Residual Risk and High-Density Lipoprotein Cholesterol Levels: Is There a Relationship?

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Statins reduce adverse cardiovascular events in both primary and secondary prevention settings. Despite their use, however, a residual burden of cardiovascular events continues to remain; in part this residual risk is related to low high-density lipoprotein (HDL) cholesterol levels. Therefore, HDL-based interventions that either raise HDL cholesterol levels or improve HDL function have become the next target for atherosclerosis management.

[Rev Cardiovasc Med. *2011;12(2):e55-e59 doi: 10.3909/ricm0565*]

Key words: Atherosclerosis • Statins • High-density lipoprotein cholesterol

Clinical trials have demonstrated that statins reduce low-density lipoprotein cholesterol (LDL-C) levels and significantly reduce atherothrombotic cardiovascular events, with a greater percentage in event reduction achieved with lower levels of LDL-C achieved.[1] However, despite high-dose statin therapy and achievement of LDL- levels approximating 70 mg/dL, a substantial number of events (referred to as residual risk) continue to occur in chronic stable coronary artery disease patients (approximately 8.7% at 4.9 years of follow-up), as well as in acute coronary syndrome (ACS) patients (22.4% after 24 months of follow-up) (Tables 1 and 2).[2-10] In a meta-analysis, the Cholesterol Treatment Trialists Collaborative compared the residual risk among 18,685 patients with diabetes to that of 71,370 patients without diabetes; the residual risk

Table 1
Residual Cardiovascular Risk in Placebo-Controlled Statin Trials

Trial	Type of Trial	Change in LDL-C (%)	Placebo Event Rate (%)	Statin Event Rate (%)
Scandinavian Simvastatin Survival Study (4S)[2]	Secondary prevention	−35	28	19.4
Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID)[3]	Secondary prevention	−25	15.9	12.3
Cholesterol and Recurrent Events (CARE)[4]	Secondary prevention	−28	13.2	10.2
West of Scotland Coronary Prevention Study (WOSCOPS)[6]	Primary prevention	−26	7.9	5.5
Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)[7]	Primary prevention	−25	10.9	6.8
Heart Protection Study (HPS)[5]	High risk	−29	11.8	8.7

LDL-C, low-density lipoprotein cholesterol.

Table 2
Residual Cardiovascular Risk in Intensive Versus Standard-Dose Statin Trials

Trial	Type of Trial	LDL-C On-Treatment Intensive Versus Standard	Standard Statin Event Rate (%)	Intensive Statin Event Rate (%)
Pravastatin or Atorvastatin Evaluation and Infection Therapy: Thrombolysis in Myocardial Infarction (PROVE-IT /TIMI) 22[10]	Acute coronary syndromes	62 vs 95 mg/dL	26.3 (2 y)	22.4 (2 y)
Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL)[9]	Stable coronary artery disease	81 vs 104 mg/dL	13.7 (5 y)	12.0 (5 y)
Treating to New Targets (TNT)[8]	Stable coronary artery disease	77 vs 101 mg/dL	10.9 (5 y)	8.7 (5 y)

LDL-C, low-density lipoprotein cholesterol.

was 29.6% in patients with diabetes as compared with 19.4% in those without (Table 3).[11] The potential contributors of residual risk may include low high-density lipoprotein cholesterol (HDL-C) and apolipoprotein (Apo) A-I levels, and possibly dysfunctional HDL, small LDL particle size, increased LDL particle number, elevated Apo B levels, elevated triglyceride levels, high lipoprotein(a) levels, diabetes and insulin resistance, and unhealthy lifestyle.

Population studies have clearly demonstrated a strong inverse relationship between HDL-C levels and cardiovascular events, suggesting that one possible reason for the residual risk in statin-treated patients may be low levels of HDL-C.[12,13] This issue was recently addressed in a post hoc analysis of the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial by

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Table 3
Residual Cardiovascular Risk in Patients With Diabetes Versus Patients Without Diabetes in a Meta-Analysis of Statin Trials

Patients	Subjects (N)	Placebo Event Rate (%)	Statin Event Rate (%)
Patients with diabetes[11]	18,685	34.9 (4.3 y)	29.6 (4.3 y)
Patients without diabetes[11]	71,370	24.8 (4.3 y)	19.4 (4.3 y)

Ridker and colleagues.[14] In the primary prevention JUPITER trial, involving 17,802 patients with elevated high-sensitivity C-reactive protein (> 2 mg/L) and LDL-C levels < 130 mg/dL, 20 mg/d of rosuvastatin led to a 44% relative risk reduction at 2 years when compared with placebo.[15] Ridker and colleagues now report that the on-treatment HDL-C levels were inversely related to cardiovascular events in the placebo-treated group, who had a median LDL-C level of 110 mg/dL (hazard ratio [HR], 0.54 at baseline; $P = .0039$; HR, 0.55 for on-treatment; $P = .0047$), but not in the rosuvastatin-treated group, whose median LDL-C levels were 55 mg/dL (HR, 1.12 at baseline; $P = .82$; HR, 1.03 for on-treatment; $P = .97$). Using Apo A-I levels in place of HDL-C levels also showed a relationship in the placebo group but not in the rosuvastatin-treated group (Figure 1).[14] These observations are comparable with those reported by Ray and associates[16] from the ACS population in the Pravastatin or Atorvastatin Evaluation and Infection Therapy: Thrombolysis in Myocardial Infarction (PROVE IT-TIMI) 22 trial, in which the Apo B to A-1 ratio, the total cholesterol to HDL-C ratio, and the non–HDL-C levels did not improve risk prediction when models included LDL-C levels. However, findings of Ridker and colleagues are at variance with those from the secondary prevention Treating to New Targets (TNT) trial.[17] Among subjects receiving statins in the TNT trial, HDL-C levels were inversely related to cardiovascular risk, when using HDL-C as a continuous variable or when HDL-C levels were stratified into quintiles.[17] In the TNT trial,

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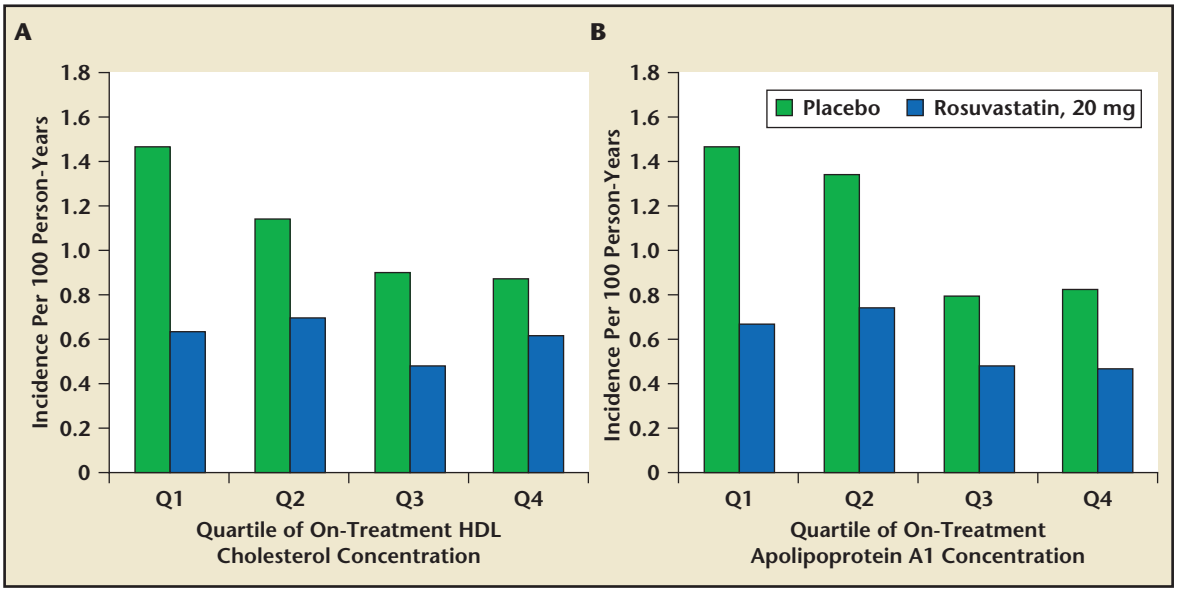
Figure 1. *Incidence of cardiovascular events based on HDL-C levels **(A)** and Apo A-I **(B)** levels in the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial. Placebo group: P = .004 for HDL-C in and P = .001 for Apo A-I. Rosuvastatin-treated group: P = .97 for HDL-C and P = .25 for Apo A-I. Apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol. Reprinted with permission from Ridker PM et al.[14]*



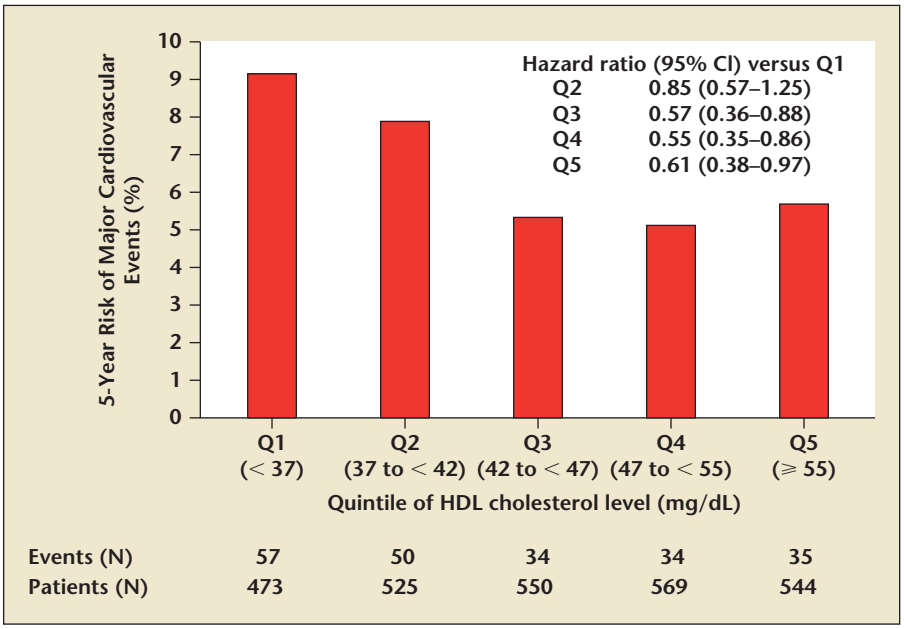


Figure 2. *The inverse relationship between quintiles of HDL-C and 5-year cardiovascular risk among patients achieving LDL-C levels < 70 mg/dL in the statin treatment arm of the Treating to New Targets trial. CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Q, quintile. Reprinted with permission from Barter P et al.*[17]

when the analysis was performed based on LDL-C levels in statin-treated subjects, HDL-C levels were related to cardiovascular events with a marginal *P* value of $P = .05$.[17] However, among subjects achieving LDL-C levels < 70 mg/dL, those in the highest quintile of HDL-C had a significantly lower risk than those in the lowest quintile of HDL-C ($P = .03$) (Figure 2).[17]

The precise reasons as to why HDL-C and Apo A-I levels failed to predict residual cardiovascular risk in the rosuvastatin-treated subjects in the JUPITER trial is not entirely clear. Potential reasons may include the very low-risk nature of the population, as well as the possibility that other risk factors beyond HDL-C may be important determinants of residual risk. Furthermore, as the complex biology of HDL continues to unfold, showing that HDL-C levels may not be a reliable indicator of the atheroprotective functionality of HDL, it may well be that markers of HDL function will turn out to be more reliable surrogates for its atheroprotective effect than simply measuring HDL-C levels; in that sense these data do not necessarily invalidate the HDL hypothesis.[12,13] The data from the JUPITER trial should not dissuade physicians from using HDL-C level as one of the biomarkers of risk (because HDL-C was negatively related to risk in the placebo group), nor should it lead to the conclusion that residual risk may not be modifiable by HDL-targeted therapies. Only appropriately designed prospective clinical trials of HDL-targeted therapies can validate or invalidate the HDL hypothesis. ■

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Main Points

- Statins significantly reduce adverse cardiovascular events in patients at risk for or with known cardiovascular disease.
- Despite statins, nearly two-thirds of adverse cardiovascular events continue to occur, leaving a significant residual risk.
- Low high-density lipoprotein cholesterol (HDL-C) level is a significant contributor to residual risk in statin-treated subjects.
- New targets to further reduce residual risk include interventions to raise HDL-C levels and enhance HDL function.

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