
Summary and Introduction

Summary

In the Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin (STELLAR) trial, the efficacy of rosuvastatin calcium (Crestor[®]) was compared with that of atorvastatin (Lipitor), simvastatin (Zocor), and pravastatin (Pravachol[®]) for lowering plasma low-density lipoprotein cholesterol (LDL-C) after 6 weeks of treatment. In this multicenter, parallel-group, open-label trial, adults with hypercholesterolemia were randomized to treatments with rosuvastatin 10, 20, 40, or 80 mg, atorvastatin 10, 20, 40, or 80 mg, simvastatin 10, 20, 40, or 80 mg, or pravastatin 10, 20, or 40 mg. Efficacy and safety results from this trial have been previously published. The additional analyses included in this report show that 53% (83/156) to 80% (125/157) of patients in the rosuvastatin 10- to 40-mg groups achieved LDL-C levels < 100 mg/dl (< 2.6 mmol/l), compared with 18% (28/158) to 70% (115/165) of patients who received atorvastatin, 8% (13/165) to 53% (86/163) of patients who received simvastatin, and 1% (1/160) to 8% (13/161) of patients who received pravastatin. Other additional analyses showed that more patients in the rosuvastatin 10- to 40-mg groups than in the comparator groups who were at high risk of coronary heart disease according to National Cholesterol Education Program Adult Treatment Panel (ATP) III, Joint European Societies, or Canadian guidelines achieved the LDL-C goals of < 100 mg/dl (< 2.6 mmol/l) (55% to 77% compared with 0 to 64%), < 3.0 mmol/l (< 116 mg/dl) (76% to 94% compared with 6% to 81%), and < 2.5 mmol/l (< 97 mg/dl) (47% to 69% compared with 0 to 53%), respectively. Results favoring rosuvastatin versus the comparators were also reported for patients: (a) who had triglycerides \geq 200 mg/dl (\geq 2.3 mmol/l), and achieved both ATP III LDL-C and non-high-density lipoprotein cholesterol (non-HDL-C) goals (80% to 84% versus 15% to 84%); (b) overall who achieved the Canadian LDL-C goals of < 2.5 (< 97 mg/dl) to < 5.0 mmol/l (< 193 mg/dl) (85% to 91% versus 44% to 86%); and (c) who achieved all 3 Canadian goals for LDL-C, triglycerides (< 3.0 mmol/l [$<$ 266 mg/dl]) to < 2.0 mmol/l [$<$ 177 mg/dl]), and the total cholesterol/high-density lipoprotein-cholesterol ratio (< 4 to < 7) (70% to 83% versus 35% to 79%).

Introduction

Much evidence supports the association between dyslipidemia and an increased risk of coronary heart disease (CHD).^[1,2] Contributing to this evidence are the large-scale, prospective, randomized clinical trials that have shown the strong association between the reductions in plasma low-density lipoprotein cholesterol (LDL-C) achieved with statins (3-hydroxy-3-methylglutaryl coenzyme A-reductase inhibitors) and reductions in CHD risk.^[3-7] These results have led to the development of treatment guidelines that identify LDL-C as the primary focus of dyslipidemia therapy and set LDL-C treatment goals.^[1,2,8] The authors of these guidelines have also recognized the associations that have been shown between CHD risk and low levels of high-density lipoprotein cholesterol (HDL-C), hypertriglyceridemia, high total cholesterol/HDL-C ratios, and high non-HDL-C (total cholesterol minus HDL-C), which represents cholesterol in the atherogenic lipoprotein components, by including these in secondary goals.

The evidence-based National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines^[1] identified an LDL-C level of < 100 mg/dl (< 2.6 mmol/l) as optimal for all adults. Since the release of the ATP III guidelines, two large prospective trials^[9,10] have contributed additional evidence for decreasing CHD risk with aggressive LDL-C reduction with statins to well below 100 mg/dl (2.6 mmol/l). Both trials included patients whose initial LDL-C levels would have been considered acceptable in the past, and both showed significant reductions in cardiovascular events, compared with placebo.

Despite the evidence for the benefit of LDL-C levels below 100 mg/dl (2.6 mmol/l), achievement of these lower levels has proven difficult.^[11,12] For example, the Lipid Treatment Assessment Project (L-TAP) study showed that only 18% of patients with an LDL-C ATP II goal of \leq 100 mg/dl (\leq 2.6 mmol/l) achieved their treatment goal with drug therapy. Factors contributing to these findings were inadequate treatment with existing therapies and the inability of these therapies to produce the large LDL-C reductions needed by many adults.^[13]

The STELLAR trial was designed to compare the lipid-modifying efficacy of statins across doses in patients with hypercholesterolemia.^[14] This trial, which was the largest of its kind to date, showed that more patients in the rosuvastatin groups reached both NCEP ATP III and European goals.^[14] The objective of this paper is to report more details regarding achievement of lipid goals than could be presented previously. We include the goal achievement results of patients considered to be at a high risk of CHD according to either ATP III or European guidelines, as well as the achievement of

the secondary ATP III non-HDL-C goals by a subset of patients with high triglycerides at baseline. The proportions of patients who achieved Canadian goals, which use a different set of criteria, and those who achieved LDL-C levels of < 100 mg/dl (< 2.6 mmol/l), regardless of risk category, are also presented.

Methods

The details regarding trial design and measurements have been published previously.^[14] This randomized, open-label, parallel-group, multicenter trial (45221L/0065) consisted of a 6-week dietary lead-in period and a 6-week randomized treatment period. Adult patients with LDL-C levels ≥ 160 mg/dl (≥ 4.1 mmol/l) and < 250 mg/dl (< 6.5 mmol/l), and triglyceride levels < 400 mg/dl (< 4.5 mmol/l), were randomized into 15 groups that received rosuvastatin calcium (Crestor[®]) 10, 20, 40, or 80 mg, atorvastatin (Lipitor) 10, 20, 40, or 80 mg, simvastatin (Zocor) 10, 20, 40, or 80 mg, or pravastatin (Pravachol[®]) 10, 20, or 40 mg.^[14] To present clinically relevant results that would be consistent with existing and proposed labeling, the results from the analyses reported here do not include rosuvastatin 80mg.

To assess the number of patients who met NCEP ATP III goals, patients were grouped according to CHD risk, as defined in the guidelines.^[1] For patients with CHD, CHD risk equivalents (such as peripheral vascular disease or diabetes), or multiple risk factors conferring a 10-year risk of CHD > 20%, the LDL-C goal was defined as < 100mg/dl (< 2.6 mmol/l). Treatment goals of < 130 mg/dl (< 3.4 mmol/l) and < 160 mg/dl (< 4.1 mmol/l) were specified for patients without CHD and with lower CHD risk. For patients with triglyceride levels ≥ 200 mg/dl (≥ 2.3 mmol/l), ATP III guidelines specify non-HDL-C levels 30 mg/dl (0.8 mmol/l) higher than LDL-C goals as secondary goals of therapy. In this study, a subset of patients who had triglyceride levels ≥ 200 mg/dl (≥ 2.3 mmol/l) at baseline were identified, and both LDL-C and non-HDL-C goal achievement was assessed in these patients.

The Second Joint Task Force of European and other Societies on Coronary Prevention guidelines^[2] specify an LDL-C goal of < 3.0 mmol/l (< 116 mg/dl) for all patients, regardless of risk. These guidelines define high-risk patients as those with CHD, diabetes, a family history of premature CHD or peripheral vascular disease, or a risk of $\geq 20\%$ over 10 years or projected to be > 20% by 60 years of age. For patients in this trial, the published charts^[2] were the basis of calculations of risk.

Canadian guidelines^[8] specify four risk categories according to an estimated coronary artery disease risk: low for patients with a 10-year risk of < 10%, moderate for those with a 10-year risk of 10% to < 20%, high for those with a 10-year risk of 20% to 30%, and very high for those with a 10-year risk of > 30% or a history of coronary artery disease or diabetes. The LDL-C goals for these risk categories are < 5.0 mmol/l (< 193 mg/dl), < 4.0 mmol/l (< 155 mg/dl), < 3.0 mmol/l (< 116 mg/dl), and < 2.5 mmol/l (< 97 mg/dl), respectively. The corresponding goals for the total cholesterol/HDL-C ratio are < 7, < 6, < 5, and < 4, respectively. Triglyceride goals are < 3.0 mmol/l (< 266 mg/dl) for the low-risk category and < 2.0 mmol/l (< 177 mg/dl) for higher-risk categories.

Statistical Analysis

Pre-specified statistical comparisons included 22 pair-wise comparisons of rosuvastatin doses with equivalent or higher doses of the comparators. The significance level was adjusted to < 0.002 to account for multiple comparisons (Bonferroni adjustment).^[15] A logistic regression model that included terms for treatment, baseline LDL-C level, and risk group was used to compare goal achievement when the data included all patients regardless of risk. For all other analyses of goal achievement, data were summarized descriptively. With the exception of the analysis of all patients (regardless of risk category) who achieved LDL-C levels of < 100 mg/dl (< 2.6 mmol/l), analyses were prospectively planned.

Results

Patients

Patient characteristics were similar among groups.^[14] Of the 2268 patients randomized to the rosuvastatin 10- to 40-mg, atorvastatin, simvastatin, and pravastatin groups, 51% were women, 29% were ≥ 65 years of age, 36% had a body mass index > 30 kg/m², 19% had a documented history of atherosclerotic disease, and 7% had diabetes.^[14] The average age was 57 years.^[14] Overall, 94% completed 6 weeks of treatment, and withdrawal rates were similar among groups.^[14]

LDL-C Levels and the Percentage Reaching LDL-C Levels < 100 mg/dl (< 2.6 mmol/l)

Table 1 shows mean LDL-C levels at 6 weeks. The percentages of all patients, regardless of risk category, who achieved an LDL-C level of < 100 mg/dl (< 2.6 mmol/l) ranged from 1% in the pravastatin 10-mg group to 80% in the rosuvastatin

40-mg group (Figure 1). The proportion of patients achieving this LDL-C level in the rosuvastatin groups was significantly higher ($p < 0.002$) than in groups receiving equivalent doses of atorvastatin, and equivalent and higher doses of simvastatin and pravastatin.

Table 1. Mean (SD) LDL-C levels at baseline and 6 weeks

Dose	Rosuvastatin	Atorvastatin	Simvastatin	Pravastatin
Baseline means*, range				
mg/dl	187 (18) to 194 (19)	189 (18) to 190 (20)	187 (16) to 190 (19)	187 (17) to 190 (19)
mmol/l	4.85 (0.47) to 5.01 (0.49)	4.89 (0.48) to 4.92 (0.51)	4.85 (0.42) to 4.93 (0.50)	4.82 (0.44) to 4.92 (0.50)
10 mg				
mg/dl	102 (25)	119 (22)	135 (27)	150 (24)
mmol/l	2.63 (0.65)	3.09 (0.57)	3.50 (0.70)	3.89 (0.61)
20 mg				
mg/dl	89 (25)	109 (30)	123 (22)	141 (25)
mmol/l	2.30 (0.64)	2.82 (0.77)	3.18 (0.57)	3.65 (0.66)
40 mg				
mg/dl	87 (26)	99 (26)	114 (26)	134 (28)
mmol/l	2.25 (0.66)	2.55 (0.67)	2.96 (0.68)	3.46 (0.71)
80 mg				
mg/dl	NA	93 (26)	103 (25)	NA
mmol/l		2.40 (0.67)	2.67 (0.66)	

NA, not applicable

*Baseline means were reported in Jones et al., Am J Cardiol 2003;92:152-6014 .

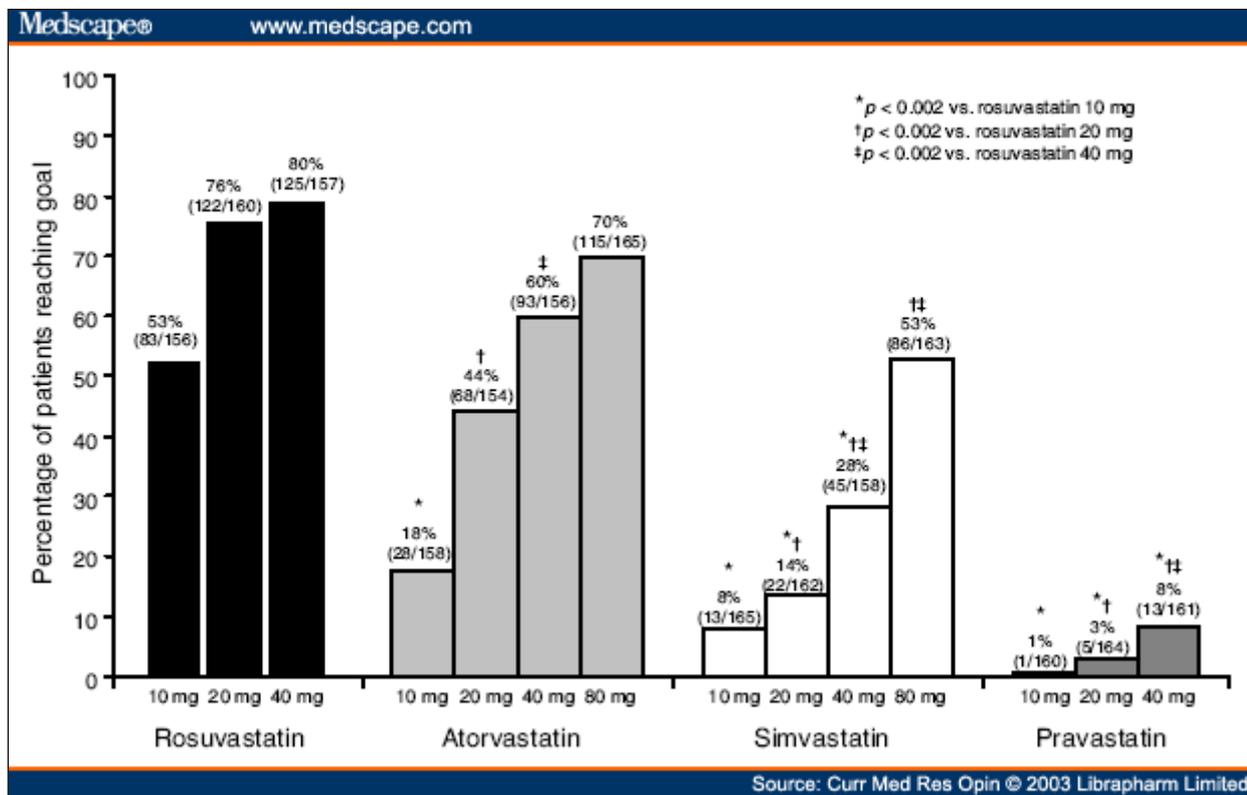


Figure 1. Proportions of all patients who had LDL-C levels < 100 mg/dl (< 2.6 mmol/l) at 6 weeks. Results of 22 pair-wise statistical comparisons between rosuvastatin doses and equivalent or higher doses of comparators are shown. (The significance level was adjusted to < 0.002 to account for multiple comparisons.)

NCEP ATP III Goal in High-risk Patients

Overall, 30% (665/2239) of the patients in this trial were classified as having a high risk of CHD according to NCEP ATP III guidelines. Achievement of an LDL-C level of < 100 mg/dl (< 2.6 mmol/l) in this subset of patients followed the pattern described above for all patients and ranged from 0 in the pravastatin 10-mg group to 77% in the rosuvastatin 20-mg group (Figure 2).

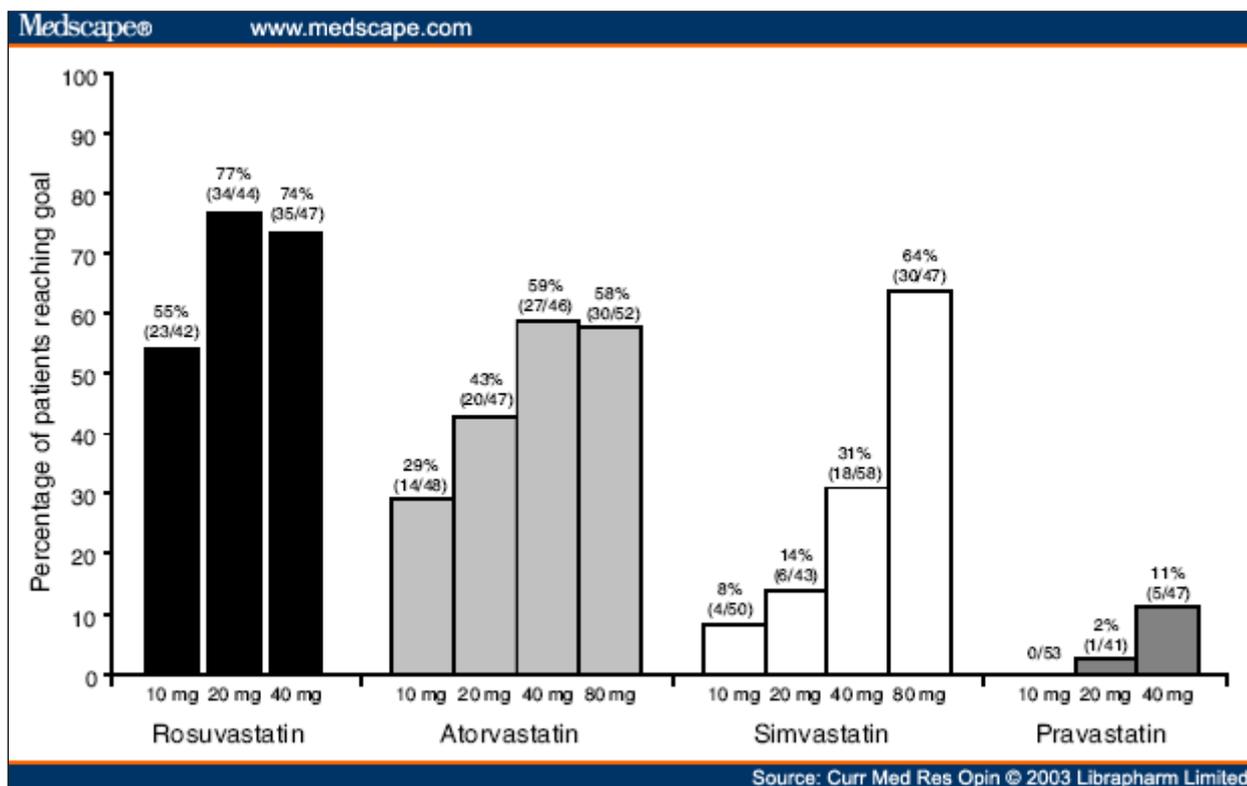


Figure 2. Proportions of patients at high risk of coronary heart disease according to NCEP ATP III guidelines who

met the LDL-C goal of < 100 mg/dl (< 2.6 mmol/l)

LDL-C and Non-HDL-C Goals in Patients with Triglycerides \geq 200 mg/dl (\geq 2.3 mmol/l)

At baseline, 35% (773/2239) of the patients in the trial had triglyceride levels \geq 200 mg/dl (\geq 2.3 mmol/l). Following ATP III guidelines, we analyzed the proportions of patients in this subgroup who achieved both LDL-C and non-HDL-C goals. Among all patients, baseline non-HDL-C treatment group means ranged from 222 to 230 mg/dl (5.73 to 5.96 mmol/l), and reductions from baseline ranged from 42% to 51% in the rosuvastatin 10- to 40-mg groups, 34% to 48% in the atorvastatin 10- to 80-mg groups, 26% to 42% in the simvastatin 10- to 80-mg groups, and 19% to 27% in the pravastatin 10- to 40-mg groups. Among patients who had baseline triglyceride levels \geq 200 mg/dl (\geq 2.3 mmol/l), the rosuvastatin 20-mg and atorvastatin 40-mg groups had the highest percentage (84%) of patients who reached both LDL-C and non-HDL-C ATP III goals (Figure 3). In the rosuvastatin 10-mg group, 80% of patients reached their goals. This percentage was significantly more ($p < 0.002$) than in the atorvastatin 10-mg group and similar to that in the atorvastatin 40- and 80-mg groups (84% and 80%). Lower percentages of patients met both goals in the simvastatin and pravastatin groups (15% to 60%).

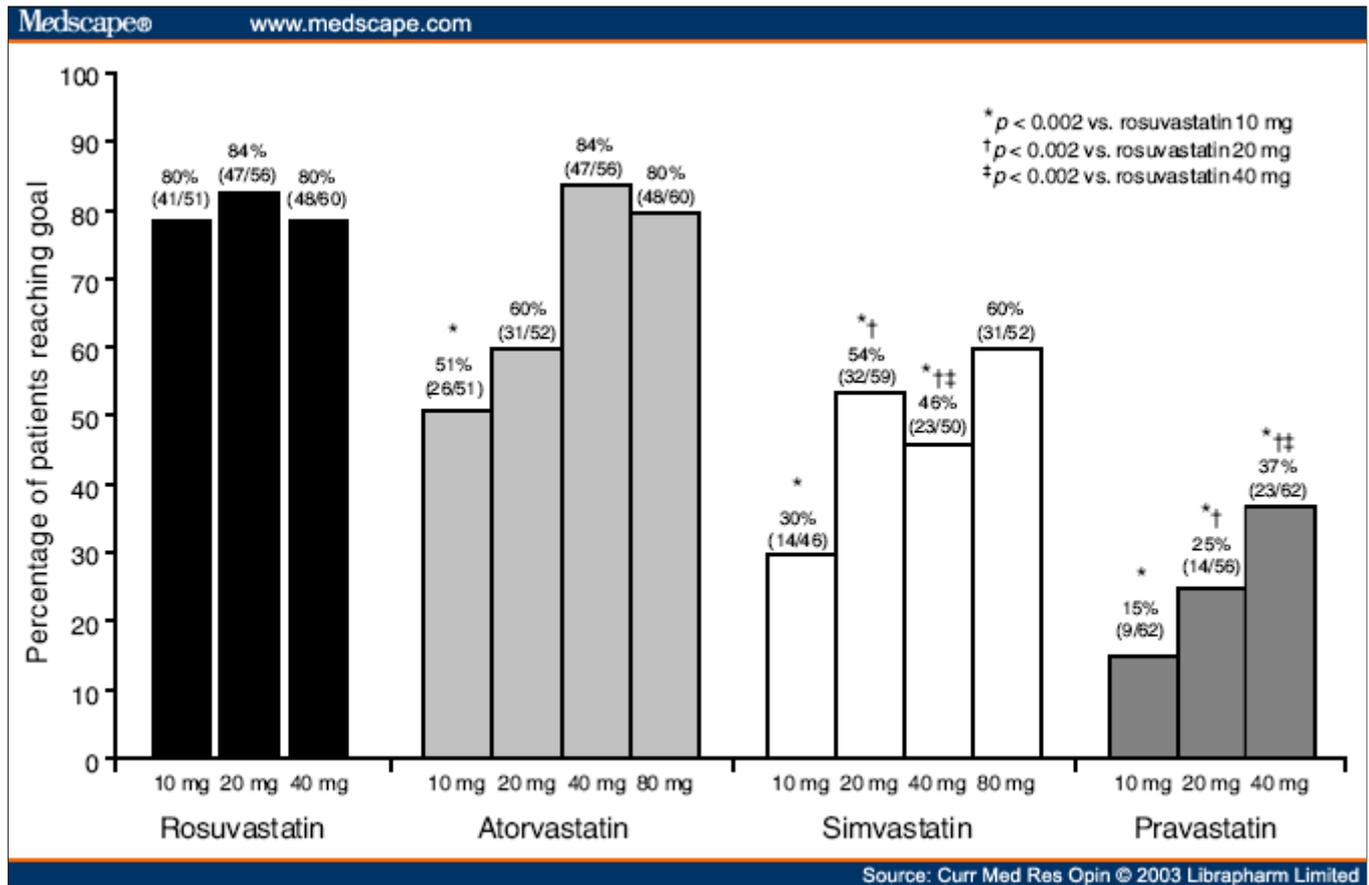


Figure 3. Proportions of patients with baseline triglyceride levels \geq 200 mg/dl (\geq 2.3 mmol/l) who met ATP III LDL-C goals and corresponding non-HDL-C goals. Results of 22 pair-wise statistical comparisons between rosuvastatin doses and equivalent or higher doses of comparators are shown. (The significance level was adjusted to < 0.002 to account for multiple comparisons.)

European LDL-C Goal in High-risk Patients

Overall, 76% of patients were classified as having a high CHD risk according to European guidelines. The proportions of these patients who achieved the European LDL-C goal of < 3.0 mmol/l (< 116 mg/dl) ranged from 76% (87/114) to 94% (105/112) in the rosuvastatin 10- to 40-mg groups, compared with 47% (58/124) to 81% (101/124) in the atorvastatin 10- to 80-mg groups, 21% (26/122) to 77% (93/121) in the simvastatin 10- to 80-mg groups, and 6% (7/125) to 23% (30/130) in the pravastatin 10- to 40-mg groups (data not shown). The results for this subset of high-risk patients were similar to those for all patients both at high risk and not at high risk in each group who achieved an LDL-C goal of < 3.0 mmol/l (< 116 mg/dl).^[14]

Canadian LDL-C Goals

According to Canadian guidelines, 27% of patients (612/2239) were considered to have a very high risk of coronary artery disease, 6% (140/2239) were considered to have a high risk, 28% (633/2239) were considered to have a moderate risk,

and 38% (854/2239) were considered to have a low risk. The highest proportions of patients who achieved their LDL-C treatment goals were in the rosuvastatin 10- to 40-mg groups (85% to 91%) and the atorvastatin 40-mg and 80-mg groups (84% and 86%) (Figure 4). Among the patients with a very high risk of coronary artery disease who had an LDL-C goal of < 2.5mmol/l (< 97 mg/dl), more patients (69% and 63%) in the rosuvastatin 20- and 40-mg groups achieved their goal than in any other group (Figure 5).

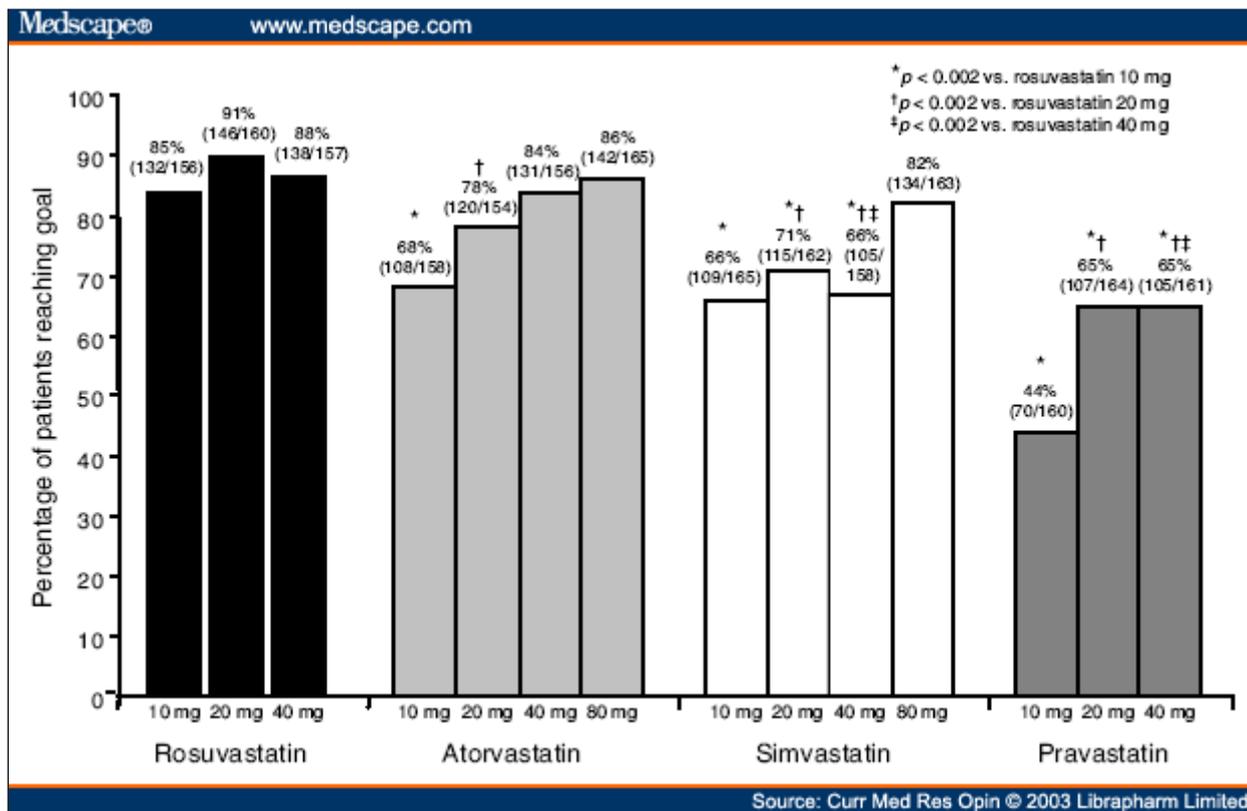


Figure 4. Proportions of patients who met Canadian guideline LDL-C goals. Results of 22 pair-wise statistical comparisons between rosuvastatin doses and equivalent or higher doses of comparators are shown. (The significance level was adjusted to < 0.002 to account for multiple comparisons.)

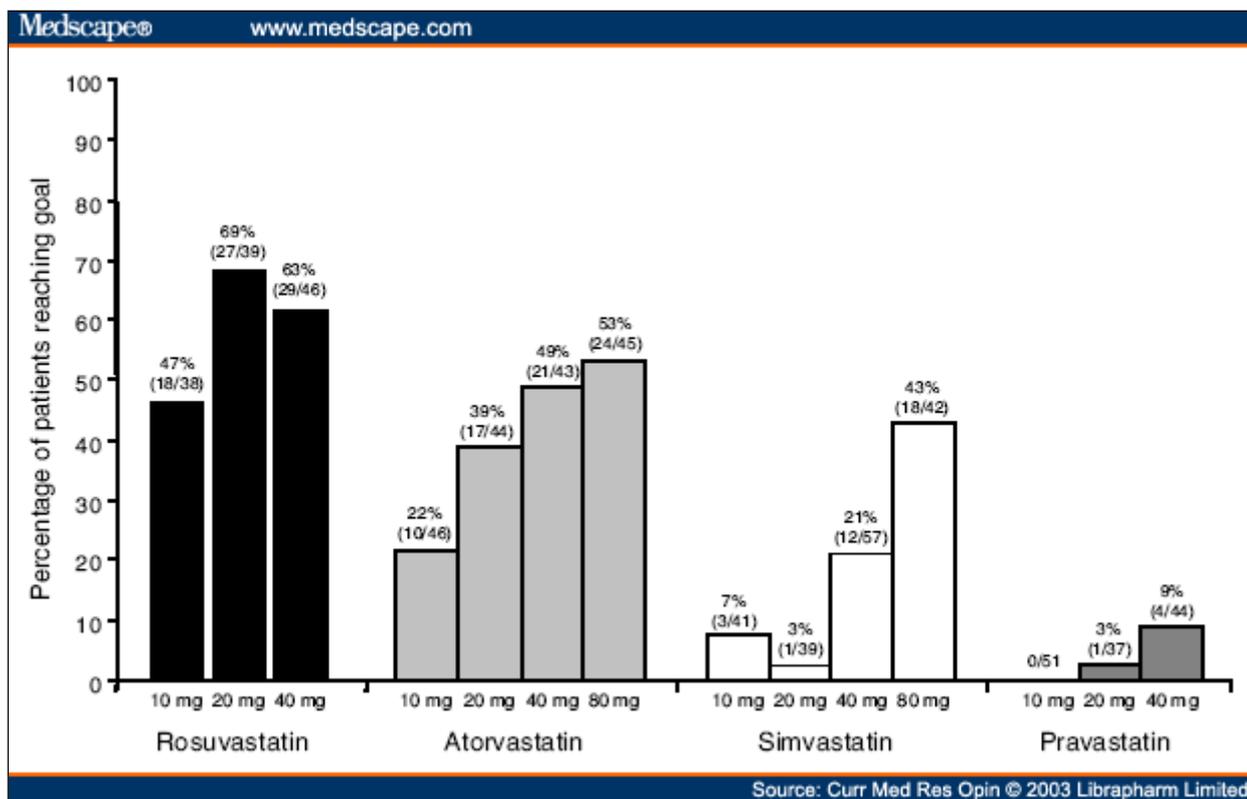


Figure 5. Proportions of patients classified as having a very high risk of coronary artery disease by Canadian

guidelines who met the LDL-C goal of < 2.5 mmol/l (< 97 mg/dl)

Canadian LDL-C, Triglyceride, and Total Cholesterol/HDL-C Ratio Goals

In the rosuvastatin 10- to 40-mg groups, the total cholesterol/HDL-C ratio was reduced by 37% to 45% from baseline, compared with 31% to 40% in the atorvastatin groups, 24% to 37% in the simvastatin groups, and 17% to 25% in the pravastatin groups. (Overall baseline was 5.7.) Triglycerides were reduced 20% to 26% in the rosuvastatin groups, 20% to 28% in the atorvastatin groups, 12% to 18% in the simvastatin groups, and 8% to 13% in the pravastatin groups.^[14] The highest proportion of patients (83%) reaching the Canadian triple goal criteria for LDL-C, total cholesterol/HDL-C ratio, and triglycerides was in the rosuvastatin 40-mg group. This proportion was not significantly different from the proportions achieving these goals in the atorvastatin 40- and 80-mg groups (75% and 79%), but was significantly different from the proportions achieving these goals in the simvastatin 40- and 80-mg (56% and 69%) and pravastatin 40-mg (55%) groups (Figure 6). Among high-risk patients with the lowest goals, 32% to 59% of patients in the rosuvastatin 10- to 40-mg groups met all three goals, compared with 17% to 44% in the atorvastatin groups, 3% to 29% in the simvastatin groups, and 0 to 3% in the pravastatin groups (data not shown).

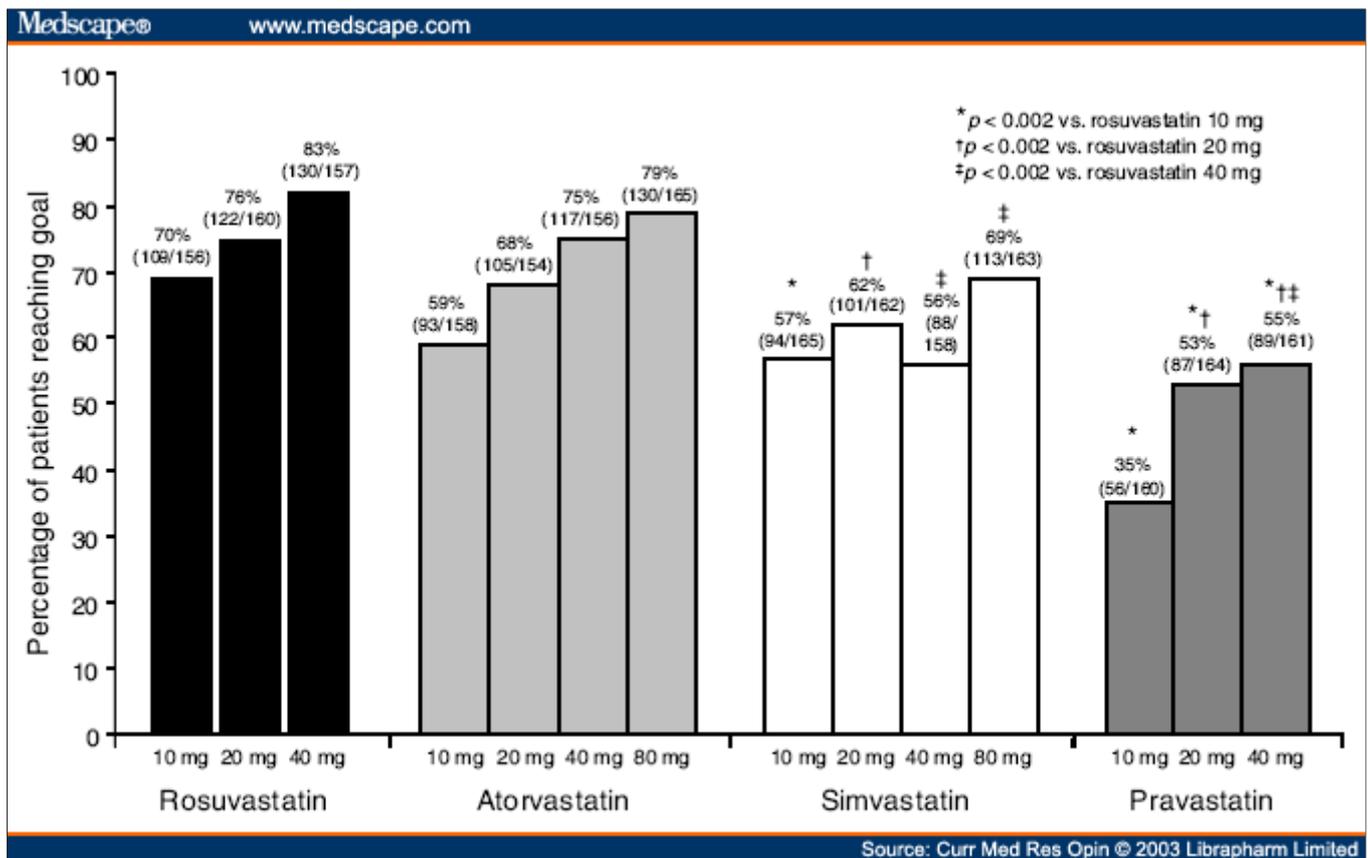


Figure 6. Proportions of patients who met Canadian LDL-C, total cholesterol/HDL-C ratio, and triglyceride goals. Results of 22 pair-wise statistical comparisons between rosuvastatin doses and equivalent or higher doses of comparators are shown. (The significance level was adjusted to < 0.002 to account for multiple comparisons.)

Discussion

The STELLAR trial is the largest trial of its kind to date to compare dose-related effects of statins on lipid goal achievement in patients with hypercholesterolemia. Trial results indicate that rosuvastatin 10 to 40 mg has greater efficacy than atorvastatin 10 to 80 mg, simvastatin 10 to 80 mg, and pravastatin 10 to 40 mg for achievement of ATP III LDL-C and non-HDL-C goals, European LDL-C goals, and Canadian LDL-C and triple goals (which also included total cholesterol/HDL-C ratio and triglyceride goals). It is particularly noteworthy that with rosuvastatin therapy, more patients achieve the most aggressive LDL-C goals of < 100 mg/dl (< 2.6 mmol/l) and < 116 mg/dl (< 3.0 mmol/l), regardless of CHD risk status. This greater goal-attaining efficacy of rosuvastatin is due in large part to its greater efficacy in lowering LDL-C, as shown previously (Figure 7).^[14] Rosuvastatin 10 mg reduced LDL-C by 46%, which was significantly greater ($p < 0.002$) than the 37% reduction achieved with atorvastatin 10 mg, the 28% to 39% reductions achieved with simvastatin 10 to 40 mg, and the 20% to 30% reductions achieved with pravastatin 10 to 40 mg.^[14] In the rosuvastatin 40-mg group, LDL-C was reduced by 55%, compared with 48% for atorvastatin 40 mg ($p < 0.002$), 51% for atorvastatin 80 mg ($p =$

0.006, NS), 39% for simvastatin 40 mg ($p < 0.002$), 46% for simvastatin 80mg ($p < 0.002$), and 30% for pravastatin 40 mg ($p < 0.002$).^[14]

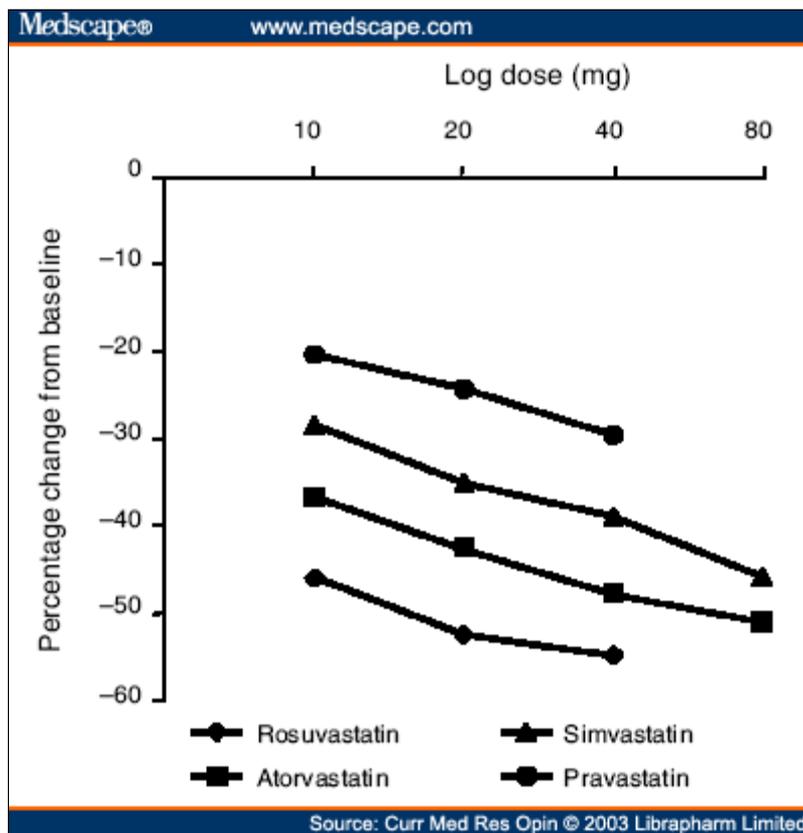


Figure 7. Least-square mean LDL-C changes from baseline. In 22 pair-wise comparisons of rosuvastatin with equivalent or higher doses of comparators using an analysis of variance, rosuvastatin 10 mg was significantly different ($p < 0.002$) from atorvastatin 10 mg, simvastatin 10, 20, and 40 mg, and pravastatin 10, 20, and 40mg; rosuvastatin 20 mg was significantly different from atorvastatin 20 and 40 mg, simvastatin 20, 40, and 80mg, and pravastatin 20 and 40 mg; rosuvastatin 40mg was significantly different from atorvastatin 40 mg, simvastatin 40 and 80 mg, and pravastatin 40mg.^[14] (Overall baseline means 189 mg/dl [4.9 mmol/l].)

As previously reported, trial treatments were generally well tolerated, and the percentages of patients who reported adverse events were similar among treatments.^[14] The most common adverse events reported were pain (6%), pharyngitis (5%), myalgia (4%), and headache (3%).

Many patients do not achieve LDL-C treatment goals in clinical practice.^[11] This failure is most pronounced in patients who require the greatest LDL-C reductions to achieve goals.^[11,12,16] Part of the reason for this observation is that most patients tend to remain on the statin dose that was initially prescribed, and statin doses often are not titrated upward.^[11,17,18] The greater efficacy of rosuvastatin 10 mg, compared with milligram-equivalent or higher doses of some other statins, should reduce the need for titration to higher doses to achieve goals and thus may reduce the frequency of medical contacts. The need for fewer titration steps with rosuvastatin is supported by the results of a trial reported by Olsson et al.^[19] In that trial, rosuvastatin and atorvastatin were titrated as needed to achieve the patient's LDL-C goal. After 52 weeks, 82% of the patients treated with rosuvastatin 10 mg initially had achieved their treatment goals at trial end while still receiving rosuvastatin 10 mg. In contrast, only 59% of patients treated with atorvastatin 10mg had achieved their LDL-C goal without titration.

The findings in the current trial are consistent with those previously reported for rosuvastatin. Pooled data from trials using usual starting doses showed that significantly more high-risk patients treated with rosuvastatin 10 mg achieved the ATP III LDL-C goal of < 100 mg/dl (< 2.6 mmol/l) than those treated with atorvastatin 10 mg (60% vs. 19%, $p < 0.001$).^[20] Differences between rosuvastatin 10 mg and simvastatin 20 mg or pravastatin 20 mg were also significant ($p < 0.001$) among high-risk patients.^[20] The LDL-C reductions achieved with atorvastatin, simvastatin, and pravastatin in the current trial were also consistent with the 6-week results in a previous trial in which atorvastatin was compared with simvastatin, pravastatin, lovastatin, and fluvastatin.^[21] However, in that trial higher percentages of high-risk patients treated with equivalent doses achieved their NCEP ATP II^[22] goal of ≤ 100 mg/dl (≤ 2.6 mmol/l) than the percentages of patients in our

trial who reached LDL-C levels of < 100 mg/dl (< 2.6 mmol/l). A likely explanation for this difference was that some patients needed less LDL-C reduction to achieve their goals in that trial, because their baseline LDL-C inclusion criteria were wider, > 130 mg/dl (> 3.4 mmol/l) and < 250 mg/dl (< 6.5 mmol/l), in contrast with our trial in which patients were required to have LDL-C levels \geq 160 mg/dl (\geq 4.1 mmol/l) and < 250mg/dl (< 6.5mmol/l).

The proportions of patients who achieved both LDL-C and non-HDL-C goals and the Canadian triple goals reflect the percentage changes from baseline observed for the secondary end points of non-HDL-C in the various groups. These results indicate that rosuvastatin not only has a significant effect on LDL-C but also has favorable effects on the atherogenic profile. A limitation in application of these results is the fact that patients in this trial were selected for their LDL-C levels and not for triglyceride levels. The patients who will benefit most from achieving these additional goals are those who have hypertriglyceridemia and related syndromes.^[1]

In summary, more patients treated with rosuvastatin 10 to 40mg achieved lipid goals, and optimal LDL-C levels as suggested by the NCEP ATP III and European guidelines, than patients treated with atorvastatin, simvastatin, and pravastatin. The proportions of patients in the rosuvastatin 10-mg group who reached the LDL-C level of < 100 mg/dl (< 2.6 mmol/l), both the non-HDL-C and LDL-C goals, and the Canadian LDL-C goals were significantly greater ($p < 0.002$) than the proportions in the atorvastatin 10-mg, simvastatin 10-, 20-, and 40-mg, and pravastatin 10-, 20-, and 40-mg groups. The highest proportions of patients who achieved NCEP ATP III, European, and Canadian goals were in the rosuvastatin groups.

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Authors and Disclosures

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