Effects of body size and hypertension treatments on cardiovascular event rates: subanalysis of the ACCOMPLISH randomised controlled trial

Michael A Weber, Kenneth Jamerson, George L Bakris, Matthew R Weir, Dion Zappe, Ying Zhang, Bjorn Dahlof, Eric J Velazquez, Bertram Pitt

Summary

Background In previous clinical trials in high-risk hypertensive patients, paradoxically higher cardiovascular event rates have been reported in patients of normal weight compared with obese individuals. As a prespecified analysis of the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial, we aimed to investigate whether the type of hypertension treatment affects patients’ cardiovascular outcomes according to their body size.

Methods On the basis of body-mass index (BMI), we divided the full ACCOMPLISH cohort into obese (BMI ≥30, n=5709), overweight (≥25 to <30, n=4157), or normal weight (<25, n=1616) categories. The ACCOMPLISH cohort had already been randomised to treatment with single-pill combinations of either benazepril and hydrochlorothiazide or benazepril and amlodipine. We compared event rates (adjusted for age, sex, diabetes, previous cardiovascular events, stroke, or chronic kidney disease) for the primary endpoint of cardiovascular death or non-fatal myocardial infarction or stroke. The analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00170950.

Findings In patients allocated benazepril and hydrochlorothiazide, the primary endpoint (per 1000 patient-years) was 30·7 in normal weight, 21·9 in overweight, and 18·2 in obese patients (overall p=0·0034). However, in those allocated benazepril and amlodipine, the primary endpoint did not differ between the three BMI groups (18·2, 16·9, and 16·5, respectively; overall p=0·9721). In obese individuals, primary event rates were similar with both benazepril and hydrochlorothiazide and benazepril and amlodipine, but rates were significantly lower with benazepril and amlodipine in overweight patients (hazard ratio 0·76, 95% CI 0·59–0·94; p=0·0369) and those of normal weight (0·57, 0·39–0·84; p=0·0037).

Interpretation Hypertension in normal weight and obese patients might be mediated by different mechanisms. Thiazide-based treatment gives less cardiovascular protection in normal weight than obese patients, but amlodipine-based therapy is equally effective across BMI subgroups and thus offers superior cardiovascular protection in non-obese hypertension.

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Introduction

Hypertension happens in people of all body sizes, ranging from lean to obese. In general, the choice of treatment to control blood pressure is made without regard to bodyweight. However, recognition of relevant clinical and prognostic differences between weight categories, which potentially could affect selection of treatment, might be important.

The association of obesity with a high incidence of major cardiovascular events, which could be caused by accompanying risk factors and by obesity itself, is widely accepted.12 Despite this knowledge, reports in patients with established cardiovascular disease, particularly those with coronary disease, have suggested that event rates in individuals with normal bodyweight are unexpectedly higher than in heavier patients.3–7

A similar finding has been noted in hypertension. Findings of epidemiological studies show that lean hypertensive individuals have a higher incidence of adverse cardiovascular outcomes than their obese counterparts.4–6 The obese phenotype of hypertension might, therefore, be a more benign or protective form of this disorder.4–11 As likely, however, is that hypertension in lean patients could be associated with the cardiovascular outcomes of greater reactivity of neuroendocrine mechanisms—in particular, the sympathetic and renin-angiotensin systems—to routine stimuli.12–18

In prospective clinical trials of hypertension treatment, increased rates of cardiovascular outcomes have been recorded in lean patients. In a recent study of hypertensive individuals with histories of clinical coronary disease, those who were overweight and obese had a lower risk of major cardiovascular outcomes than did lean people.11 However, since all patients in that trial received active treatment, the researchers could not ascertain whether the reported obesity paradox reflected innate clinical characteristics of individuals in the different weight categories or were the effects of study drugs. Furthermore, augmented risk of cardiovascular death in thin patients (body-mass index [BMI] <20) was
reported in the Losartan Intervention for Endpoint reduction in hypertension (LIFE) study, in which an increase in risk for patients who were very obese (BMI >35) was also seen.\textsuperscript{13}

Antihypertensive treatment could be an important factor in establishing how body size affects cardiovascular outcomes. In the Systolic Hypertension in the Elderly Program (SHEP), patients randomised to treatment with the diuretic chlortalidone (known also as chlorothalidone) had significantly fewer major events than did those allocated placebo; however, within the group receiving active treatment, a significantly higher rate of death and stroke was recorded in lean versus overweight individuals.\textsuperscript{14} No such relation was seen in the placebo group in that study, suggesting that the treatment itself, despite its overall benefit, might have contributed to the increased risk in lean patients.\textsuperscript{15}

The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial is a further opportunity to study the effects of bodyweight and different treatment regimens in high-risk hypertensive patients. In previous trials in which increased cardiovascular events were noted in lean patients, thiazide diuretics were used as primary or add-on therapy in all or most treated patients.\textsuperscript{11,13,14} However, in ACCOMPLISH, cardiovascular outcomes of diuretic and non-diuretic drug regimens were compared.\textsuperscript{15} The prespecified analysis of ACCOMPLISH reported here aims to provide clinical insight into the differential effects of treatment on cardiovascular event rates in hypertensive patients, categorised by BMI.

**Methods**

**Study design**

ACCOMPLISH was a multicentre trial undertaken at 548 academic centres in the USA, Sweden, Norway, Denmark, and Finland. It was designed to compare the effects of a combination of an angiotensin-converting enzyme (ACE) inhibitor (benazepril) and a calcium-channel blocker (amlodipine) with the effects of a combination of the same ACE inhibitor with a thiazide diuretic (hydrochlorothiazide). The primary endpoint was reduction of a composite of cardiac and stroke events in high-risk hypertensive patients. The design and implementation of this trial have been described elsewhere.\textsuperscript{16–18} A prespecified analysis of the study was to compare the effects on the primary endpoint of the two treatment arms in patients categorised by BMI.

The ACCOMPLISH trial was designed, supervised, analysed and interpreted by an executive committee (members were KJ, MAW, GLB, BD, EJV, and BP). The roles of key supporting committees for the trial, and the role of the original sponsor (Novartis), have been described previously.\textsuperscript{19–21} The institutional review board of every participating institution approved the study protocol. The database of adjudicated endpoints was maintained at the Duke Clinical Research Institute. The trial was registered on ClinicalTrials.gov, number NCT00170950.

**Patients**

The study population consisted of hypertensive patients at high risk of cardiovascular events. Their increased risk was established by previous records of concomitant disorders, in particular coronary events, myocardial infarction, revascularisation procedures, stroke, peripheral arterial disease, left-ventricular hypertrophy, impaired renal function, and diabetes mellitus. At study entry, we calculated BMI for every patient using the standard formula kg (body weight)/m\(^2\) (height in m) and assigned them to the relevant category: normal weight (BMI <25), overweight (≥25 to <30), or obese (≥30). All patients gave written informed consent to participate in ACCOMPLISH.

**Procedures**

ACCOMPLISH is a randomised, double-blind, two-arm trial. Immediately after eligibility was established and patients entered the study, we randomly assigned them to one of two treatment arms—either benazepril plus hydrochlorothiazide or benazepril plus amiodipine—administered in single-pill combinations. All previous antihypertensive treatments were discontinued completely at that time (or by downtitration in the days preceding randomisation) and were replaced immediately after randomisation by one of the study’s fixed-combination treatments. Randomisation was done via an automated system, which was maintained centrally by the research department at Novartis.

Starting doses were benazepril 20 mg/day plus either hydrochlorothiazide 12.5 mg/day or amiodipine 5 mg/day. The study protocol mandated an increase in the benazepril dose to 40 mg/day in both treatment arms at the following study visit. Thereafter, the hydrochlorothiazide dose could be raised to 25 mg/day or the amiodipine dose to 10 mg/day as needed, to achieve a target blood pressure goal of less than 140/90 mm Hg. For patients with diabetes or with chronic kidney disease, a target blood pressure of less than 130/80 mm Hg was recommended to investigators but not mandated.

Investigators could add other antihypertensive agents if they were needed to control blood pressure (except ACE inhibitors, angiotensin-receptor blockers, calcium-channel blockers, or thiazide diuretics), including β blockers, clonidine, α blockers, and spironolactone. Investigators could also add once-daily loop diuretics if, in their clinical judgment, these agents were needed for volume management. After an initial 3-month period, during which time all necessary treatment intensifications were made, patients returned for visits after a further 3 months and then at 6-month intervals until the end of the trial. We measured blood pressure using standard clinical trial methods described previously.\textsuperscript{15}
Endpoints
The primary study endpoint was time to first recorded event. For analyses reported here, we defined this endpoint as the composite of first occurrence of either cardiovascular death or non-fatal myocardial infarction or non-fatal stroke. Death from cardiovascular causes was defined as sudden death from cardiac events or death from myocardial infarction, stroke, coronary intervention, heart failure, or other cardiovascular causes. Only the first event in an individual patient was counted in the analysis of the primary endpoint.

Secondary endpoints for analyses reported here were cardiovascular death, total myocardial infarction (fatal or non-fatal), and total stroke (fatal or non-fatal). Secondary endpoints were measured independently of the primary endpoint analysis and were counted without censoring for previous occurrence of other endpoints.

Statistical analysis
We originally calculated the power and sample size of ACCOMPLISH based on the entire study cohort, with the intention that the trial would have 90% power to detect a 15% reduction in risk for the benazepril and amlokdipine group, assuming a 3–5% annual event rate for the benazepril and hydrochlorothiazide group. All study outcomes were adjudicated (according to standard criteria) by a clinical endpoints committee that was unaware of random assignments.15 Interim statistical analyses were done at 6-month intervals for the trial’s data safety monitoring committee, to ascertain whether a difference in outcome existed between the two treatment arms, without knowing the identity of the arms. The description of this procedure, together with a detailed explanation of the specified stopping rules of ACCOMPLISH, has been published previously.15 The data safety monitoring committee recommended early termination of ACCOMPLISH because criteria for satisfying the stopping rules were met.15

The primary analysis of this report was a comparison of outcomes between the benazepril and hydrochlorothiazide and the benazepril and amlokdipine groups within each of the three BMI categories (normal weight, overweight, and obese). Furthermore, comparisons of outcomes were made among the three BMI categories for patients treated with benazepril and hydrochlorothiazide; for patients treated with benazepril and amlokdipine; and for the pooled study cohort (benazepril and hydrochlorothiazide, and benazepril and amlokdipine, combined). All patients were included in the analyses of primary and secondary endpoints, according to the intention-to-treat principle. The primary comparison of the groups was based on a log-rank test. To compensate for differences in demographic and clinical characteristics of patients within the different BMI categories, we based analyses on hazard ratios, using a Cox’s regression model with baseline BMI group, age, sex, diabetes, and previous history of cardiovascular events, stroke, or chronic kidney disease (yes/no) as factors. We defined chronic kidney disease as an estimated glomerular filtration rate less than 60 mL/min.15 For completeness, analyses were also undertaken without making these adjustments. We did Cox’s regressions to obtain point estimates of hazard ratios and 95% CIs between comparator groups. We also undertook individual analyses for secondary endpoints without censoring for previous primary events. Finally, we compared baseline clinical and demographic data between treatment groups with the t test (for continuous variables) and the χ² test (for categorical variables). We used SAS statistical software, version 9.3.

Role of the funding source
The original ACCOMPLISH trial was funded by Novartis Pharmaceuticals, and their role in this trial has been described.15 Novartis did not provide any direct funding for the present analysis and report, although two authors (DZ and YZ) are employees of that company. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results
A total of 11482 individuals with BMI measurements underwent randomisation in ACCOMPLISH (figure 1). 5745 patients were assigned to the benazepril and hydrochlorothiazide arm and 5737 were allocated benazepril and amlokdipine (mean age 68·3 years [SD 6·9] and 68·4 [6·9], respectively). Of the entire study cohort, outcome data were unavailable in 143 patients by the end of the study: five withdrew study consent and 21 were from study sites affected by a natural disaster and had to discontinue their activities. Thus, 117 patients (1%) were lost to follow-up.

Table 1 presents the main baseline characteristics of patients in each arm according to BMI categories.

![Figure 1: Trial profile](http://dx.doi.org/10.1016/S0140-6736(12)61343-9) 3

*Some patients had more than one reason for non-randomisation.
duration of participation for patients in ACCOMPLISH was 35·7 months, at which time the trial ended prematurely when a significant inequality in clinical outcomes between treatment groups met predetermined stopping criteria. Early trial termination has been described fully elsewhere.15

In the benazepril and hydrochlorothiazide group, by 6 months (when titration of antihypertensive treatment was complete), mean doses were benazepril 36·1 mg and hydrochlorothiazide 19·3 mg; 1636 (29%) patients were receiving (or had at any point received) at least one additional drug. In the benazepril and amlodipine group, mean doses were benazepril 36·3 mg and amlodipine 7·7 mg; 1662 (29%) patients received additional agents.

Table 2 presents baseline and treatment systolic and diastolic blood pressure values. Baseline blood pressures reflected the drugs patients were receiving at study entry (11 184 [97%] were on antihypertensive agents at that time). Treatment blood pressure is the value for every patient after 6 months in the trial, when titration was complete. In general, values did not differ between treatment arms, with the exception of small but significant differences in treatment diastolic blood pressures (p<0·0001 for normal weight and overweight, p=0·0251 for obese).

Figure 2 presents the number of events recorded across all participants. 118 (7%) of 1616 patients in the normal weight group, 240 (6%) of 4157 in the overweight group, and 294 (5%) of 5709 in the obese group reached the primary endpoint. The difference in event rates was not significant between overweight and normal weight...
groups (hazard ratio 0·80, 95% CI 0·64–1·00) nor between overweight and obese groups (1·09, 0·92–1·30). However, a significant difference was recorded between obese and normal weight groups (0·74, 0·59–0·92; p=0·0066) and across all three BMI groups (overall p=0·0250). Note that these findings depend mainly on data from the benazepril and hydrochlorothiazide group.

Figure 3 shows the difference between BMI categories in event rates of primary composite and individual secondary endpoints, for patients assigned benazepril and hydrochlorothiazide. Comparing obese and overweight groups, event rates for primary and secondary endpoints were all numerically lower, yet not significantly so, in obese patients. However, primary endpoint events and cardiovascular deaths were significantly lower in the overweight group compared with normal weight individuals. Comparison of obese and normal weight categories showed event rates for the primary endpoint, cardiovascular death, and total stroke were all significantly lower in the obese group (figure 3). The primary endpoint differed significantly across the three BMI categories (overall p=0·0034).

<table>
<thead>
<tr>
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<th>Obese</th>
<th>Overweight</th>
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<tr>
<td><strong>Primary endpoint</strong></td>
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<td>137/2098 (7%)</td>
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<td><strong>Cardiovascular death</strong></td>
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<td><strong>Total myocardial infarction</strong></td>
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<td>65/2098 (3%)</td>
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<td><strong>Total stroke</strong></td>
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<tr>
<td><strong>Obese</strong></td>
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<td></td>
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<tr>
<td><strong>Hazard ratio (95% CI)</strong></td>
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<tr>
<td><strong>p value</strong></td>
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**Figure 3:** Comparison of event rates with benazepril and hydrochlorothiazide in obese, overweight, and normal weight hypertensive patients

Hazard ratio was calculated by Cox’s regression and adjusted for age, sex, diabetes, and previous history of cardiovascular events, stroke, or chronic kidney disease. BMI=body-mass index.

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<th>Obese</th>
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<tr>
<td><strong>Primary endpoint</strong></td>
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<td>75/825 (9%)</td>
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<td><strong>Cardiovascular death</strong></td>
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<td>34/825 (4%)</td>
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<td><strong>Total myocardial infarction</strong></td>
<td>65/2098 (3%)</td>
<td>28/825 (3%)</td>
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<tr>
<td><strong>Total stroke</strong></td>
<td>54/2098 (3%)</td>
<td>28/825 (3%)</td>
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<tr>
<td><strong>Obese</strong></td>
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<td><strong>Hazard ratio (95% CI)</strong></td>
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<td>0·79 (0·59–1·25)</td>
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<tr>
<td><strong>p value</strong></td>
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<th></th>
<th>Overweight</th>
<th>Normal</th>
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<tr>
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<tr>
<td><strong>p value</strong></td>
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<td>0·3152</td>
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**Figure 4:** Comparison of event rates with benazepril and amlodipine in obese, overweight, and normal weight hypertensive patients

Hazard ratio was calculated by Cox’s regression and adjusted for age, sex, diabetes, and previous history of cardiovascular events, stroke, or chronic kidney disease. BMI=body-mass index.
Figure 4 shows the difference between BMI categories in event rates of primary composite and individual secondary endpoints, for patients allocated benazepril and amlodipine. It is noteworthy that no endpoint differs when comparing obese and overweight, overweight and normal weight group, and obese and normal weight. As confirmation of these findings, the primary endpoint did not differ across the three BMI categories (overall p=0.9721).

Figure 5 shows the difference between treatment arms in event rates of endpoints, for patients in each of the three BMI categories. In the obese group, primary or secondary endpoints did not differ between treatment arms. However, in the overweight category, the primary endpoint event rate was lower in patients assigned benazepril and amlodipine than in those allocated benazepril and hydrochlorothiazide. Differences between treatment arms were greatest in the normal weight category. Event rates for both the composite primary endpoint and total myocardial infarction were lower in patients assigned benazepril and amlodipine. Figure 6 emphasises the non-significant difference in the primary endpoint event rate between treatment arms in obese patients, but shows this difference was progressively greater (and significant) in overweight and normal weight categories.

We noted some chance differences in patient’s baseline characteristics between treatment arms; thus, we adjusted the Cox’s regressions to account for possible differences in demographic and clinical characteristics. This correction did not make a major difference to our results (data available on request).

Patients in both arms tolerated treatment well. As reported previously in the full ACCOMPLISH trial,15 similar numbers of patients receiving benazepril and hydrochlorothiazide or benazepril and amlodipine discontinued treatment or had drug-related adverse events.

**Discussion**

In the pooled analysis of treatment arms, our findings show that cardiovascular deaths or non-fatal myocardial infarctions or strokes happen more frequently in normal weight than obese hypertensive patients. This result is consistent with previous reports of differential clinical event rates in obese and lean hypertensive patients.
Even so, it might not be fully generalisable and should be interpreted with caution since it was driven predominantly by findings in one (the diuretic-based) of our two treatment groups. Indeed, our main finding was that the types of treatment to which patients were randomly allocated were determinants of relations between body mass and cardiovascular outcomes.

In patients who were assigned treatment with the ACE inhibitor benazepril and the thiazide diuretic hydrochlorothiazide, a 68% higher event rate was noted for the primary endpoint in the normal weight category than in the obese group. By contrast, no difference in cardiovascular outcomes was seen between BMI categories in patients who were allocated benazepril and the calcium-channel blocker amloidine. Thus, although a major difference in event rates was not recorded between the two types of treatment in obese patients, patients in the non-obese categories assigned the amloidine combination incurred significantly fewer fatal and non-fatal events than did those allocated the thiazide combination.

How can we explain the divergent effects of the two treatment arms? Hypertension in obese and lean patients is probably mediated by different forms of underlying pathophysiology. In obese people, it seems to be characterised by increased plasma volume and cardiac output rather than by vasoconstrictor mechanisms.\(^8,10,13\) This role for volume dependency is supported by evidence of increased renal sodium reabsorption in obese patients,\(^20,23\) which in turn is most probably due to augmented renal sympathetic nerve activity, possibly a key mechanism underlying hypertension in obese patients.\(^22\) Thus, treatment incorporating a diuretic would represent a logical approach for obese individuals. Likewise, regimens that include calcium-channel blockers, which also work effectively in excess sodium states,\(^21\) would be appropriate choices in obese patients. In lean individuals, hypertension seems to be dependent on heightened reactivity of the sympathetic and renin-angiotensin systems.\(^12\) Diuretic-based treatment can have the effect of further stimulating these systems\(^24,25\) and, therefore, could potentially aggravate mechanisms that underlie vascular events. In our study, however, all patients were receiving concomitant ACE inhibitor treatment, so increased activity of the renin-angiotensin system caused by the diuretic is unlikely to have had a major role in differentiation of the two treatment arms.

Previous reports, in which cardiovascular outcomes were related to bodyweight, focused on two characteristics of hypertension.\(^10,11,14\) The first was that the increased risk of cardiovascular events in lean patients might reflect an intrinsically higher disposition to advanced vascular pathology.\(^5\) This argument is consistent with the observation of greater underlying neuroendocrine reactivity in lean individuals.\(^22\) However, the weight of some lean patients on entry into our study might have been reduced by lifestyle changes provoked by their previous cardiovascular events, thus transferring them from previously higher weight categories. The second idea is that obesity is innately a more benign form of hypertension or even provides a measure of protection against cardiovascular events.\(^4,10,27\) In fact, in patients with coronary disease (although not specifically hypertension), data from very recent reports have gone beyond conventional measures of obesity and have supported a possible direct link between increased fat mass and cardiovascular protection.\(^24,29\) Moreover, some of the risk associated with obesity could possibly be mitigated by effective management of concomitant risk factors. For instance, in the main ACCOMPLISH trial, most patients (in both treatment arms) received active treatment for dyslipidaemia and glucose abnormalities, and antiplatelet drugs.\(^31\)

Despite these speculations, our conclusions are more in keeping with those from the SHEP study.\(^4\) In that trial, by contrast with patients allocated a diuretic, those on placebo had no meaningful differences in major event rates as a function of bodyweight,\(^24\) suggesting that treatment is a determinant of outcomes in non-obese hypertensive patients.
In the original report of ACCOMPLISH, patients receiving the benazepril and amlodipine combination had a 20% lower cardiovascular event rate than did those receiving benazepril and hydrochlorothiazide. In our analysis, a 43% difference in cardiovascular events was noted between these regimens in lean patients, a 24% difference in overweight individuals, and an 11% non-significant difference in obese people. This information should be of practical value to clinicians deciding which type of combination treatment to select for individual patients.

Our findings should also help refute the argument that selection of hydrochlorothiazide in ACCOMPLISH might have provided less cardiovascular protection than if we had used the diuretic chlortalidone (known also as chlorthalidone), which was used in SHEP. In fact, findings of the SHEP study confirmed that chlortalidone was associated with an unexpectedly high cardiovascular event rate in lean patients, similar to the effect we now report for hydrochlorothiazide-based therapy in ACCOMPLISH. Thus, thiazide-like diuretic treatment, irrespective of which individual agent is considered, might not be the best choice in non-obese patients.

Although the analyses reported here were prespecified as part of the ACCOMPLISH trial, patients at baseline were not stratified into normal weight, overweight, or obese categories before randomisation took place. Although, technically, stratification would have been ideal to study the importance of body mass as a determinant of treatment outcomes, in reality, numbers of patients were sufficiently large, and the assignment to treatment groups sufficiently similar within every weight category, to make bias improbable. About 12% of the study cohort was of black ethnic origin, and numbers were not adequate to support a separate comparison of possible disparate responses between treatments within the different weight categories. However, within ACCOMPLISH as a whole, no evidence was found for differences between black and white patients in the effects of treatments on major endpoints.

Some small differences were noted in baseline clinical, demographic, and patients’ characteristics between the two treatment arms within BMI categories. We adjusted our calculations of hazard ratios for relevant comparisons by including BMI group, age, sex, presence or absence of diabetes, previous cardiovascular events, stroke, or chronic kidney disease as factors in the statistical model. Results did not differ substantially from unadjusted data, both when all adjustments were applied together and for each characteristic separately (data available on request). An apparent inequality between treatment arms in clinically measured diastolic blood pressure values was also seen: values were slightly lower in patients assigned amlodipine-based treatment compared with the hydrochlorothiazide-based group. However, this difference was not sustained throughout the day, because 24-h ambulatory blood pressure monitoring in ACCOMPLISH subsets showed that achieved 24-h blood pressure values were virtually identical in the two treatment arms.

Even though BMI has been used widely as a basis for categorisation of patients, the alternative approach using waist measurements is also of interest. However, in a longitudinal study, BMI and waist measurements were similarly predictive of changes in metabolism, blood pressure, and left-ventricular mass over a 10-year period.

In conclusion, findings of our predefined subanalysis of ACCOMPLISH show that higher cardiovascular event rates in lean patients reported in hypertension clinical trials might have reflected the types of antihypertensive treatments that were used. Diuretic-based regimens seem to be a reasonable choice in obese patients in whom excess volume provides a rationale for this type of treatment, but thiazides are clearly less protective against cardiovascular events in patients who are lean. An alternative therapeutic regimen that includes a calcium-channel blocker such as amlodipine, which works equally well across all BMI categories, provides an advantage with respect to clinical outcomes in patients who are not obese.

Contributors
All authors had access to pertinent study data, contributed to data analysis and interpretation, and reviewed and commented on drafts of the report. MAW wrote the report.

Conflicts of interest
MAW is a consultant for Boehringer Ingelheim, Daiichi Sankyo, Forest, and Takeda, and provides speaking services for Daiichi Sankyo, Forest, Novartis, and Takeda. KJ is a consultant for Boehringer Ingelheim, Forest, Novartis, XOMA Pharmaceuticals, Pfizer, and InVasc Therapeutics, provides speaking services for Daiichi Sankyo, and receives research support from NHLBI, NIH, NIDDK, and Novartis. GLB consults for Takeda, Abbott, Relpyu, Medtronic, Daiichi-Sankyo, Novartis, and Fibrogen, and has investigator-initiated grants from Forest and Takeda. MRW is a scientific adviser for Argenx, Novartis, Pfizer, Daiichi Sankyo, and MSD. DZ and YZ are employees of Novartis. BD is a consultant for Novartis, Boehringer Ingelheim, Bayer, and Vicere Pharma, owns stock in Mentina Scientific AB, and provides speaking services for Novartis, MSD, Boehringer Ingelheim, Pfizer, Kika, Bayer, and Vicere Pharma. EJV and BP are consultants to Novartis.

References
Diuretic-based regimens for obese patients?

Obesity is known to lead to hypertension and, conversely, hypertension to result in obesity; therefore, both disorders commonly coexist. However, obesity profoundly affects haemodynamic, neuroendocrine, and metabolic processes, in addition to target organ disease in hypertension. Since excess adipose tissue needs a higher cardiac output to meet metabolic demands, for any level of arterial pressure, vascular resistance will be lower in an obese than in a lean patient. Vascular resistance is the hallmark of vascular disease; because it is lower in obese individuals, obesity could paradoxically exert a protective effect on target organ disease. Indeed, the so-called obesity paradox—ie, higher cardiovascular event rates in normal weight than in obese patients—has been reported in several observational studies.

However, the increase in cardiac output and intravascular volume associated with obesity will raise left-ventricular filling pressure and volume, causing chamber dilation and ventricular hypertrophy. If both hypertension and obesity are present, the heart has to carry the double burden of a high preload from obesity and a high afterload from hypertension. Myocardial lipid content increases with obesity and might contribute to adverse structural and functional cardiac adaptations. As a result, left-ventricular dysfunction and frank heart failure are all too common features in the obese phenotype of hypertension. Data from the Framingham cohort show a doubling of the risk of heart failure in obese people, and in a systematic review of 89 studies, incident heart failure was increased by more than 70% in patients with a body-mass index (BMI) of more than 30.

In The Lancet, Michael Weber and colleagues take investigation of the obesity paradox one step further by assessing the effects of different hypertension treatments. In a subanalysis of data from the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial, the investigators classified 11,482 patients according to BMI and reported a more pronounced obesity paradox in those assigned a treatment strategy containing hydrochlorothiazide compared with individuals receiving a regimen based on amlodipine. Although amlodipine-based treatment was equally effective across all weight subgroups and was superior to the hydrochlorothiazide-based regimen in lean and overweight patients, hydrochlorothiazide was as good as amlodipine in obese individuals. Does this finding now mean that diuretic-based regimens are a reasonable choice for obese people? Before we accept this conclusion by Weber and colleagues, a few factors need to be considered.

The benefits of amlodipine in this subanalysis of ACCOMPLISH remained significant even when lean patients were excluded. Moreover, the analysis for the obese subgroup had only 35% power (based on our own calculations) to detect a 15% difference between the two groups, and the point estimate (hazard ratio 0.89, 95% CI 0.71–1.12) still favoured amlodipine over hydrochlorothiazide, although this finding was not significant. Stratification of patients by BMI is prone to enrich the highest BMI group with people at risk for heart failure.6,7 Since diuretics and angiotensin-converting enzyme (ACE) inhibitors are cornerstones for management of heart failure, whereas use of calcium-channel blockers remains contested, the relative greater efficacy of hydrochlorothiazide in the obese patient (vs lean individuals) should not be a surprise. The efficacy of diuretics for prevention of heart failure was shown in the Hypertension in the Very Elderly Trial (HYVET), in which indapamide combined with perindopril reduced this risk by 64%, by far the largest reduction of any cardiovascular event noted in the HYVET study. Similarly, chlortalidone was superior to amlodipine for prevention of heart failure.
in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),\textsuperscript{2} despite a similar reduction in blood pressure. Once the indication for diuretics expands from uncomplicated hypertension to prevention of heart failure, these drugs clearly have an edge over calcium-channel blockers.\textsuperscript{3,4} The fact that hydrochlorothiazide was equal to amlopidine in obese people\textsuperscript{1} has little if anything to do with obesity per se, but simply reflects the fact that among obese patients there was a preponderance of individuals at risk for heart failure who were prone to respond well to diuretic treatment.

However, there is more to obesity than risk of heart failure. Specifically, obese patients commonly present with the metabolic syndrome and hyperuricaemia and are at a 6–12-fold increased risk of diabetes.\textsuperscript{7} Thiazide diuretics augment insulin resistance, intra-abdominal fat accumulation, and amount of uric acid in serum. Compared with antihypertensive agents other than \( \beta \) blockers, diuretics conferred a 35\% increased risk of new-onset diabetes, and this risk rose with duration of diuretic treatment.\textsuperscript{13} Elliott and Meyer reported the odds ratio of new-onset diabetes to be 1:34 with diuretics compared with placebo.\textsuperscript{14} Admittedly, diuretic-based metabolic abnormalities are mitigated to some extent in the presence of an ACE inhibitor but seem to persist nonetheless,\textsuperscript{15} thereby contraindicating diuretics in the long term, particularly in obese patients. However, if a thiazide is to be used, it should be either chlorthalidone or indapamide, for which solid outcome data exist.\textsuperscript{11,12}

Therefore, we reject the conclusion of Weber and colleagues that diuretic-based regimens are a reasonable choice in obese patients. On the contrary, we surmise that thiazide diuretics are contraindicated in obesity, relatively speaking. If the indication is hypertension, amlopidine-based treatment should be used irrespective of body size. Conversely, if the indication is prevention or treatment of left-ventricular dysfunction, a diuretic-based regimen should be used, again irrespective of body size. This strategy relegates diuretics to third-line agents for treatment of hypertension, except in patients at risk of heart failure—a position recognised in the latest UK guidelines.\textsuperscript{16}

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