JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2017 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

VOL. 69, NO. 9, 2017
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2016.12.021

SPECIAL FOCUS ISSUE: CARDIOVASCULAR HEALTH PROMOTION

A Clinical and Biomarker Scoring System to Predict the Presence of Obstructive Coronary Artery Disease

Nasrien E. Ibrahim, MD,[a] James L. Januzzi, Jr, MD,[a,b] Craig A. Magaret, MS,[c] Hanna K. Gaggin, MD, MPH,[a,b] Rhonda F. Rhyne, BPharm, MBA,[c] Parul U. Gandhi, MD,[d] Noreen Kelly, MD,[e] Mandy L. Simon, DNP, FNP-BC,[a] Shweta R. Motiwala, MD,[e] Arianna M. Belcher, MS,[a] Roland R.J. van Kimmenade, MD, PhD[f]

ABSTRACT

BACKGROUND Noninvasive models to predict the presence of coronary artery disease (CAD) may help reduce the societal burden of CAD.

OBJECTIVES From a prospective registry of patients referred for coronary angiography, the goal of this study was to develop a clinical and biomarker score to predict the presence of significant CAD.

METHODS In a training cohort of 649 subjects, predictors of ≥70% stenosis in at least 1 major coronary vessel were identified from >200 candidate variables, including 109 biomarkers. The final model was then validated in a separate cohort (n = 278).

RESULTS The scoring system consisted of clinical variables (male sex and previous percutaneous coronary intervention) and 4 biomarkers (midkine, adiponectin, apolipoprotein C-I, and kidney injury molecule-1). In the training cohort, elevated scores were predictive of ≥70% stenosis in all subjects (odds ratio [OR]: 9.74; $p < 0.001$), men (OR: 7.88; $p < 0.001$), women (OR: 24.8; $p < 0.001$), and those with no previous CAD (OR: 8.67; $p < 0.001$). In the validation cohort, the score had an area under the receiver-operating characteristic curve of 0.87 ($p < 0.001$) for coronary stenosis ≥70%. Higher scores were associated with greater severity of angiographic stenosis. At optimal cutoff, the score had 77% sensitivity, 84% specificity, and a positive predictive value of 90% for ≥70% stenosis. Partitioning the score into 5 levels allowed for identifying or excluding CAD with >90% predictive value in 42% of subjects. An elevated score predicted incident acute myocardial infarction during 3.6 years of follow up (hazard ratio: 2.39; $p < 0.001$).

CONCLUSIONS We described a clinical and biomarker score with high accuracy for predicting the presence of anatomically significant CAD. (The CASABLANCA Study: Catheter Sampled Blood Archive in Cardiovascular Diseases; NCT00842868) (J Am Coll Cardiol 2017;69:1147-56) © 2017 by the American College of Cardiology Foundation.

From the [a]Massachusetts General Hospital, Division of Cardiology, Boston, Massachusetts; [b]Harvard Clinical Research Institute, Cardiometabolic Trials, Boston, Massachusetts; [c]Prevencio, Inc., Kirkland, Washington; [d]Yale University, Cardiology, New Haven, Connecticut; [e]Brigham and Women's Hospital, Cardiology, Boston, Massachusetts; and the [f]Department of Cardiology, Radboud University Medical Centre, Nijmegen, the Netherlands. This work was supported by a grant from Prevencio, Inc. Dr. Ibrahim is supported by the Dennis and Marilyn Barry Fellowship in Cardiology. Dr. Januzzi is supported in part by the Hutter Family Professorship in Cardiology; has received grant support from Siemens, Singulex, and Prevencio; consulting income from Roche Diagnostics, Critical Diagnostics, Sphingotec, Phillips, and Novartis; and participates in clinical endpoint committees/data safety monitoring boards for Novartis, Amgen, Janssen, and Boehringer Ingelheim. Dr. Gaggin is supported in part by the Ruth and James Clark Fund for Cardiac Research Innovation; and has received grant support from Roche and Portola; consulting income from Roche Diagnostics, American Regent, Amgen, Boston Heart Diagnostics, and Critical Diagnostics; and research payments for clinical endpoint committees for EchoSense and RadioMeter. Mr. Magaret is a consultant to Prevencio, Inc. Ms. Rhyne is an employee of Prevencio, Inc. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Ibrahim and Januzzi contributed equally to this work. Sanjay Kaul, MD, served as Guest Editor for this paper.

Manuscript received November 16, 2016; revised manuscript received November 30, 2016, accepted December 1, 2016.

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

ABBREVIATIONS AND ACRONYMS

Apo C-I = apolipoprotein C-I
AUC = area under the curve
CAD = coronary artery disease
CI = confidence interval
CT = computed tomography
HR = hazard ratio
KIM-1 = kidney injury molecule-1
MI = myocardial infarction
NPV = negative predictive value
OR = odds ratio
PCI = percutaneous coronary intervention
PPV = positive predictive value
ROC = receiver-operating characteristic

Despite efforts toward better recognition of risk factors and preventive treatments, the prevalence of coronary artery disease (CAD) in the general population remains high, with nearly 1 in 5 people >65 years of age affected by the diagnosis. Indeed, heart disease is the leading cause of death for both men and women, with CAD the most common affliction, killing >370,000 people annually (1). As such, CAD is a public health concern, and an efficient manner for its noninvasive detection could potentially result in reduction of morbidity, mortality, and cost of this disease process.

In the context of a patient with risk factors for CAD, clinicians often use stress testing with or without adjunctive imaging to assist their evaluation of obstructive CAD. Drawbacks to stress testing include variable sensitivity and specificity, limitations with respect to accuracy in certain types of body habitus (including overweight/obese patients and women), as well as the need for ionizing radiation. More recently, coronary calcium assessment by computed tomography (CT) scanning, as well as CT angiography, has been used to identify severe CAD; both techniques identify CAD presence and severity independent of and substantially incremental to clinical risk scores (2). However, CT angiography has similar drawbacks to stress testing. In addition, the application of imaging to large numbers of patients suspected of having CAD would not be practical. Lastly, both stress testing and CT imaging come with the challenge of high costs.

SEE PAGE 1157

A relatively unexplored approach for identifying significant CAD is the use of clinical and biomarker scoring systems. Wilson et al. (2) developed one of the earliest CAD risk-prediction models in the Framingham Heart Study based on traditional risk factors. Such models predict risk for events but lack discrimination for anatomically significant CAD (3). More recently, Bolton et al. (4) showed that addition of genetic testing to conventional risk factors improved prediction of CAD. Lastly, in testing 359 patients referred for coronary angiography, LaFramboise et al. (5) found significant differences in several circulating proteins in those patients with significantly obstructive CAD versus those without. These latter results provided proof of concept but were in a much smaller population of patients with low pre-test probability for disease presence.

Accordingly, the goal of the present study was to identify clinical and biomarker predictors of clinically significant CAD in an at-risk population of subjects enrolled in the CASABLANCA (Catheter Sampled Blood Archive in Cardiovascular Diseases) study undergoing coronary angiography for numerous indications (6). We hypothesized that the addition of plasma biomarkers to known clinical risk factors might increase the accuracy of predicting clinically significant CAD.

PATIENTS AND METHODS

All study procedures were approved by the Partners HealthCare Institutional Review Board and conducted in accordance with the Declaration of Helsinki.

The design of the CASABLANCA study has been described previously (6). Briefly, a convenience sample of 1,251 patients undergoing coronary and peripheral angiography with or without intervention between 2008 and 2011 were prospectively enrolled at the Massachusetts General Hospital in Boston, Massachusetts. Patients were referred for these procedures for numerous reasons, including angiography after acute processes such as myocardial infarction (MI), unstable angina pectoris, and heart failure, as well as for nonacute indications, such as the diagnostic evaluation of stable chest pain and failed stress testing or pre-operatively before heart valve surgery.

DATA ACQUISITION. After obtaining informed consent, detailed clinical and historical variables and reason for referral for angiography were recorded at the time of the procedure. Results of coronary angiography (based on visual estimation at the time of the procedure) were recorded; the left main, left anterior descending, left circumflex, and right coronary artery were each considered major coronary arteries, and the highest percent stenosis within each major coronary artery or their branches was recorded. For the purposes of this analysis, we characterized "significant" coronary stenosis as ≥70% luminal obstruction. Although less severe stenoses might be associated with risk for cardiovascular events, we elected to use a widely accepted standard for defining angiographic "significance."

FOLLOW-UP. Medical record review from time of enrollment to end of follow-up was undertaken. For identification of clinical endpoints, review of medical records as well as telephone follow-up were performed with patients and/or their managing physicians. The Social Security Death Index and/or postings of death announcements were used to confirm vital status. A detailed definition of endpoints for CASABLANCA has been published previously (6). The following clinical end events were