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Reducing Cardiovascular Risk with PCSK9 Inhibitors: Addressing Challenges and Improving Outcomes

Announcer:
Welcome to CME on ReachMD. This activity entitled “Reducing Cardiovascular Risk with PCSK9 Inhibitors: Addressing Challenges and Improving Outcomes” is provided by VoxMedia and supported by an educational grant from Amgen. Here is your host, Dr. Butler

Dr. Butler:
Greetings, and welcome to our program titled Reducing Cardiovascular Risk with PCSK9 Inhibitors. I am Dr. Javed Butler. I serve as the President of the Baylor Scott and White Research Institute in Dallas, Texas, as well as Professor of Medicine at University of Mississippi in Jackson, Mississippi. Today, to discuss the various issues related to lipid control are two of my colleagues who know a lot about this, Dr. Pam Taub and Dr. Marc Sabatine.

Dr. Pam Taub is the founder and director of the Step Family Cardiac Rehabilitation and Wellness Center, and Professor of Medicine at University of California, San Diego. Welcome, Pam.

Dr. Taub:
Great to be here.

Dr. Butler:
And also Dr. Marc Sabatine, who is the Chairman of the TIMI Study Group, Lewis Dexter, MD Distinguished Chair in Cardiovascular Medicine at the Brigham and Women's Hospital, and Professor of Medicine at Harvard Medical School. Welcome, Marc.

Dr. Sabatine:
Great. Thanks for having me.

Dr. Butler:
Great. So, we have a lot to discuss. So, let's dive right in. So, Pam, maybe I can start with you. You know, it's really interesting that just across the span of my career, I have seen lipid therapy not only completely revolutionized, but the role of statin therapy from experimental has really expanded to various forms of high-risk patients and manifests atherosclerotic cardiovascular disease, as really foundational therapy. But we also know that many patients don't reach their goals. And those who do reach the goal, may still have significant residual risk. So, can you tell us a little bit about the non-statin therapy that can be used for LDL cholesterol lowering for these patients and maybe describe their profiles a little bit?

Dr. Taub:
Great. So, as you know, statins really are the cornerstone of managing atherosclerotic cardiovascular disease. We've now had statins for over three decades. And despite having statins, we still have an unacceptably high rate of cardiovascular events. So, what that tells us is that there's more that needs to be done than what we're currently doing with statin therapy.

And what we've seen from landmark clinical trials like IMPROVE-IT is even when we get the LDL down to very low levels like in the 50s, there is still residual risk, and that comes from other biomarkers such as non-HDL, lipoprotein A, triglyceride. So, there's a lot that needs

to be done. And thankfully, we've had the introduction of multiple non-statin agents. And some of those agents include our very first non-statin agent which ezetimibe. And ezetimibe works by inhibiting the intestinal absorption of cholesterol. And on average, it's going to reduce LDL cholesterol on top of statin therapy about 10 to 15%. After ezetimibe, we had the PCSK9 inhibitors introduced on the market, and that includes evolocumab and alirocumab. And they act on the PCSK9 platform. And the PCSK9 platform consists of a PCSK9 protein, which is a bad protein that prematurely degrades the LDL receptor. And we know that the LDL receptor is really important for clearance of LDL. And so, by getting rid of the PCSK9 protein through a monoclonal antibody PCSK9 inhibitors reduce the LDL cholesterol by about 60%.

And since PCSK9 inhibitors, we've now had two additional agents introduced on the market, one is bempedoic acid, and it's an oral agent that acts upstream to where statins act. It acts on an enzyme called ATP citrate lyase. And it also contributes to decreased cholesterol synthesis like statins. And then the newest agent that was just FDA approved in December 2021 inclisiran, and that's also acting on that PCSK9 platform, but preventing synthesis of the PCSK9 protein. And that reduces LDL cholesterol by about 50%. We don't yet have outcome trials with inclisiran or bempedoic acid.

So, a lot of different options now available for treatment of residual risk and also LDL cholesterol. And what's nice is there are many patients who are intolerant to statins, and so now we have multiple options for these patients.

Dr. Butler:
And can you also tell us a little bit about evinacumab that is only approved for homozygous familial hypercholesterolemia?

Dr. Taub:
Sure. So, evinacumab acts on a protein called angiopoietin-like 3. And angiopoietin-like 3 is also another bad protein that is degrading an important - or inhibiting an important enzyme, lipoprotein lipase. So, by getting rid of angiopoietin-like 3, you allow lipoprotein lipase to do what it's supposed to do. And in a study of patients with homozygous familial hypercholesterolemia, we saw a significant reduction of LDL cholesterol around 47% with evinacumab, and that's approved now for homozygous familial hypercholesterolemia.

Dr. Butler:
So, you know, this is really great. I mean, we have a lot of options to treat LDL cholesterol. Not only do we have options with statins, but now you just told us about a lot of different non-statin LDL-lowering drugs as well. So can you tell us how some of the guidelines are assimilating all this information. And actually first, what do the guidelines say about management of LDL cholesterol, and then specifically about the role of non-statin LDL lowering therapies?

Dr. Taub:
So the American guidelines were published in 2018. And that was before some of the newer agents like bempedoic acid and inclisiran were on the market. So, the American guidelines really emphasize for our very high-risk patients, PCSK9 inhibitors and ezetimibe. And what they say is that if the LDL is greater than 70 in these high-risk patients, the next step would be to add PCSK9 inhibitors and ezetimibe. And so that's where the American guidelines were in 2018. But in the updates, we'll be seeing incorporation of bempedoic acid and inclisiran.

The European guidelines came out slightly later in 2019. And they're a little bit more aggressive in what they recommend for the very high-risk patients. And in the European guidelines, they recommend a greater than 50% reduction in LDL from the time of the event, and an LDL goal of less than 55. So more aggressive LDL targets with the European guidelines.

And so, what's exciting is there are going to be updates to the guidelines, and a lot of these newer non-statin therapies are going to be incorporated into our clinical decision-making.

Dr. Butler:
Are guidelines pretty much the same for atherosclerotic cardiovascular disease?

Dr. Taub:
The guidelines do differentiate based on the degree of risk. And so, for instance, in the European guidelines, it's low risk, moderate risk, high risk, and very high risk. And that risk category depends on some of the intrinsic characteristics of the patient, whether they have diabetes, whether they have family history, other biomarkers. So, there is a little bit more thought that goes into determining whether someone is low risk or very high risk. And depending on the risk category, both in the American and the European guidelines, our LDL threshold is lower. So those very high-risk patients, we want to be getting the LDL to a very low level. So, by the European guidelines, at least less than 55. The American guidelines not as aggressive, but it's at least saying that if it's over 70, we need to add more agents on top of statin therapy.

Dr. Butler:

So, it's interesting, you know, so far, what we're seeing is that every time you sort of set a little bit of a lower threshold, the outcome seems to get better. And that's why these non-statin LDL-lowering drugs and their role continues to become important. Can you just tell us something about real-world evidence and how we are actually doing with cholesterol control for our patients with atherosclerotic cardiovascular disease?

Dr. Taub:
Yeah, so you're absolutely right. The theme has been the lower the better, especially for our secondary prevention patients. However, what we're seeing in some of the real-world registries like the GOULD registry, is that we're really not doing a great job at just even getting patients on maximally tolerated statin therapy. So, in the GOULD registry, they looked at the number of patients post atherosclerotic cardiovascular disease events, whether it was ACS, or another high-risk event. And what they found is that only about 43% of these patients are on high-intensity statin after one year. And what was interesting in the GOULD registry is that you needed multiple agents to get patients to goal. So, most patients did not get to their LDL goal with just one agent, you needed that combination strategy with ezetimibe and PCSK9 inhibitor.

Similar to GOULD, there was another study done in Europe called the DA VINCI study. And that study also emphasized the same points from the GOULD registry, which is to really get these high-risk patients to the LDL levels that are recommended, monotherapy with statins just isn't enough. So, in this study, the patients on PCSK9 inhibitors, in addition to statins and ezetimibe, are the patients that that achieve their LDL targets.

Dr. Butler:
So Pam, we know so much about the relationship of LDL cholesterol control and subsequent atherosclerotic cardiovascular risks, that trying to achieve these goals is really, really important, and yet, in the real-world setting, we don't. Do you have a general sense, how much of this is an issue statin therapy not being used? Statin therapy being used, but not as much at the doses that it should be? The statin therapy not being tolerated? Or really statin therapy is given at the dose, which is recommended, but there is this residual LDL, and it just doesn't go down with the statin therapy?

Dr. Taub:
Well, I think it's all of the above. We know that there is true statin intolerance, and that's about 20% of patients. But we also have clinical inertia where clinicians just aren't aggressive in titrating up the statin dose. And so, the other issue sometimes is we don't measure LDL as frequently as we need to. In one study, only half the patients after an acute coronary syndrome event even had their LDL measured.

So, there's a lot that we need to do. And I think some of it is that there are so many aspects to managing that patient, that sometimes lipid management gets put on the backburner, but it's a combination of multiple factors.

Dr. Butler:
So let me ask you one last question, because I really want to ask some clinical trial data to Dr. Sabatine, but before I move on there, let me ask you one last question. If you were to look into the future, do you think that the LDL cholesterol management is going by the way of say hypertension, where if blood pressure is above a certain range, you don't even start with one, you just start with combination therapy, as opposed to trying one and see what happens? Do you think we're going to go to that level with LDL that if the levels are to a certain degree, we just start with combination therapy?

Dr. Taub:
I definitely think that's where we're headed. And those of us that are in the lipid field, we already do that. So, for instance, if I see someone with familial hypercholesterolemia, they're on a maximally tolerated statin, and their LDL is 180, I'm not going to just start ezetimibe and just wait for the next appointment. I know that I'm not - never - not going to get to where I need to be with just ezetimibe, I'm going to get a 10 to 15% lowering, I'm going to add ezetimibe and a PCSK9 inhibitor.

But I do think that's what we're going to evolve to as standard of care, especially as we have more agents that are available. And we have to change our paradigm to multiple therapies. In hypertension, we are so comfortable adding multiple agents one on top of the other, we don't even worry about starting two agents at the same time. But in lipid therapy, we're kind of fixated on just statins and we're not even doing a great job with statins. So, the new paradigm is going to be multiple agents and starting two agents at once if needed.

Dr. Butler:
Well, that's great. Let me now turn to Marc.

So, Marc, we learned a lot from Pam about the mechanism of action of these drugs and how the guidelines are sort of thinking about this. Let's turn a little bit to the clinical trials data. So, can you tell us what we have learned from clinical trials in terms of the non-statin LDL cholesterol-lowering therapies, and their effect on the major adverse cardiovascular events? Maybe you can just summarize some of the clinical trial results for us.

Dr. Sabatine:
Yeah, sure. And it's a great question. And Pam did a fabulous job summarizing, you know, how these drugs work. Certainly, LDL cholesterol is a well validated surrogate from the FDA point of view, but medicine's always humbling. And we like to have outcomes trials to be sure that these therapies are actually reducing the risk of major adverse cardiovascular events for our patients.

And so, in the IMPROVE-IT trial, which Chris Cannon in our group led, it was a large trial of over 18,000 patients who were stabilized after recent acute coronary syndrome, and either got statin alone, or a statin plus ezetimibe. And the addition of ezetimibe reduced the risk of major adverse cardiovascular events by about 6.5% or so.

A couple of points to note. First of all, the control arm was extremely well treated. So, the average LDL cholesterol in the statin alone arm was about 70 milligrams per deciliter. And that was by design for the lipid entry criteria for the trial. Because we wanted a twofer from IMPROVE-IT; we wanted to not only show that adding a non-statin to a statin could actually reduce the risk of cardiovascular events, but we also wanted to push that lower boundary which had been set at 70 after we did PROVE IT-TIMI 22. So here the control arm deliberately was set to achieve an LDL level. That was what the experimental arm was in PROVE IT-TIMI 22.

Now the magnitude of the risk reduction, about 6.5%, may seem relatively small, but that's because the spread in LDL cholesterol between the two arms was relatively small. As Pam mentioned, ezetimibe will reduce LDL cholesterol levels by, you know, roughly 20% or so. And so, the achieved LDL cholesterol in the combo arm was around 54 milligrams per deciliter.

Now we know the clinical benefit for LDL cholesterol lowering is proportional to the absolute reduction in LDL cholesterol. And if one then plots out where IMPROVE-IT sits on the meta-regression line we have for all the statin trials, it falls exactly on that line. So, while the relative risk reduction was on the modest end, that's because the LDL reduction was relatively modest.

In real practice, most of our patients actually have much higher LDL cholesterol levels, and we would accordingly expect a bigger reduction. But it also suggests that we need drugs that are more potent reducers of LDL cholesterol. And then that brings us to the PCSK9 inhibitors which can reduce levels by about 60% or so.

Two large trials done. The first was FOURIER, which we led; large trial, over 27,000 patients with prior MI, stroke, or PAD. Reductions in LDL cholesterol by about 60%, and reductions in major adverse cardiovascular events by 15 to 20%, depending on the outcome. And nice data for those reductions really happening across all the different arterial beds. So, reductions in coronary events, cerebrovascular events, and peripheral vascular events.

Very similar data for alirocumab, the other monoclonal antibody; large trial, over 18,000 patients with an ACS in the past 1 to 12 months, and again, a 15% reduction in events.

And then luckily, the good news for both the monoclonal antibodies is that the safety is really excellent. And so, no differences in the rates of adverse events or serious adverse events or allergic reactions, as one might expect for an injectable, slightly higher rate of injection site reactions, but no difference in myositis, elevated LFTs, cataracts, diabetes, or neurocognitive adverse events. So, on that front, all very good news.

Dr. Butler:
Well, that's a really great piece of information.

Now, moving on, you know, many of these patients with atherosclerotic cardiovascular disease are at a particularly very high risk. Can you describe some of those features very high-risk patient types and phenotypes in whom PCSK9 inhibitors will - have been shown to reduce the risk of cardiovascular progression?

Dr. Sabatine:
In an ideal world, we would give these drugs to basically, you know, all our patients with ASCVD, because they reduce LDL cholesterol, they reduce events, and there are no offsetting safety concerns. But we need to be mindful, just given polypharmacy costs to the healthcare system, that we might need to triage and decide which patients are going to be the ones we're most likely to first start on a PCSK9 inhibitor, so that the earlier populations we would treat, and then expand out later as availability becomes easier.

And so, with that in mind, we and others have looked at different subsets of the trials, looking for patient populations that might stand to have larger, either relative or absolute risk reductions. One of my favorite ones, because it really gets back to the biology, is looking at the subgroup of patients who have multivessel disease. And when we did that, as one might expect, in the placebo arm, the patients with multivessel disease had a higher rate of CV death, MI, or stroke. But here, for multivessel disease, I mean multivessel coronary artery disease with stenosis of at least 40% in at least two vessels. So, we're not talking about critical flow-limiting lesions, just that they had a bonafide athero in at least to two arteries.

So, one, not only individuals with multivessel coronary disease, not only were they at higher risk, but a 50% higher risk. But the relative risk reduction with PCSK9 inhibition, in this case with evolocumab, was greater- about a 30% risk reduction versus 11% in patients without multivessel disease. And if one were to look at the cumulative incidence curves, we see different patterns. In those without multivessel coronary disease, the curves diverge but it takes some time, which stands to reason, if they don't have any disease, you're helping prevent the development of disease. And that will down the road, prevent a future MI and subsequent events. But that's going to take time to see the dividends from that.

In contrast, if you have a patient in front of you who has multivessel disease, we know from imaging studies that lipid lowering can actually cause plaque regression. And so, what we see in those cumulative incidence curves is early separation, around six months or so, and then very rapid divergence of the curves. So, it certainly stands to reason then that those with multivessel disease have more athero for your LDL cholesterol-lowering therapy to get to work on. And so, if you couple a higher baseline risk and multiply it by a bigger relative risk reduction, you wind up getting a bigger absolute risk reduction, about two to three times higher in those with multivessel diseases compared to those without.

And then I would be remiss if I didn't - I should say there are other subgroup analysis from ODYSSEY OUTCOMES similarly showing that those with more risk factors have higher baseline risk, and then tend to have greater relative risk reduction. And again, multiplying the two tend to have a bigger absolute risk reduction.

I also would be remiss if I didn't mention the patients with peripheral arterial disease. And we know clinically that these patients have very aggressive athero. We don't have a lot of great therapies for them. We have a variety of antithrombotic cocktails, but all of them are limited by bleeding risk. And so, in FOURIER, we had about 3,500 or so patients with PAD. Their event rates were very high, almost twice as high as those without PAD. The relative risk reductions were robust in that group, 27% reduction in the risk of MACE. But importantly, looking just at major adverse limb events, acute limb ischemia, major amputation, urgent revascularization, a 42% risk reduction in major adverse limb events. So really good news for an additional avenue of therapy for patients with PAD.

Dr. Butler:
Boy, I mean, you have highlighted so many such important points, and one that I really want to sort of emphasize, again, for our listeners, is that, you know, when you take a very high-risk group of patients, you know, you will have absolute risk reduction, which are easy to achieve in a short-term period. And you see those differences. And because of the higher absolute risk reduction, it's relatively easier to achieve your thresholds for cost effectiveness. But the whole purpose of medicine is to start the therapies earlier in lower-risk patients and prevent development and progression of the disease in the first place. Having said that, those trials are really difficult to do, because, you know, it takes 10, 15 years to truly get to that point. I mean, do you have, Marc, any comments about the future? And are we really going to be treating relatively lower-risk patients for a much longer timeframe? Where is this field evolving to?

Dr. Sabatine:
I think we absolutely will be heading there. You know, again, if we look at the regression studies, we can see that if someone's LDL cholesterol is greater than 70 milligrams per deciliter, on average, their coronary atherosclerotic plaque is growing. So, I think those are compelling data that even for primary prevention, which is sort of a little bit outside the scope of the trials I've been showing. But to your very good question, that's actually what I think we should be targeting along with all the other risk factors. And we really need to do that early on.

And certainly, in population studies, pre-industrial societies now, which typically have LDL cholesterol levels at 70 or below, essentially have no coronary atherosclerosis. And so, I think actually, in our primary prevention, what we need to do is instead of waiting until someone is 50 or 60, and has a heavy burden of athero, and has had an MI or stroke, and then we get serious about treating them; rather, we need to start much earlier, and just make sure that their LDL cholesterol is not contributing to atherosclerosis. I think that threshold is probably around 70 milligrams per deciliter.

Dr. Butler:
Well, we all certainly look forward to the two of you leading the way and telling us in the future of how to do even better.

Now, let me ask you one more question. You know, in certain fields, like hypertension and in heart failure, not only do we very aggressively emphasize what should be done, but the sooner you do it, the better it is, and that we should not delay therapy. All these trials that you mentioned about non-LDL cholesterol management, does timing matter? I mean, if somebody comes in with acute coronary syndrome, do the therapies need to be started in the hospital setting? Can it wait for a few weeks? A few months? Does it make a difference?

Dr. Sabatine:
Yeah, it's a great question. I think, you know, largely is a function of being a clinical trialist, as you well know, you know, we want to try

to eliminate as much noise in the trial. And so there haven't been as many trials that have focused on patients who immediately come in with an acute coronary syndrome, because there's a lot of factors that lipid-lowering might not immediately affect, but obviously PROVE IT and IMPROVE-IT both looked at patients stabilized right after their ACS. FOURIER and ODYSSEY OUTCOMES waited at least four weeks before enrolling. And within FOURIER, certainly within the subgroup who had their qualifying MI within the prior year, so 1 to 12 months out, a median of around 4.8 months, they had higher event rates and tended to have even greater relative risk reductions; about a 25% relative risk reduction.

There have been trials that have looked at patients with ACS; smaller trials that have focused on LDL cholesterol as the outcomes. EVOPACS is one of them, which randomize patients with ACS on a background of atorvastatin 40 milligrams a day to get either evolocumab or placebo. And not only did, obviously, evolocumab lower the LDL cholesterol further, you know, that was certainly expected, but very nicely showed as we think about the targets, and this is what Pam nicely touched on. Think about the U.S. target of getting under 70 milligrams per deciliter, the European target of getting under 55, that, by and large, that was hard to achieve, achieved in only a small minority of patients who are just on atorvastatin 40. But if you add evolocumab to the mix, then it was achieved in greater than 90% of patients for both of those goals.

The other thing we've learned from some of these trials is to look at plaque atheroma volume. And that starts giving us some insight into what benefits we might be able to achieve early on. And so, three different trials have been done, GLAGOV, HUYGENS, and PACMAN-AMI, the latter two actually in the setting of an MI. All of them show that adding a PCSK9 inhibitor, two studied evolocumab, one alirocumab, that with that lower LDL cholesterol, the percent of atheroma volume decreased more the lower you got the LDL cholesterol. From those trials, that was the data source for what I mentioned that if you get your LDL under 70, that you start to regress plaque.

But they also gave us insight in at least two of the trials for the vulnerable plaque, not just volume of plaque. But the, if you will, the quality of the plaque. And we know that the thin-cap fibroatheromas are the so-called vulnerable plaques and will lead then to additional acute coronary syndromes. And in both trials, a treatment with a PCSK9 inhibitor caused the fibrous cap to be thicker, meaning more stable.

So that bodes well, I think, for early initiation of these therapies to try to stabilize the coronaries as soon as possible.

Dr. Butler:
Boy, I have to say, I mean, you two both have such deep knowledge based on this topic that I wish I could continue to go on, but we are at the top of our time limit here. So, before we close, maybe I can request both of you to give our listeners one key message that you would like to relate to. Maybe Pam, I can start with you?

Dr. Taub:
I want to convey just two simple points. One is, get the LDL as low as you can go for secondary prevention. And don't be afraid to use multiple agents to get to that LDL goal.

Dr. Butler:
Thank you. And Marc?

Dr. Sabatine:
Yeah, I would echo Pam's comment. And I would say lowest, and I would add for longest is best. And so, which really dovetails into a second point in terms of going with combo therapy early. You know, LDL cholesterol is a well-established risk factor, and we should treat it aggressively to maximize the benefit for our patients.

Dr. Butler:
Well, this conversation has been absolutely great. I mean, I have certainly learned a lot and I hope that our listeners and viewers have also gotten some really good pieces of information that will benefit their practice and certainly their patients and their patients' well-being.

So, thank you so much for being with us today and giving us all the information that you have. Thank you.

Announcer:
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