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Imaging Atherosclerosis in Diabetes: Current State

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Abstract

Prevalence of diabetes mellitus is rapidly increasing worldwide. Disease is an independent and important risk factor for cardiovascular disease in both men and women. Cardiovascular events including myocardial infarction and stroke are the primary causes of mortality in both type 1 and type 2 diabetes. Affected patients frequently have asymptomatic coronary artery disease. Studies have shown heterogeneity in cardiovascular risk among patients with diabetes. Imaging can help categorize patients based on their risk of future cardiovascular events by identifying those patients with atherosclerosis, rather than just relying on risk prediction based on population based studies. In this article we will review the evidence regarding use of atherosclerosis imaging in patients with diabetes.

1. Introduction

The prevalence of diabetes mellitus is rapidly increasing worldwide, with a projected prevalence of more than 350 million individuals by 2030 [1]. Diabetes mellitus is an independent and important risk factor for cardiovascular disease (CVD) in both men and women [2, 3] and patients with diabetes are at 2-4 times higher risk of coronary heart disease compared with dose free of the disease [4-6]. Besides having a higher prevalence of CVD, these patients frequently have asymptomatic coronary artery disease (CAD) [7-9].

Therefor it is pertinent to decide which patient should be treated and how aggressively. Some studies have suggested that diabetes is "coronary risk equivalent" and all diabetic patients should be treated as aggressively as nondiabetics with prior myocardial infarction.[10] But other studies have shown although diabetic patients have higher risk of CVD, their risk may not be as high. [11] [12] [13] A meta-analysis of 13 studies showed that patients with diabetes without prior myocardial infarction have a 43% lower risk of developing total coronary heart disease (CHD) events compared with patients without diabetes with previous myocardial infarction[14] Therefore it is important to categorize patients based on their disease severity and risk for progression of CVD. In this article we will review the evidence regarding use of atherosclerosis imaging in patients with diabetes.

2. CORONARY ARTERY CALCIUM

2.1. PREVALENCE OF CORONARY ARTERY CALCIUM IN DIABETIC PATIENTS

Coronary artery calcium (CAC) is a well-established marker of atherosclerosis [15]. Its relation to coronary artery atherosclerosis have been confirmed by histopathologic studies [16] and it has been shown to be strong predictor of incident coronary heart disease and improve predictive information compared to standard risk factors in large multi ethnic cohort studies. [17, 18].

Studies have shown a wide heterogeneity of atherosclerosis findings in diabetic population. [19] Substantial proportion of diabetic patients have CACS 0. In a study of 525 asymptomatic diabetic patients Van den Hoogen et al. showed that 35% of diabetic patients have CACS 0 [20]. In Multi-Ethnic Study of Atherosclerosis (MESA) 38% of diabetic individuals have 0 CACS[21] and in the HNR (Heinz Nixdorf Recall) study, 39.3% of women with diabetes and 13.4% of men with diabetes had a CAC score of 0 [22]. On the other hand, patients with diabetes have increased prevalence of CAC. In a study of 3,389 patients, Mielke et al. showed that the mean and median CAC values were much larger for those with diabetes compared to those without for all age groups and in both sexes [23]. Qu et al. studied 1,312 subjects (including 269 type 2 diabetic patients) and showed increased prevalence of CAC in diabetic patients compared with control subjects [24]. Ragi et al. studied 10,377 asymptomatic individuals (903 diabetic patients). The average CACS for subjects with and for those without diabetes was 281 ± 567 and 119 ± 341, respectively ($p < 0.0001$) [25] . It has also been sowed that asymptomatic diabetic patients have a substantial prevalence of CAC scores ≥ 400 compared with non-diabetic control subjects (25.9% vs. 7.2%, $p< 0.0005$) [26].

Patients with type I diabetes develop atherosclerosis detectable by CAC at very young age. In a study of 101 subjects 17–29 years of age with type 1 diabetes of at least 5 years' duration, 11 subjects (10.9%) were found to have calcium scores >0 [27] These patients will continue to have higher incidence of CAC compared to general population as they age. This was shown in a study of 656 patients with type 1 diabetes and 764 control subjects aged 20–55 years when patients were divided in 4 different age groups ad in each age group, diabetes was associated with a higher prevalence of any calcification ($P < 0.001$ for each gender adjusted for age) [28]. Results from this study also showed that in type 1 diabetes, coronary artery calcification is greatly increased in women and the gender difference in prevalence is lost. This parallels the risk of CVD, where women with diabetes lose the cardioprotective gender differences seen in non-diabetic cohorts.

2.2. ASSOCIATION OF CORONARY ARTERY CALCIUM WITH ISCHEMIA

CAC above 100 is associated with higher likelihood of reversible ischemia in myocardial perfusion studies. Wong et al. evaluated 1,043 patients without known CAD who underwent stress myocardial perfusion scintigraphy (MPS) and computed tomography. [29] One hundred forty patients had diabetes (with or without metabolic syndrome) and 173 who had metabolic syndrome without diabetes. They found that among patients with CAC scores ≥100, metabolic abnormalities, and even metabolic syndrome in the absence of diabetes predicted a higher likelihood of inducible ischemia.

2.3. CORONARY ARTERY CALCIUM AND CARDIOVASCULAR EVENTS:

CAC has been shown to predict cardiovascular events during a short or mid-term follow-up in diabetic patients. Anand et al. measured CAC in 510 asymptomatic type 2 diabetic subjects. During a median follow-up of 2.2 years, twenty events occurred (two cardiac deaths, nine non-fatal MIs, three acute coronary syndromes, three non-haemorrhagic strokes, and three late revascularizations). The majority of events (n=15) occurred in subjects with severe CAC (>400 AU). None of the events occurred in subjects with CAC≤10 AU. The CAC score predicted events more accurately than the UK Prospective Diabetes Study (UKPDS) and Framingham risk scores [area under the curves were 0.92, 0.74, and 0.60 for CAC, UKPDS, and Framingham risk scores, respectively ($P<0.0001$)[30]

In Prospective Evaluation of Diabetic Ischaemic Disease by Computed Tomography (PREDICT) Study, 589 patients with type 2 DM and no history of cardiovascular disease were followed for a median of 4 years. Primary endpoint of first coronary heart disease (CHD) or stroke events was reported in 66 patients. CACS was a highly significant, independent predictor of events ($P < 0.001$), with a doubling in CACS being associated with a 32% increase in risk of events. Elkeles et al. found that adding CACS to UKPDS increased the areas under the receiver operator characteristic curve from 0.63 to 0.73, respectively ($P = 0.03$). [31]

Malik et al. showed incremental association between CAC and CHD events in a large, prospective population-based study. They assessed CAC and CIMT in 6,603 people aged 45–84 years in the MESA, including 881 diabetic patients. Patients with diabetes, had low risks for CHD when CAC was not increased. . Ethnicity and RF-adjusted hazard ratios for CHD for CAC 100–399 vs. 0 was 2.9 ($P < 0.05$). For CAC 100–399 vs. 0 it increased to 3.3 ($P < 0.01$) and for CAC 400+ vs. 0 increased to 6.2 ($P < 0.001$) [21]

Similar results were found in a study of combined data from type 2 DM without clinical CVD in MESA and the Heinz Nixdorf Recall Study (N = 1343). 85 patients had events during mean follow-up of 8.5 years. Higher CAC scores had incremental increased risk of events. Compared to reference CAC score less than

25, increased CAC categories to >25 and ≤125, >125 and ≤400, and >400 relayed to increased hazard ratio to2.29 ($P < 0.09$), 3.87 ($P < 0.003$) and 5.97 ($P < 0.001$) respectively. [32] In a different study, Raggi et al. followed 10,377 asymptomatic individuals referred for EBT imaging for average 5 years including 903 diabetic patients. Primary end point was all-cause mortality. For every increase in CCS, there was a greater increase in mortality for diabetic than for nondiabetic subjects. [25] Silverman et al. studied a large cohort of 44,052 asymptomatic individuals without known CHD referred for CAC screening, including 2,384 individuals with diabetes. All subjects underwent CAC scoring at baseline and were followed for a mean of 5.6 ± 2.6 years for primary end point of all-cause mortality verified using the Social Security Death Index. They concluded that CAC independently predict cardiovascular events as well as enhance risk stratification in patients with diabetes.[33]

Diabetic patients with CAC score <10 have low mortality rate. Raggi et al. showed that patients suffering from diabetes with no coronary artery calcium demonstrated a survival similar to that of individuals without diabetes and no detectable calcium (98.8% and 99.4%, respectively, $p = 0.5$) [25]. Silverman et al. found that Most individuals with diabetes <60 years of age have a low near-term risk of <5 deaths/1,000 person-years when CAC = 0. [33]. The significance increases when we consider that large proportion of patients with diabetes have very low or 0 CAC score. In the study conducted by Raggi, from 903 diabetic patients, 351 (39 %) had CAC 0-10. [25], likewise in MESA, from 881 patients with diabetes 38% had 0 CAC [21] and in study by Silverman et al. from 2384 patients, 535 (22%) had 0 CAC.

These studies show that CAC measurement augments prediction of CHD risk in asymptomatic diabetic individuals beyond consideration non-diabetes CHD risk factors. First, a high proportion of diabetics have a CAC score of 0, which is associated with an excellent prognosis. Second, for every increasing non-zero category of CAC, the risk is higher for a diabetic than a non-diabetic patient. Based on these data, current professional societal guidelines endorse the use of diagnostic testing for selected asymptomatic individuals by means of stress testing [34] [35] or CAC scoring [36].

Long-term prognosis of asymptomatic diabetic patients according to CAC score is studied and published recently [37]. Valenti et al. followed 9715 asymptomatic subjects including 810 diabetic patients for a median 14.7 (13.9-15.6) years. Incident mortality was higher in diabetic versus nondiabetic individuals (188 [23.2%] versus 748 [8.4%]). This study extended the discrimination and reclassification benefits of adding CAC score to traditional risk factors to long-term period. For individuals with CAC=0, at 5 years the risk of mortality for diabetic patients compared with nondiabetic individuals was not different ($p = 0.088$) but at 15 years there was a nonlinear increase after 5 years ($p<0.05$).

These studies show that CAC has high discriminatory value and is a robust test in order to reclassify patients with diabetes. Presence of CAC is associated with incremental increase in near-term and long-term mortality rate in both sexes among different age categories. Patients with CAC=0 will have mortality rate similar to general population at near-term but not in long-term.

2.4. PROGRESSION OF CORONARY ARTERY CALCIUM SCORE IN DIABETES

Progression of CAC or change in quantity of CAC over time is associated with an increased risk for future hard and total CHD events as well as all-cause mortality [38-40]. Multiple studies have shown that diabetic patients have a high rate CAC progression. Budoff et al evaluated 163 asymptomatic physician referred patients with type 2 diabetes (120 men, 43 women) with 2 consecutive CACS at least 1 year apart (averaged 27 months). Patients not treated with statins demonstrated a median annual increase in CAC progression of 20% (4%-44%), whereas statin-treated patients demonstrated increase of 10% (4%-25%) (P = .0001) [41]

In a substudy of the Veterans Affairs Diabetes Trial (VADT), Saremi et al. evaluated 197 individuals with type 2 diabetes. After a mean follow-up time of 4.6 ± 0.6 years, 189 subjects (96%) had follow-up CACS. The median annualized percent change in CACS was 20% (9–41%). The extent of CAC progression increased significantly (P < 0.01) with higher baseline CAC or AAC categories and the majority (59%) of subjects with a CACS of 0 at baseline maintained a CAC score of 0 at follow-up. [42]

Gassett et al. examined cardiovascular CAC progression in MESA population. CAC was measured 1 to 4 times (mean 2.5 scans) over 10 years in 6810 adults without preexisting cardiovascular disease [43]. The overall average CAC progression was 23.9 Agatston units/year among participants with at least 2 measurements. Compared to nondiabetics, diabetic participants had higher average annual progression (31.3 Agatston units/year, P<0.001) [43]

In a different publication from MESA population, Wong et al. reported that individuals with metabolic syndrome (MetS) and DM had a greater incidence and absolute progression of CAC compared to individuals without these conditions, with progression also predicting CHD events in those with MetS and DM. [44] They evaluated 5,662 subjects (51% women, mean age 61.0 ± 10.3 years) who received baseline and follow-up (mean 2.4 years) cardiac CT scans. Relative to those with neither MetS nor DM, absolute differences in mean progression (volume score) were 7.8 (p<0.01), 11.6 (p<0.05), and 22.6 (p<0.01) for those with MetS without DM, DM without MetS, and both DM and MetS, respectively. Progression predicted CHD events in those with MetS without DM (adjusted hazard ratio 4.1, p<0.01) and DM (4.9, p<0.05) among those in highest tertile of CAC increase vs. no increase).[44]

These studies show the higher rate of CAC progression in diabetic patients compared to general population and ability of CAC progression to predict future CHD events in diabetic patients. Evaluating diabetic patients for CAC progression has the potential to identify individuals at high risk that befit from more aggressive therapy.

3. CORONARY COMPUTED TOMOGRAPHIC ANGIOGRAPHY

3.1. PREVALANCE of CORONARY ATHEROSCELEROSIS by CT ANGIOGRSPHY:

Coronary Computed Tomographic Angiography (CCTA) is a noninvasive modality for evaluation of atherosclerotic disease with high diagnostic accuracy for detection and exclusion of atherosclerosis as well as anatomic obstructive CAD [45]. Calcified plaques are the only subtype that can be detected by CAC. CCTA has extended the potential application of CT in the asymptomatic diabetic patient, by providing an accurate assessment of non-calcified coronary plaque [19]. Young patients with diabetes have high prevalence of noncalified plaque. Madaj et al. evaluated 40 patients with diabetes between ages 19 and 35. Abnormal scans were present in 57.5%; noncalcified in 35% and calcified-mixed plaque in 22.5% [46].

Studies have shown severe atherosclerotic CAD detected by CCTA in 5-10% of diabetic patients with CAC=0. Kamimura et al. evaluated 120 consecutive diabetic patients (75% male, mean age 65) by CCTA. Significant stenosis (defined as coronary artery stenosis > 70%) was present in 5% of patients whose CAC score = 0 [47]. Min et al. showed that nearly one third of asymptomatic diabetics with a CAC score of zero indeed have atherosclerosis, and that over 10% of these individuals have obstructive CAD by CCTA. [48]

Multiple studies have shown high prevalence of coronary atherosclerosis and obstructive CAD as well as higher prevalence of plaques with features of instability in patients with diabetes. In the study mentioned earlier by Kamimura et al. , coronary artery stenosis > 70% was identified in 30.5% of the patients and High-risk plaques defined as CT density < 30 Hounsfield Units (HU) were identified in 17.1% of the patients.[47] Roos et al. studied 120 asymptomatic South Asian patients with type 2 DM and matched Caucasian patients (mean age 52 years, 55% men) by multiditector CT Compared with Caucasian patients, South Asian patients had a significantly higher coronary artery calcium score and higher prevalence of significant CAD (41% vs 28%, respectively, p = 0.008), involving more coronary vessels and segments.[49] Halon et al. evaluated 427 consecutive asymptomatic diabetic patients with no history of coronary disease, (age 55–74 years, 58% women), with CCTA. Coronary atheroma was present in 76.6% of patients, multivessel coronary atheroma in 55.1% and luminal stenosis (≥50% of diameter) in 22.9%.[50] Scholte et al. evaluated 100 asymptomatic patients (aged 30 to 72 years) with type 2 diabetes mellitus and one or more risk factors for CAD with adenosine technetium-99m sestamibi SPECT imaging, CAC scoring, and 64-slice CCTA. 60 patients (60%) had positive CAC scoring (18 patients [18%] with significant CAC >401), and 70 patients (70%) had abnormal CCTS (24 patients [24%] with significant, ≥50% stenosis).[51]

3.2. CORONARY COMPUTED TOMOGRAPHIC ANGIOGRAPHY AND CARDIOVASCULAR EVENTS

Atherosclerotic coronary artery detected by CCTA is associated with higher event rates. In a study by Park et al. 557 asymptomatic type 2 diabetic patients who underwent CCTA were evaluated. Cardiac event was defined as a composite of cardiac death, nonfatal myocardial infarction, acute coronary syndrome requiring hospitalization, or late revascularization. In the follow-up period (33.7 ± 7.8 months), those with significant CAD showed more cardiac events (7.1% vs 0.5%) and lower 3-year event-free survival rates (99.2 ± 0.6% vs 90.9 ± 2.6%, p <0.001).[52]

Min et al. identified 400 asymptomatic diabetic patients without known CAD from CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter) registry. They assessed major adverse cardiovascular events (MACE) – inclusive of mortality, nonfatal myocardial infarction (MI), and late target vessel revascularization ≥90 days. At a mean follow-up 2.4 ± 1.1 years, 33 MACE occurred (13 deaths, 8 MI, 12 REV). By univariate analysis, per-patient maximal stenosis, increasing numbers of obstructive vessels and segment stenosis score (all p < 0.001) were associated with increased MACE. These findings improved the prediction of incident MACE in asymptomatic diabetic individuals beyond

CHD risk factors and CAC score, allowing for improved risk stratification, discrimination and reclassification. [48]. However, the recent multicenter study has failed to show a statistically significance of prognostic utility of CCTA. The FACTOR-64 study was a randomized clinical trial of 900 patients with type 1 or type 2 diabetes of at least 3 to 5 years' duration and without symptoms of CAD to assess weather routine screening for CAD by CCTA and CCTA-directed therapy would reduce the risk of death and nonfatal coronary outcomes. [53] Subjects were randomly assigned to CAD screening with CCTA (n = 452) or to standard national guidelines–based optimal diabetes care (n = 448). Standard therapy or aggressive therapy or aggressive therapy with invasive coronary angiography, was recommended based on CCTA findings. In CCTA arm, 61 (14%) and 36 (8%) coronary stress or noninvasive imaging tests and diagnostic coronary angiographic procedures were performed, respectively, which resulted in 26 (5.8%) coronary revascularization procedures including 7 CABG. The primary end point of death, nonfatal MI, or hospitalization for unstable angina occurred in 6.2% of CCTA screened vs 7.6% of control group patients (HR, 0.80 ; P = .38). These results were not statistically significant. A longer follow-up is underway.

These data suggest that CCTA findings of CAD can improve risk stratification, discrimination and correct reclassification in asymptomatic individuals above and beyond risk factors and CAC. Future randomized trials should be performed to determine the potential benefit of these CCTA findings in therapeutic decision making to optimize outcomes.

4. Conclusion

In this article, we reviewed the evidence regarding role of CAC and CTA in atherosclerosis imaging in diabetic patients. CAC provides strong risk stratification for diabetic patients. Presence of CAC has incremental association with long-term mortality in both men and women across different age groups. Zero CAC translates to mortality risk similar to nondiabetic for patients up to 5 years. CCTA is a noninvasive modality for evaluation of atherosclerotic disease with high diagnostic accuracy and can improve risk stratification, discrimination and correct reclassification in asymptomatic individuals above and beyond risk factors and CAC.

Reference

1. Narayan, K.M., et al., *Impact of recent increase in incidence on future diabetes burden: U.S., 2005-2050.* Diabetes Care, 2006. **29**(9): p. 2114-6.
2. Wilson, P.W., *Diabetes mellitus and coronary heart disease.* Am J Kidney Dis, 1998. **32**(5 Suppl 3): p. S89-100.
3. Giri, S., et al., *Impact of diabetes on the risk stratification using stress single-photon emission computed tomography myocardial perfusion imaging in patients with symptoms suggestive of coronary artery disease.* Circulation, 2002. **105**(1): p. 32-40.
4. Emerging Risk Factors, C., et al., *Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies.* Lancet, 2010. **375**(9733): p. 2215-22.
5. Kannel, W.B. and D.L. McGee, *Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham study.* Diabetes Care, 1979. **2**(2): p. 120-6.
6. Gu, K., C.C. Cowie, and M.I. Harris, *Mortality in adults with and without diabetes in a national cohort of the U.S. population, 1971-1993.* Diabetes Care, 1998. **21**(7): p. 1138-45.
7. Cabin, H.S. and W.C. Roberts, *Quantitative comparison of extent of coronary narrowing and size of healed myocardial infarct in 33 necropsy patients with clinically recognized and in 28 with clinically unrecognized ("silent") previous acute myocardial infarction.* Am J Cardiol, 1982. **50**(4): p. 677-81.
8. Wackers, F.J., et al., *Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study.* Diabetes Care, 2004. **27**(8): p. 1954-61.
9. Miller, T.D., et al., *Yield of stress single-photon emission computed tomography in asymptomatic patients with diabetes.* Am Heart J, 2004. **147**(5): p. 890-6.
10. Haffner, S.M., et al., *Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction.* N Engl J Med, 1998. **339**(4): p. 229-34.
11. Lotufo, P.A., et al., *DIabetes and all-cause and coronary heart disease mortality among us male physicians.* Archives of Internal Medicine, 2001. **161**(2): p. 242-247.
12. Vaccaro, O., et al., *Impact of diabetes and previous myocardial infarction on long-term survival: 25-year mortality follow-up of primary screenees of the multiple risk factor intervention trial.* Archives of Internal Medicine, 2004. **164**(13): p. 1438-1443.
13. Evans, J.M., J. Wang, and A.D. Morris, *Comparison of cardiovascular risk between patients with type 2 diabetes and those who had had a myocardial infarction: cross sectional and cohort studies.* BMJ, 2002. **324**(7343): p. 939-42.
14. Bulugahapitiya, U., et al., *Is diabetes a coronary risk equivalent? Systematic review and meta-analysis.* Diabet Med, 2009. **26**(2): p. 142-8.
15. Ardehali, R., et al., *Screening patients for subclinical atherosclerosis with non-contrast cardiac CT.* Atherosclerosis, 2007. **192**(2): p. 235-42.
16. Rumberger, J.A., et al., *Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area. A histopathologic correlative study.* Circulation, 1995. **92**(8): p. 2157-62.
17. Detrano , R., et al., *Coronary Calcium as a Predictor of Coronary Events in Four Racial or Ethnic Groups.* New England Journal of Medicine, 2008. **358**(13): p. 1336-1345.
18. Budoff, M.J., et al., *A comparison of outcomes with coronary artery calcium scanning in unselected populations: the Multi-Ethnic Study of Atherosclerosis (MESA) and Heinz Nixdorf RECALL study (HNR).* J Cardiovasc Comput Tomogr, 2013. **7**(3): p. 182-91.

19. Berman, D.S., et al., *Non-invasive imaging in assessment of the asymptomatic diabetic patient: Is it of value?* J Nucl Cardiol, 2016. **23**(1): p. 37-41.
20. van den Hoogen, I.J., et al., *Prognostic value of coronary computed tomography angiography in diabetic patients without chest pain syndrome.* J Nucl Cardiol, 2016. **23**(1): p. 24-36.
21. Malik, S., et al., *Impact of Subclinical Atherosclerosis on Cardiovascular Disease Events in Individuals With Metabolic Syndrome and Diabetes.* The Multi-Ethnic Study of Atherosclerosis, 2011. **34**(10): p. 2285-2290.
22. Moebus, S., et al., *Association of impaired fasting glucose and coronary artery calcification as a marker of subclinical atherosclerosis in a population-based cohort--results of the Heinz Nixdorf Recall Study.* Diabetologia, 2009. **52**(1): p. 81-9.
23. Mielke, C.H., J.P. Shields, and L.D. Broemeling, *Coronary artery calcium, coronary artery disease, and diabetes.* Diabetes Res Clin Pract, 2001. **53**(1): p. 55-61.
24. Qu, W., et al., *Value of coronary artery calcium scanning by computed tomography for predicting coronary heart disease in diabetic subjects.* Diabetes Care, 2003. **26**(3): p. 905-10.
25. Raggi, P., et al., *Prognostic value of coronary artery calcium screening in subjects with and without diabetes.* Journal of the American College of Cardiology, 2004. **43**(9): p. 1663-1669.
26. Schurgin, S., S. Rich, and T. Mazzone, *Increased Prevalence of Significant Coronary Artery Calcification in Patients With Diabetes.* Diabetes Care, 2001. **24**(2): p. 335-338.
27. Starkman, H.S., et al., *Delineation of Prevalence and Risk Factors for Early Coronary Artery Disease by Electron Beam Computed Tomography in Young Adults With Type 1 Diabetes.* Diabetes Care, 2003. **26**(2): p. 433-436.
28. Dabelea, D., et al., *Effect of Type 1 Diabetes on the Gender Difference in Coronary Artery Calcification: a Role for Insulin Resistance?* The Coronary Artery Calcification in Type 1 Diabetes (CACTI) Study, 2003. **52**(11): p. 2833-2839.
29. Wong, N.D., et al., *Metabolic syndrome and diabetes are associated with an increased likelihood of inducible myocardial ischemia among patients with subclinical atherosclerosis.* Diabetes Care, 2005. **28**(6): p. 1445-50.
30. Anand, D.V., et al., *Risk stratification in uncomplicated type 2 diabetes: prospective evaluation of the combined use of coronary artery calcium imaging and selective myocardial perfusion scintigraphy.* Eur Heart J, 2006. **27**(6): p. 713-21.
31. Elkeles, R.S., et al., *Coronary calcium measurement improves prediction of cardiovascular events in asymptomatic patients with type 2 diabetes: the PREDICT study.* Eur Heart J, 2008. **29**(18): p. 2244-51.
32. Yeboah, J., et al., *Development of a new diabetes risk prediction tool for incident coronary heart disease events: the Multi-Ethnic Study of Atherosclerosis and the Heinz Nixdorf Recall Study.* Atherosclerosis, 2014. **236**(2): p. 411-7.
33. Silverman, M.G., et al., *Potential Implications of Coronary Artery Calcium Testing for Guiding Aspirin Use Among Asymptomatic Individuals With Diabetes.* Diabetes Care, 2012. **35**(3): p. 624-626.
34. Hendel, R.C., et al., *ACCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM 2009 Appropriate Use Criteria for Cardiac Radionuclide Imaging: A Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the American Society of Nuclear Cardiology, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the Society of Cardiovascular Computed Tomography, the Society for Cardiovascular Magnetic Resonance, and the Society of Nuclear Medicine.* J Am Coll Cardiol, 2009. **53**(23): p. 2201-29.
35. Gibbons, R.J., et al., *ACC/AHA 2002 guideline update for exercise testing: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice*

Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). J Am Coll Cardiol, 2002. **40**(8): p. 1531-40.
36. Taylor, A.J., et al., *ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 Appropriate Use Criteria for Cardiac Computed Tomography. A Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance.* Circulation, 2010. **122**(21): p. e525-55.
37. Valenti, V., et al., *Absence of Coronary Artery Calcium Identifies Asymptomatic Diabetic Individuals at Low Near-Term But Not Long-Term Risk of Mortality: A 15-Year Follow-Up Study of 9715 Patients.* Circulation: Cardiovascular Imaging, 2016. **9**(2): p. e003528.
38. Budoff, M.J. and P. Raggi, *Coronary artery disease progression assessed by electron-beam computed tomography.* Am J Cardiol, 2001. **88**(2A): p. 46E-50E.
39. Budoff, M.J., et al., *Progression of coronary artery calcium predicts all-cause mortality.* JACC Cardiovasc Imaging, 2010. **3**(12): p. 1229-36.
40. Budoff, M.J., et al., *Progression of coronary calcium and incident coronary heart disease events: MESA (Multi-Ethnic Study of Atherosclerosis).* J Am Coll Cardiol, 2013. **61**(12): p. 1231-9.
41. Budoff, M.J., et al., *Diabetes and progression of coronary calcium under the influence of statin therapy.* Am Heart J, 2005. **149**(4): p. 695-700.
42. Saremi, A., et al., *Rates and determinants of coronary and abdominal aortic artery calcium progression in the Veterans Affairs Diabetes Trial (VADT).* Diabetes Care, 2010. **33**(12): p. 2642-7.
43. Gassett, A.J., et al., *Risk Factors for Long-Term Coronary Artery Calcium Progression in the Multi-Ethnic Study of Atherosclerosis.* J Am Heart Assoc, 2015. **4**(8): p. e001726.
44. Wong, N.D., et al., *Metabolic syndrome, diabetes, and incidence and progression of coronary calcium: the Multiethnic Study of Atherosclerosis study.* JACC Cardiovasc Imaging, 2012. **5**(4): p. 358-66.
45. Budoff, M.J., et al., *Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial.* J Am Coll Cardiol, 2008. **52**(21): p. 1724-32.
46. Madaj, P.M., et al., *Identification of noncalcified plaque in young persons with diabetes: an opportunity for early primary prevention of coronary artery disease identified with low-dose coronary computed tomographic angiography.* Acad Radiol, 2012. **19**(7): p. 889-93.
47. Kamimura, M., et al., *Role of coronary CT angiography in asymptomatic patients with type 2 diabetes mellitus.* Int Heart J, 2012. **53**(1): p. 23-8.
48. Min, J.K., et al., *Incremental prognostic value of coronary computed tomographic angiography over coronary artery calcium score for risk prediction of major adverse cardiac events in asymptomatic diabetic individuals.* Atherosclerosis, 2014. **232**(2): p. 298-304.
49. Roos, C.J., et al., *Comparison by Computed Tomographic Angiography—The Presence and Extent of Coronary Arterial Atherosclerosis in South Asians Versus Caucasians With Diabetes Mellitus.* American Journal of Cardiology. **113**(11): p. 1782-1787.
50. Halon, D.A., et al., *Pulse pressure and coronary atherosclerosis in asymptomatic type 2 diabetes mellitus: A 64 channel cardiac computed tomography analysis.* International Journal of Cardiology. **143**(1): p. 63-71.

51. Scholte, A.J.H.A., et al., *Different manifestations of coronary artery disease by stress SPECT myocardial perfusion imaging, coronary calcium scoring, and multislice CT coronary angiography in asymptomatic patients with type 2 diabetes mellitus.* Journal of Nuclear Cardiology, 2008. **15**(4): p. 503-509.
52. Park, G.M., et al., *Coronary computed tomographic angiographic findings in asymptomatic patients with type 2 diabetes mellitus.* Am J Cardiol, 2014. **113**(5): p. 765-71.
53. Muhlestein, J.B., et al., *Effect of screening for coronary artery disease using CT angiography on mortality and cardiac events in high-risk patients with diabetes: the FACTOR-64 randomized clinical trial.* JAMA, 2014. **312**(21): p. 2234-43.