Coadministered Amlodipine and Atorvastatin Produces Early Improvements in Arterial Wall Compliance in Hypertensive Patients With Dyslipidemia

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BACKGROUND

Combining statins with antihypertensive therapy has been demonstrated to provide an early reduction in cardiovascular events. This nested substudy of the AVALON trial assessed the effects of coadministered amlodipine and atorvastatin vs. either therapy alone or placebo on arterial compliance, to evaluate the vascular benefits of coadministered therapy.

METHODS

During an initial 8-week, double-blind phase, patients with concomitant hypertension and dyslipidemia were randomized into four treatment groups (placebo, amlodipine 5 mg, atorvastatin 10 mg, or coadministered amlodipine 5 mg and atorvastatin 10 mg). The sustained effect of combined therapy was evaluated during subsequent 8-week, single-blind, and 12-week, open-label periods. In the single-blind phase, all patients were coadministered amlodipine 5 mg and atorvastatin 10 mg, which were then titrated to optimize blood pressure and low-density lipoprotein cholesterol control during the open-label phase. Arterial compliance was assessed every 4 weeks using the HDI/Pulsewave CR-2000.

RESULTS

Overall, 668 patients (61% male, mean age 55 years) were randomized to treatment. A 19% improvement in small artery compliance (C2) was observed with coadministered amlodipine and atorvastatin from baseline to week 8, which was significantly greater than with either treatment alone or with placebo ($P = 0.03$ to 0.0001). After 28 weeks, C2 was increased from baseline in all groups, but the overall improvement was greatest in the group receiving coadministered drugs for the entire study period ($P < 0.05$).

CONCLUSIONS

Early and sustained improvement in small artery compliance was observed following coadministration of amlodipine and atorvastatin, thus demonstrating a vascular benefit with simultaneous treatment of hypertension and dyslipidemia.

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Therapies that lower blood pressure (BP) or lipid levels slow the progression of atherosclerosis and reduce morbidity and mortality in patients with hypertension or atherosclerotic disease.[1–6] The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) demonstrated an additive benefit of combined antihypertensive and lipid-lowering therapy on coronary events and stroke in hypertensive patients with ≥3 cardiovascular risk factors and total cholesterol levels ≤251 mg/dl (≤6.5 mmol/l).[1,7,8] Endothelial dysfunction, with associated changes in vascular function and structure, is a risk factor for cardiovascular events through its contribution to the development of atherosclerotic vascular disease.[9] Stiffening of small arteries occurs early in endothelial dysfunction and contributes to abnormal pressure oscillations or reflections within the arterial tree.[10] Recent data suggest that reduced small artery compliance is a marker for endothelial dysfunction[11] and a risk predictor for cardiovascular events independent of age and BP.[12]

Previous investigations have demonstrated improved endothelial function and arterial compliance with statins and some antihypertensive drugs.[13–15] Small vessel arterial compliance has been reported to improve with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers, but not consistently with β-blockers or diuretics.[15–18] To our knowledge, no large-scale, placebo-controlled, or multicenter trials have examined the time course of drug therapy on arterial compliance or whether

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additional vascular benefit occurs with coadministered antihypertensive and lipid-lowering therapy. Both amlodipine and atorvastatin have independently been noted to exert favorable effects on arterial compliance and endothelial dysfunction.[15] However, their additive benefits have not been thoroughly evaluated in a placebo-controlled trial.

The AVALON arterial wall compliance (AWC) trial was a nested substudy of the larger AVALON trial,[19] which investigated the efficacy and safety of coadministered amlodipine and atorvastatin in hypertensive patients with dyslipidemia. The AWC substudy assessed the effects of coadministered amlodipine and atorvastatin vs. either therapy alone or vs. placebo on arterial compliance, to evaluate the vascular benefits of coadministered therapy.

Measurements of arterial compliance were made during an initial 8-week, double-blind phase, and during subsequent 8-week, single-blind, and 12-week, open-label periods. These later phases were designed to confirm any vascular benefits observed in the double-blind phase and to determine if early vascular effects were sustained or enhanced during longer-term therapy.

METHODS

Study population. The AVALON trial[19] was a multicenter, randomized, controlled trial conducted in the United States and Canada between 14 February 2001 and 25 August 2004. The AVALON study recruited men and women, aged 18–75 years with a diagnosis of concomitant hypertension (systolic blood pressure (SBP) 130–179 mm Hg and/or diastolic blood pressure (DBP) 85–109 mm Hg) and dyslipidemia (low-density lipoprotein cholesterol (LDL-C) 101–250 mg/dl (2.6–6.5 mmol/l)). Patients were included in the AVALON-AWC substudy if they were enrolled from the AWC centers, which were supplied with AWC measurement capability.

In the AVALON-AWC substudy, patients with high cardiovascular risk (assigned to Group III in the main AVALON trial;[19] defined as those with hypertension (SBP >130 mm Hg) and dyslipidemia (LDL-C >100 mg/dl), and coronary heart disease (CHD), diabetes mellitus, or other atherosclerotic disease) were not permitted to have received lipid-lowering treatment within 6 weeks before screening, but could have been on prior antihypertensive medications. The lower risk patients (Groups I and II in AVALON;[19] defined as those with hypertension (SBP >140 mm Hg) and dyslipidemia (LDL-C >130 mg/dl) but no CHD or diabetes mellitus) could not have received lipid-lowering treatment or antihypertensives (except for diuretics or β-blockers) within 3 months before screening. Patients taking antihypertensive therapies underwent a 2- to 6-week washout period before the double-blind phase. Antihypertensive therapies in addition to the study medications and drugs known to affect lipid levels or alter the absorption/metabolism of the study medications were not permitted during the study.

AVALON-AWC conformed to Good Clinical Practice guidelines and was consistent with the Declaration of Helsinki. All patients provided written, informed consent, and each local institutional review board approved the protocol.

Study procedures. The AVALON study included three consecutive treatment phases. In an initial 8-week, randomized, double-blind, double-dummy, placebo-controlled phase, patients were randomized to one of four once-daily treatment groups: placebo + placebo (Group 1), amlodipine 5 mg + placebo (Group 2), atorvastatin 10 mg + placebo (Group 3), or amlodipine 5 mg + atorvastatin 10 mg (Group 4; **Figure 1**). The second phase was an 8-week, single-blind treatment phase, during which all patients received once-daily amlodipine 5 mg + atorvastatin 10 mg (**Figure 1**). Finally, during a 12-week, open-label phase, treatment could be up-titrated to the maximum doses of amlodipine (10 mg) and atorvastatin (80 mg) to achieve Joint National Committee VI BP[20] and National Cholesterol Education Program Adult Treatment Panel III LDL-C goals (**Figure 1**).[21] AWC substudy patients underwent BP, LDL-C, and AWC measurements every 4 weeks from baseline (week 0) to week 28.

AWC measurements. Radial arterial pulse waves were recorded noninvasively in the supine position, with the head of the bed elevated at 45°, after a 5- to 10-min rest period. A piezoelectric acoustic transducer was applied to the radial artery supported

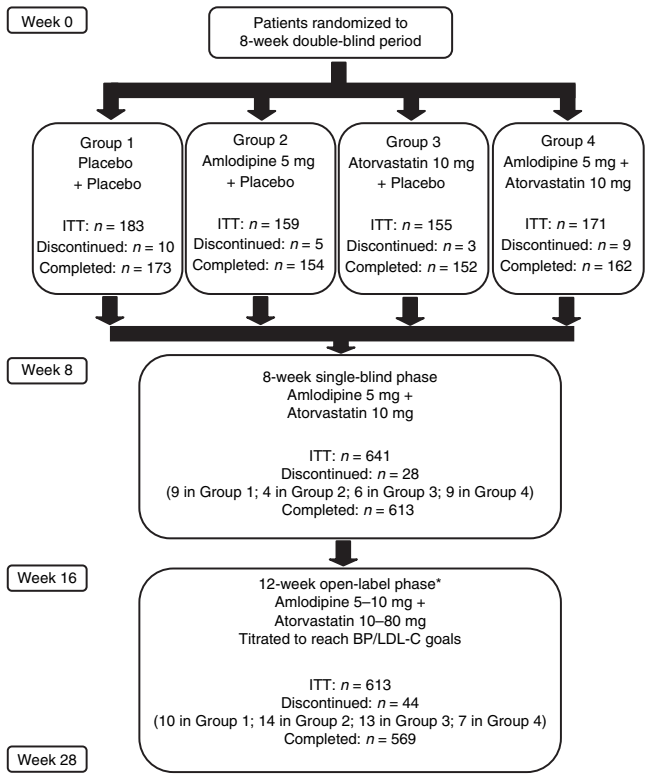

Figure 1 | AVALON-AWC substudy: design and patient disposition. *Amlodipine 5 mg and atorvastatin 10 mg once daily for the 8-week, single-blind period, up-titrated to a maximum dose of amlodipine (10 mg) and atorvastatin (80 mg), as required, during subsequent 12 weeks to achieve Joint National Committee VI blood pressure (BP) and National Cholesterol Education Program Adult Treatment Panel III low-density lipoprotein cholesterol (LDL-C) targets. Arterial wall compliance measurements using the HDI/Pulsewave CR-2000 device were obtained at baseline (week 0) and weeks 4, 8, 12, 16, 24, and 28. ITT, intent-to-treat.

by a stabilizing device around the patient's forearm (HDI/Pulsewave CR-2000 CV Profiler, Hypertension Diagnostics, Eagan, MN). Recorded waveforms were calibrated by the oscillometric method using a BP cuff on the contralateral arm and an internal device calibration system. Radial artery waveforms were recorded for 30 s and digitized at 200 samples per second. Two valid arterial compliance readings were obtained for each patient with each procedure. Diastolic waveform characteristics after the incisura were analyzed to identify exponential decay and decaying sinusoidal wave which characterizes systemic reflections or oscillations. Pulse waveforms used for compliance measurements were analyzed using a modified Windkessel model. This model includes two compliance elements (referred to as C1 (large artery elasticity) and C2 (small artery elasticity)) combined with inertia and resistance elements.[22]

Study outcomes. The primary objective was to compare changes in small artery compliance (C2) among the treatment groups after 8 weeks of double-blind treatment. Secondary measures involved assessment of the long-term effect (up to 28 weeks) of coadministered amlodipine and atorvastatin on C1 and C2.

Statistical analysis. Patients with ≥1 postbaseline AWC measurement were included in the AWC subanalysis. Last observation was carried forward for patients withdrawing prior to completion.

The sample size, based on a two-sided *t*-test ($\alpha = 0.05$), was calculated *a priori* for the primary outcome, such that a sample size of 158 patients per treatment group would have ~94% power to detect a treatment difference of at least 12.5% with coadministered amlodipine and atorvastatin vs. placebo in the mean C2 change from baseline to week 8.

Changes in arterial compliance from baseline to week 8 were analyzed using analysis of covariance with treatment as the main factor and baseline arterial compliance as the covariate. Changes in C1 and C2 were compared between coadministered therapy and placebo by constructing appropriate contrasts from the analysis of covariance model. The least squares mean

Table 1 | Demographic and baseline characteristics

		Double-blind treatment group (weeks 0–8)				
		Group 1	Group 2	Group 3	Group 4	
Characteristic	Overall (*n* = 668)	Placebo (*n* = 183)	Amlodipine (*n* = 159)	Atorvastatin (*n* = 155)	Amlodipine + atorvastatin (*n* = 171)	*P* value between groups
Gender, *n* (%)						
Male	405 (60.6)	113 (61.7)	88 (55.3)	89 (57.4)	115 (67.3)	
Female	263 (39.4)	70 (38.3)	71 (44.7)	66 (42.6)	56 (32.7)	0.12
Age (years), mean (s.d.)	55.2 (9.5)	55.3 (9.3)	55.8 (10.0)	54.7 (8.9)	55.1 (9.8)	0.78
Race, *n* (%)						
White	555 (83.1)	150 (82.0)	134 (84.3)	128 (82.6)	143 (83.6)	
Black	66 (9.9)	17 (9.3)	13 (8.2)	17 (11.0)	19 (11.1)	
Asian	14 (2.1)	3 (1.6)	3 (1.9)	2 (1.3)	6 (3.5)	
Other	33 (4.9)	13 (7.1)	9 (5.7)	8 (5.2)	3 (1.8)	0.46
Weight (kg), mean (s.d.)						
Male	94.1 (17.5)	93.4 (17.3)	92.3 (17.4)	96.4 (18.1)	94.4 (17.3)	
Female	82.0 (17.0)	81.8 (16.9)	80.4 (17.1)	82.7 (17.1)	83.3 (17.0)	0.22
Blood pressure (mm Hg), mean (s.d.)						
SBP	146.9 (11.2)	147.0 (11.0)	147.7 (10.3)	146.7 (11.1)	146.3 (12.3)	0.72
DBP	92.6 (6.6)	93.0 (5.3)	92.8 (7.0)	91.8 (7.2)	92.7 (6.7)	0.39
MAP	110.7 (6.2)	111.0 (5.4)	111.1 (6.4)	110.1 (6.6)	110.5 (6.4)	0.45
PP	54.3 (12.0)	54.0 (11.7)	54.9 (11.2)	54.9 (11.9)	53.7 (13.2)	0.74
LDL-C (mg/dl), mean (s.d.)	163.6 (24.7)	163.0 (23.7)	164.5 (25.9)	161.7 (24.7)	165.4 (24.7)	0.55
C1 (ml/mm Hg × 10)						
Mean (s.d.)	12.5 (4.1)	12.4 (3.8)	12.0 (4.5)	12.7 (4.0)	12.7 (4.1)	0.35
Range	3.4–29.2	4.3–23.1	3.7–29.2	5.0–24.9	3.4–25.6	
C2 (ml/mm Hg × 100)						
Mean (s.d.)	4.5 (2.5)	4.7 (2.6)	4.3 (2.3)	4.5 (2.5)	4.6 (2.5)	0.38
Range	1.0–16.0	1.2–13.5	1.00–16.0	1.2–14.9	1.7–12.7	

C1, large artery compliance (oscillatory compliance); C2, small artery compliance (capacitive compliance); DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; MAP, mean arterial pressure; PP, pulse pressure; SBP, systolic blood pressure; s.d., standard deviation.

within the analysis of covariance model was used for testing changes in C1 and C2 from baseline to week 28 within each treatment group. Additionally, Pearson's correlation coefficient analysis was used to assess the relationship between changes in arterial compliance variables (C1, C2) and changes in BP and LDL-C for all patients combined.

Pulse pressure (PP) was calculated as the difference between SBP and DBP. Mean arterial pressure (MAP) was calculated as ((2 × DBP) + SBP)/3.

RESULTS

Patients

Of 848 patients randomized in AVALON, 668 patients from 103 centers participated in AVALON-AWC and were included in the intent-to-treat population. Among these patients, 183 received placebo + placebo (Group 1), 159 received amlodipine 5 mg + placebo (Group 2), 155 received atorvastatin 10 mg + placebo (Group 3), and 171 received coadministered amlodipine 5 mg + atorvastatin 10 mg (Group 4). Overall, 641 patients completed the double-blind phase of the study, and 569 completed the full 28 week study period (Figure 1).

Patients were aged between 24 and 76 years (mean age, 55.2 years) and 60.6% were male. Baseline values for SBP, DBP, and LDL-C were similar across all 4 treatment groups (Table 1). Baseline arterial compliance measurements (C1 and C2) were comparable across treatment groups.

Effect of treatment on small artery compliance (C2)

After 8 weeks of double-blind therapy, C2 values were unchanged from baseline in patients receiving placebo or atorvastatin 10 mg (Figure 2a). However, patients receiving amlodipine 5 mg alone or in combination with atorvastatin 10 mg demonstrated significant increases in C2 from baseline vs. placebo ($P = 0.023$ and $P < 0.0001$, respectively). At week 8, patients coadministered amlodipine 5 mg + atorvastatin 10 mg had a 19.3% increase in C2 compared with 11.7% in those receiving amlodipine alone ($P = 0.03$), 3.1% for atorvastatin alone ($P < 0.001$), and −1.3% for placebo ($P < 0.0001$).

Subsequent changes in C2 from week 8 to week 16 and to week 28 are shown in Figure 3a. Patients receiving placebo alone during the double-blind phase exhibited an increase in C2 at week 16 after being switched to amlodipine 5 mg and atorvastatin 10 mg, thus confirming the benefits of combined therapy identified in the 8-week, double-blind phase. A similar increase in C2 was observed in the group who had been treated with atorvastatin alone during the double-blind phase.

At week 28, improvements in C2 were maintained in all patient groups (Figure 3a). Patients coadministered amlodipine + atorvastatin for the entire study exhibited significantly greater improvement in C2 compared with all the other groups ($P < 0.05$).

Effect of treatment on large artery compliance (C1)

Following 8 weeks of double-blind treatment, C1 values were unchanged in patients receiving placebo or atorvastatin 10 mg, compared with baseline (Figure 2b). However, patients receiving amlodipine 5 mg, or coadministered amlodipine

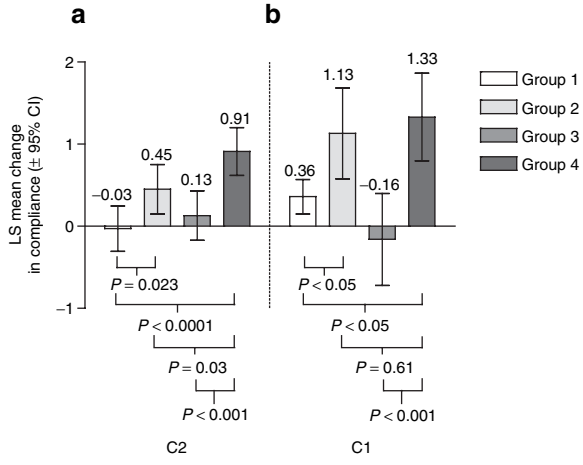

Figure 2 | Change in (**a**) small artery compliance (C2) and (**b**) large artery compliance (C1), from week 0 (baseline) to week 8. Group 1: placebo + placebo; Group 2: amlodipine 5 mg + placebo; Group 3 atorvastatin 10 mg + placebo; Group 4: amlodipine 5 mg + atorvastatin 10 mg. Coefficients of variation for C1 were 37.0, 44.2, 36.2, and 38.1 in Groups 1, 2, 3, and 4, respectively, at baseline and 41.5, 40.2, 36.7, and 38.7, at week 8. Coefficients of variation for C2 were 63.1, 61.8, 61.0, and 62.9 in Groups 1, 2, 3, and 4, respectively, at baseline and 60.7, 63.3, 62.3, and 55.8, at week 8. Compliance units: C1: ml/mm Hg × 10; C2 ml/mm Hg × 100. CI, confidence interval; LS, least squares.

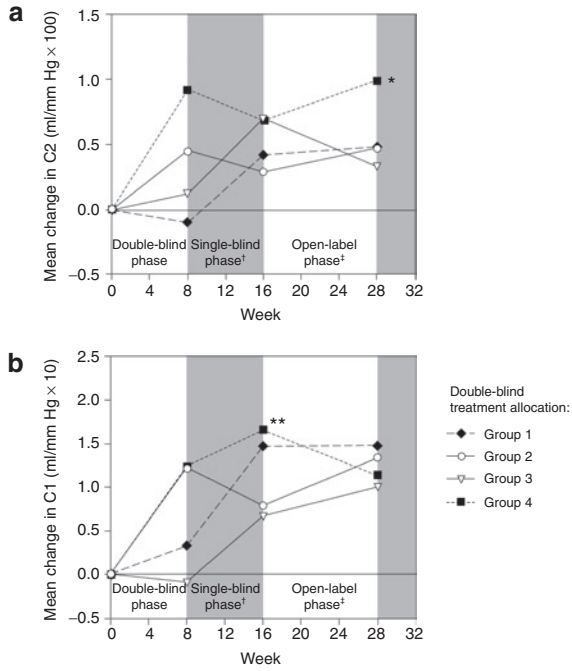

Figure 3 | Mean change in (**a**) small artery compliance (C2) and (**b**) large artery compliance (C1), from week 0 (baseline) to week 28. *$P < 0.05$ vs. Group 1, 2, and 3. **$P < 0.01$ vs. Group 2; $P < 0.05$ vs. Group 3. †All patients received coadministered amlodipine 5 mg + atorvastatin 10 mg. ‡All patients received coadministered amlodipine 5–10 mg + atorvastatin. 10–80 mg titrated to achieve blood pressure and low-density lipoprotein cholesterol goals. Group 1: placebo + placebo; Group 2: amlodipine 5 mg + placebo; Group 3 atorvastatin 10 mg + placebo; Group 4: amlodipine 5 mg + atorvastatin 10 mg.

5 mg + atorvastatin 10 mg showed significant increases in C1 of 10.3% and 10.0%, respectively, from baseline compared with placebo (both $P < 0.05$). Coadministration of amlodipine + atorvastatin resulted in an increase in C1 similar to that of amlodipine alone ($P = 0.61$; Figure 2b).

Patients who received placebo or atorvastatin 10 mg for the first 8 weeks exhibited an increase in C1 at week 16 when taking amlodipine 5 mg + atorvastatin 10 mg during the single-blind treatment phase. At week 16, patients coadministered amlodipine 5 mg + atorvastatin 10 mg during the double-blind phase had a small increase in C1, however those receiving amlodipine 5 mg alone during double-blind treatment had a small, nonsignificant reduction. At week 28, after investigator initiated up-titration of amlodipine and atorvastatin, C1 was similar in all treatment groups (Figure 3b).

Effect on BP and LDL-C

After 8 weeks, SBP and DBP reductions with amlodipine 5 mg or coadministered amlodipine 5 mg + atorvastatin 10 mg were comparable and greater than placebo ($P < 0.0001$; Figure 4a). Similarly, changes in MAP were comparable in the amlodipine (−10.9 mm Hg) and coadministered amlodipine + atorvastatin (−10.1 mm Hg) groups, although PP was reduced slightly more with amlodipine alone (−6.5 mm Hg) than with amlodipine + atorvastatin (−4.3 mm Hg) at week 8 ($P = 0.04$). Changes in MAP and PP with atorvastatin were comparable to placebo.

At weeks 16 and 28, during the period in which all patients were receiving amlodipine, there were no significant differences in mean changes in SBP or DBP between treatment groups. At week 16, mean SBP ranged from 132.7 to 133.8 mm Hg and DBP from 83.7 to 84.8 mm Hg. At week 28, BP was slightly lower, with mean SBP ranging from 130.7 to 131.1 mm Hg and DBP from 81.9 to 82.6 mm Hg. MAP and PP were also comparable between treatment groups at weeks 16 and 28 with no significant differences between groups.

At week 8, coadministered amlodipine 5 mg + atorvastatin 10 mg or atorvastatin 10 mg treatment alone had significantly greater effects on LDL-C compared with amlodipine alone or with placebo ($P < 0.001$ for both; Figure 4b). Coadministered amlodipine 5 mg + atorvastatin 10 mg led to a small, yet significantly greater reduction in LDL-C compared with atorvastatin 10 mg alone ($P < 0.01$); while patients treated with amlodipine alone exhibited a small, marginally significant reduction in LDL-C ($P = 0.057$; Figure 4b). Full details of the BP and lipid changes and patients who reached their treatment goals in the AVALON trial have been reported elsewhere.[19]

Relationship between AWC and BP or LDL-C

A modest negative correlation was observed between a reduction in BP (SBP, DBP, MAP, and PP) and LDL-C and an increase in C2. A slightly stronger relationship was demonstrated between the fall in SBP and MAP and an increase in C1, but there was no relationship between change in LDL-C and change in C1 (Table 2).

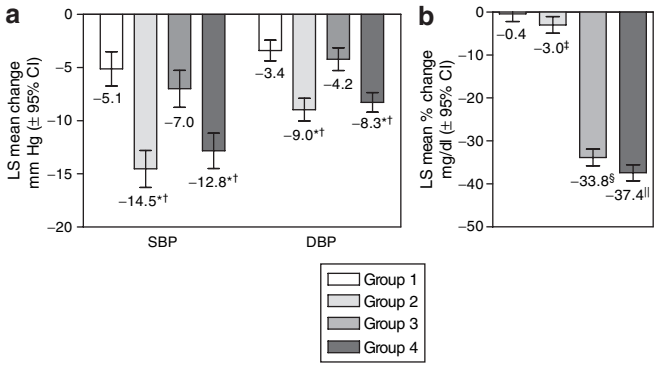

Figure 4 | Least squares (LS) mean change in (**a**) blood pressure (BP) and (**b**) low-density lipoprotein cholesterol (LDL-C), from week 0 (baseline) to week 8. *$P < 0.0001$ vs. Group 1; †$P < 0.0001$ vs. Group 3; ‡$P = 0.0571$ vs. Group 1; §$P < 0.0001$ vs. Group 2, $P < 0.0001$ vs. Group 1; ‖$P < 0.0001$ vs. Group 1, $P < 0.0001$ vs. Group 2, $P < 0.01$ vs. Group 3. Changes in BP were significant ($P < 0.001$) vs. baseline in all treatment groups. Group 1: placebo + placebo; Group 2: amlodipine 5 mg + placebo; Group 3: atorvastatin 10 mg + placebo; Group 4: amlodipine 5 mg + atorvastatin 10 mg. CI, confidence interval; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Table 2 | Pearson's correlation analysis between the changes in arterial compliance measures and the changes in blood pressure or low-density lipoprotein cholesterol at week 8 (all patients)

	C1		C2	
	R	*P* value	*R*	*P* value
SBP ($n = 640$)	−0.22	<0.0001	−0.18	<0.0001
DBP ($n = 640$)	−0.16	0.0001	−0.18	<0.0001
MAP ($n = 640$)	−0.21	<0.0001	−.20	<0.0001
PP ($n = 640$)	−0.16	<0.0001	−0.088	0.027
LDL-C ($n = 615$)	−0.018	0.65	−0.11	0.007

C1, large artery compliance (oscillatory compliance); C2, small artery compliance (capacitive compliance); DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; MAP, mean arterial pressure; PP, pulse pressure; SBP, systolic blood pressure.

DISCUSSION

The AVALON-AWC study demonstrates that in patients with hypertension and dyslipidemia amlodipine mediates early increases in small artery compliance (C2) vs. placebo, and that the coadministration of atorvastatin with amlodipine produces a more-than-additive increase in this response. Since BP has a major effect on large artery compliance (C1),[23] the increase in C1 with amlodipine but not atorvastatin can be attributed to differential BP lowering.

The observation that combination therapy has more than an additive effect on small artery compliance but not on large artery compliance can be explained by the differences between the factors controlling large and small artery function. Small artery compliance is influenced predominantly by vascular tone and structure, whereas large artery compliance is influenced more by arterial pressure and structure.[24] Potential synergistic effects on endothelial function mediated by short-term coadministration of amlodipine and atorvastatin may therefore be exerted primarily on the functionally sensitive, thin-walled small arteries,[11] whereas thick-walled large artery function

is more responsive to the amlodipine-mediated changes in BP. These differences are supported by the slightly stronger correlation between C1 and BP change than C2 and BP change in this study. Additional structural effects on the small arteries may become apparent by 28 weeks, but changes in the structure of the larger arteries may take longer to develop.

Our results are consistent with a small study by Leibovitz *et al.*[15] that demonstrated improvements in small artery compliance with amlodipine and atorvastatin at similar doses (amlodipine mean dose 5.6 mg; atorvastatin mean dose 12.7 mg) to those used in this study. Leibovitz *et al.*[15] showed that coadministration of amlodipine plus atorvastatin for 12 weeks led to an additional increase of 42% in C2 compared with amlodipine alone.

During the single-blind and open-label phases of the study from 8 to 28 weeks, when all patients were receiving combination therapy, there was a rise in C1 and C2 in all treatment groups, consistent with the effects observed in the first 8 weeks in the coadministered amlodipine + atorvastatin group. The rise in small artery compliance demonstrated within 8 weeks of instituting drug therapy is consistent with a functional effect on the vascular wall. However, the benefits on small artery compliance were more pronounced at 28 weeks among those receiving both amlodipine and atorvastatin throughout the study than in those started on placebo or either therapy alone. Because small artery compliance is reduced both by vasoconstriction and by structural alterations leading to remodeling of the microcirculation,[25] the trend for C1 and C2 to rise further during the last few months of the study could be related to several mechanisms: (i) better BP or lipid control; (ii) higher doses of the pharmacologic agents exerting effects unrelated to BP or lipids, such as anti-inflammatory effects;[26] or (iii) the influence of more slowly developing structural changes. Longer-term controlled studies and investigations after short-term withdrawal of therapy would be needed to separate short-term functional from longer-term structural effects of combination therapy.

In this study, we utilized radial artery pulse-wave analysis to monitor AWC.[27] This technique analyzes the diastolic decay of the waveform and provides a distinction between large, conduit artery stiffness and that of the small arteries that serve as sites of oscillations and reflected waves in the arterial circulation. The baseline compliance value for C1 averaged ~12.5 ml/mm Hg × 10, a low-normal value (for patients with mean age of 55.2 years, normal C1 = male >11.0, female >10.0 ml/mm Hg ×10).[27] Our findings are therefore consistent with the modest stiffening effect of elevated BP on large arteries. In contrast, the abnormally low measure for C2 at baseline (study mean = 4.5 ml/mm Hg; normal C2 = male >7.0, female >5.0 ml/mm Hg × 100)[27] is consistent with the small artery abnormality characteristic of hypertension.[28] This study also demonstrated the stability of the AWC measurements since patients randomized to placebo (n = 183) exhibited no significant change in either C1 or C2 at 4 (data not shown) or 8 weeks.

Amlodipine and atorvastatin reduce the incidence of cardiovascular events in a variety of patients.[1–4,6] This efficacy has been assumed to be based on different mechanisms: BP reduction with amlodipine and LDL-C reduction with atorvastatin. The lipid-lowering arm of ASCOT (ASCOT–LLA)[7] demonstrated that atorvastatin treatment, in addition to an amlodipine- or atenolol-based antihypertensive regimen, resulted in significant reductions in nonfatal myocardial infarction and fatal CHD (36%), stroke (27%), all coronary events (29%), and all cardiovascular events and procedures (21%) when compared with antihypertensive treatment without statin therapy.[7] However, the efficacy of atorvastatin appeared to be greater when given to patients receiving amlodipine-based antihypertensive therapy than those treated with atenolol-based therapy, despite similar reductions in BP. This suggests that there may be a treatment-specific effect with the combination of amlodipine and atorvastatin.[8]

Since reduced C2 is an independent marker for cardiovascular morbidity and mortality[12] the observed increase in C2 with coadministered amlodipine and atorvastatin in AVALON-AWC supports the hypothesis that the benefit of both amlodipine and atorvastatin on cardiovascular events may be, at least in part, mediated by this effect on vascular function.[29,30] Increased small artery compliance associated with amlodipine therapy alone at 8 weeks is potentially indicative of an improvement in vascular tone, most likely related to improved endothelial function that has previously been demonstrated with amlodipine treatment.[31] The significantly greater improvement in small artery compliance with coadministered atorvastatin, which did not by itself significantly improve small artery compliance at 8 weeks and also did not further reduce BP, is consistent with a more-than-additive effect of the two drugs on endothelial function. The additive effect of combined antihypertensive and lipid-lowering therapy has previously been demonstrated in vitro, whereby coadministered amlodipine and atorvastatin stimulated nitric oxide release from human endothelial cells in a synergistic fashion, independently of effects on LDL-C or BP levels.[29,30] Furthermore, studies in mice have revealed that the addition of amlodipine at a dose that did not affect BP levels, significantly enhanced the effect of atorvastatin to inhibit the development of atherosclerosis.[32]

The Conduit Artery Function Evaluation (CAFÉ) substudy of ASCOT[33] demonstrated a benefit of amlodipine-based therapy compared with atenolol-based therapy on calculated central aortic pressure, which the authors suggest may account for the observed decreases in cardiovascular events with an amlodipine- vs. atenolol-based antihypertensive regimen in the BP lowering arm of ASCOT (ASCOT–BPLA).[1] A recent subanalysis of CAFÉ among patients in ASCOT–LLA (CAFÉ–LLA) indicated that the addition of atorvastatin did not significantly influence central aortic pressure, thus suggesting that the benefit of atorvastatin in ASCOT–LLA was not due to pressure-related mechanisms.[34]

The AVALON-AWC study provides new insights into the vascular and pressure benefits of combined amlodipine and atorvastatin therapy. Reflected waves emanating from stiffened small arteries will augment late systolic aortic pressure if

transmitted rapidly back to the root of the aorta. An increase in small artery compliance will reduce the magnitude of the waves, whereas an increase in large artery compliance will reduce pulse-wave velocity and delay arrival in the root of the aorta. Since amlodipine increases both large and small artery compliance it would be expected to reduce central pressure augmentation, whereas the addition of atorvastatin, which has no effect on pressure or large artery compliance, will have no such effect. Nonetheless, the improvement in endothelial function leading to the increase in small artery compliance produced by the drug combination may account for the benefit in outcomes.[35] Indeed, the central BP benefit of amlodipine in CAFÉ may be largely an epiphenomenon and not the primary mechanism of the clinical benefit of the therapy.

Despite these extensive confirmatory data on the complementary vascular effects of atorvastatin combined with amlodipine, limitations in the data from the current study mandate some caution in interpretation. Although the increase in small artery compliance at 8 weeks was significantly greater in the amlodipine–atorvastatin group than in the amlodipine-alone group, the interaction statistic was not significant, thus not mathematically confirming a synergistic effect. Furthermore, addition of open-label atorvastatin to amlodipine therapy from 8 to 16 weeks did not produce a further increase in small artery compliance. Therefore, further vascular studies would be helpful in documenting this interaction.

The AVALON-AWC study has provided an opportunity to document the vascular effects of amlodipine and atorvastatin. The results support an early improvement in endothelial dysfunction associated with amlodipine therapy and a more-than-additive effect of concomitant atorvastatin therapy on the basis of observed increases in small artery compliance. The AVALON-AWC study strongly suggests that a greater early vascular benefit can be obtained from simultaneous treatment with amlodipine and atorvastatin, vs. either agent alone, in patients with hypertension and dyslipidemia.

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1. Dahlöf B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trail–Blood Pressure Lowering Arm (ASCOT–BPLA): a multicentre randomised controlled trial. *Lancet* 2005; 366:895–906.
2. Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, Hua T, Laragh J, McInnes GT, Mitchell L, Plat F, Schork A, Smith B, Zanchetti A. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet* 2004; 363: 2022–2031.
3. Nissen SE. Effect of intensive lipid lowering on progression of coronary atherosclerosis: evidence for an early benefit from the reversal of atherosclerosis with aggressive lipid lowering (REVERSAL) trial. *Am J Cardiol* 2005; 96:61–68.
4. Nissen SE, Tuzcu EM, Libby P, Thompson PD, Ghali M, Garza D, Berman L, Shi H, Buebendorf E, Topol EJ. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. *JAMA* 2004; 292:2217–2225.
5. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004; 350:1495–1504.
6. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, Gotto AM, Greten H, Kastelein JJ, Shepherd J, Wenger NK. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005; 352:1425–1435.
7. Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trail–Lipid Lowering Arm (ASCOT–LLA): a multicentre randomised controlled trial. *Lancet* 2003; 361:1149–1158.
8. Sever P, Dahlöf B, Poulter N, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen S, Kristinsson A, McInnes G, Mehlsen J, Nieminem M, O'Brien E, Ostergren J. Potential synergy between lipid-lowering and blood-pressure-lowering in the Anglo-Scandinavian Cardiac Outcomes Trial. *Eur Heart J* 2006; 27:2982–2988.
9. Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. *Nature* 1993; 362:801–809.
10. Cohn JN, Finkelstein S, McVeigh G, Morgan D, LeMay L, Robinson J, Mock J. Noninvasive pulse wave analysis for the early detection of vascular disease. *Hypertension* 1995; 26:503–508.
11. Gilani M, Kaiser DR, Bratteli CW, Alinder C, Rajala S, Bank AJ, Cohn JN. Role of nitric oxide deficiency and its detection as a risk factor in pre-hypertension. *J Amer Soc Hypertens* 2007; 1:45–55.
12. Grey E, Bratteli C, Glasser SP, Alinder C, Finkelstein SM, Lindgren BR, Cohn JN. Reduced small artery but not large artery elasticity is an independent risk marker for cardiovascular events. *Am J Hypertens* 2003; 16:265–269.
13. Higashi Y, Sasaki S, Nakagawa K, Ueda T, Yoshimizu A, Kurisu S, Matsuura H, Kajiyama G, Oshima T. A comparison of angiotensin-converting enzyme inhibitors, calcium antagonists, beta-blockers and diuretic agents on reactive hyperemia in patients with essential hypertension: a multicenter study. *J Am Coll Cardiol* 2000; 35:284–291.
14. Nazzaro P, Manzari M, Merlo M, Triggiani R, Scarano A, Ciancio L, Pirrelli A. Distinct and combined vascular effects of ACE blockade and HMG-CoA reductase inhibition in hypertensive subjects. *Hypertension* 1999; 33:719–725.
15. Leibovitz E, Beniashvili M, Zimlichman R, Freiman A, Shargorodsky M, Gavish D. Treatment with amlodipine and atorvastatin have additive effect in improvement of arterial compliance in hypertensive hyperlipidemic patients. *Am J Hypertens* 2003; 16:715–718.
16. Hayashi K, Miyagawa K, Sato K, Ueda R, Dohi Y. Temocapril, an angiotensin converting enzyme inhibitor, ameliorates age-related increase in carotid arterial stiffness in normotensive subjects. *Cardiology* 2006; 106:190–194.
17. Resnick LM, Lester MH. Differential effects of antihypertensive drug therapy on arterial compliance. *Am J Hypertens* 2002; 15:1096–1100.
18. Shargorodsky M, Leibovitz E, Lubimov L, Gavish D, Zimlichman R. Prolonged treatment with the AT1 receptor blocker, valsartan, increases small and large artery compliance in uncomplicated essential hypertension. *Am J Hypertens* 2002; 15:1087–1091.
19. Messerli FH, Bakris GL, Ferrera D, Houston MC, Petrella RJ, Flack JM, Sun W, Lee E, Neutel JM. Efficacy and safety of coadministered amlodipine and atorvastatin in patients with hypertension and dyslipidemia: results of the AVALON trial. *J Clin Hypertens* 2006; 8:571–581.
20. Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 1997; 157:2413–2446.
21. National Cholesterol Education Program (NCEP) Expert Panel on Detection E, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).

Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002; 106:3143–3421.
22. Cohn JN. Pathophysiologic and prognostic implications of measuring arterial compliance in hypertensive disease. *Prog Cardiovasc Dis* 1999; 41:441–450.
23. Bergel DH. The static elastic properties of the arterial wall. *J Physiol* 1961; 156: 445–457.
24. McVeigh GE, Bratteli CW, Morgan DJ, Alinder CM, Glasser SP, Finkelstein SM, Cohn JN. Age-related abnormalities in arterial compliance identified by pressure pulse contour analysis: aging and arterial compliance. *Hypertension* 1999; 33:1392–1398.
25. Schiffrin EL, Park JB, Intengan HD, Touyz RM. Correction of arterial structure and endothelial dysfunction in human essential hypertension by the angiotensin receptor antagonist losartan. *Circulation* 2000; 101:1653–1659.
26. Tsioufis C, Dimitriadis K, Selima M, Thomopoulos C, Mihas C, Skiadas I, Tousoulis D, Stefanadis C, Kallikazaros I. Low-grade inflammation and hypoadiponectinaemia have an additive detrimental effect on aortic stiffness in essential hypertensive patients. *Eur Heart J* 2007; 28:1162–1169.
27. Zimlichman R, Shargorodsky M, Boaz M, Duprez D, Rahn KH, Rizzoni D, Payeras AC, Hamm C, McVeigh G. Determination of arterial compliance using blood pressure waveform analysis with the CR-2000 system: reliability, repeatability, and establishment of normal values for healthy European population—the seven European sites study (SESS). *Am J Hypertens* 2005; 18:65–71.
28. Mulvany MJ, Aalkjaer C. Structure and function of small arteries. *Physiol Rev* 1990; 70:921–961.
29. Mason RP. A rationale for combined therapy with a calcium channel blocker and statin: evaluation of basic and clinical evidence. *Curr Drug Targets Cardiovasc Haematol Disord* 2005; 5:489–501.
30. Mason RP, Kubant R, Heeba G, Jacob RF, Day CA, Medlin YS, Funovics P, Malinski T. Synergistic effect of amlodipine and atorvastatin in reversing LDL-induced endothelial dysfunction. *Pharm Res* 2007; 25: 1798–1806.
31. Mason RP. Atheroprotective effects of long-acting dihydropyridine-type calcium channel blockers: evidence from clinical trials and basic scientific research. *Cerebrovasc Dis* 2003; 16(Suppl 3):11–17.
32. van de Poll SW, Delsing DJ, Wouter Jukema J, Princen HM, Havekes LM, Puppels GJ, van der Laarse A. Effects of amlodipine, atorvastatin and combination of both on advanced atherosclerotic plaque in APOE*3-Leiden transgenic mice. *J Mol Cell Cardiol* 2003; 35:109–118.
33. Williams B, Lacy PS, Thom SM, Cruickshank K, Stanton A, Collier D, Hughes AD, Thurston H, O'Rourke M. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes. Principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation* 2006; 113: 1213–1225.
34. Williams B, Lacy PS, Cruickshank KJ, Collier D, Hughes A, Stanton A, Thom S, Thurston H. Impact of statin therapy on central aortic pressures and hemodynamics—principal results of the Conduit Artery Function Evaluation study Lipid Lowering Arm: the CAFE-LLA study. *Circulation*, in press.
35. Cohn JN. Is it the blood pressure or the blood vessel?. *J Am Soc Hypertens* 2007; 1:5–16.