ERIN M. KERSHAW: OK, thank you very much and thank you for inviting me to be here today. I'm happy to talk about what has been going on in the world of lipid management. I do want to state that I have a few disclosures. I have served as a consultant for Regeneron and am currently participating in industry sponsored research primarily related to triglyceride management, which is not really the topic of today. My objectives for today are to start with the 2003 ACC AHA guidelines and to take you on a trip on what has happened beyond them. Focusing primarily on the management of hypercholesterolemia with a few brief visits to non-LDL cholesterol targets.

So as we all know, statins have made a huge impact on the treatment of atherosclerotic cardiovascular disease-- which I refer to as a ASCVD-- with multiple studies showing consistent reductions in ASCVD risk by up to 30% to 40%. However, significant, unexplained, untreated residual risk persists. And in addition to the problem with residual risk that exists with optimal statin therapy, we are nowhere near achieving this goal. Of the estimated 108 million people in the United States with hypercholesterolemia, fewer than 2/3 are actually diagnosed, and fewer 2/3 of those are treated, and fewer of 2/3 of those are optimally treated.

Subsides, lack of adequate diagnosis, factors that contribute to suboptimal treatment, are noncompliance, real or perceived statin intolerance, and inadequate response to therapies. So to address some of these issues in 2013, the ACC FEHA issued new lipid guidelines. And these guidelines are a fairly dramatic departure from the previously existing paradigms because they focus almost exclusively on statins, and exclusively on data that was present from randomized controlled trials. So for this reason, they recommended primarily statin intensity rather than treatment targets and nonstatin therapy were not extensively addressed. So just to briefly review those guidelines-- I hope by this point, you guys are all fairly familiar with these because you practice these every day, but the 2013 guidelines basically divided population into four statin benefit groups.

Patients with clinical ASCVD. Patients with LDLs greater than or equal to 190, which are presumably patients with either partial or complete familial hypercholesterolemia. Diabetic patients in the 40 to 75 year age group. And non-diabetic patients without clinic ASCVD in that age group. OK? And basically, then, they decided they recommended either high or moderate dose statins in those groups. And this is the summary of the 2003 guidelines. What they wrote that they suggested is that treatment with statins should result in an expected percent

reduction in LDL cholesterol. And based on where you were in these groups and your results on a pooled risk assessment, they would recommend either high or moderate dose statins. And those statins are listed there.

However, many people and physician groups agreed with or supported particular aspects of the 2013 guidelines. And in particular, there were a couple of things that they liked, which was the emphasis on the superiority of statins for lowering blood cholesterol and ASCVD risk. And the second thing is the reliance on random [INAUDIBLE] controlled trials. However, many lipid lowering therapies exist in our arsenal. Surely, there must be a role for them somewhere in the management of residual risk. For this and other reasons, other people and physician groups acknowledge shortcomings of the 2003 ACC AHA guidelines, notably that several lipid lowering agents had evidence of varying degrees of strength that would support their use in certain clinical situations.

And however, recommendations were not really provided on how to use them in these guidelines. Several specific but relevant situations and or patient groups were not adequately addressed in these guidelines. So while these guidelines were simple and population focused, they did not really provide specific guidance at the individual patient level. And finally, the abandonment of treatment targets, really was confusing and controversial to many. So since the 2013 guidelines, several additional guidelines have been published. Some are different country's guidelines. Some are different body's such as the American College of Endocrinology, etc.

But the body has been most vocal with alternative guidelines has been the National Lipid Association. And the National Lipid Association, what they did was, published in 2015, a very comprehensive document that addresses virtually every situation and anything you could possibly want to know. And they titled it the patient centered management of this lipidemia. And the idea is that this is a comprehensive living document that has hyperlinks to everything, that is updated in real time, and will in the future be updated every year. So these guidelines differ from the ACC guidelines in that they continue to focus on targets. And they do not rely exclusively on a randomly controlled trials.

So I'm not mentioning this because one is better or worse than the other. I just want you to be aware that most of alternative guidelines fall somewhere on the spectrum of these two governing bodies. And I think they're both useful in different situations, which we'll talk about. So they both have really good apps that you can download and use. And in particular, I will

refer you to the Statin Intolerance app from the ACC, because one of the things that I think we all struggle with at the front lines is dealing with patients who are statin intolerant or perceive themselves to be statin intolerant. And that app really provides you with the information that you need to get people on a maximally tolerated statin, which is, no matter what guideline you follow, the number one priority.

So what are the differences between these two guidelines? So the ACC guidelines has what they call the fire and forget approach. It's simple. Its population based. So the goal there is get as many people on the highest dose statin you possibly can. The problem is that at the individual level, there are some specific lack of guidance. And it tends to overtreat in primary prevention and under treat in secondary prevention. Versus the National Association philosophy which is the treat to target, lower is better philosophy. And at the time of the 2013 guidelines, there wasn't any evidence that had specifically tested the treat to target lower is better hypothesis.

However, there was a lot of circumstantial evidence, as you can see here, graphing all of the lipid trials that have been done over the years for either primary or secondary prevention, show a clear relationship between lower LDL, lower cardiovascular risk. So the first study to really address this particular question of what's better, fire and forget versus lower is better, with the IMPROVE-IT trial that was published in June, 2015, in which Ezetimibe was added to maximally tolerated statin in patients with ASCBD who were at high risk. And what they found was that addition of Ezetimibe further lowered LDL by about 24% and resulted in an absolute average LDL of 53, which was much lower than previous studies have shown.

And this study showed significant reduction in both primary and secondary composite endpoints, as well as individual endpoints, with an overall reduced risk of ASCBD risk of about 6% relative risk, 2% absolute risk, over the six year course of the study. So here, for the first time, we had evidence that treatment in addition to a statin is beneficial. Lower is better is beneficial. Which is why the study was so impactful. On the other hand, other studies using other non-statin agents suggested further caution, specifically, I'm sure you've all heard of the 2014 accord lipid [INAUDIBLE] in which [INAUDIBLE] was added to a statin in patients with diabetes who were at high risk for ASCVD events. And it did not improve the outcomes.

Although, it did show, in post-hoc analysis, a possible benefit for a subgroup of patients who were male and had high triglyceride levels. In addition, in 2014, two studies, the Aim High and the HPS To Thrive study, failed to demonstrate a benefit of niacin in combination with maximal

dose statin in preventing ASCVD outcomes. So the real game changer in this debate and reconciling these different philosophies, of course, have been the PCSK9 inhibitors, which have really not been around for long. They first came on the scene in mid-2015 with their locamab and evolocamab. So how did the PCSK9 inhibitors work?

Well, as you know, LDL binds to the LDL receptor in the liver. It's taken up. And then it's recycled to the plasma membrane. There is a molecule that circulates in the blood called PCSK9 that binds to the LDL receptor complex and targets the LDL to the lysozyme for degradation. So if you inhibit this protein, the complex can recycle more and pick up more serum LDL, and so on and so forth, thereby lowering LDL cholesterol. So this has been a very exciting year for PCSK9 inhibitors. We've learned a lot from decades of studying statins and other lipid drugs in terms of how to efficiently and very thoroughly evaluate the efficacy and safety of these drugs.

And the three available PCSK9 inhibitors, [INAUDIBLE], evolocamab, and [INAUDIBLE]-- and don't say those too fast-- have now made it through phase three. And this year, actually, all three of the outcome studies for all three of these will be reported this year. Thus far, two of three have been reported out. And we will go over those. First, I just want to basically review the overall effect, which I'm sure you guys have heard in the news. So in terms of LDL lowering, PCSK9 inhibitors have a very dramatic effect lowering LDL cholesterol by more than 50% to 60%, virtually independent of almost everything else. So whether you give them a loan, whether you give them with a statin, with high or low dose statin, with Ezetimibe whether the patient has a diagnosis of FH or ASCVD.

Whatever the clinical demographics of the patient are, whether they have comorbid illness, whether they're taking with other drugs, and also the effect over time. And this is just an example from the DESCARTES study. Blue is at 12 weeks. Red is at 52 weeks. As you can see, a 50% to 60% lowering, again, whether given with a diet, low or high dose statin, plus or minus Ezetimibe. The other thing is, these drugs also affect on non-LDL cholesterol, positive beneficial effects, raising HDL, lowering triglycerides, and importantly, lowering LPA, which is a very significant risk factor. And notably, it's one of the few if only agents that does so, niacin being the other.

We already know that [INAUDIBLE] study has shown that niacin, overall, is not helpful in addition to a statin. So the first [INAUDIBLE] and safety studies for [INAUDIBLE] and evolocamab came out in 2015. Sister articles published in the *New England Journal of*

Medicine. These agents added to maximally tolerated statined in patients. Initial starting LDLs were around 120. And they lowered them again, consistently, by 50% to 60%. Importantly to LDLs, as low as in the high 40s, 50s on average. I mean, some of these patients in these trials had LDLs in the 30s. And they demonstrated remarkable safety. In addition, for major cardiac adverse events in these studies, both the odyssey long-term with [INAUDIBLE] and [INAUDIBLE] studies with [INAUDIBLE] showed an up to 50% reduction in cardiac events.

And this just blew away the results from previous studies, such as the improvement study that I just presented to you. So what do we really care about? We really care about hard outcomes. And so several studies have been designed for each of these agents. The summary of these studies are here. As I mentioned, the first two report out with a study on [INAUDIBLE] in March 2017 and evolocamab in May 2017. And we're expecting the final one on [INAUDIBLE] in December 2017. I will mention that the first two, [INAUDIBLE] and evolocamab are human antibodies, whereas, [INAUDIBLE] is actually a humanized mouse antibody, which ended up producing ant-antibody antibodies, which subsequently resulted in the early termination of those studies and the removal of [INAUDIBLE] from the market.

Nevertheless, the results of those studies are still important in informing how we treat patients with high cholesterol. So I will first go over those studies, again, reported out in March of this year. The SPIRE one and two studies, they differed based on their initial enrollment criteria. So these were adult patients at high risk for cardiovascular disease. In SPIRE one, the patients had to have a starting cholesterol of between 70 and 100, so already fairly well treated with statin. Versus SPIRE two, where the threshold was greater than 100. So these are patients who had slightly higher cholesterols on statins.

[INAUDIBLE] was the agent of choice. And the primary and secondary endpoints are listed there. So what did these studies show? So basically, the effect on LDL was impressive, as I've previously implied, with, in SPIRE one, reducing LDL from 92 to as low as 38 with an average of 57, or 43% production over seven months. In SPIRE two, LDL at 133 to as low as 58, average of 89, which is a 61% reduction. The results of the SPIRE one, which were terminated early at seven months, did not reach their primary composite endpoints, but did show a reduction in non-fatal CVAs of 48%. However, SPIRE two did show very significant reductions in the primary and secondary composite cardiovascular endpoints as well as individual endpoints, with a reduction in the 20% to 25% range. This benefit was increased.

The lower the LDL, again, supporting the lower is better hypothesis. And it was also improved

over time. Again, the problem with this particular agent was that the effect eventually diminished due to antibodies against the therapy. The next major study to report out in May of this year was the FOURIER trial, which was of evolocamab. Similar study design. The exception is that the enrollment criteria were to have either an LDL above 70-- or equal to 70-- or a non-HDL equal to or greater than 100. Primary and secondary endpoints are noted. Here, we see, again, a pretty significant reduction in LDL from 92 to 30, which is very low, possibly one of the lowest reported in any study to date, about a 59% reduction over just two years.

And they saw, over just that short amount of time, a very significant reduction in primary and secondary composite of cardiovascular outcomes, again, of about 20-ish percent. Again, the benefit was increased with lower LDL, and increased over time, and very few, if any, side effects. So both of these studies were very important not just in demonstrating the efficacy and safety in PCSK9, but more importantly, for supporting the lower is better hypothesis. And it also established thresholds for treatment, because these studies were specifically designed for patients with LDLs at or above specific thresholds of either 70 or 100 for their LDL.

I do want to reiterate, although it's early days for these particular agents, side effects are virtually non-existent. As you can see, in all the studies done, all of the airbars cross the midline. The only one that didn't is SPIRE. And that is because it's a humanized mouse antibody and had immunologic side effects. So in general, very safe. So where does that leave us with the guidelines? So we started in 2003. Now, based on these new data, the ACC has published updated recommendations, which they call, The Expert Consensus Decision Pathway on the Role of Non-Statin Therapies. One update was in 2016. They did another update in 2017.

So in the next couple of slides, I'll just give you a sort of big overview. I know this is a busy slide that most of you probably can't see the details. So in two slides, I'm going to show you the big picture overdue of the updates in 2016, 2017. And then I'll take you through a few slides where I more specifically flesh out examples of what I'm showing in these updates. So the basic gist is we still have the four statin tolerant groups. Group one, which is people with ASCBD, group two, which is greater than 190, people with FH. Group three is your diabetics. Group four is everybody else. So now, goal, treat everyone you can with maximally tolerated statins.

If you get there. What they did first was they divided these groups into risk. And I'm telling you, this is confusing. So they further stratify these groups into high risk and low risk. So for

example, if you have ASCVD, and you're on a maximal statin therapy, you've a reasonable LDL level, and you're stable, you do not need to consider additional therapy. If you're unstable, or you have continued events, or if you have a lot of additional risk factors, or if you don't meet certain treatment thresholds, then you can consider additional therapy, in most cases, first, with Ezetimibe, [INAUDIBLE], then PCSK9 inhibitors. So one difference with 2016 is they further stratified the risk groups.

Second, is they started talking, again, about thresholds. So before, there was no talk of thresholds. Now, all of a sudden, we're confused. We've got targets. We've got thresholds. We've got goals. But because the studies set thresholds, what they did was they took the thresholds that were set by the studies and they now recommend that you consider additional therapy if you don't meet those thresholds. So for example, in the high risk group-- and, again, I'll take you through these a little more. So most of these studies showed thresholds of, say, LDL cholesterol of greater than 100, you should consider Ezetimibe therapy, in patients with ASCVD, for example.

So thresholds is the other difference. By 2016, we had not yet had the evidence for PCSK9 inhibitors. So after considering Ezetimibe, they recommended bile acid sequestrants as second line agents, and PCSK9 as third line agents, with the exception of patients with familial hypercholesterolemia. The other difference is they started introducing more things for you to consider a patient high risk. So before, there wasn't a lot of evidence for any specific things. But here, they start listing specific things that you can consider for high risk. And these are based on inclusion criteria for those studies. So if that isn't confusing enough, then the PCSK9's data came out.

And we got this. So now, it's even more confusing. Now, they changed the thresholds again. We now have evidence for PCSK9 inhibitors. So they downgraded the use of bile acid sequestrants. They added thresholds for all the different groups. And so that's sort of where we are today. So let me take you through it a little more specifically. So 2016 included new, randomized control trial evidence with Ezetimibe and niacin. They took specific situations such as statin intolerance, suboptimal response. They introduced the concept of thresholds for select high risk groups. They more carefully defined, who are those high risk groups, by further stratifying the four statin groups, and also adding specific things that you can consider high risk.

And they included some additional specific situations, which I'm not going to talk about today.

They further refine that in 2017 by including new, randomized controlled trial data with the PCSK9 inhibitors. With that additional data, they could then extend the use of thresholds to all groups. And they added even more risk factors that were based on the inclusion criteria of those studies. And since PCSK9 inhibitors showed evidence of medical benefit, whereas we still don't have that with bile acid sequestrants, bile acid sequestrants were downgraded.

Going to the concept of thresholds, in the initial 203 guidelines, there were no recommendations for thresholds. In 2016, they added the following as threshold recommendations to consider additional non-statin therapy. A percent decrease in LDL in statin benefit groups. The absolute LDL level in clinical ASCVD group one. Baseline LDL cholesterol greater than 190, group two. And primary prevention, group four. And they added both absolute values for LDL cholesterol and non-HDL cholesterol in diabetics, group three.

2017, with the new PCSK9 data, they thought they had enough data to recommend not only percent decrease in LDL cholesterol, but also absolute level of LDL and non-HDL for patients in all four benefit groups. This is an example of the group one type people with a ASCVD and maximal tolerated statin, with an LDL cholesterol in that range. In 2016, as I said, they further stratified that by risk. In 2017, they made it for all. So again, looking at percent reduction in LDL, absolute LDL cholesterol level, and absolute non-HDL cholesterol. So can you see how we're kind of getting back to where we started before 2013?

And these are the order of non-statin therapy to add. So in 2016, again, I said, it was Ezetimibe first for most groups, followed by bile acid sequestrants followed by PCSK9 inhibitors. And then, in 2017, that changed to Ezetimibe first, pcsk9 second-- depending on the level you needed to reduce-- with the exception of people with familial hypercholesterolemia. And finally, this is related to, what are you using to consider higher risk? In 2016, in addition to the pooled risk calculator, the list was very narrow in 2013, less narrow in 2016, and even less narrow in 2017. Again, sort of getting back to where we started in the first place.

So this slide really summarizes all everything I just said about where we have gone since 2013. So basically, you treat the four statin groups. If they meet the thresholds and are doing well, they're fine. If they don't, then you've got to ask yourself some questions, again, looking at treatment thresholds to consider additional therapy. That can be percent reduction in LDL. That can be absolute LDL. Or that can be non HDL. What the levels are depend on your risk groups. Group one is people with ASCVD. If they're stable, then they're considered low risk.

You add Ezetimibe first, PCSK9 secondary. If they're high risk, you can choose either Ezetimibe and, or PCSK9. If they're in group two, which is a patient with familial hypercholesterolemia, you have the same choice.

And if they're in the lower risk groups, group three or four, pretty much, Ezetimibe is the second agent if they don't meet their treatment thresholds. OK. So that tells us what to do medically. It doesn't tell us what to do practically. So now I get to where you guys probably know when you came in here, which is that what can be done medically may not be the right thing to do based on cost effectiveness. So I've included here a slide of the numbers needed to treat. And the details aren't important, but what I want to really show here is that you're really only going to be effective if you treat the highest risk groups with this PCSK9. Those are people with very high cholesterol levels greater than 190 or very high ASCVD risk.

So what they did was they looked at the incremental cost effectiveness ratio of, what is the level of cost that would make it worth prescribing a PCSK9 inhibitor using the most up to date data from the FOURIER trial. And what they found is that the cost of the PCSK9 inhibitors, which are now about $14,500 a year, would have to be reduced to a cost of about $4,000 a year for them to have an acceptable incremental cost effectiveness ratio of $100,000 for quality adjusted life year. So if that isn't confusing enough, the other thing is just to get these drugs approved is very difficult and it requires a very strategic, systematic documentation, and working your way through. They have to try at least four different statins, et cetera.

So I think at this point in time, I would still probably recommend, if you think you have a person who needs more individualized therapy who would benefit from more than a statin, that you should consider referring to a lipid specialist. So in the last couple of minutes, I just have a couple more slides just so you think that we are not just focused on cholesterol. There's a lot going on in the field in non-LDL cholesterol targets. I'm not going to go into a lot of detail because these studies, with the exception of one drug, are all still in phase one and two, not phase three trials. But the things that are mostly going on right now are looking at HDL as a target with the cholesterol ester transfer protein, CETP, using CETP as a target.

And also, there's a lot of really exciting things going on related to hypertriglyceridemia with the new identification of the ANG PTL proteins. These are proteins that interact with LDL to facilitate disposal of triglycerides. So there's a lot of other things going on. The one study that did report out this year-- I just want to review with you-- is related to CTP inhibitors. So CETP inhibitors have actually been studied for about 10 years. What this protein does is it transfers

cholesterol from HTML to other proteins and would be expected to raise HDL, which we know is associated with beneficial cardiovascular effects. The problem is, despite initial enthusiasm for these drugs, the results have not been very promising.

So in 2017, the ILLUMINATE study with Torcetrapib actually not only did not improve cardiovascular outcomes, but actually worsened cardiovascular outcomes. And then in 2012, the dal-OUTCOMES studies showed that adding dalcetrapib to statin in subjects with ASCVD did not improve ASCVD risk. So the field had pretty much given up on CETP inhibitors. And then this year, actually, just last month, this happened. So September, 2017, HPF3 to [INAUDIBLE] REVEAL study with anacetrapib in addition to a maximally tolerated statin did reach primary endpoints and showed a reduction, not only an increase in HDL, which was a relatively small effect, but a reduction in atherogenic lipoproteins, such as the [INAUDIBLE] LDL cholesterol.

So the reduction in composite outcomes was about a 9% relative risk reduction, 3% absolute risk. And they showed some beneficial effects on other cardiovascular outcomes, but no overall effect on cardiovascular death. So here we have the first study showing some possible promise of CETP inhibitor. So I'll just conclude by saying that ASCVD the risk is complex, it's a multi-factoral disease. And while this lipodemia is certainly a major contributor, it's not the only contributor. And we have a lot of work to do, biological, as well as environmental and genetic effects that influence this residual risk that persists. And with that, I'll take questions.