

# Cardiac Imaging for Risk Stratification in Diabetes

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**W**orldwide, 200 million individuals currently have diabetes, and projections by the World Health Organization and others suggest that its prevalence will exceed 300 million by 2025 and 360 million by 2030 (1,2). More than 90% of these individuals will have type 2 diabetes. Management guidelines in Europe (3) and the U.S. (4) consider type 2 diabetes to be a cardiovascular disease equivalent. These patients have a two- to fourfold higher risk of a cardiovascular event than nondiabetic patients. Importantly, cardiovascular death is the most common cause of mortality in the type 2 diabetic population (5). It has been estimated that after a myocardial infarction, 79% of diabetic patients die of cardiac complications (6). Accordingly, accurate cardiovascular risk stratification of patients with type 2 diabetes is needed. This can be problematic in that the clinical presentation and progression of coronary artery disease (CAD) differs between diabetic and nondiabetic patients. In addition to a higher prevalence of CAD (7), patients with diabetes experience more diffuse, calcified, and extensive CAD, more often have left ventricular dysfunction, often have more advanced coronary disease at the time of diagnosis, and more

often experience silent ischemia. In addition, diabetic patients generally have a less favorable response to revascularization (with frequent need for repeat percutaneous coronary intervention or coronary artery bypass grafting) and a reduced long-term survival.

Accordingly, early accurate diagnosis of CAD in patients with diabetes is needed, and reliable prognostication is mandatory. The American Diabetes Association has recommended an algorithm whereby symptomatic diabetic patients would be referred for either stress perfusion imaging or stress echo or evaluation by a cardiologist. The exception would be individuals with atypical chest pain and a normal electrocardiogram who might undergo a simple exercise stress test unless they have multiple other cardiovascular risk factors, in which case imaging studies would be preferred (8).

The purpose of the present review is to discuss the available imaging techniques in assessing CAD in symptomatic patients with diabetes (and compare observations to the accuracy of the techniques in the general population). In addition, the issue of screening CAD in asymptomatic diabetic patients is discussed.

## HOW IS CAD DIAGNOSED?

The “gold standard” for detection of CAD remains invasive angiography with vessel-selective contrast injection of the coronary arteries. Both spatial (0.2 mm) and temporal (5 ms) resolution of the technique are extremely high, and the degree of luminal narrowing can be quantified precisely. This is an invasive and expensive procedure with a small but definite risk for complications. Noninvasive testing is increasingly used to assess CAD, and multiple methods are now unavailable. These can be divided into functional imaging, which detects the hemodynamic consequences of CAD (i.e., ischemia), and anatomical imaging, which detects atherosclerosis and permits direct visualization of the coronary arteries.

## Functional imaging

The basis of functional imaging is the detection of CAD by assessing the hemodynamic consequences (i.e., ischemia) of CAD rather than direct visualization of the coronary arteries. A sequence of events occurs during induction of ischemia, referred to as “the ischemic cascade” (9). Early (within seconds) in the ischemic cascade, perfusion abnormalities occur, and systolic wall motion abnormalities follow within 10–20 s. Electrocardiogram (ECG) changes and angina occur only at the end of the cascade. Accordingly, exercise ECG is predictably not the most sensitive technique, and its diagnostic accuracy has been demonstrated to be low in patients with diabetes (10). Conversely, abnormalities in perfusion and systolic wall motion are early markers of ischemia. While perfusion abnormalities should be the more sensitive of the two for assessment of ischemia, in daily practice both phenomena are similarly sensitive.

A number of imaging techniques can assess myocardial perfusion, including nuclear techniques (i.e., positron emission tomography [PET] or single photon emission computed tomography [SPECT]), first-pass perfusion imaging with magnetic resonance imaging (MRI), and myocardial contrast echocardiography. For assessment of systolic wall motion, the following techniques are used: two-dimensional stress echocardiogra-

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**Abbreviations:** CAD, coronary artery disease; EBCT, electron beam computed tomography; DIAD, Detection of Silent Myocardial Ischemia in Asymptomatic Diabetics; ECG, electrocardiogram; MRI, magnetic resonance imaging; MSCT, multislice computed tomography; PET, positron emission tomography; SPECT, single photon emission computed tomography.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—Diagnostic accuracy imaging tests

	General population		Diabetic patients	
	Sensitivity	Specificity	Sensitivity	Specificity
Functional imaging (ref.)				
Nuclear imaging (11–14)	86	74	80–97	56–88
Stress echocardiography (15–18)	71–84	82–93	81–82	54–88
Contrast echocardiography (21,22)	89	63	89	52
First-pass perfusion MRI (21)	84	85	NA	NA
Stress cine MRI (21)	89	84	NA	NA
Anatomical imaging (ref.)				
CAC score	NA	NA	NA	NA
MRI angiography (27)	72	86	NA	NA
MSCT angiography (28,29)	91	96	95	95
EBCT angiography (30)	87	91	NA	NA

Data are percentages. CAC, coronary artery calcium. NA, not available.

phy, cine stress MRI, and stress-gated SPECT or PET imaging.

Most importantly, for ischemia assessment, imaging needs to be performed during stress and at rest. Comparison of the stress and rest images reveals whether stress-inducible perfusion or systolic wall motion abnormalities are present, indicating ischemia. The stress can be performed using bicycle or treadmill exercise or (in patients unable to exercise) pharmacological agents. Pharmacological stressors include dobutamine (a  $\beta$ -1-specific agonist), which increases heart rate, contractility, and arterial blood pressure, resulting in increased myocardial oxygen demand, and adenosine (a direct vasodilator) or dipyridamole, which act indirectly by inhibiting cellular uptake and breakdown of adenosine.

Functional imaging performed using gated SPECT (contrast) stress echocardiography and MRI allow integrated assessment of perfusion and function at rest and after stress.

### Anatomical imaging

Anatomical imaging assesses atherosclerosis by direct visualization of the coronary arteries. The several imaging modalities available include MRI, multislice computed tomography (MSCT), and electron beam computed tomography (EBCT). Since the coronary arteries are small, tortuous, and move substantially during the cardiac cycle, imaging remains technically challenging. As a result, all techniques have shortcomings and limitations, but with recent and ongoing technical advances, image quality and diagnostic accuracy are continuously improving. Besides noninvasive angiography, these techniques may

also allow assessment of plaque composition in the near future.

## DIAGNOSTIC ACCURACY OF CAD

### Functional imaging

**Nuclear imaging.** In the clinical setting, nuclear imaging (mainly with SPECT) is the most frequently used technique to assess perfusion as a marker of CAD (Table 1). Three radiopharmaceuticals are used: thallium-201, technetium-99m sestamibi, and technetium-99m tetrofosmin. Two sets of images are obtained, after stress and at rest. Perfusion defects can be divided into reversible (stress-induced) defects (reflecting ischemia) and irreversible (fixed) defects (indicating infarcted myocardium). An example is provided in online appendix Fig. 1 (available at <http://dx.doi.org/10.2337/dc06-2094>).

In the general population, the sensitivity and specificity of SPECT for detection of CAD (defined typically as  $>50\%$  stenosis on coronary angiography) are 86 and 74%, respectively (based on pooled analysis of 79 studies, 8,964 patients), as compared with invasive angiography (11). These data reflect potential patient selection biases, as patients are referred for coronary angiography after abnormal SPECT findings. In contrast, coronary angiography is usually not performed in patients with normal SPECT findings. This post-test referral bias will artificially lower the specificity, as a higher percentage of patients with normal coronary angiograms will have abnormal SPECT findings in these studies than in the general population with no CAD. A better indicator for

specificity would be the normalcy rate. This is the percentage of normal SPECT studies in a population with a low likelihood of CAD. SPECT has a normalcy rate of 89% (based on pooled analysis of 10 studies, 543 patients) (11). With the ability to acquire ECG-gated images, simultaneous assessment of regional and global function is obtainable, which increases diagnostic accuracy (12,13).

Considerably less information on diagnostic accuracy is available in diabetic patients, and studies specifically dedicated to the diagnostic accuracy of nuclear perfusion imaging in patients with diabetes are scarce. Kang et al. (14) evaluated 138 patients with diabetes who also underwent invasive angiography and reported a sensitivity of 86% with a lower specificity of 56%. The normalcy rate, however, was 89% (online appendix Fig. 2). Most important, the accuracy of SPECT was not different between patients with and without diabetes.

**Stress echocardiography.** Stress echocardiography is the most frequently used technique to assess systolic wall motion. Both physical exercise and pharmacological stress can be used. Resting wall motion abnormalities mainly represent infarcted myocardium, while those induced by stress reflect ischemia.

In the general population, as compared with invasive angiography, the sensitivity and specificity of exercise echocardiography for the detection of CAD are 84 and 82%, respectively (pooled analysis of 15 studies, 1,849 patients) (15). The sensitivity and specificity of dobutamine stress echocardiography are 80 and 84%, respectively (pooled analysis of 28 studies, 2,246 patients) (15). Though less extensively studied, the sensitivity and specificity for dipyridamole stress echocardiography (71 and 93%, respectively, in 12 studies of a total of 818 patients) appear comparable (16).

Studies that specifically addressed the topic of detection of CAD with stress echocardiography in patients with diabetes are limited to a few with small numbers of patients. Hennessy et al. (17) evaluated 52 patients with diabetes with dobutamine stress echocardiography and reported a sensitivity of 82% with a specificity of 54%. Elhendy et al. (18) evaluated 50 patients with diabetes and 240 nondiabetic patients with stress echocardiography and invasive angiography. The sensitivity and specificity in the patients with diabetes were 81 and 85%, respec-

tively, as compared with 74 and 87% in the nondiabetic patients.

#### **Myocardial contrast echocardiography.**

With recent developments in echocardiographic equipment and microbubble contrast agents, real-time perfusion imaging is now feasible (19). The infused microbubbles remain in the vascular space until they dissolve, reflecting the microvascular circulation. As with nuclear perfusion imaging, resting perfusion defects suggest infarcted myocardium, whereas stress-induced perfusion defects indicate ischemia (online appendix Fig. 3). The agreement between SPECT and myocardial contrast echocardiography for detection of perfusion abnormalities is good (20). In the general population, the sensitivity and specificity of contrast echocardiography for the detection of CAD are 89 and 63%, respectively (based on pooled analysis of seven studies, 245 patients), as compared with invasive angiography (21). One study has specifically addressed the value of contrast echocardiography in the detection of CAD in patients with diabetes. Elhendy et al. (22) evaluated 128 patients with contrast echocardiography; in 101 (79%) patients, invasive angiography detected CAD. The sensitivity and specificity were 89 and 52%, respectively. **MRI.** Myocardial perfusion is evaluated by injecting a bolus of contrast agent followed by continuous data acquisition as the contrast passes through the cardiac chambers and into the myocardium. Perfusion defects are characterized as regions of low signal intensity within the myocardium (online appendix Fig. 4). The high spatial resolution of MRI permits differentiation between subendocardial and transmural perfusion defects. Resting defects indicate infarction, and stress-induced defects indicate ischemia. In the general population, the sensitivity and specificity for detection of CAD are 84 and 85%, respectively (based on pooled analysis of 17 studies, 502 patients), as compared with invasive angiography (21).

In addition to myocardial perfusion, global and regional systolic left ventricular function can also be assessed with high accuracy using MRI. As with stress echocardiography, resting systolic wall motion abnormalities indicate infarcted myocardium and stress-induced abnormalities indicate ischemia. In the general population, the sensitivity and specificity of stress cine MRI are 89 and 84%, respectively (10 studies, 654 patients) (21). No specific studies in patients with diabetes

are currently available with MRI. Disadvantages of the technique include the relatively high costs as well as the time-consuming nature of the examination.

#### **Anatomical imaging**

**Coronary artery calcium scoring.** The two computed tomography techniques, EBCT and MSCT, both permit noninvasive detection and quantification of coronary artery calcium (online appendix Fig. 5, upper panels). The vast majority of studies published have been performed with EBCT, which has a lower radiation dose and possibly superior reproducibility (Table 1). The Agatston score is the preferred score to quantify coronary artery calcium (23). Scores <10 represent non-significant coronary artery calcium, 11–100 mild calcium, 101–400 moderate calcium, 401–1,000 severe calcium, and >1,000 extensive calcium. Although the presence of coronary artery calcium is closely correlated with the total atherosclerotic burden, it is not predictive of significant coronary stenoses and is not site specific (24). This approach is generally not used for diagnosing CAD, but rather to provide an estimate of the total atherosclerotic burden for prognostic and risk stratification purposes (see below). Observational studies revealed that diabetic patients have significantly higher coronary artery calcium scores than nondiabetic patients (25). However, coronary calcium scoring may be most valuable in risk stratification, in order to determine the intensity of primary prevention treatments. In patients with diabetes, who are already considered a coronary risk equivalent and treated with secondary prevention guidelines, assessment of advanced obstructive CAD may be more relevant.

**Noninvasive angiography with MRI.** For more than a decade, MRI has attempted to provide noninvasive images of the coronary arteries. While an initial report in 39 patients suggested a sensitivity and specificity of 90 and 92%, respectively (26), additional reports were less optimistic. Recent developments, including free breathing, navigator techniques, and three-dimensional acquisition techniques, permit superior visualization of the coronary arteries. In the general population, the sensitivity and specificity for the detection of CAD are 72 and 86%, respectively (28 studies, 903 patients) (27). However, up to 30% of all segments had to be excluded due to uninterpretability. The introduction of three Tesla imaging and newer contrast agents may

further improve diagnostic accuracy. Dedicated studies in patients with diabetes have not been published.

#### **Noninvasive angiography with MSCT.**

At present, MSCT is the technique of choice for noninvasive angiography (online appendix Fig. 5, lower panels). The technique is simple, fast, and reproducible. The technique is rapidly developing, and 64-slice MSCT is currently the clinical standard. In the general population, the sensitivity and specificity to detect CAD are 91 and 96%, respectively (nine studies, 542 patients) (28). The percentage of noninterpretable segments on 64-slice MSCT has varied from 0 to 12%, with a mean value of 4%.

At present, one study has specifically addressed diagnostic accuracy in patients with diabetes. Schuijff et al. (29) evaluated 30 patients with type 2 diabetes. Significant stenoses ( $\geq 50\%$  luminal narrowing) on MSCT were compared with invasive angiography. A total of 220 of 256 coronary artery segments (86%) were interpretable on MSCT. In these segments, sensitivity and specificity for detection of coronary artery stenoses were both 95%. When the uninterpretable segments were included, sensitivity and specificity dropped to 81 and 82%, respectively. Patients with diabetes frequently have extensive calcifications in the coronary arteries, and this hampers the interpretation of stenosis severity.

#### **Noninvasive angiography with EBCT.**

Due to high spatial and temporal resolution, this technique appears particularly useful for the imaging of coronary arteries. Instead of a mechanically rotating X-ray tube (as with MSCT), X-rays are generated through an electron beam that is guided along a 210° tungsten target ring in the gantry. As a result, a high-resolution image is acquired in 50–100 milliseconds. In the general population, the sensitivity and specificity to detect CAD are 87 and 91%, respectively (10 studies, 583 patients) (30). No specific studies in patients with diabetes are available. Data are summarized in Table 1.

### **DETECTION OF CAD**

#### **Functional versus anatomical imaging**

When interpreting the data above, it is important to realize that the original gold standard (invasive angiography) defines CAD when stenoses  $\geq 50\%$  luminal narrowing are present. In contrast, the functional imaging techniques define CAD as



Table 2—Nuclear imaging studies on prognosis in symptomatic patients with diabetes (based on ref. 39)

Year	Author (ref.)	Patients (n)	Tracer	Stressor	Abnormal MPI (%)	Mean follow-up (months)	Hard events in abnormal MPI (%/year)	Hard events in normal MPI (%/year)
1987	Felsher et al. (66)	123	<sup>201</sup> Tl	Exercise	56	36	4.8	1.3
1999	Kang et al. (14)	1,271	<sup>201</sup> Tl, MIBI	Exercise, adenosine	41	24 ± 8	3.9–7.9	1.2
2002	Schinkel et al. (67)	207	MIBI	Dobutamine	64	49 ± 29	6.6*	0.7*
2002	Giri et al. (40)	929	<sup>201</sup> Tl, MIBI	Exercise, adenosine	48	36 ± 18	5.0–6.4	3.6–3.9
2003	Berman et al. (68)	5,333	<sup>201</sup> Tl, MIBI	Adenosine	37–62	27 ± 9	4.7–9.0*	1.8–2.5
2004	Zellweger et al. (59)	911	<sup>201</sup> Tl, MIBI	Exercise, adenosine	44–51	24	5.6–13.2	2.0–3.3
2004	Miller et al. (69)	2,998	<sup>201</sup> Tl, MIBI	Exercise, adenosine, dipyridamole, dobutamine	60	70 ± 42	3.6–5.9	NA

Data are means ± SD unless otherwise indicated. Hard events include cardiac death or nonfatal myocardial infarction. <sup>201</sup>Tl, thallium-201 chloride; MIBI, technetium-99m sestamibi; MPI, myocardial perfusion imaging; NA, not available. \*Only cardiac death.

the induction of ischemia (reflected in stress-induced perfusion or systolic function abnormalities). It has been demonstrated in various studies that stenoses ≥50% luminal narrowing are not always associated with stress-inducible ischemia, while in some cases <50% luminal narrowing may be. This has been highlighted recently by Salm et al. (31), demonstrating that almost 50% of the intermediate stenoses (40–70% luminal narrowing) in bypass grafts were not associated with ischemia on SPECT.

With the introduction of noninvasive angiography, this problem has been re-emphasized. In addition to significant stenoses (≥50% luminal narrowing), the computed tomography techniques also identify stenoses <50%. In general, these techniques detect any level of atherosclerosis. Many of these lesions will not be associated with stress-inducible ischemia. Indeed, Schuijff et al. (32) recently evaluated 114 patients with MSCT and SPECT and demonstrated that 55% of the patients with atherosclerosis on MSCT do not have ischemia on SPECT (online appendix Fig. 6). Similar percentages have been reported in other studies (33,34). Thus, as a result of the recent availability of noninvasive anatomical imaging, a paradigm shift in the definition of CAD is occurring, shifting away from stenosis severity and stress-inducible ischemia to atherosclerosis in general. In addition, patients with diabetes frequently have another form of vascular malfunctioning, referred to as microvascular disease (35). This is not assessed by anatomic imaging and may or may not be assessed with functional imaging.

Apart from the discussion on the optimal definition of CAD, one needs to realize that most noninvasive imaging

studies are not performed for diagnostic but rather for prognostic purposes. The prognostic value of these imaging modalities is addressed below.

### PROGNOSIS OF CAD

For prognostication, patients are generally classified into three categories. The low-risk patients are those with an annual cardiac mortality >1%; the high-risk patients are those with an annual cardiac mortality >3% per year. Intermediate-risk patients are considered those with an annual mortality between 1 and 3%.

A wealth of prognostic data has been gathered with nuclear imaging and stress echocardiography, whereas little prognostic data with the other functional imaging techniques are available. Also, extensive prognostic data on coronary artery calcium scoring are available, but virtually no prognostic data on noninvasive angiography have been published.

### Nuclear imaging

The vast majority of studies on noninvasive imaging for prognosis have used SPECT; a meta-analysis of 31 studies including 69,655 patients was reported recently (36). These data indicate that a normal SPECT study is associated with an excellent prognosis. The average annual hard event rate (cardiac death or myocardial infarction) was 0.85%; this number is comparable with the annual event rate in the general population without CAD. In contrast, the annual hard event rate was 5.9% in patients with a moderate-severe abnormal SPECT study. The likelihood of an event increases in parallel to the extent of abnormalities on a SPECT study. Various predictive parameters on SPECT have been identified; these include (with increasing risk for events) small fixed defect

size, increasing defect size, defect reversibility, defects in multiple vascular territories, increased tracer lung uptake, and transient ischemic dilatation of the left ventricle. Additionally, in patients who were unable to perform exercise and underwent pharmacological stress, the event rates of both normal and abnormal scans were higher than in patients able to exercise (online appendix Fig. 7, upper panel).

The prognostic value of a normal scan is maintained over a long period. Schinkel et al. (37) evaluated 531 patients with SPECT over a follow-up period of 8.0 ± 1.5 years. The authors reported an annual cardiac death rate of 0.9%, with an annual cardiac death/infarction rate of 1.2% in the presence of a normal scan. This annual rate of coronary events in patients with normal scans is much higher in those with diabetes as discussed below.

Further risk stratification became possible when gated SPECT was introduced. The work from Sharir et al. (38) demonstrated that integration of perfusion data with left ventricular ejection fraction and end-systolic volume resulted in superior discrimination of low- and high-risk patients.

Seven studies with >100 patients each specifically addressed the prognostic value of SPECT imaging in symptomatic patients with diabetes using either thallium-201 and/or technetium-99m sestamibi (Table 2) (39). Two studies used pharmacological stress only, and the other studies used either exercise or pharmacological stress. The prevalence of abnormal perfusion studies was high, ranging from 37 to 64%. The results clearly confirm the higher event rate in the presence of an abnormal scan compared with a normal scan, similar to nondiabetic patients. The event rate in the

Table 3—Stress echocardiographic studies on prognosis in symptomatic patients with diabetes

Year	Author (ref.)	Patients (n)	Stressor	Abnormal stress echocardiography (%)	Mean follow-up (months)	Hard event in abnormal stress echocardiography (%/year)	Hard event in normal stress echocardiography (%/year)
2001	Elhendy et al. (48)	563	Exercise	60	36	4.7	1.5
2001	Bigi et al. (70)	259	Dobutamine, dipyridamole	42	24 ± 22	7.9	3
2001	Marwick et al. (46)	937	Exercise, dobutamine	40	3.9 ± 2.3 years	10	4
2001	Sozzi et al. (71)	396	Dobutamine	82	36	6.2	4.8
2003	D'Andrea et al. (72)	325	Dobutamine, dipyridamole	46	34	13.8	4.8

Data are means ± SD unless otherwise indicated. Hard events include cardiac death or nonfatal myocardial infarction.

presence of a normal scan also appears higher compared with the general population. Giri et al. (40) evaluated 4,755 patients (including 929 diabetic patients) with SPECT; the patients were prospectively followed for  $2.5 \pm 1.5$  years. Eighty hard events occurred in the diabetic patients (8.6%, 39 deaths and 41 infarctions), as compared with 172 (4.5%, 69 deaths and 103 infarctions) in the nondiabetic patients. The event rate was highest, both for diabetic and nondiabetic patients, in the presence of reversible defects in two or more vascular territories, with an infarction rate of 17.1% in the diabetic patients. Women with diabetes and ischemia on SPECT in two or more vascular territories were at the highest risk, with a 3-year survival rate of 60% in diabetic women. The authors subsequently demonstrated that the SPECT results provided significant incremental prognostic value over the clinical variables. They also observed that for subjects with normal SPECT studies, the event rates were significantly higher in diabetic than in nondiabetic patients. The cardiac death and infarction rates were 3.9 and 3.6%, respectively, in diabetic patients compared with 1.4 and 2.1%, respectively, in nondiabetic patients. When the survival curves for patients with a normal SPECT were compared, survival was comparable for the first 2 years after the SPECT study (online appendix Fig. 8, upper panels). Thereafter, however, diabetic patients exhibited a sharp increase in events. This could possibly be explained by the more rapid progression in atherosclerosis in patients with diabetes (41). Based on this observation, Hachamovitch et al. (42) proposed that the “warranty period” of a normal scan may be limited in high-risk subsets (e.g., diabetic patients); these patients may need repeat testing after 2 years.

### Stress echocardiography

A large number of studies have used stress echocardiography to assess prognosis in the general population. Similar to nuclear data, stress echocardiography can differentiate between low- and high-risk patients. A negative stress echocardiogram is associated with an excellent prognosis. A recent meta-analysis of 13 studies and 32,739 patients reported an annual hard event rate (death or myocardial infarction) of 1.2% for subjects with a normal stress echocardiogram (43). In contrast, the hard event rate for those with an abnormal study was 7.0% (online appendix Fig. 7, lower panel). Importantly, a recent study demonstrated a comparable prognostic accuracy of nuclear imaging and stress echocardiography (44). Similar to the nuclear studies, the severity of abnormalities determines the prognosis (44).

Five studies with >100 patients have studied the prognostic value of stress echocardiography in diabetic patients with CVD symptoms using either exercise or pharmacological stress (Table 3) (45). The prevalence of abnormal studies ranged from 40 to 60%, in line with the nuclear data. These results confirm the higher event rate in the presence of an abnormal study compared with a normal study, similar to nondiabetic patients (online appendix Fig. 8, middle panel). The largest cohort of diabetic patients undergoing stress echocardiography has been published by Marwick et al. (46). These authors evaluated the prognostic value of stress echocardiography in 937 diabetic patients. As observed with nuclear perfusion studies, survival was related to whether the patients were able to exercise, with those not able having a worse survival (online appendix Fig. 8, lower panel).

This issue of a higher event rate with a normal study in patients with diabetes

was specifically studied by Kamalesh et al. (47), who performed a follow-up study (mean 25 months) in 233 patients (144 nondiabetic and 89 diabetic) with a negative stress echocardiogram. The diabetic patients had a significantly higher incidence of nonfatal infarctions (6.7 vs. 1.4%), with a higher annual hard event rate (6.0 vs. 2.7%).

The issue of the warranty period of a normal study was addressed by Elhendy et al. (48). The authors evaluated 563 patients with diabetes with exercise echocardiography with follow-up of up to 5 years. Although the 1-year event rate was 0%, there was a gradual increase up to 7.6% at the 5-year follow-up. Considering an event rate <1% indicative for a low-risk group, the warranty period of a normal stress echo is 2 years. In addition, the authors confirmed the high event rate in patients with multivessel abnormalities on stress echocardiography. In the same study, Elhendy et al. (48) confirmed the incremental prognostic value of stress echocardiography over clinical variables.

### Coronary artery calcium scoring

In the general population, extensive data have been gathered regarding the prognostic value of coronary artery calcium but mainly in asymptomatic individuals. In one of the largest studies thus far, more than 10,000 asymptomatic patients were evaluated with EBCT and followed for the occurrence of all-cause death for 5 years (49). In patients without or with minimal coronary artery calcification, excellent survival (99%) was demonstrated. In contrast, a 5-year all-cause mortality of 12.3% was witnessed in patients with extensive (>1,000) coronary artery calcification. Importantly, risk-adjusted analysis revealed that coronary artery calcium provided information incremental to traditional risk assessment. In individ-

**Table 4—Evidence for (silent) ischemia or atherosclerosis in studies with asymptomatic diabetic patients (Only studies with >500 patients are included.)**

Author (ref.)	Patients (n)	Patient characteristics	Technique	Abnormal study	Details
Anand et al. (56)	510	Type 2 diabetes	EBCT calcium scoring	46.3%	19.6% mild calcium (score 11–100 AU); 5.5% extensive calcium (score >1,000 AU)
Sconamiglio et al. (58)	1,899	Type 2 diabetes	MCE; dipyridamole	60%	59.4% of 1,121 patients with more than two risk factors; 60% of 778 patients with at least one risk factor
Wackers et al. (57)	522	Type 2 diabetes	Nuclear imaging, SPECT; adenosine, low-level exercise	21%	16% of perfusion abnormalities involved >5% of the left ventricle
Miller et al. (69)	1,738	Diabetic patients	Nuclear imaging, SPECT; exercise, pharmacologic	59%	20% considered to represent high risk
Zellweger et al. (59)	1,737	Diabetic patients	Nuclear imaging, SPECT; exercise, pharmacologic	39–51%	39% of 826 asymptomatic patients; 51% of 151 patients short of breath; 44% of 760 patients with angina
Rajagopalan et al. (60)	1,427	Diabetic patients	Nuclear imaging, SPECT; exercise, pharmacologic	58%	20% considered to represent high risk

MCE, myocardial contrast echocardiography.

uals with an intermediate risk (according to the Framingham score), the 5-year mortality was 1.1% for individuals with minimal or no calcium, as compared with 9.0% in individuals with a similar risk profile but extensive calcifications. Even in patients with low risk (according to the Framingham score), the coronary artery calcium score allowed further risk modification, with a 3.9% mortality rate in individuals with extensive calcifications as compared with 0.9% with minimal or no calcifications. Accordingly, the coronary artery calcium score provides incremental prognostic information over traditional risk stratification (50,51). Still, controversy persists regarding the threshold for a calcium score that should be used to designate increased risk. In contrast, absence of calcification is consistently associated with excellent survival, emphasizing the power of this technique to identify low-risk patients.

Thus far, limited data are available on coronary artery calcium scoring in diabetic patients. In a large observational study of 10,377 individuals, including >900 asymptomatic diabetic patients, coronary artery calcium was the best predictor of all-cause mortality in both diabetic and nondiabetic individuals (52). Furthermore, a highly significant interaction between coronary artery calcium score and diabetes was observed, with a greater increase in mortality rate for every increase in calcium score in diabetic compared with nondiabetic patients. Importantly,

in patients without coronary artery calcium, survival was similar for individuals with and without diabetes (98.8 and 99.4%, respectively). Qu et al. (53) performed coronary artery calcium scoring in 1,312 high-risk individuals (with 269 diabetic patients) with an average follow-up of 6.3 years but failed to demonstrate the incremental value of coronary artery calcium score over diabetes for prediction of events. Raggi et al. (54) pointed out that the discrepancy may be related to differences in sample size and risk profile of the different studies. Accordingly, more studies are needed to determine whether calcium scoring allows more robust identification of high-risk patients with diabetes compared with current risk assessment strategies.

### ASYMPTOMATIC DIABETIC PATIENTS

Many diabetic patients with CAD are asymptomatic or present with atypical symptoms (55). The prevalence of atherosclerosis was evaluated using EBCT in 510 asymptomatic diabetic patients, and significant atherosclerosis (score >10 Agatston units) was noted in 46.3% (Table 4) (56). Various studies have evaluated the prevalence of silent ischemia (using either nuclear imaging or echocardiography) in both retrospective and prospective settings (39). Wackers et al. (57) evaluated 522 asymptomatic patients with at least two risk factors using gated technetium-99m sestamibi SPECT in the

Detection of Silent Myocardial Ischemia in Asymptomatic Diabetics (DIAD) study, showing a prevalence of 21% abnormal SPECT studies. The perfusion defect involved >5% of the left ventricle in 40% of patients with an abnormal SPECT study. Of note, conventional risk factors did not predict perfusion abnormalities on SPECT. A possible exception was the higher prevalence of cardiac neuropathy in patients with an abnormal SPECT study.

Three additional studies used nuclear imaging to assess ischemia in asymptomatic diabetic patients and reported perfusion abnormalities in 39 to 59% of patients (Table 4). One study used echocardiography with myocardial contrast to assess perfusion in 1,899 asymptomatic diabetic patients (58). The population was divided into patients with two or more risk factors for CAD ( $n = 1,121$ ) or one or no risk factors ( $n = 778$ ). Interestingly, the prevalence of perfusion abnormalities was almost 60% and comparable between both groups. In the patients with an abnormal contrast echocardiogram, invasive angiography was performed. These results demonstrated that the severity of CAD was less in patients with one or no risk factor, with a lower prevalence of three-vessel disease (7.6 vs. 33.3%), diffuse CAD (18.0 vs. 54.9%), and vessel occlusion (3.8 vs. 31.2%). Overall, the widely differing estimates of CAD in asymptomatic patients most likely reflect differences in study design

(retrospective vs. prospective) and inclusion criteria.

The prognostic value of nuclear imaging in asymptomatic diabetic patients has been addressed in few studies. Zellweger et al. (59) studied three subsets of patients (without symptoms, with angina, and with dyspnea) and reported that the annual hard event rates (cardiac death or infarction) were approximately threefold higher in patients with abnormal SPECT studies (5.4 vs. 1.9%). The event rates were not different between asymptomatic patients and patients with angina. Similarly, Rajagopalan et al. (60) studied 1,427 asymptomatic diabetic patients and reported that the prevalence of abnormal SPECT scans was 58% with an annual hard event rate of 5.9% for those with an abnormal scan versus 1.6% for those with a normal scan. In a smaller study, De Lorenzo et al. (61) reported an abnormal SPECT in 26% of 180 asymptomatic diabetic patients, with annual hard event rates of 9 versus 2% for abnormal and normal scans, respectively.

### Should asymptomatic diabetic patients undergo screening for CAD?

Based on the high prevalence of atherosclerosis and silent ischemia (Table 4), and the high risk for cardiovascular events, the issue of screening for CAD in asymptomatic diabetic patients has been raised and debated intensively (39,55,62,63).

At present, the American Diabetes Association consensus guidelines for screening of asymptomatic patients recommend stress imaging in patients with abnormal resting ECG (ischemia, infarction) but not in patients with, for example, cerebral/peripheral vascular disease or two or more risk factors (8). In these latter circumstances, only an exercise test (ECG) is recommended, which is known to have a low diagnostic accuracy. Moreover, the available evidence has shown that many diabetic patients with less than two conventional risk factors have perfusion abnormalities on either nuclear imaging or contrast echocardiography (Table 4). Unfortunately, clinical variables (including risk factors) do not predict which patients will have an abnormal stress imaging result (57). However, nuclear imaging and stress echocardiography may not be the ideal screening tools in terms of cost effectiveness. Anand et al. (56) have proposed a stepwise screening approach—first, patients are screened for the

presence of atherosclerosis with coronary artery calcium scoring using computed tomography techniques (either EBCT or MSCT). In patients with extensive coronary artery calcium, nuclear imaging with SPECT could be used to detect the presence or absence of ischemia. A potential algorithm illustrating a stepwise screening approach is demonstrated in online appendix Fig. 9 (39). Based on the stepwise approach, patients with severe atherosclerosis on EBCT (calcium score >400 AU) could be referred for SPECT. In patients with moderate calcium (between 100 and 400 AU), referral may depend on the presence of certain patient characteristics or comorbidities, including the presence of metabolic syndrome, duration of diabetes >10 years, or retinopathy, as patients with these characteristics may represent elevated risk, similar to those with extensive calcium scores.

Subsequently, in the presence of moderate-severe ischemia on SPECT, angiography could be considered, whereas those with small perfusion defects should be clinically evaluated by a cardiologist whether invasive coronary angiography is indicated or not. Patients without ischemia should have aggressive medical therapy, risk factor modification, and careful monitoring. This stepwise approach needs further evaluation in future studies.

Moreover, before screening can be advised, the following criteria need to be met (63). 1) The prevalence in the population should be high enough. The exact percentage of asymptomatic diabetic patients with CAD is unknown; large retrospective studies (59,60) reported abnormal SPECT studies in 39 and 58% of asymptomatic patients; the only prospective study (DIAD) (57) reported 21%. 2) The screening test needs to accurately differentiate low- and high-risk patients. In the diabetic population, SPECT can identify the high-risk patients, but the low-risk patients cannot be identified accurately; patients with a normal SPECT study still had a fairly high event rate (i.e., >1% in the available studies) (59–61). 3) Identification of asymptomatic diabetic patients should lead to treatment with better outcomes. At present, no prospective data on this topic are available, but the results from the DIAD study should provide some clues. In addition, data from the Mayo Clinic showed that patients with a high-risk SPECT study had better outcomes after CABG as compared with medical therapy (64). 4) The screening strategy should be cost-effective. At

present no data are available, but it is likely that a stepwise protocol as outlined above (EBCT first, followed by SPECT if needed) may be more cost-effective than referring all patients to SPECT immediately; data to support this hypothesis are needed.

## SUMMARY AND CONCLUSIONS

With the alarming worldwide increase in diabetes, and the associated high cardiovascular morbidity/mortality, adequate diagnostic tools are needed to detect CAD and risk stratify patients. On the one hand, functional imaging tools (nuclear techniques, echocardiography, and MRI) are available, which allow assessment of ischemia. In general, which particular technique is preferred depends on local expertise and accordingly varies among institutions. The choice for each technique may vary among institutions, and local expertise may be the best guide. On the other hand, anatomical imaging tools (computed tomography techniques) are now available, which allow assessment of atherosclerosis. Although there are less data concerning the diagnostic accuracy of functional and anatomical testing in patients with diabetes, available information suggests similar accuracies in diabetic patients compared with the general population. The advantage of anatomical testing is that both obstructive and nonobstructive (subclinical) CAD can be visualized, allowing detection of atherosclerosis at an early stage. However, information on the hemodynamic consequences of the detected lesions (needed to determine further management) is not obtained. Integration of these imaging techniques therefore may provide optimal information to guide patient management. In asymptomatic patients with diabetes, studies have observed a considerably elevated prevalence of silent ischemia and atherosclerosis, suggesting the need for screening in this population. However, no prospective data are currently available, and improved outcome based on screening has not yet been demonstrated. Large, randomized, prospective trials are therefore required to determine the potential role of screening asymptomatic patients with diabetes for CAD.

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