Pradeep Nataraj: 00:16 Thank you all for joining this podcast episode about the 2018 ACC AHA cholesterol guidelines. Today we're going to focus specifically on the role of statins for cardiovascular disease prevention as well as new incorporation of some non-statin cholesterol-lowering medications in these new guidelines.

Pradeep Nataraj: 00:32 My name is Pradeep Natarajan and I'm coming to you from Massachusetts General Hospital and Harvard Medical School. I'm delighted to be joined by Dr. Erin Michos from the Johns Hopkins school of medicine and Dr. Amit Khera from UT Southwestern Medical School.

Pradeep Nataraj: 00:45 Erin and Amit, thank you very much for joining me in this discussion, and let's get started with the questions.

Pradeep Nataraj: 00:51 So Amit, statins have been the mainstay for our clinical armament for cardiovascular disease prevention for decades. In the primary prevention category, use of these statins now appears to permit more shared decision making in selected scenarios, particularly for those with intermediate and borderline risk. Can you generally describe these new changes?

Amit Khera: 01:11 Yep, thanks Pradeep. Thanks so much for the opportunity to participate today. You know, the cholesterol guidelines in 2018 and the new 2019 primary prevention guidelines both really highlight this term shared decision making. What I'll state is that in secondary prevention, while still important, it's a bit different. In primary prevention, we have to acknowledge that we're looking at efficacy, the benefit of these therapies, but there are always side effects, and that balances is little bit more balanced, if you will. And that's where the patient's viewpoint on it becomes important.

Amit Khera: 01:39 One other point to that is, we also realize that a lot of this is based on risk, and there's uncertainty regarding risk. These tools we have aren't perfect, and I'm sure we'll talk about that. So we have to acknowledge that in talking to patients. And the third thing is adherence, that although
we prescribe these things, if patients aren't taking them and have some reluctance, and if we're not taking their thoughts in mind, then ultimately we don't get implementation and that's the ultimate goal.

Pradeep Nataraj: 02:02 Amit, thanks so much for summarizing. I think there was stronger recommendations in the 2013 guidelines for these risk categories, but the introduction of emphasis on shared decision making to help with that decision is new and I think important.

Pradeep Nataraj: 02:15 Erin, do you have a sense for why there was now formalizing shared decision making in these 2018 guidelines, or at least increased emphasis?

Erin Michos: 02:23 Yeah, so I wanted to point out that the 2013 cholesterol guidelines are really a paradigm shift that changed from targeting predominantly LDL targets to focusing, instead, making decisions based on absolute risk. And this new risk calculator, the Pooled Cohort equation, was introduced then. And I think clinicians, and often patients, are uncomfortable with change. People were used to treatment targets for thresholds for other things in medicine like blood pressure. Patients and doctors and electronic medical records like numbers. And I think there became some discomfort with relying too heavily on the Pooled Cohort equations for making risk-based decisions in primary prevention because it came to light, this calculator is known to both overestimate and underestimate risk in certain populations. And so while absolute risk is still critically important because we want to identify patients at risk enough to merit treatment, but we also want to minimize harm from over treatment in people who are unlikely to benefit.

Erin Michos: 03:18 And so I think what's nice about the 2018 guidelines is there's nice hybrid between focusing on absolute risk and also bringing back the concepts of LDL thresholds when additional non-statin therapies might be considered. And really it brings into light this uncertainty about the calculator and allows for more personalized shared decision making by considering additional risk-enhancing factors to guide decisions about preventative interventions. And for primary prevention, if risk was still
uncertain, the use of coronary artery calcium scores. And so this is where the conversation with patients really becomes critically important.

Pradeep Nataraj: 03:54 Erin and Amit, you both bring up excellent points I think about the imprecision of the risk calculators and using that to help in the discussion with patients.

Pradeep Nataraj: 04:03 Now Amit, some cost-effectiveness analyses suggest you may be able to go the extreme. Identify statin candidates just by age, and not use other risk factors. And that actually may be more cost effective. These guidelines obviously don’t endorse that catch-all approach. But can you speak a little bit more about reconciling clinical benefit, public health costs, individual preferences, and individual out-of-pocket-costs?

Amit Khera: 04:28 Yeah. I think you used the word really correctly there. The idea of this reconciling. And I don't want to use the word tension exactly, but there is a little bit of a trade off when we talk about public health and then this sort of personalized decision making or personalized health.

Amit Khera: 04:39 And what I mean by that is, a lot of these cost effectiveness analysis, or most analysis is looking at effectiveness of therapy reducing events. "Treat all," whether you use an age approach or even when we look at a "treat all" approach, you'll lower the most events because in a selective treatment, you're going to treat fewer people so by definition, you'll have prevented fewer events. The thing about all those things, and I'll speak specifically to this age as a threshold, the one thing about cost effective analysis in terms of what goes in the model, a big variable is something called disutility. Which is essentially the patient, what harm comes from the patient whether that's psychologic angst or they're not wanting to take this medicine. We can't downplay that. Patients, certainly it bothers them, for right or for wrong, about taking certain medications and there's a disutility penalty.

Amit Khera: 05:25 Now whenever disutility's brought into these analysis, the patient's viewpoint, then these cost effective analysis may change. For example, in one a "treat all" was better, but then with taking in account disutility, adding a coronary
calcium selective strategy was more cost effective. So the take home point comes back to shared decision making, that we are trading off a "treat all" where you may lower the most events, but we're paying a penalty about the patient's wishes and perceived and personal side effects. And that's the balance or the nexus we're trying to find.

Pradeep Nataraj: 05:55 Erin, Amit brought up an excellent point about disutility in statins. And a big reason in my experience in generally that patients in general are hesitant to start statins or stop statins is side effects that they may be attributing to statins. The term statin intolerance was previously used, and now statin-associated side effects is preferred, and this new term of statin associated muscle symptoms, or SAMS, why the change in terminology? And how do you discuss these issues of statin-associated risk with your patients?

Erin Michos: 06:26 Yeah. So it's really important to emphasize again that statins are both effective and generally safe. And then actually severe muscle damage, a clinical rhabdomyolysis, is incredibly rare, like .1% of patients.

Erin Michos: 06:40 People, I think, confuse intolerance with allergy. And actually many people who have muscle-associated symptoms were actually able to tolerate a statin rechallenge with an alternate statin or an alternative regimen such as reducing the dose of the statin and combining it with a non-statin like ezetimibe. So I think the word intolerance, we've moved away from this because many people can tolerate some form of statins. And really focusing on muscle-related symptoms, it's important to note that much of the symptomatic adverse events attributed to statin therapy is actually misattribution as we see in placebo-controlled trials.

Erin Michos: 07:18 The guidelines emphasize that all statin-associated symptoms should be comprehensively assessed, look for other non-statin etiologies for the muscle symptoms and predisposing factors. That's why in my patients again it's important to counsel them about that. We try to do statin holidays and do rechallenges with different statins. I start low, I've used alternate regimens such as rosuvastatin maybe three days a week, alternating with ezetimibe. But
most patients who have reported history of statin intolerance can take some form of a statin.

Pradeep Nataraj: 07:52 Amit, anything you'd like to add and do you ever routinely do CKs or LFTs after starting a statin? Or are there certain scenarios that you think about that?

Amit Khera: 08:01 Yeah. This is incredibly important because statin associated muscle symptoms are something that we all encounter frequently and end up being the bane of our existence in terms of trying to counsel. And the subjective nature of it is part of the challenge.

Amit Khera: 08:13 The point about checking biomarkers, if you will, CK and LFTs, are really assessing of any harm. So I don't check CK levels essentially almost ever, unless there's significant muscle symptoms. And I think the guidelines do endorse that if you do have significant muscle symptoms, it's reasonable. But I don't routinely check them because I find them to be more confusing than helpful.

Amit Khera: 08:31 Liver function tests, as we all know... I always like to remind people that the FDA told us years ago we don't need to routinely check liver function tests, as was mentioned with Erin as well. That these things are exceedingly rare to cause fatal or concerning liver problems. However, I do check them at baseline partly because many people have fatty liver disease, and understanding about that is helpful.

Amit Khera: 08:49 Also, in their risk overall, understanding the risk portfolio and metabolic portfolio, you know I don't routinely monitor liver function tests, but I may check them as I mentioned at baseline. And occasionally I'll check them once beyond that if they're elevated to begin with, only to see if there's a marked increment. If they're only modestly elevated, I don't worry about it at all. Two to three times the upper of limit of normal, I don't worry about it at all. And as others know, there's some data even in people with fatty liver disease that there's further improvement in their liver biomarkers with statins. So I don't routinely monitor them regularly as is endorsed by the guidelines. And I think the most important thing we can tell people is that fatal liver problems, severe liver problems, are
exceedingly rare, and that's something that we're as concerned about as we were when statins first came out.

Pradeep Nataraj: 09:33 Excellent. Let's now transition to non-statins because this is new for these guidelines. Erin, the 2013 guidelines, there wasn't that much emphasis on non-statin lipid lowering medicines because there wasn't really supportive clinical trial data at the time. So now what are the new recommendations for the 2018 guidelines with respect to non-statins?

Erin Michos: 09:54 Right. I want to remind the audience that IMPROVE-IT with ezetimibe was published in 2015, after the 2013 guidelines, and for PCSK9 inhibitors, we have FOURIER in 2017 and ODYSSEY 2018. So this was all new evidence from the prior guidelines.

Erin Michos: 10:10 So the 2018 cholesterol guidelines actually breaks secondary prevention into two categories. I think we'll talk a little bit more about that in people at very high ASCVD risk, atherosclerotic cardiovascular disease risk, and secondary prevention individuals who are more stable, who are not at very high risk. And so there's a different level of evidence of adding non-statin therapy based on that risk category. So they're all secondary prevention. For adults 40 to 75, high intensity statins is still a Class One recommendation with the goal of lowering LDL cholesterol by greater than 50%.

Erin Michos: 10:46 Now in somebody who is stable and not at very high risk, if their LDL-C threshold is still above 70 on the maximally tolerated statin, it is a 2B indication, may be considered to add ezetimibe. However, in very high-risk individuals, secondary prevention of very high risk, if the LDL threshold is still above 70 on the maximum tolerated statin, it's actually a 2A indication to add ezetimibe. And in these very high risk individuals, if you're on a high intensity statin and they recommend adding ezetimibe first, but if your LDL-C is still above 70, than PCSK9 inhibitors may be reasonable with a 2A indication.

Pradeep Nataraj: 11:32 Excellent, thanks so much for summarizing.
Pradeep Nataraj: 11:34 Now Amit, Erin touched upon some of the trial names. But can you summarize the evidence and why do we now include ezetimibe and PCSK9 inhibitors for cardiovascular disease prevention in these guidelines? And is the data sufficient to justify its incorporation in these guidelines?

Amit Khera: 11:51 Yeah. If you really look, a lot of people sort of say, "What's new from 2013 to 2018?" And I think you hit upon a really important concept of shared decision making and some additional tools. And I think the next big thing, in my view, was the addition of non-statin agents. And part of that is just evolution, that we've had a lot of new data, as Erin laid out nicely, since 2013. And so I do think they certainly are ample data to warrant including these new drugs, new agents into the guidelines.

Amit Khera: 12:18 I think the crux which people can quibble over is how they incorporated 2A versus 2B. And I think as Erin mentioned, there's this parsing of very high risk and high risk. In my opinion, I like that because it tells us who may benefit the most and who gets the most absolute risk reduction as we get diminishing returns with additional agents.

Amit Khera: 12:36 But the second part of that is this idea of 2A, 2B and the sequential nature of ezetimibe first and then PCSK9. I think there was ample nature because we know that there's significant residual risk. You always remind people that even if you... statins cut risk in half, if you will, you still have half the risk on the table. You haven't eliminated the problem in those with residual dyslipidemia, LDLs above 70 still have sufficient risk where additional agents can be helpful.

Amit Khera: 13:00 I think the nuances come in what order can be helpful. I think the nuances come in what order, level of evidence, and how those things were decided.

Pradeep Nataraj: 13:07 Great. Now, Amit and Erin, you both brought up this new term, very high-risk atherosclerotic cardiovascular disease, this new subset that's introduced in these guidelines. Erin, do you mind just giving us a working definition of what that is and what are your thoughts of now including that subset and why not just treated everybody who has athero as aggressively as possible?
Erin Michos: 13:28 Right. This is a really good question. Again, it all gets back to trying to find the people at the highest absolute risk because they benefit the most with the most aggressive therapy. You have much lower number to treat and you get more value for those cost dollars, so very high risk secondary prevention patients are patients that have had a recent acute coronary syndrome within the past 12 months.

Erin Michos: 13:52 They have a history of multiple MIs, a history of ischemic stroke with additional risk factors or they have symptomatic peripheral arterial disease. Having one of those features, having one major ASCV event and multiple high-risk conditions such as being over the age of 65 or having heterozygous familial hypercholesterolemia or having diabetes CKD, still having an LDLC above 100 despite being a maximum tolerated statin, all of these features enhance an individual's risk. We see this from secondary analysis from the trials that these higher risk individuals benefit the most.

Erin Michos: 14:32 The Fourier trial enrolled individuals with stable atherosclerotic cardiovascular disease, but you see in Fourier that evolocumab benefited more among individuals who had higher risk features, such as having a recent MI within the past two years, having more than two prior myocardial infarctions, having multivessel disease. There is both a greater relative and absolute benefit with evolocumab among this subset. Similarly, Fourier saw this with peripheral arterial disease, that individuals who had PAD also derived both greater absolute and relative benefit. When you're thinking about something that has additional cost, additional burden, who is going to benefit the most, parsing out these secondary prevention patients that are the highest risk.

Erin Michos: 15:19 Someone who's in your CCU with acute coronary syndrome is a very different phenotype than someone who had stable ischemic heart disease that maybe had a stent 5 to 10 years ago and is doing really well, and so understanding that and making treatment recommendations.
Amit Khera: 15:34 I was going to add something there. I just think this is such an important concept. It's new, but it's probably not new intuitively that amongst all patients with ASCV they're not the same. I think that's so important in practice. For example, in patients who are very high risk, as Erin laid out nicely, we have to realize those people you can't just use your usual playbook and put your high-intensity statin and kind of put your rubber stamp and say everything's fine and not appreciate that we have to think beyond that and because more aggressive because they are certainly not the same as someone who's had a stent 20 years ago and has had no recurrent events.

Amit Khera: 16:05 The reason that becomes even more important is when you're counseling a patient, you're saying we should add this or can't add that, and they're asking, "Well, how much bang for my buck do I get? What's the added value?" For that patient who's stable, that has had no problems for years, whose LDL may be 71, that's going to be a very different benefit that they'll get.

Amit Khera: 16:22 Someone who's very high risk with an LDL that's significantly higher, for example, in IMPROVE-IT you have to treat about 50 patients for seven years for one very large composite of many things. In people who are much lower risk than that there would be a much higher number needed to treat and less efficiency. I do think this is an important concept we don't think about enough.

Pradeep Nataraj: 16:42 Yeah. I think as part of the calculus of PCSK9 inhibitors and these new guidelines it's at the individual level who do you anticipate is going to maximally benefit, but the other piece of it is the cost of the medicines. Amit, let's come back to cost effectiveness because this concept is very new in these 2018 guidelines. I did word search of cost in the 2013 guidelines. It was talking about the favorable economic impact of statins, but now there's particular emphasis of cost effectiveness as it relates to PCSK9 inhibitors. There's a recommendation for us to think about this when prescribing these medicines, but it is a challenging concept when treating individual patients and having that in shared decision making, where the patient is also involved in these decisions. Will this value statement
that's in the 2018 guidelines, regarding PCSK9 inhibitors, actually change how you care for individual patients?

Amit Khera: 17:37 Yeah, I'm glad you brought this up because certainly people will notice this cost statement. I will mention, I don't recall the year, maybe it was 2014 or something, the ACHCA came out with a nice document that laid out how they would incorporate cost-effectiveness value statements in all of their guidelines. That was something that maybe wasn't there in 2013, but is beyond just cholesterol prevention, but really will pervade all of our guidelines to the extent that those data are available.

Amit Khera: 18:01 I do think in concept this is important, for us as healthcare professionals, when we're talking to patients or even thinking about treatments as gatekeepers on these a little bit, we do need to at least be aware of the relative value and cost of these different agents, so that we're using them most judiciously and for the people who can benefit the most. This is a little bit of a tricky area. As you know well, one of the challenges as this guideline is being written, things are changing by the minute. For example, a week or two before the guidelines came out the cost had dropped in half for at least one agent and now it's down in half for both.

Amit Khera: 18:35 These numbers around cost effectiveness are moving rapidly, and those involve both cost of the agent itself and also which groups that we're talking about. We've talked a lot about very high risk and can we call out the highest risk, so I think that's the challenge here. Also, we all know that there can be variabilities. There have been multiple studies looking at PCSK9 cost effectiveness, and they don't all come up with the same answer. A lot of this is modeling and how one does that. It is safe to say that PCSK9 inhibitors can be costly drugs, and so we have to be aware of that. I think in concept it's important to be aware of that in thinking about how to describe them to those who would benefit the most and have the most value.

Amit Khera: 19:11 I think in practice about putting the pen to paper and making these analyses is a little bit more challenging. Particularly since there's moving targets with the data and cost evolving.
Pradeep Nataraj: 19:22 Great. Now, Erin, assuming you're able to get a PCSK9 inhibitor approved for a patient, the cost or at least a proportion of the cost get often transferred to the patients. For some of them, the out-of-pocket costs can be high for them. Can you speak to this? Do you think about the out-of-pocket costs when thinking about the prescription? What's the relationship of these costs to the patients and their adherence?

Erin Michos: 19:44 Absolutely. There was a paper by Dr. Navar in JAMA Cardiology that found in the first year of availability in only half the patients who have been prescribed a PCSK9 inhibitor actually got approved. A third of those that had an approved prescription never ended up filling it due to copay. It's a real issue, even with the reduction in cost from about $14,000 a year to a little under $6,000 a year. They still expensive. At least, it helps, for of all, to work in a place or have access to a lipid center or a specialist pharmacist that can really help you.

Erin Michos: 20:17 Having a specialist who's really skilled in these pre-authorizations, that does it a lot, that can assist in the forms and the submission of appeal letters and patient access, one person that's sort of trained to do that, they get much better at getting this approved. Working closely with your specialist pharmacy, outsourcing the specialty pharmacies that they can help with the cost shopping around. I would encourage patients to shop around for the lowest price. There are some issues related to this new lower pricing with the PCSK9 inhibitors are linked to these new national drug codes, and if patients were prescribed the medicine before the price cut, the 60% reduction, with the original national drug codes the new prices may not be tied to their prescriptions.

Erin Michos: 20:59 It's important for patients to work with their pharmacies and find out if their out-of-pocket cost would be lower under these new national drug codes, and to shop around at different pharmacies for the lowest price, and hopefully fill these at more competitive cost.

Pradeep Nataraj: 21:15 Fantastic. Now, Amit, let's switch to a nuanced one that I found interesting. Ezetimibe is only FDA approved for cholesterol lowering for those with primary
hypercholesterolemia, but now we're recommending in these guidelines for its use in secondary prevention, including before considering a PCSK9 inhibitor, which are actually FDA approved for cholesterol lowering and for cardiovascular disease prevention. Do you agree with ezetimibe for secondary prevention and do you support its use before PCSK9 inhibitors?

Amit Khera: 21:46 Well, I think there’s a few different points in that question. The first is just FDA approval and how that impacts our thought, and then the second is just the step wise course that was endorsed. In terms of FDA approval, fortunately, we’re talking about both agents that are FDA approved for some indication, meaning the balance of harm and benefit and looking at the total portfolio around the drugs were felt to be appropriate for FDA approval. Then you get in the nuance of what’s the very specific indication. We both know that there’s, and as mentioned by Erin, there is randomized trial data. That's where essentially ezetimibe has been looked at with Improve It or outcomes looking at a secondary prevention high-risk population.

Amit Khera: 22:22 We certainly see risk reduction. Per our conversation, that risk reduction is modest, so we have to pick it in the right patients. I'd worry a little less about FDA approval. As an anecdote, I know we were just talking now we use amiodarone all the time for a-fib and it's not FDA approved for a-fib, but we do it because it's FDA approved in general for other arrhythmias. That worries me a little less about that nuance, but I do think the guideline directors had to come up with a guidance as to what to do. They had elected to say ezetimibe first and PCSK9 second.

Amit Khera: 22:50 If you look at the logic behind that, and I certainly appreciate the logic, was one that the cost issue, which certainly cannot be ignored. The second was at the time, at least, the feeling was PCSK9 was evolving and we had less experience. Certainly, it was a new delivery mechanism with a shot versus pills, so there's sort of lots of thoughts that went into that stepwise approach. My view is that people that have really high LDL levels, so I'm sure we'll talk later about familial hypercholesterolemia, but part of it's a math issue. If we're trying to achieve a low enough LDL you know you'll never get there in some
patients with ezetimibe. You can just do the math about lowering. Then those patient it seems to be a little bit of a wasted step to have to do that stepwise first of ezetimibe and then PCSK9. I don't think the guideline writers were talking to those smaller proportion of population. I think they're looking at, by and large, they didn't want overuse of PCSK9 when ezetimibe may be reasonable for many. I appreciate the point there, but they're are some nuances about specific sets where maybe that stepwise approach isn't as efficient.

Pradeep Nataraj:   23:48 Great. Erin, statins obviously are frequently prescribed in the hospital for ACS management or acute coronary syndrome management. Are there scenarios where you would recommend a new inpatient ezetimibe prescription?

Erin Michos:  24:00 Yeah. I mean keep in mind in the Improve It trial that we talked about, that forms a lot of our sort of evidence for ezetimibe, these are patients with acute coronary syndrome within the preceding 10 days. They were fresh ACS patients. I think that the setting of being admitted with an acute myocardial infarction is a vulnerable time and a time that represents an opportunity for action. I think that there is some data suggesting adherence is increased with medications when they're initiated in the hospital versus in the outpatient setting.

Erin Michos:  24:31 Now, of course, if they came in not on a statin at the time of their event I probably would just start the statin first, but many patients have had recurrent events or perhaps they're already on a statin. Maybe they're even on a high intensity statin. These patients I would certain consider adding ezetimibe in the inpatient setting before they go home to intensify their LDL lowering therapy. Again, this is an actual time that while they're spending these hours with you in your CCU you can tailor patient education, do pre-discharge planning, this is a good time to optimize patient adherence, to explain about these medications, and teaching. I think it's a good window of opportunity to get patients on appropriate therapy if indicated.
Pradeep Nataraj: 25:16 Amit, before you start ezetimibe do you talk to patients about potential side effects? If so, what do you talk to them about?

Amit Khera: 25:22 Yeah. It's always an important part of a conversation to talk about potential side effects. The short answer is there are very few. It's important for us to remind ourselves as clinicians ezetimibe is absorbed. It's metabolized, and then it's excreted, and then it's active. Unlike bile acid sequestrants, that predominantly stay in the gut, this is a systemic medication first. If you look in the package insert it's a little bit vague to call these out, but clinically you can occasionally see mild LFT abnormalities in conjunction with statins, and occasionally you might ... at least clinically, people will report some muscle symptoms, but those are pretty rare and infrequent. I don't find any severe or concerning side effects, but what is important to tell them is that the efficacy is modest, so we have to appreciate that. It does lower LDL, just modestly.

Amit Khera: 26:00 Efficacy is modest, so we have to appreciate that. It does lower LDL just modestly, so that's an important part of the conversation as to what to anticipate as well.

Pradeep Nataraj: 26:08 Now Erin, I find that from a lot of colleague's reluctance to prescribing PCSK9 inhibitors because it's an injectable, they don't have a good handle on what the side effects would be. When you're starting PCSK9 inhibitors on patients, what do you counsel them about the injection, about side effects?

Erin Michos: 26:25 Yeah, so both in a Fourier and Odyssey trial, we have about two and a half years worth of data. These are actually very safe and sort of clean medications. Some of the more common things are redness, itching, swelling, maybe a little tenderness at the injection site. This was slightly higher in the trials with the PCSK9 inhibitor compared to the placebo. Some patients will report flu-like symptoms or maybe some tenderness at the injection sites. Some of the really big things that people have worried about and worried about with statins, for example, we don't see. There has not been a signal for new onset diabetes with PCSK9 inhibitors. Similarly, the trials have not shown any excess in their cataracts,
neurocognitive decline, hemorrhagic stroke, all of the big things. They really have really a good safety profile. I reassure patients of the safety, and I do talk to them a little bit. We do training and teaching about how to do the injections. Even in the trials it was really, we were only talking about 2% or so people that had significant problems at the injection site.

Pradeep Nataraj: 27:27 Great. Now let’s switch over to primary prevention and Ahmed, you mentioned familial hypercholesterolemia. In these guidelines, PCSK9 inhibitors are felt to be reasonable as necessary. There’s a weaker 2B recommendation to target LDL cholesterol less than a 100 if the baseline LDL cholesterol is greater than 190 and there’s heterozygous familial hypercholesterolemia or FH. It’s also okay to target an LDL less than 130 if the baseline LDL is greater than 220. Why is there an actual distinction for heterozygous FH now?

Amit Khera: 27:59 Yeah, thanks Pradeep, I’ll be frank with you. I find that section of the guidelines to be a bit confusing and the nuances about LDL levels and where they start and where they end. I understand the concept. First, we’ll step back and remind ourselves that people with severe hypercholesterolemia, in the term of LDL above 190 do have a significantly increased risk. I know Don Lloyd Jones Group published a nice paper years ago, and they have a three to five fold increased risk over a long term follow up, looking at sort of lifetime risk of that phenotype. We also know that amongst those with an LDL above 190 a smaller proportion, your group has published about 2% have a genetic mutation suggestive FH. A small minority of those individuals and people looking at clinical criteria, a modified Dutch Lipid Clinic, only about 7%. Only a small minority above 190 will actually have FH.

Amit Khera: 28:44 As you all published nicely, if you have FH a mutation, a genetic mutation, your risk is incremental for the same LDL level. That may have to do with persistence of LDL since birth, so that sort of LDL gram years over your lifetime exposure may be relevant as to why that’s the case. I think the take home points are that we know in people with severe hypercholesterolemia and FH, they have very high LDL levels and may be on maximally tolerated statins
regardless, note calculating ASCV risk scores. In terms of LDL management, the one question in the FH world in my view, is sort of what LDL's acceptable beyond that. These guidelines, as you mentioned, have various thresholds of a 100. If your LDL starts at above 220, then 130 in terms of when you might add Ezetimibe. Other guidelines say something different.

Amit Khera: 29:27 The European Atherosclerosis Society has a different statement. The NLA has a different statement, and that tells you we just don't know who best warrants additional therapy and when to use PCSK9 at what threshold? I will say that, in this guidelines, if you read the text, they do refer to that there are risk factors amongst people with FH. This is from the Safe Heart Study, whether it be high LPA, a higher residual LDL beforehand, other parameters, and maybe even some imaging parameters that are evolving that help us better target PCSK9 to the right patient. The take home here is that always statins first, and then most, if you just do the math, will have significant residual LDL elevated. Then we have to maybe be more precise about who may benefit most and what exactly should our LDL targets be.

Pradeep Nataraj: 30:09 Great, yeah. Ahmed, you bring up an excellent point about a number of people have severe hypercholesterolemia, a minority have heterozygous FH as diagnosed genetically. Erin, how do you distinguish heterozygous FH among the individuals with severe hypercholesterolemia? Ahmed, brought up genetic testing also some clinical criteria. Do you consider genetic testing? If you do, at what point do you consider that?

Erin Michos: 30:34 Yeah, so FH is relatively common. We think it's about one in 250 individuals. Actually, most of the people in the United States and across the world who do have FH are actually still undiagnosed. It's important to think about, but as you both have brought up, not everybody with an LDLC above 190 has monogenic FH. They're first to look for underlying secondary causes, diets really high in saturated fats, and other causes. But there is a nice kind of a review summary, expert summary that was in JAC, I think, last year about who you consider genetic testing in. I agree with a lot of their points. This panel had recommended it
among adults who have persistently elevated LDL C levels above 190 who don't have an apparent secondary cause of these high cholesterol levels, and who have at least one or more first degree relative who has been affected by premature coronary disease, or adults who have a persistently LDL C level above 250, very high levels, again, without an apparent secondary cause of hypercholesteremia.

Erin Michos: 31:43 They had suggested a class 2A recommendation for considering genetic testing in those. It may also be even considered potentially with sort of weaker evidence with individuals with LDL cholesterols above 160 who have a strong personal or family history. I would consider it in those individuals, especially if they have a very high LDL level and have either a family history, a strong family history, or personal history, if they're in your CCU or with an acute coronary syndrome. You might consider genetic testing in these individuals because of the cascade and the downstream testing of family members once you've identified an FH program.

Pradeep Nataraj: 32:21 Awesome. Ahmed, in summary, what's your general impression of the framework for statins, and non-statin medicines, and these new cholesterol guidelines?

Amit Khera: 32:29 Yeah, I think they're very reasonable. I think, first and foremost, they build on the prior guidelines, which remind us that especially with these non-statin agents predominantly in the secondary prevention group, that we always start with statins first. Those are our backbone. Then we add on these additional therapies and try to target those that are the highest risks, whether that's in secondary prevention that have very high risk as we talked about those parameters that suggest that, or in those in primary prevention that have severe hypercholesterolemia or FH, to really targeting to the right patients. I thought they were appropriate, followed what we're learning from the data. I do think this stepwise approach of Ezetimibe and then PCSK9, in general, is appropriate too. In certain situations with very, very high LDL, again, a smaller subset of the population, things may evolve in terms of thinking on that.
Pradeep Nataraj: 33:13 Erin, what are your thoughts in foreseeing the next iteration of the cholesterol guidelines? Do you foresee other non-statin lipid lowering medicines incorporated?

Erin Michos: 33:21 Yeah, sort of depends when the next cholesterol guidelines come out, because there's a bunch of exciting therapies in the pipeline. One of the main ones now that I've actually started to use more of that is sort of icosapent ethyl. At the meeting in 2018 at AHA when the cholesterol guidelines debuted, at the same meeting, the Reduce-It trial was presented. This was as a trial of statin treated patients at elevated cardiovascular risk, either established cardiovascular disease, or diabetics, patients with multiple risk factors who were fairly well controlled on their statin. They were randomized to icosapent ethyl, which is a high dose purified EPA fish oil at four grams a day versus placebo. I think it kind of shocked a lot of us in the lipid community that this was associated with a 25% reduction in major adverse cardiovascular events with an absolute risk reduction of almost 5% in a number needed to treat of 21. That was quite remarkable.

Erin Michos: 34:18 Then just recently at the 2019 ACC meeting, we saw that the data presented that it not only reduced the first event but subsequent events 30% reduction. I would anticipate, if this is sort of confirmed with more data coming out, that we might see this role especially in patients with still elevated triglycerides, a residual risk from hypertriglyceridemia, this drug maybe even considering. Perhaps other high doses of EPA once we get data from STRENGTH and some of the trials in process. That might be in the new guidelines. Then there's several exciting classes of medicines from Phase II trials that have entered Phase III trials. Depending on whether they show cardiovascular outcome reductions, they might be making an appearance in future guidelines. The ones I'm referring to are like Inclisiran, which is a small interfering RNA that's targeting the PCSK9 messenger RNA.

Erin Michos: 35:11 Again, this was entering now into Phase III trials, cardiovascular outcome trials. We have some data on bempedoic acid, which is an ATP citrate lyase that uprights LDL receptor by reducing cholesterol synthase. That also lowers LDL cholesterol, but we're waiting the big Phase III
trials and clear outcome to see whether it can reduce events. Then, I think, one of the things, and most exciting to me, is therapy targeted at lipoprotein little A, which is a lipid marker that's associated with increased ASCV risks but does not respond to statin therapy. Now, there is an antisense oligonucleotide drug that targets lipoprotein little A's that in Phase II trials appears safe, and can actually reduce lipoprotein little A by up to 90%, which is quite remarkable. That's entering also into Phase III trials for looking at outcomes. Then there's quite a few therapies additionally for triglycerides targeting APOC3 and other markers. I think there's lots of exciting trials going on in the lipids world. Depending on whether these hit the mark, we might see an appearance in future guidelines. It will take a while to confirm their efficacy and their safety.


Erin Michos: 36:32 All right, thank you.

Amit Khera: 36:33 Thanks so much for having us.