Contrast Use in CTA Applications

Coronary artery calcified plaque for cardiovascular disease risk assessment

Not only has coronary calcified plaque now been shown to independently predict cardiovascular risk, but new research indicates that calcified plaques are intimately related to the unstable lesions responsible for myocardial infarction.

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Coronary artery calcified plaque (CACP) documents the presence of atherosclerosis and identifies patients at high risk for myocardial infarction (MI) and cardiovascular death. Moreover, the quantity of coronary calcium adds significant predictive value to traditional cardiovascular risk factors.

This article will review the current status of coronary calcium scoring, how it improves risk stratification (particularly in intermediate-risk patients) and how, together with contrast-enhanced computed tomographic angiography (CTA), it will improve our understanding of the relationship between calcified plaque, soft plaque, and the risk of cardiovascular events. This article will also review the link between coronary calcification and a genetic predisposition to atherosclerosis, an association that has the potential to aid in the development of new diagnostic tests and therapeutic interventions for the prevention of cardiovascular disease.

Calcified plaque

According to the American Heart Association classification system, calcified plaque is type Vb atheroma. Calcification is fundamental to the atherosclerotic process, with small calcified foci developing as early as the teens or 20s, immediately after formation of fatty streaks.

Figure 1 shows a patient with calcified plaque in the left anterior descending coronary artery and a diagonal branch. Many mistakenly believe that coronary calcification is a surrogate for atherosclerosis. Calcified plaque is, in fact, a key subcomponent of the atherosclerotic lesion or atheroma. It is more accurate to characterize the coronary calcium score as a surrogate for the amount or burden of total plaque (ie, calcified and noncalcified atheroma) present. Research has shown that the amount of calcified plaque detected by cardiac computed tomography (CT) is highly correlated to the overall burden of atherosclerosis in the coronary arteries, with an r² value correlation of 0.77 with histomorphometry of autopsy arteries.

Calcified plaque in the coronary arteries is not amorphous or dystrophic calcification but, rather, an active process under cellular control. Calcified plaque can recapitulate all the elements of trabecular bone, including marrow. This observation will likely have a substantial impact on research and therapeutic interventions in the next 10 to 20 years.

Inflammation in the arterial wall prompts a migration of progenitor and osteoblast-like cells, which first lay down a cartilage base and then an osteoid base and which then form trabecular bone within the walls of the arteries. There are many pathways that influence both arterial calcification and skeletal health and osteoporosis. Emerging evidence suggests there is an inverse relation between the two: As individuals lose bone mass, they tend to develop more calcified plaque in both the coronary arteries and the aorta. A recent article by Schultz et al found that women with aortic calcifications had a significantly higher risk of osteoporotic fractures.

When discussing cardiac events, emphasis is often placed on the role of vulnerable plaque, to the exclusion of calcified plaque. However, research into the biomechanics of the coronary arteries and the pathobiology of atherosclerosis suggests that certain patterns of calcification can predict the location of a culprit lesion of the acute coronary syndrome and unstable angina. Ehara et al used intravascular coronary ultrasound to evaluate patients with acute MI or unstable angina. They found that a spotty pattern of calcification could be used to identify the vascular segment of the culprit lesion. Cardiac CT easily identifies individuals with analogous patterns of calcification on both contrast-enhanced and nonenhanced examinations and should be a fertile area for future research.
Plaque measurement

The measurement of coronary calcification is straightforward. At Wake Forest University, we perform a non–contrast-enhanced CT study using a low-dose technique (Table 1). Images are electrocardiographically (ECG) triggered for the late phase of diastole. The study takes <5 minutes and yields images of very high spatial resolution. For multidetector CT systems, a gantry speed of 0.5 seconds or less is recommended. The axial or cine mode is the recommended scan mode, since it has very low radiation exposure and has been validated for cardiovascular disease risk prediction in numerous published studies.

A dedicated computer program identifies calcifications meeting the scoring criteria throughout the images. The person performing the analysis then identifies those calcified plaques in the epicardial coronary arteries and identifies the location of the plaque by the coronary vessel. The computer software sums the amount of calcification per lesion and per artery simply by adding up the pixel values and adjusting for the slice width (Figure 2). Pixel values are then converted to an Agatston score, plaque volume, or plaque mass. Each provides essentially the same information: The amount of calcified plaque in the coronary arteries. Currently, in clinical practice, Agatston scoring is used almost exclusively and has come to be known as the “coronary calcium score.” The other scoring systems have various merits but have yet to be implemented into clinical practice in a meaningful way.

Consensus statements from the American Heart Association, the American College of Cardiology, and other organizations have discussed the application of the coronary calcium score. These documents concur that coronary artery calcification is part of the development of atherosclerosis, occurs exclusively in atherosclerotic arteries, and is absent in normal vessel walls. Currently, there is no scientific debate that identification of calcified plaque in the coronary arteries indicates an individual with atherosclerosis, albeit subclinical in many cases.7-11 It is important to keep this in mind when performing non–ECG-gated chest CT studies—eg, when evaluating a patient for pulmonary embolism or examining the thoracic aorta. Reporting coronary calcified plaque can play an important role in the early identification of an individual at risk for coronary artery disease (CAD). More important, calcified plaque in this setting can serve as a trigger

| Table 1. Multidetector cardiac CT: Suggested protocol for coronary calcium scoring* |
|-----------------.|-----------------.|-----------------.|-----------------.|-----------------.|-----------------.|
| kV    | 120               |-----------------.|-----------------.|-----------------.|-----------------.|
| mAs   | 70–150            |-----------------.|-----------------.|-----------------.|-----------------.|
| Slice thickness | 2.5–3 mm         |-----------------.|-----------------.|-----------------.|-----------------.|
| Field of view  | 26–35 cm          |-----------------.|-----------------.|-----------------.|-----------------.|
| Scan mode      | Axial–cardiac     |-----------------.|-----------------.|-----------------.|-----------------.|
| Reconstruction | Partial scan,    |-----------------.|Kernel–vendor–dependent|-----------------.|-----------------.|
| ECG gating     | Prospective @ 75% or 50% of R-R interval |-----------------.|-----------------.|-----------------.|-----------------.|
| *Scan parameters are vendor- and system-specific. All scan parameters should be confirmed with manufacturers prior to implementing in a clinical situation. |
for intervention on established risk factors for CAD, such as smoking, hypertension, diabetes, and hypercholesterolemia. Implementation of prevention strategies, such as dietary modification and exercise, could save someone’s life.

Intermediate-risk patients

Cardiac CT for measuring calcified coronary plaque is a very robust test that provides standardized and reproducible results that can be applied in clinical practice. In the Multi-Ethnic Study of Atherosclerosis (MESA), funded by the National Heart, Lung, and Blood Institute at 6 sites across the United States, we have documented the implementation of a standardized protocol to measure calcified coronary artery plaque. The results were consistent and reproducible and can be applied to population screening programs. A 2005 study also showed that the amount of coronary calcification varies with ethnicity and gender, which may help us better explain the observed ethnic and gender variations in the incidence and prevalence of cardiovascular disease itself in these populations.

It is essential to target any risk-assessment tool for use in the appropriate population, and coronary calcium scoring is no different in this respect. The American Heart Association Prevention Conference V recommended grouping individuals according to their future risk of CAD, typically determined using the Framingham risk score or index. An individual is considered to be at high risk if the likelihood of developing cardiovascular disease over the next 10 years, based on traditional risk factors, is >20%. An individual with a 10% to 20% likelihood of disease is at intermediate risk, and an individual with a <10% likelihood of disease is at low risk. Coronary calcium scoring is best targeted to the screening of people who fall into the intermediate-risk category or to individuals at low risk but with other factors, such as a family history of heart disease, that may elevate their risk beyond that measured by traditional risk factors.

Unfortunately, the epidemic of cardiovascular disease in the United States has resulted in an increasingly large percentage of the adult population being at intermediate or high risk for cardiovascular disease. Most middle-aged adult men, and a growing number of middle-aged and elderly women, have elevated blood lipids, obesity, and type 2 diabetes—all of which dramatically increase the risk of coronary heart disease. It is in the evaluation of intermediate-risk patients that imaging may play an increasingly important role.

It has long been known that coronary calcified plaque predicts increased risk for MI and cardiovascular death. The question has been whether the coronary calcium score provides additional predictive information beyond that available from traditional risk factors.

The South Bay Heart Watch Study addressed that specific question in an article published in the Journal of the American Medical Association. The study involved 1461 asymptomatic individuals with coronary risk factors who underwent coronary calcium screening. Follow-up averaged approximately 8 years. Traditional risk factors performed as expected. Participants predicted to be at low risk for MI or cardiovascular death by the Framingham risk score had few cardiovascular events (1%). Those predicted to be at intermediate risk had an event rate of just under 7%, and those predicted to be at high risk had an event rate of nearly 14%.

This study demonstrated that coronary calcium screening can further improve the identification of individuals who are at high risk for MI or cardiovascular death over the next 5 to 10 years. When study participants were grouped according to an Agatston score above or below 300, those with an Agatston score ≥300 had significantly more cardiovascular events than did those with lower scores at every level of risk (low, intermediate, and high), based on the Framingham risk score. This study found that the measurement of calcified coronary plaque prospectively provided significantly more information about the likelihood of myocardial infarction or cardiovascular death than traditional risk factors alone.
The coronary calcium score is particularly valuable in intermediate-risk patients, in whom clinical decision-making is most uncertain. There is relatively little added value in scanning someone who is at very low risk of coronary artery disease. Conversely, a person with established coronary artery disease, or who is at very high risk, needs aggressive treatment regardless of the coronary calcium score.

The currently recommended approach, therefore, is to use traditional risk factors to identify patients at intermediate risk for cardiovascular disease before scheduling a CT scan. The risk assessment is then further refined according to the results of coronary calcium scoring, perhaps in combination with additional factors such as blood levels of C-reactive protein or the lipid profile.

**Genetics**

Over the last 5 years, researchers have made steady progress in elucidating the genetic basis of atherosclerosis. Some 40% to 50% of the variability in coronary calcification can be attributed to genetics, both in diabetic and nondiabetic individuals.15

Figure 3 shows coronary calcium scans from 3 sisters. The first had an Agatston score >1500 and the second, an Agatston score >1000. Both had calcified plaque in the left anterior descending coronary artery and thoracic aorta, and both had type 2 diabetes. The third sister had an Agatston score of 23 and was not diabetic. It is likely from these observations that the third sister had a different genetic profile from the other two.

The power of modern genetic techniques is the ability to obtain DNA from a large number of families and couple that with quantitative traits derived from imaging studies, such as coronary calcium scoring by CT. The information on subclinical atherosclerosis can be used to identify chromosomal regions that may be coding for the development of calcified plaque, inflammation, or a combination of the two, or other factors related to atherosclerosis.

Over the next 5 to 10 years, contrast-enhanced CTA will also provide novel information on subclinical atherosclerosis not previously available. We now know that the culprit lesion is often times not the most stenotic lesion. CT angiography and coronary calcium scoring together will play an important role in quantifying calcified and noncalcified plaque in healthy people and in determining why some are at high risk for developing vulnerable plaques that eventually rupture and cause MI and other cardiovascular events. By combining the capabilities of cardiac CT to identify and characterize individuals who have coronary artery disease with the potential to characterize plaques with cardiac MRI, intravascular ultrasound, optical imaging, and new targeted contrast agents, the potential for rapid gains in our knowledge of atherogenesis and CAD appears high. We will be able to leverage our knowledge about the relationship between calcified plaque and the future risk of cardiovascular events to improve our understanding of the natural history of this process and provide individuals with optimal diagnostic and treatment recommendations.

**Conclusion**

Research has yielded a large amount of data on calcified plaque. We know that calcified plaque documents the presence...
of coronary atherosclerosis, predicts which individuals are at highest risk for MI and cardiovascular death, and adds significant predictive value to traditional risk factors for cardiovascular disease.

Ongoing research will improve our identification of noncalcified plaque, and may link the development of calcified plaque and noncalcified plaque to specific chromosomal regions. This information will provide important opportunities to develop new diagnostic tests that will function as critical tools in the prevention of cardiovascular disease.

REFERENCES


Discussion

ELLIOT K. FISHMAN, MD:

Thanks very much, Jeff. Why don’t we open the discussion?

STEPHEN ACHENBACH, MD: I thought that the data he pointed out from the South Bay Heart Watch publication was very interesting. It seemed that a threshold of a 300 Agatston score makes a big difference in establishing a cardiovascular risk because previously, there has been a very crude classification being used, which said >400 is high risk. So I want to discuss modifying this classification. Do we really need to consider lower calcium scores as high risk?

Then the second question that goes along with it is that many experts have advocated not so much using the total Agatston score, but more looking at the percentile relative to age and gender, which, of course, did not appear at all in the data that you showed. What is your opinion on this?

J. JEFFREY CARR, MD, MSCE:

Those are great questions. As Stephan knows, the 400 threshold was really set based on correlating the amount of calcified plaque with coronary angiography, so the 400 Agatston level is a burden of calcified plaque at which there is a high likelihood of flow-limiting stenosis present at coronary catheterization. The problem with that is that, when you then apply those numbers to a screening population, it’s really two different populations, since we have limited information on coronary catherization findings with asymptomatic individuals, for obvious reasons. I think that the 300 number is the best number that we have now, based on current prospective data for indicating a significantly increased risk of hard events.

We may modify that number based on the outcome data from the NHLBI-funded Multi-Ethnic Study of Atherosclerosis (MESA) that has been going on since 2000. But, for now, I think 300 is a very reasonable number. We know it works in all 3 of the risk categories: Low, intermediate, and high risk. So, if an individual has a score of 300, we know that that individual is at a significantly higher risk of an event.

That’s not to say that the individuals with calcium <300 are necessarily at average or normal risk; I don’t want to mislead people into thinking that. In my practice, I think there are really two thresholds: The first being the transition from zero to any calcified plaque, and the second when the plaque burden reaches an Agatston score of 300.

I want to re-emphasize that, when you read your chest CTs and your PE studies with these faster scanners, you are able to stop coronary motion very well. I think that identifying any calcified plaque takes someone across a threshold from just having risk factors for coronary artery disease (CAD) to having documented subclinical atherosclerosis. So, that’s a powerful bit of information right there, in and of itself. I would use the “any calcification” and then 300 as my 2 thresholds.

I have a philosophical problem with percentiling. I think that it’s a very valuable tool in practice because it helps you gauge what’s important, for example, in a 40-year-old woman versus a 65-year-old man. We talked briefly about the differences in the epidemiology of atherosclerosis in men, women, and different ethnic groups. But the problem is that we are in the middle of an epidemic of both cardiovascular disease and obesity. So if I tell you that 60% percent of U.S. individuals are obese or overweight, and a patient is at average weight for a U.S. man, is that really optimal? Probably not. So, in the
middle of an epidemic of cardiovascular disease in Europe, the United States, and the industrialized world. I’m not sure that having the average amount of plaque for a 55-year-old man is necessarily a good thing. I don’t know that I’d take a lot of comfort in that. There will likely be a combination of those approaches.

ACHENBACH: Would they rather go the other way around? Instead of saying, “You’re on the average, so you’re fine.” We might also say, “You might have a very low calcium score of 8, but if you’re a 43-year-old woman, this puts you at the 90th percentile.”

CARR: Right.

ACHENBACH: So even if the total score is low, you could still have significantly more atherosclerosis than you would expect.

CARR: That goes along with the idea of “any versus zero.”

I did mammography for a long time, and I see coronary calcified plaque much like atypia on a biopsy—you have identified someone who is at higher risk for progressing to clinical CAD. People talk about their physiologic age or their vascular age, and there are a lot of women in their 50s, 60s, or 70s who have an extremely long life expectancy. So, if we can identify calcified plaque and these patients modify their behavior, I believe that there is a real opportunity to reduce their disease burden down the road. So I agree with you, Stephan, that it’s important.

ACHENBACH: As a cardiologist, of course, it’s obvious to me. But I am very glad to hear you as a radiologist also pointing out that while doing calcium scoring, we cannot throw away the risk factors. The first step is assessing the cardiovascular risk based on the traditional risk factors we have used for a long time. So, using the data that you showed, some patients with zero or almost zero calcium, but high risk levels based on the traditional risk factors, still have a high risk of having cardiovascular events, even if there was no evaluable calcium. So, absolutely, the first step should always be to assess the traditional risk factors.

CARR: I think that it will be even more important with coronary CTA; we need to understand who we are doing these tests on from their cardiovascular risk profile, because the pretest probability of disease is important in taking the CT results and making recommendations that will alter the likelihood of future events.

MARILYN J. SIEGEL, MD: In your presentation, you mentioned that you look at your PE studies and your routine chest CT examinations for the presence of coronary artery calcification. If you see coronary artery calcification or even noncalcified plaques, do you give more specific recommendations? Do you recommend clinical correlation?

CARR: I carry it further. Working with the residents, we have a big training job in cardiology and radiology in front of us in getting people to understand 4-dimensional cardiac anatomy with CT. So, we go through the coronary arteries on all of our PE studies. We identify if there is calcified plaque, and sometimes we can even see noncalcified plaque on our PE studies. So I’ll mention that in a conclusion: “Negative for PE, calcified plaque in the LAD. This individual is at elevated risk for coronary artery disease. Calcified plaque documents the presence of subclinical coronary atherosclerosis and elevated risk for coronary heart disease. Recommend cardiovascular risk assessment.”

Realistically, for example, for a 50-year-old woman who presents to the Emergency Department with shortness of breath and receives a PE study, finding calcified plaques in her coronary arteries can influence her longevity long term, if she begins a prevention program that includes lifestyle modifications and perhaps more aggressive management of her lipid profile.

ACHENBACH: Yes. I feel very strongly about the need for education concerning coronary calcium and the relationship between coronary calcium that has been detected and the need for an invasive angiography. That is a reflex that you sometimes see happening. An asymptomatic person has a coronary calcium assessment and is discovered to have a lot of coronary calcium. Then, the question arises: Does this person need to undergo invasive angiography just because there is lots of calcium on the CT?

CARR: Stephan’s the cardiologist, so you’ll get my answer, and then we’ll hear Stephan’s answer. There are those people who are truly asymptomatic, and then those people who may have undetected symptoms. So, realistically, if you have someone who has a calcium score above 300, they need to be assessed (depending upon their age range). They probably need to have some type of stress testing to see if they’re having unsuspected or silent ischemia. I would not recommend that they go directly to coronary angiography.

ACHENBACH: I would completely agree with that. It must not be a reflex that if there is lots of calcium the patient needs a cath. You have to bring in the cardiologist and consider the clinical situation. If there are no symptoms and there is no positive test for ischemia, there is absolutely no reason to do a cardiac catheterization because there is not necessarily a stenosis present inside the coronary artery, even with a tremendous amount of calcium.

CARR: Should they do a cardiac CTA in that case?

ACHENBACH: No. For two reasons: One is that if there is really that much calcium, the likelihood that the CTA might become uninterpretable is relatively high. Second, again, even the presence of tremendous amounts of coronary calcium does not necessarily mean that a stenosis is present, and, even if there is an asymptomatic stenosis, there is usually no need to treat it.

MICHAEL POON, MD: As the technology evolves, how are we going to quantify calcium with the various generations of multidetector CT scanners? Is there any data out there saying that the way that we quantify calcium with a 64-slice scanner is accurate compared with the electron-beam CT (EBCT) data or compared with an earlier generation multidetector CT? Christoph Becker
published data that compared EBCT with 4-slice CT, but as we’re getting faster and faster with all the different advancements, and as the resolution gets better, does that affect the calcium score? The qualitative part is unchanged, but I have a question about the quantitative part.

CARR: That’s a very good question. In MESA, we had 6 sites: 3 with C150 EBCT scanners and 3 with 4-slice multidetector CT scanners. Those studies were acquired in 2000 and 2001. We did paired scans with each of the technologies and each of the 6000 participants. What we were able to show in a paper in Radiology was that the measurement error between the 2 techniques was indistinguishable. They both were able to measure, and the precision was very high with both the EBCT and 4-slice.

If you do noncontrast, cardiac-gated studies using 2.5 to 3 mm slice collimation, regardless of your detector collimation, you will get similar results. There is the need for calibration; there’s a consortium of vendors and researchers, and we’re working on that. Realistically, that problem is close to being solved within the next year or two, and I don’t see that as a major stumbling block.

RICHARD D. WHITE, MD: We recognized this coming after some of the confusion that came out of EBCT. So, 5 years ago, we assembled all of the vendors and asked them to behave and work together. We have recently finished standardizing the acquisition and the analyses and are just now rolling it out to major clinical sites. We will collect the data, track which vendor they are coming from, and detect any slight differences in standards. But I think by starting with looking at the 4-slice technology, even if it’s using a 64-slice system functioning as sort of a 4-slice system, we can then build a solid database and evolve over time. So we hope to clarify that as it goes along.

I told you I recognize a catch-22 when it comes to understanding the increasing prevalence of calcium in the coronaries in older people, but being told at the same time that there is no aging of the coronaries. Is there an aging of the coronaries that accounts for some of the coronary calcification? Or is it purely atherosclerosis affecting most of the aging population?

CARR: The calcification is not part of the aging of the vessel. It’s not a senescence process. It is atherosclerosis, with one exception, which is individuals who are on hemodialysis. They have an altered calcium metabolism, which is incompletely understood. But individuals on dialysis can have a kind of dystrophic calcification affecting all of their arteries. The problem is that, if you look at industrialized societies and you look at the people whom we tend to see in the hospital, the presence of cardiovascular disease becomes highly prevalent as patients get into their 60s, 70s, and 80s.

WHITE: So the virtually 100% of positive calcium results we see in men 60 and older and in women 70 and older are indicative of rampant atherosclerosis.

CARR: It’s a pandemic in our society and also in the selection bias of whom we scan. If you look at who we see in the hospital, those are people who tend to have multiple medical problems. So, when you see PE studies in a 70-year-old man, why is he getting that CT scan? He’s probably not the 70-year-old healthy jogger. But with that said, we do have data from a small substudy of the Cardiovascular Health Study that 15% percent of individuals at a mean age of 80 had zero or very low amounts of coronary artery calcified plaque. In MESA, I think we’re going to see that you can live into your early 80s without calcified plaque in certain groups of individuals with lower prevalence of atherosclerosis. I think it’s just a manifestation of our society and our societal health.

FISHMAN: When we speak about colon screening, the American Cancer Society suggests 5- or 10-year follow-up. If a 50-year-old patient has a calcium score of 40 Agatston units, do you recommend getting another score in the future? Is there a time for follow-up or any other recommendations?

POON: Considering the population and the data we have, would you suggest that everyone should get a scan at age 50 to tell them where they are?

CARR: I think that everyone should go see his or her primary care physician. They should look at the National Cholesterol Education Panel, Adult Treatment Panel III (NCEP-ATP III) screen of traditional CVD risk factors. They put in the patient age, the lipid profile, the blood pressure, and it will calculate the patient’s CVD risk over the next 10 years. If you are at low risk, you don’t need to worry about it. If you are at high risk, based on a variety of factors, then you need to do cardiovascular prevention measures aggressively. Depending on an individual’s risk factors, more aggressive lipid-lowering therapy or lifestyle changes may be indicated.
If you’re at intermediate risk, the current guidelines say that physicians are obligated to reclassify your risk. So, up until now, the question has been, how do we do that? Coronary calcium currently has published data supporting it as a powerful way of reclassifying those people in the intermediate risk group into either a higher risk or lower risk group. So I would say that you should assess your risk at age 40 or 45; if you are in the intermediate risk group, you should work with your healthcare team to decide when or if you need to have that risk better classified.

FISHMAN: Thank you. I’m sure we’ll come back to that a little bit later, as well, as we get into more of the presentations on CTA of the coronaries.