# Risk Prediction Tool for Assessing the Probability of Death or Myocardial Infarction in Patients With Stable Coronary Artery Disease

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**Several risk scores in acute coronary syndromes are available, but few models exist for stable coronary artery disease to guide decision-making and prognosis. A multivariate model was developed using 23 baseline candidate variables from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Therapy EvaluationTrial (n = 2,287 patients). Discrimination of the model was evaluated by the concordance c-index. The procedure was validated using 100 random half samples. We identified 9 independent predictors of death or myocardial infarction (MI) during a 5-year follow-up. The following predictors and points contributing to the risk score were: heart failure (3), number of diseased coronary arteries (1 for each vessel), diabetes (1), age (1 for each 15 years ≥ age 45), previous revascularization (1), current smoking (1), female (1), previous MI (1), and high-density lipoprotein cholesterol (1: 31 to 40 mg/dL; 2: <30 mg/dL). The risk tool had a potential range from 0 to 15, corresponding to 5-year event rates of 5.8% to 56%. C-indices ranged from 0.67 for the full data set to 0.62 for the validating subsamples. Respective observed versus predicted 5-year event rates for 3 predefined risk strata revealed: 30% had a low-risk score of 0 to 3 (9.3% vs 9.3%, or 1.9%/year); 59% had an intermediate-risk score of 4-6 (18.0% vs 18.1%, or 3.6%/year); and 11% had a high-risk score of 7-11 (36% vs 36.5%, or 7.2%/year). This stable coronary artery disease risk score permitted a prognostic assessment of 5-year probability of death or MI with an approximate 4-fold range in event rates from the lowest (9.3%) to the highest (36%) terciles, thus enabling better clinical practice decisions that allow physicians to tailor the intensity of treatment to the level of risk.**  **(Am J Cardiol 2020;130:1−6)**

The majority of risk scores developed for patients with established coronary artery disease (CAD) have been for patients hospitalized with acute coronary syndromes or angina at rest.[1−4] Some risk scores have been developed for non-acute coronary syndromes patients, but were derived largely from drug trials of hypertension or post-myocardial infarction (MI) populations[5−9] and not from stable CAD patients, which underscores the unmet need for a risk prediction tool to assess prognosis in such patients. In the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Therapy Evaluation (COURAGE) Trial, the annual rate of death or MI was 4.1% during a median 4.6-year follow-up,[10] whereas during an extended median follow-up of 11.9 years, the all-cause death rate was 25.[11] Thus, a reliable risk prediction tool could potentially have important prognostic utility by stratifying stable CAD patients into low-, intermediate-, and high-risk strata, and would permit various therapeutic interventions to be scaled to the level of risk. Therefore, to address the need for estimating the long-term prognosis of stable CAD patients in the current era of improved medical therapy, we developed a novel risk prediction tool to assess the rate of death from any cause or nonfatal MI, using data derived from the COURAGE Trial.

## Methods

The design and results of the COURAGE trial (clinical trials number: NCT00007657) have been reported elsewhere.[10,12] In brief, COURAGE-eligible patients had stable CAD and proven angiographic CAD (≥70% diameter stenosis of at least one major epicardial coronary artery) with a class I/IIa guideline indication for percutaneous coronary intervention (PCI). All patients in the study received intensive multifaceted medical therapy and were randomly assigned to initial PCI or no PCI.[10,13] Enrolled

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patients were followed at 50 U.S. and Canadian sites for a median 4.6 years (range 2.5 to 7 years). Available baseline data included age, race, sex, previous MI, heart failure, hypertension, previous revascularization, cerebrovascular disease, diabetes, major organ system disease (hepatic, pulmonary, and renal), body mass index, smoking, regular exercise, lipid profile, current anginal symptoms and functional status, ejection fraction, the number of diseased epicardial coronary arteries at angiography, and stress test results.

Logistic survival analysis was used to develop the risk prediction tool.[14] The analysis used 23 candidate baseline variables to predict a binomial response variable for the occurrence of death or MI; for each patient, the data consisted of the number of days in the study and whether or not a death or MI event occurred by the last observed day. Although most of the baseline information was complete, a standard technique for handling missing values in a regression setting was used.[15] This method imputes missing values, assuming that the patient values are samples from a multivariate model and missing values are missing at random. Forward selection was used to develop the prediction model. Variables were added to the logistic regression one at a time until the chi-square associated with any further addition was $\leq 4$ or $\leq 2$. The latter stopping rule, the Akaike Information Criterion, is advocated for optimal prediction.[16] For each patient, a model predicted value was obtained by multiplying each coefficient in the model by the patient's value for the corresponding variable and summing the results. To develop a risk tool from the predictive model, the coefficients were multiplied by 3 and rounded, the continuous variables were cut into coefficient-based ranges, and integer contributions to the risk prediction tool for each value of each variable were obtained. The discrimination of the risk tool was evaluated by the concordance index (c-index)—the probability that a patient who had an event within 5 years had a higher risk score than a patient with no event.[17] We used 100 randomly selected subsamples (selection probability of 0.5) as the basic tool for validation.[18] For each of these subsamples, the imputation and model selection was done separately. The subsamples were used in 2 ways: first, to assess the standard errors of the coefficients in the regression, accounting for possible effects of the imputation, whereas the standard deviations of the coefficients over the 100 random subsamples were computed and compared with the nominal standard errors for these coefficients in the logistic regression; second, the c-index for each risk score procedure was cross validated.[19] For each random subsample, a model was selected and a corresponding risk formula was determined. Using the risk formula, the c-index was computed for that random subsample, and for the complementary random subsample. The difference in the 2 c-indices measured the attenuation in predictive efficiency when the risk formula was used on new data. We predefined 3 strata of prognostic risk for the purpose of subcategorizing stable CAD patients into terciles of 5-year risk for death or MI: low (COURAGE risk score of 0 to 3), intermediate (risk score of 4 to 6), and high (risk score of 7 to 15).

## Results

The COURAGE study comprised 2,287 patients with stable CAD, of whom 88% had angina at baseline. The average age was $62 \pm 10$ years, 85% were male, 86% were white, 58% had Canadian Cardiovascular Society class 2 or 3 angina, 34% were diabetic, 67% had hypertension, and 71% were dyslipidemic at baseline, whereas 39% had previous MI, 68% had angiographic multivessel CAD (of whom 30% had 3-vessel CAD), with a mean ejection fraction of 60%.[10,12]

We chose to model the COURAGE Risk Score for the 5-year estimate of death or MI, which was the trial primary end point. The observed rate of death or MI during an average 5-year follow-up was 17.3%. There were 396 death or MI events, 267 MIs, and 180 deaths, with some patients dying after having an initial nonfatal MI.[10,12] The logistic survival analysis for the composite primary end point using all the variables including the imputed values is shown in Table 1. The subsample estimates of standard errors of the coefficients were in good accord with the nominal estimates, indicating minimal effects of imputation on the standard errors. The results of the selection procedures for death or MI on the random subsamples are shown in the Appendix. Using the chi-square chi-square>4 criterion, all the variables in the final model were selected at least 50% of the time, except for high-density lipoprotein cholesterol (HDL-C), which was selected 23% of the time; heart failure and number of diseased vessels were chosen most frequently. The c-indices for the 2 selection criteria, chi-square>4 and chi-square>2, were 0.674 and 0.665, respectively. When cross validated c-indices—which estimated how the risk score would perform on a different sample from the same population—were calculated, the c-indices dropped slightly to 0.629 and 0.621.

The following predictors and integer points contributing to the risk score in the final model for death or MI, based on selection at chi-square>4, were as follows: heart failure (3), number of diseased coronary arteries (1 for each vessel); diabetes (1); age (1 for each 15 years $\geq$ age 45); previous revascularization (1); current smoking (1); female gender (1); previous MI (1); and HDL-C (1: 31 to 40 mg/dL; 2: $\leq$30 mg/dL). Heart failure was the strongest predictor, closely followed by the number of diseased vessels at coronary angiography. Table 2 also presents the corresponding odds ratios for the end points of death or MI for each predictor in the presence of the other predictors.

The risk score had a potential range from 0 to 15, corresponding to estimated 5-year event rates of 5.8% to 56%. The maximum score obtained by the patients in COURAGE was 11. Based on the cross-validation results, we expected the c-index for a new dataset would be 0.60. Although calibration was strong, discrimination was moderate, with C-indices ranging from 0.67 for the full data set to 0.62 for the validating subsamples. Figure 1 shows the risk score distributions based on the coefficients in this model for those who did and did not have a death or MI event. The

Table 1
Description of candidate variables using logistic survival analysis and their ability to predict death or MI over 5 years

| Variable (*:chi-square chi-square>2, **: chi-square chi-square>4) | Range of variable | Number missing[§] | Coefficient estimate | Nominal SE | Subsample SD | Wald chi-squarechi-square |
|---|---|---|---|---|---|---|
| Age (years)** | 33-87 | 0 | 0.025 | 0.0061 | 0.0060 | 17.3 |
| Women** | 0-1 | 0 | 0.51 | 0.15 | 0.19 | 11.9 |
| White | 0-1 | 0 | −0.049 | 0.14 | 0.14 | 0.1 |
| Previous myocardial infarction** | 0-1 | 38 | 0.27 | 0.11 | 0.13 | 5.9 |
| Diabetes mellitus** | 0-1 | 37 | 0.33 | 0.11 | 0.11 | 9.1 |
| Hypertension | 0-1 | 25 | −0.12 | 0.12 | 0.12 | 1.0 |
| Congestive Heart Failure** | 0-1 | 15 | 0.89 | 0.17 | 0.21 | 26.2 |
| Cerebrovascular Disease | 0-1 | 0 | 0.12 | 0.17 | 0.19 | 0.5 |
| Previous Revascularization** | 0-1 | 0 | 0.37 | 0.12 | 0.12 | 9.7 |
| Pulmonary Disease | 0-1 | 0 | 0.11 | 0.15 | 0.18 | 0.5 |
| Liver Disease | 0-1 | 0 | 0.35 | 0.33 | 0.29 | 1.1 |
| Renal Disease | 0-1 | 0 | 0.22 | 0.24 | 0.30 | 0.9 |
| Body Mass Index | 17-54 | 7 | 0.011 | 0.011 | 0.012 | 1.1 |
| Current Smoker** | 0-1 | 1 | 0.40 | 0.12 | 0.12 | 11.1 |
| Exercise (moderate): 5X per week | 0-1 | 45 | −0.05 | 0.13 | 0.13 | 0.2 |
| Low-Density Lipoprotein (mg/dL)* | 21-243 | 10 | 0.0025 | 0.0015 | 0.0015 | 2.7 |
| High-Density Lipoprotein (mg/dL)* | 17-100 | 5 | −0.010 | 0.0053 | 0.0055 | 3.8 |
| Triglycerides (mg/dL) | 35-860 | 5 | 0.00044 | 0.00053 | 0.00057 | 0.7 |
| CCS Angina Class | 0-4 | 5 | 0.062 | 0.053 | 0.060 | 1.4 |
| Ejection Fraction (%) | 23-90 | 4 | −0.0065 | 0.0050 | 0.0053 | 1.7 |
| ISCHEMIA | 1-3 | 898 | −0.05 | 0.072 | 0.064 | 0.5 |
| ST Segment Depression | 0-3 | 646 | −0.03 | 0.043 | 0.039 | 0.4 |
| Number of Diseased Epicardial Vessels** | 0-3 | 0 | 0.301 | 0.066 | 0.082 | 20.5 |

[§] before imputation

Table 2
Final model for prediction of death or MI and coefficients for the risk score

| Variable | Odds ratio | Coefficient estimate | SE | Wald chi-squarechi-square | Contribution to the Risk Score |
|---|---|---|---|---|---|
| Heart Failure | 2.67 | 0.98 | 0.16 | 35.45 | Add 3 if present |
| Number of narrowed coronary arteries | 1.35 | 0.31 | 0.07 | 21.61 | Add 1 for each diseased vessel |
| Age(years) | 1.02 | 0.021 | 0.006 | 13.98 | Add 1 for each 15 yrs >44 (1:45-59; 2:60-74; 3: ≥75) |
| Diabetes mellitus | 1.46 | 0.38 | 0.10 | 13.29 | Add 1 if present |
| Female | 1.70 | 0.53 | 0.15 | 13.23 | Add 1 if female |
| Current Smoker | 1.53 | 0.42 | 0.12 | 12.93 | Add 1 if smoker |
| Previous Revascularization | 1.47 | 0.39 | 0.11 | 11.24 | Add 1 if present |
| Previous myocardial infarction | 1.37 | 0.31 | 0.11 | 8.50 | Add 1 if present |
| High-Density Lipoprotein Cholesterol (mg/dL) | 0.99 | -0.011 | 0.005 | 5.76 | Add 0 if >40, 1: 31-40, 2: ≤30 |

distribution for patients who had an event is shifted to the right compared to the patients who had no event. This figure also shows the predicted probability of an end point event for each score. Table 3 shows the relationship between risk scores, observed event rates, and predicted event rates for death or MI. If a patient had a risk score of 0 to 1, the observed rate was 6.9% and the predicted rate was 5.8% whereas for a risk score of 10 to 11, the observed and predicted rates were 52.2% and 56.0%, respectively, an approximate 8-fold increase at the risk score extremes.

Finally, we formulated 3 strata of risk, which ranged from "low" (score of 0 to 3), to "intermediate" (score of 4 to 6), to "high" (score of 7 to 15). The percentage of patients in each stratum and the respective observed versus predicted 5-year rates of death or MI were as follows: 30% had a low-risk score (9.3% vs 9.3%, or 1.9%/year); 59% had an intermediate-risk score (18.0% vs 18.1%, or 3.6%/year); and 11% had a high-risk score (36% vs 36.5%, or 7.2%/year). Figure 2 shows the Kaplan-Meier plots grouped by these strata ($p < 0.001$). Using logistic survival analysis, with the 3 strata included in the risk prediction model ($p < 0.001$), randomized treatment was not significant in predicting death or MI ($p = 0.49$) and the interaction of treatment (PCI or optimal medical therapy) with the strata was also not significant ($p = 0.27$). A proposed mnemonic for the COURAGE Risk Score is shown in the Supplementary Appendix.

## Discussion

We developed a risk assessment tool to predict death or MI events from the COURAGE trial for patients with stable CAD. There was a 4-fold increase in the 5-year incidence of death or MI from 9.3% in the 30% of patients within the

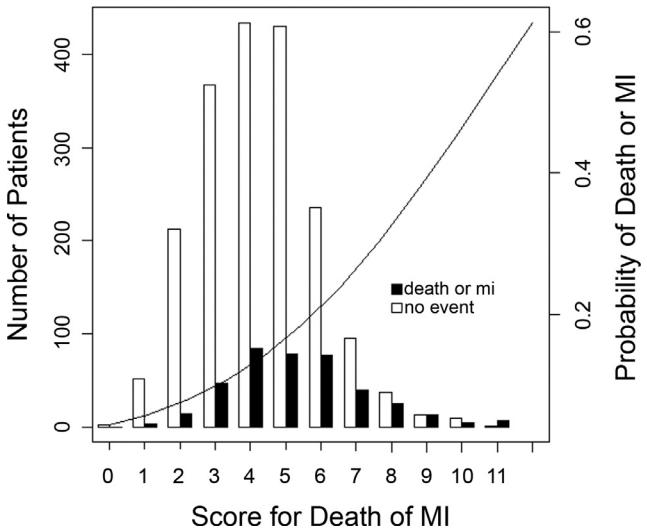


Figure 1. Distribution and performance of the COURAGE risk score in predicting death or MI within 5 years.
The bars show the number of patients with the score, the white bars are patients with no event and the solid bars are the patients with an event. The c-index for this distribution is 65%. The curve shows the predicted probability of an event for a specific score.

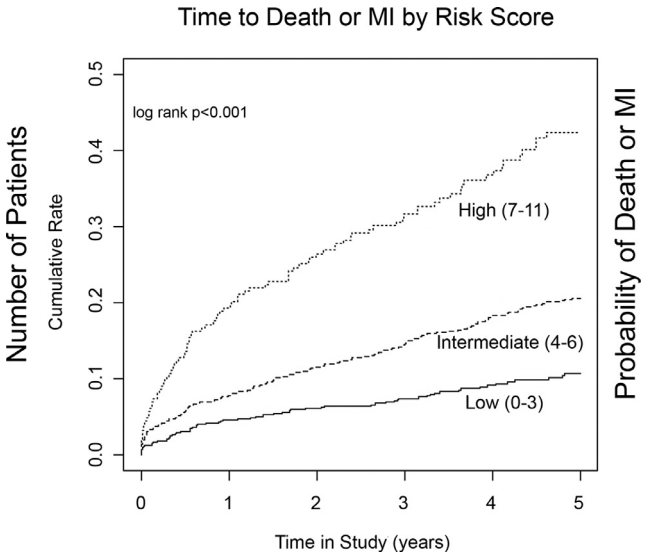


Figure 2. Time to death or MI by risk score in COURAGE trial patients. Kaplan Meier plot for the risk score divided into 3 groups. Group 1 patients (n = 699; 30%) had scores of 0-3 (solid line; Group 2 patients (n = 1,339; 59%) had scores of 4-6 (dashed line); and Group 3 patients (n = 247) had scores of 7-11 (dotted line). The difference between the risk score groups has log rank p < 0.001.

Table 3
Observed and predicted event rates over 5 years for the risk score of death or MI

| | Death or myocardial infarction | | |
|---|---|---|---|
| Risk score | Number of patients | Observed rate | Predicted rate |
| 0-1 | 58 | 6.9% | 5.8% |
| 2 | 227 | 6.2% | 7.9% |
| 3 | 414 | 11.4% | 10.6% |
| 4 | 518 | 16.4% | 14.1% |
| 5 | 509 | 15.5% | 18.5% |
| 6 | 312 | 24.7% | 23.9% |
| 7 | 136 | 29.4% | 30.2% |
| 8 | 62 | 40.4% | 37.4% |
| 9 | 26 | 50.0% | 45.2% |
| 10-11 | 23 | 52.2% | 56.0% |

lowest risk stratum of 0 to 3 (annualized rate of 1.9%); 18% in the ~60% of patients within the intermediate risk stratum of 4 to 6 (annualized rate of 3.6%); and 36% in the ~10% of patients within the highest risk stratum of 7 to 11 (annualized rate of 7.2%). Discrimination was moderate. This simple risk score, derived from readily available clinical, laboratory, and angiographic characteristics, may help clinicians determine prognosis and improve clinical decision-making in various subsets of stable CAD patients in whom the risk for subsequent clinical events may vary considerably.

We included as potential candidate variables all the risk factors for CAD available from the study population at baseline. Some variables that we expected a priori to be important did not appear in the final model. Ejection fraction, for example was highly correlated with heart failure, and not retained in the final model. Indeed, heart failure was the most powerful predictor of the risk for subsequent death or MI, which we hypothesize may be a manifestation of ischemia-mediated diastolic dysfunction given the overall normal mean ejection fraction observed in COURAGE.[10] Similarly, low-density lipoprotein cholesterol (LDL-C) was not retained in the final model of 9 independent predictors though this may, in part, relate to the 71% of patients who were already receiving a statin at baseline with a median LDL-C at baseline of 101 mg/dL, and which further decreased to 71 mg/dL on treatment during follow-up. This which could have resulted in decreased discrimination.[10] HDL-C, in contrast, is generally not affected as much by statin therapy, nor is it commonly regarded as a target of therapy, but it appeared in the subsampling procedure twice as often as did LDL-C, and hence it emerged in the final model.

A well validated risk prediction tool should help to better inform physicians and patients about prognosis and to aid in clinical decision-making in stable CAD patients. More accurately identifying personalized risk could incentivize patients and physicians to adopt management strategies tailored to the level of risk, thus making better use of evidence-based practice guidelines and promoting improved and more efficient use of healthcare resources.[20–22]

This risk score is novel as none of the currently available risk scores, including the Framingham Risk Score, which was designed to calculate long-term (10-year) risk in the general population without known CAD, have focused on intermediate- to long-term risk in patients with stable CAD.[23] However, this risk prediction tool should not be used for patients who were ineligible for COURAGE, such as those with left main coronary stenosis >50%, ejection fraction <30%, markedly abnormal exercise tests or myocardial perfusion scans, or subjects with (or unstable) angina at rest.

A potential limitation of any risk score derived from patients randomized in a clinical trial is external

generalizability to more unselected populations of so-called "real-world" patients, or that such individuals are, in general, at lower risk than patients in a routine clinical practice setting. However, as described previously, the baseline characteristics of COURAGE patients[24] showed that this was a broadly representative population of symptomatic patients who, on average, had 6 episodes of angina/week, with significant clinical co-morbidities at baseline, significant angiographic evidence of multivessel CAD in 68% of patients (mean diameter coronary stenosis of 82%),[10,12] and significant inducible ISCHEMIA on non-invasive stress testing in 85%, with 71% of patients showing multiple reversible perfusion defects on imaging.[10] Most importantly, the COURAGE trial was subsequently validated in a large observational study from the Mayo Clinic which showed similar clinical and angiographic features, as well as clinical outcomes.[25]

Although COURAGE has been criticized for not having enrolled the highest risk patients who might have derived greater proportional benefit from revascularization because randomization occurred after the results of angiography were known to investigators and could have led to potential selection bias, the large International Study of Comparative Health Effectiveness using Medical or Invasive Approaches (ISCHEMIA) trial of 5,179 stable CAD patients with moderate-to-severe baseline ischemia nonetheless showed no significant incremental benefit of an invasive strategy with revascularization compared to a conservative strategy of optimal medical therapy and lifestyle intervention alone for the composite primary outcome of cardiovascular death, MI, hospitalization for angina at rest or heart failure, or sudden cardiac death, or for the major secondary end point of cardiovascular death or MI during a median 3.2-year follow-up.[26]

In conclusion, we developed a simple risk tool consisting of 9 predictor variables that can define prognosis in patients with stable CAD for the composite of death or MI during an average 5-year follow-up. With an approximate 4-fold range from the lowest (9.3%) to the highest (36%) terciles of risk, this prognostic risk tool may help to better stratify stable CAD patients and tailor the intensity of treatment to the level of risk. The COURAGE Risk Score will need to be replicated and validated prospectively in future studies.

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Drs. William Boden and Pamela Hartigan had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Pamela Hartigan served as the senior study biostatistician at the Department of Veterans Affairs West Haven Cooperative Studies Program Coordinating Center and holds a faculty appointment in the Biostatistics Department at Yale University.

Dr. Boden affirms that each of the co-authors has provided written permission to be included as co-authors on this manuscript and each affirms that the information contained in this Acknowledgment Statement is complete an accurate. Drs. Boden, Pamela Hartigan, Teo, and Weintraub were responsible for the design and conduct of the trial, and were involved in the data analysis, manuscript preparation, and editing of the report. Drs. Mancini, Chaitman, Maron, Kostuk, Dada, Spertus, and Bates were involved in the interpretation of the data analysis and manuscript preparation. Dr. John Hartigan was involved as a consultant in the statistical analysis pertaining to the risk prediction tool.

None of the authors have conflicts of interest and relevant disclosures to report.

## Credit Author Statement

All the listed authors have contributed to the intellectual content of this report and agree with its submission to the American Journal of Cardiology.

## Author Declaration of Interest

None relevant to this submitted manuscript of the COURAGE Risk Score to the American Journal of Cardiology.

## Supplementary materials

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