Imaging to Stratify Coronary Artery Disease Risk in Asymptomatic Patients with Diabetes

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ABSTRACT: Coronary artery disease (CAD) is the leading cause of morbidity and mortality in patients with diabetes mellitus. Patients with diabetes have a higher prevalence of CAD and a larger magnitude of ischemia, and they are more likely to have silent myocardial ischemia and myocardial infarction. However, recent large cohort studies demonstrate that diabetic patients are not a homogenous group with similar high risk for cardiac events. In fact, more than 30% of asymptomatic diabetic patients do not have evidence of coronary atherosclerosis and have a very low annual cardiac event rate. Accordingly, there has been a recent paradigm shift as to whether the detection of subclinical coronary atherosclerosis through imaging can best guide therapeutic decision making. This review discusses the role of various cardiac imaging techniques for stratifying cardiovascular risk and optimizing therapy in asymptomatic diabetic patients.

INTRODUCTION

Coronary artery disease (CAD) is the leading cause of morbidity and mortality in patients with diabetes mellitus. These patients have a higher prevalence of CAD and are more likely to have silent myocardial ischemia and myocardial infarction (MI) than nondiabetics.[1,2] The goals for screening asymptomatic diabetic patients should be to (1) stratify risk beyond that estimated by clinical risk factors alone, (2) identify subclinical coronary atherosclerosis, (3) identify patients with significant obstructive CAD who have silent myocardial ischemia and are at higher short-term risk for events, and (4) guide patient management to improve long-term outcomes. Another important objective is to identify low-risk patients who may not require statin and aspirin pharmacotherapy and/or further diagnostic testing. Current American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend high-dose statin therapy for all patients with diabetes.[3] Yet large cohort studies demonstrate that asymptomatic patients with diabetes are not a homogenous group, with > 30% having no evidence of coronary atherosclerosis let alone obstructive CAD. The following review discusses the role of cardiac imaging in risk-stratifying asymptomatic diabetic patients and guiding therapeutic decision making.

CORONARY ARTERY CALCIUM SCORING

The coronary artery calcium score (CACS) is a well-established noninvasive test for identifying patients with coronary atherosclerosis; it requires no patient preparation, is easily interpretable, and can be performed within seconds with very low radiation exposure (Figure 1). In a general asymptomatic population without prior CAD, the CACS reclassifies risk beyond clinical risk models alone and, unlike functional testing, identifies the entire spectrum of subclinical coronary atherosclerosis.[4,5] A CACS of 0 predicts a very low annual risk for major adverse cardiac events (MACE) in both men and women.[5-7] This is paramount because approximately 60% of patients screened will have a CACS = 0 (more so women than men at any given age). Such low-risk patients are unlikely to benefit from further cardiac testing or statin therapy.[8,9] Conversely, an abnormal CACS identifies patients at increased risk for having myocardial ischemia[10-12] and subsequent cardiac events, particularly when atherosclerosis is severe. A recent meta-analysis of 20 studies showed a 23.6% prevalence of ischemia on single photon emission computed tomography myocardial perfusion imaging in patients with a CACS > 400.[13] Furthermore, CACS testing influences both patient and physician behavior regarding statin and aspirin use and is a strong motivator for reducing cardiac risk factors and decreasing unnecessary downstream testing.[14-16]

The CACS predicts overall MACE and all-cause mortality in both diabetic men and women.[17-20] Those who are asymptomatic have a higher median CACS across all age groups, and CACS severity is sex independent.[21,22] In an early study of 10,377 patients, Raggi et al. determined that annual all-cause mortality was similarly low for diabetic and nondiabetic patients who had a CACS = 0, whereas diabetic patients with a CACS > 0 had a significantly higher mortality rate.[17] In the Diabetes Heart Study of 1,051 diabetic patients, those with a CACS = 0 had an annual mortality of 0.9% versus 2.7% for those with a CACS ≥ 1000.[20]

A recent meta-analysis of eight studies covering 6,521 patients reported a CACS < 10 in 29% of patients with diabetes[18] who

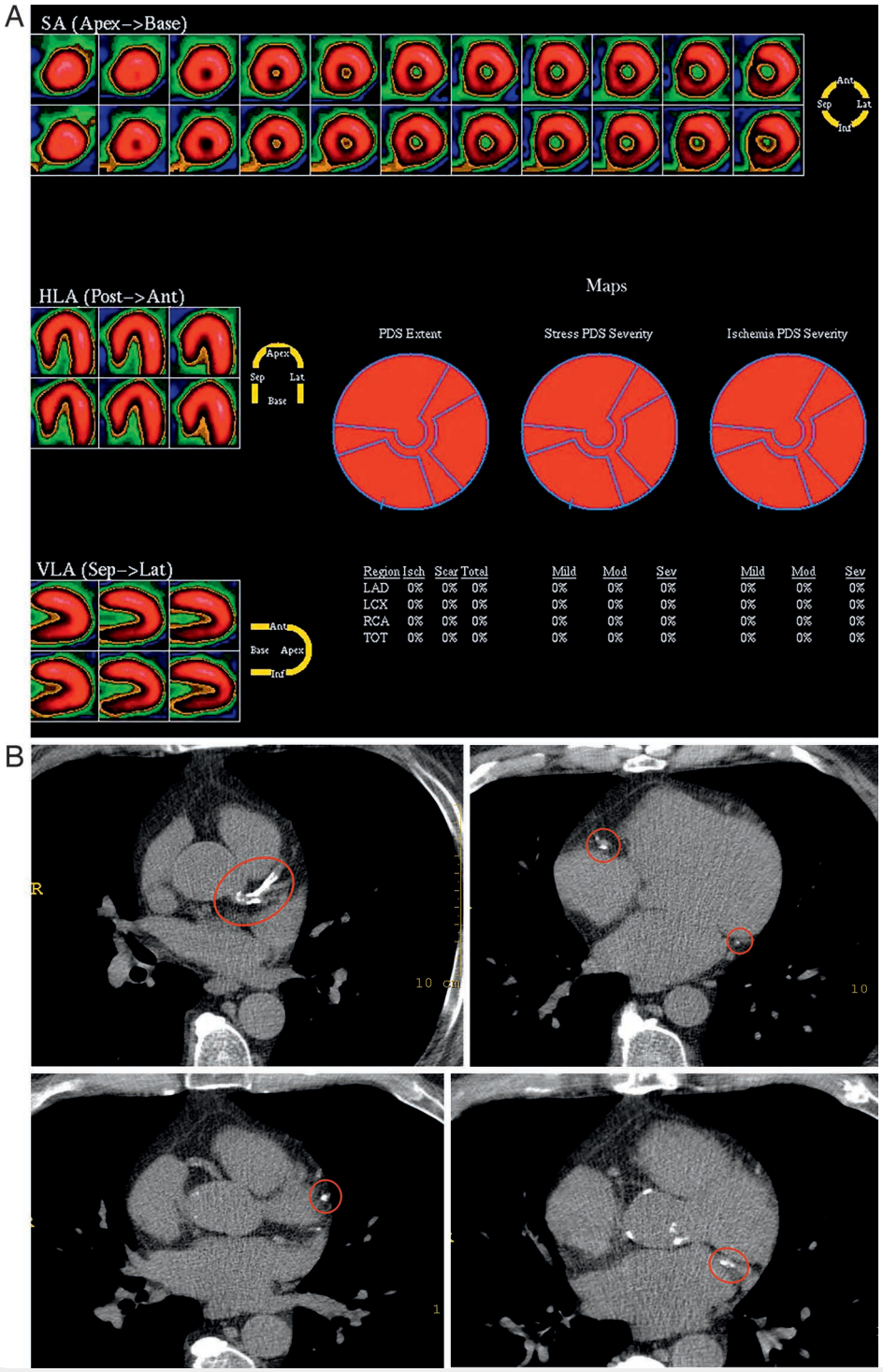

Figure 1.
A 65-year-old man with a history of hypertension, hyperlipidemia, cigarette smoking, and recent onset atypical chest pain. Exercise treadmill test results showed exercise duration of 8.5 minutes with a maximal heart rate of 125 bpm and no symptoms or ST changes. Duke treadmill score was 8.5 (low risk). (A) Stress myocardial perfusion images were normal. (B) Despite a normal functional test, the coronary artery calcium score (CACS) was severe at 740, indicating high risk for subsequent cardiac events. Red circles highlight areas of coronary calcification. SA: short axis; HLA; horizontal long axis; VLA: vertical long access; PDS: perfusion defect size; LAD: left anterior descending; LCX: left circumflex; RCA: right coronary artery; TOT: total.

then had an annual hard cardiac event rate (death/nonfatal MI) of a 0.35%, a 6.8-fold reduction from the predicted 2.4% rate. The MESA investigators reported a CACS = 0 in 45% of patients with metabolic syndrome and 38% of patients with diabetes, with a low overall annual MACE in both groups.[19] A longer follow-up analysis showed similar results but with MACE rates increasing as CACS severity increased in those with metabolic syndrome and particularly diabetes. The addition of CACS to clinical risk factors significantly improved net risk reclassification in both diabetic and nondiabetic patients and in those with metabolic syndrome.[23]

Although a CACS of 0 appears reassuring, other reports indicate that it may not confer the same low mortality risk in the long term.[24] An observational study of 9,715 asymptomatic subjects undergoing CACS and 15-year follow-up found that diabetic patients with a CACS = 0 had a 2.5-fold higher hazard ratio for all-cause mortality compared to nondiabetics, although the annual mortality rates were still relatively low. Of interest, a significant increase in mortality within the diabetic cohort began > 5 years after the baseline normal CACS, suggesting that the "warranty period" for a CACS of 0 may be shorter for diabetic patients. Two studies in the general population have shown conversion from 0 to non-0 CACS in 16% of patients over 2.4 years and 25% over 5 years.[25,26] In the latter study, the mean time of conversion was 4.1 + 0.9 years, suggesting that a repeat CACS at 4- to 5-year intervals may be prudent in patients with an initial CACS = 0.[26]

Data from the MESA investigators indicate that diabetic patients with a preexisting abnormal baseline CACS showed greater annual CACS progression compared with nondiabetic patients, regardless of sex.[27] Poor glycemic control was a predictor of both conversion and progression. An increase in cardiac events mirrored the degree of change in CACS, with continued low event rates in nonprogressors but the highest event rates in patients at the highest tertile of progression and especially among those with metabolic syndrome or diabetes. This may explain the higher event rates seen at all levels of CACS > 0 in other studies comparing diabetic and nondiabetic patients. In further support of this finding, patients with diabetes/metabolic syndrome have a higher frequency of stress-induced myocardial ischemia compared to nondiabetic patients who have a severe or moderate CACS.[28] Because myocardial ischemia predicts cardiac events, progression to even moderate CACS may be more worrisome in diabetic patients. These data support optimal glycemic control in all patients with diabetes and management of other cardiac risk factors to prevent plaque progression. Currently, CACS is considered an appropriate test in asymptomatic patients who are at intermediate or high clinical risk for CAD, a subgroup that includes the diabetic population.[29]

CT CORONARY ANGIOGRAPHY

Computed tomography coronary angiography (CTA) is highly accurate for diagnosing CAD,[30,31] detecting ischemia,[32-34] and predicting patient outcome based on the presence, extent, and severity of CAD.[35-37] In the SCOT-HEART trial, CTA was significantly better than exercise treadmill testing (ETT) at reclassifying CAD diagnosis, leading to more aggressive treatment with statins and other therapies; also, patients undergoing CTA had better outcomes than those assessed by ETT alone.[38] This is consistent with a recent observational study showing that statin therapy significantly improved outcomes in patients undergoing CTA who had extensive nonobstructive plaque.[39]

Although CTA has a potential advantage for detecting the entire spectrum of atherosclerotic plaque in asymptomatic diabetic patients, there are no data to suggest that it would perform better than a much simpler CACS. This is based on numerous studies in low-to-intermediate-risk patients with suspected CAD, wherein < 1.0% of patients had significant stenosis on CTA if the CACS was 0. At this juncture, CTA is not considered an appropriate test in asymptomatic patients.[29]

EXERCISE TREADMILL TESTING

Exercise treadmill testing predicts mortality in asymptomatic patients based on the presence of stress-induced ischemia, peak exercise capacity,[40,41] post-exercise heart rate recovery,[42] and the Duke Treadmill score (a composite of exercise duration, symptomatic status during exercise, and presence/extent of ischemia).[43,44] Exercise capacity is one of the strongest predictors of survival in both asymptomatic men and women.[40,41] In a recent study of 5,638 asymptomatic women, the Duke Treadmill score predicted total and cardiac mortality, but outcome was primarily driven by exercise capacity.[45] Currently, ETT is considered "maybe appropriate" for asymptomatic patients at intermediate risk and "appropriate" for those at high global risk, providing that the baseline electrocardiogram is normal and the patient can exercise.[29] Despite these recommendations, a normal ETT has a limited warranty period, suboptimal sensitivity and specificity for CAD detection, and does not identify subclinical coronary atherosclerosis.[5,38]

A recent observational study of approximately 1,000 generally asymptomatic patients compared the relative values of ETT and CACS for long-term risk stratification and determined that CACS severity best predicted risk[5]; it also improved risk prediction in the 85% to 90% of patients who had low-risk/normal ETT results, with subsequent event rates driven primarily by CACS severity. The results suggest that use of ETT in the general asymptomatic patient population has limited value.

However, because of its low cost, it may serve some value in diabetics with multiple other risk factors (i.e., the high-risk group) in situations where CACS is not available.

STRESS IMAGING

Stress myocardial perfusion imaging, stress echocardiography, and stress cardiac magnetic resonance imaging have all been shown to detect ischemia and predict outcome in patents with known or suspected coronary artery disease but are of limited clinical value in asymptomatic patients due to the low prevalence of a positive test result.[12,13,46-58] Furthermore, they are inferior to CACS for predicting long-term risk due to their inability to detect subclinical coronary artery atherosclerosis and may therefore lead to a false sense of security if the test result is normal.[12,13] However, targeted stress myocardial perfusion imaging is helpful in refining risk stratification in patients with a moderate (101-400) or severe (> 400) CACS because 25% to 40% will have significant silent myocardial ischemia.[12,13,29]

CLINICAL IMPLICATIONS

There is limited direct evidence showing improvement in patient outcomes through cardiac screening of asymptomatic patients, diabetic or otherwise. This is likely due to multiple issues including relatively short patient follow-up, low cardiac event rates, lack of structured protocol-directed treatment algorithms defined by imaging results, and the inability of most techniques to detect early coronary atherosclerosis. Most asymptomatic patients will have normal functional tests, but over half will have subclinical coronary atherosclerosis that will ultimately lead to a poor outcome.

Primary and secondary prevention trials have demonstrated significant reductions in cardiac event rates with statin therapy.[59] In the JUPITER trial, 17,802 asymptomatic patients with elevated C-reactive protein as a marker of high risk were randomized to rosuvastatin or placebo. There was a 63% reduction in cardiac event rates in the treated population, primarily when low-density lipoprotein level was reduced to < 50 mg/dL.[60,61] This was true irrespective of sex, age, body mass index, Framingham Risk Score, or presence of metabolic syndrome. Recently, the MESA investigators matched their patients to those in JUPITER and six other randomized primary prevention statin trials and demonstrated indirect evidence of benefit.[9] Of the patients who would qualify for statin therapy based on clinical evidence, 44% had a CACS of 0. The annual event rates in patients with a CACS of 0 were only 0.39% for total atherosclerotic disease events and 0.17% for coronary heart disease events. In this analysis, 197 patients with a CACS of 0 would need statin treatment for 10 years to prevent one coronary heart disease event. However, the number of patients decreases to 56 for a CACS of 1 through 100 and only 28 for a CACS > 100. The CACS is the only noninvasive technique that detects early coronary atherosclerosis (other than CTA), effectively redefines risk, and can better discern which patients warrant statin therapy. This has been shown even within clinical groups recommended for statin therapy in the most recent ACC/AHA guidelines.[8] The CACS appears to be an optimal initial screening test for defining the presence and extent of coronary atherosclerosis in asymptomatic diabetic patients and thereby guides patient management. In patients with a CACS of 0, statin therapy could be avoided with aggressive risk factor modification and repeat CACS testing at 3- to 4-year intervals. In patients with a CACS > 0, statin and aspirin therapy should be added to aggressive risk-factor modification, with functional testing reserved for those with silent myocardial ischemia who have a moderate to severe CACS score. Future large randomized trials should focus on how refining targeted treatment of patients with an abnormal CACS can lead to prevention of cardiac events.

KEY POINTS

- The coronary artery calcium score (CACS) is currently the preferred noninvasive imaging test for stratifying risk and guiding therapeutic decision making in asymptomatic men and women, particularly those with diabetes.
- Patients with a CACS of 0 have an exceedingly low annual event rate and can avoid statin therapy. Repeat CACS imaging is recommended at 3- to 4-year intervals.
- Patients with a CACS > 0 should undergo aggressive risk factor modification that includes aspirin and statin therapy. Repeat CACS testing in such patients is not currently recommended.
- Stress testing has limited value in asymptomatic patients with diabetes since it cannot detect subclinical coronary atherosclerosis, and a normal test result has only a 2- to 3-year warranty period. However, functional testing is recommended in the high-risk subset of patients with moderate (100-400) and severe (> 400) CACS to detect silent myocardial ischemia.

Conflict of Interest Disclosure:
Dr. Mahmarian is a consultant and serves on the Speaker's Bureau for Astellas Pharma U.S., Inc.

Keywords:
cardiac imaging, coronary artery disease, atherosclerosis, computed tomography coronary angiography, myocardial ischemia, coronary artery calcium scoring, CACS, diabetes, myocardial ischemia

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