Effects of Intensive Versus Moderate Lipid-Lowering Therapy on Myocardial Ischemia in Older Patients With Coronary Heart Disease

Results of the Study Assessing Goals in the Elderly (SAGE)

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Background—Clinical trials have demonstrated that, compared with placebo, intensive statin therapy reduces ischemia in patients with acute coronary syndromes and in patients with stable coronary artery disease. However, no studies to date have assessed intensive versus moderate statin therapy in older patients with stable coronary syndromes.

Methods and Results—A total of 893 ambulatory coronary artery disease patients (30% women) 65 to 85 years of age with ≥1 episode of myocardial ischemia that lasted ≥3 minutes during 48-hour ambulatory ECG at screening were randomized to atorvastatin 80 mg/d or pravastatin 40 mg/d and followed up for 12 months. The primary efficacy parameter (absolute change from baseline in total duration of ischemia at month 12) was significantly reduced in both groups at month 3 and month 12 (both \( P < 0.001 \) for each treatment group) with no significant difference between the treatment groups. Atorvastatin-treated patients experienced greater low-density lipoprotein cholesterol reductions than did pravastatin-treated patients, a trend toward fewer major acute cardiovascular events (hazard ratio, 0.71; 95% confidence interval, 0.46, 1.09; \( P = 0.114 \)), and a significantly greater reduction in all-cause death (hazard ratio, 0.33; 95% confidence interval, 0.13, 0.83; \( P = 0.014 \)).

Conclusions—Compared with moderate pravastatin therapy, intensive atorvastatin therapy was associated with reductions in cholesterol, major acute cardiovascular events, and death in addition to the reductions in ischemia observed with both therapies. The contrast between the therapies’ differing efficacy for major acute cardiovascular events and death and their nonsignificant difference in efficacy for reduction of ischemia suggests that low-density lipoprotein cholesterol-lowering thresholds for ischemia and major acute cardiovascular events may differ. The Study Assessing Goals in the Elderly (SAGE) demonstrates that older men and women with coronary artery disease benefit from intensive statin therapy.

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Key Words: atherosclerosis ■ electrocardiography ■ hypercholesterolemia ■ ischemia ■ statins

Atherosclerosis is a progressive disease and, consequently, coronary artery disease (CAD) is most prevalent in older persons. The risk of CAD events can be reduced by lowering low-density lipoprotein cholesterol (LDL-C), for which statins are the drug of choice. However, few trials have selectively evaluated lipid-lowering therapy with statins in older individuals.

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Transient myocardial ischemia occurs frequently in patients with extensive CAD.\(^1\) Stable CAD patients with ischemic episodes during routine daily activities have an increased risk of coronary events,\(^2,3\) with particularly high risk in older...
Efficacy Assessments

The primary efficacy parameter was the absolute change in the total duration of myocardial ischemia on 48-hour Holter monitor, normalized to 48 hours, from baseline to month 12. All Holter tests were analyzed in a blinded fashion by an experienced physician at Covance Central Diagnostics (Reno, Nev). Myocardial ischemia was defined as the period of ambulatory ECG monitoring during which ST amplitude was ≥100 μV (1 mm) below the baseline ST-segment level for ≥1 minute in ≥2 leads. The onset of each episode was defined as the time when the ST segment first deviated from baseline and the offset as the time when the ST segment returned to baseline. Ischemic burden was defined as the product of the maximum depth of ST-segment depression multiplied by the duration of the episode. A quality check of the Holter readings was conducted by an independent physician, and the comparisons were made, which yielded χ²=0.72 and Spearman correlation r=0.91 from the readings of 425 samples.

Secondary efficacy parameters included (1) the absolute change in the total duration of myocardial ischemia on 48-hour Holter monitor from baseline to month 3; (2) the percent change in the total duration of myocardial ischemia on 48-hour Holter monitor from baseline to month 3 and from baseline to month 12; (3) the absolute and percent change in the number of ischemic episodes on 48-hour Holter monitor from baseline to month 3 and from baseline to month 12; (4) the percent change in the ischemic burden on 48-hour Holter monitor from baseline to month 3 and from baseline to month 12; (5) the proportion of patients who were totally free of ischemia at month 3 and month 12; and (6) the percent change from baseline to month 3 and from baseline to month 12 in the levels of total cholesterol, LDL-C, high-density lipoprotein cholesterol (HDL-C), triglycerides, and apolipoprotein B.

Additional prespecified evaluations included the incidence and time to major acute cardiovascular events (MACE). MACE were defined as cardiovascular deaths, nonfatal myocardial infarction, resuscitated cardiac arrest, coronary revascularization procedures, fatal and nonfatal stroke, and hospitalization for unstable angina. The incidence of all-cause death was assessed post hoc. Cardiovascular events and all-cause death were adjudicated by an external cardiac adjudication committee.

Statistical Methods

An analysis of covariance (ANCOVA) model that included treatment as a fixed main effect, with the baseline total duration of ischemia as a covariate, was used to analyze the primary efficacy parameter on the modified intent-to-treat population, which was defined as all patients who took ≥1 dose of study drug and had evaluable Holter results at both baseline and follow-up. A similar ANCOVA model was used for secondary efficacy parameters with continuous variables. A χ² test was performed on the modified intent-to-treat population for the proportion of participants free of ischemia. A last-observation-carried-forward approach was used, in which values after baseline were carried to month 12 if month 12 values were missing. MACE were analyzed by Kaplan-Meier survival curves and a log-rank test for the treatment groups to summarize the time from randomization to the first occurrence of MACE. All-cause death was analyzed similarly to MACE. For the intent-to-treat population, the log-rank test and Cox model were performed to generate hazard ratios (with 95% confidence intervals) and probability values. Safety analyses included all randomized patients who took ≥1 dose of study medication and for whom follow-up information was available. All tests were performed at a 0.05 level of significance, 2 sided.

Because of the lack of direct data on the estimates of effect size and likely standard deviation for the effects of statin therapy on change in total duration of ischemia, the initial sample size estimates of the expected standard deviation were obtained from the Regression Growth Evaluation Statin Study (REGRESS) trial and data from Tzivoni and Klein. At this stage, the required sample size was estimated to be in the range of 900 to 1800 patients, depending on the standard deviation used. A further blinded analysis was performed at month 3 with data from 174 patients enrolled in SAGE. From this analysis, it was estimated that a sample size of 340 evaluable patients...
in each treatment group would provide 92% power at the 0.05 level of significance to detect a treatment difference of 15 minutes in absolute change from baseline in total duration of ischemia, with an assumption of a standard deviation of 57 minutes. With an allowance for nonevaluable data from a projected 15% of randomized patients, the required sample size to recruit was 800 patients.

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

Results

Patient Population

Of a total of 4852 screened patients, 893 patients qualified for the study and were randomized to treatment. Of these, 398 (45%) patients were receiving statin therapy before the trial (208 in the atorvastatin arm and 190 in the pravastatin arm) and entered the washout phase. A total of 751 patients completed the study (Figure 1). The majority of patients who did not qualify for randomization were excluded because they did not have an evaluable Holter at baseline (81%) or for “other” reasons (17%) (eg, withdrawal of informed consent). A total of 69 patients in the atorvastatin group withdrew prematurely from the study, Figure 1. Patient enrollment in SAGE. MITT indicates modified intention-to-treat.

~73 years in both groups, and the study included 30.5% women. Patients in the atorvastatin group had a higher body mass index ($P=0.017$) (and weight, $P=0.006$) and higher levels of apolipoprotein B 100 ($P=0.017$) at baseline than did patients randomized to pravastatin. Medical history was similar in both treatment groups, although significantly more patients in the pravastatin group had a history of stroke than did those in the atorvastatin group (27 patients and 10 patients, respectively; $P=0.004$).

Primary Efficacy Parameter

The values for the mean total duration of myocardial ischemia for both treatment groups are provided in Figure 2. The total duration of myocardial ischemia at month 12 was significantly reduced from baseline in both atorvastatin- and pravastatin-treated patients (both $P<0.001$), and improvement in ischemia was already evident at 3 months.

The least-squares mean absolute change from baseline in total duration of myocardial ischemia at month 12 was $-47.6$ minutes in the atorvastatin group and $-46.1$ minutes in the pravastatin group. Standard deviations were large, with a standard deviation of 134 minutes in the atorvastatin group and a standard deviation of 145 minutes in the pravastatin group. The difference between the intensive versus moderate

### TABLE 1. Baseline Characteristics of Patients Randomized in the SAGE Study

<table>
<thead>
<tr>
<th></th>
<th>Atorvastatin (n=446)</th>
<th>Pravastatin (n=445)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>72.4±5.1</td>
<td>72.6±5.2</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>77.4±13.2</td>
<td>75.1±11.5</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.4±4.0</td>
<td>26.8±3.5</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>225.8±36.1</td>
<td>221.9±35.9</td>
</tr>
<tr>
<td>LDL</td>
<td>147.5±30.1</td>
<td>144.0±31.5</td>
</tr>
<tr>
<td>HDL</td>
<td>45.5±11.5</td>
<td>46.4±11.1</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>164.4±71.5</td>
<td>157.1±78.0</td>
</tr>
<tr>
<td>ApoB 100, mg/dL</td>
<td>143.6±25.4</td>
<td>139.3±26.3</td>
</tr>
<tr>
<td>Duration of ischemia, min</td>
<td>113.5±122.0</td>
<td>124.3±145.3</td>
</tr>
<tr>
<td>No. of ischemia events</td>
<td>3.9±3.8</td>
<td>3.9±3.8</td>
</tr>
<tr>
<td>Men</td>
<td>307 (68.8)</td>
<td>312 (70.1)</td>
</tr>
<tr>
<td>Women</td>
<td>139 (31.2)</td>
<td>133 (29.9)</td>
</tr>
<tr>
<td>White</td>
<td>433 (97.1)</td>
<td>430 (96.6)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>24 (5.4)</td>
<td>31 (7.0)</td>
</tr>
<tr>
<td>Past smoker</td>
<td>231 (51.8)</td>
<td>243 (54.8)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>203 (45.5)</td>
<td>206 (46.3)</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>10 (2.2)</td>
<td>27 (6.1)</td>
</tr>
<tr>
<td>Coronary artery bypass graft</td>
<td>118 (26.5)</td>
<td>144 (32.4)</td>
</tr>
<tr>
<td>Angioplasty</td>
<td>141 (31.6)</td>
<td>127 (28.5)</td>
</tr>
<tr>
<td>Angina</td>
<td>421 (94.4)</td>
<td>414 (83.0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>296 (66.4)</td>
<td>279 (62.7)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>24 (5.4)</td>
<td>23 (5.2)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>100 (22.4)</td>
<td>107 (24.0)</td>
</tr>
</tbody>
</table>

Values are mean±SD or number (%). Apo indicates apolipoprotein.
treatment groups was not significant (least-squares mean difference, -1.4 minutes; 95% CI, -19.2 to 16.3 minute; \( P=0.88 \)).

Compared with male participants, female participants experienced a greater decrease in duration of myocardial ischemia from baseline to month 12; however this difference did not reach statistical significance (women: least-squares mean change of -63.1 [SE, 12.2] minutes and -65.0 [SE, 12.5] minutes in the atorvastatin and pravastatin groups, respectively; men: least-squares mean change of -40.8 [SE, 7.4] minutes and -38.0 [SE, 7.5] minutes in the atorvastatin and pravastatin groups, respectively).

Previous use of statin therapy and the 6-week washout phase did not affect the primary efficacy results. For patients with prettrial use of statins, the mean absolute changes from baseline at month 12 were -49.3 [SE=7.7] minutes in the atorvastatin group and -54.5 [SE=8.0] minutes in the pravastatin group (\( P=0.64 \)). Similarly, for patients who were not receiving statin therapy before the trial, the mean absolute changes from baseline at month 12 were -46.6 [SE=10.0] minutes in the atorvastatin group and -37.5 [SE=10.0] minutes in the pravastatin group (\( P=0.52 \)).

Consistency in patients’ activity levels over the course of the trial was assessed by measurement of mean heart rate. There were no changes in the mean heart rate over time and no differences between the 2 groups.

### Secondary Efficacy Parameters
There were no significant differences between atorvastatin and pravastatin for any of the primary or secondary efficacy parameters at month 3 or month 12. Results from the primary efficacy parameter and secondary efficacy analyses at month 12 are presented in Table 2. At month 3, probability values for the difference between atorvastatin and pravastatin ranged from \( P=0.09 \) for absolute change in total number of episodes of ischemia to \( P=0.94 \) for the percent change in ischemic burden. There was no significant difference in secondary efficacy outcomes between male and female participants.

### Lipid Parameters
Compared with pravastatin 40 mg/d, atorvastatin 80 mg/d produced significantly greater decreases in total cholesterol, LDL-C, triglycerides, and apolipoprotein B at month 3 and at month 12 (all \( P<0.001 \)) (Figure 3). Levels of HDL-C increased in both groups, with significantly larger increases in the pravastatin group at month 3 (\( P<0.001 \)) and at month 12 (\( P=0.009 \)) than in the atorvastatin group.

### TABLE 2. Summary of Results for Primary Efficacy Parameters and Secondary Efficacy Parameters at Month 12

<table>
<thead>
<tr>
<th>Changes From Baseline</th>
<th>Atorvastatin (n=408)</th>
<th>Pravastatin (n=396)</th>
<th>Absolute Treatment Difference (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LS Mean Change (SE)</td>
<td>LS Mean Change (SE)</td>
<td></td>
</tr>
<tr>
<td>Primary efficacy</td>
<td>344 -47.6 (6.3)</td>
<td>332 -46.1 (6.5)</td>
<td>-1.4 (-19.2 to 16.3)</td>
</tr>
<tr>
<td>Absolute change of total duration of ischemia, min (month 12)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary efficacy</td>
<td>344 -16.5 (15.0)</td>
<td>332 5.9 (15.3)</td>
<td>-22.4 (-64.6 to 19.8)</td>
</tr>
<tr>
<td>Percent change in total duration of ischemia (month 12)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute change in total number of episodes of ischemia (month 12)</td>
<td>344 -1.7 (0.2)</td>
<td>332 1.8 (0.2)</td>
<td>0.1 (-0.3 to 0.6)</td>
</tr>
<tr>
<td>Percent change in total number of episodes of ischemia (month 12)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent change in ischemic burden (month 12)</td>
<td>344 -40.5 (5.9)</td>
<td>332 36.4 (6.0)</td>
<td>-4.1 (-20.5 to 12.4)</td>
</tr>
<tr>
<td></td>
<td>344 -9.2 (15.3)</td>
<td>332 8.4 (15.5)</td>
<td>-17.5 (-60.3 to 25.2)</td>
</tr>
</tbody>
</table>

Proportion of patients totally free of ischemia (month 12) in the atorvastatin group was 159 (46.2%); in the pravastatin group, 150 (45.2%); \( P=0.786 \).

*Percent change and 95% CI were from an ANCOVA model that included treatment and baseline values. LS indicates least squares.
Major Adverse Cardiovascular Events

There was a favorable although nonsignificant trend for fewer atorvastatin patients to experience MACE than pravastatin patients during the 12-month treatment period (36/446 [8.1%] versus 50/445 [11.2%] of patients, respectively; HR, 0.71; 95% CI, 0.46 to 1.09; *P*=0.114) (Figure 4, Table 3). A total of 61 events were experienced by patients who received atorvastatin 80 mg/d, compared with 90 events experienced by patients who received pravastatin 40 mg/d. Three patients in the atorvastatin group were censored at month 12 because they were study completers who experienced MACE events >30 days after completion of the study. The hazard ratio when these 3 patients were included was 0.75 (95% CI, 0.49 to 1.14; *P*=0.171).

The most common MACE was urgent coronary revascularization, with a total of 22 events in the atorvastatin group and 33 events in the pravastatin group. There were no obvious relationships between MACE and change in ischemia. The small number of events and the variability of ischemia measurements precluded correlation analysis.

All-Cause Mortality

A significant 77% reduction in all-cause mortality was observed with atorvastatin 80 mg/d (1.3% incidence [6 deaths]) relative to pravastatin 40 mg/d (4.0% incidence [18 deaths]) over 12 months (HR, 0.33; 95% CI, 0.13 to 0.83; *P*=0.014) (Figure 5). The most frequent causes of death were coronary death (0.4% incidence [2 deaths] atorvastatin, 1.3% incidence [6 deaths] pravastatin) and other nonvascular death (0.4% incidence [2 deaths] atorvastatin, 1.3% incidence [6 deaths] pravastatin) and together accounted for two thirds of all deaths during the study. Death from cancer was rare and occurred in 0.2% of the total SAGE population (2 deaths in the pravastatin group). Two patients in the atorvastatin group, one of whom died from cancer, were censored because they were study completers who died >30 days after completion of the study. With these 2 patients included, the all-cause mortality hazard ratio for atorvastatin relative to pravastatin was 0.37 (95% CI, 0.16 to 0.90; *P*=0.022).

Safety

Safety analyses were performed on all randomized patients who took ≥1 dose of study medication and for whom follow-up information was available, which resulted in an analysis of data from 891 patients. The main safety findings are presented in Table 4.

The overall incidence of and discontinuations caused by all-cause adverse events were similar between the 2 treatment groups, as was the incidence of serious adverse events. In the atorvastatin group, 12.1% of patients (n=54) experienced serious adverse events that exclude MACE. The proportions of participants who experienced these events in the pravastatin group were similar to those in the atorvastatin group (11.9%, n=53). Liver function test abnormalities were more frequent in the atorvastatin 80-mg/d group than in the pravastatin 40-mg/d group (4.3% [n=19] versus 0.2% [n=1], respectively, *P*<0.001). Of these patients, only 1 patient (in the atorvastatin group) had elevations that were regarded as both clinically important and related to treatment. Liver enzyme levels returned to normal for all patients who were followed up for a repeat test or on discontinuation of study medication. Treatment-related adverse events were reported for 17.3% of the patients who received atorvastatin and 13.9% of the patients who received pravastatin (*P*=0.17). Myalgia was the most common treatment-related adverse event (3.1% of patients in the atorvastatin group versus 2.7%...
of patients in the pravastatin group, \( P = 0.70 \). There were no cases of rhabdomyolysis in either group.

**Discussion**

The SAGE trial demonstrated that lipid-lowering therapy with either atorvastatin 80 mg/d or pravastatin 40 mg/d in an older population was associated with significant reductions in the total duration of myocardial ischemia as measured by ambulatory ECG monitoring. Although there was no significant difference in benefit on total duration of ischemia between the 2 groups, secondary analyses showed that intensive lipid lowering with atorvastatin 80 mg/d was associated with greater reductions in all-cause mortality and a trend toward fewer MACE than was moderate lipid lowering with pravastatin. Therefore, the pathophysiology of clinical events related to lipid-lowering therapy may differ from that of ischemia. Indeed, improvement in ischemia is predominantly related to improvement in myocardial oxygen supply-and-demand balance, whereas MACE are more closely related to plaque rupture.

The reductions in ischemia from baseline in SAGE confirm the results from the Vascular Basis for the Treatment of Myocardial Ischemia study, which likewise revealed significant reductions in ischemia as measured by 48-hour ambulatory ECG in stable CAD patients randomized to an intensive (atorvastatin) or a moderate (lovastatin) regimen.\(^9\) In SAGE, the change in total duration of myocardial ischemia was already evident at 3 months with no further improvement at month 12 and may indicate that reduction in coronary tone preceded changes in plaque composition, which are responsible for most cardiac events. In the Vascular Basis for the Treatment of Myocardial Ischemia study, it was hypothesized that there was a threshold effect of LDL-C lowering below which there is no incremental improvement in endothelial dysfunction and episodic coronary vasoconstriction, the mechanisms that contribute to the development of ischemia, and that the on-treatment LDL-C values in both groups in the Vascular Basis for the Treatment of Myocardial Ischemia study were beneath this threshold. In contrast, the magnitude of LDL-C lowering that is effective in the improvement of the pathobiology of vulnerable plaque and the reduction of clinical events may be more continuous, such that progressively lower LDL-C values are associated with progressively lower cardiac event rates.\(^13\) This hypothesis is now further supported by the results from SAGE, which demonstrated a trend for lower clinical event rates in patients randomized to aggressive versus moderate lipid lowering.

SAGE enrolled the largest number of women (\( n = 272; 30\% \) of the SAGE population) in any trial to evaluate the effect of medications on Holter-detected ischemia in stable coronary disease. Coronary disease is as prevalent in women as in men at ages >65 years, and angina is more commonly the presenting symptom in women than in men. In the Euro Heart Survey of Stable Angina, a longitudinal cohort study of patients with a clinical diagnosis of angina, women, who constituted 42% of the population, were less likely to be treated with statins or antiplatelet therapy than men and had a higher probability of death or myocardial infarction.\(^{14} \) The SAGE results demonstrate that women 66 to 85 years of age have at least as great a reduction in total ischemia with statin therapy as do men. Moreover, the degree of lipid lowering and trends toward cardiovascular benefits observed with atorvastatin 80 mg/d but continued to progress in those treated with pravastatin 40 mg/d,\(^{16} \) and, in the Arterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol (ARBITER) trial, mean carotid intima-media thickness decreased significantly in dyslipidemic patients randomized to atorvastatin 80 mg/d versus pravastatin 40 mg/d.\(^{17} \) Results from other trials that compare intensive versus moderate statin therapy suggest that clinical events may decrease with increasing magnitudes of LDL-C lowering. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) trial, the rate of cardiovascular events in patients with acute coronary syndromes was significantly reduced in patients randomized to atorvastatin 80 mg/d compared with those randomized to pravastatin 40 mg/d,\(^7 \) and in the Treating to New Targets (TNT) trial atorvastatin 80 mg/d reduced the rate of first cardiovascular events versus atorvastatin 10 mg/d in patients with stable CAD and LDL-C <130 mg/dL (3.4 mmol/L) at baseline.\(^{18} \) SAGE demonstrated a trend toward reductions in MACE and significant reductions in all-cause mortality, despite not being designed to

<table>
<thead>
<tr>
<th>Patients who experienced ≥1 adverse event, n (%)</th>
<th>Atorvastatin (n=446)</th>
<th>Pravastatin (n=445)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients who discontinued study drug as a result of adverse events, n (%)*</td>
<td>48 (10.8)</td>
<td>46 (10.3)</td>
<td>0.84</td>
</tr>
<tr>
<td>Patients with serious adverse events, n (%)</td>
<td>90 (20.2)</td>
<td>103 (23.1)</td>
<td>0.28</td>
</tr>
<tr>
<td>Patients with ALT or AST &gt;3 times the upper limit of normal, n (%)</td>
<td>19 (4.3)</td>
<td>1 (0.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients with CPK &gt;10 times the upper limit of normal, n (%)</td>
<td>0 (0)</td>
<td>1 (0.2)</td>
<td>0.32</td>
</tr>
</tbody>
</table>

*Includes MACE. ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; and CPK, creatine phosphokinase.
detect differences in cardiovascular events between the 2 treatment groups.

In SAGE, both statin regimens were well tolerated, and adverse events were consistent with the safety profiles of each drug. It has been suggested that statin therapy should be used more conservatively in older patients (≥65 years) than in younger patients because of an increased number of concomitant illnesses and medications in the older population, which increases the risk for adverse events.19 Perhaps as a result of these concerns, older patients have remained undertreated for their CAD risk factors.20 However, the results from SAGE indicate that these concerns may be outweighed by the benefits of statin therapy. Moreover, in older patients, especially in patients with recurrent ischemia,3 the absolute risk of death is higher than in younger patients, which further emphasizes the need for intensive statin therapy in the older population.

Limitations
The reduced frequency and duration of ischemia may have been caused by generally enhanced patient care associated with a clinical trial setting rather than by the benefits of lipid-lowering therapies. However, regression to the mean has not been observed in other studies of ischemia as measured by serial ambulatory ECG assessments in CAD patients during daily life.21,22 It is also possible that improvements in ischemia were due to patients’ being less active during follow-up than at baseline. However, mean heart rates were similar at baseline and month 12 in both the atorvastatin and pravastatin groups, which suggests that patients had not changed their activity levels between baseline and month 12 in either group.

Although it appears that ischemia and clinical events may have differing LDL-C thresholds for cardiovascular benefit, it is also possible that reductions in ischemia did not differ significantly between the 2 treatment groups because ambulatory ischemia is not an adequately sensitive measure of change in cardiovascular event risk. Moreover, although an effect size of 15 minutes with a standard deviation of 57 minutes was estimated from the initial analysis, in the final analysis the effect size was 1.5 minutes with a standard deviation of 134 to 145 minutes. As a result, the study may have been underpowered to detect differences between the 2 treatment groups. In addition, the number of events for the mortality analysis was small and was analyzed post hoc. For these reasons, the results from this trial need to be confirmed in prospective studies.

Conclusions
SAGE compared the effects of intensive versus moderate statin therapy on the reduction of myocardial ischemia in older individuals. Both statin regimens were equally effective in the reduction of the frequency and duration of myocardial ischemia. Intensive atorvastatin therapy more effectively improved lipids and reduced all-cause death than moderate pravastatin. These results, together with a trend toward reductions in MACE with atorvastatin versus pravastatin, support the concept that mechanisms of ischemic events, which are related to oxygen supply and demand, may differ from acute coronary events, which are related to plaque stability.

These findings, together with the greater cardiovascular risk in the elderly population, suggest that intensive statin therapy should be considered routinely in the elderly population.

Acknowledgments
We acknowledge the many coinvestigators, subinvestigators, and coordinating investigators who participated in this trial by randomizing patients but who are not listed individually here because of space limitations. We also thank Dr Robert Lester of Covance for his expertise and hard work in reading all of the Holter readings for the SAGE study. We are also grateful for the expert judgments of Jeffrey Breall, James Carter, Glen Cooke, Sanjay Rajagopalan, and Mirek Sochanski, who served on the adjudication committee. Editorial support was provided by Dr Fiona Steinkamp of Envision Pharma, Ltd.

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Disclosures
Dr Deedwania has received research grants and consulting fees/other remuneration from Pfizer and AstraZeneca. Dr Stone has received research grants from Pfizer, Novartis, CV Therapeutics, and Boston Scientific. He has given educational lectures sponsored by Pfizer and CV Therapeutics, and is a consultant to CV Therapeutics. Dr Bairey Merz has received honoraria from Pfizer for educational lectures related to treatment of dyslipidemia and previously has served as a consultant to Pfizer. She has given educational lectures sponsored by Bayer, Kos, Merck, CV Therapeutics, Sanofi-Aventis, and Astellas. She receives research grants from Merck and Pfizer. She owns stock in Johnson and Johnson, Boston Scientific, Eli Lilly, and Medtronic. Dr Cosin-Aguilera has received consulting fees from Pfizer and Roche. Dr Koylan has received consulting honoraria from Pfizer, Novartis, Merck, Sanofi-Aventis, and Boehringer Ingelheim. He has also received consultancy fees from Pfizer, Merck, Sanofi-Aventis, and Boehringer Ingelheim. Dr Luo is an employee of Pfizer. Dr Ouyang previously has served as a consultant to Pfizer. She has received honoraria from CV Therapeutics and Kos for development of educational lectures. She receives research grants from Glaxo Smith Kline, Scios Inc., and PreMD, Inc. She has served on an advisory board for Atherogenics. Dr Piotrowicz has no conflicts of interest. Dr Schenck-Gustafsson has served on advisory boards for AstraZeneca and Guidant, received lecture fees from Pfizer, MSD, AstraZeneca, and Guidant, and is an international coordinator for a study supported by Eli-Lilly. Dr Sellier has received consulting fees from Pfizer and Servier. Dr Stein has received honoraria from Pfizer for educational lectures related to treatment of dyslipidemia, and previously has served as a consultant to Pfizer. He also has given educational lectures sponsored by Kos, Merck, Schering-Plough, and Takeda. He receives research grants from Astra-Zeneca, Bristol-Myers Squibb, and Sanofi-Aventis. Dr Thompson has received honoraria from Pfizer for educational lectures related to treatment of dyslipidemia. He has also given educational lectures for Astra Zeneca, Bristol Myers Squibb. He has received research grants from Bristol Myers Squibb, Merck, Pfizer, and has served on advisory boards for Astra Zeneca, Bristol Myers Squibb and Sanofi Aventis. Dr Tzivoni has no conflicts of interests.

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Antiischemic Efficacy of Statins in the Elderly

Clinical Perspective

Clinical trials have demonstrated that, compared with placebo, intensive statin therapy reduces ischemia in patients with acute coronary syndromes and in patients with stable coronary artery disease. However, no studies to date had assessed intensive versus moderate statin therapy in older patients with stable coronary syndromes. The Study Assessing Goals in the Elderly (SAGE) compared the effects of intensive versus moderate statin therapy (atorvastatin 80 mg/d versus pravastatin 40 mg/d) on the reduction of myocardial ischemia, as assessed by ambulatory ECG, in older men and women with stable coronary artery disease. The results demonstrated that both treatment regimens reduced ischemia but that atorvastatin 80 mg/d was also associated with reductions in cholesterol, all-cause death, and a trend toward a reduction in major cardiovascular events as compared with pravastatin 40 mg/d. The contrast between the therapies’ efficacy for the reduction of major cardiovascular events and death and the similarity of their efficacy for the reduction of ischemia suggests that low-density lipoprotein cholesterol-lowering thresholds for major cardiovascular events may differ from those for ischemia. The results from SAGE demonstrate that intensive statin therapy is beneficial in older men and women with coronary artery disease.


Effects of Intensive Versus Moderate Lipid-Lowering Therapy on Myocardial Ischemia in Older Patients With Coronary Heart Disease: Results of the Study Assessing Goals in the Elderly (SAGE)
Prakash Deedwania, Peter H. Stone, C. Noel Bairey Merz, Juan Cosin-Aguilar, Nevres Koylan, Don Luo, Pamela Ouyang, Ryszard Piotrowicz, Karin Schenck-Gustafsson, Philippe Sellier, James H. Stein, Peter L. Thompson and Dan Tzivoni

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