Effects of blood pressure lowering on cardiovascular risk according to baseline body-mass index: a meta-analysis of randomised trials

Blood Pressure Lowering Treatment Trialists’ Collaboration*

Summary

Background The cardiovascular benefits of blood pressure lowering in obese people compared with people of normal weight might depend on choice of drug. We compared the effects of blood pressure-lowering regimens on cardiovascular risk in groups of patients categorised by baseline body-mass index (BMI).

Methods We used individual patient data from trials included in the Blood Pressure Lowering Treatment Trialists’ Collaboration to compare the effects of different classes of blood pressure-lowering regimens for the primary outcome of total major cardiovascular events (stroke, coronary heart disease, heart failure, and cardiovascular death). We used meta-analyses and meta-regressions to assess interactions between treatment and BMI when fitted as either a categorical variable (<25 kg/m², 25 to <30 kg/m², and ≥30 kg/m²) or a continuous variable.

Findings Analyses were based on 135 715 individuals from 22 trials who had 14 353 major cardiovascular events. None of the six primary comparisons showed evidence that protection varied by drug class across the three BMI groups (all p for trend >0·20). When analysed as a continuous variable, angiotensin-converting-enzyme inhibitors gave slightly greater protection for each 5 kg/m² higher BMI than did calcium antagonists (hazard ratio 0·93, 95% CI 0·89–0·98; p=0·004) or diuretics (0·93, 0·89–0·98; p=0·002). The meta-regressions showed no relation between BMI category and the risk reduction for a given fall in systolic blood pressure. By contrast with a previous report, we noted no relation between BMI and the efficacy of calcium antagonists compared with diuretics.

Interpretation We found little evidence that selection of a particular class of blood pressure-lowering drug will lead to substantially different outcomes for individuals who are obese compared with those who are lean.

Funding None.

Introduction High blood pressure is the leading risk factor for cardiovascular disease worldwide and more frequently occurs in obese individuals than in those of normal weight. Treatment to lower blood pressure can substantially reduce cardiovascular risk in diverse patient groups, but debate continues about how obesity changes the link between blood pressure and cardiovascular risk. This uncertainty is underpinned by the suggestion that the pathogenesis of hypertension differs between lean and obese individuals.

Investigators did a series of post-hoc analyses comparing the effects of blood pressure-lowering drugs at different levels of baseline body-mass index (BMI) for large-scale trials of blood pressure lowering, with inconsistent findings. Three trials reported no interaction between BMI and reductions in blood pressure on vascular risk, and one suggested greater protection with enalapril than with placebo in individuals with high BMI (25–30 kg/m²). In 2013, an analysis of the ACCOMPLISH trial reported that hydrochlorothiazide was less effective than amlodipine in normal-weight patients with hypertension, but of similar efficacy in obese patients when used with an angiotensin-converting-enzyme (ACE) inhibitor. On the basis of these findings, a strong recommendation was made for body size to be a key consideration for clinicians when choosing drugs to lower blood pressure, although management guidelines do not contain specific recommendations, and investigators have noted a need for better evidence.

The Blood Pressure Lowering Treatment Trialists’ Collaboration was established to undertake a series of overviews of trials investigating the effects of blood pressure-lowering drugs on cardiovascular mortality and morbidity, including assessments of the comparative effects of drugs between patient subgroups. We compared the effects of different blood pressure-lowering regimens on cardiovascular risk in groups of patients categorised by baseline BMI.

Methods

Search strategy and selection criteria We searched Ovid Medline, Embase, and the Cochrane Central Register of Controlled Trials for reports published from Jan 1, 1966, to May 1, 2014, to identify randomised controlled trials of drugs to lower blood pressure that have reported treatment by BMI interactions for effects on major vascular events or mortality, but not provided individual participant data to...
one did not include long-term cardiovascular outcomes; one was an unpublished conference abstract; one compared two types of patient referral rather than two blood-pressure-lowering drugs; one has since been withdrawn from press (retracted); one did not report an interaction term between body-mass index groups; and one was already included in the BPLTTC database.

Figure 1: Study selection

†12 reports were excluded on the basis of the following: four analysed the control and treatment groups as one; one did not include long-term cardiovascular outcomes; one was an unpublished conference abstract; one compared two types of patient referral rather than two blood-pressure-lowering drugs; one has since been withdrawn from press (retracted); one did not report an interaction term between body-mass index groups; and one was already included in the BPLTTC database.

Table: Baseline patient characteristics and difference in blood pressure by body-mass index category

<table>
<thead>
<tr>
<th>BMI category</th>
<th>n</th>
<th>Mean age (years)</th>
<th>Baseline SBP (mm Hg)</th>
<th>Baseline DBP (mm Hg)</th>
<th>Men (%)</th>
<th>Diabetes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor vs placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25 kg/m²</td>
<td>10,250</td>
<td>63.8</td>
<td>140.4</td>
<td>80.5</td>
<td>69.6%</td>
<td>57.1%</td>
</tr>
<tr>
<td>25 to &lt;30 kg/m²</td>
<td>16,975</td>
<td>63.1</td>
<td>141.9</td>
<td>82.2</td>
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<td>≥30 kg/m²</td>
<td>9,187</td>
<td>62.5</td>
<td>144.8</td>
<td>83.3</td>
<td>64.7%</td>
<td>87.4%</td>
</tr>
<tr>
<td>Calcium antagonist vs placebo</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25 kg/m²</td>
<td>1,803</td>
<td>69.5</td>
<td>167.3</td>
<td>84.2</td>
<td>41.0%</td>
<td>11.6%</td>
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<tr>
<td>25 to &lt;30 kg/m²</td>
<td>2,896</td>
<td>67.1</td>
<td>165.6</td>
<td>84.8</td>
<td>44.6%</td>
<td>19.5%</td>
</tr>
<tr>
<td>≥30 kg/m²</td>
<td>1,377</td>
<td>64.8</td>
<td>162.9</td>
<td>85.5</td>
<td>35.1%</td>
<td>30.0%</td>
</tr>
<tr>
<td>More intensive vs less intensive</td>
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<td>4,404</td>
<td>62.6</td>
<td>169.0</td>
<td>104.3</td>
<td>45.7%</td>
<td>10.9%</td>
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<tr>
<td>25 to &lt;30 kg/m²</td>
<td>9,801</td>
<td>61.3</td>
<td>168.2</td>
<td>104.4</td>
<td>58.5%</td>
<td>14.6%</td>
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<tr>
<td>≥30 kg/m²</td>
<td>6,636</td>
<td>59.8</td>
<td>167.1</td>
<td>103.7</td>
<td>50.5%</td>
<td>24.8%</td>
</tr>
<tr>
<td>ACE inhibitor vs diuretic or β blocker</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>&lt;25 kg/m²</td>
<td>11,386</td>
<td>66.6</td>
<td>160.5</td>
<td>89.9</td>
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<td>25 to &lt;30 kg/m²</td>
<td>19,205</td>
<td>65.1</td>
<td>158.0</td>
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<td>20.1%</td>
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<td>≥30 kg/m²</td>
<td>15,263</td>
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<td>153.4</td>
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<tr>
<td>Calcium antagonist vs diuretic or β blocker</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>&lt;25 kg/m²</td>
<td>10,365</td>
<td>67.2</td>
<td>162.6</td>
<td>92.4</td>
<td>44.5%</td>
<td>14.2%</td>
</tr>
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<td>25 to &lt;30 kg/m²</td>
<td>17,347</td>
<td>65.5</td>
<td>160.2</td>
<td>92.8</td>
<td>56.4%</td>
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<tr>
<td>≥30 kg/m²</td>
<td>14,191</td>
<td>64.3</td>
<td>155.0</td>
<td>90.2</td>
<td>45.1%</td>
<td>35.0%</td>
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<tr>
<td>ACE inhibitor vs calcium antagonist</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25 kg/m²</td>
<td>6,379</td>
<td>70.4</td>
<td>158.5</td>
<td>86.3</td>
<td>51.1%</td>
<td>21.0%</td>
</tr>
<tr>
<td>25 to &lt;30 kg/m²</td>
<td>9,842</td>
<td>68.4</td>
<td>155.5</td>
<td>87.0</td>
<td>56.8%</td>
<td>32.8%</td>
</tr>
<tr>
<td>≥30 kg/m²</td>
<td>9,174</td>
<td>65.5</td>
<td>150.7</td>
<td>86.4</td>
<td>45.1%</td>
<td>46.8%</td>
</tr>
</tbody>
</table>

SBP=systolic blood pressure. DBP=diastolic blood pressure. ACE=angiotensin-converting enzyme.

We used keywords including variations on “obesity”, “body-mass index”, “antihypertensive agent”, “cardiovascular event”, and “mortality”. A full list is available in the appendix. Results were limited to trials published in English. To supplement the electronic search, we manually searched the reference lists of identified reports for additional trials.

We identified four relevant studies. Three studies were done in patients with hypertension and in patients immediately after myocardial infarction with mean follow-up durations between 5 months and 5 years. Comparisons, subgroups, and outcomes reported were different and meta-analyses were not possible.

The Trialists Collaboration included trials that randomly assigned patients to a drug to lower blood pressure versus placebo, to different intensities of drugs, or to groups given regimens based on different classes of drug. Trials had to have a minimum of 1000 patient-years of planned follow-up in each randomised group and not to have had their main results published before our protocol was finalised in July 31, 1995. Studies from the Trialists Collaboration were included in this study if individual participant data, including BMI, had been provided by Jan 31, 2013. When a trial included more than two treatment groups, we calculated estimates of effect for all possible comparisons except when early termination of one group made such estimates impossible. We gauged quality of the included trials according to the inclusion criteria of the Blood Pressure Lowering Treatment Trialists’ Collaboration, and used the Cochrane instrument to assess the risk of bias.

### BMI categories

We calculated BMI with the standard formula of weight in kg divided by height in m². We used BMI groupings based on standard criteria that divides individuals into three groups: normal (<25 kg/m²), overweight (25 to <30 kg/m²), or obese (≥30 kg/m²). The analyses were restricted to individuals with a BMI between 10 kg/m² and 100 kg/m² to exclude potentially erroneous outliers. We also did analyses for BMI of 15–60 kg/m² with no effect on our conclusions (data not shown).

### Outcomes

The primary outcome was total major cardiovascular events, comprising stroke (non-fatal stroke or death from cerebrovascular disease), coronary heart disease (non-fatal myocardial infarction or death from coronary heart disease including sudden death), heart failure (causing death or resulting in admission to hospital), and cardiovascular death. Secondary outcomes were the cause-specific outcomes of stroke, coronary heart disease, heart failure, and cardiovascular death, and total mortality (appendix). These outcomes are those prespecified in the original protocol.
Procedures
The primary analyses were of the six prespecified comparisons of treatments: ACE-inhibitor-based regimens versus placebo, calcium-antagonist-based regimens versus placebo, more intensive versus less intensive regimens, ACE-inhibitor-based regimens versus diuretic-based or β-blocker-based regimens, calcium antagonist-based regimens versus diuretic-based or β-blocker-based regimens, and ACE-inhibitor-based regimens versus calcium antagonist-based regimens. We did not do a meta-analysis of comparisons between angiotensin-receptor blockers and controls (included in a previous analysis) because BMI data were available for only one study (MOSES). We also excluded HYVET, a trial of diuretics versus placebo in elderly people, since it was the only trial making this comparison. In addition, in view of previous findings of possible differential effects of calcium antagonists compared with diuretics, we did additional analyses comparing calcium-antagonist-based or ACE-inhibitor-based regimens to β-blocker-based regimens only and to diuretic-based regimens only.

Statistical analysis
We did all analysis according to the principle of intention to treat, with the first event of each type included in each analysis. We used a p value of 0.05 or less for statistical significance, and made no corrections for multiple testing. We used STATA (version 11.0) and SAS (version 9.2). To estimate effects on blood pressure in each BMI subgroup, we used the same weighting strategy that has been used in previous subgroup analyses done by the collaboration—the blood pressure difference in each BMI subgroup within each trial was multiplied by the number of individuals contributing data to that BMI subgroup within that trial. For each specific analysis, we summed the products of these differences in each BMI subgroup within each trial was multiplied by the number of individuals contributing data to that BMI subgroup within that trial. For each specific analysis, we summed the products of these differences to get the overall effect for each comparison. Negative values indicate lower mean follow-up blood pressure in first listed group than in second listed group. SBP= systolic blood pressure.

Figure 2: The effect of different blood-pressure-lowering regimens on total major cardiovascular events according to baseline BMI

Figure 3: Proportionate higher relative risk of major cardiovascular events for every 5 kg/m² higher BMI for patients given the first-listed treatment compared with those given the second-listed treatment

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We did three sets of analyses to explore possible interactions between BMI and magnitude of reduction in cardiovascular risk for each of the six comparisons. First, we did meta-analyses to estimate the proportionate risk reductions with different blood pressure-lowering regimens in each of the three BMI subgroups. For each trial, and for each outcome, we calculated estimates of the relative risk and its variance separately for each of the BMI subgroups. We calculated overall estimates of effect and corresponding 95% CIs separately for each BMI subgroup with random-effects models with inverse-variance weighting. We did a test for linear trend of treatment effects across the three BMI categories by regressing each log relative risk on an ordinal variable for BMI category. We also did this test for trend on data extracted from the ACCOMPLISH trial. Furthermore, we pooled the ACCOMPLISH trial results with the corresponding data from trials in the Blood Pressure Lowering Treatment Trialists’ Collaboration with a random effects meta-analysis with inverse-variance weighting.

Second, we tested for evidence of an interaction between treatment regimen and BMI (in units of 5 kg/m²) as a continuous variable with Cox regression models, including treatment, continuous BMI, and their interaction term for each trial. The regression coefficient (β) for the interaction term represents the log ratio of relative risks of one treatment compared with the other for a 5 kg/m² difference in BMI. We pooled log ratios of relative risks (regression coefficient for interaction terms between treatment and continuous BMI) across trials for each comparison with inverse-variance weighted random-effects meta-analysis. We exponentiated the pooled summary to represent the ratio of relative risks of one treatment compared with the other for a 5 kg/m² difference in BMI.

Third, we did random-effects meta-regression analyses to examine the association between reductions in blood pressure and relative risk of events for each BMI subgroup. We plotted the differences in follow-up systolic blood pressure between randomised groups for each comparison in each BMI subgroup against the log relative risk for major cardiovascular events. We fitted meta-regression lines to the data separately for the three BMI subgroups and compared the slopes to test for a differential effect of reduction in blood pressure on risk reduction between BMI subgroups. The model included an interaction term between BMI subgroup and systolic blood pressure. With standard graphical methods, we tested assumptions of linear associations between differences in follow-up blood pressure and log relative risk. Because trial participants could contribute only once to a given meta-regression analysis, for factorial trials that included randomisation to different intensities of blood pressure lowering and allocation to different drugs, we included only the results of the randomisation to different intensities of blood pressure lowering. Similarly, for trials with randomisation to three treatment groups, only two of the possible three treatment comparisons were included with the control group participants divided equally between the two comparisons.

To estimate the likely absolute effect of regimens that have been identified as significantly differentially effective at higher BMIs compared with at lower BMIs, we calculated event rates for patient groups with BMI grouped by 5 kg/m². We made separate estimates by assuming baseline 5 year risks of 2.5% and 10.0%. We obtained the effects of treatment by first reducing the baseline risks for both the higher and lower BMI groups by the effect of the referent therapy. The risk in the higher BMI group was then further reduced by the risk reduction identified by the interaction term.

Role of the funding source
None of the funding sources were involved in the data collection, analysis or writing of this research. HA and AY had access to the raw data. AY and BN had the decision to submit the manuscript for publication.

Results
The analyses are based on data from 135715 individuals drawn from 22 trials included in 31 different comparisons of treatments (appendix). 14353 major cardiovascular events occurred, on which the primary analyses are based. Participant characteristics for BMI groupings are shown for each of the six primary comparisons (table), with higher baseline BMI being associated with younger age, greater incidence of type 2 diabetes, and lower blood pressure. We considered the risk of bias in the included studies to be low (appendix).

For the composite outcome of total major cardiovascular events, none of the six primary comparisons showed evidence that the protection from a blood pressure-
lowering regimen varied across BMI subgroups (all p for trend >0.20; figure 2). This finding was true for comparisons of drugs with placebo, for comparisons between more intensive versus less intensive treatment regimens, and for comparisons between regimens based on different drug classes (figure 2). For the 30 comparisons for the secondary outcomes, difference in benefit between the BMI subgroups was significant for only two calculations—there was greater protection against coronary heart disease in patients with lower BMI for ACE inhibitors compared with placebo (p=0.02; appendix) and greater protection against all-cause mortality in patients with higher BMI when using a calcium antagonist compared with placebo (p=0.04; appendix).

Analyses using BMI as a continuous measure showed no evidence that the effects of ACE inhibitors or calcium antagonists compared with placebo had different effects on major cardiovascular outcomes in patients with different levels of BMI (figure 3). The same was also true for the comparison of more intensive versus less intensive blood-pressure-lowering regimens and for the head-to-head comparisons of calcium antagonist-based regimens compared with diuretics or β blockers combined (figure 3). For the comparison of ACE inhibitor-based regimens against calcium antagonist-based regimens, there was evidence that ACE inhibitors provided greater protection in patients with higher BMI (figure 3). When the head-to-head comparisons between drug classes were further subdivided by separating out groups of trials comparing diuretics, those comparing β blockers, and those comparing either, we noted two further significant observations. For the trials that compared ACE inhibitors against either a diuretic or a β blocker, ACE inhibitors had a greater protection in patients with higher BMI (figure 3), which was driven by a similar effect in the comparison of ACE inhibitors against diuretics (figure 3). We noted no such effect for the comparison of ACE inhibitors versus β blockers regimens (p=0.78) or for any of the comparisons, including those with calcium antagonists (all p >0.65).

The meta-regressions showed no evidence of a difference in the association between reductions in systolic blood pressure and risk reduction across groups defined as normal, overweight, or obese for total major cardiovascular events (p=0.49; figure 4). The same was also true for all secondary outcomes (all p>0.15; appendix).

The trend towards greater protective effects of calcium antagonists compared with diuretics at lower BMIs identified by the ACCOMPLISH trial (n=11 482) was not statistically significant (p=0.12), nor was the estimate obtained from the 24 604 individuals included in the two studies from our dataset that made this same comparison (p=0.91; figure 5). Combining the two sets of data identified no association between BMI and the comparative effectiveness of calcium antagonists and diuretics (p=0.25; figure 5).

We identified two interactions between treatment and BMI (figure 3) for which estimates of absolute effects were made—ACE inhibitors versus calcium antagonists and ACE inhibitors versus diuretics. For ACE inhibitors versus calcium antagonists, the overall proportional risk of cardiovascular events with calcium antagonists compared with placebo was reduced by 25% (95% CI 8–39) with no evidence that effects differed by BMI group (figure 2). For individuals with a baseline 5 year risk of 2.5%, use of a calcium antagonist would result in risks being reduced from 25·00 per 1000 to 18·75 per 1000 for both lower and higher BMI groups. The additional risk reduction inferred by the BMI–treatment interaction for ACE inhibitor versus calcium antagonist would further

### Table 1: Effects of calcium antagonists versus diuretics on major cardiovascular events for the ACCOMPLISH trial, the corresponding trials included in the Trialists Collaboration, and baseline BMI

<table>
<thead>
<tr>
<th>BMI Category</th>
<th>Events/patients</th>
<th>Calcium antagonist</th>
<th>Diuretic</th>
<th>Risk ratio (95% CI)</th>
<th>p for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25 kg/m²</td>
<td>75/825</td>
<td>43/791</td>
<td>0.57 (0.39–0.84)</td>
<td>0.121</td>
<td></td>
</tr>
<tr>
<td>≥25 to &lt;30 kg/m²</td>
<td>142/1287</td>
<td>103/2059</td>
<td>0.76 (0.59–0.94)</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>≥30 kg/m²</td>
<td>152/2822</td>
<td>142/2887</td>
<td>0.90 (0.71–1.12)</td>
<td>0.25</td>
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</tr>
<tr>
<td>BPLTCC</td>
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<td></td>
</tr>
<tr>
<td>&lt;25 kg/m²</td>
<td>572/3345</td>
<td>360/1969</td>
<td>1.10 (0.97–1.23)</td>
<td>0.908</td>
<td></td>
</tr>
<tr>
<td>≥25 to &lt;30 kg/m²</td>
<td>941/5816</td>
<td>561/3450</td>
<td>0.90 (0.85–1.00)</td>
<td>0.247</td>
<td></td>
</tr>
<tr>
<td>≥30 kg/m²</td>
<td>964/6243</td>
<td>634/3781</td>
<td>1.09 (0.99–1.20)</td>
<td>0.30</td>
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<tr>
<td>Pooled estimate</td>
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</tr>
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<td>&lt;25 kg/m²</td>
<td>647/4170</td>
<td>403/2760</td>
<td>0.87 (0.52–1.46)</td>
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</tr>
<tr>
<td>≥25 to &lt;30 kg/m²</td>
<td>1078/7914</td>
<td>664/5509</td>
<td>0.88 (0.67–1.14)</td>
<td>0.62</td>
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</tr>
<tr>
<td>≥30 kg/m²</td>
<td>572/3345</td>
<td>776/6668</td>
<td>1.01 (0.84–1.22)</td>
<td>0.90</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 5:** Effects of calcium antagonists versus diuretics on major cardiovascular events for the ACCOMPLISH trial, the corresponding trials included in the Trialists Collaboration, and baseline BMI

Patients grouped by BMI as standard: normal (<25 kg/m²), overweight (25 to <30 kg/m²), or obese (≥30 kg/m²). BMI=body-mass index. BPLTTC=Blood Pressure Lowering Treatment Trialists’ Collaboration.
reduce 5 year risk in the group with higher BMI from 18.75 per 1000 to 17.45 per 1000) if an ACE inhibitor was used instead of a calcium antagonist. Additional risk reduction for patients with a baseline 5 year risk of 10% would result in risk being further reduced by the use of ACE inhibitor instead of calcium antagonist in the high BMI group from 75.00 per 1000 patients to 69.75 events in 1000 patients. We estimated quantitatively similar absolute effects for the observed interaction between ACE inhibitors versus diuretics that were of directly similar magnitude (data not shown).

Discussion

With use of individual participant data from more than 130 000 individuals, this meta-analysis has identified benefits of blood pressure lowering for individuals with different levels of BMI. However, the analyses did not convincingly show that particular drug classes were substantially more or less effective among patients with different BMIs. We noted a small additional benefit for individuals with a higher BMI with ACE inhibitors, although this observation could have arisen by chance because we made many comparisons. It was not possible to replicate the widely reported findings of greater protection with calcium antagonists than with diuretics in patients with lower BMIs.46

Greater protection with ACE inhibitors in obese people might be anticipated on the basis of the upregulated state of the renin-angiotensin system in obesity-mediated hypertension.47,48 A study done in patients after myocardial infarction reported greater protection against total mortality with ACE inhibitors compared with placebo in overweight individuals.49 In other studies, angiotensin-receptor blockade in obese patients was associated with greater reductions in proteinuria50 and a lower incidence of new-onset diabetes, although not with protection against other important clinical outcomes.51

The absence of any interaction between BMI and the comparative effects of calcium antagonist regimens and diuretic regimens in the Trialists’ Collaboration data seems to conflict with the findings of the ACCOMPLISH trial. However, the disparity might be a result of chance with either the ACCOMPLISH trial results (n=11482, 652 events) being a false-positive finding or the corresponding Trialists’ Collaboration analyses (n=24691, 4059 events) failing to detect a true effect. On balance, the relatively few events and the absence of clear statistical support for an interaction of BMI and treatment effect within the ACCOMPLISH trial suggests a false-positive report from that study. The much higher numbers of patients and events included in the analyses of the Trialists’ Collaboration provide for a more robust test of the hypothesis. It is also possible that the discrepancy between the results could be due to differences in the characteristics of the populations studied, which could have further modified the effects of the different drug regimens. For example, the ACCOMPLISH trial included background ACE-inhibitor therapy for all participants, whereas ACE inhibitors were provided to only some of the individuals in the Trialists’ Collaboration dataset.

The many different analyses that we have done for this report are a strength of this study. In particular, the estimates obtained by fitting BMI as a continuous variable increased the statistical power to detect interactions between BMI and the effects of the different treatment regimens. The presence of significant findings for the analyses of BMI fitted as a continuous variable, which are not apparent when BMI is treated in a categorical manner, might show the different levels of statistical power provided by the two methods. That said, precise estimation for the power available for the investigation of treatment interactions is difficult, and the large number of comparisons made without formal adjustment for multiplicity means that the results must be interpreted with some caution. Accordingly, we have focused on the results for the primary composite cardiovascular outcome and the most extreme findings.

The systematic differences between the characteristics of patients with different BMIs add an additional dimension of complexity to the interpretation of the study results, and are a further weakness. However, with previous analyses showing little effect of characteristics such as age, diabetes, and baseline blood pressure on the relative effectiveness of the treatments studied,52–54 the findings reported here might be taken to be accurate. Additionally, the correlations between diabetes, age, and BMI shown in this cohort are broadly comparable to those seen in groups in the general population and therefore the findings reported here are probably generalisable to clinical practice, irrespective of how they arose.44 Patients at the extremes of the BMI range (<18.5 kg/m² or >60.0 kg/m²) were few and it was not possible to investigate effects separately for these groups of patients, who often have substantial metabolic abnormalities and have particularly high risks. Blood pressure reductions in the head-to-head comparisons between drug classes in which we noted interactions between BMI and treatment across BMI subgroups were similar and the interactions are therefore unlikely to be mediated by blood pressure. Finally, despite the volume of data available for these analyses, the effect estimates for several remain wide and no data were available for drug classes such as angiotensin-receptor blockers and aldosterone antagonists.52 Access to more individual participant data from completed trials would be an asset to future analyses.

In conclusion, these analyses substantially add insight into the probable effect of BMI as a modifier of the effects of treatments to lower blood pressure. ACE inhibitors seem most likely to have effects that differ by BMI, possibly providing slightly greater levels of cardiovascular protection in individuals with higher BMI. However, the evidence is not entirely convincing and the data do not provide a strong case for a change in clinical practice...
such that particular drug classes are directed specifically towards obese patients.

Contributors
SC, RH, FT, VP, MW, and BN contributed to the study design. Ay, HA, and BN did the data analysis and interpretation. Ay and BN drafted the manuscript. SC, RH, FT, VP, and MW revised the manuscript.

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Declaration of interests
BN is on the steering committee for Janssen, Dr Reddy’s Laboratories, and Servier; his institution has received grant funding from AboVie, AboVie, Novartis, Pfizer, Roche, and Servier; and he has received honoraria for meeting presentations from Abbott, AstraZeneca, Novartis, Pfizer, Roche, and Servier. VP has received honoraria for meeting presentations and/or advisory board participation from AboVie, AstraZeneca, Baxter, Boehringer Ingelheim, Servier, and Vitae, and his employer has received trial funding from AboVie, Baxter, Janssen, Novartis, Roche, and Servier. SC received honoraria for meeting presentations from Coviden, Servier, Novonordisk, and Sanofi; research grants from Novonordisk; and attended board meetings of AstraZeneca and Coviden. HA has received honoraria for meeting presentations from Takeda Pharmaceutical Company. MW is on a trial advisory committee for Novartis. Ay, FT, and RH declare no competing interests.

Acknowledgments
HA is supported by an Australian Research Council Fellowship. BN is supported by an Australian Research Council (ARC) Future Fellowship. BN and MW are supported by National Health and Medical Research Council of Australia (NHMRC) Senior Research Fellowships. VP has received grants from The Heart Foundation of Australia. BN, MW, and VP have received grants from the NHMRC. This work received no specific funding support.

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Optimum antihypertensive therapy: does adiposity matter?

Given that at least 75% of patients with hypertension are obese, it is no coincidence that the continuing obesity epidemic is driving the increasing incidence of hypertension. Physicians have questioned whether the benefits of blood pressure lowering for cardiovascular disease might depend, in part, on choice of antihypertensive drugs (as shown in ACCOMPLISH) and that the choice of drugs should vary with the state of adiposity.

This issue motivated the report in The Lancet by Andrew Ying and the Blood Pressure Lowering Treatment Trials’ Collaboration, who used meta-analysis and meta-regression to explore the cardiovascular effects of various regimens to lower blood pressure according to baseline body-mass index (BMI), dividing participants into lean (normal), overweight, or obese BMI groups. The analyses were done for 135715 individuals from 22 trials who had 14353 cardiovascular events. Six prespecified comparisons were done: angiotensin-converting-enzyme (ACE) inhibitors versus placebo; calcium antagonists versus placebo; more intensive versus less intensive drug treatment; ACE inhibitors versus diuretics or β blockers; calcium antagonists versus diuretics or β blockers; and ACE inhibitors versus calcium antagonists.

None of the six primary comparisons, when done categorically, showed special cardiovascular event protection across the three BMI categories. However, investigators reported differences when analysed as continuous variables: ACE inhibitors (vs calcium antagonists) provided greater protection for each 5 kg/m² increase in BMI (relative risk of major cardiovascular event reduced by 7% [95% CI 2–11], p=0.004); as did ACE inhibitors (vs diuretics; 7% [2–11], p=0.002). The Collaboration conclude, on the basis of their overall analyses, that the apparent advantages of ACE inhibitors over other drugs in terms of decreases in cardiovascular events in obese patients versus lean individuals are probably false-positive findings. Furthermore, Ying and colleagues could not replicate an interaction between BMI and the comparative effects of calcium antagonist regimens versus diuretic regimens, and conclude that the results of the ACCOMPLISH trial could be a chance finding.

In this context, it is not surprising that Ying and colleagues’ report did not show differences between the major antihypertensive drug classes in their effects on outcomes across obese, overweight, and normal-weight patient groups. Interestingly, the Trialists note the difference in their findings from those reported from the ACCOMPLISH trial. In ACCOMPLISH, treatment with calcium-antagonist-based treatment (combined with an ACE inhibitor)—similar to Ying and colleagues’ data—had equal outcome effects across the three BMI categories. But, by contrast, diuretic-based treatment (combined with an ACE inhibitor) in ACCOMPLISH was associated...
Comment

with lower rates of cardiovascular events in the obese BMI subgroup than in overweight, and especially in normal-weight, BMI subgroups; thus, diuretics seem to be less effective for cardiovascular protection than calcium-antagonist regimens in leaner patients.

Since the Trials1 did not see this differential diuretic effect in their own analysis, they argue that the ACCOMPLISH results might have been a chance finding. However, their speculation is open to question because the ACCOMPLISH diuretic findings largely reproduced those of an earlier trial—The Systolic Hypertension in the Elderly Program (SHEP)—in which the thiazide-like diuretic chlorthalidone was also less effective (particularly in women) in reduction of events (strokes and death) in lean patients.1,2 Given the clarity and transparency of rigorous individual clinical trials, we believe that it is reasonable to assert the concepts raised by the SHEP and ACCOMPLISH findings.

Ying and colleagues1 note that there were insufficient data available about the effect of aldosterone antagonists (spironolactone and eplerenone) on cardiovascular outcomes to include them in their analysis. Nevertheless, there is evidence that central obesity (through adipocyte secretion of aldosterone-releasing factors) stimulates adrenal cortical secretion of aldosterone,8 which directly acts on mineralocorticoid receptors in vascular smooth muscle cells. Adipocyte-induced release of aldosterone occurs early in association with normotension,9 later (perhaps with worsening obesity and development of the metabolic syndrome) in incident hypertension,10 and eventually in resistant hypertension with hyperaldosteronism,11 which responds well to aldosterone inhibitors.12

Indeed, Ying and colleagues’ equivocal finding of ACE inhibitor showing benefit to decrease cardiovascular event rates in obese patients could result from aldosterone breakthrough during ACE inhibition, which might attenuate the action of ACE inhibitors to lower serum aldosterone concentrations.12 Importantly, however, there have been no randomised controlled trials to test the hypothesis of better cardiovascular protection with aldosterone inhibitors in overweight or obese hypertensive patients who have high cardiovascular risk.

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We declare no competing interests.

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Published online November 4, 2014 http://dx.doi.org/10.1016/S0140-6736(14)61336-2