

AHA 2010 - Debate over benefits of raising HDL set to continue



[Amy Brown](#)

Fighting cardiovascular disease by boosting levels of high density lipoprotein (HDL) or 'good cholesterol' is widely expected to emerge as an effective treatment strategy; definitive evidence that this will help save lives has yet to emerge. Two high-profile studies at the American Heart Association meeting in Chicago this week of two novel agents seeking to raise HDL - Merck & Co's anacetrapib and Resverlogix's RVX-208 - threw the spotlight on this debate.

Speaking to *EP Vantage* on the sidelines of the AHA meeting, most experts agree that raising HDL remains a plausible target. Some are more sceptical than others, but ultimately studies like the 30,000 patient Reveal trial of anacetrapib will provide more definitive answers. Or as Dr Christopher Cannon of the Brigham and Women's Hospital puts it: "This is the HDL decade".

Questionable marker

In contrast to the widely accepted notion that reducing levels of low density lipoprotein (LDL), or 'bad cholesterol', significantly cuts a patient's risk of cardiovascular events like heart attack and stroke, the relevance of raising HDL is more debatable.

The evidence of epidemiology studies indicate that high levels of HDL reduces cardiovascular risk, on the basis that HDL helps to clear LDL from the bloodstream. However, there is a big difference between identifying a marker of disease and assuming that targeting that marker has a clinical benefit.

"It has not been shown that raising HDL matters a whole lot", says Dr Robert Bonow, Feinberg School of Medicine at Northwestern University. Although niacin does raise HDL and has been shown to improve clinical outcome, Dr Bonow points out that the mechanism of niacin is "clouded by the fact niacin also lowers LDL".

Dr Bonow uses the following analogy in questioning the need to raise HDL, although he admits it is somewhat simplistic: "If LDL is the garbage and HDL is the garbage men, if you create less garbage you need fewer garbage men".

Dr Bonow also points to data from the Jupiter trial of Crestor which showed that, in patients with very low LDL, also having low HDL did not appear to be related to a higher cardiovascular risk.

Dr Harlan Krumholz, professor of medicine at Yale University School of Medicine, concurs with this view: "The truth is we really don't know. We don't have that proof-of-concept yet, particularly not from contemporary research".

More convinced

Others are more convinced that raising HDL levels holds the key to improving treatment of heart disease, particularly in patients who have had LDL lowered dramatically by statins, but still suffer heart attacks and strokes.

Dr Jean-Louis Dasseux, chief executive of Cerenis, says that as the reverse lipid transport process is the only way to clear cholesterol from arteries, a process driven by HDL, booster therapies are the way forward.

"We can reduce cholesterol to a certain level, but we still need to do more as patients are left with cholesterol in the wall of arteries that will cause heart attacks. If we can find an agent to fight the plaque it will help.

"The jury is still out what is best way to promote plaque regression. But no doubt the function of HDL is a target."

Dr Dasseux has a vested interest in the hypothesis - Cerenis is developing an HDL mimetic, CER-001, that is about to enter a large phase II trial in patients recently suffered a heart attack ([EP Vantage Interview - Cerenis](#))

[adds €40m to the HDL debate, July 27, 2010](#)).

Testing the thesis

Ultimately these concerns about the relevance of raising HDL can only be tested in large scale clinical outcome trials.

One such trial is the Reveal study of anacetrapib announced at AHA which will aim to enrol 30,000 patients and last up to six years, although there is a chance it will be stopped early if safety and efficacy data is particularly compelling ([AHA 2010 - Benefits of Merck's HDL booster could be revealed by 2014, November 18, 2010](#)).

“An exciting feature of this (the Reveal trial) is that it is going to be a terrific proof of concept”, says Dr Christopher Granger of the Duke Heart Center. “If this doesn’t improve clinical outcomes then it really will challenge the whole paradigm that raising HDL is important”.

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