DONALD LLOYD-JONES: Well, good morning. It's a pleasure to be here. I was really pleased to receive the invite, and I knew the timing would work out so I suggested this title, because I thought it might be helpful. And I haven't been in St. Louis for 25 years, and I think I was telling Justin yesterday when he picked me up that the last time I was here, it was sort of one of those really bad college road trip movies, because I had picked up my college roommate, and I was driving him out to UCLA for graduate school, and we stopped and spent a couple days sampling the two carbon molecules of Saint Louis, and it was a great time, but there were fire alarms pulled in the hotel and late nights and all sorts of sordid stories, but it was a really good time, but it's great to be back and in a more academic environment, shall we say. So it's a pleasure to be with you today.

I'm going to talk mostly about the updated guidelines for cardiovascular risk assessment, but to do that I really need to give you some context about what the cholesterol guidelines have done in their update. I'm not going to go into super huge depth on those, because I know Ann's going to talk about those in January, but I do want to start there, basically so that you'll have a context and a framework, and I have no disclosures.

So just to put the guidelines in context, you're all quite well aware that the last round of NHLBI-sponsored guidelines came out in the late '90s, early 2000s. ATP-III in 2001, JNC7 in 2002, and the first obesity guideline came out in 1998, all sponsored by NHLBI. And so the original plan for NHLBI was to do updates and the next round of these guidelines and they convened panels in 2008, really focusing on what they saw as-- and what turned into an IOM-level guideline, meaning really strict adherence to understanding relationships with industry and conflicts of interest.

An independent group that actually went and did the systematic evidence reviews, sampled them, judged them on quality, and then turned them over to the panel so that the panels could make evidence statements from those data and then recommendations from those data that would be really rock solid in terms of your confidence level in understanding the quality of the evidence behind any given recommendation.

After that, it went through five layers of peer review with literally dozens of external and governmental reviewers. Some of you are actually in the room, I know, as reviewers. The guidelines were actually completed in 2012 and, as you then know, in June 2013 NHLBI decided they wanted out of the guidelines business, and that was an interesting process. Fair to say that one came a little bit out of left field. We didn't expect it, but I think one can understand that increasingly over the last few years, with things like mammography guidelines, guidelines for pediatric lipid management, there's been a lot of politics around guidelines, and I think NHLBI has said-- and I totally get it-- that they should probably be out of this business and leave it up to the professional societies. And so in August 2013, ACC AHA, in negotiation with NHLBI, picked up the guideline documents, moved them forward.

And, as you then know, in November 2012 four executive summaries from this process were published. Full reports are also published. Those are really long, if you're interested, or need an Ambien substitute, they're really great documents for both academic interest and Ambien substitution. But there are guidelines on lifestyle management, management overweight and obesity, treatment of blood cholesterol and assessment of cardiovascular risk. Those are out there.

There is also a BP guidance that was published by AHA, ACC and ASH, talking about how you can use systems of care to improve blood pressure control, and that's actually a very nice document as well, and I would recommend that to you. That's online in circulation and going to be published hard copy. But interestingly enough, the JNC panel that was convened by NHLBI did not choose to go with AHA ACC, and they chose to publish separately. They've submitted their document to JAMA, and my understanding is that that will actually be published online tonight, so stay tuned, keep your eyes peeled for that. It should be interesting to see where they ended up.

So I'm going to start to dive in, as I said, first on a sort of brief overview of the cholesterol guidelines, because they really provide the context for why you would want a risk calculator and a risk assessment approach. Hopefully you can find these online. I won't spend time letting you see those URLs, because they are almost unreadable. But really, I have to say, this was one of the most fun things I've ever done. It was long, tortuous, and painful, but just an amazing process, and you can see here a number of people, who are really true leaders in the field, were on those panels, and it was a joy, especially to work with Ann, who was our real guru on familial hypercholesterolemia and how to approach that. So if you ever get the chance to be a part of a panel like this, it's really a remarkable experience, and I think I was one of the more junior members of the panel and really learned a ton from a remarkable group of colleagues.

Because this has been out there, I will spend just a moment saying that we were rigorous about conflict of interest. That means, first, we were all vetted for conflicts of interest, and we had to stop them before joining the panel. Second, if we had any conflicts of interest or relationship with industry, every time we deliberated we had to both state them and update them. And third, any time we voted on either an evidence statement or a recommendation for clinical care, anybody with a relationship with industry had to recuse themselves, and that was held firmly. So nobody with a relationship with industry ever voted on an evidence statement or a guideline recommendation. They could contribute to the conversation, of course, after stating their conflicts, but they never got to vote on any of these, so only those of us who had no conflicts or no relationships were allowed to vote.

So what was the charge to the expert panel for cholesterol? We were supposed to use critical questions in the context of systematic evidence reviews in order to develop the evidence for our guideline recommendations. I talked about the independent body that did the evidence reviews and provided us with quality of evidence ratings, and then we were supposed to develop those recommendations.

When we switched over to the AHA ACC model, we moved out of the NHLBIs evidence grading system and into a different evidence grading system, which I think is probably more familiar to all of you. In AHA ACC speak, of course, you give a class of a recommendation, class I, class IIa or IIb, class III, and then you give the level of evidence on which that's based.

So class I recommendations are those where benefit far outstrips the potential risk of the recommendation, IIa where benefit is clearly still greater than risk, IIb where benefit-risk are perhaps equivalent, and then class III, you could say don't do this, either because it's associated with harm or don't do this, because we have enough evidence to say that there's no benefit. So class III recommendations come as class III harm or class III, no benefit. And then for every recommendation, you get a level A, B or C. Level A meaning we have multiple randomized clinical trials to say this is solid evidence, level B evidence is either one randomized clinical trial or a lot of observational data, and level C means we have some data here, but largely this is an expert consensus recommendation.

OK. So the scope of the cholesterol guideline was treating blood cholesterol to reduce cardiovascular risk in adults, specifically atherosclerotic cardiovascular disease risk, because that's what cholesterol, of course, is associated with. There's a big focus on adherence to heart healthy lifestyle and a link to the lifestyle guidelines which, again, I would recommend to you. And we really tried to focus in-- you know, in ATP-III they talked about risk equivalents. We really wanted to focus in on benefit groups. Where is there solid evidence that we know a patient in this group is going to benefit from cholesterol reducing therapy?

And in the end, we found four such groups that were clear net clinical benefit. That is, the benefit and risk reduction far outstrips any potential harm from going on a drug therapy. And we spent a great deal of time, and I'm going to leave all that to Ann, thinking about safety issues for each of the drug classes that we use to reduce cholesterol.

So this is the big finding. It's probably not a surprise, but remember these guidelines are largely targeted at primary care physicians, and we wanted to give them a signal that these are the four groups where you can have rock-solid confidence that a patient in this group is very likely to benefit, but clearly have net benefit, that is, benefits far exceeding risks from going on a therapy to reduce their cholesterol.

So first group, those who already have clinical atherosclerotic cardiovascular disease. Probably a no brainer for everybody in this room, but I think there may have been some doubt out there in the primary care area. Second, LDL cholesterols of 190 or higher that appear to be genetic in origin. So you should rule out hypothyroidism as a cause of very high LDL before you consider a patient to be this group. But if their LDL cholesterol is over 190, they clearly have genetically extreme high level of LDL. We know that's a very high-risk group for development of, particularly, coronary heart disease at younger ages.

Third group. Patients with diabetes who are at least age 40, and the clinical trial data actually can limit the diabetics between the ages of 40 and 75, so that's where we have the best evidence for sure. And there's a lot of evidence about treating diabetics and part of that of course is because, especially type 2 diabetes never travels alone. Type 2 diabetics almost always have hypertension. They almost always have dyslipidemia-- not the classical high LDL, but more of a metabolic syndrome picture. All of those things pile on risk, so diabetes is really a marker of substantial cardiovascular risk and fortunately we have enough clinical trial data to say this is a very high benefit group as well.

And then the final group is people who don't have any of those first three conditions but are in primary prevention, and we were able to look at the clinical trial data and say, if that 10-year risk is above 7 and 1/2% for heart attack or stroke, that's again a net clinical benefit group, where you're far above the likelihood of developing a side effect from statins. Things like diabetes or very low risk of things like myositis, but you're in a group where there is net clinical benefit, where the number needed to treat actually is pretty reasonable, so you should consider it.

But here's what has been totally lost in the media. A 10-year risk over 7 and 1/2% for heart attack or stroke does not mean we mail you a prescription if your patient. It means that's your starting point for having a discussion with your doctor about where does you risk come from? Is a statin going to appropriately reduce that risk? Is there more we should do with lifestyle first? So this is really the start of a risk discussion, it's not the start of writing a prescription. And I think that's been completely missed in the media. It'd be nice to say, everybody gets this prescription up there. That makes it easy for people who want to do quality improvement metrics and performance measures, but that's not what we said, because that's not clinical practice, right?

These guidelines, especially the cholesterol guideline, really try to put the patient and the doctor back in the middle of this equation. We give you tools to understand the patient's risk, and we give you guidance about where the benefit groups are, but we don't mandate prescriptions in primary prevention at all. We mandate a discussion, and that's what's been missed, so we'll go through that just briefly. So Neil Stone, who is our chair, put this together. I think these are patients we often will see in practice, and they should give you a sense for the person who's in the sweet spot of these recommendations.

A 63-year-old guy who's just had a STEMI-- I heard you guys had a STEMI last night. I hope it went well-- who should be discharged on a maximal intensity dose of a statin, right? We know lots of clinical data for secondary prevention for this gentleman.

A 26-year-old woman who clearly has FH levels of LDL cholesterol. She's at risk earlier in life than the rest of us. We need to get her started on therapy as soon as possible.

A 44-year-old woman with diabetes. She has hypertension. It is controlled. That's great, but she's got some end-organ damage. She's got microalbuminuria. That's a patient who is going to benefit from statins. We know that from multiple clinical trials, both cards and trials focused specifically on diabetes, but also many, many large secondary analyses of large clinical trials that included diabetics.

And then finally a 56-year-old African-American woman, primary prevention. She's got multiple atherosclerotic cardiovascular disease risk factors, and she's African-American, which puts her-- and she's a woman-- which puts her at significant risk for stroke even before her risk of coronary heart disease starts to pop up. We'll talk a little bit more about that. She's going to be in a group that would benefit from a statin. Does she specifically need a statin? Well, that's the conversation that you have to have with her.

So a lot of questions. This is a big change. We're not focusing on an LDL level that tells you you have to start therapy and an LDL level you have to get to to assure quality therapy. Why? There's no evidence for that. You all know. There have been no titration clinical trials to get to a certain LDL goal. None. So we couldn't recommend that that's the best approach, because there's absolutely no data to suggest, for example, that getting to an LDL of 68 is better than being at an LDL of 78.

So the real problem is, while there might be high-risk patients where you still want to do that, because lower pretty much always is better, we can't tell you that there's a specific combination that you should pile on two or three more drugs to get there. We can't show you any benefit, and the best example I can give you of that is two-- one large and one very large trial, putting long-acting niacin preparations on top of quite adequate statin therapy. Absolutely no benefit, clear harm.

In HPS2-THRIVE, clear harm to adding long-acting niacin preparation on top of good statin therapy, and the harm came in the form GI bleeds, it came in the form of infections, atrial fibrillation, gout, and almost a statistically significant increase in total mortality, with no benefit for cardiovascular disease. So there are still patients, and I have them in my clinic, where I am going to be more aggressive over and above a maximally tolerated dose of a statin, because they're at such high risk, and I think lower will be better, but I have to admit to myself that I am in a data-free zone. I have to, and I also have to admit I'm probably piling on extra side effects, and I don't know what the benefit will be. I think it's there, but I have to have a conversation with the patient about that if I'm being honest, right?

So that's really why we moved away from those LDL targets, and really put this back on the clinical judgment area. Guidelines are guidelines, and they never replace clinical judgment. So we hope to give you some good frameworks, but you and the patient know best what the right thing to do is and whether more medications over and above that maximally tolerated dose of statin are likely to give you some net clinical benefit. So I kind of I think just went through that.

These are really important data to understand the primary prevention approach. In 2012 in the Lancet, the cholesterol treatment trial answered the question that I think we all wondered, which was, OK, none of the trials has really taken a risk-based approach, but if we look at the totality of data, what we understand about statins is that statins reduce risk. They reduce risk largely-- perhaps not exclusively-- but largely by reducing LDL cholesterol, but what they treat is risk. So we need to put this in the risk framework, and the other thing that's important is that understanding side effects has to be done in an absolute risk plane also.

So if you want to compare the net clinical benefit, the absolute reduction in cardiovascular events, with the likelihood that my patient might develop a new case of diabetes or myositis, you can't compare that in relative risks. It's not doable mathematically or conceptually. You have to do that on absolute risk plane. So understanding the absolute benefits is really, really important.

So these are data from that cholesterol treatment trial. It's individual level meta analysis. And they calculated the predicted five-year risk for a cardiovascular event in all the participants, and they laid it up here, as you can see. And overall, the relative risk reduction is basically similar, regardless of your baseline risk. So there are people in here who have LDLs of 70, and there are people in here who have LDLs of over 190, but the relative risk production lines up pretty well based on the baseline risk.

No matter who you are, you're going to benefit from being on a statin if you're in these groups, but that doesn't tell you much. This tells you everything. Now what you see is those same baseline predicted risk groups, and here's the amount of LDL reduction achieved. Notice that the most events are prevented in people at the highest risk who get the most LDL reduction. What does that mean? Highest baseline predicted risk, maximal intensity of statin. That's what these data will tell you.

If you want to focus on really low-risk people, you're not going to get nearly as much bang for your buck as if you focus on high-risk people, and when we dug in on the clinical trial data, again, we found that threshold actually at 5% there's net clinical benefit, but we backed it off to 7 and 1/2%, because we thought, one, there needs to be a buffer. At 5% you're getting a little bit closer to the marginal zone of benefit-risk, and we also wanted to create a buffer in case, interestingly enough, there a little bit of overprediction by the risk calculator. So we built in this buffer for discussion, for understanding individual clinical patient characteristics, and just to hedge our bets. We know there's clear benefit above that 7 and but, again, the real concept here is you have to understand the absolute risk to the patient in order to understand what your benefit's likely to be and match that up with potential harms.

So this is the key, if you aren't going to read the guidelines-- and I really would love you to read the guidelines, but if you're not, this is the figure you have to read, and it's figure four in the cholesterol guidelines. And basically it says, OK, if we're in a primary prevention setting, and we've ruled out secondary causes of dyslipidemia, then figure out if you're in one of those four benefit groups. So we've already kind of taken out the people with ASCVD. We take out then, in this flow diagram, we take out the diabetes, we take out the people with LDL over 190.

Here's our primary prevention group then, and we take them forward, and we put them through the risk calculator, and we generate their predicted 10-year risk for heart attack or stroke, and as I'll show you, those are sex and race specific estimates. Now notice the next thing that happens is not mail a prescription to the patient. The next thing that happens, regardless of which of these three groups you're in is think about, is there anything else we need to talk about to color in their risk, like their family history, for example? We'll talk about that in a second. And then here it is, engage in a discussion of the potential for risk reduction benefits, adverse effects, drug-drug interactions, and patient preferences.

This is the mandated discussion. It's not the mandated prescription. And only then if that discussion results in it do you initiate statin therapy. And that's, I think, again been completely missed in people's interpretations of the guidelines so far. So to estimate that 10-year risk is where we'll spend most of the rest of time. We use these new Pooled Cohort Risk Equations that are providing sex and race specific 10-year risks for white and black men and women for heart attack and stroke, and really then that discussion should focus the statin therapy for those that are most likely to benefit. So I think we've kind of gone through this.

Here's a really important thing that nobody has covered in the media. Nobody. We keep getting these cases thrown at us. Well, what about a 38-year-old or a 42-year-old with a family history and an LDL of 180? Here they are. You're going to get a 10-year risk estimate in them that's less than 7 and because they're 42, they're young, but you're not done. You're still a clinician, and you need to consider that family history, which is not in the risk prediction equations. You need to consider that that LDL is over 160, and that is putting them at risk, particularly in the context of a family history. You might have measured their CRP. If it's over 2, that's going to push them to the higher side of risk as well, indicating if it's repeated and appropriate, indicating they may have some subclinical inflammation in their atherosclerosis.

You may have chosen, because of family history in this young person, to get a coronary calcium score. Really in this person, any coronary calcium if they're 42 is going to put them above the 90th percentile for their age. They're way ahead of their sex cohort and their race cohort if they have any coronary calcium. The average white man develops coronary calcium at age 53, so if you're a 42-year-old with a family history and an LDL of 180 and has coronary calcium today, they are way ahead of where they should be, and you better be treating that patient.

So again, we gave you guidance in these guidelines to say, not everybody who's at risk is going to be above that 7 and threshold. You will have patients who have specific issues that you must consider in that risk discussion, and this list of six things, I think, is really important to help you color in that risk estimate which is, again, just a starting point. It's not the finishing point.

This is the last thing I'll say about cholesterol, because I think Ann will dig into detail here. We didn't say, put them on a statin and say sayonara. We said, get them back, measure that LDL cholesterol, think about whether it's low enough for that patient's specific scenario, but particularly look at that LDL to give you some guidance on, one, is the patient actually taking the medication? We know that many patients stop taking their medication within the first year after prescription. This is a really nice biomarker of whether they're taking their statin, right? It's also a really nice biomarker of whether you're doing everything you possibly can with their lifestyle to reduce their LDL.

If you're confident that they're taking the medication and they're doing everything they can with lifestyle, and you're still not at an LDL where you'd like to be for this particular scenario, great. You have every right and reason to perhaps aggress with further therapy, but you have to admit to yourself you're in a data-free zone. Why am I doing this? Am I going to get more benefit by doing it than harm? And if you think you are, terrific. And the guidelines will say, go for it. And then I'm going to let Ann talk about, there's some really terrific data on the safety of statins and all the other medication classes as well, so if you want kind of a nice review article about safety, we did a good job for you.

So just to wrap, this up, three principles. Don't focus on LDL cholesterol levels as therapy goals. Use proven medications. Really, that means first-line therapy is statins for almost every patient, except for maybe those patients with very high triglycerides. And make decisions on drug treatment in the primary setting, based on the patient and based on that risk discussion that hopefully you're going to have with them, armed with the tools that we've given you.

So let's dig in on the risk calculator. Again, you can find this on the web. I'll show you the best way to Google search it in a moment. And again, I had the honor of co-chairing this with David Goff, who has become a partner, a bunker-mate and good friend through this process, but a really terrific group of people as well. And what you'll see is there are people there from all the other guideline panels as well, because we really wanted to try to incorporate their needs and views as well. Same kind of thing, we had 5 out of 17 folks on our panel had relationships with industry. Same transparency, same lack of ability to vote on any of our evidence statements or reviews or clinical recommendations.

So what was our charge? Well, we were charged specifically with looking at risk assessment, obviously, and particularly in primary prevention settings. That's what we were asked to do is create, as you see here, a quantitative risk assessment tool that can be used to help guide care, and then also to do literature reviews that could address what we felt were critical issues in the area of risk assessment. So that's what we did. So first of all we said, what should we do about quantitative risk assessment? Well, is it good enough to get the patient's assessment of where they think they are in the spectrum of cardiovascular risk? Well, there's some actually great data out there.

Here's one study where they took a bunch of primary care patients and they just gave them a scale, and they said point to the scale between 0 and 100%. What do you think your risk is of having a heart attack within the next 10 years? Somewhere between 0 and 100%. Well, it turned out that about 45% of them were more than 20% percent higher on that absolute scale than their predicted 10-year risk for either a heart attack or a stroke. So they were way high, and a number of others were actually significantly lower than their predicted risk.

So patients were all over the map, and they were really poor, and if you looked at the average, they missed their predicted risk target by 23% on that scale. Absolute value, not relative 23%. Absolutely on average they missed by 23%. So patients do a terrible job of understanding by eyeball what their risk is for heart attack and stroke, and unfortunately we're not much better. If you only focus on that LDL cholesterol level, you miss risk completely. There are people at extraordinarily low risk with LDL cholesterols of 160, there are people at extraordinarily high risk of LDL cholesterols of 95, and it's about risk. It's not about one LDL number.

So when they gave these physicians 12 different scenarios and they looked at over and underestimation, only about a quarter of the time were the physicians within a reasonable boundary around the actual predicted risk for that given scenario. And as you can see, much of the time they were overestimating risk as well, leading to potentially over-treatment, because they didn't understand what the risk actually was. So knowing those kinds of data in background context and knowing that our major constituency was going to be the cholesterol panel, we really worked closely with them to understand what would be the best tool that we could provide to help them understand their benefit group in primary prevention.

And we endorsed the paradigm, which has really been the paradigm since 1996 and the 27th Bethesda Conference, that we should use absolute risk estimation over the next 10 years as a way to gauge finding the people who are going to benefit the most. That is, patients who are at higher absolute risk deserve more intensive therapy, because they are at higher absolute risk. Patients who are at low absolute risk certainly still need lifestyle intervention when appropriate-- everybody should stop smoking-- but we're probably not going to use drug therapy in those people at lower absolute risk, because they're not as likely to benefit, but they're just as likely have side effects.

So we endorsed that sort of basic paradigm, and then we really dug in in the literature on all of the existing published risk scores that are out there, and there are a lot. If you've been alive for the last decade, you know pretty much every few months we get another risk score to help predict cardiovascular risk, and that's a nice exercise, but when you really want to look at what's the most useful risk score, there a number of things you have to consider. First of all, is it derived from a population that is useful to clinicians in the United States, representative of the broad US population? And that has issues of, does it cover the ages that are of interest? Is it done in both men and women? Does it cover more than just Caucasian Americans? What's the birth cohort, meaning are these people relevant to today, or were they only seen in 1948? Very different world in 1948, obviously. And are they actually from the US, or are they from Europe? Where are the risks? We know the baseline risks are very different.

Many of the risk scores use different types of inputs. All of them-- all of them-- use the traditional risk factors, not because there's a bias toward including the traditional risk factors, but when you actually create these models, the strongest predictors are the traditional risk factors. That's why they were discovered first, and that's what we found as well. We took an unbiased approach to our models, and the first things that came in as strong predictors were the traditional risk factors. Shouldn't surprise anybody, right? But some of them also included family history, some of them include BMI, some of them include measures of socioeconomic status, region. Some of them include, as you know, CRP levels as well.

So we looked at all of those, and there's some very good risk scores out there, there's no question about it, but the other question that's really important is, do they tell you about an outcome that is reliable and that is of interest? And this is where a lot of the risk scores, I think, gave us some problems. First, if it's only predicting cardiovascular death, you are really undervaluing your patients. There are a lot of non-fatal cardiovascular events that occur out there that we really need to be preventing and that we can prevent. We know this. So we didn't like any of the scores that only predicted cardiovascular death.

There are some nice scores that include total coronary heart disease, and they include revascularizations. Now, we all know revascularizations are very important clinical events, but it's really hard to predict who's going to get a revascularization. It's really, really hard. I have a great slide I didn't bring that shows you that there is a tenfold gradient in rates of elective coronary revascularization across this country, and it has nothing to do with the risk levels in the population. It has everything to do with the density of catheterization labs in those zones. And I'm not casting aspersions against our interventional colleagues, but elective interventions-- we have great guidance on those-- but there's a huge practice variation, and you can't predict who's going to get a revascularization. So we didn't think that was an appropriate endpoint. While clinically important, it's not something we should try to predict. We should try to predict clinical events that might lead to a revascularization, but we should not be trying to predict elective revascularizations in the primary prevention setting, obviously.

Hard CHD. The Framingham and ATP-III models have focused on fatal and nonfatal coronary events, right? Really important endpoint, but really important endpoint of you're a white man. If you're a woman or an African-American, your risk for stroke goes up much earlier than your risk for a coronary event. So in the ATP-III framework where we only focus on CHD, we left a ton of risk on the table, specifically for women and specifically for African-Americans. That's why we thought this endpoint must include stroke, because stroke is a preventable atherosclerotic event.

Total CVD endpoints, again, include revascularization, and some endpoints include heart failure. Heart failure is another thing that's really hard to predict. Heart failure is like pornography, and I said this at the AHA, so I'll say it again here. You know it when you see it, but you can't define it. And that's really true in clinical studies. It's really hard to predict heart failure, and every study has defined it differently. We had a lot of difficulty finding one common definition that everybody would agree on as something to predict. Furthermore, statins don't really prevent heart failure except through preventing atherosclerosis. Antihypertensive therapy, absolutely, but direct prevention of heart failure with statins doesn't happen. It happens through atherosclerosis.

So when we ended up we said, we need a risk calculator that predicts heart attack risk and stroke risk combined, and there's no calculator out there that does that. We want to revisit a population that will be broadly representative of the US, as contemporary as possible, and pick up particularly more women and particularly more African-Americans. We would have loved to pick up more Hispanic and Asian-Americans as well, but just aren't cohort data out there. It's a funny thing, when you want to predict 10-year risk, you actually have to follow people for 10 years before you can predict 10-year risk, right? Some people in the media haven't really gotten that. So we used as contemporary data as possible from representative US-based cohorts that included whites and African-Americans.

Most of the data come from followup times from the '90s to 2000, and here's the other thing that happens when you want to predict risk. You must predict natural history. You're not trying to predict statin therapy because, again, that's subject to wide clinical variation. So downstream therapy will contaminate your natural history prediction, and I'm going to show you a great example of that.

So we judge the new risk tool as needed. Again, we wanted to include African-Americans. We wanted to include stroke, and we wanted to get a new look. What things should be included, including we needed new risk markers. We really scoured for representative US population-based cohorts, and in the end we created these Pooled Cohort Risk Equations, including data from the Atherosclerosis Risk in Communities study, about 16,000 white and African-American men and women. Cardiovascular Health Study of older Americans-- again, white's and African-Americans. CARDIA, which is a younger cohort, whites and African-Americans, and then updated data from the Framingham Original and Offspring cohorts, as you know, just Caucasians.

We focused on this hard atherosclerotic endpoint, fatal or nonfatal CHD and stroke. We looked at what should come in, and the data told us that traditional risk factors were still the best predictors, and then we did extensive internal and external validation. About 25,000 people in the models. Age range, where we had robust data, was 40 to 79. Pretty darn good C statistics, indicating we can tell it who's at higher versus lower risk. As always, we actually discriminate risk better in women than men. That's a huge myth that's out there. Always do better in women than men. And these calibration chi squared statistics say, we're actually right on point for our cohorts if we think that a group has about a 7 and 1/2% 10-year risk and, in fact, when we look at the observational data, that's about where they land. So we were quite well calibrated.

So then we did what no other risk score has ever done before. We actually validated our data in an external cohort in the publication in which we first published this risk score. No other risk score has actually ever done this. So we went to two cohorts. Here's the data from MESA. MESA is a cohort of asymptomatic individuals. We just looked at the whites and African-Americans, and they started in 2000.

What happened in 2000 was, they got a very careful assessment of their risk factors, and they got their coronary calcium measured, and those data were sent to the patient and their physician. So we looked at predicting their risk based and what they looked like in 2000, the information then went to their physicians, and 60% of people who were over 7 and 1/2% 10-year risk for a cardiovascular event got put on a statin. What's going to happen to the high-risk individuals? Are they going to live out their natural history for cardiovascular disease? No way, right? They know they have a high coronary calcium score, and a lot of them got prescriptions for statin, so what we found in our validations was, we were overpredicting what the natural history was going to be, particularly in those high-risk groups.

To us this said proof of principle. We know that about 60% of these people up here are actually starting a statin after we've characterized them, and look what happened? It's not that we overpredicted, it's that they underperformed. They didn't have event rates that they were destined to have, precisely because they got put on a statin. And, in fact, a lot of these people got elective revascularizations as well, which probably also contributed to them not having as many events as they might have.

So if you want to find the risk calculator, you can just Google "prevention guidelines risk calculator." You'll get this page. The other thing that happens a lot is people click right on the red button, and they don't read the text. Please read the text. It will save me a lot of emails. How you use this is really well described in there. So you click on that red button, and you'll get a spreadsheet which looks and feels just like the ATP-III risk calculator, by design. We want you to sort of-- if you played with ATP-III calculator, you should feel very comfortable with this one.

It'll ask you to input values for your patient on the sex, age, race, total and HDL cholesterol, systolic blood pressure, whether that's a treated or an untreated value, diabetes status, and smoking status. You'll put the values in in this column, and here's an example. We have a 55-year-old woman, she's African-American, she's got an average total cholesterol for an African-American woman, which is 210, an average HDL cholesterol of 56. I made her a hypertensive who is treated but not controlled, but she does not have diabetes or smoking.

So then you'll get the output. Here's your output. Her 10-year risk for atherosclerotic cardiovascular disease is 7.7% percent. If she had all optimal levels of risk factors, it would have been 1.8%. So relative to her cohorts, she's actually pretty advanced in her risk status. She's over our magic threshold of 7.5%, so I give her a prescription for a statin, right? Wrong. I sit down with her and I say, look, your cholesterol levels are actually not optimal, but you also have hypertension that' not controlled yet.

What should we work on? Where are we going to get the most benefit for our buck? Well, for her, her risk for stroke is probably the chief risk she has in the next couple years. I would aggress on her blood pressure personally first, and I would actually lean strongly towards getting her on a statin at some point in the near future, because I think it's going to benefit her too, but that's a discussion. So I would push hard on her blood pressure first, because I think stroke risk reduction is the main thing I would do for her.

Interestingly, here are the same numbers now plugged in for a white woman, same age, same risk factor levels. Her 10-year risk is only 3.6%. That shows you it's really important to understand risk separately by race. So I think that's a really important part of our risk tool. So we recommended that we use these risk tools to estimate 10-year risk for her first hard ASCVD event for whites and African-Americans. We don't have specific good guidance if you have an Asian-American or Hispanic-American patient. What we say is, you can use the white equations, but if they are Hispanic-American or East-Asian, you will be overestimating their risk. So just know that. If they're South-Asian, you might be underestimating their risk, but at least this can perhaps start to get you in the ballpark. But know that in those other groups, you're not going to be precise for sure.

So the guidelines come out, and then there's a little bit of breathlessness in the media, and Paul and Nancy published unfortunately first in *The New York Times* and subsequently in the *Lancet* some non-peer-reviewed data from three cohorts, the Women's Health Study, the Physicians' Health Study, and the Women's Health Initiative, and what they showed here is a typical kind of calibration curve. The red is the risk predicted by our risk calculator, the blue was the 10-year absolute event rates in these cohorts. Fair enough.

So we want to put these out there so they can get validated and road tested and checked in other cohorts, usually in the scientific literature, not so much in *The New York Times,* but here's the thing. We looked at these cohorts to think about whether we should use them to drive the risk equations, and we rejected them. And there are a bunch of reasons for that. One, they are not at all representative of the US population. They are overwhelmingly white, they are incredibly healthy with historically low rates of smoking-- historically low rates of smoking. And we know already they have extremely low event rates that are not representative of the US population.

So we said, hmm, probably not the best things to use to make our risk equations. Furthermore, two of the three cohorts actually didn't measure risk factors. They asked their participants to mail in reports of their risk factor levels, and they didn't actually report their risk factor levels, they reported ranges of risk factor levels. So there's a real precision problem with some of these cohorts. We don't actually know what the actual value of cholesterol, actual value of blood pressure was in these cohorts. Another reason why we chose not to use these for derivation and why you might not therefore think you would use them for validation either.

Last thing, even though these are really healthy cohorts, they are medical cohorts, at least in the Women's Health Study and Physicians' Health Study. They're highly statinized-- highly statinized-- even though they're healthy, right? Downstream therapy. So they're not living out their natural history that they otherwise would. So a lot of controversy, a lot of discussions. Love it. I can tell you there are papers already in the works that are already submitted to journals looking at these. There is much more to come. Stay tuned, but I haven't heard what's better yet. I've heard a lot of criticism. Nobody's been able to tell me what's better, and I love the discussion. You got something better, I'm all ears. Remember, we had five years to think about this, and we had lots of reviewers, and nobody came up with anything better. Just something to think about.

Just in the last couple minutes, we did do some systematic evidence review to say, how should we flavor risk assessment? Are there other things we should be doing? So we had the opportunity to address two critical questions. First, what other risk markers, even if independently associated with cardiovascular risk, are they adding clinical value to our risk assessment, and we looked at nine of them. CRP, ApoB, GFR, microalbuminuria, family history, fitness, ABI, CIMT, and CAC score.

There are other things that could be on this list? Absolutely. No question about it, but these were the nine that we chose to focus on. Four of them we really didn't see enough data to make any recommendation on, and those were microalbuminuria, fitness, GFR, and ApoB. We just said, need more data. We're not going to make a recommendation up or down on those, but we did make recommendations on the others, and we said, if after you've calculated your 10-year risk as your starting point, if you have further evidence about their family history, their CRP, their CAC score, their ABI, please use those, as was done in the cholesterol guidelines, plus LDL over 160. Please use those to help color your risk assessment. These are things that show added benefit over and above a predicted 10-year risk score.

We particularly put our quarter down on family history, if you have it reliably, as a helpful guide, and coronary counseling. And the reason we saw-- I think, the reason we saw the best data for coronary calcium was, remember, all these other things are risk markers. Coronary calcium actually is the disease of interest. Of course it's going to be a really helpful marker. We don't have great data yet about how it should be used as a screening tool, but if you have it or if you choose to measure it, it can be really helpful if you're on the fence. If it's 0, that's a really low-risk individual. If they're ahead of their age, sex, and risk cohort, you've got to be thinking pretty hard about it, because they actually have the disease that you're worried about.

We found a lot of evidence suggesting that CIMT does not actually add much benefit, and so we said, class III don't do this in clinical practice. It may be a useful research tool. We would not recommend using this in clinical practice, not because it causes harm, but because there's evidence that there's really no benefit. So that was our recommendation for CIMT.

Next thing we did-- and I'm not going to spend a lot of time on this, but happy to answer your questions-- was we said, if you have an individual at low 10-year risk, can you reclassify them, if you will, if you also consider their long-term risk? Are there people out there with a low predicted 10-year risk who have a high lifetime risk? And the answer was, you bet there are. In fact, one of the papers, more than half of Americans who have a low 10-year risk-- less than 10%-- have a lifetime risk that's over 40%. So it may help you in your risk discussion to understand that whether low risk in the near term, perhaps because they're young, they may be at extremely high risk in the long term.

So flow diagram kind of walks you through who should get a risk assessment with the calculator and how to use it which is, again, the starting point for discussion, not the starting point for prescription. And we recognize that there's a lot of work that needs to be done in this area, and ask for specific research to address these evidence gaps.