
Welcome. I’m Doctor Robert Henry and I’m Professor of Medicine at the University of California, San Diego, in San Diego, California. I’d like to welcome you to this lipid management in Type 2 Diabetes Mellitus podcast during which I will discuss current concepts in lipid management of Type 2 diabetes to reduce cardiovascular disease. This podcast is a course in the Type 2 Diabetes Mellitus curriculum program.

So generally what I’m going to talk about today is lipid management and I’m going to break this into two parts. Part one I’m going to talk about the general concepts in lipid management of Type 2 diabetes, and then the second part, discuss the therapies for dyslipidemia in Type 2 diabetes. So with that let’s first go to the risk factors related to diabetes. And for that I just look at the Framingham Study, which clearly shows that both LDL cholesterol and HDL cholesterol are coronary heart disease risk factors. They clearly show over a wide range of both LDL cholesterol levels and HDL cholesterol levels that the risk for coronary heart disease goes up significantly with increasing LDL cholesterol and with decreasing HDL cholesterol.

In terms of early aggressive lipid lowering, we know that lipid lowering reduces coronary heart disease risk, and I’m going to talk about this a little later on, but the early aggressive lipid lowering trials support the value of reducing cardiovascular and coronary heart disease risk. It appears that elevated—as I’ve told you, from the Framingham and now from additional information—that serum LDL cholesterol appears to be, or have, the largest role in premature and early atherosclerosis and coronary heart disease development. And as we’ll talk about, clinical trials show that aggressive lowering of LDL cholesterol reduces cardiovascular risk. And that there’s also, which is a very important feature and we’re going to talk about this, that there’s no apparent threshold for the reduction in cardiovascular risk. And that the benefits are seen in both men and women.

So let’s first of all look at the goals of therapy. Where are we trying to strive? Well, the two major recommendations that are followed are the American Diabetes Association and the National Cholesterol Education Program. Both of those associations or
recommendations are for an LDL cholesterol of less than 100 milligrams per deciliter overall. But in patients at highest risk, that is patients with a strong family history who’ve had a prior cardiac event and other risk factors, that they should be striving to achieve an LDL cholesterol of less than 70 milligrams per deciliter. The American Diabetes Association also recommends that HDL cholesterol be greater than 40 milligrams per deciliter in men, and greater than 50 milligrams per deciliter in women. And as well, the triglycerides should be less than 150 milligrams per deciliter. In contrast, the National Cholesterol Education Program focuses on non-HDL cholesterol as a major lipid component that needs to be reduced, and advocates that non-HDL cholesterol should be less than 130 milligrams per deciliter in patients with diabetes.

Now, what additional predictors of cardiovascular risk do we have beyond LDL and HDL cholesterol? Well clearly, apolipoprotein B is an extremely good predictor in diabetes even with patients who are on statin therapy. So an elevated Apo B is, again, a very strong predictor of cardiovascular disease in diabetes. Why it’s beneficial is it has less biologic variation and its repeated measures are very reliable. You don’t need a fasting sample, but unfortunately the cost is higher so it hasn’t been widely used, but it certainly is a very important risk predictor.

The elevated triglycerides and low HDL are, again, additional risk factors that have been identified in individuals with Type 2 diabetes, particularly when it’s associated with the metabolic syndrome. LDL particle size and number is important, however, it is technically difficult and expensive, but we know that Type 2 diabetic subjects, who are usually insulin resistant, have abnormalities in the LDL in terms of it being a small and dense LDL particle, which is prone to oxidative modification and increased risk for atherosclerosis. There’s also a number of inflammatory markers that can be of some help in patients in intermediate risk. This would be highly sensitive C-reactive protein primarily. But generally this has proven to be unhelpful in the very high risk patients.

So let’s then look at lipid management in diabetes and what kind of management should be introduced. First of all, in adult patients we should test for lipid disorders in diabetic Type 2 diabetic patients at least annually. Clearly in addition to pharmacologic therapy the grounds are sort of the most important—that lifestyle therapy be instituted because it’s been undoubtedly shown to have beneficial effects on the lipid profile. For example, a diet that is low in saturated and trans fat has been shown to be clearly beneficial on reducing cardiovascular risk. A weight reducing diet with caloric restriction is also important, as is the implementation of an exercise regimen that has been approved by the primary care provider.

In patients with diabetes who do not have any evidence of overt cardiovascular disease, again the primary goal is an LDL cholesterol less than 100 milligrams per deciliter. If
over the age of 40, the patient should be on a statin at a dose sufficient to reduce the LDL cholesterol 30 to 40%. When a patient has an LDL of over 100 milligrams at baseline after lifestyle intervention has been tried, patients should be started on a statin. Under the age of 40 but with other cardiovascular risk factors and who do not reach lipid goals with lifestyle modification, pharmacological therapy is also appropriate. Now in individuals with overt cardiovascular disease, and this is a large number of patients with Type 2 diabetes, these patients should all be treated with a statin. And in fact, a lower LDL cholesterol of less than 70 milligrams per deciliter, often requiring a high dose of statin, is certainly an option.

I would say one of the biggest problems in the management of Type 2 diabetics is that the primary care provider is often accepting an LDL cholesterol of less than 100 but still greater than 70, and this is in individuals with clear evidence of cardiovascular disease. I think that at least most of the information now suggests that—the lowering of the LDL cholesterol—the lower you go the better. And generally to get the LDL cholesterol less than 70 should really be the focus for the majority of patients with diabetes.

**Part 2. Therapy for Dyslipidemia in Type 2 Diabetes Mellitus**

Now if you look at the second part of our talk today it’s about the lipid modifying effects of the available agents. And we clearly have a number of agents, not only the statins and the fibric acid derivatives, [but] nicotinic acid, bile acid sequestrants, and the cholesterol absorption inhibitors. And all have variable effects on the components of the lipid profile—the total cholesterol, the LDL cholesterol, HDL cholesterol, and triglycerides. Clearly, we know that you are able to reliably achieve reductions in LDL cholesterol more than 50% with current statin dose regimens. Triglyceride lowering appears to be roughly proportional to LDL cholesterol lowering with statins, and there tends to be generally a modest rise in HDL cholesterol with statins, usually in the range of 5, perhaps 10%, occasionally greater in individuals. You can see with the fibric acid derivatives, primarily significant reductions in triglycerides of 25 to 50%. They can also get increases in HDL cholesterol of 10 to 20% and reductions in LDL cholesterol of 10 to 15%.

Nicotinic acid—which is an excellent drug but has to be used with some caution in patients with diabetes because it can worsen the glycemic control—but is very effective and has across the board benefits in lowering triglycerides, and LDL cholesterol, and also increasing HDL cholesterol. The bile acid sequestrant can lower LDL cholesterol 15 to 30% with small increases in HDL cholesterol. Unfortunately, sometimes they have some increases in triglycerides that can occur. And finally, the cholesterol absorption inhibitors reduce LDL cholesterol 15 to 20% with small reductions in triglycerides and very small increases in HDL cholesterol.
Now if we look at the results—and the statins are, of course, the major therapy for increases in LDL cholesterol in patients with Type 2 diabetes—the results of the Heart Protection Study, together with the results of the WASCOPS study and the AFCAPS/TexCAPS study, show that the benefits of LDL cholesterol lowering with statin therapies in primary prevention are seen across a broad range of baseline plasma LDL cholesterol concentrations. Together with the results from 4S and CARE, and the LIPID Trial, the Heart Protection Study has also established the benefits of LDL cholesterol reductions with statin therapy in secondary prevention, again, over a wide range of baseline LDL cholesterol levels. There’ve really been four LDL lowering trials in diabetes that have provided consistent evidence that aggressive LDL cholesterol lowering reduces cardiovascular risk significantly in patients with diabetes, irrespective of their baseline cholesterol level—a very important comment.

Now the TNT, which is the Treating to New Target Study, which was conducted in over about five years in patients with coronary heart disease and diabetes, looked at Atorvastatin, 80 milligrams, and showed that it resulted in a 25% reduction in cardiovascular events compared to Atorvastatin, 10 milligrams. And end of treatment LDL cholesterols in these studies were 77 milligrams on the 80 milligrams of Atorvastatin compared to 99 milligrams per deciliter in the 10 milligrams per day of Atorvastatin.

The ASCOT Study, which was the Anglo-Scandinavian Cardiac Outcomes Trial, looked at the separate and combined effects of blood pressure and lipid lowering on primary prevention of cardiovascular disease in hypertensive patients with diabetes. In this study—the lipid lowering arm of ASCOT—the group allocated 10 milligrams of Atorvastatin per day had a 23% reduction in major cardiovascular events and procedures compared to placebo. In the CARDS study, which is the Collaborative Atorvastatin Diabetes Study, in patients with Type 2 diabetes and no cardiovascular disease history, patients randomized to Atorvastatin 10 milligrams per day had a 37% reduction in major cardiovascular events compared to placebo. And finally in the Heart Protection Study, allocation to Simvastatin 40 milligrams per day resulted in reductions of 22% in major vascular events in all patients with diabetes, and 33% in those with diabetes without cardiovascular disease compared to placebo.

So clearly what we’ve seen, I think it’s unequivocal, that statin doses and statins are very effective, and really their use should be encouraged in most diabetics who don’t have any of the side effects and to get the LDL low. And in those who are at highest risk, and I personally believe that virtually all Type 2 diabetics are at high risk, one should push for the LDL cholesterol levels of less than 70 milligrams per deciliter.
Now what do we have in terms of recently completed lipid trials and ongoing lipid combination trials? There are really two studies that I want to talk about. The first is the AIM HIGH Study and this is a study that is in patients with coronary artery disease. All patients are on Simvastatin and then going to be randomized either to Niacin slow release or placebo and then look at the long-term cardiovascular outcomes. The other study, which was just recently completed and the results of which are really quite interesting, was the ACCORD Lipid Arm. Now the ACCORD study had three major components, both the glycemic and blood pressure trials as well as a lipid trial which was placebo controlled. In the lipid trial or the lipid arm in Type 2 diabetics, all patients were on Simvastatin, 20 to 40 milligrams per day, and were randomized either to Fenofibrate, a fibric acid derivative, or placebo, and then they were to look at the long-term cardiovascular outcome.

Now the results of the ACCORD Lipid Trial were quite interesting. They basically in these, Type 2 diabetics, who were treated with the Simvastatin—as I stated earlier the individuals were treated with Simvastatin 20 to 40 milligrams daily—and then when they were randomized to Fenofibrate or placebo they were followed up for a mean of nearly five years; 4.7 years. Interestingly, the results showed that cardiovascular mortality, myocardial infarction, or stroke was 2.2% per year with the Fenofibrate versus 2.4% per year with placebo. And the primary outcome plus revascularization or hospitalization for congestive heart failure was 5.4% per year with Fenofibrate versus 5.6% per year with placebo. All cause mortality was 1.5% versus 1.6%. So the conclusions of the ACCORD Lipid Arm were that among Type 2 diabetics treated with a statin, there was no long-term benefit from Fenofibrate compared to placebo. And the composite cardiovascular outcomes were similar between the two groups.

Now this is really quite important because many of us who take care of patients with diabetes often feel compelled to add a fibric acid derivative to a statin to get additional reductions of triglycerides, small additional reductions in LDL cholesterol, and small additional increases in HDL cholesterol. But I think this data from the ACCORD study clearly showed that the combination of Fenofibrate and Simvastatin, while it did show trends for improvement in the cholesterol profile, it did not reduce the rates of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke as compared with Simvastatin alone. And therefore, the results of the ACCORD Lipid Study do not support the routine use of combination therapy with Fenofibrate and Simvastatin to reduce cardiovascular risk in the majority of high risk patients with Type 2 diabetes.

So in closing, I want to just emphasize that one of the biggest problems that I perceive is that the care providers for patients with Type 2 diabetes have to understand that aggressive lipid lowering of LDL cholesterol particularly, and efforts to increase HDL cholesterol and lower triglycerides—significant effort should be put into that. After
efforts at lifestyle modification, a therapy with statins is clearly indicated to get the LDL cholesterol, and that often will require, as I told you from some of those trials, they require high dose statin levels in order to get LDL cholesterol levels low. And although we had hoped that there would be significant benefit from the addition of Fenofibrate or fibric acid derivatives to the statins in people with diabetes, that unfortunately, at least in this one trial, did not translate to reductions in cardiovascular events. With that I’m going to wrap things up and I thank you very much for listening to me.