Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/optimizing-ldl-c-management-post-mi-patient/12664/

Released: 07/15/2021
Valid until: 07/15/2022
Time needed to complete: 30 minutes

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Optimizing LDL-C Management in the Post-MI Patient

Announcer Introduction:
You're listening to CME on ReachMD. This activity, titled "Optimizing LDL-C Management in the Post-MI Patient," is brought to you by Voxmedia and supported by an educational donation from Amgen.

Before beginning this activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Here's your host, Dr. Hector Chapa.

Dr. Chapa:
Low density lipoprotein cholesterol, or LDLC for short, is a primary cause of atherosclerosis, and LDL-C reduction continues to be a central focus of cardiovascular risk reduction. Fortunately, clinicians can significantly reduce patients' cardiovascular risk after a myocardial infarction by lowering their LDL-C. But how exactly can clinicians go about doing so? Welcome to CME on ReachMD. I'm Dr. Hector Chapa, and joining me today is Dr. Marc Sabatine. Dr. Sabatine is chairman of the TIMI Study Group, and he's also the Lewis Dexter Chair in Cardiovascular Medicine at Brigham and Women's Hospital. He's also a professor of medicine at Harvard Medical School in Boston, Massachusetts. Dr. Sabatine, it's a real pleasure and an honor to have you. Welcome to the program.

Dr. Sabatine:
Oh, thanks so much, Dr. Chapa. It's a pleasure to be here today.

Dr. Chapa:
A very, very important topic. So, to start us off, Dr. Sabatine, can you please summarize the pharmacological therapies for lowering LDL-C, and how effective are they?

Dr. Sabatine:
Luckily we're blessed by having multiple different approved therapies. I'll start with statins, which are the foundation for our LDL cholesterol lowering therapy. They inhibit HMG-CoA reductase – that's an enzyme responsible for cholesterol synthesis inside hepatocytes. And so, by decreasing the intrahepatocyte cholesterol content, that then triggers up-regulation of the LDL receptor, and then more LDL is cleared from the circulation. These drugs reduce LDL cholesterol by up to 50%, if you're giving, a high-intensity statin, so around the 50-55%, depending on which particular drug you give and the dose. Then we have our non-statin therapies. The first among them is ezetimibe. This is a drug that inhibits Niemann-Pick C1-like 1 protein. That's a protein that's involved in absorption of dietary cholesteroland ezetimibe lowers LDL cholesterol by about 24% or sort of a moderate LDL cholesterol lowering drug. Then we have the PCSK9 inhibitors. Two of them are currently approved evolocumab and alirocumab. Both monoclonal antibodies. As the name would suggest, these inhibit PCSK9. That's a protein that normally helps chaperone the LDL receptor to its destruction in hepatocyte after it's internalized an LDL particle. By inhibiting PCSK9, that allows the LDL receptor to recirculate back to the surface of the hepatocyte, where it can then clear more LDL out of the circulation. These drugs are very potent LDL cholesterol lowering drugs. They lower levels by about 60%, and in fact, really a high degree of consistency. So the vast majority of patients will be right around that 60% reduction range. And then lastly, we have bempedoic acid. This is a drug that inhibits ATP citrate lyase –that's another enzyme in the

cholesterol synthesis pathway in hepatocytes, and so like statins, then, triggers increased expression of LDL receptors on hepatocytes and more clearance of LDL from the circulation. It reduces LDL cholesterol by about 18% or so, so again, kind of a moderate LDL cholesterol lowering drug.

Dr. Chapa:
You see, and this is amazing to me. This is why I think these programs have such value, because statins were just a foundation for so long, and it's great to see that other things are available to help these patients. But now, Dr. Sabatine, I wanted to really get into a specific high-risk group, which are those who have experienced, an MI. So if we specifically focus on lowering LDL-C in patients who have experienced an MI, what do the guidelines recommend for this patient population?

Dr. Sabatine:
So we have two sets of guidelines that we could turn to, for guidance. The AHA/ACC multi-society guidelines, that came out in 2018, as well as the European guidelines that came out the subsequent year, in 2019. Let's start with the U.S. guidelines. For patients, as you described, with an MI or even more broadly, with clinical atherosclerotic cardiovascular disease, those patients are then put into two bins. One bin are the patients who are considered very high risk. Those are individuals who have had a major event – by that we mean a myocardial infarction just as you described, or a stroke, or symptomatic peripheral arterial disease, with typically some high-risk conditions, or they've had two multiple major ASCVD events. For those individuals, there is a clear mandate for high-intensity statin therapy. After that, the guidelines are a little more conservative, and so they give a 2A recommendation if a patient's LDL cholesterol is above a threshold of 70 milligrams per deciliter, to add ezetimibe. But really clear with the basis for that threshold was it doesn't match what we studied in the IMPROVE-IT trial that we can talk about in a few minutes, but if the LDL cholesterol is higher than that, then there's a 2A recommendation for considering to add ezetimibe, probably 2A, because as we'll see, the LDL lowering, therefore the risk reduction, is relatively modest, but nonetheless it gives patients a benefit. And then there's also a 2A recommendation then, to add a PCSK9 inhibitor, again if the LDL cholesterol is at or above 70 milligrams per deciliter.

And then, sort of the other limb of that guideline is ASCVD not at very high risk, and then there's some ages in there, where if you're at or under 75 years, it's recommended to get a high intensity statin. If you're older than 75 years, then – , one could just initiate a moderate intensity statin. There's really no scientific basis for them. All these patients should ge a high intensity statin. I'll say that the European guidelines, which came out the subsequent year – I had the privilege of being on the writing committee for that as the sole American, amongst the Europeans there it was a fun experience. And I really have to give them credit for putting together, really, all of the data, not just sort of narrowly, importing in the specific clinical trials designs. And so, you know, their approach for high risk patients is to target a more aggressive goal and rather than having a threshold to initiate therapy, they talk about a target, which I think makes more sense for a risk factor, and so their target is an LDL cholesterol under 55 milligrams per deciliter, for patients, for example who've had an MI. I'll say in the – the back room conversations, there was a discussion that the data, and we'll, I think, get to this in a little bit, really would support even lower targets – even under 40 milligrams per deciliter, but the 55 was already a major step forward, and so that gets the ClassOne recommendation. But there's also a clause we have in there that for patients who are experiencing recurrent vascular events, despite taking a maximally tolerated statin therapy, that they really do need more LDL cholesterol lowering, and then for them the target is actually under 40 milligrams per deciliter. So those are the guidelines we have on both sides of the Atlantic.

Dr. Chapa:
So Dr. Sabatine, that's why we have people like you, because these guidelines, which are ever-changing, and honestly, quite varied from American to the European, that's why we need these reminders, so thank you for doing that. that was a great reminder of what these guidelines say. But that leads me to my next question. Now that we know what the guidelines say, and we know those are key, but here's a real question: Are those goals actually being met by the treatments that are out there? So, what can you say about that? Again, clinical practice is one thing, and guidelines are the other, but what does it really look like in practice? How are we doing?

Dr. Sabatine:
You're absolutely right, Dr. Chapa. There is the chasm between doing the clinical trial, which is what we do for a living here at the TIMI Study Group, and, showing the benefit. Then the guideline committees say yes, this is, you know, great, advantage here and a great advance for the field. So now it's in the guidelines, but the point you raised is, okay but what's happening for our patients? Are clinicians actually prescribing it, or patients actually taking it?

Because obviously, you know, in our country, there's a series of barriers between what's in the guideline, the patient actually taking the medicine, including our health care system which is, you know, quite byzantine and complicated. And so, people have studied this issue and the results are, quite frankly, very disappointing, and so, in a variety of different registries and cohorts you know, probably about half or so of the patients will get to the, less stringent, if you will, U.S., threshold or target, to be under 70 milligrams per deciliter. And it's not for a lack of ability to do it's just that it's not happening. They're not being prescribed the high-intensity statins. They're not being prescribed the non-statin therapy that, – as I mentioned, we'll talk about, has been shown to be beneficial. And so, in a variety of

registries, one the GOULD registry – the two-year data just published that and just following individuals. You know, again, it was under half of patients, had an LDL cholesterol under 70. And so, there's a lot of clinical inertia out there, which is really a shame, because we have these therapies and yet they're not being used.

Dr. Chapa:
I totally agree, and it's the same thing, I think, in any discipline, whether it's, you know, internal medicine, family medicine, cardiovascular health, OB/GYN for me. We have guidelines, and it's just so hard for us, for a variety of reasons, as you very well stated to get there, which again, goes into my next point, is especially for these patients, that we're the most concerned about, and the ones that give us the most, fear and worry are those patients who have already had a cardiovascular event, like a myocardial infarction. So if we're not meeting these goals, what does that mean as the risk factor for a cardiovascular event, in the early period after somebody's had one of these issues, like an MI? What's their risk of having another one if we're not meeting these guidelines?

Dr. Sabatine:
Yep. Unfortunately, it's simply too high, and we know that patients are at risk after they have an event for a variety of reasons. One – having the event just already puts them in a higher risk group. In the setting of a myocardial infarction, there can be a increased degree of inflammation that can lead to plaque instability and a higher risk of plaque rupture,– in the near term. And so, looking at the risk for events, in the next year or two after the MI, that a sizable proportion of patients I'd say ten to fifteen percent of patients are going to have another myocardial infarction, or a stroke, or a cardiovascular death, or need some type of cardiovascular revascularization.

We have the tools to prevent this, and yet the patients remain undertreated, and we're seeing that the event rates are high. You know, these are serious conditions, which do require, attention to the therapeutic regimen.

Dr. Chapa:
That's a great reminder, we've really got to do much better, in getting where we need to be, specifically with regards to lowering LDL cholesterol.

For those of you just tuning in, you're listening to CME on ReachMD, and I'm Dr. Hector Chapa, and here with me to discuss how we can lower LDL cholesterol in patients who have experienced myocardial infarction is really a world leader in this area, Dr. Marc Sabatine.

So, Dr. Sabatine, now that we have a better understanding of a patient's cardiovascular risk after myocardial infarction, I want to take a look at the data behind some of these new treatment options. What is the data using ezetimibe for cardiovascular risk reduction in the early period after myocardial infarction?

Dr. Sabatine:
Thanks for that question. When we studied this in the IMPROVE-IT trial, which was led by Chris Cannon in our group, and the notion here was to see, would adding a non-statin, LDL cholesterol lowering drug, like ezetimibe, we know it lowered LDL cholesterol. The question is would it make a difference in cardiovascular, events? And so, in the IMPROVE-IT trial,we enrolled over 18,000 patients who had had a recent acute coronary syndrome, within the past 10 days. Their LDL was at least 50 milligrams per deciliter. All of them got background statin therapy. They were all on simvastatin. And then, randomly allocated to get either ezetimibe or not. And so, ezetimibe, first of all, lowered LDL cholesterol levels, we deliberately designed the inclusion criteria in the trial, so that the simvastatin alone arm would achieve an LDL cholesterol of 70 milligrams per deciliter, because that's what the guidelines, had as the new target. And so, we really wanted a twofer, from IMPROVE-IT. First, to show that adding a non-statin to a statin would reduce events, and secondly, to challenge that notion that 70 was the threshold, that there was some sort of hockey stick shaped relationship, that once you got your LDL to 70, there'd be no further benefit. And so, the experimental arm, the simvastatin plus ezetimibe arm then achieved an LDL cholesterol in the mid to low 50, milligrams per deciliter range. And so, with that difference in LDL cholesterol, there was a significant reduction in the risk of cardiovascular events. Now, the magnitude of that reduction was just a 6.4% relative risk reduction.

Now that may seem small, but that's also because the delta – the difference – between the two arms was relatively small, because ezetimibe, as I mentioned, is a relatively weak to moderate LDL cholesterol lowering drug, – and we enrolled patients who already had very low LDL cholesterol levels, you know, far lower than – in practice where, for people with ASCVD, their LDL cholesterol levels are kinda 90-100 milligrams per deciliter. We set a high bar for ourselves, but the magnitude of reduction was exactly what one would expect given the amount of LDL lowering. So people have looked at this relationship with statins and shown that for each millimole per liter – that's close to 40 milligrams per deciliter – each millimole per liter reduction in LDL cholesterol translates to about a 20% or so reduction in clinical events. Because we reduced LDL cholesterol by about a third of that, we saw about a third of that, or, you know, about a 7% risk reduction. So all that was good for reducing risk, and luckily the drug was extremely well-tolerated, so in this large trial, over 18,000 patients, followed for a mean of six years no difference in any of the safety outcomes. LFTs were fine, no gall bladder

related issues, no difference in myopathy between the two arms.

All very reassuring for ezetimibe.

Dr. Chapa:
That's fantastic, and I gotta tell you, I've read many LDL, papers, and there's nothing like hearing it from somebody closely involved with these trials, so I really do appreciate you getting into that. Now I wanna change tracks a little bit, because I wanna zero in on PCSK9 inhibitors. So what does the data for cardiovascular risk reduction in the early period after MI look like for those drugs?

Dr. Sabatine:
Great question. To set the stage, two drugs have been studied in cardiovascular outcomes trials – evolocumab, that we studied in the FOURIER trial, and alirocumab, that was studied in ODYSSEY OUTCOMESFOURIER came out first, in 2017. We studied over 27,000 patients, with a prior MI, prior stroke or PAD. Evolocumab reduced LDL cholesterols by 60% - that's on top of statin therapy. We got a patient down, on average, to LDL cholesterol levels of 30 milligrams per deciliter – the lowest of any cardiovascular outcomes trial that's been done to date. So, amazingly low levels of LDL cholesterol. This then translated into, highly significant reductions in cardiovascularevents. The 15% reduction in a broad, primary endpoint, and more importantly, a 20% reduction in the risk of CV death, MI or stroke. I'll also point out that as has been well-documented for statins, that the benefit of LDL cholesterol lowering grows with time, and we saw, for example 16% reduction in CV death, MI or stroke in the first year, but beyond the first year, there was a 25% risk reduction. And so that probably more closely approximates the benefit that would be seen long-term with such therapy.

As I mentioned, the other trial was ODYSSEY OUTCOMES. That looked at patients with an acute coronary syndrome, anywhere from one to twelve month earlier. It too reduced LDL cholesterol levels, in their case, down to about 40 milligrams per deciliter. Also showed a significant reduction in major adverse cardiovascular events, a 15% reduction. And for a trial that went longer, our median follow-up was only 2.2 years – theirs was closer to 3 years, a nominal reduction in all-cause mortality. So overall, for these two very large trials, you know, in toto, over 40,000 patients in the trials, highly significant reductions in major adverse cardiovascular events.

And the flipside, for safety, very reassuring data. So no imbalances for serious adverse events, allergic reactions. Slight excess of injection site reactions, not unexpected for an injectable drug, but relatively modest, and then for the some of the adverse events that, rightly or wrongly, we worry about with statins and/or with LDL cholesterol lowering, no difference in myositis, elevated aminotransferases, cataracts, new onset diabetes, neurocognitive – all very reassuring for all of that.

Now, before getting into the recent MI, I will comment on what I think is my favorite subgroup from the trial. That's the 2,000 patients from FOURIER who came in with a baseline LDL cholesterol under 70 milligrams per deciliter. Now, as we discussed earlier, those would be patients who, per the current U.S. guidelines, we'd say they don't need any further therapy, beyond a statin, because they're under this artificial bar here of 70 milligrams per deciliter. In this group here, their median was 66 milligrams per deciliter. Evolocumab dropped the LDL cholesterol levels by over 60%, so the achieved LDL cholesterol, in the evolocumab arm was a median of 21 milligrams per deciliter. So amazingly low levels, and the question is, "Did these patients benefit?" And the answer is yes. And they enjoyed just as much clinical benefit as their counterparts who came in with higher levels of LDL cholesterol. So, 30% reduction in CV death, MI or stroke in these individuals, so I think these data point to the fact that the U.S. guidelines really are too conservative, and that having this threshold of 70 for treatment is not supported by the data. Patients who are under 70 can benefit from further LDL cholesterol lowering, and – and in fact, in analyses we did, looking at the association now, between achieved LDL cholesterol and the risk of CV death, MI or strokes, so using FOURIER like a Framingham art study as an observational cohort now, there was a monotonic, nearly linear relationship. The lower the LDL cholesterol, the lower the risk of CV death, MI or stroke. And it was not the hockey stick shape relationship. It was essentially a straight line going all the way down, even to LDL cholesterol levels in the teens. And likewise, for those who achieved LDL cholesterol levels below 20 milligrams per deciliter, no excess risk for any of the safety events. So really, I think very powerful and reassuring data for lowering LDL cholesterol.

Now you asked a great question: What about those who are closest to their MI? We talked earlier about how those individuals are at higher risk for events, and that's what we saw in FOURIER. So for individuals, within the first year from their MI, their risk was higher, and their benefit, tended to be greater. Their relative risk reduction for CV death, MI or stroke was 25%. So reducing the risk of events by a quarter, and given the higher baseline risk at 3% absolute decrease, over three years, so meaning a number needed to treat, to prevent a cardiovascular death, MI or stroke of only 32 patients, treated for three years.

Dr. Chapa:
And that's a big thing. We always know number needed to treat, and that's an incredible that means that's good to know, because usually you get a one in 200, one in 300, but this is really striking numbers. Now I also want to talk about initiation of this therapy. So we know that some of these medications, of course, can be started in a hospital setting. But what about the PCSK9 inhibitors? Is there any evidence for PCSK9 inhibitor initiation in the hospital setting?

Dr. Sabatine:
Yeah, well that's another great question, because, you know, when we do these large cardiovascular outcomes trials, in general, it's prudent to study stable patients, at least for the first big outcomes trial, and that's what was done in – in both FOURIER and ODYSSEY OUTCOMES, where we waited for patients to be at least four weeks out from their acute coronary syndromes, or, you know, after the dust has settled, if you will. But, there's really no reason why one would think that the benefit wouldn't start accruing immediately in these individuals, and so several studies have looked at that. One is the EVOPACS trial led by Francois Mach and colleagues from Europe. They looked at several hundred patients with an acute coronary syndrome, and randomized them, right during their ACS, which is a wonderful time to look at these patients – sort of a intervenable, teachable moment. And so, all patients got background therapy of atorvastatin, 40 milligrams, so a high-intensity statin. And then, one arm got placebo and the other got evolocumab added to it, and then looked at what the changes were in LDL cholesterol. As one might imagine, the group that got evolocumab then had much lower levels of LDL cholesterol. The group without it, their LDL cholesterols were in sort of the 80 milligrams per deciliter range. It's actually somewhat better than what we see in the United States, because not everyone's on a high-intensity statin. But it still doesn't even meet the U.S. target, and certainly doesn't meet the European target, whereas in the arm that got evolocumab, right by week four, already their LDL cholesterol was down to about 30 milligrams per deciliter, and so, you know, they would then get the levels down to what not only the U.S. but also the European guidelines would recommend, and if you analyze the data that way, in terms of what fraction of the patients then fall into that bin. If you're just treated with a high-intensity statin then only about a third or so achieve the U.S. target and only about 10% achieve the European target of under 55 milligrams per deciliter. But, if you add a PCSK9 inhibitor, then that's greater than 90% for both targets. So, very, very striking data there.

Dr. Chapa:
Incredible. Alright, Dr. Sabatine, as we are rounding the bend here, coming towards the end of our time together, I really want you to bring this all together. So, can you summarize key management steps for clinicians treating LDL-C, and what specifically should they be telling their patients about LDL-C after a myocardial infarction?

Dr. Sabatine:
Happy to summarize it. These are such important points. So, I think if one were to have one take home point, it really is that for LDL cholesterol, lowest for longest is best. You really can't get it too lowand the longer you have it low, the better the outcomes, and we didn't get into that today, but you can see that for plaque progression on imaging studies, and we see it for clinical outcomes. So, that translates into early intensive lowering of LDL cholesterol. Certainly, our foundation remains high-intensity statin therapy. You know, that can give your patients about a 50% reduction. But then, to achieve the targets that we've shown are beneficial for patients one is likely going to need to add non-statin therapy. And we've talked about ezetimibe, which lowers LDL cholesterol by about 24%, and then the PCSK9 inhibitors – evolocumab, alirocumab – which lower LDL cholesterol by about 60%. And so, both of those classes have been shown to further reduce cardiovascular risk in these patients. And then, as we think about – from a patient centric point of view, it's so important to tell them why lowering LDL cholesterol is important, to help, keep their arteries open, to prevent the risk of heart attack and stroke and to remind them that LDL cholesterol lowering therapies are a lifelong therapy. I'm always struck by how, for our patients, we take care of them when they come in with their acute coronary syndrome, we put them on these medications, they go home and, a month later, three months later, they're on the phone with the clinic, saying, "I feel great now. Do I really need to be on these medications?" Well, you know, hypercholesterolemia, like hypertension – it's a silent killer. You're not symptomatic with it, but it is a killer, and they need to stay on these therapies, and by doing so, they will live longer and they'll feel better.

Dr. Chapa:
Well, I definitely learned something, and honestly, Dr. Sabatine, it's been an incredible pleasure talking with somebody who's just so knowledgeable and so closely tied to these trials. I've really enjoyed this time together.

So with those important management strategies in mind, I'd like to thank my guest, Dr. Marc Sabatine, for speaking with me and our ReachMD audience. Dr. Sabatine, an incredible program. Thank you for your leadership in this area and for your time.

Dr. Sabatine:
It was an absolute pleasure to be here today.

Announcer Close:
This activity was brought to you by Voxmedia and was supported by an educational donation from Amgen. To receive your free CME credit or to download this activity, go to ReachMD.com/CME. This is CME on ReachMD. Be part of the Knowledge.