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DIABETES AND CARDIOVASCULAR DISEASE (S MALIK, SECTION EDITOR)

Subclinical Cardiovascular Disease Assessment in Persons with Diabetes

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Abstract Patients with diabetes mellitus are at particularly high risk for cardiovascular disease. Although global risk factor scoring systems, such as the Framingham Risk Score, are well established for screening asymptomatic adults, they are not as predictive in diabetics. Therefore, there has been considerable interest in new screening tests to establish cardiovascular risk in diabetics. Coronary artery calcium assessment, both baseline levels and progression, have been shown to be additive to risk factor scoring systems and are independently predictive of cardiovascular mortality in diabetics. Current American Heart Association/American College of Cardiology Foundation guidelines recommend coronary calcium scoring for asymptomatic diabetics. Myocardial perfusion studies are recommended for patients with a coronary calcium score >400 but the level of evidence is poor. The data for other screening tests is limited. Further research is required into assessing what would be an appropriate follow-up duration for serial coronary calcium scanning.

Keywords Type 2 diabetes mellitus · Coronary calcium · Framingham risk score · Primary prevention · Cardiovascular disease

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Introduction: The Burden of Cardiovascular Disease in Type 2 Diabetes Mellitus

Type 2 diabetes mellitus (T2-DM) places an extraordinary burden on the population of the United States. According to data collected by the National Health and Nutrition Examination Survey (NHANES), 18.3 million American adults carry a diagnosis of DM, an additional 7.1 million are undiagnosed, and about 81.5 million Americans (36.8% of total US population) have pre-diabetes [1]. T2DM accounts for about 99% of DM in adults according to data from the Framingham Heart Study [2]. Patients with DM are at particularly high risk for cardiovascular disease. Adults with DM are 2–4 times more likely to die of cardiovascular disease (CVD) compared with nondiabetic controls, with 65% of diabetics experiencing death due to heart disease or stroke [3]. The financial fallout of this epidemic is also significant, with direct and indirect costs related to DM and its complications costing about $174 billion dollars in 2007 [4], and with the prevalence of DM expected to almost double by 2050 to 12.0% of the population [5], the importance of identifying higher risk patients becomes increasingly crucial.

The Natural History of Atherosclerotic Cardiovascular Disease

CVD is the most common cause of death in the world, with atherosclerosis the underlying pathology in the vast

majority of cases [6]. While classically considered a disease of developed countries, the prevalence of CVD is increasing in the developing world with about 80% of cardiovascular mortality predicted to occur there [7]. Atherosclerosis is a systemic process that involves the infiltration of fatty deposits, inflammatory mediators and cells, and subsequent calcification, and scarring in the intima of the arteries. The natural history of atherosclerosis unfolds over decades, beginning in childhood with fatty streaks. Thus CVD has a long latent period during which it remains subclinical therefore making it an ideal target for screening tests. About half of all patients who die of coronary artery disease do not have any preceding symptoms or cardiac diagnoses [8]. Furthermore, the presentation of myocardial infarction can be atypical in patients with DM, more so in women [9].

Assessing the Predictive Value of Screening Tests and Risk Factors

The characteristics of an ideal screening test should include several factors [10]. The test should be inexpensive and should result in a decrease in downstream expenses as well. The test should be easily reproducible and interpretable. The test should have a positive effect on the patient's behavior, motivating the patient to reduce modifiable risk factors and adopt efficacious therapies. The test should not induce any harm to the patient. The test should result in a meaningful change in patient management. The test should be adequately calibrated, which means that it should correctly predict the proportion of patients in a specific risk category who will have the event of interest. The test should also be discriminant, which means that the patient should be able to adequately differentiate between patients who are high risk, and patients who are low risk. This can be calculated by using the receiver operating characteristic (ROC) curve, which is a plot of true-positive rate vs false-positive rates against the entire range of a continuous random variable. The area under the curve (AUC), also referred to the c-statistic, is a measure of discrimination, with a value of 0.5 indicating no discrimination vs a value of 1.0, which indicates perfect discrimination. The c-statistic is also used to evaluate the additive utility of a new test, which can be measured by the increase in the c-statistic if a new test is combined with an existing one. Another parameter to assess the benefit of a new test is its ability to correctly reclassify patients into categories that truly reflect their level of risk [11]. Finally, the test should be evaluated in large population based, multi-ethnic cohort studies that include large numbers of outcome events for all of the above characteristics.

Global Risk Factor Scoring

Global risk factor scoring uses multivariate analyses to combine "classic" cardiovascular disease risk factors to predict the risk of cardiovascular disease events in asymptomatic patients. These risk factors include both unmodifiable factors such as age and gender as well as modifiable risk factors that can be targeted by interventions such as blood pressure, smoking, diabetic status, and cholesterol level (total cholesterol, LDL, and/or HDL). While several scores have been developed including the United Kingdom Prospective Diabetes Study (UKPDS) score [12], the Munster Heart Study (PROCAM) score [13], and the Systematic Coronary Risk Evaluation (SCORE) score [14], the Framingham Risk Score (FRS) is the most commonly used global risk score [15]. These scores have been validated by large epidemiologic studies in diverse patient populations and therefore, obtaining these systems to estimate risk and target interventions is a class 1 recommendation in the ACCF/AHA Guidelines for Assessment of Cardiovascular Risk in Asymptomatic Adults [16••]. These scoring systems are useful in avoiding both underestimating risk [17, 18], as well as potentially avoiding overestimation of risk [19], and/or excessive testing in the general population. FRS-type risk models have yielded high c-statistic values (0.83 in women and 0.78 in men) [20] in the general population [21].

However, while these scoring models are considered the standard of care, they can still miss 20%–35% of future cardiovascular events [22], resulting in preventable harm to a very large population of adults. Furthermore, these risk assessment algorithms are not as predictive in diabetics as opposed to the general population. In different studies, the FRS has been shown to both over- and under-estimate cardiovascular event risks in patients with diabetes by a significant margin [23–26]. Therefore, there has been considerable interest in the incorporation of new screening tests into the current paradigm of risk stratification in a way that there is a meaningful improvement over current measures, particularly in the asymptomatic diabetic population.

Coronary Calcium Measurement in Asymptomatic Adults

Coronary artery calcium (CAC) scoring used to be obtained using electron beam tomography, which has now been replaced by non enhanced computed tomography (CT). CAC is a reflection of an individual's global atherosclerotic burden and is reported either in Agatston units (AU) or by the volume scoring method, both of which correlate well with each other [27]. CAC has been shown to be independently associated with cardiovascular morbidity and mortality [28]. Furthermore, CAC has been consistently additive to FRS [28–32], results in improved reclassification [33–35], and in some

studies has predicted cardiovascular events by itself even more accurately than FRS [24]. Having a CAC score of 0 is 1 of the significant negative risk factors indicating a very low risk of future cardiovascular events [36–38]. Furthermore, in a recent prospective trial that randomized 2137 healthy volunteers to CAC scanning vs conventional FRS based risk stratifications, patients randomized to CAC scanning showed a significant net positive change in systolic blood pressure, LDL cholesterol, and reduction in waist circumference in patients with increased abdominal girth and weight loss in overweight patients [39]. A statistically significant dose-response improvement was noted in systolic and diastolic blood pressure, total and LDL cholesterol, triglycerides, weight, and FRS. Downstream testing and costs were balanced between lesser cost in low CAC patients and increased cost in patients with higher CAC resulting in no difference compared with the conventional FRS arm. In the Rotterdam study, however, CAC scanning was shown to only be cost-effective for male patient with intermediate FRS risk [40]. This was so because in this study, more intermediate risk men were reclassified as higher risk, as opposed to women who were more likely to have their risk profile lowered [40].

This powerful body of literature culminated in the incorporation of CAC screening in the ACCF/AHA Guidelines for Assessment of Cardiovascular Risk in Asymptomatic Adults [16••] (Table 1). A summary of notable studies assessing CAC screening in asymptomatic adult diabetics is provided in Table 2.

Coronary Calcium Measurement in Asymptomatic Diabetic Adults

Population-based studies have confirmed that patients with diabetes have a high prevalence of CAC before the onset of symptoms. CAC screening has been used to demonstrate the presence of atherosclerosis in 44%–81% of asymptomatic diabetic adults [41–44]. Severe atherosclerosis, defined as AU>400, has been reported in 17%–25% [41, 43, 45•] of patients in 3 large population based studies, however the prevalence was 42% in 1 German cohort [42] and 7% in a British cohort that was 56% of South Asian origin [44]. Absence of CAC has been noted in 15%–38% of patients [42, 43, 45•, 46, 47]. Patients with 0 CAC represent a very important cohort as their CVD event rate was found to be similar to patients without diabetes [45•, 48]. These patients' risk of CVD events is similar to that of patients without diabetes therefore challenging the notion that diabetes is a CVD equivalent, an already controversial concept [49, 50]. CAC was consistently additive to global risk scores such as FRS and

Table 1 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Guidelines for Assessment of Cardiovascular Risk in Asymptomatic Adults [16••]

ACCF/AHA Guidelines for Assessment of Cardiovascular Risk in Asymptomatic Adults	
➢ Computed tomography for coronary calcium	
Class IIa	Measurement of CAC is reasonable for cardiovascular risk assessment in asymptomatic adults at intermediate risk (10% to 20% 10-year risk (level of evidence: B))
Class IIb	Measurement of CAC may be reasonable for cardiovascular risk assessment in persons at low to intermediate risk (6% to 10% 10-year risk) (level of evidence: B)
Class III (no benefit)	Persons at low risk (<6% 10-year risk) should not undergo CAC measurement for cardiovascular risk assessment (level of evidence: B)
➢ Coronary computed tomography angiography	
Class III (no benefit)	Coronary computed tomography angiography is not recommended for cardiovascular risk assessment in asymptomatic adults (level of evidence: C)
➢ Recommendations for patients with diabetes	
Class IIa	In asymptomatic adults with diabetes, 40 years of age and older, measurement of CAC is reasonable for cardiovascular risk assessment (level of evidence: B)
Class IIb	1. Measurement of Hba1c may be considered for cardiovascular risk assessment in asymptomatic adults with diabetes (level of evidence: B)
	2. Stress MPI may be considered for advanced cardiovascular risk assessment in asymptomatic adults with diabetes or when previous risk assessment testing suggests a high risk of coronary heart disease, such as a CAC score of 400 or greater (level of evidence: C)

Class IIa suggests benefit is much greater than risk, and that 'it is reasonable' to perform modality. Class IIB suggests benefit is greater than or equal to risk and that modality 'may be considered'. Class III indicates no benefit.

Level of evidence B suggests limited populations evaluated with data derived from a single randomized trial or nonrandomized trials. Level of evidence C is based only on consensus opinion of experts, case studies, and/or standard of care.

CAC coronary artery calcium, *MPI* myocardial perfusion imaging.

Table 2 Notable studies studying the role of coronary calcium in asymptomatic adult patients with diabetes mellitus

Study	Design	Results
Silverman et al, 2012 [51]	Prospective, population-based self referred, n=2384 diabetics, mean age 58±11 (52% male), median follow up 5 yrs	CAC can identify diabetics at high risk (10 year CVD risk >10%) better than traditional risk factors who would benefit from aspirin per recent guidelines [72]. Patients who are ≥60 years with any additional risk factors have CVD risk >10% and thus don't benefit from CAC scanning.
Malik et al 2011 [45•]	Prospective, multi ethnic population, n=6603 (881 diabetics), mean age of diabetics 65±10, median follow-up 6.4 y	38% of patients had AU of 0, 17% >400. Event rate <1%/y in CAC 0 patients. CAC substantially additive to risk factors alone in diabetics for coronary heart disease (c statistic 0.78 vs 0.72, P<0.0001) compared with CIMT (c statistic 0.74 vs 0.72, P<0.002). Unlike CAC, CIMT not additive to cardiovascular disease risk.
Becker et al 2008 [42]	Observational, referred from diabetes clinic, n=716, mean age 55.2±15, mean follow-up 8.1 y	15% had AU of 0, 81% of patients had AU >10, 42% >400. CAC significantly associated with CVD events. CAC had higher c statistic than UKPDS and FRS (0.77 vs 0.68 and 0.71, P<0.01). Patients had negative resting EKG, stress EKG, and echocardiogram.
Elkeles et al 2008 [43]	Prospective, referral based, n=589, mean age 63.1, median follow-up 4 y	23% of patients had AU 0, 77% of patients had AU>10, 25% >400. CACS independently predicted CVD events. Insulin resistance was the only other factor that independently predicted CVD events. CACS increased c-statistic of UKPDS risk engine from 0.63 to 0.73.
Anand et al 2006 [41]	Prospective, recruitment from diabetic clinics, n=510, mean age 52.7±8, median follow-up 2.2 y	46.3% of patients had AU>10, 21.2% >400. CAC had the greatest AUC compared with UKPDS and FRS (both of which did not predict abnormal myocardial perfusion). Showed that myocardial perfusion scintigraphy was higher yield if performed in patients with AU >100.
Raggi et al 2004 [48]	Observational, referred from PCP for EBT, n=10,377 (903 diabetics), mean age of diabetics 57±10, median follow-up 5 y	Increasing CAC was more strongly predictive of mortality in diabetics compared with nondiabetics. However, survival of patients with 0 CAC was similar regardless of diabetic status. FRS didn't predict mortality (c-statistic 0.5, P=1 .0), compared with CAC (c statistic 0.72, P<0.0001)
Qu et al 2003 [73]	Prospective, population based, n=1312 (269 diabetics), mean age of diabetics 66.4±7, median follow-up 6.3 y	CAC scores greater in diabetics but Cox regression revealed that CAC score was significantly associated with events in nondiabetics (RR≥2.6, P<0.01) but not diabetics (RR≤1.7, P<0.05). However, CAC scanning method used had lower sensitivity than other studies [74].
Wong et al 2003 [46]	Cross-sectional, self or physician referred, n=1823 (36% female, 150 diabetics), mean age 57.2±9	CAC was present in 75.3% of men and 52.6% of women. Diabetics have both higher prevalence of any CAC as well as CAC >75th percentile compared with patients with metabolic syndrome as well as those with neither.
CAC Progression Studies		
Wong et al 2012 [56•]	Prospective, multi ethnic population, n=5662 (708 diabetics), mean age 61±10, mean follow-up scan 2.4 y, mean CVD follow-up 7.3 y	Diabetics have greater incidence and progression of CAC than patients with metabolic syndrome and those without either. However, greatest incidence and progression noted in patients with both diabetes and metabolic syndrome. Both baseline CAC and CAC progression were predictive of future CVD events.
Blaha et al 2011 [54]	Prospective, population-based, n=5464, mean age 62±10, follow-up scan at an average 1.6 and 3.2 y in 2 groups	Homeostasis model assessment of insulin resistance did not independently predict CAC incidence and progression after adjustment for metabolic syndrome.
Lee et al 2009 [58]	Observational, recruited from Kaiser Permanente, n=1024, mean age 65.8±3, median follow-up scan 2 y	Diabetes was strongest predictor of CAC progression in multivariate analysis. Insulin resistance, reflected by fasting insulin, was independently associated with CAC progression after controlling for other confounders.
Anand et al 2007 [44]	Prospective, recruited from diabetic clinics, n=398 diabetics, mean age 52±8 (54% South Asian), mean follow-up scan 2.5 y	56% had CAC <10, 7% had CAC >400. In multivariate analysis CAC>400 (OR 6.38, 95% CI 2.63-15.5, P<0.001), HbA1c >7 (OR 1.95, 95% CI 1.08–3.52, P=0.03) and statin use (OR 2.27 95% CI 1.38–3.73, P=0.001) were the only independent predictors of CAC progression. CAC progression was frequent in patients with baseline CAC compared with those with 0 CAC (29.6% vs 12%).
Kronmal et al 2007 [57]	Prospective, multi-ethnic population based, n=5756 (518 diabetics), mean age 62 (48% male), follow-up scan after 2.4 y	51.2% of general population had 0 CAC at baseline. Incidence was 6.6% overall and 10.3% in white mails. Diabetes had highest OR for CAC progression, even after adjustment for baseline CAC. This effect of diabetes was strongest in blacks, and weakest in Hispanics.
Budoff et al 2005 [55]	Observational, diabetics referred from primary care clinic, n=163 diabetics, mean age 65±10, mean follow-up scan 2.3 y	Only 6% of patients had 0 CAC. Statin treatment reduced CAC progression by 50% (10% vs 20%, P=0.0001). Hba1c was weakly associated with CAC progression (r=0.34, P=0.05).

Table 2 (continued)

Study	Design	Results
Raggi et al 2005 [47]	Retrospective, physician-referred for CAC scoring, n=1310 (157 diabetics), mean age 56±10, mean follow-up scan 2.2 and 2.7 for diabetics and non diabetics	23% had 0 CAC. Diabetes most powerful predictor of CAC progression. Statins reduce CAC progression by about 50% but are associated with higher risk of MI. Progression of CAC greater in diabetics than non diabetics. Statins slow progression in diabetics but are not as effective in patients who experience MI compared with patients without diabetes.

AU Agatston unit, *AUC* area under the curve, *CAC* coronary artery calcium, *CI* confidence intervals, *CIMT* carotid intimal-medial thickness, *CVD* cardiovascular disease, *FRS* Framingham risk score, *MI* myocardial infarction, *OR* odds ratio, *UKPDS* United Kingdom Prospective Diabetes Study risk engine.

UKPDS [41–43, 45•, 48] and in many cases the c-statistic for CAC alone exceeded that for FRS [42, 48]. CAC was also able to appropriately risk stratify patients with diabetes who would benefit from primary prevention with aspirin therapy [51]. Patients with CAC >100, regardless of their risk profiles otherwise, have been shown to have a 10 year CVD risk of >10%, and would likely benefit from aspirin therapy. However, a study of active-duty United States Army personnel that CAC measurement did not motivate patients to bring about an improvement in modifiable CVD risk factors at 1 year [52].

The progression of CAC over time has also been found to be associated with increased CVD and all-cause mortality, independent of patients' baseline CAC [53]. CAC progression is increased in diabetes compared with patients without diabetes [44, 54, 55, 56•]. Furthermore, many studies have demonstrated that progression of CAC over time is the single most powerful independent predictor of CVD events [47, 57, 58]. Amongst ethnic groups, diabetes had the highest odds ratio for progression in blacks, with the least in Hispanics [57]. Diabetics with 0 CAC were much less likely to experience progression in CAC compared with nondiabetics (29.6% vs 12%) [44]. Progression is more pronounced in diabetics compared with patients with metabolic syndrome, although the greatest rate of progression is in patients with both disorders [56•]. HbA1c level >7 was associated with increased CAC progression in 1 study [44], although the association was weaker in another (r=0.34, P= 0.05) [55]. While fasting insulin was found to be independently associated with increased CAC progression, the homeostasis model assessment of insulin resistance was not found to be associated with CAC progression after adjusting for confounders such as metabolic syndrome [54, 58].

The effect of statin therapy has also been extensively investigated in this population and the results have been mixed. Statin treatment has been shown to reduce progression of CAC in some studies in patients with diabetes by about 50% [47, 55], similar to reduction in nondiabetics [59]. However, other studies have found that statins were associated with both increased incidence and progression of CAC, including the large Multi Ethnic Study of Atherosclerosis (MESA) study [44, 57]. Although it is presumed that this may reflect the fact that patients on statins represent higher risk patients, it has been suggested that at the molecular level, the removal of lipid deposits by statins may induce vascular calcification by macrophages, smooth muscle cells, and osteoclast-like cells [60, 61]. In 1 study that did show reduction in CAC progression, statins were noted to be not as effective in diabetics who experienced myocardial infarctions as compared with nondiabetics [47]. However, this study was limited by the fact that it did not study the effect of statins on other CVD endpoints other than myocardial infarction.

Based on this extensive evidence, the ACCF/AHA recommended the use of CAC to risk stratify adults >40 years of age with diabetes (Table 1). This recommendation also acknowledges that diabetes is not necessarily a CVD equivalent and that the degree of CAC may be more important to assess the risk of these patients. However, the guidelines do not recommend serial scanning to assess for progression. This might be based on the fact that several large studies analyzing the significance of CAC progression in patients with diabetes had not been published at the time of the writing of this guideline. We believe that information obtained from follow-up CAC scanning will further help risk stratify patients, particularly those with intermediate CAC scores between AU 10 and 400.

Role of Other Screening Tests: Myocardial Perfusion Imaging, HbA1c, Carotid Intimal-Medial Thickness

The role of stress myocardial perfusion imaging (MPI) in asymptomatic diabetic patients remains controversial [62]. In the study by Anand et al CAC>100 was used as a cut off to increase the yield for MPI to 8.4% of asymptomatic diabetics that had a moderate-severe defect, compared with 6.3% in the DIAD study, which imaged all comers, and failed to show any benefit [63]. This strategy of screening patients with CAC scoring also reduced the number of MPI studies to only 25% of the number used in the DIAD study [41, 63]. Therefore, while stress MPI is recommended by the AHA/ACCF in patients with CAC >400 in this asymptomatic diabetic adults, this recommendation is based on expert consensus only (level of evidence C) [16••]. This recommendation differs from that

of the American Diabetes Association (ADA). The ADA initially recommended asymptomatic diabetics with risk factors to be screened for coronary artery disease with MPI [64], however since subsequent randomized data [63, 65] failed to show any benefit with this strategy their most recent guidelines do not suggest MPI in this population [66]. CAC screening, however, is suggested as the initial test in selected patients in a related ADA consensus statement [67].

With regards to the HbA1c, which is predictive of CVD in asymptomatic diabetics [44, 68], lower HbA1c levels were not associated with improved macrovascular complications in large trials [69–71]. However, per the AHA/ACCF guidelines, HbA1c should be considered for risk assessment in diabetics. Carotid intimal-medial thickness, has not been shown to be significantly additive to risk factor based stratification compared with CAC in the MESA population [45•].

Conclusions

Asymptomatic diabetic adults with subclinical cardiovascular disease represent a group at high risk for cardiovascular morbidity and mortality. While risk factor scoring systems such as the FRS are useful in the general population, they may not be as predictive in diabetics as compared with the general population. CAC scoring, however, is consistently additive and helps positively reclassify patients and is therefore recommended in this population. Follow-up CAC screening particularly in patients with intermediate CAC scores at baseline could provide further useful information data regarding CAC progression in these patients. MPI remains controversial but may have a role in patients with higher CAC scores.

Conflict of Interest Haider Javed Warraich declares that he has no conflict of interest.

Khurram Nasir declares that he has no conflict of interest.

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- • Of importance
- •• Of major importance

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