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IN THIS ISSUE



# Redefining the At-Risk Cardiovascular Patient—Who Should Receive Statins for Primary Prevention?

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Approximately 1 of 6 deaths among adults in the United States is caused by complications of coronary heart disease (CHD).[1] CHD typically is the culmination of the lifelong accumulation of atherosclerotic lesions in coronary arteries.[2] A major challenge for reducing the high mortality rate associated with CHD lies in the silent nature of atherosclerotic disease progression. Most individuals with atherosclerosis experience no significant symptoms before the occurrence of a first major cardiovascular event, including fatal myocardial infarction. Therefore, any primary prevention strategy has to include proper assessment of a person's risk, together with effective tools to reduce that risk. Fortunately, in recent years, tremendous progress has been made on multiple fronts in meeting the challenges of primary prevention, including the development of noninvasive imaging technologies for assessing preclinical artery disease, the identification of new biomarkers that aid in risk classification, and the availability of new, effective lipid-modifying treatment options.[2] Most important, results from large, randomized primary prevention studies are starting to provide a clear picture of what it takes to reduce cardiovascular risk in individuals with no or only mild to moderate dyslipidemia.[3–6] Findings suggest that controlling serum levels of low-density lipoprotein cholesterol (LDL-C) and non–high-density lipoprotein cholesterol (non–HDL-C) is essential for successful primary prevention and that LDL-C and non–HDL-C targets that an individual must attain to receive clinical benefit are determined by the totality of the person's risk.

## Who Is At Risk?

Most of our current understanding of cardiovascular risk has come from data collected during the Framingham Heart Study, a large, ongoing population study initiated in 1948 by the National Heart, Lung, and Blood Institute and Boston University.[7] Findings of this study led to the development of the Framingham risk score (available online at http://www.framinghamheartstudy.org/risk/gencardio.html), a risk classification algorithm that is used to determine a person's 10-year risk for coronary artery disease events based on his or her age, lipid parameters (total cholesterol and HDL-C), lifestyle (smoking), and relevant morbidities (eg, diabetes, hypertension). The Framingham Study identified elevated levels of total cholesterol (of which LDL-C is the largest component) and low levels of HDL-C as important risk factors for CHD.[8] Findings of the Framingham Study form the basis for the risk classification system developed by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III; http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm) and for the ATP III recommendations of specific LDL-C targets to reduce cardiovascular risk.[9,10]

Although the Framingham risk score today remains a cornerstone of cardiovascular risk assessment, the marked increase in the prevalence of obesity and its associated comorbidities (mixed dyslipidemia, diabetes, and hypertension) in recent years has prompted attempts to refine risk classification.[11] Because of the important contribution of metabolic syndrome to cardiovascular risk, a disadvantage of the Framingham risk

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score is that it does not include a direct biomarker of the metabolic syndrome (**Table 1**) and consequently seems to underestimate the total risk associated with this growing epidemic.[11] This omission may explain why many patients who experience cardiovascular events had no traditional Framingham risk factors before the event.[12] In this context, it is important to note that the pathogenesis of atherosclerosis is characterized by inflammatory responses to growing atherosclerotic lesions. Visceral adiposity causes systemic inflammation, and visceral adipose volume has been shown to be correlated with the serum concentration of high-sensitivity C-reactive protein (hsCRP), a biomarker of inflammation.[13,14] Elevated concentrations of hsCRP, which is present only in trace amounts in healthy individuals, have been associated with increased risk of cardiovascular events.[15] The Reynolds risk score is an improved risk assessment algorithm, originally developed in women[16] and subsequently validated in men,[17] that recognizes hsCRP and parental history of myocardial infarction at age <60 years as important independent risk factors, in addition to the traditional Framingham risk factors (**Table 1**). The Reynolds risk score replaces LDL-C and HDL-C with other indicators of dyslipidemia, notably apolipoprotein B (apoB).[16] ApoB is a measure of the total number of circulating atherogenic particles and therefore is considered a more accurate indicator of total atherosclerotic burden than LDL-C, especially in patients with metabolic syndrome. Moreover, results from clinical studies suggest that risk assessment that includes apoB as a nontraditional risk factor, compared with assessment based solely on the Framingham risk score, may improve the prediction of cardiovascular risk in young, clinically healthy men with a low-risk profile for atherosclerosis.[18]

## How to Reduce Risk of CHD—The Importance of Meeting Lipid Targets

In 2002, the Heart Protection Study convincingly demonstrated that lowering LDL-C significantly improves cardiovascular outcomes in high-risk patients.[19] Since that time, it has become the consensus among experts that lowering LDL-C to specific targets is the cornerstone of a successful strategy to reduce cardiovascular risk. Current CHD risk reduction guidelines put forth by the NCEP ATP III, originally published in 2001 and updated in 2004, recommend LDL-C as the primary target of lipid-lowering therapy.[9,10] The underlying principle of the ATP III recommendations for prevention of cardiovascular events is that, for each individual, the intensity of intervention has to match the person's global CHD risk. This means that the LDL-C goal recommended for each person depends on the risk category to which the person has been assigned.[10] Updated ATP III guidelines recommend a target LDL-C of <100 mg/dL for individuals at high risk, including those who do not have CHD but who do have a CHD risk equivalent, such as diabetes or noncoronary clinical atherosclerosis, and those who have 2 or more risk factors and a 10-year Framingham CHD risk >20%.[10] In addition, the guidelines recommend LDL-C <70 mg/dL and non–HDL-C <100 mg/dL as targets for individuals at very high risk, including those with established cardiovascular disease who have severe and poorly controlled risk factors, such as cigarette smoking, and those with multiple risk factors associated with the metabolic syndrome, such as hypertriglyceridemia or HDL-C <40 mg/dL.[10] The ATP III guidelines emphasize that therapeutic lifestyle interventions such as smoking cessation, low-cholesterol diet, weight management, and physical activity have the potential

### Table 1. Reynolds Risk Score Versus Framingham Risk Score[16]

| Framingham Risk Score | Reynolds Risk Score (Full) | Reynolds Risk Score (Simplified) |
|---|---|---|
| Age | Age | Age |
| Blood pressure | HbA1c, with diabetes | HbA1c, with diabetes |
| Diabetes | Blood pressure | Blood pressure |
| Smoking | Smoking | Smoking |
| Total cholesterol | ApoB | HDL-C |
| HDL-C | ApoA-I | Total cholesterol |
| | Lp(a), if apoB >100 mg/dL | hsCRP |
| | hsCRP | Parental history of MI for age <60 years |
| | Parental history of MI for age <60 years | |

ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; Lp(a), lipoprotein A; MI, myocardial infarction.
Adapted with permission from Davidson MH. Assessing cardiovascular risk one patient at a time. *J Fam Pract.* 2009;58(11 Suppl):S26-S31.

to reduce cardiovascular risk and remain an essential modality in clinical management.[10] However, in practice, many individuals may be unable to achieve recommended lipid targets without receiving lipid-lowering pharmacotherapy.

## Primary Prevention—The Role of Statins

Results from a large number of studies have demonstrated the efficacy and safety of statins as lipid-lowering agents and the benefits they can provide for patients at high risk of CHD or with established coronary artery disease.[20] As a result, statin therapy has become an integral part of secondary prevention and treatment of high-risk patients.[10] More recently, a meta-analysis of primary prevention trials provided evidence that statin therapy is also beneficial for individuals without established cardiovascular disease but with cardiovascular risk factors.[21] However, although this analysis demonstrated that statin use was associated with significant risk reduction in all-cause mortality, a more recent meta-analysis that included previously unpublished data found a numeric reduction in mortality that missed statistical significance.[22] What, then, is the appropriate role of statins in the long-term prevention of cardiovascular events in seemingly healthy individuals with no clinical symptoms of CHD and no or mild hypercholesterolemia? Is statin therapy able to slow down atherosclerotic disease progression in patients with subclinical atherosclerosis? If so, what appropriate lipid targets have to be met?

The first demonstration of the benefits of statin therapy in primary prevention was provided by the results of the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), conducted throughout most of the 1990s at 2 outpatient clinics in Texas.[4] This randomized placebo-controlled study of long-term therapy with lovastatin included 6605 middle-aged or elderly (<74 years old) men and women with average LDL-C concentrations (placebo group mean after 1 year, 156 mg/dL) and low HDL-C concentrations. After follow-up of more than 5 years, study participants who received lovastatin had a 37% reduced risk of experiencing a first major cardiovascular event, such as myocardial infarction, sudden death, or unstable angina, compared with those who received placebo ($P < 0.001$; **Table 2**, *Figure 1*).[4] The cardiovascular benefits of lovastatin therapy were accompanied by a highly significant improvement in lipid profile, including a 25% reduction in LDL-C (versus a 1.5% increase with placebo, $P < 0.001$) and a 6% increase in HDL-C (versus a 1.2% increase with placebo, $P < 0.001$) after 1 year of treatment. The mean LDL-C value achieved after 1 year of treatment with lovastatin was 115 mg/dL. An important aspect of the study design was that participants had no clinical signs of CHD, no uncontrolled hypertension, and no significant diabetes-associated hyperglycemia.[4]

Findings of 2 primary prevention studies of pravastatin in individuals with hypertension and additional risk factors suggest that more intensive statin therapy may be necessary for patients with multiple risk factors but with no severe dyslipidemia. The first study, the lipid-lowering trial component of the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT), evaluated the effects of pravastatin in ethnically diverse North and Central American hypertensive patients with moderate hypercholesterolemia.[23] Pravastatin was associated with statistically nonsignificant risk reductions in CHD events after almost 5 years of follow-up ($P = 0.16$; **Table 2**). The mean LDL-C goal achieved after 2 years of treatment with pravastatin was 111 mg/dL compared with 135 mg/dL achieved with usual care (**Table 2**).[23] The second study was a subgroup analysis of the Management of Elevated cholesterol in the primary prevention Group of Adult Japanese (MEGA) study. In the original study conducted in 7832 Japanese patients with mild dyslipidemia, addition of low doses of pravastatin to dietary restriction resulted in a significant reduction in CHD events (33%, $P = 0.01$) after 5 years of follow-up (**Table 2**).[24] A subgroup analysis in 3277 patients with mild to moderate hypertension showed a significant reduction in cardiovascular disease events (33%, $P = 0.01$) and a nonsignificant reduction in CHD events (29%, $P = 0.12$) for pravastatin plus diet versus diet alone.[26] Although pravastatin significantly reduced LDL-C, the achieved target was only 124 mg/dL compared with 147 mg/dL for diet alone.[26] In contrast to these findings, participants in the large Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA), who had hypertension and at least 3 additional risk factors but no or only mild dyslipidemia (mean LDL-C at baseline, 131 mg/dL), had a 36% reduced risk of nonfatal myocardial infarction or fatal CHD if they received atorvastatin instead of placebo for a median period of 3.3 years ($P = 0.0005$; **Table 2**).[6] A notable finding of the study was the low mean LDL-C value of 87 mg/dL achieved by those who received atorvastatin (compared with 133 mg/dL in the placebo group; **Table 2**).[6] Thus, results of the ASCOT-LLA study suggest that individuals with multiple risk factors may benefit from low levels of LDL-C, even if they have no or mild dyslipidemia.

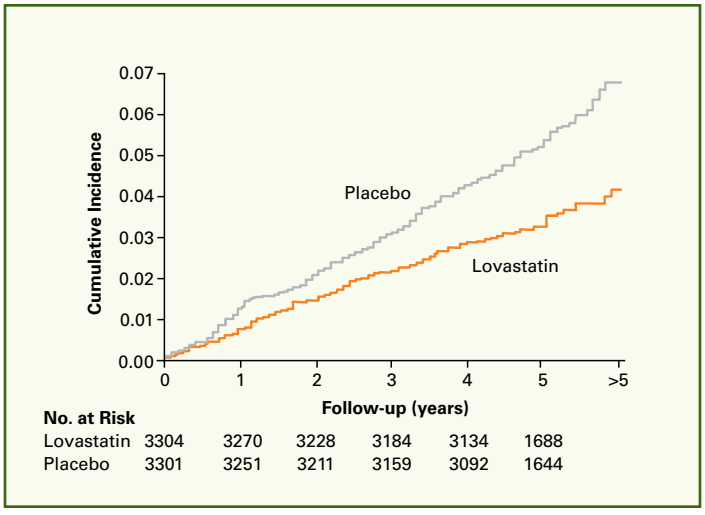


**Figure 1.** Cumulative incidence in AFCAPS/TexCAPS of fatal and nonfatal myocardial infarction, sudden death, and unstable angina. Lovastatin compared with placebo was associated with a 37% risk reduction ($P < 0.001$). Adapted with permission from Downs et al.[4]

Further support for this idea was provided by results of the Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study.[3] JUPITER was a large placebo-controlled study that evaluated the effects of intensive therapy with rosuvastatin on cardiovascular outcomes in 17,802 seemingly healthy individuals with normal LDL-C levels (<130 mg/dL). Patients with diabetes or uncontrolled hypertension were excluded. The only mandatory risk factors in the study were age (men, ≥50 years; women, ≥60 years) and elevated hsCRP (≥2 mg/L), but approximately 40% of the study population had metabolic syndrome and 16% were smokers.[3] Median LDL-C in the placebo group was approximately 110 mg/dL throughout the treatment period. In contrast, participants who received rosuvastatin achieved a median LDL-C level of 55 mg/dL after 1 year of treatment. The trial was stopped by an independent Data Safety Monitoring Board after a median follow-up of 1.9 years when it became apparent that rosuvastatin was associated with a highly significant reduction in the risk of major cardiovascular events, including myocardial infarction and stroke (**Table 2**, *Figure 2*).[3,27]

## Table 2. Summary of Major Primary Prevention Trials of Statin Therapy

| | | | | LDL-C (mg/dL)[a] | | Primary end point | |
|---|---|---|---|---|---|---|---|
| Study | Follow-up (years)[a] | Population | Treatments | Baseline | On treatment[b] | Event | Hazard ratio (95% CI) |
| AFCAPS/TexCAPS[4] (US; 1990–1993) | 5.2 | N = 6605 Low HDL-C | Lovastatin 20–40 mg (n = 3304)<br>Placebo (n = 3301) | 150<br>150 | 115<br>156 | MI, unstable angina, or sudden death | 0.63 (0.50–0.79) $P < 0.001$ |
| ALLHAT-LLT[23] (US, Canada; 1994–2002) | 4.8 | N = 10,355 Hypertension | Pravastatin 40 mg (n = 5170)<br>Usual care (n = 5185) | 129<br>129 | 111[c]<br>135[c] | All-cause death | 0.99 (0.89–1.11) $P = 0.88$ |
| MEGA[24] (Japan; 1994–1999) | 5.3 | N = 7832 Hypercholesterolemia | Diet + pravastatin (n = 3866)<br>Diet (n = 3966) | 156<br>156 | 127<br>153 | First occurrence of CHD | 0.67 (0.49–0.91) $P = 0.01$ |
| ASCOT-LLA[6] (UK, Ireland, Scandinavia; 1998–2000) | 3.3[d] | N = 10,305 Hypertension, ≥3 other risk factors | Atorvastatin 10 mg (n = 5168)<br>Placebo (n = 5137) | 131<br>131 | 87<br>133 | Nonfatal MI or fatal CHD | 0.64 (0.50–0.83) $P = 0.0005$ |
| CARDS[25] (UK, Ireland; 1997–2003) | 3.9[d] | N = 2838 Type 2 diabetes | Atorvastatin 10 mg (n = 1428)<br>Placebo (n = 1410) | 117<br>117 | 72<br>120 | Acute CHD, coronary revascularization, or stroke | 0.63 (0.48–0.83) $P = 0.001$ |
| JUPITER[3] (Americas, Europe, South Africa; 2003–2008) | 1.9[d] | N = 17,802 LDL-C <130 mg/dL, hsCRP ≥2 mg/L | Rosuvastatin 20 mg (n = 8901)<br>Placebo (n = 8901) | 108[d]<br>108[d] | 55[d]<br>110[d] | MI, stroke, arterial revas-cularization, hospitalization for unstable angina, or CV death | 0.56 (0.46–0.69) $P < 0.00001$ |

AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT, Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial–Lipid-lowering trial component; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm; CARDS, Collaborative Atorvastatin Diabetes Study; CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; JUPITER, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; MEGA, Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; MI, myocardial infarction.

[a]Values are means except where otherwise indicated.

[b]At 1-year follow-up except where otherwise indicated.

[c]At 2-year follow-up.

[d]Median value.

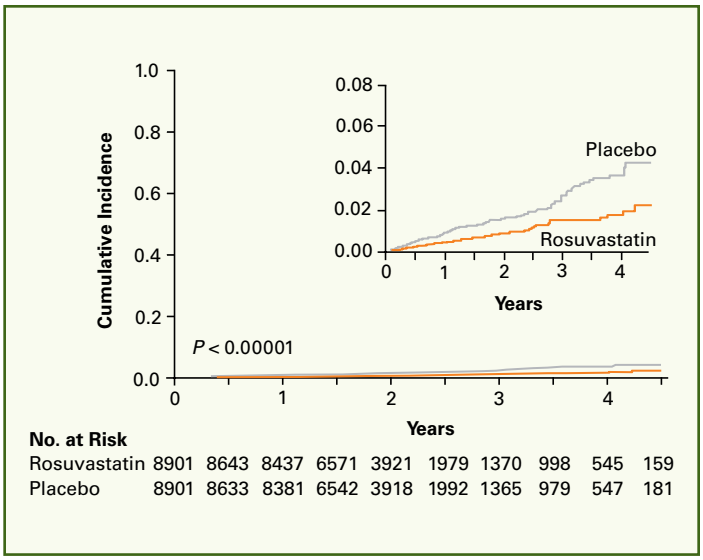


**Figure 2.** Cumulative incidence in JUPITER of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. The hazard ratio for rosuvastatin versus placebo was 0.53 (95% confidence interval, 0.40–0.69; $P < 0.00001$). The inset shows the same data on an enlarged y-axis and a condensed x-axis.
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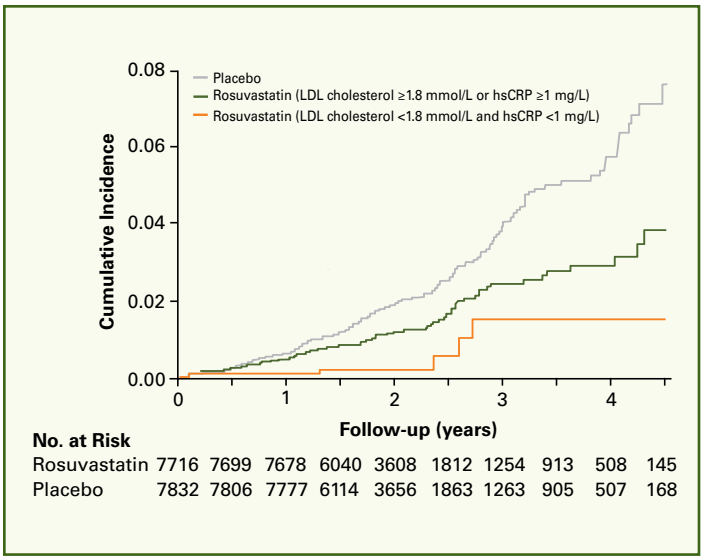


**Figure 3.** Cumulative incidence of cardiovascular events in JUPITER for rosuvastatin versus placebo based on achievement of reductions in both LDL cholesterol (to <1.8 mmol/L) and high-sensitivity C-reactive protein (hsCRP) (to <1 mg). Adapted with permission from Ridker et al.[5]

In addition, participants who received rosuvastatin had a 54% reduced risk of myocardial infarction, a 48% reduced risk of stroke, and a 46% reduced risk of arterial revascularization compared with those who received placebo.[3] In a prospective analysis of trial results, the authors evaluated whether meeting specific targets of LDL-C and hsCRP would be associated with increased cardiovascular benefit.[5] Investigators found that participants who reached LDL-C goals of <70 mg/dL had greater risk reduction than those who did not. The greatest risk reduction in major cardiovascular events (79%) was observed in participants who achieved both LDL-C <70 mg/dL (1.8 mmol/L) and hsCRP <1 mg/L with rosuvastatin (*Figure 3*).[5] The meta-analysis by Baigent et al[20] also evaluated the safety of statin therapy in patients with or without CHD. The results suggested that patients treated with statins for 5 years had no increased risk of cancer or death from nonvascular causes. Importantly, statin therapy compared with placebo did not significantly increase the risk of rhabdomyolysis, a rare but serious adverse event (5-year absolute risk excess for statins versus placebo, 0.01%; $P = 0.4$). Similarly, a large meta-analysis of 76 randomized, controlled primary and secondary prevention studies that included a total of 170,255 patients found no significant risk of cancer or rhabdomyolysis associated with statin therapy.[28] Available data from 17 studies (including 111,003 patients) found that statin therapy compared with placebo was associated with an increased risk of incident diabetes (9%; $P = 0.008$). This result is similar to that of JUPITER, in which statin versus placebo was associated with increased incidence of diabetes ($P = 0.01$).[3] For patients at risk for CHD, the benefits of statin therapy in reducing the risk of cardiovascular events and revascularization procedures may outweigh this risk.

## Primary Prevention in Patients With Type 2 Diabetes

A particular challenge in primary prevention is the treatment of patients with type 2 diabetes. Diabetes is recognized by ATP III guidelines as a CHD risk equivalent, and patients with diabetes are considered to be at high risk of cardiovascular events even in the absence of additional risk factors.[9] A recent clinical study evaluating the benefits of intensive glycemic control in primary prevention yielded inconclusive results, mainly because of an unexpectedly high mortality rate in the active treatment arm of the Action to Control CardiOvascular Risk in Diabetes (ACCORD) trial, which essentially remains unexplained.[29] By contrast, the primary prevention benefits of lipid-lowering statin therapy for diabetic patients are well established.[25,30] Notably, results of the Collaborative Atorvastatin Diabetes Study (CARDS) demonstrated a significant reduction (37%, $P = 0.001$) in major cardiovascular events with atorvastatin versus placebo in 2838 diabetic patients without high LDL-C (mean LDL-C at baseline, 117 mg/dL) after a median follow-up of less than 4 years.[25] Patients in the atorvastatin arm achieved a mean LDL-C value of 72 mg/dL (1.86 mmol/L) after 1 year of treatment.

The ACCORD lipid study evaluated the benefits of triglyceride-lowering therapy in addition to statin therapy in diabetic patients by comparing the effects of simvastatin monotherapy and of combination therapy with simvastatin and fenofibrate on cardiovascular outcomes in 5518 diabetic patients with normal overall LDL-C values (mean, 101 mg/dL).[31] The primary analysis showed that combination treatment versus monotherapy overall was significantly more effective in improving HDL-C and triglyceride levels but provided no significant cardiovascular benefit (hazard ratio for major cardiovascular events, 0.92; $P = 0.32$). In a subgroup of patients (n = 941) with high triglyceride levels

(≥204 mg/dL) and low HDL-C (≤34 mg/dL), combination therapy was associated with a lower rate of cardiovascular events (12.4%) compared with monotherapy (17.3%); however, these results did not achieve statistical significance ($P = 0.06$).[31] These findings of the ACCORD lipid study suggest that adding fenofibrate to statin therapy may provide primary prevention benefits for diabetic patients with signs of atherogenic dyslipidemia. In addition, the ACCORD study demonstrated that diabetic patients with high triglycerides and low HDL-C on statin therapy have a high residual cardiovascular risk (event rate of 17.3%) compared with those who have no mixed dyslipidemia (event rate of 10.1%).[31]

**Together, the results of primary prevention trials confirm the current ATP III recommendation that reaching specific lipid goals is critical to reduce CHD events in patients with other cardiovascular risk factors.**

## Does Intensive Statin Therapy Affect Atherosclerotic Disease Progression?

Results of the METEOR (Measuring Effects on intima-media Thickness: an Evaluation Of Rosuvastatin) study make a strong case that the use of intensive statin therapy directly influences the course of atherosclerotic disease progression in at-risk patients with subclinical atherosclerosis. The METEOR Study Group conducted a 2-year placebo-controlled trial of intensive therapy with rosuvastatin in 984 patients with elevated cholesterol (~154 mg/dL), a 10-year Framingham CHD risk <10%, and modestly increased carotid intima-media thickness indicative of atherosclerosis.[32] Although rosuvastatin generally did not induce regression of atherosclerosis in this low-risk population, disease progression during the 2-year treatment period was significantly reduced in participants who received rosuvastatin compared with those who received placebo ($P \leq 0.02$).[32]

In addition, evidence supporting disease regression with aggressive statin therapy was seen in the results of A Study To Evaluate the effect of Rosuvastatin On Intravascular ultrasound-Derived coronary atheroma burden (ASTEROID). This 24-month prospective, open-label, blinded end point study of rosuvastatin 40 mg/d in statin-naïve patients with symptoms of coronary artery disease demonstrated that achieving average LDL-C levels of 61 mg/dL and HDL-C increases of 15% was associated with significant regression of coronary atherosclerosis, as determined by various intravascular ultrasound parameters ($P < 0.001$).[33] To further evaluate the effects of high-intensity statin therapy on coronary atherosclerotic burden, a large, randomized, double-blind study is under way to compare the efficacies of rosuvastatin (40 mg/d) and atorvastatin (80 mg/d) in reducing atheroma volume in patients with coronary artery disease and modifiable risk factors.[34]

## CONCLUSION

**Over the last decade, results of a number of large, controlled clinical studies have provided compelling evidence that lipid-lowering statin therapy significantly reduces the risk of first major cardiovascular events. The efficacy of statins in primary prevention has been demonstrated in different study populations representing a broad range of disease characteristics and risk factors, including patients with diabetes, hypertension, dyslipidemia, and/or metabolic syndrome. In particular, ASCOT-LLA, CARDS, and JUPITER demonstrated that achieving low levels of LDL-C can reduce the risk of CHD derived from risk factors other than dyslipidemia and hypercholesterolemia. For example, results of the JUPITER study suggest that LDL-C levels as low as 55 mg/dL may benefit seemingly healthy individuals who have LDL-C <130 mg/dL but who have multiple other CHD risk factors. Together, the results of primary prevention trials confirm the current ATP III recommendation that reaching specific lipid goals is critical to reduce CHD events in patients with other cardiovascular risk factors.**

**Another essential part of a successful prevention strategy is complete understanding of a person's global risk. Since the conception of the Framingham risk score, our understanding of and ability to measure atherosclerotic disease progression have greatly improved. The recent results of the ACCORD lipid study suggest that, in diabetic patients with atherogenic dyslipidemia, elevated triglyceride levels and low HDL-C substantially increase residual cardiovascular risk on statin therapy. The JUPITER results further suggest that traditional risk factors do not fully capture the risk of individuals with elevated hsCRP, a biomarker of inflammation that has been associated with visceral adiposity. The Reynolds risk score, which incorporates nontraditional risk factors, may provide a more accurate measure of an individual's risk for cardiovascular disease. The key strategy for effective primary prevention is to understand a patient's absolute lifetime risk for cardiovascular disease and apply comprehensive lipid management that is likely to improve the outcome.**

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