Effect of Amlodipine on the Progression of Atherosclerosis and the Occurrence of Clinical Events

Bertram Pitt, MD; Robert P. Byington, PhD; Curt D. Furberg, MD, PhD; Donald B. Hunninghake, MD; G.B. John Mancini, MD; Michael E. Miller, PhD; Ward Riley, PhD; for the PREVENT Investigators*

**Background**—The results of angiographic studies have suggested that calcium channel–blocking agents may prevent new coronary lesion formation, the progression of minimal lesions, or both. This could be important in view of data that suggest acute coronary events are often due to plaque rupture of minimal lesions rather than to the progression of advanced lesions. These findings were, however, based on retrospective analyses and should be viewed as hypothesis generating.

Amlodipine besylate (Norvasc) is a long-acting dihydropyridine calcium channel–blocking agent that is lipophilic, has antioxidant effects, and prevents experimental atherosclerosis. We postulated that amlodipine would alter the progression of early coronary atherosclerosis in 825 patients with angiographically documented coronary artery disease. The primary outcome was the average 36-month angiographic change in mean minimal diameters of segments with a baseline diameter stenosis of 30%. A secondary hypothesis was whether amlodipine would reduce the rate of atherosclerosis in the carotid arteries as assessed with B-mode ultrasonography, which measured intimal-medial thicknesses (IMT). The rates of clinical events were also monitored. The placebo and amlodipine groups had nearly identical average 36-month reductions in the minimal diameter: 0.084 versus 0.095 mm, respectively (P=0.38). In contrast, amlodipine had a significant effect in slowing the 36-month progression of carotid artery atherosclerosis: the placebo group experienced a 0.033-mm increase in IMT, whereas there was a 0.0126-mm decrease in the amlodipine group (P=0.007). There was no treatment difference in the rates of all-cause mortality or major cardiovascular events, although amlodipine use was associated with fewer cases of unstable angina and coronary revascularization.

**Conclusions**—Amlodipine has no demonstrable effect on angiographic progression of coronary atherosclerosis or the risk of major cardiovascular events but is associated with fewer hospitalizations for unstable angina and revascularization.

Amlodipine ■ atherosclerosis ■ angiography ■ ultrasonics ■ trials ■ angina ■ revascularization

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**Key Words:** amlodipine ■ atherosclerosis ■ angiography ■ ultrasonics ■ trials ■ angina ■ revascularization

**A**ngiographic studies suggest that calcium channel–blocking agents prevent new coronary artery lesion formation, the progression of minimal coronary lesions, or both. This could be important in view of data that suggest acute coronary events are often due to plaque rupture of minimal lesions rather than to the progression of advanced lesions. These findings were, however, based on retrospective analyses and should be viewed as hypothesis generating.

Amlodipine besylate (Norvasc) is a long-acting dihydropyridine calcium channel–blocking agent that is lipophilic, has antioxidant effects, and prevents experimental atherosclerosis. We postulated that amlodipine would alter the progression of coronary and carotid artery atherosclerosis and therefore reduce the risk of events without the major adverse clinical effects found in previous studies of dihydropyridine calcium channel–blocking agents. This report describes the results of the Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT).

**Methods**

**General Design Features**

The design features have been previously reported and are summarized here. PREVENT was a multicenter, randomized, placebo-controlled, double-masked clinical trial of 825 patients who had angiographic evidence of coronary artery disease. The objectives were to evaluate the effect of amlodipine in slowing the 3-year progression of early coronary atherosclerotic lesions as well as the progression of intimal-medial thickness (IMT) in the carotid arteries of a subset of 377 patients. Men and women (30 to 80 years old) were randomized if there was angiographic evidence of 1 focal coronary lesion of ≥30% diameter stenosis (nonintervened and noninfarcted) and the presence of ≥1 lesion with a 5% to 20% stenosis (judged qualitatively) that was not in a vessel with a ≥60% lesion. Other eligibility criteria included diastolic blood pressure of...
<95 mm Hg, total cholesterol of <325 mg/dL, and fasting blood glucose of <200 mg/dL. Randomization was stratified according to clinical center and history of PTCA.

Study medication was initiated at 5 mg QD and increased to 10 mg QD after 2 weeks if tolerated. The final study angiogram was scheduled 36 months after randomization, 7 to 10 days after the study medication was stopped. If a patient had a cardiac procedure performed during follow-up, an “interim” angiogram obtained before the procedure could serve as the final film if a 36-month film could not be obtained and if the interim film occurred no earlier than 35 months after randomization.

Angiographic Methods and Outcomes

The primary objective was to determine whether amlodipine would reduce the progression of early atherosclerotic segments as measured on the basis of a change in mean minimal diameter with quantitative coronary angiography (QCA).9,10 Atherosclerotic segments were defined as coronary segments with a diameter stenosis of ≥30% at baseline. Up to 12 coronary segments were used in the analysis of disease progression.6 Vessels that underwent a procedure at or before baseline were excluded from the analyses. The baseline and follow-up films were centrally read pairwise by a certified reader who was blinded to treatment assignment and the temporal sequencing of films.

Ultrasonographic Methods and Outcomes

A secondary hypothesis tested whether amlodipine reduced the progression of atherosclerosis in the carotid arteries as assessed with B-mode ultrasonography. Progression was based on the mean of the 3-year regression slopes of the maximum IMT measurements estimated in each of the 12 separate wall segments (near and far walls of the common carotid, bifurcation, and internal carotid arteries, on the right and left sides of the neck).11 This outcome required fewer participants (377) than the angiographic outcome (825). There were 2 ultrasound examinations at baseline and 1 every 6 months thereafter for 36 months. Certified readers who were blinded to treatment assignment centrally read videotapes.

Monitoring for Clinical Events and Adverse Experiences

The prespecified clinical events were all-cause mortality and the occurrence of major fatal/nonfatal vascular events or procedures. Death, myocardial infarction, stroke, hospitalized heart failure, and hospitalized episodes of unstable angina were classified by an external events classification committee blinded to treatment assignment with the use of definitions that were used in other studies.12–14 Confirmation of unstable angina required hospitalization for typical chest pain and either evidence of myocardial ischemia (ECG or stress test evidence, or new angiographic findings of disease) or an indication that this pain was similar to that of previously documented evidence of ischemia. The PREVENT adverse experience database was retrospectively reviewed for terms that suggest cancer or bleeding. All suspected cancers were classified by an external oncology committee. The a priori definition for an incident cancer was a new pathologically confirmed cancer diagnosed at least 1 year postrandomization.

Statistical Analyses

Analysis of the primary end point was performed with a mixed-effects ANCOVA model that accounted for correlation among segments measured within patients.15 Treatment effects are presented in terms of the mean difference and 95% CIs in 3-year change for both minimum diameter and percent diameter stenosis. In addition to treatment group assignment, the mixed-effects model included effects that represent segments, clinical centers, PTCA status at baseline, and random effects for participants. Secondary analyses of 3-year change in minimal diameter and percent diameter stenosis were performed within predefined subgroups after stratification of segments by baseline stenosis of 0%, >0% to ≤30%, >30% to 50%, >50%, and all segments. For analysis of all segments, baseline stenosis was included as a covariate. Correlation among segments was accounted for by fitting models to allow different variances for each segment and a common covariance between segments (heterogeneous compound symmetry). Segments having undergone revascularization during follow-up were excluded from analyses of 36-month angiograms.

The progression of atherosclerosis in the carotid arteries was measured on the basis of the slope of the maximum IMT measurements averaged over 12 separate wall segments as a function of time.11 For this analysis, a mixed-effects model was fit to the maximum IMT measured within each segment at each follow-up. In addition to including random intercepts and slopes for participants, this model contained fixed effects for clinic, treatment, segment, time, and a time × treatment interaction. Treatment effects are presented in terms of the mean difference and 95% CIs on the mean difference in 36-month change in maximal IMT. Analyses of time until the occurrence of clinical outcomes were carried out by log-rank statistics and proportional hazards models to adjust for covariates.16 For clinical outcomes, treatment effects are presented in terms of hazard ratios (HRs) and associated 95% CIs. Simple tests of proportions and means were conducted to evaluate treatment group differences in baseline characteristics. HRs and associated 95% CIs were used to estimate treatment group differences in the 36-month occurrence of adverse events, including cancer and bleeding episodes.

To protect against the increased probability of a type I error, tests of statistical significance were performed at the 0.05 level for the primary angiographic outcome and the overall ultrasonic analysis. Because the 5 clinical event outcomes were selected at least in part to address safety concerns,12–14 hypothesis tests were interpreted at the 0.05 level so potentially important differences would not be overlooked. In contrast, 95% CIs of treatment effects were calculated for all other secondary outcomes.

Results

There was good treatment group comparability of baseline characteristics (Table 1).

Angiographic Results

Evaluable follow-up angiograms were obtained from 82% (678 of 825) of the participants. There was no evidence that any baseline characteristic was distributed differentially between treatment groups. For the primary outcome measure (mean 3-year change in the minimum diameter in segments of ≥30% stenosis), the placebo and amlodipine groups had nearly identical average reductions in the minimal diameter: 0.084 versus 0.095 mm, respectively (P=0.38, Table 2). Amlodipine also failed to show any significant effect for each of the other angiographic outcomes.

Ultrasonographic Results

In contrast, amlodipine had a significant effect on the progression of carotid atherosclerosis (Table 3): the placebo participants had a 0.033-mm increase in IMT during 3-years of follow-up, and the amlodipine participants had a 0.013-mm decrease (P=0.007). When stratified according to carotid segment, the estimated 3-year changes in the common carotid were −0.046-mm regression for amlodipine versus +0.011-mm progression for placebo (95% CI on difference −0.090 to −0.024 mm).

Clinical Event Results

Table 4 presents the rates and Figure 1 presents the life-table curves for the major clinical events by treatment group. Vital status was unknown for 2 placebo and 4 amlodipine patients.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Amlodipine (n=417)</th>
<th>Placebo (n=408)</th>
<th>Overall (n=825)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>56.8</td>
<td>57.0</td>
<td>56.9 (range 30–78)</td>
</tr>
<tr>
<td>Women, %</td>
<td>20.1</td>
<td>19.6</td>
<td>19.9</td>
</tr>
<tr>
<td>White, %</td>
<td>88.3</td>
<td>89.2</td>
<td>88.7</td>
</tr>
<tr>
<td>Mean lipid values, mg/dL*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>217.3</td>
<td>217.4</td>
<td>217.3 (range 107–398)</td>
</tr>
<tr>
<td>Estimated LDL-C</td>
<td>140.7</td>
<td>139.3</td>
<td>140.0 (range 39–302†)</td>
</tr>
<tr>
<td>HDL-C, Men</td>
<td>44.3</td>
<td>43.5</td>
<td>43.9 (range 20–95)</td>
</tr>
<tr>
<td>HDL-C, Women</td>
<td>52.2</td>
<td>55.4</td>
<td>53.8 (range 29–104)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>189.3</td>
<td>188.5</td>
<td>188.9 (range 46–500†)</td>
</tr>
<tr>
<td>Mean blood pressure, mm Hg:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>128.8</td>
<td>130.0</td>
<td>129.4</td>
</tr>
<tr>
<td>Diastolic</td>
<td>78.8</td>
<td>78.9</td>
<td>78.8</td>
</tr>
<tr>
<td>Mean body mass index, kg/m²</td>
<td>28.1</td>
<td>27.9</td>
<td>28.0</td>
</tr>
<tr>
<td>Prior history, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>44.4</td>
<td>45.3</td>
<td>44.9</td>
</tr>
<tr>
<td>Stroke</td>
<td>3.1</td>
<td>2.9</td>
<td>3.0</td>
</tr>
<tr>
<td>Angina</td>
<td>67.9</td>
<td>69.4</td>
<td>68.6</td>
</tr>
<tr>
<td>Family history, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>29.5</td>
<td>34.3</td>
<td>31.9</td>
</tr>
<tr>
<td>Sudden death</td>
<td>14.4</td>
<td>15.7</td>
<td>15.0</td>
</tr>
<tr>
<td>History of cigarette smoking, %</td>
<td></td>
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<td></td>
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<tr>
<td>Current smoker</td>
<td>22.8</td>
<td>26.7</td>
<td>24.7</td>
</tr>
<tr>
<td>Past smoker</td>
<td>54.2</td>
<td>54.4</td>
<td>54.3</td>
</tr>
<tr>
<td>Never smoker</td>
<td>23.0</td>
<td>18.9</td>
<td>21.0</td>
</tr>
<tr>
<td>Medication use at 1st screening visit, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>33.1</td>
<td>34.6</td>
<td>33.8</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>8.2</td>
<td>10.0</td>
<td>9.1</td>
</tr>
<tr>
<td>Diuretic</td>
<td>11.5</td>
<td>12.0</td>
<td>11.8</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>60.0</td>
<td>65.7</td>
<td>62.8</td>
</tr>
<tr>
<td>Nitrates</td>
<td>64.5</td>
<td>63.1</td>
<td>63.8</td>
</tr>
<tr>
<td>Lipid-lowering agent</td>
<td>25.7</td>
<td>28.9</td>
<td>27.3</td>
</tr>
<tr>
<td>PTCA associated with qualifying angiogram, %</td>
<td>42.9</td>
<td>41.2</td>
<td>42.1</td>
</tr>
<tr>
<td>Clinic-defined angiographic disease (vessels &gt;30% stenosed), %‡</td>
<td>44.9</td>
<td>44.8</td>
<td>44.8</td>
</tr>
<tr>
<td>1-vessel disease</td>
<td>34.6</td>
<td>34.5</td>
<td>34.5</td>
</tr>
<tr>
<td>2-vessel disease</td>
<td>20.5</td>
<td>20.7</td>
<td>20.6</td>
</tr>
<tr>
<td>Mean minimum diameter, mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In 0–30% stenosed segments</td>
<td>2.468</td>
<td>2.443</td>
<td>2.456</td>
</tr>
<tr>
<td>In all segments combined</td>
<td>2.147</td>
<td>2.149</td>
<td>2.148</td>
</tr>
<tr>
<td>Mean percent diameter stenosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In 0–30% stenosed segments</td>
<td>15.326</td>
<td>15.465</td>
<td>15.390</td>
</tr>
<tr>
<td>In all segments combined</td>
<td>26.600</td>
<td>26.583</td>
<td>26.592</td>
</tr>
<tr>
<td>Mean maximum IMT from B-mode, mm</td>
<td></td>
<td></td>
<td>1.2586</td>
</tr>
</tbody>
</table>

*Averaged over 3 possible values per patient before randomization.
†Twenty-five participants with triglycerides >500 mg/dL are excluded (7 amlodipine, 18 placebo).
‡Vessels include left main, left anterior descending, diagonal, left circumflex, oblique, and right anterior descending arteries.
§Based on 678 baseline films read as part of baseline/follow-up paired readings.
||In subset of 373 participants.
Amlodipine had no effect on all-cause mortality. When fatal and nonfatal coronary and cerebrovascular events are combined, there were 23 amlodipine and 28 placebo participants who experienced an event (HR 0.82 [95% CI 0.47 to 1.42]). Amlodipine reduced the occurrence of the combination of hospitalized nonfatal congestive heart failure and unstable angina (61 amlodipine versus 88 placebo, HR 0.65 [0.48 to 0.93]), a difference primarily due to a reduction in the rate of unstable angina (60 versus 85, HR 0.67 [0.48 to 0.93]). Amlodipine also reduced coronary revascularizations (53 versus 86, HR 0.57 [0.41 to 0.81]) regardless of the use of β-blocker, nitrates, or lipid-lowering therapy. When the major and other events and procedures were combined, there were fewer events in the amlodipine group (86 versus 116, HR 0.69 [0.52 to 0.92]), mostly attributable to a difference in unstable angina and revascularization.

Table 5 presents adverse experiences for which there was a treatment group difference with a nominal P value of ≤0.10. Twenty-three confirmed incident cancers were reported during the second and third years of follow-up: 15 amlodipine and 8 placebo (HR 2.13 [0.90 to 5.21]). In the first year postrandomization, there were 7 and 4 cancers, respectively. This treatment difference is consistent with reports from observational studies that link calcium channel blockers to an increased risk of cancer during the long term, although other studies have not reported an association.7 There were 10 participants who were hospitalized for bleeding: 5 in each group. All were on their study medications within 3 days of the hospitalization, none were on an open-labeled calcium channel blocker, and 1 amlodipine patient was on warfarin. During follow-up, 40 amlodipine and 28 placebo participants reported at least 1 bleeding episode, mostly nosebleeds (HR 1.42 [0.88 to 2.30]), similar to the bleeding risk reported from larger observational studies.8

Other Follow-Up Results
Pill count compliance was 79% for amlodipine versus 83% for placebo. After 4 months of treatment, both systolic and diastolic blood pressures were lower in the amlodipine group. Mean changes in carotid mean maximum IMT are presented in Table 3.

### Table 2. Mean Changes in Angiographic Outcome Measures During 3 Years of Follow-Up by Treatment Group

<table>
<thead>
<tr>
<th>Mean±SEM Change*</th>
<th>95% CI for Treatment Group Difference in Mean Change</th>
<th>Amlodipine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean change in minimum diameter, mm</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All segments ≤30% diameter stenosis</td>
<td>1771/348</td>
<td>−0.095±0.009</td>
<td>1548/319</td>
</tr>
<tr>
<td>Segments stenosed &gt;30% and ≤50%</td>
<td>918/333</td>
<td>−0.040±0.012</td>
<td>818/296</td>
</tr>
<tr>
<td>Segments stenosed &gt;50%‡</td>
<td>242/155</td>
<td>0.085±0.025</td>
<td>221/139</td>
</tr>
<tr>
<td>Segments stenosed 0%‡</td>
<td>447/226</td>
<td>−0.080±0.017</td>
<td>373/195</td>
</tr>
<tr>
<td>Segments stenosed &gt;0% and ≤30%‡</td>
<td>1324/345</td>
<td>−0.098±0.009</td>
<td>1175/314</td>
</tr>
<tr>
<td>All segments‡</td>
<td>2931/354</td>
<td>−0.063±0.008</td>
<td>2587/324</td>
</tr>
<tr>
<td><strong>Mean change in percent stenosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All segments ≤30% diameter stenosis</td>
<td>1770/348</td>
<td>2.94±0.22</td>
<td>1548/319</td>
</tr>
<tr>
<td>Segments stenosed &gt;30% and ≤50%</td>
<td>918/333</td>
<td>0.18±0.39</td>
<td>818/296</td>
</tr>
<tr>
<td>Segments stenosed &gt;50%</td>
<td>241/155</td>
<td>−4.74±0.91</td>
<td>221/139</td>
</tr>
<tr>
<td>Segments stenosed 0%</td>
<td>447/226</td>
<td>2.79±0.37</td>
<td>373/195</td>
</tr>
<tr>
<td>Segments stenosed &gt;0% and ≤30%</td>
<td>1323/345</td>
<td>3.03±0.26</td>
<td>1175/314</td>
</tr>
<tr>
<td>All segments</td>
<td>2929/354</td>
<td>1.49±0.21</td>
<td>2587/324</td>
</tr>
</tbody>
</table>

*Adjusted for clinical center and angioplasty at baseline. **Prespecified primary outcome measure (P=0.38) †Prespecified secondary outcome measure (additional covariate=baseline diameter stenosis).

### Table 3. Mean Change in Carotid Mean Maximum IMT During 3 Years of Follow-Up by Treatment Group

<table>
<thead>
<tr>
<th>Mean±SEM Change, mm</th>
<th>95% CI for Treatment Group Difference in Mean Changes</th>
<th>Amlodipine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Over 12 walls†</strong></td>
<td>−0.0126±0.0120</td>
<td>0.0030±0.0120</td>
<td>−0.0789 to −0.0123</td>
</tr>
<tr>
<td><strong>Common carotid (4 walls)</strong></td>
<td>−0.0456±0.0120</td>
<td>0.0114±0.0120</td>
<td>−0.0903 to −0.0240</td>
</tr>
<tr>
<td><strong>Bifurcation (4 walls)</strong></td>
<td>0.0270±0.0222</td>
<td>0.0543±0.0222</td>
<td>−0.0888 to 0.0342</td>
</tr>
<tr>
<td><strong>Internal carotid (4 walls)</strong></td>
<td>−0.0123±0.0222</td>
<td>0.0408±0.0222</td>
<td>−0.1146 to 0.0081</td>
</tr>
</tbody>
</table>

*Adjusted for clinical center and carotid wall segment. †Prespecified secondary outcome (P=0.007).
Although the use of calcium channel blockers and ACE inhibitors was discouraged during follow-up, 91 amlodipine and 120 placebo patients were receiving a nonstudy calcium channel blocker for at least some portion of follow-up, and 32 amlodipine and 67 placebo group participants were receiving an ACE inhibitor. The use of diuretics was almost equal between treatment groups during follow-up: 111 amlodipine and 93 placebo. After the Scandinavian Simvastatin Survival Study (4S) results, an effort was made to get appropriate participants to use lipid-lowering agents. The use of statins increased from 27% at baseline (Table 1) to 52% for any use during the course of follow-up (50% amlodipine versus 54% placebo).

**Discussion**

These results fail to support the hypothesis that amlodipine altered the development or progression of minimal coronary artery lesions. There also was no effect of amlodipine on the progression of moderate or advanced coronary artery stenoses (Table 2).

In contrast, amlodipine had a significant effect on the progression of carotid artery atherosclerosis, as assessed with B-mode ultrasonography. One explanation for this discrepancy may be a difference in the sensitivity of B-mode ultrasonography and coronary angiography for the detection of early arterial disease. Experimental studies show that the growth of atherosclerotic lesions initially affects the vessel wall or external arterial diameter without encroachment on the lumen. Another explanation is that the blood pressure-lowering action of amlodipine: reduction in wall stress may have different effects on the carotid and coronary circulation. Regardless, the extent of carotid atherosclerosis as measured by B-mode ultrasonography is associated with increased risk of cardiac mortality and morbidity.

Amlodipine had no effect on the risk of all-cause mortality or major cardiovascular events (myocardial infarctions and strokes). However, the statistical power for the detection of a treatment difference in mortality and major morbidity rates was low because of the relatively low incidence rates (eg, 2%/y for myocardial infarction or death). Of possible importance is the finding that amlodipine significantly reduced the rates of unstable angina and coronary revascularization. An improvement in coronary vasmotor tone could be due to a direct effect on vascular smooth muscle or endothelial function. These reductions in hospitalization for angina pectoris and revascularization were seen in patients on a β-blocker, nitrate, or lipid-lowering agent. A reduction in the incidence of unstable angina pectoris could result in lower rates of coronary angiography and revascularization. These beneficial effects were not seen in previous angiographic trials with nifedipine or nicardipine in patients with stable coronary artery disease, even though these agents have proved antianginal effects, suggesting that amlodipine may have additional effects.

Of additional importance is the finding that the event curves for unstable angina pectoris and coronary revascularizations diverge early. Although lipid lowering with statins and ACE inhibition with ramipril have reduced total mortality rates, nonfatal myocardial infarction, and revascularizations in patients with stable coronary artery dis-

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**TABLE 4. Events and Procedures Occurring During 3 Years of Follow-Up by Treatment Group**

<table>
<thead>
<tr>
<th>Event</th>
<th>Amlodipine Group (n=417)</th>
<th>Placebo Group (n=408)</th>
<th>HR (Amlodipine/Placebo)</th>
<th>95% CI for HR</th>
<th>Life-Table P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Participants With Event</td>
<td>Annualized Rate per 100</td>
<td>No. of Participants With Event</td>
<td>Annualized Rate per 100</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>6</td>
<td>0.5</td>
<td>8</td>
<td>0.7</td>
<td>0.74</td>
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<tr>
<td>Major vascular events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal/nonfatal MI</td>
<td>19</td>
<td>1.5</td>
<td>20</td>
<td>1.6</td>
<td>0.94</td>
</tr>
<tr>
<td>Fatal/nonfatal stroke</td>
<td>5</td>
<td>0.4</td>
<td>5</td>
<td>0.4</td>
<td>0.99</td>
</tr>
<tr>
<td>Other fatal vascular events</td>
<td>0</td>
<td>0.0</td>
<td>4</td>
<td>0.3</td>
<td>...</td>
</tr>
<tr>
<td>Any major vascular event</td>
<td>23</td>
<td>1.8</td>
<td>28</td>
<td>2.3</td>
<td>0.82</td>
</tr>
<tr>
<td>Other documented nonfatal vascular events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
<td>0.1</td>
<td>5</td>
<td>0.4</td>
<td>0.20</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>60</td>
<td>4.8</td>
<td>85</td>
<td>6.9</td>
<td>0.67</td>
</tr>
<tr>
<td>Either event</td>
<td>61</td>
<td>4.9</td>
<td>88</td>
<td>7.2</td>
<td>0.65</td>
</tr>
<tr>
<td>Major vascular procedures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>17</td>
<td>1.4</td>
<td>29</td>
<td>2.4</td>
<td>0.57</td>
</tr>
<tr>
<td>Other major procedure†</td>
<td>40</td>
<td>3.2</td>
<td>67</td>
<td>5.5</td>
<td>0.56</td>
</tr>
<tr>
<td>Either major vascular procedure</td>
<td>53</td>
<td>4.2</td>
<td>86</td>
<td>7.0</td>
<td>0.57</td>
</tr>
<tr>
<td>Any major/documentured vascular event or procedure</td>
<td>86</td>
<td>6.9</td>
<td>116</td>
<td>9.5</td>
<td>0.69</td>
</tr>
</tbody>
</table>

*From proportional hazards models (P values presented only for prespecified composite event outcomes).
†Includes angioplasty, stenting, and arthrectomy.
‡Prespecified event of interest.
ease, there is a lag of 1 year before the event curves for these strategies diverge. The addition of amlodipine could produce an early benefit and further reduce revascularization and hospitalization for unstable angina. It may be hypothesized that this would allow statins or ACE inhibitors a chance to reduce “hard” ischemic events by altering the underlying pathophysiology of atherosclerosis, plaque rupture, or thrombosis and thereby possibly avoid coronary revascularization. Thus, amlodipine might further reduce the need for coronary revascularizations observed in previous randomized trials of medical therapy versus coronary angioplasty, such as Randomised Intervention Treatment of Angina (RITA-2) and Atorvastatin Versus Revascularization Treatment (AVERT). This strategy, however, requires prospective testing.

Appendix: PREVENT Participating Investigators and Institutions

Clinical Centers
David C. Booth, MD (University of Kentucky Medical Center); Anthony Chapekis, MD (Midwest Cardiology); Vivian Clark, MD (Henry Ford Hospital); Gilles Côté, MD (Montreal Heart Institute); Robert Feldman, MD (Mediquest Research Group); David Herrington, MD, MHS (Wake Forest University School of Medicine); Lyall A.J. Higginson, MD (University of Ottawa Heart Institute); Craig Hjemdahl-Monsen, MD (New York Medical College); Donald B. Humminghake, MD (University of Minnesota Hospital/Clinic); Glen J. Kowalchuk, MD (Carolina Medical Center); Stephen Mallon, MD (University of Miami School of Medicine); Michael Miller, MD (University of Maryland Hospital); K.B. Ramanathan, MD (University of Tennessee); Donald Ricci, MD (Vancouver Hospital/Health Sciences Center); David Waters, MD.
TABLE 5. Events Recorded in Adverse Experience Logs During 3 Years of Follow-Up by Treatment Group

<table>
<thead>
<tr>
<th>Specified Adverse Event</th>
<th>Amlodipine Group (n=417)</th>
<th>Placebo Group (n=408)</th>
<th>HR* (Amlodipine/Placebo)</th>
<th>95% CI for HR*</th>
<th>Risk Difference/100/y (Amlodipine—Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Participants With Event</td>
<td>Annualized Rate per 100</td>
<td>No. of Participants With Event</td>
<td>Annualized Rate per 100</td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>170</td>
<td>13.6</td>
<td>68</td>
<td>5.6</td>
<td>3.12</td>
</tr>
<tr>
<td>Vertigo</td>
<td>17</td>
<td>1.4</td>
<td>3</td>
<td>0.2</td>
<td>6.55</td>
</tr>
<tr>
<td>Constipation</td>
<td>19</td>
<td>1.5</td>
<td>9</td>
<td>0.7</td>
<td>2.11</td>
</tr>
<tr>
<td>Erythematous rash</td>
<td>13</td>
<td>1.0</td>
<td>5</td>
<td>0.4</td>
<td>2.57</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>10</td>
<td>0.8</td>
<td>3</td>
<td>0.2</td>
<td>3.29</td>
</tr>
<tr>
<td>Gout</td>
<td>4</td>
<td>0.3</td>
<td>10</td>
<td>0.8</td>
<td>0.29</td>
</tr>
<tr>
<td>Seborrhea</td>
<td>2</td>
<td>0.2</td>
<td>9</td>
<td>0.7</td>
<td>0.22</td>
</tr>
<tr>
<td>Asthenia</td>
<td>25</td>
<td>2.0</td>
<td>37</td>
<td>3.0</td>
<td>0.66</td>
</tr>
<tr>
<td>Headache</td>
<td>72</td>
<td>5.8</td>
<td>89</td>
<td>7.3</td>
<td>0.76</td>
</tr>
<tr>
<td>Coughing</td>
<td>43</td>
<td>3.4</td>
<td>63</td>
<td>5.1</td>
<td>0.67</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17</td>
<td>1.4</td>
<td>39</td>
<td>3.2</td>
<td>0.41</td>
</tr>
<tr>
<td>Chest pain, angina</td>
<td>202</td>
<td>16.1</td>
<td>222</td>
<td>18.1</td>
<td>0.82</td>
</tr>
</tbody>
</table>

Events with a monitoring P of ≤0.10 are presented here.

*From proportional hazards model.

(Hartford Hospital); Steven W. Werns, MD (University of Michigan Medical Center).

Steering Committee Cochairmen
Curt D. Furberg, MD, PhD (Wake Forest University School of Medicine); Bertram Pitt, MD (University of Michigan Medical Center).

Angiography Reading Center
G.B. John Mancini, MD (University of British Columbia).

Ultrasound Reading Center
Ward Riley, PhD (Wake Forest University School of Medicine).

Data Coordinating Center
Robert P. Byington, PhD, Michael E. Miller, PhD (Wake Forest University School of Medicine).

Central Laboratory
Smithkline Beecham Clinical Laboratories.

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References


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