Effect of Antihypertensive Agents on Cardiovascular Events in Patients With Coronary Disease and Normal Blood Pressure

The CAMELOT Study: A Randomized Controlled Trial

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Context The effect of antihypertensive drugs on cardiovascular events in patients with coronary artery disease (CAD) and normal blood pressure remains uncertain.

Objective To compare the effects of amlodipine or enalapril vs placebo on cardiovascular events in patients with CAD.

Design, Setting, and Participants Double-blind, randomized, multicenter, 24-month trial (enrollment April 1999-April 2002) comparing amlodipine or enalapril with placebo in 1991 patients with angiographically documented CAD (>20% stenosis by coronary angiography) and diastolic blood pressure <100 mm Hg. A substudy of 274 patients measured atherosclerosis progression by intravascular ultrasound (IVUS).

Interventions Patients were randomized to receive amlodipine, 10 mg; enalapril, 20 mg; or placebo. IVUS was performed at baseline and study completion.

Main Outcome Measures The primary efficacy parameter was incidence of cardiovascular events for amlodipine vs placebo. Other outcomes included comparisons of amlodipine vs enalapril and enalapril vs placebo. Events included cardiovascular death, nonfatal myocardial infarction, resuscitated cardiac arrest, coronary revascularization, hospitalization for angina pectoris, hospitalization for congestive heart failure, fatal or nonfatal stroke or transient ischemic attack, and new diagnosis of peripheral vascular disease. The IVUS end point was change in percent atheroma volume.

Results Baseline blood pressure averaged 129/78 mm Hg for all patients; it increased by 0.7/0.6 mm Hg in the placebo group and decreased by 4.8/2.5 mm Hg and 4.9/2.4 mm Hg in the amlodipine and enalapril groups, respectively ($P<.001$ for both vs placebo). Cardiovascular events occurred in 151 (23.1%) placebo-treated patients, in 110 (16.6%) amlodipine-treated patients (hazard ratio [HR], 0.69; 95% CI, 0.54-0.88 [$P=.003$]), and in 136 (20.2%) enalapril-treated patients (HR, 0.85; 95% CI, 0.67-1.07 [$P=.16$]. Primary end point comparison for enalapril vs amlodipine was not significant (HR, 0.81; 95% CI, 0.63-1.04 [$P=.10$]). The IVUS substudy showed a trend toward less progression of atherosclerosis in the amlodipine group vs placebo ($P=.12$), with significantly less progression in the subgroup with systolic blood pressures greater than the mean ($P=.02$). Compared with baseline, IVUS showed progression in the placebo group ($P<.001$), a trend toward progression in the enalapril group ($P=.08$), and no progression in the amlodipine group ($P=.31$). For the amlodipine group, correlation between blood pressure reduction and progression was $r=0.19$, $P=.07$.

Conclusions Administration of amlodipine to patients with CAD and normal blood pressure resulted in reduced adverse cardiovascular events. Directionally similar, but smaller and nonsignificant, treatment effects were observed with enalapril. For amlodipine, IVUS showed evidence of slowing of atherosclerosis progression.

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DESPITE MORE THAN 30 YEARS of clinical trials, uncertainty still exists regarding the optimal use of antihypertensive drugs in patients with coronary artery disease (CAD).[1-3] Several classes of pharmacological agents have shown benefits in patients with CAD, but most studies enrolled patients with an elevated or borderline blood pressure. Recent clinical trials have demonstrated benefits for both angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers in patients with CAD with relatively normal or borderline blood pressures.[4-6]

However, few studies have specifically targeted patients with angiographically documented coronary obstructions and restricted enrollment to patients with entry blood pressures significantly less than 140/90 mm Hg.

For editorial comment see p 2271.

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Therefore, no consensus exists regarding administration of antihypertensive drugs to normotensive patients with CAD.[7]

Antihypertensive drugs have a variety of potentially beneficial properties that might favorably affect cardiovascular event rates. We sought to address these issues by studying the effects of antihypertensive drugs in patients with CAD and customary blood pressure of less than 140/90 mm Hg. The Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study compared treatment using either of 2 classes of antihypertensive drugs, a calcium channel blocker (amlodipine) and an ACE inhibitor (enalapril), with placebo in normotensive patients with CAD. The primary end point was the time to first occurrence of an adverse cardiovascular event. In addition, a subset of patients underwent serial intravascular ultrasound (IVUS) to determine if either or both agents exhibited antiatherosclerotic effects.

METHODS

Study Design

The CAMELOT study was a multicenter, double-blind, placebo-controlled randomized trial involving 100 study sites in North America (United States and Canada) and Europe. The institutional review boards of participating centers approved the protocol and all patients provided written informed consent. Men and women, aged 30 through 79 years, requiring coronary angiography for evaluation for chest pain or percutaneous coronary intervention were eligible. During a screening period, sitting and standing blood pressures were measured using a manual cuff and stethoscope. Study eligibility required a diastolic pressure lower than 100 mm Hg, with or without treatment. ACE inhibitors, angiotensin receptor blockers, and calcium channel blockers were discontinued over a 2- to 6-week period and were prohibited during the study (with the exception of study medications). β-Blockers, α_1-blockers, and diuretics were permitted. Angiographic inclusion criteria required 1 or more lesions in a native coronary artery with greater than 20% stenosis by visual (angiographic) estimation. Patients with a left main coronary artery obstruction greater than 50%, left ventricular ejection fraction (EF) less than 40%, or moderate to severe congestive heart failure were excluded. Information on race/ethnicity was collected via self-report by the patient. This information was thought pertinent to the study because antihypertensive agents may have different effects on different racial groups.

Intravascular Ultrasound Substudy

At 38 sites, an IVUS substudy was performed. Following diagnostic angiography, ultrasound examination was performed in the longest and least angulated target vessel meeting inclusion criteria. The "target vessel" for interrogation must not have undergone angioplasty nor have a luminal narrowing of more than 50% throughout a segment with a minimum length of 30 mm. The IVUS procedure has been described in detail previously.[8,9] After a 24-month treatment period, actively participating patients underwent repeat IVUS of the originally imaged vessel.

Treatments

All patients participated in a 2-week placebo run-in period. Patients were instructed to take 1 placebo tablet and 1 placebo capsule daily (in the morning) and return in 2 weeks. Patients demonstrating at least 80% compliance by pill count were randomly assigned to 1 of the following combinations of study medications: 1 amlodipine tablet (5 mg) plus 1 placebo enalapril capsule, 1 placebo amlodipine tablet and 1 enalapril capsule (10 mg), or 1 placebo amlodipine tablet plus 1 placebo enalapril capsule. At the end of the second week, if the initial dose level was tolerated, the participant was instructed to double the daily dose of study medication. If during the treatment period a participant was taking the full dose and experienced an intolerable adverse effect believed to be related to the study drug, he/she was instructed to take only 1 tablet and 1 capsule of study medication each day. Investigators attempted to reinstitute the higher dose of study medication at a later date, if possible.

Randomization and Allocation Concealment

The patients and all study personnel were blinded to treatment assignment. The randomization code was generated using a block size of 6 (stratified in 3 groups: no coronary intervention, stent placement, or non-stent intervention at baseline). Patients participating in the IVUS substudy were separately randomized in the same 3 strata.

Outcomes

All events were independently adjudicated by a blinded end point committee. The primary outcome was the incidence of adverse cardiovascular events in patients treated with amlodipine compared with placebo. Events included in the end point were cardiovascular death, nonfatal myocardial infarction, resuscitated cardiac arrest, coronary revascularization, hospitalization for angina pectoris, hospitalization for congestive heart failure, fatal or nonfatal stroke or transient ischemic attack (TIA), and any new diagnosis of peripheral vascular disease. Secondary outcomes included the incidence of adverse events for enalapril treatment compared with placebo and comparison of the amlodipine treatment group with the enalapril group. Additional prespecified secondary end points included all-cause mortality and the incidence of revascularization in vessels that had undergone previous stent placement.

The end point for the IVUS substudy was the nominal change in percent atheroma volume (PAV) for all slices of anatomically comparable segments of the target coronary artery from baseline to month 24 visit calculated as follows:

$$\mathrm{PAV} = [\Sigma(\mathrm{EEM}_{\mathrm{area}} - \mathrm{LCS}_{\mathrm{area}})/\Sigma\mathrm{EEM}_{\mathrm{area}}] \times 100$$

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where EEM represents external elastic membrane area and LCS represents lumen cross-sectional area. Nominal change in PAV = (PAV month 24 – PAV baseline).

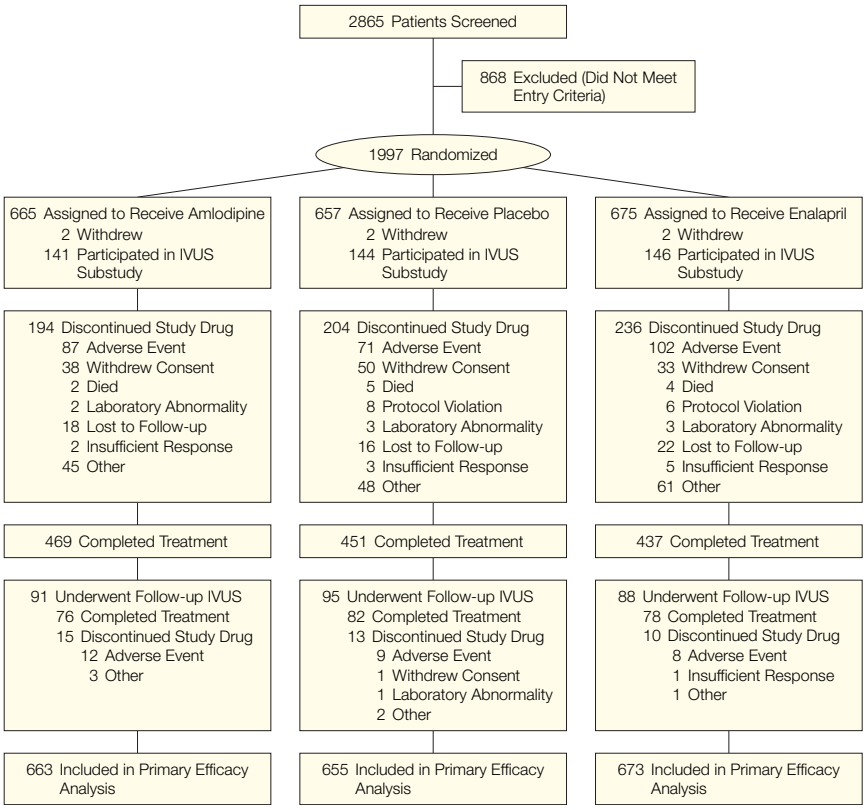
Statistical Methods

Baseline characteristics are reported as means (SDs) and percentages with *P* values calculated by 1-way analysis of variance (ANOVA) or χ^2 test. Data were analyzed according to patients' treatment assignments regardless of their subsequent medications (intent-to-treat analysis). The log-rank test and Cox proportional hazards model were used for the three 2-treatment comparisons (amlodipine vs placebo, enalapril vs placebo, and amlodipine vs enalapril).

The IVUS results are reported as means (SDs). IVUS efficacy analysis was tested using analysis of covariance (ANCOVA), adjusting for baseline values and randomization strata as covariates. To further describe the bivariate relationship between blood pressure and IVUS progression rates, the locally weighted scatterplot smoothing (LOWESS) technique was used.[10] This technique is designed to produce a smooth fit to the data that also reduces the influence of extreme outliers. Analyses were performed using SAS version 8.2 (SAS Institute Inc, Cary, NC). Statistical significance was set a priori at $P<.05$.

The study was originally powered at 90% for a sample size of 3000 patients. However, enrollment progressed slowly following the publication of a clinical trial suggesting a benefit for routine administration of ACE inhibitors to high-risk patients.[4] The data and safety monitoring board observed a greater than anticipated rate of accumulation of events and recommended that the steering committee reduce the sample size to 2000 patients and power to 80%. The amended protocol assumed a dropout rate lower than 1% and an incidence rate of adverse outcomes after 24 months of 0.229 for placebo and 0.167 for amlodopine. Using the log-rank test, a sample size of 672 randomized patients per treatment group was specified to provide 80% power to detect a difference between the groups.

Figure 1. Flow of Patients Through the Study



IVUS indicates intravascular ultrasound.

RESULTS

Baseline Characteristics

Between April 1999 and March 2004, 1997 patients, aged 32 to 82 years, were randomized and 1856 completed the protocol (1991 included in the efficacy analysis). The placebo group included 655 participants, the enalapril group 673, and the amlodipine group 663. Of the 1991 participants in CAMELOT, 274 completed the IVUS substudy: 95 in the placebo group, 88 in the enalapril group, and 91 in the amlodipine group. The numbers of patients screened, randomized, and reasons for discontinuation are reported in FIGURE 1. The baseline characteristics of patients included in efficacy analyses are reported in TABLE 1. There were no clinically meaningful differences in characteristics between treatment groups.

Treatments and Blood Pressure Changes

Table 1 also shows the treatments and concomitant medications for patients in the 3 treatment groups. Crossover rates were low with 7.4% of amlodipine patients receiving an angiotensin-converting enzyme (ACE) inhibitor, 1.7% receiving an angiotensin II receptor blocker (ARB), and 6.1% of enalapril patients receiving a calcium channel blocker. More patients in the placebo group received a calcium channel blocker, ACE inhibitor, or ARB.

FIGURE 2 illustrates the mean systolic and diastolic blood pressures for the 3 treatment groups. Mean sitting blood pressure at baseline averaged 128.9/77.6 mm Hg in the placebo group, 128.9/77.2 mm Hg in the enalapril group, and 129.5/77.7 mm Hg in

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the amlodipine group. The mean blood pressure during follow-up increased 0.7/0.6 mm Hg in the placebo group and was reduced 4.8/2.5 mm Hg in the amlodipine group and 4.9/2.4 mm Hg in the enalapril group ($P<.001$ for both vs placebo).

Primary Efficacy Measure

Amlodipine vs Placebo. Cardiovascular events occurred in 151 (23.1%) patients in the placebo group and 110 (16.6%) in the amlodipine group. TABLE 2 illustrates the point estimates and 95% confidence intervals (CIs) for the primary end point, individual components of this end point, and secondary end points. The primary efficacy measure was reduced in the amlodipine group compared with placebo, a hazard ratio (HR) of 0.69 (95% CI, 0.54-0.88, $P=.003$). The most frequent component of the primary end point, coronary revascularization, was reduced in the amlodipine group from 15.7% to 11.8% (HR, 0.73; 95% CI, 0.54-0.98, $P=.03$). Hospitalization for angina was reduced in the amlodipine group from 12.8% to 7.7% (HR, 0.58; 95% CI, 0.41-0.82, $P=.002$). FIGURE 3 illustrates the cumulative event rates for the primary composite end point for all 3 treatment groups.

Amlodipine vs Enalapril. Table 2 illustrates the comparisons between amlodipine and enalapril. In comparison with enalapril, the primary end point was reduced in the amlodipine group, from 20.2% to 16.6% (HR, 0.81; 95% CI, 0.63-1.04, $P=.10$). For components of the primary end point, only the rate of hospitalization for angina showed a statistically significant difference between amlodipine and enalapril (HR, 0.59; 95% CI, 0.42-0.84, $P=.003$). A trend toward fewer episodes of revascularization in patients undergoing intervention at baseline was observed (HR, 0.66; 95% CI, 0.40-1.06, $P=.09$).

Enalapril vs Placebo. Table 2 also illustrates the comparisons of enalapril with placebo. Cardiovascular events were reduced from 23.1% to 20.2% of patients in the enalapril treatment group (HR, 0.85; 95% CI, 0.67-1.07, $P=.16$). Individual components of the primary end point and secondary end points generally showed fewer events with enalapril treatment, but none of the comparisons reached statistical significance.

Table 1. Baseline Characteristics, Treatments, and Concomitant Medications

Baseline Characteristics	No. (%) of Patients			*P* Value*
	Amlodipine (n = 663)	Placebo (n = 655)	Enalapril (n = 673)	
Age, mean (SD), y	57.3 (9.7)	57.2 (9.5)	58.5 (9.9)	.02
Men	506 (76.3)	478 (73.0)	484 (71.9)	.16
White race	593 (89.4)	583 (89.0)	601 (89.3)	.97
Weight, mean (SD), kg	89.7 (18.3)	88.4 (16.4)	88.5 (18.4)	.31
Body mass index, mean (SD)†	29.9 (5.5)	29.7 (5.0)	29.7 (5.5)	.72
Low-density lipoprotein cholesterol, mean (SD), mg/dL	104 (32)	100 (32)	101 (31)	.04
Blood pressure, mean (SD), mm Hg				
Systolic	129.5 (15.5)	128.9 (15.8)	128.9 (16.3)	.76
Diastolic	77.7 (9.1)	77.6 (8.9)	77.2 (9.4)	.54
Medical history				
Hypertension	407 (61.4)	395 (60.3)	402 (59.7)	.82
Stroke	24 (3.6)	27 (4.1)	30 (4.5)	.74
Diabetes	115 (17.3)	130 (19.8)	118 (17.5)	.42
Class 4 angina‡	54 (8.1)	65 (9.9)	56 (8.3)	.45
Vessel disease§				
1	203 (30.6)	185 (28.2)	187 (27.8)	.47
2	217 (32.7)	223 (34.1)	243 (36.1)	.42
3	230 (34.7)	239 (36.5)	234 (34.8)	.74
Percutaneous intervention	173 (26.1)	199 (30.4)	192 (28.5)	.22
Coronary artery bypass graft surgery	54 (8.0)	54 (8.2)	46 (6.8)	.59
Myocardial infarction	248 (37.4)	247 (37.7)	271 (40.3)	.50
Current smoker	178 (27.0)	182 (27.9)	166 (24.8)	.41
Treatment received				
Titrated to full target dosage	575 (86.7)	588 (89.8)	567 (84.3)	.01
Dose received, mean (SD), mg	8.6 (2.0)	NA	17.4 (3.7)	NA
Completed trial	619 (93.4)	614 (93.7)	622 (92.4)	.62
Discontinued study medication	194 (29.3)	204 (31.1)	236 (35.1)	.07
Concomitant medications				
Statin	551 (83.1)	552 (84.3)	550 (81.7)	.46
Diuretic	213 (32.1)	219 (33.4)	180 (26.8)	.02
β-Blocker	492 (74.2)	516 (78.8)	503 (74.7)	.11
Aspirin	626 (94.4)	625 (95.4)	637 (94.7)	.69
Angiotensin-converting enzyme inhibitor	49 (7.4)	84 (12.8)	47 (7.0)	<.001
Angiotensin receptor blocker	11 (1.7)	15 (2.3)	11 (1.6)	.61
Calcium channel blocker	33 (5.0)	79 (12.1)	41 (6.1)	<.001

Abbreviation: NA, not applicable.
SI conversion factor: to convert cholesterol to mmol/L, multiply values by 0.0259.
*Calculated by analysis of variance or χ^2 test.
†Calculated as weight in kilograms divided by the square of height in meters.
‡Canadian Cardiovascular Society class 4 (angina at any level of physical exertion).
§Number of vessels with at least 1 stenosis >20% by visual estimation

Subgroup Analyses

The outcomes for prespecified subgroups for the primary end point comparing amlodipine with placebo are reported in FIGURE 4. Most point estimates showed similar HRs. There was no statistical heterogeneity among subgroups.

IVUS Results

TABLE 3 summarizes the IVUS results. The mean (SD) change in PAV was 0.5% (3.9%) for amlodipine, 0.8% (3.7%) for enalapril, and 1.3% (4.4%)

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for placebo. Comparison of amlodipine with placebo showed a trend toward statistical significance ($P=.12$). Comparison of enalapril with placebo was not statistically significant ($P=.32$). In the prespecified subgroup with systolic blood pressure greater than the mean, the amlodipine group showed significantly slower progression (0.2% [3.9%]) compared with placebo (2.3% [4.7%]) ($P=.02$). No treatment effects were evident in the subgroup with baseline blood pressure below the mean. Paired analyses comparing change from baseline in each of the treatment groups showed progression for placebo ($P=.001$), a trend toward progression for enalapril ($P=.08$), and absence of progression for amlodipine ($P=.31$).

FIGURE 5 shows the relationship (LOWESS plots) between IVUS-derived progression rates and change in systolic blood pressure for the combined drug treatment groups. Using linear regression analysis, adjusting for baseline blood pressures, the correlation between blood pressure reduction and progression rate was $r=0.19$, $P=.07$ in the amlodipine group. In the enalapril and placebo groups, there was no statistically significant correlation between blood pressure reduction and progression rate.

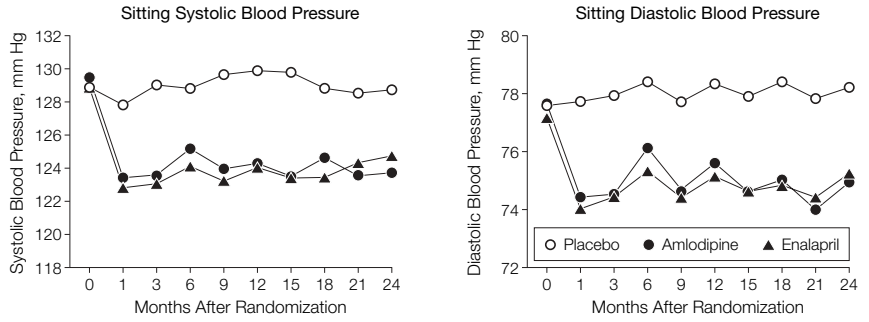
Exploratory (Post Hoc) Analyses

The event rates for the more restrictive end point of all-cause mortality, nonfatal myocardial infarction, and nonfatal stroke were also computed. The event rate was 3.3% in the amlodipine group, 4.7% in the placebo group, and 3.4% in the enalapril group. Comparison of amlodipine vs placebo revealed an HR of 0.70 (95% CI, 0.41-1.21; $P=.20$). Comparison of enalapril vs placebo revealed an HR of 0.71 (95% CI, 0.41-1.21; $P=.20$). Comparing the combined treatment groups (amlodipine or enalapril) vs placebo, the HR was 0.70 (95% CI, 0.45-1.11; $P=.13$). In the subgroup of patients with diabetes at baseline, the primary composite end point occurred in 19.1% of amlodipine-treated patients, 29.2% of placebo patients, and 29.7% of enalapril-treated patients (amlodipine vs enalapril: HR, 0.58; 95% CI, 0.34- 0.99 [$P=.04$]).

Adverse Events

Both active treatment regimens were well tolerated. Discontinuation from the study for treatment-emergent adverse events was low, averaging 0.4% and not

Figure 2. Mean Patient Blood Pressure at Baseline and During Treatment



Over time, the SDs for systolic blood pressure ranged from 13.3 to 15.5 mm Hg for the amlodipine group, 15.6 to 16.5 mm Hg for the placebo group, and 16.1 to 18.0 mm Hg for the enalapril group. The SDs for diastolic blood pressure ranged from 8.4 to 9.5 mm Hg for the amlodipine group, 8.9 to 9.8 mm Hg for the placebo group, and 9.4 to 10.5 mm Hg for the enalapril group.

Table 2. Cardiovascular Event Rates and Hazard Ratios

Outcomes	Cardiovascular Event Rates, No. (%)			Amlodipine vs Placebo		Amlodipine vs Enalapril		Enalapril vs Placebo	
	Amlodipine	Placebo	Enalapril	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
Primary end point									
Adverse cardiovascular events	110 (16.6)	151 (23.1)	136 (20.2)	0.69 (0.54-0.88)	.003	0.81 (0.63-1.04)	.10	0.85 (0.67-1.07)	.16
Individual components									
Coronary revascularization	78 (11.8)	103 (15.7)	95 (14.1)	0.73 (0.54-0.98)	.03	0.84 (0.62-1.13)	.24	0.86 (0.65-1.14)	.30
Hospitalization for angina	51 (7.7)	84 (12.8)	86 (12.8)	0.58 (0.41-0.82)	.002	0.59 (0.42-0.84)	.003	0.98 (0.72-1.32)	.87
Nonfatal MI	14 (2.1)	19 (2.9)	11 (1.6)	0.73 (0.37-1.46)	.37	1.32 (0.60-2.90)	.49	0.55 (0.26-1.15)	.11
Stroke or TIA	6 (0.9)	12 (1.8)	8 (1.2)	0.50 (0.19-1.32)	.15	0.76 (0.26-2.20)	.61	0.66 (0.27-1.62)	.36
Cardiovascular death	5 (0.8)	2 (0.3)	5 (0.7)	2.46 (0.48-12.7)	.27	1.07 (0.31-3.70)	.91	2.33 (0.45-12.1)	.30
Hospitalization for CHF	3 (0.5)	5 (0.8)	4 (0.6)	0.59 (0.14-2.47)	.46	0.78 (0.17-3.47)	.74	0.78 (0.21-2.90)	.71
Resuscitated cardiac arrest	0	4 (0.6)	1 (0.1)	NA	.04	NA	.31	0.24 (0.03-2.15)	.17
New-onset peripheral vascular disease	5 (0.8)	2 (0.3)	8 (1.2)	2.6 (0.50-13.4)	.24	0.63 (0.21-1.93)	.41	3.91 (0.83-18.4)	.06
Secondary end points									
Revascularization after baseline PCI	27 (4.1)	52 (7.9)	42 (6.2)	0.49 (0.31-0.78)	.002	0.66 (0.40-1.06)	.09	0.75 (0.50-1.13)	.17
All-cause mortality	7 (1.1)	6 (0.9)	8 (1.2)	1.14 (0.38-3.40)	.82	0.92 (0.33-2.53)	.87	1.26 (0.44-3.65)	.67

Abbreviations: CHF, congestive heart failure; CI, confidence interval; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

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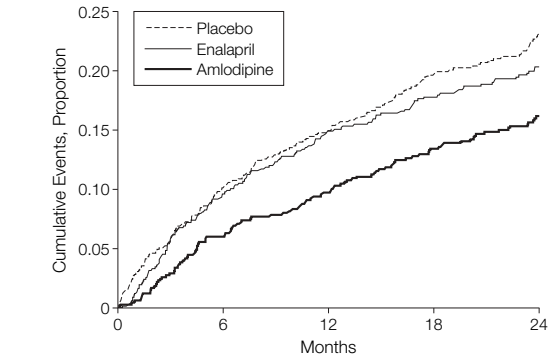
statistically different between the 3 treatment groups. Discontinuations of study drug for adverse events occurred in 13% of patients (Figure 1). Investigators reported hypotension in 3.3% of amlodipine-treated patients, 3.2% of placebo patients, and 9.5% of enalapril-treated patients. Peripheral edema occurred in 32.4% of amlodipine-treated patients, 9.6% of placebo patients, and 9.5% of enalapril-treated patients. Amlodipine was discontinued for edema in 5.0% of patients. Cough occurred in 5.1% of amlodipine-treated patients, 5.8% of placebo patients, and 12.5% of enalapril-treated patients. Enalapril was discontinued for cough in 3.9% of patients.

COMMENT

Recent studies have demonstrated benefits for both ACE inhibitors and calcium channel blockers in patients with established CAD and relatively normal blood pressures.[3-5] However, the optimal strategy for administration of these agents to patients with CAD has not been established. Most large hypertension trials restricted enrollment to patients with blood pressures higher than 140/90 mm Hg, and few trials studied patients with angiographically documented CAD.[1-3] Strong epidemiological data suggest that the lowest cardiovascular event rates occur in patients with systolic blood pressures much lower than the current treatment guidelines.[7,11] The CAMELOT trial was designed to determine whether either or both of these 2 therapeutic approaches would reduce adverse cardiovascular events in patients with CAD and a "normal" blood pressure by current standards.

The results of this study showed a relatively large treatment effect for the primary efficacy measure. For patients with a baseline systolic blood pressure averaging only 129/78 mm Hg, amlodipine reduced blood pressure an average of 5/3 mm Hg and produced a 31% relative reduction (6.5% absolute reduction) in cardiovascular events ($P = .003$). The number needed to treat for amlodipine is 16, ie, for every 16 patients who receive amlodipine, there will be on average 1 adverse cardiovascular event avoided during the 2-year period compared with patients who receive placebo. The most frequent com-

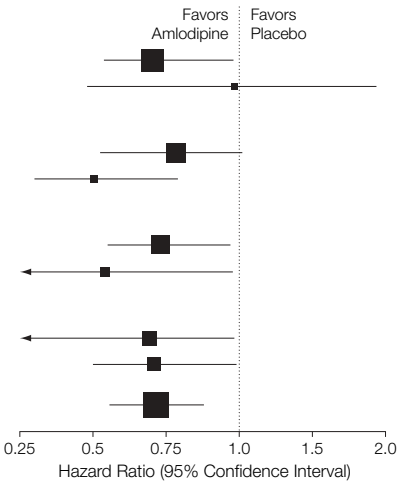
Figure 3. Cumulative Event Rates for All 3 Treatment Groups



No. at Risk					
Placebo	655	588	558	525	488
Enalapril	673	608	572	553	529
Amlodipine	663	623	599	574	535

Figure 4. Adverse Cardiovascular Events in Amlodipine vs Placebo Groups, by Subgroup

	2-Year Event Rates, No./Total (%)			
Lipid-Lowering Therapy	Amlodipine	Placebo	*P* Value	Relative Risk Reduction, %
Treated With Statin	93/551 (16.9)	135/552 (24.5)	.002	33.9
Not Treated With Statin	17/112 (15.2)	16/103 (15.5)	.91	4.1
Age, y				
<65	84/487 (17.2)	109/498 (21.9)	.07	22.9
≥65	26/176 (14.8)	42/157 (26.8)	.006	49.3
Sex				
Male	88/506 (17.4)	110/478 (23.0)	.03	26.8
Female	22/157 (14.0)	41/177 (23.2)	.03	42.8
Sitting Systolic Blood Pressure				
≤Mean	51/340 (15.0)	77/359 (21.4)	.03	32.2
>Mean	59/323 (18.3)	73/295 (24.7)	.04	29.6
All Patients	110/663 (16.6)	151/655 (23.1)	.003	30.9



Box sizes indicate proportion of the total study population (ie, smaller boxes have fewer patients relative to other subgroups).

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Table 3. Intravascular Ultrasound (IVUS) Results

	Percent Atheroma Volume, Mean (SD)			*P* Value*		
	Amlodipine (n = 91)	Placebo (n = 95)	Enalapril (n = 88)	Amlodipine vs Placebo	Enalapril vs Amlodipine	Enalapril vs Placebo
All patients completing IVUS						
Baseline	39.9 (10.5)	42.1 (9.3)	41.6 (9.8)	.14	.25	.75
Follow-up	40.4 (10.8)	43.4 (9.6)	42.4 (10.4)	.05	.20	.50
Change	0.5 (3.9)	1.3 (4.4)	0.8 (3.7)	.12	.59	.32
P value compared with baseline†	.31	.001	.08			
Patients with baseline systolic blood pressure >mean	**(n = 47)**	**(n = 49)**	**(n = 40)**			
Baseline	41.6 (10.3)	42.0 (10.3)	43.7 (10.3)	.82	.34	.46
Follow-up	41.8 (11.1)	44.3 (10.3)	44.5 (11.3)	.25	.25	.94
Change	0.2 (3.9)	2.3 (4.7)	0.8 (3.7)	.02	.47	.12
P value compared with baseline†	.76	<.001	.20			

**P* value by ANCOVA (adjusting for randomization stratum and baseline values as covariates).
†*P* value for change from baseline from least squares mean using the same ANCOVA model. Since there were only 5 to 7 patients per treatment group in the stent stratum, the stent and non-stent intervention groups were combined into a stratum with coronary intervention for the ANCOVA model.

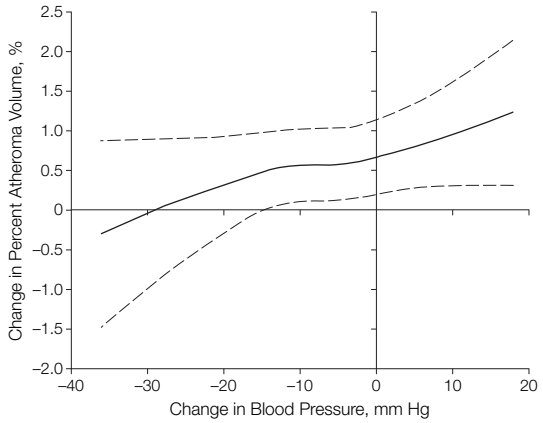
ponent of the primary end point, need for revascularization, was reduced by 27.4% (absolute reduction, 3.9%). Amlodipine treatment reduced hospitalization for angina by 42.2% (absolute reduction, 4.1%), nonfatal myocardial infarction by 26% (absolute reduction, 0.8%), and stroke or TIA by 50.4% (absolute reduction, 0.9%) (Table 2). Importantly, the improved clinical outcome was observed in the setting of optimal treatment of lipids (a mean baseline low-density lipoprotein cholesterol level of approximately 100 mg/dL [2.59 mmol/L]) and very high use of concomitant therapies such as aspirin (95%), statins (83%), and β-blockers (76%) (Table 1).

Enalapril treatment also reduced blood pressure by an average of 5/2 mm Hg. However, the observed 15.3% relative reduction (2.9% absolute reduction) in events was not statistically significant. None of individual components of the composite end point reached statistical significance; however, most event rates (Table 2) showed directional changes favoring enalapril treatment compared with placebo.

The mechanism of action of amlodipine in reducing events in patients with CAD remains uncertain. Two mechanisms seem likely. Since the most frequent component of the composite outcome was coronary revascularization, the anti-ischemic properties of amlodipine may have played an important role. Amlodipine is approved for treatment of angina.[12] Conceivably, a reduction in ischemic chest pain may have prevented hospitalization and subsequent revascularization procedures. Although enalapril produced similar blood pressure reductions, it is not approved for treatment of angina, which may explain its smaller effect on the primary end point. Alternatively, blood pressure reduction may have contributed to the observed benefits. Supporting the importance of antihypertensive effects is the observation of a relative risk reduction similar to the primary outcome for the composite of all-cause mortality, myocardial infarction, and stroke—end points not likely driven by antianginal efficacy. Furthermore, in the IVUS substudy, for patients with systolic blood pressures greater than the mean, amlodipine treatment significantly slowed atherosclerosis progression. A continuous relationship between reductions in blood pressure and atherosclerotic progression was observed in the LOWESS plot for the combined amlodipine and enalapril treatment groups.

The blood pressures in the current trial are, to our knowledge, the lowest ever studied in a major trial of antihy-

Figure 5. LOWESS Plot of Change in Percent Atheroma Volume vs Change in Blood Pressure in the Combined Drug Treatment Groups



The solid line represents the continuous relationship, surrounded by the dashed lines representing 95% confidence intervals. LOWESS indicates locally weighted scatterplot smoothing.

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pertensive drug therapy, averaging only 124 mm Hg during active treatment. The 2 trials using ACE inhibitors in patients with vascular disease studied patients with initial blood pressure values approximately 10 mm Hg higher than those in the current study.[4,5] In CAMELOT, although initial blood pressures appeared "normal," a 5/3-mm Hg decrease in blood pressure during amlodipine treatment was accompanied by a 31% relative reduction in morbidity. Although we cannot directly attribute the observed reduction in cardiovascular events to blood pressure reduction, these findings suggest the possibility that current target levels for blood pressure are too high for patients with established CAD. Our findings support the hypothesis that, even within the normal range, blood pressure represents a continuous risk factor for adverse cardiovascular outcomes. Although we consider the current findings important, we acknowledge that our findings are insufficient to recommend routine administration of antihypertensive agents to all "normotensive" patients with CAD without further confirmatory trials.

The IVUS substudy provides useful insights into potential mechanisms of benefit of antihypertensive treatments in a CAD population (Table 2). A trend toward reduced progression was evident for the amlodipine group compared with placebo ($P=.12$). However, in the subgroup with baseline blood pressures above the mean, significant reduction in progression was observed in the amlodipine group compared with placebo ($P=.02$). Furthermore, paired analysis of each regimen compared with baseline revealed progression in the placebo group ($P<.001$) and no progression in either the amlodipine or enalapril treatment groups (Table 3). The LOWESS plot shows a continuous relationship between reduction in blood pressure and IVUS-derived progression rates (Figure 5). Linear regression analysis also provides evidence of a relationship for the amlodipine treatment group. Although not definitive, the current study provides the first clinical trial evidence that reduction in blood pressure may decrease progression of coronary atherosclerosis.

The reduction in clinical events with amlodipine, but not enalapril, will be surprising to many. The value of ACE inhibitors in patients with CAD has received considerable attention following publication of 2 trials showing benefits in patients with evidence of vascular disease.[4,5] Both sets of investigators concluded that the benefits observed were unlikely due to antihypertensive effects of the tested agents, ramipiril and perindopril. However, neither trial included a treatment group assigned a non–ACE inhibitor antihypertensive agent. Accordingly, it was difficult to assess whether the apparent benefits of ACE inhibition were drug-specific or merely a reflection of the impact of blood pressure reduction. The CAMELOT study deliberately included both an ACE inhibitor group and calcium channel blocker group to further elucidate the relative benefits of these 2 therapeutic strategies in normotensive patients with CAD. It should be recognized that post hoc analysis using the more restrictive "hard" combined end point of death, myocardial infarction, and stroke showed comparable reductions using either active treatment.

The current study is consistent with other recent clinical trials that failed to show superior outcomes for antihypertensive agents that modulate the renin angiotensin system. The Antihypertensive and Lipid Lowering to Prevent Heart Attack Trial (ALLHAT) showed similar event reduction with lisinopril, diuretic, and amlodipine therapy.[13] The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) study showed smaller reduction in blood pressure and less decrease in early events for valsartan compared with amlodipine.[14]

However, unlike VALUE and ALLHAT, the current study observed nearly identical blood pressure reductions in the ACE inhibitor and amlodipine groups. Amlodipine has a 50-hour half-life, resulting in nearly constant blood pressure reduction, whereas enalapril has an 11-hour half-life.[15] The current study measured blood pressure during the daytime clinic visits and may have underestimated nighttime and early morning differences. Since many coronary events occur in the early morning hours, just prior to awakening, the continuous effects of amlodipine may have proven advantageous. It is also possible that twice-daily administration of enalapril might have improved outcomes in this treatment group, resulting in similar benefits to amlodipine. A recent study of sustained-release nifedipine failed to show similar benefits.[16] However, amlodipine has additional biological effects not mediated through blood pressure reduction, including antioxidant activity, inhibition of smooth muscle cell proliferation, and enhancement in endothelial nitric oxide production.[17] Some of these pleiotropic effects are not shared with all other calcium channel blockers.[17]

We are cognizant of the limitations of the current study. The sample size, approximately 2000 patients, was modest and the CIs around the point estimates for event reductions are relatively large. The application of an extended composite end point, rather than the narrower end point of cardiovascular death, nonfatal myocardial infarction, and stroke, is a potential weakness. However, in recent years, addition of hospitalization for angina and/or revascularization to the composite end point has become increasingly common.[6,18] There is a reasonable rationale for using a broader end point. Hospitalization for chest pain and revascularization are undesirable outcomes for patients and consume substantial health care resources. Because the current study planned to enroll patients with "normal" blood pressures and appropriate concomitant therapies, use of a narrow end point would have required a prohibitively large sample size and longer treatment exposure. Nonetheless, clinical trials are always more convincing when pow-

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ered for the traditional narrower end point of death, myocardial infarction, and stroke.

Despite these limitations, the current study provides important new findings regarding the administration of antihypertensive agents to patients with CAD and a "normal" blood pressure. In patients with CAD treated with a "standard of care" regimen including high rates of statin and aspirin use, addition of amlodipine for 24 months resulted in a 31% relative reduction and a 5.6% absolute reduction in adverse cardiovascular outcomes. In the amlodipine treatment group, the IVUS substudy provides evidence of a relationship between the magnitude of blood pressure reduction and the rate of disease progression. These results suggest that the optimal blood pressure range for patients with CAD may be substantially lower than indicated by current guidelines. Accordingly, larger and perhaps longer-term studies of antihypertensive therapies in patients with CAD and a "normal" blood pressure are essential to further explore these potential benefits.

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*Indicates IVUS site.

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