expert roundtable »

The Role of CETP Modulation and Inhibition in the Progression of Coronary Heart Disease

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Moderated by **Michael Davidson, MD[1]**
Discussants: **Christie Ballantyne, MD[2]; Stephen Nicholls, MD, PhD[3]; Robert S. Rosenson, MD[4]**

The following Expert Roundtable Discussion was held on November 11, 2011. Dr. Michael Davidson from the University of Chicago Medical Center moderated the topic "The Role of CETP Modulation and Inhibition in the Progression of Coronary Heart Disease." with Drs. Christie Ballantyne from the Baylor College of Medicine, Stephen Nicholls from the Cleveland Clinic, and Robert S. Rosenson from the Mount Sinai Hospital Medical Center.

The discussion focused primarily on: (1) how CETP inhibitors/modulators modify HDL cholesterol levels; (2) the role of CETP inhibitors in dyslipidemia; (3) CETP modulation compared to inhibition; (4) HDL particle concentration compared to HDL cholesterol; (5) why did torcetrapib increase cardiovascular and total mortality; (6) newer CETP inhibitors in development and how they differ from torcetrapib (*Med Roundtable Cardiovasc Ed.* 2012;3(1):38–44) ©2012 FoxP2 Media, LLC

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STUDIES MENTIONED:
dal-PLAQUE, dal-VESSEL, DEFINE, Heart Protection Study, ILLUMINATE, ILLUSTRATE, RADIANCE-1, RADIANCE-2

COMPOUNDS MENTIONED:
Anacetrapib, dalcetrapib, evacetrapib, torcetrapib

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DR. DAVIDSON: Cholesteryl ester transfer protein (CETP) has been a target for the management of risk for cardiovascular disease. This effort began a number of years ago when it was noted that this protein transfers cholesteryl ester in exchange for triglyceride from different lipoproteins, specifically apolipoprotein (apo)B-lipoproteins to high-density lipoproteins (HDL). It's an exchange that provides equilibrium between the concentration gradients between the different lipoproteins. It also significantly modulates our levels of what we consider HDL and low-density lipoprotein (LDL) cholesterol.

Animals who lack CETP have very high HDL levels and very low LDL levels. Interestingly, human deficiencies of CETP are similar to other mammals who do not have CETP, in other words, they have very high HDL levels and very low LDL levels. There is evidence that inhibiting CETP would raise HDL levels and lower LDL levels and that this is associated with reduction of atherosclerosis in animal models.

Based on these findings, CETP became an intriguing target for the inhibition of atherosclerosis and led to the clinical development of the first CETP-inhibitor, torcetrapib. We'll discuss torcetrapib in detail in regards to that specific molecule for inhibiting CETP, but I think we're all aware that the use of this drug was shown to result in increased mortality and was stopped from clinical development in Phase III.

To set the stage, we have new CETP inhibitors in development that do not potentially share the adverse off-target effects of torcetrapib. These new thera-

pies that affect CETP function may have an important therapeutic role in the reduction of atherosclerosis progression. I'm joined today by three experts in this field. Dr. Steve Nicholls, from the Cleveland Clinic; Dr. Christie Ballantyne from the Baylor College of Medicine; and Dr. Robert Rosenson from the Mount Sinai Medical Center in New York City. we will put into clinical context the issues that we wrestle with and hopefully come up with some ideas. These might help us interpret the ongoing clinical trials that will be completing over the next couple of years, and that will determine whether CETP inhibition does in fact represent an important therapy for reducing cardiovascular disease events.

Let me start with you, Bob. What are CETP modulators or inhibitors and how do they work to modify HDL-C levels?

DR. ROSENSON: CETP mediates the transfer of core lipid between lipoproteins, such that the cholesterol cargo in HDL particles is exchanged for the core triglyceride in very low- density lipoprotein (VLDL) particles and core cholesterol in LDL particles. CETP also facilitates the remodeling of plasma HDL particles by converting α HDL to pre-β HDL and transferring cholesteryl ester among HDL sub particles in a process called HDL remodeling. This remodelling of HDL is an important aspect in reverse cholesterol transport and the removal of excess cholesterol from tissue and delivery to the liver.[1] The CETP reaction results in reduced cholesterol content in HDL particles and thus smaller HDL particles, which are filtered through the glomerulus and excreted in the urine. Through CETP inhibition, this lipid transfer is blocked resulting in larger cholesterol-containing HDL particles. The heterotypic agents, CETP inhibitors that block cholesterol transfer between lipoprotein classes, increase the cholesterol content of LDL particles, and a conformational change in apoB that facilitates LDL receptor mediated hepatic clearance of larger versus smaller LDL-C particles. This results in reduction in LDL and increases in HDL-C. CETP modulators like dalcetrapib modulate CETP activity by increasing HDL-C while maintaining HDL function. Dalcetrapib also reduces the transfer of cholesterol ester towards apoB containing lipoproteins.[2] More importantly dalcetrapib maintains the CETP mediated exchange between HDL (HDL remodeling).

"Cholesteryl ester transfer protein has been an important target for the management of risk for cardiovascular disease. It began a number of years ago when it was noted that this protein transfers cholesteryl ester in exchange for triglyceride from different lipoproteins specifically, apoB-lipoproteins to HDL lipoproteins."

– Michael Davidson, MD

DR. DAVIDSON: Christie, can you give us some kind of background about how CETP inhibitors might work in the treatment of dyslipidemia?

DR. BALLANTYNE: Well, the hope is that we know that there is a very strong epidemiological association between levels of HDL-C and atherosclerosis and coronary events. The higher the level, the fewer coronary events. There are some genetic polymorphisms in the gene that encodes for CETP where people have a slight reduction in CETP activity, they have an increase in HDL-C and they have fewer cardiovascular events. The hope is that these inhibitors will have a beneficial effect on the process of atherosclerosis development and progression and that they would also significantly reduce atherothrombotic cardiovascular events.

DR. DAVIDSON: Bob, please explain the differences between an inhibitor and a modulator and also the differences between the two CETP therapies that are in development right now, anacetrapib and dalcetrapib?

DR. ROSENSON: The two CETP inhibitors that have entered Phase III clinical trials differ dramatically with regard to the effects on lipids and lipoproteins. Agents such as torcetrapib and anacetrapib can be categorized as heterotypic CETP inhibitors or agents that work on lipid exchange between the various lipoprotein classes.

Through the effects of CETP inhibition with a heterotypic CETP inhibitor, there is a reduction in VLDL triglyceride and cholesterol, LDL-C, and an increase in HDL-C. In contrast, dalcetrapib is a CETP modulator that can increase HDL-C while still preserving the CETP mediated exchange between HDL particles.

Although this agent has a negligible effect on reducing LDL particles, it expands the pool of HDL particles by 10% and the cholesterol content in those particles by about 34%.[3] In contrast, the heterotypic CETP inhibitor torcetrapib more effectively increases HDL-C but it is less effective than dalcetrapib in increasing HDL particle concentration. Thus, HDL quantity changes differently with homotypic as compared to heterotypic CETP inhibtors. From this perspective, CETP inhibitors cannot be categorized simply in the same group even though they "inhibit" CETP. This is why I prefer this term heterotypic CETP inhibitor and homotypic CETP inhibitor that was initially advanced by Niesor and colleagues.

DR. DAVIDSON: Bob, you said something important. Dalcetrapib increases HDL particle number and torcetrapib does not. What do you think that means as far as potential effects on cardiovascular risk?

DR. ROSENSON: Observational studies and secondary analysis of clinical trials have shown that HDL particle concentration is a more robust predictor of cardiovascular events than is HDL-C. For reasons of analytical simplicity, we focus on the cholesterol cargo in the HDL particles, e.g., the HDL-C concentration, but the total number of HDL particles appear to be more important in human biology.

From Glomset's initial hypothesis for reverse cholesterol transport in 1964, there has been a focus on HDL-C as a surrogate marker for efflux of cholesterol from the tissues before disposition in the feces. We know that these large cholesterol-containing HDL particles formed from the lecithin:cholesterol acyl transferase reaction have been considered a biomarker of efficient reverse cholesterol transport, but macrophage cholesterol efflux represents only one aspect of the functionality of HDL. For example, small cholesterol depleted HDL particles bind the antioxidant protein paraoxanse with greater affinity than large HDL particles. These small particles have been shown by John Chapman and Anatol Kontush to be more important in mediating the antioxidant and anti-inflammatory effects of HDL particles.

Again, by focusing on HDL-C or the large HDL particles, we may overlook the contributions that small or cholesterol-depleted HDL particles have in mitigating the risk. This may be one of the reasons that a measure of the total HDL particle concentration appears to be a better predictor of cardiovascular events. The total HDL particle concentration accounts for all the various HDL sub-classes involved in its anti-atherothrombotic properties.

DR. DAVIDSON: Torcetrapib was the the first CETP inhibitor in development and Dr. Nicholls was involved with an imaging trial with torcetrapib called ILLUSTRATE.[4] What did torcetrapib show in the three imaging trials—RADIANCE 1,[5] RADIANCE 2,[6] and ILLUSTRATE[4]? Is there anything that we can take out of those trials that can help us mechanistically regarding torcetrapib? Question number two is, what do we know about torcetrapib now that we didn't know then that lets us believe it was an off-target effect that may have caused increased cardiovascular and total mortality?

> ***"We certainly have seen a very strong epidemiological association between levels of HDL-C and atherosclerosis and coronary events."***
>
> *~Christie Ballantyne, MD*

DR. NICHOLLS: We've now used arterial wall imaging in a number of clinical trials over the last 20 years to look at the effects of various medical therapies. Many of us had considerable hope that torcetrapib, a drug that had the ability to raise HDL-C well in excess of 50% to 60%, in addition to lowering LDL-C 20% to 25% on top of a statin, should have a fairly profound anti-atherosclerotic effect. In fact, one could postulate that the effect that one would want to see is really disease regression.

We knew that if you treat patients with a statin you get their LDL down to about 80 mg/dL, you could pretty much arrest disease progression. In the clinical development program for torcetrapib in parallel to a very large outcome study were three imaging studies. There was one that looked at coronary atherosclerosis using intravascular ultrasound we performed at the Cleveland Clinic called ILLUSTRATE. There were two studies performed in Europe, one was called RADIANCE 1; one was called RADIANCE 2. They both used serial measures of carotid intima-media thickness, and one of those studies was performed in a cohort with familial hypercholesterolemia; the other in patients with atherogenic dyslipidemic phenotype high triglycerides, low HDL. What was really striking was the complete lack of any effect on disease burden in all three of the studies.

There was no regression at all in lesions, and in fact, the use of this medication didn't have an impact in slowing disease progression. So in fact, when you look at the results of those studies, which had finished just before we pulled the plug on the outcome study due to the mortality problems, it really gave you an interesting snapshot of what torcetrapib was doing. We have a large outcome study showing us that there is clearly no cardiovascular benefit, in fact, there is this adverse impact on mortality, cardiovascular, and non-cardiovascular events. The drug really just wasn't doing what we had anticipated that it would do.

I think in some ways the imaging studies at least complemented the information. We then scratched our heads, and we debated for a long time, and, while many of us had thought that inhibiting CETP would be a good thing for the reasons that Bob and Christie have outlined, there were many who still weren't sure. One could argue that if you inhibit CETP too much that you were going to generate "dysfunctional" HDL. You'd make the HDL particles so full of cholesterol they'd become engorged and they would no longer promote cholesterol efflux. Was that fundamentally a potential problem?

When you have a mortality problem and a problem with excess clinical events, certainly those arguments came to the forefront. What we've subsequently learned is that it really does appear that torcetrapib has a number of off-target toxicities. First of all, it has an adverse effect on blood pressure. We saw that story evolve during the development program. What we learned was that as each study progressed, the blood pressure signals seemed to become more prominent, instead of a couple of millimeters, it ended up 5–6 millimeters of mercury.

That was one problem. There were a number of problems at the level of the adrenal gland increasing aldosterone levels, increasing cortisol levels. Finally, there were some interesting studies in animals suggesting that endothelin, which we think is a potent vascular toxic factor seems to be up-regulated in the artery wall in some animal models. There seem to be a number of off-target toxicities that have got nothing to do with CETP at all.

We know that if you give torcetrapib to people, examine blood and isolate and evaluate the impact of HDL to promote cholesterol efflux in lab studies, it looks intact. That would suggest that the HDL is not dysfunctional. We went back and looked at our own imaging studies and what we found with coronary atherosclerosis in the intravascular ultrasound studies was that patients treated with torcetrapib who achieved the very highest levels of HDL-C actually regressed.

We thought that was a pretty compelling argument to suggest that the HDL was still functional. It still retained the capacity to move the lipid out of the vessel wall, and shrink the size of the plaque. We saw that on ultrasound. Putting that all together I think we've now got to this point where we think that there is enough to suggest that if there is another agent that we think lacks the types of toxicities of torcetrapib, then it remains a reasonable question to move forward in large outcome studies to test the hypothesis whether inhibiting CETP would be beneficial.

In 2011 there are two agents that are already in Phase III, and a third agent that is also being studied.

DR. DAVIDSON: There was evidence in ILLUMINATE[7,8] as well that the higher the HDL-C in the treated group appeared to have less of a cardiovascular risk than those that did not have higher HDL-C, is that correct?

DR. NICHOLLS: Yes.

> ***"If you keep in mind that the cardiovascular field in general has had numerous examples of therapeutic classes where the first drug failed. In fact, the very first statin failed. It is really important for us to be able to elucidate what happened with torcetrapib so that we can get this path moving forward."***
>
> *~Stephen Nicholls, MD*

DR. DAVIDSON: Therefore the ILLUMINATE study supported the findings in the ILLUSTRATE trial that the higher the on-treatment HDL-C the greater the potential cardiovascular benefit.

DR. NICHOLLS: That's right, and I think that one of the criticisms in the early stages of this process was the question, did the imaging miss the signals? I think that in two ways it didn't because first of all, the only real legitimate impact we expected to see was regression of lesions. We didn't see that at all.

When you look at these findings, it really does look that there was a potential cardiovascular benefit in patients who actually achieved the higher levels of HDL, at least suggesting that it wasn't dysfunctional.

DR. DAVIDSON: Let's move on to the two new CETP inhibitors that are in development and touch on the third, evacetrapib, that was recently discussed. Christie, talk about anacetrapib and the Determining the Efficacy and Tolerability of CETP Inhibition with Anacetrapib (DEFINE) trial[9] and how things are moving forward with that compound for cardiovascular risk reduction.

DR. BALLANTYNE: After the first experience with torcetrapib where there were off-target effects, I think it was very important to show that the other compounds were safe. A study with anacetrapib, the DEFINE trial[10] looked at the lipid effects, and reported very impressive lipid effects of raising HDL 138.1%, and reducing LDL 40%.[10]

There was not a problem with blood pressure as compared to torcetrapib; an aldosterone effect was not seen and there was no difference in aldosterone levels. If we looked at cardiovascular events it was also safe. If you look at the issue of revascularization there was a clearly marked reduction. If you were to have some regression of atherosclerosis one might predict that revascularization could be affected favorably.

I think that the data were sufficient; that the study met its end point of showing lipid efficacy without any evidence of harm. That the decision has been to go forth with the REVEAL study,[11] which is being led by the Oxford and the Thrombolysis in Myocardial Infarction (TIMI) groups, and is now underway.

DR. DAVIDSON: Bob, please discuss dalcetrapib and the clinical trials to date in regards to its cardiovascular safety and also the outcome trials that are underway?

DR. ROSENSON: Yes, dalcetrapib has been investigated in two vascular studies that were designed to evaluate the safety of the compound. The dal-VESSEL trial[12] was the multi-centered trial that evaluated blood pressure and brachial reactivity. In this study there was no change in blood pressure and no adverse change on vascular reactivity.

The dal-PLAQUE study was a trial that randomized individuals to dalcetrapib or placebo and evaluated changes in carotid plaque burden quantified by magnetic resonance imaging and vascular inflammation quantified by fluorodeoxyglucose (FDG)-positron emission tomography (PET) scanning. In this trial, treatment with dalcetrapib decreased carotid plaque burdensuggesting regression of the atherosclerosis.[13]

Because of the critical importance of HDL as an anti-inflammatory molecule they did evaluate vascular information by FDG-PET, but there were no overall group differences in this measure. Individuals, however, who had the greatest increase in HDL-C had the least amount of vascular inflammation. It is worth noting that dal-PLAQUE study was a relatively small study and some of the power to detect differences was limited because of the small size.

Christie was one of the authors, and maybe he wants to comment more about the dal-PLAQUE study from his perspective.

DR. BALLANTYNE: The first point was to examine with novel imaging modalities if dalcetrapib was safe, and there was not a safety concern. There was an effect in regard to total reduction of the total vessel area with dalcetrapib, which is the most accurate measure by MRI.[14]

However, I want to emphasize that this was a safety trial for the primary end points, and we looked at a number of secondary end points here that I think ought to be considered hypothesis generating. It was a small study. There were suggestive data that people who have worse plaque, defined by the highest uptake of deoxyglucose measured by PET/computed tomography, had the most benefit. The drug was safe in this study and the endothelial function study. The lack of any safety concerns in these studies supports the rationale for the outcomes trial, which is in progress.

"By focusing on HDL-C or the large HDL particles, we may overlook the contributions that small or cholesterol-depleted HDL particles have in mitigating the risk. This may be one of the reasons that a measure of the total HDL particle concentration appears to be a better predictor of cardiovascular events."

~Robert S. Rosenson, MD

DR. DAVIDSON: Steve, what is your perspective on both CETP inhibitors, because you weren't involved with the DEFINE trial or the dal-PLAQUE or dal-VESSEL trials. How do you think these two CETP inhibitors compare? How should clinicians think about them as the larger trials start reporting?

DR. NICHOLLS: Well, I think that they should be optimistic that the field has moved forward. If you go back to the end of 2006, early 2007, the rug had really been pulled out from under all of us. It was certainly quite conceivable that there wouldn't be a path forward for a CETP inhibitor at all.

Keep in mind that the cardiovascular field in general has numerous examples of therapeutic classes where the first drug failed. In fact, the very first statin failed. It was important for us to be able to elucidate what we did about torcetrapib so that we could get this moving forward. Investigators and clinicians who are watching from the sidelines could be confident that we were moving forward with a class of drugs that is potentially safe, and potentially effective.

I think that's what we've seen. DEFINE was a very elegant study; it was almost the first of its kind. It's almost a small outcome study. It's not quite a Phase II study; it's not quite a Phase III study. It gave a pretty clean bill of health to anacetrapib. This drug has impressive lipid effects and there is a lot of confidence not only in its ability to raise HDL, but its ability to lower LDL. As Christie said, just purely its LDL lowering of 35% to 40%, is something that I think would be attractive in clinical practice.

The dalcetrapib program includes several programs where we'll see the results in the next few years. This drug, while it raises HDL-C less than anacetrapib, still has a fairly robust increase in HDL-C levels. Ultimately we have to see if they prevent cardiovascular events. If they do that then we will have an additional class of drugs on top of the statins to help reduce cardiovascular morbidity and mortality.

DR. DAVIDSON: You want to mention the third CETP inhibitor, evacetrapib?

DR. NICHOLLS: We performed a 12-week lipid study[15] to define the effects of the compound on both HDL and LDL levels, both as mono-therapy and in combination with a range of statins at their commonly prescribed doses. What we observed was a dose-dependent increase in HDL by up to 129%

and decrease in LDL by up to 36%. We observed robust changes with the submaximal dose in combination with the most commonly prescribed statins at their typically used doses. We did not observe adverse effects on blood pressure or mineralocorticoid activity. I suspect that ultimately, like the statins, we'll end up with a number of CETP inhibitors.

DR. DAVIDSON: Let's close by reviewing what's going to happen over the next several years as the CETP inhibitor outcome trials complete. Christie, I'll start with you.

DR. BALLANTYNE: Well, the first thing we're going to find out now is clinical outcomes. Will there be a reduction in events? Will we see any safety signals? I think that there are enough differences between the drugs we have discussed, that one cannot assume that the results with dalcetrapib will be applicable to anacetrapib.

We will have to wait until the results of the outcomes for all the studies, including anacetrapib and evacetrapib to really know the differences in these drugs. It's one of these things where it's truly the scientific method. One does experiments and you don't know what the answer is going to be until they are completed.

DR. DAVIDSON: It's fair to say that even if one doesn't work, another one might. It's really different than the statins. Each of these CETP inhibitors act differently and so we'll have to see how each one turns out. It might not be a class effect at all for CETP inhibitors. We know the first drug of the class, torcetrapib was toxic but hopefully the new CETP inhibitors that do not share the adverse effects of torcetrapib on blood pressure and steroidogenesis will be beneficial.

DR. BALLANTYNE: Yes.

DR. DAVIDSON: We have explanations about why it was toxic, but yet I think each of the other CETP inhibitors in development have differences that may affect their outcomes as well.

DR. BALLANTYNE: Correct.

DR. DAVIDSON: Bob, how do you see things comparing going forward in the next five years with the field?

DR. ROSENSON: The clinical trials are key and clearly the different CETP inhibitors vary with respect to their lipid and lipoprotein effects. Dalcetrapib is an agent that will allow us to more adequately test the HDL hypothesis than any other therapy that we have had other than the apoA1 mimetics and apoA1 inducers because this agent works essentially on HDL particles. Thus far, we have not discussed the effects of dalcetrapib on increasing the pre-beta HDL fraction, which is the HDL fraction that interacts with the quintessential ABCA1 transporter. We know how important the ABCA-1 transporter is for macrophage cholesterol efflux. At the same time, we also know from work by Laurent Yvan-Charvet and Alan Tall that the heterotypic CETP inhibitors form very large HDL particles that can remove cholesterol from the cell membrane via the ABCG1 pathway. These data provide another example as to how these agents differ even at the level of the cholesterol transporters.

Moving forward, it will be interesting to see how these different CETP inhibitors impact clinical cardiovascular events. Through its effects on HDL, dalcetrapib works mainly on the anti-atherothrombotic side of cardiovascular risk, whereas anacetrapib works on reducing atherogenic lipoproteins. In statin-treated patients with the metabolic syndrome and type 2 diabetes, anacetrapib may be very useful to reduce residual risk.

Whether anacetrapib will be effective because of its effects on increasing HDL-C is not necessarily clear to me, whereas the potential benefits of reducing the atherogenic particles is more widely accepted. The translation of these clinical trials into different subgroups of individuals who may benefit from one agent compared to another is going to be one of the great challenges that we have as clinicians and educators.

DR. DAVIDSON: This has been a fascinating discussion about a novel class of therapies on the horizon that may not be pertinent to your practice today as clinicians, but addresses an important topic by focusing on the HDL pathway for reducing atherosclerosis.

I want to thank everyone. It's going to be an exciting several years in this field. Thank you very much.

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