European Society of Cardiology–Recommended Coronary Artery Disease Consortium Pretest Probability Scores More Accurately Predict Obstructive Coronary Disease and Cardiovascular Events Than the Diamond and Forrester Score

The Partners Registry

BACKGROUND: The most appropriate score for evaluating the pretest probability of obstructive coronary artery disease (CAD) is unknown. We sought to compare the Diamond-Forrester (DF) score with the 2 CAD consortium scores recently recommended by the European Society of Cardiology.

METHODS: We included 2274 consecutive patients (age, 56±13 years; 57% male) without prior CAD referred for coronary computed tomographic angiography. Computed tomographic angiography findings were used to determine the presence or absence of obstructive CAD (≥50% stenosis). We compared the DF score with the 2 CAD consortium scores with respect to their ability to predict obstructive CAD and the potential implications of these scores on the downstream use of testing for CAD, as recommended by current guidelines.

RESULTS: The DF score did not satisfactorily fit the data and resulted in a significant overestimation of the prevalence of obstructive CAD (P<0.001); the CAD consortium basic score had no significant lack of fitness; and the CAD consortium clinical provided adequate goodness of fit (P=0.39). The DF score had a lower discrimination for obstructive CAD, with an area under the receiver-operating characteristics curve of 0.713 versus 0.752 and 0.791 for the CAD consortium models (P<0.001 for both). Consequently, the use of the DF score was associated with fewer individuals being categorized as requiring no additional testing (8.3%) compared with the CAD consortium models (24.6% and 30.0%; P<0.001). The proportion of individuals with a high pretest probability was 18% with the DF and only 1.1% with the CAD consortium scores (P<0.001).

CONCLUSIONS: Among contemporary patients referred for noninvasive testing, the DF risk score overestimates the risk of obstructive CAD. On the other hand, the CAD consortium scores offered improved goodness of fit and discrimination; thus, their use could decrease the need for noninvasive or invasive testing while increasing the yield of such tests.
Individuals with stable coronary artery disease (CAD) experience lower quality of life and higher rates of adverse cardiovascular events and mortality compared with healthy individuals. In individuals with chest pain, both non-invasive and invasive investigations of CAD are often used to establish prognosis and to guide treatment. However, studies have shown a relatively low prevalence of either ischemia or obstructive CAD on noninvasive imaging and invasive angiography (IA) in this population. Therefore, additional methods are needed to improve patient selection for such testing.

US and European guidelines recommend using a diagnostic strategy tailored to the individual's pretest probability of obstructive CAD. Although individuals with a very low probability may not need further investigation, among those with an extremely high pretest probability, it may be reasonable to proceed directly to IA for risk stratification. For individuals with an intermediate probability of obstructive CAD, guidelines recommend further evaluation with noninvasive cardiovascular imaging. The first score to calculate the pretest probability of obstructive CAD, introduced >3 decades ago in a seminal work by Diamond and Forrester, is a simple, easy score recommended in the American College of Cardiology/American Heart Association (ACC/AHA) guidelines and appropriate use criteria for stable CAD. However, a recent European study demonstrated that although the predictors selected by Diamond and Forrester are robust, their calibration was not adequate for the modern population of patients investigated for CAD. Recognizing these limitations, the most recent European Society of Cardiology (ESC) guidelines for stable CAD have replaced the DF score with 2 new revised scores.

As a result, significant differences now exist between European and US guidelines for evaluating individuals with chest pain. However, the implications resulting from these differences have not yet been evaluated. Moreover, no study to date has evaluated the potential role of these clinical scores in predicting adverse cardiovascular events. In the present study, we compared the ACC/AHA–recommended DF score with the 2 scores recommended by the ESC in respect to their ability to predict the presence of obstructive CAD and the association of these scores with adverse cardiovascular events in a cohort of individuals with no prior CAD referred for coronary computed tomography angiography (CTA).

**METHODS**

**Study Population**

We included in a registry all consecutive subjects ≥18 years of age who underwent a clinically indicated coronary CTA for the evaluation of suspected CAD at the Massachusetts General Hospital or Brigham and Women's Hospital from 2004 to 2011. We excluded patients who were missing any of the clinical information needed to calculate the pretest probability, who had nondiagnostic coronary CTA images, or who had incomplete follow-up information. Patients with congenital heart disease, heart transplantation, or prior CAD, defined as prior percutaneous coronary interventions, coronary artery bypass graft surgery, or myocardial infarction (MI), were also excluded (Figure 1 in the online-only Data Supplement). The Human Research Committee of both institutions approved the study. Retrospective review of previously existing clinical data was considered exempt by the Partners Institutional Review Board in accordance with standard practice. Institutional Review Board permission was granted to contact patients, if indicated, by mail or phone, who then voluntarily provided consent at the time of contact.

**Ascertainment of Risk Factors**

Systemic arterial hypertension was defined as a systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or diagnosis/treatment of hypertension. Dyslipidemia was defined as total cholesterol >240 mg/dL, serum triglycerides >150 mg/dL, high-density lipoprotein cholesterol <40 mg/dL (men) or <50 mg/dL (women), or diagnosis/treatment of dyslipidemia. Diabetes mellitus was defined by a hemoglobin A1c ≥6.5%, physician-based diagnosis, or use of glucose-lowering medications. Smoking was defined as current (tobacco products used within the last month), former, or never. Family history of premature CAD was defined as a self-reported history of any first-degree family member with a history of MI, percutaneous
coronary intervention, or revascularization before 60 years of age. Ethnicity was self-reported and identified as white, black, Hispanic, Asian, other, unknown, or refused.

CTA Examination Acquisition and Interpretation
All scans were performed with 64-row computed tomography scanners or newer technologies. The studies were performed according to established guidelines17,18 and institutional protocols at the time of the scan. After each scan, the images were reconstructed in single-phase or multiphase data sets, and images were interpreted with the use of axial and multiplanar reformations.

All scans were analyzed by level III–trained cardiologists or radiologists with extensive experience in coronary CTA analysis. The coronary CTAs were interpreted according to current guidelines18 with a previously published 18-segment model.18 Each coronary segment with a >2-mm diameter was analyzed for the presence of coronary atherosclerosis, and each lesion was quantified by visual estimation into 3 categories: normal, nonobstructive disease (1%–49% stenosis), and obstructive disease (≥50% stenosis). Obstructive CAD was defined as at least 1 segment with a lesion with ≥50% stenosis.

Pretest Probability Scores
The DF pretest probability was calculated on the basis of the chest pain type (nonanginal chest pain, atypical angina, or typical angina), sex, and age. This score was developed using conditional probability and modeled to predict a lesion with ≥50% stenosis for individuals between 30 and 69 years of age.8 We used a revised version of the DF score that allows the inclusion of patients >69 years of age and incorporates age as a continuous variable (Table 1).14

We compared the DF score with 2 CAD consortium models according to the coefficients provided by Genders et al.13 The first model, called the CAD consortium basic, was based on age, sex, and chest pain type (typical, atypical, or nonanginal chest pain). Although the score uses the same parameters as the original DF, the model was developed to detect a ≥50% stenosis on IA or coronary CTA. The score was developed using more advanced statistical modeling strategies that were not available when the DF model was derived. Additionally, the population had a lower prevalence of disease than the original DF derivation cohort did (Table 1). The second model, called the CAD consortium clinical, included the same characteristics as the CAD basic but also included the following clinical risk factors: diabetes mellitus, smoking status, hypertension, and dyslipidemia (Table 1). Moreover, for the clinical model, the presence of typical chest pain was weighted less in diabetics than in nondiabetics. The CAD consortium clinical was developed with logistic regression and was validated for populations with a lower prevalence of disease than the population used in the derivation of DF. Prior studies have provided detailed definitions and validation for each parameter in the model.13

Cardiovascular Outcomes
For the survival analysis, we used the primary composite end point of the major adverse cardiovascular events (MACEs) composed of cardiovascular mortality, nonfatal MI, late coronary revascularization (>90 days), and unstable angina requiring hospital admission.

All patient charts were reviewed for the adjudication of cardiovascular events by 2 cardiologists who were blinded to coronary CTA results. To ensure that events outside our healthcare network were captured, a standardized questionnaire was mailed to each patient. Additionally, patients had the option of completing a web-based version of the questionnaire via the REDCap (Research Electronic Data Capture) system,19 which is encrypted, secure, and Health Insurance Portability and Accountability Act compliant. For patients who did not reply to the questionnaire on repeated mailings, scripted phone interviews were performed based on the questionnaire. All self-reported events were verified via outside medical record review by 2 cardiologists blinded to coronary CTA results with discordant events adjudicated by consensus.

Deaths were confirmed by the Social Security Death Index. For all patients who died, the cause of death was obtained from the National Death Index. When data were not available, records from the Massachusetts Department of Vital Statistics were obtained. In addition, other pertinent clinical records (eg, death notes, autopsy findings, hospice notes) related to the cause of death were reviewed. Using all available data, 2 cardiologists blinded to the coronary CTA results adjudicated the cause of death for each patient. The cause of death was considered to be of cardiovascular origin if the primary cause was defined as acute MI, atherosclerotic coronal vascular disease, congestive heart failure, valvular heart disease, arrhythmias, stroke, or other structural or primary cardiac cause of death. MI was defined when at least 2 of the following 3 criteria were met: chest pain or equivalent symptom complex, positive cardiac biomarkers, or typical ECG changes.20 For revascularizations, the time to the first coronary revascularization procedure (percutaneous coronary intervention or coronary artery bypass graft surgery) was evaluated. Early revascularizations (<90 days after coronary CTA) were censored in the survival analysis to minimize verification bias21–23 because patients with ≥50% stenosis by coronary CTA may be referred for IA and revascularization on the basis of the coronary CTA results alone. On the other hand, late revascularizations (>90 days after coronary CTA) are more likely to be associated with CAD progression and were therefore included as part of the composite end point. Unstable angina requiring admission was defined as chest pain or chest pain equivalent with dynamic ECG changes such as ST depression or T-wave inversion but without abnormal cardiac biomarkers and characterized by rest symptoms, new-onset angina (<2 months’ duration), or increasing duration or severity of previously stable anginal symptoms.24

Planned Strategy According to Guidelines
To evaluate how the results of each score might influence the use of downstream noninvasive and invasive testing, we stratified each score result as low (<5%), intermediate (5%–70%), or high (>70%) pretest probability of obstructive CAD, defined as ≥50% stenosis in at least 1 vessel. Those cutoff values were based on the 2012 ACC/AHA guidelines,6 which state that individuals with a low (<5%) pretest probability are unlikely to benefit from additional testing and those with an intermediate probability (5%–70%) are most likely to benefit from an initial noninvasive test. Lastly, individuals with a high...
The pretest probability might be considered to have presumed CAD, although additional testing, including direct referral for IA, should be considered for further risk stratification.

**Statistical Analysis**
Continuous variables are expressed as mean±SD except for time of follow-up, which is expressed as median and interquartile range. Categorical variables are presented as absolute numbers and frequencies. Differences between groups were tested with χ² or the Fisher exact test for discrete variables and 1-way ANOVA for continuous variables.

For each of the pretest probability scores (DF, CAD consortium basic, and CAD consortium clinical), we plotted the pretest probability across deciles of the population versus the actual observed presence of obstructive disease on coronary CTA. Additionally, we calculated the Hosmer-Lemeshow goodness of fit for each of the prediction models. In this analysis, models with a value of P<0.05 were considered to have adequate fit of the data, whereas higher P values signified inadequate fit. To evaluate model discrimination, we constructed receiver-operating characteristics curves and compared the area under the receiver-operating characteristics curve (AUC) for each model using the presence of obstructive (>50% stenosis) as the outcome. The positive predictive value of each score was defined as the proportion of patients with obstructive CAD among those classified as high pretest probability by the score, whereas the false-negative rate was defined as the proportion of individuals with obstructive CAD among those classified as low pretest probability by each score.

To evaluate the ability to predict future MACEs, we built univariable Cox proportional hazard models for each of the 3 scores, constructed receiver-operating characteristics curves, compared the AUC for the 3 models using the Harrel c index, and calculated the confidence intervals using the Somers D statistics. Additionally, we evaluated the goodness of fit using the Gronnesby and Borgan test in which a nonsignificant P value indicates adequate fit of the model. The assumption of proportional hazards was tested with a formal significance test based on the unscaled and scaled Schoenfeld residuals and resulted in nonsignificant findings in all analyses.

To compare the prevalence of individuals stratified as low (<5%), intermediate (5%–70%), or high (≥70%) pretest probability of obstructive CAD, defined as ≥50% stenosis in at least 1 vessel, we performed χ² tests. Statistical analysis was performed with Stata version 12 (StataCorp, College Station, TX), and statistical significance was defined as a 2-tailed value of P<0.05.

**RESULTS**

**Patient Population and Baseline Characteristics**
Among 2274 patients who met our inclusion and exclusion criteria and had all clinical information needed to calculate all scores, the mean age was 56±13 years, 1289 (57%) were male, and 501 (22%) had obstructive CAD. Other baseline characteristics are presented in Table 2. Information on the differences between included and excluded individuals is presented in [Table I in the online-only Data Supplement](http://circ.ahajournals.org/content/134/20/204.full.pdf).

When stratified by the presence or absence of obstructive CAD on coronary CTA, the presence of obstructive disease was associated with older age, male sex, symptoms, and all traditional cardiovascular risk factors except family history of premature CAD (Table 2). The pretest probability of CAD in individuals with obstructive disease was higher than for those with no obstructive disease for all 3 scores (DF, CAD consortium basic, and CAD consortium clinical; Table 2).

**Comparison of Pretest Probability Scores to Predict Obstructive CAD**
Although higher scores were associated with a higher probability of obstructive disease for all 3 scores (Figure 1), the DF score demonstrated a poor model fit (P<0.001), leading to an important overestimation of disease prevalence, mainly for individuals with higher scores. For example, in the second blue dot from right to left in Figure 1A, the pretest score estimated a probability of disease of 0.70, although the actual observed prevalence of obstructive CAD was only 0.30 on the basis of the coronary CTA. For the CAD consortium basic score, no significant lack of fitness was noted, although small deviations cannot be excluded because of the borderline value of P=0.08, whereas the CAD consortium clinical score provided adequate goodness of fit (P=0.39; Figure 1B and 1C).

The DF score was also less capable of discriminating between individuals with and without obstructive CAD. The DF had a lower discrimination than the other mod-

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<th>Table 1. Information on How the DF, CAD Consortium Basic, and CAD Consortium Clinical Scores Were Derived</th>
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ACC/AHA indicates American College of Cardiology/American Heart Association; CAD, coronary artery disease; CTA, computed tomography angiography; DF, Diamond-Forrester; and ESC, European Society of Cardiology.
Comparison of Pretest Probability Scores to Predict Adverse Cardiovascular Events

During a median follow-up of 3.3 years (interquartile range, 1.9–4.7 years), the primary outcome of MAC-Es occurred in 148 individuals (6.5%). This included 38 (1.7%) cardiovascular deaths, 33 (1.5%) MIs, 27 (1.3%) unstable angina cases, and 67 (3%) late revascularizations.

Although these scores were not designed to predict future cardiovascular events, we have compared their ability to discriminate between individuals who experienced incident MAC-Es and those who did not. The DF score had the worst discriminatory ability for MAC-Es (AUC, 0.623; 95% confidence interval, 0.578–0.668); the CAD consortium basic score had a significantly higher AUC (0.638; 95% confidence interval, 0.593–0.682); and the CAD consortium clinical score had the highest AUC (0.687; 95% confidence interval, 0.646–0.728).

Implications of Pretest Probability Scores on the Use of Cardiac Testing

With the use of DF, only 188 individuals (8.3% of the entire cohort) were classified as low risk and thus would not need additional testing according to guidelines. This proportion increased to 560 (24.6%; P<0.001) with the use of the CAD consortium basic model and to 6823 (30.0%; P<0.001) with the use of the CAD consortium clinical model (Figure 3). The use of the DF score also resulted in a significantly larger proportion of individuals with a high pretest probability compared with the CAD consortium scores (410 individuals [18.0%] versus 1.1% for both CAD consortium scores; Figure 3).

Importantly, although the positive predictive value was only 44% (180 of 410) with the DF, it was higher for...
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Figure 1. Predicted vs observed probability of coronary artery disease (CAD) for the Diamond-Forrester (A), CAD consortium basic (B), and CAD consortium clinical (C) risk scores.

The blue dots represent the deciles of pretest probability according to each scores, and the red line represents the fitted line of pretest probability to observed prevalence of obstructive CAD. The dotted line is where the line would be if agreement were perfect.

**DISCUSSION**

In the present study, we have demonstrated that estimation of the pretest probability of CAD as recommended by the ACC/AHA guidelines or by the ESC guidelines results in significantly different risk estimations, which may influence the use of downstream testing and medical therapies for a significant proportion of individuals evaluated for chest pain. The DF score resulted in a significant overestimation of the prevalence of obstructive CAD compared with the 2 models recommended by the ESC. Thus, the use of this risk score may result in the overuse of noninvasive and invasive diagnostic testing in individuals with a low prevalence of disease. In addition, the DF score had a lower discrimination for obstructive disease compared with the ESC-recommended scores.
Our results suggest that because of the differences in risk classification observed in our study, replacing the DF risk score by the CAD consortium clinical score would result in as much as a 95% reduction in the number of individuals categorized as having a high pretest probability. Because this is a subgroup who, per guideline recommendations, would subsequently be treated as having presumed CAD and could be referred directly to IA, a reduction in this subgroup could significantly decrease the use of testing in a group of individuals unlikely to have significant disease. At the same time, our study estimates that using the CAD consortium clinical score could result in a 3-fold increase in the number of individuals who would be categorized as low risk and subsequently would not require any additional testing (9% to 31%). Moreover, the use of the CAD consortium clinical score would increase the yield of testing (ie, the proportion of individuals referred for testing who are found to have abnormal results) among those with a high pretest probability from 44% to \(\approx 80\%\). Interestingly, although these scores were not designed to predict incident cardiovascular events, the CAD consortium scores recommended by the ESC also had a significantly better discrimination for incident cardiovascular events.

The DF risk score represents a seminal achievement in clinical reasoning and has built the foundation for the
assessment of pretest probability of CAD using bayesian reasoning. However, the original validation of the DF risk score occurred decades ago among patients referred for IA or on autopsy, whereas contemporary patients are more likely to undergo noninvasive testing and may be of lower probability of disease. Several factors may account for this trend: wider availability and use of noninvasive testing, increased awareness and recognition by patients of anginal symptoms and thus a higher likelihood of presenting earlier in the disease course, and increased use of preventive medical therapies even before the clinical presentation starts. Our results are consistent with several studies investigating the accuracy of the DF risk score in the current era. One important study occurred in the international CONFRIM (Coronary CT Angiography Evaluation For Clinical Outcomes: An International Multicenter) Registry. This study evaluated 14,048 subjects with suspected CAD who underwent CTA and determined that the DF score markedly overestimated the likelihood of obstructive CAD at all centers in the cohort and across all age and sex groups. For example, patients presenting with atypical angina had an observed prevalence of 15% obstructive CAD versus 47% predicted. Similarly, those with typical angina had 29% observed versus 86% predicted probability. This overestimation was also demonstrated in other studies. Emphasizing the implications of risk scores on the appropriate use criteria, a study by Wasfy et al suggested that the choice of pretest probability scores could reclassify the level of appropriateness in a significant proportion of patients referred for noninvasive testing for CAD symptoms. This study concluded that the Duke Clinical Score was more accurate in predicting obstructive CAD and that this could significantly affect the classification of test appropriateness based on published criteria. However, their cohort was much smaller than in the present study, and the data precede the development of the CAD consortium scores.

On the basis of these limitations of the DF scores, the CAD consortium developed and validated new clinical risk scores that were based not only on patients referred for IA, who are likely to have higher pretest probabilities, but also on individuals with low and intermediate pretest probability who were referred to coronary CTA. Both scores developed and validated by this consortium were based on multicenter registries of patients in the United States and Europe. Although their study performed internal validation of the scores, to the best of our knowledge, the present data are the first external validation of their scores in the literature, and the results are remarkably similar. Despite differences in data collection, secular trends, and local patterns for referrals and other potential differences between studies, our findings support the CAD consortium scores as extremely robust scores for the prediction of obstructive disease. These scores were better calibrated than the DF score in our sample, with notable improvement in goodness of fit for the CAD consortium clinical score. Additionally, they had a significantly better discrimination for obstructive disease compared with the DF score.

Our finding that contemporary risk scores classify fewer patients as high and more patients as low pretest probability carries substantial economic implications. Although <10% of our cohort would be considered at low enough pretest probability to defer additional testing by DF, >30% could potentially defer further testing by the CAD consortium scores. Likewise, a sizeable reduction in the individuals who would be presumed to have obstructive CAD and might be considered candidates for invasive risk assessment, from 16.3% to 1% of the population, was noted. Reducing the overestimation of pretest risk among individuals being evaluated for potential testing could lead to a reduction in noninvasive and invasive testing. In the current era of cost containment, and given the low prevalence of obstructive CAD among patients referred for invasive and noninvasive CAD testing, even if the reduction in further testing is smaller than anticipated by the above estimates, it could still have important economic implications.

Another important finding of our study was the evaluation of prognosis according to the pretest probability scores. Our study suggests that although the CAD consortium clinical score had a somewhat better discrimination for future cardiovascular events compared with both the DF and the CAD consortium basic scores, none of the models had a good discrimination for future cardiovascular events. Although this finding supports this score as the most appropriate pretest probability score for the investigation of stable CAD, this was not unexpected because the main difference between this score and the other 2 scores is that it also incorporates clinical risk factors for CAD (eg, diabetes mellitus, hypertension, smoking, and dyslipidemia), which are well known markers of future cardiovascular events. Nevertheless, a key finding on prognosis in the present study is the fact that regardless of the pretest probability score used, the rate of MACEs in individuals with a low pretest probability score is equally low. This finding further supports the safety of withholding additional testing in this population.

Our study must, however, be read within the context of its design. First, the ACC/AHA guidelines suggest that either the DF score or the Duke Clinical Score can be used to estimate the pretest probability score. Although we did not have all the clinical information such as ECG findings to calculate the Duke Clinical Score, prior data suggest that both studies have comparable performance. Additionally, although the present findings corroborate data from other studies and validate previously developed scores, the actual reductions in the use of additional testing may be highly variable and depend on local clinical practice patterns. Even though our analysis assumes that patient management will be dictated by guidelines, the real-life impact of these scores depends on the actual implemen-
tation of those recommendations in actual practice and variability in physician and patient preferences. Furthermore, we used coronary CTA as the reference standard to establish the diagnosis of obstructive CAD. Because coronary CTA may overestimate the prevalence of obstructive disease, the use of IA could have resulted in an even lower observed prevalence of disease (and possibly need for additional testing) than predicted by our study. Additionally, Hosmer-Lemeshow goodness of fit has known limitations for the evaluation of calibration. Although our results are most applicable to patients referred for coronary CTA, we anticipate that these findings would have important implications for patients who are considered for other noninvasive or invasive testing because the absence of obstructive CAD on coronary CTA has a very high negative predictive value to exclude ischemia on functional testing and because the consortium clinical score was validated both for individuals undergoing coronary CTA and for those undergoing IA. Nevertheless, our results may be less applicable to higher-risk cohorts and should not be extrapolated to the emergency department setting.

CONCLUSIONS

Use of the CAD consortium pretest probability scores, particularly the CAD consortium clinical score, results in improved model goodness of fit and provides better discrimination for the detection of obstructive CAD than the DF risk score. Although warranting further validation with both invasive and noninvasive testing, our results, which are based on coronary CTA, suggest that the use of the CAD consortium scores could potentially reduce unnecessary referrals for noninvasive cardiovascular imaging tests and IA for the investigation of stable chest pain. Although requiring additional external validation, our findings suggest that such a reduction in testing may be accompanied by an increase in the yield of both noninvasive and invasive testing. Thus, the present study supports the replacement of the DF risk score by the CAD consortium clinical score as the recommended pretest probability score for the investigation of patients with suspected obstructive CAD.

SOURCES OF FUNDING

Dr Bittencourt was supported by the J.P. Lemann Foundation as a Jorge Paulo Lemann Harvard Medical School Cardiovascular Fellow at Brigham and Women’s Hospital.

DISCLOSURES

The opinions and assertions contained herein are the authors’ alone and do not represent the views of Walter Reed National Military Medical Center, the US Army, or the Department of Defense.

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FOOTNOTES

Received January 4, 2016; accepted June 13, 2016.

The online-only Data Supplement is available with this article at http://circ.ahajournals.org.

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European Society of Cardiology–Recommended Coronary Artery Disease Consortium Pretest Probability Scores More Accurately Predict Obstructive Coronary Disease and Cardiovascular Events Than the Diamond and Forrester Score: The Partners Registry Marcio Sommer Bittencourt, Edward Hulten, Tamar S. Polonsky, Udo Hoffman, Khurram Nasir, Suhny Abbara, Marcelo Di Carli and Ron Blankstein

*Circulation*. 2016;134:201-211; originally published online July 13, 2016; doi: 10.1161/CIRCULATIONAHA.116.023396

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://circ.ahajournals.org/content/134/3/201

Data Supplement (unedited) at:

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Supplemental material

Supplemental figure 1: flowchart of the patient selection
Supplemental table 1. Baseline demographic characteristics according to the presence and severity of CAD.

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*: results are presented as means and standard deviation