DR. WENGER: Let me welcome you all to the Expert Medical Roundtable on high-density lipoprotein (HDL) cholesterol and triglycerides in the year 2011, I am Dr. Nanette Wenger, Professor of Medicine in the Division of Cardiology at the Emory University School of Medicine. With me are Dr. Michael Davidson, who is Clinical Professor of Medicine and the Director of Preventive Cardiology at the University of Chicago School of Medicine, and Dr. Christie Ballantyne, Chief of the Sections of Cardiology and Cardiovascular Research at the Baylor College of Medicine.

The last official published guidelines regarding cholesterol management date back a decade, to the 2001 National Cholesterol Education Program Adult Treatment Panel III recommendations for lipid management,1 with a small modification a few years later just lowering the LDL goal optionally for patients at high risk. Excitingly, during the past decade, we have experienced remarkable levels of LDL control with statin therapy and many reports of subsequent declines in coronary events. Yet coronary events still occur, even in the presence of optimal levels of low-density or LDL lipoprotein cholesterol. Many have termed this occurrence “residual risk,” which is not a bad term. Many patients with residual risk have type II diabetes, metabolic syndrome, or obesity, so that we considered it was now time to readdress the implications of low levels of HDL cholesterol, high levels of triglyceride and potential therapies for these lipid abnormalities.

Dr. Davidson, let me start with you. As you know, the NCEP ATP III focused only on LDL, and, when the triglyceride levels were greater than 200, on non-HDL cholesterol. Look into your crystal ball and tell me what
you might anticipate the changes will be when NCEP ATP IV is published, hopefully later this year.

**DR. DAVIDSON:** I think it's going to be hard to say exactly what the ATP IV is going to recommend, but I believe one important change is going to be the emphasis on non-HDL cholesterol (LDL and triglycerides) being potentially a co-primary goal of therapy with LDL cholesterol. One of the big disappointments about non-HDL cholesterol in the ATP III guidelines was that doctors don't look at it and it's not on the lab sheet. So consequently, if you look at surveys of treatment, you'll find that although LDL cholesterol goals are much improved over what they were a decade ago, the treatment to non-HDL targets is still much more suboptimal. So I think one key modification of ATP IV will be to focus on non-HDL cholesterol as a treatment target equal to that of LDL cholesterol, so you don't have a secondary target type of priority for non-HDL cholesterol, but move it to a co-primary with LDL cholesterol.

The reason for this is the fact that, in all the most recent trials, it is more likely that you're going to find that non-HDL cholesterol predicts better than LDL cholesterol when it comes to recurrent cardiovascular events, especially on statin treatment. So therefore there is an evidence-based rationale to shift more priority to non-HDL cholesterol. One potential is to do away with LDL cholesterol and to focus only on non-HDL cholesterol. I don't think the ATP IV panel will go that far, but certainly, the elevation of non-HDL cholesterol to a co-primary target will be a likely part of the new guidelines.

**DR. WENGER:** For practicality, both for the patient and for the clinician, non-HDL-C is a non-fasting measurement, which makes it so much more attractive in terms of actual use. Any other changes that you might anticipate?

**DR. DAVIDSON:** I think another benefit of utilizing non-HDL cholesterol as a target is that it can be accurately measured non-fasting. I should point out, the main reason why non-HDL cholesterol is becoming more predictive than LDL cholesterol is because, in the last ten years, we've seen this tremendous change with the type of patient presenting for an acute coronary syndrome (ACS). Patients with ACS are now far more likely to have metabolic syndrome, diabetes and high triglycerides with low HDL. They're also the patients who are more likely to have events on a statin. Therefore, non-HDL cholesterol, which incorporates both LDL and VLDL (triglycerides) into a single number as a target, is a better measurement of risk in the patients who will more likely present with an acute coronary event.

With regard to other changes, I think ATP IV will include lifetime risk instead of just ten-year risk as a tool to initiate therapy earlier in some high-risk individuals. Based on clinical trial evidence, the treatment of people with diabetes over age 40 or those with established coronary disease, ATP IV will likely recommend the initiation of statin therapy regardless of the baseline LDL cholesterol. ATP III did not recommend initiation of therapy regardless of the baseline LDL cholesterol.

The JUPITER study also supports that in high risk patients, defined as men and women over 50 and 60, respectively, with an additional risk factor of a high sensitivity CRP (hs-CRP) over 2 mm/L, giving a statin reduces events, regardless of the baseline LDL cholesterol. Therefore another potential important change may be to measure hs-CRP in patients with an LDL cholesterol <130 mg/dL, and initiate statin therapy regardless of their baseline LDL cholesterol. The clinical trial evidence would support at least a 35%–50% LDL cholesterol reduction to achieve a significant clinical benefit in this population.

**DR. WENGER:** Dr. Ballantyne, let me ask you the next question. The epidemiologic data are rather powerful, showing that the risk is greater for women than for men with both high triglyceride and low HDL levels. Based on these epidemiologic data, and acknowledging that we don’t have clinical trial data, do you think there should be a gender-specific recommendation?

**DR. BALLANTYNE:** I agree with the recent AHA guidelines that looked at prevention of cardiovascular disease in women’ where an HDL cut point for HDL cholesterol of 50 mg/dL defined risk. Now that’s different than ATP III, which mentioned less than 40 mg/dL. ATP III made the argument that for men and women, the absolute risk was similar with low HDL levels.

Even in ATP III, though, when they discussed the metabolic syndrome, they moved to a higher HDL of less than 50 mg/dL. So let’s look at some of the reasons for the 50 mg/dL level. I think this is the key issue for women—we need to look at not only the absolute risk over ten years, but also the lifetime risk, which really is similar to what we used to call the relative risk. In a younger person with a high relative risk, over a long period of time, they have a high lifetime risk. When you see an HDL of less than 50 mg/dL, that is low for women. It’s very often associated with concomitant comorbidities, hypertension, obesity, elevated triglycerides, and insulin glucose resistance.
These are individuals where lifestyle modification can have a major impact, so I’m highly supportive of that.

One of our goals in prevention is to try to motivate people to modify their lifestyle and comply with their medications. In particular, when we’re talking to women and you tell a woman, “Well, you’re at low risk.” In the Framingham risk profile it’s less than 10% for CHD, let’s say it’s 8% over ten years. That ignores the risk for stroke. It also ignores the risk for revascularization and for angina. Most of our patients would consider these to be pretty serious problems. I certainly would consider it a serious problem for myself. I really don’t understand why we underestimate the total cardiovascular risk in patients when we’re trying to motivate them. So I was very pleased that your guidelines noted that we should be looking at the cardiovascular risk. I think we should include both hard and soft cardiovascular risk, because there really is a big difference. The risk for nonfatal MI and death from MI might be 8%, but if you throw in everything else for women, the number is much higher. Stroke is actually quite common in women, as compared to CHD events and revascularization is much more common. You might tell someone that they’re low risk when they can be over 20%, if you look at total events.

Another important thing I liked in those guidelines was the mention of triglycerides. This is a little bit tricky, in terms of whether they are even a risk factor, but certainly they’re a good risk marker. When you see a triglyceride of over 150 in a woman, we should be thinking about the same things I mentioned: metabolic syndrome, hypertension, insulin resistance and diabetes.

DR. WENGER: I am delighted that you were as pleased with the new women’s prevention guidelines as we, the Writing Committee, were. A new aspect of the 2011 update to the women’s prevention guidelines is the emphasis on cardiovascular disease and not solely on coronary disease, of course, continuing the emphasis of the prior guideline on lifetime risk as truly important. But again, in the guideline we emphasized lifestyle, lifestyle, lifestyle first, for all women, and then other interventions.

Dr. Davidson, let’s examine diabetic compared to non-diabetic patients. What type of clinical trial data do we have for the role of therapy of high triglycerides and low HDL levels and the difference in diabetic and non-diabetic populations?

DR. DAVIDSON: Unfortunately, we don’t have a lot of evidence to focus on in the studies that compare one to the other. We do know that, for example, in the Heart Protection Study, the diabetic patient population, which is at high risk, benefit significantly with statins, regardless of the baseline LDL cholesterol. We also know that low HDL and high triglycerides confer additional risk for subsequent events for those with or without diabetes, but the presence of diabetes elevates the risk significantly.

So if you look at rating risk, the metabolic syndrome patient is at increased risk, compared to those without the metabolic syndrome. Then once you go to diabetes, their risk appears to be increased. In patients with diabetes and the metabolic syndrome, which is most of the people with diabetes, their risk is even higher. Then if you add in coronary disease, the risk is even greater. Patients with both coronary disease and the metabolic syndrome or diabetes have the greatest risk. Therefore patients with metabolic syndrome or diabetes deserve special attention when it comes to and treating assessing risk factors.

As a part of the ADA/ACC Consensus Conference Statement of Lipoprotein Management in 2008, we had a lot of debate about the lipid targets for patients without CVD, with diabetes or the metabolic syndrome. We came up with a recommendation for an LDL cholesterol target less than 70 mg/dl, and non-HDL cholesterol target less than 100 mg/dl if the patient has evidence of the metabolic syndrome/diabetes and an additional risk factor. There wasn’t significant trial evidence to support this recommendation, but we believed there was considerable evidence that these patients are destined to have an event in the future. Their lifetime risk is high, so why wait for the event to start treating them more aggressively? Once they have an event, their prognosis remains much less optimistic, and the long-term prognosis is poor.

What we were hoping to do with a prevention strategy like this is to target the highest risk patient, get their LDL cholesterol down to at least 70 mg/dl, and the non-HDL cholesterol below 100 mg/dl. Consider ApoB measurements once they have achieved those LDL and non-HDL targets to make sure that they are truly at the ApoB target, which may not be concordant with their LDL cholesterol and non-HDL cholesterol. You’ll frequently see discordance between ApoB and non-HDL cholesterol and LDL cholesterol in those high-triglyceride, low-HDL patients. Hopefully we can prevent an event.

DR. WENGER: Of course, this emphasizes the importance of the detection of diabetes, because there is so much unrecognized diabetes in the population at large. Once you identify a patient, man
or woman, as diabetic, there are totally different intensity goals for so many of their risk factor managements.

Let’s move on to some of the clinical trials that have been quoted and misquoted, interpreted and misinterpreted. Dr. Ballantyne, I will ask you first to talk about ACCORD. Let’s just confine this discussion to the lipid component of ACCORD\textsuperscript{8,10} and tell me what you think ACCORD has taught us?

**DR. BALLANTYNE:** As you know, ACCORD was an ambitious trial, which followed diabetic patients and looked at important questions in regard to glucose control, blood pressure control and lipid therapy. Maybe one thing that we learned is, if you try to look at too many things at one time, you don’t always get a very clear answer. Unfortunately, when you design these trials, they’re hard to recruit. So there was some compromise here, in that they enrolled patients with diabetes who were on statins. The study tested whether the combination of fenofibrate plus simvastatin conferred more benefit than statin alone. To make recruitment easier, patients were admitted to the study who didn’t have the typical lipid criteria that we use when we use a fibrate. Typically, fibrates, at least for most of us, are reserved for patients who have a high triglyceride and a low HDL cholesterol or a very high triglyceride. Those were not the criteria. Overall there was no benefit from the combinations used in this study.\textsuperscript{10}

There was a subgroup that had elevated triglycerides and low HDLs. This group had an event reduction following aggressive lipid-lowering therapy. Now the \( P \) for the interaction for treatment effect for this subgroup compared to the overall study was 0.057,\textsuperscript{10} so that was not significant, but it’s consistent with data from numerous other trials. It appears the benefits of fibrates are greater in patients who have a combination of low levels of HDL and high triglycerides with little or no benefit in patients with normal triglycerides and HDL levels. Another consideration is the presence of very high triglycerides but as you know, this is a less common condition and they weren’t entered into this study.

**DR. WENGERT:** Again, the message is that we need information on the combination of a fibrate and a statin in a randomized study, in people who have high triglycerides. That information was not truly imparted by the full ACCORD cohort.

**DR. BALLANTYNE:** It’s frustrating for those of us who are in this field that we’ve yet to have a true triglyceride trial. Hopefully we’ll finally get one in the near future.

**DR. WENGERT:** This is the concern that so many have voiced of the difference between trial populations and community populations. Here we see the trial data being extrapolated to the community, where often the community (these are patients we see in our offices) differs markedly from the highly selected group in clinical trials.

Let me ask you to return to another trial, though, and that is the VA-HIT\textsuperscript{11} trial. Obviously, the concern with VA-HIT is that it was a single-sex trial, confined to men, but tell me what we have learned from VA-HIT that’s applicable to our male patients.

**DR. BALLANTYNE:** I think this is consistent, when you have people who enter into a trial with low levels of HDL cholesterol. In the VA-HIT study, a different fibrate was tested, gemfibrozil and there was benefit in regards to cardiovascular event reduction. So gemfibrozil worked when there were low levels of HDL cholesterol. An old study with fibrates was the Helsinki Heart Study.\textsuperscript{12} Interestingly, these patients were enrolled by high levels of non-HDL cholesterol, not by high levels of LDL cholesterol. In that trial, the group that had the greatest benefit were individuals with high triglycerides and low HDL cholesterol.

Overall, there’s a fairly consistent theme that, at least in regard to fibrates, the patient population that benefits needs to have a low HDL cholesterol and high triglyceride. So there are some differences compared to statins. These have benefitted in a wide variety of patients. They’re uniquely easy agents to use as compared to fibrates. I think fibrates are like some other therapies—you’ve got to target more specifically the patients to get benefit.

**DR. WENGERT:** What’s fascinating, if you recollect the history of statin use and review the early requirements for substantial laboratory testing that had to be done pre-therapy, and with change of therapy, etc., virtually all those test requirements have proved unnecessary as we’ve increasingly used statins in clinical practice. The clinical use of statin therapy today is totally different than it was a decade ago.

Let’s proceed to another category of drugs. Dr. Davidson, the CETP drugs and raising of HDL cholesterol levels. There has been a longtime interest in trying to raise HDL cholesterol. It’s been an elusive target. Should we be excited or should we be worried about the recent clinical trial data?

**DR. DAVIDSON:** CETP inhibition is an interesting target. CETP is the protein that transfers cholesterol from HDL back to the ApoB containing particles VLDL and LDL. So by blocking CETP, HDL increases significantly and if you block it enough, LDL also decreases significantly. Animals that lack CETP, such as mice, rats, and dogs have very high HDL and low LDL. So in that sense, it’s a very attractive target.

The first CETP inhibitor that went into human trials was torcetrapib, and, as expected, it raised HDL and lowered LDL, but also raised blood pressure. A very large outcome study with...
this agent (ILLUMINATE),\textsuperscript{13} was stopped early due to increased mortality, so that cast a pall over the whole CETP inhibition mechanism as a target of therapy. There was concern that by inhibiting CETP, HDL becomes large and dysfunctional and no longer athero-protective.

Fortunately, two additional CETP inhibitors are being studied. One is called dalcetrapib that’s produced by Roche Genentech. It works by modulating the actual protein itself. It does not bind HDL and leads to about a 30\% increase in HDL. The drug has been studied and does not raise blood pressure. There is now a large outcomes study with this agent that will be completed in 2013.

The study dal-HEART\textsuperscript{14} is designed to look at high-risk acute coronary syndrome patients and see if the drug improves outcomes in all patients, regardless of their baseline HDL. Dalcetrapib is also being evaluated for the effects on atherosclerosis as measured by carotid MRI and coronary IVUS. We’ll be seeing more data in the near term in regard to its effects on blood pressure and endothelial function. From what we can tell from the data so far, there has not been an adverse effect on blood pressure. Because it works with a different mechanism from torcetrapib, it might maintain better HDL functionality. We’ll have to wait and see what happens as the clinical trials proceed over the next few years.

The second CETP inhibitor is anacetrapib. It’s a potent CETP inhibitor. It raises HDL by about 100\% and it lowers LDL by about 30\%. So it’s very effective in modifying the values of HDL and LDL on the lab sheet. The question about anacetrapib—because it is closely related to torcetrapib in structure—is safety. Anacetrapib was evaluated in a very large safety trial called DEFINE.\textsuperscript{15,16} There were 2757 high-risk patients in the study, comparing anacetrapib with placebo for 18 months. The study showed that there was no torcetrapib-like effect on blood pressure, and, in this patient population, that the drug was safe.

**DR. WENGER:** No increase in blood pressure.

**DR. DAVIDSON:** No increase in blood pressure, there was no increase in cardiovascular events, no increase in mortality. So the DEFINE study ruled out a torcetrapib adverse effect on cardiovascular events. On the positive side, the cardiovascular events seemed to go in the right direction, especially revascularization, which was eight events on anacetrapib, compared to 28 events in the statin control group. We’re talking about those already at their well-treated LDL targets. The DEFINE study has given us a lot of confidence that the problems with torcetrapib may have been molecule-specific and not mechanistically based.

It doesn’t necessarily mean that CETP inhibition is going to work on reducing cardiovascular events, but we now have more optimism that these drugs may, in fact, provide significant cardiovascular benefits. If anacetrapib does work, and it appears to work in relationship to how much it lowers LDL, we still may not know whether it’s the HDL raising effect that causes the benefits. This is a complex field, and we may not have an answer to whether raising HDL is beneficial with CETP inhibition.

There are going to have to be drug-specific studies, because the drugs are different in how they work. We’re not going to be able to draw any broad conclusions about raising HDL and what this means when it comes to cardiovascular benefits. This is truly a situation where I believe in a class effect for supporting the LDL hypothesis, but when it comes to this particular area, we’re going to be basing more of our evidence on the specific drug that was used in the trial.

**DR. WENGER:** The challenging aspect is that we now see HDL raising through two different mechanisms by these two different drugs. It opens a new vista. Let me ask you to continue from the viewpoint of the clinician. For the clinician in practice, what should he or she be alert for as research data begin to emerge? On one hand, we see trials in acute coronary syndromes. Other research trials are outside the setting of an acute event, more comparable to office practice. What should the clinician look for as lipid trial data emerge in the next several years?

**DR. DAVIDSON:** I think the key thing is not to over-interpret things that may not be powered sufficiently to give us an answer. For example, we’re going to have the dal-VESSEL\textsuperscript{17} study come out first, which is an endothelial function trial with dalcetrapib. That really was a safety trial to make sure there was no adverse effects on blood pressure or endothelial function. So if it doesn’t work on improving endothelial function, I don’t think we should jump to the conclusion that it’s not going to work when it comes to cardiovascular outcomes.

One word is caution. We need to make sure the trials are designed appropriately to answer questions that we want answered in regard to HDL therapies. The key thing is, we have to be patient, and I know that’s hard sometimes, but we have to be patient for the studies to finish and give us the right answers for how these drugs can be most effectively utilized.

We do have two niacin trials that will be coming out in the next few years, too. One is AIM-HIGH,\textsuperscript{18} with 3,000 patients, looking at niacin on top of a statin, compared to a higher-dosed statin. The LDL cholesterol levels should be about the same in both arms, but we’ll be able to compare the effects of triglyceride lowering and HDL cholesterol raising to that of the equivalent LDL cholesterol levels. Whether it will have enough events is hard to say, but as
we mentioned early on, that group of patients that does have high triglycerides, low HDL, metabolic syndrome and heart disease, do have a high risk even on a statin. My hope is it will be sufficiently powered to see enough event difference and that in the absolute event differences. To me, this is probably the most interesting trial evaluating niacin treatment.

The other trial is Heart Protection II, or THRIVE. The study will compare a statin in the control group to a combination of niacin and laropiprant to reduce the flushing with the niacin. The study will evaluate a similar population as HPS I, which includes those with CVD, diabetes and high Framingham risk. The THRIVE population will not have only low HDL/metabolic syndrome patients like AIM-HIGH, and therefore it may be hard to compare the two trials. I think when someone looks at those two trials, they shouldn’t jump to the conclusion that one niacin formulation is better than the other because they were treated in different populations. With AIM-HIGH focusing on the more at-risk group that can benefit the greatest from a niacin product, they may likely have a greater relative risk reduction. While the other study will hopefully show still a benefit, the relative risk reduction won’t be quite as robust. So we need to be careful again how we interpret the difference in these trials and what it means for us to use these drugs clinically.

DR. WENGER: It’s fascinating to see the resurgence of interest in niacin, which was really the only drug that survived and thrived following the age-old Coronary Drug Project. Now we see niacin as the focus of many clinical trials. I expect that for clinical practice, clinicians are now looking askance, actually, as are the regulatory agencies, at intermediate or surrogate trial outcomes. What we really require is clinical outcome information. That will be important.

But I expect that clinicians also have concern in terms of the trial populations because many patients seen in clinical practice may be older. Of course, this group has either been systematically excluded from or underrepresented in many clinical trials, and in particular if they have comorbidities. That’s one of the challenges that clinicians face daily in the office. How are they to make decisions for an elderly population, which is the most rapidly growing component of our cardiology practices, with limited data. I hope that the newer trials at least will have a representative component of older people.

Dr. Ballantyne, let’s return to some of the historical data from the Framingham Heart Study, which was the landmark prevention study. Many years ago, Framingham showed us that determination of HDL was important in the risk evaluation for cardiovascular disease and that the total cholesterol to HDL ratio was probably the best indicator of risk. In Framingham, for example, a ratio of more than four of total cholesterol to HDL was defined as a good indicator of high risk. Somehow, this observation seems either to have been lost or to have disappeared from view over the past 20 or 30 years because of our focus on LDL reduction. How do you view this?

DR. BALLANTYNE: I think we’re coming back to it. One of the things that’s always been fascinating is, why does that ratio do so well? Mathematically the ratio of total cholesterol to HDL cholesterol is exactly the same as non-HDL cholesterol to HDL cholesterol. It’s not the same as using LDL cholesterol. Basically, what drives the ratio is the non-HDL cholesterol and HDL cholesterol. So that’s one of the reasons as we begin to focus on non-HDL cholesterol, as Mike’s already mentioned, it’s a better marker for risk and probably a better target for therapy than LDL cholesterol.

The other one that is coming back is the focus on HDL. I’m hopeful that at the ACC in 2013, we might be hearing the results of some of these studies with niacin and our first CETP inhibitor, and there’s more in the pipeline beyond this. The challenge has been, as you know, that it hasn’t been very easy to raise HDL. Niacin is not the easiest drug to take. We do have an extended release formulation, and there’s a development of a niacin flushing pathway inhibitor available in Europe. But the challenge has been to achieve major increases in HDL cholesterol or improvements in HDL function, and the therapeutics for this have lagged far behind that for reducing LDL and non-HDL cholesterol.

DR. WENGER: Dr. Davidson, do you think this concentration on LDL was because we did not have an HDL enhancer that could be taken with reasonable safety or was there just loss of interest in the molecule?

DR. DAVIDSON: I think that’s right. I believe that every risk factor becomes more and more important once we find effective treatments to modify that risk factor, and modification of that risk factor yields outcome benefits. So I think that once we find that effective HDL-raising or triglyceride-lowering therapies provide clinical benefits, we’ll start focusing more and more on those particular risk factors. We can say with certainty that the LDL cholesterol lowering with multiple types of approaches results in cardiovascular benefits. If we
could demonstrate that HDL-raising-specific therapies or triglyceride-lowering-specific therapies also provide clinical benefits, then we could start addressing this high residual risk that people do have on statins.

In the ACCORD trial, there was a 17.3% primary outcome rate in the placebo group who had high triglycerides, low HDL, compared to 10.1% primary outcome rate for those that did not have a high triglyceride, low HDL in both study groups. That’s a 70% higher event rate in that one subgroup, which represented about 20% of the patients. We know that they are at high risk, so once we can identify effective therapies that can modify that risk, it will become much more important when it comes to management of the overall global risk for patient with diabetes or cardiovascular disease.

**DR. WENGER:** Dr. Ballantyne, obviously, with a low HDL and high triglycerides as important components of the metabolic syndrome, we have to correct these, if we are to reduce the risk. Are there trials that provide any relevant information?

**DR. BALLANTYNE:** We do have some data. For example in AFCAPS/TexCAPS,21 patients were recruited by low HDL cholesterol levels and they had benefit with statin therapy. There was a large number of people with metabolic syndrome in the JUPITER trial who did not have high LDLs. They benefitted from statin therapy. So I think we have pretty good indicators that patients with the metabolic syndrome benefit from statin therapy if their risk is sufficient to be treated.

Unfortunately, what we don’t have is therapies with drugs that really target triglyceride, HDL or even obesity. In fact, we are still waiting for the results of Look AHEAD,22 which is our lifestyle trial on obese diabetics. So it’s a case where we recognize there’s a terrible problem here. I would point out we do have pretty good data with regard to lifestyle changes. These patients have high risk for heart disease and diabetes. We have data that lifestyle modification is terrific for reducing the onset of diabetes.

**DR. WENGER:** Again, certainly that was important, but would you like to comment on lifestyle modifications for raising HDL?

**DR. BALLANTYNE:** I think this is something that we have to look at more seriously. For example, we have gotten very aggressive with statin therapy. We’ve seen that with more aggressive therapy, you get greater benefits. Now in terms of HDL raising, lifestyle modifications usually are fairly modest, but the more exercise you do and the more weight you lose, the greater the benefits. There is a dose response for diabetes prevention and also some for exercise. It takes a lot, but I think our concepts of prescribing exercise in the past would say, 30 minutes a day, six days a week. That’s really the minimum. I’d be like prescribing ten milligrams of lovastatin.

In fact, you see better efficacy with around an hour a day of exercise. People say that’s not realistic. In my case, I have a family history of both heart disease and diabetes and I find the time to get an hour a day of exercise, on average, in a week. It is a choice that busy people can make. I think the benefits are great, if we look at diabetes prevention, blood pressure control, improving the lipid profile and also probably in my case, mental health when you have a high stress job, there’s nothing better than a vigorous workout.

**DR. WENGER:** Dr. Davidson, what about the women who have very high HDL levels, in the range of 80 or 90, and consequent elevated total cholesterol levels? Should they be treated with medication despite their high levels of HDL? Do we have any data that could guide those decisions?

**DR. DAVIDSON:** We really don’t have data. I actually believe that this is a situation where it’s very valuable to talk to the woman yourself and get a feeling for where she stands on the issue of drug treatment. I know a lot of people don’t like you to do that. They’d rather you tell them what to do, but I think the situation where when you have a high HDL and a high LDL, your risk is actually quite low—lifetime risk is low, and often we find these people live to be quite old and live healthy lives. We need to be cognizant of that issue, that there is no evidence of benefit. The risk is generally quite low in these women.

What frequently is kind of a tie-breaker is that if the LDL is above 190 mg/dl, then you’re kind of above the threshold of where the ATP guidelines say you should initiate therapy. Or if you have another risk factor—hypertension or a bad family history or high LPA, that I think would also weigh more towards treatment. Then if you want to do an assessment, such as carotid IMT or coronary calcium and look for evidence of subclinical disease, that can help you if the woman is old enough. A woman with high HDL should be at least 50 before considering a coronary calcium scan to assess risk.
But my general view is very conservative in how I treat women in that situation. I try to be cognizant of the fact that they are at low risk. We should try lifestyle approaches first, and then if necessary have them go onto treatment, but in general, I like to hear what the woman has to say, too, before I decide which way to go.

**DR. WENGER:** The final question, actually for both of you, is given the variety of rather powerful statin drugs that enable reducing LDL cholesterol levels to be extremely low values, is there any level of LDL below which any other interventions may not provide significant benefit?

**DR. BALLANTYNE:** There are a few things. First of all for the clinician, at least, using therapies lowering LDL cholesterol to brittle levels like 20 or 30 mg/dl does not seem to cause harm to the patient. Now the question that comes up is, are there ever people in whom you have treated LDL to very low levels and they are still at increased risk for CHD? Unfortunately the answer is yes. These tend to be people with other comorbidities, such as low levels of HDL cholesterol, high triglyceride, diabetes, or kidney disease. But we don’t really have the answer yet, in regard to whether, if you have LDLs on average down to 25 or 30, you would still have much risk from other lipoprotein abnormalities such as involving HDL.

From what we saw in the large collaborative trial—and they looked at more intensive compared to less intensive statin therapy—and these were LDLs that were in the 70s and 60s—there was still benefit for the patients who got aggressive LDL treatment, but they still had the increased residual risk by having a low HDL. So there appears to be some risk still with low HDL even with intensive statin therapy and that was seen in TNT.

**DR. WENGER:** Dr. Davidson, your comment?

**DR. DAVIDSON:** I agree with everything Christie said. I think lower is better, as a general rule of thumb. Sometimes when I have really low HDL cholesterol, I just drive the LDL cholesterol down to equal to HDL cholesterol as a target in these very high-risk patients. So there’s one approach to take. I really can’t say what’s better, an LDL cholesterol of 30 mg/dl with HDL of 30 mg/dl or LDL of 60 mg/dl with and HDL of 60 mg/dl. They both have the same one-to-one ratio. So one strategy for a very low HDL cholesterol is to really drive the LDL cholesterol down quite low, and as Christie mentioned, we don’t have any evidence that there’s harm. We have a lot of evidence that these people do fine. In the JUPITER trial, what was reassuring was that when the LDL cholesterol was treated to below 50 mg/dl, people actually had lower mortality including lower cancer mortality. So it shows that treating to lower levels of LDL does not appear to increase your risk of any adverse effects.

**DR. WENGER:** That’s a very short-term trial, though, remember.

**DR. DAVIDSON:** Right.

**DR. WENGER:** This concludes a roundtable that has probably posed as many questions as it has answered. Nonetheless, there appears to be promise from ongoing clinical trials. I thank both of you for participating in this discussion.

### REFERENCES


HDL and Triglycerides in 2011


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