ORIGINAL ARTICLE

Searching for the optimal strategy for the diagnosis of stable coronary artery disease. Cost-effectiveness of the new algorithm

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Abstract

Background: *Coronary arteriography is still widely accepted as a gold standard for the diagnosis of coronary artery disease (CAD), despite emerging methods such as multi-slice computed tomography. None of the presently available non-invasive diagnostic tests is perfect. The aim of the article was to make a comparison of the value and limitations of history, resting electrocardiography, exercise electrocardiography and dobutamine stress echocardiography in the diagnosis of CAD, and to create a simple algorithm for non-invasive diagnosis of CAD to optimize indications for coronarography.*

Methods: *Prospective, multicentre trial. The collection of clinical data, resting electrocardiography, exercise treadmill electrocardiography, dobutamine stress echocardiography and catheterization data was performed on 600 patients with chest pain regarded as angina pectoris and no previous history of myocardial infarction. CAD was defined as ≥ 50% narrowing of at least one major vessel. Final results were obtained in 551 patients, 65% male. The studied population was divided into three groups on the basis of pre-test likelihood of CAD: 1. high (> 70%), 2. intermediate (10–70%) and 3. low (< 10%).*

Results: *Sensitivity and specificity of resting electrocardiography, exercise treadmill electrocardiography, dobutamine stress echocardiography and created algorithm were calculated: 23%, 87% and 93%, 21% and 85%, 69% and 96%, 44%, respectively. The prevalence of CAD in the studied population was 61%.*

Conclusions: *The diagnostic value of resting electrocardiography in stable CAD is low. Dobutamine echocardiography has comparable sensitivity but significantly higher specificity than exercise treadmill test. Our algorithm is simple, reasonably cost-effective and may be useful in decision making. When the probability of CAD is high, non-invasive testing is not indicated before coronary angiography; when it is intermediate or low, a first choice test should be different in female (stress echocardiography) and male (exercise electrocardiography).* (Cardiol J 2007; 14: 544–551)

Key words: coronary artery disease, cost-effectiveness, diagnosis

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Introduction

Coronary arteriography is widely accepted as a gold standard for the diagnosis of coronary artery disease (CAD) and the evaluation of the extent and severity of vessel stenoses. Non-invasive diagnostic tests detect the consequences of ischemia: impaired cell membrane function, decreased perfusion and impaired myocardial contractility. None of these techniques e.g. single-photon emission computed tomography (SPECT), positron emission tomography (PET), exercise electrocardiography (ET), stress echocardiography (DE) and others is perfect [1–3]. Some of these methods are useless since up to 40% of patients are unfit for adequate exercise [4], some are expensive and thus discussed in terms of cost-effectiveness ratio and some patients undergoing a non-invasive test have an indeterminate result (indeterminacy rate is up to 40% for exercise electrocardiography and up to 10% for exercise echocardiography) [5]. For patients presenting with chest pain regarded as angina pectoris, estimation of the probability of the disease is a crucial issue [6]. This clinical evaluation helps the physician to choose the optimal non-invasive diagnostic technique, or when the probability of CAD is high, some clinicians regard coronary angiography as a single reasonable strategy without prior testing. On the other hand, the use of coronary angiography routinely as a first-choice test is not accepted due to the risk of complications and death and its obviously high costs.

On the basis of the remarks above, we decided to analyse the value of different non-invasive techniques used in CAD diagnosis, to compare them and to optimize indications for cardiac catheterization. Many algorithms and nomograms have been created for this purpose, but they are time consuming, complicated, difficult to apply at the patient's bedside and often require a computer, so clinicians are sceptical about using them [7–11]. Our goal was to create a simple diagnostic algorithm useful in clinical practice for patients complaining of chest pain, and to estimate its value by comparing cost-effectiveness with routine non-invasive strategies.

Methods

Materials

Five hundred fifty one patients (49 cases were excluded from 600 due to lack of full data): 359 men (65%, mean age 51.1 ± 8.9) and 192 women (35%, mean age 53.1 ± 8.9) with chest pain suspected of CAD were referred by general practitioners. All enrolled patients subsequently underwent coronary angiography. Patients with previous myocardial infarction (Q wave on ECG), unstable angina, severe heart failure > II NYHA class, significant valve heart disease, cardiomyopathy, uncontrolled hypertension (BP $\geq$ 200/ /100 mm Hg) and permanent ventricular pacing were excluded. The characteristics of the study group are given in Table 1.

Table 1. Characteristics of the study groups.

	Coronary artery disease (+) (n = 336)	Coronary artery disease (–) (n = 215)	p
Male (n = 359)	268 (80%)	91 (42%)	< 0.001
Female (n = 192)	68 (20%)	124 (58%)	
Mean age (years)	53.3 ± 8.6	49.6 ± 8.9	< 0.001
Body mass index [kg/m^2]	26.5 ± 3.4	25.9 ± 3.1	NS
Cigarette smoking (n = 262)	194 (58%)	68 (32%)	< 0.001
Family history of atherosclerosis (n = 222)	143 (43%)	79 (37%)	NS
Diabetes (n = 59)	43 (13%)	16 (7%)	< 0.05
Hyperlipidemia (n = 295)	197 (59%)	98 (46%)	< 0.001
Total cholesterol	236 ± 45	220 ± 41	0.001
LDL cholesterol	159 ± 40	146 ± 65	< 0.05
HDL cholesterol	40 ± 12	45 ± 12	< 0.001
Triglycerides	173 ± 82	161 ± 95	NS
Peripheral or cerebral vascular disease (n = 16)	13 (4%)	3 (1%)	< 0.05
Hypertension (n = 298)	189 (56%)	109 (51%)	NS
Duodenal or gastric ulcer (n = 74)	41 (12%)	33 (15%)	NS
Mitral valve prolapse (n = 30)	9 (3%)	21 (10%)	< 0.005
Degenerative spondylopathy (n = 72)	31 (9%)	41 (19%)	0.001

History

On the basis of history analysis the pre-test probability of CAD was assessed. For chest pain classification a special questionnaire was used with three categories: typical, atypical or nonanginal chest pain as proposed by Diamond and Forrester [12]. The likelihood of CAD was estimated on the combination of age, sex and date of symptoms according to Diamond and Forrester's results [12, 13].

Resting electrocardiography

The resting routine electrocardiogram (ECG) was interpreted by two cardiologists independently and assigned to one of three categories: normal, nonspecific abnormalities or typical ischemia pattern [14].

Exercise stress test

Symptom limited treadmill exercise electrocardiography was performed with the use of the Bruce protocol. Classic criteria for test positivity were used, that is more than 0.1 mV or equal of ST segment depression from baseline horizontal or downsloping at 0.08 seconds from the J point. The patients taking beta-blocking agents or calcium antagonists were instructed to stop medication 72 hours before the test, but if the treatment was regarded as necessary by the referring physician it was continued. The exercise was considered adequate if the patient achieved 85% of the age-predicted maximal heart rate. During the exercise test a 12 lead electrocardiogram was monitored continuously. Blood pressure was measured at baseline and at 1.5-minute intervals during the exercise and for 3 minutes after its termination. The exercise electrocardiography test result was regarded as non-diagnostic if the criterion for electrocardiographic positivity was not present without obtaining 85% of the target heart rate [15].

Dobutamine stress echocardiography

Baseline echocardiography and electrocardiography were performed. Dobutamine was infused through a peripheral intravenous line with a mechanical pump starting at a dose of 5 μg/kg/min. The dose was increased every 3 minutes by 5 μg/kg/min. The end point of the test was the achievement of the peak dose 40 μg/kg/min, 85% of the target heart rate. If this rate was not reached, atropine (0.5–1 mg) was infused. Cross sectional echocardiographic examination was performed during drug infusion and up to 10 minutes after the infusion was stopped. Dobutamine infusion was terminated if any of the following occurred: target heart rate, new segmental wall motion abnormalities, complex ventricular ectopy or sustained supraventricular tachycardia, hypotension ($\geq$ 20 mm Hg decrease from baseline), hypertension (systolic BP $\geq$ 220 mm Hg), severe chest pain or other intolerable symptoms [16–18]. A 12-lead ECG was recorded at the end of each 5-minute stage and at recovery. The left ventricle was divided into 16 segments for analysis as recommended by the American Society of Echocardiography. The ischemia was defined as new or worsening wall motion abnormalities. Dobutamine stress echocardiography test results were regarded as non-diagnostic if the target heart rate was lower than 85%. Patients with an insufficient 'acoustic' window were not included in the study.

Coronary angiography

All patients underwent selective coronary angiography (CA) by the Judkins technique with multiple projections. Images were recorded on cine film. Significant coronary artery disease was defined as > 50% in a major epicardial artery (in one or more of the major vessels or in their main branches: diagonal branch of left anterior descending marginal branch of the left circumflex coronary artery and posterior descending branch were regarded as separate vessels) or $\geq$ 50% in the left main artery. When an intermedius artery was present, it was considered equivalent to the major diagonal branch of left anterior descending [19]. CA was performed within 8 weeks of non-invasive tests, irrespective of the obtained results, and was evaluated qualitatively by two independent and experienced physicians.

Statistical analysis

The comparison of pre-test probability of CAD in the studied population and in Diamond-Forrester's group was performed [12]. For correlation, the Pearson correlation coefficient was applied (r = 0.85).

The accuracy of non-invasive tests with the use of coronary angiography as the reference method was made in the standard way, calculating sensitivity and specificity according to standard definitions. Continuous variables were expressed as mean (SD) and were compared by the Student's T-test. Qualitative variables were expressed as percentages and were compared with the χ^2 test. The Fisher test was used when indicated. Statistical significance was set at a probability (p) value of < 0.05.

Development of the algorithm

After the calculation of the sensitivity and specificity of the exercise stress test and dobutamine echocardiography, on the basis of Bayes theorem

Table 2. Comparison of the sensitivity and specificity of electrocardiography (ECG), exercise treadmill test (ET), dobutamine echocardiography (DE) and algorithm.

Study	Sensitivity (%)			Specificity (%)		
	Female (n = 68)	Male (n = 268)	All patients (n = 336)	Female (n = 124)	Male (n = 91)	All patients (n = 215)
ECG	33	20	23	81	93	87
ET	91	94	93	16	27	21
DE	79	87	85	71	66	69
The algorithm (A)	88	99	96	55	30	44
p — ET *vs*. DE	NS	< 0.05	< 0.005	< 0.0001	< 0.0001	< 0.0001
p — A *vs*. ET	NS	< 0.05	NS	< 0.0001	NS	< 0.0001
p — A *vs*. DE	NS	< 0.0001	< 0.0001	< 0.05	< 0.001	< 0.0001

of conditional probability, the post-test likelihood of CAD was estimated by using equations given in the appendix. ET and DE were regarded as independent tests and the post-test probability of CAD calculated from the former became the pre-test likelihood for the second test. On the basis of pre-test variables (age, gender, symptoms-Diamond classification) and the results of one or two non-invasive tests, the algorithm was developed by applying a computer program. The algorithm was modified to achieve a model of the best sensitivity and acceptable specificity. Our goal was to make a simple algorithm applying a combination of clinically relevant data, not requiring a computer and easy to use for the physician. The derived algorithm was tested in the studied population, and the percentage of patients correctly classified was calculated and compared to traditional non-invasive testing based on the exercise stress test and dobutamine echocardiography. In the proposed algorithm, the pre-test likelihood of CAD was arbitrarily divided into three groups: low (< 10%), intermediate (10–70%) and high ≥ 70% [20, 21], intermediate in men divided into intermediate-high: 30–70% and intermediate-low: 10–29%.

After calculation of the probability of CAD based on age, gender and chest pain classification, 2% was added for each risk factor in the history and 5% was added for the presence of changes typical of ischemia in resting ECG in men. This method was implemented in other studies and was concordant with results of the analysis of the value of resting ECG in our population [14]. This approach is based on the assumption that if a given patient has risk factors typical of CAD, a more aggressive diagnostic strategy is required.

The study was approved by the National Institute of Cardiology Ethical Committee on Human Research in Warsaw. Informed, written consent was obtained from each patient. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Results

The results of the sensitivity and specificity of ECG, ET, DE and algorithms are shown in Table 2. The created algorithms for women and men are shown in Figure 1. Cost-effectiveness analysis for five different strategies of CAD diagnosis is presented in Figure 2. The calculation is based on cost-data of the Polish National Health Fund (26, 138 and 320 Euro for ET, DE and CA, respectively). Reimbursements for these procedures include technical and professional components.

The strategy called 'Angio' assumes the performance of coronary angiography in each patient suspected of CAD regardless of the other tests and pre-test probability.

The second and the third strategies, called ET and DE, make use of only one non-invasive test, i.e. exercise treadmill electrocardiography or dobutamine echocardiography, respectively.

The fourth strategy (DE + ET) is based on the results of two tests, i.e. DE and ET, performed independently. Coronary angiography is not performed only if the results of these two tests are negative. If the results are discordant or positively concordant, patients undergo coronary angiography.

The fifth strategy, based on the probability analysis, implements an algorithm derived from our study. An algorithm, based on probability analysis and the strategy called 'angio' without prior non-invasive testing, resulted in reasonable cost-effectiveness ratios. The per-test cost of DE exceeds that of ET, but the total cost of strategy per correctly diagnosed patient using DE and ET in
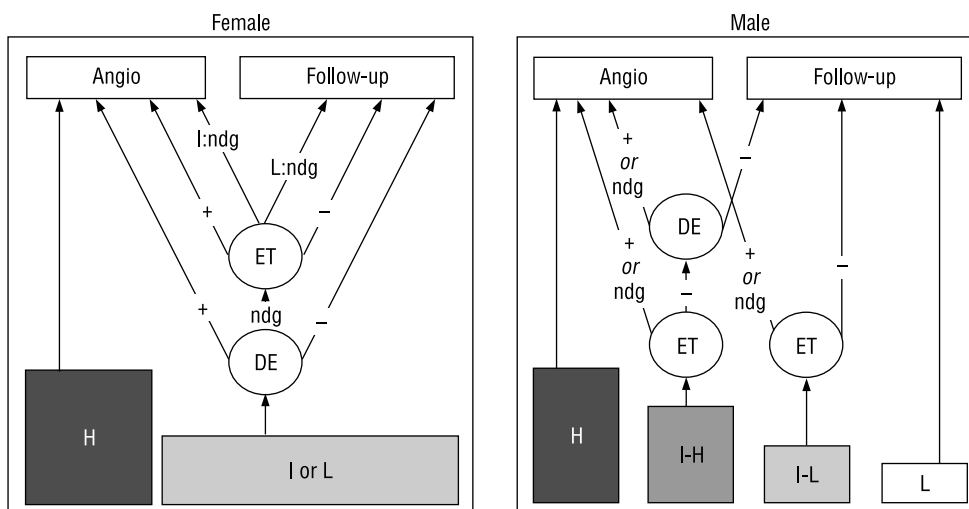
Figure 1. Algorithms for coronary artery disease diagnosis. Pre-test probability of coronary artery deisease: H — high, I — intermediate, L — low, I-H — intermediate-high, I-L — intermediate-low. Diagnostic tests: DE — dobutamine stress echocardiography, ET — exercise stress test, + positive test result, – negative test result, ndg — non--diagnostic test result.
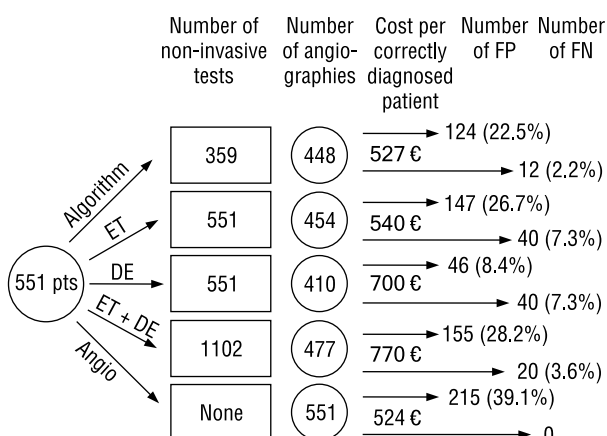

Figure 2. Comparison of different strategies in coronary artery disease diagnosis based on coronary angiography (CA), exercise stress test (ET), dobutamine stress echocardiography (DE) and the algorithm derived in the study; FP — false positive, FN — false negative.

association with pre-test probability (algorithm) is about the same as the cost of ET strategy with greater accuracy and less than the cost of DE implemented first. The total cost of this strategy that implicates DE first is less than the cost of exercise testing and, subsequently, echocardiography.

Discussion

It is widely accepted and proved in many trials that non-invasive tests performed for diagnostic purposes are almost useless in populations with very high or very low probabilities of the disease [22]. Nevertheless, clinical routine is different. Many physicians think of non-invasive techniques as good tools to screen for CAD. Before sending a patient for ET, for example, one should answer the question of whether the management would be changed by a positive or negative test result. One must keep in mind data from the CASS [23] showing that with high probability of CAD in the population, the incidence of false negative results is highest. Therefore, if the test is negative in a certain patient whose symptoms are typical of angina, indications for catheterization are obvious. On the other hand, if the ET test is positive in young women with atypical chest pain (that is with low probability of CAD), we know that the proportion of angiography studies performed in such a situation often reveal normal coronary arteries [24].

The spectrum of new medical diagnostic technologies today gives physicians an opportunity to use different tests on one patient [25]. Sometimes results of two or even more tests are discordant, so the diagnosis is still uncertain, forcing the physician to use a new test or to decide to use a gold standard method, which in the diagnosis of CAD is still angiography. This situation leads to high expense; the process of diagnosis is time-consuming and, what is often forgotten, increases patient anxiety. Our results document the clinical applicability of the above-mentioned remarks.

Sensitivity of ET in our study is concordant with mean values found in the biggest meta-analyses, but the specificity is surprisingly low (85% of women with positive ST response had normal coronary arteries) [1]. This gave us the idea that the diagnostic CAD strategy in women based on exercise testing as a first-choice test leads to worse results. High sensitivity and very low specificity of ET can be explained by the fact that patients with previously positive tests are more frequently referred for catheterization. The studied population probably reflects post-test referral bias, because we do not know if the ET performed in this study was the first in the patient's lifetime [15]. Of course, patients with heart disease other than CAD, which might predispose them to false positive results, were excluded, but subclinical ventricular hypertrophy due to treated hypertension might also be the reason for the low specificity of ET. Using different criteria for positive ET (i.e. more than 1 mm ST depression), an investigator can get greater specificity and slightly lower sensitivity. Several currently available tests for non-invasive diagnosis of CAD are more accurate than traditional exercise electrocardiography, i.e. SPECT or PET, but they are also more expensive and thus their clinical use is limited.

Sensitivity and specificity of DE are satisfactory and concordant with different publications [26]. Values obtained for these two techniques (DE and ET) are typical of the clinical practice in our country; they are based on the biggest prospective trial in this field in Poland. Echocardiography is more physician dependent; nevertheless, it possesses higher sensitivity and specificity. A unique feature of DE is the detection of forms of heart disease other than CAD associated with chest pain (hypertrophic cardiomyopathy, mitral valve prolapse). This method is even superior to angiography for the prediction of subsequent cardiac events [18].

Dobutamine echocardiography is two times more expensive than ET, so it should be reserved for cases difficult to diagnose [27]. We decided to use it for women and only for those men in whom the probability of CAD is < 70% (intermediate or low), while ET is good enough as a first-choice test in men.

Our algorithm is characterised very good sensitivity and acceptable specificity. In patient subgroups with a high probability of CAD, we found coronary angiography without previous non-invasive testing successful in terms of the correctness of the diagnosis and reasonably cost-effective. This is a lower cost testing strategy than the algorithm but the cost difference is negligible. The application of our scheme reduces the amount of angiographies by 19%. We propose to use the non-invasive diagnostic testing in cases of a moderate risk of CAD (when the probability is intermediate or low). A first-choice test should be different in women-DE and men-ET. Detection of CAD in women is more difficult due to lower prevalence of the disease in the population at the same age. In addition, chest pain symptomatology differs between women and men. So the pre-test probability of CAD should be considered first [28, 29]. Guidelines for the management of patients with CAD suspicion stratify the probability of disease into three groups, i.e. low, intermediate and high. Within the literature are found numerous models; the cut-off points between probability groups are drawn arbitrarily [20, 21].

Dobutamine echocardiography and the derived algorithm have been shown to be superior to exercise electrocardiography in diagnostic performance [30–33]. An important limitation of this study is the relatively small number of women in comparison with that of men. We analysed 12 false negative cases for CAD diagnosis after application of the algorithm. Even if the result was false-negative, the extent of jeopardized myocardium was relatively small (angiography revealed small coronary branch stenosis, or significant stenosis was present in the distal part of the major artery).

We welcome future evaluation of the proposed algorithm in different populations.

Appendix

The probability of coronary artery disease in a patient with a positive test was calculated by the equation:

$$P\,(CAD/_{T+}) = \frac{Sensitivity \times Prevalence}{(Sensitivity \times Prevalence) + (1 - Specificity) \times (1 - Prevalence)}$$

The probability of coronary artery disease in a patient with a negative test was calculated by the equation:

$$P\,(CAD/_{T-}) = \frac{(1 - Sensitivity) \times Prevalence}{(1 - Sensitivity) \times Prevalence + Specificity \times (1 - Prevalence)}$$

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