Is a systolic blood pressure target <140 mmHg indicated in all hypertensives? Subgroup analyses of findings from the randomized FEVER trial

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Aims
Major guidelines recommend lowering systolic blood pressure (SBP) to <140 mmHg in all hypertensives, but evidence is missing whether this is beneficial in (i) uncomplicated hypertensives, (ii) grade 1 hypertensives, and (iii) elderly hypertensives. Providing this missing evidence is important to justify efforts and costs of aggressive therapy in all hypertensives.

Methods and results
Felodipine Event Reduction (FEVER) was a double-blind, randomized trial on 9711 Chinese hypertensives, in whom cardiovascular outcomes were significantly reduced by more intense therapy (low-dose hydrochlorothiazide and low-dose felodipine) achieving a mean of 138 mmHg SBP compared with less-intense therapy (low-dose hydrochlorothiazide and placebo) achieving a mean of 142 mmHg. FEVER included older and younger patients, and patients with and without diabetes or cardiovascular disease. In the analyses here reported, Cox regression models assessed outcome differences between more and less-intense treatments in groups of patients with different baseline characteristics. Significant reductions in stroke were found in uncomplicated hypertensives (23%, P = 0.002), in hypertensives with randomization SBP >153 mmHg (29%, P = 0.03), and in elderly hypertensives (44%, P < 0.001), when their SBP was lowered by more intense treatment. Significant reductions (between 29 and 47%, P = 0.02 to <0.001) were also found in all cardiovascular events and all deaths. Achieving mean SBP values <140 mmHg by adding a small dose of a generic drug prevented 2.1 (uncomplicated hypertensives) and 5.2 (elderly) cardiovascular events every 100 patients treated for 3.3 years.

Conclusions
These analyses provide strong support, missing so far, to guidelines recommending goal SBP <140 mmHg in uncomplicated hypertensives, individuals with moderately elevated BP and elderly hypertensives.
The FEVER trial has been registered on www.clinicaltrials.gov, n. NCT01136863

Keywords
Antihypertensive therapy • Cardiovascular disease • Elderly • Stroke • Systolic blood pressure • Trials

Introduction
A recent document¹ reappraising the 2007 European Society of Hypertension—European Society of Cardiology guidelines for management of hypertension² points out that the recommendation, common to all major guidelines,²-⁴ to lower systolic blood pressure (SBP) to values <140 mmHg in all hypertensive patients is not founded on undisputable evidence. Indeed, most trials showing morbidity and mortality benefits by achieving mean SBP values <140 mmHg were only on patients at high cardiovascular risk,⁵ and in no trial of antihypertensive treatment in the elderly was a mean SBP <140 mmHg achieved in the actively treated group.⁵ Therefore, efforts and costs of intense drug therapy to lower SBP <140 mmHg in millions of uncomplicated

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or elderly hypertensives are still based on opinion rather than evidence.

In the Felodipine Event Reduction (FEVER) randomized trial, lowering SBP to a mean of 138 mmHg by more active treatment was accompanied by significant 25–35% reductions in cardiovascular outcomes when compared with SBP lowering to a mean of 142 mmHg by less active treatment.6 However, the FEVER cohort included 42% of hypertensives with previous cardiovascular events and 13% of diabetics, and its results cannot safely be extended to uncomplicated moderate hypertensive patients1,5 unless specific subgroup analyses are provided.

The FEVER study6 was of sufficiently large size (9711 patients) and outcome differences between the two treatment arms conspicuous enough (average 28% reduction) to allow separate analyses in different risk groups, and the analyses here reported help clarifying some of the problems the ESH Task Force has found still open: is aiming at SBP <140 mmHg beneficial in (i) uncomplicated hypertensive patients, (ii) individuals with moderately elevated BP, and (iii) elderly hypertensives?

Methods

Study population and treatment

Details on the FEVER study design and organization have been published.6 After approval by local Ethics Committees, and obtaining patients’ written consent 10 426 Chinese patients, aged 50–79 years, of either sex, with a screening SBP of 210 mmHg or less and diastolic blood pressure (DBP) <115 mmHg if under antihypertensive treatment, or SBP 160–210 mmHg or DBP 95–115 mmHg if untreated, and other inclusion criteria (one previous cardiovascular event or two additional risk factors if aged 60 years, one additional risk factor if >60 years) were switched to or received open label hydrochlorothiazide 12.5 mg once daily. A total of 9800 subjects who, after 6 weeks, had SBP 140–180 mmHg or DBP 90–100 mmHg were assigned randomly and blindly to add either felodipine (5 mg, once daily) or identical placebo, for an average follow-up of 40 months. Randomization was done centrally with stratification based on enrolling unit, gender, age (> vs. ≤65 years), presence or absence of diabetes mellitus, presence or absence of clinical evidence or history of cardiovascular disease. Follow-up was double-blind until trial end. According to protocol (if blood pressure ≥160/95 mmHg for two consecutive visits) added antihypertensive therapy was given open label: 33.9% of felodipine patients and 42.3% of placebo patients received added therapy (mostly intensification of diuretic therapy and addition of angiotensin converting enzyme-inhibitor). During treatment SBP/DBP averaged 142.1/84.5 mmHg in the placebo group and 137.9/82.5 mmHg in the felodipine group with significant reductions (26–35%) of each of all major cardiovascular outcomes in the felodipine group.6

Classification by individual risk factors or disease

The effects of the two randomized treatments on outcomes were compared in FEVER patients grouped according to the presence or absence at randomization of each of five major risk factors, two signs of asymptomatic organ damage, and two coconcomitant diseases: gender (men vs. women); SBP (higher or lower than median 153 mmHg); age (> vs. ≤65 years); smoking (current smokers vs. non-smokers plus ex-smokers); serum total cholesterol (> vs. ≤5.5 mmol/L); presence vs. absence of left ventricular hypertrophy (LVH) (Sokolow and Lyon electrocardiographic voltage and S-T T-wave criteria); presence or absence of isolated systolic hypertension (SBP ≥140 mmHg and DBP <90 mmHg); presence vs. absence of diabetes (fasting plasma glucose ≥7.0 mmol/L or current use of antidiabetic therapy); presence or absence of clinical evidence or history of one cardiovascular event (myocardial infarction or stroke; stable angina or clinical evidence of coronary heart disease; congestive heart failure ≥ New York Heart Association class II; peripheral arterial disease; transient ischaemic attack); presence of either diabetes or cardiovascular disease or absence of both. Subgroups based on variables used for randomization stratification (men vs. women, older vs. younger, patients with vs. without diabetes, patients with vs. without cardiovascular disease) were prespecified, the others were post hoc.

Definition of outcomes

Primary outcome was time to first stroke (fatal or non-fatal). Prespecified secondary outcomes were time to: (i) first cardiovascular event (death from cardiovascular disease, non-fatal stroke, non-fatal myocardial infarction, dissecting aortic aneurysm, heart failure requiring additional treatment, percutaneous transluminal coronary angioplasty, or coronary by-pass graft, angioplasty or surgical procedures for peripheral vascular disease, serum creatinine ≥355 μmol/L), (ii) first cardiac event (death from coronary heart disease, including sudden death, non-fatal myocardial infarction, death from heart failure, heart failure requiring additional therapy, percutaneous transluminal coronary angioplasty or coronary by-pass graft); (iii) death from any cause; (iv) death from cardiovascular disease, a composite of death from coronary heart disease, fatal stroke and death from heart failure.

All outcomes were validated by an independent Event Adjudicating Committee, blind to randomized treatment. Only validated outcomes were included in the analyses.

Statistical methods

All analyses were performed according to the intention-to-treat principle. Cox regression models were used to assess outcome differences between treatments within any given group, with calculation of hazard ratios (HRs) and their 95% confidence intervals (CIs). Cumulative event rates over time were illustrated by Kaplan–Meier curves. Only time to first event was considered for composite outcomes, but a single patient could have a first event counted in each individual outcome category. Heterogeneity of hazard ratios among groups defined by baseline characteristics was investigated by interaction analyses. All tests were two-sided and the significance level chosen was P < 0.05. Statistical analyses used the SAS System (version 8.2: SAS Institute, Inc., Cary, NC, USA).

Results

On-treatment blood pressures achieved by randomized treatment in various groups of patients

The baseline characteristics of patients in each risk group were presented in a previous paper.7 In all groups considered, average on-treatment SBP achieved mean values <140 mmHg in the felodipine arm, whereas SBP mean remained >140 mmHg on placebo. Only in patients with higher SBP at randomization (mean 164.5 mmHg) mean SBP remained >140 mmHg in both treatment arms, whereas in those with lower randomization SBP (mean
144.2 mmHg) this decreased to <140 mmHg in both arms. In all groups, on-treatment DBP averaged <84 mmHg in the felodipine, and commonly >84 mmHg in the placebo arm (with the exception of subjects with isolated systolic hypertension). In all groups, SBP was lower by 3.7–6.5 mmHg and DBP by 1.6–3.1 mmHg in the felodipine arm (Table 1).

Effects of randomized treatment on the primary outcome (fatal and non-fatal stroke)

Kaplan–Meier curves with cumulative strokes in patients randomized to felodipine or placebo are illustrated in Figure 1 for the three groups of patients for whom benefits of reducing SBP <140 mmHg are yet unknown1,5: (i) uncomplicated hypertensives; (ii) hypertensives with randomization SBP <153 mmHg (mean 144/89 mmHg); (iii) elderly hypertensives (mean age 69.5 years). Significant reductions in stroke incidence were observed in these groups. In absolute terms, further lowering of SBP/DBP by a few millimeters of mercury over an average treatment period of 3.3 years led to the prevention of 1.6, 1.1, and 3.8 strokes every 100 patients with uncomplicated hypertension, moderately elevated BP, and elderly hypertension, respectively.

In all other groups, both those with and those without a given risk factor or disease, the HRs were consistently below unity, with values between 0.54 and 0.91, i.e. favouring the treatment (felodipine) achieving a lower average SBP. In most of the groups, HRs were statistically significant (Table 1). Statistical significance was not achieved in younger patients (mean age 57.6 years), those with baseline cardiovascular disease, smokers, patients with higher cholesterol, and with isolated systolic hypertension. However, interaction analyses indicated that there was no major between-group difference in stroke reduction by lower SBP/DBP values (P always >0.05), except for age (P = 0.005).

Effects of randomized treatment on secondary outcomes

Table 2 and Figure 2 illustrate that greater lowering of SBP/DBP was beneficial not only on stroke, but also on secondary outcomes in the elderly, in individuals with moderate blood pressure elevation at randomization and in hypertensives with neither cardiovascular disease nor diabetes (uncomplicated hypertensives), as well as in women. In absolute terms, 2.1, 1.6, and 5.2 cardiovascular events could be prevented over 3.3 years every 100 patients with uncomplicated hypertension, moderate blood pressure elevation, and elderly hypertension, respectively.

In most other groups, HRs for secondary outcomes were consistently below unity: 0.53–0.93 for all cardiovascular events, 0.36–0.93 for all cardiac events, 0.63–0.86 for death by any cause (but 1.0 in diabetics), 0.51–0.97 for cardiovascular death

### Table 1  Fatal and non-fatal stroke (primary endpoint) in various groups of patients with different baseline characteristics, achieving different on-treatment blood pressure according to randomized treatment

| Baseline characteristics | Patients’ number | On-treatment SBP/DBP (mmHg) | Strokes/1000 pt.y | HR (95% CI) | P   | P
<table>
<thead>
<tr>
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<td></td>
<td></td>
<td>Felodipine</td>
<td>Placebo</td>
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<tr>
<td>All patients</td>
<td>9711</td>
<td>137.9/82.5</td>
<td>142.1/84.5</td>
<td>11.2</td>
<td>15.9</td>
<td>0.73 (0.60–0.89)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
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<tr>
<td>&gt;65</td>
<td>3179</td>
<td>139.7/81.2</td>
<td>145.5/83.6</td>
<td>12.3</td>
<td>23.7</td>
<td>0.56 (0.41–0.75)</td>
</tr>
<tr>
<td>≤65</td>
<td>6532</td>
<td>137.5/83.2</td>
<td>141.7/85.1</td>
<td>10.1</td>
<td>11.5</td>
<td>0.91 (0.71–1.18)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
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<td></td>
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<tr>
<td>≥153</td>
<td>4856</td>
<td>141.4/83.6</td>
<td>146.1/85.7</td>
<td>13.2</td>
<td>19.0</td>
<td>0.74 (0.58–0.95)</td>
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<td>&lt;153</td>
<td>4855</td>
<td>134.7/81.6</td>
<td>138.4/83.8</td>
<td>8.4</td>
<td>11.7</td>
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<td>1241</td>
<td>139.0/82.3</td>
<td>143.6/84.1</td>
<td>13.4</td>
<td>19.8</td>
<td>0.56 (0.34–0.92)</td>
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<tr>
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<td>141.9/84.9</td>
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<td>14.6</td>
<td>0.77 (0.62–0.96)</td>
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<tr>
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<td>CVD or DM</td>
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<tr>
<td>Men</td>
<td>5920</td>
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<td>142.4/85.3</td>
<td>13.0</td>
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<td>140.2/84.2</td>
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<td>14.5</td>
<td>0.71 (0.56–0.90)</td>
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<td>141.5/85.0</td>
<td>8.6</td>
<td>12.2</td>
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<td>142.4/84.6</td>
<td>11.5</td>
<td>16.4</td>
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<td>15.0</td>
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<td>ISH</td>
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<tr>
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<td>2161</td>
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<td>142.1/80.6</td>
<td>9.0</td>
<td>13.9</td>
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<td>11.3</td>
<td>15.7</td>
<td>0.71 (0.57–0.87)</td>
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CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; HR, hazard ratio; ISH, isolated systolic hypertension; LVH, left ventricular hypertrophy; pt. y, patients years; Rand, randomization; SBP, systolic blood pressure; P, P-value for HR; Pia, P-value for interaction between subgroups.
Figure 1  Kaplan–Meier curves for incident strokes (fatal and non-fatal). FEVER hypertensive patients with baseline characteristics indicated on the top of each set of curves. Blue lines: placebo treatment; red lines: felodipine treatment. Hazard ratios with 95% confidence intervals are also indicated. The number of patients at risk at each of the times indicated in the abscissa is listed at the bottom of each set of curves. CVD, cardiovascular disease; SBP, systolic blood pressure.
(but 1.0 in diabetics). For the numerically most important outcome, all cardiovascular events, in 16 of 20 groups the upper 95% CI did not cross the line of unity (Table 2). Interaction tests did not reach statistical significance (P > 0.05) for the comparison of most subgroups and outcomes, with the notable exception of the subgroups based on age (P < 0.001 for all cardiovascular events, but P > 0.05 for all cardiac events, all deaths and cardiovascular mortality). There was an occasional significance in the numerous comparisons between patients with or without cardiovascular disease, likely due to chance.

### Discussion

#### Uncomplicated hypertensive patients

Reduction in hard cardiovascular outcomes by aiming at SBP <140 mmHg in uncomplicated hypertensives is a relatively unexplored area, evidence being limited to the Medical Research Council mild hypertension trial, which included very low-risk hypertensives (8.2% cardiovascular events in 10 years on placebo), but found that lowering SBP/DBP to mean values of 138/86 rather than 149/91 mmHg significantly reduced stroke and all cardiovascular events, but neither coronary events nor mortality. The Hypertension Detection and Follow-up Program also showed benefits of SBP lowering to mean values <140 mmHg, but in hypertensives who could hardly be classified as low risk since their cardiovascular risk was three times greater than in the Medical Research Council trial. In the Hypertension Optimal Treatment (HOT) study, including individuals with an overall cardiovascular risk of ~10% in 10 years mean SBP remained >140 mmHg in all treatment groups. In Cardio-Sis tighter BP control in non-diabetic hypertensives significantly reduced the rate of LVH, but information on hard outcomes was limited by their low number in this small study. In FEVER among the 4850 hypertensives with neither cardiovascular disease nor diabetes incident cardiovascular events were 13.6% in 10 years (16.8% on placebo and 10.7% on felodipine), and SBP/DBP reduction to mean values of 138.1/82.8 mmHg rather than 141.9/85.1 was accompanied by significant 40% reductions in stroke, cardiovascular events, cardiac events, and all cause mortality.

We also found that in FEVER achieving mean SBP <140 mmHg significantly reduced stroke and cardiovascular events in women whose 10-year cardiovascular risk was only 13.9%. Current evidence of benefits of antihypertensive treatment in women is largely based on meta-analyses, significant data from individual trials being scanty. Also hypertensives with randomization SBP <153 mmHg and 10-year cardiovascular risk 13.8% significantly benefited from lowering SBP to a mean of 134.7 mmHg rather than 138.4 mmHg.

Because these analyses were deliberately restricted to moderate risk hypertensives, absolute benefits could not be large, but prevention of 1.6–2.1 cardiovascular events (the majority being strokes) every 100 patients over 3.3 years appears worth aiming at a slightly lower blood pressure by the addition of a small dose of a generic antihypertensive drug, such as 5 mg felodipine.

### Table 2

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>All CV events</th>
<th>All cardiac events</th>
<th>All deaths</th>
<th>Cardiovascular death</th>
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<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
<td>P&lt;sub&gt;ia&lt;/sub&gt;</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>All patients</td>
<td>0.73 (0.61–0.86)</td>
<td>&lt;0.001</td>
<td>0.65 (0.47–0.89)</td>
<td>0.007</td>
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<tr>
<td>Age &gt;65 (years)</td>
<td>0.53 (0.41–0.69)</td>
<td>&lt;0.001</td>
<td>0.49 (0.31–0.77)</td>
<td>0.002</td>
</tr>
<tr>
<td>SBP ≥153 (mmHg)</td>
<td>0.73 (0.59–0.91)</td>
<td>0.05</td>
<td>0.61 (0.41–0.91)</td>
<td>0.12</td>
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<td>Diabetes Yes</td>
<td>0.80 (0.54–1.17)</td>
<td>0.26</td>
<td>0.53 (0.52–1.67)</td>
<td>0.82</td>
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<td>CVD Yes</td>
<td>0.77 (0.61–0.98)</td>
<td>0.03</td>
<td>0.56 (0.37–0.85)</td>
<td>0.07</td>
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<td>CVD or DM Yes</td>
<td>0.80 (0.65–0.99)</td>
<td>0.04</td>
<td>0.55 (0.52–1.08)</td>
<td>0.13</td>
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<td>Gender Men</td>
<td>0.75 (0.61–0.91)</td>
<td>0.005</td>
<td>0.54 (0.44–0.92)</td>
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<td>Smoking Yes</td>
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<td>0.005</td>
<td>0.56 (0.19–0.67)</td>
<td>0.01</td>
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<td>Cholesterol &gt;5.7 (mmol/L)</td>
<td>0.77 (0.52–1.15)</td>
<td>0.21</td>
<td>0.62 (0.29–1.44)</td>
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<td>LVH Yes</td>
<td>0.69 (0.42–1.13)</td>
<td>0.15</td>
<td>0.71 (0.36–1.79)</td>
<td>0.60</td>
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<tr>
<td>ISH Yes</td>
<td>0.76 (0.45–0.95)</td>
<td>0.03</td>
<td>0.33 (0.16–0.71)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; HR, hazard ratio; ISH, isolated systolic hypertension; LVH, left ventricular hypertrophy; pt, patients years; Rand, randomization; SBP, systolic blood pressure; P, P-value for HR; P<sub>ia</sub>, P-value for interaction between subgroups.
Elderly hypertensives

In no previous trial of antihypertensive therapy in the elderly did SBP achieve mean values < 140 mmHg, since all studies aimed at < 150 mmHg. Therefore, our finding that in hypertensives aged > 65 years (at a mean age similar to that in most previous trials) lowering of SBP by felodipine to a mean just < 140 mmHg (rather than 145 mmHg in the placebo arm) significantly reduced stroke, cardiovascular events, cardiac events, and all death by 40–50% (with prevention of 3.8 strokes and 5.2 cardiovascular events every 100 patients over 3.3 years) is the first evidence in favour of aiming at a SBP < 140 mmHg also in the elderly. Admittedly, the mean SBP achieved on felodipine in the elderly was just < 140 mmHg (139.7 mmHg), but it was definitely lower than mean values achieved in all other trials on the elderly (never < 143 mmHg and often > 150 mmHg).

It should be acknowledged that in younger patients (< 65 years) achievement of a mean SBP < 140 mmHg did not significantly reduce any type of event, and that age was the only subgroup in which interaction analyses indicated significant differences between older and younger individuals, at least for stroke and all cardiovascular events (though not for mortality). However, HRs were always lower than unity, and the low cardiovascular risk (less than half that of the elderly) made significance difficult to be reached.

High-risk hypertensives

Doubts were recently raised about the foundation of recommending SBP values < 130 in diabetics or patients with previous cardiovascular events, an issue supported by subsequent publication of the ACCORD trial in diabetics. Even evidence favouring SBP < 140 mmHg in these patients is scanty. In diabetics, MicroHOPE reported a 25% reduction in primary outcome by reducing SBP to a mean of 139 rather than 142 mmHg, and ADVANCE a 9% reduction in primary outcome (mostly microvascular events) for a SBP mean of 134 rather than 140 mmHg. Among patients with previous stroke, the benefits of reducing SBP to a mean of 132 rather than 141 mmHg, and PROGRESS a 9% reduction in primary outcome (mostly microvascular events) for a SBP mean of 134 rather than 140 mmHg.

The often reported opinion that the benefit of antihypertensive therapy is proportionally greater in high-risk patients is not based on direct comparisons in trials, and contrasts with the meta-analysis by Law et al. showing the same proportional reduction in coronary events, and a slightly lower prevention of strokes in subjects with history of vascular disease than in subjects without. Several of our analyses of the FEVER study add information in higher vs. lower risk hypertensives. In diabetic patients,
we found a significant 44% reduction in strokes with more intense treatment, but a 20% reduction in cardiovascular events and a 7% in cardiac events did not achieve statistical significance, and no change was found in all and cardiovascular deaths. On the other hand, all types of outcomes were significantly reduced in non-diabetics. However, the group of diabetics was relatively small (n = 1241), and all P-values for interactions >0.05. In patients with higher serum cholesterol values more intense BP lowering had similar benefits as in the subgroup with lower cholesterol, except for mortality which was more markedly reduced in the higher cholesterol subgroup. However, FEVER patients with cholesterol >5.7 mmol/L were not found at an increased cardiovascular risk,7 an observation consistent with epidemiological data from Asia showing that high cholesterol adds little cardiovascular risk, particularly for stroke, at SBP >150 mmHg.29 Anyway, in FEVER this was not due to the use of statins, which were taken by <1% of the patients. In the relatively large group of patients with a previous cardiovascular disease (n = 3894), there were significant reductions in all cardiovascular events, cardiac events, all deaths, and cardiovascular deaths. However, with the exception of the elderly, in higher risk groups of FEVER, the relative reduction in cardiovascular events tended to be somewhat lower and absolute event reduction similar to that in lower risk groups (either/neither cardiovascular disease or diabetes –4.7/–6.1, men/women –5.9/–5.7, with/without LVH –6.2/–5.5 cardiovascular events per 1000 patient years).

Strengths and limitations

The strength of the analyses here reported is that FEVER included a large cohort of hypertensives (n = 9711), the number of incident cardiovascular events was high (n = 575), benefit of more intense blood pressure lowering was large (27% outcome reduction) and highly significant (P < 0.002). Furthermore, reports of benefits of lowering SBP to a mean <140 mmHg are not only based, as frequent in subgroup analyses of trials, on the finding that subgroup HRs are not heterogeneous, even when formal significance is lost. In our analyses, the statement that SBP lowering to a mean <140 mmHg was beneficial in a given subgroup was based on the fact that statistical significance was achieved. Because of the descriptive values of our analyses, correction for multiple testing was done, but in many cases, e.g. in elderly patients and in those without any previous cardiovascular disease, HRs for stroke had P-values <0.001.

Limitations are those inherent in subgroup or post hoc analyses, although gender, age, diabetes, and cardiovascular disease were used to stratify randomization, and therefore randomization was preserved and most covariates were satisfactorily controlled in groups based on these variables. Not all individuals allocated to felodipine had their SBP reduced <140 mmHg, and not all individuals receiving placebo had SBP >140 mmHg; therefore, the different outcome incidences refer to average rather than individual SBP values below or above 140 mmHg. Hypertensives with randomization SBP <153 mmHg cannot be defined as grade 1 because at randomization FEVER patients were on low-dose hydrochlorothiazide (12.5 mg daily), and their untreated blood pressure was unknown. However, average SBP under very mild therapies was only 144 mmHg, and it is unlikely that a consistent part of these patients had more than a moderate BP elevation.

In all subgroups SBP means achieved under felodipine were only slightly <140 mmHg, therefore the present analyses cannot shed light on a possible J-shaped relationship between achieved BP and outcomes, suggested by recent post hoc analyses of randomized trials, which are, at best, hypothesis generating.30 Finally, this study included Chinese subjects only. This gives homogeneity to the trial, and provides evidence on stroke prevention in a population heavily contributing to stroke burden worldwide. These results can be extrapolated to Caucasian or African American patients only with reservations. The relationship between BP and stroke is steeper in Chinese than in Western populations,11 and it is likely that in the latter a SBP difference >4 mmHg may be needed to obtain similar reductions in stroke. Stroke is one of the main causes of disease burden in Western populations also, and its reduction is one of the major benefits of antihypertensive therapy. Incidence of secondary outcomes (all cardiac events, death by any cause) was also significantly reduced in FEVER,6 as well as in relevant subgroups analysed in this paper, thus indicating stroke prevention was not the only benefit of BP lowering, and this suggests that benefits of aiming at a SBP <140 mmHg may be obtained in other population groups in the world.

Throughout this paper, the benefits of more intense treatment have been attributed to the albeit small BP difference, in line with evidence from trial meta-analyses that the benefits of all antihypertensive agents are due to BP lowering.13,28 A specific contribution of felodipine cannot be excluded, however, especially since calcium antagonists may have a slightly greater effectiveness in stroke prevention than other agents,28 and stroke was the most frequent outcome in our Chinese cohort.

Conclusions

These current analyses of FEVER give evidence of outcome reduction by targeting SBP <140 mmHg in hypertensive patients at old age, or without diabetes, or without concurrent cardiovascular disease, or with neither diabetes nor cardiovascular disease, as well as in individuals with moderate initial elevation of blood pressure, thus providing well-needed support to the guidelines recommendation of a goal SBP <140 mmHg in the elderly and uncomplicated hypertensive patients. The size of the benefit is greater in the elderly than in low-to-moderate-risk uncomplicated hypertensives, but even in the latter group it appears to justify the small and modestly expensive increment of drug therapy required in FEVER to achieve goal SBP. Analyses in patients with high risk, because of diabetes, previous cardiovascular disease and LVH, also support a SBP goal <140 mmHg in these patients, but it remains open whether these high-risk patients may have greater benefit from even lower BP targets or run the risk of excessive BP reduction (J-shaped curve) because of a more elevated threshold for organ underperfusion.13,30

Although these analyses provide support, entirely missing so far, to the prudent recommendation to lower SBP <140 mmHg in all hypertensive patients independently of their overall risk or baseline characteristics, they are subgroup analyses, a part of them are
post hoc, and therefore require confirmation in prospectively planned trials.

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Left ventricular outflow tract pseudoaneurysm compromising blood flow through the left main coronary artery after mechanical aortic valve implantation

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A 73-year-old male with a history of mechanical aortic valve replacement and DDD pacemaker implantation was referred to our hospital with progressive anginal complaints. Invasive coronary angiography (CA) revealed systolic compression of the left main coronary artery (LMCA), suggesting an extra-cardiac mass compromising blood flow. Single photon emission computed tomography (SPECT) and multislice computed tomography-CA (MSCT-CA) were obtained which revealed a pseudoaneurysm originating from half the circumference of the left ventricular outflow tract (LVOT) extending over the aortic root. The main stem of the left coronary artery and its proximal circumflex and anterior descending branches were embedded in the aneurysm. Stress SPECT images did not reveal ischaemia. The extensive dehiscence of the aortic root, also depicted by the tilting of the mechanical aortic valve on the invasive angiogram, was the reason to perform a re-operation with implantation of a Bentall prosthesis. A Bio-Valsalva 25 mm prosthesis was implanted on the remaining LVOT at the level of the mitral valve annulus. Cultures obtained during the operation grew coagulase-negative staphylococci; the pseudoaneurysm might be caused by a low-grade infectious process. Post-operatively, antibiotics were continued for 6 weeks. Currently, 10 months after the operation, the patient is doing reasonably well; follow-up MSCT-CA revealed no paravalvular cavities or valvular abnormalities.

Left ventricular outflow tract pseudoaneurysm is a rare and serious complication after implantation of a mechanical aortic valve. It is associated with a history of endocarditis and the development of anginal complaints. Surgery is the first-line therapeutic option. Reports exist on successful stent implantation in the LMCA and percutaneous closure of the pseudoaneurysm.

Panel A. Invasive coronary angiogram right caudal view, showing systolic compression of the left main coronary artery.

Panel B. Multislice computed tomography image, showing a large pseudo aneurysm originating from the left ventricular outflow tract just below the mechanical aortic valve.

Panel C. Volume rendered multislice computed tomography coronary angiography image, showing the left main coronary artery and its proximal anterior descending and circumflex branches embedded in the pseudoaneurysm. The pseudoaneurysm extends over half the circumference of the aortic root.

Panel D. Multislice computed tomography image showing the post-operative situation with the Bentall prosthesis implanted at the level of the mitral valve annulus. No evidence of residual paravalvular aneurysm formation.