Pharmacologic Treatment of Hyperlipidemia

Hyperlipidemia & ASCVD: Overview, Guidelines, and Statin Therapy

Statin Intolerance

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PHARMACOLOGIC TREATMENT OF HYPERLIPIDEMIA

DR. PAM R. TAUB: It's great to be here today as part of the Foundations of Cardiometabolic Health Certification Course. I am Pam Taub. I am a Cardiologist Professor of Medicine, and Director of Cardiac Rehabilitation and Wellness at UC Sand Diego. I am going to be talking to you today about the pharmacologic treatment of hyperlipidemia. These are my disclosures. I am going to start my talk by giving you an overview of statin therapy and statin intolerance. Then I will delve into the mechanism of action of non-statin agents, and I will go into each of these agents in depth. And those agents include ezetimibe, PCSK9 inhibitors, bempedoic acid, inclisiran, evinacumab, and icosapent ethyl. But before we go into these agents, I do want to provide an overview of atherosclerotic cardiovascular disease and the pathogenesis of this disease, and then briefly delve into the guidelines and foundational therapy for hyperlipidemia, which is statins.

HYPERLIPIDEMIA & ASCVD: OVERVIEW, GUIDELINES, AND STATIN THERAPY

Before we delve into the different therapeutic options for the management for hyperlipidemia, we need to look at the fundamental pathophysiology of atherosclerotic cardiovascular disease in detail. So, when we think about atherosclerotic cardiovascular disease we think about plaque, and the plaque is composed of lipids, mainly LDL cholesterol. So, I love to term the fuel for the fire as LDL, and so, when we look at how this plaque impacts the artery, what we see is that the plaque is very sneaky. And the artery actually expands to accommodate that plaque. So in this particular figure, if we took out this thrombus and we did an angiogram on this patient, we wouldn't pick up any significant stenosis. Similarly, if we did a stress test on this particular patient, we may not pick up that there is a hemodynamically significant stenosis because of how the artery accommodates this plaque. So this is where we need to be using biomarkers such as LDL, non-HDL, and APO-B, LDL particle number to really look at this plaque burden that patients have because plaque in the initial stages can be very sneaky, and not be recognized on stress testing, and even angiography. When we've done serial angiographic studies, what we have seen is the majority of heart attacks are coming from stenosis that is <50%. So we often think of myocardial infarctions coming from very high grade stenosis, but what we actually see when we follow people serially through angiograms is many times myocardial infarctions are resulting from <50% stenosis. So, going back to this figure, this is a particular patient that would have <50% stenosis who has this sneaky plaque that is hiding. And so this is why it is really important to manage hyperlipidemia very aggressively, and to address this plaque that is hiding in the arterial wall.

What we know from many large studies is that when we focus on LDL cholesterol there is a significant impact on overall cardiovascular outcomes. But there is still work to be done, and that work is what I refer to as residual risk. And so residual risk refers to the risk that persists despite optimization of LDL. And what this tells us is that, yes, LDL is important. But we also need to be looking at other risk factors such as low HDL, elevated triglycerides, LPa, and so LDL lowering is one part of our management, there are a lot of other things that we need to also take into account.

The other point that I want to emphasize is how atherosclerosis is a systemic disease. We used to think about it as a focal disease where you could put a stent in a coronary artery, or do a bypass surgery, and you are fixing the disease. But what we have learned from numerous clinical trials is that that is not enough. There is plaque throughout the vasculature, and just putting a stent in one focal area doesn't

fix the disease. And so we really need to be thinking about it as a systemic disease that needs systemic treatment, and that's where medical therapy such as statins are so important because they address the systemic nature of the disease. One of these landmark trials that really demonstrated the systemic nature of atherosclerosis is the Ischemia Study. And this was a large study of over 5,000 patients who had stable atherosclerotic cardiovascular disease, and they were randomized to either medical therapy, or invasive therapy with stents. And what they found is that medical therapy was equal to a percutaneous coronary intervention with stents and/or bypass surgery. And this study was a follow-up to the landmark Courage Study, which also showed that medical therapy is very beneficial for the treatment of atherosclerotic cardiovascular disease in patients with stable coronary artery disease. Of course, when someone has an acute coronary syndrome, that is a completely different category, and those patients do need stenting or bypass surgery.

Now let's look at the guidelines for the treatment of these patients. So the cornerstone of therapy for our patients with atherosclerotic cardiovascular disease is statin therapy. And we now have >30 years of data showing that statins are very efficacious in the treatment of atherosclerotic cardiovascular disease. But what we are realizing is there are many patients that need more than just statin therapy. And some of that is because they may not tolerate statin therapy. But in many cases statin therapy alone is not enough to get them to the LDL levels we need to achieve. And, so, other categories of medications can be added.

These guidelines are from 2018, and in many ways they are outdates because, since then, we have had so many new medications on the market. But, just based on these guidelines, when you have a patient who is very high risk for atherosclerotic cardiovascular disease, so, they may have had a recent event, or they've had multiple events, and they are maximized on statin therapy, then the next step would be to add ezetimibe and PCSK9 inhibitors. And, so this set of guidelines will be updated with some of the newer agents that I am going to highlight in this talk.

When we look at patients who are very high risk for future atherosclerotic cardiovascular disease events, we do want to keep in mind those that have had a recent event, those who have had a history of MI or stroke, and we cannot forget about patients who have peripheral arterial disease, TIA, because these patients are sometimes not thought of as having coronary disease, but we do need to keep in mind that peripheral arterial disease and TIAs are also part of atherosclerotic cardiovascular disease. In addition, we also need to be thinking about patients who have very high risk conditions when we are thinking about what therapy to institute. And some of those high risk conditions include heterozygous familial hypercholesterolemia, which is defined as a baseline LDL without treatment >190, and usually a family history.

Now let's talk about statins. We have had incredible data that shows that statins are very efficacious in lowering LDL. There are many different statins on the market, and it is important to note that they have different potency. So the most potent statin is rosuvastatin with about a 60% reduction in LDL. And the least potent statin would be pravastatin which has about a 40% LDL-lowering at the highest dose, and in the 20 mg. dose it is about 27%. So we need to understand within statins that each one has some unique properties and different potency, and you can think of rosuvastatin being the most potent, followed by atorvastatin. Those are the two most commonly prescribed statins.

The other characteristics we need to keep in mind about statins is some of them are what we call lipophilic. And some of them are what we call hydrophilic. So the lipophilic statins are more easily

absorbed into skeletal muscle, and they tend to have more musculoskeletal effects versus the hydrophilic statins which have less bioavailability in skeletal muscle, and tend to have less musculoskeletal side effects. And so one of the things that you want to think about is, let's say you have someone on atorvastatin 40 mg., and they complain to you of myalgias or muscle weakness. The first thing you want to do is switch the statin from atorvastatin to either pravastatin or rosuvastatin, which is more hydrophilic. So it is important to understand that not all statins are created equal. They are different in their potencies, and also in their pharmacokinetics and their bioavailability in skeletal muscle.

STATIN INTOLERANCE

Now that we've talk about the pathogenesis of atherosclerotic cardiovascular disease and how statins are really the cornerstone of the management of hyperlipidemia and atherosclerotic cardiovascular disease, let's delve into a very important topic that we face every day in our clinical practice, and that's statin intolerance. We used to think that statin intolerance was not real, and we really thought that it was just patients complaining about statins, or having some really mild symptoms. But what we have learned with subsequent clinical trials is that it is real, and that up to 20% of patients who are prescribed a statin stop it because of side effects. And a recent trial called the Gauss-3 Study, really studied statin intolerance from a very rigid scientific method in which there was a placebo-controlled statin re-challenge, and it really established how statin intolerance is real. In this study, and alarming 43% of patients had statin intolerance. So, when our patients tell us that they are having problems with statins, if they can't tolerate it, we need to take them seriously, and we need to come up with some alternatives to lower their LDL and address their cardiovascular risk. And, when we talk about statin intolerance, it can be multiple side effects. So, the most common are muscle aches, muscle pain, muscle weakness, decreased exercise tolerance, sometimes it's joint pain or tendon pain. But the key is when people give you a specific side effect that occurs after a statin is started, we want to take them seriously and attribute that particular side effect to the statin, and see if we can try an alternative statin, or maybe add some non-statin agents.

As I mentioned earlier, there are different properties of statins, and the lipophilic statins such as simvastatin and atorvastatin tend to have more muscle-related side effects. And the hydrophilic statins like pravastatin, pitavastatin and rosuvastatin have less musculoskeletal side effects. One other aspect of starting statin therapy that we need to keep in mind is there are some data that show that patients who have vitamin D deficiency, or who are hypothyroid, tend to have more statin-related musculoskeletal effects. So it is also important to make sure that vitamin D levels and thyroid levels are normal in these patients who have statin intolerance.

What we know about statin intolerance is that it actually adversely impacts outcomes. So the reason we have to take this very seriously is because when patients have statin intolerance, it results in higher rates of myocardial infarction in these patients. And so there are multiple reasons for patients having statin intolerance, and it's something that needs to be addressed very quickly, whether it's switching the statin, or trying another non-statin agent, especially in our patients who are very high risk, or have had a recent event.

This is another study that shows that when there is early statin discontinuation in patients that are under the umbrella of secondary prevention, that there is an increased risk of future myocardial

infarction and death. So, statin intolerance is a major problem that leads to adverse outcomes that needs to be taken seriously and addressed promptly.

NON-STATIN AGENTS: MECHANISMS OF ACTION & REVIEW OF KEY DATA

Now that we have reviewed statin intolerance, let's talk about some options for our patients. The good news is there are a lot of non-statin agents that are now available to us. I am going to highlight the mechanism of action of some of these agents, and review the key data that supports the use of these agents.

When we look at the timeline of when some of these agents were introduced, we see that many of these agents have been recently introduced. So, the first statin agent that we had was the ezetimibe, and there were multiple outcome trials including Improve-It that showed that ezetimibe is an important non-statin agent that can reduce cardiovascular events. After ezetimibe, the next class that was introduced was the PCSK9 inhibitors. And now we have multiple outcome trials with the PCSK9 inhibitors, showing that they are beneficial in reducing cardiovascular outcomes. The newer agents that are on the market are bempedoic acid, which has LDL lowering, but we are awaiting the results of the outcome trial, and inclisiran in the Orion Study. Inclisiran was just introduced to the US market. It was FDA approved in December of 2021. So, now we see that there is an evolving landscape of non-statin agents, and we have a lot of different agents to choose from.

Let's delve into the mechanism of action of some of these non-statin agents. We know that our good friend, the statin, works on HMG-CoA reductase. And by inhibiting this enzyme, it decreases cholesterol synthesis. Well, upstream to HMG-CoA reductase is an enzyme called ATP citrate lyase. And this is where bempedoic acid works. And, by inhibiting this enzyme, and working upstream to where statins currently work, it also decreases cholesterol synthesis.

The other platform that we want to look at is the PCSK9 platform. What we discovered is that PCSK9 protein is a very bad protein that results in the deprivation of the LDL receptor. And we have PCSK9 inhibitors that are monoclonal antibodies that get rid of PCSK9 protein, thereby allowing the LDL receptor to do what it is supposed to do, which is to clear LDL cholesterol from circulation.

In addition to this monoclonal antibody strategy, we now have inclisiran which interferes with the synthesis of the PCSK9 protein by acting at the messenger RNA level. And this ultimately results in decreased PCSK9 protein, which then allows the LDL receptor to work more effectively.

Then, we also have ezetimibe which works in the intestine and prevents the dietary absorption of cholesterol. The reason I like this figure is because it shows all the different sites some of these non-statin agents work. And these agents can be used together. So there are many patients that I have on statins that work here. PCSK9 inhibitors that work here. Ezetimibe that works on the intestinal villi, and bempedoic acid that works on ATP citrate lyase. So we need to understand that these non-statin agents can be used effectively with statins. And we also need to get comfortable with using multiple agents together for LDL optimization. When we talk about blood pressure management, we are very comfortable using multiple categories of medications together. So, for instance, we will have many patients on a diuretic, and ACE inhibitor, calcium channel blocker, a beta blocker, and we use these agents together. They all work on different targets, and work well together. Similarly, these non-statin agents can be used together, and work very well in conjunction with statin therapy. What I hope to see

evolve with more and more data coming out with these non-statin agents, is for us to have comfort in adding multiple agents on as needed to optimize LDL cholesterol.

Let's start with one of the older non-statin agents, which is ezetimibe. In the landmark clinical trial that was conducted that showed the efficacy of ezetimibe was the Improve-It Study, in which a combination of ezetimibe and simvastatin was compared to simvastatin alone. And, in this study what we saw was this combination of ezetimibe and simvastatin did reduce the event rate in terms of cardiovascular death, nonfatal MI, or nonfatal stroke. And this was a landmark trial because this was the first non-statin agent that showed clinical benefit. And it also proved the LDL hypothesis that lower is better. And, so I like to say that it's not a hypothesis anymore; it is a conclusion that the lower the LDL the better, in terms of reduction of cardiovascular events.

Now let's talk about the next non-statin agent that was introduced after ezetimibe, and that is the PCSK9 inhibitors. And PCSK9 inhibitors really represents rapid progress from discovery of the protein and the mutation to development of a drug, clinical trials, and FDA approval. It was just very remarkable and rapid progress in introducing the drug to the market. PCSK9 mutations were initially discovered, and it was noted that people who were blessed to have PCSK9 mutations had very low LDL cholesterol levels, and very low rates of atherosclerotic. Cardiovascular disease. And, so, when that was recognized, PCSK9 protein became a target of drug development. And what really gave the drug developers confidence to target PCSK9 are that there are natural mutations that occur in the population, and these people that have these mutations in the PCSK9 gene where they produce no PCSK9 protein, really don't have any other adverse sequelae of having no PCSK9 protein. And, so, the PCSK9 monoclonal antibodies were rapidly developed, and in 2015 were introduced into the market. So, when we look at the PCSK9 platform, the initial strategy that was developed was a monoclonal antibody to inhibit, or get rid of, the PCSK9 protein.

There are multiple therapeutic strategies that act on this PCSK9 platform. The PCSK9 inhibitors were the first that were introduced, and their monoclonal antibody. In addition, inclisiran is now on the market, which is acting on the RNA in preventing synthesis of the protein. But there are a lot of other novel technologies, including CRISPR technology, which is gene editing, and vaccine strategy, as well as adnectins that we will all be seeing data on, both in animal models, and early human clinical trials. So, there are going to be a lot more drugs that are acting on this PCSK9 platform.

And here is just a comparison of some of the different methods of inhibiting PCSK9. And, as you can see, many of these new technologies are in very early clinical trials, Phase 1, or pre-clinical. This is a little bit of an older slide, because the small interferon RNA (siRNA) is now on the market, both in the US and Europe.

Let's look a little bit more in depth into exactly what the PCSK9 inhibitors are doing. So here is a great depiction of the LDL particle, and the LDL receptor. So this receptor is very important in the clearance of LDL. LDL binds to this receptor, and this is the way it is cleared from circulation.

So, when you have PCSK9 protein floating around, it basically degrades that LDL receptor. It basically marks that LDLR for degradation. And if you don't have PCSK9 protein around attaching to the LDLR, then the LDLR becomes recycled and goes back to the cell surface, which is what it is supposed to do. So PCSK9 protein is a very bad protein that prematurely kills the LDLR, and prevents it from what it is supposed to do, which is to get rid of LDL. So, you can see why attacking that PCSK9 protein through the

multiple different strategies, including monoclonal antibodies, help decrease LDL cholesterol levels in the blood.

After we had PCSK9 inhibitors introduced on the market, we quickly had outcome studies that showed that use of PCSK9 inhibitors was also associated with improved cardiovascular outcomes, both in a population that had a recent acute coronary syndrome in the Odyssey Trial, and in patients with stable atherosclerotic cardiovascular disease in the Fourier Study. PCSK9 inhibitors reduce LDL cholesterol by 50-60%, and in these trials, on top of statin therapy, we saw that that translated into improved cardiovascular outcomes. And here are the results from both Fourier and Odyssey showing a reduction in cardiovascular outcomes.

We also have some great mechanistic data from studies conducted with PCSK9 inhibitors, in terms of what is actually happening at the level of that atherosclerotic plaque. In the Glagov Study, they used a technique called IVIS, or intravascular ultrasound, to look at what was happening in terms of the plaque in the coronary arteries. And what they saw is that patients on PCSK9 inhibitors had a decrease in atheroma volume, and plaque regression, compared to patients that did not have PCSK9 inhibitors. And here is some of the data showing the reduction in atheroma volume. What is very insightful about this study is that it really shows the lower, the better. It is not that you get the maximal benefit in terms of plaque regression and an LDL of 70. You continue to see changes in plaque when you go to lower LDLs. So this also illustrates that, for patients who have had an event under the umbrella of secondary prevention, the lower the better in terms of the LDL. Most recently, we have had the Huygens study which also shows some changes in terms of plaque morphology after a PCSK9 inhibitor is given. And what we see here is that, when patients are given evolocumab that there is an increased thickness of the fibrous cap, making this plaque less vulnerable. And, so multiple benefits of PCSK9 inhibitors in terms of not only LDL-lowering, but actual fundamental changes in plaque morphology that make a plaque less vulnerable, and less prone to rupture.

Currently we have two PCSK9 inhibitors on the market, evolocumab, and alirocumab, and they are both indicated for similar patient populations, patients who have heterozygous familiar hypercholesterolemia, and those who also have homozygous familial hypercholesterolemia, and for patients who have atherosclerotic cardiovascular disease. And that encompasses patients who have peripheral arterial disease, TIAs, and stroke.

Now let's talk about a newer non-statin agent, which is bempedoic acid. It acts on an enzyme called ATP citrate lyase, which is upstream to where HMG-CoA reductase is, which is the target for statins. And bempedoic acid decreases the synthesis of LDL. It also results in upregulation of the LDL receptor, which is very beneficial because the LDLR is important for clearance of LDL cholesterol. What is nice about bempedoic acid is it is not active at all I the skeletal muscle. So, one of the nice aspects of this drug is you do not see some of the stat-related musculoskeletal side effects with bempedoic acid. So there have been multiple studies done looking at bempedoic acid alone, or bempedoic acid on top of ezetimibe, or on top of statin therapy. And in all of those studies, there has been a benefit in terms of LDL reduction. Different populations have been looked at in these various studies, including patients with atherosclerotic cardiovascular disease, and heterozygous familial hypercholesterolemia. And what we see is that bempedoic acid has about a 15-24% reduction in LDL lowering. We see more of an LDL reduction when there is no background statin therapy. So when patients are not on background statins, you see a more significant reduction in LDL. And, when you look at bempedoic acid in combination with

ezetimibe, you get about a 36% reduction in LDL. So bempedoic acid is very efficacious in LDL lowering, either alone, or in combination with ezetimibe, and there are very minimal safety concerns, and you do not see the musculoskeletal side effects that you do with statin therapy. Overall, a really great safety profile. There is a small increase in uric acid, and so you do have to be cautious in starting bempedoic acid in patients who have active gout, or gout that is poorly controlled.

We do have an outcome study that is ongoing with bempedoic acid, and we hope to get the results of this study in the next year or so.

Now let's talk about the real recent new player on the market, and that is inclisiran, which was just FDA-approved in the US in December of 2021, and is now just entering the market. And, as I mentioned before, it is targeting the RNA and preventing synthesis of the PCSK9 protein. And we have had multiple Phase 3 clinical studies to support the use of inclisiran for LDL lowering in both patients with atherosclerotic cardiovascular disease, and heterozygous familial hypercholesterolemia. And this is the result of the Orion Study. In the Orion Study, patients were on background statin therapy, and 90% were on some sort of statin, whether it was, 67 were on high intensity statins. And what we see in Orion-10 is about a 52% reduction in LDL. So the beauty of inclisiran is the infrequent dosing. It can be given every six months. So that really is a game-changer in terms of compliance. We have compliance issues with many of our patients, not only because of side effects, but because they just forget to take it, or they have a very high pill burden. And, so, this is a medication that you can give every six months, and you can even give it in the office as part of their visit, and it's going to have persistent LDL-lowering over that time period.

In summary, we are seeing great safety and efficacy with inclisiran. On average, you are going to have an LDL lowering of about 50%.

Let's look at another agent that has been introduced on the market. That agent is evinacumab, and that acts on a protein called angiopoietin-like 3 (ANGPTL3). So, similar to PCSK9, ANGPTL3 is a bad protein. And when there is a deficiency of ANGPTL3, we have seen in multiple lines of clinical and animal studies that there is benefit in terms of decrease in atherosclerotic plaque. So this also has become a target of drug development. ANGPTL3 inhibits an important enzyme called lipoprotein lipase, which is responsible for the degradation of triglyceride-rich lipoproteins. And so when you don't have ANGPTL3, lipoprotein lipase is able to do its job.

Evinacumab was tested in a Phase 3 trial in patients with homozygous familial hypercholesterolemia, and these are patients that usually have an LDL level >400. In this study, what we see is on top of good background therapies such as status, PCSK9 inhibitors, evinacumab had a significant impact on LDL lowering, and it was recently approved for homozygous familial hypercholesterolemia. One novel aspect of evinacumab is it does not require functioning LDL receptor to exert its effect. If you remember, when we talk about PCSK9 inhibitors, we do need some LDL receptor present for PCSK9 inhibitors to work, because what PCSK9 inhibitors do is they prevent that LDL receptor from being degraded prematurely. But evinacumab does not require the presence of any LDL receptors. So it is useful in patients with homozygous familial hypercholesterolemia who many times have almost no LDL receptors. Another interesting aspect of evinacumab is it does have great impact on triglyceride lowering. And so there are studies that are currently in progress, looking at the impact of evinacumab on triglyceride lowering.

Now let's talk about a novel agent, and that is icosapent ethyl, which is derived from fish oil. And the reason that this agent is very novel is it has an impact on triglycerides, a little bit of an impact on LDL, but it also has a significant impact in lowering high sensitivity CRP. And all of the pleotropic effects of this agent has really translated into significant reduction in cardiovascular events. So the landmark clinical trial that was conducted is the Reduce-It Trial, with >8,000 patients. And these are patients that are on background statin therapy with a mean LDL of 75, and they either have established atherosclerotic cardiovascular disease, or they are high-risk, with diabetes, age >50, and one or more risk factors for cardiovascular disease. And in this study, they were randomized to either a placebo or statin with icosapent ethyl. What is important here is the baseline LDL was in very good range at 75. And this really gets to the point about residual risk that, even after we optimize LDL, there are still other things that we can do to reduce cardiovascular risk. And, in this study, what we saw was a dramatic reduction in cardiovascular events. It was a 25% relative risk reduction, a 4.8 absolute risk reduction, and a number needed to treat of 21 in this study. So, a very powerful agent for lowering cardiovascular risk. And, as I mentioned earlier, we can't really pin the efficacy of this drug to one particular biomarker. It impacts multiple biomarkers. For instance, there is a 20% reduction in triglycerides, there's about a 6% reduction in LDL, a 40% in high-sensitivity CRP. So this is truly a pleotropic agent that exerts benefits on multiple biomarkers that are very important in terms of the pathogenesis of atherosclerotic cardiovascular disease.

I want to focus on high sensitivity CRP because inflammation is a big driver and substrate for atherosclerotic cardiovascular disease.

Now let's look at some of the different agents that I have gone over, and juxtapose some of their benefits, so you can determine which agent you want to reach for your patient. When we look at LDL-lowering, the most potent lowering agents are the PCSK9 inhibitors and the PCSK9 small interferon RNA agents that is inclisiran. And you are going to get, on average, about 50-60% LDL lowering with PCSK9 inhibitors, about 50% with inclisiran. Statins lower LDL 25-55%. There are different potencies in statins with rosuvastatin being the most potent. With ezetimibe you are going to get about a 10-18% more, and bempedoic acid alone 15-25% lowering. If patients are not on background statins, you are going to get more LDL lowering, about 25%. When bempedoic acid is added to ezetimibe, about a 35% LDL lowering, and with icosapent ethyl a very small LDL lowering effect of about 6.6%. When you look at inflammation, the agents that are going to give you lowering high sensitivity CRP are statins, bempedoic acid, and icosapent ethyl. In terms of triglycerides, you are going to get the most triglyceride lowering from evinacumab, but it not yet FDA-approved for this indication. Icosapent ethyl is going to give you a 20% lowering of triglycerides. And with statins, you are going to get 7-30%. And with PCSK9 inhibitors and inclisiran, you are looking at a 7-15% range.

In terms of dosing, the injectables are PCSK9 inhibitors, inclisiran, and evinacumab. And we have outcome studies with statins, ezetimibe, PCSK9 inhibitors, and we are awaiting the outcome studies with bempedoic acid, inclisiran, and evinacumab. Also, the outcome study with icosapent ethyl, which I just highlighted the Reduce-It Trial was positive.

Now that we've gone over some of the non-statin agents, let's go back to where we began, and that is fundamentally at the level of the atherosclerotic plaque. And, what we see is there are many pharmacologic strategies to reduce cholesterol deposition, and ultimately result in plaque regression. But we can't forget about the importance of lifestyle strategies such as exercise. Exercise increases

nitric oxide levels in the body, and improves endothelial function. And when you use exercise along with a healthy diet, such as a Mediterranean diet, you definitely see an impact on plaque. There have been many imaging studies that show that just lifestyle alone, which includes exercise and healthy diet, can result in plaque regression. When we look at some of the pharmacologic strategies, what we are looking at ways to reduce the fuel for the fire, which is to reduce the LDL cholesterol that deposits in plaque, and those strategies include statins, ezetimibe, PCSK9 inhibitors, and inclisiran. In addition, we can look at ways to reduce inflammation because inflammation is a big driver of turning a stable plaque to an unstable plaque. And those agents that can help with that include icosapent ethyl. So a lot of different strategies to get plaque to regress, and we need to be using all of these strategies concomitantly, and they work synergistically. Like, for instance, lifestyle strategies work very synergistically with pharmacologic strategies.

So, in conclusion, statins are the cornerstone of therapy in our patients with hyperlipidemia. Ezetimibe is a very useful non-statin adjunct, and it is also generic, and very cheap, so easy to add on to generic statins, and cost effective. PCSK9 inhibitors are a very potent way to lower LDL cholesterol 50-60%, and they have a beneficial safety profile, and also favorable effects on plaque remodeling. Bempedoic acid, evinacumab, and inclisiran are all now FDA-approved, and are promising new agents for LDL lowering. We are awaiting outcome trials from bempedoic acid, evinacumab, and inclisiran. Icosapent ethyl is a very novel agent that should be thought of overall as a risk reducing agent. It does lower triglycerides, but it also results in significant improvement in cardiovascular outcomes. And we should be targeting low LDLs. And in patients who have established atherosclerotic cardiovascular disease, we need to be getting the LDL as low as we can.

CASE #1

This is a case of a 66-year-old woman who has coronary artery disease and recent stent placement to the LAD in the setting of acute coronary syndrome. She also has a history of hypertension, type 2 diabetes, atrial fibrillation, hypothyroidism, and pancreatitis. Her current medications are amlodipine for hypertension, aspirin and clopidogrel given that she had a recent stent, levothyroxine for her hypothyroidism, apixaban which is an anticoagulant for her atrial fibrillation, and metformin for her diabetes. She has tried multiple statins including lipophilic statin such as atorvastatin, that can cause more musculoskeletal side effects, and she was switched to a hydrophilic statin like rosuvastatin and pravastatin which also caused side effects. So all of these statins caused side effects to the point that she had weakness just getting up from a chair. She was also tried on ezetimibe, but that caused some GI side effects. Currently she is on evolocumab every two weeks, and her current lipid profile reveals a total cholesterol of 170 mg/dL, HDL-C 28 mg/dL, LDL 60 mg/dL, and triglycerides of 180. Her hemoglobin A1C is 7.9%. What would you add? Would you try another statin like simvastatin? Would add inclisiran, icosapent ethyl, or bempedoic acid?

The point of this case is that her LDL is in good range with the PCSK9 inhibitor. So we need to be looking at other biomarkers of residual risk. And so her triglycerides are elevated at 180, and the agent that is going to target her triglycerides is going to be icosapent ethyl. So this would be the most appropriate agent for this particular patient whose LDL is in good range.

CASE #2

Now let's go to case #2. We have a 48-year-old female with hypertension, metabolic syndrome, and NSTEMI a week ago, and also another stent placement in the LAD. Her father had an MI at age 42. On physical exam she has a blood pressure of 139/85. Her heart rate is 75, BMI elevated at 30, and she also has a mid-peaking systolic murmur at the RUSB. Current medications are lisinopril and aspirin. She was also started on ticagrelor given her recent stent placement. She was started on atorvastatin during her recent admission, and she is also on metoprolol. So, two months after discharge with atorvastatin 80 mg., her total cholesterol is 261, LDL is 120, HDL is 40, triglycerides 180, and her L-(a), which is another biomarker of cardiovascular risk, is elevated at 200 mg/dL, and that is not surprising given her family history. So, what is your next best step? Would you add ezetimibe and bempedoic acid? Would you add icosapent ethyl? Would you add ezetimibe and alirocumab? Or, would you add evinacumab?

So, this is a patient who has had a recent event. She has good statin therapy. She is on a high-intensity statin with atorvastatin 80. And, despite the atorvastatin, she still has a high LDL of 120. Her triglycerides are elevated. And she also has an elevation of her lipoprotein A. So, in this patient we want to first focus on LDL lowering. And the best agents to target LDL would be a combination of ezetimibe and alirocumab. One additional side-benefit of alirocumab, which is a PCSK9 inhibitor, is you will get some lowering of the lipoprotein A. This is not an FDA-indication for lipoprotein A lowering. Alirocumab is indicated for LDL lowering, but this is something that has been seen in clinical trials is LDP-lowering with PCSK9 inhibitors. So the combination of ezetimibe and alirocumab is going to give you the most potent LDL lowering. You will also get some impact on triglycerides with alirocumab.

Now that I've given you an overview of statins, statin intolerance, non-statin agents, and also application to clinical cases, I hope that some of the things that you heard will help you with your clinical practice. Thank you for your time.