Efficacy of Patient Selection for Diagnostic Coronary Angiography in Suspected Coronary Artery Disease

Francisco Flávio Costa Filho, Áurea Jacob Chaves, Lourenço Teixeira Ligabó, Eduardo Moreira dos Santos, Danillo Taiguara da Silva, Marcelo Aguiar Puzzi, Sérgio Luiz Braga, Alexandre Abizaid, Amanda GMR Sousa
Instituto Dante Pazzanese de Cardiologia, São Paulo, SP – Brazil

Abstract

Background: **Guidelines recommend that in suspected stable coronary artery disease (CAD), a clinical (non-invasive) evaluation should be performed before coronary angiography.**

Objective: **We assessed the efficacy of patient selection for coronary angiography in suspected stable CAD.**

Methods: **We prospectively selected consecutive patients without known CAD, referred to a high-volume tertiary center. Demographic characteristics, risk factors, symptoms and non-invasive test results were correlated to the presence of obstructive CAD. We estimated the CAD probability based on available clinical data and the incremental diagnostic value of previous non-invasive tests.**

Results: **A total of 830 patients were included; median age was 61 years, 49.3% were males, 81% had hypertension and 35.5% were diabetics. Non-invasive tests were performed in 64.8% of the patients. At coronary angiography, 23.8% of the patients had obstructive CAD. The independent predictors for obstructive CAD were: male gender (odds ratio [OR], 3.95; confidence interval [CI] 95%, 2.70 - 5.77), age (OR for 5 years increment, 1.15; CI 95%, 1.06 - 1.26), diabetes (OR, 2.01; CI 95%, 1.40 - 2.90), dyslipidemia (OR, 2.02; CI 95%, 1.32 - 3.07), typical angina (OR, 2.92; CI 95%, 1.77 - 4.83) and previous non-invasive test (OR 1.54; CI 95% 1.05 - 2.27).**

Conclusions: **In this study, less than a quarter of the patients referred for coronary angiography with suspected CAD had the diagnosis confirmed. A better clinical and non-invasive assessment is necessary, to improve the efficacy of patient selection for coronary angiography. (Arq Bras Cardiol. 2015; 105(5):466-471)**

Keywords: **Coronary Artery Disease; Cardiac Catheterization; Patient Selection; Efficacy.**

Introduction

Despite major advances in the identification of risk factors and diagnostic approach, defining the presence of coronary artery disease (CAD) with significant obstruction using only clinical and noninvasive methods, is often a difficult task for the physician. It is well known that the standard procedure for studying the coronary anatomy is the coronary angiography. Nevertheless, this test should be judiciously requested, as it is an invasive procedure and not free from complications[1].

For patients in stable clinical condition, the current guidelines recommend straight forward coronary angiography in those considered to have a high probability of CAD, and clinical follow-up in those with low probability of CAD[2-4]. However, the majority of patients are classified as having an intermediate probability of CAD and, in these cases the need for the invasive procedure is subject to the non-invasive test results or the assistant physician's judgment.

In a recent North-American Registry[5], only 37.6% of the stable patients without previous CAD diagnosis and referred for coronary angiography had significant obstructive lesions, suggesting that better risk stratification strategies are needed. As far as we know, there are no such data available in Brazil.

The objective of the present study is to analyze, in a population of consecutive patients, the efficacy of patient selection for coronary angiography for suspected stable CAD. Moreover, we aim to estimate obstructive CAD probability based on available clinical data before the invasive procedure, as well as determine the incremental diagnostic value of previous non-invasive tests.

Methods

Design

This is a cross-sectional observational study that collected prospective data from consecutive patients referred by physicians from centers included in the Brazilian Unified Health System (*Sistema Único de Saúde* - SUS) network to a tertiary cardiology center to undergo coronary angiography between July 2012 and January 2013.

Mailing Address: Francisco Flavio Costa Filho •
Av. Dr. Dante Pazzanese, 500, Ibirapuera. Postal Code 04012-909, São Paulo, SP – Brazil
Email: flavioamerica@yahoo.com.br
Manuscript received March 11, 2015; manuscript revised April 20, 2015; accepted June 11, 2015.

DOI: 10.5935/abc.20150099

Study Population

The eligible patients had suspected stable obstructive CAD, and were electively referred for coronary angiography. Patients with ongoing acute coronary syndromes (ACS), patients with ≥ 50% obstruction in a previous coronary angiography, patients with a history of myocardial infarction, surgical or percutaneous myocardial revascularization were excluded. We also excluded patients who were being evaluated for valvular surgery or heart transplantation.

The information on demographic characteristics, risk factors for CAD, symptoms and the results of non-invasive tests were collected by a team of cardiologists before coronary angiography was performed.

Symptoms were categorized as typical angina, atypical chest pain, ischemic equivalent or no symptoms. The typical angina was defined as (1) substernal chest pain or discomfort that is (2) caused by exertion or emotional stress and (3) relieved by rest and/or nitroglycerine. Atypical chest pain included patients with atypical angina (only two out of the above mentioned criteria) and those with non-anginal chest pain (one or none of the above mentioned criteria)[6,7]. Ischemic equivalents were considered as any collection of clinical findings (dyspnea, dizziness, arrhythmias) that the physician thought to be consistent with obstructive CAD.

The presence or absence of classical risk factors for CAD was established according to the patients´ information. Non-invasive diagnostic tests were considered to be any test suggesting ischemic disease, performed before the coronary angiography, such as resting electrocardiogram, ECG stress testing, myocardial radionuclide imaging, rest or stress echocardiogram, or coronary computed tomography angiography.

Obstructive Artery Disease

Obstructive CAD was defined as stenosis ≥ 70% in a major epicardial vessel or its branches, or ≥ 50% in the left main coronary artery, according to recommendations from AHA/ACC[6,8].

Statistical Analysis

Baseline demographic characteristics, risk factors for CAD, symptoms and non-invasive test results of patients with or without obstructive CAD were compared. The continuous variables were presented as medians and interquartile ranges; the categorical variables were presented as absolute numbers and percentages. The continuous variables were compared using the non-parametric Mann-Whitney test and the categorical variables were compared using the chi-square test.

Models for logistic regression (univariate and multivariate analysis) were adjusted to identify associated factors and independent predictors for obstructive CAD. The variables with $p < 0.10$ in the univariate analysis were selected for the multivariate analysis. To assess if the risk factors and the performance of previous non-invasive tests had any incremental power for predicting the presence of obstructive CAD, three models were considered: a basic model (with gender, age and symptoms); a clinical model, which is the basic model added by risk factors (diabetes, dyslipidemia, hypertension, and smoking); and a third model called the extended model, which adds the performance of previous non-invasive tests to the clinical model. The area under the ROC (receiver operating characteristics) curve was used to compare the discriminatory capacity of the 3 models and a non-parametric test was used to compare the values of the statistical C among the models[9].

P values < 0.05 were considered statistically significant in the multivariate analysis. Statistical analyses were performed using the software SPSS for Windows version 13.0.

Ethical Aspects

This study was approved by the Institutional Ethics Committee (protocol number 4250).

Results

Between July 2012 and January 2013, 3,817 coronary angiographies were performed at the Invasive Cardiology Service of *Instituto Dante Pazzanese de Cardiologia*, which had been requested by 118 different centers of the SUS network. Of these patients, 2,987 (78.3%) were excluded from this analysis, as the test had been requested during ongoing ACS, for patients with a previous diagnosis of CAD, or for pre-surgical assessment for heart surgery. Our study analyzed 830 patients submitted to elective coronary angiography with suspected obstructive CAD, which represented 21.7% of all patients referred for coronary angiography during this period.

Baseline Characteristics

The median age was 61 years (interquartile interval 54 – 69 years), and 49.3% of the patients were males. The prevalence of hypertension was 81.0%, dyslipidemia was 66.6%, diabetes was 35.5% and 16.5% of them declared being current smokers (Table 1).

Of the patients referred for coronary angiography, 33.5% had typical angina, 23.9% had atypical chest pain (atypical angina or non-anginal chest pain), a similar proportion, 23.9%, had ischemic equivalent symptoms (dyspnea, dizziness, arrhythmias), and 18.8% had no symptoms.

It was observed that 538 patients (64.8%) had been submitted to non-invasive diagnostic tests before the coronary angiography, but only 464 of them (55.9%) had undergone cardiac stress tests (ECG stress testing, stress echocardiography, and radionuclide stress myocardial perfusion imaging). The most frequently performed test was the ECG stress testing, in 32.5% of them.

Prevalence of Obstructive Coronary Artery Disease

Obstructive CAD (stenosis ≥ 50% on the left main coronary artery, or ≥ 70% in a major epicardial vessel) was found in only 198 (23.8%) patients. Of these patients, 54.5% had single–vessel disease, 27.8% had two–vessel disease, 13.1% had three–vessel disease lesions, and 5.6% had a significant lesion in the left main coronary artery. Considering

Table 1 – Baseline Characteristics of the patients

Characteristic	Total
	n = 830
Age, years	
Median	61
Interquartile range	54-69
Male gender, n (%)	409 (49.3)
Body mass index, kg/m2	
Median	27.8
Interquartile	24.9-31.2
Smoking, n (%)	
Current	137 (16.5)
Former	318 (38.1)
Diabetes, n (%)	295 (35.5)
Hypertension, n (%)	672 (81.0)
Dyslipidemia, n (%)	553 (66.6)
Creatinine clearance *, mg/dL	
Median	83.2
Interquartile range	64.0-103.9
Peripheral arterial disease, n (%)	23 (2.8)
Cerebrovascular disease, n (%)	20 (2.4)
Chronic obstructive pulmonary disease, n (%)	76 (9.2)
Clinical presentation, n (%)	
No symptoms	156 (18.8)
Typical angina	277 (33.5)
Atypical chest pain †	198 (23.9)
Ischemic equivalent ‡	198 (23.9)
Non-invasive diagnostic test §, n (%)	538 (64.8)
ECG Stress testing	270 (32.5)
Myocardial radionuclide imaging	182 (21.9)
Stress echocardiography	12 (1.4)
Computed tomography coronary angiography	9 (1.1)
Resting electrocardiogram	30 (3.6)
Resting echocardiography	33 (4.0)

**Cockcroft-Gault formula was used to estimate creatinine clearance. †Atypical symptoms were defined as atypical angina and non-anginal chest pain. ‡ Ischemic equivalent was defined as dyspnea, dizziness or arrhythmias. § Resting electrocardiogram, resting echocardiography, computed tomography coronary angiography, ECG stress testing, myocardial radionuclide imaging or stress echocardiography.*

the alternative definition of obstructive CAD as a lesion with stenosis ≥ 50% in any epicardial vessel, the prevalence increased to 32.2%. Therefore, two thirds (67.8%) of the patients submitted to the invasive coronary angiography for suspected stable obstructive CAD did not have significant lesions at the coronary angiography.

Predictors for the Obstructive Coronary Artery Disease

The univariate analysis showed 6 variables significantly associated ($p < 0.10$) with the presence of obstructive CAD: age, male gender, diabetes, dyslipidemia, presence of typical angina, and having undergone some previous non-invasive test. The patients that reported arterial hypertension (OR, 1.23; CI 95% 0.81 – 1.88, p = 0.33) or current smoking (OR, 1.06; CI 95% 0.70 – 1.63, p = 0.77) were associated with a greater probability of obstructive CAD, but without statistical significance.

In the multivariate analysis (Table 2), male gender (OR, 3.95; CI 95%, 2.70 – 5.77, $p < 0.001$), age (OR for each 5 incremental years, 1.15; CI 95%, 1.06 – 1.26, p = 0.002), diabetes (OR, 2.01; C I 95%, 1.40 – 2.90, $p < 0.001$), dyslipidemia (OR, 2.02; CI 95%, 1.32 – 3.07, $p < 0.001$), typical angina (OR, 2.92; CI 95%, 1.77 – 4.83, $p < 0.001$), and having undergone some non-invasive test (OR, 1.54; CI 95%, 1.05 – 2.27, p = 0.027), were shown to be independent predictors for obstructive CAD.

Models for Predicting CAD

Table 3 summarizes the performance of each of the 3 prediction models. The basic model, which only uses the clinical variables age, gender and the presence of typical angina, showed a statistical C of 0.703 (CI 95%, 0.652 – 0.0754). The clinical model, which added the presence of risk factors (diabetes, dyslipidemia, hypertension, and active smoking) to the basic model, had a statistical C of 0.728 (CI 95%, 0.678 – 0.778). The third model, the extended one, which added the performance of non-invasive tests to the clinical model, revealed a statistical C of 0.739 (CI 95%, 0.701 – 0.778). The comparative analysis of the area under the ROC curve did not show any significant difference among them (Table 4).

Discussion

In this study, which included patients without known CAD submitted to coronary angiography, the efficacy of patient selection for coronary angiography was low.

Table 2 – Predictors of obstructive CAD (stenosis ≥ 50% in left main coronary artery or ≥ 70% any epicardial vessels)

Variable	Odds Ratio	Confidence interval 95%	p Value
Age, every 5 years increase	1.15	1.06-1.26	0.002
Male gender	3.95	2.70-5.77	< 0.001
Diabetes	2.01	1.40-2.90	< 0.001
Dyslipidemia	2.02	1.32-3.07	0.001
Typical angina*	2.92	1.77-4.83	< 0.001
Non-invasive diagnostic test †	1.54	1.05-2.27	0.027

**Compared with asymptomatic patients. † Resting electrocardiogram, resting echocardiography, computed tomography coronary angiography, ECG stress testing, myocardial radionuclide imaging or stress echocardiography.*

Table 3 – Odds ratio and 95% confidence intervals of the prediction model for the presence of obstructive CAD (stenosis ≥ 50% in left main coronary artery or ≥ 70% any epicardial vessels)

	Basic Model	Clinical Model	Extended Model
Age by 5 years	1.09 (0.98-1.21)	1.07 (0.96-1.20)	1.07 (0.96-1.20)
Male gender	4.31 (2.69- 6.90)	4.44 (2.75-7.18)	4.39 (2.71-7.10)
Typical angina	3.00 (1.83- 4.94)	2.80 (1.68- 4.69)	2.94 (1.75-4.93)
Diabetes	-	1.90 (1.20- 3.02)	1.91 (1.20-3.03)
Dyslipidemia	-	1.80 (1.06- 3.07)	1.82 (1.07- 3.10)
Hypertension	-	0.66 (0.36- 1.22)	0.66 (0.36-1.20)
Current smoker	-	0.90 (0.48- 1.70)	0.92 (0.49- 1.75)
Non-invasive diagnostic test*	-	-	1.43 (0.87- 2.34)
C statistic	0.703 (0.652 a 0.754)	0.728 (0.678 a 0.778)	0.739 (0.701 a 0.778)

** Resting electrocardiography, resting echocardiography, computed tomography coronary angiography, ECG stress testing, myocardial radionuclide imaging or stress echocardiography*

Table 4 – Comparison of areas under the ROC curve between the basic, clinical and extended models

Model	p Value
Basic* *versus* clinical†	0.12
Basic *versus* extended‡	0.09
Clinical *versus* extended	0.62

** Basic model: gender, age, stable angina. † Clinical model: gender, age, stable angina, hypertension, diabetes, current smoker and dyslipidemia. ‡ Extended model: gender, age, stable angina, hypertension, diabetes, current smoker, dyslipidemia and any previous non-invasive diagnostic test.*

Of the 830 patients assessed for suspected clinical significant CAD (stenosis ≥ 50% in the left main coronary artery or ≥ 70% on any other epicardial vessel), only 198 (23.9%) had this hypothesis confirmed by the coronary angiography. The percentage was a little higher (32.3%) when the CAD definition was expanded to include stenosis ≥ 50% in any other epicardial vessel. In approximately two thirds of the patients (67.7%), coronary angiography revealed coronaries without any obstructive atherosclerotic process.

The comparison of our results with the ones found in other studies is difficult because of the different definitions used for obstructive CAD, as well as different inclusion criteria. Most previous publications report information on populations from high-income countries, and just a few of them were carried out in middle-income countries, such as Brazil. Galon et al[10] conducted an overview of the clinical-angiographic profile of 1,282 patients submitted to 1,410 coronary angiographies in São Paulo, Brazil, between March 2007 and May 2008. In this study, 72.7% of the procedures showed coronary arteries with significant obstructive lesion. However, approximately half of the patients submitted to coronary angiography had ACS, and 16% had already been diagnosed for previous CAD. Besides that, the authors considered obstructive CAD as the presence of lesions with stenosis ≥ 50%.

The CASS (Coronary Artery Surgery Study) Registry, published in 1986, involving 21,487 coronary angiographies, showed that 81.2% of the patients had a coronary obstruction, defined as a lesion ≥ 50% in any vessel[11]. More recently, Patel et al[5] published a registry with 398,978 patients without a previous CAD diagnosis, in the absence of ACS, submitted to coronary angiography in 663 hospitals, between January 2004 and April 2008. As in our study, the presence of obstructive CAD (stenosis ≥70%) found was low (37.6%). Absence of coronary disease was found in 39.2% of the patients.

Not surprisingly, we observed that the stronger independent predictors for the presence of obstructive CAD at the coronary angiography were the traditional risk factors age, male gender, presence of diabetes and dyslipidemia, in addition to the presence of typical angina. On the other hand, in our study, reported arterial hypertension and smoking did not show any association with obstructive CAD in the univariate analysis. Regarding hypertension, a possible explanation could have been the high prevalence detected in our sample in both groups. As for smoking, it was assessed only qualitatively through patient reports, whereas quantitative characteristics such as exposure time and intensity of consumption were not considered.

It is well known that non-invasive tests are useful tools for the decision-making process in daily clinical practice, due to its important negative predictive value in patient populations with intermediate pre-test probability[2], preventing these individuals from being unnecessarily exposed to the risks of the invasive test.

In our study, we observed that approximately 35% of the individuals were directly referred to coronary angiography, without any previous non-invasive tests. This percentage represents approximately twice the one found by Patel (16%)[5]. Many are the possible reasons for, in the SUS network context, a patient with suspected stable CAD to be directly referred to coronary angiography before a functional test is performed. Although the official data show that the number of non-invasive tests performed by the SUS network[12] has almost doubled, it is likely that there is still a great repressed demand, increasing the delay to performing these tests, thus making it longer than that observed for coronary angiography.

The Forrest and Diamond classification[13], created in 1979, is still currently recommended by the cardiology societies for assessment of pre-test probability of finding obstructive CAD (stenosis ≥ 50%) at the coronary angiography, using only age, gender and type of chest pain. Although it is useful for being practical, it is criticized for not considering the presence of other traditional factors[14]. In our study, we observed that the statistical C value was greater (from 0.703 to 0.728) when the presence of traditional risk factors such as diabetes and dyslipidemia were added to the basic model (age, gender and symptoms), but without significant statistical difference. In a study that assessed models for estimating the presence of CAD (stenosis > 50%) in a low prevalence population, Genders et al[15] found results similar to ours. Adding traditional risk factors (diabetes, dyslipidemia, hypertension and smoking) to the basic model (age, gender, symptoms) showed a greater discriminatory capacity (statistical-C from 0.77 to 0.79).

It should be mentioned that our study had several limitations. We could not assess the performance of the non-invasive stress test (ECG stress testing, stress echocardiogram, myocardial radionuclide imaging) as we did not have any information on patients submitted to noninvasive testing that were not referred for catheterization. Moreover, the interpretation of the test results was performed by the assistant physician. Important information, such as maximum heart rate, Duke score, percentage of ischemic area, which help the interpretation of the non-invasive stress testing, was not available. Furthermore, the characterization of chest pain was simplified to typical angina or atypical symptoms (atypical angina or non-anginal chest pain).

To our knowledge, this is the first study that describes the clinical approach for patients with suspected stable CAD in the context of the Brazilian SUS network. Although it was conducted in a single center, it represents the reality of the clinical decision making process of more than 100 secondary and tertiary centers.

Conclusions

In a scenario of clinical practice of the Brazilian SUS network, the efficacy of patient selection without previous diagnosis of CAD for coronary angiography was low, with the diagnosis being confirmed in less than a quarter of the patients. The incremental diagnostic value of a previous non-invasive test was low and non-significant. A better clinical and non-invasive assessment is needed and it should be available for SUS patients to improve the efficacy of the selection for the invasive test.

Author contributions

Conception and design of the research and Acquisition of data: Costa Filho FF, Chaves AJ, Ligabó LT, Santos EM, Silva DT, Puzzi MA; Analysis and interpretation of the data, Statistical analysis e Writing of the manuscript: Costa Filho FF, Chaves AJ; Critical revision of the manuscript for intellectual content: Costa Filho FF, Chaves AJ, Ligabó LT, Santos EM, Silva DT, Puzzi MA, Braga SL, Abizaid A, Sousa AGMR.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

References

1. Johnson LM, Lozner EC, Johnson S, Krone R, Pichard AD, Vetrovec GW, et al. Coronary arteriography 1984-1987: a report of the Registry of the Society for Cardiac Angiography and Interventions. Cathet Cardiovasc Diagn. 1989;17(1):5-10.

2. Meneghelo RS, Araújo CGS, Stein R, Mastrocolla LE, Albuquerque PF, Serra SM, et al/Sociedade Brasileira de Cardiologia. III Diretrizes da Sociedade Brasileira de Cardiologia sobre Teste Ergométrico. Arq Bras Cardiol. 2010; 95(5 Supl. 1):1-26.

3. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS. Guideline for the diagnosis and management of patients with stable ischemic heart disease. J Am Coll Cardiol.2012;60(24):e44-164.

4. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Buday A, et al. 2013 ESC guidelines on the management of stable coronary artery disease. The Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J.2013;34(38):2949-3003.

5. Patel MR, Peterson ED, Dai D, Brennan JM, Redberg RF, Anderson HV, et al. Low diagnostic yield of elective coronary angiography. N Engl J Med. 2010;362(10):886-95.

6. Weintraub WS, Karlsberg RP, Tcheng JE, Boris JR, Buxton AE, Dove JT, et al. ACCF/AHA 2011 key data elements and definitions of a base cardiovascular vocabulary for electronic health records: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Data Standards. J Am Coll Cardiol. 2011;58(2):202–22.

7. Patel MR, Bailey SR, Bonow RO, Chambers CE, Chan PS, Dehmer GJ, et al. ACCF/SCAI/AATS/AHA/ASE/ASNC/HFSA/HRS/SCCM/SCCT/SCMR/STS 2012 Appropriate use criteria for diagnostic catheterization: a report of the American College of Cardiology Foundation. Appropriate use criteria Tak Force, Society for Cardiovascular Angiography and Interventions, American Association for Thoracic Surgery. *J Am Coll Cardiol*. 2012;59(22):1995-2027.

8. Hendel RC, Budoff MJ, Cardella JF, Chambers CE, Dent JM, Fitzgerald DM, et al. ACC/ACR/ASE/ASNC/HRS/NASCI/RSNA/SAIP/SCAI/SCCT/SCMR/SIR 2008 key data elements and definitions for cardiac imaging: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Clinical Data Standards for Cardiac Imaging). J Am Coll Cardiol. 2009;53(1):91-124.

9. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988;44(3):837–45.

10. Galon MZ, Meireles GCX, Kreimer S, Marchiori GG, Favarato D, Almeida JA, et al. Clinical and angiographic profile in coronary artery disease: hospital outcome with emphasis on the very elderly. Arq Bras Cardiol. 2010;95(4):422-9.

11. Kemp HG, Kronmal RA, Vlietstra RE, Frye RL. Seven year survival of patients with normal or near normal coronary arteriograms: a CASS registry study. J Am Coll Cardiol. 1986;7(3):479-83.

12. Ministério da Saúde . Portal da saúde. Datasus. Departamento de Informatica do SUS. Brasília; 2012. em portugues

13. Diamond GA, Forrester JS. Analysis of probability in the clinical diagnosis of coronary-artery disease. N Engl J Med. 1979;300(24):1350–8.

14. Genders TS, Steyerberg EW, Alkadhi H, Leschka S, Desbiolles L, Nieman K, et al. A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension. Eur Heart J. 2011;32(11):1316-30.

15. Genders TS, Steyerberg EW, Hunink MM, Nieman K, Galema TW, Mollet NR, et al. Prediction model to estimate presence of coronary artery disease: retrospective pooled analysis of existing cohorts. BMJ. 2012;344:e3485.