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ORIGINAL ARTICLE

Yield of contemporary clinical strategies to detect patients with obstructive coronary artery disease

Pedro Rio, Ruben Ramos, Tiago Pereira-da-Silva, Carlos Barbosa, Duarte Cacela, António Fiarresga, Lídia de Sousa, Ana Abreu, Lino Patrício, Luís Bernardes, Rui Cruz Ferreira

Cardiology Department, Santa Marta Hospital, Centro Hospitalar de Lisboa Central, Lisbon - Portugal

ABSTRACT

Purpose: Noninvasive ischemia testing (NIST) is recommended for most patients suspected to have stable coronary artery disease (CAD) before invasive coronary angiography (ICA). We sought to assess the diagnostic predictive ability of NIST over clinical risk profiling in a contemporary sample of patients undergoing the currently recommended diagnostic triage strategy.

Methods: From 2006 to 2011, 2,600 consecutive patients without known CAD undergoing elective ICA in a single tertiary-care center were retrospectively identified and the prevalence of obstructive CAD determined. To understand the incremental value of frequently used clinical parameters in predicting obstructive CAD, receiver operating characteristic curves were plotted for six sequential models starting with Framingham risk score and then progressively adding multiple clinical factors and finally NIST results.

Results: At ICA 1,268 patients (48.8%) had obstructive CAD. The vast majority (85%) were classified in an intermediate clinical pretest probability of CAD and NIST prior to ICA was used in 86% of the cohort. The most powerful correlate of obstructive CAD was the presence of severe angina (odds ratio (OR) = 9.1; 95% confidence interval (CI) 4.3-19.1). Accordingly, the incorporation of NIST in a sequential model had no significant effect on the predictive ability over that achieved by clinical and symptomatic status model (C-statistic 0.754; 95% CI 0.732-0.776, p = 0.28).

Conclusions: Less than half the patients with suspect stable obstructive CAD referred to a tertiary-level center for elective ICA had the diagnosis confirmed. In this clinical setting, the results of NIST may not have the power to change the discriminative ability over clinical judgment alone.

Keywords: Angiography, Coronary disease, Diagnosis

Introduction

It is estimated that care for coronary artery disease (CAD) results in annual direct and indirect costs of around €50 billion within the European Union (1). A sizable proportion of this expenditure results from procedures used with the sole intention to confirm the diagnosis. Invasive coronary angiography (ICA) is still the gold standard for establishing the presence of CAD. Despite some variations in the diagnostic workflow among international guidelines, most algorithms usually recommend noninvasive ischemia testing (NIST) before referral for ICA in stable patients with low to intermediate risk (2, 3). Accordingly, use of NIST has grown substantially in recent years (4). However, it is unknown whether this strategy contributes incrementally to diagnostic efficiency. A contemporary observational study from the United States comprising almost 400,000 patients submitted to ICA found that even for those with prior positive NIST, the diagnostic yield of ICA for obstructive CAD was only 41% (5). It is acknowledged, however, that there may be significant populational and geographic variation on this figure ranging from 33 to 73% of obstructive CAD (1, 5, 6). This discrepancy may reflect not only different baseline risk of the studied population but also the diagnostic strategy used. Nonetheless, it is estimated that each year, in the European Union, about 400,000 patients undergo unnecessary ICA (1).

We sought to perform a clinical audit to determine the diagnostic yield of ICA in a tertiary center from Western Europe. We used a sample of patients following the usual risk stratification strategy based on clinical judgment complemented with NIST. We also assessed the incremental diagnostic predictive ability of NIST over clinical risk profiling alone.

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Corresponding author:
Pedro Rio
Santa Marta Hospital
Rua de Santa Marta
1169-024, Lisbon, Portugal
pedrosantosrio@gmail.com

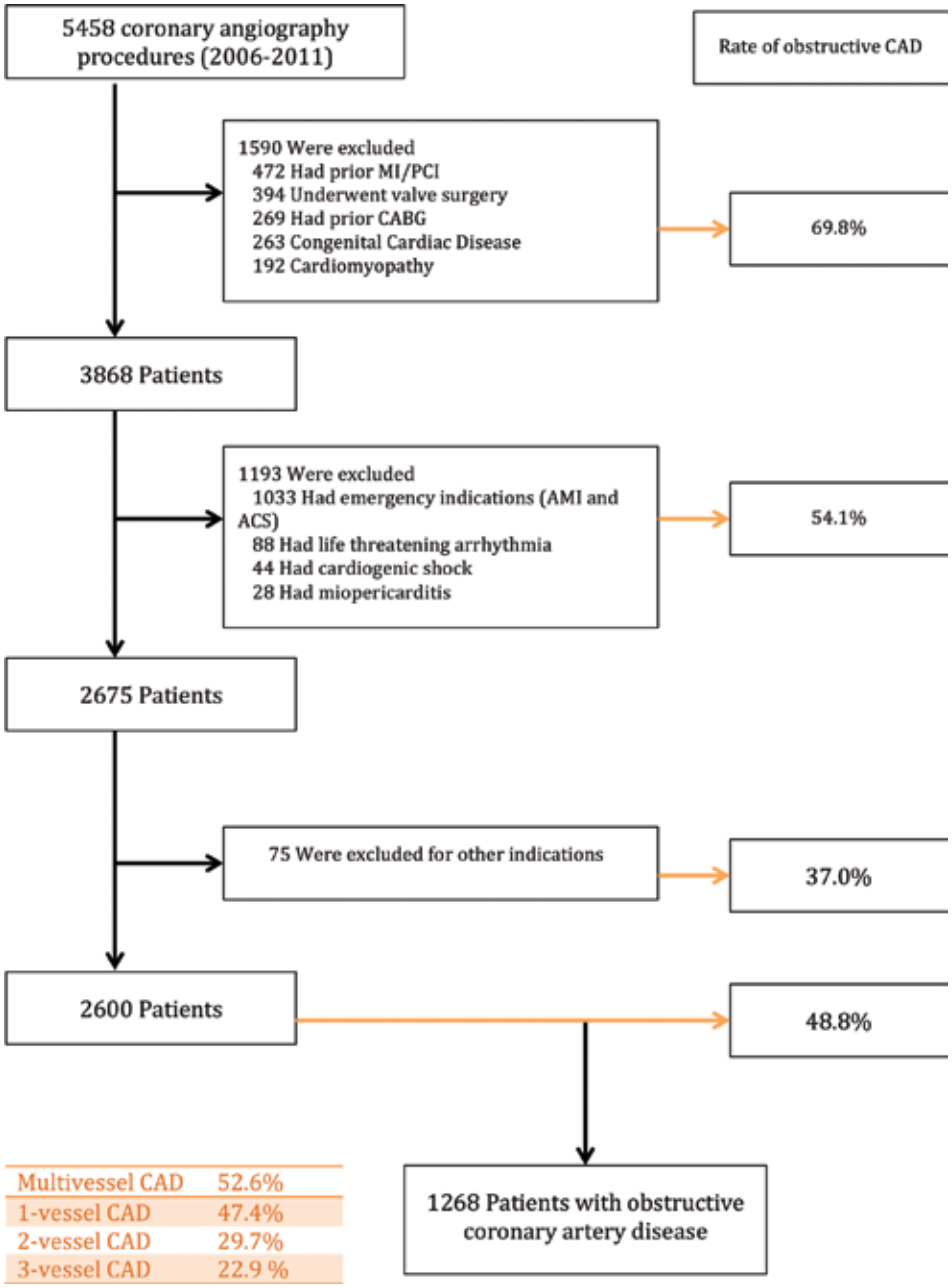

Fig. 1 - Study population selection. ACS = acute coronary syndrome; AMI = acute myocardial infarction (MI); CABG = coronary artery bypass grafting; CAD = coronary artery disease; PCI = percutaneous coronary intervention.

Methods

Patient selection

This was a retrospective, cross-sectional study performed at a single public hospital from January 2006 through December 2011. All data were entered prospectively into the departmental patient information system (SIGUS_, Cardiology Department - Central Lisbon Medical Center) and retrospectively analyzed. Consecutive patients with suspected stable CAD (with or without a previous NIST) who were referred for their first elective ICA were included (Fig. 1). Therefore, patients with known heart disease (documented coronary stenosis ≥50% on previous ICA, previous myocardial infarction, percutaneous coronary intervention, coronary artery bypass surgery or undergoing ICA as routine workup before cardiac noncoronary surgery were excluded, as were patients with indications for emergency or urgent cardiac catheterization (acute coronary syndromes, cardiogenic shock or life-threatening ventricular dysrhythmia). The study protocol conforms to the ethical guidelines of the Declaration of Helsinki.

Patient evaluation

Data on demographic characteristics, classic and nonclassic CAD risk factors [including peripheral artery disease (PAD), chronic obstructive pulmonary disease (COPD), cerebrovascular

disease (CVD) and renal dysfunction (chronic kidney disease, CKD)], symptomatic status, type and results of NIST as well as the results of the first ICA performed in the study period were prospectively collected. Symptomatic status was categorized as 1) nonanginal symptoms, 2) atypical chest pain (including dyspnea, fatigue or equivalent) or 3) typical angina. Pretest probability for CAD was retrospectively calculated using an update Diamond-Forrester classification (7). Intermediate probability was arbitrarily defined as pretest risk between 15% and 85% of ischemic heart disease. The modalities of NIST routinely used were exercise treadmill test (ETT) and stress myocardial single-photon emission computed tomography (SPECT). Only tests performed before the ICA were considered. The results were categorized as positive, negative or equivocal. Degree of positivity of the NIST results was not considered. Information on left ventricular systolic function (LVSF) was considered whenever available. For patients with more than one LVSF assessment method, the preferred method was nuclear ventriculography, after echocardiography and finally was invasive ventriculography. Normal LVSF was defined as LV ejection fraction >55%. A modified Framingham risk score (FRS) (8) was calculated for nondiabetic individuals on the basis of available clinical data, with a moderate score (i.e., 1 point) imputed for either a history of dyslipidemia or the use of statins and for the presence of hypertension or a history of medication use for the treatment of high blood pressure.

Invasive coronary angiography

Interpretation of ICA was based on visual assessment only. No quantitative coronary angiogram was performed and data from intracoronary imaging, like fractional flow reserve, intravascular ultrasound or optical coherence tomography, were not considered. Obstructive CAD was defined as stenosis ≥50% of the left main coronary artery or stenosis ≥70% of a major epicardial vessel or branch vessel with at least 1.5 mm in diameter. Normal coronary artery was defined as complete absence of any luminal narrowing detectable by angiography. Nonobstructive CAD was defined as CAD not meeting the criteria for obstructive CAD or normal coronary arteries.

Statistical analysis

We determined the rate of obstructive CAD in the overall population and also according to clinical pretest probabilities and results of NIST. In order to identify variables associated with obstructive CAD, the population was divided into two groups, patients with and without obstructive CAD. We compared the baseline demographic characteristics, cardiovascular risk factors, symptoms and results of NIST between the groups. Normally distributed continuous variables were compared using Student's *t*-tests and are expressed as mean ± SD; continuous variables not normally distributed were compared using Mann-Whitney tests and are expressed as medians and interquartile ranges. Variables that showed association with obstructive CAD in univariate analysis ($p<0.10$) were included in a multivariate logistic regression model to identify independent correlates ($p<0.05$).

To study the incremental value of different parameters in predicting obstructive CAD, a stepwise (six steps) logistic regression analysis was carried out, starting with (1) FRS alone and then sequentially adding, (2) nonclassic risk factors, (3) symptomatic status, (4) pretest probability of CAD, (5) LVSF and finally (6) NIST result. The receiver operating characteristic curves of each model were compared using a nonparametric method (9). A p value of less than 0.05 was considered statistically significant. All data were analyzed using SPSS 16.0.

Results

Study population

The study population consisted of 2,600 patients with suspected CAD who were undergoing their first elective ICA, 13.6% of them without any previous NIST. This final cohort represented 47.6% of a total of 5,458 ICA procedures performed during the 7 years of the study period. Reasons for patients' exclusion were known history of heart disease in 1,590 (29.1%), urgent ICA indication in 1,193 (21.9%) and other reasons such as routine workup based on institutional defined protocols in 75 (1.3%) patients (Fig. 1).

Prevalence of obstructive CAD

The prevalence of obstructive CAD was 48.8% (n = 1,268). Normal coronary arteries as defined per protocol were found in 1,035 (39.8%) patients and the remaining represents patients with nonobstructive CAD (10.4%). Multivessel disease was present in 735 patients representing 58% of all obstructive CAD and 28.3% of the entire population. Left main and/or three-vessel disease was present in 323 patients (12.4% of the entire population).

Demographic and clinical characteristics

Detailed population characteristics are described in Table I. In general, the study cohort consisted of a predominantly male population (60%), with a low (5.7%) prevalence of associated comorbidities. Except for COPD and CKD, all traditional and nontraditional cardiovascular risk factors were significantly associated with the presence of obstructive CAD in univariate analysis (Tab. II). One third of the cohort had no anginal symptoms but was sent for ICA due to perceived high risk, high FRS and/or a positive NIST. Most patients (85.1%) were classified in an intermediate clinical pretest probability of ischemic heart disease. Patients with low and high pretest probabilities represented 3.4% and 11.5% of the whole population, respectively. Typical symptoms of angina were present in half the population and were also significantly associated with obstructive CAD. After adjustment however, only severe symptoms (Canadian Cardiovascular Society (CCS) 3 or 4) were independently associated with obstructive CAD (OR 9.1; 95% CI 4.33-19.1).

Noninvasive ischemia test and LVSF

From the 2,600 patients included, the vast majority (86.4%) had at least one NIST prior to ICA. Considering that ischemia testing would be justified only in patients in an intermediate pretest risk category, an NIST was appropriately used in 73.4% of the whole population. ETT was the single test performed

TABLE I - Population characteristics

Characteristic	Total (N = 2,600)	Obstructive coronary artery disease (N = 1,268)	No obstructive coronary artery disease (N = 1,332)	p-Value
Age (years)	65 ± 9.9	67 ± 9.7	64 ± 9.8	<0.001
Female sex (%)	1057 (40.7)	374 (29.5)	683 (51.3)	<0.001
Clinical risk factors				
Body mass index Kg/m^2	28.2 ± 4.3	28.0 ± 4.1	28.4 ± 4.4	0.035
History of smoke (%)	461 (17.7)	272 (21.5)	189 (14.2)	<0.001
Current (%)	229 (8.8)	134 (10.6)	95 (7.1)	0.001
Diabetes (%)	704 (27.1)	409 (32.3)	295 (22.1)	<0.001
Hypertension (%)	1933 (74.3)	971 (76.6)	962 (72.2)	0.012
Dyslipidemia (%)	1603 (61.7)	825 (65.1)	778 (58.4)	0.001
Peripheral vascular disease (%)	53 (2.0)	38 (3.0)	15 (1.1)	0.001
Cerebrovascular disease (%)	48 (1.8)	34 (2.7)	14 (1.1)	0.001
Chronic obstructive pulmonary disease (%)	29 (1.1)	18 (1.4)	11 (0.8)	0.19
Chronic kidney disease (%)	20 (0.85)	13 (1)	7 (0.5)	0.18
Framingham risk score				<0.001
Low (<10%) (%)	771 (29.7)	288 (22.7)	483 (36.3)	
Intermediate (%)	1064 (40.9)	525 (41.4)	539 (40.5)	
High (>20%) (%)	765 (29.4)	455 (35.9)	310 (23.3)	
Left ventricular systolic dysfunction (%)	241 (11.1)	169 (16.3)	72 (6.3)	<0.001
Clinical status				<0.001
No angina (%)	868 (33.4)	332 (26.1)	536 (40.2)	
Atypical angina (%)	435 (16.7)	52 (4.1)	383 (28.8)	
Stable angina (%)	1297 (49.9)	884 (69.7)	413 (31.0)	
Clinical pretest probability	55.6 ± 24.1	66.0 ± 21.3	45.8 ± 22.5	<0.001
Low (<15%) (%)	89 (3.4)	11 (0.9)	78 (5.9)	
Intermediate (%)	2213 (85.1)	1028 (81.1)	1185 (89)	
High (>85%) (%)	298 (11.5)	229 (18.1)	69 (5.2)	

in 1,201 (46.2%), SPECT only in 782 (30.1%) and 262 patients (10.1%) had both. Only 2 patients in the low-risk category did not receive a previous NIST. Likelihood of receiving an NIST before ICA was not significantly different in the intermediate and high-risk categories (86.4% vs 82.6%, respectively, p = 0.08). Ninety-three percent of patients had a positive result in at least one NIST. Inconclusive and negative results in one or both tests were found in 5% and 2%, respectively. Rate of obstructive CAD did not differ after a patient has made a SPECT or an ETT (47.2% and 46.3%, respectively, p = 0.68). Also, rate of obstructive CAD did not differ after a positive SPECT or ETT (49.0% and 48.4%, respectively, p = 0.83). Figure 2 shows the rate of obstructive CAD according to pretest likelihood and NIST results. As expected, there was a progressive increase in the rate of obstructive CAD from low to high pretest likelihood. Interestingly though, in the intermediate risk category where an NIST is usually considered necessary, observed rate of obstructive CAD did not differ significantly for those with positive or negative NIST (47% vs 43%, respectively, p = 0.66). Equivalent rates of obstructive CAD were also found in the high pretest risk category, when patients with positive NIST were compared to those with no previous NIST (77.6% vs 78.8%).

For 262 patients ETT and SPECT were used sequentially and both tests resulted positive for ischemia in 47%. The prevalence of obstructive CAD was not significantly different when only one NIST resulted positive versus both positive, 43.4% and 49.4% (p = 0.23).

An assessment of LVSF was available for analysis in 2,170 patients (83.4% of the study population). From these patients, normal LVSF was found in 89% and moderate to severe LV systolic dysfunction was present in 3.3%. Prevalence of obstructive CAD in patients with any degree of LV systolic dysfunction was 70.1%.

Correlates of obstructive CAD

Increasing age, male sex, history of smoke, diabetes, left ventricular dysfunction and severe angina were independent

TABLE II - Predictors of obstructive coronary artery disease, univariate analysis

Variable	Odds ratio	CI (95%)	p-Value
Age, per 5-year increase	1.16	1.12-1.21	<0.001
Male sex	2.52	2.14-2.96	<0.001
Body mass index, per 5-unit increase	0.91	0.83-0.99	0.033
History of smoke	1.65	1.35-2.03	<0.001
Diabetes	1.67	1.41-1.99	<0.001
Hypertension	1.26	1.05-1.50	0.011
Dyslipidemia	1.33	1.13-1.55	<0.001
High Framingham risk score	1.85	1.56-2.19	<0.001
Peripheral vascular disease	2.71	1.49-4.96	0.001
Cerebrovascular disease	2.59	1.39-4.86	0.003
Left ventricular dysfunction	2.88	2.15-3.84	<0.001
Clinical status			
Atypical angina	0.10	0.08-0.14	<0.001
Stable angina	5.64	4.74-6.71	<0.001
CCS Class 3 or 4	5.19	3.18-8.47	<0.001
High clinical pretest probability	4.03	3.05-5.35	<0.001
Noninvasive stress test			
Positive result	1.85	1.33-2.58	<0.001
Equivocal result	0.5	0.36-0.69	<0.001

CCS = Canadian Cardiovascular Society; CI = confidence interval.

correlates of obstructive CAD (Tab. III). A positive NIST was associated with obstructive CAD in univariate analysis, but after adjustment this association was no longer significant (OR 1.69; 95% CI 0.952-3.09). The strongest correlate of obstructive CAD was the presence of severe angina (class 3 or 4 of CCS) (OR = 9.1; 95% CI 4.3-19.1), left ventricular systolic dysfunction (OR = 3.3; 95% CI 1.7-6.3) and male sex (OR = 3.04; 95% CI 2.09-4.44).

A stepwise analysis was performed to study the incremental value of different parameters in predicting obstructive CAD (Fig. 3). Predictive power of each model is given by the C-statistic value over a 95% CI. The first model included only a modified FRS as initial approach for general CV risk assessment irrespective of symptomatic status (0.595, 0.569-0.620). In the second model, nonclassic risk factors and comorbidities such as PAD, CVD, CKD and COPD were added. The C-statistic for this model remained unchanged (0.601, 0.576-0.627). With the incorporation of the symptomatic status there was a significant increase in the model's predictive ability (0.735, 0.712-0.758; p<0.001). When we added the pretest probability (obtained by the Diamond-Forrester method) no change was noted. In the fifth step, inclusion of the LVSF caused a slight, albeit not significant (p = 0.29), increase in the predictive ability (0.751, 0.729-0.773). Finally, the sixth step consisted in the addition of the noninvasive ischemia test results, which had no significant effect on the model's predictive ability over that already achieved by previous steps (0.754, 0.732-0.776, p = 0.28).

Discussion

In this study including 2,600 patients with suspected CAD undergoing their first elective ICA in a single tertiary care, urban and public European center, the rate of obstructive CAD was 48.8%. This occurred despite appropriate use (but not necessarily interpretation) of noninvasive stress tests in more than 70% of the patients.

The incidence of obstructive CAD as diagnosed by ICA in elective patients has been suggested as a health care performance measure (10) and the 2013 catheterization and percutaneous coronary intervention standards from the Accreditation for Cardiovascular Excellence organization suggests this figure should be above 60% (11). However, strategies to achieve this goal are not simple. Most international guidelines, largely based on prognostic reasons, suggest that patients in pretest intermediate risk category should be selected for ICA according to NIST results (2, 3). However, despite geographic and temporal variations in the rate of no obstructive disease after ICA, most contemporary studies using NIST strategies for patient selection fail to show success in increasing the yield of ICA. Genders et al (7) in a multicenter study involving 11 European hospitals reported a rate of obstructive CAD of 58% (ranging from 39.4% to 75.5%). Patel et al (5) in the USA reported a rate of 37.6% of obstructive CAD among patients who underwent elective ICA in the National Cardiovascular Data Registry. There was however a wide regional variation among the hospital referral regions, from 23% to 100% (12).

Several factors may influence the diagnostic performance of ICA. The increased availability and more liberal use of ICA may be one explanation. The 30-year-old Coronary Artery Surgery Study (CASS) (13) with more than 20,000 angiograms showed 81% of patients with obstructive CAD. This is in contrast with the more recent data from registries showing that this rate is between 38% and 50% (5, 14). Even though this may suggest a temporal decrease in ICA yield, it is difficult to draw definite conclusions since past studies included patients with varying cut points to define obstructive CAD, with previous myocardial infarction or revascularization procedures, with urgent indications and failure to report on the used noninvasive ischemia test strategy, if any.

Also, the impact of NIST on the ICA performance is not entirely clear. A recent published study (4) suggests that despite the increasing availability of noninvasive tests through the years, the proportion of patients with normal coronary arteries or undergoing revascularization remains unchanged. One of the often pointed reasons for this is the overall low pretest probability of obstructive CAD in the studied population. In our cohort more than 85% fell in the intermediate risk category and thus an NIST would be considered appropriately indicated. Germane to this discussion is not just the appropriate indication for NIST but also the appropriate interpretation of the results. Notwithstanding the fact that NIST has intrinsic accuracy and referral strategy limitations, there may be several other factors driving use of ICA after NIST. These

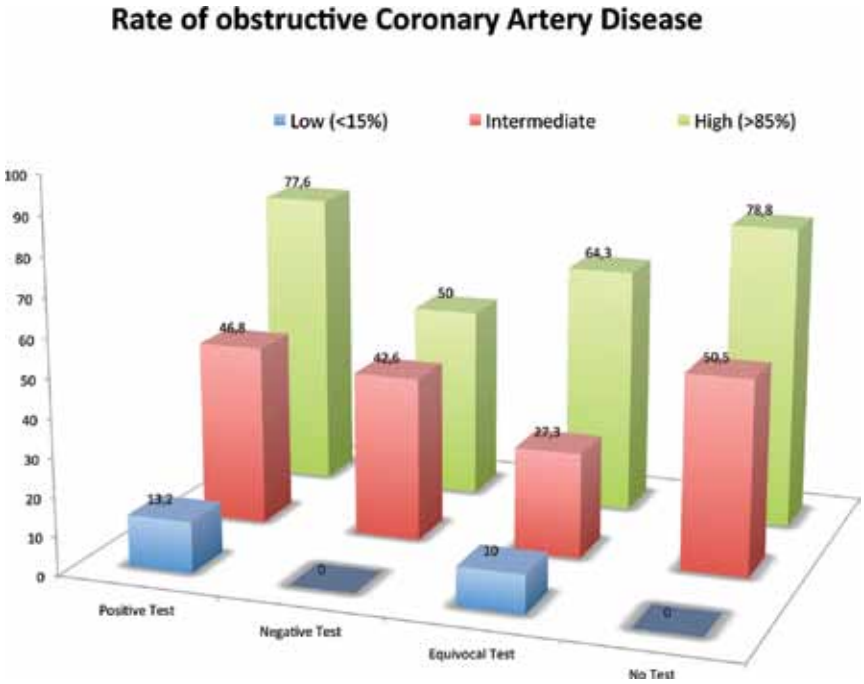

Fig. 2 - Prevalence of obstructive coronary artery disease, according to clinical pretest probability and noninvasive test results.

TABLE III - Predictors of obstructive coronary artery disease, multivariate analysis

Variable	Wald chi-square statistic	Adjusted odds ratio	CI (95%)	P value
Age, per 5-year increase	9.91	1.12	1.06-1.30	0.002
Male sex	33.47	3.04	2.09-4.44	<0.001
Body mass index, per 5-unit increase	6.94	0.79	0.66-0.94	0.008
History of smoke	4.68	1.62	1.05-2.52	0.031
Diabetes	9.59	1.74	1.23-2.47	0.002
Left ventricular dysfunction	12.91	3.30	1.72-6.33	<0.001
Clinical status				
CCS Class 3 or 4	33.85	9.10	4.33-19.15	<0.001

CCS = Canadian Cardiovascular Society; CI = confidence interval.

may include the role of the patients', family and colleagues' expectations, fear of liability and, importantly, a feeling, albeit debatable, that prognostic risk stratification is not complete until the coronary anatomy is known (15, 16). If we are to take this last factor into account, coronary computed tomography angiography (CCTA) may have an important role (17, 18). The ongoing ISCHEMIA trial is evaluating the best management strategy for patients with stable ischemic heart disease. Most patients are required to undergo CCTA before randomization both to confirm the presence of obstructive CAD and to exclude left main disease. Preliminary results (after enrolling 1,078 patients) have found that even for these high-risk patients with core-lab adjudicated moderate to severe ischemia, 13.6% were found to have no obstructive CAD (19). Even though these findings may represent true flow limitation due to small vessel disease or endothelial dysfunction, it illustrates the thesis that even in an optimal environment, patient selection based on NIST may not be sufficient to increase the diagnostic yield of ICA.

In this study we also sought to determine factors associated with the presence of obstructive CAD as defined by ICA. Demographic and symptom characteristics are generally used to estimate pretest risk of CAD based on clinical risk assessment models (15, 20). The original populations from which these data were derived as well as the validation cohort data used are now over 30 years old and were obtained before the current wide availability of ICA. Thus, it is acknowledged that risk assessment in these stratification models may be now overestimated at least in the primary care setting (21). Nonetheless, our data confirm that typical angina was the strongest independent predictive factor for obstructive CAD followed by other traditional risk factors such as older age, male sex, use of tobacco, diabetes, as well as the presence of abnormal LVSF. In fact, in our stepwise construct, the only significant increment in the ability to predict obstructive CAD was observed when symptomatic status was considered (increase in area under the curve (AUC) from 0.60 to 0.74). Moreover, use of NIST did not significantly add predictive power over demography and symptoms, especially when LVSF was also considered (AUC change from 0.73 to 0.74). This remained true irrespective of Framingham baseline risk (data not shown).

These observations suggest that there is room for improvement and better strategies for patient stratification, before undergoing ICA, are desirable. The incremental value of NIST is limited and therefore other methods of functional and/or anatomic assessment to increase the yield of ICA are

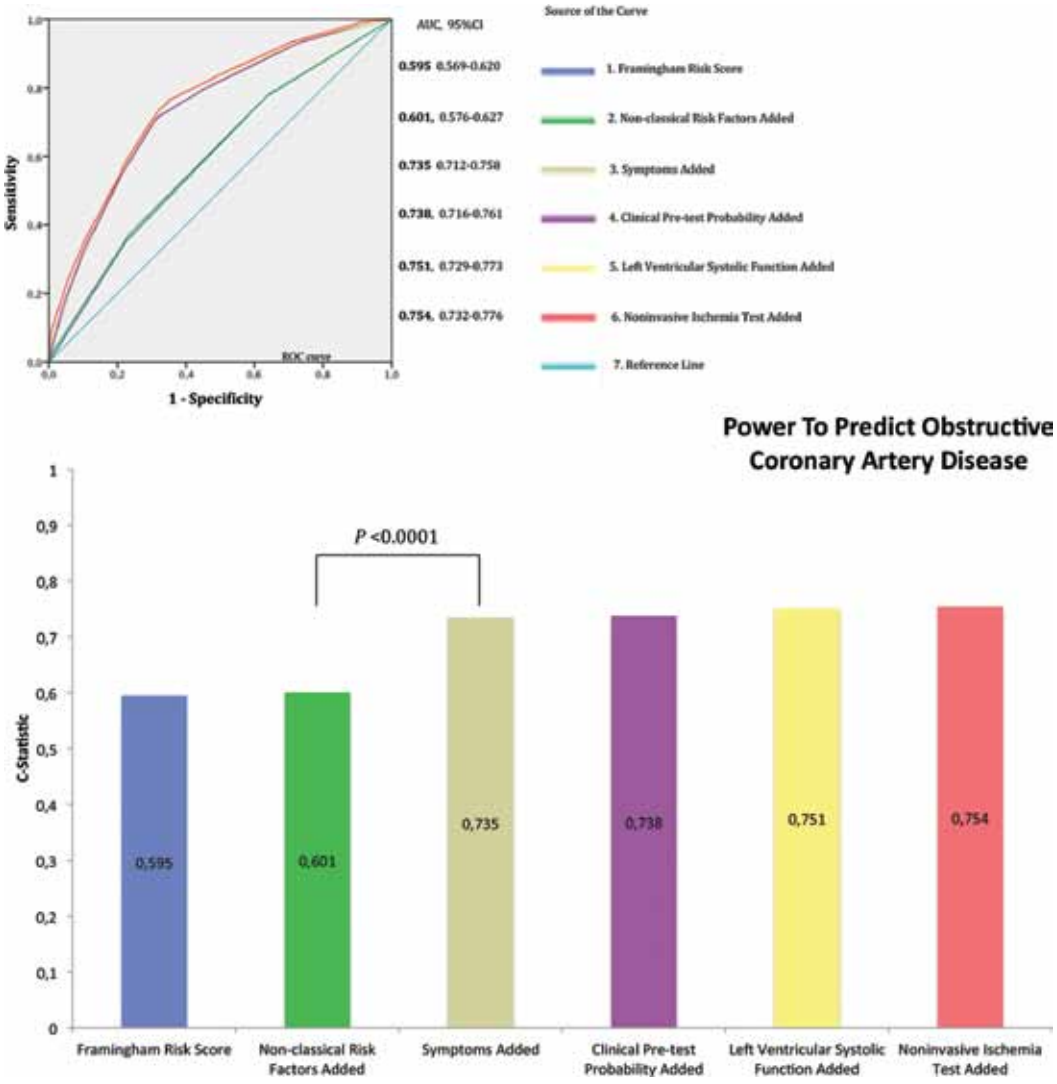

Fig. 3 - Predictive ability of each model to detect obstructive coronary artery disease is given by the area under the curve (AUC). The only significant increment was observed when symptoms were added to baseline clinical risk.

necessary (17, 18, 22-24). Finally, in this era of increasing use and even dependence on medical technology our study shows that careful history taking for the accurate elucidation of symptoms, especially typical angina, should not be overlooked in the evaluation of patients with CAD.

Limitations

First, this is a retrospective analysis. It is possible that there might have been variables used by clinicians to direct patients for ICA namely rest ECG abnormalities, nonclassified symptoms or other hidden confounders not reflected in pretest risk estimation or NIST results. Also, FRS may be underestimated because in our database dyslipidemia and hypertension are classified as categorical variables and therefore a modified FRS was used using imputed values for lipid levels and blood pressure. Second, patients were subjected to referral bias. This analysis was focused exclusively in patients referred for ICA. Thus, we have no data on subjects evaluated for presence of CAD that for any reason did not receive ICA. Therefore, we could determine the incremental value of NIST in confirming CAD diagnosis but we could not determine the overall performance of the NIST, and most notably its ability to exclude CAD. Third, the database was not powered to provide information on details of NIST results. Information such as high-risk features, extent or ischemia location or reason for equivocal results was not available. Fourth, even though data on symptomatic status was prospectively collected at the initial clinical interview, the database is also a clinical tool and thus it is susceptible to posttest symptom reclassification bias. Hence, it is not unlikely that an initially designated typical angina would be reclassified as atypical or absent after an ICA showing normal epicardial coronaries, particularly if symptoms are inconsistent. Fourth, angiographic findings were not adjudicated and lesion severity assessment was based on operator's semiquantitative angiographic classification. Also, we did not correlate ischemic territories with distribution of lesions in the coronary tree. Thus, lack of use of invasive fraction flow reserve in this cohort is a limitation given its demonstrated reclassification potential. Fifth, only ETT and SPECT were used

so these results cannot be extrapolated to other functional tests such as stress echocardiography or magnetic resonance imaging. Sixth, although we used a standard definition of obstructive CAD (stenosis >70%), often angiographically moderate stenosis, especially in long lesions, may be flow limiting.

Conclusions

In this retrospective study, less than half the patients with suspect CAD referred to a tertiary-level center for elective ICA were found to have obstructive CAD. In this clinical setting, results of noninvasive ischemia test did not have significant discriminative power over clinical judgment alone to predict obstructive CAD. Better strategies or tests need to be designed to improve the diagnostic yield of ICA.

Disclosures

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