

The External Validity of Prediction Models for the Diagnosis of Obstructive Coronary Artery Disease in Patients With Stable Chest Pain

Insights From the PROMISE Trial

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ABSTRACT

OBJECTIVES This study sought to externally validate prediction models for the presence of obstructive coronary artery disease (CAD).

BACKGROUND A better assessment of the probability of CAD may improve the identification of patients who benefit from noninvasive testing.

METHODS Stable chest pain patients from the PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial with computed tomography angiography (CTA) or invasive coronary angiography (ICA) were included. The authors assumed that patients with CTA showing 0% stenosis and a coronary artery calcium (CAC) score of 0 were free of obstructive CAD ($\geq 50\%$ stenosis) on ICA, and they multiply imputed missing ICA results based on clinical variables and CTA results. Predicted CAD probabilities were calculated using published coefficients for 3 models: basic model (age, sex, chest pain type), clinical model (basic model + diabetes, hypertension, dyslipidemia, and smoking), and clinical + CAC score model. The authors assessed discrimination and calibration, and compared published effects with observed predictor effects.

RESULTS In 3,468 patients (1,805 women; mean 60 years of age; 779 [23%] with obstructive CAD on CTA), the models demonstrated moderate-good discrimination, with C-statistics of 0.69 (95% confidence interval [CI]: 0.67 to 0.72), 0.72 (95% CI: 0.69 to 0.74), and 0.86 (95% CI: 0.85 to 0.88) for the basic, clinical, and clinical + CAC score models, respectively. Calibration was satisfactory although typical chest pain and diabetes were less predictive and CAC score was more predictive than was suggested by the models. Among the 31% of patients for whom the clinical model predicted a low ($\leq 10\%$) probability of CAD, actual prevalence was 7%; among the 48% for whom the clinical + CAC score model predicted a low probability the observed prevalence was 2%. In 2 sensitivity analyses excluding imputed data, similar results were obtained using CTA as the outcome, whereas in those who underwent ICA the models significantly underestimated CAD probability.

CONCLUSIONS Existing clinical prediction models can identify patients with a low probability of obstructive CAD. Obstructive CAD on ICA was imputed for 61% of patients; hence, further validation is necessary. (J Am Coll Cardiol Img 2017;■:■-■)
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**ABBREVIATIONS
AND ACRONYMS****CAC** = coronary artery calcium**CAD** = coronary artery disease**CI** = confidence interval**CTA** = computed tomography
angiography**ICA** = invasive coronary
angiography

Every year, millions of patients in the United States with stable chest pain undergo noninvasive diagnostic testing to investigate the presence of obstructive coronary artery disease (CAD) (1). The decision to proceed to invasive coronary angiography (ICA) is often based on the results of such noninvasive tests. However, 59% of stable symptomatic patients referred for elective ICA in the United States are free of obstructive CAD (2). A better strategy to select patients who might benefit from invasive testing is needed, which should begin by better risk-stratifying patients who should undergo noninvasive testing (3).

The clinical value of a diagnostic test for CAD depends on the pre-test probability of CAD (4-7). Current guidelines uniformly recognize this and recommend considering the pre-test probability before deciding whether to test. However, due to a lack of evidence on comparative effectiveness of imaging strategies, for a given pre-test probability and other factors, the test of choice may vary across countries (8-10). The traditional Diamond and Forrester model (11), which in combination with the model based on the CASS (Coronary Artery Surgery Study) study data (12) is currently recommended by the American College of Cardiology Foundation/American Heart Association stable ischemic heart disease guidelines (8), significantly overestimates the pre-test probability of obstructive CAD (13-15). Improved estimates of the pre-test probability may be obtained using updated prediction models that were developed by the CAD Consortium (13), and they can potentially help clinicians make better decisions as to which patients should undergo noninvasive testing. The current study aims to externally validate the CAD consortium prediction models for the presence of obstructive CAD in chest pain patients from the United States.

METHODS

STUDY POPULATION. Our study population consisted of patients enrolled in the PROMISE (Prospective

Multicenter Imaging Study for Evaluation of Chest Pain) trial, which has been described in detail previously (16,17). In brief, the PROMISE trial was a pragmatic, multicenter randomized trial that compared outcomes of initial anatomic testing with the use of coronary computed tomography angiography (CTA) versus initial functional testing (exercise electrocardiography, nuclear stress testing, or stress echocardiography) for patients with suspected CAD. Enrollment began on July 27, 2010, and was completed on September 19, 2013. Patients were symptomatic outpatients; men were ≥ 55 years of age, or ≥ 45 to 54 years of age with ≥ 1 cardiac risk factor (diabetes, peripheral arterial disease, cerebrovascular disease, current or past smoking, hypertension, or dyslipidemia) and women were ≥ 65 years of age, or ≥ 50 to 64 years of age with ≥ 1 cardiac risk factor. Patients with a history of acute myocardial infarction, known CAD, or revascularization were excluded. For the current study we selected PROMISE trial patients who were assigned to the anatomic testing strategy, presented with chest pain, and underwent CTA, ICA, or both.

The Duke University Health System Institutional Review Board approved this study. A waiver of informed consent was granted for the current analysis. Patients previously consented for enrollment in the PROMISE trial.

RISK FACTOR DEFINITIONS IN THE PROMISE TRIAL.

Chest pain symptoms were defined as typical, atypical, or noncardiac. Typical chest pain was defined as: 1) substernal chest pain or discomfort; that was 2) provoked by exertion or emotional stress; and 3) relieved by rest or nitroglycerine. Atypical chest pain was defined as 2 of the previously mentioned criteria. If 1 or none of the criteria was present, chest pain symptoms were categorized as noncardiac (18). Hypertension was defined as a blood pressure $>140/90$ mm Hg on at least 2 occasions ($>130/80$ mm Hg for patients with diabetes or chronic kidney disease) or requiring antihypertensive treatment. Diabetes was defined as a history of diabetes, an elevated fasting serum glucose >126 mg/dl (7

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