Impact of Statin Therapy on Central Aortic Pressures and Hemodynamics. Principal Results of the Conduit Artery Function Evaluation Lipid-Lowering Arm (CAFE-LLA) Study

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Impact of Statin Therapy on Central Aortic Pressures and Hemodynamics

Principal Results of the Conduit Artery Function Evaluation–Lipid-Lowering Arm (CAFE-LLA) Study

Bryan Williams, MD, FRCP; Peter S. Lacy, PhD; J. Kennedy Cruickshank, MD, FRCP; David Collier, MBBS, PhD; Alun D. Hughes, MBBS, PhD; Alice Stanton, PhD, FRCPI; Simon Thom, MD, FRCP; Herbert Thurston, MD, FRCP; for the CAFE and ASCOT Investigators

Background—Statins reduce the risk of cardiovascular events in people with hypertension. This benefit could arise from a beneficial effect of statins on central aortic pressures and hemodynamics. The Conduit Artery Function Evaluation–Lipid-Lowering Arm (CAFE-LLA) study, an Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) substudy, investigated this hypothesis in a prospective placebo-controlled study of treated patients with hypertension.

Methods and Results—CAFE-LLA recruited 891 patients randomized to atorvastatin 10 mg/d or placebo from 5 centers in the United Kingdom and Ireland. Radial artery applanation tonometry and pulse-wave analysis were used to derive central aortic pressures and hemodynamic indices at repeated visits over 3.5 years of follow-up. Atorvastatin lowered low-density lipoprotein cholesterol by 32.4 mg/dL (95% confidence interval [CI], 28.6 to 36.3) and total cholesterol by 35.1 mg/dL (95% confidence interval, 30.9 to 39.4) relative to placebo. Time-averaged brachial blood pressure was similar in CAFE-LLA patients randomized to atorvastatin or placebo (change in brachial systolic blood pressure, −0.1 mm Hg [95% CI, −1.8 to 1.6], $P=0.9$; change in brachial pulse pressure, −0.02 mm Hg [95% CI, −1.6 to 1.6], $P=0.9$). Atorvastatin did not influence central aortic pressures (change in aortic systolic blood pressure, −0.5 mm Hg [95% CI, −2.3 to 1.2], $P=0.5$; change in aortic pulse pressure, −0.4 mm Hg [95% CI, −1.9 to 1.0], $P=0.6$) and had no influence on augmentation index (change in augmentation index, −0.4%; 95% CI, −1.7 to 0.8; $P=0.5$) or heart rate (change in heart rate, 0.25 bpm; 95% CI, −1.3 to 1.8; $P=0.7$) compared with placebo. The effect of statin or placebo therapy was not modified by the blood pressure–lowering treatment strategy in the factorial design.

Conclusions—Statin therapy sufficient to significantly reduce cardiovascular events in treated hypertensive patients in ASCOT did not influence central aortic blood pressure or hemodynamics in a large representative cohort of ASCOT patients in CAFE-LLA. **(*Circulation*. 2009;119:53-61.)**

Key Words: blood pressure ■ hypertension ■ statins ■ vasculature

We recently reported the principal results of the Conduit Artery Function Evaluation (CAFE) study,[1] which showed that blood pressure (BP)–lowering drugs could influence the relationship between brachial and central aortic pressures, thereby demonstrating that brachial BP was not always a good surrogate for the hemodynamic effects of drug therapies on the central circulation. Moreover, central pulse pressure (PP) was identified as an independent predictor of clinical outcomes.[1] This latter finding, supported by recent data from the Strong Heart Study,[2] has generated much interest in the impact of cardiovascular drug therapies on central aortic pressures and hemodynamics.[3]

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The CAFE study was a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), which had a factorial design.[4,5] ASCOT, in addition to examining the impact of different BP-lowering strategies, examined the impact of statin therapy (atorvastatin 10 once daily) versus placebo on clinical outcomes. The lipid-lowering arm of

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From the Department of Cardiovascular Sciences, University of Leicester, Leicester, UK (B.W., P.S.L., H.T.); University Department of Medicine, Manchester Royal Infirmary, Manchester, UK (J.K.C.); Barts and the London, Queen Mary's School of Medicine, London, UK (D.C.); International Centre for Circulatory Health, Imperial College, London, UK (A.D.H., S.T.); and Beaumont Hospital and Royal College of Surgeons, Dublin, Ireland (A.S.).

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Correspondence to Bryan Williams, MD, FRCP, FAHA, Department of Cardiovascular Sciences, University of Leicester, Clinical Sciences Building, Leicester Royal Infirmary, Leicester, LE2 7LX, UK. E-mail bw17@le.ac.uk

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ASCOT (ASCOT-LLA)[6] showed that atorvastatin reduced the primary outcome (nonfatal myocardial infarction and fatal coronary heart disease) by 36% compared with placebo. Stroke also was reduced by 27%.

Interest in the mechanisms accounting for the clinical benefits of statins has been considerable, much of it no doubt relating to the impact of cholesterol lowering on atherosclerotic plaque burden and stability. A clear relationship exists between the magnitude of cholesterol lowering in clinical trials and cardiovascular risk reduction.[7] However, there has also been interest in the hypothesis that statins might modulate large-artery function and thereby central aortic pressures via mechanisms dependent on or independent of cholesterol lowering. Such mechanisms have implicated improved endothelial function and/or reduced large-artery stiffness, both of which could influence central aortic pressures and hemodynamics beyond any potential impact on brachial BP.[8–11] If this were so, the resulting reduction in central aortic pressures might contribute to a reduced risk for cardiovascular events, especially in people with hypertension.

Thus far, the studies cited above that have assessed the impact of statins on large-artery function have mostly been small scale and have not directly reported the effects of statins on central aortic pressures. Moreover, the results of studies of statins on large-artery function have been conflicting, limited in many cases by a lack of statistical power. In addition, analyses of the impact of statins on brachial BP have suggested the possibility of a small beneficial effect of lowering brachial BP, an action attributed to improvements in endothelial function and, by inference, large-artery function.[12]

Because statins are so widely used in clinical practice, it was important to clarify their impact on central aortic pressures and hemodynamics, especially in people with treated hypertension. Thus, a prespecified analysis of the CAFE study took advantage of the factorial design of ASCOT to prospectively assess the impact of statin therapy on the relationship between brachial and central aortic pressures and hemodynamics in patients with treated hypertension in a major clinical outcomes trial.[4] We report here the principal results of the CAFE study lipid-lowering arm (CAFE-LLA).

Methods

Study Design

The CAFE-LLA study, a substudy of ASCOT, was designed to assess the impact of lipid-lowering therapy with atorvastatin versus placebo on central aortic pressures and hemodynamics. ASCOT had a 2×2 factorial design comprising a BP-lowering arm that compared 2 different BP-lowering strategies (atenolol with or without bendroflumethiazide-K versus amlodipine with or without perindopril) and a lipid-lowering arm comparing atorvastatin and placebo.[5] Briefly, people were eligible for ASCOT if they were 40 to 79 years of age with either untreated hypertension (systolic BP [SBP] ≥160 mm Hg or diastolic BP [DBP] ≥90 mm Hg) or treated hypertension with a BP ≥140/90 mm Hg and 3 additional cardiovascular risk factors but no prior history of coronary heart disease. The majority (>80%) were receiving treatment for hypertension immediately before randomization.

Of the 19 257 individuals recruited into ASCOT, 10 305 also were eligible for randomization into the lipid-lowering arm of the study (ie, ASCOT-LLA).[6] To be eligible for ASCOT-LLA, patients had to be untreated with any lipid-lowering medication with a total blood cholesterol concentration of ≤250 mg/dL at randomization. In addition to their randomized BP-lowering medication, the-LLA patients were randomized to receive either atorvastatin (10 mg once daily) or placebo in a prospective double-blind study design. Titration of the statin did not occur and no lipid-lowering goal was set.

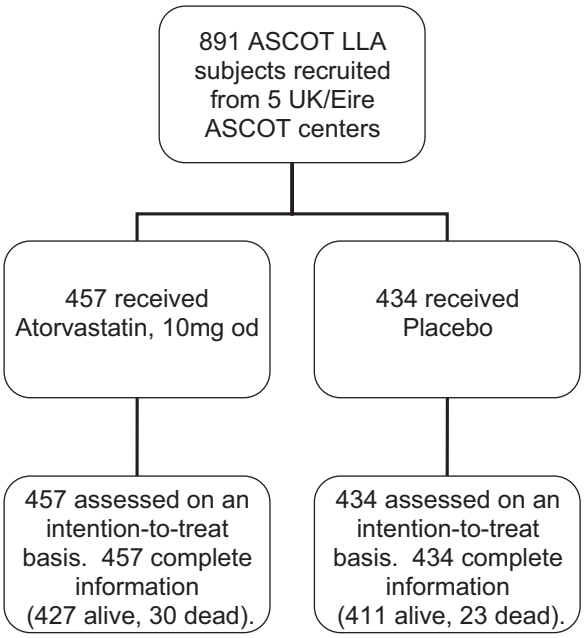

Figure 1. CAFE-LLA study profile.

CAFE-LLA recruited 891 patients already randomized into ASCOT-LLA from 5 CAFE study centers in the United Kingdom and Ireland (see Figure 1 and Figure I of the online-only Data Supplement). All patients recruited into CAFE-LLA gave their written informed consent. Approval for the study was granted by regional research ethics committees at each ASCOT center and by the UK multicenter ethics committee.

Procedures

Brachial Artery BP Measurement and Radial Artery Pulse-Wave Analysis

In CAFE-LLA, central aortic pressures and hemodynamic parameters were derived from radial artery applanation tonometry and pulse-wave analysis (SphygmoCor, Atcor, Sydney, Australia) performed at the patients' regularly scheduled ASCOT follow-up visits as previously described.[1] Brachial BP was measured according to the ASCOT protocol with a validated device (Omron 705CP, Kyoto, Japan). Immediately after measurement of brachial BP, radial artery waveforms were sampled in the same arm, calibrated to the brachial BP, and transformed into a central aortic waveform using a validated generalized transfer function. Hemodynamic parameters derived from the central waveform are shown in the online-only Data Supplement (Figure II). Typical interobserver variability for CAFE tonometry measurements has been published.[1]

Timing of Measurements

As in the main CAFE study,[1,4] central aortic pressure and hemodynamics were not recorded at baseline in CAFE-LLA. The reason is that the design of ASCOT meant that >80% of patients were being treated for hypertension at the time of randomization and were directly "rolled over" onto their randomized BP-lowering medication at baseline without any washout period; thus, no off-treatment baseline was present. As part of the factorial design, the BP-lowering treatment was then uptitrated over the next 12 months until the BP goal was reached. Thus, by design, we elected to begin measure-

ments of central aortic pressures and hemodynamics for CAFE-LLA at a time when the patients' BP-lowering medication had stabilized at goal, thereby avoiding the turbulence of the titration phase; this was ≈1 year after randomization. This design suited our purpose of examining our primary hypothesis, which was focused on the differences in central aortic pressures between atorvastatin- and placebo-treated patients at a time when brachial BP levels were similar, thereby removing the confounding of differences in brachial BP during the titration phase of the study. Our prespecified objective was to obtain at least 2 measurements per patient during the subsequent follow-up period.

ASCOT-LLA was terminated earlier than anticipated (after 3.5 years) on the recommendation of the Data Safety Monitoring Board because of clear benefit of atorvastatin therapy versus placebo on the primary end point.[6] An average of 2.0 tonometry measurements per patient had been recorded by the end of CAFE-LLA and did not differ between treatment arms (atorvastatin, 2.0 measurements; placebo, 2.1 measurements). The median follow-up time from initial tonometry measurement to study end was 1.3 years (atorvastatin, 1.3 years; placebo, 1.3 years), and the total period of exposure to study drug was similar for both atorvastatin (1455 patient-years) and placebo (1392 patient-years).

Biochemical Measurements

Fasting and nonfasting blood samples collected at scheduled ASCOT visits were analyzed at a central laboratory for serum lipids and other biochemical and hematologic parameters as previously described.[5]

Primary Hypothesis

The primary hypothesis stated that in patients with treated hypertension, we would observe a greater difference between central aortic and brachial BPs (brachial SBP or PP minus central aortic SBP or PP) after treatment with atorvastatin 10 mg/d compared with placebo. Clinical significance was defined as an SBP or PP difference (brachial minus central) of ≥3 mm Hg for either parameter.

Data and Statistical Analyses

Data were collated at the CAFE coordinating center (Leicester, United Kingdom) by researchers blinded to treatment allocation and subsequently merged with ASCOT demographic and follow-up data. The data were analyzed by intention to treat according to treatment allocation.

Sample Size and Statistical Power

Data from the CAFE study[1] indicate that a sample size of <50 patients per treatment arm would be required to give 90% power to distinguish a difference ($P<0.05$) of at least 3 mm Hg in central SBP or PP relative to brachial pressures in CAFE-LLA (for details, see Table I of the online-only Data Supplement). One hundred patients per treatment arm would be sufficient to distinguish a difference of only 2 mm Hg with 90% power. Thus, with >400 patients per treatment arm, the CAFE-LLA study was adequately powered to test the primary hypothesis and to eliminate the possibility of a type II error concealing a clinically important effect.

Statistical Analysis

All statistical analyses were performed at A-Plus Science (ASCOT Coordinating Center, Goteborg, Sweden) with SAS version 9.13 (SAS Institute Inc, Cary, NC). Nonpaired Student *t* tests were used for between-treatment comparisons of continuous variables. Two-way ANOVA was used to evaluate the main effects of treatment with amlodipine/atenolol and atorvastatin/placebo as main effects and peripheral and central pressures and hemodynamics as dependent variables. All significance tests were 2 tailed and conducted at the 5% significance level. Details of the calculation of area under the curve values have previously been published.[1]

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

Results

Demographic Parameters

In total, 891 patients with baseline total cholesterol levels ≤250 mg/dL were recruited into CAFE-LLA and assigned to treatment with atorvastatin or placebo. The study profile is shown in Figure 1. The CAFE-LLA participants were well matched between treatments arms (atorvastatin versus placebo) and were similar to the ASCOT-LLA population (Table 1).

Blood Lipid Concentrations

Six months after randomization to atorvastatin (10 mg once daily), total and low-density lipoprotein (LDL) cholesterol levels were significantly reduced relative to placebo (LDL cholesterol change, 47.1 mg/dL [95% confidence interval {CI}, 43.2 to 51.0]; total cholesterol change, 50.6 mg/dL [95% CI, 46.3 to 54.8]; both $P<0.0001$). Total and LDL cholesterol levels remained significantly reduced throughout the remainder of the follow-up despite a trend toward a reduction in patients receiving placebo (Figure 2). The overall dropout rate for statin use in atorvastatin-treated patients was 10%, whereas the maximum "drop-in" rate for statin use in placebo-treated patients was 13%. Atorvastatin also lowered blood triglyceride levels (triglyceride change, 32.7 mg/dL; 95% CI, 21.8 to 42.7; $P<0.0001$) but had no effect on high-density lipoprotein (HDL) levels relative to placebo (HDL change, −1.2 mg/dL; 95% CI, −3.1 to 0.8; $P=0.25$).

Hemodynamic Measurements: Impact of Statin Therapy on Brachial BP

CAFE-LLA could not directly assess the impact of statins on brachial BP because patients were concurrently receiving BP-lowering therapy as a part of the ASCOT factorial design. Slightly fewer add-on BP-lowering treatments were used in patients randomized to atorvastatin to achieve similar brachial BP levels (mean area under the curve number of BP-lowering drugs: placebo−atorvastatin=0.09; Table II). This is indirect evidence that atorvastatin may have had a small BP-lowering effect. However, the main focus of CAFE-LLA was whether statins influenced the relationship between brachial and central pressures and hemodynamics.

Primary Outcome: Impact of Statin Therapy on the Relationship Between Brachial and Central Pressures and Hemodynamics

Brachial and central pressures throughout CAFE-LLA are shown in Figure 3 (top). Brachial and central aortic pressures did not differ between patients receiving atorvastatin or placebo at any time point. This is shown clearly in the bottom portion of Figure 3, which shows that the difference between brachial and central pressures did not differ in patients receiving either atorvastatin or placebo. These data are also summarized as the area under the curve for these parameters in Table 2. As expected, brachial SBP and PP were higher than derived central pressures, indicating pressure amplification. However, PP amplification was unmodified in patients receiving atorvastatin versus placebo (PP amplification area under the curve change, 0.01; 95% CI, −0.01 0.03; $P=0.3$; Table 2).

Table 1. Baseline Demographic Parameters for Patients Recruited Into CAFE-LLA and All Patients Recruited Into ASCOT-LLA

	CAFE		ASCOT	
	Atorvastatin (n=457)	Placebo (n=434)	Atorvastatin (n=5168)	Placebo (n=5137)
Demographics and clinical characteristics				
Women, n (%)	65 (14.2)	63 (14.5)	979 (18.9)	963 (18.7)
Age, y	62.6 (8.0)	62.9 (8.4)	63.1 (8.5)	63.2 (8.6)
<60, n (%)	171 (37.4)	158 (36.4)	1882 (36.4)	1853 (36.1)
>60, n (%)	286 (62.6)	276 (63.6)	3286 (63.6)	3284 (63.9)
White, n (%)	394 (86.2)	366 (84.3)	4889 (94.6)	4863 (94.7)
Current smoker, n (%)	115 (25.2)	107 (24.7)	1718 (33.2)	1656 (32.2)
Alcohol consumption, units/wk	12.4 (14.5)	11.6 (15.0)	8.0 (11.3)	8.2 (12.0)
SBP, mm Hg	159.6 (16.7)	160.3 (17.5)	164.2 (17.7)	164.2 (18.0)
DBP, mm Hg	92.5 (9.7)	92.9 (9.2)	95.0 (10.3)	95.0 (10.3)
Heart rate, bpm	70.8 (12.3)	70.9 (12.4)	71.3 (12.8)	71.8 (12.6)
BMI, kg/m^2	29 (4.7)	28.9 (4.6)	28.6 (4.7)	28.7 (4.6)
Weight, kg	85.4 (15.6)	84.2 (14.3)	85.1 (15.5)	85.0 (15.4)
Height, cm	171.6 (8.7)	170.7 (9.4)	NA	NA
Total cholesterol, mg/dL	208.8 (30.9)	212.7 (30.9)	212.7 (30.9)	212.7 (30.9)
LDL cholesterol, mg/dL	131.5 (27.1)	131.5 (27.1)	131.5 (27.1)	131.5 (27.1)
HDL cholesterol, mg/dL	50.3 (15.5)	50.3 (15.5)	50.3 (15.5)	50.3 (15.5)
Triglycerides, mg/dL	141.7 (79.7)	141.7 (70.9)	150.6 (79.7)	141.7 (79.7)
Glucose, mg/dL	106.2 (34.2)	106.2 (34.2)	111.6 (37.8)	111.6 (37.8)
Creatinine, mg/dL	1.1 (0.17)	1.13 (0.19)	1.12 (0.19)	1.12 (0.19)
Medical history				
Previous stroke/TIA, n (%)	36 (7.9)	33 (7.6)	497 (9.6)	525 (10.2)
Diabetes mellitus, n (%)	85 (18.6)	73 (16.8)	1258 (24.3)	1274 (24.8)
LVH (echo or ECG), n (%)	87 (19)	98 (22.6)	744 (14.4)	729 (14.2)
Peripheral vascular disease, n (%)	14 (3.1)	21 (4.8)	261 (5.1)	253 (4.9)
Risk factors, n	3.5 (0.8)	3.6 (0.8)	3.7 (0.9)	3.7 (0.9)
Drug therapy				
Previous antihypertensive treatments, n (%)				
0	44 (9.6)	38 (8.8)	1021 (19.8)	996 (19.4)
1	239 (52.3)	200 (46.1)	2314 (44.8)	2279 (44.4)
≥2	174 (38.1)	196 (45.2)	1833 (35.5)	1862 (36.2)
Lipid-lowering therapy	1 (0.2)	2 (0.5)	41 (0.8)	52 (1.0)
Aspirin use	102 (22.3)	107 (24.7)	929 (18.0)	902 (17.6)

BMI indicates body mass index; TIA, transient ischemic attack; and LVH, left ventricular hypertrophy. Data are mean (SD) when appropriate.

Secondary Outcomes: Central Hemodynamic Parameters

Central SBP and PP represent the summation of outgoing and reflected pressure waves. Table 2 shows that no differences were present in the magnitude of either the outgoing (P1 height) or reflected (augmentation or augmentation index) pressure waves between atorvastatin- and placebo-treated patients. Thus, atorvastatin did not influence the magnitude or composition of central pressure waves in patients recruited into CAFE-LLA.

Impact of Statin Therapy on Arterial Stiffness

The impact of statins on arterial stiffness, determined by measurement of pulse-wave velocity, was not formally assessed in CAFE-LLA. Time to the appearance of the reflected wave for the arterial waveform (Figure II of the online-only Data Supplement) has been shown to be proportional to pulse-wave velocity. Time to the appearance of the reflected wave did not differ between patients treated with atorvastatin or placebo (Table 2).

Impact of Statin Therapy on Central Aortic Pressure and Hemodynamics According to BP Treatment Strategy

Examination of the data from CAFE-LLA through the use of ANOVA clearly showed a significant differential impact of BP-lowering treatment (amlodipine-based versus atenolol-based treatment) on central aortic pressures and hemodynam-

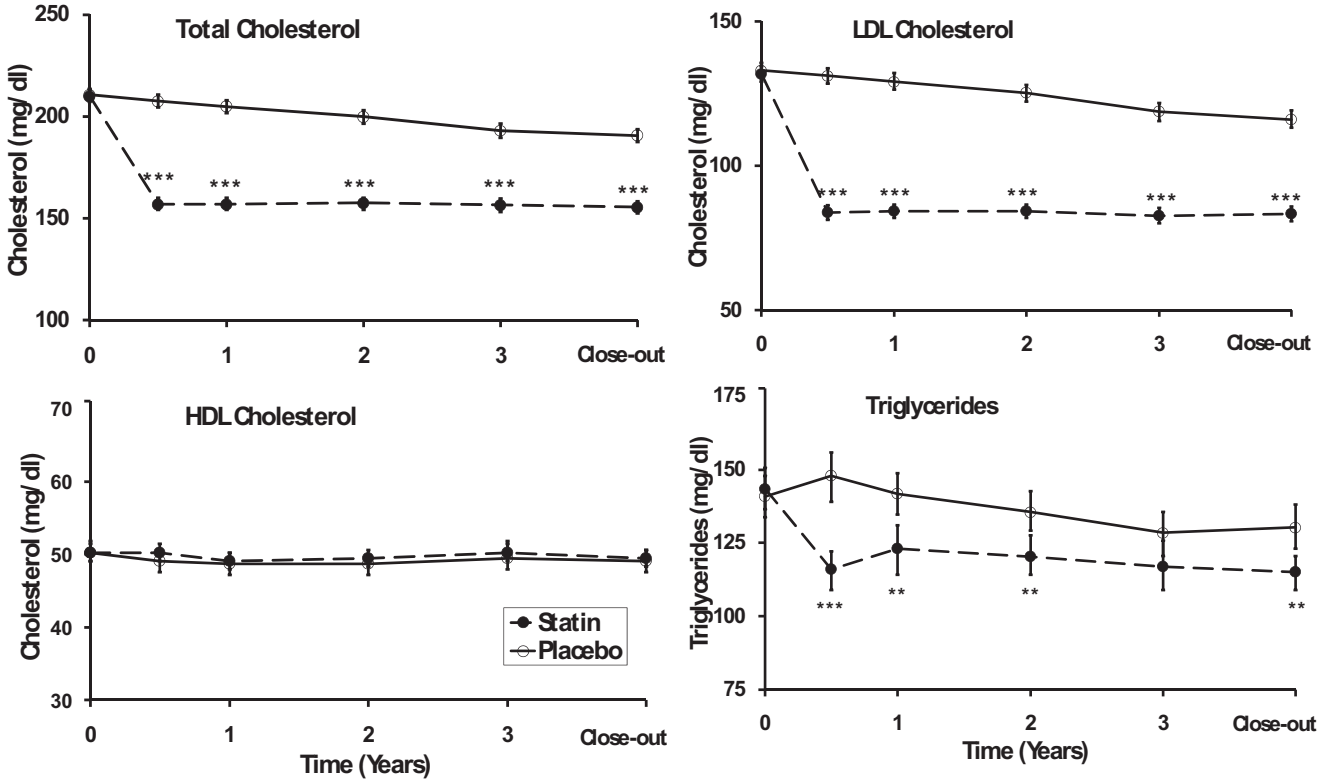

Figure 2. Serum lipid concentrations from time of recruitment into ASCOT-LLA for patients who subsequently went on to be recruited into CAFE-LLA. Time represents the duration from randomization into ASCOT to the patient follow-up visit at which a tonometry measurement was made in the CAFE-LLA study. Top left, Total cholesterol; bottom left, HDL cholesterol; top right, LDL cholesterol; bottom right, triglycerides. $^{**}P<0.01$; $^{***}P<0.001$.

ics despite no difference in brachial BP (Table 3). This is consistent with data from our previously published CAFE study.[1] In contrast, no impact of atorvastatin versus placebo on these parameters was found in the lipid-lowering arm of the study. Moreover, the magnitude of the F values for the differential effects of BP-lowering treatments was maintained after adjustment for treatment with either atorvastatin or placebo.

Influence of Statin Add-On Therapy on Placebo-Treated Patients After ASCOT-LLA Closeout

After ASCOT-LLA closeout, patients previously treated with placebo were offered atorvastatin (10 mg once daily). As a consequence of the factorial design, these patients continued follow-up under clinical trial conditions as part of the BP-lowering arm of ASCOT. This provided a second opportunity to evaluate the impact of introducing statin in a stable clinical trial population. We identified 147 patients previously treated with placebo who subsequently received atorvastatin and had no change in their BP-lowering medication after ASCOT-LLA closeout. The mean time between visits was 1.4±0.8 years. Predictably, total and LDL cholesterol levels were reduced by atorvastatin (total cholesterol change, −52.2±25.1 mg/dL, $P<0.0001$; LDL cholesterol change, −50.6±23.9 mg/dL, $P<0.0001$). Table 4 shows that despite the addition of statin in patients previously treated with placebo throughout CAFE-LLA, no difference in brachial or central pressures or indices of wave reflection were found during the further follow-up period.

Discussion

The CAFE-LLA study is the first large-scale, placebo-controlled study to prospectively evaluate the impact of statin therapy on the relationship between brachial and central aortic pressures in the context of a major clinical outcomes trial. The primary aim was to test the hypothesis that atorvastatin (10 mg once daily) compared with placebo would have favorable effects on central aortic pressures and hemodynamics and that this might serve as a potential explanation, at least in part, for the beneficial effects of statins in reducing cardiovascular and stroke risk in people with hypertension. Importantly, the results of CAFE-LLA are unequivocal: When atorvastatin is used at a dose sufficient to reduce total cholesterol by a quarter and LDL cholesterol by a third, no impact is seen on central aortic pressures, pulse-wave augmentation, augmentation index, pressure amplification, or any other central hemodynamic parameter. This finding indicates that the clinical outcome benefits of atorvastatin in this group of treated hypertensive patients were not mediated by direct effects on central aortic pressure and hemodynamics.

CAFE-LLA was not powered to relate statin-mediated differences in central pressures or hemodynamics to clinical outcomes. Nevertheless, atorvastatin in ASCOT-LLA was associated with substantial reductions in cardiovascular

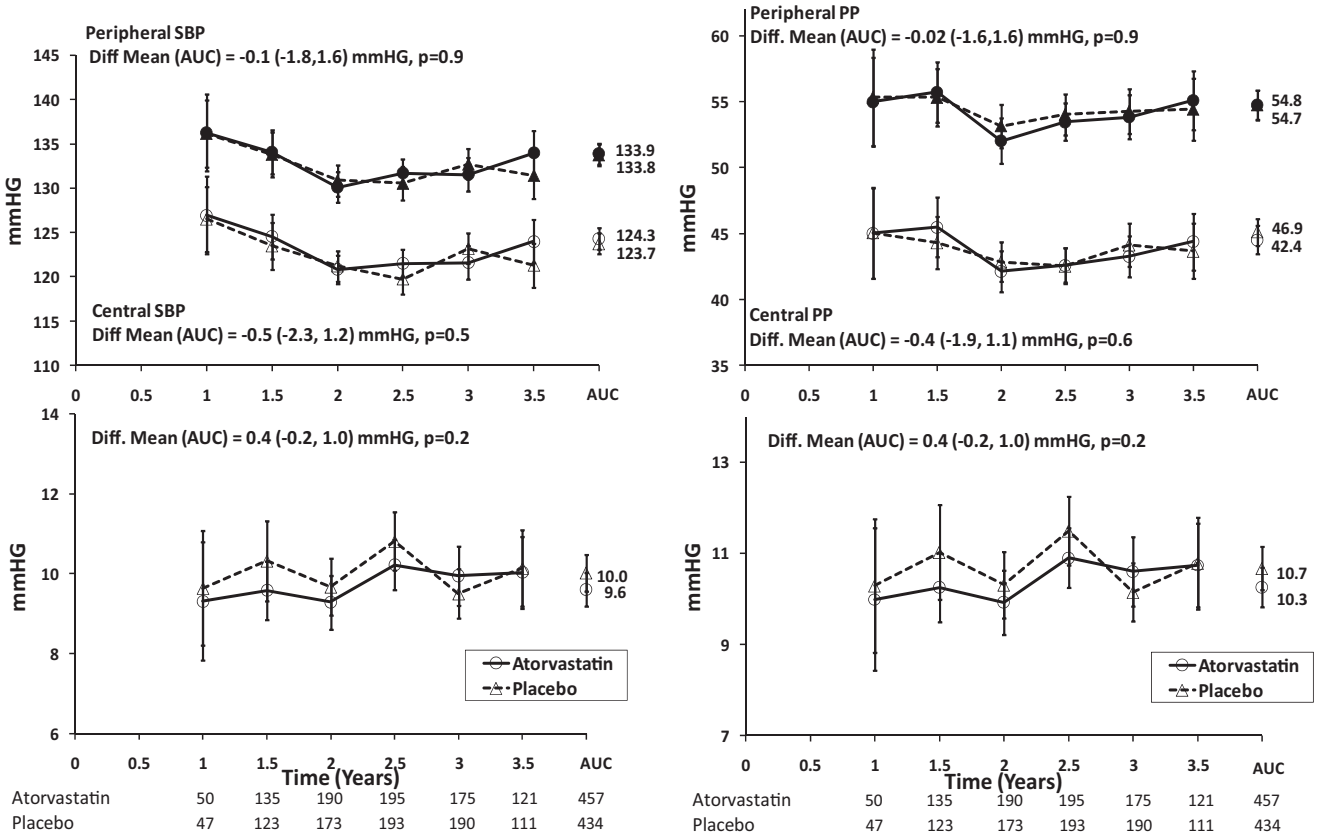

Figure 3. Top, Brachial and derived central aortic SBP (left) and PP (right) with time (mean, 95% CI) for patients receiving atorvastatin or placebo. Bottom, Difference between brachial and central SBP (left) and PP (right) (brachial−central aortic; mean, 95% CI) with time. Numbers below the abscissa represent the number of patients seen at each time point. Time (top and bottom) represents the duration from randomization into ASCOT to the patient follow-up visit at which a tonometry measurement was made in the CAFE-LLA study. AUC indicates area under the curve (mean, 95 % CI).

events compared with placebo.[6] The demographics and treatment of patients within CAFE-LLA were similar to those in ASCOT-LLA, suggesting that the hemodynamic data from the CAFE-LLA study are likely to be representative of the ASCOT-LLA population. In this regard, the cardiovascular benefits of atorvastatin in ASCOT-LLA were most likely mediated through the effects of cholesterol-lowering and/or potential pleiotropic effects (eg, effects on oxidized LDL,

Table 2. Hemodynamic and Pulse-Wave Analysis Parameters for the CAFE-LLA Study Population

Parameter	Atorvastatin (n=457)	Placebo (n=434)	Difference	*P*
Brachial SBP, mm Hg	133.9 (132.7–135.1)	133.8 (132.5–135)	−0.1 (−1.8–1.6)	0.88
Brachial DBP, mm Hg	79.1 (78.3–79.9)	79 (78.2–79.8)	−0.1 (−1.2–1.0)	0.85
Brachial PP, mm Hg	54.8 (53.7–55.9)	54.7 (53.6–55.9)	−0.02 (−1.6–1.6)	0.98
Central SBP, mm Hg	124.3 (123.1–125.5)	123.7 (122.5–124.9)	−0.5 (−2.3–1.2)	0.53
Central DBP, mm Hg	79.8 (79.0–80.6)	79.7 (78.8–80.5)	−0.1 (−1.2–1.0)	0.85
Central PP, mm Hg	44.5 (43.4–45.6)	44.1 (43.1–45.1)	−0.4 (−1.9–1.0)	0.56
ΔSBP (peripheral−central), mm Hg	9.6 (9.2–10.0)	10.0 (9.6–10.5)	0.4 (−0.2–1.0)	0.18
ΔPP (peripheral−central), mm Hg	10.3 (9.8–10.7)	10.7 (10.2–11.1)	0.4 (−0.2–1.0)	0.2
Augmentation, mm Hg	13.5 (12.8–14.1)	13.0 (12.4–13.6)	−0.4 (−1.3–0.4)	0.34
P1 height, mm Hg	31.0 (30.4–31.6)	31.0 (30.4–31.7)	0.0 (−0.9–0.9)	0.99
Augmentation index, %	28.9 (28.0–29.8)	28.5 (27.6–29.4)	−0.4 (−1.7–0.8)	0.49
PP amplification	1.25 (1.24–1.26)	1.26 (1.25–1.27)	0.01 (−0.01–0.03)	0.31
Ejection duration, ms	316.0 (313.3–318.7)	313.3 (310.6–316)	−2.7 (−6.4–1.1)	0.17
Diastolic duration, ms	675.9 (661.2–690.5)	674.6 (659.3–689.8)	−1.3 (−22.4–19.8)	0.9
Heart rate, bpm	62.7 (61.6–63.8)	63.0 (61.9–64.1)	0.25 (−1.3–1.8)	0.74
Time to foot of reflected wave, ms	140.3 (139.3–141.3)	139.5 (138.6–140.5)	−0.8 (−2.2–0.6)	0.25

Data are mean (95% CI) where appropriate.

Table 3. Main Effects of Amlodipine/Atenolol and Atorvastatin/Placebo on Hemodynamic Parameters by ANOVA

		Amlodipine/Atenolol		Atorvastatin/Placebo	
Dependent Variable	n	F Statistic	*P*	F Statistic	*P*
Peripheral SBP	891	0.06	0.81	0.02	0.88
Central SBP	891	22.0	<0.0001	0.56	0.46
Peripheral PP	891	4.3	0.038	0.01	0.98
Central PP	891	10.9	0.001	0.44	0.51
ΔSBP (peripheral−central)	891	182.1	<0.0001	3.23	0.07
ΔPP (peripheral−central)	891	200.2	<0.0001	3.13	0.08
Heart rate	891	308.2	<0.0001	0.67	0.41
Augmentation	891	76.3	<0.0001	1.47	0.23
Augmentation index	891	134.1	<0.0001	1.04	0.31
Outgoing pressure-wave height	891	8.3	0.004	0.01	0.93
PP amplification	891	194.3	<0.0001	2.14	0.14
Time to reflected wave	891	13.3	0.003	1.55	0.21

F values and *P* values are adjusted for the other variable in the analysis (with type III SS).

thrombosis, or inflammation) rather than hemodynamic effects resulting from changes in relationships between central and brachial pressures.

Heretofore, no conclusive data have been found on the effects of statin on central aortic pressures and hemodynamics. We originally hypothesized that elevated plasma cholesterol values might increase central aortic pressures relative to brachial pressures by affecting large-artery function and increasing the stiffness of large conduit arteries.[4] Since CAFE-LLA was designed and initiated, a number of studies examining the relationship between plasma cholesterol and large-artery stiffness have been published. Most of these studies have been small and observational, and the results have been conflicting, reporting reduced, maintained, or increased arterial stiffness associated with elevated plasma cholesterol. For example, the augmentation index and indices of arterial stiffness have been shown to be independent of cholesterol levels in patients with hypertension and/or hypercholesterolemia.[13,14] Furthermore, cholesterol lowering with statin did not change the augmentation index or central arterial compliance in patients with hypercholesterolemia.[15,16] In contrast, elevated LDL cholesterol has been associated with increased central PP, augmentation index, and PP amplification in various patient groups.[17,18] Statin treatment also has been linked to reduced arterial stiffness, assessed as systemic arterial compliance or pulse-wave velocity.[9,19] Statins also have been shown to improve indices of endothelial function in some animal[20,21] and human studies[22,23] but not all.[24,25]

In the largest study of older patients with hypertension (65 to 84 years of age), no relationship was observed between baseline total cholesterol and indices of large-artery function, including pulse-wave analysis and direct measurements of aortic distensibility, in >800 patients.[13] Of interest, the mean total cholesterol concentrations in that study were similar to that of the CAFE-LLA cohort reported here, and the range of total cholesterol (≈100 to 400 mg/dL) was sufficiently wide to determine a relationship between plasma cholesterol and arterial stiffness if it existed.

However, CAFE-LLA goes further than any previous study and directly examines the impact of therapeutic lowering of cholesterol in a prospective randomized controlled trial and demonstrates no effect of cholesterol lowering on central aortic pressures relative to brachial pressures or any hemodynamic index in the population studied. Moreover, the findings of CAFE-LLA are robust: When atorvastatin is compared with placebo, CAFE-LLA had ample power to detect even small differences in central pressure relative to brachial pressure, excluding the likelihood of a type II statistical error.

We did not measure aortic stiffness directly in the CAFE-LLA study. However, time to arterial wave reflection is regarded by some as a surrogate for pulse-wave velocity, with a shorter time to wave reflection indicating accelerated pulse-wave velocity and stiffer arteries.[26,27] This interpretation is more robust when no differences are present in heart rate, pressures, or augmentation indices between treatments, as was the case here. No difference was found in time to the appearance of the reflected wave between statin and placebo treatment (Tables 2 and 4); thus, it is reasonable to conclude

Table 4. Difference in Peripheral and Central Hemodynamic Parameters After Add-In of Atorvastatin (10 mg/d) in Patients Previously Treated With Placebo Throughout CAFE-LLA

Parameter	Value at or Before LLA Closeout (n=147)	Value After Statin Add-In (n=147)	Change	*P*
Brachial SBP, mm Hg	131.7 (129.8–133.7)	131.6 (129.5–133.6)	−0.2 (−2.3–1.9)	0.87
Central SBP, mm Hg	122.6 (120.6–124.6)	121.9 (119.8–123.9)	−0.7 (−2.8–1.3)	0.48
ΔSBP (peripheral−central), mm Hg	9.1 (8.4–9.9)	9.7 (8.8–10.6)	0.6 (−0.1–1.2)	0.07
ΔPP (peripheral−central), mm Hg	9.8 (9–10.6)	10.4 (9.5–11.3)	0.6 (0–1.2)	0.06
Augmentation, mm Hg	13.1 (12–14.2)	13.7 (12.7–14.8)	0.6 (−0.3–1.6)	0.19
Augmentation index, %	29.4 (27.7–31.1)	29.4 (27.7–31.1)	0.0 (−1.3–1.3)	0.98
PP amplification	1.25 (1.2–1.3)	1.25 (1.2–1.3)	0.0 (−0.04–0.04)	0.54
Heart rate, bpm	61.5 (59.7–63.3)	62.0 (60–64)	0.5 (−0.7–1.7)	0.43
Time to reflected wave, ms	139.2 (137.3–141.1)	138.0 (136.2–139.8)	−1.2 (−3.3–0.9)	0.25

Mean (95% CI) comparisons are with a paired Student *t* test.

that atorvastatin had no major effect on aortic stiffness in CAFE-LLA. This conclusion is consistent with other published data showing no impact of cholesterol on the local mechanical properties of the aorta and carotid and radial arteries.[13,14]

The design of ASCOT without a treatment washout period before randomization meant that we were unable to obtain baseline central pressure measurements in the absence of antihypertensive therapy. Therefore, we are, by design, unable to report central pressure changes from baseline. However, in a large randomized study, it is unlikely that central pressures differed between groups at baseline. This finding, together with our finding that central pressures did not differ between treatments at any time point beyond baseline (Figure 3), supports our conclusions.

So, how do we reconcile the reported differences in the relationship between plasma cholesterol and large-artery function and hemodynamics in the context of the present study? First, some studies report univariate relationships between cholesterol values and indices of aortic stiffness that are inevitably confounded by the impacts of age, BP, and heart rate. Second, it is conceivable that the relatively low dose of statin (atorvastatin 10 mg once daily) used in CAFE-LLA was too low to reveal potentially beneficial effects on central aortic pressures. Although this remains possible, it is unlikely to be an important explanation for the beneficial effects of statins on clinical outcomes because this dose of atorvastatin was sufficient to reduce coronary and stroke events significantly in ASCOT-LLA.[6] Third, the patients in CAFE-LLA had a mean age of 63 years at study entry. It is possible that older patients may have too much established vascular damage to reveal an impact of statin therapy on central aortic function/pressures and that such effects might be apparent in younger people in whom the potential is greater to improve endothelial and arterial function. Fourth, CAFE-LLA recruited patients on the basis of cardiovascular risk rather than elevated cholesterol levels, which were only modestly elevated. It is possible that a more obvious effect of statins on central aortic pressures might be observed in patients with a higher baseline cholesterol values and a greater reduction in cholesterol with treatment, eg, in younger patients with familial hypercholesterolemia. Finally, it is inevitable that data demonstrating a beneficial effect of statin therapy on endothelial function, arterial stiffness, and central pressures are more likely to be published. In this regard, whatever the explanation for the inconsistency in previous findings, it should be recognized that CAFE-LLA is by far the largest study to evaluate the impact of statin therapy on central aortic pressures and hemodynamics. The study was conducted with the rigor of clinical trial conditions and had ample statistical power to address the hypothesis: CAFE-LLA has produced an unequivocal result. Moreover, the findings of the main study were reproduced in the analysis of the extended observational follow-up of patients who previously received placebo therapy and subsequently received atorvastatin.

Conclusions

Although atorvastatin 10 mg/d significantly reduced major cardiovascular events compared with placebo in ASCOT-LLA,[6] CAFE-LLA demonstrated no important effects of atorvastatin on central aortic pressures or hemodynamic indices. Therefore, the benefits of statins in reducing cardiovascular events are most likely a direct consequence of lipid-lowering and/or pleiotropic effects rather than any important action on central aortic hemodynamics.

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Disclosures

Dr Williams has received travel grant support and honoraria from Pfizer for lectures at international conferences. Dr Hughes has received research funding and honoraria and acted in a consultant/advisory board capacity for Pfizer. Dr Thom reports receiving research funding and acting in a consultant/advisory board capacity for Pfizer. Dr Cruickshank has received honoraria and served as a consultant/advisory board member for Pfizer. Dr Stanton has received honoraria from Pfizer. Drs Lacy, Collier, and Thurston report no conflicts.

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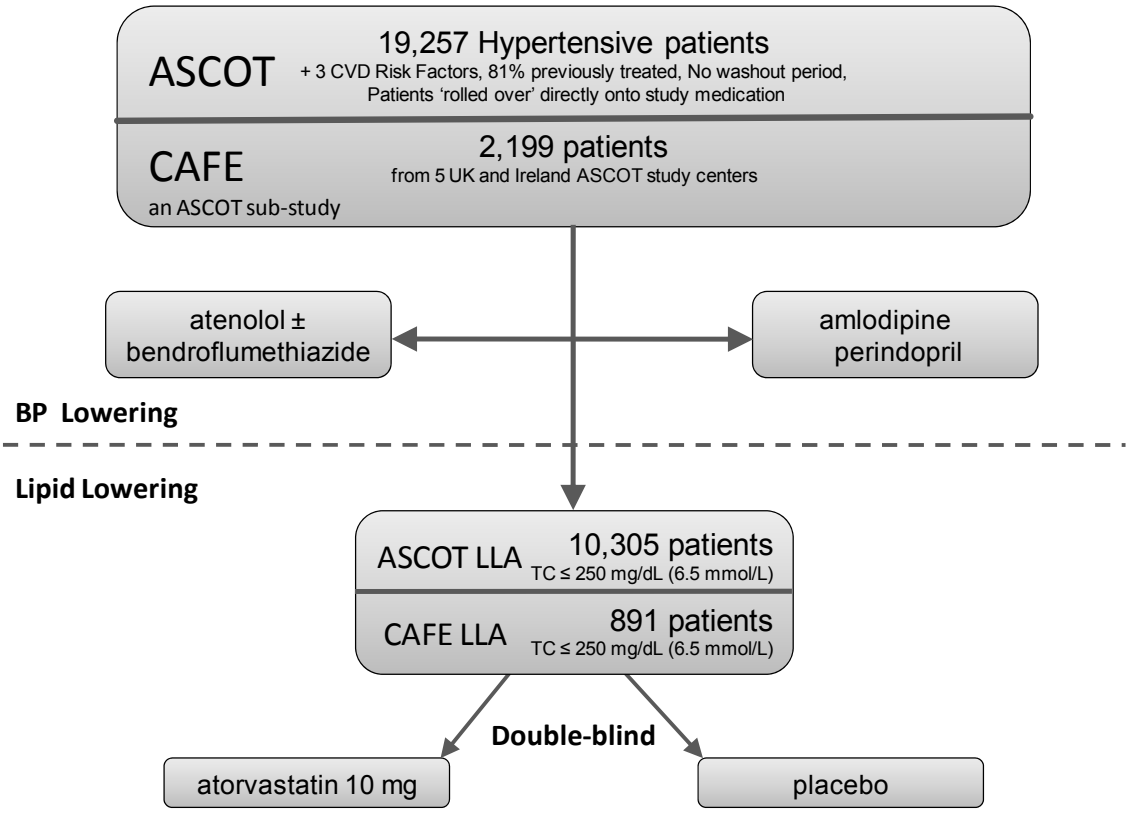
CLINICAL PERSPECTIVE

There has been much interest recently in the impact of cardiovascular drugs on central aortic pressures because this impact may influence clinical outcomes. The Conduit Artery Function Evaluation–Lipid-Lowering Arm was a randomized placebo-controlled trial that prospectively examined the impact of atorvastatin (10 mg once daily) on central aortic pressures in hypertensive patients. Atorvastatin did not influence central aortic pressures or hemodynamics in these patients. Thus, the favorable effects of statins on cardiovascular outcomes in hypertensive patients are via mechanisms that are independent of important effects on large-artery function and central pressures. For this reason, the benefits of statins in hypertensive patients are unlikely to be replicated by blood pressure lowering alone.

Online supplement.

1. On-line supplement figure 1: Design of ASCOT and CAFE studies. 8,952 ASCOT patients and 1,308 CAFE patients were not entered into the lipid-lowering study due to serum cholesterol >250mg/dl or because of treatment with lipid-lowering therapy at time of randomization. These patients however, continued participation in the blood pressure-lowering study (BPLA).



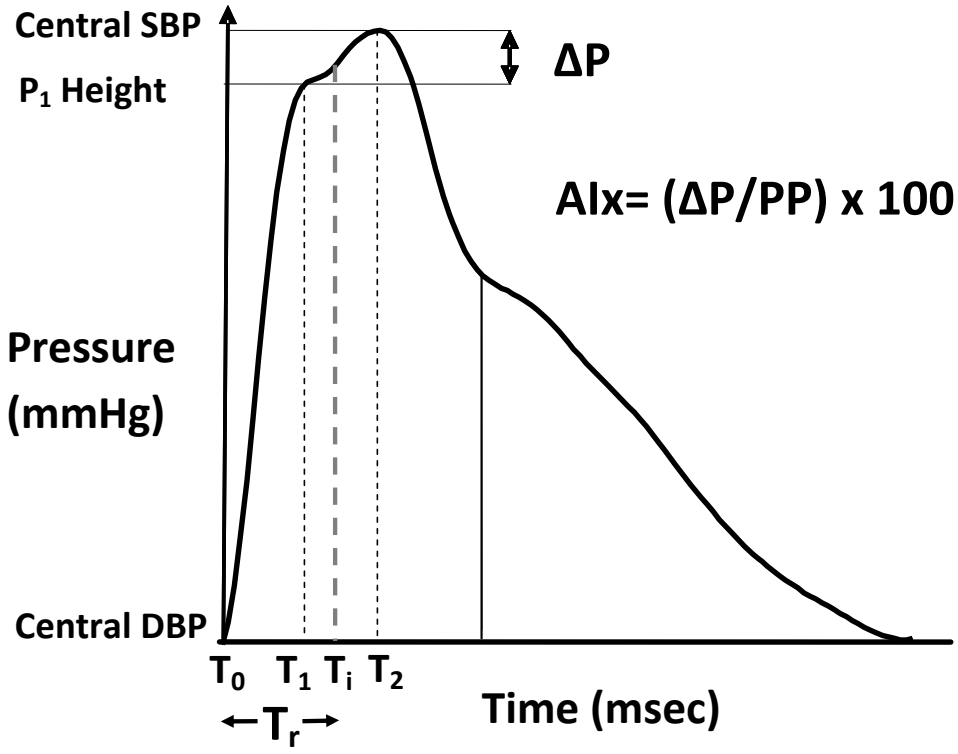
2. Definition of variables derived by applanation tonometry and pulse wave analysis.

Central pressure waveforms were analysed using the SphygmoCor software (SphygmoCor version 8, Atcor Medical, Sydney Australia) to define the following parameters (see on line supplement fig 2).

T_0	Time at the start of the waveform.
T_1	Time at the first peak/shoulder during systole (outgoing pressure wave).
T_2	Time at the second peak/shoulder during systole (reflected pressure wave).
T_i	Time at the inflection point on the systolic up-stroke
T_r	Duration from start of waveform to the inflection point (reflected wave).
ED	Ejection duration.
Central SBP	Central systolic pressure, maximum pressure of the central waveform.
Central DBP	Central diastolic pressure, minimum pressure of the central waveform.
Central PP	Central pulse pressure, height of the central waveform (Central PP=Central SBP-Central DBP).
P1 Height	Difference between the minimum pressure and the pressure at the first peak/shoulder (T1).
Augmentation	Pressure difference (ΔP) between the 1st peak/shoulder (P1 Height) and the second peak/shoulder (Central SBP) for the central waveform.

AIx	Augmentation Index proportion of the central pressure wave height attributable to augmentation (ΔP). AIx =(ΔP/PP)x100.
PP amp	Pulse pressure amplification ratio of peripheral to central pulse pressure (PPA=Peripheral PP/Central PP).

On-line supplement figure 2: The Central Arterial Pressure Wave with Derived Parameters.



3. CAFE LLA Power Calculations.

Power calculations for CAFE LLA were performed retrospectively using data from the CAFE study (4). On-line supplement table 1 shows the number of patients required with 80 and 90% power to detect a difference of 1 – 3mmHg in the primary endpoint for CAFE LLA, the difference between central and brachial pressures at the p=0.05 level. Power calculations are also shown to calculate the number of patients required with 80 and 90% to detect differences of 2-4mmHg for central systolic and pulse pressure and 1.5 – 4% for augmentation index at the p=0.05 level. The magnitude of these differences in the CAFE study is also shown.

On-line supplement Table 1. Power calculations for the CAFE LLA study.

1. Difference between brachial and central PP (ΔP-C PP): CAFE study difference; 3.9mmHg					
Power (%)	Difference (mmHg)				
	2.0	**2.5**	**3.0**	**3.5**	**4.0**
80	77	49	34	25	20
90	102	66	46	34	26
2. Difference between brachial and central SBP (ΔP-C SBP): CAFE study difference; 3.6mmHg					
Power (%)	Difference (mmHg)				
	2.0	**2.5**	**3.0**	**3.5**	**4.0**
80	73	47	33	24	19
90	98	63	44	32	25
3. Central pulse pressure: CAFE study difference; 3.0mmHg					
Power (%)	Difference (mmHg)				
	2 .0	**2.5**	**3.0**	**3.5**	**4.0**
80	450	288	200	147	113
90	602	386	268	197	151
4. Central systolic pressure: CAFE study difference; 4.3mmHg					
Power (%)	Difference (mmHg)				
	2.0	**2.5**	**3.0**	**3.5**	**4.0**
80	594	381	264	194	149
90	796	509	354	260	199
5. Augmentation Index: CAFE study difference; 6.5%					
Power (%)	Difference (%)				
	1.5	**2.0**	**2.5**	**3.0**	**3.5**
80	533	311	200	139	102
90	741	417	267	186	136

4. On-Line Supplement Table 2. Mean (SD) number of antihypertensive drugs required to achieve target blood pressure, with time for CAFE LLA patients receiving atorvastatin or placebo.

	Mean Number of All Antihypertensive Drug Classes*			
Time Since Study Start	**Atorvastatin (n=457)**	**Placebo (n=434)**	**Difference**	**p**
Baseline	1.25 (0.48)	1.28 (0.49)	0.03 (0.49)	0.3
1 Year	2.03 (0.8)	2.15 (0.8)	0.12 (0.79)	0.03
1.5 Years	2.1 (0.8)	2.2 (0.8)	0.1 (0.82)	0.06
2 Years	2.15 (0.8)	2.24 (0.86)	0.1 (0.83)	0.09
2.5 Years	2.17 (0.82)	2.3 (0.87)	0.13 (0.84)	0.03
3 Years	2.24 (0.82)	2.33 (0.86)	0.08 (0.83)	0.21
Close-out	2.23 (0.82)	2.31 (0.87)	0.08 (0.84)	0.16
AUC N^{o} drugs	2.05 (0.69)	2.14 (0.73)	0.09 (0.71)	0.06

* ACEI, AIIA, Ca++ blockers, ß blockers, Diuretics, α blockers, vasodilators

5. CAFE Investigators and CAFE study Centers.

University Hospitals of Leicester - Leicester Royal Infirmary, Leicester, UK.
B. Williams, P.S. Lacy, H. Thurston, D O'Brien, P Swales, S Nanayakkara, A Stanley, K Edwards, W Gamble, V Garratt, J Harris, A Kirkham, Y Revell-Smith, L Bernhardt.

St Mary's Hospital, Paddington, London, UK.
S. Thom, A Whitehouse, A. D. Hughes, J Macduff, S Leech, L Kinsley, O Trainor, Y Chim, A Jack, S Murphy, R Baruah, F Harrison, R Fernandez, A Strain, M Liboro.

The Beaumont Hospital, Dublin, Ireland.
A. Stanton, E. O'Brien, E Dolan, D Farrell, OB Gallagher, S Lyons, G McCarthy.

Manchester Royal Infirmary, Manchester, UK.
K. Cruickshank, S Dean, J Dunkerley, M Banerjee, M Holland, M Hart, M Cullen, L Hardstaff, J Reynolds, J Collins, K Peters, M Luckson.

St Bartholomew's Hospital, London, UK.
D. Collier, M Caulfield, C Waleczko, G Salahi-Ali, J Sheil, B Scott, S Wilson, C David, H Fok.