DIAGNOSIS AND NON-INVASIVE RISK STRATIFICATION OF CORONARY ARTERY DISEASE IN DIABETIC PATIENTS

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Abstract

Diabetic patients have an increased risk of developing coronary artery disease (CAD). Risk factor aggregation is prevalent in the diabetic population and it is responsible for increased cardiovascular morbidity and mortality. A number of methods for diagnosing CAD in asymptomatic patients have been extensively used in the general population and some could be as well implemented in the diabetic population. Every diabetic patient must be included in a workup plan that should consist of initial evaluation of symptoms and risk factors, noninvasive cardiac testing, and eventually referral to coronary angiography unit if and when needed.

Keywords: diabetes mellitus, coronary artery disease, screening, risk stratification, exercise ECG.

Patients with diabetes mellitus have an increased relative risk of developing cardiovascular disease as compared to non-diabetics. The Framingham trial has proven that diabetics have an excess of risk of 2 to 5 times greater of angina, myocardial infarction (MI) or heart failure (HF) than non-diabetics of the same age and sex. Moreover, this risk excess is especially evident in young patients (relative risk of over 11 in patients aged <45 years)[12]. Recently it has become a well recognized fact that the prognosis of a diabetic patient is similar to that of a non-diabetic that had already suffered a MI[11]. Moreover, diabetes seems to abate the gender difference favoring women as far as the cardiovascular risk is concerned, as a greater relative increase in risk has been documented in diabetic women than in diabetic men[4]. In addition to a higher prevalence of CAD, patients with diabetes experience more diffuse and extensive CAD at the time of diagnosis, and develop silent ischemia more often. The complications of CAD account for approximately 65% of deaths in diabetic patients.

It is recognized that the preponderance of data regarding risk factor modification and screening for CAD comes from trials that included mainly type 2 diabetes cases. However, evidence from epidemiological studies exists that people with type 1 diabetes have a greater prevalence of CAD than age-matched individuals from the general population, and they presumably respond similar to risk-reduction interventions[6]. Conclusively, this discussion also applies to patients with type 1 diabetes mellitus.

A combination of risk factors such as systemic arterial hypertension, central obesity, dyslipidemia and microalbuminuria is a common finding in diabetics. About 50% have dyslipidemia, and over 80% are obese. A high-risk (proatherogenic) lipid profile is present, consisting of small and dense LDL particles, hypertrigliceridemia and low HDL-cholesterol. Hypertension is found in over 50% of the patients, and associated chronic renal disease is also a common finding. The presence of proteinuria, from early stages of microalbuminuria is an independent risk factor for CAD. However, the "traditional" risk factors only account for 50% of the excessive risk noticed in diabetics, a finding that emphasizes the concept of "hyperglycemic environment" as a promoter for atherosclerosis progression and, although the need for a multifactorial approach of the diabetic patient has been well established, underlines the importance of treating hyperglycemia itself [20].

A number of therapeutic interventions are proven to reduce the incidence of coronary events in diabetics, such as control of hypertension, statin treatment for dyslipidemia, and the use of aspirin, β-blockers and ACE-inhibitors or angiotensin receptor blockers. The use of certain oral antidiabetic agents, as metformin and pioglitasone, has also brought about a reduction in macrovascular events.

Even when adequately treated, the diabetic patient has a worse prognosis. This is proved by the statistics regarding post-MI and post-revascularization procedures mortality, which have shown an excess of events in diabetic patients[13].

The diabetes epidemic has an enormous impact on health systems worldwide, as far as the need for human and financial resources is concerned.

Therefore, for the cardiovascular management to reach its maximum potential, the early identification of diabetic patients with CAD is important. The finding of a previously undiagnosed MI or of silent ischemia has an impact on the type and intensity of therapeutic intervention. In diabetic patients without proven CAD, the physician must decide when screening is necessary, what methods to use and what time to follow-up depending on the prior results of the chosen tests.

Guidelines by the American Diabetes Association have been issued in 1998 addressing this problem. In asymptomatic diabetic patients screened for CAD, the ADA expert panel focused on risk factor burden (i.e. number of risk factors as opposed to severity of anyone risk factor), resting ECG and evidence of vascular disease at other sites. The ADA position was largely expert opinion based since evidence from large prospective randomised trials was lacking. A revision of these guidelines has been published by ADA in 2008, recognizing that risk factor burden (i.e. two or more cardiovascular risk factors; see below) is not always predictive of inducible ischemia at stress testing. Efforts have been made to develop computer models (risk engines) that can identify individuals at high risk for CAD. They have the limitation of being based on cohorts of patients (e.g. Framingham, UKPDS) not always representative for the general population. Also, newer methods like CT angiography, coronary artery calcium scoring, and cardiac magnetic resonance imaging, have been investigated for their usefulness in screening for CAD[6]. A joint task force of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD) issued a common guideline on diabetes and cardiovascular diseases in 2007 recommending an even more aggressive approach to diagnosing CAD in people with diabetes. The ESC/EASD guideline recommends cardiac screening, including exercise ECG, in all patients that are diagnosed with diabetes mellitus, irrespective of risk factor and comorbidities configuration. The reader is directed to the respective references for further data[2-4, 20].

The main methods employed for detection of asymptomatic CAD are the treadmill exercise electrocardiography (ECG), pharmacological stress echocardiography and myocardial perfusion studies. Newer imagistic methods such as non-invasive coronary computed tomographic angiography have also proven useful in the general as well as in the diabetic population.

Initial risk stratification. Value of resting electrocardiography

The presence of already known CAD in a diabetic, possibly with a previous cardiovascular event, implies the necessity of cardiac testing for risk stratification. Despite the significant number of diabetic patients with silent ischemia, a large number have chest pain (approximately 16% of patients with type 2 diabetes over 65 years of age by an estimate). Sometimes, atypical symptoms as dyspnea, fatigue and even gastrointestinal complaints can be elicited by exertion and often impose cardiac testing. The use of resting ECG has greater value in diabetics than in their non-diabetic counterparts. The finding of a pathological Q wave warrants, apart from the initiation of β-blockade, also exercise testing. Other findings on the resting ECG that could be used as indicators for further evaluation are deep inverted T waves and left bundle branch block. Some pathological findings on the resting ECG make the exercise testing uninterpretable. These are: left bundle branch block, WPW syndrome or other conduction disturbances, digitalis induced changes or preexistent ST downward deviation >1 mm.

A more important issue is that of cardiac testing in individuals without a prior MI or without symptoms suggestive of CAD. Silent ischemia is present in 20-30% of diabetic patients, as are painless MI, asymptomatic ST depression during Holter monitoring or in the setting of treadmill exercise ECG testing. A substudy of Coronary Artery Surgery Study (CASS) has shown that the presence of silent ischemia is linked to a reduction in survival at 6 years in diabetics, when compared to non-diabetics [13].

Co-existent peripheral arterial disease (PAD) is a risk factor for CAD and justifies further testing, especially since the majority of diabetics with PAD are known to succumb to a cardiovascular event. Clinical findings such as the absence of distal pulse or femoral murmurs, or an ankle-brachial index of <0,9 have a satisfactory sensibility for the identification of PAD[13]. Evidence of carotid atherosclerotic disease, as antecedent ischemic brain attacks, clinical findings (e.g. carotid murmurs), or by echographic examination (measurement of intimal-medial thickness) constitutes another risk factor for CAD.

Physical exercise is an important therapeutic approach in type 2 diabetes[3]. The gradual initiation of moderate physical exercising could be employed without prior cardiac testing. But for the subset of patients older than 35 years, that had a sedentary lifestyle and at present wish to engage in sustained physical training, exercise ECG testing is useful in identifying those at high risk of developing a cardiovascular event during physical effort, and to help individualize the exercise program.

The presence of urinary albumin excretion is an independent risk factor in diabetics, not only for overt kidney disease, but also for macrovascular events (especially in type 2 diabetes). The prevalence of CAD shoots up significantly in diabetics with associated chronic renal disease[4]. Patients with type 1 diabetes and impaired renal function often develop extensive atherosclerosis[6]. The risk is 8-15 times greater in diabetics with proteinuria compared to those without, and 37 times greater as compared to the general population[13]. A value of 30 mg/g of albumin/creatinine ratio in a spontaneous urine sample is defined as the threshold for microalbuminuria. The coexistence of persistent microalbuminuria in a diabetic aged >35 years warrants cardiac testing.

The clustering of multiple cardiovascular risk factors like dyslipidemia, hypertension, or family history characterizes diabetic patients. Cardiac testing was indicated by the ADA 1998 guidelines when more that two "traditional" risk factors were present (see table 1). Subsequent recommendations (ESC/EASD 2007 and ADA 2008) are putting less emphasis on risk factor burden (as shown above). The failure of risk factor burden to accurately predict future events in diabetics may reflect the inability of clinical trials to account for the severity, duration, and effect of treatment of both lipid abnormalities and hypertension in people with long-standing type 2 diabetes[6].

Left ventricle systolic dysfunction (LVD) is diagnosed when the left ventricular ejection fraction is less than 50%. The left ventricle is typically dilated by the effect of increased parietal tension on myocardial wall. The patient stratification according to the presence and stage of alteration of left ventricle function parameters has prognostic significance. Migrino et al (1997) have shown that in post-MI patients, a telesystolic volume less than 40 ml carries a mortality percent of less than 2%, whereas if the same parameter exceeds 120 ml the prognosis is far worse (20% mortality)[17]. The importance of screening for LVD has been also underlined by a recent study, in which the prevalence of LVD in post-MI patients and/or patients with ECG signs of left ventricular hypertrophy was as high as 15,4% [5]. The evaluation of left ventricular systolic dysfunction by transthoracic echography is indicated in diabetics as a method of risk stratification.

Other markers of cardiovascular risk have been identified, but sufficient data are lacking in order for them to be included in the guidelines[2]. Plasma homocystein levels have been independently correlated with all-cause mortality and especially with cardiovascular mortality in a study on 587 patients with angiographicaly determined CAD, followed-up a median of 4,6 years[18]. Homocystein levels tend to increase in diabetic individuals especially in the setting of chronic renal disease. It has also been proven that the values of a number of subclinical inflammation markers as C reactive protein (CRP), and to a lesser extent fibrinogen, Von Willebrand factor and plasminogen activation inhibitor 1 (PAI-1) are predictive for cardiac events. These markers can serve to identify the subset of patients at high risk of "destabilization" of CAD (with vulnerable atherosclerotic plaques). In clinical practice high sensitivity-CRP (hsCRP) levels are more reproducible than fibrinogen levels and less susceptible to laboratory errors. It is possible for the patients with stable angina and hsCRP levels >3 mg/l to be a high risk group, in which detailed evaluation and aggressive therapy is warranted[13]. The clinical use of all the biomarkers mentioned is constrained mainly by financial reasons.

A risk factor unique to diabetic patients is autonomic neuropathy. Clinical findings of autonomic neuropathy have been linked with worse prognosis in several studies. In the *Detection of Silent Myocardial Ischemia in Asymptomatic Diabetic Subjects (DIAD)* trial, autonomic neuropathy was the single most powerful predictor for the presence of ischemic myocardium areas diagnosed on perfusion studies, while "traditional" risk factors added little predictive value (see below for other details)[7]. Screening for the presence of autonomic neuropathy is recommended by ADA upon diagnosis in type 2 diabetes and within 5 years of diagnosis for type 1 diabetes. Autonomic neuropathy is a complication of long-standing diabetes, often associated with other chronic complications, and is an indication of cardiac testing in patients >35 years old, with diabetes diagnosed >25 years.

Table 1. Indications for cardiac testing in diabetic patients. After ADA, 1998. (See text).

1. Typical or atypical angina
2. Resting ECG suggestive of ischemia or infarction
3. Peripheral or carotid artery disease
4. Patients with sedentary lifestyle who begin a sustained program of physical exercise
5. Two or more of the following risk factors (a-e) apart from diabetes
a. Total cholesterol ≥ 240 mg/dl, LDL-cholesterol ≥ 160 mg/dl, or HDL-cholesterol < 35 mg/dl
b. Blood pressure > 140/90 mmHg
c. History of smoking
d. Positive family history for premature CAD
e. Micro/macroalbuminuria

Treadmill exercise electrocardiography

Physical exercise causes an increase in myocardial oxygen demand by augmenting heart rate, contractility, wall stress and blood pressure. In the setting of diminished coronary reserve, stenotic arteries cannot respond adequately by a concomitant increase in blood flow. As a consequence, myocardial regions supplied by these arteries become ischemic, and this phenomenon is detected by the surface ECG because of the modifications in repolarization currents. This method employs a graded exercise test. The patients begin with a low workload that he or she is able to perform without difficulty, which is then increased in small amounts. Perhaps the most widely used graded exercise protocol is that of Bruce and Hornsten, with a common variation known as the "modified Bruce protocol" used in patients with limited effort capacity. The estimated workload is reported in METs (metabolic equivalents), expressing the energy cost of activity in multiples of resting oxygen consumption (1 MET = 3,5 ml/min/kg).

A metaanalysis on 132 trials, including 24074 patients, determined a sensibility of 68% and a specificity of 77% of exercise ECG for the detection of CAD. However, the results vary considerably between the trials, probably because different positively criteria have been used and the prevalence of CAD was different in the tested populations[15].

Exercise ECG identifies most of the patients with significant left main coronary stenosis and those with multivascular disease. The latter usually have decreased effort tolerance and develop important ST deviation during testing, or an inadequate hypotensor response.

Pharmacological therapy with anti-ischemia drugs (e.g. β-blockers) can delay the occurrence of cardiac ischemia, and blunt heart response to exercise influencing the results, and if the purpose of testing is diagnosis of CAD, any such medication should be withdrawn prior to testing.

Although useful in many clinical circumstances, this method has proven lacking in certain situations. The exercise ECG has too low a specificity to be cost-effective when used in low-risk populations[12]. This is not a particular problem for the diabetic population because of its high pre-test probability. The sensibility of the test is too low to be highly predictive in high-risk populations. In conclusion, exercise ECG is particularly useful in patients stratified as intermediate risk. Moreover, certain problems, such as exercise incapacity linked to obesity, PAD, diabetic polineuropathy, or concurrent neurological or orthopedic conditions further limit the use of this method. Some pathological features on the resting ECG can mask effort elicited signs, as shown above.

A patient's incapacity of reaching 85% of target heart rate: 220-age (years) bpm considerably diminishes the method's positive predictive value, and in this case alternative tests should be considered even in case of a negative result.

Absolute and relative contraindications of treadmill exercise ECG are shown in table 2.

The interpretation of exercise ECG is done according to the patient's effort capacity, ECG changes, the hemodynamic response to exercise and the occurrence of symptoms. The Duke treadmill scoring (DTS) can be used for this purpose: duration of exercise (min) - 5 x maximal ST deviation from baseline during or after exercise (mm) - 4 x angina index. The angina index is considered 0 if no chest pain occurs during testing, 1 if typical angina occurs, and 2 if angina causes the interruption of testing (limiting angina). The score improves prognostic accuracy of exercise ECG compared to single use of ECG changes[15]. In accordance with this score, the patients can be stratified as low (DTS ≥ +5), moderate (DTS between –11 and +4), or high risk (DTS < -11).

A negative test, despite its low sensitivity for the detection of univascular coronary disease, confers good prognosis. The patients that can sustain a physical effort longer that 9 min during Bruce protocol (stage 3 or higher), or other physical exercise equivalent to 10 METs, are at low risk, with a 4-year mortality <1%. Such a result should assure the physician and the patient that the probability of significant CAD is low. However, retesting at 1-2 years is warranted in patients with a high pretest probability because of the risk for false-negative results, and atherosclerosis being a progressive disease.

Table 2. Contraindications of exercise testing.
After Crawford, DiMarco and Paulus, 2004 (8).

Absolute contraindications	Acute myocardial infarction in the last two days
	High-risk unstable angina
	Uncontrolled symptomatic arrhythmia or arrhythmia associated with hemodynamic compromise
	Severe symptomatic aortic stenosis
	Severe uncontrolled heart failure
	Acute pulmonary thromboembolism or infarction
	Acute myocarditis or pericarditis
	Acute aortic dissection
Relative contraindications	Left main coronary artery stenosis
	Moderate valvular stenosis
	Electrolyte disturbances
	Severe arterial hypertension (SBP>200 mmHg and/or DBP>110 mmHg)
	Tahi or bradiarrhythmias
	Hypertrophic-obstructive cardiomyopathy or any other form of outflow tract obstruction
	Exercise incapacity as a result of a psychical or physical condition
	High grade atrioventricular block

Asymptomatic diabetic patients with a borderline positive result (e.g. ST depression of 1-1,5 mm with moderate/high effort) are, as a rule, at low risk. An alternative method for diagnosis of CAD, usually myocardial perfusion scan or stress echocardiography, should be used in patients that have a low pretest probability (for the exclusion of false-positive cases).

A moderate positive exercise ECG result warrants further testing with an alternate (imagistic) method. Normal or near normal myocardial perfusion scans indicate low-risk (approximately 2% per year), while moderate or large perfusion defects, pulmonary caption of the radioactive trasor or left ventricular dilation during effort places the patient in the high-risk group, and warrants invasive evaluation (see below). Moreover, invasive evaluation is cost-effective in patients with moderate positive exercise ECG and high pretest probability (4-5 risk factors).

A marked positive exercise ECG testing is defined by hypotension during physical effort, positivity criteria at a heart rate <120 bpm, effort capacity <6 min (Bruce protocol stages 2-3 or 5 METs during other protocol), ST segment deviation in 5 or more derivations, a.o. (see also table 4).

The patients unable to sustain a physical effort of 3 min have a mortality of over 5% per year, and as high as 20%. Such a result should prompt immediate referral for coronary angiography. Invasive evaluation defines the location and severity of CAD, and also the configuration of coronary vasculature, that determines the revascularisation method needed (percutaneous coronary angioplasty or coronary artery by-pass graft) (see also table 4).

Table 3. High risk indicators in exercise ECG testing. After Crawford, DiMarco and Paulus, 2004 (8).

Incapacity of reaching >6 METS during effort
Lack of increase in SBP>120 mmHg or decrease of ≥10 mmHg during exercise
ST depression of ≥2 mm with low effort (stage 1)
ST depression of ≥1 mm in 5 or more derivations
ST depression of ≥1 mm lasting more than 5 min during the recovery period
ST elevation in derivations without Q waves
Limiting angina
Sustained or unsustained ventricular tachycardia

Table 4. Indications for further evaluation after screening with exercise ECG testing in accordance with pretest risk and result of testing. Modified after ADA 1998

Pretest risk	Result of exercise ECG testing			
	Negative	Borderline	Moderate positive	Marked positive
High *4-5 risk factors*	Reevaluation after 1-2 years	Reevaluation by imaging method	Coronary angiography	Coronary angiography
Moderate *2-3 risk factors*	Reevaluation after 3-5 years	Reevaluation by imaging method	Reevaluation by imaging method	Coronary angiography
Low *0-1 risk factors*	Reevaluation after 3-5 years	Reevaluation by imaging method	Reevaluation by imaging method	Coronary angiography

Myocardial perfusion scan

This method uses radioactive compounds such as thalium-201 or technetium-99m-sestamibi, and detects changes in myocardial blood flow due to diminished coronary reserve during exercise or pharmacological challenge (e.g. with adenosine or dipiridamole). The technique has a high success rate (less than 1% of images are noninterpretabile).

Visualizing hypoperfused areas of myocardium (perfusion defects) boosts the diagnostic accuracy of classic exercise testing, and also makes possible estimating the localization and size of myocardial areas that are at risk, even in case of univascular disease, sometimes associated with a false-negative exercise ECG. The possibility of quantitative estimation of hypoperfused myocardium is an important feature of this type of test and allows risk stratification[12].

The risk for future coronary events is directly proportional to the severity, dimension and number of perfusion defects, as well as with the reduction of left ventricular ejection fraction (that can be measured when certain isotopes, like Tc-99m-sestamibi, are used), increased pulmonary distribution or temporary ventricular dilation during effort. For a similar amount of at risk myocardium, diabetic patients have a greater rate of coronary events, by comparison to nondiabetics, reaching 4-10% per year[13].

Clinical data has shown that normal perfusion scans, even in patients with angiographically proven CAD, are associated with a favorable prognostic (<1% risk of death or MI per year). Interestingly, in patients with a normal coronary angiography, the presence of perfusion defects is predictive for future coronary events, probably being associated with endothelial dysfunction.

In the *DIAD* trial, 1123 patients with type 2 diabetes mellitus, aged between 50-75 years, without known CAD, have been randomized to Tc-99m-sestamibi single photon emission computed tomography (SPECT) imaging and follow-up at 5 years (n=522), or just follow-up at 5 years (n=601). Silent ischemias of some sort, regional perfusion defects or other modifications (e.g. resting left ventricular dysfunction) have been diagnosed in 22% of the patients. The most powerful predictors for an abnormal scan were duration of diabetes and the presence of autonomic neuropathy. The referral for cardiac testing only of patients that met ADA 1998 criteria for screening, would have resulted in missing the diagnosis of silent ischemia in 41% of the patients[7].

Nuclear perfusion scans are especially indicated in patients with known CAD, with moderate positive exercise ECG tests, for quantification of the extension of lesions, stratification of risk for future events and need for revascularisation procedures. They are particularly useful in medium risk patients, where they bring additional data over exercise ECG (13).

The limit of this method is lack of controlled clinical trials for determining its utility especially in the diabetic population.

Stress echocardiography

Pharmacological stress echography uses 2D ultrasonographic study before and after intravenous dobutamine infusion, which augments contractility and myocardial oxygen consumption. It detects regional wall movement abnormalities generated by local ischemia (ischemic areas become hypocontractile), that can be quantified by a simple score. The positive predictive value of this method in the general population is well known (see table 5).

As well as in the case of nuclear perfusion imaging, controlled clinical trials to address its predictive value in the diabetic subpopulation are few. A trial by Sozzi et al certifies the capacity of this method to predict the composite end point of cardiac death or non-fatal MI, in a cohort of 396 diabetics, followed up for 3 years (19).

Exercise ability in diabetic patients is frequently decreased; therefore stress echography could find a place in their evaluation. It must be noted that when pharmacological stress is used, potential important data are lost, data that could be obtained with classical exercise testing: true effort ability of the patient and the angina threshold (12).

New echocardiographic techniques are being evaluated: e.g. myocardial contrast echography, which, on a sample of 128 patients that have been further evaluated angiographically, has proven to be satisfactorily sensible, specific and gave only a few false-positive results in a recent trial (10).

Stress echocardiography is, as any echographic method, highly dependent on operator expertise.

Table 5. Rates of cardiovascular events and catheterisation in accordance with results of stress echocardiography. After Crawford, DiMarco and Paulus, 2004 (8).

	Total	Result (score)			
		Normal (0-3)	Mild abnormal (4-8)	Moderate abnormal (9-13)	Severe abnormal (>13)
Cardiovascular events (% per year)	4,9	1,6	3,5	5,7	10,6
Cardiac deaths (% per year)	6,6	0,9	0,9	3,4	7,4
Emergency catheterisation (%)	14,1	3,8	9,7	23,1	27,2

Non-invasive coronary computed tomographic angiography

This relatively new imaging method employs multislice spiral computed tomography (MSCT) for the assessing of coronary vessels greater than 1,5-2 mm in size. It is a promising diagnostic procedure for the identification of significant coronary stenosis. MSCT angiography was compared in a number of trials with invasive angiography, the present gold standard for the detection of CAD.

In a well conducted prospective study on 243 intermediate-risk patients (the *CACTUS* trial) this method provided a sensitivity of 99%, a negative predictive value of 99% and a specificity of 75% for the detection of CAD when compared to invasive angiography. Only 15,2% of the included patients were diabetics, but the overall population was, as mentioned above, at intermediate-risk of having CAD (11).

A systematic metaanalysis on 27 trials including 1740 patients confirmed the high diagnostic accuracy of MSCT angiography in a variety of clinical settings such as diagnosis of CAD on native coronary arteries, assessing of coronary artery by-pass grafts or coronary stent restenosis (1).

This new imaging method allows both accurate CAD detection, and ruling out, and it is considered a very promising future technique for initial screening of patients suspected of CAD. Direct comparisons between coronary CT angiography and other non-invasive diagnostic modalities are still warranted to prove the superiority of one method over the others.

Limitations of MSCT angiography include the pre-requisite of sinus rhythm, the application of potentially nephrotoxic contrast dyes, and the associated radiation exposure.

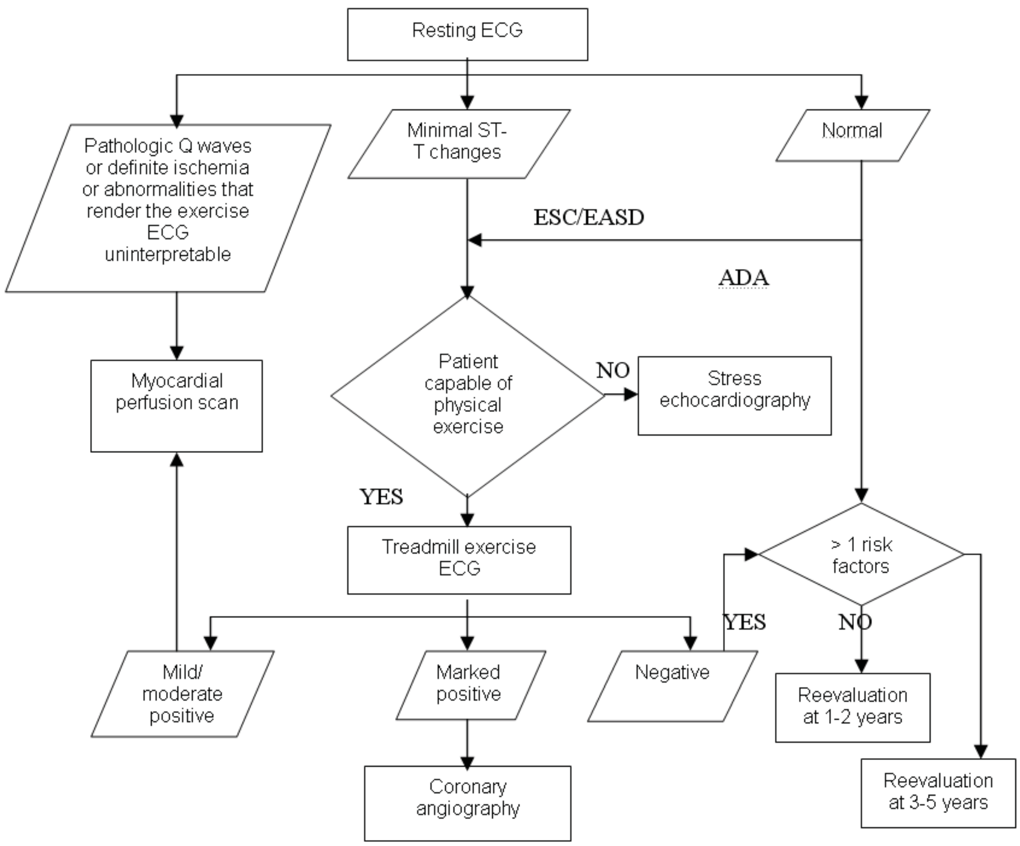

Figure 1. Algorithm for the evaluation of asymptomatic diabetic patients, for diagnosis of CAD and risk stratification.

Evaluation of asymptomatic diabetic patients

As it has been shown above, *symptomatic* diabetic patients with unstable angina, antecedent MI, or angina and HF should be promptly referred to an invasive cardiology unit. The presence of atypical angina recommends exercise ECG testing if no baseline characteristics on the resting ECG that would render it uninterpretable exist (in this case a myocardial perfusion scan or a stress echography would be warranted, in accordance with the individual patient characteristics and clinical experience in the respective institution).

Based on ADA and ESC/EASD recommendations and other data from the literature we propose the algorithm in figure 1 for the purpose of diagnosis and initial evaluation of diabetic *asymptomatic* patients. Cardiac exercise testing in asymptomatic diabetics with normal ECG is warranted when using ESC/EASD guidelines. Some expert opinions recommend the screening of asymptomatic individuals to be considered in those patients in which medical intervention goals could not be met, and in those with a high clinical suspicion of very high risk CAD (6). New methods such as MSCT angiography were not included here because of lack of trials on patients with diabetes, and scarcity of direct comparisons with the other non-invasive methods.

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