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Prediction of Coronary Artery Disease Severity in Patients Referred for Coronary Angiography

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Summary

Background: Diagnostic coronary angiography is often followed by coronary stenting. Therapy with aspirin and clopidogrel is currently the standard treatment for patients undergoing coronary stenting. Clopidogrel loading is usually given prior to the procedure. Some pretreated patients, however, are found to have triple-vessel disease (3VD) or left main disease (LMD) that requires referral for coronary artery bypass graft (CABG) surgery. Surgery in patients pretreated with clopidogrel may be complicated by excessive bleeding or delayed to avoid that risk.

Hypothesis: A risk factor-based formula may predict the likelihood that patients referred for coronary angiography will have 3VD or LMD.

Methods: Consecutive patients (n = 2,180) referred for coronary angiography constitute the training subset (n = 1,296) used to build the model, and the validation subset (n = 884) used to test the model. Logistic regression models selected five variables showing strong associations with the presence of 3VD or LMD: age, gender, diabetes, hypercholesterolemia, and prior myocardial infarction (MI). A formula based on these variables and on the training subset was constructed to calculate the probability of 3VD or LMD.

Results: Applying this model to the validation subset predicted 3VD or LMD with 79% sensitivity, 53% specificity, 45% positive predictive value, and 83% negative predictive value.

Conclusions: This simple formula based on five clinical variables is helpful in predicting the likelihood that patients, referred for coronary angiography, will have 3VD or LMD. Use of this formula can help decide in which patients clopidogrel loading prior to angiography should be avoided.

Key words: clopidogrel, coronary stenting, coronary artery bypass graft

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Introduction

Combination therapy of aspirin and clopidogrel is currently the standard treatment for patients undergoing coronary artery stenting.[1, 2] Since the antiplatelet activity of clopidogrel is delayed for up to 6 h,[3] a loading dose of clopidogrel 300 mg is usually given up to 24 h prior to the procedure.[1, 2, 4] This early loading dose is indicated in patients undergoing planned percutaneous coronary intervention (PCI). However, it is common practice to perform diagnostic catheterization followed by PCI, when indicated, in the same session. In this case pretreatment is controversial since, if the diagnostic angiography reveals that coronary artery bypass graft (CABG) is indicated, the surgery may be complicated by excessive bleeding or be delayed to avoid that risk.[5–7] To avoid this problem, there is a need for a simple way to predict the likelihood that patients referred for coronary angiography will have coronary disease requiring CABG.

Patients with one or two diseased vessels usually undergo PCI while those with more extensive disease, triple-vessel disease (3VD) or left main disease (LMD), are more likely to be referred for CABG.

In this manuscript, we describe a formula based on five readily available clinical variables that predicts the likelihood of 3VD or LMD versus two or fewer diseased vessels in a cohort of unselected patients referred for diagnostic coronary angiography. Using this formula to predict coronary disease severity prior to the procedure may help decide which patients are more likely to benefit from clopidogrel loading and in which patients it should be avoided.

Methods

Patients

The study population included consecutive patients referred to our hospital for coronary angiography from February 1999 to April 2003. Patients referred from February 1999 to December 2000 constitute the training subset (used to build the model) (n = 1,296), whereas patients referred from January 2001 to April 2003 constitute the validation subset (used to test the model) (n = 884). In patients who underwent more than one procedure during the specified time period, only the first one was included in the analysis.

The following variables were recorded prospectively: (1) Coronary risk factors: age, gender, the presence of hypertension, diabetes mellitus (DM), hypercholesterolemia, smoking, and documented old myocardial infarction (MI); (2) indication for referral for angiography: stable angina, unstable angina, acute MI, congestive heart failure, positive exercise test; (3) coronary angiography findings: nonsignificant, single-vessel, double-vessel, triple-vessel, or left main disease.

The variables under headings (1) and (2) above were included in the initial phase of the model construction.

Coronary Angiography

Coronary angiography was performed by the femoral approach according to standard clinical practice. Coronary arteries were cannulated by the Judkins technique. Selective coronary injections were filmed in standard projections.

Significant coronary disease was defined as the presence of ≥70% diameter stenosis in any vessel or ≥50% left main stenosis.

Statistical Analysis

The outcome variable representing an indication for CABG was the dichotomy indicating whether "three vessels diseased and/or left main diseased" was observed at angiography. In addition to age, all explanatory variables were also dichotomies. The analysis constituted five steps; the first three were directed toward the development of the most parsimonious (in terms of variables involved) diagnostic tool.

In patients who underwent more than one procedure, only the first one was selected, both for the training (used to build the model) and the validation subsets.

Development of the diagnostic tool: First, univariate associations of each dichotomous explanatory variable with the outcome were examined and tested by Fisher's exact test. Concerning age, logistic regression models were used to determine whether to enter age as a numeric variable or grouped; the former showed a better fit. All variables showing a statistically significant association entered the second step, a multiple logistic model constructed by means of a stepwise backward likelihood ratio procedure. In the third step, a final model was built with a multiple logistic regression using those statistically significant variables in the previous step. This step was meant to maximize the number of patients utilized by eliminating the deletion of those with any missing data. The final diagnostic tool is based on a formula for the predicted probability of the event (alternatively and equivalently a formula for the log [odds] of the event) and a cut-off value above which the subject will be classified as a candidate for CABG. An interval of values around the suggested cut-off point was declared as a region of uncertainty.

Evaluation: Receiver operating characteristics (ROC) curves were constructed and plotted. This curve gives the sensitivity and specificity for each cut-off value of the predicted probability. The area under the curve serves as a measure of the usefulness of the tool: for an absolutely useless tool, this area will be 0.5; a greater area reflects a better tool. A statistical test to determine whether the area of the ROC curve is significantly greater than 0.5 was performed.

Validation: Sensitivity, specificity, positive and negative predictive values, as well as the percentage of patients for whom no prediction is made (i.e., falling in the region of uncertainty), were calculated for the validation subset.

Results

The clinical characteristics of the training and validation subsets were similar (Table I). Table II shows the distribution of the angiographic severity of coronary disease in the training subset.

Training subset variables showing a statistically significant univariate association with the presence of 3VD or LMD (i.e.,

TABLE I Clinical characteristics in the training and validation sets

Variable	Test set n = 1,296 (%)	Validation set n = 884 (%)	p Value
Females	383 (30)	233 (26)	0.2
Hypertension	578 (45)	391 (44)	0.9
DM	351 (27)	191 (22)	< 0.03
Hypercholesterolemia	595 (46)	465 (53)	0.1
Smoking	334 (26)	259 (29)	0.1
S/P MI	369 (28)	232 (26)	0.4
Acute MI	151 (12)	115 (13)	0.4
Stable angina	586 (45)	380 (43)	0.5
Unstable angina	363 (28)	239 (27)	0.7
CHF	73 (6)	62 (7)	0.2
Age			
< 40	38 (3)	21 (2)	0.5
40–59	413 (32)	343 (39)	< 0.03
60–69	410 (32)	261 (30)	0.5
70–79	347 (27)	209 (24)	0.2
80 +	88 (7)	50 (6)	0.4
0, 1, 2 VD	778 (60)	586 (66)	0.2
3VD&/or LM	515 (40)	298 (37)	< 0.06

Abbreviations: N = number of patients, DM = diabetes mellitus, S/P MI = status post myocardial infarction, CHF = congestive heart failure, VD = vessels disease, LM = left main.

TABLE II Angiographic severity of coronary disease in the training set patients

Number of diseased vessels	Left main disease No	Left main disease Yes	Total
0	277	0	277 (21)
1	237	0	237 (18)
2	266	14	280 (22)
3	464	38	502 (39)
Total	1,244	52	1,296

TABLE III Association of the explanatory variables, with the presence of 3VD or LMD in the training set (by univariate analysis)

Variable	N	3VD or LMD (%)	p Value
Gender			
Male	911	406 (44.6)	< 0.00001
Female	383	109 (28.5)	
Hypertension			
No	693	247 (35.6)	0.0004
Yes	578	263 (45.5)	
DM			
No	921	334 (36.3)	0.00001
Yes	351	177 (50.4)	
Hypercholesterolemia			
No	675	239 (35.4)	0.0002
Yes	595	271 (45.5)	
Smoking			
No	937	393 (41.9)	0.03
Yes	334	117 (35.0)	
S/P MI			
No	904	291 (32.2)	< 0.00001
Yes	369	219 (59.3)	
Acute MI			
No	1133	454 (40.1)	0.99
Yes	151	60 (39.7)	
Stable angina			
No	698	268 (38.4)	0.23
Yes	586	245 (41.8)	
Unstable angina			
No	920	358 (38.9)	0.23
Yes	363	155 (42.7)	
CHF			
No	1210	482 (39.8)	0.90
Yes	73	30 (41.1)	
Positive EST			
No	990	381 (38.5)	0.04
Yes	293	133 (45.4)	
Age			
< 40	38	5 (13.2)	
40–59	413	116 (28.1)	
60–69	410	187 (45.6)	< 0.00001
70–79	344	159 (46.2)	
80 +	88	48 (54.5)	
Age, mean ± SD			
0, 1, 2 VD	778	61.2 ± 12.3	< 0.00001
3VD&/or LM	515	66.5 ± 10.6	

Abbreviation: EST = exercise stress test. Other abbreviations as in Table I.

with the indication for CABG) were age, gender, hypertension, DM, hypercholesterolemia, old MI, and positive exercise test (Table III). These variables entered the second step as explained above under Statistical Analysis. All these variables were found to be independently associated with the presence of 3VD or LMD; however, when the third step (see Statistical Analysis) was performed, we noted that hypertension and positive exercise test added no predictive value to the final diagnostic tool. Step 2, therefore, was repeated after the exclusion of hypertension and positive exercise test (Table IV).

The final diagnostic tool (e.g., the formula for the predicted probability of 3VD or LMD) is, therefore, based on age, male gender, and the presence of DM, hypercholesterolemia, and old MI:

(1) $b = -4.86 + 0.0485 \times \text{age} + 0.95 \times I(\text{male}) + 0.61 \times I(\text{DM}) + 0.92 \times I(\text{s/pMI}) + 0.46 \times I(\text{hypercholesterolemia})$.
Each I (variable) is an indicator receiving the value 1 for "yes" and 0 for "no;" s/p status post.

(2) $$\text{3VD \&/or LM probability} = p = \frac{1}{1 + \exp(-b)}$$

In constructing the model, we aimed for higher sensitivity in selecting the cut-off points, believing that giving clopidogrel to a patient requiring surgery is a less desirable clinical outcome than withholding pretreatment in a patient undergoing PCI. Thus, we considered $p < 0.3$ as double-vessel disease or less (e.g., no indication for CABG), $p > 0.35$ as 3VD or LMD (e.g., indication for CABG), and the range of $p \geq 0.3$ to $p \leq 3.5$ as the uncertainty zone.

Applying the formula with these cut-off points to the training subset to predict presence of 3VD or LMD resulted in a

TABLE IV Association of five selected variables, with the presence of 3VD or LMD in the training set (by multivariate logistic regression analyses)

Variable	N	OR	95% CI	p Value
Age	1263	1.05	1.04–1.06	< 0.00001
Gender				
Female	376	1		
Male	887	2.58	1.93–3.45	< 0.00001
DM				
No	913	1		
Yes	350	1.85	1.41–2.42	0.00001
Hypercholesterolemia				
No	671	1		
Yes	592	1.59	1.24–2.04	0.0003
S/P MI				
No	900	1		
Yes	363	2.50	1.92–3.27	< 0.00001

Abbreviations: OR = odds ratio, CI = confidence interval. Other abbreviations as in Table I.

TABLE V Association of five selected variables, with the presence of 3VD or LMD in the validation set (by multivariate logistic regression analyses)

Variable	N	OR	95% CI	p Value
Age	881	1.04	1.02–1.05	< 0.00001
Gender				
Female	232	1		
Male	649	1.46	1.02–2.08	< 0.04
DM				
No	690	1		
Yes	191	1.92	1.35–2.71	0.0002
Hypercholesterolemia				
No	417	1		
Yes	464	1.39	1.03–1.89	0.04
S/P MI				
No	650	1		
Yes	231	2.85	2.05–3.97	< 0.00001

Abbreviations as in Tables I and III.

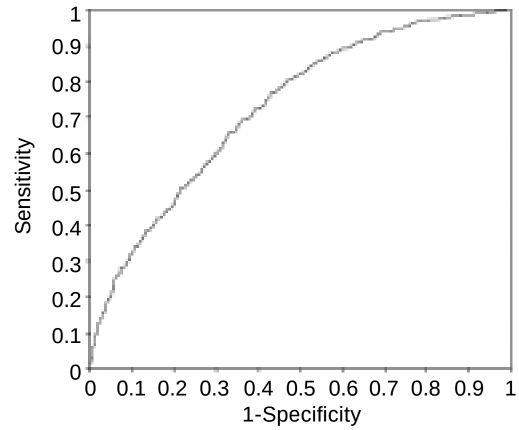

FIG. 1 Receiver operator characteristic (ROC) curve for the validation subset. The area under the curve is 0.73, which is significantly greater than 0.5 ($p < 0.0001$). As detailed in the Methods section, the bend of the ROC curve toward the upper left point (0,1) where the specificity and the sensitivity are unity, is evidence of the discriminating power of the test. A greater area under the curve reflects this.

TABLE VI Statistical characteristics of the prediction tool

Set %	Training	Validation
Sensitivity	82	79
Specificity	53	53
Uncertainty	10	9.5
Positive PV	54	45
Negative PV	82	83

Abbreviation: PV = predictive value.

sensitivity of 82% and a specificity of 53%, with 10% of patients falling into the uncertainty zone.

Validation subset variables entered the first and second steps of statistical analysis as described above for the training subset. The variables that showed a statistically significant multivariate association with the presence of 3VD or LMD were the same noted in the training subset analyses (Table V). Applying the formula with the cut-off points described above to the validating subset patients resulted in a sensitivity of 79%, a specificity of 53%, a positive predictive value of 45%, and a negative predictive value of 83% for predicting presence of 3VD or LMD. Of the patients tested, 9.5% fall in the uncertainty zone (Table VI).

As detailed in the Methods section, the bend of the ROC curve toward the upper left point (0,1), where the specificity and the sensitivity coincide, is evidence of the discriminating power of the test; a greater area under the curve reflects this. The ROC curve (for the validation subset) is shown in Figure 1; its area is significantly greater than 0.5 ($p < 0.0001$). The ROC curve for the training subset (not shown) was very similar.

To simplify the formula, we calculated the b values corresponding to the p cut-off points 0.3 and 0.35.

The formula used for calculating the b values was

$$(3) \qquad b = \ln\left(\frac{p}{1-p}\right)$$

(ln = natural logarithm).

For $p = 0.3$ the corresponding value for b was $b = (-0.847)$, and for $p = 0.35$ the corresponding value for b was $b = (-0.619)$. The patient b value should be calculated according to formula 1. Thus if $b < (-0.847)$ (e.g., $p < 0.3$), the prediction favors double-vessel disease or less (e.g., no indication for CABG); if $b > (-0.619)$ (e.g., $p > 0.35$), the prediction favors 3VD or LMD (e.g., an indication for CABG); and if b falls in the range of $\geq(-0.847)$ to $\leq(-0.619)$ (e.g., $p \geq 0.3$ and ≤ 0.35), the patient falls in the uncertainty zone.

Thus it is enough to calculate the b value (using formula 1) to predict the presence of 3VD or LMD.

How to Use the Formula

$$b = -4.86 + 0.0485 \times \text{age} + 0.95 \times I(\text{male}) + 0.61 \times I(\text{DM}) + 0.92 \times I(\text{s/p MI}) + 0.46 \times I(\text{hypercholesterolemia})$$

The cutoffs for b were as follows:

	2 VD or less	Uncertainty zone	3VD or LMD
b ◄──	──── (−0.847)	(−0.619) ────	──►

Example 1: A 50-year-old man with no other risk factors referred for coronary angiography:

$$b = -4.86 + 0.0485 \times \text{age} + 0.95 \times I(\text{male}) = -4.86 + 0.0485 \times 50 + 0.95 = -1.485$$

This patient will most likely have 2VD or less.

Example 2: A 60-year-old woman with diabetes and a history of MI referred for coronary angiography:

$$b = -4.86 + 0.0485 \times \text{age} + 0.61 \times I(DM) + 0.92 \times I(s/p\ MI) = -4.86 + 0.0485 \times 60 + 0.61 + 0.92 = -0.42$$

This patient will most likely have 3VD or LMD.

Discussion

Combination therapy of aspirin and clopidogrel has been shown to be safe and effective in preventing ischemic complications following PCI; it is currently the standard treatment for patients undergoing coronary artery stenting.[1, 2, 4] Clopidogrel antiplatelet activity is delayed for up to 6 h from the initial dose.[3] A loading dose of clopidogrel 300 mg is usually given up to 24 h prior to the procedure[1, 2, 4] and is recommended in patients undergoing planned PCI.[8] A recent retrospective analysis of the Do Tirofiban And ReoPro Give similar Efficacy outcome Trial (TARGET) population suggested that in patients undergoing coronary stent placement, clopidogrel pretreatment is associated with a reduction of death and MI.[9] However, such pretreatment is not routinely recommended in patients who have not yet undergone diagnostic cardiac catheterization and in whom CABG would be performed within 5 to 7 days, if warranted, based on findings at the time of cardiac catheterization.[8] This is based on the concern that surgery in pretreated patients will either be complicated by excessive bleeding or will need to be delayed for 7 days to avoid that risk.[5–7]

In this article we present a formula that may serve as a diagnostic tool for predicting the severity of coronary artery disease in patients referred for coronary angiography. This formula has a sensitivity of 79%, a specificity of 53%, a positive predictive value of 45%, and a negative predictive value of 83% for predicting presence of 3VD or LMD, when applied to the validation subset. The striking similarity between the sensitivity and specificity obtained for the two subsets (training and validation, Table VI) confirm the reliability of the formula.

We believe that the most important statistical characteristic of the formula is its negative predictive value: high negative predictive value, in this case, will minimize the number of patients who erroneously will be predicted to have nonsurgical disease and therefore be inappropriately premedicated with clopidogrel; only 17% of patients will fall into this category using our formula. The possible error of withholding clopidogrel pretreatment from patients who eventually will undergo stent placement is a lesser problem since these patients may be loaded with 600 mg clopidogrel immediately post procedure. This results in significant platelet inhibition within 2 h after loading, versus 6 h after conventional 300-mg loading.[10, 11]

This formula should be useful when diagnostic coronary angiography has not been undertaken, coronary anatomy is unknown, and the angiographer plans on performing PCI in the same session if feasible. It should help limit the number of patients with surgical disease who are pretreated with clopidogrel, and therefore limit the number of surgeries being delayed, as well as the number of surgeries that might be complicated by excessive bleeding.

Study Limitations

Like other diagnostic modalities, the formula is not perfect in terms of sensitivity or specificity; however, it has a statistically significant predictive value for predicting severity of coronary disease in a selected group of patients who are referred for coronary angiography.

We assumed in the model that patients with one or two diseased vessels will undergo PCI, while those with 3VD or LMD will be referred for CABG. We believe this is the current practice in most institutions; occasionally, however, clinical decision-making may be different.

Conclusion

A simple formula based on five clinical variables is helpful in predicting the likelihood that patients, referred for coronary angiography, will have 3VD or LMD. This may help decide which patients are likely to benefit from clopidogrel loading prior to angiography and in which patients it should be avoided.

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