SURGERY FOR ACQUIRED CARDIOVASCULAR DISEASE

PREDICTION OF CORONARY ARTERY DISEASE IN PATIENTS UNDERGOING OPERATIONS FOR MITRAL VALVE DEGENERATION

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Objectives: We sought to develop and validate a model that estimates the risk of obstructive coronary artery disease in patients undergoing operations for mitral valve degeneration and to demonstrate its potential clinical utility.

Methods: A total of 722 patients (67% men; age, 61 ± 12 years) without a history of myocardial infarction, ischemic electrocardiographic changes, or angina who underwent routine coronary angiography before mitral valve prolapse operations between 1989 and 1996 were analyzed. A bootstrap-validated logistic regression model on the basis of clinical risk factors was developed to identify low-risk ($\leq 5\%$) patients. Obstructive coronary atherosclerosis was defined as 50% or more luminal narrowing in one or more major epicardial vessels, as determined by means of coronary angiography.

Results: One hundred thirty-nine (19%) patients had obstructive coronary atherosclerosis. Independent predictors of coronary artery disease include age, male sex, hypertension, diabetes mellitus, and hyperlipidemia. Two hundred twenty patients were designated as low risk according to the logistic model. Of these patients, only 3 (1.3%) had single-vessel disease, and none had multivessel disease. The model showed good discrimination, with an area under the receiver-operating characteristic curve of 0.84. Cost analysis indicated that application of this model could safely eliminate 30% of coronary angiograms, corresponding to cost savings of \$430,000 per 1000 patients without missing any case of high-risk coronary artery disease.

Conclusion: A model with standard clinical predictors can reliably estimate the prevalence of obstructive coronary atherosclerosis in patients undergoing mitral valve prolapse operations. This model can identify low-risk patients in whom routine preoperative angiography may be safely avoided. (J Thorac Cardiovasc Surg 2001;121:894-901)

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Although a substantial number of patients undergo valvular operations in the United States each year (>200,000 since 1990), there is no validated approach for routine evaluation of possible obstructive coronary artery disease (CAD) in this population. Current American College of Cardiology/American Heart Association practice guidelines for presurgical coronary angiography include the following: male patients 35 years of age or older; female patients who are postmenopausal or premenopausal and 35 years of age or older with coronary risk factors; and patients with chest pain, objective evidence of ischemia, one or more risk

factors for CAD, previous CAD, or decreased left ventricular systolic function.¹ Considering that the estimated mean ages of patients who underwent mitral and aortic valve operations in the United States between 1990 and 1996 were 64 and 68 years of age, respectively,² with more than half of 31,000 patients undergoing mitral valve operations not requiring concurrent coronary artery bypass grafting, these guidelines recommend coronary angiography for the vast majority who ultimately will not undergo revascularization. Although coronary angiography is generally a low-risk procedure, a validated model for preoperative coronary angiography may be helpful by eliminating the cost and morbidity of unnecessary studies.

The present study was undertaken to (1) construct and validate a model to estimate the risk of obstructive CAD on the basis of clinical predictors in a large series of patients undergoing operations for degenerative mitral valve disease, (2) propose an algorithm for coronary angiography before the operations in these patients, and (3) compare the use of this algorithm with current practice guidelines.

Methods

Patient selection. We identified 1178 consecutive patients from the Cleveland Clinic Foundation Cardiovascular Information Registry³ who underwent operations for degenerative mitral valve disease (998 myocardial mitral valve repairs and 180 replacements) between 1989 and 1996. This prospectively collected and validated database provides comprehensive descriptions of clinical and surgical characteristics of all patients undergoing cardiac operations at the institution since 1971. One hundred three patients who did not undergo coronary angiography at the discretion of the attending staff cardiologist were excluded. In addition, 353 patients with previous myocardial infarction ($n = 158$), ischemic electrocardiographic changes ($n = 99$), angina ($n = 195$), or some combination thereof were excluded from analysis because these patients clearly were reasonable candidates for preoperative coronary angiography. Thus, 722 patients were included in our study.

Clinical data. Angina was limited strictly to symptoms with at least two of the following characteristics: (1) substernal chest discomfort with characteristic quality and duration that is (2) provoked by exertion or emotional stress and (3) relieved by rest or nitroglycerin.⁴ Ischemic electrocardiographic changes were strictly defined as the presence of diagnostic Q waves or abnormal baseline ST segment changes of 0.1 mV or greater consistent with ischemia unrelated to metabolic abnormalities, drug effects, conduction disturbances, or ventricular hypertrophy. Previous myocardial infarction was defined by means of clinical history, diagnostic Q waves, or thinned akinetic segments on resting echocardiography.

Risk factor selection. Established CAD risk factors, including age, sex, diabetes mellitus, smoking, family history

of CAD, hypertension, and hyperlipidemia, were recorded systematically according to standard definitions elucidated in detail elsewhere.⁵ In addition, abnormal left ventricular function defined as an ejection fraction of 50% or less by means of echocardiography or contrast ventriculography and New York Heart Association class III or IV were also designated a priori for analyses. The presence of obstructive CAD was defined as 50% or greater luminal narrowing in one or more major epicardial vessels by means of coronary angiography.

Statistical analysis

Model development and validation. All designated clinical variables were initially entered into univariable analyses. Predictors of obstructive CAD in the univariable analyses were entered into a forward stepwise multivariable logistic regression model.⁶ All variables except age were analyzed categorically. Only independent predictors ($P < .05$) were included in the multivariable model:

$$\text{Model score (Ln OR)} = \alpha + x_1\beta_1 + x_2\beta_2 + x_3\beta_3 + x_4\beta_4 + \dots + x_k\beta_k$$

in which Ln OR is the natural logarithm of the odds ratio; α is a constant; $x_1, \dots$, and x_k are independent predictors; and $\beta_1, \dots$, and β_k represent respective parameter coefficients. A model score based on the sum of parameter coefficient variable products and the α term in the model was calculated to identify patients with 5% or lower predicted risk of CAD. On the basis of the regression equation, the odds ratio is related to risk of obstructive CAD by the following equation:

$$\text{Risk of CAD} = e^{\text{OR}} / (e^{\text{OR}} + 1)$$

A model score of 2.95 corresponds to approximately 5% risk of CAD. This subgroup is defined as having a low risk of CAD.

The multivariable logistic model was validated and further refined by using the bootstrap technique.⁷ By using this computer-intensive approach, 1000 random resamplings and respective multivariable analyses were performed to assess the stability of odds ratio estimates with sampling variation. The bootstrap-validated 95% confidence interval was defined by the lower 2.5 and upper 97.5 percentile values and was compared with original logistic model estimates.

Model validity was examined by assessing model discrimination and precision. Discrimination reflects the model's ability to distinguish patients with CAD from those without CAD. Receiver-operating characteristic curves were used to compare discrimination of the original and bootstrap models.^{7,8} Precision refers to how closely predicted fit observed outcomes; this was assessed by comparing the predicted versus observed prevalence of CAD according to deciles of predicted risk and quantified by the Hosmer-Lemeshow goodness-of-fit statistic, the coefficient of determination (r^2) with the Spearman rank correlation, and the Brier score.

Comparison with current practice guidelines. Use of the bootstrap model was compared with class I indications from current American College of Cardiology/American Heart Association Practice Guidelines for the Management of

Fig 1. Sex-specific correlation of unadjusted age versus the prevalence of CAD in 772 patients who underwent coronary angiography before operations for degenerative mitral valve disease.

Patients with Valvular Heart Disease.¹ Cost analysis was performed on the basis of 1998 Medicare reimbursement of outpatient coronary angiography (\$1424) for the Cleveland area. Cost per patient with obstructive CAD identified was calculated for each strategy relative to the study population.

Continuous variables are expressed as mean values $\pm$ SD. Categorical variables are expressed as frequencies, percentage, or both. All statistical analyses were performed with SAS 6.12 software (SAS Inc, Cary, NC).

Results

Clinical characteristics. Clinical characteristics of the study population are summarized in Table I. One hundred thirty-nine (19%) patients in the study population had obstructive CAD. Sex-specific prevalence of CAD relative to the unadjusted age in the study cohort is summarized in Fig 1. Both prevalence curves increased in a curvilinear fashion with age, although there was delayed onset of CAD of greater than 10 years in female patients. Of note, the prevalence of obstructive CAD in both male patients 35 years of age or female patients of perimenopausal age range was extremely low.

Of 103 patients (47 men; age, 36 ± 12 years) in the exclusion subset ($n = 456$) who did not undergo coronary angiography, diabetes mellitus was present in 6, hypertension in 11, hyperlipidemia in 21, family history in 8, and smoking history in 23. None had more than one established risk factor. Two hundred twenty-one

Table I. Clinical characteristics of the study population

Variable	Study population ($n = 722$)
Age (y)	61 ± 12
Male (%)	484 (67.0)
Diabetes mellitus (%)	32 (4.4)
Hypertension (%)	179 (24.8)
Hyperlipidemia (%)	237 (32.8)
Smoking (%)	87 (12.0)
Family history of CAD (%)	166 (23.0)
NYHA class	
I or II (%)	598 (82.8)
III or IV (%)	124 (17.2)
Abnormal LV function*	232 (32.1)
Concurrent AV operation (%)	41 (5.6)
Concurrent TV operation (%)	45 (6.2)
CAD (%)	139 (19.3)
CABG (%)	128 (17.7)

Continuous variables are given as means $\pm$ SD. Categorical variables are given as frequency (%). NYHA, New York Heart Association; LV, left ventricular; AV, aortic valve; TV, tricuspid valve; CABG, coronary artery bypass grafting.

*Abnormal left ventricular function defined as an ejection fraction of 50% or less.

(61%) of 353 patients in the high-risk exclusion subset with ischemic electrocardiographic changes, angina, or previous myocardial infarction had obstructive CAD.

Model development and validation. Table II shows the univariable association between obstructive CAD and the prespecified factors evaluated as potential predictors. All variables, except for abnormal left ventricular function, functional class, and family history, were predictors in univariable analyses. Male sex, age, diabetes mellitus, hyperlipidemia, and hypertension were also predictors in the logistic multivariable analysis and further validated as predictive in the bootstrap validated model as follows:

$$\begin{aligned} \text{Model score (Ln OR)} = & (0.105 \times \text{Age}) + (1.177 \\ & \times \text{Male sex}) + (1.475 \times \text{Diabetes mellitus}) + (1.750 \\ & \times \text{Hyperlipidemia}) + (0.483 \times \text{Hypertension}) - 10.070. \end{aligned}$$

Comparisons between bootstrap and estimated confidence intervals are shown in Table III. There was a strong similarity between the odds ratios of the original and the bootstrap model, supporting the validity of the model. On the basis of the bootstrap model scores, 220 patients were designated as having a low predicted risk for obstructive CAD ($\leq 5\%$; model scores, < -2.95). Of these patients, only 3 (1.3%) had single-vessel disease, and none had high-risk CAD (ie, left main trunk, proximal left anterior descending, or multivessel disease). Ninety percent stenosis

Table II. Univariable association between obstructive coronary artery disease and prespecified categoric factors

Variable	OR	95% CI	χ^2	P value
Age*	2.58	2.06-3.23	68	<.0001
Male sex	2.02	1.31-3.11	10.08	<.005
Diabetes mellitus	5.28	2.74-10.17	24.68	<.005
Hypertension	1.88	1.29-2.72	10.91	<.005
Hyperlipidemia	4.22	2.88-6.20	54.02	<.005
Smoking	1.02	0.84-1.21	1.89	.169
Family history of CAD	1.17	0.80-1.73	0.64	.424
NYHA class III or IV	1.77	1.14-2.76	6.42	.011
Abnormal LV function	1.39	0.95-2.04	2.83	.092

OR, Odds ratio; CI, confidence interval; NYHA, New York Heart Association; LV, left ventricular.

*Per 10-year increase.

of the mid-left anterior descending artery was present in one patient (46-year-old man), 70% stenosis of the midcircumflex artery was present in another patient (57-year-old man), and 50% stenosis of the distal circumflex artery was present in the third patient (38-year-old man). None had established risk factors for CAD. Obstructive CAD was present in 136 (27%) of the 502 patients in the intermediate and high-risk groups (>5%; model scores, ≥ -2.95).

Model discrimination was examined by constructing receiver-operating characteristic curves for the original and bootstrap models in Fig 2. Areas under the curves were nearly identical, being approximately 0.84 for both models. Validation of the bootstrap model according to deciles of predicted CAD risk is shown in Fig 3. There was excellent agreement between observed and predicted prevalences of disease across the predicted risk, with no evidence of systematic overestimation or underestimation. The Hosmer-Lemeshow statistic was 1.9 ($P = .98$). The coefficient of determination (r_3) between the predicted and observed prevalence was 0.99 ($P < .001$). The mean Brier score was quite low at 0.11, the median was 0.014, and the 25th to 75th percentiles were 0.002 and 0.11.

Comparisons between current practice guidelines and the bootstrap model. In this study population, if coronary angiography would have been performed in all patients, the calculated cost per case of CAD identified would be \$104,427 ($220 \times \$1,424 \div 3$) in the low-risk group and \$5256 per case of CAD ($502 \times \$1,424 \div 136$) among those with intermediate or high-risk profiles. The proposed algorithm based on the logistic model for presurgical coronary angiography is shown in Fig 4. Application of this model could safely elimi-

Fig 2. Receiver-operating characteristic (ROC) curves from the original and the bootstrap models.

nate 30.5% of coronary angiograms, with a high negative predictive value of 98.7%. This corresponds to a cost saving of \$433,906 per 1000 patients. Under current American College of Cardiology/American Heart Association practice guidelines, 97.9% should undergo coronary angiography. No patient with obstructive CAD would be missed, but the specificity and positive predictive value of this approach were only 2.6% and 19.7%, respectively.

Comparing the cost difference between the 2 strategies on the basis of the number of catheterizations recommended divided by the total cases of CAD identified with each approach, there is a cost saving of \$1990 per case of CAD identified with the logistic model. Cost analyses, rates of coronary angiography, and accuracy for both strategies are summarized in Table IV.

Discussion

Our study is the first to develop a validated model that shows that patients with surgical mitral regurgitation caused by myxomatous disease who are at low risk of obstructive CAD can be easily identified on the basis of routine clinical information gathered during preoperative evaluation. The ability of our model to discriminate patients with CAD from those without CAD is demonstrated by the almost identical high areas (0.84) under the receiver-operating characteristic curves derived from the original and bootstrap models. The high coefficient of determination ($r_3 = 0.99$, $P < .001$) between the predicted and observed prevalence of CAD (Fig 3), along with the low Brier score, validate the predictive value of the model.

Several previous studies have developed purely clinical models to predict the risk of obstructive angio-

Table III. Multivariable predictors of obstructive CAD: Odds ratios and confidence intervals from original regression model estimates and the bootstrap model

Variable*	Original model, OR (95% CI)	Wald χ^2	P value	Bootstrap model, OR (95% CI)
Hyperlipidemia	5.51 (3.48-8.72)	53	<.0001	5.75 (3.45-9.14)
Diabetes mellitus	3.67 (1.44-9.37)	7	.007	4.37 (1.55-10.12)
Male sex	3.10 (1.87-5.15)	19	<.0001	3.24 (1.94-5.28)
Hypertension	1.56 (1.01-2.46)	4	.05	1.62 (0.98-2.47)
Age (10 y)	2.81 (2.18-3.62)	64	<.0001	2.81 (2.18-3.62)

OR, Odds ratio; CI, confidence interval.

*Smoking and family history were not predictors in the multivariable model.

graphic CAD in symptomatic patients with chest pain.⁹⁻¹⁴ Diamond and Forrester¹³ proposed a rule to predict CAD on the basis of age, sex, and nature of chest pain. Subsequently, Pryor and associates¹⁰ developed and validated a model based on established risk factor profiles, chest pain characteristics, and electrocardiographic criteria. Application of these models to patients with degenerative mitral valve disease may be constrained by differences in baseline characteristics. Patients with typical or atypical angina were excluded from this analysis, whereas previous studies consisted primarily of patients who presented for evaluation of chest pain. The prevalence of CAD in previous models ranged between 60% and 83%,^{8,9,11-13} which was roughly 3 to 4 times that found in our study. The strength of prediction and respective relationships between predictors derived in previous analyses may be lost in a population with a lower prevalence and lesser severity of CAD.

Predictors of CAD in patients undergoing operations for degenerative mitral valve disease. Previous surgical series have suggested that age of 40 years or greater was a reliable predictor of CAD in patients undergoing valve operations.^{15,16} Chest pain has also been reported as a predictor in several studies.^{15,17-21} In this low-prevalence cohort free of clinical and electrocardiographic evidence of CAD, the risk for obstructive CAD was above low levels (>5%) beyond 56 and 68 years of age for male and female patients, respectively, independent of other predictors. Likewise, family history and smoking were not predictive, although other commonly recognized risk factors, including male sex, hyperlipidemia, hypertension, and diabetes mellitus, remained predictive in the bootstrap model.

Revascularization of CAD during valvular operations. Whether a selective catheterization approach based on risk stratification adversely affects surgical outcome is unclear. Although the presence of coexisting CAD has been clearly linked to a worse prognosis in patients undergoing valvular operations,²²⁻²⁵ the incremental benefit from concurrent revascularization

in patients with nonsurgical disease is not definitive.^{22,26,27} Although the current practice is to revascularize coexisting CAD in these patients, randomized trials in nonvalve populations have revealed that only patients with multivessel CAD in the presence of proximal left anterior descending artery disease, left ventricular dysfunction, or left main trunk disease derived survival benefit from surgical revascularization.²⁸⁻³⁰ In addition, revascularization of flow-limiting CAD may not prevent myocardial infarction. Angiographic studies have documented that plaque composition and morphology, rather than severity of luminal narrowing, are the major determinants of subsequent acute coronary syndromes.³¹⁻³³ Alternatively, coronary bypass of non-flow-limiting lesions may lead to accelerated venous bypass graft closure³⁴ or proximal native vessel atherosclerosis.³⁵ Finally, despite advances in surgical techniques and myocardial protection,^{36,37} combined myocardial revascularization and valvular operations are still associated with a higher operative mortality compared with isolated valvular operations.²

Comparisons between current guidelines and the model. Although both strategies maintained relatively high negative predictive values for the prediction of CAD, an approach with greater discrimination and cost reduction is an attractive alternative. Application of the derived model would have eliminated nearly one third of 722 angiographic studies, without missing any patients with high-risk CAD. The accuracy was more than 2-fold higher with this approach versus that with existing guidelines, which corresponded to a substantial cost reduction approaching 25% on the basis of conservative measures of cost.

Limitations. This model was developed and validated in patients undergoing operations for degenerative mitral valve disease. For that reason, the size of our study group was limited, and the observed prevalence of obstructive coronary artery disease was low. Although its findings are potentially applicable to those of other valvular populations, given the vari-

Fig 3. Comparison of the observed versus predicted prevalence of CAD according to deciles of predicted risk. r^2 , Coefficient of determination. Range of probabilities: *decile 1*, 0.0001-0.014; *decile 2*, 0.014-0.029; *decile 3*, 0.029-0.049; *decile 4*, 0.050-0.074; *decile 5*, 0.075-0.108; *decile 6*, 0.108-0.163; *decile 7*, 0.165-0.229; *decile 8*, 0.231-0.334; *decile 9*, 0.343-0.508; and *decile 10*, 0.525-0.901.

Fig 4. Proposed algorithm to risk stratify patients undergoing operations for degenerative mitral valve disease operations. *MI*, Myocardial infarction; *ECG*, electrocardiogram.

ability of baseline characteristics among different valvular lesions, extrapolation should be avoided until further validation. Patients in our study who underwent concomitant tricuspid valve operations, aortic valve operations, or both were few and had

these listed as secondary conditions. Similar results were obtained, however, when we repeated analysis after excluding those patients. Second, our definition of low risk is arbitrary and not universally accepted. We arrived at a cutoff value of less than 5% on the

Table IV. Cost analyses, rates of preoperative coronary angiography, and accuracy of different strategies

Strategies	Coronary angiography (%)	Negative studies (%)	NPV (%)	Accuracy* (%)	Cost/CAD identified (dollars)
ACC/AHA guidelines	97.9	80.3	100	22.3	7243
Bootstrap model	69.5	73.1	98.7	48.6	5256

NPV, negative predictive value; ACC/AHA, American College of Cardiology/American Heart Association.

*Accuracy = Specificity + Positive predictive value.

basis of (1) optimal positive and negative predictive values calculated for cutoffs of 1%, 5%, and 10% and (2) minimal acceptance level agreed on by a group of practicing cardiologists and cardiothoracic surgeons. Nevertheless, by using this cutoff point, not even one patient with high-risk CAD (ie, left main trunk, proximal left anterior descending, or multivessel disease) was missed. Furthermore, the bootstrap validated model allows the clinician to quantify the risk of obstructive CAD by using routine information gathered preoperatively and recommend coronary angiography on the basis of individual definition of low risk. Nevertheless, further validation of our model in an independent patient population is warranted before recommending its widespread adoption in the clinical practice. Finally, despite the substantial reduction in the number of low-yield angiographic studies, there is still a sizeable cohort with intermediate risk who may benefit from additional noninvasive risk stratification (ie, exercise echocardiography). Future studies are required to explore this issue.

Conclusions

A model based on routine clinical predictors gathered preoperatively provided reliable estimates of CAD risk in patients undergoing degenerative mitral valve disease operations. Considering the increasing constraint on health care resources, an evidence-based approach of using coronary angiography for patients who have an intermediate or high likelihood of CAD is an attractive and rational alternative. Greater diagnostic yield at a lower cost was achieved with the derived model than with current practice guidelines. Future large-scale prospective studies are required to confirm these results and determine their applicability to other types of non-ischemic surgical heart disease.

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Appendix

Example 1. A 40-year-old man with severe mitral regurgitation presents for surgical evaluation. He is classified as being in functional class I and has hyperlipidemia.

$$\begin{aligned} \text{LN (Multivariable odds ratio)} &= -10.070 + (0.105 \times \text{Age}) \\ &\quad + (1.177 \times \text{Male sex}) + (1.475 \times \text{Diabetes mellitus}) \\ &\quad + (1.750 \times \text{Hyperlipidemia}) + (0.483 \times \text{Hypertension}) \\ &= -10.070 + (0.105 \times 40) + (1.177 \times 1) + (1.750 \times 1) \\ &= -2.35 \end{aligned}$$

$$\text{Probability of CAD} = e^{(-2.35)} / e^{(-2.35)} + 1 = 8.7\%.$$

On the basis of the proposed algorithm, the patient is at higher than low risk and should undergo coronary angiography before mitral valve operations.

Example 2. A 60-year-old woman presents for surgical evaluation of severe mitral regurgitation. She has no clinical predictor for CAD.

$$\begin{aligned} \text{LN (Multivariable odds ratio)} &= -10.070 + (0.105 \times 60) \\ &= -3.77 \end{aligned}$$

$$\begin{aligned} \text{Probability of coronary artery disease} &= e^{(-3.77)} / e^{(-3.77)} \\ &\quad + 1 = 2.0\%. \end{aligned}$$

On the basis of the proposed algorithm, the patient does not require routine coronary angiography before mitral valve operations.