Goals for Diabetes and Dyslipidemia Treatment and Its Challenges

I will start with the glycemic and lipid goals in our patients. The American Diabetes Association (ADA) standards of care are very well thought out and they remind us that the goal of glycemic control in all of our patients should be an A1C level of less than 7%.

In some patients, it might be desirable to get the control of glycemia as close to normal as possible. I think the secret behind this whole strategy is to consider at what stage of a patient’s life you are seeing them. The sooner you begin treatment, the more likely you will achieve the goal as close to normal as possible, which will provide dividends in the long run. But if you have patients in the late stages, who have cardiovascular complications and already have major morbidity, the goal may not have to be as close to normal as possible. This is something that is being sorted out now in studies such as the Action to Control Cardiovascular Risk in Diabetes (ACCORD).

The same applies to the lipid goals. Shown here are the low-density lipoprotein cholesterol (LDL-C) targets for patients with diabetes. According to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines, the ideal goal in all patients should be less than 100 mg/dL, whether you have diabetes or not. If you are high-risk, because of family history, multiple risk factors, or the presence of cardiovascular disease, the minimum goal is LDL-C less than 100 mg/dL. But if you have cardiovascular disease along with other risk factors, such as diabetes, history of smoking, multiple risk factors from the metabolic syndrome, etc, you need to try to achieve an LDL-C goal of less than 70 mg/dL.

The ADA, in 2008, came up with their update of the guidelines, which is very similar. I would like to point out a couple of important points that were made in the ADA guidelines. One is that not only should we be trying to achieve these goals of LDL-C less than 100 mg/dL or less than 70 mg/dL, but once we start therapy we should try to lower the LDL-C by 40% or more, if the above targets are not met. It used to be 30% to 40%, but now there is more evidence to suggest that we should consider a 40% reduction from baseline.

In younger patients, less than 40 years of age, we have much less data. Therefore, you need to individualize treatment and you need to think about patients who have multiple risk factors. Even in that younger population, you may want to think about starting pharmacotherapy if diet alone does not work. We would all like to see diet alone work but it does not always get us to goal.

Unfortunately, there are data from various sources saying that
we are not doing very well at achieving our goals. Noteworthy are the data from the National Health and Nutrition Examination Survey (NHANES) as recently as year 2000. The A1C goal of less than 7% was being met in the year 2000 in about 37% of all patients with diabetes; 2 out of 3 did not achieve goal. Blood pressure of less than 130/80 mm Hg was being met in about 35% of patients, and total cholesterol of less than 200 mg/dL in 48% of patients. Remember, this is total cholesterol less than 200 mg/dL, which is roughly equivalent to LDL-C of 130 mg/dL. They did not even look at an LDL-C of less than 100 mg/dL, and even at the cutoff of 130 mg/dL, less than half of the patients were achieving that goal.

We hope that these numbers are changing because a few more years have passed since this report came out. But we certainly are very aware of the fact that a majority of patients with diabetes are not achieving these 3 goals at the same time. We have a lot more work ahead of us to achieve those goals.

Looking at these numbers sometimes you wonder, "How can this be right? My patients are doing better than this," but this is the country as a whole, and patients are from all different ethnic and racial backgrounds.

What is the difficulty in achieving these goals? First look at glycemic control, the A1C targets. We know that we diagnose diabetes too late. By the time diabetes is diagnosed, you probably have had the disease for about 5 to 8 years. This is why we need to look for diabetes; we need to screen people for diabetes and diagnose it as early as possible.

There is therapeutic inertia. We keep saying to our patients, "Let us work on your diet some more. Go and exercise, lose some weight, and come back in 3 months." But the patient does not show up 3 months later, sometimes another appointment is canceled, and years can go by.

There are not many effective lifestyle intervention methodologies available, and there is often secondary failure to the drugs that get started.

Sometimes patients are only focusing on fasting blood glucose level and their A1C might be 8.2% while their fasting blood glucose is less than 130 or 120 mg/dL. That is because they are not checking postprandial glucose levels, and these patients often might have a high postprandial glucose. So the complexity of care certainly adds to these challenges in achieving these A1C goals.

**Current Tools to Treat Hyperglycemia**

We now have 9 varieties of agents we can use with patients with type 2 diabetes. Prior to 1995, it was either a sulfonylurea; and if that did not work, the next choice was insulin.

We now have the benefit of many agents that help enhance endogenous insulin secretion. In addition to sulfonylureas, we have meglitinides and nateglinide, dipeptidyl peptidase-IV (DPP-IV) inhibitors, and exenatide.

At the level of the muscle, in stimulating glucose uptake, we have thiazolidinediones (TZDs). At the level of the liver, we have metformin, which reduces glucose output; and at the level of the gut, we have alpha-glucosidase inhibitors, such as miglitol and acarbose, which may limit postprandial glucose
Still, about 50% of the patients with type 2 diabetes, in order to reach those goals, will end up requiring an injectable preparation. Besides exenatide, we now have a variety of insulins to choose from. We are very fortunate to have newer, long-acting insulin analogs that provide us basal insulin, such as glargine and detemir.

We have several short-acting insulin analogs, including lispro, aspart, and glulisine. The availability of these analogs has helped us in achieving better control with less hypoglycemia, although we have not overcome hypoglycemia.

We even have some very specialized drugs, such as pramlintide. Some type 1 diabetes patients and some type 2 diabetes patients who have marked fluctuations in blood glucose levels can use an agent such as pramlintide.

We have come a long way in treating type 2 diabetes. The important thing is to use these agents judiciously. Start with one agent and if control is not achieved, proceed to the second agent, and sometimes the third agent. If necessary, proceed to insulin as soon as possible rather than waiting, especially because type 2 diabetes is a progressive disease.

The large United Kingdom Prospective Diabetes Study (UKPDS) used a number of different strategies. They used various oral agents, including sulfonylureas and metformin, as well as insulin at modest doses. Initially all of the patients got better; A1C levels came down within the first 6 months to 2 years. Then the blood glucose levels begin to progressively rise; one agent will not suffice after a few years of diabetes duration. So combination therapy becomes very important in achieving glycemic goals.

There are various types of combination therapy, some of which are shown here. When sulfonylureas or metformin alone does not work, you combine the two and get another 1.5% reduction in A1C. The same can occur with a combination of a sulfonylurea and a TZD, whether you use rosiglitazone or pioglitazone. The same applies to other combinations, such as TZDs and metformin. They may not give you the same reduction in the A1C, but fairly significant reductions can be achieved by various combinations.

But once again, after several years of diabetes, a number of patients, whether they have failed to stay with their dietary plan or because they are failing with multiple agents, they end up requiring insulin. Use of basal insulin allows us to keep some of these patients on oral agents while only having 1 injection of insulin a day, which will be acceptable to a lot of patients versus a multiple insulin-injection regimen.

A relatively new approach in type 2 diabetes pharmacotherapy is the result of understanding incretin physiology. Briefly, after eating a meal, certain gut hormones are released that sensitize the beta cell to secrete more insulin. One of the most important gut hormones is glucagon-like peptide-1 (GLP-1), which goes into the circulation and stimulates insulin secretion in a glucose-dependent manner.
In addition, this pathway has the added benefit of suppressing glucagon secretion, which has a role in the pathophysiology of diabetes. GLP-1 is also involved in slowing gastric emptying and in working on the central nervous system causing early satiety, leading to some beneficial effects in glycemic control. The problem is that GLP-1 is very rapidly degraded through the very important enzyme, DPP-IV. This leads to rapid inactivation of GLP-1, making its use impractical in patients who have type 2 diabetes.

It is also interesting to note that in some animal models, and in in-vitro studies, there are some exciting observations that this pathway may also help beta-cell differentiation. This has been shown to increase beta-cell mass, and the formation of new beta cells, but is not yet proven in humans. It is an exciting new concept that is still being explored.

Coming back to this pathway of GLP-1 degradation through DPP-IV, one of the ways to use this physiologic knowledge is to develop a drug that might block DPP-IV activity, which has been done with the DPP-IV inhibitors. They sustain GLP-1 level in the circulation longer, which then stimulates pancreatic insulin secretion and suppresses glucagon secretion. Another strategy that one can employ is to develop a GLP-1-like substance synthetically that is not recognized by DPP-IV. That is the approach underlying the GLP-1 analogs that are not degraded through this pathway, and you can then use that substance in the treatment of type 2 diabetes.

These are the 2 concepts behind the development of the new drugs. Incretin mimetics, which are analogs of GLP-1, are synthetically produced. Exenatide is one of these drugs used to treat patients with type 2 diabetes. Because of the protein, you have to inject exenatide subcutaneously; you cannot give it orally. Another drug in this class, liraglutide, is under US Food and Drug Administration (FDA) review and might be approved in the near future.

The second way to use this physiology is to develop DPP-IV inhibitors. One such agent, sitagliptin, has been on the market for 2 years. There are several other drugs in this class undergoing clinical trials. This is an important area to pursue, and many of the pharmaceutical companies are trying to develop these agents that will be easy to use in the oral form to improve glycemic control.

This shows a summary of the effects of the incretin therapies. With exenatide, a twice-daily injection, you can lower A1C by about 0.8% to 1%. The main side effect is nausea, sometimes vomiting. There may be appreciable weight loss, which is a desirable side effect of this drug. We do not have another approved drug yet that improves glycemic control and results in weight loss at the same time. The only medication that came close to it was metformin, but metformin is relatively weight-neutral; it does not cause weight loss in most patients.

Sitagliptin has very similar effects on A1C reduction as exenatide, except it does not cause weight loss. This drug is
weight-neutral, but at least it does not cause weight gain. Another advantage of these drugs is that they do not cause gastrointestinal side effects, such as nausea.

Both GLP-1 agonists and DPP-IV inhibitors are being utilized in the strategy of combination therapy to achieve better glycemic control.

**Current Tools to Treat Dyslipidemia

Statins**

We have various agents for treating dyslipidemia, particularly elevated LDL-C, the most atherogenic risk factor. First of all, there is the dietary approach. No drug works very well unless our patients meet us halfway in watching their dietary factors.

In terms of LDL-C, there are 3 major points that one has to keep in mind. One is, reduce saturated fats. If the patient is not willing to reduce total fat, the most important thing is to reduce saturated fat, which is twice as effective in lowering LDL-C as raising the unsaturated fat. If you lower the saturated fat to less than 7% of total calories, cholesterol intake will follow.

Second is to limit trans fat. Thankfully, many states in the United States have already started banning trans fat. Trans fat is just as harmful as saturated fat, if not worse.

Finally, add certain plant sterol and stanol esters to your diet. The only margarine I ever recommend to my patients is plant stanol/sterol margarine. Two grams a day, basically three pats, will lower LDL-C by about 8% to 10%. All of these dietary strategies together, along with increase in viscous fiber, may give you a significant 10% to 15% reduction in LDL-C, which is worthwhile, rather than trying to get all of that 40% reduction that we were trying for by administering drugs.

This is all easier said than done, because patients are not following this kind of a simple diet strategy in most cases. Another problem in patients with diabetes is total calories. My advice to patients is that if they enjoy eating something, they can still do that but in as moderate an amount as possible, keeping the total saturated fat down. Basically, I want them to downsize, as opposed to supersize. I think this is a very important concept. It is beneficial even if patients start with downsizing, forgetting about saturated fat and all the calculations. But, of course, they can learn by meeting with the nutritionist, who is a very important part of the diabetes treatment team.

As I said, we are looking for 40% reduction in LDL-C in high-risk patients, such as those with diabetes, where we are trying to prevent cardiovascular problems. Therefore, we have to use drugs in most cases. The best drugs to do that are statins. Statins are the drug of choice because they block the key enzyme HMG CoA Reductase, which is involved in cholesterol synthesis, thereby turning on the LDL receptors in the liver and in other tissues.

Statins, at various dosages depending on which statins you use, can lower LDL-C by up to 50% to 60%. They have modest effects on raising high-density lipoprotein cholesterol (HDL-C) or lowering triglycerides. Based on clinical trials, for every 40 mg reduction in LDL-C, you reduce the risk of cardiovascular events by about 25% to 30% over 5 years. There are very few contraindications to the use of statins. It is very important to tell our patients that regardless of what they read in any
newspaper, these drugs are very safe, even in older patients or patients with other systemic illness, as long as you are careful with some of the drug interactions.

A potent statin, such as atorvastatin or rosuvastatin, will give you the desired 40% reduction in LDL-C at a relatively low dose of 10 mg/day. If you use less potent statins, such as pravastatin, simvastatin, or fluvastatin, you have to go to much higher dosages to get that 40% reduction in LDL-C. However, some patients cannot tolerate the higher doses. In this case, combining statins with other drugs may be necessary.

Some patients develop liver enzyme changes while on statins. Alanine aminotransferase (ALT) more than 3 times the upper limit of normal is seen in 1% or less of patients with the starting doses of statins. But if you go to the maximum dose, the range is 1% to 3%, maybe even up to 5%. The 1% to 3% number is from clinical trials, which exclude patients who have a history of liver disease or previous statin-induced liver enzyme changes. In the real world, this number is about 5% to 6%. So there are a small number of patients who cannot tolerate high-dose statins; with those patients, you have to be a bit more careful as to what to do next.

It is a good idea to check ALT at baseline and then recheck periodically and every time you escalate the dose of a statin, because the risk is somewhat dose-dependent. This risk is reversed after dose reduction or drug discontinuation.

Myopathy, seen in a very small number of patients on statins, is defined by an increase in creatine kinase (CK) by 10-fold above the upper limit of normal, along with myalgia or muscle weakness. That increase in CK is seen in less than 1 in 1000 people. But muscle pain, or myalgia of various degrees, is much more common. We estimate about 10% to 15% of the patients on statins will complain of muscle pain, but it has no relation with CK level. In fact, it is not even necessary to measure routinely unless you think there is a good reason to measure CK serially in a given patient.

Risk factors associated with these muscle pains or myopathy include higher statin doses, advanced age, patients with multisystem disease -- particularly renal disease -- and drug-drug interactions. If you are using drugs that are HIV protease inhibitors, antifungals, etc, you have to be careful. In the package insert, it is clearly mentioned not to use the high-dose statin in those patients; try to get away with the lowest dose possible. Other drugs, such as cyclosporine, can also result in drug-drug interactions.

Combining fibrates with statins also increases the risk of myopathy. It is important to let the patient know that if they develop severe muscle pains, they should stop the drug first and then call you. These are relatively infrequent problems, but they can occur in susceptible patients.

Fibrates, Niacin

In addition to statins, there are many other drugs to choose from for dyslipidemias. There are 2 fibrates approved in the United States, gemfibrozil and fenofibrate, of which there are several preparations. These drugs are primarily suited for triglyceride reduction. They reduce the very low-density lipoprotein (VLDL) synthesis and improve VLDL hydrolysis, leading to reduction in triglycerides by about 25% to 50%, depending on baseline.
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Fibrates have no significant effect on LDL-C, which actually may sometimes go up slightly when you use a fibrate alone. In some cases, however, there might be a slight decline such as with the newer fibrate, fenofibrate.

Finally, you have to be aware that they all can occasionally cause some gastrointestinal side effects, promote gallstone formation, and in combination with statins, they can increase the incidence of myositis; the incidence is small but has been reported in the literature.

Niacin is a great drug that has been around for a long time. It is the cheapest drug around if you want to use the over-the-counter crystalline niacin. There is also extended-release prescription niacin. There are a number of other preparations on the market. It is the best agent to increase HDL-C; no other drug currently exists that will raise HDL-C as much. At the same time, it also has effects on lowering LDL-C, which is a dose-dependent effect, and also helps lower triglycerides. In fact, in some of the older studies, niacin was shown to reduce coronary events.

Niacin monotherapy, however, is not extremely effective in lowering LDL-C. You have to use it as an adjunct, when statins alone will not work, or when HDL-C is quite low. The main side effect is flushing, which affects most patients who go on niacin. One solution is to gradually increase the dose or have patients take it at bedtime. The other way to combat flushing is to take an aspirin before the niacin pill because flushing is caused by a prostaglandin-mediated phenomenon. Still, many people find this a limiting factor. A new drug is being developed that will be combined with niacin and will reduce flushing. It is now undergoing clinical trials.

Niacin can have some liver side effects and you cannot use it in patients who have gout or active peptic ulcer disease, so there are some problems in using niacin in some patients, but overall it is a very effective drug.

Bile Acid Sequestrants

Finally, there is a class of drugs that we sometimes forget about that are referred to as gastrointestinally acting, lipid-lowering agents. Before the statins became available in the early 1980s, how did you lower cholesterol? The only drugs that did that effectively were the bile acid sequestrants, of which there are several examples: cholestyramine, colestipol, and now more recently one that has been around for the last several years, colesevelam. All of these are bile acid sequestrants.

Bile acid metabolism is very intimately involved with cholesterol metabolism, as discussed previously (in Dr. Tolia's presentation). By binding to the bile acid, these agents are increasing the excretion of cholesterol from the gut, which in turn reduces the hepatic cholesterol pool, and that turns on the LDL receptor. Therefore the bile acid sequestrants are very effective in lowering LDL-C. However, there have been some
The bile acid sequestrants can lower LDL-C by up to 30% with the right dose. They can also increase HDL-C very modestly. But they are contraindicated in people who have high triglycerides, because they can raise triglycerides to some extent. Cholestyramine is a powder and you have to use 4 to 6 scoops per day. In a study done many years ago, even when they gave this powder free for clinical trial, half the people took less than half the dose, which is the reason this drug could not be used. Colestipol is very similar.

The newest agent, colesevelam, is a little easier to take because it is in tablet form; and you take 3 pills twice a day. But all the bile acid sequestrants have the same property of lowering cholesterol. For statin-intolerant patients who cannot increase the dose of their statin, you have to consider these agents.

The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) showed that these agents can actually lower coronary events. The main side effects, particularly with the older preparations, are gastrointestinal, such as constipation and bloating, and the gritty taste of the powder can be bothersome. There are some drug interactions, particularly with the older sequestrants, including that they bind to the negatively charged drugs. Consequently, you have to take other drugs either an hour before or 4 hours after you take your bile acid sequestrant. This is an important caveat.

The newest bile acid sequestrant, colesevelam, is a little different chemically than cholestyramine. It has a hydrophobic chain, which is optimized to interact with the bile acid in such a way that it is more effective at a relatively lower dose in achieving the same LDL-C reduction as cholestyramine.

How do they work? When you use a bile acid sequestrant, you lower the bile acid pool. This results in the increased synthesis of the bile acid from the cholesterol in the liver, resulting in a lower intrahepatic cholesterol pool. When the intrahepatic cholesterol pool is reduced, the LDL receptor expression is turned on; and once there are more LDL receptors, you lower the LDL-C by “sucking the cholesterol out” from the circulation into the liver.

There is only one problem: when you lower the cholesterol pool in the liver, the liver turns on the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase enzyme and its own cholesterol synthesis, which tries to undo what you are trying to achieve by increasing the LDL-C receptor expression. Consequently, these drugs may not work well after a while. The best way to overcome that is to use a drug that actually suppresses the liver enzyme and reduces cholesterol synthesis, and that drug is a statin. Combining a statin with a bile acid sequestrant is an ideal strategy to get away with a lower dose of each and achieve greater reduction in LDL-C. This is an old concept and was being practiced for years with cholestyramine and niacin before we had statins.
What is the effect of colesevelam, or any other bile acid sequestrant on lipids? The main effect is LDL-C reduction in a dose-response manner. At the full dose, you can lower LDL-C by about 20%, as shown. There is a modest increase in HDL-C and a slight increase in triglycerides when you use the colesevelam at the full dose of 3.8 g/day (6 pills/day), which you need to get a significant effect on cholesterol reduction.

What is the evidence that cholesterol reduction by bile acid sequestrants is helpful? In the LRC-CPPT study in 1984 where the subjects took only half the dose, half the time, the LDL-C was lowered by 13% with cholestyramine. This was accompanied by a 24% reduction in congestive heart disease (CHD) deaths, a 19% reduction in the CHD death and/or nonfatal myocardial infarction (MI), and a 19% reduction in nonfatal MI. It worked, even when the LDL-C reduction was modest. This old study needs to be reproduced with the combination with statins.

The ENHANCE study (Effect of Combination Ezetimibe and High-Dose Simvastatin vs Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia) was published in the April 3, 2008 issue of the New England Journal of Medicine. This study was done in 720 patients with familial hypercholesterolemia. Such patients have very high cholesterol levels from the time they are born, and may suffer an MI at age 30 to 40 years or younger. The mean LDL-C in these patients was 320 mg/dL. These are the hardest individuals to treat. Half of the patients in this trial received simvastatin 80 mg, and the other half simvastatin 80 mg along with ezetimibe 10 mg. The endpoint was carotid intima-medial thickness (CIMT), because it was thought this would be a good way to assess the atherosclerotic burden over a short period of time.

Over 2 years, LDL-C was lowered quite effectively by 58% in those who received the combination of simvastatin and ezetimibe vs 41% with simvastatin alone. What happened to the CIMT? Those who received the combination, their CIMT went up slightly. It went up with both regimens, but more so in those who got the combination. These are minute differences, not statistically significant, but the fact remains that a 0.011 increase in CIMT is about twice as much as 0.0058.
Clinically, is CIMT a good surrogate for cardiovascular endpoints? We are not sure. In fact, there is a large study of 10,000 people ongoing in a more typical hypercholesterolemic population to see what happens to cardiovascular events.

**Combination Therapy for Low-Density Lipoprotein Cholesterol Management**

This is the same diagram previously shown, but in this case, you are combining a bile acid sequestrant with a statin, which is blocking cholesterol synthesis. You can get more out of the cholesterol reduction from the bile acid sequestrant, because the liver is not poised to increase cholesterol synthesis. This results in greater LDL-C reduction, partly from the statin and partly from the bile acid sequestrant.

Looking at this another way, when you increase the dose of a statin, it takes almost 3 cycles of doubling the dose to get about a 16% reduction in LDL-C beyond what you achieve with the initial statin dose. You need to go from 10 to 20 to 40 mg of atorvastatin, and 20 to 40 to 80 mg of simvastatin to get that 16% reduction in the LDL-C.

You can also do that by simply staying with the initial statin dose and adding a bile acid sequestrant, which gives you that additional 16% or 18% reduction in LDL-C. The concept is very good; it makes sense. Yet, we try to get our patients on a statin and increase the dose of statin as long as the patient can tolerate it. That is what the guidelines all tell you, because the best evidence for cardiovascular risk reduction is from statins, and the trials have all been primarily done with statins so far.

What happens if you combine the 2 agents in clinical trials? In this example, they took patients with LDL-C greater than 160 mg/dL, put them on a diet, and gave them colesevelam, atorvastatin 10 mg, a combination of the two, the highest dose atorvastatin (80 mg), or placebo for 4 weeks to determine the lipid effect.

Atorvastatin 80 mg/day gave a 53% reduction in LDL-C. But there was almost the same reduction in LDL-C with atorvastatin 10 mg/day combined with colesevelam 3.8 g/day; very synergistic as you might have expected. HDL-C goes up modestly with statins as well as the combination of these 2 drugs. The triglyceride level went down mainly because of the effect of the statin in addition to colesevelam, which may sometimes raise triglycerides modestly in monotherapy.
of atorvastatin and 47% taking the combination of atorvastatin and colesvelam reached the goal of LDL-C less than 100 mg/dL.

A Coincidental Finding With Bile Acid Sequestrants in Type 2 Diabetes: Lipid and Glycemic Control

A new observation came to light about 15 years ago, an entirely serendipitous finding. A study was being done in patients with type 2 diabetes using cholestyramine, the old bile acid sequestrant, to determine its effect on lipid management in type 2 diabetes. In a relatively small study of 21 subjects, half of them received cholestyramine 16 g/day or placebo, and 6 weeks later the groups crossed over. Investigators saw something very unexpected.

Fasting glucose went down when they gave cholestyramine to patients with type 2 diabetes. It went down about 20 mg/dL, a significant drop.

At the same time, their A1C decreased by about 0.5%. That was also quite unexpected.

The GLOWS Study: Glucose-Lowering Effect of WelChol Study

Based on this observation, colesvelam's manufacturer conducted an interesting small study called the Glucose-Lowering Effect of WelChol Study (GLOWS). They looked at a group of patients with type 2 diabetes over the course of 12 weeks, where they evaluated parameters of glycemic control in addition to the lipid effects.
There were 65 patients with a mean age of 56 years. Most of them were on metformin, with or without a sulfonylurea, and their LDL-C at baseline was greater than 100 mg/dL.

In terms of glucose control, those on placebo saw their A1Cs go up, and those on colesevelam saw their A1Cs go down. In the course of 3 months, the mean difference between the two groups was an A1C reduction of 0.5%. With this knowledge, it was imperative to do a larger clinical trial, and there are several clinical trials that have been completed in the past few years.

The GLOWS study also showed a significant decrease in postprandial glucose levels in response to colesevelam.

**Colesevelam and Glycemic Control**

Another study looked at 316 patients with type 2 diabetes on a metformin-based regimen. They were randomized to either placebo or colesevelam. Compared with placebo, again, colesevelam resulted in an approximately 0.5% reduction in A1C.
Another study was done with a group of 461 patients on sulfonylureas who were randomized to receive either colesevelam or placebo. Once again, the drop in A1C associated with colesevelam was on the order of about 0.5% to 0.6% compared with placebo.

What happened to other individual glycemic parameters in the previous 2 studies? When adding colesevelam to the original metformin protocol, more patients achieved a reduction in fasting glucose of greater than 30 mg/dL, had a reduction in A1C of greater than 0.7%, and had an overall better glucose response compared with placebo. The same thing happened in the group originally on sulfonylurea therapy.

Interestingly, by reducing the glycemic control, one of the inflammatory markers of atherosclerosis, C-reactive protein (CRP) was also affected favorably. For those on the metformin protocol, compared with placebo, there was a significant decrease in the CRP level for those who got colesevelam. Likewise for those on the sulfonylurea protocol.

Most recently, there was a study of about 290 patients with type 2 diabetes who were on an insulin-based program. Half of these patients were randomized to colesevelam, and the other half to placebo. Over the course of 16 weeks, there was a 0.5% reduction in A1C with colesevelam compared with placebo. With all this evidence, it appears that the bile acid sequestrant, in this case, colesevelam, improves glycemic control.
Summarizing the 4 trials, in each case, the mean reduction in A1C associated with colesevelam was 0.5% to 0.55% over the course of 12 to 24 weeks.

Patients on colesevelam also had the expected reduction in LDL-C. In each of these studies, the LDL-C reduction was significant; approximately 15% across all 4 clinical trials.

What is the mechanism by which the bile acid sequestrants may lower glucose levels? There are a number of possibilities that are listed here. We think they may alter bile acid composition and affect intestinal glucose absorption. There may be some effect on the gut hormones such as cholecystokinin, which is involved in pancreatic insulin secretion.

By turning on liver X receptor (LXR) activity, bile acid sequestrants might result in suppression of hepatic gluconeogenesis and improvement in glucose utilization. Finally, there may be some other nuclear signals that get turned on in the liver that may promote pancreatic insulin secretion, such as hepatocyte nuclear factor (HNF)-4 alpha.

**Colesevelam: Indications and Limitations**

With all this clinical trial evidence, the FDA recently approved colesevelam for reduction of blood glucose in patients who are already on other therapies for glycemic control. The drug had been approved in the past by the FDA for lowering LDL-C. Now patients who have been on other drugs can add colesevelam, not only to improve glycemic control, but also to improve LDL-C levels.

Colesevelam is not approved for use in patients with type 1 diabetes. It has not yet been studied in patients with type 2 diabetes as monotherapy or in combination with the DPP-IV inhibitors. Combinations with sulfonylureas, metformin, and insulin have been studied. Finally, in patients who have significant hypertriglyceridemia, the drug is contraindicated, particularly when triglycerides are greater than 500 mg/dL.
Pleiotropic Effects of Drugs in Managing Diabetes

We now have some examples in our clinical acumen of using the same drug for multiple purposes. Statins not only lower LDL-C, but there has also been a lot of discussion in the literature that statins have pleiotropic effects including improving endothelial function, antithrombotic effects, anti-inflammatory effect, and improved plaque stability. Some of these pleiotropic effects are explained by the reduction in LDL-C, but some may be independent from LDL-C reduction.

Angiotensin-converting enzyme (ACE) inhibitors are not only drugs for blood pressure improvement, but they also have a direct effect on the vessel wall. They have been shown to reduce the risk of stroke, cardiovascular mortality, nonfatal MI, and even all-cause mortality, independent of their effect on blood pressure control. ACE inhibitors are frequently employed in patients with type 2 diabetes.

Now we have bile acid sequestrants, which not only have an effect on LDL-C lowering, but also on glucose lowering.

Summary

To summarize this discussion on glycemic control and lipid management in patients with type 2 diabetes, we have a strong need for further improvement in glycemic, lipid, and blood pressure control. LDL-C remains the primary target of lipid-altering therapy. Combination therapy may be needed to safely achieve current LDL-C targets in patients with or without cardiovascular disease, particularly when you cannot increase the dose of a statin or, in some cases, where other limitations might exist for using statins.
We also know that even a small increase in HDL-C may confer substantial benefit, and that interventions to increase HDL-C should be considered in high-risk patients. Recent data from bile acid sequestrant trials support their dual value in optimizing lipid and glycemic goals. Unfortunately, currently defined goals for well-established risk factors are being met in only a minority of patients with diabetes. Therefore, we have a lot of work ahead of us, but we have much better tools than we had in the past.

Contents of Reducing Cardiovascular Risk: Multiple Risk-Factor Intervention

1. Diabetes and Dyslipidemia: Interrelationships and Clinical Implications
2. Treating Diabetes and Dyslipidemia: Achieving Therapeutic Targets
3. Clinical Approach to Achieving Treatment Targets: Case Vignette Discussion