

## Safety and Tolerability of Pravastatin in Long-Term Clinical Trials

### Prospective Pravastatin Pooling (PPP) Project



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**Background**—Therapeutic decisions regarding pharmacological therapy should be based on safety and tolerability as well as efficacy data. Clinical trials designed to assess efficacy are often insufficiently powered to generate reliable safety data.

**Methods and Results**—The West of Scotland Coronary Prevention Study (WOSCOPS), the Cholesterol and Recurrent Events (CARE), and Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) studies collectively accumulated >112 000 person-years of exposure in double-blind randomized trials comparing placebo and pravastatin (40 mg once daily). During 5 years of exposure, the incidence of fatal and nonfatal cancers was similar between pravastatin and placebo groups. No differences in noncardiovascular serious adverse events were detected. With >243 000 blood sample analyses, the percentage of patients with any abnormal liver function test after baseline sampling was similar (>3× the upper limit of normal for alanine aminotransferase: 128 [1.4%] versus 131 [1.4%] patients for pravastatin versus placebo, respectively). Study medication was withdrawn in 3 pravastatin and 7 placebo patients due to creatine phosphokinase elevations; no cases of mild or severe myopathy were reported. A Cox regression model considering treatment group, age, diabetes, smoking, whether primary or secondary prevention study, and cardiovascular serious adverse events indicates that the likelihood of discontinuing pravastatin was less than placebo.

**Conclusions**—This prospective analysis indicates that during prolonged exposure, 40 mg of pravastatin is well tolerated, with no excess of noncardiovascular serious adverse events, including liver function abnormalities and laboratory and clinical evidence for myositis. These extensive safety and tolerability data provide important information for therapeutic decisions regarding this pharmacological agent. (*Circulation*. 2002;105:2341-2346.)

**Key Words:** statins ■ pravastatin ■ safety ■ rhabdomyolysis ■ myositis

Reductions in the prevalence and severity of cardiovascular risk factors have been prominent contributors toward the decline in cardiovascular morbidity and mortality observed in the last several decades.<sup>1,2</sup> Favorable lifestyle modifications such as avoidance of smoking, weight reduction, dietary modifications, and increasing physical activity are based on sound epidemiological data and raise no safety concerns. However, a strategy that uses long-term pharmacological therapy for cholesterol lowering as well as for other risk factors, such as hypertension, should be based on definitive data concerning efficacy and the safety and tolerability of the therapy to derive a rational risk-benefit assess-

ment. In many respects, safety and tolerability are as important as efficacy in defining the clinical thresholds to initiate long-term pharmacological therapy to modify a risk factor.

Large scale, well-conducted, placebo-controlled, randomized clinical trials have established conclusive evidence that the long-term use of certain 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) results in important reductions in the risk of experiencing major cardiovascular events in patients with a wide range of lipid levels, both<sup>3</sup> with<sup>4-6</sup> and without<sup>7,8</sup> a history of heart disease. These major clinical trials were designed with sufficient statistical power to detect the efficacy of the particular statin in reducing

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predefined cardiovascular events. However, individually, these studies generally do not provide sufficient exposure to uncover relatively uncommon safety issues. Indeed, before these studies, the safety of earlier pharmacological strategies to lower cholesterol had been questioned<sup>9</sup> when nonsignificant increases in noncardiovascular deaths were reported with cholestyramine and gemfibrozil therapy in some studies.<sup>10,11</sup> Rodent toxicity data raised questions concerning the possible carcinogenesis of lipid-lowering agents.<sup>12</sup> Because statins inhibit a major liver enzyme, hepatic safety has been an ongoing concern. Marked elevations in plasma levels of certain statins metabolized by CYP3A4 have been experienced with coadministration of other agents that inhibit this pathway.<sup>13</sup> Indeed, reports of rhabdomyolysis with the coadministration of mibefradil and statins sharing this metabolic pathway led to the withdrawal of this antihypertensive agent. The recent worldwide withdrawal of cerivastatin as a consequence of postmarketing reports of a relatively high rate of fatal rhabdomyolysis has appropriately heightened concerns about the use of statins.<sup>14</sup>

The investigators from the West Of Scotland Coronary Prevention Study (WOSCOPS), the Cholesterol And Recurrent Events (CARE) study, and the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study formed the Prospective Pravastatin Pooling (PPP) project to combine the cumulative experience of their 3 major long-term, large, placebo-controlled trials of a single dose of pravastatin.<sup>15</sup> The objective was to prospectively and cooperatively pool data to derive more precise quantitative estimates of the efficacy of pravastatin in predefined subgroups,<sup>16</sup> for less common events such as stroke,<sup>17</sup> and to evaluate potential safety issues.<sup>15</sup> Collectively, these 3 studies amassed >112 000 person-years of experience comparing pravastatin (40 mg once daily) with placebo in a rigorous double-blind manner. This report describes the tolerability and safety analyses of the PPP project.

## Methods

The protocol for the PPP collaboration has been described previously,<sup>15</sup> as have the major subgroup,<sup>16</sup> stroke analyses,<sup>17</sup> and mortality data.<sup>18</sup> The individual data sets from these 3 large double-blind trials were combined for statistical analysis. Previous PPP analyses were based on the intent-to-treat principle, including all 19 768 patients randomized into any of the 3 trials. This prespecified safety analysis includes the 19 592 patients who received at least one dose of blinded study medication (n=9809 for pravastatin; n=9783 for placebo) and excludes 176 patients (<1%) who were not exposed to study medication. The duration of exposure to study drug was calculated from the day of the first dose to the last day taken, without adjustments for temporary treatment interruptions.

## Safety Analysis

Safety was evaluated by multiple analyses using the frequency of all reported fatal and nonfatal serious adverse events. A serious adverse event was defined as an adverse event that was fatal, immediately life-threatening, permanently disabling, a congenital anomaly, cancer, an overdose, or that required overnight or prolonged hospitalization. Fatal events, whether cardiovascular or noncardiovascular, were previously described for the PPP cohort.<sup>15</sup> To analyze cancers, the incidence of primary malignancies reported during and within 30 days after study completion was compared.

to the incorporation of protocol-directed laboratory evaluations of alanine aminotransferase (ALT) and creatine phosphokinase (CPK) in all 3 studies. Central laboratories were used for WOSCOPS and CARE, but the LIPID study used local laboratory evaluations. During the first year, all 3 studies measured ALT at baseline and at the 3, 6, 9, and 12-month visits. In WOSCOPS and LIPID, liver function was then tested biannually and in CARE annually. From 18 637 participants, a total of 243 506 samples were analyzed for ALT, representing a mean of 13 evaluations per patient. An ALT abnormality was defined as any postrandomization value (regardless of baseline) that exceeded 1.5× the upper limit of normal (ULN), and the incidence of postbaseline abnormalities is expressed as the total number of subjects with at least one abnormality in that measurement on any postrandomization sample. Aspartate aminotransferase was also analyzed in a similar fashion to ALT; however, it was not routinely obtained in the LIPID study. Concomitant measures of CPK were performed except in LIPID, in which CPK measurements were obtained annually. Because normal ranges for CPK were not specified in the local laboratories in the LIPID study, these data are presented for CARE and WOSCOPS only. Prespecified analyses were also performed to examine the severity of abnormalities ( $\geq 1.5 < 3 \times \text{ULN}$ ,  $\geq 3 < 5 \times \text{ULN}$ ,  $\geq 5 < 7 \times \text{ULN}$ ,  $\geq 7 < 9 \times \text{ULN}$ , and  $\geq 9 \times \text{ULN}$ ). Frequency of events or incidence of abnormalities between the pravastatin and placebo-treated groups were compared.

## Tolerability

The number of patients who permanently discontinued their study medication for any reason was ascertained. Tolerability was expressed as a percent of exposed patients remaining on their assigned study medication. Patients who completed the study on blinded medication or who died within 7 days of a dose of study medication were considered tolerant of medication. Adverse events leading to discontinuation were classified by body systems and by cardiovascular and noncardiovascular causes. Because pravastatin use had a major impact in reducing the risk of experiencing a cardiovascular event, a separate exploratory analysis of tolerability was conducted in a subgroup defined as having or not having experienced a cardiovascular event after randomization.

## Statistical Analysis

Cancer incidence and laboratory abnormality occurrence differences were calculated with associated probability values and 95% confidence intervals using either  $\chi^2$  or Fisher's exact tests. The time to discontinuation of study medication was analyzed using a Cox proportional hazards model with baseline terms for treatment group (pravastatin or placebo), sex, primary (WOSCOPS) or secondary (CARE and LIPID) prevention study, history of diabetes, smoking status, and treatment by primary or secondary prevention study interaction, as well as the presence of a serious cardiovascular event after randomization. Hazards ratios for risk of discontinuation of study medication and 95% confidence intervals are presented.

## Results

Demographics and baseline characteristics of the 19 592 patients in the safety analysis of the PPP were very similar to those previously reported in the overall PPP cohort.<sup>16</sup> Of the 19 592 patients, 13 173 were enrolled in either CARE or LIPID (secondary prevention studies) and 6419 patients were enrolled in WOSCOPS (primary prevention study). The median age of the overall population was 59 years, with a maximum of 75 years at the time of study drug initiation. Approximately 25% of the population was  $\geq 65$  years at randomization. The overall population was 89% male and 11% female (WOSCOPS was confined to men). The mean

**TABLE 1. Total Extent of Exposure to Study Medication**

	40 mg of Pravastatin (n=9809)	Placebo (n=9783)
Extent of exposure to study medication		
Mean±SD, y	4.6±1.7	4.5±1.8
Median, y	5.0	5.0
Minimum, d	1	1
Maximum, y	7.1	7.1
Extent of exposure to study medication, n (%)		
<1 year	755 (8)	826 (8)
1-<2 years	431 (4)	538 (5)
2-<3 years	339 (3)	449 (5)
3-<4 years	579 (6)	710 (7)
4-<5 years	2527 (26)	2465 (25)
5-<6 years	3488 (36)	3322 (34)
≥6 years	1690 (17)	1473 (15)

Percentages for extent of exposure are based on the number of subjects who received at least one dose of study medication; 1 year=365.25 days.

**Safety**

**Deaths and Cancer**

Fewer pravastatin-treated patients died. This was due to a reduction in cardiovascular deaths in those assigned to pravastatin (n=394) compared with placebo (n=502; *P*<0.001), with no difference observed in noncardiovascular deaths. There was no category of noncardiovascular death in which the proportion of deaths differed between the pravastatin and placebo-assigned groups. Fatal primary cancers occurred in 455 of the 19 592 (2.3%) patients, with no differences between treatment groups in these relatively infrequent events. Adding the incidence of nonfatal cancers increased the number of patients in whom at least one primary cancer was diagnosed to 9.5% of the population (1860 of 19 592; Table 2). There were no differences between the pravastatin and placebo groups for any primary cancer as categorized by body system, except in musculoskeletal/connective tissue, which were composites of different histological types and anatomic sites with no pattern according to treatment assignment.

The incidence of breast cancer was 0.2% (n=22) in the pravastatin-treated group and 0.1% (n=11) in those assigned to placebo (*P*=0.080). An imbalance in breast cancer had previously been noted in the CARE study.<sup>5</sup> The LIPID study, compared with CARE, enrolled a larger number of women: 756 were in the pravastatin-treated group and 760 were in the placebo-treated group. In the LIPID study, there were 10 reports (1.3%) of breast cancer in pravastatin-treated women and 8 reports (1.1%) in placebo-treated women. In addition, 2 cases of breast cancer were reported in men; both were assigned placebo.

**Serious Adverse Events**

**TABLE 2. Primary Cancer: Incidence by Body System**

Body System	Treatment Group		<i>P</i> *
	Pravastatin, n (%)	Placebo, n (%)	
Total number of subjects with at least one primary cancer adverse event†	946 (9.6)	914 (9.3)	0.480
Dermatological	357 (3.6)	330 (3.4)	0.313
Endocrine‡/metabolic/electrolyte imbalance	24 (0.2)	12 (0.1)	0.065
Gastrointestinal	137 (1.4)	149 (1.5)	0.475
General	16 (0.2)	21 (0.2)	0.417
Hematopoietic	38 (0.4)	52 (0.5)	0.140
Hepatic/biliary	10 (0.1)	6 (<0.1)	0.454
Musculoskeletal/connective tissue	9 (<0.1)	1 (<0.1)	0.021
Nervous system	16 (0.2)	12 (0.1)	0.571
Renal/genitourinary	266 (2.7)	247 (2.5)	0.421
Respiratory	122 (1.2)	133 (1.4)	0.489
Special senses	4 (<0.1)	3 (<0.1)	>0.999

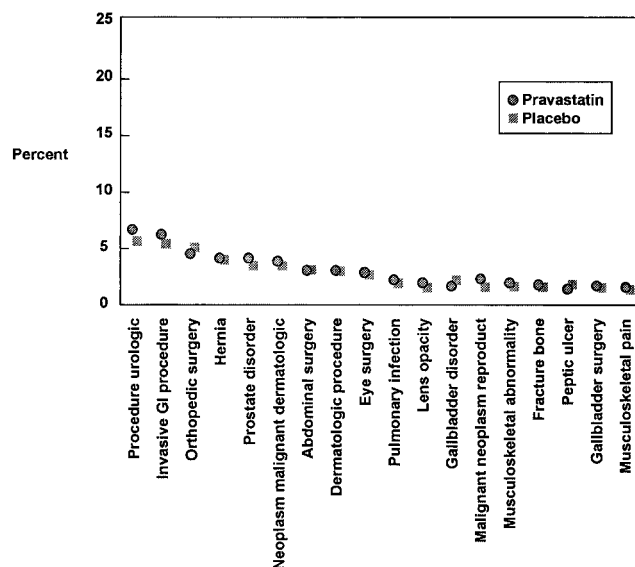
\*Difference of incidence.

†A total of 48 pravastatin and 107 placebo-treated patients had >1 body system cancer; ‡including breast.

There were no differences in the number of serious adverse events reported for noncardiovascular reasons (Figure 1).

**Hepatic Safety**

There was no difference in serious adverse events related to the hepatobiliary system between the pravastatin (n=255; 2.6%) and the placebo-treated subjects (n=297; 3.0%). The most common reported serious adverse event related to the hepatobiliary system was gallbladder disorders, which was reported in 186 (1.9%) of pravastatin-treated and 208 (2.1%) of placebo patients. The incidence of any abnormality of ALT after baseline was similar between the pravastatin and the



**TABLE 3. Serum Chemistry Abnormalities**

	ALT Abnormalities			CPK Abnormalities		
	Pravastatin 40 mg (n=9185), n (%)	Placebo (n=9152), n (%)	95% CI of Difference	Pravastatin 40 mg (n=5245), n (%)	Placebo (n=5233), n (%)	95% CI of Difference
Any value >1.5×ULN	804 (8.8)	746 (8.2)	−0.21, 1.42	587 (11.2)	563 (10.8)	−0.78, 1.65
>1.5×ULN to ≤3×ULN	676 (7.4)	615 (6.7)	−0.11, 1.39	480 (9.2)	460 (8.8)	−0.75, 1.48
>3×ULN to ≤5×ULN	84 (0.9)	90 (1.0)	−0.36, 0.22	84 (1.6)	79 (1.5)	−0.40, 0.59
>5×ULN to ≤7×ULN	24 (0.3)	19 (0.2)	−0.10, 0.21	8 (0.2)	16 (0.3)	−0.36, 0.05
>7×ULN to ≤9×ULN	6 (<0.1)	9 (<0.1)	−0.13, 0.06	6 (0.1)	6 (0.1)	−0.15, 0.15
>9×ULN	14 (0.2)	13 (0.1)	−0.11, 0.13	9 (0.2)	2 (<0.1)	−0.02, 0.28

ULN=upper limit of normal.

placebo groups (Table 3). Moreover, there were no differences in severity of abnormality of ALT. Similarly, no differences in postbaseline abnormalities of aspartate aminotransferase were observed.

The risk of exacerbating an already existing liver function abnormality was evaluated by a subgroup analysis of the 579 patients who were randomized with an abnormal ALT value. At baseline, 317 (3.2%) of the pravastatin-treated subjects and 262 (2.6%) of the placebo-treated subjects had ALT elevations that exceeded baseline (between 1 and 3×ULN). The number of these patients who subsequently showed an increase that was between 1.5 and 3×ULN was comparable (127 of 317 [40.1%] versus 101 of 262 [38.5%] for pravastatin and placebo, respectively). Importantly, the number of these patients with baseline abnormalities in whom ALT was subsequently >3×ULN on any postrandomization sample was 16 of 317 (5.0%) in the pravastatin-treated subjects versus 19 of 262 (7.3%) for placebo-treated subjects.

#### Musculoskeletal Safety

There were no cases of myopathy, which was defined as muscle aching or muscle weakness in conjunction with increases of CPK >10×ULN, or confirmed cases of rhabdomyolysis reported for either pravastatin or placebo-treated groups. The incidence of adverse events due to myalgia and/or myositis was comparable between treatment groups. Although women reported myalgia and myositis more frequently than men, there was no treatment effect. No differences were observed between older versus young subjects. Postbaseline abnormalities of CPK occurred with similar frequencies in the placebo- and pravastatin-treated groups (Table 3).

#### Renal Safety

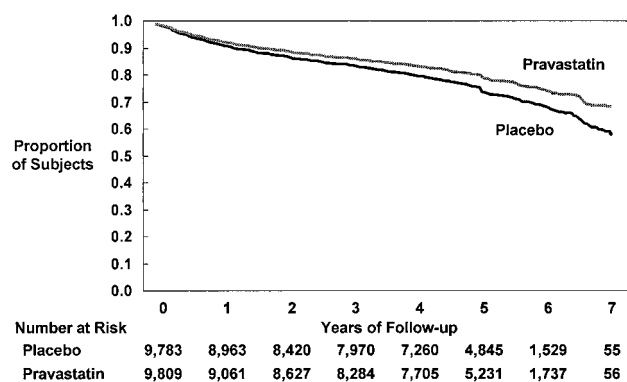
Renal failure or chronic renal failure was designated as a serious adverse event in 78 of 9783 (0.79%) placebo and 48 of 9809 (0.49%) pravastatin subjects. Although more detailed evaluations were not conducted, there was at the least no suggestion of drug-induced severe renal problems.

#### Tolerability

Discontinuation of the blinded study medication for any

for pravastatin versus placebo, respectively;  $P<0.001$ ; Figure 2). An analysis of reported adverse experiences leading to drug discontinuation by body system did not reveal any increase in discontinuation rate attributed to pravastatin therapy for any body system. Indeed, patients taking placebo were more likely to discontinue due to an adverse event classified as related to the cardiovascular, endocrine/metabolic, and general body systems. Therefore, an additional exploratory analysis that excluded patients who discontinued medication after a cardiovascular event still indicated that discontinuation of the blinded study medication was less frequent in the pravastatin than in the placebo group (2050 of 9642 [21.3%] versus 2451 of 9506 [25.8%] for pravastatin versus placebo, respectively;  $P<0.001$ ).

The likelihood of discontinuing study medication was analyzed with a Cox proportional hazards model, which in addition to treatment group used covariates of age, enrollment in either the primary or secondary prevention studies, history of diabetes, smoking status, presence of a serious adverse event attributed to the cardiovascular body system, and treatment by primary or secondary prevention study interaction. Despite the attempts to adjust for potential confounders for long-term continuation on study medication, assignment to pravastatin remained a significant determinant of reduced likelihood to discontinue study medication (increased tolerability; Table 4). Individuals with a history of diabetes, smokers, and those in the primary prevention study were more likely to discontinue study medication, whereas those





**TABLE 4. Factors Affecting Discontinuation of Study Medication: Results From the Multivariate Cox Regression Model**

Parameter	Hazard Ratio	95% CI	P
Treatment group (pravastatin)	0.69	0.64, 0.74	0.001
Age	1.00	1.00, 1.01	0.471
Male sex	0.83	0.76, 0.91	0.001
Primary/secondary prevention	1.15	1.04, 1.26	0.004
History of diabetes	1.34	1.21, 1.49	0.001
Smoking status	1.25	1.16, 1.36	0.001
Presence of a serious adverse event in the cardiovascular body system*	0.76	0.71, 0.81	0.001
Treatment by primary/secondary prevention interaction	1.40	1.24, 1.57	0.001

\*Time-dependent covariate.

experiencing a serious adverse cardiovascular event or who were men were more likely to continue their assigned medication. Independent of these and other factors, assignment to pravastatin was associated with a higher likelihood of continuing study medication (Table 4).

### Discussion

The safety of a pharmaceutical agent is a relative term. Safety concerns for agents used long-term in the treatment of relatively well individuals as preventive therapies would differ from those for agents used for the treatment of life-threatening illnesses for shorter durations. Statins are generally used for long-term exposure. Indeed, even in a secondary prevention study such as LIPID, which enrolled patients with previous acute coronary syndromes who had a median age of 62 years, the averaged modeled life expectancy was  $\approx 15$  years. Even longer durations of therapy would be anticipated in younger patients with less overt vascular disease. Acquisition of safety data are also cumulative, because the safety profile of a pharmaceutical agent becomes more precise with increasing exposure of the molecule to subjects. During initial drug development, animal toxicology is used to recognize those compounds that have already raised possible safety concerns before clinical evaluation. Early short-term clinical efficacy studies, as designed, can only be expected to detect adverse events that occur with relatively high frequency. Indeed, it is acknowledged that regulatory approval for clinical use “does not and cannot guarantee safety.”<sup>19</sup> Large-scale, placebo-controlled trials with long durations provide a greater degree of comfort regarding drug safety and are again dependent on the duration of exposure and the absolute level of risk for the specific safety concern. As the result of major clinical trials involving thousands of patient years of exposure, the first generation of statins (lovastatin, pravastatin, and simvastatin) have not only proven their efficacy but also provided important quantitative safety information. Cerivastatin did not have this degree of exposure from long-term clinical trials and the heightened risk of rhabdomyolysis was only detected after marketing.

Statins decrease intracellular cholesterol production in the liver by partial inhibition of this rate-limiting enzyme for cholesterol biosynthesis. As such, the potential for hepatic toxicity has been a concern since their early development, as has their potential to produce myopathy and rhabdomyolysis. Given these concerns about skeletal muscle and liver function abnormalities, relevant assays for safety surveillance were incorporated into the protocols of these large-scale trials. Indeed, in many respects, patients in clinical trials generally have much closer surveillance than those in general practice. Trial protocols require frequent visits and, depending on the study, surveillance laboratory evaluations. As a result, in the combined PPP experience,  $\approx 243\,000$  blood samples were obtained and analyzed. On the basis of this extensive experience, we were able to quantitate that the risk of developing elevations in hepatic transaminase levels while taking pravastatin (40 mg once daily) was no greater than placebo. Similarly, in the Air Force/Texas Coronary Atherosclerosis Prevention Study, the frequency of detection of consecutive  $3\times\text{ULN}$  elevations in hepatic transaminase was not significantly increased with lovastatin compared with placebo.<sup>20</sup> In the Scandinavian Simvastatin Survival Study, the finding of any  $3\times\text{ULN}$  value of ALT during frequent surveillance was slightly higher in the simvastatin group compared with placebo. However, there was no difference in the groups with respect to the number of patients who had therapy discontinued because of elevated hepatic enzymes (8 of 2221 simvastatin patients and 5 of 2223 placebo patients).<sup>21</sup> The recent report of the Heart Protection Study, which has  $>20\,000$  patients (10 269 on simvastatin and 10 267 on placebo) who were followed for  $\approx 5$  years, reported ALT  $>3\times\text{ULN}$  in only 77 (0.8%) of the patients assigned the statin and 65 (0.6%) of those assigned placebo.<sup>3</sup>

Similarly, despite prestudy concerns about statin-induced myotoxicity, increased rates of rhabdomyolysis or creatinine kinase  $>10\times\text{ULN}$  were not detected in these large-scale clinical trials of first-generation statins (lovastatin, pravastatin, and simvastatin).<sup>22</sup> As a result of major clinical trials with  $>100\,000$  patient-years of exposure, a reliable safety profile of these well-studied agents was available.

With the administration of any pharmacological compound, safety must always be a consideration. Acquisition of safety data is a continuous process that should never be considered complete. At this time, our extensive pooled data had a 99% chance of detecting events that had a frequency  $>1$  in 1000 and a 62.5% chance for events with a frequency of  $\geq 1$  in 10 000 during the period of monitoring. The postmarketing detection of an excessive risk of fatal rhabdomyolysis associated with cerivastatin serves to reinforce the need for specific safety information for each molecule. Because this particular agent was not used in long-term morbidity/mortality trials, the available safety information was much less robust. Although differences in lipophilicity, drug metabolism by the hepatic cytochrome P-450 system, and drug interactions have been postulated to explain the different safety profiles of statins, there should be no substi-

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