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. **(*Circulation*. 2007;115:700-707.)**

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.

Editorial p 681
Clinical Perspective p 707

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

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patients. The presence of myocardial ischemia is a marker for high risk of cardiac events and death.[2–9] Monitoring changes in frequency and duration of ischemia by ambulatory ECG may provide a means to assess the effectiveness of therapeutic interventions.

In clinical trials in patients with acute coronary syndromes, reductions in ischemic events were observed with intensive statin therapy versus placebo[5,6] and versus a more moderate statin regimen.[7] In patients with stable CAD, too, statin therapy was associated with reductions in ambulatory ischemia, as compared with placebo in a randomized pilot study[8] and in a nonrandomized database study.[9] The recent Vascular Basis for the Treatment of Myocardial Ischemia Study[10] further demonstrated that both intensive and more moderate lipid-lowering regimens reduced the duration of ischemia from baseline as measured by ambulatory ECG in patients with stable CAD. However, the mean age of the participants in these studies ranged from 56 to 67 years, participants were predominantly male, and none of the studies addressed the unique group of older patients with stable CAD—a population that is at highest risk of cardiac events and mortality. The purpose of the Study Assessing Goals in the Elderly (SAGE) was to compare the effects of intensive versus moderate statin therapy on the reduction of myocardial ischemia, as assessed by ambulatory ECG, in older men and women with stable CAD.

Methods

The design and full methodology of SAGE have been published previously.[11]

Study Overview

SAGE was a 12-month, prospective, international, multicenter, randomized, double-blind, double-dummy, parallel-arm trial that compared the effect of atorvastatin 80 mg/d with that of pravastatin 40 mg/d on the total duration of myocardial ischemia as assessed by 48-hour ambulatory ECG. Enrollment occurred at 192 sites worldwide in 16 countries.

Patient Population

Study participants were 65 to 85 years of age and had a documented history of CAD, baseline LDL-C levels between 100 mg/dL (2.6 mmol/L) and 250 mg/dL (6.5 mmol/L), and ≥1 episode of myocardial ischemia with a total duration of ≥3 minutes during 48-hour ambulatory ECG monitoring at the screening visit. SAGE was originally designed to enroll patients in a 4:1 female:male ratio, but because of slow enrollment (after 40 patients), this criterion was withdrawn. This did not impact the statistical analyses, because SAGE was not designed exclusively to detect efficacy in women.

Study Design

Before proceeding to the screening visit, eligible patients who were already receiving lipid-lowering therapy entered a washout period of ≥6 weeks, and patients on digitalis glycosides underwent a 4-week washout period (atrial fibrillation and heart failure New York Heart Association [NYHA] III and IV were exclusion criteria). Baseline measurements were defined as the assessments taken at the screening visit. Clinically stable patients who met the recruitment criteria at baseline were subsequently randomized in a double-blind fashion to atorvastatin 80 mg/d or pravastatin 40 mg/d and were followed up for 12 months. A 48-hour ambulatory ECG monitoring assessment by Holter monitor was conducted again at 3 and 12 months after randomization.

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 $\kappa=0.72$ 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 χ^2 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.[12] 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

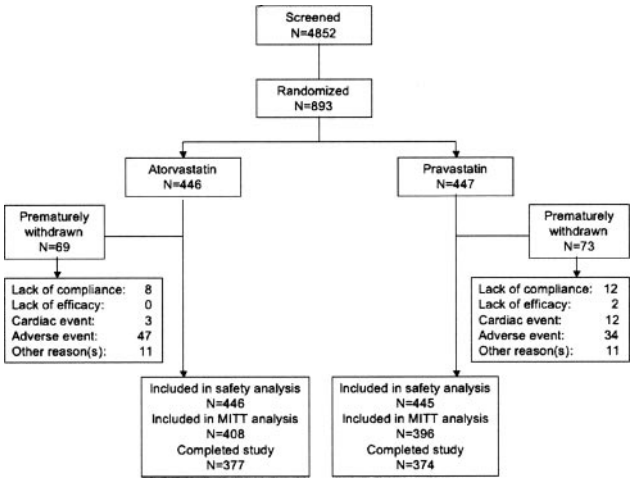

Figure 1. Patient enrollment in SAGE. MITT indicates modified intention-to-treat.

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. The most frequent adverse events experienced by >1 patient that led to study drug discontinuation were abnormal liver function tests (n=11); diarrhea and myalgia (each n=8); asthenia and pain (each n=3); and flatulence, shock, angina pectoris, and cardiac arrest (each n=2). In the pravastatin group, 73 patients withdrew prematurely from the study, again largely because of adverse events. In this group, the most common adverse events that led to study discontinuation were myocardial infarction, nausea, and myalgia (each n=5); angina pectoris (n=4); pain and shock (each n=3); and sudden death, dyspepsia, gastritis, gastrointestinal hemorrhage, dizziness, and pneumonia (each n=2).

Baseline data for the total SAGE population have been presented in detail previously[11] and were generally found to be similar across the 2 treatment groups (Table 1). Holter readings did not differ significantly between patients who had entered the statin washout phase and patients who had never received statin therapy. The mean age of participants was ≈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).

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

	Atorvastatin (n=446)	Pravastatin (n=445)
Age, y	72.4±5.1	72.6±5.2
Weight, kg	77.4±13.2	75.1±11.5
Body mass index, kg/m^2	27.4±4.0	26.8±3.5
Cholesterol, mg/dL		
Total	225.8±36.1	221.9±35.9
LDL	147.5±30.1	144.0±31.5
HDL	45.5±11.5	46.4±11.1
Triglycerides, mg/dL	164.4±71.5	157.1±78.0
ApoB 100, mg/dL	143.6±25.4	139.3±26.3
Duration of ischemia, min	113.5±122.0	124.3±145.3
No. of ischemia events	3.9±3.8	3.9±3.8
Men	307 (68.8)	312 (70.1)
Women	139 (31.2)	133 (29.9)
White	433 (97.1)	430 (96.6)
Smoking status		
Current smoker	24 (5.4)	31 (7.0)
Past smoker	231 (51.8)	243 (54.6)
Myocardial infarction	203 (45.5)	206 (46.3)
Cerebrovascular accident	10 (2.2)	27 (6.1)
Coronary artery bypass graft	118 (26.5)	144 (32.4)
Angioplasty	141 (31.6)	127 (28.5)
Angina	421 (94.4)	414 (93.0)
Hypertension	296 (66.4)	279 (62.7)
Congestive heart failure	24 (5.4)	23 (5.2)
Diabetes mellitus	100 (22.4)	107 (24.0)

Values are mean±SD or number (%). Apo indicates apolipoprotein.

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

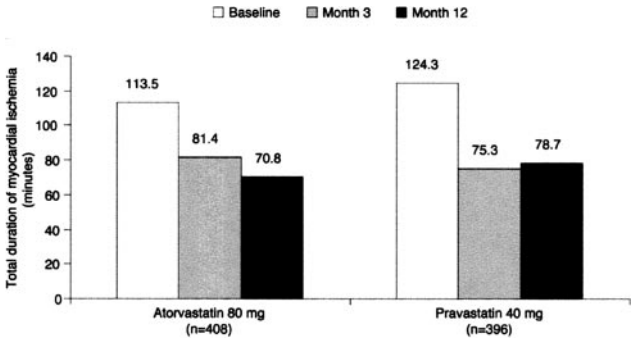

Figure 2. Mean total duration of myocardial ischemia over 48 hours at baseline, month 3, and month 12 in the modified intent-to-treat population. *$P<0.001$ versus baseline; no difference between atorvastatin 80 mg/d and pravastatin 40 mg/d.

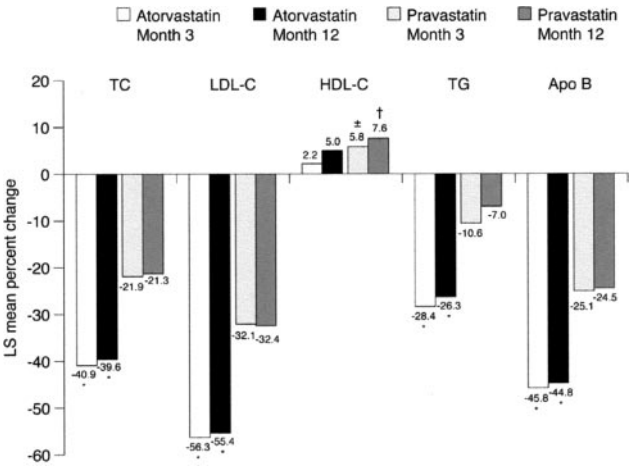

Figure 3. Least-squares mean percent changes in lipid parameters from baseline. *$P<0.001$ versus pravastatin; ‡$P<0.001$ versus atorvastatin; †$P=0.009$ versus atorvastatin. Apo indicates apolipoprotein; LS, least squares; TC, total cholesterol; and TG, triglycerides.

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 pretrial 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

	Atorvastatin (n=408)		Pravastatin (n=396)		
Changes From Baseline	No.	LS Mean Change (SE)	No.	LS Mean Change (SE)	Absolute Treatment Difference (95% CI)*
Primary efficacy					
Absolute change of total duration of ischemia, min (month 12)	344	−47.6 (6.3)	332	−46.1 (6.5)	−1.4 (−19.2 to 16.3)
Secondary efficacy					
Percent change in total duration of ischemia (month 12)	344	−16.5 (15.0)	332	5.9 (15.3)	−22.4 (−64.6 to 19.8)
Absolute change in total number of episodes of ischemia (month 12)	344	−1.7 (0.2)	332	−1.8 (0.2)	0.1 (−0.3 to 0.6)
Percent change in the total number of episodes of ischemia (month 12)	344	−40.5 (5.9)	332	−36.4 (6.0)	−4.1 (−20.5 to 12.4)
Percent change in ischemic burden (month 12)	344	−9.2 (15.3)	332	8.4 (15.5)	−17.5 (−60.3 to 25.2)

Proportion of patients totally free of ischemia (month 12) in the atorvastatin group was 159 (46.2%); in the pravastatin group, 150 (45.2%); $P=0.786$.
*Treatment difference and 95% CI were from an ANCOVA model that included treatment and baseline values. LS indicates least squares.

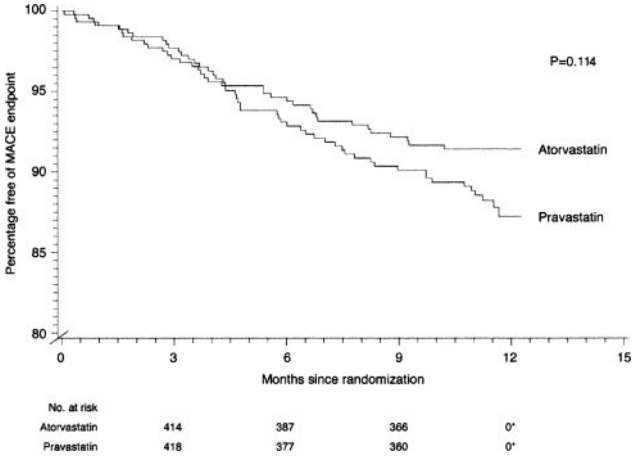

Figure 4. Kaplan-Meier plot for the time to the first MACE end point up to month 12. *At risk at month 12 plus 8 days.

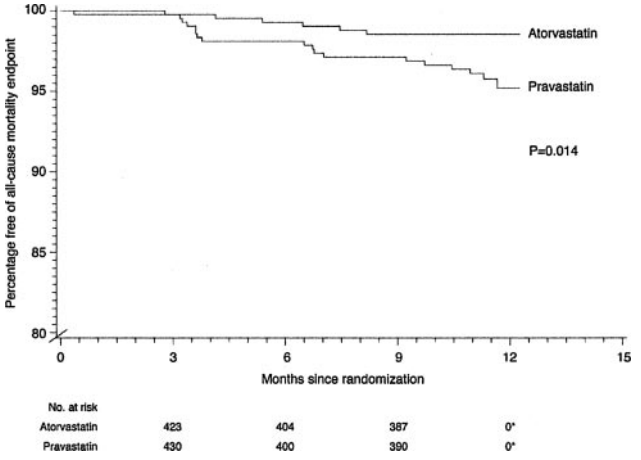

Figure 5. Kaplan-Meier estimates of time to all-cause death during the 12-month treatment period. *At risk at month 12 plus 8 days.

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; $P=0.022$).

TABLE 3. Summary of MACE During the SAGE Study

	Atorvastatin 80 mg/d (n=446)		Pravastatin 40 mg/d (n=445)	
	n (%)	Events	n (%)	Events
MACE	36 (8.1)	61	50 (11.2)	90
Cardiovascular death	4 (0.9)	4	10 (2.2)	10
Nonfatal myocardial infarction	16 (3.6)	18	16 (3.6)	17
Resuscitated cardiac arrest	1 (0.2)	1	0 (0.0)	0
Urgent coronary revascularization	20 (4.5)	22	29 (6.5)	33
Hospitalized for unstable angina	14 (3.1)	15	22 (4.9)	29
Stroke	1 (0.2)	1	3 (0.7)	3

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%

TABLE 4. Summary of All-Cause Safety Results

	Atorvastatin (n=446)	Pravastatin (n=445)	*P*
Patients who experienced ≥1 adverse event, n (%)	273 (61.2)	287 (64.5)	0.31
Patients who discontinued study drug as a result of adverse events, n (%)*	48 (10.8)	46 (10.3)	0.84
Patients with serious adverse events, n (%)	90 (20.2)	103 (23.1)	0.28
Patients with ALT or AST >3 times the upper limit of normal, n (%)	19 (4.3)	1 (0.2)	<0.001
Patients with CPK >10 times the upper limit of normal, n (%)	0 (0)	1 (0.2)	0.32

*Includes MACE. ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; and CPK, creatine phosphokinase.

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 more 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) statin regimen.[10] 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 statin therapy in the older population in SAGE are consistent with those in older patients in other clinical trials and thus further support guideline recommendations for statin therapy in older patients with or at risk of cardiovascular disease.[15]

SAGE was the first trial to assess intensive versus moderate therapy in older patients. Recent trials indicate that, in the general population of CAD patients, intensive statin therapy has a more beneficial effect on atherosclerotic progression than does moderate statin therapy. In the Reversing Atherosclerosis with Aggressive Lipid-Lowering (REVERSAL) study, atherosclerotic progression halted in CAD patients treated 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 more 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

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.

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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.