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Inappropriate testing for the diagnosis of coronary artery disease

Giuseppe Di Pasquale, Gloria Vassilikì Coutsoumbas, Silvia Zagnoni

Department of Cardiology, Maggiore Hospital, Bologna, Italy

ABSTRACT

In the last three decades also in our country there has been a huge growth in the use of non-invasive testing for diagnosis of coronary artery disease (CAD). Therefore, appropriateness of prescription in diagnostic testing is crucial. Clinical evaluation is mandatory before a diagnostic test, including the evaluation of pre-test probability of the disease based on symptoms, age, sex and cardiovascular risk factors. The main benefit of testing is in patients with an intermediate pre-test probability. Testing for diagnosis of CAD is rarely appropriate in asymptomatic subjects, except for electrocardiogram exercise test in intermediate and high risk individuals, while stress or anatomic imaging is preferable in higher risk individuals. Coronary calcium score should not be used as screening test in asymptomatic subjects, except for excluding CAD in those with low pre-test probability. As far as diabetic patients are concerned, available evidence indicates an unfavorable risk-benefit ratio of extensive CAD screening, except in the presence of high clinical suspicion.

Introduction

The early diagnosis of coronary artery disease (CAD) for a long time has been a major issue, given the high prevalence of CAD in the general population and its burden of mortality and morbidity. The number of non-invasive diagnostic tools has grown up in recent years, but their indiscriminate use not guided by clinical judgement, can give false positive/negative results, generating a cascade of further tests and inappropriate prescriptions with clinical and economic negative implications.

Therefore, appropriateness of prescription in the assessment of CAD is crucial. Reasons for inappropriateness are many. In the general population the awareness of the risk of CAD as a consequence of educational programs aimed to reduce risk factors could generate the request of a screening test to be reassured about the absence of the disease. General practitioners could also inappropriately prescribe diagnostic test as a consequence of patient's claim and of the work overload, with limited time to evaluate the correct indication and pre-test probability of the disease in the individual patient.

In prescribing diagnostic test it is important to evaluate also the risk-benefit ratio correlated to the test itself and related to exertion, use of inotropes and vasodilators, contrast, invasive procedures, radiation's exposure. Particularly, the procedural risk should be carefully evaluated in comparison to the risk related to a delayed diagnosis of CAD.[1] Furthermore, the choice of a diagnostic tool is affected by the local availability and welfare organization.

The perfect diagnostic test should be widely available, with high reproducibility, low incidence of false positive or negative results, low risk and low cost.

The international guidelines point out the available evidence in prescribing diagnostic tests, based on clinical trials, metanalyses and experts' opinion.[1-4]

Correspondence: Giuseppe Di Pasquale, Department of Cardiology, Maggiore Hospital, L.go Bartolo Nigrisoli 2, 40133 Bologna, Italy.
Tel.: +39.051.6478318 - Fax: +39.051.6478635.
E-mail: giuseppe.dipasquale@ausl.bo.it

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Pre-test clinical evaluation

Clinical evaluation is mandatory before a diagnostic test, including the evaluation of pre-test probability (PTP) of the disease based on symptoms, age, sex and cardiovascular risk factors. This dramatically affects the accuracy of the diagnostic test.

The PTP increases with age and in the presence of typical angina, most of all in patients with CAD risk factors. In patients with chest pain, clinical characteristics allow to identify patients at low risk of CAD (PTP<15%), moderate risk (PTP 15-65%), high risk (PTP 66-85%) and very high risk (PTP>85%).[5] In pa-

tients at low risk no diagnostic test for CAD is indicated. In high-risk patients, in whom CAD is almost certain, it is more important to use tests for prognostic stratification rather than a simple test to confirm the diagnosis of CAD.

The main benefit of testing is in patients with an intermediate pre-test probability (PTP 15-85%). In these patients guidelines suggest the use of exercise electrocardiogram (ECG), if feasible, in the moderate risk subgroup (lower PTP) and non-invasive functional test in the high risk subgroup.[2]

Anatomical and morphological tests

Coronary computed tomography angiography

Coronary computed tomography angiography (CTA) is a useful test, considering its high negative predictive value, if no coronary stenoses are detected.[6,7] Even if CTA is a non-invasive test, radiation dose and contrast use is a matter of concern in selecting the diagnostic approach in the single patient. Moreover, coronary CTA is an expensive and not widely available diagnostic test. For these reasons CTA is a useful test especially for patients at low-intermediate PTP.[8] On the contrary, the positive predictive value in high risk population seems to be limited, because of the risk of overdiagnosis in highly calcified coronary stenosis. Coronary CTA could be indicated in patients with intermediate probability of CAD in which stress test results equivocal or contradicts clinical judgment, and in patients with dilative cardiomyopathy and low PTP.[8]

Key message: coronary CTA is not indicated in low risk asymptomatic patients and in patients with high pre-test probability of CAD.

Calcium score

Quantitative evaluation of coronary calcium (CACS) has a high negative predictive value in the diagnosis of CAD. However, recent studies reported that the incidence of false negative is not negligible, ranging from 13 to 18%.[9-11] The amount of calcium correlates to the total amount of atherosclerosis present in the coronary arteries, but correlation with the degree of luminal narrowing is poor. In the absence of prospective trials on the value of CACS in prognostic stratification and also considering the probability of false positive results and the radiation exposure, CACS is not suitable as screening tool for low risk population.

Key message: CACS is not indicated as a screening test in asymptomatic patients and high pre-test probability of CAD for the presence of risk factors.

Coronary angiography

Coronary angiography (CA) represents the gold standard in CAD diagnosis but it is not considered a first-line diagnostic test in stable patients, because of risks related to invasive procedure even if reduced by current techniques such as the radial access. Moreover, the anatomical information derived from CA could be misleading when not supported by a functional assessment in order to identify lesions potentially feasible for revascularization. Furthermore guidelines suggest the use of functional invasive test if the degree of coronary narrowing at CA is equivocal.[12] The use of CA not preceded by functional test could be considered in patients with high clinical suspicion of CAD, in patients who cannot undergo stress imaging techniques or with reduced left ventricular ejection fraction (<50%) and typical angina.[12] CA should not be performed in patients not suitable for percutaneous coronary intervention and coronary artery bypass (irrespective to symptoms) or in whom revascularization is not expected to improve functional status or quality of life.[2]

Key message: the use of CA not preceded by functional test should be considered in selected patients with high clinical suspicion of CAD and without contraindications to coronary revascularization.

Functional tests

Electrocardiogram exercise testing

Exercise ECG is a simple and widespread non-invasive test for CAD detection. For these reasons the test is often overprescribed. The use in asymptomatic patients with low pre-test probability of CAD leads to a high incidence of inconclusive or false positive results with the needs of further tests. On the contrary, in high risk patients a negative result may represent a false negative result with possible dangerous implication. In higher risk populations it should be used only for prognostic purposes. Exercise ECG is recommended as the initial test for establishing diagnosis of CAD in symptomatic patients with intermediate PTP. Therefore guidelines advice against the routine use of exercise ECG in asymptomatic patients, with the exception of sedentary individuals with high risk profile (*i.e.*, diabetes) who want to start physical activity, with a class of recommendation IIb.[13] In a large registry population of 400,000 patients without prior CAD diagnosis, symptoms and clinical risk profile predicted the presence of CAD better than provocative tests.[14]

Exercise ECG has sensitivities between 45-50% and specificities of 85-90%, if all bias are avoided. The main diagnostic criteria during ECG exercise testing consists of horizontal or downsloping ST-segment depression ≥0.1 mV (1 mm), persisting for at least 0.08" after J point, in one or more ECG leads.[15] More lenient interpretation of ECG could be misleading and

reduces test sensitivity. Exercise ECG testing is less sensitive and specific in women.[16] However, a recent randomized trial comparing an initial diagnostic strategy of exercise myocardial perfusion imaging (MPI) with standard treadmill testing in symptomatic women with suspected CAD who were able to exercise, did not show an incremental benefit of MPI strategy on clinical outcome.[17] Moreover ECG exercise test has no diagnostic value in patients with left bundle branch block, paced rhythm and Wolff-Parkinson-White syndrome. False positive results are more frequent in patients with abnormal resting ECG in the presence of left ventricular hypertrophy, electrolyte imbalance and use of digitalis.

Key message: exercise ECG test is not indicated as screening test in asymptomatic low risk patients.

Myocardial perfusion scintigraphy (single photon emission computed tomography and positron emission tomography)

Exercise or pharmacological stress single-photon emission computed tomography (SPECT) testing shows a higher sensitivity and specificity compared to exercise ECG alone (85-90% and 70-75%, respectively).[1] SPECT allows to detect also functional information, such as transient ischemic left ventricular dilation or reduced post-stress ejection fraction, increasing test sensitivity. The use of radiopharmaceuticals makes the test less available and not completely safe, mainly in young people. In a large retrospective study on 39,515 patients who underwent stress-rest SPECT between 1991 and 2009, positive results fall to only 2.9% among patients without typical angina; thus this test is not indicated in asymptomatic patients.[18]

Key message: myocardial SPECT is not indicated in asymptomatic patients and in symptomatic patients with low and intermediate PTP with normal baseline ECG and preserved functional capacity, who are able to perform exercise ECG.

Stress echocardiography

Stress echocardiography has a higher sensitivity and specificity than exercise ECG test (80-85% and 84-86%, respectively); compared to SPECT it avoids biohazards for the patient and the physician.[1] Technical issues must be evaluated when choosing this test: the need of an adequate acoustic window, the involvement of a physician with appropriate expertise, the use of adequate monitoring instruments and the potential risks connected to pharmacological stress make this test less suitable for screening purpose. The advantages of stress echocardiography over SPECT include higher specificity, despite lower sensitivity, in the detection of CAD.[19] Stress echocardiography should be considered for diagnosis of CAD in women with childbearing potential, for the absence of radiations.

Key message: Stress echocardiography is not indicated in asymptomatic patients and in symptomatic patients with low PTP or intermediate PTP with normal baseline ECG and preserved functional capacity.

Electrocardiogram Holter monitoring

ECG Holter monitoring is mainly used for arrhythmias detection, but the use of this test to detect ST segment alterations (particularly in spontaneous angina and silent ischemia) has been widely employed. In practice however, Holter monitoring adds no additional information to exercise tests.[12] Moreover the availability of a limited number of ECG leads in the currently used facilities limits the possibilities of ST segment alterations analysis.

Key message: the use of ECG Holter monitoring as routine test for the diagnosis of CAD should be discouraged.

Detection of coronary artery disease in patients with diabetes

CAD is the major cause of mortality and morbidity in patients with type 2 diabetes, with a risk of cardiovascular events 2-3 fold higher than the general population and comparable to patients with a known diagnosis of CAD.[11] Moreover, CAD can be frequently silent in these patients. For these reasons, the use of test for the detection of CAD in diabetic patients is apparently reasonable. The largest study conducted to compare the extensive research of ischemia with MPI in asymptomatic patients *versus* the standard of care (symptoms driven), is the DIAD study, enrolling 1123 patients.[20] Cardiac event rates were low (2.9% at 4.8 years; P=0.73) and were not significantly reduced by MPI screening for myocardial ischemia over 4.8 years in the two groups (2.7% in MPI group, 3% in standard of care group), confirming the unfavorable risk-benefit ratio of extensive CAD screening in diabetic patients. According to this evidence, the cardiological societies (European Society of Cardiology, American College of Cardiology/American Heart Association) guidelines indicate the use of test for CAD screening with IIa class of recommendation; the American Diabetes Association (ADA) recommends the research of ischemia only in the presence of high clinical suspicion.[21] The use of MPI is preferable because of the prognostic value given by the ischemia extent.[22]

Conclusions

In the last three decades also in our country there has been a huge growth in the use of non-invasive testing for the diagnosis of CAD. The recent widespread

availability of CTA, without rigorous education for appropriate use represents a further threat for inappropriate testing. There is no evidence that the detection of CAD in asymptomatic subjects may have a favourable impact on public health, besides the active treatment of traditional coronary risk factors.

Moreover, an inappropriate use of non-invasive testing for the diagnosis of silent CAD represents a serious burden for the risk of false positive results leading to coronary angiography and in some cases to inappropriate coronary revascularization.

Finally, also the issue of containing health costs with a wise allocation of resources should be considered by the responsible physician in the era of limited resources.

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