DANIEL FORMAN: Thank you. It's a great pleasure to be here. And we're running a little late, which means that you've all been sitting a long time. Actually, one of the nicest things about giving the talk is that I get to stand. So I would not be put off if anyone wanted to stand up and stretch for a moment as I start my talk since this has become kind of an endurance morning for you.

So I imagine most of you have had some experience of the conundrum, do I put this patient that's on so many pills-- we've heard about all these cardiovascular disease with the prevalence climbing with age, and so many other diseases, prevalence coming with age.

And then do we think about cholesterol? How important is cholesterol? You hear a lot about it. Dr. Mathier talked about the impact of television commercials. We hear a lot about cholesterol, and our patients think about it. They come to you.

So I want to put this notion of cholesterol issues in context of longevity, that I really think the demographics are enormously important just in terms of who we're treating. And all of you treat older patients. But there are more and more older patients. People are living longer, so the population over 65 that was only about three million in 1900 now is about 50 million. By 2030, one out of five, 70 million, are going to be over 65, and with numbers going beyond that.

So that's the driving issue, that people are living longer and we have this epidemic of aging. And the older population, those over 85, is the most rapidly growing demographic in the world. So all of us are treating patients that are kind of a growth industry as we're doing such a good job in helping people live longer.

So what does that mean? People are living into their 70s and 80s and beyond. So you have this issue of time. Tomorrow you're going to hear Dr. Finkel, who's going to talk about what does age itself do, the physiology of aging. It has an impact on our whole bodies. And focusing particularly on the vasculature in terms of some of the impact or implications of cholesterol I think, is a good place to start because you're living longer and you're exposed to this physiology, this notion of inflammation, reactive stress in the system, and downstream molecular changes.

Cells are not working the same way. And it's compounded by some of the things that are happening simultaneously, the growing prevalence of diabetes and hypertension and cholesterol, oxidized LDL, the environment with tobacco, diseases like amyloid and calcium. All these things are accruing in this growth industry of aging.

So typical aging means disease. You've heard about heart failure. You saw those graphs skyrocketing with age. Pulmonary hypertension skyrocketing with age. Tomorrow you're going to hear about hypertension. Everything goes up with age. That becomes a problem. And there's guidelines-based care. Each thing is treated, in many diseases. And so most of your patients, as a result, just by living longer, are subject to polypharmacy by well-meaning clinicians. You, me, we're doing everything right. But for the patient it's bewildering.

And whether or not you have team-based care, as we heard from Dr. Schindler, it's still bewildering to our patients. Lots of pills, lots of doctors, lots of caregivers, everyone well-meaning. But the experience for most of our patients-- perhaps for you, perhaps for your parents-- bewildering.

So here we have coronary heart disease skyrocketing as a function of age, skyrocketing as a function of what we're now living with among all of our patients and in our own lives. And when we talk about the burdens, coronary heart disease deaths are an issue of aging. It's not just the pathophysiology. It's the pathophysiology in the context of an aging demographic.

So when we talk about the importance of yes, there's another pill, a statin pill, another thing to give to our patients, it really is driven by the context that with increased longevity-- with this fact that by 2030 we have this new population that is growing-- the projected increase in coronary heart disease is enormous, 43% increase by 2030, five million new cases, costs going up almost 200%. Enormous burden.

So sure, if we have a pill with lots of data, because this data's been driven for the last decade or two, much of it driven by the pharmaceutical companies who want to sell this drug, so they do lots of trials and they say it works, and we extrapolate. It works in middle aged adults, and then we look at a few older adults and we say it works. It's powerful. It's predominantly safe. What a great thing to give statins, this fancy name that changes the way cholesterol is produced in our bodies.

So it's not just what you eat, it's really how our bodies synthesize cholesterol. And it has substantial benefit in terms of its potential to provide effective and inexpensive prevention. It's true for coronary heart disease. It's true for strokes or cardiovascular accidents. And it's true for peripheral arterial disease, true heart failure, true for so many cardiovascular issues.

And I want to drive home the point with this particular graph. But it's really in many different things you've probably read that this notion that if you give a drug like statin-- and this represents giving it at a higher dose for the 40% relative risk reduction, or even a lower dose at a 20% relative risk reduction. So you're saying, I'm going to give statin light. Is it really good for our older patients?

So you see in the top graph that if you look at the younger patients, those that are 40, the statins really work, particularly the 40%. It cuts down the risk of the number of events overall by more than half. And the 20% doesn't work quite as well. But it's still a very substantial number. The blue is really cut down very much by using these statin drugs.

And it doesn't work quite as well to the right for those that are older. The relative risk reduction is less. The efficacy is not quite as powerful. But if you look at the lower graph, the number of prevented events, and actually you see on the right, whether you use the lower or the higher dose of the statins, the number of events vastly exceeds those that are in the younger adults.

The meaning is that when you have the greater ambient risk, if you have, within a population that's so prone to cardiovascular disease, anything-- in this case, statins-- to modify those risks, the actual effect is very powerful. And it translates into the sense that you don't have to treat many people to see an effect. In the younger adults, despite the fact that the drug works relatively well, you have to treat a lot of people because then the prevalence of disease isn't that high.

But in the older populations, where the prevalence of disease is so high-- in this case, of coronary heart disease, but this could be strokes, this could be a lot of other things-- you see that even a little drug goes a long way in modifying events. What a strong rationale for primary prevention and certainly secondary prevention. We should be doing this. It seems logical.

And so Nanette Wanger, someone I really like to champion, who herself is in her 80s, and she is going off to Europe and China giving talks. She's very active and dynamic. And so she's a wonderful spokesperson talking about the paradox of under treatment with statins. She's a big believer and a proponent.

So the contemporary statin treatment risk paradox is striking, she says, despite the high attributable risk of hypercholesterolemia at an older age and the powerful stain-associated reduction in all causes of mortality in this population, statin use declines sharply in older adults.

Shame on all of us. Shame on me, because I think there's a little bit more complexity to it. And despite the fact that I really admire Dr. Wanger, I would say, when I look at this patient, when I think of my patients, when I think of parents, when I think of grandparents, these issues are not so black and white. If you give this patient-- who may have pulmonary hypertension, may have heart failure, he might have many different problems that I think you all struggle with with your patients-- is giving them another pill a good thing? Is there insidious harm? Is there a diminished quality of life, perhaps, with myalgias or some other kind of effect that's really not widely reported? Is there a cost burden? Another pill, another thing to struggle with. I think these are the realities for our patients.

So if you Google statins-- and I'm sure many of you have, and certainly many of your patients have, or their granddaughters or grandsons-- they would come back saying, why are you doing this to us? So just in the context of this morning, this issue of multi-morbidity, because most people that have issues with cholesterol have lots of other things going on because it's part of that aging phenomenon.

And you have this polypharmacy, where giving a statin can exacerbate the calcium channel blockers, or the antibiotic, the cost. Is it really worth it when someone's 85 to be giving them this drug? So just staying on the right side of the graph, the context of old age is not simple. But then you add in the left side of the slide, some of the things that are particular to the statins. There's literature that says you give statins, they get more frail, more enfeebled, weak.

And it has to do, perhaps, with muscle. It makes sarcopoenia, this notion of muscle weakening, a little bit more of an issue. It creates pain in many patients. They swear by it. The literature says no, but they say I feel pain. They might describe confusion. I'm not quite as sharp as I used to be. This is a very common complaint. The greater susceptibility to falls, especially if they have muscle weakness, especially if they're on something for their heart failure or hypertension. So these things kind of compound one another.

There's literature that says if somebody has things that are metabolic in nature like hypertension, like changes to their body composition with more fat, they're going to have more diabetes when you put them on a statin. There's literature or even in some of the Prosper, the geriatric-related statin trial that says you could even have more cancer.

These things have all been controversial. They've all been disputed and denied by the drug companies and by people who do the research. And yet they're out there. And I would say that I have dozens of patients who have complained about these things. And they're not reassured by the fact that I say the literature says otherwise because their experience.

So can we simply extrapolate data that were collected in trials of predominantly younger adults, or super healthy older adults that were enrolled? And do the existing trials and registries capture data that are relevant for our older patients, for ourselves? Many older doctors or nurses and other care caregivers do not want to be on a statin. So it's not just what we do to our patients. It's how we treat ourselves.

This was a study that was recently in the cardiology literature by this guy Martin Mortensen from Denmark. And so he is not a geriatrician. And he was really kind of enamored with this notion of giving statins for an older population. And in Europe, they really only recommend giving statins through 65. And after 65 there's really no guidelines. So Dr. Mortensen has been very critical of that.

And so he looks at the European scoring system, which is based upon who's going to die from events that could be modified by statins. And he looks at this graph and he says, well, these numbers are impressive. They go up with aging. But is that the whole story? And he says if you look at people that don't actually die of cardiovascular events-- he's looking particularly at myocardial infarctions and strokes-- he says the risk of getting older is huge.

And that's really his issue. He says it's not dying that we should be worrying about as caregivers. It's the fact that by not treating cholesterol aggressively with statins, that we expose our patients to all of these non-lethal events and thereby predispose them to disability, to going to long term care living, and all kinds of dependencies that could be avoided. So he feels that there should be a mandate for a population that's aging in Europe and throughout the world.

And in the same breath, he kind of reaches equipoise because he's very strident saying we should be doing this, and then he takes a step back and says, but we really still have these issues that patients do complain of diminished physical function and cognitive impairments and pain, especially for those in this growth industry of 85 plus. We really don't have all the answers.

So I want to really highlight work that's been in the geriatric literature for a while. Mary Tinetti has been a prominent spokesperson coming from Yale, but she speaks for a voice that I think many geriatricians share, perhaps many of you, that we need a different metric. We need a metric that's really holistic in having a sense of the patient's overall experience.

What does the cholesterol number mean for somebody who is 82 and has a lot of other things going on in his or her life? We need a metric to gauge a patient's experience across conditions as a better index for aggregate clinical decisions, symptom burden, function, self-related health. That's really the holy grail.

And in a related kind of statement by a colleague of Tinetti's also at Yale, Terry Fried, she talks about would a patient really-- now you see it on TV, and taking a statin looks really great, you know? Patients seem very happy and they're all smiling. But would a patient, would your patient, would you take a pill that really was possibly going to cause fatigue or fuzzy thinking and would could possibly affect functioning.

So in Fried's work--and she surveyed patients-- very few would do this. And it's really how the pill is pitched and whether patients have a total understanding of what these things are going to do. And this is why the impact of Google and other things is so prominent because I think patients and patients' families are really concerned about what we're doing as part of presumably good care.

This issue of cognition has really percolated for quite a while, and it still continues to be very controversial. There's been many comprehensive analyses, including this Cochrane analysis. And it concludes-- and again, this is kind of a theme-- with good evidence that statins given late in life to people at risk for vascular disease do not prevent cognitive decline or dementia.

So they do not prevent it, but they do not exacerbate it either. It's not a causal agent of cognitive impairment. And so it's something which we should be giving as something where we feel that this is a reasonable thing to do for our patients. But even in these very powerful analytic efforts, they admit that the actual indices that were used in the literature, or in their analyses, are suboptimal, that there were limitations in the actual cognitive assessments that were used both to assess changes of cognition and to assess any conclusions that were made thereof.

And likewise this issue of myalgias. This has been a particular interest of mine. I have a strong interest in physical function in aging. And so we tell our patients with cardiac disease to come to cardiac rehabilitation so we can increase their function. And we tell them to take their statins because we think it's doing well by preventing disease. But are we inadvertently exacerbating their functional decline?

And so again, as I've mentioned several times, there's many trials that have looked at this issue and concluded uniformly that myalgias are not exacerbated by giving statin therapy, even high dose statin therapy. Very minimal effects of the statins themselves.

But this work by Paul Thompson, who had been much of his career in Pittsburgh, highlights the patient experience. He's looking at actigraphy data, people wearing these device that track their function. And he shows the impact of Atorvastatin on different age strata. And he shows that once people are over 55, if they're taking a statin, the amount of activity just goes down. So it doesn't correlate to blood levels that were measured. It doesn't correlate to other things that were really obviously consistent with known science. But yet there's this pattern that seemed to be unmistakable. Age seems to be relevant in terms of statin effects.

And so Paul Thompson has really spent much of his career looking at this. He's been really fixated on this, looking at all kinds of cellular, subcellular, metabolic impacts of statins on our patients, and really has not come to a conclusion. He's still going strong in his 70s looking at this. And he's on many different panels and very sophisticated thought initiatives. And yet it still remains an unclear issue.

Does that mean it doesn't exist? Does that mean we can tell our patients no, there's no problem? Because many patients complain.

So then I want to just conclude this thought by Michelle Oden's work. She's a geriatrician from Canada. And the first part of this slide, she kind of recapitulates this notion that there's a strong rationale for prevention with statins, in this case, looking at primary prevention. And she talks about reducing the numbers of deaths, modifying the costs associated with this treatment. Again, she acknowledges it.

But then she counterpoints by saying that there are geriatric risks that are just as common, and that by giving a pill when you have a chance of increasing functional limitation or cognitive impact, that has to be incorporated into the calculation. And so she writes that even a small increase in geriatric-specific adverse events can offset the cardiovascular benefit. Improved data on potential benefits and harms of statins are needed to inform decision making.

So despite all of these drug trials, funded in large part by drug companies, we need data that really are patient-specific for people that are old and very old that are not typically included in these big trials. So what do the guidelines say? Actually, I think it's been an interesting pattern for all of you to watch this sea of cardiologists because they always show the guidelines. And I suspect that your experience with your patients may not always mesh with the guidelines. And that's a huge tension because the cardiovascular world looks at guidelines.

And I should say I have no conflicts, but I'm actually on the guideline committee. And I'm not going to tell you what the guidelines are going to say in 2018, but I can tell you what some of the thought processes were that are there. But these are you live with now, from 2013, and they've been rife with controversy because they don't fit with most clinicians' experiences.

And it's interesting to note that this guideline, which is 80 pages, has one paragraph on patients over 75 on page 46. You know, that in itself says a lot. And as I showed in my first demographic slides, this is endemic with aging. This is an aging phenomenon. You've heard that for all these cardiovascular stories. And yet we get one paragraph for all these issues that you all struggle with with all of your patients every day. So that's a problem.

And the guidelines start with primary prevention, patients without atherosclerotic vascular disease. And it talks about those that have high risk, which is everyone, by virtue of age. That lecture you're going to hear tomorrow by Toren Finkel-- everyone who's old has a high risk. That's everyone. So they say from 65 to 75, there's data from these big trials that say statins should be given, this condition of class one data. So moderate to high intensity statins. But after 75, it's your best guess. So there's the guidelines. It's your best guess.

So what do we do for primary prevention? So just a little bit about that. And I want to go back to that Mortensen article I showed where he was developing a strong rationale for treating aggressively with cholesterol-lowering agents, particularly statins, from a European perspective.

And what he does is he first starts out with the American ACCHA guidelines. And he shows, based upon the notion of risk that was established by this notion of the pooled cohort equations, which is a sense of risk that is aggregated by hypertension and some of the other risk factors that are very familiar to you. And so once patients are over 75, everyone has risk just by age. But even at younger ages, there is high risk subgroups.

And he says that up until 75, those with high risk should be on the statins. And then once you're over 75, you see a number one, it's really not so clear. And he shows that there are other guidelines from Canada and the United States Preventive Task Force, number four, that are kind of similar. They say up until 75, the data from trials are clear. Then once you're over 75, it's somewhat ambiguous.

The United States Preventive Task Force is the most ambiguous because after 75 they have no recommendations. They just stop. Nothing. So he points out what, really, the conclusion from this kind of perspective, this is just so messy. So again, this started with 2013, but even in the years since, '14, '16, they're the same. We've gotten no better. All these smart people sitting in a room coming out to ambiguity. And he says this is a problem.

And he points to the difference. The second one, which is the British system, the nice system, uses a different scoring system, the Q Risk Score System, and it says you give statins till 85. And then it says we're not so certain, but you should probably give Lipitor, Atrovastatin, at 20 milligrams thereafter.

Now they had no more data in the UK than we have here. They just looked at the same studies and they came out to different conclusions based upon their Gestalt. And in Europe-- this is where Mortensen was so critical-- they say up until 65 you should be giving statins. And then we don't know.

So such a diverse approach to the same issue. So that's a problem. So again, we know up until about 75, or in the case of Europe, 65, strong data, should be given. But then once you're over 65 in Europe, or 75 in most of the other places, it is reasonable or may be considered much more ambiguous.

So what's been happening recently? And what should you do now? And what do you know? So this is important literature to highlight, in my opinion. This is Paul Ridker's work. Dr. Ridker is a very opinionated individual, someone I know well. And he has lots of bravado. He's powerful because he's very good at numbers. So you may think he's absolutely right or you may not be certain.

So he looks at this. He pulled data from the Jupiter trial and the Hope trial, two trials that used Rosuvastatin, Crestor at different doses. And when he pulled together the data from the two, looking at the older subgroups, he showed a statistically significant 26% relative risk reduction to those over 70 for this powerful endpoint of a composite of non-fatal MI stroke and cardiovascular death. And to his mind, it was unequivocal.

And it's mirrored by many meta analyses that have gone on in the recent years looking for primary prevention. And this one by Savarese is one of several that kind of come to similar conclusions that show is that if you look, in this case, at about 25,000 patients, that by the various statin trials, you see this significant reduction in heart attack and strokes. No overall increase of death. But the point being that for an older population, reducing heart attacks and strokes is a great thing.

And this is the schematic from the same work, again, showing this predominant benefit in favor of statins. So primary prevention with statins is really well supported by data.

But the counterpoint-- and this is where I think we struggle in our offices, still-- the Prosper trial. I mentioned this earlier. This was a trial specifically focusing on patients that were older, 70 to 82. And it looked at patients that had both risk factors for atherosclerotic heart disease as well as those with disease. And it showed benefit, but only in those that already had disease. The ones that were at risk showed no benefit in the composite endpoint. So what's wrong with this?

And likewise recently, very recently, the ALLHAT trial. This is old data coming back from the 1990s, was reassessed by Caroline Plum and a group at NYU, a geriatric group looking at Pravastatin versus usual care. And it said in those that were over 75, there was no benefit.

Now I frankly don't like this trial. It's an older trial, and it was done when Simvastatin was being released, so a lot of the people that were in the control group took Simvastatin, and then the older group was only 7% of the population. I don't know what it really means. But the conclusions were pretty strong. No benefit was found. And there was even a non-significant direction towards increased overall mortality in those that were older.

And when you look at this online in terms of the literature search in PubMed, this is cited extensively. I heard about this trial for the first time when I was driving home. It came on NPR. The next day it was *The New York Times* and *The Wall Street Journal.* This small, bad trial got huge press.

So what does this say about our struggles and our patients and what our thoughts are? I think people really don't know. And when they find a trial like this, they feel like it's validating of their experience, which their doctors, their well-meaning doctors, don't really validate.

So what do we know about secondary prevention? Maybe that's less ambiguous. Maybe we really know more about treating cholesterol in those that are over 75. And these guidelines say 65 to 75, high intensity statin, good drug. Over 75, all of a sudden moderate intensity statin, because why? Gestalt.

Dr. Stone, who is my friend, who wrote these guidelines-- he was the lead author to this-- well, he just didn't want to hurt anyone. So very well-meaning.

So if you look at the data, they're unequivocal. These statins, across the board, this meta analysis by John Afflalo, everything that we worry about. Coronary heart disease, mortality, heart attacks, revascularization strokes. Everything is going down with statin therapy. A strong endorsement. But why moderate intensity?

So this is an important trial to know. This came out, again, since the guidelines, 2017. It's a VA analysis. It was done very rigorously, propensity analysis, looking at those that were on a moderate dose versus those who were on a high intensity dose, and unequivocally shows high intensity doses work better without any notable increase of side effects.

So this is very controversial. You could find 10 cardiologists and get 20 opinions about this. And I'm sure you have your own versions of some of the controversies. Is it right? But it's compelling. I think that's the issue that I really want to emphasize, that it's really compelling to use the higher dose. The patients that are older got relatively greater benefit than those that are young from the higher dosing.

And along with that trial, which was this propensity analysis, are these new data, a prospective trial from Chris Cannon looking at the utility of combining Simvastatin with Zetia or Ezetemide, the impact, meaning that you actually get a lower LDL effect, a lower LDL effect, which is very topical in cardiology now because we have a whole new class of drugs getting very, very low cholesterol.

But looking at this in the older population, it shows by getting the lower effect of these combined things, you get a better impact in reducing stroke and heart attacks. Good things. And he showed, particularly in those that were older than 75, the effects were the greatest. A very compelling rationale for going after the older population with the most aggressive therapy.

But this is the issue that we already know. It's kind of saying what I've already kind of assessed earlier, that they're two side of the same coin. There are benefits. There are predictable, well-known, well-studied therapies that you can reduce, perhaps mortality. But certain events of heart attacks and strokes, you can reduce claudication. I haven't gone through that literature, but there's quite a bit. Perhaps, in some literature, you can increase function by increasing vasculature. Some literature says you can diminish frailty and increase cognition by using statins. Particularly Australian literature kind of makes these points.

But then, on the other side of the coin, in terms of function, frailty, and cognition, there's lots of literature that goes the other way and saying, well, maybe these things aren't so good with statins. And maybe these issues of polypharmacy and costs and myaglias are really the overriding issues.

And none of these studies really look at universal health outcomes, this thing that Mary Tinetti talked about as being so important. We don't have it yet.

So the things-- we heard this a little bit before in the other lectures-- that we should be thinking about patient preferences. We don't really know the right answer. So we should really ask our patients, what do they want? And so your patients are already in 10 pills. It's a lot to ask them about this drug that they might not even understand. But it's really important.

And actually, one of the big things in cardiology now is to develop tools. The American College of Cardiology has a whole unit developing towards helping clinicians to really better engage with their patients so that it goes beyond just a number but a concept. And you really try to find wording and a thought process that really meshes better with our patients. And those resources will be available to all clinicians, not just cardiologists.

The other really important topic in cardiology right now is this notion of de-risking. If you look at this picture to the left, you see that in the middle aged adult, the issue is that we find all kinds of things to increase stratification of risk. You get a BNP. You get a troponin. You get some kind of imaging study. You say you're a greater risk. I'm going to treat you.

But as you go to the right, by virtue of age, everyone's at high risk because age is the driving risk for coronary heart disease. Does that mean that everyone should get everything? So the thought process in cardiology now, and much of medicine, is to de-risk. Who can we untreat? Who can we find a rationale not to treat? And there's many candidate variables. Many people have looked at inflammatory markers and other-- intimal-medial thickening.

But for the sake of time, I just want to focus on what's really, I think, the most topical right now in cardiology, is this notion of looking at the coronary artery calcium score, that if you find someone that has no coronary artery calcium, it really is a marker of very low vascular risk. So if we find those people, there's a very good rationale, certainly, for primary prevention, for not treating with statins.

So it's really helpful in terms of thinking about our patients. So as you think of old age, almost everyone who's older is at risk for atherosclerotic vascular disease. But if you find those that have no calcium in this group, we say we can really down risk those patients so that when we actually start to think of who we're going to treat with statins, we only treat it with those that remain calcium eligible in terms of having some calcium available or visible that we think may be a source of risk. So we really have a different thought process in relation to our older adults.

And then another controversy among many clinicians, among many families, is that if you're on this drug-- perhaps you've been on this drug for 10, 20 years-- do you really want to stop it? Is that going to be a death sentence? Are you going to go spiraling to something bad?

And so the palliative care literature, this particular study by Kutner, really highlights something quite different. Her work, Jean Kutner, shows that when you stop statins, true with much of the palliative care literature, people actually do better. And so these are people that are in advanced stages of disease with shortened lifespan prognosis. But showing that when you stop the statins, patients actually live longer, as we see here.

And in related schematics, they show they live better. Quality of life and a variety of other indices all improve, providing really strong rationale for taking away statins when somebody has predominant issues that really confound the utility for using a statin.

So in terms of thought processes, these aren't guidelines, but these are driving thoughts that are going to contribute, I suspect, to guidelines that in patients that are older, 75 plus, without atherosclerotic disease, it's reasonable, and it should be considered, to give a moderate intensity statin, not statin light because some of those trials, the Prosper trial, things they've tried to use, Pravachol, really didn't work.

But giving the higher intensity statin in the primary prevention trials like the Paul Ridker trials did show benefit. But, but, but-- asking your patients. Don't just throw them a pill at discharge from the hospital, but really engaging with a patient. Do you want to be on this other pill, this other cost, this other complexity? Do you want to deal with the risk that this might make you weaker?

I think patients need to be engaged, and I think that has to be hardwired into any recommendations. And likewise, once you have atherosclerotic disease, your secondary prevention-- and then there's a whole smorgasbord of things that are atherosclerotic from strokes to peripheral arterial disease to heart attacks. So there's a strong rationale for moderate and even high intensity statins in our older patients. Treat aggressively, but talk to your patients, and really make sure that they're engaged with the thought process that you're initiating.

And if someone is on a high intensity statin, which is consistent with the guidelines, don't just cut back because they're 75, which is what they currently say to do, but really, if they're tolerating it, I would say it's reasonable to continue.

And likewise, now, thinking about using Zetia or Ezetemide as an adjunct to really drive up the LDL lowering properties. The data are quite strong. The things which I think are really topical, new, and I hope are incorporated in guidelines, which I hope are incorporated in your thought processes regardless, is to think about de-risking, to think about the the coronary artery calcium score as a way of thinking who doesn't need to be in a cholesterol lowering agent. So that's a very, I think, useful adjunct to the thought process of care.

And finally, this notion that just as it's important to start a statin-- I've heard many prominent cardiologists kind of banging on the podium saying push the statins-- I would say it's important to stop the statins when they're really not having a predominant benefit. So I think being just as critical as stopping for the sake of the patients is really a very prudent and reasonable thought process. Thank you very much.