Welcome and thank you for joining us as we launch a new and informative podcast series on cholesterol management for health care professionals. This series is being developed as part of the American Heart Association’s "Check. Change. Control. Cholesterol” initiative. The goal of this podcast series is to offer expert insights and discussion on the prevalence of high cholesterol, and the risk and prevention of CVD. Improving cholesterol management in high-risk and cholesterol patients, and to identify lifestyle and treatment plans as standard of care. This cholesterol podcast series is brought to you by Sanofi-Regeneron, the national supporter of American Heart Association’s "Check. Change. Control. Cholesterol” initiative.

Thank you all for joining this podcast episode about the 2018 ACC/AHA cholesterol guidelines. Today, we'll focus on the assessment of coronary artery calcification to help guide prognosis and management. My name is Pradeep Nataraja and I'll be your host today. I'm the Director of Preventative Cardiology at Massachusetts's General Hospital, and Assistant Professor of Medicine at Harvard Medical School.

Today, I'm joined by Drs. Ron Blankstein and Khurram Nasir. Ron is the Director of the Cardiac CT program at Brigham and Women's Hospital, where he's also a Preventative Cardiologist, and he's Associate Professor of Medicine at Harvard Medical School. Khurram is Associate Professor of Medicine at the Yale School of Medicine where he's also a Preventative Cardiologist. Khurram also directs the Population Health and Health System's research at the Center for Outcomes Research and Evaluation at Yale. Ron and Khurram, many thanks for joining. I've prepared some questions, so why don't we get started?

Ron, to kick this off, can you summarize the changes in 2018 guidelines compared to the 2013 guidelines, specifically with respect to coronary artery calcium scoring?

Sure. The 2018 guidelines really, first of all, rely on the same risk equation, based on the pooled cohort equation that was used previously, but it now divides individuals into distinct risk groups focusing specifically on those between the age of 40 to 75, where if their risk is less than 5%, they would be low risk; 5-7.5% they would be characterized as borderline risk; the individuals that have a risk between 7.5-20% would be intermediate risk; and a 10-year score more than 20% would be...
considered high risk. One of the big areas of focus is to have a risk discussion between patients and clinicians in order to decide on the role of therapy.

Ron: 02:57 The guidelines do advocate that for the patients who fall into intermediate risk, which is the large proportion of patients with a risk score between 7.5-20%, to actually initiate moderate-intensity statins; but they recognize that there's a lot of variability and uncertainty in terms of risk, and in terms of patients' preferences to be or not to be on statin therapy; and it therefore goes on to state that if the risk is unclear, then individuals can consider, or clinicians can consider, measuring a calcium score in selected individuals. They specifically then state that if the calcium score is zero, that it would be reasonable to withhold statin therapy, and perhaps reassess risk in 5-10 years, as long as other high-risk conditions are absent.

Ron: 03:43 In individuals who are found to have a calcium score of 1-99, they then state it is reasonable to initiate statin therapy for those who are over the age of 55. Then, for anyone with a calcium score more than 100, or those who are over the 75th percentile, that it would also be reasonable to initiate statin therapy. In essence, it now gives us the option of not just calculating the risk score; but also in selected patients, using more of a shared decision-making, and using the calcium score as a tie-breaker, so to speak, to decide on whether to initiate statin therapy.

Pradeep: 04:21 Many thanks for summarizing. What I found particularly interesting, between the 2013 and 2018 guidelines, is now the use of the absence of coronary artery calcification as an actionable data point. Now, Khurram, what's the evidence base for now this increasing emphasis of the absence of coronary artery calcification and disease management?

Khurram: 04:42 So, Pradeep, calcium testing, as we all know, has come a long way since 1991 when Arthur Agatston first described its unique ability to noninvasively estimate the burden of coronary subclinical disease, which we now know is a strong mediator for the majority of preventable cardiovascular disease. With evidence that emerged in the early part of the last decade, the traditional approaches, which rely on clustered risk factors and surrogate biomarkers, lack precision for individual patient management decisions. At that time, aspirations for calcium screening for disease detection that could guide preventative therapy did not appear ambitious.
Khurram: 05:23 Now, as you mentioned about the changes in the 2013 guidelines, we saw a significant shift that broadened the eligibility criteria for preventative therapy, especially statins; and from that perspective, the utility of the preferred rule of calcium testing at that time, which was claimed to identify additional individuals for treatment, again became less than valid. In that time, in spite of being an avid calcium advocate, we were definitely challenged with the imprecise guesstimate that crowd, the statin island, it made us all pause to question the utility of screening presence of disease, to identify individuals for preventative therapy when two thirds of the adult population may be a candidate; however, at the same time, all was not lost, and we felt that rather than abandoning coronary calcium testing, stakeholders may be well-served by acknowledging a key, yet underappreciated, information afforded by it, that is absence of disease.

Khurram: 06:26 Now, using this, in 2015 we provided the first insights on implication of calcium testing that could inform statin decisions within the framework of existing guidelines. As you know, in the prospective MESA study, we were the first ones to establish that nearly half of statin candidates, based on the current guidelines, either who were recommended or considered, had no detectable calcium testing, especially among those in the intermediate 5-20% 10-year risk range. The power of zero was able to reclassify the risk to a category in which the guidelines no longer recommended treatment. Now, these findings were subsequently verified by other prospective study; and in 2015, we explicitly for the first time projected a paradigm shift in the conventional calcium testing... which is screen, detect disease, and treat rule... to one where we felt it would be primarily deployed as a decision aid to de-risk in uncertain patients.

Khurram: 07:25 Now, fast-forward that three years: based on our proposed approach, eventually the new guidelines adopted these findings, and it formed the backbone of the new stance by the Cholesterol Management Guidelines, as well as the Primary Prevention Risk guidelines. I think they took a bold step by emphasizing the role of calcium testing is to guide flexible choices of statin therapy, rather than as a screening tool; it upgraded its role back to a 2a; and for the first time acknowledged that in the absence of calcium, that is a score of 0, can afford you flexible choices when treatment could be deferred or avoided. So, this is a short summary how, over the last 30 years, when Dr. Agatston identified calcium testing for the first time, and the role of it being proposed in the mid-2000s as a screening test, that got momentum in 2010,
eventually it got reversed to where this test may be the most useful when it's 0 in identifying those who don't need a statin.

Pradeep: 08:28 Khurram, thank you very much for the summary. The epidemiology is very compelling.

Pradeep: 08:33 Now, Ron, clinicians often prefer high-quality randomized control trial data, evaluating efficacy and safety when guiding their management. Now, critics of the notion of withholding statins, when coronary artery calcification is absent, often point to the lack of randomized control trial data. What's your impression? What do you think?

Ron: 08:53 Yes, this is a common discussion point and a good question, and we have to think about a couple points. First of all, trials in this space certainly have been proposed; in fact, about a decade ago I had the pleasure of participating in a big effort led by Phil Greenland to propose to the NIH a trial comparing the use of calcium to allocate therapy versus standard of care. Unfortunately, the trial wasn't funded, and today it would be impossible to actually do that trial, at least the way it was powered, to show a reduction in heart events, because statins now are so much a part of standard of care.

Ron: 09:30 The role of calcium scoring today is really very different than it was in that era to tell us who to treat; it's really now where we use it as part of shared decisions-making to identify who perhaps not to treat among individuals that have a strong preference to avoid statins. So, the role of calcium scoring is never to actually say nobody with a calcium score needs to be treated, and there's certainly individuals with a calcium score of 0 that all three of us would agree need to be treated, or patients that perhaps don't mind taking long-term statins and recognize that their risk is low, but they still want to reduce it even if it's for a small amount.

Ron: 10:06 When we use calcium scoring in the context of shared decision-making, the type of trial and the type of evidence I think is very different, and we have to recognize that. I think it's also important to know, though, that many other tools we use in preventative cardiology have not been studied in trials; for example, the pooled cohort equation, the Framingham Risk Score, decisions based on all those risk scores have never been evaluated in prospective trials, so I think that's important for folks to recognize that does not mean that they're not useful; I think all of us use them and we find value in them.
Ron: 10:39 But I think one of the most important aspects, if you're trying to think about what kind of data perhaps is needed for those who say there's no data, but withholding statins, and intermediate risk patients with a calcium score of 0, is the fact that even if you wanted to conduct such a trial, the event rate in patients with a calcium score of 0 is so low... and this is the observed event rate in many of the trials that Khurram just described, and many of the trials that Khurram and other have led... we're talking about event rates of 0, or at times less than 0.1% per year, that if you actually were to calculate the number of individuals needed and the follow-up needed, it becomes a trial that is incredibly difficult, if not impossible, to conduct. I would state that the onus is actually on those who say that a trial like that is needed to put forward a trial like that. These would be trials that would have hundreds of thousands of individuals with very long follow-up in order to possibly show a difference.

Ron: 11:34 To summarize all those thoughts, I think in the current era where we're using calcium scoring more so for shared decision-making, and in selected individuals who have a preference not to be on a statin, this is why I actually don't think we need, for example, large prospective randomized trials to use calcium in that particular role.

Pradeep: 11:54 Khurram, would love to get your thoughts on this. What's your impression on the absence of randomized controlled trial data, commenting also on the logistical challenges? Is there even a need for a randomized control trial?

Khurram: 12:07 Again, while I understand the motivation to confirm the lack of benefit with statins, especially among those with a calcium score of 0 within the intermediate risk group in a randomized setting, at the same time I'm glad that the guidelines did not remain a silent bystander, and did not choose to take refuge behind the pretense of lack of RCT data and maintain status quo, so I have a different take. First, we need to understand why we perform randomized clinical trials. Usually, they're in the context where: a) we have identified a high-risk group; and b) there is a proposed intervention; and finally, we need to assess whether it works in reducing events or not. Now, let's say we come up with a strategy that identifies that many among those whom we considered high risk are actually at a much lower risk than anticipated, I don't think you need a randomized clinical trial to show that withholding therapy in that group is safe or not. It's very simple, as Ron pointed out. We need events to prevent events; and when in a group with those with a
calcium score of 0, we know historically they have very few events; it's very unlikely that statin will reduce them.

Khurram: 13:18 Now, I will also like to point you to another data, although it's not in a randomized clinical trial; however, a recent retrospective analysis showed that among intermediate-risk group individuals with a 10-year risk of 5-20%, statin utilization in those with a calcium score of 0 did not prevent any event as compared to those who did not take over a period of 10 years, again confirming and reassuring what the current guidelines have suggested. So, in the end, I will again echo Ron's thought that the burden of proof, that withholding statins in such a low-risk group is going to be harmful, lies on those who are asking for that evidence.

Pradeep: 14:00 Thank you, Khurram.

Pradeep: 14:01 Ron, now given the stronger recommendation for cardiac CT and selected settings in the guidelines, do you think insurance companies will come around to starting to cover this test?

Ron: 14:12 I think the answer is yes here. There's already coverage of this test, but it's quite variable. There are some states... like Texas, for example... where actually it's mandated to cover this test for the right individuals, and then there's other parts of the country where it's not covered; as a result, a market has emerged where patients actually pay out of pocket, and the price has actually gone down, ironically, as a result. So, this test is now available in many places for $50 to $100 with out-of-pocket payment. Now, I do think there will be movement now for insurance companies to cover this test, and I do know that there are several payers that are actively now thinking about how to change our coverage plans as a result of the guidelines.

Pradeep: 14:55 Khurram, throughout this podcast so far we've talked about selected patients for cardiac CT. Now, how do you actually select people who are good candidates for coronary artery calcification testing?

Khurram: 15:07 For this, again I'll refer you back to the guidelines, and I think they have made very pragmatic and practical choices. Considering that calcium is now being used as a shared decision-asking tool rather than a screening tool, it needs to focus where there is the highest uncertainty. Now, based on ours and many others, we have clearly shown that the uncertainty is significantly less of risk at the extreme of estimated 10-year risk scores; however, the greatest
uncertainty of future risk we have seen lies in those who are in the intermediate group, almost 50% of those individuals who have a 10-year risk of 5-20%. Now, if you look at the guidelines, it clearly suggests that one in two of these individuals actually have a calcium score of 0 that will push them below the threshold where, from our societal standpoint, we are considering statin, and just the mere presence of calcium will push them at the risk that is at the higher level or the threshold where we should be considering a statin. Now, that doesn't mean everyone in this score range is a candidate for calcium testing.

Khurram: 16:20 Practically speaking, you have to advocate for each patient who's sitting in front of you, and you start that with the estimation of individual risk scores. Now, let's assume that somebody comes in with an estimated 10-year risk of 12%; they would be recommended to consider statin based on the given data, but we have an option to personalize that risk, thankfully, which is introduced by the current guidelines, for the patient who's sitting in front of us; for that, you have to try to understand their personal goals, preferences and value; and if these individuals remain uncertain, and understand that there is one in two chance that they will have no coronary artery calcium... and their 10-year threshold risk is not on an average 12%, but 4%... and if that's good enough for them to avoid commitment to a lifelong therapy and just pursue lifestyle optimization, then we should consider calcium; however, some of the patients would like to do anything and everything, as one of the patients we discussed earlier; for them, that's not where the calcium testing should be done.

Khurram: 17:22 So, again, I would refer you back to the guidelines where it's clearly suggested that it should be considered in those who have a 10-year estimating risk of 5-20% and are uncertain of their risk. If you're certain that you're going to take a statin whatever the risk is, or you're not going to take a statin whatever your risk is, then this test is not for you.

Pradeep: 17:44 Thanks, Khurram.

Pradeep: 17:45 Now, Ron, the guidelines do support some scenarios where a coronary artery calcification score of 0 may not be appropriate as a basis for deferring a statin; and you alluded to this earlier, but they specifically state cigarette smoking, family history of premature atherosclerotic cardiovascular disease, and diabetes. What are your thoughts? Is this appropriate? Are there others that we should consider?
Ron: 18:09  Good question, and I certainly think that in high-risk individuals, whether by the pooled cohort equation, if they have a 10-year risk that's greater than 20%, or for other reasons, perhaps there are other risk factors, and in our mind we think someone is high risk, it's certainly very reasonable to not withhold statin therapy even with a calcium score of 0, or in fact not to even perform the calcium score; because if you're not going to use it to withhold therapy, there's really not a lot of need to do it in many of these individuals.

Ron: 18:37  When it comes to these three specific groups, I have to say that I was a little perplexed to see this, in some respects. Certainly, most diabetics, most individuals with diabetes, are high risk, especially if they're on insulin or they've had longstanding diabetes. So, certainly, in select patients with diabetes, there could be a role. Again, if they have a strong preference to avoid statins, and will be willing to take statins if they are found to have atherosclerosis. The other one is cigarette smoking, and that's because we know patients who smoke have more noncalcified plaques, or a calcium score of 0 may not be as protective in them; and of course, we should always remind everyone that the most important intervention in cigarette smokers is not necessarily the statins, but it's stopping to smoke, which would cut the risk by 50%, more so than any other intervention.

Pradeep: 19:26  Khurram, I'd love to get your thoughts. What do you think about these three categories? You've contributed to some of the observations of coronary calcium score distributions among diabetics, and also recently among patients with familial hypercholesterolemia. Are there setting where you would not get a coronary artery calcium test, looking for a score of 0?

Khurram: 19:46  Pradeep, I understand and mostly agree with the guidelines, and the data suggests that the value of testing is minimal at the extreme spectrum of the 10-year calculated risk, but let me remind you it's not negligible. For example, the guidelines suggest that we should not perform calcium testing if you have a 10-year risk of less that 5% and I am onboard; however, there are going to be some individuals, some exceptions, especially those with a very strong family history of premature cardiovascular disease. Now, it's well-known that even among those who are considered traditionally low risk, and have a strong family history of premature cardiovascular disease, they are more likely to have presence, as well as a higher burden, of atherosclerosis. So, that would be an exception, in my view, and something that is also considered by the Society of Cardiac CT
Khurram: 20:48 Now, the other population that I think would be very helpful is those with a familial hypercholesterolemia, genetically determined familial hypercholesterolemia. Now, don't get me wrong: the whole idea here is not to considered using a calcium score of 0 to identify those who are not statin candidates. In our view, and as per the guidelines, everyone with genetically determined familial hypercholesterolemia, especially heterozygous, should be on high-dose statin; however, as you will recall, recently we published a paper with our colleagues in Brazil where we showed that a significant proportion of those patients, vulnerable patients, almost 48% had a calcium score of 0. Even about 1:3 age 50 and above, those with genetically confirmed heterozygous familial hypercholesterolemia, had a calcium score of 0. When we followed them for a median of four years, extended up to seven, we did not identify any cardiac event.

Khurram: 21:45 Now, the implications here are all of these patients would be candidates for aggressive treatment with PCSK9 inhibitors; however, these findings need to be confirmed in other studies.

Pradeep: 21:58 Excellent. So, Ron, if a score is 0, do you repeat it? How do you decide? Do you use clinical risk factors? When do you repeat a score, if you're repeating at all?

Ron: 22:09 I will sometimes repeat it, not automatically in everyone, and generally repeated in around five to 10 years. First of all, if I make that decision whether I want to repeat a calcium score, I obviously would want to make sure that that scan is going to have a potential impact on how I manage a patient; for example, if a patient had a calcium score of 0, but over the years I think the risk has gone up, perhaps we're going to start statin therapy despite a calcium score of 0 over time; and at that point there's not as much role for repeating it, perhaps, if there's uncertainty about the intensity of therapy; but if I've already made the decision for another reason to start therapy, the role of a calcium score will be lower. Also, some patients I see have had issues with statin therapy; and no matter what score, they're not going to want to be on statin therapy, and I'm not going to... If they were fortunate enough to have a cal score of 0, I'm less likely to repeat it if I don't think it's going to change practice.
Ron: 23:04 One of the things I do look at, when I decide whether to repeat it, is also the age of the patient when the score was obtained. Sometimes, we'll do calcium scores on young individuals at age 40, and they have a higher likelihood of converting to having atherosclerosis or having calcium on a repeat scan; as compared to if an individual in their 70s has a calcium score of 0, perhaps with those folks I'm less likely to repeat it down the road; knowing that if you've made it to a certain age and did not develop any calcium in your arteries, you're probably less likely to have calcium upon the repeat. Those are generally the different factors that I have to think about. I do occasionally repeat calcium score. I certainly don't do it for everyone that has a calcium score of 0; and when I do repeat a calcium scan, it would generally be in five to 10 years.

Ron: 23:50 There's various factors that I will consider when making that decision whether to repeat the calcium score; for instance, I would like to know what is the impact of repeating the scan on patient management. If an individual has already started statin therapy since the calcium score of 0 that was performed a couple years before, there would be less of the utility to repeating the scan; they're already on therapy. In another case perhaps someone is very resistant to being on statin therapy, and maybe they were fortunate to have a calcium score of 0, but they absolutely would not want to take statin, and I think less of a utility for repeating it in that particular scenario. I also look at patient age, because some individuals when they have their calcium score are young; so individuals that have a calcium score of 0 at the age of 40, they may be more likely to develop calcium over a follow-up. Conversely, a person in their 70s, if they've made it that far and never developed any calcifications, less likely to develop calcium over time.

Ron: 24:49 Finally, you have to put it also in the context of all the other risk factors, so patients that have multiple risk factors and generally have a higher risk score to begin with... not the calcium score, but the ASCVD risk score... they're going to be more likely to convert and to have calcium on subsequent exams, as opposed to low-risk patients are likely to stay without calcium. These are all factors that I would look at, but I think the most important factor is that I want to make sure that the scan, if I repeat it, will actually change how I'm managing that patient; and if the answer is, "I don't think it will make a big difference," then I'm less likely to repeat it.

Pradeep: 25:23 Now, Ron brought up an important observation that younger individuals often have a lower prevalence of coronary artery
calcium; and it's often hard to identify patients who sustain premature events, because they have low 10-year risk, often purely driven by age. Now, Khurram, are there times that you consider coronary artery calcium scoring in young individuals, or those with low 10-year risk, for the purposes of classifying risk and starting a statin?

Khurram: 25:48 Pradeep, as we discussed earlier, that while the greatest utility still remains among the uncertain patients who are in the intermediate risk range, above the age of 45, I think there are some patient populations that even at a younger age, or at a risk group that's less than 5%, would be appropriate candidates. The first one, as we had discussed earlier, are those with a family history of premature cardiovascular disease. I would definitely undertake calcium testing anywhere from age 40 and above, and especially if their 10-year risk is less than 5%, a case common in young women. Second, those with established metabolic syndrome, they have a higher prevalence of positive calcium even at a younger age. Thirdly, diabetics, although are not a group where calcium testing should be performed to guide management, we feel that there is no extensive data that potentially tells us that an absence of calcium score could be reassuring and guide flexible choices in this group. Finally, those with genetically confirmed heterozygous hypercholesterolemia where an absence of calcium score can allow some flexible choices for consideration of PCSK9 inhibitors, whereas those who have a very high calcium score and at a much higher risk, can help us work with insurance companies to get the appropriate therapies for these vulnerable patients.

Ron: 27:16 Basically, this is a common question, "When do you start doing calcium scoring?" and even though the guidelines and most of the data now suggests age above 40, and some high-risk patients I will actually give a calcium score above age 35. There are some data, for instance in the CARDIA study, Jeff Car led a study looking at the impact of calcium scoring in very young individuals, and I think one of the important points of any amount of calcium at a young age is strongly predictive of risk and automatically puts the patient above the 90th percentile for their age, especially if they’re under the age of 40. So, if calcium is found in young individuals... perhaps it's not because they had a calcium score, perhaps they had a chest CT or a CT for another reason... any calcium in a young person needs to be taken very seriously, and I think should be a call for treatment. That's just an important message that may not necessarily be in the guidelines, but it's good for people to know that any calcium in young folks is a really ominous sign.
Excellent. Thanks to you both for that summary. Now, this was mentioned earlier: statins are very available, they're pretty cheap, they lower cardiovascular disease risk across baseline risk categories; and Khurram, you did mention something about cost-effectiveness. A big change between the 2013 and 2018 guidelines was more emphasis on cost, but really as it related to PCSK9 inhibitors. Cardiac CT is another test. So, given these data about statin: Ron, could you give us a sense of the cost-effectiveness of coronary artery calcification scoring for allocating statin prescriptions?

Sure. There have been several studies on this, at least three studies... in fact, Khurram has led some of these... and basically these studies collectively they show that the use of calcium score is actually very favorable from a cost-effectiveness analysis, but only when certain assumptions are met, and this is typical of cost-effectiveness analysis. There's always assumptions that can be highly influential in the analysis; those assumptions are, of course, with statins being cheap and being generic it makes the use of statins for everyone more favorable; but calcium scoring becomes particularly beneficial when the cost of a calcium score is $100 or less, which it is right now in many places in the US that have active programs.

It's also more favorable to do calcium scoring if there's reluctance on behalf of a patient for being on a statin; this is what we call an economic analysis, the disutility of being on a statin, and how much value individuals have in not being on a statin? There's certainly data on this; in fact, it's always remarkable to me to look at some of these studies showing that people are willing to give up a number of months of their life just not to be on a medication; and certainly in those people, calcium scoring may be more effective if there's a real value for not being on a statin. So, I think as long as these assumptions are met, that there is a disutility for being on a statin, that it's not a free drug that has no side effects and nobody cares about taking it: as long as there's a value for not being on it, a calcium score becomes attractive from a cost perspective, especially when we're looking at a society perspective.

Pradeep, I would just like to add on this. I totally agree with Ron here. One of the key things that we need to understand is that we are trying to look at whether calcium testing approach is more cost-effective. I think another approach should be: is it as cost-effective as compared to the current recommendations of treat-all in that 5-20% 10-year risk range? Now, even if you take into account all rigid assumptions, including that the outcome
of treating those with a calcium score of 0 with statin will almost be similar to those who have a fair amount of subclinical atherosclerosis; however, even if we take that, as Ron pointed out, what we have seen is that this approach is going to be as cost-effective, especially when the patients are uncertain; and when they are uncertain, there is a higher disutility. Secondly, if you're able to keep the prices at an average of $150 or less, and especially less than $100, a scenario that we're seeing in many places in this country, we can reassure you that the calcium testing approach to guide statin therapy actually becomes more cost-effective than the treat-all for those who are recommended, based on their 10-year risk scores.

Pradeep: 31:31 Now, Khurram, I have many patients who are already on statins for primary prevention and they really want to know what their underlying [inaudible 00:31:39] atherosclerosis is. So, these are patients who are already on statins, and they're coming and starting to ask about coronary artery calcium scoring. What would you tell them?

Khurram: 31:47 Pradeep, this is a tough one. While we all appreciate that the true value of calcium testing still remains among the statin naïve patient; but at the same time, it's a reality that we see many patients who are already on statins now having doubts. So, what I usually try to do is understand what was really the underlying motivation for starting statin in the first place. Was it that they had a significantly higher baseline risk? Or was it maybe to an upgrade of the recommendation, that we also in 2013 now remember with that upgrade, anybody with one to two risk factors after a certain age group could be a candidate of statin in the first place. Now, if that's because of that, and now that it appears that the patient will rather not oblige to commit for a lifetime utilization of statin, calcium testing may not be inappropriate.

Khurram: 32:38 Let's assume if they have a calcium score of 0, it can guide them about their choices; but at the same time there is an additional benefit. What we have seen is an excellent study by, Ron Blankstein's group, that recently showed that among individuals who have a positive calcium and a higher burden, they are more likely to remain adherent to their medication, so it provides two great options; and if you do not have a calcium-positive, then it may allow you to have flexible choices. But once you are able to see that you have disease in your coronaries and early progression, I think it provides strong motivation for these individuals not only to adhere to the guidelines recommended with therapy, but also optimize their lifestyle, which is going to
be a key factor in preventing future cardiovascular disease events.

Ron: 33:29 I may add here the fact that there could be a role. I generally agree with Khurram; but at times, I don’t really know their burden of atherosclerosis; by doing a calcium scoring, knowing how much plaque they have, and thereby knowing their risk, if I think that can impact the intensity of therapy... perhaps they’re just on a low-dose statin, their LDL is only around 90-100... and if we’re finding a large burden of disease, we would intensify therapy; to me, that’s one potential reason for doing it.

Ron: 33:57 The other one, as Khurram mentioned, it’s not just about medical therapy, but we have shown that patients that actually are found to have atherosclerosis are more likely to exercise and they’re more likely to in fact lose weight, and they’re more likely to change their diet; unfortunately, the data has not shown that they’re more likely to quit smoking quite yet, so we need to work on that one, but there’s definitely beneficial lifestyle changes that happen when patients have calcium, and in my mind also has to do with how we communicate that risk, which is a separate story.

Ron: 34:26 Finally, the other thing that may apply to this scenario is whether they need to be on aspirin. I think we’re all getting calls these days, after the new prevention guidelines, from patients asking whether they need to continue their aspirin therapy; and if patients are found to have severe amounts of coronary atherosclerosis or a calcium score greater than 100, I would say there is some data that tells us that they may be more likely to benefit from aspirin, or at least enough so to overcome the risk of bleeding. I think we used to say once you’re on a statin there’s really no role for calcium scoring, but I do see now selected cases where that information can be very helpful.

Pradeep: 35:02 Great. This issues comes up a lot. Another issue that comes up... Ron, you alluded to this earlier... is that patients often get non-gated chest CTs for a variety of reasons, more commonly than getting cardiac CTs. How reliable is the absence or presence of coronary atherosclerosis calcification in this setting, and can you use this data in place of cardiac CT derived coronary artery calcification score?

Ron: 35:27 This is a good question because chest CTs are being done for so many different reasons. Lung cancer screening, for example, is becoming more popular. Generally, when you see calcium on those CT scans that are not gated to the heart, it’s real and you
can visually look and estimate how much calcium there is there. You can even quantify the calcium score off of a chest CT that's not gated to the heart, and there's some research showing that that score actually is fairly accurate. So, when we see calcium, especially if there's a lot of it, we can identify the patient as having atherosclerosis and requiring more intensive therapy. On the other hand, if we don't see evidence of calcium, the data to support that being the equivalent of a calcium score of 0 is not as robust; in fact, you can have minimal amount of calcified plaque and perhaps not see it on a non-gated CT.

Ron: 36:18 If anything, if you're missing calcium it's probably a small amount, so the concern is to truly say that you have a calcium score of 0 today still requires, for the most part, a calcium score, which is a gated scan; however, if the CT is done for another reason and you see plaque on it, I think it's important obviously to report that plaque. There's a lot of research showing that that is often under-reported or not reported at all; but if we know that it's there, we should be acting on it.

Pradeep: 36:46 Khurram, when you're practically talking to patients about coronary artery calcium scoring, what downsides or risks do you end up discussing? What do you talk about with regard to radiation exposure, incidental findings? Do you talk about out-of-pocket costs?

Khurram: 37:02 This is a great question, Pradeep. Apart from identifying the right individuals who may be candidates for statin therapy, the choice of getting it is not straightforward. There are pros and cons, and the things that I discuss with the patient. First and foremost, it's the cost. The average national cost for getting a calcium testing is around $100, ranging anywhere from places I've seen that do it for $50 up to $150... which may be equal to almost two years of generic statin, if that's $5 a month... so that's definitely a conversation that we should have with the patient. The chances of that being negative, and whether a negative test would help them avoid taking a pill a day, is that cost worth it? Now, based on my experience I can tell you, irrespective of the socioeconomic status, most of the patients tend to have a disutility of taking a pill every day however cheap, effective, and [inaudible 00:37:58].

Khurram: 37:59 A cost around the $50 to $100 has never been a major issue even out of pocket. We should all disclose that the radiation is equivalent to a bilateral mammogram that most women get every year after a certain age. It's almost also an equivalent dosage of whether you would fly back and forth from the East
Coast to LA a couple of times. So, from my perspective, I get this information and usually I don't see that to be a major issue; however, one of the challenges that I feel is the highest consideration is going to be among those, if you are dealing with the low socioeconomic patients, for example Medicare, which is definitely expanding, and we know that even when making $45 to $50 out of pocket could be a challenge for them. That's why when Ron pointed out that there is a significant need for the national reimbursement policy to be pushed out, I cannot emphasize it enough; because if it doesn't happen, it's likely going to become a burden for those who cannot afford to pay, and we definitely need to do something about it.

Pradeep: 39:11 Ron, anything to add about discussing downsides and risks with patients?

Ron: 39:16 No. I think Khurram got all the key points there. I mean, yes, there are sometimes incidental findings that require follow-up, and certainly those can be of concern. To me as a clinician they're a concern. Patients rarely if ever say, "I will not have the test because I'm concerned about [inaudible]." As clinicians, we are all concerned about those. Patients certainly are concerned about radiation; and I think as much as the dose is low, it's going to keep on going down. There are now various techniques being developed that will make the radiation dose, or the calcium score, even lower.

Ron: 39:48 The other thing is to put all of this into perspective with the fact that cardiovascular disease is still the number one killer in the US; and overall in the US, most people are undertreated both with respect to whether they're on statin therapy when they need it, and also the intensity of therapy. So, I do like to remind patients about the benefits and about the importance of preventing heart disease not just with calcium score, but everything else we do in preventative cardiology, that in my mind at least the value of knowing your risk is so important. Certainly, yes, there are downsides to the test; but I think they, for the most part, fail in comparison to the true value of the exam.

Pradeep: 40:23 Ron, overall in summary, are you happy with how coronary artery calcification is incorporated in these guidelines? Is there room for improvement?

Ron: 40:32 I really think the guidelines, for the most part, got this right; and I really salute all the authors of the guidelines, both the cholesterol guidelines, and more recently the prevention
guidelines, a really thoughtful group of individuals. I know they spend a lot of time thinking about these topics, and this is not easy. I tell you on a guideline committee, being faced with the evidence, being faced with the data and knowing, "How are we going to phrase this?" is certainly challenging because this has been a controversial topic over the years, but I think they really got it right. They are endorsing now, the guidelines are endorsing, calcium scoring... not for everyone, but for selected individuals, as it should be... and really focusing in on the fact that when patients or physicians are uncertain about risk, and therefore using this particular test as a decision aid tool. I think as long as we use it in that context, it has a lot of value because it allows us to pick who are the individuals that really would benefit from a calcium score, as opposed to just applying it in a blanket fashion.

Ron: 41:30 Then, there's always some nuances in the guidelines about what we would do, "How do we act on the results of the calcium score?" And there's certainly agreement that if the calcium score is over 100, to treat; but I would state that even in most intermediate risk patients with a risk score of 7.5-20%, the presence of any calcified plaque, any evidence of atherosclerosis, automatically would put them above the 7.5% threshold. So, I see room for treating anyone that's found to have calcium, as long as their pre-test risk is in that intermediate risk group. I think that's more maybe a small area that perhaps needs more thought for future guidelines, but it is a small area, and for the most part I was very impressed with these guidelines. I'm already seeing adoption of these in my own institution. I know clinicians don't always follow the guidelines, but these are guidelines that have really been embraced by the general cardiovascular community.

Pradeep: 42:24 Khurram, just in the weeks before the guidelines were released, you published an editorial in JACC with the subtitle saying, "Time takes up the power of zero," and this was a direct comment to the authors of the cholesterol guidelines. Did they accept the power of zero? Are you happy with how coronary artery calcium scoring is incorporated? Also, do you have any thoughts on improvements for the future?

Khurram: 42:47 That's a very interesting observation, Pradeep. Before the guidelines came in, I wasn't too sure that they would adopt such a dramatic change; however, if you ask me, I'm really pleased. I think, just looking through the lens of the calcium testing, it's really modernized its role from the initial proposal where most of us were considering it as a screening test, to now adopted by
the guidelines finally as a tool, a shared decision-making tool, that would guide risk assessment and informed treatment choices. So, from my perspective, we have made significant progress out here, and it was great that the guidance acknowledged all the evidence that came over the previous five years. At the same time, I don't think our work is done. We have to look at the future because that's where we'll all be spending most of our time.

Khurram: 43:34 Now, among the things that are still pending and needs to be addressed, the number one is trying to get national coverage for the reimbursement of calcium testing because we cannot exaggerate the existing disparities among who need it versus who can afford it. At the same time, there are certain things: their need for a pragmatic statin clinical trial to see whether this approach works or not, and I'm for that; but when it comes to the application for a pragmatic trial, I think that we need to be mindful that our outcomes need to be also pragmatic beyond the traditional outcomes where we are not emphasizing around cost, shared decision-making, quality of life, and utility. The third item, a significant role that has not yet been explored, though will be extremely useful, is how calcium testing can identify candidates for more expensive preventative therapies, such as PCSK9, the EPAs, that eventually will need to be assessed and randomized controlled trials.

Khurram: 44:35 Now, what about also the more advanced antidiabetic therapies? This is where we all believe there is a significant valuable calcium testing as an accompanying tool to identify those who are at the highest risk, a double screening, such as a calcium score of greater than 100. It will have two benefits: first, it will avoid enrolling patients who have a calcium score of 0, unlikely to have any event in the next five years; and secondly, it will enroll patients who are at the highest risk where there is enough residual risk for these expensive therapies to act.

Khurram: 45:14 Finally, I think while the power of zero is now well-established in the primary prevention settings, I think we need to start pushing and giving attention to the extensive literature that deserves its value of a calcium testing as a gatekeeper for more advanced testing, such as stress testing, and coronary CT angiogram, and truly lower-risk symptomatic patients. Ron is working on those guidelines, so I may eventually request him an opportunity to write another perspective piece before the guidelines come in, ensuring that the new guideline authors accept the power of zero in the symptomatic work.
Pradeep: 45:55 Excellent.

Ron: 45:56 I second that, Khurram. I think we need you to write one on that when the time comes, but I think Khurram makes a really important point here because in cardiology we are moving more and more towards more aggressive LDL lowering. There's a pipeline of new therapies; there's new trials ongoing with PCSK9 inhibitors to lower risk populations that may benefit, or perhaps even benefit more, from PCSK9, and there's other therapies on the horizon. I think the guidelines currently appropriately focus on statins; but as we look into the future, I see calcium scoring as not just a way for telling us how to allocate statin, but how to allocate some of the more expensive therapies that we are currently struggling distributing, especially given their higher cost.

Pradeep: 46:40 Well, Ron and Khurram, thank you very much for the enlightening discussion, and thank you all for tuning in to this deep dive into coronary artery calcium scoring, and your general interest in improving your clinical practice. Thanks very much.

Ron: 46:55 Thank you, Pradeep.

Khurram: 46:55 Thank you, Pradeep. It was great having this conversation.

Pradeep: 47:00 Thank you for listening, and please stay tuned for upcoming podcasts, and American Heart Association's "Check. Change. Control. Cholesterol" podcast series.