Rising to the Challenge of Treating High-risk Patients

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Abstract

Guidelines from the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) focus the need for the most intensive efforts to lower low-density lipoprotein cholesterol (LDL-C) in the patients at greatest risk of a major future clinical coronary heart disease event. Major clinical trials, such as Pravastatin or Atorvastatin Evaluation and Infection Therapy and the Heart Protection Study, demonstrated the value of lowering LDL-C levels in high-risk patients to well below the ATP III target of <100 mg/dL. In 2004, the NCEP writing group suggested that a more aggressive LDL-C goal of <70 mg/dL is an option when treating high-risk patients, particularly those with the presence of established cardiovascular disease plus major multiple risk factors (especially diabetes), severe and poorly controlled risk factors (ie, cigarette smoking), multiple criteria of the metabolic syndrome, or an acute coronary syndrome. With stricter targets, high-risk patients are less likely to achieve their cholesterol goals than lower risk patients. Recent large trials comparing rosuvastatin with other statin monotherapies have shown a greater LDL-C reduction and better attainment of goals with rosuvastatin. In addition, the MERCURY [Measuring Effective Reductions in Cholesterol Using Rosuvastatin Therapy] trials demonstrate that switching to rosuvastatin significantly increased the percentage of patients who achieved their ATP III LDL-C targets.

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Guidelines from the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III)[1] focus the need for the most intensive efforts to lower low-density lipoprotein cholesterol (LDL-C) in the patients at greatest risk of a major future clinical coronary heart disease (CHD) event.

According to ATP III, the highest-risk group is comprised of individuals with known CHD, diabetes mellitus, noncoronary atherosclerosis, abdominal aortic aneurysm, and patients with a 10-year global risk of an event that exceeds 20%, grouped together as patients with "CHD risk equivalents." The target LDL-C in these groups is <100 mg/dL.

Another high-risk group specifically identified for intensive management are patients with metabolic syndrome, a constellation of central obesity, insulin resistance, glucose intolerance, hypertension, and dyslipidemia. Metabolic syndrome is extremely prevalent, affecting about 1 in 3 US adults older than 50 years.[2]

After publication of ATP III, major clinical trials demonstrated the value of lowering LDL-C levels in high-risk patients to well below the ATP III target of <100 mg/dL. An examination of such evidence led ATP III authors to issue an interim report, a focused white paper on 5 trials completed subsequent to ATP III. In this update in 2004, the NCEP writing group suggests that a more aggressive LDL-C goal of <70 mg/dL is an option for physicians when treating very high-risk patients.[3] The authors defined *very high risk* as the presence of established cardiovascular disease plus major multiple risk factors (especially diabetes), severe and poorly controlled risk factors (ie, cigarette smoking), multiple criteria of the metabolic syndrome, and an acute coronary syndrome (ACS). Other groups that may benefit from a more aggressive strategy are unclear but might include patients with remote ACS and possibly CHD risk equivalents such as type 2 diabetes, cerebrovascular disease, peripheral arterial disease, and a global risk score greater than 20%. Space does not permit inclusion of all 5 clinical trials reviewed in the NCEP writing group's white paper, because they did not apply to the focus of this article.

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With increasing evidence in high-risk patients that the lower the LDL-C, the better, intensive research has been devoted to maximizing LDL-C–lowering drug therapy.

This article will examine the evidence to support aggressive approaches to lipid-lowering therapy in high-risk patients and will review the relative efficacy of current therapies to lower LDL-C to the targets for high-risk patients.

Lowering the Threshold—HPS and PROVE IT

Heart Protection Study (HPS). Evidence for initiating therapy in high-risk patients with statin monotherapy that provides effective LDL-C reduction is provided by the HPS.[4] In HPS, 20 536 adults with diabetes or vascular disease were allocated to simvastatin 40 mg or placebo. There was no threshold LDL-C value below which a statin ceased to provide therapeutic benefit in high-risk patients. HPS showed that treatment of patients with a baseline LDL-C <130 mg/dL, with reduction of LDL-C to far below 100 mg/dL, achieved significant reductions in cardiovascular risk. A subanalysis of HPS demonstrated that high-dose statin monotherapy among patients with an LDL-C <100 mg/dL produced statistically significant reductions in all-cause mortality and highly significant reductions in cardiovascular disease end points.

Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT). In the PROVE IT trial,[5] 4162 patients who had been hospitalized for an acute coronary syndrome (ACS) within the previous 10 days were randomized to intensive lipid-lowering therapy with atorvastatin 80 mg or a moderate-intensive strategy with pravastatin 40 mg. The median achieved LDL-C was 62 mg/dL in the patients assigned to atorvastatin versus 95 mg/dL in those assigned to pravastatin (P <.001).

The primary end point—a composite of all-cause mortality, myocardial infarction, documented unstable angina requiring hospitalization, revascularization, or stroke—occurred in 22.4% of patients randomized to atorvastatin and 26.3% of patients assigned to pravastatin (P = .005), representing a 16% relative risk reduction favoring high-dose atorvastatin. The reduction in clinical events with the more intensive lipid-lowering therapy emerged as early as 30 days after the start of therapy.

PROVE IT demonstrated that aggressive lipid lowering initiated at discharge in patients hospitalized for an ACS significantly reduced the risk of long-term adverse cardiovascular outcomes, compared with lipid lowering that met ATP III guidelines at the time (<100 mg/dL).

According to the NCEP ATP III update authors, HPS supports the current ATP III goal for high-risk patients (<100 mg/dL), and PROVE IT makes a strong case for achieving the optional goal (<70 mg/dL).[3]

Clinical Trials Comparing Intensity of Lipid Lowering: Reduction of Risk for Future Events

Treating to New Targets (TNT). In the TNT study,[6] 10 001 patients with stable CHD and LDL-C values <130 mg/dL were randomly assigned to 10 or 80 mg of atorvastatin. The average exposure to treatment was 4.9 years.

The primary end point—a composite of death from CHD, nonfatal myocardial infarction, resuscitation from cardiac arrest, or fatal or nonfatal stroke—was reduced by 22% (P = .0002) with high- versus low-dose atorvastatin. The outcome of stroke was reduced by 25% in the 80-mg group (P = .02).

Incremental Decrease in Clinical End Points Through Aggressive Lipid Lowering (IDEAL). The IDEAL study[7] compared atorvastatin 80 mg/day with simvastatin 20 to 40 mg in 8888 patients with stable CHD.

The primary end point was a composite of myocardial infarction, CHD death, or cardiac arrest with resuscitation, the rate of which was not significantly different between the 2 treatment groups.

The group randomized to atorvastatin suffered 11% fewer such events over the 5-year course of the study, narrowly missing statistical significance (P = .07). Several secondary end points did achieve significance in favor of atorvastatin, including a 13% reduction in major cardiovascular events (P = .02), a 16% reduction in any CHD event

(P <.001), and a 16% reduction in any cardiovascular event (P <.001).

Atherosclerotic Regression as End Point—REVERSAL and ASTEROID

Using the latest imaging tools, 2 recent trials explored the effect of aggressive lipid lowering on degree of occlusion present in the arteries of patients with CHD.

Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL). Intravascular ultrasound was used in REVERSAL to assess coronary artery plaque burden in 502 patients with symptomatic CHD who were randomized to either aggressive treatment with atorvastatin 80 mg/day or less aggressive treatment with pravastatin 40 mg/day for 18 months.[8] Assignment to pravastatin resulted in a final mean LDL-C level of 110 mg/dL (–25.2% change from baseline); assignment to atorvastatin treatment resulted in a final mean LDL-C of 79 mg/dL (–46.3% change from baseline). The primary end point of the study was the percent change in atheroma volume, which increased by 2.7% (median) from baseline in pravastatin-treated patients and did not change in atorvastatin-treated patients. The pravastatin group demonstrated a 1.6% median increase in obstructive atheroma volume, whereas the atorvastatin group had a 0.2% increase in obstructive volume from baseline. Therefore, REVERSAL showed that progression of atherosclerosis could be halted. However, REVERSAL stopped short of demonstrating regression of atherosclerosis with an intensive lipid-lowering strategy.

A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID). Intensive statin therapy using 40 mg of rosuvastatin led to regression of coronary atherosclerosis in patients with CHD in ASTEROID.[9]

Using intravascular ultrasound, patients with CHD were assessed at baseline and after 24 months of open-label treatment with rosuvastatin 40 mg. Their mean LDL-C level at baseline was 130.4 mg/dL, which was lowered 53% by the end of the study. Their mean high-density lipoprotein cholesterol (HDL-C) increased from 43.1 mg/dL at baseline to 49.0 mg/dL.

Atheroma volume decreased by a mean of 0.98% and a median of 0.79% from baseline (P <.001), and 63.6% of the study group experienced some regression of their atherosclerosis.

In the most diseased 10-mm segments of the patients' arteries, atheroma volume regressed by a mean of 6.1 mm^3 and a median of 5.6 mm^3 (P <.001), representing a median reduction of 9.1%.

ASTEROID represents the first trial to show that regression of coronary atherosclerosis is possible with intensive lipid lowering.

Achieving Maximal LDL-C Reduction

With stricter targets, patients with CHD or at high risk of CHD are less likely to achieve their cholesterol goals than lower risk patients. The previously mentioned data support the clinical benefit of achieving lower LDL-C levels in high-risk patients. Finding therapies that are successful in achieving these lower targets in high-risk populations is therefore essential. Several clinical trials have compared statin monotherapies in achievement of LDL-C goal in various patient populations, and the effect of switching therapies on goal achievement.

Comparative Study with Rosuvastatin in Subjects with Metabolic Syndrome (COMETS). In COMETS,[10] 397 patients who qualified for a diagnosis of metabolic syndrome were randomized after a 4-week run-in to rosuvastatin 10 mg, atorvastatin 10 mg, or placebo once daily for 6 weeks. Patients in the rosuvastatin and placebo groups then received 20 mg/day of rosuvastatin for the next 6 weeks, whereas those started on atorvastatin had their atorvastatin dosage titrated to 20 mg/day for the following 6 weeks.

After 6 weeks, by intent-to-treat analysis of treatment as allocated, rosuvastatin 10 mg was associated with a significantly larger reduction in LDL-C compared with atorvastatin 10 mg (42.7% vs 36.6%; P <.001). After 12 weeks, LDL-C was reduced by 48.9% in the combined rosuvastatin group (including those switched from placebo)

whereas LDL-C was reduced by 42.5% in the atorvastatin recipients (P <.001).

The 1998 European Atherosclerosis Society (EAS) LDL-C goal (<115 mg/dL)[11] was achieved by 79% of rosuvastatin recipients compared with 71% of atorvastatin recipients (P <.05) at 6 weeks, which increased to 90% and 83% (P <.05), respectively, after 12 weeks. The more stringent 2003 EAS LDL-C goal (<100 or <115 mg/dL depending on the patient's risk category)[12] was achieved by the same proportion of patients in each group.

Study to Compare the Effects of Rosuvastatin with Atorvastatin on apoB/apoA1 Ratio in Patients with Type 2 Diabetes Mellitus and Dyslipidemia (CORALL). In CORALL,[13] 263 patients with type 2 diabetes who were being treated with oral agents or insulin were randomized after a dietary run-in period to open-label rosuvastatin 10 mg/day or atorvastatin 20 mg/day. The dosages of each medication were doubled after 6 weeks, and doubled again after another 6 weeks, so that patients were taking either rosuvastatin 40 mg/day or atorvastatin 80 mg/day by study end.

The primary end point, the apolipoprotein B (apoB)/apolipoprotein A-1 (apoA1) ratio, was chosen because this ratio has been found to be a more powerful predictor of cardiovascular risk than LDL-C.[14]

The reductions in the apoB/apoA1 ratio were 34.9%, 39.2%, and 40.5% with rosuvastatin 10, 20, and 40 mg/day, respectively. The reductions were 32.4%, 34.7%, and 35.8% with atorvastatin 20, 40, and 80 mg/day, respectively. The difference in the changes between the rosuvastatin and atorvastatin groups was significant at weeks 12 and 18 (P <.05).

LDL-C reductions were also significantly greater with rosuvastatin compared with atorvastatin (P <.05), with maximum reductions of 53.6% with rosuvastatin and 47.8% with atorvastatin.

More patients treated with rosuvastatin achieved goal LDL-C levels established by the American Diabetes Association (<2.6 mmol/L, or 100 mg/dL)[15] and the EAS (<2.5 mmol/L, or 100 mg/dL),[12] with the difference being significant (P <.05) at the highest dosage levels.

Rosuvastatin and Atorvastatin in Different Dosages and Reverse Cholesterol Transport (RADAR). A low level of HDL-C has been identified as an independent predictor of CHD events. The RADAR study[16] was an open-label study in which 461 patients with established cardiovascular disease and an HDL-C <40 mg/dL were randomized to therapy starting with either rosuvastatin 10 mg or atorvastatin 20 mg for 6 weeks. Dosages were uptitrated at 6 weeks to rosuvastatin 20 mg or atorvastatin 40 mg, and at 12 weeks to rosuvastatin 40 mg or atorvastatin 80 mg, for a total treatment duration of 18 weeks.

The primary end point of the study was the change from baseline in the LDL-C/HDL-C ratio. At 6 weeks, rosuvastatin 10 mg was associated with a mean reduction in the LDL-C/HDL-C ratio of 47.0%, compared with a 41.9% mean reduction with atorvastatin 20 mg (P <.05).

At 12 weeks, rosuvastatin 20 mg was associated with a mean reduction in the ratio of 53.0%, compared with a mean 47.9% reduction associated with atorvastatin 20 mg (P <.01).

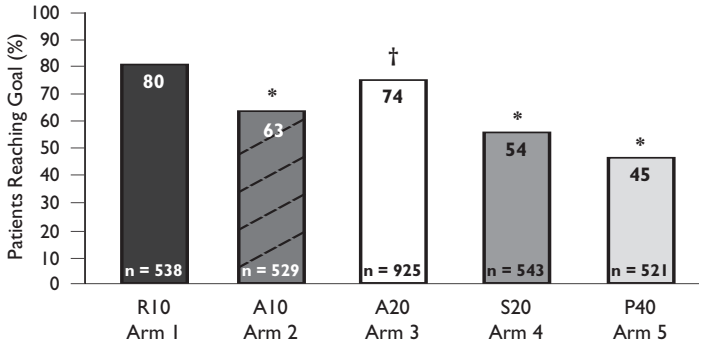
At study end (18 weeks), reductions in the LDL-C/HDL-C ratio were 57.3% in patients randomized to rosuvastatin, 40 mg, compared with 49.6% in those assigned to atorvastatin, 80 mg (P <.001).

The proportion of patients achieving the 2003 European LDL-C treatment goal (<100 mg/dL) was significantly greater at week 18 with rosuvastatin compared with atorvastatin (94% vs 85%; P <.01).

Measuring Effective Reductions in Cholesterol Using Rosuvastatin Therapy (MERCURY I). Switching CHD patients from one statin to another is an option to help achieve lipid goals. MERCURY I was a 5-arm open-label study[17] that assessed 3140 patients with CHD or other atherosclerotic disease, type 2 diabetes, or a CHD risk greater than 20% over 10 years.

After a 6-week dietary run-in during which any lipid-lowering therapy was discontinued, patients were randomized to 8 weeks of treatment with 1 of the following: rosuvastatin 10 mg, atorvastatin 10 mg, atorvastatin 20 mg, simvastatin 20 mg, or

Figure 1. Patients Achieving ATP III LDL-C Goal at Week 8



*P <.0001 (R10 vs A10, S20, and P40).
†P <.01 (R10 vs A20).
Proportions of patients achieving the 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). 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 a 10-year CHD risk >20%).
ATP III indicates Adult Treatment Panel III; LDL-C, low-density lipoprotein cholesterol; R10, rosuvastatin 10 mg; A10, atorvastatin 10 mg; A20, atorvastatin 20 mg; S20, simvastatin 20 mg; P40, pravastatin 40 mg; CI, confidence interval; CHD, coronary heart disease.
Source: Adapted with permission from Reference 17.

pravastatin 40 mg. At 8 weeks, patients in the rosuvastatin 10-mg arm remained on this treatment for 8 weeks; patients in the other arms remained on these treatments or were switched to rosuvastatin.

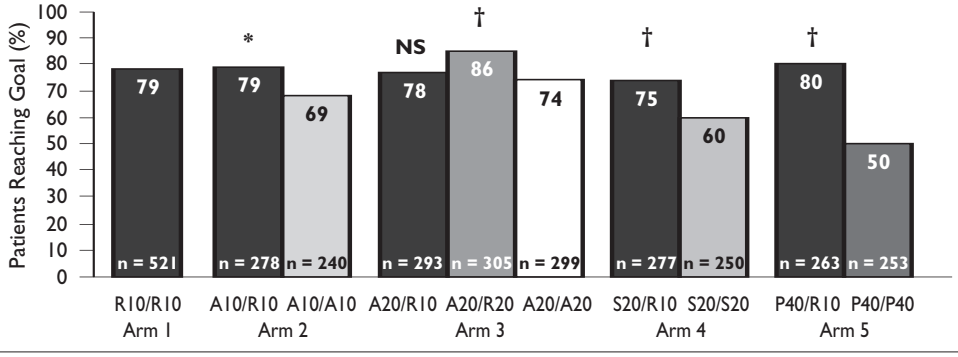
At week 8, a significantly greater proportion of patients assigned to rosuvastatin 10 mg achieved the NCEP ATP III LDL-C goals than did patients assigned atorvastatin 10 mg, atorvastatin 20 mg, simvastatin 20 mg, or pravastatin 40 mg **(Figure 1)**.

Switching to rosuvastatin 10 mg allowed significantly more high-risk patients to achieve their NCEP ATP III LDL-C goal compared with continuing treatment with atorvastatin 10 mg, simvastatin 20 mg, or pravastatin 40 mg (**Figure 2**).

Switching to rosuvastatin 20 mg allowed significantly more high-risk patients to achieve their NCEP ATP III LDL-C goal compared with continuing treatment with atorvastatin 20 mg (Figure 2).

MERCURY II. The MERCURY II study[18] had a similar design as MERCURY I but involved assignment of 1993 high-risk subjects with hypercholesterolemia to 1 of the

Figure 2. Patients Achieving ATP III LDL-C Goal at Week 16



*P <.001.
†P <.0001 (R10 vs A10, S20, and P40 or R20 vs A20).
P = NS (R10 vs A20).
Proportions of patients achieving the 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). 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%).
ATP III indicates Adult Treatment Panel III; LDL-C, low-density lipoprotein cholesterol; R10, rosuvastatin 10 mg; A10, atorvastatin 10 mg; A20, atorvastatin 20 mg; S20, simvastatin 20 mg; P40, pravastatin 40 mg; CI, confidence interval; CHD, coronary heart disease.
Source: Adapted with permission from Reference 17.

following treatment arms in an open-label fashion: rosuvastatin 20 mg, atorvastatin 10 mg, atorvastatin 20 mg, simvastatin 20 mg, or simvastatin 40 mg for 8 weeks. After 8 weeks, all subjects were randomly assigned within each treatment arm to either an additional 8 weeks of treatment on their original study medication, or were switched to rosuvastatin.

Compared with continuing treatment with either atorvastatin or simvastatin, switching to rosuvastatin significantly increased the percentage of patients who achieved their ATP III LDL-C targets. Switching to rosuvastatin 10 or 20 mg was associated with a significantly greater reduction in LDL-C compared with continued treatment with twice the dose of simvastatin.

Conclusion

Recent clinical trials with statin therapy provide a rationale for lower target LDL-C levels and the use of more intensive LDL-C–lowering therapy in high-risk individuals as defined by ATP III.

Members of the NCEP believed that the results of these trials were compelling, had important implications for moderately and very high-risk patients, and justified the development of the Interim Report. Among the modifications to the current NCEP ATP III guidelines recommended by the writers of the interim report[2]:

- In high-risk patients, the recommended LDL-C goal is <100 mg/dL;
- In high-risk patients, an LDL-C goal <70 mg/dL is a therapeutic option, especially for those patients considered to be at very high risk;
- For patients at moderately high risk, LDL-C goal <100 mg/dL is a therapeutic option.

An abundance of comparative data indicate that rosuvastatin monotherapy is superior at equivalent doses to other statin monotherapies for achieving goal LDL-C levels in various high-risk populations, including those with vascular disease, diabetes, and metabolic syndrome, and that patients not at their goal LDL-C level on other statins may derive further benefit from switching to rosuvastatin.

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