



A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension

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Aims

The aim was to validate, update, and extend the Diamond–Forrester model for estimating the probability of obstructive coronary artery disease (CAD) in a contemporary cohort.

Methods and results

Prospectively collected data from 14 hospitals on patients with chest pain without a history of CAD and referred for conventional coronary angiography (CCA) were used. Primary outcome was obstructive CAD, defined as $\geq 50\%$ stenosis in one or more vessels on CCA. The validity of the Diamond–Forrester model was assessed using calibration plots, calibration-in-the-large, and recalibration in logistic regression. The model was subsequently updated and extended by revising the predictive value of age, sex, and type of chest pain. Diagnostic performance was assessed by calculating the area under the receiver operating characteristic curve (*c*-statistic) and reclassification was determined. We included 2260 patients, of whom 1319 had obstructive CAD on CCA. Validation demonstrated an overestimation of the CAD probability, especially in women. The updated and extended models demonstrated a *c*-statistic of 0.79 (95% CI 0.77–0.81) and 0.82 (95% CI 0.80–0.84), respectively. Sixteen per cent of men and 64% of women were correctly reclassified. The predicted probability of obstructive CAD ranged from 10% for 50-year-old females

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with non-specific chest pain to 91% for 80-year-old males with typical chest pain. Predictions varied across hospitals due to differences in disease prevalence.

Conclusion

Our results suggest that the Diamond–Forrester model overestimates the probability of CAD especially in women. We updated the predictive effects of age, sex, type of chest pain, and hospital setting which improved model performance and we extended it to include patients of 70 years and older.

Keywords

Coronary artery disease • Stable chest pain • Angina pectoris • Pre-test probability • Prediction model • Validation

Introduction

In patients presenting with chest pain suggestive of stable angina pectoris, numerous diagnostic strategies can be used. The reference standard for diagnosing coronary artery disease (CAD) is conventional coronary angiography (CCA). However, CCA is expensive and involves a small risk of complications and death.¹ Therefore, non-invasive testing is recommended to select patients who will benefit from CCA.^{2–4} The clinical value of non-invasive diagnostic tests depends on the test sensitivity, the specificity, the potential gain from making the correct diagnosis, the potential harm caused by false-positive test results, and the pre-test (prior) probability of the suspected disease.^{5–7} In choosing the appropriate test for a particular patient with chest pain suggestive of CAD, the pre-test probability of CAD is crucial.⁷

Diamond and Forrester⁸ demonstrated the importance of the pre-test probability on interpreting test results in their classic paper in 1979. Using estimates from autopsy and cross-sectional studies, they developed a simple but elegant model that considers age, sex, and type of chest pain to estimate the probability of obstructive CAD in patients between 30 and 70 years old. In spite of its limitations, the Diamond–Forrester model is still used in current guidelines.^{2–4} Although other cardiovascular risk factors such as diabetes, smoking and dyslipidaemia have been included in, e.g. the Duke Clinical Score,^{9,10} the predictive effects of other risk factors in diagnostic models are often small compared with the predictive effects of age, sex, and type of chest pain. Furthermore, complicated models are less likely to be used by physicians in clinical practice especially since non-invasive diagnostic tests are commonly ordered immediately at the first visit. The Diamond–Forrester model allows the immediate calculation of an estimate of the patients' pre-test risk of CAD, without the need to wait for laboratory findings or exercise test results.

Since the Diamond–Forrester model was developed >30 years ago and based on data from the USA only, our aims were to study the validity of the Diamond–Forrester predictions in estimating the probability of obstructive CAD, to update the predictions using recently collected data, and to extend the model for patients beyond the age of 70, using data from contemporary cohorts.

Methods

The CAD Consortium

The CAD Consortium is part of the European network for the Assessment of Imaging in Medicine (EuroAIM), which is an initiative of the

European Institute of Biomedical Imaging Research (EIBIR).¹¹ The main goal of EuroAIM is to perform pooled analyses of existing prospectively collected data, which will improve power of the studies and increase generalizability of the results obtained.

Data collection

A consortium of researchers from various countries in Europe and the USA was formed. An existing database with prospectively collected data on 80 or more eligible patients was required for participation in this consortium. All patients included in this consortium had to be enrolled in single-centre studies, for which local approval from the Institutional Review Board and signed informed consent had been obtained. Participation in the consortium did not involve any financial incentives.

Patient population

Our patient population consists of patients with chest pain, suggestive of stable angina pectoris. Patients were eligible for the analysis if they presented with stable chest pain (typical, atypical, or non-specific chest pain) and if CCA was performed. Patients were excluded if they met one of the following criteria: (i) acute coronary syndrome or unstable chest pain, (ii) history of myocardial infarction or previous revascularization (percutaneous coronary intervention or coronary artery bypass graft surgery), and (iii) no informed consent.

Only patients who underwent CCA were eligible for this analysis, implying that our population was highly selected. To explore the effect of selection bias (i.e. verification bias) in this study population, we performed a separate analysis using inverse probability weighting on each patient in the data set. Based on an independent registry data set (not included in our consortium) consisting of unselected outpatients presenting to the cardiologist who were intended to undergo both stress-ECG and coronary CT angiography (CCTA) for the evaluation of chest pain,^{12,13} a logistic regression analysis was performed to calculate the probability of undergoing CCA (i.e. the probability of verifying the presence of CAD with CCA) depending on age, sex, and type of chest pain. Each patient was subsequently weighted with the inverse of the probability of verification which corrects for verification bias (Appendix, Correction for verification bias).^{14,15}

Clinical definitions

Data on age, sex, type of chest pain, and the presence of CAD were collected. Type of chest pain was classified as being typical, atypical, or non-specific. Typical chest pain was defined as having (i) substernal chest pain or discomfort, that is (ii) provoked by exertion or emotional stress and (iii) relieved by rest and/or nitroglycerine. Atypical chest pain was defined as having two of the before-mentioned criteria. If one or none of the criteria was present, the patient was classified as having non-specific chest pain.^{4,16}

The presence of obstructive CAD was defined as one or more vessels with $\geq 50\%$ lumen diameter reduction on CCA. As we used

existing databases, CCA was performed at each institution according to local protocols; both visual assessment and quantitative assessment were allowed for interpretation of the CCA. Indicator variables for hospital were used to allow adjustment for hospital.

Data analysis

Validation and updating of the Diamond–Forrester model was performed using state-of-the-art methods,^{17–19} by one of the authors (T.S.S.G.). See Appendix for a more detailed description of the methods.

Validation

The Diamond–Forrester model takes into account age, sex, and type of chest pain and was developed for patients between 30 and 70 years. For validation, we therefore excluded both patients below the age of 30 and patients above the age of 69.

The observed frequency of CAD in our data set was calculated stratifying for 10-year age category, sex, and type of chest pain (i.e. equivalent to the Diamond–Forrester categories). Observed frequencies of CAD were compared with the estimates according to Diamond and Forrester and subsequently tabulated and presented by means of calibration plots.

Calibration-in-the-large

When assessing the validity of a prediction model, the first step is to check whether the average prediction is equal or close to the average observed outcome. This concept is referred to as ‘calibration-in-the-large’. Hereto, we compared the mean observed frequency of CAD with the mean prediction according to Diamond and Forrester.

Recalibration

The second step is to test whether the overall effect of the predictors in the Diamond–Forrester model is valid for the consortium data.

Re-estimation

The third step is to re-estimate the predictor effects in the consortium data and to compare the effects with the original effects according to Diamond and Forrester. Subsequently, we calculated the difference between the re-estimated and the original effects (Appendix, Table A1).

Updating and extension

For updating the Diamond–Forrester model, we used all data including patients <30 and >69 years. Age, sex, and type of chest pain were entered simultaneously in a logistic regression model. All analyses were performed both unadjusted and adjusted for hospital.

Separately, we extended the model with a random intercept to allow for heterogeneity in CAD prevalence across different hospitals (Appendix, Table A3). Because of potential differences in symptom classification across hospitals, we also tested random effects for type of chest pain between different hospitals.

Diagnostic performance was quantified by calculating the area under the receiver operating curve (*c*-statistic). Calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test and a calibration plot (Appendix, Figure A2).

Reclassification was assessed by cross-tabulating the probability classification of patients according to the Diamond–Forrester model vs. the updated model. We analysed reclassification with the commonly used cutoffs of 30 and 70% (Appendix, Table A4, A6).²⁰ In a second reclassification analysis, we analysed the cutoff 40% (Appendix, Table A5, A7), which is the threshold below which CCTA is cost-effective.⁷ Furthermore, we determined the reclassification calibration statistic and the net reclassification improvement (Appendix, Table A8).^{21,22}

Validation of the updated model

As mentioned, the CAD Consortium population is highly selected based on referral to CCA. To assess the performance of the updated model in a low-risk population, we validated the updated model in an independent data set (not included in our consortium) consisting of outpatients presenting to the cardiologist who were intended to undergo both stress-ECG and CCTA for the evaluation of chest pain.^{12,13} These data were also used to perform the ‘correction for verification bias’. We followed the step-wise approach as described above. Since not all patients in this population underwent CCA, the CCTA results were used as a proxy for the reference standard in patients who did not undergo CCA.

A *P*-value <0.05 was considered statistically significant. Statistical analyses were performed using Stata/SE 10.1 (StataCorp, TX, USA). Reclassification was assessed by using syntax made available by Cook et al.²² in SAS Enterprise Guide v3 (SAS, Inc., NC, USA).

Results

Data collection and study population

Existing databases with prospectively collected data were retrieved from 14 hospitals (Table 1). After excluding 12 cases because of missing values, the total study population consisted of 2260 patients [1521 men, 739 women, mean age 62 (range 21–93, IQR 55–70)], of whom 1319 (58.4%) were found to have obstructive CAD on CCA.

For validation, we excluded patients below the age of 30 (*n* = 7) and above the age of 69 (*n* = 570). Therefore, 1683 patients [1159 (68.9%) men, 524 women] and 937 (55.7%) with obstructive CAD were left for validation.

Data analysis

Validation

Table 2 and Figures 1 and 2 show the average observed frequency of CAD in men and women, respectively, as observed in our data set, compared with the prediction according to Diamond and Forrester. In men, we observed a slight overestimation of the probability of CAD by Diamond and Forrester for patients with atypical and typical chest pain. In women, the overestimation was more pronounced. The validation of predictions for men <40 and women <50 years old was less reliable, due to the limited number of patients in these subgroups.

Calibration-in-the-large

We found that the average predicted probability according to Diamond and Forrester was higher compared with the CAD frequency in the consortium data (*P* < 0.001).

Recalibration

Recalibration demonstrated that the overall effect of the predictors in the Diamond–Forrester model was higher compared with the overall effect of the predictors in the consortium data (*P* < 0.001).

Re-estimation

The effects of age (*P* < 0.001) and type of chest pain (*P* < 0.001) were significantly larger in the Diamond–Forrester model,

Table 1 Patient characteristics, ordered according to the prevalence of coronary artery disease

Hospital, country	Medical University of South Carolina, Charleston, USA	Turku University Hospital, Finland	Innsbrück Medical University, Austria	Maasstad Ziekenhuis, Rotterdam, The Netherlands	Leiden University Medical Center, The Netherlands	Erasmus University Medical Center, The Netherlands	Charité Medical School, Berlin, Germany	University Medical Center Utrecht, The Netherlands	Papworth Hospital NHS Foundation Trust, Cambridge, UK
<i>n</i>	99	98	101	90	99	289	186	85	83
Mean age (SD)	60.3 (10.4)	64.4 (6.8)	61.2 (8.6)	59.0 (9.9)	62.1 (10.9)	59.4 (10.6)	62.7 (9.4)	60.5 (5.4)	65.5 (10.8)
Male sex (%)	49.5	58.2	58.4	58.9	56.6	68.5	71.0	67.1	65.1
Typical CP (%)	76.8	50.0	21.8	10.0	62.6	50.2	57.0	55.3	41.0
Atypical CP (%)	20.2	42.9	78.2	27.8	35.4	26.0	29.0	18.8	36.1
Non-specific CP (%)	3.0	7.1	0	62.2	2.0	23.9	14.0	25.9	22.9
CAD on CCA (%)	39.4	42.9	45.5	50.0	51.5	52.2	54.8	57.6	59.0
Hospital, country	University Hospital Parma, Italy	The Essex Cardiothoracic Centre, UK	University Hospital Leuven, Belgium	University Hospital Zurich, Switzerland	Federal Center for Medicine and Rehabilitation, Moscow, Russia	Total (CAD+)	Total (CAD-)	Total	
<i>n</i>	277	110	100	549	106	1325	947	2272	
Mean age (SD)	59.9 (11.4)	63.2 (9.5)	64.0 (10.7)	65.6 (10.9)	59.7 (8.4)	63.8	60.3 (10.9)	62.3 (10.4)	
Male sex (%)	67.9	68.2	59.0	74.5	76.4	78.0	52.2	67.2	
Typical CP (%)	65.0	52.7	58.0	53.4	56.6	69.3	30.2	53.0	
Atypical CP (%)	35.0	24.5	28.0	10.9	24.5	19.1	37.3	26.7	
Non-specific CP (%)	0	22.7	14.0	35.7	18.9	11.6	32.5	20.3	
CAD on CCA (%)	60.0	61.8	63.0	68.1	75.5	100	0	58.3	

SD, standard deviation; CP, chest pain; CAD, coronary artery disease; CCA, conventional coronary angiography.

Table 2 Head-to-head comparison of the pre-test probability according to Diamond and Forrester

	Men			Women		
	Diamond and Forrester	Observed frequency of CAD	Updated model ^a	Diamond and Forrester	Observed frequency of CAD	Updated model ^a
Typical chest pain						
30–39	69.7	90.0	59.1	25.8	b	27.5
40–49	87.3	73.2	68.9	55.2	41.4	36.7
50–59	92.0	82.0	77.3	79.4	38.5	47.1
60–69	94.3	86.1	83.9	90.6	56.9	57.7
70–79	—	88.6	88.9	—	70.8	67.7
>80	—	86.2	92.5	—	92.3	76.3
Atypical chest pain						
30–39	21.8	16.7	28.9	4.2	b	9.6
40–49	46.1	28.9	38.4	13.3	19.2	14.0
50–59	58.9	45.9	48.9	32.4	24.2	20.0
60–69	67.1	53.9	59.4	54.4	30.1	27.7
70–79	—	63.6	69.2	—	35.6	37.0
>80	—	83.3	77.5	—	b	47.4
Non-anginal chest pain						
30–39	5.2	14.3	17.7	0.8	b	5.3
40–49	14.1	20.9	24.8	2.8	0.0	8.0
50–59	21.5	28.6	33.6	8.4	22.2	11.7
60–69	28.1	50.5	43.7	18.6	18.0	16.9
70–79	—	62.1	54.4	—	22.0	23.8
>80	—	45.0	64.6	—	20.0	32.3

The observed frequency of CAD in the CAD consortium data and the prediction according to the updated model. Subgroup estimates that are overestimated by the Diamond–Forrester model are printed in boldface.

^aProbabilities shown reflect the estimates for patients aged 35, 45, 55, 65, 75, and 85 years.

^bData on subgroups with less than five observations are not shown.

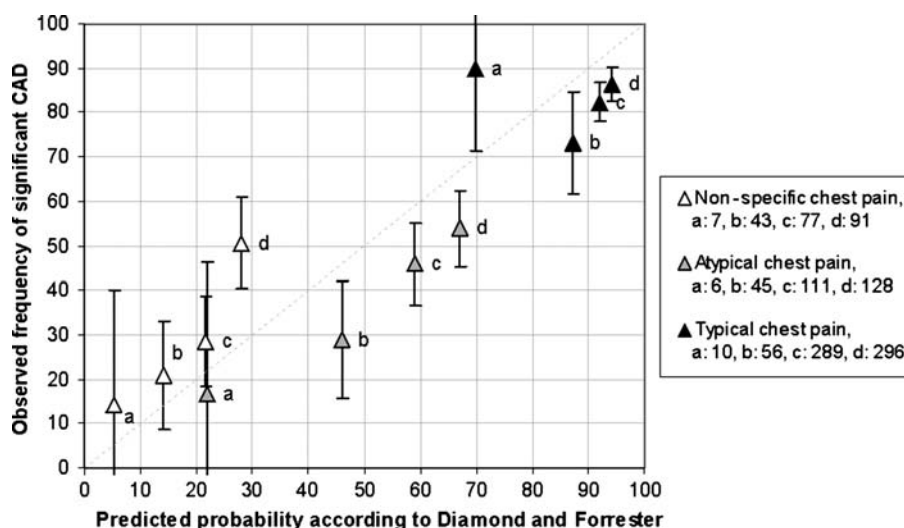


Figure 1 Predicted probability of obstructive coronary artery disease in men (triangles) for the Diamond–Forrester age categories a: 30–39, b: 40–49, c: 50–59, and d: 60–69, vs. the observed frequency of obstructive coronary artery disease in our data. The legend provides the number of patients per age category for each type of chest pain. The bars indicate the 95% confidence interval of the observed frequency.

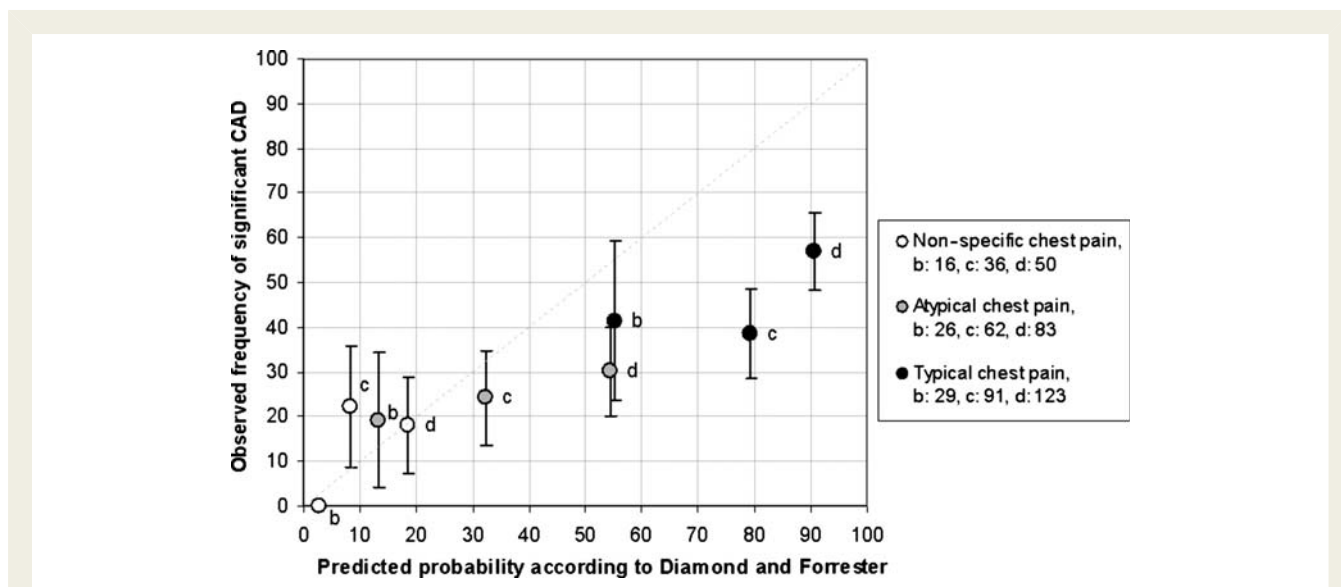


Figure 2 Predicted probability of obstructive coronary artery disease in women (circles) for the Diamond–Forrester age categories a: 30–39, b: 40–49, c: 50–59, and d: 60–69, vs. the observed frequency of obstructive coronary artery disease in our data. The legend provides the number of patients per age category for each type of chest pain. Data on subgroups with less than five observations are not shown. The bars indicate the 95% confidence interval of the observed frequency.

compared with the effects in the consortium data. We conclude that these predictors require updating.

Updating and extension

The updated model (Table 3) showed highly significant effects for age, sex, and type of chest pain, with similar effect sizes after adjustment for hospital (not shown). The area under the receiver operating characteristic curve demonstrated good performance (c-statistic: 0.79, 95 CI: 0.77–0.81). After correction for verification bias, the regression coefficients were similar (Appendix, Table A3).

Interactions between the main effects did not show statistical significance (not shown). We found significant interactions between ‘typical chest pain’ and hospital (not shown), implying that the effect of having typical chest pain on the predicted probability is different across hospitals.

Finally, a random effects logistic regression model showed that there was substantial heterogeneity in disease prevalence across hospitals. The model could not be improved by adding a random effect for atypical chest pain, whereas a random effect for typical chest pain showed statistical significance (Appendix, Table A3). The random effects model is available for online use (Figure 3). The test for a non-linear age effect was not statistically significant, which is why we assumed a linear effect for age in all models.

Analysis of reclassification in 30–69-year-old patients demonstrated that 16% of men and 64% of women reclassified correctly, when using the probability categories <30, ≥30–70, and ≥70% (Figures 4 and 5). The net reclassification index was negative for both men and women, which is explained by the fact that the updated model predicts less high probabilities compared with Diamond and Forrester, resulting in down-classification of patients among both cases and non-cases (Appendix, Table A8).

Table 3 Updating and extension of the Diamond–Forrester model (random effects model)

	Coefficient	Odds ratio	95 % CI lower limit	95 % CI upper limit
Age	0.04	1.04	1.03	1.05
Male sex	1.34	3.82	3.08	4.74
Typical chest pain	1.91	6.72	3.97	11.37
Atypical chest pain	0.64	1.89	1.38	2.59
Non-specific chest pain ^a	—	—	—	—
Intercept	−4.37	—	—	—
c-Statistic (95% CI ^b)	0.82	—	0.80	0.84

^aReference category.

^bEstimated by bootstrapping with 1000 repetitions.

Validation of the updated model

Calibration-in-the-large

The average predicted probability according to our updated model was significantly higher compared with the CAD frequency in the independent data set ($P < 0.001$).

Recalibration

Recalibration demonstrated that the overall effect of the predictors in the updated model is similar to the overall effect of the predictors in the independent registry of outpatients ($P = 0.79$). From

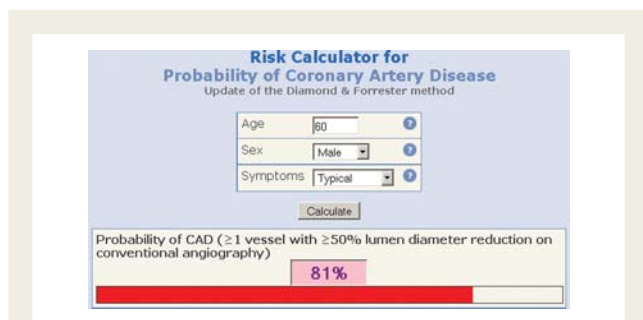


Figure 3 Online calculator example. Here, the probability of obstructive coronary artery disease is calculated for a 60-year-old male with typical chest pain. The calculator is based on the random effects model (Table 3) and is available for online use via <http://rcc.simpal.com/RCEval.cgi?Owner=tgenders&RCName=CAD%20consortium>. The recalibrated model for the low-risk populations is available via <http://rcc.simpal.com/RCEval.cgi?RCID=7TO293>.

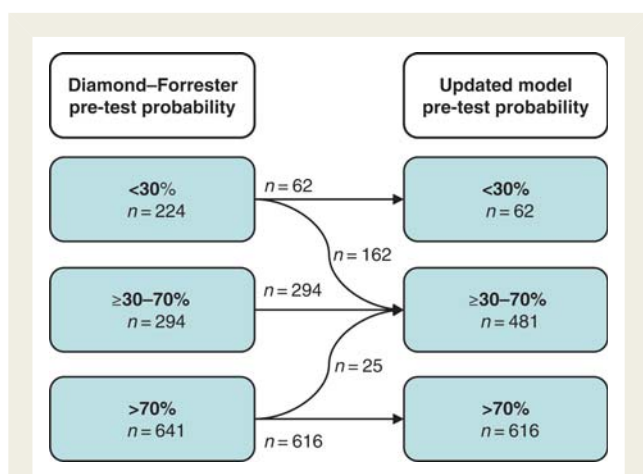


Figure 4 Reclassification flow chart for men between 30 and 70 years old. See Appendix, Table A8 for reclassification statistics.

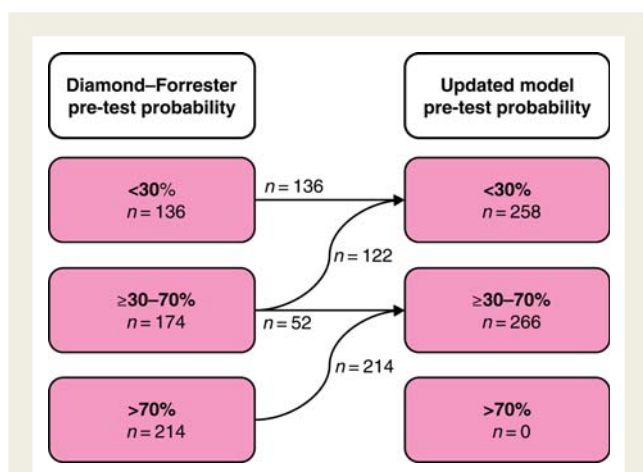


Figure 5 Reclassification flow chart for women between 30 and 70 years old. See Appendix, Table A8 for reclassification statistics.

this, we conclude that the predictor effects are valid and do not require updating (Appendix, Table A9).

The model, adjusted for the lower disease prevalence, is available for online use (Figure 3).

Discussion

Using recently collected data and modern statistical methods, we assessed whether the Diamond-Forrester model is valid in a contemporary mainly European cohort (Box 1). Furthermore, we updated and extended the model by re-estimating the predictive effects of age, sex, and type of chest pain. We observed that the prevalence of CAD was different across hospitals and adjusted for this difference.

Box 1 Study strengths and weaknesses

Strengths

- A large contemporary cohort was studied.
- Multicentre collaboration of 14 hospitals.
- Modern statistical methods were used for validation, updating, and extension of the Diamond-Forrester model.
- In contrast to the Diamond-Forrester model, the updated model uses age as a continuous predictor and also predicts probabilities for patients 70 years and older.
- An easy-to-use online probability calculator was developed.

Weaknesses

- Only age, sex, and type of chest pain were considered predictors.
- The primary outcome was limited to obstructive CAD vs. no obstructive CAD.
- Existing databases designed for other research objectives were combined.
- A high-risk population was selected by including only patients referred for coronary angiography.
- Heterogeneity across hospitals with respect to the assessment of chest pain, adherence to guidelines, and interpretation of the coronary angiographies.

In short, we validated the Diamond-Forrester predictions in patients between 30 and 70 years old. By comparing the Diamond-Forrester predicted probabilities with the average observed frequencies of obstructive CAD in our data using calibration plots, we demonstrated that there is a tendency for the Diamond-Forrester model to overestimate the prevalence of CAD in a contemporary cohort. We showed that the Diamond-Forrester model needs to be updated according to the overall disease prevalence for the current European situation. Furthermore, we demonstrated that the predictor effects in the consortium data are not as extreme as the model by Diamond and Forrester suggests.

It is important to note that the Diamond-Forrester model is based on 30–40-year-old data from the USA. To some extent,

the differences we demonstrated are explained by changes in the risk factor distributions over the past decades, as well as by the differences between populations from the USA and Europe.

All-in-all, we demonstrated that the validity of the Diamond–Forrester model for current practice is limited, which justifies updating. Furthermore, Diamond and Forrester did not provide any estimates for patients above the age of 69. Nowadays, a substantial proportion of patients with chest pain will be at least 70 years old, which motivated the extension of the Diamond–Forrester model. Therefore, we re-estimated the predictive effect of age, sex, and type of chest pain in all patients and confirmed the importance of these in the prediction of obstructive CAD. We also demonstrated that predictions may vary across different hospitals. The performance of the updated model improved discrimination and calibration, as indicated by the *c*-statistic and the non-significant Hosmer–Lemeshow test. Measures of reclassification indicated correct reclassification by the updated model of a substantial proportion of patients, especially in women. Updated predicted probabilities of obstructive CAD ranged from 10% for a 50-year-old female with non-specific chest pain to 91% for an 80-year-old man with typical chest pain. Prior studies assessed the performance of the Diamond–Forrester model²³ or developed new models to estimate the pre-test probability of CAD.^{9,10,24} However, in spite of efforts to develop new prediction models, the Diamond–Forrester model remains a common method for estimating the probability of obstructive CAD.^{2,4}

Limitations

The study population was derived from existing databases, some of which were designed for other research objectives (e.g. to investigate the diagnostic accuracy of non-invasive imaging tests for CAD). In some studies, all patients underwent the reference standard test, whereas in other studies, patients were selected for CCA based on the results of an index non-invasive test. When evaluating the diagnostic performance of the index non-invasive test, selection based on the test results may lead to ‘verification bias’ or ‘referral bias’ which may bias estimates of sensitivity and specificity of such a test. In the current study, however, we did not assess the diagnostic performance of a non-invasive test, making bias less likely. To explore the potential effect of verification bias, we used inverse probability weighting on each individual with the probability of verification based on age, sex, and type of chest pain. The analyses with or without correction for verification bias yielded similar results, indicating that our results are unlikely to be biased by selected verification.

The fact that we only included patients who underwent CCA indicates the selection process that occurred in this study. Some of the patients will have had prior positive stress testing or another non-invasive imaging test. However, the association between age, sex, type of chest pain, and the presence of obstructive CAD on CCA does not depend on whether another diagnostic imaging test was performed and whether it was positive or not. The elderly, males, and patients with typical chest pain are more likely to undergo stress testing. Such patients are therefore over-represented in our population. Incorporating the test results from the non-invasive test in the prediction model would influence

the prediction of the probability of obstructive CAD. However, our aim was to predict the presence of obstructive CAD on initial presentation prior to diagnostic testing to provide decision support for the decision to test.

The presence of obstructive CAD was determined by CCA. As existing databases were used, CCAs were carried out at each individual hospital according to local protocols. Some institutions used quantitative coronary angiography to determine the degree of stenosis, whereas others used visual assessment. All in all, heterogeneity due to differences between protocols and guidelines across hospitals could have influenced our results.

One could argue that our study population does not represent the target population of the Diamond–Forrester model because of the high prevalence of CAD. It might be more reasonable to apply the model in patients without a clinical indication for CCA and a lower probability of disease. However, despite the overall high prevalence of disease in our study population, we showed that the Diamond–Forrester model tends to overestimate the probability of CAD. The overestimation will be even larger, if the model would be applied to lower risk populations. As expected, validation of the updated model in the independent data consisting of outpatients presenting with chest pain demonstrated an overestimation of the probability of CAD, although to a lesser extent than the overestimation by Diamond and Forrester would be. Recalibration results did not justify updating of the predictor effects, suggesting that after adjusting the intercept, our updated model would be valid for the estimation of the pre-test probability of CAD in this low-risk population.

Furthermore, the Diamond–Forrester model predicts the probability of the presence vs. the absence of obstructive CAD. In validation and updating, we focused on this dichotomous outcome. This is a limitation of our study design, since detecting severe CAD (e.g. $\geq 70\%$ stenosis, multi-vessel disease, left main disease) would have different clinical implications, as those patients would be eligible for revascularization.

Although our total sample size was large, some analyses involved stratification for several variables. This resulted in small numbers of patients in the lower age categories, especially for women because women represented only 30% of the total population.

Clinical implications

According to our analysis, the Diamond–Forrester model overestimates the probability of obstructive CAD in a contemporary cohort. Thus, the pre-test probability for today’s patients can be estimated with more precision if the updated model is used.

The clinical value of a diagnostic test depends largely on the pre-test probability. A better estimate of the pre-test probability will therefore help clinicians make better decisions as to whether and which diagnostic test is indicated in a particular patient and to decide on further management based on the results of such tests. In patients with a (very) low pre-test probability of disease, a wait-and-see strategy without any testing is preferable. In patients with a high pre-test probability of disease, a direct invasive strategy is optimal. The main benefit of testing is in patients with an intermediate pre-test probability, in which a negative test rules out the presence of obstructive CAD, whereas a positive test justifies further testing.

Since the updated model predicts less high probabilities compared with the Diamond–Forrester model, using the updated model could lead to decreased referral to CCA, a higher yield of angiography, and increased use of non-invasive testing for risk stratification. This would be a welcome response to the issue brought to light by Patel et al.,²⁵ who reported that the diagnostic yield of elective coronary angiography in the USA was only 41% (i.e. only 41% was found to have obstructive CAD) and concluded that better risk-stratification tools are needed.

Finally, the revised model is user-friendly and requires only three inputs from the physician. The model can be used via the website, or it could be implemented in electronic patient records or electronic order entry systems.

Future research

Our study focused on the prediction of obstructive CAD according to age, sex, type of chest pain, and hospital only. Other risk factors such as smoking, diabetes, hypertension and dyslipidaemia have previously been demonstrated to be associated with the presence of CAD.²⁶ Therefore, other known cardiovascular risk factors should be considered in future prediction models. On the other hand, the predictive effects of cardiovascular risk factors (in diagnostic models) are probably small in comparison with the predictive effects of age, sex, and type of chest pain, and care should be taken to minimize the number of variables, because simple prediction tools are more likely to be used by physicians in clinical practice.

Prospective data should be collected for the development and validation of prediction models, including a more heterogeneous study population. For example, including populations with a lower overall probability of obstructive CAD would improve the generalizability of the results.

Conclusion

All-in-all, we updated and extended the predictive effects of age, sex, and type of chest pain, based on a contemporary cohort and using modern statistical methods. We demonstrated that the Diamond–Forrester model can be improved for the current European situation. The updated model is available online.

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Appendix

Validation and updating of the Diamond–Forrester model was performed by T.S.S.G., using state-of-the-art methods.^{17–19}

Validation

The Diamond–Forrester model takes into account age, sex, and type of chest pain and was designed for patients between 30 and 70 years only. For the validation of the Diamond–Forrester model, we therefore excluded both patients below the age of 30 and patients above the age of 69.

'Original' Diamond–Forrester coefficients

The Diamond–Forrester model⁸ is based on a Bayesian analysis. Therefore, it does not provide regression coefficients for the effects of age, sex, and type of chest pain on the probability of CAD. To unravel the implicit coefficients of the predictors in this model, we performed a weighted linear regression on the log odds of the Diamond–Forrester predictions per subgroup. The weights were proportional to the inverse of the standard errors reported by Diamond and Forrester. The coefficients obtained by the weighted linear regression are further referred to as the 'original coefficients' of Diamond and Forrester.

The observed frequency of CAD in our data set was calculated stratifying for 10-year age category, sex, and type of chest pain (i.e. equivalent to the Diamond–Forrester categories). Observed frequencies of CAD were compared with the predicted probabilities of CAD according to Diamond and Forrester and were subsequently tabulated (Table 2) and presented by means of calibration plots (Figures 1 and 2).

1. $\text{Logit}(p\text{CAD})_{\text{data}} = \alpha_{\text{new}} + \text{offset}(lp_{\text{D\&F}})$
2. $\text{Logit}(p\text{CAD})_{\text{data}} = \alpha_{\text{new}} + \beta_{\text{miscalibration}} \cdot lp_{\text{D\&F}} + \text{offset}(lp_{\text{D\&F}})$
3. $\text{Logit}(p\text{CAD})_{\text{data}} = \alpha_{\text{new}} + \delta_{\text{age}} \cdot X_{\text{age}} + \delta_{\text{sex}} \cdot X_{\text{sex}} + \delta_{\text{typical}} \cdot X_{\text{typical}} + \delta_{\text{atypical}} \cdot X_{\text{atypical}} + \text{offset}(lp_{\text{D\&F}})$
4. $\text{Logit}(p\text{CAD})_{\text{data}} = \alpha_{\text{new}} + \beta_{\text{age}} \cdot X_{\text{age}} + \beta_{\text{sex}} \cdot X_{\text{sex}} + \beta_{\text{typical}} \cdot X_{\text{typical}} + \beta_{\text{atypical}} \cdot X_{\text{atypical}}$
5. $\text{Logit}(p\text{CAD})_{\text{data}} = \alpha_{\text{new}}^* + \beta_{\text{age}} \cdot X_{\text{age}} + \beta_{\text{sex}} \cdot X_{\text{sex}} + \beta_{\text{typical}} \cdot X_{\text{typical}} + \beta_{\text{atypical}} \cdot X_{\text{atypical}}$
6. $\text{Logit}(p\text{CAD})_{\text{data}} = \alpha_{\text{new}}^* + \beta_{\text{age}} \cdot X_{\text{age}} + \beta_{\text{sex}} \cdot X_{\text{sex}} + \beta_{\text{typical}}^* \cdot X_{\text{typical}} + \beta_{\text{atypical}}^* \cdot X_{\text{atypical}}$

Figure A1 Equations. Logit, natural log odds of the probability; pCAD, probability of obstructive coronary artery disease; α , intercept of logistic regression model; offset, regression coefficient fixed at unity; β , regression coefficient; δ , difference between β_{new} and β_{original} (See Table A1 for ‘original’ coefficients); $lp_{\text{D\&F}}$, linear predictor of Diamond and Forrester; *, random effect.

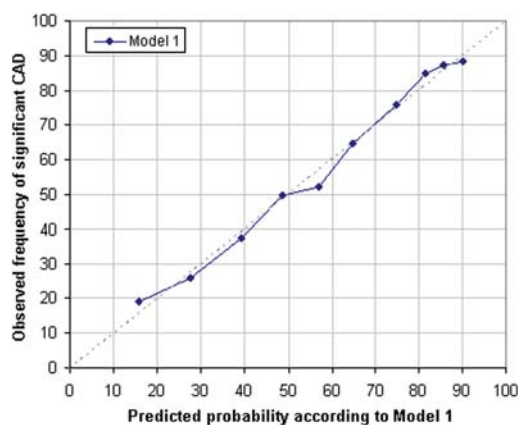


Figure A2 Calibration plot of the updated model (See Table A3, Model 1).

Calibration-in-the-large

In the consortium data, patients aged 30–69 (Diamond–Forrester age range) were assigned the log odds of obstructive CAD as estimated by the weighted linear regression model, i.e. the linear predictor. A model (Equation 1 in Figure A1) was fitted to calculate the log odds of obstructive CAD as observed in our data set. The linear predictor of Diamond and Forrester ($lp_{\text{D\&F}}$) was included in the model and its coefficient was fixed at unity. In this way, the original absolute and relative effects of the original Diamond–Forrester model are maintained. The intercept (α_{new}) is the only free parameter in the model, which allows us to quantify the ‘calibration-in-the-large’ and adjust for difference in disease prevalence. The intercept (α_{new}) can be interpreted as the difference in log odds between the mean observed outcome and the mean predicted probability of CAD according to Diamond and Forrester.¹⁹ In other words, we assessed calibration-in-the-large by comparing the mean observed frequency of CAD with the

Table A1 Validation of the Diamond–Forrester model

Model	Diamond and Forrester (weighted linear regression ^a) ‘original’ regression coefficients		δ coefficients ^b (Equation 3 in Figure A1) (in patients aged 30–69, n = 1683)	
	Coefficient	P-value	Coefficient	P-value
Baseline analysis	α	–7.52	$\delta \alpha$	2.97 <0.001
	Age	0.09	δ Age	–0.04 <0.001
	Male sex	1.35	δ Male sex	0.05 0.67
	Typical CP	3.77	δ Typical CP	–1.78 <0.001
	Atypical CP	1.70	δ Atypical CP	–1.20 <0.001
c-Statistic (95% CI) ^c	0.78 (0.76–0.79)		0.78 (0.76–0.81)	
HL P-value	<0.001		0.36	
Analyses adjusted for hospital ^d			$\delta \alpha$	2.05 <0.001
			δ Age	–0.04 <0.001
			δ Male sex	–0.02 0.88
			δ Typical CP	–1.21 <0.001
			δ Atypical CP	–0.96 <0.001
c-Statistic (95% CI) ^c			0.81 (0.79–0.83)	
HL P-value			0.06	

CP, chest pain; HL, Hosmer–Lemeshow goodness-of-fit test (significant result indicates lack of model fit, poor calibration); α , intercept; $lp_{\text{D\&F}}$ linear predictor of Diamond and Forrester.

^aRegression coefficients were approximated by weighted linear regression (see Appendix, *Original Diamond-Forrester coefficients*).

^bDifference between Diamond–Forrester coefficients and refitted coefficients.

^cEstimated by bootstrapping with 1000 repetitions.

^dReference category is Erasmus University Medical Center.

Table A2 Logistic regression predicting the probability of verification with conventional coronary angiography

Variable	Odds ratio	95% CI		P-value
Age	1.04	1.02	1.07	<0.01
Male sex	2.18	1.34	3.55	<0.01
Typical chest pain	3.09	1.47	6.50	<0.01
Atypical chest pain	1.23	0.58	2.61	0.58
Non-specific chest pain	Reference			

Table A3 Updating and extension of the Diamond–Forrester model

	Coefficient	Odds ratio	95% CI lower limit	95% CI upper limit
Model 1: Baseline analysis				
Age	0.04	1.04	1.03	1.05
Male sex	1.34	3.82	3.11	4.70
Typical chest pain	1.99	7.33	5.69	9.43
Atypical chest pain	0.50	1.65	1.26	2.16
Non-specific chest pain ^a	—	—		
Intercept	−4.32	—		
c-Statistic (95% CI ^b)	0.79		0.77	0.81
HL P-value	0.52			
Model 2: Corrected for verification bias				
Age	0.04	1.04	1.02	1.06
Male sex	1.16	3.20	2.47	4.15
Typical chest pain	1.99	7.31	5.62	9.52
Atypical chest pain	0.63	1.87	1.40	2.51
Non-specific chest pain ^a	—	—		
Intercept	−4.09	—		
c-Statistic (95% CI ^b)	0.78		0.76	0.80
Model 3: Random intercept + random slope 'typical chest pain' ^c				
Age	0.04	1.04	1.03	1.05
Male sex	1.34	3.82	3.08	4.74
Typical chest pain	1.91	6.72	3.97	11.37
Atypical chest pain	0.64	1.89	1.38	2.59
Non-specific chest pain ^a	—	—		
Intercept	−4.37	—		
c-Statistic (95% CI ^b)	0.82		0.80	0.84

^aReference category.

^bEstimated by bootstrapping with 1000 repetitions.

^cGroup variable is 'hospital'.

mean of the predicted probabilities according to Diamond and Forrester in a logistic regression model. We tested whether the difference (i.e. the intercept) was significantly different from zero.

Recalibration

Next, we recalibrated the model by comparing the average regression slope of Diamond and Forrester with the average regression slope in the consortium data. A second linear predictor variable was added to the model (while maintaining both the previous linear predictor as offset variable and the new intercept), and its coefficient $\beta_{\text{miscalibration}}$ (Equation 2 in Figure A1) was estimated. This coefficient reflects the miscalibration of the Diamond–Forrester predictor effects when compared with the predictor effects in the consortium data.¹⁹ We tested whether $\beta_{\text{miscalibration}} = 0$, corresponding to the hypothesis that the Diamond–Forrester prediction (adjusted for calibration-in-the-large) fits the data well. If significant, we conclude that the overall effects of age, sex, and type of chest pain together are different in our data and that model revision is justified.

Re-estimation

Finally, we re-estimated the predictor effects in a model including the linear predictor as offset and the new intercept (Equation 3 in Figure A1). The coefficients from this analysis refer to the difference between the re-estimated and the original coefficients (i.e. δ -coefficients). We tested whether these differences were significantly different from zero. From these analyses, we can judge which predictor effects are different in our data compared with the model according to Diamond and Forrester.

All analyses were performed both unadjusted and adjusted for hospital.

Updating and extension

To update the Diamond–Forrester model, we performed a logistic regression analysis (Equation 4 in Figure A1), using all data, including patients below the age of 30 and above the age of 69. All variables (age, sex, and type of chest pain) were entered simultaneously in the model ('baseline analysis') (Table A3). To judge whether interaction terms should be considered, we performed an overall test for interaction using second-order interactions of the main effects (i.e. age, sex, and type of chest pain). Significant interaction terms were tested one-by-one and omitted if non-significant. Similarly, interactions between main effects and hospital were tested.

Separately, we extended the model with a random intercept to allow for heterogeneity in CAD prevalence across different hospitals (Equation 5 in Figure A1). Because of potential differences in symptom classification across hospitals, we also tested random effects for type of chest pain across different hospitals (Equation 6 in Figure A1). The linearity assumption for the continuous variable age was checked graphically and tested statistically by including a restricted cubic spline function (with three knots (2 d.f.)).

Diagnostic performance was quantified by calculating the area under the receiver operating curve (c-statistic), and confidence intervals were obtained by bootstrapping with 1000 repetitions. Calibration was estimated by the Hosmer–Lemeshow goodness-of-fit test and by constructing a calibration plot (Figure A2).

Table A4 Reclassification table using probability categories <30, ≥30–70, and ≥70% (men)

Probability category based on Diamond and Forrester	Probability category based on updated model			Total
	0–30%	30–70%	70–100%	
0–30%				
<i>n</i> (%)	62 (27.7)	162 (72.3)	—	224 (19.3)
Observed probability, %	17.7	42.0	—	35.3
30–70%				
<i>n</i> (%)	—	294 (100.0)	—	294 (25.4)
Observed probability, %	—	48.3	—	48.3
70–100%				
<i>n</i> (%)	—	25 (3.9)	616 (96.1)	641 (55.3)
Observed probability, %	—	64.0	84.3	83.5
Total				
<i>n</i> (%)	62 (5.4)	481 (41.5)	616 (53.2)	1159 (100.0)
Observed probability, %	17.7	47.0	84.3	65.2

Table A5 Reclassification table using probability categories <40 and ≥40% (men)

Probability category based on Diamond and Forrester	Probability category based on updated model		Total
	0–40%	40–100%	
0–40%			
<i>n</i> (%)	150 (67.0)	74 (33.0)	224 (19.3)
Observed probability, %	26.0	54.1	35.5
40–100%			
<i>n</i> (%)	22 (2.4)	913 (97.6)	935 (80.7)
Observed probability, %	27.3	73.5	72.4
Total			
<i>n</i> (%)	172 (14.8)	987 (85.2)	1159 (100.0)
Observed probability, %	26.2	72.0	65.2

A *P*-value <0.05 was considered statistically significant. Statistical analyses were performed using Stata/SE 10.1, StataCorp, TX, USA.

Correction for verification bias

To correct for verification bias in our study population, we performed inverse probability weighting on each individual in our data set, using the probability of verification.

For this purpose, we used registry data^{12,13} of 471 outpatients who presented to the cardiologist for the evaluation of chest pain. All patients in this registry were intended to undergo both stress-ECG and CT coronary angiography. Of the 471 patients, 98 were referred for CCA based on clinical parameters and the non-invasive test results.

A logistic regression analysis was performed, predicting the probability of undergoing CCA based on age, sex and type of chest pain (Table A2). Subsequently, the probability of verification was calculated for each individual in the CAD Consortium. The inverse of the probability of verification was used to weigh each individual, which corrects for verification bias.

Reclassification

To assess the clinical utility of the updated Diamond–Forrester model, we assessed reclassification of patients between the ages of 30 and 69 for men (Table A4, A5) and women (Table A6, A7) separately, comparing the original Diamond–Forrester probability prediction (i.e. according to age category, sex, and type of chest pain) with the updated model in the

Table A6 Reclassification table using probability categories <30, ≥30–70, and ≥70% (women)

Probability category based on Diamond and Forrester	Probability category based on updated model			Total
	0–30%	30–70%	70–100%	
0–30%				
<i>n</i> (%)	136 (100.0)	—	—	136 (25.9)
Observed probability, %	17.6	—	—	17.6
30–70%				
<i>n</i> (%)	122 (70.1)	52 (29.9)	—	174 (33.2)
Observed probability, %	27.0	36.5	—	29.9
70–100%				
<i>n</i> (%)	—	214 (100.0)	—	214 (40.8)
Observed probability, %	—	49.1	—	49.1
Total				
<i>n</i> (%)	258 (49.2)	266 (50.8)	—	524 (100.0)
Observed probability, %	22.1	46.6	—	34.5

Table A7 Reclassification table using probability categories <40 and ≥40% (women)

Probability category based on Diamond and Forrester	Probability category based on updated model		Total
	0–40%	40–100%	
0–40%			
<i>n</i> (%)	198 (100.0)	—	198 (37.8)
Observed probability, %	19.7	—	19.7
40–100%			
<i>n</i> (%)	105 (32.2)	221 (67.8)	326 (62.2)
Observed probability, %	32.4	48.9	43.6
Total			
<i>n</i> (%)	303 (57.8)	221 (42.2)	524 (100.0)
Observed probability, %	24.1	48.9	34.5

Table A8 Reclassification statistics

Cutoffs		Overall reclassification percentage	%Correct ^a	χ^2 model 1 ^b	<i>P</i> -value	χ^2 model 2 ^c	<i>P</i> -value	NRI ^d , %	<i>P</i> -value for NRI
<30, ≥30–70, ≥70%	Men	16.1	100.0	125.5	0	10.9	0.01	–14	<0.001
	Women	64.1	100.0	261.7	0	4.25	0.12	–19	0.02
<40, ≥40%	Men	8.3	100.0	99.1	0	6.98	0.03	0	0.99
	Women	20.0	100.0	24.0	0	4.0	0.04	2	0.64

NRI, net reclassification improvement.

^aIf the predicted probability of obstructive CAD of the updated model was closer to the observed probability of CAD compared with the prediction of the original model, the reclassification was considered to be correct.

^bReclassification calibration (Hosmer–Lemeshow) statistic for the original model, using cells from the reclassification table with at least 20 observations. The significant *P*-value indicates poor calibration of the original model.

^cReclassification calibration statistic for the updated model, using cells from the reclassification table with at least 20 observations. The higher *P*-value indicates better fit of the updated model compared with the original model.

^dThe net reclassification improvement is defined as the difference in proportions of patients moving up and down for cases and non-cases separately and it is interpreted as the percentage reclassified, adjusted for the reclassification direction. Here, the net reclassification index is negative because, on average, most individuals are being downclassified by the updated model (i.e. less overestimation by the updated model compared with the Diamond–Forrester model), irrespective of their disease status.

Table A9 Validation of the updated model

	Calibration-in-the-large		Recalibration	
	Coefficient	P-value	Coefficient	P-value
α	-0.92	<0.001	-0.92	<0.001
$lp_{\text{Consortium}}$	1	—	-0.03	0.79
$lp_{\text{Consortium}}$			1	—
c-Statistic (95% CI ^a)	0.76 (0.71–0.81)		0.76 (0.71–0.81)	

α , intercept; $lp_{\text{Consortium}}$, linear predictor of the updated model (random effects model, see Table 3).

^aEstimated by bootstrapping with 1000 repetitions.

online calculator [i.e. according to age (continuous), sex and type of chest pain; Table A3, Model 3].

Validation of the updated model

The CAD Consortium population is highly selected based on referral to CCA. To assess the performance of the updated model in a lower risk population, we attempted to validate the model in an independent registry data set (not included in our consortium) consisting of unselected outpatients presenting to the cardiologist who were intended to undergo both stress-ECG and CCTA for the evaluation of chest pain.^{12,13} (This data set was also used to perform the correction for verification bias.)

For this purpose, we followed the step-wise approach as described above (Table A9). Since not all patients in this population underwent CCA, the CCTA results were used as proxy for the reference standard in patients who did not undergo CCA. Out of 471 patients, 17 did not undergo either CCTA or CCA and were therefore excluded from the analysis.

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CARDIOVASCULAR FLASHLIGHT

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Saphenous vein graft aneurysm connected to lung parenchyma: a very unusual cause of haemoptysis

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A 74-year-old man, with a coronary artery bypass surgery 12 years before, was referred for a life-threatening episode of haemoptysis. Chest X-ray showed mild cardiomegaly and a right pulmonary mass (Panel A, arrow) located close to the pulmonary hilum. Computed tomography angiogram (Panel B) demonstrated an aortic pseudoaneurysm with thrombus (arrow) placed at the proximal anastomosis of a saphenous vein graft to circumflex artery that was occluded. Three-dimensional computed tomography reconstruction (Panel C) showed the anterolateral position of the aneurysm (long arrow) that was connected to lung parenchyma (short arrow) with no evidence of aorto-bronchial fistula. This was also observed in aortography where we could appreciate complete absence of blood flow to lung or bronchi after injection of contrast (Panel D). Surgery was performed and intraoperative transoesophageal echocardiography showed the ascending aortic dilatation (Panel E); Panels F and G show the large saphenous vein graft aneurysm at the proximal anastomosis connected to lung parenchyma corrected with a Gore Tex patch.

