Non-Invasive Technology for Coronary Artery Plaque Analysis Evidence Review Contractor Advisory Meeting

Meeting Details	
Meeting Date:	May 25, 2023
Facilitator:	Dr. Denise Nachodsky (WPS Government Health Administrators) and Dr. Meredith Loveless (CGS Administrators, LLC)

Dr. Loveless: Welcome everyone to the Multi-Jurisdictional Contractor Advisory Committee meeting regarding Non-invasive Technology for Coronary Artery Plaque Analysis. I'm Dr. Meredith Loveless, CMD with CGS Administrators and I'm joined by contract medical directors from NGS, WPS, Noridian and Palmetto, and we all welcome you to this meeting.

We thank you for taking time out of your day and practices to be part of this process. Only the panelist and CMDs have speaking capacity on this call. All others will be in listen only mode.

This meeting is recorded, and audio and written transcript will be available on all of the participating MACs websites in about three to four weeks after the meeting and for anyone who is hearing impaired, you have the ability to turn captions on. If you go up to the top, where there's three little dots and there's a more tab that can be used as a drop down to access the transcript option.

Part of the LCD modernization as a result of the 21st Century Cures Act is a call for Local Coverage Determinations to be based on robust scientific evidence. The purpose of this meeting is for our expert panel to serve in an advisory capacity to review the quality of evidence used in the development of an LCD.

Our CAC is advisory in nature and final decision on all issues due rest within the MAC. While our experts represent vast clinical experience, since the process demands a focus on evidence, we'll ask our panelists only share evidence-based feedback.

I understand there are many experts that are not on our panel today and CAC members from across the country who are listening to this meeting. For our jurisdictional CAC members who join us, we value your input and feedback and assure you that you were part of the process. We welcome you to invite your comments in writing to your local MAC, accompanied with a completed conflict of interest for.

For all other interested parties, if a draft policy is developed and released, you will have an opportunity to submit written comments as well as provide presentations, if desired, at your jurisdictional open meeting.

All feedback and comments through the open meeting process and open comment process are considered in any final policy development.

I now want to welcome and thank our panelists for their time and willingness to share their expertise. This panel was nominated by their respective medical societies and peers, and they have a broad representation in terms of geography, practice, settings, background and medical specialties.

The next slide is a disclosure slide, stating everything that we share today is accurate as of today. Of course, Medicare changes rapidly. So, we only can guarantee up till today. Now I'm going to ask for our panelists to introduce themselves and I'm starting in alphabetical order and were asking each of our panelists just to give a brief background as well as their conflicts of interest.

And I do not believe Dr. Bhakta is on. If I'm not correct, if you can please speak up.

So, we're going to move straight to Dr. Calnon.

Dr. Calnon: Yeah, I'm Dennis Calnon.

I'm I have no financial disclosures at all or relevant to this topic. Did you say you want a little bit of background?

Dr. Loveless: Yes.

Dr. Calnon: OK, I'm a cardiac imaging specialist cardiologist in Columbus, Ohio and I'm Level 3 trained and board certified in Echo, Nuclear and Cardiac CT and a member of all three organizations.

Dr. Loveless: Thank you. That's a great introduction for everyone to hear you because I know this is new for almost everyone on.

Dr. Calnon: And I forgot to say I'm also here as a representative of the ACC.

Dr. Raible: I'm at Norton Healthcare in the Louisville, Kentucky, and I'm a multi-modality imager to include echo, nuclear, CT and MRI. As far as financial disclosures, I have some done some consulting for Heart Flow and our health system was one of the Beta sites for the plaque AI analysis and we participated in plaque review.

Dr. Rose: Yeah. Hi, good afternoon, Jeff Rose. I'm an echocardiographer with Atrium Health in Charlotte, NC.

I have no financial disclosures relevant to this. Our organization has worked with Heart Flow on various projects, but I have no personal conflicts.

Dr. Slim: Hi, I'm Ahmad Slim. I'm a multi-imaging modality cardiovascular imager. I'm the regional chief medical officer for Pulse Heart Institute in Washington and I'm the SCCT representative with no financial disclosure.

Dr. Thompson: I'm Randy Thompson. I'm a multimodality imager in Kansas City and Professor of Medicine at the University of Missouri, Kansas City. I'm representing ASNIC.

I am also an advisor to the MAC PT editorial panel for the ACCI, and I was one of the presenters for the current Category 3 code for Plaque Analysis 0623T and that that family of codes.

I don't have any financial conflicts of interest. I am a middle author and some of the papers that were in the bibliography was enrolled in the Credence study.

And the number of the papers were in our scientific background.

Dr. Tukaye: I'm Deepali Tukaye, I'm an interventional cardiologist with Duran Medical in Houston, TX with a special interest in coronary Physiology and sorry, I'm running a little late because of a STEMI, so I'll be getting to my office in 5 minutes. I'm in my car right now, but nice being here.

Dr. Winchester: I am David Winchester, professor of Medicine, University of Florida College of Medicine, Multimodality Imaging, primarily CT, Nuclear, and echo. No financial disclosures.

Dr. Woodard: Yes, thank you. I'm a radiologist specializing in cardiovascular imaging at Washington University in Saint Louis.

I and I am an NIH funded researcher and I study targeted plaque imaging with various imaging modalities looking at vulnerable plaque. I am representing the ACR.

I have no disclosures, no conflicts of interest.

Dr. Loveless: And we appreciate all of you and because we have an ambitious agenda and turning things over to begin our questions.

Dr. Nachodsky if you can begin.

She will read off each question aloud for anyone who is joining us by audio only.so hey can understand what we're talking about.

But for anyone who is on the screen, the questions are present on the screen and again, somebody jump in and answer and then if you have additional information, we'll use the hand raise.

Dr. Nachodsky: Great, Thank you so much, Dr. Loveless.

Right from the start though, I'd like to echo what Dr. Loveless said in the beginning that I personally want to thank the panel experts in advance for your time today.

and sharing your expertise and your willingness to educate and provide insight regarding this innovative cardiac non-imaging modality.

It is so much appreciated prior to us starting our questions though our collaborative multi-jurisdiction MAC cardiology workgroup would appreciate some consistency and clarity among the panel experts regarding the definition of the acronym AI-QCT during our medical literature review, we have seen some discrepancy of different definitions for this acronym.

The majority of our research reviews, particularly the Clarify and the Credence Multi-Center International Studies and the subsequent medical literature that references these studies, they define AI-QCF as artificial intelligence enabled quantitative coronary computed tomography angiography.

So, the AI stands for artificial intelligence and QCT is quantitative computed tomography. However, there have been some references that we have seen where they have made reference to AI-QCT as Atherosclerosis imaging-quantitative computed tomography.

And so, our collaborative work group we have acknowledged this acronym definition in all of our research as referencing it as the artificial intelligence and enabled quantitative coronary computed tomography angiography unless otherwise directed from the group here.

So, any comments on that would be greatly appreciated.

Dr. Slim: If you don't mind, Can I go ahead and start?

I really appreciate the definition that you provided.

However, the technology itself is primarily used for plaque quantification, which is a lot more expensive than degree of stenosis. Provide information on plaque burden, plaque volume, plaque composition, fibrotic, fiber, fatty plaque, Necrotic Core.

There is some additional component of quantification of stenosis, but it's an additional benefit.

But the primary utility of it is an identification of the high-risk plaque that even in non-obstructive disease it can lead to increased outcomes as we've seen in many trials.

Dr. Woodard: Yeah, I want to echo what Dr. Slim has said.

You know, while there are a lot of tools to assess percent diameters of stenosis, what we are defining today is a tool, while it may also do that, really looks at the plaque composition, whether or not there's a non-calcified plaque versus calcified plaque.

In order to determine what type of and the volume of this plaque in order to determine what type of risk the patient is at. Literature for decades has demonstrated that non-calcified plaque is more vulnerable to rupture and to give you a major adverse cardiovascular event. So, to give you a heart attack, calcified plaque and as the non-calcified plaque becomes more calcified, it becomes more stable. And so those patients are less likely to have an acute event.

They may have angina, chest pain, chronic chest pain with exertion, but they don't have what people might think of as the big one that gives you that heart attack and kills you.

So, the definition of the AI-QCPA is really to characterize the composition of the atherosclerotic plaque, not just the percent diameter stenosis. Which you know might tell you whether you'll have. You have angina, but whether or not you may have an event down the road, so the definition is a little different than what you currently have here.

Dr. Raible: I agree with the last two speakers and just to echo their points when you say QCT to me that you're talking about diameters stenosis a particular part of the vessel where you're trying to determine whether that stenosis is responsible for ischemia Do we need to do anything about it?

Where the plaque analysis as, the other two have mentioned, is really an assessment for a total disease burden and whether there's aspects of that disease burden which put the patient at higher risk and has relevance in sort of your short-term management as well as your long-term management goals.

Dr. Nachodsky: Thank you all.

So therefore, just for consistency, then if we say AI-QCT-QCPA, this would be interpreted as the artificial intelligence enabled quantitative computed tomography-qualitative and quantitative computed plaque analysis.

Are we in agreement if we were to say so, as we are reading and pursuing writing policy, that would be our definition and consistency with the panel here is AI-QCT -QCPA?

Dr. Slim: That that's reasonable. But I would say, A_-QCPA in the in the front because really that's the primary function of the technology.

Dr. Woodard: Yeah, I agree. This is principally for plaque component analysis.

Dr. Nachodsky: OK. Thank you so much. Very helpful everyone.

OK, we can now go on to the second question, that was quick.

The second question here is what is the current gold standard for measurement or characterization of atherosclerosis?

I mean, we know that there is IVUS and there's OCT and there's also now the near infrared spectroscopy IVUS Are these considered the gold standards currently today?

Dr. Slim: This is really the gold standard outside of an autopsy where you're looking at a histological cross section of a blood vessel. IVUS has data that that puts it as the gold standard near infrared has some follow up data that she will changes in outcomes as it relates to the type of block.

The fiber fatty block within a necrotic core with increased risk. So, from a gold standard to compare outside of an autopsy, this will be it with this one caveat.

This approach is invasive, so it only applies to patients to undergoing coronary angiography which becomes a very smaller group of patients as compared to you know Cardiac CT which is less invasive when comes with less complications.

Dr. Raible: I would add that the current plaque analysis programs of which are several.

All were sort of standardized or subsequently adjudicated by the OCT studies where they measured a segment of plaque volume by ultrasound and then looked at the same segment of that artery on CTA and measured the plaque there. And that was how they adjudicated the current plaque analysis programs, the non-invasive ones, by using the 3D information from an ultrasound.

Since the AI plaque analysis takes into account the whole vessel, you could almost argue that that is the new gold standard. But its segment segments were verified with IVUS 3D volumes, not just two orthogonal views of angiography.

Dr. Woodard: Yeah, I think. What Dr. Raible is saying that the gold standard currently is IVUS. You know the true gold standard is autopsy, but you know that there are certainly issues with that and so in clinical care IVUS which is invasive is the principal modality if you would like to determine the plaque component.

It has gradually been shifting to CT where you can very easily without invasion look at the components of the plaque, and so this particular technology is essentially attempting to take the place of IVUS in that you have a non-invasive modality that can tell you what the volume of the non-calcified non-fibrous. The softer tissue plaque, the non-calcified plaque that provides the risk.

Dr. Winchester: If I could chime in for just one moment, I was going to say that I have a little bit of trouble with the question and my problem with the question is that I'm not sure that there is one gold standard and then I think the other a problem I have with it is whether or not atherosclerosis needs a gold standard.

And when I say that I mean that sort of implies that every patient should have it and maybe not. Maybe I'm just reading it the wrong way, we can do IVUS in patients and we've talked about how that's very good at doing plaque composition. But most of the folks that that I've worked with and Cath labs here at my institutions we use IVUS, but it's not like something when the Cath gets done and everybody also gets a full coronary tree IVUS.

And so, if you're looking at an individual plaque would say IVUS is one of the best options we have, but that's the that's the only thing so that kind of makes this question a little a little weird for me. I think it's not quite the defining exactly what we want for patients and unless I'm just reading it wrong.

Dr. Nachodsky: I think the purpose of this question, Dr. Winchester, was for us to be able to use when comparing studies and results for efficacy or sensitivity and specificity, we wanted to know what is the current gold standard that is used that we might be able to compare with some studies is what probably the indication for this question was.

Dr. Thompson: AI-QCT-QPCA has been a validated against intravascular ultrasound and to a lesser extent against histology and therefore its conclusion would be that it's been validated against what would be considered the gold standard.

Dr. Nachodsky: Thank you very much for that comment. Do we have any other or any other comments?

Dr. Rose: There's another element here too that perhaps we're going to get into and that is the gold standard of AI in assessing this, as opposed to human beings assessing atherosclerosis through CT.

So, yes, the correlations I agree with the other speakers in terms of using IVUS as the principal modality, but then we also have the separate question of expert readers using CT to be able to quantify plaque volumes versus automated algorithms being able to achieve that same end.

Dr. Nachodsky: Thank you Dr. Rose and I think that some of our other questions are pointing to that as you see in the list, but much appreciated.

Any more comments for Question 2? Otherwise, I'm going to proceed to the next question.

Question three: Given the current available medical literature is their sufficient evidence to validate the use of AI- QCT or let's say AI-CPA?

For consistency here in the repertoire of the many non-invasive imaging techniques that we have to include it in the standards of medical practice, and also to include it in our specialty society guidelines such as guidelines for CAD evaluation or chest pain evaluation, what evidence do we have that can support and what limitations exist?

So, our concern or is we know CCTA is invaluable to us. It's non-invasive. It offers a significant amount of data for us to treat or direct the treatment of our patients, but we're talking now if we use AI-QCT-CPA, not just for CCTA. Is there enough evidence that we think we should be able to put it into our specialty society guidelines and included in our standards of medical practice?

Dr. Slim: SCCT shared before the meeting a compendium of data on publications to include data from iconic data from Scot Heart, Promise, Paradigm trials as well as guideline recommendation on the utility and the non-obstructive disease patients with which has been a recommendation as well 2021 consensus document from SCCT.

Happy to go over some of some of the trials if that's needed to share with the group, but I want to be cognizant of time, but there is definitely data and clinical trials to support the utility. We know that the high-risk plaque, we do know that the low attenuation of plaque spotty calcification, the volume of plaque and the stage that it applies correlates with significant three-to-four-fold increase in cardiovascular outcomes and we do have some data on a plaque progression. There's data for follow-up CTAs showing plaque changes and some associated outcome changes.

So, there is data to support it that we shared with the with the group, but we're happy to go through it 1 by 1 if needed.

Dr. Thompson: I would add that some believe this sufficient evidence to be included in for evaluation of coronary heart disease, but not evidence to be included in chest pain guidelines yet, Regarding the question asked him about limitations I'm not sure if that's an opening to list all the limitations of and what's not known about AI QPCA, but I'll call your attention to a state of the art review that appeared in JAC earlier this year, and some of those are spelled out there.

For example, there's evidence lacking and the variability by location, order size, or image quality available. Data is also limited in how technical or patient specific factors result in measurement variability, but composition subgroups, diverse patient groups have not been tested. There are some technical issues that are important. There's an inverse relationship between two potential and higher two voltage scanning between 80 and 120 associated with decrease in luminal attenuation. You really require good action on image quality. Derivation cohorts have generally been highly selected, and with all these kinds of predictive models, performance will deteriorate when applied to images that differ from training sets. Different disease problems, artifacts change, the luminal vessel of all varied scanners and there's also a fair amount of overlap between unit density for the categories of atherosclerotic plaque. And there are others, but I think that probably it ought to be in the record of there are some are some limitations and that relevant to whether we can apply this in broad groups of patients and whether they're very close to being in chest pain guidelines for example.

Dr. Slim: Now I was just going to say there is some validation with some of the publications done where there's comparison between expert readers, Level 3 readers, and AI algorithm.

And it does take an average of eight to 10 hours for an expert reader to generate the same data as compared to AI algorithm and there is over 50% more detection of high risk compared to Level 3 expert readers. So there is some publications out there that identifies and support the utility of the AI and it's accuracy with a good sensitivity over 88% with 92% for specificity.

There is there is some data to say with every technology that we have, there are limitations and some of it that was brought up earlier is limited to CCTA per se and which equipment you're using, not necessarily the AI algorithm by itself.

So, it's a pyramid and at the top of the pyramid is just kind of generate as bunch of data. But when we apply it to the right population, as we do with any technology, and this is where the medical expertise comes in, then it will provide us with a more accurate representation of the whole blood vessel and better representation and a better pickup of high-risk plaque from an expert Level 3 reader.

Dr. Woodard: The FDA has become relatively rigorous in its assessment of AI algorithms in terms of what it requires for AI.

In other words, continuous learning AI where the algorithm has a potential to change over time. They are not looking for autonomous AI. They're looking for defined algorithms that have undergone, not only have been developed on a rigorous set, but also have been tested in a separate, more heterogeneous test set, and maybe even multiple test sets.

So, as AI has become more popular in many of our technologies, the FDA has become more rigorous in assessing that the algorithm is accurate.

Dr. Raible: I agree with all the above comments, just to mention in the chest pain guideline from October of 2021 or November, the concept of looking at plaque burden was introduced.

It's under section 5.2 and patients with no non-obstructive disease with stable chest pain. That's at 2A recommendation that patients with non-obstructive sees CCTA is reasonable for the determining atherosclerotic plaque burden and the progression to obstructive CAD in terms of guiding therapeutic decision making.

So, they didn't necessarily mention an AI program for defining all the quantitative things that we're talking about, but certainly the guidelines do suggest the concept that we should be that looking at the plaque burden and plaque composition to guide our therapy.

Dr. Slim: Just to highlight the obvious, at the end of the day, this is an AI augmented algorithm and the keyword is augmented. We still have a reader that's going to analyze the algorithm and the analysis and generate a report talking about the quality, the quantification and the methodology. It’s not an automated report that just carries through.

So there is there is second layer of review evaluation that to account for any variance and just to add one more, we don't want to forget about the CAD-RADS reporting system now incorporating the plaque analysis discussion in this final reporting. So, there is some support from a few guidelines.

Dr. Winchester: I just wanted to add that if I think about different software packages for analyzing coronary CT and over the years, the software’s have gotten a lot better and made us much more efficient at being able to quickly analyze the scan.

And you know, some of the earliest options we have are basically just looking at the cross-sectional images or something that lets you add a little trail down of coronary so that the software can attempt to come up with some sort of model. And now the most modern stuff that we have you click one button and it shows you all the coronaries and you’re under the responsibility of still going back and checking the original data, but that's certainly does help to facilitate reading and to come up with a very comprehensive report on all the findings. And so, to the extent that an AI augmented software package could make that even easier to be even more thorough about exactly how much plaque is there and the characterization of the plaque that would be potentially a useful tool to have.

Dr. Thompson: So, let me sort of ask a question about this utility that you mentioned Dr. Winchester. With many with all imaging modalities that we use in acute coronary syndromes, for example the test is used to inform a treatment like coronary calcium score, a number of publications show that doctors changed the treatment based on the coronary calcium score. I'm not aware of any published information that shows that using AI-QCPA, have people have documented they changed the treatment? Does it change the treatment and if so, has that been published or known, or is that still a limitation?

Dr. Winchester: I totally agree with you that's my understanding- the next step that this sort of thing needs to go to.

Dr. Thompson: It makes sense. This is the whole idea here. You're going to give more intense treatment to patients that have high risk features and so forth.

Dr. Slim: Yes. So, there is definitely data out there as far as treatment changes and plaque composition when done in clinical trials, you know for example the PARADIGM with statins and there's data on PCSK 9 inhibitors and even colchicine.

But as far as the AI itself, I know there is stuff coming in the pipeline that they are working on before the end of the year that potentially under embargo, but there is at least from the AIP's I can't speak to it, but at least from the analysis itself, the plaque analysis there is changes.

The article by Freeman that highlights the impact of different treatment and how you can escalate therapy based on the findings of non-calcified plaque and even the plaque volume to a higher level and to different stages and different treatments based on that.

Randall Thompson: Those are research studies, not clinical practice reports or documentation, aren't they?

Dr. Slim: Yes.

Dr. Rose: Perhaps even the Scot Heart trial helps us in this regard, even though it wasn't about quantitative plaque. You know the outcomes are there at five years and you know a higher degree of treatment was shown based on the on the images.

So I think the lines of logic follow as we go forward in terms of seeing plaque quantifying it, compelling treatment and influencing outcomes.

Dr. Slim: And if you look even at the Scot Heart, when they looked for lower attenuation and plaque burden over 4%, there was fivefold increase of risk for that population as compared to everyone else.

So, when you're looking there is on this a large trial over a very long period with significant reduction that was independent of the synopsis.

Dr. Calnon: Where you're talking about changes, I think what you're saying is that there are changes in plaque volume and plaque characteristics with medical therapy.

But what I think Randy or maybe it was David Winchester was asking is what change would you make?

I'm trying to envision using this and saying, well, the calcium score is 300, but they also have quite a bit of vulnerable looking non-calcified plaque. I'm going treat that patient aggressively already with high intensity statin therapy and aspirin and aggressive risk factor modification in every possible way.

I'm trying to envision how this would in any way change what I'm already going to do for that kind of patient.

Now you can envision, someone with minimal to no calcification detected and then yet has a whole lot of non-calcified dangerous looking soft, vulnerable plaque that you might treat them more aggressively than you would based on a calcium score alone.

That's my question is compared to visual estimation of a coronary CTA, this may be more quantitative and more measurable and more accurate and comparison to IVUS, but I'm trying to figure out how I would use it differently to manage the patient right now based on what we know now?

Dr. Slim: Going back to the recommendation of the Prevention Work Group, there are different categories based on the plaque volume and the associated risk that comes with it and different interventions to include escalation of care, adding Zetia, adding PCSK 9 inhibitor, antiplatelet therapies and escalation of care that's based on clinical trials that shows changes in the plaque morphology.

Now I see where you're coming from as far as the aspirin and statins across the board, but that's what we're trying to figure out, right, the Holy Grail. In the in the past, we see two non-obstructive lesions, we treat them the same, but then six months later, there's that one patient that comes back with the massive MI. So this is the technology that's going to allow us to identify one patient had a calcific block where aspirin and statin by itself is enough and the other patient is the one with the high risk block that requires the escalation of therapy with Zetia, with PCSK and inhibitor, and even with colchicine in some of the trials. Now, there is no outside identification within a 4% within the Scot Heart subgroup when you when you look at it, there is follow up studies like Paradigm where they looked at the statins versus non-statins and the changes in in the plaque volume and the other studies mentioned earlier where there's correlation. But we also know in patients whose plaque continue to get worse, their outcomes

got worse. We're trying to connect the dots and we're still need direct hard endpoints, but we do have a significant amount of literature that's out there that correlates the changes in plaque morphology that we do know that in the long run leads to worse outcomes with aggressive therapies.

Dr. Thompson: Do we answer your questions after this asking, Dr. Nachodsky?

Dr. Nachodsky: Yes, this very same question was actually further, so I'm glad we have an intro to it. One thing I just wanted, Dr Slim, the one study you mentioned, I didn't quite hear the other study when you were talking Scot Heart. I was writing down notes here and thank you much appreciated.

Dr. Slim: You know, and I'm happy to share it with you at the end of the meeting.

Dr. Nachodsky: The input from all of you is amazing here and the professionalism with which it is handled between all of us, the academic learning environment here is wonderful. It's much appreciated as we go into the next set of questions.

The next question is really in the scan preparation technique. Now we know that many of the studies when you start with doing your CCTA, we use a beta blocker and nitroglycerin and that can alter when the patient comes in with chest pain. If you're going to give them a beta blocker, you're going to give them nitryl. Is that is going to change their clinical physiologic presentation? It changes your heart rate, blood pressure and has an anti-ischemic effect. It vasodilates the vessels versus when the patient may have come in with the symptoms.

So, AI-QCPT, I'm trying to say the right initials here. We know it's very beneficial for the patients atherosclerotic plaque burden and it's composition and what's in the plaque and we know that these medications are not going to change the plaque composition, but we're concerned versus how would it affect if we're using this modality to decide if we're going to go on to more invasive procedures in regards to ischemia. The use of this technology as I said for morphology, genotype, vessel stenosis at rest data processing, and increasing the expediency with which you can read and the type of plaque that you can read of this technology versus just CCTA would be great for CAD prevention and some medical therapy, but in regards to using this with ischemia, will not these drugs alter the results in when you're trying to compare to other non-imaging modalities or invasive coronary angiography?

Dr. Slim: So, just to highlight the one thing though is when it comes for plaque morphology, right now, the standard of care is IVUS, correct me if I am wrong.

We do radio and when you're doing radio, you do Nitro, you do verapamil and that does not in any way shape or form affect your IVUS result, what we are comparing to the gold standard because the plaque morphology is a plaque morphology.

And there is really not statistically significant change even when you're using these drugs in quantification of the stenosis. If anything, what we're trying to capture here, you know which is the high-risk block that sometimes is missed in stress testing because it's designed to capture the obstructive lesion.

Now there there's other technologies that we can talk that measure cardio blood flow and so on and so forth.

But at least in the sense of stress testing, if there is a higher risk block that's not obstructive, is not going to be picked up in that environment.

But if we're trying just to compare apples to apples when we're doing invasive angiography and IVUS as compared to CTA using the nitrates and the AI QCA it, we're comparing the same mechanisms and if it's going to affect one, it should affect the other one and you know vice versa. So, I don't see the preparation of the for the CTA impacting the final outcome or the result of the algorithm.

Dr. Tukaye: So, I actually agree with that statement that question I give Nitro even before I get started with the FFR IFR. Primarily because that'll give you the true assessment of what the flow would be if the patient was an optimal medical therapy. Basically, that's what you are assessing. You need to intervene only if optimal medical therapy is not sufficient, so the premedication for the CTA for assessment of will not affect what the downstream outcomes will be.

Dr. Calnon: I was just going to say that I certainly agree. In fact, I just wanted to point out that the opposite is actually true. If you don't use beta blockers and don't get good heart rate control, image quality may suffer and then the accuracy of the quantitative plaque assessment may be reduced. And if you don't give nitroglycerin, the studies that validated the use of nitroglycerin as part of the CTA. So, in fact, the opposite is true. You need to use beta blockers and nitroglycerin to ensure adequate image quality and accurate quantification. And I was just

going to mention while I have the microphone that our reference number five was the Scot Heart article that he was mentioning that was included in our references that were provided, Dr. Williams's first author.

Dr. Thompson: I was going to say something similar to what Dr. Calnon said is that the technique for AI-QCPA? I guess we're saying was validated using best practices for coronary CT angiography including beta blockers and nitroglycerin.

And I've seen some writers expressed concern that nitroglycerin is not given, which usually that happens with the coronary CTA, the patients' blood pressure is low or whatever.

Dr. Woodard: And I also want to concur with Dr. Conlon that you need to give a beta blocker and sublingual Nitro. The better the image quality, the better your AI algorithm will perform.

So, and really the goal of this software is not to predict ischemia, we have other tools to predict ischemia. The goal of this software is to characterize the plaque in order to predict event. So, not ischemia but an actual an acute event.

Dr. Nachodsky: Thank you so much, Dr. Woodard. That was just to the point in what we needed here. Really the goal of this software is the analysis, the morphology, the quantifying it and the use of those medications would be good for but not in regard to if you're trying to evaluate for ischemia. So much appreciated everyone. Is there anybody else? I still see maybe one hand up that will need to speak.

OK, I thought that was going to be more troublesome, so thank you.

So, this question ask medical profession specialties will perform this and interpret these AI-QCT studies and what medical training and certification will be required not only from the physicians but as well as your technical staff?

Dr. Slim: You would need to follow the same criteria for reading cardiac CT because you need to understand the cardiac CT, you need the same level of training.

So historically speaking radiologist with cardiovascular training or cardiologists with cardiovascular imaging training fulfilling their code requirement to read Cardiac CTs and like I said, the algorithm is generated but it's AI augmented and you need someone to be able to compare and adjust and provide the final report. We should have that training.

Dr. Nachodsky: Great, so for all the physicians out there that are not in fellowship programs and are not going to go back into another fellowship program, besides our academicians and physicians like you who are experts, what do you think it's going to require so that many other clinical cardiologist and cardiology radiologist can do this?

Dr. Winchester: When CT first came on the scene for cardiology, academic institutions put together training programs for people in practice that they could go and then do to learn the technology. When the transcatheter valves came on the market, we didn't have any influx of invasive cardiologists coming back and redoing training.

They did an appropriate amount of workshop training and if this is something that becomes widespread, then I'm sure we'll have agreement amongst the people that develop in the professionals that set academic standards that will come up with. If you're going to do this, you need to this to be familiar with it.

Dr. Nachodsky: Thank you very much. Then as far as your technician staff, do you believe also that there will be additional training or certification that they will be required to do?

Dr. Calnon: What my understanding is, there is a little bit of quality control required by the technologist, but it would be similar where they are trained for coronary CT angiography.

It would just be a little updated training, just like for the physicians who use it.

The technologists would need to as well, but my understanding is there is some technologists sort of intervention required to ensure that the acquisition is accurate and that the quantification will be accurate.

Dr. Thompson: Yes, currently all the systems are cloud based. They're sent off rather than the analysis performed by this technologist.

Dr. Nachodsky: Great. Alright, I think we'll proceed on to the next one. So, if we have any invasive cardiologist here to be able to help with this question. So, what is the average number of views at an invasive cardiologist uses to determine coronary stenosis when you're in clinical practice?

The reason why we're asking this is because some of the Medicare articles that were comparing AI-QCPA stated that in their studies was compared to only two views of invasive coronary angiography views.

I know that in the Cath lab, if you have difficult lesions and all that, I believe that the invasive cardiologist may use more views to determine if they're going to proceed doing an intervention or not. And so, our concern is if the studies have only compared it to two invasive coronary angiography views, would that affect the accuracy or the sensitivity and specificity reporting from these studies when they compared it to ICA?

Dr. Slim: If you don't mind, I'll answer it in two ways.

The QCPA is, like we mentioned earlier, is in comparison to IVUS and OCT, which is not based on the two orthogonal views. It's based on the image rendered in a 360 view, and that's what you're obtaining and comparing to.

There are some vendors that did some studies that compare that capability to compare QCT and do some diameter stenosis, but I'd like to describe that as the icing on the cake, but not the primary function of the algorithm, the primary function of the algorithm is independent of the orthogonal views.

It's an evaluation within the lumen and outside the lumen to determine the plaque burden and there's 360 views if compared to IVUS, but of the whole blood vessel, which is independent of the orthogonal views.

Dr. Calnon: I would just add that the two fundamental differences between coronary CT and invasive coronary angiography would be the three dimensional nature of coronary CTA versus more of a two dimensional nature of invasive coronary angiography, but then on the other hand, the spatial resolution differences where CT does not have quite as good of a spatial resolution as invasive coronary angiography.

So, those are sort of the two fundamental differences that would affect any comparisons of stenosis severity, for example.

Dr. Nachodsky: Thank you very much.

OK, if we'll go on to Question 7 what is the quality of evidence on plaque burden and role in the management of patients at risk for coronary artery disease or acute coronary syndrome?

So, it is their evidence to support that non-invasive imaging is accurate for this evaluation? I think this was one of the questions that we had started to get to in question two, when we were talking about what do you do with this data and how does it change in the role of management for patients who have CAD RADs coronary syndrome.

Dr. Rose: So, I think that you know, again I think if we go back to the Scot Heart trial, the answer is yes, where we're seeing five-year outcomes survival advantage in a greater degree of preventive therapies in the cohort that underwent CT evaluation correlating with plaque burden. So that's before we even get into specifics of plaque volume and plaque characteristics, but just your plaque burden. So, I think that there's a clear role for assessing plaque burden in chronic coronary disease.

Dr. Slim: Yes, and as you mentioned earlier, we shared the compendium of data, you got articles, you got trials like iconic Scot Heart, and PROMISE identifying the type of plaque and the high-risk plaque carries higher event rates compared to the calcified stable plaque.

There is an acute chest pain, _____ one and two identifying the type of plaque increased the incidence of ACS in the short term. You have data from PARADIGM, so we know that the type of plaque makes a big difference in the outcomes. The calcified stable plaque is not going to generate higher adverse events as much as the high-risk plaque and high volume of the of disease within a chronic course.

So there is a lot of data that shows having these plaques is bad and you know for a while this is the one thing that we've always tried to figure out when we do a Cath and we have two lesions that look the same, yet one patient has an event and the other doesn't. These are the things that we're trying to figure out.

That's not delivered through calcium score and other modalities, that is the plaque composition, the plaque burden, which tells us where these population is that we're able to aggressively treat and have more discussions with the patients to alter course.

Dr. Calnon: I would just say that I feel very convinced that detecting and quantifying atheromatous plaque is clearly a way to identify high risk patients and then treat them more aggressively than you would if they do not.

The only question I I'm wondering still in the back of my mind is, if I have a coronary CTA angiogram which I can visually assess and see that there's calcified and non-calcified plaque and there's extensive based on a calcium score plaque. I'm trying to still imagine, how I will

treat them differently if I get a quantitative measure as well, and whether that would actually change things?

And I guess that will just be determined in the future, but I agree this was certainly give you a more automated and quantitative measure of plaque burden, but you do get a lot of that by visually looking at a coronary CT angiogram as well.

Dr. Raible: There was a study published earlier this year. The Architect study, which patients were just given high intensity statins and the other the other group got the PCSK 9 inhibitors at the end of 78 weeks.

They actually showed a quantitative decrease in the amount of plaque between those two groups. So, this is an example where they were following these patients with an AI plaque determination and they documented the improved results with the therapy.

And so, as everybody else has said, identifying the patients with the high risk lack and then applying therapies and then perhaps even checking them several years later to see whether the therapy is hanging as desired effect.

Dr. Nachodsky: So, Dr. Raible, in that study that you were just speaking in regard to, so you said that then you know giving a data change to therapy maybe became more aggressive or used other type of medical therapy.

And you said that they studied them later, did it show a change in the plaque from, let's say, a very vulnerable high-risk plaque to one that was more calcified or less chance of, eroding and having an acute event?

Dr. Raible: I have to go back and look at the specifics. I remember a 4% absolute reduction in plaque volume, but I can't remember about the plaque.

Dr. Nachodsky: If we change the characteristics of it where it is no longer a high-risk plaque that was a gooey type of plaque versus our hard plaque. My definition is it gooey or is it not?

Dr. Slim: So there is data from PARADIGM, with a follow up CT that shows that there is a change in plaque composition with statin therapy, there is articles on icosapent ethyl PCSK 9 inhibitor with evolocumab and even _____ and all of these are listed in a table in the Fremont article or happy to share that at the end of the meeting.

Dr. Thompson: I have, in addition, to what Dr Slim says. They're also is the IVUS literature showing that aggressive treatment with statins at least aggression or less progression with and this AI QCT has been partially validated against.

I was also going to jump in about what Dr. Calnon had about what does the doctor do with the individual patient? I would just point out those robust literature showing that coronary plaque, plaque burden are based on coronary calcium scoring is very robust and the doctors do act on it and it's so there was sort of getting this when I'd say this presumption that the detection, the high risk features on the CTA would then lead us to change treatment and reclassify patients in both directions as higher risk or perhaps if there's no high risk features and not very much soft plaque that the patient would be reclassified as less risky.

Dr. Woodard: And I should also point out that what's nice about knowing how much non-calcified plaque there is and what the patient's risk is that you may not want to provide aggressive therapy in all patients.

In other words, if you have a middle-aged woman who's trying to get pregnant, they're going to be classes of patients where it might be easy enough to say let's just give aggressive therapy to everyone. Not everybody is going to be a prime candidate for aggressive optimal medical therapy. If you know that there's a lot of plaque, you know you then you might say, well, you know in this patient, we really need to go ahead and provide this therapy regardless.

Dr. Slim: Now, I'm sorry, I didn't mean to interrupt, but I was just going to say, I mean, the whole PARADIGM shift in our mentality in all of our guideline recommendation is having a discussion with the patient and coming up with a plan that applies to them. Not all patients tolerate therapies well, and you know, we've all have stories about some patients not tolerating the maximum dose of statins.

And before you sit and have a conversation with someone to talk about additional therapies on top of the existing therapies they have, knowing that they are at the high risk spectrum and showing to the patient they are the high end of the risk of the spectrum makes that conversation a lot easier than you know broad brush stroke saying you're just high risk and we're going to throw the kitchen sink at you and that conversation is very difficult for anyone in practice trying to have that conversation with the patient.

Dr. Raible: The Architect data did show a decrease in the gooey plaque is then the chronic plaque from 4.1% to 1%.

Dr. Nachodsky: I think Question 8 is very much very similar to what we are talking about right now.

If there's anyone who wants to speak further, but it is, what is the clinical benefit that AI-QCPA, which would bring to clinical care? And does this technology change clinical management and how?

And I think several of our questions have been addressing as to the different type of therapies that we might use, knowing what the plaque is like. Should we give them this therapy? Should we not? Risk stratifying them, I understand.

Is there anything different from question seven that others would like to add for additional information?

I think we kind of added some of these questions knowing that we were so fortunate to have so many experts in the different specialties who are willing to provide us some information and insight that we thought if we had it just tweak the question a little different way. It would make sure that everybody gets an opportunity on the panel to be able to speak, so I'm going to proceed into question #9, OK, which may take a little bit longer discussion.

So, in the clinical decision pathways for patients who present with chest pain and suspected acute coronary syndrome, coronary artery stenosis quantification and ischemia, these two concepts are significant determinants that guide the disposition of the patient's either being discharged, putting in observation or in a chest pain unit.

It may direct the type of conservative medical therapy versus proceeding with other non-invasive diagnostic imaging or advancing directly to ICA with potential intervention.

So please comment on the accuracy and the indications of AI-QCPA versus the other current imaging modalities. Regarding these following two issues.

So, for sub question A, coronary arteries stenosis quantification? Discuss the method and accuracy of this technology for stenosis quantification in patients who would have diffuse non-focal, coronary artery disease, such as our diabetics or our transplant patients or sometimes very elderly, frail thin female patients who may have that just diffuse vessels.

How will we be able to use this technology to accurately assess for stenosis quantification?

Dr. Slim: I think we're already answered the question prior about this stenosis piece and then ischemia. I think when we're talking stenosis and ischemia completely different discussion than plaque composition in diabetic and cardiac plants transplant, if you're still going to get the same information in our population, again there is data that shows even in the high risk population identifying and finding a high risk block incur even higher incidents of event rates.

So yes, and I know some folks will say well diabetics carry a high risk of events, but there is data to show that high risk plaque and high volume of high risk plaque and high risk population incur higher event rates.

But for ischemia this is not the QCPA functionality, it's the plaque composition.

Dr. Calnon: I was just going to say that in patients who have diffuse disease or coronary microvascular disease, for example, and transplant vasculopathy is a good example.

All of the anatomic tests, including invasive coronary angiography, are somewhat limited and that's where functional testing, for example, preferably myocardial blood flow reserve assessment with pet or cardiac MRI or better in that situation.

So again, it's not really a good application for this kind of a technology is sort of the microvascular disease.

Dr. Thompson: I was going to add that yes, the real strength of AI QCT is plaque characterization.

It can accurately and reproducibly measure corner synopsis compared to expert readers, so it there might be some usefulness there for as a second reader, second opinions sort of thing or perhaps if the synopsis is close to a 50% threshold, that kind of thing.

So there's some added value there, but it's less than the catheterization.

Dr. Nachodsky: OK. I think we're beating a dead horse or how many times I'm going to still ask the same question that yes, it's for plaque analysis and I'm getting it's very good, and our group appreciates this very much because we need to find the niche for this technology and not try

to take away from some of the other non-invasive technology that is very helpful in directing therapy for our patients.

So, I'm getting the just here from the answers of our experts here that AI QCT PA is really this modality is really for determining the analysis, the quantification, the morphology of the plaque.

It really is not the modality to be used for stenosis or for ischemia evaluation, where you should rely more on a functional study such as a stress echo, stress nuclear, MRI, PET studies with pharmacologic agents etcetera.

So, my next question leading to ischemia evaluation was basically just to reinforce that thought that if you're going to use this technology versus the other non-invasive imaging modalities that I've just stated.

Stress echocardiography, PET, MPI, CMR which can detect perfusion abnormalities. It can measure the changes in the EF. It can identify new wall motion abnormalities or transient ischemic dilatation as part of their ischemia evaluation.

Those are the studies that we should rely on for that versus that would not be the role of this technology. Am I getting that picture from you all?

Dr. Slim: So, AIQCPA is there for the plaque morphology.

You know that if we're going to talk about comparison and the CT world, there's other codes like CT-FRR.

So, there is some other ways utilizing CT to determine that, but for the purpose of this technology is really plaque analysis.

Dr. Nachodsky: Great. I really appreciate where we're finding the niche for this technology.

Dr. Thompson: Just to clarify. At least one of the vendors at Clearly has an ischemia evaluation product based on AI that would then be reported with a different CPT code though that's not part of this billing code or concept.

Dr. Nachodsky: OK. So, can you just extrapolate on that in regard to what other vendor, I mean not to see the name of the vendor, but what other thing is being added that you can event?

So that's where this question then comes into play. How could this AI CCTA, then let's put it that way, be able to compare to these other modalities for an ischemic evaluation?

Dr. Thompson: I was referring to a product that's not FDA approved, but I believe it's a different category. It's using AI and this analysis with machine learning to predict myocardial ischemia. In compared to invasive FFR. That would be comparable to CT-FFR and, you know, presumably reported once FDA approved reported in the same way with that CPT code.

Dr. Nachodsky: OK, so that's coming down the pike is what you're telling me.

Dr. Thompson: So, I hear.

Dr. Slim: Yeah. So that's a that's a different algorithm to generate flow, but not necessarily in this scenario.

Dr. Nachodsky: So, we're saying, that I mean with the advances in cardiology as they are, that there will be some eventually down the road. This is the niche for AIQCPA, let's find out what the plaque is like. Let's have this, perhaps as our gold standard, but now that down the road there may be some other AI related algorithms that will be able to be compared against like fractional flow reserve in the future.

Thank you for clarifying that and giving me an update on what to expect in the future.

Let's go to 10 what would be the role and indication for AI-QCPA versus just CCTA alone?

Dr. Slim: Again, it goes back to CCTA provides a lot of information, not necessarily just, you know, coronary evaluation, but it will provide the stenosis piece, part of the expert reader. The process itself to generate plaque analysis is extensive and even in the research world, it can take 8 to 10 hours of work where with the AI augmented piece it can deliver the same quality if not higher quality of picking up high risk plaque and providing the analysis for the reader to review which is unique to it the. But as you know cardiac CT has a lot of applications coronary evaluation is one of them.

Dr. Calnon: One thing that I would say, so if you're asking how would you add AI QCPA to coronary CTA?

I would say that it would be most youthful. It still needs to be defined, but in people where a quantitative plaque analysis and plaque characterization would change your management

and that will have to be determined based on changes and advances in medical therapy and everything else.

But I would say that at this point in time, if the coronary CTA is completely normal with no detectable plaque whatsoever visually, I imagine that the benefit of adding this would be relatively low.

To add the quantitative plaque analysis, just to confirm some plaque, and similarly it may be maybe I'm wrong that when there's very, very, very severe and extensive obvious, visually evident, calcified and non-calcified plaque and severe stenosis on coronary CTA and you know for sure you're going to manage this person, very aggressive medically and with invasive coronary angiography.

I would think that the benefit of adding quantitative plaque analysis might be relatively less too, although maybe there's some advantage still in this population.

So in my opinion it would be in more of the intermediate range of people where there's some plaque, not very, very severe. And quantitative analysis might really change your management.

Dr. Slim: Yeah, I couldn't agree more because we do expect about 40% of CTs to be normal and then within a group that's abnormal, really, it's the Holy Grail for those that you want to identify, the high-risk plaque, especially in a non-obstructive population.

There are smaller groups in the obstructive that appears high risk on visual inspection, but really the Holy Grail is in the group that you know is the best intervention is medical intervention and you're trying to figure out from the two groups that look similar, which one really needs that aggressive bombardment with medications to make a difference in their outcome.

Dr. Nachodsky: OK. Thank you everyone. Dr. Woodard, did you have a response? It looks like you wanted to talk.

Dr. Woodard: Well, you're right. Actually, I agree with both Dr Calnon and also Dr. Slim it will be a select patient population. It's not like you would take this and use this AI algorithm on every coronary CTA that you performed.

There would be some where you would say that there's so much non-calcified plaque here that we want to go ahead and perform aggressive treatment.

There will be some that have no place whatsoever. It's going to be in the patient populations where you know there's a moderate amount of plaque and those individuals you where you're trying to decide do you really want to provide aggressive therapy?

Dr. Nachodsky: OK. Thank you. We're getting lower down. Can coronary CTA with this technology reduce the need for invasive angiography? If yes, I think we're starting to lean to which patients do you feel confident that you can rely on this data and not proceed with invasive angiography? And then what evidence is there to support this to ensure the new technology does not miss legions that would have been detected on invasive angiography?

Dr. Slim: So, I would have to divide it into elective and I guess _____.

And the reason that I'm saying that is if you focus on therapy and decrease the event rates and decrease the MI, your subsequently decreasing invasive interventions, right.

But if we're talking about elective cases, when there is a flow limiting blockage, that's assessed by whichever mechanism for ischemia, this technology is not going to play a role. But in interim and secondary prevention and decreasing that down the road.

I don't know if that makes any sense, so I say yes and no, depending on which situation that you're looking at.

Dr. Rose: Yeah, I might say it could be a yes and yes, in the sense that you know, certainly if we're intervening earlier, we're going to reduce subsequent events and reducing the need for invasive angiography.

But I think in clinical practice today with a lot of the modalities we use to assess our patients, we're still left wanting for an answer in those patients wind up going to the Cath lab for "the gold standard" and we have data from CT alone without augmentative technologies on reducing the need for invasive angiography in that regard.

And I think that that's only further complemented when we can provide more incremental information about plaque burden.

Dr. Winchester: I think this is an interesting question. Again, about reference standards, gold standards.

Because we think about it's sometimes as you said and basic angiography is considered the gold standard.

I think that's more when we're not quite sure what's going on in in regard to a degree of stenosis, but when the question here asks how do we ensure this technology doesn't miss lesions that would be detected on invasive angio.

I would argue that invasive angio misses plaques more than coronary CT does.

You're looking at the lumen of the angiogram, and unless you do a full triple vessel OCT or IVUS and you're only looking at the lumen, you're going to miss plaques on an invasive angiogram that you might otherwise spot on a CT, where maybe the positive remodeling has not resulted in a stenosis yet.

Dr. Nachodsky: Thank you for that. That was actually a very good answer Dr. Winchester.

Anybody. Pamela?

Dr. Woodard: OK. Yeah, I'll just add to that that like Dr. Slim mentioned and also Dr. Winchester added, it's, you know essentially this is sort of a 2-level approach.

Coronary CTA in and of itself, reduces the need for invasive angiography.

And so we know that we've demonstrated it and now that's why it's part of the guidelines as the first you know imaging test. The QPCA could reduce the need for invasive procedures with IVUS.

So, you know by having the coronary CTA together with this methodology, as David said, you're eliminating the need to go ahead and if you wanted to fully understand what the risk burden was of performing a 3 vessel IVUS, which is really highly impractical.

Dr. Nachodsky: OK and so I think for question 12, we can just add on to this current question because we're comparing it with invasive angiography and then just to bring on using this technique with or without FFRCT or invasive FFR.

Are there situations where we're going to need both measurements? I mean, as Dr. Loveless has said at the very beginning of this meeting, cost is not part in our policy making. We have to see that we are doing the best for a beneficiary with evidence-based medicine. However, there comes a point where you have to say I'm not going to do 10 non-invasive tests on a patient and then I'm ultimately still going to put them in the Cath lab. And all of the associated risk and then subsequently the cost that maybe with it I know I'm over exaggerating with the number 10 test. But my point being is that when can we just rely on just using this technology without having to use FFRCT and then ultimately still going to the Cath lab? And probably using IVUS and or FFR in the Cath lab.

Dr. Woodard: Yes, if you had had this methodology, you wouldn't need the IVUS.

I'm quite sure that there would be no indication to perform this first and then and then IVUS. However, in terms of, you know whether or not you would perform FFRCT and this methodology together, I think you know there are certain and percent diameter stenosis where by performing FFRCT you clearly keep them out of the Cath lab because you can identify whether or not the flow of mutation is significant and requires a stent or not which would then keep them out of the Cath lab.

This additional tool might be performed in some of those patients and some of those patients it might not if you don't have a lot of you know if you have let's say a lot of calcified plaque. So, there may be some subset of patients where you would perform both, but you wouldn't be performing both in every patient in which you would perform the FFRCT.

Dr. Tukaye: I have a comment. You know, I don't completely agree with saying that if I had a data from the AIPA CT analysis that an IVUS would be completely irrelevant. There are still cases where doing an intravascular direct imaging prior to implantation of stent is absolutely necessary. No test is perfect. So, you know, you may get inflammation from the CT and then visually if it looks different your graphically, it will still merit an intravascular and IVUS or an OCT.

Dr. Slim: Just to follow up on that. So again, it goes back to what are we talking about? Are we talking about plaque composition or stenosis for plaque composition, for outcome reduction and secondary prevention? There is there is not likely a need to repeat an IVUS and double the cost because we're not trying to determine if we're going to put a stent in there or not.

So, if I have someone let's say I know I don't need a FFRCT and I don't need any stenosis quantification for and they're not going to go to the cath lab for stenting, but they happen to have even though they have not as obstructive of lesion, but they have tons of lesions everywhere that are high risk.

These are the people that will extremely benefit, for example, of the technology, because even though it's not obstructive and doesn't need stenosis evaluation, the abundance of disease and the high risk of the disease, this technology would help me have a conversation with the patient to escalate their therapy and treat them more aggressively versus if we, if we're talking about stenosis, if we got someone with an intermediate lesion that's a completely different question is that intermediate lesion obstructive or not and do they need CT FFR to determine? No, it's not obstructive or yes, it is obstructive. That's a completely different scenario. And a different question and this is where doing, potentially IVUS in the Cath lab or doing FRR and IFR in the Cath lab or doing the CTFFR by itself without doing it on any of the above might be useful.

So, I'm trying to separate into two separate questions. Again, back to the to the QCPA itself. Its benefits where in what population and it's that population where the question is how can we decrease future events and not necessarily how can we intervene on them tomorrow with a stent?

Dr. Nachodsky: Thank you Dr. Loveless, I see your hand raised.

Dr. Loveless: Yes. I'm asking our experts if you were for instance writing guidelines or in our position where you're considering policy based on our current evidence, how do you decide who needs this? What do we know so far about who needs additional studies and who this might reduce the need for additional studies? Do we have any specified patients that that you could clarify, or we just don't know that yet?

Dr. Slim: It's kind of tough to build guidelines on the on the whim, but with that said, it's not applicable in the patients with CAD RADS 0 or no plaque disease.

So, if my memory serves me right, that's about 40% of the CCTAs that are being done.

There is questionable applicability in the CAD RADs 5 and potentially maybe the CAD RADs 4 for, but there's definitely benefits within the non-obstructive population. Some component of the obstructive population that you really identify, they have abundance of the high-risk plaque. When we look at the CT, we know there is some high-risk plaque, but like I said earlier, it's going to take 8 hours to sit there in an academic center to do it. And if I have that capability as a reader to say I'm looking at a high-risk plaque and this technology is going to help me to be able to inform the patient and treat them better, I think this is where the applicability will work based on the data that we have right now. I don't know if that makes any sense.

Dr. Loveless: It does. Thank you. I appreciate it.

Dr. Thompson: I would add that patients that have normal coronary CT angiography don't need CTFFR, don't need AIQCT. Patients that have high grade stenosis, you know clearly high-grade stenosis, severe stenosis like corner CTA don't need CTTFR and they might or might not need AIQCT, but it's sort of the real benefits. The patients in in the middle of that have moderate disease, moderate plaque that you might use either both AIQCT and CTFFR, especially if it's a possibly significant stenosis for the CTFFR.

Dr. Nachodsky: Thank you so much everyone. As you can see, I'm diligently writing notes down here. All alright. Anybody else have comments on that one?

I think we are now moving on to question 13 we want to pinpoint more which ones in addition to the moderate or intermediate risk patients. Are there specific patients that are contraindications that we can't do this. So, what specific patient population would this modality be utilized, like for risk stratifying? It sounds more of our intermediate risk patients versus people who have established CRD already. Patients with symptomatic chest pain or angina like symptoms once they've ruled out with cardiac enzymes, patients who have cardiac devices, you know ICD's or pacemakers. Are there any contraindications, patients with stents, multiple stents with prosthetic valves? What degree of stenosis on CCTA would you advise going on to this technology? A patient who's had a recent MI and is coming back with symptoms or someone comes into the lab, or they come into the into the hospital they present and their enzymes are positive.

Is this still the patient that once they're stable and along having chest pain, can we proceed to this, a patient with severe cardiomyopathy and these are just some of the examples? Which ones do we think that this technology would benefit?

Dr. Slim: Do you mind if I just add one thought to the question because it's kind of tough to answer the question because we're trying to identify the population that needs it.

But if we say yes to certain population, but they're CT is CAD RADs zero and they don't have any plaque it just not going to be beneficial.

So, this is unfortunately one of these situations where the indications are the indications for the CT and then if the CT is normal then there is no need for the test.

It's really a CT gateway entry point, not necessarily population-based entry point, if that makes sense.

I think we'll be doing you a disservice if we say, this population and then it turns out to be that they had a normal CT, then really it's not right, because then we're increasing the cost and we're going to lead to IQCA being ordered than a normal CT just because we said this is the right population.

This is a situation where the CT findings really determine the next step, but not necessarily the population that led to the CT. I would say the CT itself is just driven by the guideline recommendation.

As long as we're appropriately following the guideline recommendation for this CT as a gateway, then identify and if this is normal CT then this technology doesn't apply and in the non-obstructive disease is perfect and in some group of the obstructive disease is beneficial but really it's a CT based gateway but not necessarily population, I could be wrong.

Dr. Calnon: I agree with Dr. Slim that it would really be sort of in my opinion, low to intermediate likelihood patients with symptoms suggestive of coronary disease who undergo coronary CTA and who are then found to have non-obstructive plaque that is felt that quantification and characterization of the plaque would be helpful in further risk stratification and management of the patients.

Some of the things listed here, in my opinion at least, (see what others think) patients with previous revascularization, for example, I think there would be less benefit of applying this technology to those patients, particularly with bypass surgery and stents.

And as far as I am aware, a lot of these specific indications like cardiomyopathies and heart failure recent MI have not really been studied very well at this point to suggest that it's helpful in those situations out there.

Dr. Slim: Yep, but there is data though on CCTA as a utility, there is appropriate use criteria for CCTA as a test for new onset heart failure. So, I wouldn't exclude it completely.

My take would be I would follow the guideline for CTA indications. The most appropriate guideline at the time as the gateway and really is the CT result that dictates the AIQCT and not the population, because whatever we recommend right now, if there's a new guideline 2 years later that changes that recommendation, we'll be limiting you to that.

You know to our recommendation versus just simply saying the follow the appropriate guidelines, appropriate use criteria on current guidelines that least CCTA.

But really, if you have a normal CCTA, you don't need the technology.

Dr. Thompson: I would think that very low utility in patients that have had coronary bypass surgery, most of these patients have very heavy coronary calcifications diffuse disease and you already know it and it seems like you ought to be giving the full court press for preventive all not preventive therapies. I guess I would just ask Dr. Slim and Dr. Woodard to confirm that you don't think that coronary stents, coronary devices and pacemakers should be necessarily an exclusion.

Dr. Woodard: In terms as long as the image quality is good, the presence of a stent you certainly would be able to assess all the other coronaries and you know and devices as long as the image quality is good it shouldn't be an exclusion.

I do think bypass grafting, though I agree with you, that would be a full court press.

You know, very different patient population.

Dr. Nachodsky: Great. And then #14 to further assess for the progression or the regression of disease in the effectiveness of their of medical therapy or recommendations based off of this, how often would we repeat this technology to be performed?

Now I did hear, I think it was Dr. Slim who had mentioned, or someone said that currently we don't have guidelines. We don't have recommendations on how often we should repeat this. However, if we're using, my thought is if we're going to going to use this because it is so great and telling us what the plaque is like and the morphology if you are at risk or not, and then we say, OK, we're going to throw this bucket of drugs at you now, but then we don't study them later on. How do we know that we have been effective as clinicians? I put you through this study not that it's a difficult study, but I've put you through this and the cost of it, I'm telling you to take all these medicines. Let's see, somewhere down the road, how often might we be able to repeat this study to be determined for the future if we're going in the right direction.

Dr. Slim: So, there is no consensus as far as how often do we repeat it and what's the space time.

There is some data that's published out there with follow up and subsequent CTs, and the impact on plaque composition. There is the Motoyama study and it was around 3000 patients average follow up about four years and it showed that change in plaque composition led to 14% higher incidence of major events.

The PARADIGM study looked at an average of 3.8 year follow up and then changes in plaque composition as it relates to statin therapy versus no statin therapy. So, on average, some of the studies that looked at follow-up CTs, they were around four years, but there is no consensus and because any consensus in in the world of cardiovascular imaging is based on abundance of data. There is no abundance of data to simply tell us this is this is the follow up.

This is this is definitely something to come that we anticipate will be something that everyone will study now that we know that there is a change in composition.

You know when you repeat the scan, but I don't think there is any society that will endorse it at this moment based on the data that we have.

Dr. Thompson: I would add this is a very exciting potential application here. It makes sense that if you have a high risk and high-risk features and you repeat the study sometime later if they've not regressed or you're not seeing the change you want, that you would somehow advance your treatment, add some of the preventive therapies that we don't use quite so commonly. But there's a very little experience with it in terms of the exact interval and so forth. I did put three studies I found in my written answers to the questions too, with statins and one with _____ that Dr. Slim mentioned before, and the two statin studies followed up CTA's at over at least two years.

So, two years plus in the third study, _____ was 18 months or more. So, I guess it to throw out a number to be at least that amount of time.

Dr. Calnon: I would say that as a general rule, there's a trend towards trying not to do serial testing with imaging on people who are stable and asymptomatic. As a general rule, especially when the testing involves radiation, especially, and so in general that's not recommended.

Although I do see sort of enormous potential for this compared to calcium scoring where repeating calcium scoring is very unhelpful when it's elevated to begin with because it typically goes up even if the patient's plaque becomes more stable and more low risk, their calcium score tends to rise.

So, and that's discouraging for patients and not really helpful in changing treatment in any way, but in this case I could see that it potentially could be, although again with the caveat that testing people who are asymptomatic and stable with a repeat serial imaging that involves radiation and contrast is not typically recommended by guidelines at this point.

Dr. Woodard: I tend to agree with Dr. Calnon. You know, I mean right now the guidelines don't suggest that you would go ahead and do serial imaging in someone. You know that maybe that down the line with experience in a more experience with this.

And then when with our history or information, that plaque morphology does change overtime 18 months, two years, three years, you know that somebody might do this.

But I think initially you wouldn't just go ahead and do this without having a patient with symptomatic and that's more my opinion than anything else. I think Randy has his hand raised.

Dr. Nachodsky: OK, great answers from everyone. I'm very helpful for us and then our last question for the day is again, there might be some redundancy and I'm sorry if we've done that, it is just a force it into our heads, but is there evidence to support this non-invasive plaque analysis for the following patients?

You've all done very well in trying to say really which ones would it should stand and where we can find this niche. Would it be considered first line or add adjunctive testing for elevated risk for major cardiac event within ASCVD greater than 7.5%?

As an example, to further assess patients with significant non-calcified plaque who had a recent CCTA which this was adequately and very nicely explained by many of you on the panel. If you do have that on a CCTA that will dictate then further going on to having this added technology for monitoring disease progression or assessment for CAD on recent CCTA that is of uncertain physiologic significance or assessment of CAD in patients with a family history of ischemic heart disease or an early MI would we consider this as a screening test?

Dr. Rose: So I think I was just going to say I think this goes back to what Dr. Slim was saying before we really need to follow what the guidelines are for coronary CT and then if those

guidelines are fulfilled, then you know whether or not it's appropriate to add on this as was said, if there's no coronary disease, there's no reason to do it.

I would call that we just kind of answered C around the monitoring disease in the previous question and then you know, the only other point to bring back up is that this is not a modality that we really look at for assessing physiology. It is a, you know an anatomic and prognostic test.

Dr. Slim: Yeah, I can agree, and I wouldn't even exclude the ASCVD over 7.5% because there is about four articles and four different trials that were done and they looked at the different ASCVD risk and high-risk block was present in abundance in across the spectrum and it's the block that dictates the risk and restratify. So, we, as we mentioned earlier, it's really the CT that gateway and the guidelines is that gateway to the CT.

Dr. Raible: I agree with everything that's been said, sub subgroup B, I think is a very fertile ground for how this may be used if a patient has a CTA for an accepted indication, but those patients that have a greater amount of non-calcified plaque, or actually the ones that are higher risk and as the other speaker mentioned, the risk scores don't risk scores don't really agree that well with total plaque volume or non-calcified plaque volumes and you may help you deciding whether somebody could have a coronary syndrome in terms of the indication for CT. But you certainly can't gauge your therapy based on just in their risk score, they would need the plaque analysis to tailor or make the therapy more precise for an individual patient.

Dr Calnon: I would just say that one thing to clarify both, yes, can you hear me? Oh, that, that both.

No, not I don't. Not clarifying you. You were fine.

I'm just clarifying question B and Question D talk about recent CTA and in my opinion, this would always be performed on the current CTA as additional analysis to the current CTA, you would not do another test again on another day to obtain this information.

And the other thing I'd say, is for letter A, the elevated risk of major cardiac event.

I could see that as the data is further emerging about this technique and the benefits of this technique compared to calcium scoring, it may potentially have a role in sort of the asymptomatic patient, where ordinarily today we would use calcium scoring.

This potentially could become something used in that primary prevention population when we ordinarily might use calcium scoring today, we might potentially do this despite the extra cost and the extra the contrast dye requirements.

Dr. Raible: Hopefully radiation exposure will go down as the technology progresses.

Dr. Woodard: And it already has since we began the coronary CTA saga in the mid-2000s.

Dr. Nachodsky: Do we have any other hands up? No, I think this is the conclusion of the questions. I do want to say that this has been very informative. You are such great experts and you provided a great wealth of data that our group will be able to look at when we relook at our articles and having your expert opinion is certainly, is extremely helpful.

Once again, taking your time here, your willingness to teach us here and provide insight is not only benefit for all of us for all the MACs and the CMDs here, but it is ultimately at the end of the day it is for the benefit of our patients or our beneficiaries and that's why we're all here in medicine. And with that, I know that Dr. Loveless had a hand up, and so did Dr. Thompson.

Dr. Thompson: Just a procedure question. Many of us wrote out the written the answers to the question you just sent. Should we just email those to Angela Calisi?

Dr. Loveless: Yes, that would be great. If you can send to send to Angela and that way we have those, it's very helpful.

Dr. Loveless: And for I am so unbelievably impressed with this panel. I never expected to make it to question 15 before 4:00 o'clock I honestly didn't think we'd make it before 5:00 PM.

Outstanding job and you answered all of our questions with expertise and with so much appreciated. I just had one question.

When we asked you about provider qualifications. Is there any role for cardiologist or non-cardiology trained radiologist to be utilizing this test at all? And then I do want to allow if any of the other medical directors that are on the call if they have any other questions before we before we close.

Dr. Slim: I would argue this is an AI augmented algorithm and you need someone trained in reading CTs to augment that read and evaluate it for accuracy and limitations and provide a

report back to the referring provider. So, I do not see a utility outside a well-trained individual in reading cardiac CT to report on that technology.

Dr. Thompson: Yeah, I agree. I don't know of any coronary CT readers who are not cardiologists or radiologists are in the nuclear medicine space. There used to be some internal medicine docs that would read nuclear medicine and so forth, but I think they're not any other specialties that are in this space in a in a well-trained way.

Dr. Calnon: I was just going to say to simplify things from your standpoint, I would just simply say that the criteria are anyone who has credentials to read coronary CTA should be able to do this procedure.

Dr. Woodard: This is true and by saying that our training indicates that these are individuals who are board certified cardiologists or radiologists.

Dr. Loveless: Thank you.

Dr. Nachodsky: And we don't have to go really. I mean the regulations do they have to be level? We should just look at that and say or is it just suffice to say, if you're CT certified cardiologist or radiologist, it doesn't have to be level two or three.

Dr. Woodard: That's correct.

Dr. Nachodsky: OK. Thanks.

Dr. Slim: Yeah, it doesn't have to. Otherwise, you're grabbing a small piece of the pie and making it even smaller.

Dr. Nachodsky: You wouldn't. Smaller. Yes.

Dr. Loveless: And to any of our other CMDs have any questions? I don't see any hands up, so I figured we asked enough questions for everyone.

So, in closing, I just want to thank the panel again for educating us and for your time and your services for the Medicare program and if you have any additional comments that you think of after the close, we welcome those. You can email that to the same email we've been communicating with Angela Calisi and again, just thank you so much.

We really appreciate all your time and expertise and with that, we'll conclude.