

## Assessment of cardiovascular risk in diabetes: Risk scores and provocative testing

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morbidity and mortality among patients with diabetes mellitus, who have a risk of cardiovascular mortality two to four times that of people without diabetes. An individualised approach to cardiovascular risk estimation and management is needed. Over the past decades, many risk scores have been developed to predict CVD. However, few have been externally validated in a diabetic population and limited studies have examined the impact of applying a prediction model in clinical practice. Currently, guidelines are focused on testing for CVD in symptomatic patients. Atypical symptoms or silent ischemia are more common in the diabetic population, and with additional markers of vascular disease such as erectile dysfunction and autonomic neuropathy, these guidelines can be difficult to interpret. We propose an algorithm incorporating cardiovascular risk scores in combination with typical and atypical signs and symptoms to alert clinicians to consider further investigation with provocative testing. The modalities for investigation of CVD are discussed.

**Key words:** Diabetes; Cardiovascular risk; Risk scores; Provocative testing; Silent ischaemia; Atypical symptoms

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**Core tip:** Current guidelines focus on testing for cardiovascular disease in symptomatic patients. However, patients with diabetes often present with atypical features of underlying vascular disease. An individualised approach to cardiovascular risk estimation and management is needed in patients with diabetes. We propose an algorithm incorporating cardiovascular risk scores in combination with typical and atypical signs and symptoms to alert clinicians to consider further investigation with provocative testing. The modalities for investigation of cardiovascular disease are discussed.

### Abstract

Cardiovascular disease (CVD) is the leading cause of

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## INTRODUCTION

The incidence of diabetes mellitus is increasing globally. The World Health Organisation estimated there were 30 million people who had diabetes worldwide in 1985. This number increased to 217 million in 2005, and by the year 2030, it is predicted this number will increase to at least 366 million<sup>[1]</sup>.

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality among people with diabetes mellitus, who have a risk of cardiovascular mortality two to four times greater than that of people without diabetes<sup>[2]</sup>. Diabetes is commonly associated with other cardiovascular risk factors, interacting with these to accelerate atherogenesis<sup>[3-6]</sup>. Multifactorial interventions, such as those targeting hyperglycaemia, hypertension and hypercholesterolaemia, significantly reduce the risk of both fatal and non-fatal CVD<sup>[7]</sup>. The National Cholesterol Education Programme Adult Treatment Panel III (NCEP-ATPIII) has listed diabetes as a coronary heart disease (CHD) equivalent, which would obviate the need for risk stratification. However, clearly not all patients with diabetes have the same cardiovascular risk. An individualised approach to cardiovascular risk estimation and management is needed<sup>[8]</sup>. Furthermore there is a high prevalence of asymptomatic coronary artery disease (CAD), and higher incidences of silent ischaemia and of atypical symptoms<sup>[9]</sup>.

Over the past two decades, there has been a significant reduction in the incidence of diabetes-related complications. The greatest absolute decline was in the number of cases of acute myocardial infarction, likely reflecting a combination of enhanced awareness, detection and early management of risk factors<sup>[10]</sup>. The development of statistical models, such as the Framingham equations, has allowed the probability of future cardiovascular events to be calculated based on multiple risk factors<sup>[11]</sup>. This allows targeted preventative therapy for those with highest absolute risk<sup>[12]</sup>. However, the majority of these risk equations have not been validated enough in the diabetic population, and either overestimate or underestimate cardiovascular risk.

## USE OF CARDIOVASCULAR RISK SCORES IN DIABETES MELLITUS: PREDICTORS, VALIDATION AND IMPACT ON CLINICAL OUTCOME

There have been a multitude of risk scores developed

over the past decades, but only a few have been specifically developed for use in the diabetic population. In a systematic review of prediction models for CVD risk in type 2 diabetes<sup>[13]</sup>, 12 of 45 prediction models were specifically developed for patients with type 2 diabetes. The majority of these predicted 5-year risk of CHD or total CVD, with the most commonly used predictors being age, sex, duration of diagnosed diabetes, HbA1c (glycosylated haemoglobin A1c) and smoking. Non-traditional risk factors, such as novel biomarkers and low birthweight, have generally not been incorporated into these models, and are of questionable clinical significance<sup>[14,15]</sup>. Prediction models derived from the general population, in which diabetes was used as a predictor, included other risk factors such as age, sex, systolic blood pressure, smoking and cholesterol. Of the risk scores, only a third had been externally validated in a diabetic population<sup>[13]</sup>.

The International Diabetes Federation recommends calculating cardiovascular risk in patients with type 2 diabetes with prediction models that can be applied to the diabetes population, including the United Kingdom Prospective Diabetes Study (UKPDS) risk engine<sup>[16]</sup>. This risk engine provides a comprehensive model for predicting CHD risk in patients with type 2 diabetes. The Australian National Vascular Disease Prevention Alliance<sup>[17]</sup> recommends using both the Framingham prediction model and UKPDS risk engine. However, certain subgroups (Table 1) are at high risk of cardiovascular events because of their comorbidities, and a calculation of absolute CVD is not considered necessary<sup>[17]</sup>.

Kengne *et al*<sup>[11]</sup> evaluated the performance of the Framingham and UKPDS models in a cohort of patients with established type 2 diabetes, and found both models to overestimate the 4-year risk of CHD; by 146% and 198% respectively. The Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation model<sup>[18]</sup> was developed from a contemporary multinational cohort of diabetic patients, and includes both retinopathy and microalbuminuria as risk predictors. They are both significantly associated with CVD. It has largely outperformed the Framingham models in validation studies, with only a modest risk underestimation<sup>[19]</sup>. Similarly, the Fremantle prediction model<sup>[20]</sup>, developed from a type 2 diabetic cohort, had good positive and negative predictive values, but requires further validation<sup>[13]</sup>.

Very few studies have examined the impact of applying a prediction model in clinical practice. In a cohort of patients with type 2 diabetes at high risk of CVD, clear documentation of a cardiovascular risk prediction score on patient medical records was associated with more intensive intervention through prescription of lipid-modifying or antihypertensive medications<sup>[21]</sup>. Furthermore, use of risk scores has resulted in improvements in lipid profiles and significant reductions in risk of CHD<sup>[22]</sup>.

The use of cardiovascular risk scores has been

**Table 1 Clinical features suggesting diabetes patients at high risk**

Diabetes and age > 60 yr
Diabetes and microalbuminuria (> 20 mcg/min or urine albumin to creatinine ratio > 2.5 mg/mmol for males, > 3.5 mg/mmol for females)
Diabetes and moderate or severe chronic kidney disease (persistent proteinuria or eGFR < 45 mL/min per 1.73 m <sup>2</sup> )
Diabetes and a previous diagnosis of familial hypercholesterolaemia in the individual
Diabetes and systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 110 mmHg
Diabetes and serum total cholesterol > 7.5 mmol/L

Albumin to creatinine ratio - confirmed on second test and not due to another cause (*e.g.*, urinary tract infection).

**Table 2 American Diabetes Association guidelines on stress testing in diabetic patients<sup>[23]</sup>**

Typical or atypical cardiac symptoms
Resting electrocardiogram suggestive of ischaemia or infarction
Peripheral or carotid occlusive arterial disease

**Table 3 Signs and symptoms of concern in an otherwise asymptomatic patient**

Symptoms suggestive of cardiovascular autonomic neuropathy
Resting tachycardia
Postural hypotension
Signs/symptoms suggestive of coexisting vascular disease
Erectile dysfunction
Claudication symptoms
Carotid bruit
Diminished/absent peripheral pulses
Inappropriate exercise tolerance
Shortness of breath without clear pathology

incorporated into multiple guidelines, and may be a useful initial step towards CVS risk stratification. However, given the modest performance of most prediction models, and need for more extensive validation studies, further decision-making may be useful before proceeding to provocative testing.

### PROVOCATIVE TESTING: FACTORS INFLUENCING DECISION MAKING

The onset of microvascular and macrovascular complications in diabetic patients is frequently insidious, with the absence of typical symptoms often delaying diagnosis. Studies have demonstrated that a significant percentage of patients with diabetes who have no symptoms of CAD have abnormal stress tests, either by stress electrocardiogram (ECG), stress echocardiogram or stress nuclear perfusion imaging<sup>[23]</sup>. CAD in patients is often silent, more advanced and associated with less favourable prognosis than those in the non-diabetic population<sup>[23]</sup>. Diabetic cardiovascular autonomic neuropathy (CAN) resulting in damage to the neural fibres responsible for innervation of the heart and cardiac vessels can lead to atypical clinical manifestations, hence the concept of screening an asymptomatic patient is complex<sup>[24]</sup>. However, the American Heart Association recommends against routine screening in diabetic patients who are asymptomatic, as there is currently no outcome data to support stress

testing in this group of patients<sup>[25]</sup>. In contrast, the American Diabetes Association (ADA) recommends exercise stress testing in both symptomatic and asymptomatic patients with specific criteria (Table 2).

There are further specific guidelines for screening for CVD before beginning moderate to vigorous exercise training program which expand to include the length of disease; 15 years for type 1 diabetes and 10 years for type 2 diabetes, and age ≥ 35 for type 2 diabetes. Given we encourage all our patients to exercise as part of a general care plan for diabetes, it may be argued that all patients should be screened prior to this recommendation.

Furthermore, given symptoms may be atypical in the diabetic patient, there may be some clues to the presence of CVD to alert the treating clinician to investigate (Table 3). Symptoms of exercise intolerance and erectile dysfunction may suggest underlying coronary artery disease and may prompt further investigation. Peripheral arterial disease and the presence of Q waves and or ST/T wave abnormalities on ECG have also been shown to predict presence of coronary artery disease<sup>[26]</sup>.

#### Erectile dysfunction

Erectile dysfunction may be the manifestation of endothelial dysfunction in many cases and is recognised to represent the coexistence of vascular disease in other areas<sup>[27]</sup>. It has been documented that men with

**Table 4** Sensitivity and specificity of provocative tests in patients with diabetes

Diagnostic test	Sensitivity (%)	Specificity (%)
Exercise stress test <sup>[33]</sup>	47	81
Stress echo <sup>[35]</sup>	82	54
Stress nuclear perfusion study <sup>[36]</sup>	86	56
CT coronary angiogram <sup>[40]</sup>	76	90
Coronary calcium score <sup>[39]</sup>	64-75	75-83

CT: Computed tomography.

no cardiac symptoms and erectile dysfunction have increased risk of cardiac events over the following 3-5 years<sup>[28]</sup>. Furthermore a large meta-analysis found patients with erectile dysfunction have an increased risk of CVD, cerebrovascular disease, stroke and all-cause mortality independent of traditional risk factors<sup>[29]</sup>. The suggestion that patients with erectile dysfunction are likely to be vasculopathic validates the investigation of cardiovascular and peripheral vascular disease, even in the absence of typical symptoms. We therefore propose that patients with a history of erectile dysfunction be investigated further for underlying vascular disease.

#### **Exercise tolerance and CAN**

Autonomic dysfunction in diabetes leads to exercise intolerance. Suboptimal cardiac output in times of exertion can be a result of CAN as well as vascular disease and silent ischaemia<sup>[30]</sup>. Signs and symptoms of CAN may include resting tachycardia due to impaired vagal tone or orthostatic hypotension<sup>[30]</sup>. CAN significantly increases the risk of fatal or non-fatal cardiovascular event<sup>[24]</sup>. The suspicion of CAN may therefore justify further investigation for coronary vascular disease.

#### **Claudication symptoms**

Symptoms of claudication in the diabetic patient justify consideration of investigating other vascular disease including coronary artery disease, even in the absence of symptoms. Patients with peripheral vascular disease have increased mortality from cardiovascular causes<sup>[31]</sup>. Assessment of peripheral pulses should be performed in all patients, given this is a simple method of screening. If abnormal, further investigation with ankle brachial indices and provocative testing for cardiac ischaemia may be warranted<sup>[31]</sup>.

### **CHOICE OF INVESTIGATION FOR RISK STRATIFICATION IN DIABETIC PATIENTS WITH SUSPECTED CVD**

The choice of investigation will depend on a number of factors including mobility, exercise tolerance, plans for future increases in exercise and potentially gender. As a baseline investigation, the American Heart Association recommends that a resting electro-

**Table 5** Sensitivity and specificity of provocative testing in women<sup>[44]</sup>

Diagnostic test	Sensitivity (%)	Specificity (%)
Exercise electrocardiogram	31-71	66-78
Exercise echocardiogram	80-88	79-86
Pharmacological echocardiogram	76-90	85-94
Nuclear perfusion study	78-88	64-91
Computed tomography coronary angiogram	97	79

cardiogram (ECG) is a reasonable tool for risk assessment in asymptomatic adults with diabetes<sup>[32]</sup>. Beyond this, the factors influencing selection of a particular modality for provocative testing are similar between diabetic and non-diabetic patients and include availability, sensitivity and specificity and risk. Each modality has varying performance accuracy in terms of sensitivity and specificity with some specific differences in patients with diabetes (Table 4).

#### **Exercise ECG**

Exercise ECG (stress testing) is widely regarded as the first line test in mobile patients with a normal baseline electrocardiogram and it has been found to have similar predictive value between diabetic and non-diabetic populations<sup>[33]</sup>. However sensitivity is variable, and in some studies is less than 50%<sup>[33]</sup>. A positive test will identify the majority of patients with left main or significant multi-vessel coronary artery disease<sup>[33]</sup>. One study found a positive predictive value of 94% in a cohort of asymptomatic older males with poorly controlled diabetes<sup>[34]</sup>.

Stress ECG is less sensitive and specific in asymptomatic populations, *i.e.*, where there is a lower pre-test probability. The test is highly dependent on the patient's capacity to exercise long enough to provide a valid test. Whilst a patient reaching above expected exercise capacity provides useful prognostic and clinical information, many diabetic patients with obesity, peripheral neuropathy, decreased physical conditioning or other co-morbidities are unable to exercise long enough to determine low cardiovascular risk. It can therefore be argued that this form of investigation is suboptimal for patients with diabetes who are unlikely to be able to reach an appropriate workload owing to co-morbidities. In women, the test may also be less useful, with quoted sensitivities of 31%-71% (Table 5).

#### **Stress echocardiography**

In the general population addition of imaging modalities such as echocardiography to stress testing provides greater diagnostic accuracy. Addition of echocardiography gives additional information about regional wall motion abnormalities (suggesting prior infarcts) and ventricular dysfunction, both of which are more common in people with diabetes. However data regarding diagnostic accuracy of stress echocardiography specifically in diabetic populations is relatively limited. Hennessy *et al.*<sup>[35]</sup> evaluated

dobutamine stress echo in 52 patients with diabetes, finding a sensitivity of 82% but a specificity of only 54%. The positive predictive value was 84% with a poor negative predictive value of 50%<sup>[35]</sup>. Availability may be limited by cost and operator expertise.

### **Nuclear perfusion scans**

Stress nuclear imaging has been the most widely investigated modality for the detection of CAD in people with diabetes. The sensitivity of this tool has been quoted as 86% with a specificity of 56% in patients with diabetes<sup>[36]</sup>. Wackers *et al.*<sup>[37]</sup> examined asymptomatic patients with diabetes using adenosine Single Photon Emission Computed Tomography (SPECT) imaging and found positive test results for CAD in 22%. Interestingly, 41% of these patients with abnormal imaging findings would not have met usual criteria for further investigation of coronary disease according to previous ADA guidelines. Thus, use of stress imaging in selected people with diabetes who have high absolute cardiovascular risk is reasonable even if they are asymptomatic. Nuclear imaging studies can be performed with exercise, or in subjects with limited exercise capacity with other modalities to increase coronary flow such as adenosine. This modality provides information about coronary flow at rest, with exercise or stimulated stress, as well as regional wall motion, although the last is much less precise than the information obtained with echocardiography.

### **Computed tomography coronary angiogram and coronary calcium score**

Computed tomography (CT) coronary angiogram (CTCA) may provide information on the vascular lumen and the arterial wall<sup>[38]</sup>. In people without diabetes it has been reported to have high sensitivity<sup>[39]</sup>. However, a study comparing the use of CTCA in diabetic vs non-diabetic patients found reduced sensitivity and specificity in people with diabetes, due to differences in artefacts and calcification<sup>[40]</sup>. While coronary calcium score may be able to predict coronary disease beyond standard risk factors, significant stenosis can occur in the absence of calcification, so this tool should not be used in isolation<sup>[31,41,42]</sup>.

A study by Maffei *et al.*<sup>[42]</sup> showed that coronary plaque burden and coronary calcium scores were higher in diabetic vs non diabetic patients. Furthermore it has been shown that asymptomatic patients with diabetes with high coronary artery calcium scores have a high prevalence of inducible ischaemia on stress imaging<sup>[43]</sup>. The American Heart Association acknowledges that measurement of coronary artery calcium score is reasonable for cardiovascular risk assessment in patients with diabetes who are asymptomatic and age over 40<sup>[32]</sup>. The efficacy of this test in women with diabetes is less clear, see below.

### **Gender effects**

Both symptoms and pathophysiology of coronary

artery disease can differ between males and females. Women, whether diabetic or not, are more likely to have atypical symptoms and are often older at the time of onset of disease or events. Prognosis is poorer in women than men with higher mortality rates from acute myocardial infarction<sup>[44]</sup>. Detection of disease in women is more difficult given the lower likelihood of obstructive coronary disease and apparently lower levels of clinical suspicion<sup>[45]</sup>.

As well as these issues, currently available provocative tests are both less sensitive and less specific in women<sup>[44]</sup>. Information regarding the characteristics of coronary artery disease in diabetic women vs the general female population is surprisingly sparse. To date, guidelines suggest the use of exercise ECG testing as first line investigation in women with symptoms of coronary disease with a normal baseline ECG<sup>[46]</sup>. If either the baseline ECG or exercise ECG is abnormal, the addition of stress testing with imaging is recommended<sup>[46]</sup>. However, these investigations are well known to have limitations in the female population due to interference from breast soft tissue and differences in coronary anatomy in women<sup>[45]</sup>.

Stress SPECT and stress echo are considered superior to exercise ECG in women for both sensitivity and specificity. Adenosine stress nuclear imaging has similar prognostic ability in men and women, though it has been shown that women have worse clinical profiles for the same degree of imaging abnormality<sup>[47]</sup>. However, the ultimate decision may be limited by cost and local expertise. Table 5 summaries the sensitivity and specificity of the different provocative investigations in women.

### **Risks associated with different testing modalities**

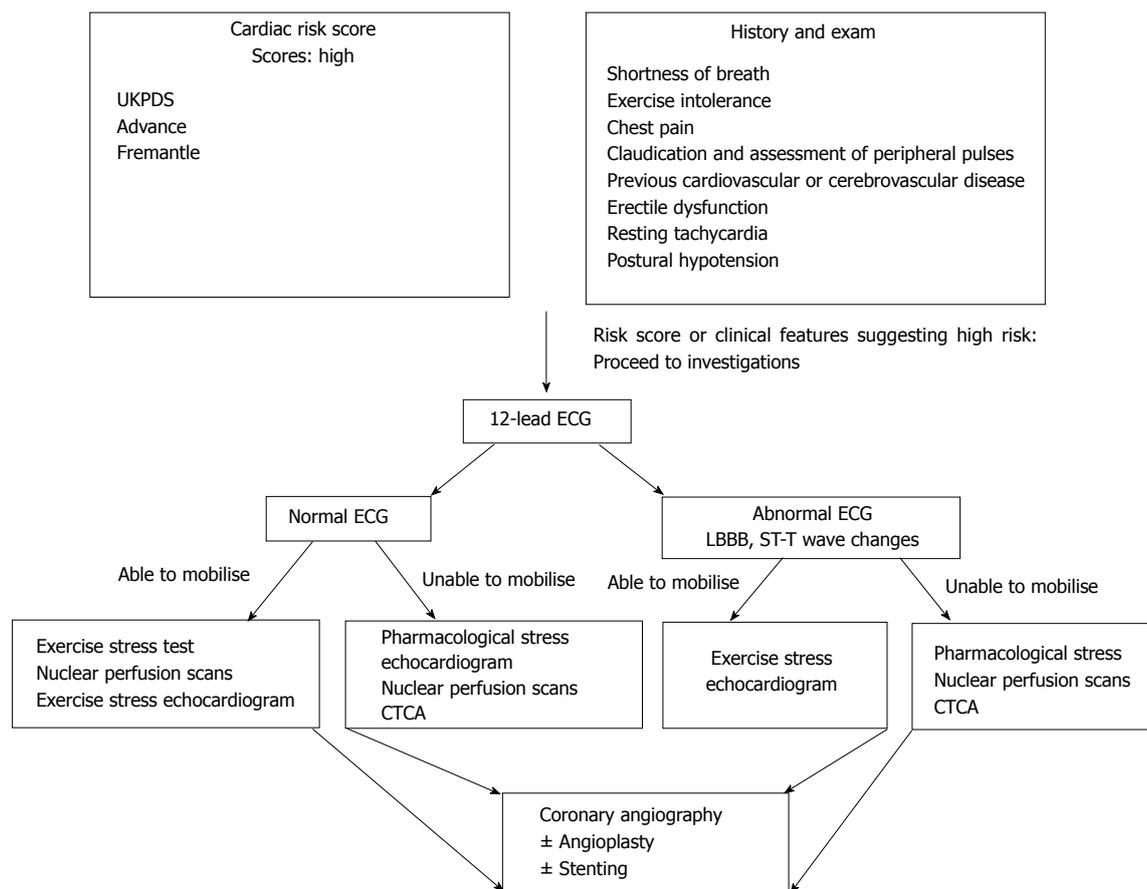
There are risks associated with each of the tests discussed. For non-invasive stress testing such as exercise stress tests and exercise stress echo, 5% of patients may experience mild angina, shortness of breath or musculoskeletal pain. Less commonly (< 5%) chest pain, hypotension or syncope may occur and rarely (< 1%) there is a risk of acute myocardial infarction, stroke or arrhythmia<sup>[45]</sup>. Investigations requiring contrast such as CTCA carry risks of associated renal toxicity or allergic reaction, and exposure to significant radiation with resultant cancer risk. Nuclear perfusion scans may employ the use of agents such as adenosine, which are known to induce asthma in some individuals and also involve some radiation exposure. Each of these factors must to be considered in the decision to utilise a certain modality. In women who are considering pregnancy, stress ECG or stress echocardiography are radiation-free, which is an important consideration.

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## **SUGGESTED ALGORITHM**

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The decision to proceed with provocative testing should be based on a combination of cardiovascular risk



**Figure 1 Suggested algorithm for investigation of cardiovascular disease in patients with diabetes.** Since a 12-lead ECG is a safe and cheap test, it should be performed in people with diabetes with a low threshold. At each layer of testing, if the test is normal or unchanged from previous testing, consider whether the next level of testing is needed. ECG: Echocardiogram; LBBB: Left bundle branch block; CTCA: CT coronary angiogram; UKPDS: United Kingdom prospective diabetes study.

score and suspicious features on clinical history and or examination. As discussed above, risk calculators do not consider specific features such as erectile dysfunction or cardiac autonomic neuropathy. Therefore, risk calculators may fail to identify potential high risk features when used in isolation.

Firstly, a baseline 12-lead ECG should be performed in all patients considered at risk. Following this, the choice of modality for provocative testing will depend on factors such as abnormal resting ECG (left bundle branch block or ST-T wave changes at baseline), mobility including ability to perform exercise testing, gender, cost and access to local expertise. There is a need to highlight and alert the treating clinician to recognise novel markers of disease that have been previously under-recognised by traditional risk scores. Considering these risk factors, we propose the algorithm in Figure 1.

## CONCLUSION

Patients with diabetes are at high risk of mortality from CVD. Given this group of patients often present with atypical symptoms and silent ischaemia, traditional recommendations for screening in symptomatic individuals may not be applicable. National guidelines

recommend incorporation of a cardiovascular risk score in risk stratification. Risk scores have arguably suboptimal performance when used in isolation and have not been extensively validated. Additionally, to date such clinical signs as erectile dysfunction or autonomic neuropathy have not been incorporated into cardiovascular risk prediction models, though it is well recognised that these pathologies represent underlying cardiac disease. We propose the use of a combination of a risk score and relevant clinical findings in the overall assessment of cardiovascular risk. The algorithm (Figure 1) presented may provide treating clinicians with various clues to prompt further investigation with provocative testing. There is an ongoing need for re-evaluation of guidelines for screening in this high risk patient group.

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