Prognostic value of blood pressure in patients with high vascular risk in the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial study

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Background Hypertension guidelines advise aggressive blood pressure (BP) lowering in patients with diabetes or high cardiovascular risk, but supporting evidence is limited. We analysed the impact of BP on cardiovascular events in well treated high-risk patients enrolled in a large clinical trial (Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial).

Methods Twenty-five thousand five hundred and eighty-eight patients with atherosclerotic disease or diabetes with organ damage, tolerant to angiotensin-converting enzyme inhibitors, were randomized to ramipril, telmisartan or both. We related the primary composite outcome and its components to: baseline SBP; SBP changes from baseline to event; and average in-trial SBP.

Results The risk of myocardial infarction did not increase with baseline SBP and was unaffected by subsequent SBP change. In contrast, stroke risk progressively increased with baseline SBP (P for trend <0.0001) and decreased with reduction. In patients with baseline SBP less than 130 mmHg, adjusted for several covariates, cardiovascular mortality increased with further SBP reduction (P<0.0001). A J-curve (nadir around 130 mmHg) occurred in the relationship between in-treatment SBP and all outcomes except stroke.

Introduction In healthy populations, long-term epidemiological studies [1,2] showed a log-linear relationship between usual blood pressure (BP) and the risk of serious cardiovascular events. Lowering BP reduces both morbidity and mortality, especially in those with SBP of at least 160 mmHg [3]. The BP goal for maximal benefit is debated, but current guidelines recommend to lower BP to less than 140/90 mmHg for all individuals and to even less than 130/80 mmHg in patients at higher risk [4,5], particularly those with known vascular disease or diabetes.

Some evidence exists for a goal of 140/90 mmHg, or even lower for uncomplicated hypertension [6] but, for BP control below 130/80 mmHg, the uncertainty is larger and may be due both to lack of robust data and also to the different impact on stroke versus other cardiovascular events. In patients with previous stroke, the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) [7] showed cardiovascular mortality and morbidity benefit from BP reduction to 132/79 mmHg rather than 141/83 mmHg. The European trial on Reduction of cardiac events with Perindopril in stable coronary artery disease (CAD) (EUROPA) [8] and the International Verapamil–Trandolapril Study (INVEST) [9] both showed benefit from BP reduction to these levels. In the ADVANCE study [10] in diabetes, a BP difference of 5/2 mmHg translated into a reduction of events (mainly microvascular); major vascular events were not reduced.

Conclusion In high-risk patients, the benefits from SBP lowering below 130 mmHg are driven mostly by a reduction of stroke; myocardial infarction is unaffected and cardiovascular mortality is unchanged or increased. Future trials should be designed to test the value of BP lowering in high-risk patients with SBP in the range of 130–150 mmHg.


Keywords: blood pressure lowering, death, dialysis, high-risk patients, hypertension guidelines, J-curve, mortality, myocardial infarction, stroke

Abbreviations: BP, blood pressure; PP, pulse pressure

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In the INVEST trial, when in-trial BP was considered as a continuous variable, a nadir of the J-curve was observed at 119 mmHg systolic and 84 mmHg diastolic [11].

The recently published Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) [12] provided the opportunity to investigate the relationship between BP and outcome in a large population (>25,000) of high-risk patients. The study [12] did not show any statistical differences in the primary composite outcome and its components between three randomized treatments (telmisartan, ramipril or their combination). Therefore, we analysed the relationship between baseline BP and its changes with treatment (excluding BP after an event) on subsequent cardiovascular outcomes in the pooled study patients with both baseline and at least one further measure.

**Methods**

Between November 2001 and June 2004, 25,588 patients (with baseline and at least one follow-up measure from the original 25,620 patients), older than 55 years and with coronary, peripheral or cerebrovascular disease or diabetes with end-organ damage, were enrolled in a multicentre, double-blind randomized trial in 40 countries with three study arms: ramipril, telmisartan or both (ONTARGET; detailed eligibility criteria of the patients have been described [12]). Briefly, after written informed consent, patients entered a single-blind run-in period in which they received ramipril and telmisartan in progressive doses for 3–4 weeks. The continuation of other antihypertensive drugs other than angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) was allowed. Patients were randomized to receive 80 mg of telmisartan once daily, 5 mg of ramipril once daily or their combination for 2 weeks. Then the dose of ramipril was increased to 10 mg in the two relevant arms. Investigators were encouraged to adhere to accepted hypertension treatment guidelines, with goals of less than 130/80 mmHg for patients with chronic kidney disease or diabetes and less than 140/90 mmHg for the others. Follow-up visits occurred at 6 weeks, at 6 months and then every 6 months until the last scheduled visit. BP values from baseline to the time of the event or to the final protocol visit were used for the analysis. At each of the visits, BP was measured in duplicate after 3 min rest in the sitting position using an automated validated [13] device (OMRON: Model HEM-757; Omron Corp., Kyoto, Japan).

The primary outcome of the study [12] was a composite of cardiovascular death, myocardial infarction (MI), stroke or hospitalization for heart failure [congestive heart failure hospitalization (CHFHI)] adjudicated by a central committee. As mentioned previously, we pooled the data from the three randomized treatment groups (in the 25,588 patients with baseline and follow-up data), as the interaction between outcomes and treatment allocation in Cox regression models showed no significant differences.

**Statistical analysis**

We used the Statistical Analysis Software (SAS) 8.2 release (SAS Institute, Cary, North Carolina, USA). Standard parametric and nonparametric tests were used to compare the main characteristics of patients across the four quartiles of baseline SBP. The potential impact of DBP, and indirectly of pulse pressure (PP), was tested by relating the risk of events to average in-trial SBP for each quartile of in-trial DBP.

In order to explore the relationship between baseline SBP and risk of subsequent events, we first related baseline SBP, divided into quartiles, to the risk of primary study outcome and other outcome events. Then, in order to test the impact of serial changes in BP at any given level of SBP at entry, we tested the relationship between the magnitude of BP change from baseline to follow up, divided into tertiles, and risk of events within each quartile of baseline SBP.

The average SBP change from baseline to follow up (average 56 months) in each patient was calculated as the average of all the BP differences between the first visit and each of the subsequent visits up to an incident event of censoring. Finally, in order to provide more insight into the impact of in-trial SBP, we tested the relationship of primary study outcome and its components with in-trial SBP, excluding baseline SBP from analysis divided into deciles. For each decile, the risk of event and the hazard ratio were adjusted by age, sex, current smoker, diabetes, history of CAD, stroke and peripheral artery disease, use of aspirin, statins, diuretics and β-blockers.

We used the multivariate Cox proportional hazard model to test the relationships between baseline SBP, SBP changes and in-trial SBP. In addition to unadjusted estimates, we adjusted by age (years) and sex, and then also by the following covariates, all included into the model: diabetes (yes, no), current smoking (yes, no), ethnicity (white, Asian, black and other), BMI (kg/m²), serum creatinine (mmol/l), history of CAD, stroke and peripheral artery disease (yes, no), use of aspirin, statins, diuretics and β-blockers (yes, no). We did not adjust the prognostic impact of SBP by PP because of the strong collinearity between the two BP measures. In order to account for PP, we examined the association between achieved DBP, divided into quartiles, and the risk of primary outcome at any level of achieved SBP.

As we pooled the data of the three randomized treatment groups, we also tested the interaction between baseline SBP (quartiles) and treatment allocation (telmisartan versus ramipril and combination versus ramipril) in...
Cox regression models. In two-tailed tests, \( P \)-values less than 0.05 were considered significant.

**Results**

**General characteristics of the study population**

The general characteristics of the study population, and treatment additional to the trial medication, have been published [12]. The high baseline risk of the patients is shown by a mean age of 66 years, 75% with known CAD, 49% prior MI, 21% previous stroke, 69% prior hypertension or 37% with high-risk diabetes (Table 1). Prior CHF was an exclusion criterion. The patients were well treated, both for hypertension (57\% \(-\)-blockers, 28\% diuretics and 33\% calcium channel blockers) and for other cardiovascular risks (60\% on statins and 80\% on antiplatelet therapy). The mean baseline SBP ranged from 120.4 to 163.7 mmHg (Table 1), whereas, as expected, the range of in-trial SBP in these quartiles was lower, 125.9–144.5 mmHg (Table 2), partly because of not only added treatment but also from reduced regression dilution bias [14].

**Events**

Overall, there were 1145 new cases of stroke, 1290 of MI (fetal or nonfatal) and 1079 first admissions for CHF. There were 1816 cardiovascular deaths (total deaths were 3061). A first primary outcome occurred in 4214 patients. The separate components of the primary outcome were 1121 cardiovascular deaths, 1139 MIs, 1023 strokes and 931 CHFHs.

**Outcomes related to baseline SBP**

Table 2 shows the unadjusted and adjusted hazard ratio for the primary outcome and its four components by quartiles of baseline SBP. The unadjusted and adjusted hazard ratio for stroke progressively increased along the four quartiles of SBP. In contrast, the unadjusted and adjusted hazard ratio for the primary study outcome and other outcome events either decreased or did not show any statistical change when moving from the first to the second quartile of SBP. None of the interactions between baseline SBP (quartiles) and treatment allocation (telmisartan versus ramipril and combination versus ramipril) was statistically significant.

Table 1 | Main features of the population
<table>
<thead>
<tr>
<th></th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66.4 (7)</td>
<td>65.2 (7)</td>
<td>66.0 (7)</td>
<td>66.7 (7)</td>
<td>67.9 (7)</td>
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<tr>
<td>Age ≥65 years, %</td>
<td>57.1</td>
<td>49.8</td>
<td>54.7</td>
<td>58.7</td>
<td>66.1</td>
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<tr>
<td>Female sex, %</td>
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<td>23.0</td>
<td>25.3</td>
<td>27.8</td>
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<td>Ethnicity</td>
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<td>73.9</td>
<td>73.9</td>
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<td>White</td>
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<td>14.2</td>
<td>14.0</td>
<td>14.4</td>
<td>12.4</td>
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<tr>
<td>Black African</td>
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<td>2.1</td>
<td>2.0</td>
<td>2.3</td>
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</tbody>
</table>

**Table 2**

<table>
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<th>Baseline SBP (quartiles)</th>
<th>I ≤130 mmHg</th>
<th>II 130–142 mmHg</th>
<th>III 142–154 mmHg</th>
<th>IV &gt;154 mmHg</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66.4 (7)</td>
<td>65.2 (7)</td>
<td>66.0 (7)</td>
<td>66.7 (7)</td>
<td>67.9 (7)</td>
</tr>
<tr>
<td>Age ≥65 years, %</td>
<td>57.1</td>
<td>49.8</td>
<td>54.7</td>
<td>58.7</td>
<td>66.1</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>26.7</td>
<td>23.0</td>
<td>25.3</td>
<td>27.8</td>
<td>30.9</td>
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<tr>
<td>Hypertension</td>
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<td>54.2</td>
<td>66.3</td>
<td>74.7</td>
<td>81.4</td>
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<tr>
<td>Diabetes</td>
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<td>31.9</td>
<td>36.1</td>
<td>40.5</td>
<td>42.3</td>
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<tr>
<td>Current cigarette smoking</td>
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<td>14.9</td>
<td>13.0</td>
<td>11.8</td>
<td>10.5</td>
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<tr>
<td>Coronary artery disease</td>
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<td>81.9</td>
<td>75.3</td>
<td>71.1</td>
<td>68.1</td>
</tr>
<tr>
<td>Myocardial infarction</td>
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<td>58.5</td>
<td>50.2</td>
<td>44.7</td>
<td>41.5</td>
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<td>Coronary revascularization</td>
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<td>50.6</td>
<td>46.5</td>
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<td>Stroke or TIA</td>
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<td>17.0</td>
<td>20.2</td>
<td>22.3</td>
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<td>11.2</td>
<td>12.8</td>
<td>14.0</td>
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<tr>
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<td>67.1</td>
<td>62.8</td>
<td>58.8</td>
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</table>

ACE, angiotensin-converting enzyme; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation; TIA, transient ischaemic attack.
Figure 1 shows the unadjusted Kaplan–Meier plots for all the outcomes except CHFH (which showed no significant differences between quartiles, and so is subsequently omitted from the results; Table 2 and Fig. 4). A statistically significant and consistent trend between baseline SBP and risk of events was noted for stroke ($P < 0.0001$). For cardiovascular mortality, the statistically significant trend ($P = 0.0227$) was driven by the upper SBP quartile. No significant trend emerged between baseline SBP and the risk of MI. The progressive increase in the risk of primary outcome with baseline SBP was largely driven by stroke.

**Outcomes related to SBP reduction from baseline to follow up**

Within each quartile of SBP at entry, the relationship between the changes in SBP from baseline to follow up...
and outcome are shown in Fig. 2 (unadjusted for baseline imbalances) and Fig. 3 (adjusted for 14 covariates as well as baseline SBP and baseline DBP; see Statistical analysis).

In the majority of patients, in-trial SBP was lower than the corresponding baseline value, but in many of the patients with SBP at baseline equal or lower than 130 mmHg (first quartile), the average in-trial SBP actually increased during the trial. The benefit of SBP reduction on the primary composite endpoint was largely driven by stroke, although some benefit was also noted with cardiovascular mortality (Fig. 3).

The effects of statistical adjustment for the 10 risk factors are complex. For the primary composite outcome and for stroke, adjustment lessens the apparent benefits of treatment for the lower two quartiles of baseline SBP. For cardiovascular mortality, adjustment results in a significantly worse outcome for BP reduction in those in the lowest quartile of baseline SBP.

In patients with baseline SBP higher than about 130–140 mmHg, greater reductions in SBP resulted in a significant reduction in the primary endpoint and stroke but not MI (Figs 3 and 4). In patients with baseline SBP of 130 mmHg or less, a reduction in SBP from baseline to follow up or an increase by less than 10 mmHg were both associated with an excess risk of cardiovascular mortality when compared with a SBP increase by 10 mmHg or more (P for trend <0.0001). In each quartile of baseline SBP, there was no relationship between the changes in SBP from baseline to follow up and the risk of CHFH (Fig. 4).

For the primary outcome, Fig. 5 shows a J-shaped pattern (nadir 130 mmHg) in the relationship between on-treatment SBP, categorized into deciles, and adjusted risk of events or hazard ratio. The pattern of curve differed among the components of the primary outcome; although a J-curve was apparent for cardiovascular mortality (nadir 130 mmHg) and MI (126 mmHg), it did not hold for stroke.
Influence of in-trial DBP

The association between in-trial DBP and the risk of primary outcome at any level of achieved SBP is reported in Fig. 6. The highest risk occurred in patients with the lowest in-trial DBP (67 mmHg average), followed by those with the highest in-trial DBP (87 mmHg), with quartiles 2 and 3 lowest and almost superimposable (DBP 75 and 79 mmHg, respectively).

Discussion

Our findings, obtained in a large population of well treated patients with established cardiovascular disease or complicated diabetes, show for the first time the effects of a further BP lowering, by adding additional drugs acting on the renin–angiotensin system to their existing BP lowering treatments. Our data question the uncritical application of the generally accepted view that ‘lower is better’ in high-risk individuals.

This may be true for lower risk patients with higher baseline BP (e.g. over 160 mmHg), as enrolled in most hypertension trials. However, this may not hold in older patients with more advanced atherosclerotic disease. The 25,620 elderly patients with a high or very high cardiovascular risk enrolled in the ONTARGET trial [12], with about 4500 events and normal or only mildly raised BP at baseline, provided an opportunity to examine the relationship between BP values, mainly SBP, and cardiovascular risk. The large use of antihypertensive drugs at baseline may explain the normal or near normal BP values in these patients. The trial also allowed investigation of the impact on cardiovascular outcomes of further reduction of SBP by an ACEi, ramipril, an ARB, telmisartan or their combination. Although the trial showed a similar outcome in the three arms, the combination arm showed no greater benefit in terms of the main outcomes but rather some harm in other outcomes, despite a 2 mmHg average lower BP.

Outcomes related to SBP

For stroke, ‘the lower the SBP the lower the risk’ assumption was correct, but for other cardiovascular outcomes, this did not apply for several reasons. First, no relationship was found between SBP reduction and risk
of MI, CHF and cardiovascular mortality. Second, there was a J-curve, with a nadir around 130 mmHg, in the relationship between achieved SBP and event risk for all outcome events except stroke. The observed J-shaped relationship between achieved SBP and the primary outcome does not establish a causal relationship, nor does it allow the conclusion that an inappropriate decrease in SBP with antihypertensive therapy causes an excessive morbidity and mortality. However, these findings emphasize that patients with extensive vascular disease, such as those enrolled in the ONTARGET study, might have an increased risk when SBP is inappropriately lowered beyond a certain critical level. The potential role of concurrent low DBP beyond levels that could compromise myocardial perfusion cannot be excluded (see below). The nadir of the J-curve for DBP, found in clinical studies to be around 78 mmHg diastolic, is well above the value achieved by BP lowering in clinical trials that showed benefit from active treatment versus placebo, possibly because SBP has greater importance for prognosis [2].

Third, there was an excess risk of cardiovascular mortality associated with a further reduction in SBP, or even an increase by less than 10 mmHg, in the subset of patients with baseline SBP of 130 mmHg or less (Fig. 3). This might reflect an occult progression towards CHF or the selection of sicker patients. Such a hypothesis would appear consistent with the statistical significance of the excess risk of mortality in these patients only after adjustment for the baseline imbalances in SBP and other covariates and the concomitant trend towards an excess risk of CHF (Fig. 4).

There were striking differences in the gradient of risk for specific endpoints versus SBP; stroke showed a much steeper gradient than other serious outcomes. Hypertension trials, carried out in generally lower risk patients and with higher baseline BP than those enrolled in ONTARGET, showed a stroke reduction of around 35–40% [2], which was quite similar to observational epidemiology [1] (and our findings), whereas reduction in MI was somewhat less (around 14% in trials versus 20–25% from epidemiological data). A meta-analysis by Staessen et al. [15] in treated and untreated elderly patients with isolated systolic hypertension also found a large difference between the greater benefit for stroke and the very small benefit for MI.

Similarly, in previous trials of secondary prevention that included patients with stroke (PROGRESS [7]) or with coronary heart disease (EUROPA [8] and INVEST [9]), ‘lower is better’ was true for stroke (down to an SBP of about 130 mmHg or even lower) but was not true for...
cardiovascular death or MI. We found that lower SBP was associated with higher cardiovascular mortality (and even total mortality – data not shown) not only as a possible marker of reversed causality, but also possibly due to reduced coronary or renal perfusion in the presence of occult arterial stenoses [11]. In our elderly high-risk population, the well accepted linear relationship (on a doubling scale of risk) between usual BP and outcomes seen in epidemiologic studies did not apply for most outcomes, except stroke.

**Outcome related to in-trial DBP**

For any given level of SBP, the risk of primary outcome was higher with the lowest DBP. Although this might be due to reduced flow from occult stenoses, it might also be an artefact caused by regression to the mean [14], in which extreme BP values (either high or low) are artefacts caused by random noise, or the fact that patients with the lowest DBP (and highest SBP) were those with already diseased arteries (stiff and lacking elastic recoil) [16,17]. Whether or not low BP is a marker of existing disease rather than low pressure causing more events remains unresolved. Another possibility could be a regression dilution bias [14]. This error can be considerably reduced if the BP is re-measured and the bias corrected. We, therefore, used multiple measures of in-trial SBP (before any event) to calculate the hazard associated with differing baseline SBP.

**Limitations**

Although an analysis of BP effects was prespecified, the details of our analysis have been defined posthoc and are therefore open to bias and confounding. A large proportion of patients were on treatment with antiplatelet drugs, β-blockers and statins, all of which reduce cardiovascular risk. In addition, a high proportion of patients...
were also receiving other drugs to lower BP, and so the current population differs in many ways from the individuals included in the epidemiologic studies of apparently healthy people. The use of so many other drugs that could affect either outcomes or BP, or both, might in part mask the potential benefit of BP reduction.

Although the treatment was based on drugs that block the renin–angiotensin–aldosterone system, it is unlikely that the actual drug regimen is relevant. Still, the recent Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial [18] performed in high-risk hypertensive patients, all receiving the same ACEi, suggested that for the same BP effects, adding one drug type compared with another (amlodipine versus hydrochlorothiazide) significantly affected fatal and nonfatal cardiovascular event rates.

Although we used automated BP measurements that minimized the potential errors in BP measurement, alerting reactions might still occur. Patients categorized into groups by BP showed marked differences in other risk factors. Despite extensive adjustments for known factors, such as age, weight and so on, the adjustment might have been inadequate or did not include other unknown factors. Around 70% of the population had a history of hypertension – and were generally well treated for this – but these patients all had advanced cardiovascular disease or were at very high risk, and therefore, our results should not be generalized to all hypertensive patients.

Despite these limitations, our data do suggest that the uncritical enthusiasm for ‘lower is better’ may not be justified for older, sicker patients whose BP is reasonably well controlled, particularly if at lower risk of stroke. The European guidelines correctly emphasize those areas in which the evidence for recommendations is suboptimal. There is a need to gather more evidence from randomized trials similar to the Hypertension Optimal Treatment (HOT) study [19] but using SBP rather than DBP. Particularly for those with SBP in the range of 130–150 mmHg, we need more evidence that balances benefits versus risk in different populations. Until more evidence is available, the present data suggest that we should avoid excessive SBP reduction during treatment in older high-risk patients. We need more evidence for more aggressive treatment (below 130 mmHg SBP) and also more evidence for pressures in the range of 130–150 mmHg, as today the majority of patients seen in practice have SBP in this range – in which the existing evidence for treatment is not as robust as needed [20].

Acknowledgements

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