

# expert roundtable »

## The Role of HDL-C in the Management of Atherosclerosis



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Moderated by **Daniel J. Rader, MD<sup>1</sup>**

Discussants: **H. Bryan Brewer, MD<sup>2</sup>; Jean-Claude Tardif, MD<sup>3</sup>; Peter P. Toth, MD, PhD<sup>4</sup>**

**DR. RADER:** Our topic today is high-density lipoprotein (HDL); HDL as a target for new therapies. This is a topic that's been of great interest to a lot of people, and not without its controversy. What we'll do is talk a little bit about current approaches to raising HDL, or to targeting HDL, and then talk about new treatments in development.

So let's first talk briefly about the epidemiology. There is incredibly strong epidemiologic association of low HDLs with coronary disease. That's why we're interested. But there have been recent issues that suggest that certain types of genetic causes of low HDL don't seem to be necessarily associated with increased risk; as well as of course, some well known drug trials that were not all positive. There has been some questioning about HDL and its importance.

Peter, I wonder if you could start and address the issue of the epidemiology of HDL and the issue of causality versus association. What's your take on the strong epidemiologic association of HDL levels and coronary disease?

**DR. TOTH:** The epidemiologic relationship between HDL and cardiovascular disease is remarkably consistent when you look at both genders, and people irrespective of race or ethnicity, throughout the world. We know that when it comes to HDL, when levels are low, risk for cardiovascular events is high. And, with some excep-

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The discussion focused primarily on: (1) The epidemiologic association of HDL with coronary disease: causality versus association; (2) HDL metabolism; (3) niacin and the results of the AIM-HIGH trial; (4) additional trials that looked at niacin in raising HDL; (5) the role of fibrates in the management of low HDL; (6) new therapies in development for lowering HDL; (7) lifestyle changes; and (8) the role of CETP inhibitors and modulators. (*Med Roundtable Cardiovasc Ed.* 2012;3(1):27-37) ©2012 FoxP2 Media, LLC

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#### STUDIES DISCUSSED:

ACCORD, AFREGS, AIM-HIGH, ARBITER 2, CHI-SQUARE, dal-OUTCOMES, dal-PLAQUE, dal-VESSEL, DEFINE, ERASE, FATS, FIELD, Framington study, HATS, Helsinki Heart Study, HERITAGE family study, HPS2-THRIVE, HPS3, ILLUMINATE, ILLUSTRATE, PREVENT, REGRESS, REVEAL, TNT, VA-HIT

#### COMPOUNDS DISCUSSED:

anacetrapib, dalcetrapib, evacetrapib, torcetrapib, RVX208

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tions, when HDL is high, risk tends to be lower.

So ultimately what is it about HDL particles that give rise to this apparent atheroprotectiveness? Is the relationship between HDL cholesterol (HDL-C) and risk for coronary artery disease (CAD) biologically plausible? We believe the most important atheroprotective function of HDL is to drive reverse cholesterol transport (RCT): the process by which excess cholesterol is mobilized from the interior of macrophage foam cells resident within the sub-endothelial space of arterial walls, bound, and transported back to the liver for disposal. RCT has been verified in a variety of animal models and in humans.

Recently, it was demonstrated in humans that the capacity of HDLs to induce cholesterol efflux from foam cells is related to risk for coronary heart disease. For each one standard deviation increase in flux capacity, there is a 25% reduction in risk for coronary heart disease. It's very impressive and confirms the importance of HDL functionality. We also know that HDL has a very complex proteasome, up to 75 different proteins, including apoproteins, enzymes, globulins, complement components, that influence its functionality. The HDLs are also important vehicles for delivering micro RNAs and sphingolipids to systemic tissues.

At least in vitro we know that HDL can exert a broad variety of anti-atherogenic effects, including reducing low-density lipoprotein (LDL) oxidation, modulating thrombotic capacity, regulating inflammation and insulin sensitivity, and participating in immunity. So there is biological plausibility to the epidemiological findings. And I think there is a body of evidence that in fact it does play into what goes on in vivo in humans.

**DR. RADER:** Bryan, I wonder if you could just give a very brief overview of the key players in HDL metabolism and then maybe give your take on this issue of flux and function compared to simple plasma levels of HDL.

Dr. Brewer: I think there was a big breakthrough in our understanding of how HDL removes excess cellular cholesterol with the discovery of the adenosine triphosphate-binding cassette (ABC) A1 transporter as the genetic defect in Tangier disease. The discovery of the ABCA1 transporter provided us with a mechanism by which HDL is able to efflux or remove cholesterol from cholesterol loaded cells. For a long period of time it was not

**"Many clinicians for years have prescribed niacin for people with low HDL ... so we recently had a shock ... when AIM-HIGH was stopped because [there was] no evidence of benefit."**

*-Daniel Rader, MD*

clear how HDL was able to remove cholesterol from the cell. We also recently discovered that the major ligand for the ABCA1 transporter was pre- $\beta$ -HDL or the lipid poor newly synthesized A-I.

After the discovery of the ABCA1 transporter, a second-transporter, ABCG1, was identified and shown to facilitate cholesterol efflux from cholesterol loaded cells. The ligand for the ABCG1 transporter is the mature  $\alpha$ HDL. An additional major component of the cholesterol flux from the peripheral cells to the liver involves the lecithin-cholesterol acyltransferase (LCAT) enzyme, which esterifies plasma cholesterol and converts the pre  $\beta$ -HDL to the spherical  $\alpha$ HDL.

There has also been a major conceptual change in our understanding of the pathway of HDL cholesterol transport back to the liver. Approximately half of the HDL cholesterol is transported to the liver via the cholesteryl ester transfer protein (CETP) to the  $\beta$  containing lipoproteins and ultimately back by the LDL receptor. The remaining approximately 50% of the HDL-C goes back directly from  $\alpha$ HDL to the liver following binding to the hepatic scavenger receptor class B type 1 receptor. In the transport of cholesterol from peripheral cells it is important to note that the half-life of the apolipoprotein (apo) A-I HDL protein is about four days, whereas the cholesterol has a half-life of only hours. Thus the HDL particles load and unload cholesterol several time during the half life of the HDL particles.

There are two difficulties in looking at HDL, and specifically HDL-C in terms of the efficiency of RCT. The first problem was the discovery that approximately 95% of the HDL-C is synthesized by the liver and intestine and <5% of the HDL-C is coming from peripheral cells including the cholesterol from the coronary arteries. The second difficulty as we have discussed is that the cholesterol flux through the HDL pathway from peripheral cells to the liver is not reflected in the plasma HDL-C level.

You can have low HDL with a very efficient system and effective HDL remodeling. A low plasma HDL-C level suggests that there is reduced RCT when in fact it could be normal or even increased. In addition, a high HDL-C level may mean that the system is not fluxing very effectively. Thus, the level of cholesterol in HDL is not very useful in evaluating the potential efficiency of the RCT process.

**DR. RADER:** The drug that we primarily use in clinical practice for raising HDL is niacin. This is certainly the most effective HDL raising drug we

have. And many clinicians for years have prescribed niacin for people with low HDL including, I suspect the four of us around this table. So we recently had a bit of a shock when a trial designed to test the benefit of niacin added to a statin, in people with coronary disease and low HDL, the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial<sup>1</sup> was stopped because, basically there was no evidence of benefit.<sup>2</sup>

Jean-Claude, I wonder if you could give us your take on that trial; what's known, which at this particular point is not much. Based on what we know now, what is your take currently on the use of niacin in clinical practice based on that result?

**DR. TARDIF:** Well first, before going directly to the AIM-HIGH trial, there had been a lot of data generated with niacin over the last decades, so it's not only looking at AIM-HIGH, but I think it's putting a lot of data into perspective. I'm thinking of the Familial Atherosclerosis Treatment Study (FATS)<sup>3</sup> and the HDL Atherosclerosis Treatment Study (HATS)<sup>4</sup> that Greg Brown had led that had suggested that niacin would induce favorable effects in terms of the progression of disease with different imaging modalities. There was also a non-invasive carotid ultrasound study called Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2 that also suggested that you could favorably alter carotid atherosclerosis using niacin.<sup>5</sup>

Then finally there was also the long-term follow-up of the Coronary Drug Project that had suggested significant benefits of niacin, both in terms of non-fatal myocardial infarctions and mortality in the long-term.<sup>6</sup> Now these studies were conducted, especially in the Coronary Drug Project, in a different era, but there have been

a lot of data suggesting that niacin would work.

Then there was the news that AIM-HIGH was stopped because of no benefit. AIM-HIGH was a study of 3,300 patients with vascular disease, low HDL, and high triglycerides that were randomized to either simvastatin 40 mg alone, or simvastatin plus niacin.<sup>1</sup> The primary endpoint was a composite of hard outcomes; the study is going to be presented within the next two days and published in a major journal.

**"You can have low HDL with a very efficient flux of cholesterol to the liver and effective HDL remodeling. Thus a low HDL-C suggests low cholesterol flux and it could in fact be normal or increased. "**

*-H. Bryan Brewer, MD*

We know that there was no trend in the right direction for the primary endpoint, which was the composite of cardiovascular events, non-fatal myocardial infarction, and non-fatal stroke. And there was also a trend in the wrong direction for strokes. Several of these strokes actually occurred after patients had been off medication for a while.

There are a couple of issues in terms of the study design of AIM-HIGH that may have had an impact on these findings. The investigators were not blinded to the LDL cholesterol (LDL-C) values; that means that we'll need to be looking carefully at imbalances in terms of statin use and dosage, as well as the use of ezetimibe. It would not be surprising, for example, that more patients in the placebo or simvastatin alone arm would have used higher

doses or more ezetimibe. So what part this could have played into what was observed needs to be rethought.

Since your question was also what to make of these findings, there is also a major study called HPS2-THRIVE that's ongoing, with more than 25,000 patients.<sup>7</sup> These 25,000 patients are treated to goal first, and then are randomized to either niacin with laropiprant or placebo. There will not be further adjustments in terms of LDL lowering. I think this is probably a significant methodological issue. If implied in your question was, "Does niacin have an effect on other HDL raising drugs?" I think niacin has a number of other effects, not only in HDL but on triglycerides and LDL-C, perhaps on the vessel and inflammation, so I think it's impossible to say that the HDL hypothesis was really tested in this study.

In terms of how to use niacin after AIM-HIGH, these methodological issues I think will have a serious impact, and we'll probably have to wait until Treatment of High Density Lipoprotein to Reduce the Incidence of Vascular Events (HPS2-THRIVE)<sup>7</sup> reports to really know exactly. I don't want to avoid the question, but I would not personally stop niacin in patients. I may be slightly less inclined to start new patients on the medication.

**DR. RADER:** Peter, do you have a comment on that?

**DR. TOTH:** Yes, I think we have to be very careful in our interpretation of AIM-HIGH because the temptation is now to discount niacin as an agent that is of therapeutic value and efficacy. That's the wrong thing to do because AIM-HIGH was light years beyond the other studies that we've seen.

You're talking about patients who, at the time of randomization, have an LDL of 71, non-HDL 106, and an apoB of 81, and intensive background therapy with aspirin and thi-

enopyridenes, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, and intensive regulation of blood sugars among diabetic patients (mean a1c 6.6%), it is going to be challenging to observe incremental benefit from yet another drug. Moreover, a lot of these patients had already been chronically treated with statin plus or minus ezetimibe. HDL-C was only mildly reduced at 35 mg/dL. This is not the same population as what you encountered in HATS, FATS, the Armed Forces Regression Study (AFREGS), or the Coronary Drug Project. I think when you look at patients who approximate what you saw in other trials, the patients who have atherogenic dyslipidemia, niacin clearly is therapeutically beneficial.

I think another temptation we have to avoid is that AIM-HIGH was a definitive test of whether or not the results of HATS were real. That's wrong because HATS was a placebo-controlled study with a mean starting LDL-C of 124 and HDL-C of 31. Clearly there was benefit with an 89% reduction in risk for the primary composite endpoint (when comparing simvastatin/niacin therapy to placebo) and evidence for coronary atherosclerotic plaque regression as assessed by quantitative coronary angiography. The study was small. But they're very different studies.

I think if we ask the question, if I saw a patient with the same level of background therapy as we see in AIM-HIGH, would I give that patient niacin? No. But that probably represents about 12% or 15% of the total patient population in the US and elsewhere with coronary disease.

I guarantee you that the average patient you encounter in community practice is not this intensively treated. We know that the percentage of patients who hit a very high risk target of LDL less than 70 and a non-HDL ap-

proximating 100 is around 13 or 14%. So I think we have to be very careful about drawing conclusions.

**DR. RADER:** So I get the feeling you haven't given up on niacin yet?

**DR. BREWER:** I haven't given up on niacin as yet. I think two aspects of the AIM-HIGH trial that we need to look at very carefully are the difference between the placebo group and the treated group in terms of changes in their HDL lipoproteins, and the fact that the study was designed with a projected goal of a significant reduction in clinical events as great as 25%.

***"The epidemiologic relationship between HDL and cardiovascular disease is remarkably consistent when you look at both genders, people irrespective of race or ethnicity throughout the world."***

*-Peter P. Toth, MD, PhD*

There was only a final difference of 4 mg in HDL-cholesterol between the niacin treated group and the control group. This difference in HDL-C levels would not be able to achieve a 25% reduction in clinical events. Some of these points are going to be very important parameters to review in order to decide whether this trial effectively tested the HDL hypothesis, or the role of niacin per se in the treatment of high risk cardiovascular patients.

**DR. TOTH:** I reject the proposition that this study rigorously tested "the HDL hypothesis." And I think the other thing we have to be careful about is that during the trial they talked about a numerical excess risk of ischemic stroke, but on therapy this was

only 19 compared to 12 in the niacin and placebo groups, respectively. That's seven excess events, and I'm afraid that's not going to convince anyone that there's an excess hazard attributable to niacin for ischemic stroke. Moreover, no other trial has ever shown an excess risk of ischemic stroke attributable to niacin.

**DR. RADER:** Bryan, could I ask you to address the theoretical issue of maybe the HDL raising with niacin doesn't promote flux and doesn't promote a good form of HDL raising? It's purely theory, but could you just comment on that?

**DR. BREWER:** I think that's an interesting question, because you need to look at not only the HDL-C level, but also the HDL particle number, which is another parameter that we're beginning to use to evaluate the changes in the lipoprotein profile with the use of a given drug. Obviously what we'd like to do is increase the number of HDL particles as well as increase the cholesterol flux through the HDL pathway. Based on the currently available data with niacin there is a minimal increase in the number of HDL particles but what you have with niacin treatment is very large cholesterol filled HDL particles with an increase in lipid content per particle. Whether those large HDL particles will be able to function in a number of different ways and reduce atherosclerosis is not clear. It would be interesting to test these particles in the in vitro cholesterol efflux system that you and George Rothblat have used to see how effective these particles are in removing cholesterol from cholesterol loaded cells. We also don't know if the cholesterol flux through the HDL pathway to the liver is increased with niacin treatment.

**DR. RADER:** Jean-Claude, could we talk briefly about fibrates, which also raise HDL modestly? There have also been some disappointments with fibrate trials recently. Do fibrates have any role in the management of patients with low HDL?

**DR. TARDIF:** Well, yes. Again there have been trials that excited us. I'm referring to the Helsinki Hearts Study<sup>8</sup> and the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT),<sup>9</sup> where gemfibrozil provided good results both in primary and secondary prevention. But then there has been a series of fairly major disappointments, and I'm referring to the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study<sup>10</sup> with fenofibrate, which was a fairly large study, and more recently the Action to Control Cardiovascular Risk in Diabetes (ACCORD) that also failed to demonstrate benefits of adding fenofibrate to statin.<sup>11</sup>

Actually in the FIELD study the result was a bit strange in a sense that there was actually a trend in the right direction for reduced rates of myocardial infarction, but that was counterbalanced by a trend in the wrong direction for mortality, the overall result was disappointing. And then in the ACCORD Study,<sup>11</sup> the overall result was neutral. Some people have made a case from the subgroup analysis where the subgroup of patients with high triglycerides and low HDL had a trend in the right direction for clinical events with a *P* value of 0.06. I think we need to be careful with that. When you've spent all your alpha on the primary point that failed, and then you start looking at sub-groups with a nominal *P* value of 0.06, this is strictly hypothesis generating.

So I think that some people have made too much of a case of *P* value. So to answer your question, I think fibrates can still have a role for patients who have very high triglyceride values, for example to prevent pancreatitis. As far as the addition of a fibrate to a statin for secondary prevention of cardiovascular events, especially following the results of FIELD and ACCORD, the place of fibrates for the time being is fairly limited. I would change my mind if there was a prospective study

testing fibrate in patients with high triglycerides, low HDL that would prospectively demonstrate on a pre-specified endpoint that we improve outcomes. For the time being I don't think we have that.

**DR. RADER:** It would be nice if someone would fund that study.

**DR. TARDIF:** Absolutely.

**DR. RADER:** So before we move on to new therapies in development, I wonder if we could just briefly address the question, what's the general approach in clinical practice at this time in the patient with coronary disease and low HDL? Is it primarily or purely aggressive reduction of LDL and apoB-containing lipoproteins, or is there a role for adding something like niacin or fibrate? Could I just quickly ask each of you to give your take on where we are currently before we talk about new therapies? Peter?

**DR. TOTH:** Yes, I think the approach for patients with coronary disease and low HDL is to treat with a statin plus niacin. But we have to remember that aggressive lifestyle modification in patients with low HDL can also be very helpful. We know that cigarette smoking is associated with lower HDL-C,<sup>12</sup> while cessation can raise HDL 15% to 20%.<sup>13</sup> There is evidence to suggest that in cigarette smokers LCAT is inhibited to some degree. When LCAT is inhibited, cholesterol transported out of cells is not esterified, leading to impaired maturation of HDL and increased clearance from the circulation. We also know that cigarette smoking potentiates insulin resistance by augmenting tumor necrosis factor- $\alpha$  production by adipocytes. This also results in less HDL biogenesis by the liver and adipose tissue and increased rates of HDL clearance secondary to hepatic lipase dependent lipolysis of triglyceride enriched HDL particles.

In addition to smoking cessation, exercise can increase serum levels of

HDL-C in a dose-response manner.<sup>14</sup>

The Health, Risk Factors, Exercise Training and Genetics (HERITAGE) Family Study<sup>15</sup> showed that for patients with baseline insulin resistance, exercise reduced insulin resistance, promoted weight loss, and induced HDL elevation. Dietary alterations can promote HDL elevation, so I think lifestyle modification is important. Does it always work? No.

Beyond that, of course statin, niacin, and then plus or minus fibrate if the patient still has residual hypertriglyceridemia. There are no clinical trial data that demonstrates that triple therapy provides incremental risk reduction over and above one or two drug therapy. However, if we pay attention to guideline recommendations where we have to meet risk stratified LDL and non-HDL targets, most certainly there are more complex CAD patients who warrant therapy with two, three, or even more drugs if they have any hope of attaining their risk stratified goals for all of their lipoprotein fractions.

**DR. RADER:** Bryan, your general take on that?

**DR. BREWER:** I would agree completely. I think that we have to maximize all the ways to change the lifestyle of the patient and try to increase the HDL. I think that in many patients, particularly with diabetes, or the metabolic syndrome, the practicing cardiologist is only looking at the LDL-C level. I think in the management of these patients we have to achieve the LDL goal but it is also important to reach the non-HDL-C, or apoB goal, or LDL particle number goal. Reducing all of the atherogenic apoB lipoproteins is of great importance to try to reduce the significant residual risk in the statin treated diabetic and metabolic syndrome patient.

It is important to remember that in those patients in whom you have reached the LDL-C target goal, such

as the patients in the Treating to New Targets (TNT) trial<sup>16</sup> that Phil Barter reviewed, the HDL remains an independent risk factor. So even if we maximize the LDL-C and triglyceride reduction, I think that HDL remains an important risk factor. In those patients with a strong family history of CAD, I think that they are still a candidate for niacin. There are less data to support the use of a fibrate in these patients but I think that you still have to consider HDL as an important independent risk factor. Thus, the high risk cardiovascular patient may require the addition of a second and third drug to reduce the risk of cardiovascular events.

**DR. RADER:** Jean-Claude, anything to add?

**DR. TARDIF:** Well, very little. I think it's aggressive use of statins, and as Peter said, lifestyle changes, so that includes smoking cessation, weight reduction, exercise, but as we all know it's very difficult to induce ongoing changes in lifestyle for many of our patients.

**DR. RADER:** None of you mentioned my favorite way to raise HDL and that's alcohol. So my questions are, does the HDL raising of alcohol contribute to the apparent benefit of alcohol in terms of reducing cardiovascular risk? In other words does it raise a good form of HDL? And do you ever consider suggesting alcohol to patients with coronary disease and low HDL?

**DR. TOTH:** That's an interesting question, Dan, because Framingham<sup>17</sup> has also shown that among the patients who drink moderately, there is a dose response relationship between amount of alcohol consumed daily and level of serum HDL-C.<sup>18</sup> Some people believe this underlies the so-called French Paradox, but there is skepticism about that. Alcohol appears to be a weak inhibitor of CETP and has also been shown to potentiate hepatic apoA-1 production and HDL biogenesis.

I actually wrote a paper in *Circulation* about five years ago on approaches to raising HDL.<sup>19</sup> One of the things I mentioned toward the end was consideration of four to six ounces of wine with the evening meal because the average adult is responsible enough to handle this. I was assailed through emails with people accusing me of being irresponsible and promoting alcoholism. What was I thinking?

It was such a disproportionate response because if you think about it, can the average person responsibly drink one or two glasses of wine? The answer is in fact, yes, they can. So in some cases I don't think it's such an unreasonable recommendation.

**DR. BREWER:** It's a tricky business.

**DR. TARDIF:** It is a tricky business.

**DR. RADER:** So I'd like to turn now to new HDL therapies and spend a fair amount of time on the gorilla in the room, which is CETP inhibition. So I wonder if we could just start, Bryan, maybe you can take this and just remind us of the initial discovery of CETP deficiency and essentially what led to the concept that CETP inhibition would raise HDL, and if you could also comment on CETP deficient patients and their cardiovascular risk.

**DR. BREWER:** There was a great deal of interest generated in terms of the HDL hypothesis with the discovery of patients who had complete CETP deficiency. The lipoprotein profile in patients with complete CETP deficiency was very exciting in the sense that these individuals had very high levels of HDL, greater than 100 mg/dL,<sup>20</sup> and low levels of LDL. So it looked like the ideal lipoprotein profile. Unfortunately it was not easy to conclude whether the presence of the high HDL lipoprotein profile was associated with reduced atherosclerosis and clinical events since there were only a small number of patients,

primarily in Japan, who were identified with complete CETP deficiency. Secondly, a number of the CETP deficient patients also had other comorbidities including defects in hepatic lipase. So it became difficult to use the CETP deficient patients to effectively assess whether the inhibition of CETP in fact would lead to a significant reduction in cardiovascular risk, even though the lipoprotein profile looked very encouraging,

Nevertheless, the lipoprotein profile in the CETP deficient patients led to a great deal of interest in trying to develop a small molecule to inhibit CETP to change the lipoprotein profile to reflect what is present in the patients with complete CETP deficiency. There was also a great deal of discussion of whether the HDL generated with CETP inhibition was in fact good HDL or was it a bad HDL. It ultimately became clear that the only way we would definitively answer the question of whether CETP inhibition was a good target for reducing cardiovascular events disease would be clinical morbidity and mortality trials.

**DR. RADER:** So with that discovery many companies developed programs for CETP inhibition, and the first CETP inhibitor that basically got into full scale clinical development was torcetrapib. Jean-Claude, I wonder if you could just briefly trace for us the history of torcetrapib.

**DR. TARDIF:** Torcetrapib was a powerful CETP inhibitor<sup>21</sup> that raised HDL-C values by about 100% on higher dosages. Early on in the program there was a signal in terms of blood pressure raising, but the consensus was that if we lowered the dosage we could find sort of a sweet spot between HDL-C elevation and minimal impact on blood pressure. So the gamble or the hypothesis was that raising of HDL-C with this drug would much more than offset the downside of a slight increase in blood pressure.

So torcetrapib entered a large drug development program. There were three imaging studies; two in the carotid circulation using carotid intima-media thickness, called RADIANCE 1<sup>22</sup> and RADIANCE 2,<sup>23</sup> and there was one coronary intravascular ultrasound (IVUS) study called the ILLUSTRATE study.<sup>24</sup> There was also one large clinical outcome study called the ILLUMINATE study.<sup>21,25</sup> All three imaging studies failed to demonstrate a benefit on the primary endpoint. There was no evidence of benefit of adding torcetrapib to statin therapy to reach a reasonable LDL-C goal in terms of slowing atherosclerosis progression in the coronary or the carotid circulation. Even in the smaller imaging studies, compared to the large outcome study, there was also a trend in the wrong direction for clinical events.

Then on December 2, 2006 the study was stopped. There was a 25% increase of the primary endpoint of hard outcomes with torcetrapib added to atorvastatin compared to atorvastatin alone. There was a 58% increase in the risk of dying with the combination of torcetrapib plus atorvastatin compared to atorvastatin alone. Actually when you look at event curves, the curves diverge, not in favor of torcetrapib, early, in a matter of months. When this study was stopped the median exposure to torcetrapib was about 18 months.

So the question was, was it the molecule, was it the class, was it the HDL hypothesis all together? I think what we've learned is that certainly torcetrapib was not a clean drug; it was turning on a number of bad genes and turning off a number of good genes. In a nutshell, it was, for example, turning on the CYP11B2 aldosterone synthase gene that was resulting in an increase of aldosterone secretion by adrenal glands, leading to electrolyte changes, a blood pressure increase, and potential deleterious vascular and ventricular negative effects.

What part that off-target toxicity played in the disappointing results of torcetrapib is not certain, but certainly these effects that I just described, probably at least in part, explain the negative findings with torcetrapib. Now, what we have learned is that there are a number of newer CETP inhibitors or modulators that are not associated with this target toxicity. And now I think we have the right tools, drugs to test the hypothesis that inhibiting CETP is going to have favorable effects on atherosclerosis in clinical outcomes.

**DR. RADER:** Could I just ask you, as an IVUS expert—there was a post-hoc analysis of the torcetrapib IVUS trial<sup>24</sup> with torcetrapib suggesting that the greater the increase in HDL, the less progression of disease. So it's been interpreted that this is at least evidence for the benefit of the HDL raising associated with CETP inhibition. How do you interpret that?

**DR. TARDIF:** Well I have to be careful because I was a co-author on that paper. But that being said, simply put, I think one needs to be very careful when you're trying to find a positive finding, or put a positive spin on a neutral or negative study, because at the end of the day you spent your alpha on your primary endpoint and you fail. So the rest, in my opinion, needs to be taken with a grain of salt.

**DR. TOTH:** At least you're consistent.

**DR. TARDIF:** Yes, absolutely. I think we need to be careful. Some people say the hypothesis makes sense, but that there was something else preventing the full blown beneficial effects on torcetrapib, which is a nice hypothesis. I think the proof of the pudding will be in these cleaner CETP drugs that we have that will be tested. I think ultimately that will be the answer. I mean there are other hypotheses generating results that have been observed. For example, even the ILLUMINATE study went in the right direction.

**DR. RADER:** Remarkably, despite this, there have been additional drugs that have continued in development. The one that is the furthest along in its outcomes trial is dalcetrapib. Peter, I wonder if you could just briefly review what we know about dalcetrapib,<sup>26-28</sup> its lipid effects, mechanism, and where we are with the clinical trials.

**DR. TOTH:** Dalcetrapib is a second generation CETP inhibitor and, unlike torcetrapib, does not form a stable covalent complex with CETP and HDL. It appears to be a modulator of CETP activity. It has shown very nice safety—it does not raise blood pressure, doesn't activate aldosterone synthase, does not disturb electrolyte balance—and it does provide a maximum 31.42% increase in HDL when used at 600 mg and a maximum 36.45% increase in HDL when used at 900 mg.<sup>27</sup>

Anacetrapib is going to be the competing drug. Dalcetrapib is capable of regenerating pre-beta HDL.<sup>26</sup> This regeneration of pre-beta HDL potentiated a significant increase in the recovery of fecal bile acids and neutral sterols, whereas anacetrapib, another inhibitor, which did not regenerate pre-beta HDL, did not result in a significant increase in the recovery of bile acids or neutral sterols in the gastrointestinal tract.

Despite the fact that dalcetrapib raises HDL somewhat modestly compared to the anacetrapib (which raises HDL-C about 140%),<sup>30</sup> consistent with what Bryan had said earlier, we are probably shooting for the augmentation of RCT rather than some absolute level of HDL-C targeting.

**DR. RADER:** Could you please briefly cover dal-VESSEL,<sup>31</sup> dal-PLAQUE,<sup>32</sup> and then maybe just sort of give a description of the dal-OUTCOMES trial<sup>33</sup> in terms of the general design?

**DR. TOTH:** In order for any of these drugs to be approved, they are going to have to have hard cardiovascular outcome data coupled with demonstrable long-term safety. dal-OUTCOMES is enrolling about 15,600 patients with established CAD and they're being randomized to dalcetrapib plus statin versus statin alone.<sup>33</sup> Hopefully this trial will constitute a rigorous test of whether or not the addition of dalcetrapib to statin in patients with established CAD will provide incremental risk reduction.

It is important to point out that dal-OUTCOMES will not be a rigorous test of the HDL hypothesis. If it works it's just going to show that dalcetrapib provides incremental risk reduction. dal-VESSEL basically turned out to be a safety study. What the investigators were hoping to show was that the use of dalcetrapib will impact endothelial function and promote vasodilatory capacity. In the end it turned out to be a neutral study. dal-PLAQUE used a variety of imaging modalities to determine whether or not dalcetrapib impacts plaque volume and configuration. But again, the impact was relatively modest.

**DR. RADER:** You referred to anacetrapib, a very different CETP inhibitor with a different profile. Can you summarize anacetrapib's lipid effects and the outcome trial that's currently going on?

**DR. BREWER:** Anacetrapib is a more potent inhibitor of CETP than dalcetrapib. As a result of the more consistent inhibition of all of the facets of CETP's functionality, anacetrapib increases HDL about 140% and reduces LDL approximately 35%. In the Determining the Efficacy and Tolerability of CETP Inhibition with Anacetrapib (DEFINE) study<sup>34,35</sup> anacetrapib was not associated with the adverse side effect previously observed with torcetrapib. Based on the positive safety profile in DEFINE, a 30,000 patient

morbidly and mortality trial, Randomized Evaluation of the Effects of Anacetrapib Through Lipid Modification (REVEAL),<sup>36</sup> has been initiated to determine if CETP inhibition is associated with a decrease in cardiovascular clinical events.

There is also the development of a third CETP inhibitor, evacetrapib,<sup>37</sup> which has a similar lipoprotein profile to anacetrapib. There will ultimately be several CETP inhibitors developed, and we will have the opportunity to see if these inhibitors will reduce the residual cardiovascular risk in our patients that are taking statins.

**DR. RADER:** And I'll just add briefly they also seem to lower lipoprotein(a) (Lp[a]) levels for reasons that are totally unclear.

**DR. BREWER:** I think that's really a very exciting facet of the CETP inhibitors, in that they also lower LDL as well as Lp(a). We still do not know the definitive mechanism for the reduction in LDL or Lp(a). However, for the first time we may have a drug that will lower LDL, increase HDL and lower Lp(a), which should be of great use in the treatment of the high risk patient with cardiovascular disease.

**DR. TOTH:** It is a continuous linear relationship as a function of time. It will be interesting to see how low Lp(a) goes over the course of 3–5 years.

**DR. RADER:** So as you all have pointed out, these two CETP inhibitors are actually very different drugs which have very different effects on the lipid profile, and it's important that they're both being tested in large clinical trials. The only thing we're missing is they're not being tested head-to-head.

But having said that, Jean-Claude, you get the fun question. There's a lot of discussion about whether you would want to inhibit CETP more or less. No one knows the right answer. But what's your take on the concept

that maybe there's a sweet spot for CETP inhibition and maybe it's not the more inhibition the better. I mean, is there validity to that?

**DR. TARDIF:** Well I think you already said it. These are very elegant hypotheses and positions, but it's dal-OUTCOMES and REVEAL<sup>38</sup> that will really tell us the clinical significance of this. The only thing I would add is that, yes, people are saying, do you need more potent or less potent inhibitors? I think the question is whether or not we need complete inhibition versus selective modulation.

So said differently, is it more beneficial to simply block or only block the transfer of cholesterol esters from HDL to apoB containing lipoproteins, and let CETP do its work on the remodeling of HDL particles that generate pre-beta particles? Or is it better to get complete CETP than blockade in terms of its effects on transfer to apo B containing lipoproteins and the effects of CETP on HDL remodeling. I think nobody really knows; certainly anacetrapib not only has effects on HDL-C, but has major effects on LDL-C.

Most people would think that this is a good thing, but you could argue that perhaps the reason by which it's doing that may not necessarily be a good thing. We don't really know the clinical significance of these different mechanisms.

**DR. RADER:** Peter, do you have any comments on CETP inhibition?

**DR. TOTH:** I just want to add a little bit of sense of balance to the whole CETP discussion because I want them to work, because we need novel therapies. But on the other hand we have to introduce a little bit of a note of skepticism just because we've got so many recent studies that have interjected notes of caution.

The Framingham Offspring Study recently showed that low CETP activ-

ity was associated with increased risk for cardiovascular events in Framingham.<sup>17</sup> The Prevention of Recurrent Venous Thromboembolism (PREVENT)<sup>42</sup>, the Ludwigshafen study in Germany and then the Copenhagen City Heart Study<sup>40-42</sup> all have shown that decreased CETP activity is associated with increased risk in their studies. Counterbalancing some of these findings are other studies like the Womens' Health Study,<sup>43</sup> and then the Emerging Risk Factors Collaboration,<sup>44</sup> which showed modest reductions in risk if CETP activity was low.

It's a very messy area and I think one particular concern for me is recent data from the Regression Growth Evaluation Statin Study (REGRESS),<sup>45</sup> where they showed if you were on a statin and your CETP was below the median, your risk for disease progression and for cardiac events increased dramatically compared to people whose CETP activity was above the median. It's all going to come down to the dal-OUTCOMES<sup>34,46</sup> and then also to REVEAL<sup>36</sup> and Heart Protection Study 3 (HPS3).

**DR. BREWER:** I think that's good, because I think that we need to put in the appropriate problems associated with the simple conclusion that raising HDL is a great target. Although that makes it more confusing to the cardiologist, we still don't know the answer based on anything other than the outcomes studies.

**DR. RADER:** I'd like to take one more minute just to briefly touch on a few other things that are much earlier in potential clinical development and then we'll wrap things up.

Jean-Claude, let's start with apoA-1 infusions since you have a history with that. Can you tell us something; what's going on with the concept of apoA-1 infusion?

**DR. TARDIF:** Very simply put, there have been three small clinical studies,

all less than 200 patients that have all shown the same thing. One with a mutant form of apoA-1, called apoA-1 Milano, 47 patients<sup>47</sup>; one with the wild type form of apoA-1 called the Effect of Reconstituted HDL on Atherosclerosis and Efficacy (ERASE) study;<sup>48</sup> and a third approach called HDL delipidation that was led by Bryan Brewer.<sup>49</sup> All studies basically came back with almost identical results; that is significant reduction of plaque burden versus baseline, but not significant compared to placebo because these studies were too small.

And in the study we did, ERASE, we saw favorable changes in plaque composition and position.<sup>47</sup> I think none of these studies are definitive. We're doing a large study now, 500 patients called the Can HDL Infusion Significantly Quicken Natural Atherosclerosis Regression (CHI-SQUARE) trial. Next year we'll be able to tell you whether it works or not.

**DR. RADER:** Exciting. So there's also endogenous up-regulation of apoA-1. Peter, are you comfortable talking about what's happening there?

**DR. TOTH:** Yes, RVX-208<sup>50,51</sup> is an interesting novel compound, and it exerts a variety of effects including increasing hepatocyte driven apoA-1 production and HDL biogenesis. The other facet of this is it has also been shown to stimulate ABCA1 expression on the surface of macrophages, and the combination of these two effects may provide for a powerful approach toward altering HDL metabolism and RCT kinetics. In the safety studies done to date by Jacques Genest and co-workers, it also appears to have some promise that will have to be tested in larger scale trials.

And there is an ongoing IVUS trial, too that will be interesting.

Finally, Bryan, you know the concept of getting the macrophage to up-regulate efflux pathways is attractive. If

you could comment briefly on two approaches; one would be LXR agonists; are they dead or is there still a possibility? And the second would be miR-33 antagonism.

**DR. BREWER:** I think both of these new approaches are very exciting ways to further look at the question of reducing cardiovascular disease. It would be interesting to be able to specifically increase macrophage ABCA1, which could be achieved with macrophage specific LXR agonists. I don't think that LXR agonists are dead and further research in this area may provide some new drugs with greater macrophage specificity.

A very exciting new area for modulation of HDL-C levels and cholesterol metabolism are microRNA antagonists; microRNAs are short, double-stranded RNAs that bind to complementary target sites in the three untranslated regions of mRNA, resulting in translational repression of gene expression. Of particular interest is miR-33, which down-regulates expression of ABCA1 and ABCG1, as well as reduces fatty acid degradation. An antagonist to mi-R33 is a potential novel mechanism to regulate HDL metabolism and atherosclerosis.<sup>52</sup>

**DR. RADER:** What I've heard in this time is that despite the setbacks and despite the uncertainty, the HDL therapeutic field is alive and well. If the CETP inhibitor trials are positive this class is going to be a big deal. We're still waiting for the final word on niacin. And then they are several other things that are in an earlier stage of development, so it will be fascinating to see how all of this pans out over the next decade. Thanks very much everybody.

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Genentech, Roche, Lilly, InfraReDx, AstraZeneca; he has a financial interest/stock ownership in HDL Therapeutics, The Medicines Company, and InfraReDx. Dr. Tardiff has received research grants and honoraria from Roche and Merck. Dr. Toth has served as a consultant and on a speakers' bureau for Abbott, AstraZeneca, Kowa, and Merck; and as a consultant for Amylin, Atherotech, Genentech, and Genzyme.

## REFERENCES

- 1 The role of niacin in raising high-density lipoprotein cholesterol to reduce cardiovascular events in patients with atherosclerotic cardiovascular disease and optimally treated low-density lipoprotein cholesterol Rationale and study design. The Atherothrombosis Intervention in Metabolic syndrome with low HDL/high triglycerides: Impact on Global Health outcomes (AIM-HIGH). *Am Heart J*. 2011;161:471–477 e2.
- 2 Gundry SR, Epstein J. Abstract 16318: Niacin dramatically raises the endothelial inflammatory marker Lp-PLA2: the reason the AIM-HIGH trial failed despite improvements in HDL and triglycerides. *Circulation*. 2011;124:A16318.
- 3 Brown BG, Hillger L, Zhao XQ, Poulin D, Albers JJ. Types of change in coronary stenosis severity and their relative importance in overall progression and regression of coronary disease. Observations from the FATS Trial. Familial Atherosclerosis Treatment Study. *Ann N Y Acad Sci*. 1995;748:407–417; discussion 417–418.
- 4 Zhao XQ, Morse JS, Dowdy AA, et al. Safety and tolerability of simvastatin plus niacin in patients with coronary artery disease and low high-density lipoprotein cholesterol (The HDL Atherosclerosis Treatment Study). *Am J Cardiol*. 2004;93:307–312.
- 5 Taylor AJ, Sullenberger LE, Lee HJ, Lee JK, Grace KA. Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2: a double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. *Circulation*. 2004;110:3512–3517.
- 6 Canner PL, Berge KG, Wenger NK, et al. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. *J Am Coll Cardiol*. 1986;8:1245–1255.
- 7 Borgel J, Sanner BM, Bittlinsky A, et al. Obstructive sleep apnoea and its therapy influence high-density lipoprotein cholesterol serum levels. *Eur Respir J*. 2006;27:121–127.
- 8 Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med*. 1987;317:1237–1235.
- 9 Robins SJ, Collins D, Wittes JT, et al. Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomized controlled trial. *JAMA*. 2001;285:1585–1591.
- 10 Keech A, Simes RJ, Barter P, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet*. 2005;366:1849–1861.
- 11 Ginsberg HN, Bonds DE, Lovato LC, et al. Evolution of the lipid trial protocol of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *Am J Cardiol*. 2007;99:56i–67i.
- 12 Garrison RJ, Kannel WB, Feinleib M, et al. Cigarette smoking and HDL cholesterol: the Framingham offspring study. *Atherosclerosis*. 1978;30:17–25.
- 13 Cullen P, Schulte H, Assmann G. Smoking, lipoproteins and coronary heart disease risk. Data from the Munster Heart Study (PROCAM). *Eur Heart J*. 1998;19:1632–1641.
- 14 Kokkinos PF, Fernhall B. Physical activity and high density lipoprotein cholesterol levels: what is the relationship? *Sports Med*. 1999;28:307–314.
- 15 Kee P, Caiazza D, Rye KA, et al. Effect of inhibiting cholesteryl ester transfer protein on the kinetics of high-density lipoprotein cholesteryl ester transport in plasma: in vivo studies in rabbits. *Arterioscler Thromb Vasc Biol*. 2006;26:884–890.
- 16 LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med*. 2005;352:1425–1435.
- 17 Gorshkova IN, Liu T, Kan HY, et al. Structure and stability of apolipoprotein a-I in solution and in discoidal high-density lipoprotein probed by double charge ablation and deletion mutation. *Biochemistry*. 2006;45:1242–1254.
- 18 Schaefer EJ, Lamon-Fava S, Ordovas JM, et al. Factors associated with low and elevated plasma high density lipoprotein cholesterol and apolipoprotein AI levels in the Framingham Offspring Study. *J Lipid Res*. 1994;35:871–82.
- 19 Toth PP. High-density lipoprotein and cardiovascular risk. *Circulation*. 2004;109:1809–1812.
- 20 Inazu A, Brown ML, Hesler CB, et al. Increased high-density lipoprotein levels cause by a common cholesteryl-ester transfer protein gene mutation. *N Engl J Med*. 1990;323(18):1234–1238.
- 21 Barter PJ, Caulfield M, Eriksson M, et al. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med*. 2007;357:2109–2122.
- 22 Kastelein JJP, van Leuven SI, Burgess L, et al. Effect of torcetrapib on carotid atherosclerosis in familial hypercholesterolemia. *N Engl J Med*. 2007;356:1620–1630.
- 23 Bots ML, Visseren FL, Evans GW, et al. Torcetrapib and carotid intima-media thickness in mixed dyslipidaemia (RADIANCE 2 study): a randomised, double-blind trial. *Lancet*. 2007;370:153–160.
- 24 Nissen SE, Tardif J-C, Nicholls SJ, et al. Effect of torcetrapib on the progression of coronary atherosclerosis. *N Engl J Med*. 2007;356:1304–1316.
- 25 Hu X, Dietz JD, Xia C, et al. Torcetrapib induces aldosterone and cortisol production by an intracellular calcium-mediated mechanism independently of cholesteryl ester transfer protein inhibition. *Endocrinology*. 2009;150:2211–2219.
- 26 Niesor EJ, Magg C, Ogawa N, et al. Modulating cholesteryl ester transfer protein activity maintains efficient pre-beta-HDL formation and increases reverse cholesterol transport. *J Lipid Res*. 2010;51:3443–3454.
- 27 Stein EA, Stroes ES, Steiner G, et al. Safety and tolerability of dalcetrapib. *Am J Cardiol*. 2009;104:82–91.
- 28 Niesor EJ, Chaput E, Staempfli A, et al. Effect of dalcetrapib, a CETP

- modulator, on non-cholesterol sterol markers of cholesterol homeostasis in healthy subjects. *Atherosclerosis*. 2011;219(2):761–767.
- 29 Stein EA, Roth EM, Rhyne JM, Burgess T, Kallend D, Robinson JG. Safety and tolerability of dalcetrapib (RO4607381/JTT-705): results from a 48-week trial. *Eur Heart J*. 2010;31:480–488.
- 30 Cannon CP, Shah S, Dansky HM, et al. Safety of anacetrapib in patients with or at high risk for coronary heart disease. *N Engl J Med*. 2010;363:2406–2415.
- 31 Lüscher TF, Taddei S, Kaski JC, et al., on behalf of the dal-VESSEL Investigators. Vascular effects and safety of dalcetrapib in patients with or at risk of coronary heart disease: the dal-VESSEL randomized clinical trial. *Eur Heart J*. 2012 Feb 16. [Epub ahead of print].
- 32 Fayad ZA, Mani V, Woodward M, et al. Safety and efficacy of dalcetrapib on atherosclerotic disease using novel non-invasive multimodality imaging (dal-PLAQUE): a randomised clinical trial. *Lancet*. 2011;378:1547–1559.
- 33 Schwartz GG, Olsson AG, Ballantyne CM, et al. Rationale and design of the dal-OUTCOMES trial: efficacy and safety of dalcetrapib in patients with recent acute coronary syndrome. *Am Heart J*. 2009;158:896–901 e3.
- 34 Cannon CP, Dansky HM, Davidson M, et al. Design of the DEFINE trial: determining the Efficacy and tolerability of CETP INhibition with AnacEtrapib. *Am Heart J*. 2009;158:513–519 e3.
- 35 Brinton E, Liu S, Stepanavage M, et al. Abstract 9649: Lipid-modifying Effects of Anacetrapib in Patients with Lower versus Higher Baseline Levels Of HDL-C, LDL-C, And TG: Pre-Specified Subgroup Analyses of the DEFINE (Determining the Efficacy and Tolerability of CETP INhibition with AnacEtrapib) Trial. *Circulation*. 2011;124:A9649.
- 36 Najjar SS, Rao SV, Melloni C, et al., the REVEAL Investigators. Intravenous erythropoietin in patients with ST-segment elevation myocardial infarction: REVEAL: a randomized controlled trial. *JAMA*. 2011;305(18):1863–1872.
- 37 Nicholls SJ, Brewer HB, Kastelein JJP, et al. Effects of the CETP inhibitor evacetrapib administered as monotherapy or in combination with statins on HDL and LDL cholesterol. *JAMA*. 2011;306:2099–2109.
- 38 Ji J, Watts GF, Johnson AG, et al. High-density lipoprotein (HDL) transport in the metabolic syndrome: application of a new model for HDL particle kinetics. *J Clin Endocrinol Metab*. 2006;91:973–979.
- 39 Ridker PM. Long-term, low-dose warfarin among venous thrombosis patients with and without factor V Leiden mutation: rationale and design for the prevention of recurrent venous thromboembolism (PREVENT) trial. *Vascular Med*. 1998;3:67–73.
- 40 Agerholm-Larsen B, Nordestgaard BG, Steffensen R, Jensen G, Tybjaerg-Hansen A. Elevated HDL cholesterol is a risk factor for ischemic heart disease in white women when caused by a common mutation in the cholesteryl ester transfer protein gene. *Circulation*. 2000;101:1907–1912.
- 41 Agerholm-Larsen B, Tybjaerg-Hansen A, Schnohr P, Steffensen R, Nordestgaard BG. Common cholesteryl ester transfer protein mutations, decreased HDL cholesterol, and possible decreased risk of ischemic heart disease: The Copenhagen City Heart Study. *Circulation*. 2000;102:2197–2203.
- 42 Ritsch A, Scharnagl H, Eller P, et al. Cholesteryl ester transfer protein and mortality in patients undergoing coronary angiography: the Ludwigshafen Risk and Cardiovascular Health study. *Circulation*. 2010;121:366–374.
- 43 Ridker PM, Pare G, Parker AN, et al. Polymorphism in the CETP gene region, HDL cholesterol, and risk of future myocardial infarction: Genome-wide analysis among 18245 initially healthy women from the Women's Genome Health Study. *Circ Cardiovasc Genet*. 2009;2:26–33.
- 44 Thompson A, Di Angelantonio E, Sarwar N, et al. Association of cholesteryl ester transfer protein genotypes with CETP mass and activity, lipid levels, and coronary risk. *JAMA*. 2008;299:2777–2788.
- 45 Barth JD, Zonjee MM. Regression growth evaluation statin study (REGRESS): study design and baseline characteristics in 600 patients. The REGRESS Research Group. *Canadian J Cardiol*. 1992;8:925–932.
- 46 Stalenhoef AF, Davidson MH, Robinson JG, et al. Efficacy and safety of dalcetrapib in type 2 diabetes mellitus and/or metabolic syndrome patients, at high cardiovascular disease risk. *Diabetes Obes Metab*. 2012;14(1):30–39.
- 47 Nissen SE, Tsunoda T, Tuzcu EM, et al. Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial. *JAMA*. 2003;290(17):2292–2300.
- 48 Tardif JC, Gregoire J, L'Allier PL, et al. Effects of reconstituted high-density lipoprotein infusions on coronary atherosclerosis: a randomized controlled trial. *JAMA*. 2007;297:1675–1682.
- 49 Sacks FM, Rudel LL, Conner A, et al. Selective delipidation of plasma HDL enhances reverse cholesterol transport in vivo. *J Lipid Res*. 2009;50(5):894–907.
- 50 Bailey D, Jahagirdar R, Gordon A, et al. RVX-208: a small molecule that increases apolipoprotein AI and high-density lipoprotein cholesterol in vitro and in vivo. *J Am Coll Cardiol*. 2010;55:2580–2589.
- 51 [No authors listed]. Rvx 208. *Drugs R D*. 2011;11:207–213.
- 52 Fernandez-Hernando C, Suarez Y, Rayner KJ, Moore KJ. MicroRNAs in lipid metabolism. *Curr Opin Lipidol*. 2011;22:86–92.

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