Differential Impact of Blood Pressure–Lowering Drugs on Central Aortic Pressure and Clinical Outcomes

Principal Results of the Conduit Artery Function Evaluation (CAFE) Study

The CAFE Investigators, for the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) Investigators

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Background—Different blood pressure (BP)–lowering drugs could have different effects on central aortic pressures and thus cardiovascular outcome despite similar effects on brachial BP. The Conduit Artery Function Evaluation (CAFE) study, a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), examined the impact of 2 different BP lowering-regimens (atenolol±thiazide-based versus amlodipine±perindopril-based therapy) on derived central aortic pressures and hemodynamics.

Methods and Results—The CAFE study recruited 2199 patients in 5 ASCOT centers. Radial artery applanation tonometry and pulse wave analysis were used to derive central aortic pressures and hemodynamic indexes on repeated visits for up to 4 years. Most patients received combination therapy throughout the study. Despite similar brachial systolic BPs between treatment groups (Δ0.7 mm Hg; 95% CI, −0.4 to 1.7; P=0.2), there were substantial reductions in central aortic pressures with the amlodipine regimen (central aortic systolic BP, Δ4.3 mm Hg; 95% CI, 3.3 to 5.4; P<0.0001; central aortic pulse pressure, Δ3.0 mm Hg; 95% CI, 2.1 to 3.9; P<0.0001). Cox proportional-hazards modeling showed that central pulse pressure was significantly associated with a post hoc–defined composite outcome of total cardiovascular events/procedures and development of renal impairment in the CAFE cohort (unadjusted, P<0.0001; adjusted for baseline variables, P<0.05).

Conclusions—BP-lowering drugs can have substantially different effects on central aortic pressures and hemodynamics despite a similar impact on brachial BP. Moreover, central aortic pulse pressure may be a determinant of clinical outcomes, and differences in central aortic pressures may be a potential mechanism to explain the different clinical outcomes between the 2 BP treatment arms in ASCOT. (Circulation. 2006;113:1213-1225.)

Key Words: aorta ■ arteries ■ blood pressure ■ hemodynamics ■ hypertension

When blood pressure is measured conventionally over the brachial artery, it is assumed that these measurements accurately reflect pressures in the central circulation. This assumption is supported by irrefutable observations that brachial blood pressure parameters are powerful predictors of cardiovascular structural damage, morbidity, and mortality.1 However, central aortic pressure parameters and left ventricular load are determined not only by cardiac output and peripheral vascular resistance but also by the stiffness of conduit arteries and the timing and magnitude of pressure wave reflections.2–6 Short-term studies have shown that various classes of blood pressure–lowering drugs may have
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profundely different effects on pulse wave morphology and thus central hemodynamic parameters despite similar effects on brachial artery pressures. This observation is relevant to the debate about how much of the benefit of blood pressure-lowering drugs in clinical trials can be attributed to blood pressure lowering per se or to alternative mechanisms “beyond blood pressure.” This debate is fundamental because it defines the principles of clinical practice for the treatment of hypertension.

**Editorial p 1162 Clinical Perspective p 1225**

The discussion about the impact of blood pressure-lowering drugs on central aortic hemodynamic parameters has been hindered by a remarkable lack of data from large-scale clinical trials on anything other than periodic brachial blood pressure measurements. This is despite the fact that emerging evidence suggests that central aortic pressures may be independent predictors of cardiovascular structural damage and clinical outcomes.

A clinical study was therefore required to define whether different blood pressure-lowering treatment strategies would have different effects on central aortic pressures and thus cardiovascular outcome despite similar effects on brachial blood pressures. We thus designed the Conduit Artery Functional Evaluation (CAFE) study as a large substudy within the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT). ASCOT was an ideal setting for this purpose because it prospectively examined the impact of 2 blood pressure-lowering regimens on derived central aortic pressures and other hemodynamic parameters.

The prespecified primary objective of the CAFE study was to test the hypothesis that different blood pressure-lowering regimens would produce different effects on central aortic pressures despite similar effects on brachial blood pressures. A secondary objective of the CAFE study was to examine whether there was a relationship between measurements of central aortic pressure and cardiovascular-related outcomes within the CAFE study cohort. The primary results of the Blood Pressure Lowering Arm of ASCOT have recently been reported. This report describes the principal results of the CAFE study.

**Methods**

**Patient Recruitment**

Participants already recruited into ASCOT were eligible for recruitment into the CAFE study. Recruitment began in 2001, and a total of 2199 participants were recruited from 5 ASCOT study centers in the United Kingdom and Ireland (Figure 1). (Study centers are listed in the online-only Data Supplement.) Recruitment into the CAFE study began 1 year after randomization into ASCOT to avoid the turbulence of the early blood pressure changes and uptitration of treatment, so patients were studied when their treatment regimens were stable. Those consenting to inclusion into the CAFE study were progressively recruited over the duration of the remaining ASCOT follow-up (4 years), and by the end of follow-up, ~70% of ASCOT patients at each CAFE study center had been recruited. Within the first year, 36% of the CAFE cohort had undergone at least 1 CAFE study measurement (see below). This increased to 67% by year 2 and to 87% by year 3.

All patients gave written informed consent; approval for the study was granted by local research ethics committees at each ASCOT center. Ethical approval was also granted by the UK Multicenter Ethics Committee.

**Study Design: Blood Pressure and Lipid Lowering in ASCOT**

The ASCOT protocol including study design has been published. Briefly, people were eligible for the blood pressure-lowering arm of ASCOT if they were 40 to 79 years of age at randomization and had either untreated hypertension (systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg) or treated hypertension with a systolic blood pressure of ≥140 mm Hg or diastolic blood pressure of ≥90 mm Hg. To be eligible, patients had at least 3 additional cardiovascular risk factors: male sex, smoker, age >55 years, left ventricular hypertrophy, ECG abnormalities consistent with evidence of ischemic changes, type 2 diabetes, peripheral arterial disease, cerebrovascular disease, microalbuminuria or proteinuria, a ratio of plasma total cholesterol to HDL cholesterol of ≥6, or a family history of premature coronary heart disease. People were not eligible for ASCOT if they had evidence of previous myocardial infarction, treated angina at the time of randomization, a cerebrovascular event in the 3 months before randomization, fasting triglycerides >400 mg/dL, heart failure, uncontrolled arrhythmias, or any clinically important hematological or biochemical abnormality on

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**Figure 1. CAFE study profile.**
Table 1. Study Blood Pressure-Lowering Drug Regimens

<table>
<thead>
<tr>
<th>Step</th>
<th>Calcium Channel Blocker Regimen</th>
<th>β-Blocker-Based Regimen</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Amlodipine 5 mg</td>
<td>Atenolol 50 mg</td>
</tr>
<tr>
<td>2</td>
<td>Amlodipine 10 mg</td>
<td>Atenolol 100 mg</td>
</tr>
<tr>
<td>3</td>
<td>Amlodipine 10 mg + perindopril 4 mg</td>
<td>Atenolol 100 mg + bendroflumethiazide K 1.25 mg</td>
</tr>
<tr>
<td>4</td>
<td>Amlodipine 10 mg + perindopril 8 mg (2 × mg)</td>
<td>Atenolol 100 mg + bendroflumethiazide K 2.5 mg</td>
</tr>
<tr>
<td>5</td>
<td>Amlodipine 10 mg + perindopril 8 mg (2 × 4 mg) + doxazosin gastrointestinal transport system 4 mg</td>
<td>Atenolol 100 mg + bendroflumethiazide K 2.5 mg + doxazosin gastrointestinal transport system 4 mg</td>
</tr>
<tr>
<td>6</td>
<td>Amlodipine 10 mg + perindopril 8 mg (2 × 4 mg) + doxazosin gastrointestinal transport system 8 mg</td>
<td>Atenolol 100 mg + bendroflumethiazide K 2.5 mg + doxazosin gastrointestinal transport system 8 mg</td>
</tr>
</tbody>
</table>

Further treatment to achieve blood pressure goal is outlined at http://www.ascotstudy.org. All drugs were given orally.

Procedures

The detailed CAFE study protocol has been published.19 The CAFE study used radial artery applanation tonometry and pulse wave analysis24-28 to calculate derived central blood pressures and other parameters using a commercially available system (SphygmoCor). Applanation tonometry measurements were obtained at scheduled ASCOT follow-up visits. Our objective was to obtain at least 2 measurements for each participant in the CAFE study over the course of the ASCOT follow-up. By the end of the CAFE study, an average of 3.4 measurements per patient had been recorded, and the average value did not differ by treatment arm (atenolol/HD1006 vs. perindopril-based treatment, 2.9 years; amlodipine/HD1006 + bendroflumethiazide K 2.5 mg).

Through the use of a factorial design, people also were eligible for randomization to the lipid-lowering arm of ASCOT (ASCOT-LLA) if they had a total blood cholesterol concentration of ≤250 mg/dL and were not taking a statin or fibrate at the time of randomization. Patients recruited into ASCOT-LLA were randomized to receive atorvastatin 10 mg daily or matching placebo. The results of ASCOT-LLA have been reported.23

Statistical Analysis

In powering the CAFE study, we set as our primary objective a comparison of the effects of the 2 treatment regimens on central
clinical outcomes in all people from the time of the first central aortic pressures/hemodynamic indexes measured to central aortic pressures derived from applanation tonometry. When the study was designed, there were no published data from studies of appropriate size using these drug regimens to undertake a formal power calculation. From studies in Leicester, we defined the variability in the tonometry measurement of central aortic pressure from various populations that included people with normal blood pressure, treated hypertension, and diabetes. Using these data, we calculated that to detect a difference in central aortic systolic or pulse pressure of 5 mm Hg between treatment arms, 250 patients per treatment arm would be required to show this difference with 90% power at the P<0.01 level of significance. However, an additional consideration was recruiting a sufficiently large sample (>10% of the total ASCOT population) so that our findings would be more representative of the whole ASCOT population.

All statistical analyses were performed at the Scandinavian Cardiovascular Research Institute (ASCOT coordinating center) using the SAS computer program version 8.2 (SAS Institute Inc). Non-paired Student t tests were used for between-treatment-arm comparisons of continuous data variables.

As a secondary objective of the CAFE study, we prespecified that we would examine the relationship between central aortic pressures and the primary and secondary outcomes of ASCOT. Post hoc, we defined a composite clinical outcome comprising all cardiovascular events and procedures and development of renal impairment for events as defined and validated by the ASCOT end-points committee (see the Data Supplement for details). Three Cox proportional-hazards models were constructed to evaluate whether central aortic pressures/hemodynamic indexes measured during the CAFE study follow-up were associated with this composite clinical outcome. The first model (model 1) analyzed composite clinical outcomes in all patients recruited into CAFE from the time of randomization into ASCOT (305 events recorded). To assess whether there was a disproportionate influence of the titration phase of ASCOT on clinical outcomes, ie, before the beginning of central blood pressure measurements in CAFE, 2 further Cox proportional-hazards models were constructed. Model 2 evaluated composite clinical outcomes in all people from the time of the first central aortic pressure measurement in CAFE (245 events recorded). Model 3 evaluated composite clinical outcomes from the time of the first central aortic pressure measurement in CAFE but excluded patients with documented events before this time; ie, it evaluated only first events occurring during CAFE follow-up (225 events recorded). All models were adjusted for age and baseline risk factors and were updated (ie, time dependent) for blood pressures and central hemodynamic indexes throughout the follow-up period. Analyses were on an intention-to-treat basis.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Demographic Data

The profile for the 2199 patients recruited into the CAFE study is shown in Figure 1. Before data analysis, 126 patients were excluded because their radial arterial pressure waveforms were of insufficient quality as a result of abnormal heart rhythms or low-amplitude pulses. Table 2 shows the baseline characteristics of the 2073 patients in the CAFE study who were included in the intention-to-treat analysis, along with the baseline characteristics for the 19 257 patients recruited into ASCOT. The CAFE participants were well matched between the 2 treatment arms and well matched with all participants in ASCOT. Most patients recruited into the CAFE study and ASCOT had previously been treated for hypertension at the time of randomization (≈90% in the CAFE study and 81% in ASCOT). The use of lipid-lowering therapy and aspirin was slightly higher in the CAFE study cohort. There were also fewer smokers and alcohol consumption was slightly higher for patients recruited into CAFE compared with all participants in ASCOT. These small differences reflect differing regional demographics between patients recruited from the United Kingdom and Ireland (CAFE) and those recruited from the United Kingdom, Ireland, and the Nordic countries (all ASCOT). As in ASCOT, the CAFE participants were mainly white men, with a mean age of 63 years. The baseline seated brachial blood pressure of the CAFE participants was 160/93 mm Hg, which was slightly lower than that of the total ASCOT population.

Hemodynamic Data

At the end of the CAFE study, brachial blood pressures were similar between the 2 treatment groups and had fallen substantially from baseline: −26/−13.8 mm Hg for atenolol±thiazide versus −27.8/−15.7 mm Hg for amlopidine±perindopril (Tables 2 and 3). By the end of the study, 85% (amlopidine±perindopril) and 80% (atenolol±thiazide) of patients remained on treatment with their original randomized allocation (Data Supplement Table I). Most patients (95%) were taking at least 2 blood pressure–lowering drugs, with 56% and 60% receiving the predefined combination therapy of amlopidine±perindopril or atenolol±thiazide, respectively (Data Supplement Table I). Only 3.5% (atenolol) and 7.0% (amlopidine) remained on monotherapy throughout the CAFE study.

Figure 3 shows representative averaged radial artery waveforms and the resulting derived central aortic waveforms from individual patients with similar brachial blood pressures treated with either atenolol or amlopidine monotherapy.
differences in the morphology of both the radial and central aortic arterial waveforms. Atenolol monotherapy was associated with a broader peripheral waveform and a more prominent late systolic peak in the central aortic waveform.

**Primary Outcomes**

Brachial systolic pressures and derived central aortic systolic pressures at various time points throughout the CAFE study are shown in Figure 4. The average age and gender of the patient cohorts at each sampling time point in these analyses did not differ between treatment arms; this was consistent with time throughout the study.

A summary of the blood pressure load for each treatment arm is also presented as the mean area under the curve (AUC) for each parameter. Despite insignificant differences in brachial systolic blood pressures throughout the CAFE study (AUC difference, 0.7 mm Hg; 95% CI, −0.4 to 1.7; P = 0.2), derived central aortic systolic pressure was substantially lower with amlodipine/ perindopril-based therapy (AUC difference, 4.3 mm Hg; 95% CI, 3.3 to 5.4; P < 0.0001) (Figure 4). Moreover, these differences between brachial and central aortic blood pressures were consistent with time throughout the CAFE study.

**TABLE 2. Baseline Characteristics by Treatment Arm for the CAFE Cohort and the ASCOT Population**

<table>
<thead>
<tr>
<th>Demographics and clinical characteristics</th>
<th>CAFE</th>
<th>ASCOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62.6 (8.3)</td>
<td>62.9 (8.2)</td>
</tr>
<tr>
<td>&lt;60, n (%)</td>
<td>381 (37)</td>
<td>367 (35.2)</td>
</tr>
<tr>
<td>&gt;60, n (%)</td>
<td>650 (63)</td>
<td>675 (64.8)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>886 (85.9)</td>
<td>892 (85.6)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>251 (24.3)</td>
<td>267 (25.6)</td>
</tr>
<tr>
<td>Alcohol consumption, units/wk</td>
<td>11.5 (14.3)</td>
<td>11.8 (14.9)</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>159.9 (16.6)</td>
<td>161 (18.4)</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>92.4 (9.6)</td>
<td>92.6 (9.8)</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>71.8 (12.3)</td>
<td>71.2 (12.4)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29.0 (4.5)</td>
<td>29.1 (4.7)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>84.6 (14.7)</td>
<td>84.3 (15.7)</td>
</tr>
<tr>
<td>height, cm</td>
<td>170.7 (8.7)</td>
<td>170.2 (9.4)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>224.3 (38.7)</td>
<td>224.3 (42.5)</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>143.1 (34.8)</td>
<td>134.1 (34.8)</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>50.3 (15.5)</td>
<td>50.3 (15.5)</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>159.4 (88.6)</td>
<td>159.4 (88.6)</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>110 (38)</td>
<td>110 (38)</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.08 (0.18)</td>
<td>10.9 (0.19)</td>
</tr>
</tbody>
</table>

Medical history, n (%)

| Previous stroke/TIA | 76 (7.4) | 101 (9.7) | 1063 (11.1) | 1050 (10.9) |
| Diabetes | 252 (24.4) | 251 (24.1) | 2578 (26.8) | 2567 (26.6) |
| LVH (echo or ECG) | 237 (23) | 256 (24.6) | 2076 (21.6) | 2091 (21.7) |
| Atrial fibrillation | 9 (0.9) | 6 (0.6) | 113 (1.2) | 117 (1.2) |
| ECG abnormalities other than LVH | 271 (26.3) | 272 (26.1) | 2249 (23.4) | 2206 (22.9) |
| Peripheral vascular disease | 61 (5.9) | 59 (5.7) | 613 (6.4) | 586 (6.1) |
| Other relevant CV disease | 22 (2.1) | 27 (2.6) | 486 (5.1) | 533 (5.5) |
| Mean (SD) risk factors, n | 3.7 (0.9) | 3.7 (0.9) | 3.7 (0.9) | 3.7 (0.9) |

Drug therapy

| Previous antihypertensive treatments, n (%) | 109 (10.6) | 100 (9.6) | 1825 (19) | 1841 (19.1) |
| Lipid-lowering therapy | 482 (46.8) | 496 (47.6) | 4283 (44.5) | 4280 (44.4) |
| Aspirin use | 440 (42.7) | 446 (42.8) | 3510 (36.5) | 3518 (36.5) |
| Lipid-lowering therapy | 120 (11.6) | 120 (11.5) | 1004 (10.4) | 1046 (10.9) |
| Aspirin use | 244 (23.7) | 274 (26.3) | 1837 (19.1) | 1851 (19.2) |

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; TIA, transient ischemic attack; LVH, left ventricular hypertrophy; and CV, cardiovascular.

Baseline characteristics (mean ±SD) for the CAFE study cohort and the ASCOT population for comparison. Definition of diagnoses: LVH by echocardiography was assessed as ≥116 g/m² in men and ≥104 g/m² in women. ECG LVH was defined using either Cornell voltage duration product (≥2440) or Sokolow Lyon criteria (≥38 mm). ECG abnormalities excluding LVH included evidence of LV strain pattern, abnormal Q-waves, evidence of left bundle branch block, and ST-T changes compatible with ischemic heart disease (ST-T depression, negative or biphasic T-waves). Peripheral vascular disease was assessed using a validated questionnaire or from evidence of a recent history of surgical intervention for peripheral vascular disease.
There were small differences in central aortic diastolic pressure in favor of amlodipine ± perindopril-based therapy (AUC difference, 1.4 mm Hg; 95% CI, 0.6 to 2.1; P<0.0001; Table 3), indicating that an important difference between the 2 treatment regimens was the impact of treatment on central aortic systolic pressure.

Central aortic pulse pressure also was significantly lower with time throughout the CAFE study with amlodipine ± perindopril-based therapy (AUC difference, 3.0 mm Hg; 95% CI, 2.1 to 3.9; P<0.0001). This was seen despite a slightly higher brachial pulse pressure with amlodipine ± perindopril-based therapy (Table 3 and Data Supplement Figure panel B); it was lower perindopril-based therapy in the CAFE study did not result from an increase in the outgoing systolic pressure wave (P1 height) (Table 3 and Data Supplement Figure panel B). It was lower with amlodipine ± perindopril-based therapy compared with atenolol ± thiazide-based therapy (AUC difference, 0.8 mm Hg; 95% CI, 0.3 to 1.4; P<0.01). However, central aortic systolic pressure wave augmentation was markedly increased with atenolol ± thiazide-based therapy compared with amlodipine ± perindopril-based therapy (AUC difference, 3.8 mm Hg; 95% CI, 3.3 to 4.4; P<0.0001) (Table 3 and Data Supplement Figure panel C), and the percentage of

![Figure 3](http://circ.ahajournals.org/)

**Figure 3.** Examples of peripheral (A) and corresponding derived central aortic (B) waveforms from patients of equal age treated with atenolol (solid line) or amlodipine (broken line) as monotherapy, achieving equivalent brachial blood pressures.
the systolic pressure wave attributable to wave reflection (augmentation index) was also increased by atenolol±thiazide-based therapy (AUC difference, 6.5%; 95% CI, 5.8 to 7.3; P<0.0001) (Table 3 and Data Supplement Figure panel D).

Heart rate, as expected, was significantly lower with atenolol±thiazide-based therapy (AUC difference, 10.7 mm Hg; 95% CI, 9.8 to 11.5; P<0.0001; Table 3). This was associated with prolonged time to both the outgoing pressure wave peak (T1) and the reflected pressure wave (T2; Table 3).

We measured PWV<sub>c</sub> in a cohort of the CAFE study participants at the Leicester center (n=114). The data from this cohort are shown in Data Supplement Table II. The older age of this cohort reflects the fact that the PWV<sub>c</sub> measurements were obtained in the final year of the CAFE study when the patients had been stable on treatment for almost 5 years. PWV<sub>c</sub> did not differ between treatment groups (difference, 0.5 m/s<sup>−1</sup>; 95% CI, −0.2 to 1.2; P=0.3; Data Supplement Table II).

**Secondary Outcomes**

To evaluate whether blood pressure and tonometry-derived hemodynamic indexes were related to clinical outcomes in the CAFE cohort, we used Cox proportional-hazards modeling, updated with time for blood pressures and hemodynamic indexes, and the post hoc–defined composite clinical end point. Three models were constructed, evaluating composite clinical outcomes from time of randomization into ASCOT (model 1), from time of the first central aortic pressure measurement in CAFE (model 2), and from time of the first central aortic pressure measurement in CAFÉ with patients with events before this time excluded (model 3).

As shown in Table 4, central aortic pulse pressure, central aortic pressure wave augmentation, and outgoing pressure wave height (P1 height), along with brachial pulse pressure, were significantly associated with the composite clinical outcome (<i>P</i>&lt;0.01) in all models. The Cox regression models were then adjusted for age and baseline risk factors (see the Table 4 legend for details). After adjustment, central pulse pressure remained significantly associated with the composite clinical outcome in all 3 models. In addition, augmentation and/or peripheral pulse pressure were significantly associated with the composite clinical outcome after adjustment in models 2 and 3. All the hemodynamic factors tested in the adjusted and unadjusted models are listed in the legend for Table 4. Only those factors significantly associated with hazard for the composite clinical outcome before adjustment for age and baseline risk factors are shown in the Table.
Discussion

The CAFE study derived central aortic blood pressures and hemodynamic indices contemporaneously with brachial blood pressure measurements in 2073 ASCOT participants for up to 4 years of follow-up. These measurements showed substantial and consistent differences in central aortic pressures and hemodynamics in favor of the amlodipine–perindopril-based therapy versus atenolol–thiazide-based therapy despite similar brachial systolic blood pressure between treatment arms. Our finding that different blood pressure–lowering drugs might differentially affect central aortic pressures/hemodynamics despite similar effects on brachial blood pressure is consistent with data from previous smaller-scale studies of shorter duration.8,9,11,30–33 The CAFE study, however, is the first study to evaluate this hypothesis in a major cardiovascular outcomes trial with repeated measurements throughout the study in a very large cohort of patients.

The higher central aortic systolic and pulse pressures with atenolol–thiazide-based therapy could have resulted from an increase in the outgoing pressure wave (P1 height) and/or increased pressure wave reflection, leading to augmentation of the outgoing pressure wave. The magnitude of the outgoing pressure wave (P1 height) was not increased by atenolol–thiazide-based therapy compared with amlodipine–perindopril-based therapy (Table 3 and Data Supplement Figure panel B); thus, the increase in central systolic and pulse pressure must be attributable to increased pressure wave reflection from distal reflection sites. This conclusion is supported by our findings that (1) central aortic systolic pressure wave augmentation was much higher with atenolol–thiazide-based therapy (Table 3 and Data Supplement Figure panel C) compared with amlodipine–perindopril-based therapy and (2) the percentage of the systolic pressure wave attributable to wave reflection (augmentation index) was substantially higher with atenolol–thiazide-based therapy (Table 3 and Data Supplement Figure panel D).

The differences in aortic systolic pressure wave reflections between the 2 treatment arms in the CAFE study could have resulted from at least 3 mechanisms: (1) differences between treatment arms in arterial pulse wave velocity as a consequence of changes in arterial stiffness, (2) differences in the proximity of pressure wave reflection sites, and (3) differences in the timing of systolic ejection resulting from differences in heart rate.

With regard to the first mechanism, our finding that PWVc was similar between treatment arms in a small cohort of
patients suggests that differences in aortic pressure wave reflections were not due to important differences in arterial stiffness and/or velocity of the pressure wave. The relatively small sample size used in the measurement of pulse wave velocity means that we cannot rule out the possibility of a type 2 statistical error in this analysis; however, our findings are supported by other studies that have shown no difference in aortic pulse wave velocity when β-blocker–based therapy has

### TABLE 4. Updated Cox Proportional-Hazards Modeling for the Composite Clinical End Point in the CAFE Cohort

<table>
<thead>
<tr>
<th>Model</th>
<th>Peripheral PP</th>
<th>Central PP</th>
<th>Augmentation</th>
<th>P1 height</th>
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<tbody>
<tr>
<td>Model 1 (305 events)</td>
<td>21.0</td>
<td>17.8</td>
<td>7.1</td>
<td>19.0</td>
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<tr>
<td>Model 2 (245 events)</td>
<td>19.7</td>
<td>17.2</td>
<td>8.9</td>
<td>15.4</td>
</tr>
<tr>
<td>Model 3 (225 events)</td>
<td>18.0</td>
<td>15.5</td>
<td>7.7</td>
<td>14.3</td>
</tr>
</tbody>
</table>

**Updated Cox proportional-hazards model adjusted for age and baseline risk factors**

<table>
<thead>
<tr>
<th>Model</th>
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<th>Central PP</th>
<th>Augmentation</th>
<th>P1 height</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1 (305 events)</td>
<td>3.83</td>
<td>3.91</td>
<td>2.26</td>
<td>3.04</td>
</tr>
<tr>
<td>Model 2 (245 events)</td>
<td>4.5</td>
<td>5.0</td>
<td>4.2</td>
<td>2.5</td>
</tr>
<tr>
<td>Model 3 (225 events)</td>
<td>4.1</td>
<td>4.1</td>
<td>3.1</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Cox proportional hazards regression models updated for blood pressure and hemodynamic indices with time. Hazard ratios are presented per 10 mm Hg. The composite clinical outcome variable was all cardiovascular events and procedures plus development of renal impairment (see Data Supplement for details). Model 1 evaluates composite clinical outcomes in all patients from time of randomization into ASCOT. Model 2 evaluates composite clinical outcomes in all patients from time of first central aortic pressure measurement in CAFE. Model 3 evaluates composite clinical outcomes in all patients from time of first central aortic pressure measurement in CAFE excluding patients with events occurring prior to this time. Where indicated, models were adjusted for age and baseline risk factors including presence of peripheral vascular disease, diabetes mellitus, left ventricular hypertrophy on echocardiogram or ECG, ECG changes compatible with ischemic heart disease, history of cerebrovascular disease, microalbuminuria/proteinuria, plasma total:high-density lipoprotein cholesterol ratio greater than 6, family history of coronary artery disease, male sex, age over 55 years, or smoking status (current/recent). Blood pressures and hemodynamic factors were entered into the model individually and included brachial systolic blood pressure, central systolic blood pressure, difference between brachial and central systolic blood pressure, brachial pulse pressure, central pulse pressure, pulse pressure amplification, augmentation, augmentation index, and outgoing pressure wave height (P1 Height). Factors showing a significant association with the composite end point are shown.
been compared with vasodilator-based blood pressure–lowering treatments.\textsuperscript{11,30,31,34}

With regard to the second mechanism, atenolol±thiazide-based treatment could have resulted in a shift of arterial reflection sites proximally, eg, via a relative vasoconstriction, compared with amlodipine±perindopril-based therapy.\textsuperscript{33,35} This would result in earlier wave reflection despite similar pulse wave velocities, thereby enhancing central aortic systolic augmentation. Additionally, amlodipine±perindopril-based treatment may have had a beneficial functional effect, shifting pressure wave reflection sites distally as a consequence of small artery remodeling\textsuperscript{36} and thereby reducing pressure wave reflections during systole. Support for the remodeling and wave reflection hypothesis comes from the REASON study.\textsuperscript{31}

The third mechanism, ie, differences in timing of systolic ejection, is likely to be a function of the slower heart rate resulting from atenolol±thiazide-based therapy. This prolongs systolic ejection time and delays the peak of the outgoing pressure wave (T1) (Table 3), thereby increasing the likelihood that pressure wave reflections will augment the outgoing pressure wave during systole. We suggest that this is the principal mechanism accounting for the differences in central aortic pressures between treatment arms in the CAFE study.\textsuperscript{30,31,37}

Support for the hypothesis that central aortic pressures are higher with \( \beta \)-blocker–based therapy compared with alternative blood pressure–lowering regimens comes from short-term, in vivo catheterization studies in humans\textsuperscript{34,35} and previous analyses of cardiovascular structural changes in response to blood pressure lowering. It has been well recognized from experimental animal and human studies that despite similar reductions in blood pressure, \( \beta \)-blocker–based treatment regimens have been less effective than alternatives at regressing left ventricular hypertrophy, carotid intimal thickness, and resistance artery structure.\textsuperscript{38–45} It is plausible that this differential structural regression relates to less effective lowering of central aortic pressures. The changes in waveform shape and central aortic pressures seen in our study are unlikely to represent an epiphenomenon resulting from structural change because differential effects of blood pressure–lowering drugs have been shown to occur early,\textsuperscript{34,35} before the onset of structural change in humans.

Additional support for the concept that central aortic pressures are higher with \( \beta \)-blocker-based therapy comes from studies of the changes in plasma brain natriuretic peptide (BNP) levels in response to blood pressure lowering. Various classes of blood pressure–lowering drugs produce a fall in circulating BNP, a response that has been regarded as a surrogate for reduced central aortic pressures and reduced left ventricular end-diastolic pressure.\textsuperscript{32} In contrast, numerous studies have reported that \( \beta \)-blocker–based treatments are associated with an increase in BNP levels despite similar reductions in brachial blood pressure.\textsuperscript{32,46–49} This divergent BNP response to blood pressure lowering supports our conclusion that \( \beta \)-blocker–based therapy is associated with elevated central aortic pressures and, by inference, increased left ventricular wall stress.

The differences in central aortic pressures between treatment arms persisted throughout the CAFE study regardless of add-on therapy (thiazide diuretics and vasodilator drugs in the atenolol±thiazide regimen). This suggests a powerful effect of atenolol-based therapy on central arterial hemodynamics in hypertensive patients that is not reversed by add-on blood pressure–lowering therapy. The dependence of this effect on heart rate slowing suggests that these findings may be applicable to other \( \beta \)-blockers in people with hypertension. This conclusion is supported by similar effects observed in acute studies, by direct catheter measurements, with an alternative \( \beta \)-blocker (propranolol).\textsuperscript{34}

An important question is whether the differences in central aortic pressures between treatment arms in the CAFE study are clinically important.

First, it is not unreasonable to assume that pressures within the central aorta are more relevant to cardiovascular outcomes than pressures in the brachial artery. Second, the aforementioned data showing less cardiovascular structural regression and higher circulating BNP levels with \( \beta \)-blocker–based therapy imply persistence of a greater hemodynamic stress within the central circulation compared with other blood pressure–lowering regimens. Third, a previous study in patients with end-stage renal disease, a condition associated with enhanced pressure wave reflections,\textsuperscript{50} demonstrated a direct relationship between central aortic pulse pressure and adverse cardiovascular outcomes. In that study, central aortic pulse pressure was of greater predictive value for cardiovascular outcomes than brachial pulse pressure.\textsuperscript{14,15} Fourth, using updated Cox regression modeling, we showed a relationship between central aortic pulse pressure and a post hoc–defined composite of cardiovascular and renal outcomes that was consistent after adjustment in three separate Cox regression models. Finally, ASCOT showed significant reductions in total coronary events, cardiovascular death, and stroke with amlodipine±perindopril-based therapy compared with atenolol±thiazide-based therapy.\textsuperscript{21} An analysis of the factors contributing to the differential clinical outcomes in ASCOT concluded that conventional risk factors and differences in brachial blood pressure may not fully account for the better cardiovascular outcomes with amlodipine-based therapy.\textsuperscript{51}

The authors and the accompanying editorial\textsuperscript{52} speculated that a differential effect on central aortic pulse pressure might have contributed to the benefit of amlodipine±perindopril-based therapy. Unsurprisingly, the baseline characteristics of the CAFE study cohort were similar to those of ASCOT overall. It is therefore likely that the differences in central aortic pressures and hemodynamics observed in CAFE are representative of those for all patients in ASCOT. By demonstrating that amlodipine±perindopril-based therapy is associated with substantially lower central aortic pressures than atenolol±thiazide-based therapy, the results of the CAFE study provide a plausible and novel mechanism to explain the effects of the different treatment arms on the ASCOT outcomes. Importantly, these differences would not have been appreciated from the measurement of brachial blood pressure alone.

The CAFE study has limitations that require consideration. For obvious practical reasons, central aortic pressure indices
were not measured directly but were derived from peripheral radial artery waveforms with applanation tonometry. The values for central aortic systolic and pulse pressures depend on the validity and applicability of the generalized transfer function used to generate the central aortic waveforms. The correspondence between calculated central aortic and directly recorded systolic and pulse pressures has been found to be within 1 mm Hg.\(^{28,53,54}\) The transfer function used to derive the central aortic pressures is founded on the observation that pressure wave transmission in the upper limb is remarkably consistent under different conditions. This includes the effects of aging, disease, drug therapy, and variation in heart rate, thereby allowing a generalized transfer function to be used to convert the radial to an aortic pressure wave.\(^{27}\) This principle is used by the SphygmoCor device used in the CAFE study and gained US Food and Drug Administration approval in 2004.\(^{54,55}\) A potential weakness of this technology is that the calibration of central aortic pressures depends on the accuracy of the brachial pressure measurements.\(^{56,57}\) However, this is less relevant to the CAFE study because we were evaluating relative differences between brachial pressures and the derived central aortic pressures; ie, the denominator was the same throughout.

The use of a generalized transfer function in large study cohorts with differing heart rates may have introduced a potential bias. However, no heart rate bias has been apparent in extensive testing of the transfer function. Moreover, consistency in performance of the transfer function at different heart rates and blood pressure has been demonstrated during the Valsalva maneuver.\(^{27}\) It is also important to note that in acute studies comparing \(\beta\)-blockers with vasodilator therapies, measurement of pressure wave reflections by direct catheterization showed similar divergent effects of treatments.\(^{34,35}\)

The patients in the CAFE study cohort volunteered for participation in the study after randomization into ASCOT. There may therefore have been a potential for bias in recruitment of patients into the CAFE study. By ensuring that we recruited the majority of ASCOT patients at each CAFE study center, we reduced the potential for systematic bias and imbalances between treatment arms. This is indicated by reference to the baseline demographics and treatment allocation of the CAFE cohort, which were very well balanced for each treatment arm and similar to the total ASCOT cohort (Table 2).

Our objective was to obtain repeated measurements of central aortic pressures from as many patients as possible within the 5 study centers, within the constraints of maintaining high-quality and moderately complex data acquisition within a large clinical outcomes trial. This approach could have limited collection of data during follow-up and introduced potential bias. However, almost 80% of the CAFE cohort had repeated measurements, with an average of 3.4 measurements per patient through the 4-year follow-up period of the CAFE study. Moreover, at each time point throughout the CAFE follow-up, the age and gender compositions of the cohorts were consistent between treatment arms.

We recognize that it may not be warranted to extrapolate our findings beyond this specific patient population. The CAFE study cohort was predominantly white men, reflecting the ASCOT cohort; however, differential effects of the 2 treatment arms on central aortic pressures and hemodynamics were observed, regardless of gender. The patients randomized into ASCOT and CAFE were hypertensive with 3 additional cardiovascular risk factors, but their 10-year cardiovascular disease risk according to the Framingham risk function was \(<20\%\) over 10 years; thus, they represented a moderate, not-high-risk cohort relative to many recent studies of patients with hypertension.\(^{12}\)

The CAFE cohort had a mean age of 63 years. Patients of that age are likely to have had stiffer conduit arteries, which could exacerbate any differential drug effects on central aortic pressure. Whether similar results would have been seen in much younger patients and in nonwhite populations is unknown and merits further investigation.

Finally, as a secondary objective, we undertook Cox regression modeling to examine whether central hemodynamic parameters measured in the CAFE cohort were associated with clinical outcomes. Our interpretation of these analyses is cautious because the composite clinical end point was defined post hoc and because the CAFE study was not powered primarily to examine clinical outcomes. We undertook 3 Cox models, and all revealed central pulse pressure as significantly associated with hazard for the composite end point after adjustment for age and baseline risk factors. Mindful of the necessary caution in interpreting this data as a secondary outcome measure, we should note that this is the first report of an association between central pulse pressure and clinical outcomes in a major clinical outcomes trial. It is also remarkable that the magnitude of hazard per 10-mm Hg change in central pulse pressure is very similar to that recently reported in preliminary data from the Strong Heart Study.\(^{58}\) an epidemiological population study of risk factors and cardiovascular outcomes. In future analyses, we plan to use the regression equations relating brachial to central aortic pressures for each treatment arm to model the impact of central aortic pressure differences between treatment arms on cause-specific outcomes for the whole ASCOT cohort.

We believe that the findings of the CAFE study have important implications. The CAFE study provides a plausible mechanism to explain, at least in part, the better clinical outcome for patients treated with amlodipine-\(\pm\)perindopril-based therapy in ASCOT. Moreover, we speculate that the central blood pressure hypothesis might also explain the differential effects of blood pressure-lowering drugs on cardiovascular structure and clinical outcomes in other recent outcome trials.\(^{47,59,60}\)

In conclusion, the CAFE study is the largest prospective evaluation of the effects of cardiovascular drugs on derived central aortic pressures and hemodynamics. The results show that brachial blood pressure is not always a good surrogate for the effect of blood pressure-lowering drugs on arterial hemodynamics. In the CAFE study, atenolol-\(\pm\)thiazide-based treatment was much less effective than amlodipine-\(\pm\)perindopril-based treatment at lowering central aortic pressures. These findings suggest a mechanism to support recent meta-analyses that have challenged the recommendation for \(\beta\)-blockers as an optimal treatment for uncomplicated hypertension.\(^{51–64}\)
Disclosures

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References


Blood pressure is conveniently measured over the brachial artery and is assumed to faithfully represent pressures within the central circulation, ie, aortic pressures. The CAFE study tested the hypothesis that different blood pressure–lowering treatments in hypertension could differentially affect central aortic pressures despite similar effects on brachial pressure. This study suggests a mechanism by which different drug treatments in hypertension trials could differentially affect central aortic pressure waveform characteristics.
Differential Impact of Blood Pressure–Lowering Drugs on Central Aortic Pressure and Clinical Outcomes: Principal Results of the Conduit Artery Function Evaluation (CAFE) Study

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