The effect of statin therapy on vessel wall properties in type 2 diabetes without manifest cardiovascular disease

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Chapter 2

Non-invasive cardiac imaging techniques and vascular tools for the assessment of cardiovascular disease in type 2 Diabetes Mellitus

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ABSTRACT

Cardiovascular disease is the major cause of mortality in type 2 diabetes mellitus (DM2). The criteria for the selection of those asymptomatic patients with DM2 who should undergo cardiac screening and the therapeutic consequences of screening remain controversial.

Non-invasive techniques as markers of atherosclerosis and myocardial ischemia may aid risk stratification and the implementation of tailored therapy for the individual patient with DM2. 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 DM2. These vascular tools are therefore most likely to be useful in identification of 'at risk' patients in early stages of atherosclerotic disease. The additional value of these tools in risk stratification and tailored therapy in DM2 remains to be proven.

Cardiac imaging techniques are more justified in individuals with a strong clinical suspicion of advanced coronary artery disease (CAD). Asymptomatic myocardial ischemia 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 CAD, and can therefore be used to screen asymptomatic patients with DM2, 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.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of mortality in DM2[1]. Current guidelines on the treatment of dyslipidemia 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 ischemia 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 ischemia:* ambulatory electrocardiography (AECG), exercise electrocardiography, 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 DM2, as the value of these techniques has scarcely been studied in type 1 diabetes.

SURROGATE MARKERS OF ATHEROSCLEROSIS

Carotid Intima-Media Thickness (CIMT)

Since its introduction in the early 1990s, intima-media thickness (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 carotid arteries (common carotid, bifurcation and internal carotid); and 2) automated computerized measurement of CIMT restricted to the far wall of the distal common carotid artery. Computerized 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 multicenter 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 (CE) and stroke in the general population [5-6].

Carotid Intima-Media Thickness in DM2

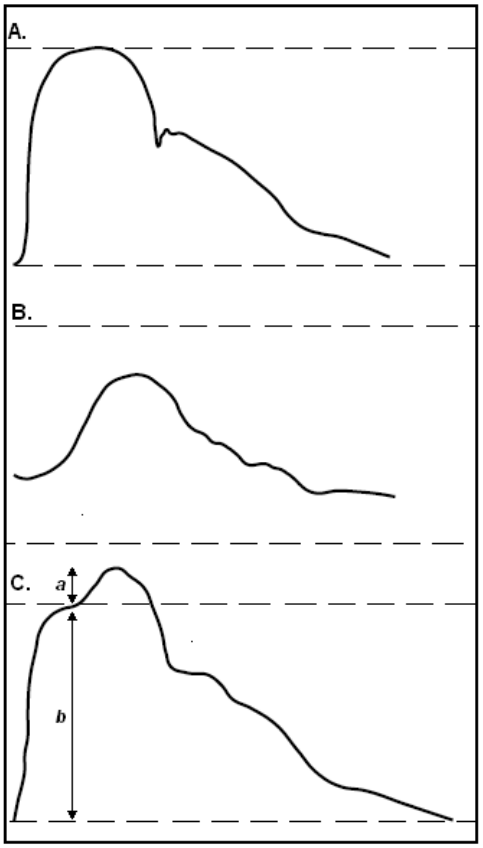
Mean common CIMT in middle aged individuals is reported to range from 0.71-0.98 mm in diabetic patients versus 0.66 – 0.85 mm in control patients [7-9]. In diabetic individuals without a history of myocardial infarction CIMT is similar to that in non-diabetic individuals with a history of myocardial infarction [9]. Progression of maximal CIMT in the IRAS study was twice as high in persons with diabetes versus controls [10], but other studies report lower rates [11]. In DM2, 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 analyzed CIMT in a large cohort with 1500 diabetic participants, they found that CIMT has predictive value for future CE only in combination with several other novel risk factors [14].

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/sec in the third decade to 10 m/sec 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 (Figure 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 related to angiographic coronary atherosclerosis [17]. In a cohort of men aged > 70 years, baseline arterial distensibility predicted cardiovascular mortality during a two 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].

Figure 1. The pulse pressure wave form.



A. The incident wave generated by the left ventricle (in ascending aorta). **B.** Waves reflected back from the peripheral vascular bed (ascending aorta). **C.** Resultant wave in the ascending aorta which is a combination of **A** and **B**. The augmentation index (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****)*] *x 100*.

Arterial stiffness in DM2

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 DM2 patients have a higher PWV than matched controls [17,25]. Arterial stiffness in DM2 is related to prevalent CVD [16] and has shown to be an independent predictor of CAD [26].

Baseline distensibility did not predict mortality in 140 indiviuals 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 DM2 [24].

Flow Mediated Dilation (FMD)

Flow Mediated Dilation (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 visualized in the elbow, and by inflating a cuff (mostly distal to the elbow) for 4 minutes, hypoxia is created. After deflation, reactive hyperemia induces shear stress, thereby stimulating nitric oxide (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 dilation 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 of 14-50% [29-30]. In spite of the biological variation, there is good intra- and interobserver reproducibility for measurements of baseline and maximum post-ischemia brachial artery (diameter variations approximately 4%) [30].

FMD ranges from about 10% in young adults to 0% in patients with established CAD and it has proven to be predictive for the presence of CAD [31] and for future CE 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 CE in patients at lower risk [33].

Flow Mediated Dilation in DM2

DM2 is associated with endothelial dysfunction. The underlying mechanisms are suspected to be related to hyperglycemia (sorbitol, hexosamine, PKC-, and AGE-pathways) and insulin resistance, which result in mitochondrial superoxide overproduction, and thus decreased NO availability [34-35]. Clustering of risk factors such as dyslipidemia, hypertension and obesity in the metabolic syndrome play an additional role. Insulin-mediated vasodilation 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 CE [36]. However, to our knowledge, no studies to date have evaluated the relationship between FMD and prediction of CE in DM2.

DIRECT ANATOMIC ASSESSMENT OF CORONARY ATHEROSCLEROSIS

Coronary Artery Calcium (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 Computed Tomography (EBCT), and more recently by Multi-slice Computed

Tomography (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].

Coronary Artery Calcium scores in DM2

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 DM2 than in non diabetic patients [44].

In a study by Raggi et al. 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. who found no significant relationship between CE and CAC scores during a six year follow-up of 269 diabetic patients [46].

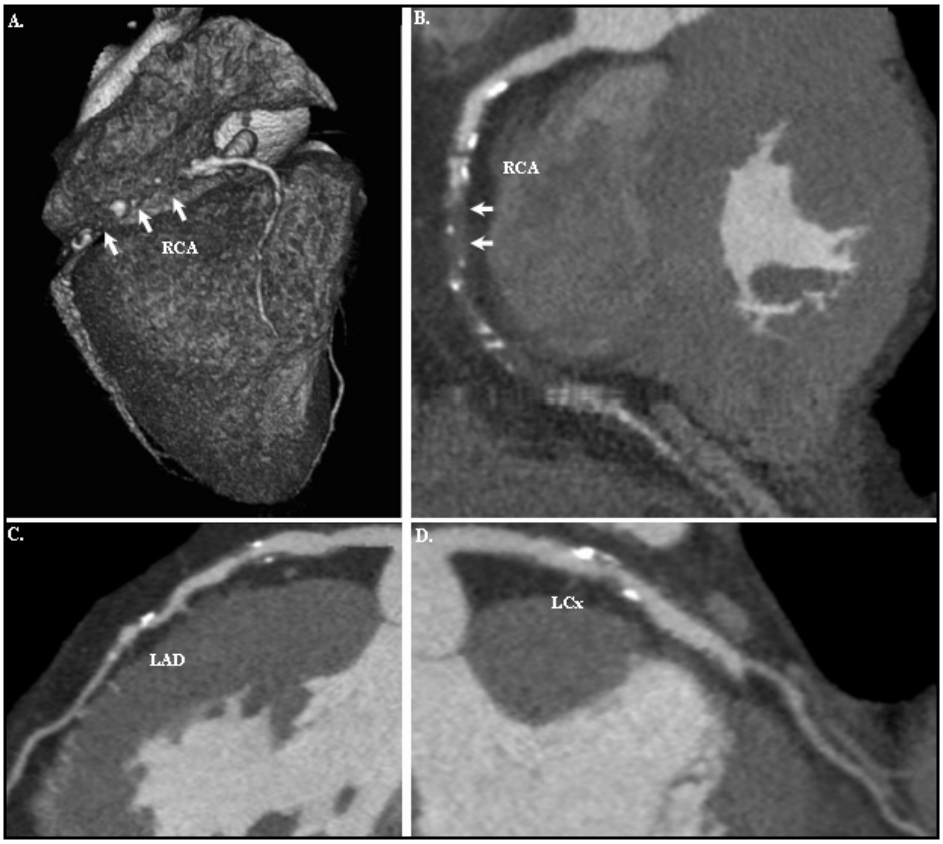
Multi-Slice Computed Tomography (MSCT) Coronary Angiography

The application of MSCT scanners for non-invasive coronary angiography has developed rapidly over recent years. Employment of 16 and 64 slice systems has demonstrated a sensitivity ranging from 83-99% and specificity of 93-98% [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 CAD.

Besides visualization of the coronary artery lumen (Figure 2), CT angiography allows the identification of non-stenotic atherosclerosis and 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 CE; 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 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 CAD in patients of intermediate risk.

Figure 2. An asymptomatic patient with DM2 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.** and **D.** multiplanar reconstruction of the left anterior descending (LAD) and left circumflex (LCx) coronary arteries.

MSCT Coronary Angiography in DM2

MSCT angiography has demonstrated a higher percentage of non-calcified and calcified plaques and a relatively lower percentage of mixed plaques in DM2[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 on 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 DM2 was found to be 98% and 100% on segmental and patient basis, respectively [55]. The prevalence of CAD has been assessed by

MSCT angiography in 70 asymptomatic patients with DM2. The majority of the patients (80%) had atherosclerosis (obstructive CAD (luminal narrowing ≥ 50%) in 26%, non-obstructive CAD in 54% of the patients) [56]. Thus, results on the use of non-invasive MSCT angiography for CAD screening and as a prognostic indicator in the diabetic population appear promising, but further studies in larger population groups are needed.

FUNCTIONAL TESTS IN ASSESSMENT OF CORONARY ARTERY DISEASE

Functional tests detect myocardial ischemia 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 ischemia (SMI), which can be detected with Ambulatory ECG (AECG), precede a first coronary event. AECG monitoring can be performed with a three-channel recording system for a continuous period of 48 hours. Transient myocardial ischemia is defined as the presence of episodes showing more than 0,1 mV (1mm) horizontal or downsloping ST-segment depression. The sensitivity of AECG for detecting CAD is poor, ranging from 19-62% [57-59]. Compared with coronary angiography, the specificity of AECG ranged from 54- 92% [57-60]. Frequent episodes of transient ischemia detected by AECG have shown to be a marker for an increased coronary event rate in asymptomatic middle-aged men and in patients with known CAD [61].

Ambulatory ECG in DM2

The prevalence of SMI as assessed by AECG in DM2 varies between 35-58% [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 ACIP study, illustrated lower rates of asymptomatic ischemia in DM2, despite more extensive and diffuse coronary disease in the latter group [65]. A study comparing exercise ECG with AECG for detection of SMI in DM2 reported that AECG identified ischemia only in diabetic patients with three-vessel disease whereas exercise ECG also revealed ischemia in one- and two-vessel disease [66]. In one study, patients with previously detected silent ischemia had a higher incidence of new CE (87%) than those with no silent ischemia (51%) during a 40 months follow-up period[63]. Further studies are needed to validate the prognostic value of SMI detected by AECG.

Exercise Electrocardiography (ECG)

The exercise ECG is considered positive for myocardial ischemia if horizontal downsloping or upsloping ST-segment depression of ≥ 0.1mV 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 [67]. Sensitivity was higher in three-vessel disease [67]. In addition to myocardial ischemia, the exercise ECG provides information on exercise capacity and hemodynamic response, which both have prognostic value [68].

The prognostic significance of exercise-induced myocardial ischemia 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. The risks of acute CE 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 [69].

Exercise ECG in DM2

The use of an exercise ECG for diagnosing myocardial ischemia specifically in the setting of DM2 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 CAD in DM2 because of the presence of microvascular disease.

Abnormal ECG stress tests have shown to be independent predictors of CE [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 end points [74]. Gerson et al., showed that exercise ECG successfully identified all diabetic patients who developed clinical CAD within 50 months, but provided little prognostic information after the first 50 months, suggesting the need for serial testing [75].

Stress echocardiography

Stress Echocardiography (SE) is a well-established functional technique for assessing CAD 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 hemodynamic response, which are beneficial prognostic factors. A potential hindrance may be rapid resolution of ischemia after exercise,

and therefore normalization of any wall motion abnormality prior to echocardiography. Pharmacologically induced SE 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 CAD[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 ischemia on SE and the number of ischemic segments predict the likelihood of CE during long-term follow-up in the general population with known or suspected CAD [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 CE [81].

Stress echocardiography in DM2

The diagnostic accuracy of SE for significant CAD in DM2 has been verified in two studies. In one study in which 55 diabetic patients underwent dobutamine SE and invasive angiography, sensitivity and specificity of SE were 81% and 85%, respectively [82]. Another study that compared SE with coronary angiography in 52 DM2 patients reported a similar sensitivity (82%), but a much lower specificity (54%) [83].

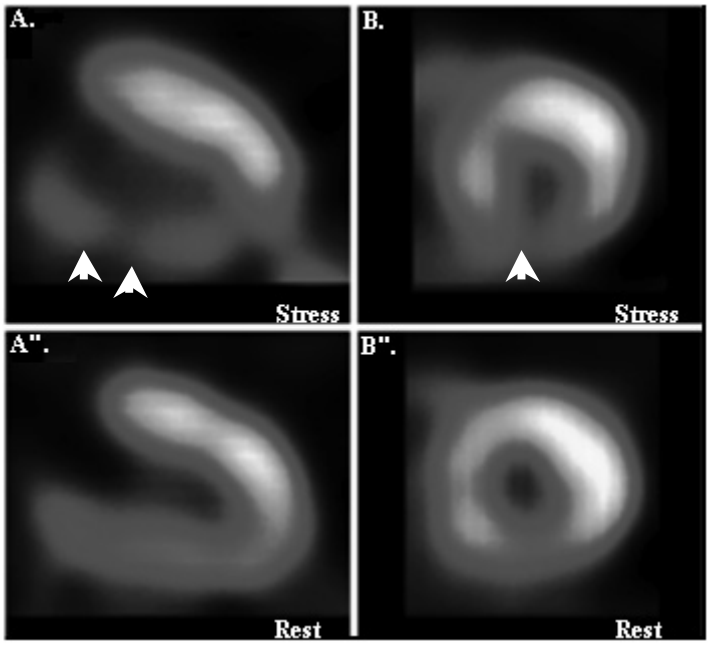
In a prospective study, SE plus an exercise ECG were used to screen 71 DM2 patients with unknown asymptomatic cardiac disease and ≥ 2 cardiovascular risk factors. Those who obtained an abnormal result in one test underwent coronary angiography, and if necessary, revascularization. Compared with patients randomized to the control arm (n=70), CE were significantly reduced in the screening arm during follow-up [84]. The preclinical diagnosis of CAD 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 DM2 patients.

Nuclear SPECT Myocardial Perfusion Imaging (MPI)

The majority of studies on ischemia have used SPECT MPI. This imaging modality reveals the the presence and extent of perfusion defects. Images are taken following exposure to stress (exercise or pharmacological) and at rest, allowing the identification of fixed and reversible defects(Figure 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 CE in patients with known or suspected CAD [86]. However, over a follow-up period of 4,6 years the presence of perfusion defects did

Figure 3. Myocardial perfusion imaging was carried out in the patient described in Figure 2, in whom coronary abnormalities had been observed on MSCT angiography.



A. A perfusion defect was observed in the posterolateral segment (indicated by arrows) during stress, which did not exist during rest as shown in **A"**, indicating ischemia. **B.** Partial ischemia was observed during stress, shown by an increase in size of the defect in the inferior segment (indicated by arrow), in comparison to the rest scan **B".**

not independently predict CE in a purely asymptomatic group of volunteers [87]. Normal MPI results have shown a low CE rate (1%) over a 5 year follow-up period[88]. Significant predictors of future CE 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 Imaging in DM2

To our knowledge, the diagnostic accuracy of MPI in DM2 has only been studied by Kang et al., who performed MPI and conventional coronary angiography in 138 DM2 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 DIAD study, which included 1,123 asymptomatic patients with DM2, the occurrence of perfusion defects was not significantly associated with the traditional risk factors for CVD [92].

Table 1. Comparison of studies which have used SPECT MPI to detect silent ischemia in diabetic patients.

Study Group	No. of patients	Patient characteristics	Study nature	Abnormal results (percentage)	Other details
Rajagopalan et al.[90]	n = 1427	No known cardiac history. Patients with abnormal resting ECG included.	Retrospective	58% abnormal scans 18% high-risk scans (high-risk: SSS ≤ 47)*	High-risk scans were associated with ECG Q waves, PAD*, HbA1c, male gender, age, LDL cholesterol.
Miller et al. [91]	n = 1738	No known cardiac history. Patients with abnormal resting ECG included.	Retrospective	59% abnormal scans	High-risk scans in 19.7%.
Wackers et al. [92] (DIAD study)	n = 522	No known cardiac history. Patients with abnormal resting ECG excluded.	Prospective	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]	n = 419	No known cardiac history. ≥ 1 traditional cardiac risk factor besides DM2. Patients with abnormal resting ECG included.	Prospective	17% abnormal scans (abnormal: defect ≥ 3/20 segments)	Male gender, triglycerides, low creatinine clearance, HbA1c > 8%, were independent predictors of abnormal scans.
Zellweger et al. [94]	n = 826	No known cardiac history.	Prospective	39% abnormal scans (abnormal: SSS < 4 or SDS ≥ 2)*	
Valensi et al. [95]	n = 370	No known cardiac history. ≥ 2 traditional cardiac risk factors besides DM2. Patients with abnormal resting ECG excluded.	Prospective	26% abnormal scans	Silent ischemia was associated with higher age, triglycerides and lower HDL levels.

* PAD = peripheral arterial disease; SSS = summed stress score; SDS = summed difference score.

During an intermediate follow-up period, persistent and reversible perfusion defects have shown to be predictors of CE in asymptomatic diabetic patients [93-95]. Rajagopalan et al, categorized diabetic patients according to SPECT imaging scans, as 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 analyzed. It is speculated that concurrent abnormalities of perfusion imaging scans in diabetic patients with normal coronary angiograms may be due to microangiopathy or endothelial dysfunction, and therefore represent an increased likelihood of future CE [96].

CONCLUSIONS

CIMT, arterial stiffness and variably FMD are abnormal long before the onset of DM2.

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 CAD, cardiac imaging techniques are more warranted. When functional techniques are compared, AECG and exercise ECG are less sensitive and specific than functional cardiac imaging tests for the detection of ischemia in DM2. Head-to-head comparison has revealed that SPECT MPI has a higher sensitivity than SE for the detection of multi-vessel and single-vessel CAD [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 coronary angiography allow quantification of atherosclerotic burden. CAC scores have been shown to predict CE [56]. MSCT coronary angiography has good sensitivity for the identification of prevalent CAD and can therefore enable more widespread screening in combination with CAC scores in DM2, but its use is limited by radiation exposure and costs.

We propose an algorithm for the screening of asymptomatic diabetic patients (Figure 4). A selection strategy with a CAC score >100 AU has 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 CAD in DM2 [56]. Based on this, the initial step of our algorithm involves the combined use of CAC assessment and exercise ECG to maximize sensitivity for detection of CAD. 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 ischemia according to stress MPI

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

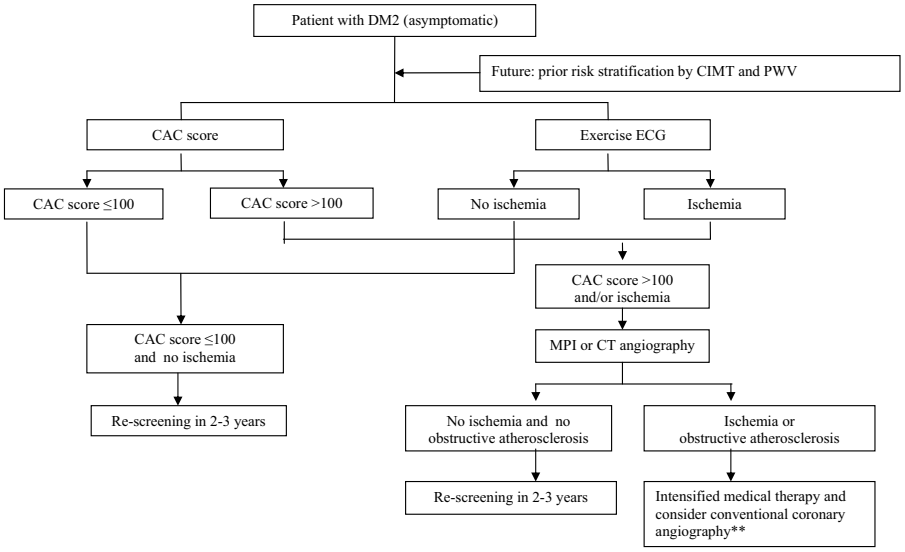
		Reproducibility	Detection of prevalent CAD		Prediction of CAD events		Details
			non-DM2	DM2	non-DM2	DM2	
I	**Vascular Tools**						
	IMT	Good: variability <5%	++[4]	+[9]	++[5,6]	+[12-14]	
	Vascular Stiffness	Mediocre: variability 11-15%	++[17]	+[16,26]	+[22,23]	+[18,24]	
	FMD	Poor: variability up to 50%	++[31]	Unknown	±[32,33]	Unknown	High intersession variability
II	**Anatomical Tests**						
	CAC scores	Good	++[37]	++[56]	++[100]	±[45,46] Limited studies	
	MS-CT angiography	Good	++[47-51]	++[54-60]	Unknown	Unknown	High radiation dosis
III	**Functional Tests**						
	AECG	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
	Stress Echocardiography	Good	+[76-78] Good Sensitivity Good Specificity	+[82,83] Limited studies Good Sensitivity Good Specificity	±[79-81]	±[84] Limited studies	Relative 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, or only one available study, in multivariate analysis; ± association in some studies, or association only in univariate analysis.

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 DM2 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 ADA guidelines, failed to accurately identify a large number of patients with ischemia in the DIAD study [92]. Future studies may prove non-invasive vascular tools such as CIMT, PWV and FMD to be more effective in identification of patients at risk who should be screened for CAD(Figure 4).

Figure 4. Proposed algorithm for screening of asymptomatic diabetic patients.



* Choice of test according to availability and patient characteristics (in patients with severely impaired kidney function or atrial fibrillation, CT angiography should be avoided).
** Conventional coronary angiography can be considered in the presence of obstructive atherosclerosis in a proximal segment of a coronary artery or extensive ischemia.

The future

In DM2 patients , plaque development is not only accelerated, but also distinct, exhibiting more lipid-rich atheroma, macrophage infiltration and a higher thrombogenic potential compared with 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 DM2. However, the application of magnetic resonance angiography as a screening tool is not feasible in the near future because of high costs and complex methodology involved.

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