Achieved blood pressure and cardiovascular outcomes in high-risk patients: results from ONTARGET and TRANSCEND trials

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Summary

Background Studies have challenged the appropriateness of accepted blood pressure targets. We hypothesised that different levels of low blood pressure are associated with benefit for some, but harm for other outcomes.

Methods In this analysis, we assessed the previously reported outcome data from high-risk patients aged 55 years or older with a history of cardiovascular disease, 70% of whom had hypertension, from the ONTARGET and TRANSCEND trials investigating ramipril, telmisartan, and their combination, with a median follow-up of 56 months. Detailed descriptions of randomisation and intervention have already been reported. We analysed the associations between mean blood pressure achieved on treatment; prerandomisation baseline blood pressure; or time-updated blood pressure (last on treatment value before an event) on the composite outcome of cardiovascular death, myocardial infarction, stroke, and hospital admission for heart failure; the components of the composite outcome; and all-cause death. Analysis was done by Cox regression analysis, ANOVA, and χ². These trials were registered with ClinicalTrials.gov, number NCT00153101.

Findings Recruitment for ONTARGET took place between Dec 1, 2001, and July 31, 2008. TRANSCEND took place between Nov 1, 2001, and May 30, 2004. 30 937 patients were recruited from 733 centres in 40 countries and followed up for a median of 56 months. In ONTARGET, 25 127 patients known to be tolerant to angiotensin-converting-enzyme (ACE)-inhibitors were randomly assigned after a run-in period to oral ramipril 10 mg/day (n=8407), telmisartan 80 mg/day (n=8366), or the combination of both (n=8334). In TRANSCEND, 5810 patients who were intolerant to ACE-inhibitors were randomly assigned to oral telmisartan 80 mg/day (n=2903) or placebo (n=2907). Baseline systolic blood pressure (SBP) 140 mm Hg or higher was associated with greater incidence of all outcomes compared with 120 mm Hg to less than 140 mm Hg. By contrast, a baseline diastolic blood pressure (DBP) less than 70 mm Hg was associated with the highest risk for most outcomes compared with all DBP categories 70 mm Hg or more. In 4052 patients with SBP less than 120 mm Hg on treatment, the risk of the composite cardiovascular outcome (adjusted hazard ratio [HR] 1·14, 95% CI 1·03–1·26), cardiovascular death (1·29, 1·12–1·49), and all deaths (1·28, 1·15–1·42) were increased compared with those in whom SBP was 120–140 mm Hg during treatment (HR 1 for all outcomes, n=16099). No harm or benefit was observed for myocardial infarction, stroke, or hospital admission for heart failure. Mean achieved SBP more accurately predicted outcomes than baseline or time-updated SBP, and was associated with the lowest risk at approximately 130 mm Hg, and at 110–120 mm Hg risk increased for the combined outcome, cardiovascular death, and all-cause death except stroke. A mean DBP less than 70 mm Hg (n=5352) during treatment was associated with greater risk of the composite primary outcome (HR 1·31, 95% CI 1·20–1·42), myocardial infarction (1·55, 1·33–1·80), hospital admission for heart failure (1·59, 1·36–1·86) and all-cause death (1·16, 1·06–1·28) than a DBP 70–80 mm Hg (14 305). A pretreatment and mean on-treatment DBP of about 75 mm Hg was associated with the lowest risk.

Interpretation Mean achieved SBP less than 120 mm Hg during treatment was associated with increased risk of cardiovascular outcomes except for myocardial infarction and stroke. Similar patterns were observed for DBP less than 70 mm Hg, plus increased risk for myocardial infarction and hospital admission for heart failure. Very low blood pressure achieved on treatment was associated with increased risks of several cardiovascular disease events. These data suggest that the lowest blood pressure possible is not necessarily the optimal target for high-risk patients, although it is not possible to rule out some effect of reverse causality.

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Introduction Guidelines recommend a target blood pressure of less than 140/90 mm Hg to reduce cardiovascular events.4–9 However, cardiovascular outcomes including stroke and heart failure are more sensitive to systolic blood pressure (SBP) reduction than are other outcomes, such as coronary events.4–7 Risk is also higher for some cardiovascular events at low SBP, resulting in a J-curve of
Evidence before the study
Guidelines recommend a blood pressure target of less than 140/90 mm Hg to reduce cardiovascular events but the degree to which blood pressure should be lowered to achieve the lowest risk of cardiovascular disease events is unknown. In May, 2016, we searched PubMed with the terms “SPRINT”, “high cardiovascular risk patients”, “J-curve”, “blood pressure control”, and “blood pressure target”. Articles published in English were included, with no date restriction.

Added value of the study
The ONTARGET and TRANSCEND was conducted in high-risk patients, with 70% of patients hypertensive after cardiovascular events such as stroke or myocardial infarction. Since the treatment effects were neutral, we pooled data from 30,937 patients from ONTARGET and TRANSCEND. In this analysis, we studied the lower boundary of achieved blood pressure in this group of patients on evidence-based treatments. Mean achieved systolic blood pressure less than 120 mm Hg was associated with an increase in cardiovascular death and all-cause death. This was not observed for myocardial infarction and stroke providing the lowest risk at approximately 130 mm Hg, and mean achieved diastolic blood pressure less than 70 mm Hg increased risk for myocardial infarction and hospital admission for heart failure.

Implications of all the available evidence
Our study suggests that reduction of systolic blood pressure to less than 120 mm Hg or diastolic blood pressure to less than 70 mm Hg is associated with an increase in cardiovascular death and all-cause death events, and with no reduction in myocardial infarction or stroke. In high-risk patients, a target blood pressure of 120–130 mm Hg systolic and 70–80 mm Hg diastolic is associated with lowest rates of cardiovascular disease events.

Methods
Study design
In this analysis, we assessed the previously reported outcome data of high-risk patients aged 55 years or older with a history of cardiovascular disease, 70% of whom had hypertension, from the ONTARGET and TRANSCEND trials investigating ramipril, telmisartan, and their combination, with median follow-up 56 months.

Patients
The design, treatments, algorithms, and results of the ONTARGET and TRANSCEND studies have been reported previously. Patients aged 55 years or older without symptomatic heart failure at entry, with a history of coronary artery disease, peripheral artery disease, transient ischaemic attack, stroke, or diabetes mellitus complicated by organ damage were recruited from 733 centres in 40 countries and followed up for a median of 56 months. Inclusion and exclusion criteria are described in the appendix. All patients gave written informed consent, and the study protocols were approved by the ethics committees at the participating centres. In ONTARGET, patients known to be tolerant to angiotensin-converting-enzyme (ACE) inhibitors were randomly assigned to oral ramipril 10 mg/day, telmisartan 80 mg/day, or both at the same doses (double dummy design) after a run-in period (ONTARGET had a single-blind run-in period with oral ramipril 2.5 mg/day for 3 days followed by oral telmisartan 40 mg/day and oral ramipril 2.5 mg/day for 7 days, then 5 mg ramipril plus 40 mg telmisartan for 11 to 18 days. TRANSCEND had a single-blind run-in with placebo for 7 days followed by open-label treatment with either oral telmisartan 40 mg/day or oral ramipril 5 mg/day for 24 weeks.)
by oral telmisartan 80 mg/day). In TRANSCEND, patients who were intolerant to ACE inhibitors were randomly assigned to telmisartan 80 mg per day or placebo. Study medication was given on top of standard treatment used by the treating physicians according to best clinical practice. Investigators were advised to maintain and (when necessary) to adjust pre-existing blood pressure medications. Visits were scheduled at 6 weeks and 6 months after random assignment, and every 6 months thereafter. Results from ONTARGET showed similar outcomes in the composite of cardiovascular death, myocardial infarction, stroke, or hospital admission for heart failure (time to first event) in the three active treatment groups. In TRANSCEND, there was a lower event rate in patients treated with telmisartan, but this was not significant.

Procedures
Because there were no differences in the primary composite outcomes and individual components between the treatment groups, data from all patients were pooled, allowing an adequately powered comprehensive post-hoc analysis of the associations of blood pressure at baseline, blood pressure achieved on treatment, and time-updated blood pressure (blood pressure value before an event or at the end of the study period) and changes in SBP in relation to the primary composite outcomes and its components.

At each visit, brachial SBP was measured in a sitting position after resting for 3 min using an automated validated device (Omron model HEM 757, Omron, Kyoto, Japan), attended by the study nurse or investigator. Only patients with complete data were included in the analysis. The flow of the study and treatment assignment are summarised in the appendix. Of the 31,546 patients randomly assigned, those with no recorded SBP at baseline or before a first event or those with missing covariates were excluded from our analysis. 30,937 patients were available for the analyses. All primary and secondary outcome events were assessed by a blinded central committee according to standard criteria. An average of 8.3 (SD 2.6) blood pressure measurements were available before an event measured over 54.8 months (SD 10.8).

Outcomes
The primary composite outcome of cardiovascular death, myocardial infarction, stroke, and hospital admission for heart failure was used in the analysis, along with the separate outcome of all-cause death.

Statistical analysis
Given that there were no differences in outcomes between the randomised groups, they were combined for this analysis. Patients were divided into subgroups on the basis of baseline and mean achieved in-trial seated clinic blood pressure according to the following cutoffs for SBP: less than 120 mm Hg, 120 to less than 140 mm Hg, 140 to less than 160 mm Hg, and 160 mm Hg, or more. For DBP, cutoffs were less than 70 mm Hg, 70 to less than 80 mm Hg, 80 to less than 90 mm Hg, and 90 mm Hg or more. Groups were tested for differences

### Table 1: Baseline characteristics of patients assigned to telmisartan 80 mg/day (proportion of patients)

<table>
<thead>
<tr>
<th>Variable</th>
<th>&lt;120 mm Hg</th>
<th>≥120 &lt;140 mm Hg</th>
<th>≥140 &lt;160 mm Hg</th>
<th>≥160 mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td>3006</td>
<td>5177</td>
<td>13143</td>
<td>4271</td>
</tr>
<tr>
<td><strong>SBP, sitting (mm Hg; mean, SD)</strong></td>
<td>111.3 (6.5)</td>
<td>120.4 (5.7)</td>
<td>140.9 (5.9)</td>
<td>168.2 (9.9)</td>
</tr>
<tr>
<td><strong>DBP, sitting (mm Hg; mean, SD)</strong></td>
<td>69.7 (8.0)</td>
<td>78.5 (8.2)</td>
<td>85.0 (8.7)</td>
<td>90.4 (5.7)</td>
</tr>
<tr>
<td><strong>Pulse rate, sitting (bpm; mean, SD)</strong></td>
<td>67.0 (12.2)</td>
<td>68.0 (11.9)</td>
<td>68.4 (12.0)</td>
<td>67.6 (12.4)</td>
</tr>
<tr>
<td><strong>Age (years; mean, SD)</strong></td>
<td>65.0 (7.1)</td>
<td>65.6 (7.2)</td>
<td>66.3 (7.2)</td>
<td>68.4 (7.1)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>2275 (76%)</td>
<td>7687 (73%)</td>
<td>8984 (68%)</td>
<td>2804 (66%)</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>731 (24%)</td>
<td>2830 (27%)</td>
<td>4159 (32%)</td>
<td>1467 (34%)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Asian</strong></td>
<td>524 (17%)</td>
<td>1627 (16%)</td>
<td>2031 (16%)</td>
<td>539 (13%)</td>
</tr>
<tr>
<td><strong>Black</strong></td>
<td>58 (2%)</td>
<td>222 (2%)</td>
<td>298 (2%)</td>
<td>135 (3%)</td>
</tr>
<tr>
<td><strong>White</strong></td>
<td>336 (11%)</td>
<td>1135 (11%)</td>
<td>1390 (11%)</td>
<td>374 (9%)</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>1631 (54%)</td>
<td>5306 (51%)</td>
<td>6500 (50%)</td>
<td>2132 (50%)</td>
</tr>
<tr>
<td><strong>Body-mass index (kg/m²; mean, SD)</strong></td>
<td>27.6 (5%)</td>
<td>28.1 (5%)</td>
<td>28.3 (5%)</td>
<td>28.3 (5%)</td>
</tr>
<tr>
<td><strong>Obese</strong></td>
<td>855 (28%)</td>
<td>3412 (32%)</td>
<td>4447 (34%)</td>
<td>1431 (34%)</td>
</tr>
<tr>
<td><strong>eGFR MDRD (mL/min per 1.73 m²; mean, SD)</strong></td>
<td>74.0 (20%)</td>
<td>74.1 (20%)</td>
<td>73.3 (20%)</td>
<td>72.1 (20%)</td>
</tr>
<tr>
<td><strong>Physical activity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mainly sedentary</strong></td>
<td>646 (22%)</td>
<td>2371 (23%)</td>
<td>3099 (24%)</td>
<td>991 (23%)</td>
</tr>
<tr>
<td><strong>Less than once per week</strong></td>
<td>338 (11%)</td>
<td>1209 (12%)</td>
<td>1502 (11%)</td>
<td>496 (12%)</td>
</tr>
<tr>
<td><strong>2–4 times per week</strong></td>
<td>684 (23%)</td>
<td>2436 (23%)</td>
<td>2993 (23%)</td>
<td>979 (23%)</td>
</tr>
<tr>
<td><strong>5–6 times per week</strong></td>
<td>257 (9%)</td>
<td>822 (8%)</td>
<td>976 (7%)</td>
<td>306 (7%)</td>
</tr>
<tr>
<td><strong>Every day</strong></td>
<td>1081 (36%)</td>
<td>3679 (35%)</td>
<td>4573 (35%)</td>
<td>1499 (35%)</td>
</tr>
<tr>
<td><strong>Formal education</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>≤8 years</strong></td>
<td>958 (32%)</td>
<td>3362 (32%)</td>
<td>4581 (35%)</td>
<td>1533 (36%)</td>
</tr>
<tr>
<td><strong>9–12 years</strong></td>
<td>895 (30%)</td>
<td>3186 (30%)</td>
<td>3807 (29%)</td>
<td>1251 (29%)</td>
</tr>
<tr>
<td><strong>Trade or technical</strong></td>
<td>516 (17%)</td>
<td>1844 (18%)</td>
<td>2360 (18%)</td>
<td>801 (18%)</td>
</tr>
<tr>
<td><strong>College or university</strong></td>
<td>637 (21%)</td>
<td>2125 (20%)</td>
<td>2395 (19%)</td>
<td>868 (16%)</td>
</tr>
<tr>
<td><strong>Alcohol consumption</strong></td>
<td>1158 (39%)</td>
<td>4091 (39%)</td>
<td>5022 (38%)</td>
<td>1721 (40%)</td>
</tr>
<tr>
<td><strong>Tobacco use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Current</strong></td>
<td>435 (15%)</td>
<td>1410 (13%)</td>
<td>1472 (11%)</td>
<td>408 (10%)</td>
</tr>
<tr>
<td><strong>Former</strong></td>
<td>1631 (54%)</td>
<td>5306 (53%)</td>
<td>6500 (50%)</td>
<td>2322 (50%)</td>
</tr>
<tr>
<td><strong>Never</strong></td>
<td>940 (31%)</td>
<td>3801 (36%)</td>
<td>5171 (39%)</td>
<td>1721 (41%)</td>
</tr>
<tr>
<td><strong>History of hypertension</strong></td>
<td>1483 (49%)</td>
<td>6956 (62%)</td>
<td>10991 (77%)</td>
<td>3548 (83%)</td>
</tr>
<tr>
<td><strong>History of diabetes</strong></td>
<td>895 (30%)</td>
<td>3528 (34%)</td>
<td>5284 (40%)</td>
<td>1780 (42%)</td>
</tr>
<tr>
<td><strong>History of myocardial infarction</strong></td>
<td>1888 (6%)</td>
<td>5548 (53%)</td>
<td>5786 (44%)</td>
<td>1774 (42%)</td>
</tr>
<tr>
<td><strong>History of stroke or transient ischaemic attack</strong></td>
<td>496 (17%)</td>
<td>1988 (19%)</td>
<td>3007 (23%)</td>
<td>1003 (24%)</td>
</tr>
<tr>
<td><strong>Rhythm</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sinus</strong></td>
<td>2785 (93%)</td>
<td>9851 (94%)</td>
<td>12327 (94%)</td>
<td>3989 (93%)</td>
</tr>
<tr>
<td><strong>Atrial fibrillation</strong></td>
<td>124 (5%)</td>
<td>364 (4%)</td>
<td>393 (3%)</td>
<td>128 (3%)</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>87 (3%)</td>
<td>302 (3%)</td>
<td>413 (3%)</td>
<td>154 (4%)</td>
</tr>
</tbody>
</table>

(Table continues on next page)
using ANOVA for continuous data and the χ² test for categorical data. Yearly event rates and Kaplan–Meier curves for all outcomes were analysed by SBP categories and tested for differences using Cox regression, adjusting for baseline patient characteristics. The associations between the various blood pressure measures and their changes expressed as continuous variables were also analysed non-parametrically with restricted cubic splines that allowed exploration of non-linear relationships. The Vuong test was used to assess which of the three blood pressure measures, baseline, mean achieved in-trial, or time-update, was best for prediction of each outcome. The Vuong test has been developed for the comparison of non-nested models, and it is based on the individual log-probabilities in the respective models to assess which of them is closer to the true model. All analyses were done using SAS version 9.4 (SAS Institute, NC, USA).

Role of the funding source
The funder of the trials had no role in the design and interpretation of this analysis. The authors had full access to all data of the study with final responsibility to submit this manuscript for publication.

Results
Recruitment for ONTARGET took place between Dec 1, 2001, and July 31, 2008. Recruitment for TRANSCEND took place between Nov 1, 2001, and May 30, 2004. 30 937 patients were recruited from 733 centres in 40 countries and followed up for a median of 56 months. In ONTARGET, 25127 patients known to be tolerant to ACE-inhibitors were randomly assigned after a run-in period to oral ramipril 10 mg/day (n=8402), telmisartan 80 mg/day (n=8386), or the combination of both (8334). In TRANSCEND, 5810 patients who were intolerant to ACE-inhibitors were randomly assigned to oral telmisartan 80 mg/day (n=2903) or placebo (n=2907).

Table 1 shows the demographic and clinical characteristics of the ONTARGET and TRANSCEND populations grouped by SBP at baseline. Patients with higher baseline SBP were older, had higher body-mass index, and higher prevalence of hypertension, diabetes, or history of stroke. Randomised treatments with placebo, ramipril, telmisartan, or ramipril with telmisartan were similarly distributed between the groups according to SBP at baseline.

Kaplan-Meier curves in the appendix show the association of SBP and DBP at baseline to the combined primary outcome of cardiovascular death, myocardial infarction, stroke, and hospital admission for heart failure; plus the primary outcome of all-cause death. The lowest risk for the combined primary outcome, cardiovascular death, hospital admission for heart failure, and all-cause death was seen at a baseline SBP 120–140 mm Hg, and those with SBP of more than 140 mm Hg or less than 120 mm Hg showed higher event rates for stroke and myocardial infarction. The calculated yearly events and the adjusted hazard ratios are shown in figure 1 (SBP 120–140 mm Hg used as reference). HR at baseline SBP less than 120 mm Hg was not significantly different from the reference for all outcomes. Risk was highest at a baseline DBP less than 70 mm Hg for all outcomes except stroke, where no clear relationship to the cumulative incidence was recorded. Significantly higher event rates were recorded in patients with a baseline SBP of 140–160 mm Hg and 160 mm Hg or higher for all outcomes except myocardial infarction, in which risk was only increased for SBP 160 mm Hg or more. DBP 90 mm Hg or higher at baseline was associated with lower risk for the composite outcome, myocardial infarction, and hospital admission for heart failure compared with all lower DBP values (figure 1A,C,E). At baseline DBP less than 70 mm Hg, all outcomes were more frequent except stroke (figure 1A–F).

Next, we assessed mean achieved SBP and DBP values during treatment (mean in-trial SBP and DBP at all study visits before an event or censoring). By contrast with baseline SBP, the lowest level of risk occurred at SBP values of 120–140 mm Hg for all outcomes except myocardial infarction (figure 2). For the combined primary outcome, cardiovascular death, hospital admission for heart failure, and all-cause death, there was an increased risk at an SBP less than 120 mm Hg during treatment.
outcome, all its components, and all-cause death, an increase in risk was observed at SBPs 140–160 mm Hg and 160 mm Hg or more. Separately adjusted analyses for baseline, achieved, and time-updated SBP were done and the strength of model fit was compared using the Vuong test. The mean achieved SBP provided the highest predictive value (appendix).

Similar patterns were observed with DBP. Achieved DBP less than 70 mm Hg was associated with an increased risk of the primary composite outcome, myocardial infarction, hospital admission for heart failure, and all-cause death compared with DBP 70–80 mm Hg. DBP during treatment was associated with an increased risk of the primary composite endpoint and stroke if 80 mm Hg or more. For cardiovascular death, myocardial infarction, hospital admission for heart failure, and all-cause death, risk was higher when mean achieved DBP was 90 mm Hg or more, compared with DBP 70–80 mm Hg (figure 2).

To exclude the possibility that blood pressure falls are more pronounced in those with concomitant morbidities, indicating that these groups might have inherently higher mortality (reverse causality), we separated the analysis by comorbidities that were present at baseline or before an event. As expected, non-fatal events like myocardial infarction, stroke, new heart failure, and known malignancies adversely affected outcomes (appendix). After excluding patients with these comorbidities (appendix) our results were essentially unchanged. Furthermore, to address non-detected background comorbidities acting on blood pressure, we excluded patients with a blood pressure reducing drugs and active study drugs, ie, excluding all patients without blood pressure lowering drugs. There was no difference from the main analysis of this study (appendix).

Analysis taking SBP as a continuous variable and using cubic spline regression revealed that the
relationship between endpoints and baseline SBP (and achieved SBP) were non-linear. Figure 3 shows HRs for the combined primary outcome, cardiovascular death, myocardial infarction, stroke, hospital admission for heart failure, and all-cause death according to baseline SBP and achieved SBP after adjusting for all variables in the table. SBP 140 mm Hg was used as reference (HR=1). The risk for the primary outcome increased from a mean achieved SBP of 140 mm Hg to lower SBP. Similar results were observed for the other outcomes except for myocardial infarction and stroke. For an achieved SBP less than 120 mm Hg, risk increased compared with higher SBP. This J-shape curve was not observed for myocardial infarction and stroke. Similar results were observed for mean achieved DBP (figure 4). Low baseline and achieved DBP of less than about 75 mm Hg was associated with decrease in the combined primary outcome, myocardial infarction, hospital admission heart failure, and death; however, stroke rates were lower at lower achieved DBP.

**Discussion**

Our study shows that in a population of patients with cardiovascular disease, with a high prevalence of
hypertension, most of whom were taking antihypertensive medication, the lowest risk for the composite primary cardiovascular outcome and all its components was observed at achieved SBP between 120–140 mm Hg. A significantly higher risk was observed for cardiovascular death, hospital admission for heart failure, and all-cause death when SBP was greatly reduced. DBP followed a similar pattern with low DBP (<70 mm Hg) being associated with a higher risk of myocardial infarction and hospital admission for heart failure. Patients with SBP values at baseline of approximately 130 mm Hg showed an increased risk for all outcomes except stroke, for which the lowest risk was at baseline SBP of less than 120 mm Hg on treatment.

US and European guidelines recommend a SBP goal less than 140 mm Hg for most patients, as there is conflicting evidence whether a more intensive SBP lowering is associated with greater reduction of cardiovascular events. Our results suggest that reductions of SBP to less than 110 mm Hg were associated with increased cardiovascular death and myocardial infarction risk with the lowest risk at a SBP...
of around 130 mm Hg. In patients with and without diabetes,8,20,21 patients with coronary heart disease,8,21 and patients studied in the ACCORD study,13 risk of the composite cardiovascular disease outcome was not reduced, when SBP of less than 120 mm Hg compared with more than 130 mm Hg was achieved. This was supported by data from the CLARIFY registry in patients with stable coronary artery disease.11 Parallel results were observed in average risk patients (few with diabetes) in the Heart Outcomes Prevention Evaluation-3 (HOPE 3) study.31 We extend those findings by investigating a larger and broader population in a controlled trial, where more standard conditions for blood pressure measurements were used. When we compared achieved in-trial SBP values in relation to outcomes, the SBP risk-nadir was also at about 130 mm Hg, with an increase in risk for several cardiovascular outcomes other than stroke. This is supported by a previous analysis from ONTARGET, where an increase of cardiovascular death and myocardial infarction was observed with SBP values less than 110 mm Hg20 and is in line with previous

![Figure 4: Hazard ratios according to baseline and mean achieved DBP](image-url)

Cubic splines for the adjusted hazard ratios for baseline DBP (left) and achieved DBP (right) for (A) primary endpoint, (B) cardiovascular death, (C) myocardial infarction, (D) stroke, (E) hospital admission for chronic heart failure, and (F) all-cause death. Shaded areas indicate 95% CIs. 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 or transient ischaemic attack, heart rhythm, concomitant medications, study, and study medications. DBP=diastolic blood pressure.
Figure 5: Hazard ratios according to changes from baseline in mean achieved SBP, separately for SBP groups at baseline.

Cubic splines for the adjusted hazard ratios for changes in SBP for different groups at baseline for (A) primary endpoint, (B) cardiovascular death, (C) myocardial infarction, (D) stroke, (E) hospital admission for chronic heart failure, and (F) all-cause death. Shaded areas indicate 95% CIs. 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 or transient ischaemic attack, heart rhythm, concomitant medications, study, and study medications. SBP=systolic blood pressure.
suggestions that excessive blood pressure lowering in higher risk patients is potentially hazardous. Analyses from the ACCOMPLISH trial and the VALUE trial showed a reduction of stroke but no reduction in other cardiovascular events or death when treated SBP was less than 120 mm Hg, suggesting that different outcomes have individual optimal SBP targets. A meta-analysis in patients with diabetes showed a reduction of cardiovascular mortality by antihypertensive treatment when baseline SBP was more than 140 mm Hg, and there was a significant or nominal risk increase at lower baseline (<140 mm Hg) or attained (<130 mm Hg) SBP. The average SBP during treatment had a greater potential to predict outcomes than baseline SBP or the last value before an event. In the SPRINT study, achieved SBP after 1 year was 121-4 mm Hg in the intensive treatment group compared with 136-2 mm Hg in the standard treatment group. The risk reduction in patients with SBP at baseline of 145 mm Hg or more and 132 mm Hg or less were similar, but data at lower achieved SBP have not been reported. In a meta-analysis on 44,989 patients from 19 trials, there was a significant reduction in events in high-risk patients when blood pressure was reduced to 133/76 mm Hg compared with 140/81 mm Hg. The risk reduction by SBP control was greater in patients at higher global cardiovascular risk. The achieved SBP-risk ratio might also change in patients at different levels of risk. The HOPE-3 trial reported no reduction of outcomes in intermediate-risk patients without evident cardiovascular disease with a baseline SBP of 138 mm Hg. However, a significant risk reduction in individuals with SBP more than 143.5 mm Hg at baseline by 24% (p<0.009 for interaction) was significantly different compared with the outcomes in individuals less than 131.5 mm Hg. Renin-angiotensin blockade might influence the SBP risk ratio by providing blood-pressure-independent effects in low SBP patients, however, in HOPE-3, the angiotensin-receptor blocker candesartan did not provide benefits in patients at low baseline SBP. Furthermore, results were similar when only patients actually taking the study drug or at least one blood pressure reducing agent were assessed. Supporting the role of SBP, reduction of SBP was associated with reduced risk at high baseline SBP (eg, >160 mm Hg), but an increase in SBP was associated with reduced risk for the combined primary endpoint, cardiovascular death, all-cause death, and hospital admission for heart failure when baseline SBP was low. Changes in antihypertensive medications by the investigators or changes in patients’ condition might play a part in increases of SBP in the trial. Achieved DBP 90 mm Hg or more was negatively associated with all outcomes. DBP less than 70 mm Hg was significantly associated with increases in the primary composite endpoint, myocardial infarction, hospital admission for heart failure, and all-cause death. Unlike low SBP, low DBP was significantly associated with myocardial infarction and chronic heart failure. At low DBP, reduced myocardial perfusion pressure might facilitate ischaemia and events when substantial coronary lesions are present. Furthermore, this association and arterial stiffness resulting in pulse wave reflection into myocardial systole might have increased myocardial afterload, remodeling, and hospital admission for heart failure. Similar results for the composite of cardiovascular death, myocardial infarction and stroke, all-cause death, and hospital admission for heart failure was reported in a real life registry in patients with known coronary artery disease. Taken together, these data indicate that achieved blood pressure values have diverse benefit for different outcomes and this probably differs according to baseline risk in hypertensive patients. Consequently, people with a particular risk for a specific outcome—eg, stroke, might benefit from lower blood pressure than those who are more prone to develop myocardial infarction or cardiovascular death—the challenge, however, is how to predict who is most likely to develop each of these events. In SPRINT, patients had a low mean SBP at baseline of 139.7 mm Hg. The analysis was done in high-risk patients with similar SBP at baseline (ONTARGET 141.7–141.9 mm Hg, TRANSCEND 140.7–141.3 mm Hg). Although these SBP values are similar, in previous hypertension trials, SBP values were considerably higher, leading also to higher achieved SBP values. These results are similar to real world scenarios, where less than 50% of patients achieve guideline-recommended target SBP values. Due to the specific method of measuring blood pressure (unattended measurements after 5 min of quiet rest) in SPRINT, the values are probably 10–15 mm Hg lower compared with conventionally measured SBP, which challenges any comparison of unattended blood pressure values with other prospective trials using different blood pressure measurement modalities. Patients with previous stroke or diabetes were excluded from SPRINT, due to competing recruitment into the ACCORD and the SPS3 studies. One ongoing trial explicitly recruits patients with characteristics that were mainly excluded in previous trials, specifically around 7500 patients aged 65 years or older with diabetes and stroke or transient ischaemic attacks, and will provide complementary data. In our analysis, patients were not randomly assigned to specific treatments. However, the rigorous measurement of SBP at baseline and at all follow-up visits to establish achieved SBP allowed a robust analysis of cardiovascular outcomes in more than 30,000 patients at risk. In this analysis, we cannot completely rule out some effect of reverse causality indicating that morbidities cause decreases in blood pressure and morbidity and mortality during the trial. However, we tried to address this
In conclusion, in patients at high cardiovascular risk, lowering blood pressure to less than 130 mm Hg SBP or less than 75 mm Hg DBP is associated with increased rates for cardiovascular death, myocardial infarction, and heart failure, but not stroke. Risk of cardiovascular disease events other than stroke increased for SBP less than 120 mm Hg and DBP less than 70 mm Hg. Physicians might be less aware of this concern because they focused on high SBP values. According to our analysis, in higher risk patients, achieving a SBP less than 130 mm Hg but not lower than 120 mm Hg should be safe for most and result in improved outcomes. The findings suggest that in some patients at low SBP on treatment, blood pressure medication might have to be reduced to avoid adverse outcomes because treat to target does not mean treat under target.

Contributors
All authors participated in the design of the study, the interpretations of the data and the writing of the Article. The statistical analysis was done by HS. MB drafted the manuscript. All authors were members of the steering committee of ONTARGET and TRANSCEND chaired by SY.

Declaration of interests
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References
   Eur Heart J 2013; 34: 2159–219
2. Rydén L, Grant PJ, Anker SD, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology [ESC] and developed in collaboration with the European Association for the Study of Diabetes (EASD).
   Eur Heart J 2013; 34: 3055–87
   JAMA 2003; 289: 2334–44.
7. Zanchetti A. Blood pressure targets of antihypertensive treatment: up and down the J-shaped curve.
   JAMA 2010; 304: 61–68.
10. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 20,566 individuals with previous stroke or transient ischaemic attack.
19. Vuong QH. Likelihood ratio tests for model selection and non-nested hypotheses.
    Eur Heart J 2016; 37: 955–64.
27. Brunstrøm M, Carlberg B. Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses.
    BMJ 2016; 352: i717.


