More from JUPITER: HDL not predictive of risk at very low LDL levels

JULY 21, 2010 | Lisa Nainggolan

Boston, MA - A post hoc analysis of the JUPITER trial has shown that when patients have very low concentrations of LDL cholesterol attained through the use of potent statin therapy, "good" HDL cholesterol may no longer be predictive of cardiovascular risk [1].

This is the first time this has been observed in a primary-prevention population, although there are similar data from contemporary secondary-prevention statin trials, say Dr Paul M Ridker (Brigham and Women's Hospital, Boston, MA) and colleagues in their paper published online July 21, 2010 in the Lancet.

They emphasize, however, that HDL was predictive of cardiovascular risk in patients taking placebo in JUPITER, so "our data should not reduce enthusiasm for measurement of HDL-cholesterol concentration as part of an initial cardiovascular risk assessment."

In an accompanying comment [2], Drs Derek J Hausenloy (University College London, UK), Lionel Opie (University of Cape Town, South Africa), and Derek Yellon (University College London) say that it is "unclear" why HDL concentrations did not predict cardiovascular risk at very low concentrations of LDL cholesterol in those treated with rosuvastatin (Crestor, AstraZeneca) in JUPITER. But given that more potent drugs for raising HDL cholesterol are on the horizon, the issue will require more research and needs to be examined in large randomized trials, they say.

The findings from this study "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; the problem, in most cases, is how to achieve this strategy," they stress.

Little evidence that HDL is predictive of risk when LDL very low

JUPITER participants were adults without diabetes or previous cardiovascular disease who had baseline LDL-cholesterol levels <3.37 mmol/L and high-sensitivity C-reactive protein levels ≥2 mg/L. In all, 8900 participants were randomized to receive rosuvastatin 20 mg per day, and 8900 to receive placebo.

In the new analysis, HDL-cholesterol concentrations were inversely related to vascular risk in the patients given placebo (who had a median on-treatment LDL-cholesterol level of 2.8 mmol/L) both at baseline (hazard ratio 0.54; p=0.0039) and on treatment (HR 0.55; p=0.0047).

In contrast, among those on rosuvastatin (who had a median on-treatment LDL-cholesterol level of 1.42 mmol/L), there was no significant relation between quartiles of HDL-cholesterol concentration and vascular risk, either at baseline (HR 1.12; p=0.82) or on treatment (HR 1.03; p=0.97).
A similar analysis for apolipoprotein A1 showed an equivalent strong relation to frequency of primary outcomes in the placebo group but little association in the rosuvastatin group.

Ridker et al say their findings are "consistent with data from two secondary-prevention trials"—the TNT trial and PROVE-IT TIMI 22—and "provide little evidence to support the hypothesis that HDL-cholesterol levels predict risk of vascular events in the setting of high-dose statin therapy."

**But some data do suggest HDL still predictive at low LDL levels**

But in their comment, Hausenloy, Opie, and Yellon say the data are conflicting on whether HDL is predictive of risk in the face of low LDL levels. Although they agree that some secondary-prevention statin trials have illustrated null data for HDL and residual risk, they cite other studies in which HDL was predictive of risk even in patients with quite low LDL levels (ranging from 1.6 to 2.0 mmol/L).

It possible that at "very low" LDL levels, other lipid measures will provide more accurate prediction of cardiovascular risk than HDL concentrations, they note.

"Studies of secondary prevention of cardiovascular disease are needed to confirm whether the predictive value of HDL-cholesterol concentrations for cardiovascular risk are diminished in the presence of very low LDL cholesterol and whether other lipid measurements might offer greater predictive accuracy of cardiovascular risk," they conclude.

Ridker et al agree: "Randomized trials of potent HDL-cholesterol-raising agents will be needed to definitively test this clinically important hypothesis."

**Biology of HDL "complicated," further analysis needed**

Asked to comment on the study for heartwire, Dr Emil M deGoma (University of Pennsylvania, Philadelphia), who was not involved with this trial but has published research on the topic, said he believes it "highlights the limitations of serum HDL cholesterol as a measure of HDL-related risk in patients receiving pharmacotherapy."

"The biology of HDL is far more complicated than that of LDL," deGoma said a parallel can be drawn here to on-treatment LDL-cholesterol levels, which numerous trials—including AFCAPS/TexCAPS, LIPID, TNT, and IDEAL—"have shown no longer predict risk on statin treatment; only measures of LDL particle concentration using [nuclear magnetic resonance] NMR or [apolipoprotein B] assays correlated with residual risk."

And "the biology of HDL is far more complicated than that of LDL," deGoma said. "I suspect that mass-based assays alone will be inadequate. Measures of functionality . . . are likely needed to further illuminate HDL-related risk, particularly in the setting of drug therapy. The results of planned studies by the JUPITER investigators examining metrics of HDL functionality are eagerly awaited," he noted.

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conflicts to declare.

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- [ApoB and non-HDL better than LDL cholesterol for risk prediction: TNT and IDEAL](http://www.thelancet.com/database/article/1103731/print.do) ([Lipid/Metabolic > Lipid/Metabolic]; Jun 19, 2008]

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