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REVIEW

# Non-invasive cardiac imaging techniques and vascular tools for the assessment of cardiovascular disease in type 2 diabetes mellitus

**R. Djaberi · E. D. Beishuizen · A. M. Pereira · T. J. Rabelink · J. W. Smit · J. T. Tamsma · M. V. Huisman · J. W. Jukema**

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**Abstract** Cardiovascular disease is the major cause of mortality in type 2 diabetes mellitus. The criteria for the selection of those asymptomatic patients with type 2 diabetes who should undergo cardiac screening and the therapeutic consequences of screening remain controversial. Non-invasive techniques as markers of atherosclerosis and myocardial ischaemia may aid risk stratification and the implementation of tailored therapy for the patient with type 2 diabetes. In the present article we review the literature on the implementation of non-invasive vascular tools and cardiac imaging techniques in this patient group. The value of these techniques as endpoints in clinical trials and as risk estimators in asymptomatic diabetic patients is discussed. Carotid intima–media thickness, arterial stiffness and flow-mediated dilation are abnormal long before the onset of type 2 diabetes. These vascular tools are therefore most likely to be useful for the identification of 'at risk' patients during the early stages of atherosclerotic disease. The additional value of these tools in risk stratification and tailored therapy in type 2 diabetes remains to be proven. Cardiac imaging techniques are more justified in individuals with a strong clinical suspicion of advanced coronary heart disease (CHD). Asymptomatic myocardial ischaemia can be detected by stress echocardiography and myocardial perfusion imaging. The more recently developed non-invasive multi-slice computed tomography angiography is recommended for exclusion of CHD, and can therefore be used to screen asymptomatic patients with type 2 diabetes, but has the associated disadvantages of high radiation exposure and costs. Therefore, we propose an algorithm for the screening of asymptomatic diabetic patients, the first step of which consists of coronary artery calcium score assessment and exercise ECG.

**Keywords** Cardiac imaging · Cardiovascular disease · Diabetes mellitus · Review · Risk stratification · Vascular tools

**Abbreviations**

| | |
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| AIx | augmentation index |
| CAC | coronary artery calcium |
| CIMT | carotid intima–media thickness |
| CVD | cardiovascular disease |
| DIAD | Detection of Ischemia in Asymptomatic Diabetics |
| FMD | flow-mediated dilation |
| IMT | intima–media thickness |
| MPI | myocardial perfusion imaging |
| MSCT | multi-slice computed tomography |

R. Djaberi and E. D. Beishuizen contributed equally to this review.

R. Djaberi (✉) · J. W. Jukema
Department of Cardiology, C5-P33, Leiden University Medical Center, Postbus 9600, 2300 RC Leiden, the Netherlands
e-mail: R.Djaberi@LUMC.nl

E. D. Beishuizen · J. T. Tamsma · M. V. Huisman
Department of General Internal Medicine, Leiden University Medical Center, Leiden, the Netherlands

A. M. Pereira · J. W. Smit
Department of Endocrinology, Leiden University Medical Center, Leiden, the Netherlands

T. J. Rabelink
Department of Nephrology, Leiden University Medical Center, Leiden, the Netherlands

J. W. Jukema
Eindhoven Laboratory of Experimental Vascular Medicine, Leiden University Medical Center, Leiden, the Netherlands

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| PWV | pulse wave velocity |
| SE | stress echocardiography |
| SMI | silent myocardial ischaemia |
| SPECT | single photon emission computed tomography |

## Introduction

Cardiovascular disease (CVD) is the leading cause of mortality in type 2 diabetes mellitus [1]. Current guidelines on the treatment of dyslipidaemia and hypertension in diabetes recommend rigorous primary prevention, with target lipid and blood pressure levels similar to those used for secondary prevention in non-diabetic patients [2]. To date, there is much debate as to whether all diabetic patients will benefit from this strategy and whether risk stratification should be attempted.

Non-invasive imaging techniques as markers of atherosclerosis and myocardial ischaemia may help risk stratification and the implementation of tailored therapy for the individual patient. However, many of these tools have not been validated in diabetic individuals. In this article we will review the reproducibility and predictive value of the following surrogate markers of atherosclerosis: intima–media thickness (IMT), arterial stiffness and flow-mediated dilation (FMD). We will discuss the diagnostic accuracy and predictive value of imaging techniques used for direct anatomic assessment of coronary atherosclerosis (coronary artery calcium [CAC] scores and multi-slice computed tomography [MSCT] angiography) and functional tests that detect myocardial ischaemia (ambulatory ECG, exercise ECG, stress echocardiography (SE) and nuclear myocardial perfusion imaging (MPI) by single photon emission computed tomography (SPECT). Finally, the value of these non-invasive techniques as endpoints in clinical trials and as risk estimators in diabetic patients will be discussed. We will concentrate on methods of risk stratification and the implementation of non-invasive techniques in patients with type 2 diabetes, as the value of these techniques has scarcely been studied in type 1 diabetes.

## Surrogate markers of atherosclerosis

### Carotid IMT

Since its introduction in the early 1990s, IMT, especially carotid IMT (CIMT), has increasingly been used as a surrogate marker of atherosclerotic disease. IMT can be assessed non-invasively using B-mode ultrasound. Two approaches are used: (1) multiple measurements of CIMT in the near and far walls of the three main segments of the carotid arteries (common carotid, bifurcation and internal carotid); and (2) automated computerised measurement of CIMT, restricted to the far wall of the distal common carotid artery. Computerised measurement of CIMT is superior in terms of precision and reproducibility, with an approximately 3% difference between two successive measurements [3]. As a result, common CIMT has become a valid tool for large-scale multicentre studies. However, the common carotid artery is less likely to have intrusive plaque than the bifurcation and internal segments of the carotid arteries.

CIMT correlates with prevalent CVD and with risk factors for CVD [4]. In prospective studies, CIMT has proven to be a consistent and independent predictor for coronary events and stroke in the general population [5–6].

*CIMT in type 2 diabetes* Mean common CIMT in middle-aged individuals is reported to range from 0.71–0.98 mm in diabetic patients vs 0.66–0.85 mm in controls [7–9]. In diabetic individuals without a history of myocardial infarction CIMT is similar to that in non-diabetic individuals with a history of myocardial infarction [9]. Progression of maximal CIMT in the Insulin Resistance Atherosclerosis Study was twice as high in persons with diabetes vs controls [10], but other studies report lower rates [11]. In type 2 diabetes, prevalent CVD is associated with higher CIMT [9]. In two prospective studies, baseline CIMT was shown to be an independent predictor of cardiovascular events [12–13]. However, when Folsom and colleagues analysed CIMT in a large cohort that included 1500 diabetic participants, they found that CIMT has predictive value for future coronary events only in combination with several other novel risk factors [14].

CIMT measurements show good reproducibility. CIMT is increased in type 2 diabetic patients with CVD and is an independent predictor of coronary events. However, the magnitude of its predictive value when added to other risk factors is questionable

### Arterial stiffness

Whereas IMT is a marker of structural vessel wall properties, arterial stiffness reflects functional wall properties. Stiffness can be measured in many ways, including distensibility, pulse wave velocity (PWV) and augmentation index (AIx). Distensibility, defined as the change in arterial lumen diameter during the cardiac cycle, can be evaluated by ultrasound imaging using wall-tracking systems based on Doppler shift or using B- or M-mode. The change in arterial diameter

during the cardiac cycle varies by about 5–6% in middle-aged individuals [15]. PWV is the speed with which the arterial pressure wave progresses through the arterial tree, and this increases with increasing vascular stiffness. The PWV can be determined either by placing a probe on two sites and recording the waveform simultaneously, or by recording the waveforms independently and comparing the time delay at both sites with a simultaneously measured QRS complex. PWV gradually increases with age, from about 4 m/s in the third decade to 10 m/s in the ninth decade. The AIx, which is the augmentation of aortal pressure as a percentage of pulse pressure, has also emerged as a parameter for arterial stiffness (Fig. 1) [16–17]. Studies report excellent reproducibility of PWV, with a CV of approximately 3.2%, which is lower than that for distensibility indices (CV 5.3%) or AIx (CV 10.1%) [17–19].

In cross-sectional studies, arterial stiffness is strongly associated with age and classical risk factors for CVD [15, 20–21], and it has been reported to be related to angiographic coronary atherosclerosis [17]. In a cohort of men aged >70 years, baseline arterial distensibility predicted cardiovascular mortality during a 2 year follow-up, but added little to clinical risk estimation [22]. However, in a Danish population study, aortic PWV predicted a composite of cardiovascular events outcome above and beyond traditional risk factors [23].

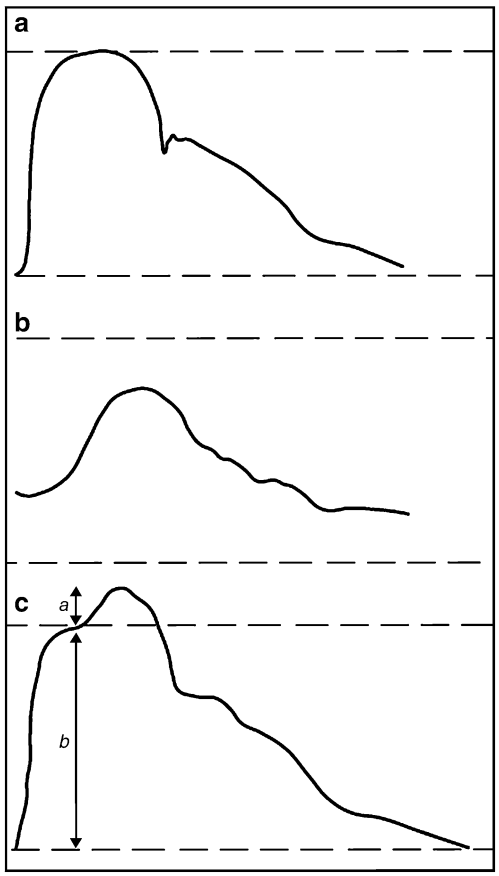


**Fig. 1** The pulse pressure wave form. **a** The incident wave generated by the left ventricle (in the ascending aorta). **b** Waves reflected back from the peripheral vascular bed (ascending aorta). **c** The resultant wave in the ascending aorta, which is a combination of (**a**) and (**b**). AIx is the measure of additional pressure to which the left ventricle is subjected as a result of wave reflection and is calculated as: $AIx=(a/[b+a])\times 100$

*Arterial stiffness in type 2 diabetes* Diabetic patients have increased arterial stiffness [17, 24]. Compromised carotid distensibility and PWV have been demonstrated even before the onset of diabetes, in patients with impaired glucose tolerance. Healthy offspring of type 2 diabetic patients have a higher PWV than matched controls [17, 25]. Arterial stiffness in diabetes is related to prevalent CVD [16] and has shown to be an independent predictor of CHD [26].

Baseline distensibility did not predict mortality in 140 individuals with impaired glucose tolerance during a follow-up period of 6.6 years [18]. Conversely, PWV does seem to have a reasonable predictive value for mortality in patients with impaired glucose tolerance and type 2 diabetes [24].

The reproducibility of PWV is superior to that of AIx and distensibility. Therefore, PWV is the most accepted method for estimating vascular stiffness. Vascular stiffness is increased in type 2 diabetic patients with CVD and has been shown to predict cardiovascular mortality

## FMD

FMD of the brachial artery is a non-invasive technique for measuring endothelial function. FMD is measured with B-mode ultrasound or a wall-track system. The brachial artery is visualised in the elbow, and by inflating a cuff (mostly distal to the elbow) for 4 min, hypoxia is created. After deflation, reactive hyperaemia induces shear stress, thereby stimulating NO synthesis, resulting in NO-dependent dilation [27]. FMD is thus defined as the percentage change in the diameter of the brachial artery after hypoxia, estimated to be 5–10% in healthy individuals. The observed brachial artery dilatation has shown to be closely related to coronary vasoreactivity [28].

FMD fluctuates during the day and is influenced by the temperature, stress, diet, glucose levels and the menstrual cycle [29]. Within-subject variability of FMD is therefore often poor, with CVs ranging from 14–50% [29–30]. In spite of the biological variation, there is good intra- and interobserver reproducibility for measurements of baseline

and maximum post-ischaemia diameter in the brachial artery (diameter variations of approximately 4%) [30].

FMD ranges from about 10% in young adults to 0% in patients with established coronary heart disease (CHD), and it has proven to be predictive for the presence of CHD [31] and for future coronary events in high-risk populations [32]. High sensitivity and high negative predictive values were calculated using cut-off points of 8.1–10% [32]. FMD has not been independently associated with coronary events in patients at lower risk [33].

*FMD in type 2 diabetes* Type 2 diabetes is associated with endothelial dysfunction. The underlying mechanisms are suspected to be related to hyperglycaemia (sorbitol, hexosamine, protein kinase C, and AGE pathways) and insulin resistance, which results in mitochondrial superoxide overproduction, and thus decreased NO availability [34–35]. Clustering of risk factors such as dyslipidaemia, hypertension and obesity in the metabolic syndrome play an additional role. Insulin-mediated vasodilatation is at least in part NO-dependent, thus explaining how insulin resistance may cause endothelial dysfunction.

The predictive value of endothelial dysfunction in epicardial coronary arteries of diabetic patients has been established for long-term coronary events [36]. However, to our knowledge, no studies to date have evaluated the relationship between FMD and prediction of coronary events in diabetes.

FMD is a marker of endothelial function. It should only be assessed under strictly constant external and physical circumstances, so that reproducibility is optimised. The potential of FMD for the identification of type 2 diabetic patients at risk for CVD is as yet unknown

## Direct anatomic assessment of coronary atherosclerosis

### CAC scores

Anatomical and intravascular studies have illustrated that the presence of coronary calcium is indicative of coronary atherosclerosis [37]. Coronary calcification can be detected non-invasively by electron beam CT (EBCT), and more recently by MSCT. Agatston et al. developed a coronary calcium scoring algorithm, based on calcification volume and density, that is now widely used in clinical practice [38]. The extent of coronary calcium increases with age, and is, on average, higher in men than in women [39–40].

*CAC scores in type 2 diabetes* Diabetic patients without manifest CVD have a higher CAC score than non-diabetic individuals, independent of classical risk factors [41–43]. In addition, CAC scores show significantly more progression over time in patients with diabetes than in non-diabetic patients [44].

In a study by Raggi et al. [45], 10,377 patients (903 with diabetes) were followed for a period of 5.0±3.5 years after CAC imaging. Mortality increased with increasing baseline CAC levels for both diabetic and non-diabetic individuals. However, despite similar CAC scores, there was a greater increase in mortality in diabetic than non-diabetic patients for every increase in CAC score [45]. The predictive value of CAC scores in diabetes has been questioned by Qu et al. [46], who found no significant relationship between coronary events and CAC scores during a 6 year follow-up of 269 diabetic patients [46].

CAC score is associated with prevalent CVD in diabetes. However, CAC scores may underestimate the risk for CVD in type 2 diabetic patients

### MSCT coronary angiography

The application of MSCT scanners for non-invasive coronary angiography has developed rapidly over recent years. Employment of 16 and 64 slice systems have demonstrated a sensitivity ranging from 83–99% and a specificity of between 93% and 98% [47–51]. Several studies have demonstrated that CT angiography has a high negative predictive value of 99% on average [47–51]. Therefore, the technique is currently most suited to exclude CHD.

Besides visualisation of the coronary artery lumen (Fig. 2), CT angiography allows the identification of non-stenotic atherosclerosis and the various types of plaques. In addition, chronic myocardial infarction and left ventricular ejection fraction can be assessed. Non-stenotic atherosclerosis may prove to be a predictor of coronary events; however, this remains to be determined in prospective long-term clinical studies. Plaques can be classified as non-calcified, mixed or calcified. Initial comparisons have shown that calcification may represent the duration of atherosclerosis, whereas non-calcified and mixed lesions are more frequently observed in patients with an acute coronary syndrome [52].

MSCT is subject to a number of limitations, including exposure to a relatively high dose of radiation, currently in the range of 9–12 mSv [47, 51], lower accuracy in the presence of severe calcification and movement artefacts, and limited application possibilities in case of irregular

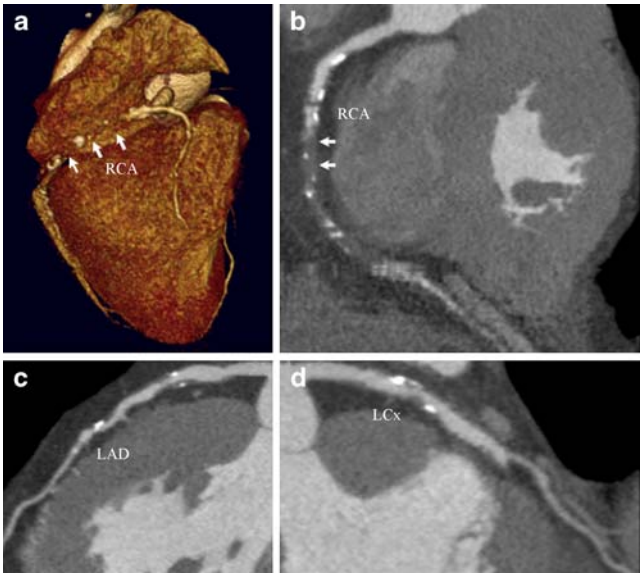


**Fig. 2** An asymptomatic patient with type 2 diabetes was screened for CAD using MSCT angiography. **a** The occluded right coronary artery (RCA) is easily visible using the three-dimensional volume rendering technique, which provides an overview of coronary anatomy. Arrows indicate occlusion. **b** Multiplanar reconstruction of the RCA gives a more precise overview of abnormalities. **c**, **d** Multiplanar reconstruction of the left anterior descending (LAD) and left circumflex (LCx) coronary arteries

heart rate [49–51]. Taking the radiation exposure and the high negative predictive value of MSCT angiography into consideration, this technique is recommended for excluding CHD in patients of intermediate risk.

*MSCT coronary angiography in type 2 diabetes* MSCT angiography has demonstrated a higher percentage of non-calcified and calcified plaques and a relatively lower percentage of mixed plaques in diabetes [53], which can be explained by the rapid progression of atherosclerosis. Schuijf et al. have reported a sensitivity and specificity of 95% for detection of stenosis. Inclusion of uninterpretable segments reduced sensitivity and specificity to 81% and 82%, respectively [54]. In an evaluation of the diagnostic accuracy of 16 slice MSCT angiography, there were no statistically significant differences between the diabetic and non-diabetic individuals in the study population [55]. Importantly, negative predictive value of MSCT angiography in diabetes was found to be 98% and 100% on segmental and patient basis, respectively [55].

The prevalence of CHD has been assessed by MSCT angiography in 70 asymptomatic patients with type 2 diabetes. The majority of the patients (80%) had atherosclerosis (obstructive CHD [luminal narrowing ≥50%] in 26%, non-obstructive CHD in 54% of patients) [56]. Thus, results on the use of non-invasive MSCT angiography for CHD screening and as a prognostic indicator in the diabetic population appear promising, but further studies in larger population groups are needed.

MSCT angiography has good sensitivity, specificity and negative predictive value for identification of CHD in diabetic patients. However, assessment of CHD by MSCT in asymptomatic type 2 diabetic patients should be limited to patients at high risk, because of exposure to high radiation and contrast as well as cost factors

## Functional tests in assessment of coronary artery disease

Functional tests detect myocardial ischaemia which is the physiologic consequence of coronary obstruction. These include: ambulatory ECG, exercise ECG, stress echocardiography and nuclear myocardial perfusion imaging.

### Ambulatory ECG

It has been postulated that periods of silent myocardial ischaemia (SMI), which can be detected with ambulatory ECG, precede a first coronary event. Ambulatory ECG monitoring can be performed with a three-channel recording system for a continuous period of 48 h. Transient myocardial ischaemia is defined as the presence of episodes showing >0.1 mV horizontal or downsloping ST-segment depression. The sensitivity of ambulatory ECG for detecting CHD is poor, ranging from 19–62% [57–59]. Compared with coronary angiography, the specificity of ambulatory ECG ranged between 54% and 92% [57–60]. Frequent episodes of transient ischaemia detected by ambulatory ECG have shown to be a marker for an increased coronary event rate in asymptomatic middle-aged men and in patients with known CHD [61].

*Ambulatory ECG in type 2 diabetes* The prevalence of SMI in diabetes as assessed by ambulatory ECG varies between 35% and 58% [62–64]. Although the prevalence of SMI determined by this method is expected to be higher in diabetic than non-diabetic individuals, findings have been inconsistent. Comparison of diabetic and non-diabetic patients in the Asymptomatic Cardiac Ischemia Pilot (ACIP) study, illustrated lower rates of asymptomatic ischaemia in diabetes, despite more extensive and diffuse coronary disease in the non-diabetic group [65]. A study comparing exercise ECG with ambulatory ECG for detection of SMI in diabetes reported that ambulatory ECG identified ischaemia only in diabetic patients with three-vessel disease, whereas exercise

ECG also revealed ischaemia in one- and two-vessel disease [66]. In one study, patients with previously detected silent ischaemia had a higher incidence of new coronary events (87%) than those with no silent ischaemia (51%) during a 40 month follow-up period [63]. Further studies are needed to validate the prognostic value of SMI detected by ambulatory ECG.

The diagnostic value of ambulatory ECG for CHD is poor. The predictive value of ischaemia detected by ambulatory ECG in type 2 diabetic patients has not been extensively studied

## Exercise ECG

The exercise ECG is considered positive for myocardial ischaemia if horizontal downsloping or upsloping ST-segment depression of ≥0.1 mV occurs at least 0.08 s after the J point. In a pooled meta-analysis of 24,074 patients who had undergone both an exercise ECG and conventional coronary angiography, mean sensitivity and specificity were calculated to be 68% and 77%, respectively, for the diagnosis of CHD by exercise ECG [67]. Sensitivity was higher in three-vessel disease [67]. In addition to myocardial ischaemia, the exercise ECG provides information on exercise capacity and haemodynamic response, which both have prognostic value [68].

The prognostic significance of exercise-induced myocardial ischaemia has been evaluated in prospective studies [69–70]. In a population-based study, an average follow-up period of 10 years was completed in 1,769 asymptomatic men who had undergone an exercise ECG [69]. The risks of acute coronary events and cardiac death were increased 1.7- and 3.5-fold, respectively, in men with SMI compared with men without SMI, after adjusting for conventional factors.

*Exercise ECG in type 2 diabetes mellitus* The use of an exercise ECG for diagnosing myocardial ischaemia specifically in the setting of diabetes has not been assessed in large studies. In an evaluation of the correlation between the ECG exercise test and coronary angiography for the identification of significant coronary artery stenosis in 59 diabetic patients, the sensitivity and specificity were 75% and 77%, respectively [71]. The mean positive predictive value of the exercise ECG for predicting angiographic coronary disease varies between 70% and 90% [72–73]. However, the test is often inconclusive or unfeasible in diabetic patients (approximately 32%) because exercise capability may be impaired by peripheral vascular or neuropathic disease [72]. Furthermore, the specificity of this method is lower for detecting significant coronary artery disease in diabetes because of the presence of microvascular disease.

Abnormal ECG stress tests have shown to be independent predictors of coronary events [74–75]. A 38 month follow-up of 262 asymptomatic diabetic patients who had undergone a maximal ECG stress test showed a good negative predictive value (97%) for major cardiac endpoints [74]. Gerson et al. [75] showed that the exercise ECG successfully identified all diabetic patients who developed clinical CHD within 50 months, but provided little prognostic information after the first 50 months, suggesting the need for serial testing.

Exercise ECG has moderate sensitivity and specificity for detection of CHD. During intermediate follow-up exercise ECG has been shown to have a good predictive value for coronary events. Application of exercise ECG as a screening tool in type 2 diabetes is limited as the test is often inconclusive

## SE

SE is a well-established functional technique for assessing CHD that can be used to demonstrate inducible wall motion abnormalities in the general population. Exercise or a pharmacological form of stress can be used. In the case for the former, echocardiography is performed shortly after exercise. This method provides additional information on exercise capacity, symptoms and haemodynamic response, which are beneficial prognostic factors. A potential hindrance may be the rapid resolution of ischaemia after exercise, and therefore normalisation of any wall motion abnormality prior to echocardiography. Pharmacologically induced stress echocardiography is preferred in those with a limited exercise capacity. An additional advantage is that images are obtained during stress. In a meta-analysis of 10,817 patients in which dobutamine was compared with stress testing with adenosine or dipyridamole, dobutamine echocardiography had the highest combination of sensitivity (80%) and specificity (84%) for the diagnosis of coronary disease [76]. The accuracy of the method is dependent on the degree of stenosis, the amount of myocardium at risk and the degree of induced wall motion abnormality [77]. False-negative results are more likely with submaximal exercise (in the case of exercise-induced stress), single-vessel disease and moderate stenosis (50–70%) [78].

The presence of ischaemia on SE and the number of ischaemic segments predict the likelihood of coronary events during long-term follow-up among members of the general population with known or suspected CHD [79–80]. However, in a 10 year follow-up of 1,832 asymptomatic patients who underwent SE, exercise testing and a resting echocardiogram, SE did not offer additional prognostic information in terms of identifying patients at a higher risk of coronary events [81].

*SE in type 2 diabetes* The diagnostic accuracy of SE for significant CHD in diabetes has been verified in two studies. In one study in which 55 diabetic patients underwent dobutamine SE and invasive angiography, the sensitivity and specificity of SE were 81% and 85%, respectively [82]. Another study that compared SE with coronary angiography in diabetic patients ($n$=52) reported a similar sensitivity (82%) but a much lower specificity (54%) [83].

In a prospective study, SE plus an exercise ECG were used to screen 71 diabetic patients with unknown asymptomatic cardiac disease and two or more cardiovascular risk factors [84]. Those who obtained an abnormal result in one test underwent coronary angiography, and if necessary, revascularisation. Compared with patients randomised to the control arm ($n$=70), coronary events were significantly reduced in the screening arm during follow-up [84]. The preclinical diagnosis of CHD by SE may therefore be effective. However, more studies are needed to determine the prognostic role of SE in screening for cardiac disease in asymptomatic diabetic patients.

The sensitivity and specificity of SE for diagnosing extensive CHD are satisfactory. However, the predictive value of a positive test in type 2 diabetes needs to be further analysed

## Nuclear SPECT MPI

The majority of studies on ischaemia have used SPECT MPI. This imaging modality reveals the presence and extent of perfusion defects. Images are taken following exposure to stress (exercise of pharmacological) and at rest, allowing the identification of fixed and reversible defects (Fig. 3). The dimensions of the left ventricle and ejection fraction can also be determined. An analysis of the diagnostic accuracy of pharmacologically induced stress MPI in a pooled meta-analysis of 10,817 patients with angiographic data reported a mean sensitivity and specificity of 88% and 77%, respectively [85].

Perfusion defects are significant predictors of coronary events in patients with known or suspected CHD

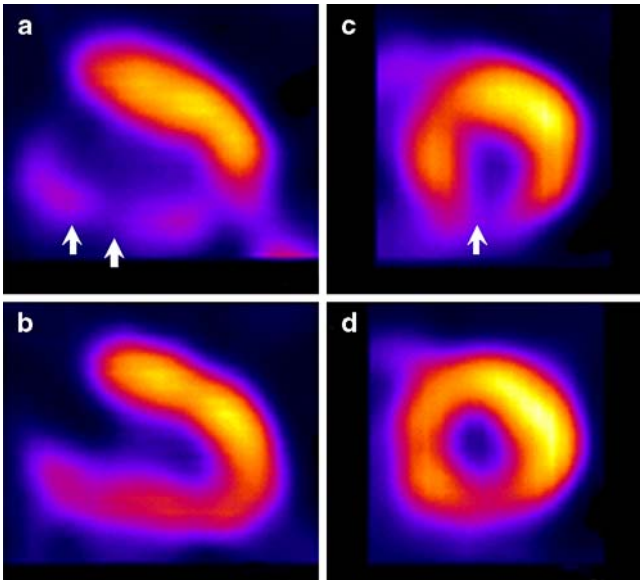


**Fig. 3** Myocardial perfusion imaging was carried out in the patient described in Fig. 2, in whom coronary abnormalities had been observed on MSCT angiography. **a** A perfusion defect was observed in the posterolateral segment (indicated by the arrows) during stress, which did not exist during rest (**b**), indicating ischaemia. **c** Partial ischaemia was observed during stress, shown by an increase in the size of the defect in the inferior segment (indicated by the arrow) compared with the rest scan (**d**)

[86]. However, over a follow-up period of 4.6 years the presence of perfusion defects did not independently predict coronary events in a purely asymptomatic group of volunteers [87]. Normal MPI results have shown a low coronary event rate (1%) over a 5 year follow-up period [88]. Significant predictors of future coronary events after pharmacologically induced stress MPI include large defects, defects in multiple coronary artery territory suggestive of multi-vessel disease, major irreversible defects, left ventricular dilatation and decreased resting left ventricular ejection fraction [86].

*Nuclear SPECT MPI in type 2 diabetes* To our knowledge, the diagnostic accuracy of MPI in diabetes has only been studied by Kang et al. [89], who performed MPI and conventional coronary angiography n 138 diabetic patients. Mean sensitivity and specificity were 86% and 56%, respectively, for ≥50% coronary stenosis, and 90% and 50% for ≥70% coronary stenosis [89].

In asymptomatic diabetic patients, the rate of SMI diagnosed by stress MPI ranges from 17–59% (Table 1) [90–95]. In general, a higher percentage of perfusion defects has been detected in retrospective studies [90–91]. In the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study, which included 1,123 participants, the occurrence of perfusion defects was not significantly associated with the traditional risk factors for CVD [92].

During an intermediate follow-up period, persistent and reversible perfusion defects have been shown to be predictors of coronary events in asymptomatic diabetic patients [93–95]. Rajagopalan et al. [90], categorised diabetic patients, according to SPECT imaging scans, as being at high, intermediate or low risk. The annual mortality rate was 5.9%, 5.0% and 3.6%, respectively, with a significant difference in mortality ($p<0.001$) between the three groups [90]. The long-term prognostic value of MPI in asymptomatic diabetic patients needs to be further analysed. It is speculated that concurrent abnormalities of perfusion imaging scans in diabetic patients with normal coronary angiograms may be caused by microangiopathy or endothelial dysfunction, and therefore represent an increased likelihood of future coronary events [96].

MPI shows good sensitivity but poor specificity (possibly because of microvascular disease) for diagnosing CHD in diabetes. Intermediate follow-up has shown a good predictive value of MPI for coronary events in type 2 diabetes

## Conclusion

CIMT, arterial stiffness and perhaps FMD are abnormal long before the onset of diabetes. Therefore these measurements are the most likely to be useful for the identification of at risk patients during the early stages of atherosclerotic disease, when functional wall properties are still reversible. However, further studies are necessary to evaluate whether these tools provide any additional prognostic value when used in combination with clinical risk scores (Table 2) before they can be implemented on large scale in clinical practice.

In individuals with a strong clinical suspicion of advanced CHD, cardiac imaging techniques are more warranted. When functional techniques are compared, ambulatory ECG and exercise ECG are less sensitive and specific than functional cardiac imaging tests for the detection of ischaemia in type 2 diabetes. Head-to-head comparison has revealed that SPECT MPI has a higher sensitivity than SE for the detection of multi-vessel and single-vessel CHD [97]. Furthermore, the predictive value of SPECT MPI in the diabetic population has been studied more extensively than that of SE (Table 2). CAC scoring and the more recently developed MSCT non-invasive

**Table 1** Comparison of studies which have used single-photon emission-computed tomography myocardial perfusion imaging to detect silent ischaemia in diabetic patients

| Study group | No. of patients | Patient characteristics | Study nature | Abnormal results (%) | Other details |
|---|---|---|---|---|---|
| Rajagopalan et al. [90] | 1,427 | No known cardiac history<br>Patients with abnormal resting ECG included | R | 58% abnormal scans<br>18% high-risk scans (high risk: SSS ≤47) | High-risk scans were associated with ECG Q waves, PAD, $HbA_{1c}$, male sex, age, LDL-cholesterol |
| Miller et al. [91] | 1,738 | No known cardiac history<br>Patients with abnormal resting ECG included | R | 59% abnormal scans | High-risk scans in 19.7% |
| Wackers et al. [92] (DIAD study) | 522 | No known cardiac history<br>Patients with abnormal resting ECG excluded | P | 22% abnormal results (out of which, 73% abnormal scans and 37% other abnormalities) | Abnormal test result was not associated with traditional cardiac risk factors; 50% of patients were incapable of exercise |
| Sultan et al. [93] | 419 | No known cardiac history<br>Besides DM, ≥1 traditional cardiac risk factor<br>Patients with abnormal resting ECG included | P | 17% abnormal scans (abnormal: defect in ≥3/20 segments) | Male sex, triacylglycerol, low creatinine clearance, $HbA_{1c}$>8% were independent predictors of abnormal scans |
| Zellweger et al. [94] | 826 | No known cardiac history | P | 39% abnormal scans (abnormal: SSS <4 or SDS ≥2) | |
| Valensi et al. [95] | 370 | No known cardiac history<br>Besides DM, ≥2 traditional cardiac risk factors<br>Patients with abnormal resting ECG excluded | P | 26% abnormal scans | Silent ischaemia was associated with higher age and triacylglycerol and lower HDL levels |

DM, diabetes; P, prospective; PAD, peripheral arterial disease; R, retrospective; SDS, summed difference score; SSS, summed stress score

coronary angiography allow quantification of atherosclerotic burden. CAC scores have been shown to predict coronary events [56]. MSCT coronary angiography has good sensitivity for the identification of prevalent CHD and can therefore enable more widespread screening in combination with CAC scores in diabetes, but its use is limited by radiation exposure and costs.

We propose an algorithm for the screening of asymptomatic diabetic patients (Fig. 4). A selection strategy using a CAC score >100 AU has been shown to be an effective way of identifying patients with moderate to large perfusion defects [98]. Nevertheless, recent observations have shown that low CAC scores do not exclude CHD in diabetes [56]. Based on this, the initial step of our algorithm involves the combined use of CAC assessment and exercise ECG to maximise sensitivity for the detection of CHD. MPI or MSCT coronary angiography seem to be justified for individuals with a CAC score >100 or a positive exercise ECG. Conventional coronary angiography can then be considered in the presence of ischaemia according to stress MPI or obstructive atherosclerosis illustrated by MSCT angiography. Prospective studies may be conducted to evaluate the effectiveness of such a screening approach.

The criteria for the selection of those asymptomatic patients with type 2 diabetes who should undergo non-invasive cardiac screening for risk stratification remain controversial. The 'two or more risk factors' criterion for screening, as suggested by the 1998 American Diabetes Association guidelines, failed to accurately identify a large number of patients with ischaemia in the DIAD study [92]. Future studies may prove non-invasive vascular tools such as measurement of CIMT, PWV and FMD to be more effective for the identification of patients at risk who should be screened for CHD (Fig. 4).

**Table 2** Comparison of various non-invasive vascular tools and cardiac imaging techniques

| Tool/technique | Reproducibility | Detection of prevalent CAD | | Prediction of CAD events | | Details |
|---|---|---|---|---|---|---|
| | | Non-DM2 | DM2 | Non-DM2 | DM2 | |
| 1. Vascular tools | | | | | | |
| IMT | Good: variability <5% | ++ [4] | + [9] | ++ [5, 6] | + [12–14] | |
| Vascular stiffness | Mediocre: variability 11–15% | ++ [17] | + [16, 26] | + [22, 23] | + [18, 24] | |
| FMD | Poor: variability up to 50% | ++ [31] | Unknown | ± [32, 33] | Unknown | High intersession variability |
| 2. Anatomical tests | | | | | | |
| CAC scores | Good | ++ [37] | ++ [56] | ++ [100] | ± [45, 46] Limited studies | |
| MSCT angiography | Good | ++ [47–51] | ++ [54–56] | Unknown | Unknown | High radiation doses |
| 3. Functional tests | | | | | | |
| Ambulatory ECG | Unknown | ± [57–60] Reasonable sensitivity Low specificity | ± [65, 66] Low sensitivity | + [61] | ± [63] Limited studies | |
| Exercise ECG | Unknown | + [67] Reasonable sensitivity Reasonable specificity | + [71–73] Reasonable sensitivity Low specificity | + [69, 70] | + [74, 75] | Not feasible in 32% of patients with DM2 |
| Nuclear MPI | Good | + [85] Good sensitivity Reasonable specificity | + [89] Good sensitivity Low specificity | ++ [86–88] | ++ [90, 93–95] Based on intermediate follow-up | More long-term follow-up studies in DM2 are needed |
| SE | Good | + [76–78] Good sensitivity Good specificity | + [82, 83] Limited studies Good sensitivity Good specificity | ± [79–81] | ± [84] Limited studies | Relatively high false-negative rate in single-vessel disease and moderate stenosis |

++, strong and consistent association in several studies in multivariate analysis; +, association in most studies in multivariate analysis; ±, association in some studies or association only in univariate analysis DM2, type 2 diabetes

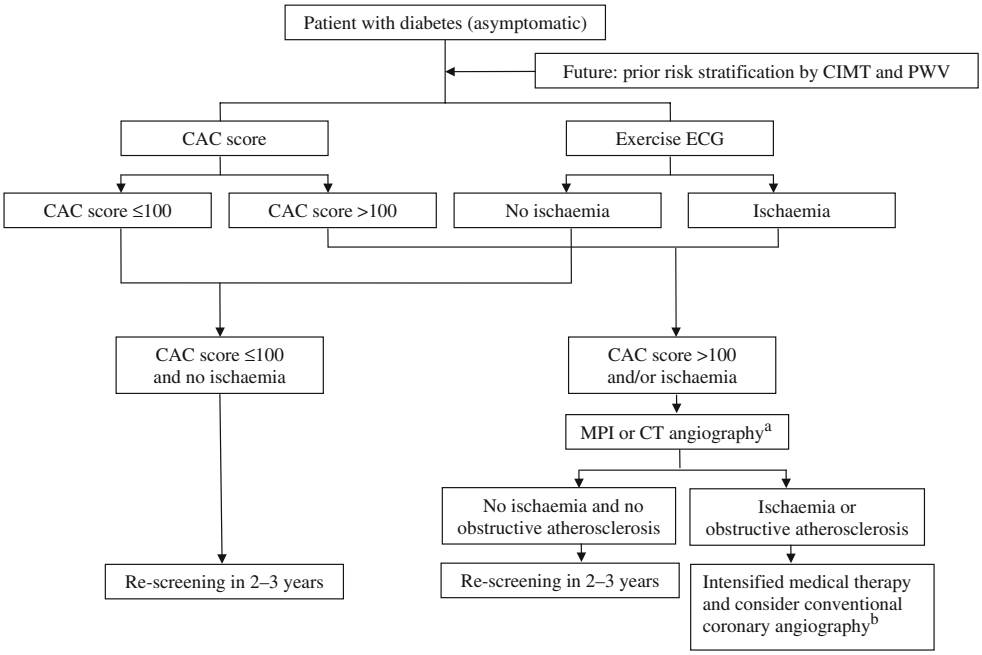


**Fig. 4** Proposed algorithm for the screening of asymptomatic diabetic patients. [a]Choice of test according to availability and patient characteristics (in patients with severely impaired kidney function or atrial fibrillation, CT angiography should be avoided). [b]Conventional coronary angiography can be considered in the presence of obstructive atherosclerosis in a proximal segment of a coronary artery or extensive ischaemia

## The future

In type 2 diabetic patients, plaque development is not only accelerated but also distinct, exhibiting more lipid-rich atheroma, macrophage infiltration and a higher thrombogenic potential compared with development in non-diabetic individuals [99]. This implies that screening tools such as magnetic resonance angiography, which enable assessment of plaque composition and may reflect the real culprit, i.e. plaque vulnerability, could emerge as more potent risk predictors in diabetes. However, the application of magnetic resonance angiography as a screening tool is not feasible in the near future because of the high costs and complex methodology involved.

**Duality of interest** The authors declare that there is no duality of interest associated with this manuscript.



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