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.

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*Members are listed at the end of the paper

Correspondence to: Mr Andrew Ying, The George Institute for Global Health, University of Sydney, Australia **aying@georgeinstitute.org.au**

Introduction

High blood pressure is the leading risk factor for cardiovascular disease worldwide[1] and more frequently occurs in obese individuals than in those of normal weight.[2,3] Treatment to lower blood pressure can substantially reduce cardiovascular risk in diverse patient groups,[4–6] but debate continues about how obesity changes the link between blood pressure and cardiovascular risk.[7,8] This uncertainty is underpinned by the suggestion that the pathogenesis of hypertension differs between lean and obese individuals.[9–11]

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[12–14] reported no interaction between BMI and reductions in blood pressure on vascular risk, and one[15] 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.[16] 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,[17,18] and investigators have noted a need for better evidence.[16,19]

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.[20] 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 the Blood Pressure

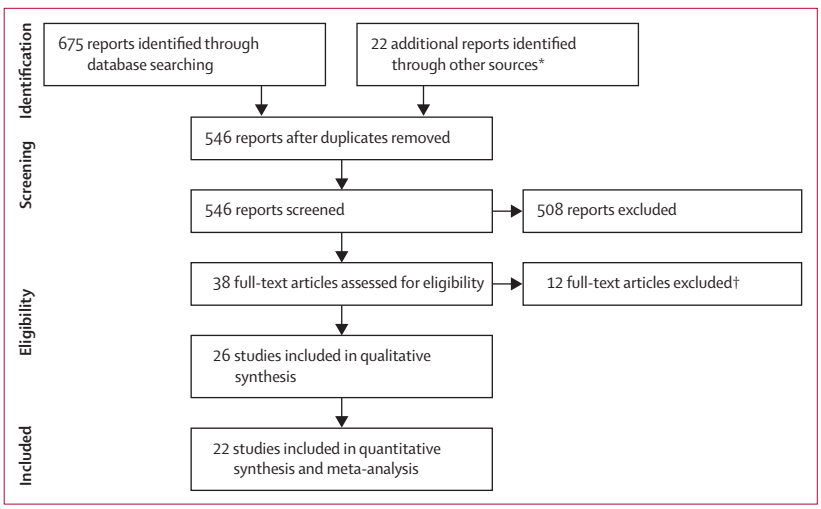

Figure 1: **Study selection**
*Studies identified from existing Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTCC) database. †12 reports were excluded on the basis of the following: four analysed the control and treatment groups as one group in the style of a cohort study;[21–24] two used other measures of obesity to group patients (waist-hip ratio[25] or presence of metabolic syndrome[26]); one did not include long-term cardiovascular outcomes;[27] one was an unpublished conference abstract;[28] one compared two types of patient referral rather than two blood-pressure-lowering drugs;[29] one has since been withdrawn from press (retracted);[30] one did not report an interaction term between body-mass index groups;[31] and one was already included in the BPLTTC database. [32]

	n	Mean age (years)	Baseline SBP (mm Hg)	Baseline DBP (mm Hg)	Men (%)	Diabetes (%)
ACE inhibitor *vs* placebo						
<25 kg/m²	10 250	63·8	140·4	80·5	69·6%	57·1%
25 to <30 kg/m²	16 975	63·1	141·9	82·2	75·7%	71·6%
≥30 kg/m²	9387	62·5	144·8	83·3	64·7%	87·4%
Calcium antagonist *vs* placebo						
<25 kg/m²	1803	69·5	167·3	84·2	41·0%	11·6%
25 to <30 kg/m²	2896	67·1	165·6	84·8	44·6%	19·5%
≥30 kg/m²	1377	64·8	162·9	85·5	35·1%	30·0%
More intensive *vs* less intensive						
<25 kg/m²	4404	62·6	169·0	104·3	45·7%	10·9%
25 to <30 kg/m²	9801	61·3	168·2	104·4	58·5%	14·6%
≥30 kg/m²	6636	59·8	167·1	103·7	50·5%	24·8%
ACE inhibitor *vs* diuretic or β blocker						
<25 kg/m²	11 386	66·6	160·5	89·9	45·4%	13·3%
25 to <30 kg/m²	19 205	65·1	158·0	90·5	57·6%	20·1%
≥30 kg/m²	15 263	63·6	153·4	88·9	46·4%	33·4%
Calcium antagonist *vs* diuretic or β blocker						
< 25 kg/m²	10 365	67·2	162·6	92·4	44·5%	14·2%
25 to <30 kg/m²	17 347	65·5	160·2	92·8	56·4%	21·2%
≥30 kg/m²	14 191	64·3	155·0	90·2	45·1%	35·0%
ACE inhibitor *vs* calcium antagonist						
<25 kg/m²	6379	70·4	158·5	86·3	51·1%	21·0%
25 to <30 kg/m²	9842	68·4	155·5	87·0	56·8%	32·8%
≥30 kg/m²	9174	65·5	150·7	86·4	45·1%	46·8%

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

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

Lowering Treatment Trialists' Collaboration (figure 1).[12,21–31] 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.[13–16] 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.[20] 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.[32] 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.[33]

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[34] 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.[20]