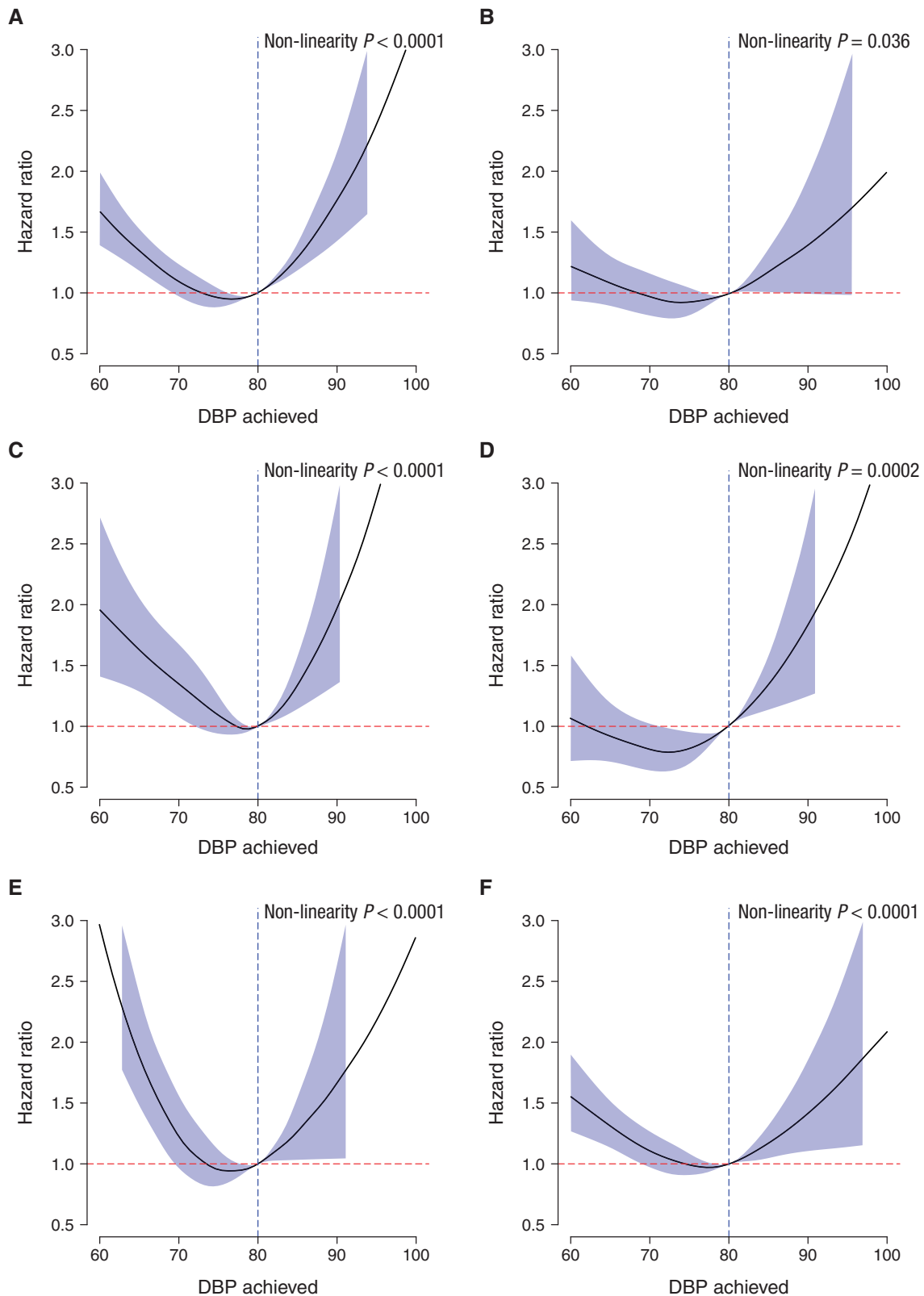
**Figure 1** Consolidated Standards of Reporting Trials (CONSORT) diagram showing patient selection and treatment allocation.



**Figure 2** Adjusted hazard ratios for mean achieved diastolic blood pressure and outcomes at optimal systolic blood pressure achieved (120 to <140 mmHg) for primary endpoint (A), cardiovascular death (B), myocardial infarction (C), stroke (D), hospitalization for heart failure (E), and all-cause death (F). The reference is 70 to <80 mmHg diastolic blood pressure. Yearly event rates and the  $P$ -values for global effects of diastolic blood pressure are also given. The analysis was adjusted for heart rate, age, sex, body mass index, renal function, physical activity, education, alcohol consumption, tobacco use, history of hypertension, history of diabetes, myocardial infarction, stroke, transient ischaemic attack, heart rhythm, concomitant medications, study, and study medications.

for the primary outcome, stroke, and hospitalization for heart failure (DBP $\geq$ 80 mmHg) and for myocardial infarction (DBP $\geq$ 90 mmHg). With lower achieved DBP (<70 mmHg) risk increased for the primary endpoint, myocardial infarction, hospitalization for heart failure, and all-cause death but not for CV death and stroke (Figure 2A–F).

In order to account for the non-linear relationships observed, DBP was evaluated as a continuous variable using cubic spline regression. Figure 3 shows HRs of the combined primary outcome, CV death, myocardial infarction, stroke, hospitalization for heart failure, and all-cause death. Adjusting for all variables according to Supplementary material online, Table S1, an achieved DBP of 80 mmHg was used as



**Figure 3** Hazard ratios according to mean achieved diastolic blood pressure. Cubic splines for the adjusted hazard ratios for mean achieved diastolic blood pressure for primary outcome (A), cardiovascular death (B), myocardial infarction (C), stroke (D), hospitalization for heart failure (E), and all-cause death (F). Shaded areas indicate 95% confidence intervals. The analysis were adjusted for heart rate, age, sex, body mass index, renal function, physical activity, education, alcohol consumption, tobacco use, history of hypertension, history of diabetes, myocardial infarction, stroke, transient ischaemic attack, heart rhythm, concomitant medications, study and study medications. DBP, diastolic blood pressure.

reference. The risk for the primary outcome increased beyond a mean DBP of lower than 70 mmHg and higher than 90 mmHg. Similar results for myocardial infarction, hospitalization for heart failure, and all-cause death were observed, while no such J-curved relationship was detected for CV death and stroke. Similar associations were observed for achieved PP which expectedly shows mirror-inverted patterns notably at SBP 120 to <140 mmHg (Figure 4).

We also analysed changes of DBP relative to DBP at baseline. A decline of DBP on-treatment at baseline DBP of 80 to <90 mmHg or DBP  $\geq$ 90 mmHg was associated with less risk for the primary outcome (Figure 5), CV death (Figure 5B, right), stroke (Figure 5D for 80 to <90 mmHg), heart failure (Figure 5E, right), and all-cause death (Figure 5F). When baseline DBP was <80 mmHg, a further decrease in DBP on-treatment associated with an increased risk for the primary outcome (Figure 5A), hospitalization for heart failure (Figure 5E), or all-cause death (Figure 5F). The numbers of participants and outcomes in those with DBP <70 mmHg were too low for valid conclusions (Figure 5).

The range of SBP 120 to <140 mmHg chosen for this evaluation is rather wide and current discussion focus on a goal in the lower parts of this range. Therefore, we further subdivided the population of 16 099 individuals according to an on-treatment SBP of 120 to <130 mmHg ( $n=6988$ ) and 130 to <140 mmHg ( $n=9011$ ). Patient characteristics of these subgroups are given in [Supplementary material online, Table S2](#). The event rates were lowest when SBP was 120 to <130 mmHg vs. 130 to <140 mmHg ([Supplementary material online, Figures S1 and S2](#)). The event rates were also lowest at 70–80 mmHg DBP ([Supplementary material online, Figures S1 and S3](#)) with a similar J-shape pattern with SBP 120 to <130 mmHg or SBP 130 to <140 mmHg ([Supplementary material online, Figure S3](#)) with the HRs increased for stroke and myocardial infarction compared to 70 to <80 mmHg ([Supplementary material online, Figure S3](#)). [Supplementary material online, Figures S4 and S5](#) show that association to risk was similar for achieved DBP and achieved PP in the two SBP groups.

## Sensitivity analyses addressing reverse causality

We evaluated the possibility that low DBP is more prevalent in individuals with prevalent or incident comorbidities suggesting a 'per se' higher mortality (a phenomenon referred to as 'reverse causality'). In addition to the baseline characteristics reflecting morbidities such as history of hypertension, diabetes, myocardial infarction, stroke, or arrhythmias ([Supplementary material online, Table S1](#)), we also adjusted our analyses for events occurring during the observation and before the outcome of interest. Such new or existing morbidities included new congestive heart failure (CHF) revascularization, new diabetes, new onset of atrial fibrillation, renal function decline, angina (unstable, new, or worsening), transient ischaemic attack, new malignancies, and laser therapy for diabetic retinopathy, all of which were collected in ONTARGET and TRANSCEND. For the death outcomes prior non-fatal events such as myocardial infarction, stroke, and CHF hospitalization were included in the analysis of reverse causality. Likewise, for myocardial infarction, information regarding prior stroke or CHF hospitalization was included. An analogous approach was taken for the other non-fatal outcomes. [Supplementary material online, Table S2](#) shows to what extent the mortality risk was affected

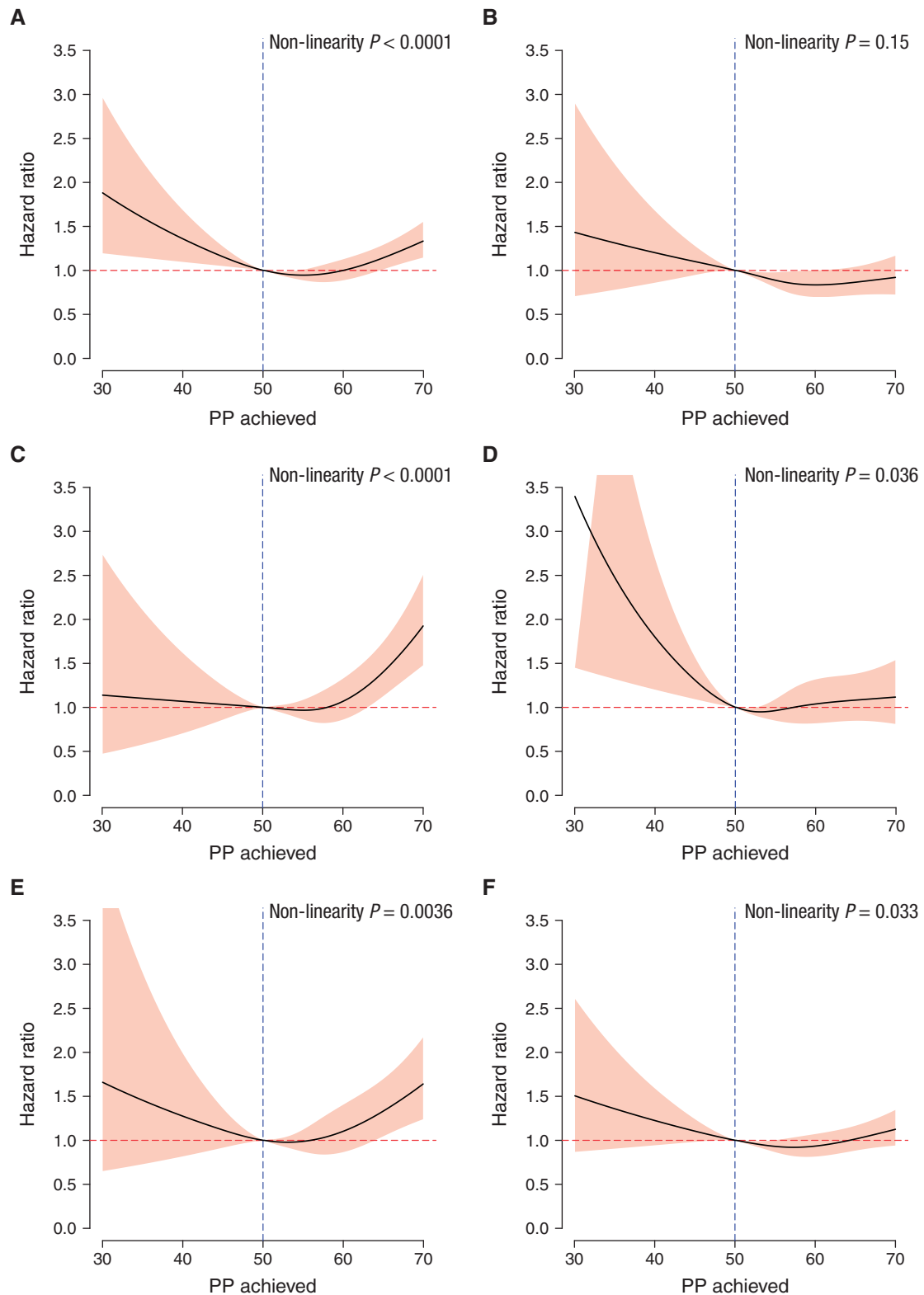
by all of the above events, the incidence in the total population as well as in the four categories for mean achieved DBP. As expected, major events such as myocardial infarction, stroke, new hospitalizations, new diagnosed CHF and especially detection of malignancies had a high negative impact on the mortality risk. Conversely, some of the new diagnoses and therapies for comorbidities had a positive impact.

To further evaluate our findings and to address the possibility of reverse causality, further sensitivity analyses were conducted. We excluded all patients with a non-fatal event, which could have impacted on all or most of the investigated outcomes of interest, i.e. non-fatal myocardial infarction, non-fatal stroke, CHF, new hospitalization, and malignancies in order to derive a population that showed stable morbidity status during the trial. This approach yielded 12 977 (80.6%) of the 16 099 patients for all-cause mortality analyses. We next excluded all patients with a baseline SBP <120 mmHg (not on-treatment SBP) in order to exclude patients with potentially non-detected background comorbidities acting on SBP yielding 14 648 (91.1%) of the 16 099 population for this analysis. Finally, we excluded patients not on antihypertensive drugs at baseline. Here, a total of 15 783 patients remained (98.0%) of the 16 099 patient population. [Supplementary material online, Table S3](#) shows the HRs for the DBP categories in the population with optimal achieved SBP (120 to <140 mmHg) and the restricted populations of the sensitivity analyses. The results of the main analysis are supported by all sensitivity analyses. This was true not only for the mortality outcome but also for all other outcomes. The effect of low or high DBP on risk is even more pronounced if patients with new serious morbidities are excluded ([Supplementary material online, Table S3, first sensitivity analysis](#)).

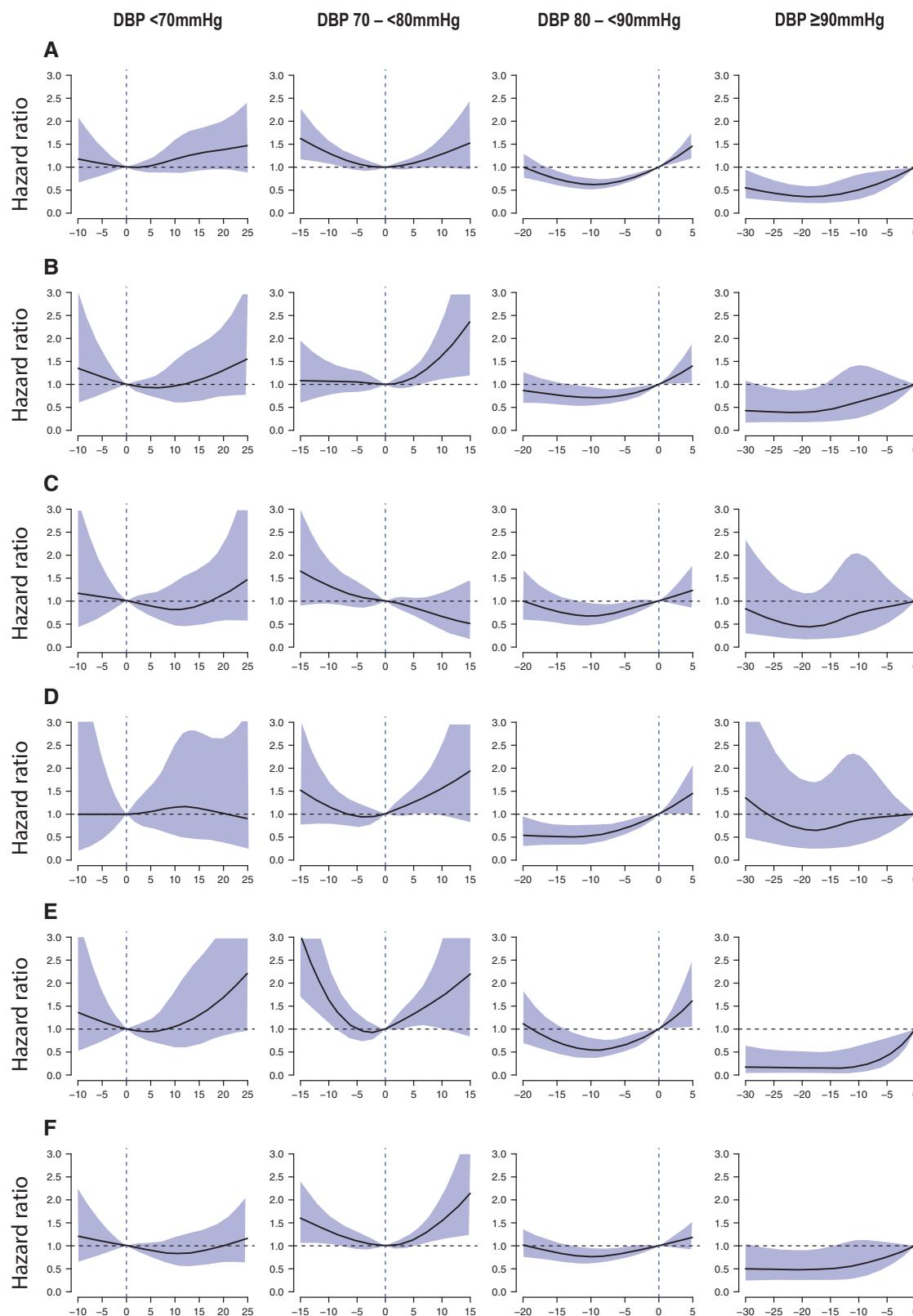
## Discussion

In this study, we have extended previous findings by exploring the relationship between DBP and outcome in patients with high CV risk and a high prevalence of hypertension, most of whom were taking anti-hypertensive medication. We specifically studied patients with an achieved SBP associated with the lowest risk (120 to <140 mmHg).<sup>11</sup> The lowest risk within these SBP boundaries was documented by an achieved mean DBP 70<80 mmHg, whereas at lower (<70 mmHg) and higher ( $\geq$ 80 mmHg) DBP risk increased for the primary outcome, myocardial infarction, stroke, heart failure hospitalization, and total death. Similar associations were detected with achieved PP. These analyses were robust after several sensitivity analyses addressing the possibility of 'reverse causality'.

Current international guidelines recommend a target BP of less than 140/90 mmHg to reduce CV events and to prolong life.<sup>3–5</sup> This was recently challenged by the SPRINT study, which reported a further reduction in event rates with stricter SBP control of <120 mmHg albeit targeting automated office BP, while almost all other trials in hypertension used attended office BP.<sup>7</sup> The method of BP measuring may be pivotal, because other analyses of the SBP–risk relationship suggest an increase of risk when clinic SBP is reduced to <120 mmHg or DBP to <70 mmHg, in particular risks for CV death, all-cause death, and myocardial infarction but not stroke.<sup>10,11</sup> However, it is unclear whether DBP, which usually declines when high SBP is treated, modulates risk in the presence of achieved SBP



**Figure 4** Hazard ratios according to mean achieved pulse pressure. Cubic splines for the adjusted hazard ratios for mean achieved pulse pressure for primary outcome (A), cardiovascular death (B), myocardial infarction (C), stroke (D), hospitalization for heart failure (E), and all-cause death (F). Shaded areas indicate 95% confidence intervals. The analysis were adjusted for heart rate, age, sex, body mass index, renal function, physical activity, education, alcohol consumption, tobacco use, history of hypertension, history of diabetes, myocardial infarction, stroke, transient ischaemic attack, heart rhythm, concomitant medications, study, and study medications. PP, pulse pressure.



**Figure 5** Hazard ratios according to changes from baseline in mean achieved DBP separately for diastolic blood pressure groups at baseline. Cubic splines for adjusted hazard ratios for changes in diastolic blood pressure for different groups at baseline for primary outcome (A), cardiovascular death (B), myocardial infarction (C), stroke (D), hospitalization for heart failure (E), and all-cause death (F). Shaded areas indicate 95% confidence intervals. The analyses were adjusted for heart rate, age, sex, body mass index, renal function, physical activity, education, alcohol consumption, tobacco use, history of hypertension, history of diabetes, myocardial infarction, stroke, transient ischaemic attack, heart rhythm, concomitant medications, study, and study medications. DBP, diastolic blood pressure.



associated with lowest event rates.<sup>10,11</sup> Whilst DBP was perceived as the primary and reproducibly measurable driver of CV risk in hypertension in the past,<sup>16</sup> it has since become clear from epidemiological studies that SBP is the most important determinant of CV outcomes such as stroke and myocardial infarction.<sup>17–19</sup> Though SPRINT supports claims for lower SBP targets (<120 mmHg),<sup>7</sup> the Heart Outcomes Prevention Evaluation trial (HOPE-3),<sup>20</sup> exhibits a trend for harm in patients with a baseline SBP <130 mmHg. Notably, SPRINT and HOPE-3 were using different techniques to measure BP. It is unclear whether increased harm at low SBP might be also due to lower DBP as intense SBP reduction is associated with lower DBP values. In particular in patients with coronary artery disease,<sup>21,22</sup> a drop in coronary perfusion pressure driven by a reduction in DBP during diastole may result in myocardial damage and CV events.<sup>23</sup> Accordingly, a J-shape curve has been reported in hypertensive subjects with coronary artery disease.<sup>8,15,21,22</sup> Consistent with these findings, an increased risk for myocardial infarction and hospitalization for heart failure was detected at low achieved DBP values but controlled SBP with the present analysis in high-risk patients. These analyses were robust to sensitivity analyses addressing reverse causality taken into consideration new onset of comorbid conditions before the event of interest. In agreement, an analysis of the Atherosclerosis Risk in Communities (ARIC) observational cohort study demonstrated increased hs-cTnT values being associated with incident coronary vascular events and mortality but not with stroke at low DBP values despite low SBP.<sup>24</sup> Therefore, even at optimal SBP, considerable amount of risk can be due to DBP. In support of the relevance of this finding, it has recently been shown that the majority of CV events occur in patients at rather low and well controlled SBP,<sup>12</sup> where DBP could become important.

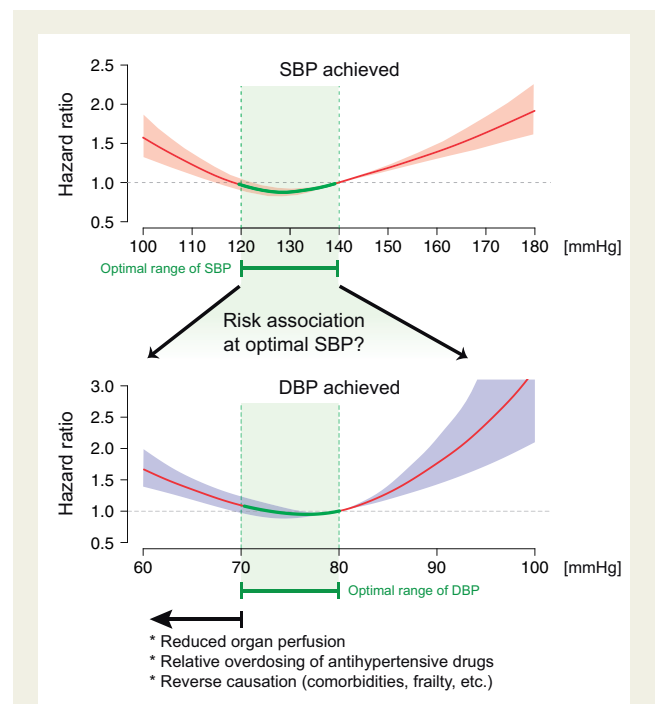
Although PP is not addressed by guidelines as a target, it is known to be associated with outcomes in the general population,<sup>25</sup> high-risk patients<sup>26</sup> and in elderly individuals where it reflects age-associated vascular stiffness<sup>27</sup> and represents the interaction of SBP, DBP, pulse wave reflection, reduced systolic vascular reservoir (reduced 'Windkessel function'), and ejection volume.<sup>28</sup> Pulse pressure is related to the extent of atherosclerosis.<sup>29</sup> Therefore, high PP besides low DBP could also predict risk even beyond low DBP. In a meta-analysis, risk was increased above a PP of 60 mmHg at a SBP of 162/90 mmHg.<sup>30</sup> It appears that risk increases at higher PP the higher SBP is.<sup>25,30</sup> Our studies extend those findings in showing that at SBP 120 to <140 mmHg the DBP, and PP risk associations are similar.

The present findings might have important clinical implications. Since DBP follows SBP when BP-lowering therapies are initiated, it might be important for future guidelines to not only focus solely on upper boundaries but also appreciate lower boundaries of SBP<sup>11</sup> and DBP as shown herein. Adjusting BP-lowering medication within the range optimal SBP (between 120 and 140 mmHg) could also provide space for optimal DBP adjustment. Future studies will have to scrutinize whether such precise adjustments of SBP and DBP are feasible at all and might provide further benefit for patients with pre-existing CV disease.

This study obviously has limitations but also strengths. It is a retrospective observational analysis, which was not subject to randomization. Therefore, it is hypothesis-generating by nature. A low DBP (<70 mmHg) at high SBP is a frequent clinical condition. We could not rule out that patients with low DBP exhibited more vascular stiffness and more vascular disease at baseline, because they were older

(Supplementary material online, Table S1). Reverse causality can neither be completely ruled out nor proven. However, the large number of individuals and a rigorous control and examination of BP in a broad population of high-risk patients on contemporary treatments are the strengths of this analysis.

In conclusion, our study indicates that low DBP at <70 mmHg is associated with CV risk, in particular myocardial infarction, hospitalization for heart failure, and all-cause death in individuals low achieved SBP values associated with the lowest CV risk (between 120 and <140 mmHg) providing the lowest risk. These findings support the appreciation of DBP control in the presence of optimal SBP control in high-risk CV patients. Setting lower boundaries of SBP and DBP might become important in future treatment recommendations (Take home figure).



**Take home figure** J-curve relationship between achieved mean on-treatment systolic blood pressure (SBP) and the primary outcomes (cardiovascular death, myocardial infarction, stroke, and hospitalization for heart failure) (above) is shown in the total ONTARGET/TRANSCEND population (see also reference<sup>11</sup>). At an optimal achieved on-treatment systolic blood pressure range (120 to <140 mmHg), a J-shape curve for the achieved on-treatment diastolic blood pressure (DBP) was explored. The increased risk at low diastolic blood pressure (even at optimal on-treatment systolic blood pressure levels) might be due to reverse causation (comorbidities, frailty, and progression of cardiovascular disease), adverse effect of overdosing of antihypertensive drugs or organ hypoperfusion potentially leading to cardiac damage. Concomitant low diastolic blood pressure at optimal systolic blood pressure might be associated with cardiovascular outcomes and physicians should be aware of the signal of increased risk. Guidelines should take into consideration lower boundaries of achieved on-treatment systolic blood pressure, diastolic blood pressure, and diastolic blood pressure even at optimal systolic blood pressure.

## Supplementary material

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

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