Effects of switching statins on achievement of lipid goals: Measuring Effective Reductions in Cholesterol Using Rosuvastatin Therapy (MERCURY I) study

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Background In a multinational trial (4522IL/0081), we assessed the effects of switching to low doses of rosuvastatin from commonly used doses of atorvastatin, simvastatin, and pravastatin on low-density lipoprotein cholesterol (LDL-C) goal achievement in high-risk patients.

Methods Hypercholesterolemic patients (n = 3140) with coronary heart disease, atherosclerosis, or type 2 diabetes were randomized to open-label rosuvastatin 10 mg, atorvastatin 10 or 20 mg, simvastatin 20 mg, or pravastatin 40 mg for 8 weeks. Patients either remained on these treatments for another 8 weeks or switched treatments from atorvastatin 10 mg, simvastatin 20 mg, and pravastatin 40 mg to rosuvastatin 10 mg or from atorvastatin 20 mg to rosuvastatin 10 or 20 mg. The primary efficacy measure was the proportion of patients reaching the Joint European Societies' LDL-C goal (<116 mg/dL) at week 16. For measures of cholesterol goal achievement, treatment arms were compared using logistic-regression analysis.

Results Significant improvement in LDL-C goal achievement was found for patients who switched to rosuvastatin 10 mg, compared with patients who remained on atorvastatin 10 mg (86% vs 80%, $P < .05$), simvastatin 20 mg (86% vs 72%, $P < .0001$), and pravastatin 40 mg (88% vs 66%, $P < .0001$), and between patients switched to rosuvastatin 20 mg and those who remained on atorvastatin 20 mg (90% vs 84%, $P < .01$). Similar results were found for achievement of the European combined LDL-C and total cholesterol goals and National Cholesterol Education Program Adult Treatment Panel III LDL-C goals. All statins were well tolerated over 16 weeks.

Conclusions We demonstrated that switching to a more efficacious statin is an effective strategy to improve lipid goal achievement in patients requiring lipid-lowering therapy. (Am Heart J 2004;147:705–12.)

Achievement of cholesterol goals is an important objective of lipid-lowering therapy in clinical practice.[1,2] However, many patients receiving lipid-lowering therapy fail to achieve their cholesterol goals, with such failure being particularly prevalent in patients with coronary heart disease (CHD) or at elevated risk for CHD.[3–5] Statins are the most widely used lipid-lowering therapy, and low doses of these agents are most commonly used in clinical practice.[4,5] Statins differ with regard to their effectiveness in lowering low-density lipoprotein cholesterol (LDL-C), and thus their ability to enable patients to achieve their individual LDL-C goal.[6–8] In clinical practice, switching patients from one statin to another that is more effective in lowering LDL-C is a therapeutic option for managing high blood cholesterol; however, this practice has not been adequately investigated. The Measuring Effective Reductions in Cholesterol Using Rosuvastatin Therapy (MERCURY I) study was designed to evaluate the effects of switching statins on cholesterol goal achievement and lipid measures in a large, well-defined population of

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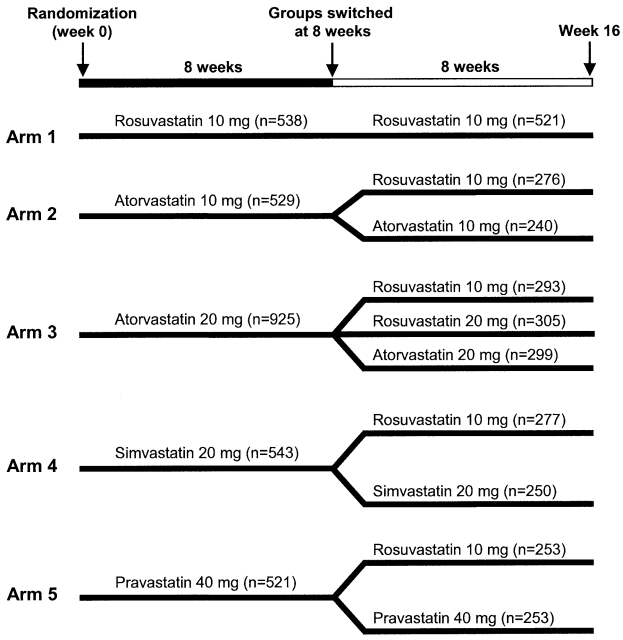
Figure 1



Trial design.

patients requiring lipid-lowering therapy. We assessed the effects of switching from commonly used doses of atorvastatin, simvastatin, and pravastatin to low doses of rosuvastatin (licensed to AstraZeneca, Alderley Park, Cheshire, UK, from Shionogi & Co, Ltd, Osaka, Japan), a new statin that has previously demonstrated greater LDL-C reductions and better LDL-C goal achievement when compared with these statins.[8–13]

Methods

Trial design

This was a randomized, open-label, 5-arm, parallel-group, 2-period multicenter trial (4522IL/0081) conducted at 224 centers in Europe, Canada, and Australia. This trial was designed and conducted in accordance with the Declaration of Helsinki (version amended in October 2000) and in compliance with the ethical principles of good clinical practice. Appropriate ethics committees or institutional review boards approved the trial, and all patients gave their written, informed consent before initiation of any trial procedure.

After a 6-week dietary lead-in period during which patients discontinued all lipid-lowering therapies and were instructed in and assessed for compliance with the National Cholesterol Education Program Step I diet,[14] eligible patients were randomized as follows for 8 weeks (period 1): rosuvastatin 10 mg (arm 1), atorvastatin 10 mg (arm 2), atorvastatin 20 mg (arm 3), simvastatin 20 mg (arm 4), or pravastatin 40 mg (arm 5) (Figure 1). Thereafter, patients in arm 1 continued receiving rosuvastatin 10 mg for another 8 weeks (period 2), and patients in other treatment arms either remained on these treatments for 8 weeks or switched treatments from atorvastatin 10 mg, simvastatin 20 mg, and pravastatin 40 mg to rosuvastatin 10 mg or from atorvastatin 20 mg to rosuvastatin 10 or 20 mg. The original trial protocol included a cerivastatin 0.3-mg treatment arm; however, after cerivastatin was withdrawn from the market approximately 3 months after the start of the MERCURY I study, the cerivastatin arm was removed from the trial by protocol amendment. Patients were randomized by assignment to treatment on the basis of sequential patient numbers using a randomization scheme generated by SAS statistical software (version 6.12, SAS Institute, Cary, NC). A separate randomization scheme was used at each center, with patients being allocated to treatment in balanced blocks.

Study population

Patients eligible for randomized treatment were those who qualified for lipid-lowering therapy according to the Joint European Societies' cholesterol management guidelines.[1] Patients were aged ≥18 years with a history of CHD or other established atherosclerotic disease, type 2 diabetes, or a CHD risk >20% over 10 years,[1] and had fasting levels of LDL-C ≥2.99 mmol/L (≥115 mg/dL) and triglycerides <4.52 mmol/L (<400 mg/dL); LDL-C measurements had to be within 15% of each other during the lead-in period. Pregnant or lactating women, women of childbearing potential not using a reliable form of contraception, and patients with a history of homozygous familial hypercholesterolemia or known type III hyperlipoproteinemia were ineligible for this trial. Additional exclusion criteria included active arterial disease (eg, unstable angina, myocardial infarction, transient ischemic attack, cerebrovascular accident, or coronary revascularization procedures within 2 months of screening), uncontrolled hypertension, active liver disease or hepatic dysfunction (hepatic transaminases or bilirubin levels ≥1.5 times upper limit of normal), unexplained serum creatine kinase elevation >3 times upper limit of normal, and serum creatinine >220 μmol/L.

Efficacy and safety assessments

The efficacy analyses were performed on data from the intention-to-treat population (ie, all patients who received randomized treatment and had at least 1 baseline and post-baseline lipid measurement for an appropriate period) with the last observation carried forward. The primary efficacy measure was the proportion of patients in treatment groups reaching the Joint European Societies' LDL-C goal of <116 mg/dL (<3.0 mmol/L) at 16 weeks.[1] Secondary efficacy measures included proportions of patients meeting the European LDL-C goal at 8 weeks, European combined goals for LDL-C and total cholesterol (<193 mg/dL; <5.0 mmol/L) at 8 and 16 weeks, and National Cholesterol Education Program Adult Treatment Panel III (ATP III) LDL-C goals[2] at 8 and 16 weeks, as well as changes from baseline in plasma LDL-C, total cholesterol, HDL-C, triglycerides, and other lipid measures at 8 and 16 weeks. Baseline values for LDL-C and other lipid measures were calculated by averaging the measurements obtained at weeks −2, −1, and 0; lipids were measured subsequently at weeks 8 and 16.

Standard safety assessments included adverse event reports, clinical laboratory data, vital signs, and results of physical examinations. All randomized patients who received at least 1 dose of trial medication were evaluated for safety.

Laboratory methods

Analysis of all laboratory samples was performed at 2 certified central laboratories (Clinical Research Laboratory Europe, Zaventem, Belgium, for all European centers and Medical Research Laboratories, Highland Heights, Ky, for Canadian and Australian centers), which maintain Centers for Disease Control and Prevention and National Heart, Lung, and Blood Institute part III lipid standardization.[15] Blood samples were obtained after a 12-hour fast. Triglycerides and total cholesterol were analyzed by enzymatic methods using a Hitachi 747 (Boehringer Mannheim Diagnostics, Indianapolis, Ind) as described previously.[16] Very-low-density lipoproteins were separated from LDL and HDL by preparative ultracentrifugation at a density of 1.006 g/mL (β-quantification method).[17] Cholesterol and triglyceride levels in the "bottom" fraction (density >1.006 g/mL) were measured directly. HDL-C was then isolated by precipitation of LDL with heparin/2M manganese chloride.[18] LDL-C values were obtained by subtraction of HDL-C.

Statistical analysis

For the primary efficacy measure and secondary efficacy measures involving cholesterol goal achievement, treatment arms were compared using logistic-regression analysis, including inter-arm comparisons for period 1 and intra-arm comparisons for period 2. Treatment, center, treatment-by-center interaction (period 2 analyses), and (when appropriate) ATP III risk category were fitted as factors in the analysis, and baseline LDL-C was included as a covariate. For period 2 analyses, period 1 response (goal achievement/no achievement) was also fitted as a factor. Results are shown as proportions of patients reaching goal with the odds ratio (OR), CI, and *P* value for pairwise comparisons from the logistic-regression analysis.

Inter- and intra-arm comparisons of percentage change in lipids from baseline for rosuvastatin groups and comparator groups were performed using analysis of variance (ANOVA) models. The models included factors for treatment and center. Results are shown as least squares means percentage changes, differences in least squares means, CIs, and *P* values from ANOVA. The Bonferroni correction[19] was applied for multiple comparisons for primary and secondary efficacy measures. Pairwise comparisons for 16-week goal achievement and lipid change data were performed at a 2-sided significance level of .05, except for a significance level of .025 for intra-arm pairwise comparisons in arm 3 (Bonferroni correction applied). Pairwise comparisons for all 8-week goal achievement and lipid change data were performed at a 2-sided significance level of .0125. Safety data were summarized by descriptive statistics.

Results

Of 6508 patients entering the dietary lead-in period, 3161 were randomized to study treatment, including 21 patients randomized to cerivastatin 0.3 mg who were subsequently withdrawn from trial treatment. Of the remaining 3140 patients, 122 patients (3.9%) were withdrawn from the trial in period 1 (by week 8), representing 2.6% to 4.9% of the individual treatment arms, and 62 patients (2.0%) in period 2 (by week 16), representing 1.1% to 3.0% of individual treatment arms. Withdrawal due to an adverse event was the main reason for withdrawal in both periods (69 and 36 patients, respectively); other reasons included informed consent withdrawn (18 and 13 patients), patient did not meet the eligibility criteria (14 and 4 patients), and protocol noncompliance (10 and 2 patients). For the efficacy analysis, the intention-to-treat population of patients with at least 1 baseline and postbaseline lipid measurement in a given period consisted of 3056 patients for period 1 and 2967 patients for period 2. A total of 3128 patients received at least 1 dose of trial medication and were included in the safety analysis.

The period 1 treatment groups were well balanced with regard to demographic and baseline characteristics (Table I), including baseline LDL-C levels. In terms of defining the overall patient population according to CHD risk equivalents or risk factors, 55.4% of the patients had atherosclerotic disease, 27.2% had diabetes mellitus, 71.1% were hypertensive, 25.5% had a family history of CHD or peripheral vascular disease, and 88.7% were either men aged ≥45 years or women aged ≥55 years.

Cholesterol goal achievement

At the end of period 1 (8 weeks), as shown in Figure 2, *A*, rosuvastatin 10 mg (arm 1) enabled statistically significantly more patients to achieve the Joint European LDL-C goal than did atorvastatin 10 mg, simvastatin 20 mg, or pravastatin 40 mg, and a similar proportion of patients compared with atorvastatin 20 mg. Rosuvastatin 10 mg brought more patients to the European combined LDL-C and total cholesterol goals (83%) than did atorvastatin 10 mg (69%, $P < .0001$), atorvastatin 20 mg (77%, $P < .0125$), simvastatin 20 mg (60%, $P < .0001$), and pravastatin 40 mg (49%, $P < .0001$). Similarly, as shown in Figure 2, *B*, statistically significantly more patients receiving rosuvastatin 10 mg achieved ATP III LDL-C goals, compared with those receiving atorvastatin 10 mg, atorvastatin 20 mg, simvastatin 20 mg, and pravastatin 40 mg.

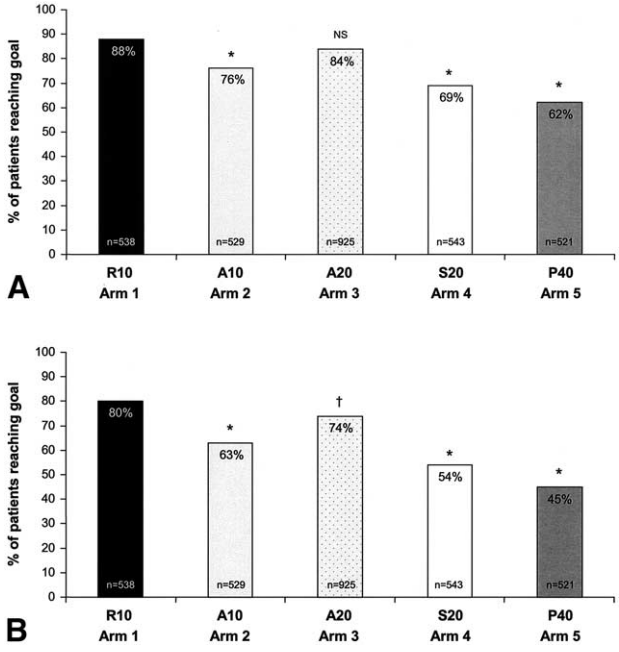
At 16 weeks, a statistically significantly greater percentage of patients who were switched to rosuvastatin 10 mg achieved the Joint European LDL-C goal, compared with patients remaining on atorvastatin 10 mg, simvastatin 20 mg, or pravastatin 40 mg (treatment arms 2–5) (Figure 3, *A*), and significantly more patients who were switched to rosuvastatin 20 mg achieved this goal, compared with patients receiving atorvasta-

Table I. Demographic and baseline characteristics by period-1 treatment

	Arm 1, rosuvastatin 10 mg (n = 552)	Arm 2, atorvastatin 10 mg (n = 539)	Arm 3, atorvastatin 20 mg (n = 952)	Arm 4, simvastatin 20 mg (n = 559)	Arm 5, pravastatin 40 mg (n = 538)
Male*	314 (56.9)	324 (60.1)	563 (59.1)	315 (56.4)	293 (54.5)
Age (y)†	62.0 (10.7)	61.8 (10.4)	62.2 (10.2)	61.9 (10.6)	62.7 (10.1)
≥65 y*	241 (43.7)	209 (38.8)	402 (42.2)	230 (41.1)	250 (46.5)
Weight (kg)†	79.7 (14.0)	81.3 (15.9)	80.3 (14.0)	80.1 (15.5)	79.4 (16.4)
Body mass index (kg/m^2)†	28.5 (8.8)	28.9 (12.9)	28.3 (4.4)	28.2 (4.5)	28.5 (11.3)
>30 kg/m^2*	153 (27.7)	154 (28.6)	284 (29.8)	155 (27.7)	159 (29.6)
White*	544 (98.6)	536 (99.4)	941 (98.8)	554 (99.1)	530 (98.5)
LDL-C (mg/dL)†‡	164.9 (31.0)	162.2 (27.7)	167.5 (31.4)	165.5 (29.1)	163.8 (31.0)

*Values presented as number (%)
†Values presented as mean (SD).
‡Baseline low-density lipoprotein cholesterol (LDL-C) values are from the intention-to-treat population in period 1 (n = 3056); all other baseline data are from the randomized population (n = 3140).

Figure 2



Proportions of patients achieving the (**A**) Joint European and (**B**) ATP III LDL-C goal at week 8 by treatment arm (intention-to-treat population; logistic-regression analysis). Significance defined as $P < .0125$ for all comparisons (98.75% CI). R10, rosuvastatin 10 mg; A10, atorvastatin 10 mg; A20, atorvastatin 20 mg; S20, simvastatin 20 mg; P40, pravastatin 40 mg. **A**, European LDL-C goal is <116 mg/dL (<3.0 mmol/L). *$P < .0001$ (R10 vs A10, S20 and P40). NS (R10 vs A20) **B**, ATP III LDL-C goals are low risk <160 mg/dL (<4.1 mmol/L) for 0 or 1 risk factor; medium risk <130 mg/dL (<3.4 mmol/L) for multiple risk factors and 10-year CHD risk ≤20%; and high risk <100 mg/dL (<2.6 mmol/L) for CHD or CHD risk equivalents (type 2 diabetes, other atherosclerotic disease, or multiple risk factors with 10-year CHD risk >20%) *$P < .0001$ (R10 vs A10, S20, and P40). †$P < .01$ (R10 vs A20).

tin 20 mg (arm 3). The difference in goal achievement between patients switched to rosuvastatin 10 mg and those patients receiving atorvastatin 20 mg (arm 3) was not statistically significant.

At 16 weeks in arm 2, European combined LDL-C and total cholesterol goals were achieved in 80% of patients who were switched to rosuvastatin 10 mg versus 73% of patients who remained on atorvastatin 10 mg ($P < .05$). Results at 16 weeks in arms 3 to 5 for these cholesterol goals were as follows: 79% of patients receiving rosuvastatin 10 mg (P = not significant [NS]) and 87% of those receiving rosuvastatin 20 mg ($P < .0001$) versus 75% of patients receiving atorvastatin 20 mg; 80% of patients receiving rosuvastatin 10 mg ($P < .0001$) versus 61% of those receiving simvastatin 20 mg; and 83% of patients receiving rosuvastatin 10 mg ($P < .0001$) versus 50% of those receiving pravastatin 40 mg.

As expected because of the predominantly high-risk patient population with an ATP III goal below 100 mg/dL, relatively fewer of these patients overall achieved their ATP III LDL-C goal than those achieving the European LDL-C goal at week 16; however, the pattern of goal achievement for the various switch groups was similar (Figure 3, *B*). In general, rates of ATP III LDL-C goal achievement statistically favored rosuvastatin over the other treatments.

Lipid changes

At 8 weeks, rosuvastatin 10 mg (arm 1) reduced LDL-C by 47.0%, compared with reductions of 37.2%, 43.7%, 35.4%, and 31.0%, respectively, in patients treated with atorvastatin 10 and 20 mg, simvastatin 20 mg, and pravastatin 40 mg ($P < .0001$ for all comparisons vs rosuvastatin). Similarly, reductions in total cholesterol with rosuvastatin 10 mg were 32.5% versus 25.8%, 30.9%, 24.3%, and 20.7% for atorvastatin 10 and 20 mg, simvastatin 20 mg, and pravastatin 40 mg, re-

spectively ($P < .0001$ for all comparisons, except $P < .01$ vs atorvastatin 20 mg). HDL-C was increased by 9.2% with rosuvastatin 10 mg, 6.8% with atorvastatin 10 mg ($P < .01$), 5.7% with atorvastatin 20 mg ($P < .0001$), 8.0% with simvastatin 20 mg (P = NS), and 7.6% with pravastatin 40 mg (P = NS). Triglycerides were reduced by 18.9% with rosuvastatin 10 mg versus 15.9%, 18.3%, 13.5%, and 10.5%, respectively, for atorvastatin 10 and 20 mg (P = NS), simvastatin 20 mg ($P < .01$), and pravastatin 40 mg ($P < .0001$).

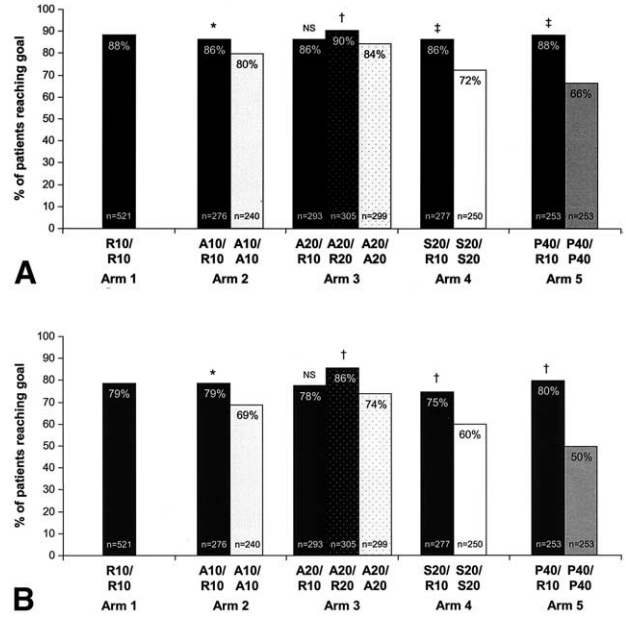
Table II summarizes the changes from baseline at the end of period 2 (week 16) in LDL-C, total cholesterol, HDL-C, and triglycerides for all treatment arms. For LDL-C and total cholesterol, the effects seen after the patients were either switched to rosuvastatin or allowed to remain on atorvastatin generally favored rosuvastatin over atorvastatin statistically and were consistent with the cholesterol goal data reported above. HDL-C was increased more in rosuvastatin-treated patients than in atorvastatin-treated patients, with statistically significant differences noted as listed in the table. For triglycerides, the treatment differences between rosuvastatin and atorvastatin were not statistically significant. Rosuvastatin 10 mg reduced LDL-C and total cholesterol statistically significantly more than simvastatin 20 mg and pravastatin 40 mg, increased HDL-C more than both ($P < .05$ vs pravastatin), and reduced triglycerides more than both ($P < .01$ vs pravastatin).

Safety

Throughout this 16-week, 2-period trial, all study treatments were well tolerated. In periods 1 and 2, the overall occurrence of adverse events associated with each treatment was generally similar, and the occurrence of deaths, serious adverse events, and withdrawals from the trial due to adverse events was low, with no differences noted among the treatment groups. Eight patients died during the trial from causes that would be expected in such a patient population (ie, cardiovascular events in 4 patients, malignancy in 2, pneumonia and subdural hematoma in 1 each). No treatment-related adverse events leading to death or serious adverse events were reported in any of the treatment groups.

The occurrence of myalgia was low and similar between treatments, occurring in 1.9% of patients in period 1 and 0.9% of patients in period 2. No cases of myopathy were reported (ie, creatine kinase >10 times the upper limit of normal and muscle symptoms). Asymptomatic increases in creatine kinase >10 times the upper limit of normal were observed in 1 patient receiving atorvastatin 20 mg and 1 receiving rosuvastatin 10 mg (arm 2); these elevations resolved during continued study treatment. No patients had clinically significant elevations in hepatic transaminases (ie, >3 times the upper limit of normal at ≥2 consecutive measurements).

Figure 3



Proportions of patients achieving the (**A**) Joint European and (**B**) ATP III LDL-C goal at week 16 by treatment arm (intention-to-treat population; logistic-regression analysis). Significance defined as $P < .05$ for all comparisons (95% CI), except in arm 3, in which $P < .025$ is significant (97.5% CI). R10, rosuvastatin 10 mg; A10, atorvastatin 10 mg; A20, atorvastatin 20 mg; R20, rosuvastatin 20 mg; S20, simvastatin 20 mg; P40, pravastatin 40 mg. **A**, European LDL-C goal is <116 mg/dL (<3.0 mmol/L). *$P < .05$, †$P < .01$, ‡$P < .0001$ (R10 vs A10, S20, and P40 or R20 vs A20). NS (R10 vs A20). **B**, ATP III LDL-C goals are low risk <160 mg/dL (<4.1 mmol/L) for 0 or 1 risk factor; medium risk <130 mg/dL (<3.4 mmol/L) for multiple risk factors and 10-year CHD risk ≤20%; and high risk <100 mg/dL (<2.6 mmol/L) for CHD or CHD risk equivalents (type 2 diabetes, other atherosclerotic disease, or multiple risk factors with 10-year CHD risk >20%) *$P < .001$, †$P < .0001$ (R10 vs A10, S20, and P40 or R20 vs A20). NS (R10 vs A20).

Discussion

In clinical practice, most hypercholesterolemic patients requiring aggressive statin therapy remain on lower doses, and many patients with CHD or an elevated risk of CHD do not achieve their cholesterol goals despite increased utilization of statins. In the current trial, statistically significantly more patients achieved their Joint European and ATP III LDL-C goals after being switched from 10- or 20-mg doses of atorvastatin, previously recognized as the most effective

Table II. Lipid changes from baseline for arm 1 and rosuvastatin vs atorvastatin arms at 16 weeks (period 2)

	Arm 1 (period 1/period 2)	Arm 2 (period 1/period 2)		Arm 3 (period 1/period 2)	
	Rosuvastatin 10 mg/ rosuvastatin 10 mg (n = 521)	Atorvastatin 10 mg/ atorvastatin 10 mg (n = 240)	Atorvastatin 10 mg/ rosuvastatin 10 mg (n = 276)	Atorvastatin 20 mg/ atorvastatin 20 mg (n = 299)	Atorvastatin 20 mg/ rosuvastatin 10 mg (n = 293)
Low-density lipoprotein cholesterol					
Baseline (mg/dL)*	164.9 (31.0)	162.7 (28.7)	161.6 (26.5)	166.7 (30.1)	168.9 (30.6)
LSM change†	−47.5 (15.2)	−38.5 (0.9)	−46.2 (0.9)	−44.0 (1.0)	−46.9 (1.0)
P value	NA	NA	<.0001	NA	.0252
Total cholesterol					
Baseline (mg/dL)*	246.6 (34.5)	242.4 (31.4)	243.9 (32.5)	248.3 (37.9)	248.7 (33.8)
LSM change†	−32.6 (11.7)	−26.6 (0.7)	−31.3 (0.7)	−30.8 (0.8)	−32.5 (0.8)
P value	NA	NA	<.0001	NA	.0995
High-density lipoprotein cholesterol					
Baseline (mg/dL)*	48.6 (10.9)	48.7 (11.6)	49.1 (13.2)	49.9 (11.8)	49.7 (10.8)
LSM change†	+10.3 (15.7)	+8.0 (1.0)	+10.8 (1.0)	+5.7 (1.0)	+9.1 (1.0)
P value	NA	NA	.0317	NA	.0142
Triglycerides					
Baseline (mg/dL)*	165.5 (64.7)	160.4 (67.8)	161.5 (61.4)	158.6 (62.1)	162.7 (65.4)
LSM change†	−18.4 (27.9)	−16.1 (1.9)	−17.7 (1.8)	−17.2 (1.8)	−19.1 (1.8)
P value	NA	NA	.5161	NA	.4272
Baseline, median (mg/dL)	156	147	153	147	150
Median change (%)	−22.9	−18.1	−21.4	−22.9	−21.3

Baseline levels are reported as mean values for all measures, except triglycerides, for which both mean and median baseline values are reported. Change values correspond to the LSM (or median) of percentage change from baseline at week 16 with SD (arm 1) or SE (arms 2–5). Analysis of variance was conducted on 16-week data using the last observation carried forward from the intention-to-treat population. Significance defined as $P < .05$ for all comparisons (95% CI), except in arm 3, in which $P < .025$ is significant (97.5% CI). To convert baseline low-density lipoprotein cholesterol, total cholesterol, and high-density lipoprotein cholesterol values from mg/dL to mmol/L, multiply by 0.02586; to convert baseline triglyceride values from mg/dL to mmol/L, multiply by 0.01129. *LSM,* least squares mean; *NA,* not applicable.
*Values presented as mean (SD).
†Values presented as percent (SE).

statin in enabling patients to reach their LDL-C goals,[7,20,21] to milligram-equivalent doses of rosuvastatin. Similarly, the switch from simvastatin 20 mg or pravastatin 40 mg to rosuvastatin 10 mg significantly improved LDL-C goal achievement. Previous findings also indicated that rosuvastatin brought more hypercholesterolemic patients to their Joint European and ATP III LDL-C goals than did atorvastatin, simvastatin, and pravastatin.[22] Moreover, in this trial, the greater efficacy achieved by switching to rosuvastatin occurred without having patients undergo a drug washout period, which mimics the prescribing practices of physicians and makes this strategy highly applicable to the actual conditions of clinical practice.

In addition, the MERCURY I study is the first large-scale, prospectively designed switching trial to evaluate several widely used statins at their most commonly used doses. The statin comparators and doses evaluated were selected on the basis of prevailing prescribing patterns and product labeling for starting doses of these agents at the time this trial was initiated. Previously, in a 1-way crossover trial in 80 patients with CHD, switching to atorvastatin 10 mg produced statistically significantly greater reductions in LDL-C compared with simvastatin 20 mg and pravastatin 20 and 40 mg, and improved ATP II LDL-C goal achievement, compared with simvastatin 20 and 40 mg and pravastatin 20 and 40 mg.[23] In a single-blind trial of 378 patients with or without CHD in which those receiving simvastatin 20 or 40 mg were randomized to continued treatment or a switch to milligram-equivalent atorvastatin,[24] atorvastatin 20 and 40 mg produced statistically significant additional reductions in LDL-C, a significantly greater rate of achievement of the Joint European LDL-C goal in patients not initially at goal at both doses, and a significantly greater rate of achievement of ATP II LDL-C goals in the 20-mg comparison. A large observational study (n = 980), involving a US Department of Defense formulary conversion program, showed that patients were successfully converted from their current statins (usually atorvastatin or pravastatin) to simvastatin 80 mg or cerivastatin 0.4 or 0.8 mg.[25]

In the current trial, compared with the other statins, rosuvastatin treatment reduced LDL-C and total cholesterol more effectively and produced greater increases in HDL-C and comparable decreases in triglycerides at

Arm3 (period 1/period 2)	Arm 4 (period 1/period 2)		Arm 5 (period 1/period 2)	
Atorvastatin 20 mg/ rosuvastatin 20 mg (n = 305)	**Simvastatin 20 mg/ simvastatin 20 mg (n = 250)**	**Simvastatin 20 mg/ rosuvastatin 10 mg (n = 277)**	**Pravastatin 40 mg/ pravastatin 40 mg (n = 253)**	**Pravastatin 40 mg/ rosuvastatin 10 mg (n = 253)**
166.8 (33.2)	165.1 (28.9)	165.8 (29.3)	164.3 (31.9)	163.1 (29.9)
−53.0 (1.0)	−37.4 (1.0)	−45.6 (1.0)	−32.4 (0.9)	−46.6 (0.9)
<.0001	NA	<.0001	NA	<.0001
250.6 (37.0)	248.3 (33.7)	247.4 (34.0)	246.7 (36.4)	244.4 (32.6)
−37.3 (0.7)	−25.6 (0.8)	−31.1 (0.75)	−21.9 (0.7)	−31.8 (0.7)
<.0001	NA	<.0001	NA	<.0001
48.3 (10.8)	48.8 (11.9)	48.3 (11.6)	49.8 (12.7)	50.0 (12.6)
+8.2 (1.0)	+8.4 (1.2)	+10.0 (1.1)	+7.3 (1.0)	+10.1 (1.0)
.0682	NA	.2782	NA	.0301
167.2 (59.3)	170.8 (67.8)	164.4 (63.2)	164.2 (65.5)	156.0 (62.6)
−21.4 (1.8)	−13.6 (1.9)	−15.1 (1.8)	−11.3 (1.8)	−17.6 (1.8)
.0700	NA	.5377	NA	.0057
162	156	153	154	144
−25.3	−18.6	−17.6	−15.9	−20.9

8 weeks and, after switching, 16 weeks. These findings and the magnitude of the changes in lipid measures are consistent with previous trials comparing rosuvastatin with atorvastatin, simvastatin, and pravastatin at commonly used doses in hypercholesterolemic patients.[8-12,26]

Overall, the statin treatments were well tolerated in this trial. There were no obvious differences between treatment groups with regard to adverse events. None of the adverse events reported was unexpected, given the age and underlying medical conditions of the patient population studied. Moreover, transient elevations in hepatic transaminases and asymptomatic increases in creatine kinase were infrequent and were not indicative of hepatotoxicity or myotoxicity.

Compliance is an important issue in an open-label trial, where the investigators and their patients are aware of the medications dispensed and taken, and thus the possibility exists that differential compliance between rosuvastatin and the other statins may have influenced the results seen. However, compliance with all trial medications was assessed by tablet counts at each patient visit and mean compliance was found to be ≥95% during both periods 1 and 2, with similar standard deviations among the treatment groups. Therefore, the likelihood of such bias influencing the results is considered small.

In summary, the current trial shows that the therapeutic strategy of switching patients from a statin to milligram-equivalent or potentially lower doses of a statin with a greater ability to lower LDL-C can be successful in improving cholesterol goal achievement and the overall lipid profile in patients with CHD or at high risk for CHD, who require relatively aggressive lipid-lowering therapy.

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