With Very Low LDL, HDL Is Not a Marker

BY SHARON WORCESTER

FROM THE LANCET

High-density lipoprotein cholesterol concentrations are inversely associated with risk for cardiovascular events, but this association does not persist in patients who achieve very low concentrations of low-density lipoprotein cholesterol on statin therapy, according to an analysis of data from the JUPITER (Justification for the Use of Statins in Primary Prevention) trial.

In 8,901 patients in the study who received placebo and who had a median LDL cholesterol level of 2.8 mmol/L (108 mg/dL), HDL cholesterol levels were inversely associated with risk for cardiovascular events both at baseline and on placebo (hazard ratios, 0.54 and 0.55, respectively, for the top vs. the bottom quartiles of HDL cholesterol levels).

However, in 8,900 patients in the study who were treated daily with 20 mg rosuvastatin (Crestor) and who had a median LDL cholesterol level of 1.42 mmol/L (55 mg/dL) on treatment, there was no significant association between HDL cholesterol concentrations and vascular risk at baseline or on treatment (hazard ratios, 1.12 and 1.03, respectively, for the top vs. bottom quartiles of HDL cholesterol levels), Dr. Paul M. Ridker of Brigham and Women's Hospital, Boston and his colleagues reported.

They also noted that, like HDL cholesterol levels, apolipoprotein A1 levels were strongly and inversely associated with risk for cardiovascular events in the placebo group, but these associations were attenuated and not statistically significant in the treatment group.

Patients were part of the JUPITER trial, which enrolled 17,802 participants from March 2003 to December 2006 to investigate whether rosuvastatin lowered the rate of first-ever cardiovascular events.

Study participants had LDL cholesterol levels of less than 3.4 mmol/L (130 mg/dL) and were at high vascular risk because of elevated high-sensitivity C-reactive protein (hsCRP) concentrations of 2 mg/L or more, but were otherwise healthy, without cardiovascular disease or diabetes.

Indeed, rosuvastatin reduced LDL levels to a median of 1.4 mmol/L (55 mg/dL), with 25% of patients achieving concentrations of less than 1.1 mmol/L 44 mg/dL) in the trial, and treatment was associated with a 54% reduction in MI, a 48% reduction in stroke, a 46% reduction in revascularization, and a 20% reduction in total mortality (N. Engl. J. Med. 2008;359:2195-20), the investigators noted.

Now, based on the findings of the current analysis of data from the JUPITER primary prevention trial, it appears that treatment also reduces the clinical relevance of HDL cholesterol concentrations, they said (Lancet 2010 July 22 [doi:10.1016/So140-6736(10)60713-1]).

"This analysis provides little evidence that residual risk after aggressive use of

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Major Finding: In 8,900 patients treated daily with 20 mg rosuvastatin and who had a median LDL cholesterol level of 1.42 mmol/L on treatment, there was no significant association between HDL levels and vascular risk at baseline or on treatment (hazard ratios, 1.12 and 1.03, respectively, for the top vs. bottom quartile of HDL levels).

Data Source: An analysis of the randomized, double-blind, placebo-controlled JUPITER trial.

Disclosures: AstraZeneca, maker of the trial drug, funded the study. Dr. Ridker reported receiving grant support and/or consulting and lecture fees from AstraZeneca and other drug manufacturers. He is listed as a co-inventor on patents held by the Brigham and Women's Hospital, which relate to the use of inflammatory biomarkers in cardiovascular disease and have been licensed to AstraZeneca and other entities. Some authors also reported receiving research support and/or consulting and lecture fees from AstraZeneca and numerous drug manufacturers.

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statin therapy is related to HDL-cholesterol concentration," the investigators wrote, noting that their findings are supported by similar findings in one other primary prevention trial and two secondary prevention trials involving high-dose statin therapy.

The current study is strengthened by the investigators' ability to adjust for a wide range of covariates, including age, sex, smoking status, metabolic syndrome, family history of premature atherosclerosis, body mass index, systolic blood pressure, fasting glucose, and estimated glomerular filtration rate. Analyses of HDL cholesterol were controlled for baseline concentrations of LDL cholesterol, triglyceride, and hsCRP (and in the case of on-treatment HDL cholesterol, for changes in the latter three), they said.

The study is limited, however, by the exclusion of diabetic patients and the inclusion of patients with LDL cholesterol of less than 3.4 mmol/L. Generalization of the findings should therefore be done with caution, they noted.

The investigators concluded that their primary prevention data, along with data from other primary and secondary prevention studies, provide little evidence in support of the hypothesis that HDL cholesterol concentrations predict risk of vascular events in patients on high-dose statins.

They noted, however, that their findings should not "reduce enthusiasm for measurement [of HDL cholesterol concentration] as part of an initial cardiovascular risk assessment."

Future randomized trials of potent HDL cholesterol–raising agents are needed to determine if such treatment would provide added benefit in terms of cardiovascular risk reduction in patients whose LDL levels are successfully lowered on statin therapy, they said.

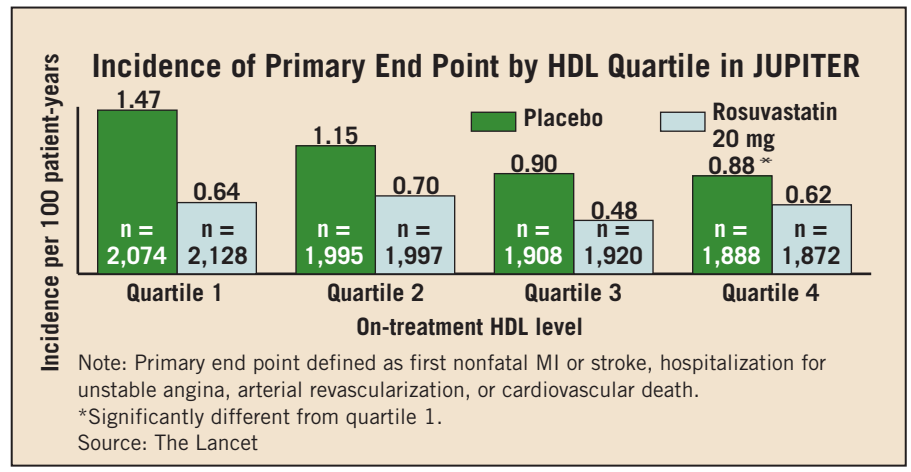
In an accompanying editorial comment, Dr. Derek Hausenloy of the Hatter Cardiovascular Institute at University College London Hospital and his colleagues noted that although the researchers had shown that HDL cholesterol concentrations do not predict residual cardiovascular risk in patients with very low LDL cholesterol concentrations, the reasons for this observation remain unclear (Lancet 2010 July 22 [doi:10.1016/S0140-6736(10)61021-5]).

"Perhaps, in patients with a low cardiovascular risk … who are treated to very low concentrations of LDL cholesterol, the relation between HDL cholesterol and cardiovascular risk is lessened; however, [the researchers] were not able to find a relation between apolipoprotein A1 and reduced cardiovascular risk," the commentators wrote.

They added that in the setting of very low LDL cholesterol, other lipid measures, such as apolipoprotein B to A1 ratio, may provide a better prediction of cardiovascular risk.

Regardless, the findings should not "detract from the fact that raising HDL cholesterol remains a major treatment strategy for the reduction of cardiovascular risk in the large majority of patients who do not have very low LDL cholesterol," wrote Dr. Hausenloy and his colleagues, none of whom had any disclosures to make in relation to the study.

It still needs to be determined in large randomized trials whether increasing HDL cholesterol in patients with very low LDL cholesterol is of benefit, they noted, adding that such trials will be particularly important given that two new inhibitors of cholesterol ester transfer proteins—anacetrapib and dalcetrapib—are now in clinical testing. ■



Note: Primary end point defined as first nonfatal MI or stroke, hospitalization for unstable angina, arterial revascularization, or cardiovascular death.
*Significantly different from quartile 1.
Source: The Lancet

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