Modeling and Risk Prediction in the Current Era of Interventional Cardiology

A Report From the National Heart, Lung, and Blood Institute Dynamic Registry

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Background—Validation of in-hospital mortality models after percutaneous coronary interventions using multicenter data remains limited.

Methods and Results—This study evaluated whether multivariable mortality models developed during the pre-stent era by New York State, American College of Cardiology (ACC)–National Cardiovascular Data Registry, Northern New England Cooperative Group, Cleveland Clinic Foundation, and the University of Michigan are relevant in patients undergoing percutaneous coronary intervention in the 1997 to 1999 National Heart, Lung, and Blood Institute Dynamic Registry. Of 4448 Dynamic Registry patients, 73% received stent and 28% received a IIB/IIIA receptor inhibitor. In-hospital mortality occurred in 64 patients (1.4%). The New York state model predicted mortality in 69 patients (1.5%; 95% confidence bounds [CI], 0.89% to 1.70%); Northern New England predicted mortality in 60 patients (1.3%; 95% CI, 1.0% to 1.7%); and Cleveland Clinic predicted mortality in 76 patients (1.7%; 95% CI, 1.3% to 2.1%). Among high-risk subgroups, with these 3 models, observed and predicted in-hospital mortality rates in general were not different. The other 2 models yielded different results. The University of Michigan predicted fewer deaths (n=47; 1.1%; 95% CI, 0.7% to 1.3%), and the ACC Registry model predicted 603 deaths (13.5%; 95% CI, 12.6% to 14.4%). Using the ACC Registry model, predicted mortality was higher than observed in each subgroup.

Conclusions—Application of 5 mortality risk models developed from different data sets to patients undergoing percutaneous coronary intervention in the Dynamic Registry predicted, in 3 models, mortality rates that were not significantly different than those observed. In both high and low risk subgroups, the University of Michigan slightly underpredicted mortality, and the ACC Registry predicted significantly higher mortality than that observed. (Circulation. 2003;107:1871-1876.)

Key Words: interventional cardiology ■ coronary disease ■ stents

Outcome analysis and quality control are important in interventional cardiology.1–6 Benchmarking raw outcome data is difficult and is complicated by variations in case mix, referral patterns, procedural techniques, and adjunctive therapy. Multivariable adjustment may overcome some of these limitations.7 In the mid-1990s, in-hospital multivariable mortality models after percutaneous coronary intervention (PCI) procedures began to be published.2,8–12 These models have been used for risk adjustment when comparing results from different operators and institutions and for predicting an individual’s risk of death after PCI. Most models, however, have been validated using internal patient populations only.2,8,10–12 External validation of the New York State, the Northern New England Cooperative group, and the Cleveland Clinic Foundation multicenter in-hospital mortality models have been previously evaluated by single-center data.3,6,13 The applicability of these models to a broader range of patients from multiple centers is uncertain.3,12 This study evaluated the ability of 5 such models, two8,9,11 in which patients were treated with conventional angioplasty only, two10,12 from the modern era in which stents were used, and one2 that spanned both eras, to predict procedural in-hospital mortality after PCI from patients enrolled in the multicenter National Heart, Lung, and Blood Institute (NHLBI) Dynamic Registry.

Methods

The institutional review board–approved NHLBI Dynamic Registry14,15 was developed to obtain periodic updates of interventional
cardiology emphasizing patient and lesion selection criteria, procedural performance, and early and intermediate term outcome. For this analysis, consecutive patients undergoing PCI at each of the 17 participating sites during two enrollment periods (July 1997 to February 1998 and February to June 1999) were studied. Standard data forms were obtained and analyzed at the University of Pittsburgh coordinating center. PCI patient selection criteria were site-specific, as was periprocedural adjunctive therapy. Core laboratory quantitative coronary angiographic analysis was not available, although on-site analysis was usually performed.

Definitions
Any in-hospital death occurring after PCI was considered procedure-related. Lesion success was an achievement of residual luminal diameter stenosis of <50% with ≥20% improvement. Procedural success was defined as at least one successful lesion without in-hospital death, Q-wave infarction, or emergency coronary bypass surgery. Myocardial infarction was defined by evidence of ≥2 of the following: (1) typical chest pain lasting >20 minutes not relieved by nitroglycerin; (2) serial ECG readings showing new changes in ST-T segments and/or Q-waves in ≥2 contiguous leads; (3) serum enzyme elevation of creatine kinase-MB >5% of total creatine kinase, total creatine kinase greater than twice the normal value, lactate dehydrogenase (LDH) subtype I greater than LDH subtype 2, or troponin >0.2 μg/L; and (4) new wall motion abnormalities. Unstable angina was defined as rest angina, new onset of exertional angina of at least 1 CCSC class to at least class III.

Single vessel disease was defined as ≥50% diameter stenosis in the right coronary, the left anterior descending, or the left circumflex artery systems; multivessel disease was defined as ≥50% stenosis in ≥2 major epicardial vessels. If the left main coronary artery had ≥50% stenosis, then 2-vessel disease was present. Left ventricular ejection fraction was recorded when measured at each center per site-specific protocols using angiographic, echocardiographic, and/or radionuclide techniques.

Five previously described multivariable in-hospital mortality models were studied: the New York State (NY State),9 the American College of Cardiology (ACC)—National Cardiovascular Data Registry (ACC),10 the Northern New England Cooperative Group (Northern New England),2 the Cleveland Clinic Foundation Multicenter (Cleveland Clinic),11 and the University of Michigan consortium (Michigan)12 models. All 5 included similar but not identical clinical, angiographic, and planned procedural variables (Appendix 1-13). The NHLBI Dynamic Registry collected all data included in each of the models except use of an intra-aortic balloon pump (NY State, ACC, and Northern New England), hemodynamic instability (NY State), salvage versus elective PCI (ACC), and history of cardiac arrest (Michigan). These variables were set to “no” or the lowest level for all patients. The NHLBI Registry recorded history of renal disease and used this variable as a surrogate for elevated creatinine values, which were not collected.

The NHLBI Registry enrolled 4625 patients from 1997 to 1999. Patients missing lesion data (n=168) or age at baseline (n=9) were excluded. The ACC, Northern New England, and Michigan models were developed using imputed left ventricular ejection fraction data and, thus, missing ejection fraction data (n=1849) was imput using a linear regression model that included sex, race, angina class, prior myocardial infarction, acuteness of PCI, number of significant lesions, presence of total occlusion, renal disease, and history of congestive heart failure, diabetes, and prior CABG. All other missing categorical responses (<1% of data), such as history of heart failure or renal disease, were set to “no” or the lowest level.

Statistical analysis results were presented as either mean ± SD or as a percentage of the total. Risk scores from all 5 mortality models were calculated from coefficients derived from the multivariable risk factor equation for in-hospital death.6–12 The probabilities of in-hospital death were then summed to determine an expected number of deaths for the overall NHLBI Registry sample, as well as for low and high-risk patient groups for each specific model. The 95% confidence bounds (CI) around the expected death rate were calculated with the normal approximation to a binomial distribution. Observed versus expected mortality by rank-ordered deciles of risk were plotted (ie, calibration). The relationship between each calculated risk score and in-hospital mortality was examined using logistic regression. Each model’s goodness-of-fit was assessed using the Hosmer-Lemeshow method,6 and fit was considered adequate (P>0.05). Model discrimination was assessed using the area under the receiver operator curve (ROC), and the area under each ROC curve was compared statistically using the Mann-Whitney test.

Results
The majority of patients were male with a mean age of 62.7 years (Table 1). The primary indication for PCI was unstable angina. In addition, 10.3% of patients underwent PCI within 24 hours of an acute myocardial infarction. Other high-risk features included a history of heart failure (9.5%), prior coronary artery bypass surgery (16.3%), and renal disease (4.2%). Among patients with measured left ventricular ejection fraction, ~88% of these patients had an ejection fraction >40%, whereas <1% had an ejection fraction <20%.

Although two (32.8%) or three (25%) vessel disease was most common, the majority of revascularization procedures involved a single vessel (88.6%). Stent implantation was common at 73.2%. A glycoprotein IIb/IIIa agent was admin-

| TABLE 1. Demographics and Medical History Characteristics in the Dynamic Registry |
|--------------------------|---|---|
| Factor                  | n  | %  |
| Male sex                | 2851 | 64.1 |
| Age, y (n=4448)         | 62.7±11.8 |
| Diabetes                | 1234 | 27.7 |
| Unstable angina         | 2066 | 46.5 |
| History of hypertension | 2710 | 61.6 |
| Renal disease           | 187 | 4.2 |
| Congestive heart failure| 424  | 9.5 |
| History                 | 338  | 7.6 |
| Peripheral vascular disease | 316  | 7.0 |
| History of stroke/CVA   | 275  | 6.2 |
| Prior PCI               | 1285 | 29.0 |
| Prior CABG              | 723  | 16.3 |
| Shock                   | 75   | 1.7 |
| Prior MI                | >7 days | 618 | 13.9 |
|                       | <6 hours | 258 | 5.8 |
|                       | 6–23 hours | 200 | 4.5 |
|                       | 1–7 days  | 1284 | 28.9 |
|                       | >7 days   | 618  | 13.9 |
| LVEF*                   | 1842 | 70.9 |

Values are number of patients and percent, except for age, which is mean ± SD. CVA indicates cerebrovascular accident; MI, myocardial infarction; and LVEF, left ventricular ejection fraction.

*Includes only patients with observed values.
istered either before or during the procedure in 27.8% of patients.

In-hospital outcomes other than death were also evaluated. Angiographic success (≥1 lesion treated successfully) and procedural success were achieved in 96.6% and 95.3% of patients, respectively. Myocardial infarction after PCI occurred in 2.9% of patients; 34 patients required CABG within 24 hours after their index procedure (0.8%).

Sixty-four patients (1.4%) died during hospitalization (Table 2). Three of the risk models accurately predicted this in-hospital mortality, with the observed rate falling within the 95% CI: the NY State model predicted 69 deaths (1.5%; 95% CI, 1.2% to 1.9%); the Northern New England model predicted 60 deaths (1.3%; 95% CI, 1.0% to 1.7%); and the Cleveland Clinic model predicted 76 deaths (1.7%; 95% CI, 1.3% to 2.1%). The Michigan model underestimated mortality in the entire group, predicting only 47 deaths (1.1%; 95% CI, 0.7% to 1.3%). In contrast, the ACC model markedly overestimated mortality, predicting 603 deaths (1.3%; 95% CI, 1.2% to 1.4%).

For most subgroups, both high and low risk (Table 2), observed and predicted mortalities were not significantly different for NY State, Northern New England, and Cleveland Clinic models. These models were accurate, not only for high risk patients such as those with acute infarction and shock, but were also very accurate for low-risk patients. In patients without acute infarction, 34 deaths were observed (0.8%); the NY State model predicted 42 (1.0%), Northern New England model predicted 34 (0.8%), and Cleveland Clinic predicted 38 (0.9%). The ACC model significantly overestimated in-hospital mortality rates for each subgroup. In general, the Michigan model underestimated mortality, although the significant differences were restricted to the high-risk groups. For example, the Michigan model predicted 26 deaths (0.6%; 95% CI, 0.4% to 0.9%) in patients with no acute infarction. For the patients with shock, the Michigan model significantly underpredicted 16 deaths (21.3%; 95% CI, 12.0% to 30.7%) versus the 26 deaths observed (34.7%).

The relationship between the observed and predicted in-hospital mortality by rank-ordered decile of risk in the entire sample is important. The plots for NY State, Northern New England, and Cleveland Clinic models were similar and show a strong correlation between observed and expected mortality by risk decile (Figure). The slope of observed and predicted death using the ACC model, however, is markedly steeper, indicating a significant overprediction of mortality in each risk decile. In the higher risk deciles, the Michigan model underpredicted mortality.

![In-hospital mortality by risk decile observed in the NHLBI Dynamic Registry and predicted using the NY State, Northern New England, Cleveland Clinic, ACC, and University of Michigan models.](http://circ.ahajournals.org/)
With univariate logistic regression models, the association between each of the risk scores and in-hospital mortality was similar across the 5 models, with a 1-point increase in the calculated score associated with an $\approx$3-fold increase in risk of in-hospital mortality among NHLBI Registry patients (Table 3). Model discrimination measured by the C statistic ranged between 0.84 to 0.89, and there was little departure in model fit on the basis of the Hosmer-Lemeshow’s goodness-of-fit statistic ($P$>0.05). The area under the ROC curve was significantly lower ($P$≤0.01 for each comparison) for the Cleveland Clinic model compared with the NY State, the ACC, and the Northern New England models.

**Discussion**

This study assessed the accuracy of both pre-stent and modern era in-hospital mortality models using a multicenter external data source; it documents that risk stratification models developed from data collected in the early and mid-1990s are relevant to our multicenter registry of consecutive patients treated with current techniques. In the NHLBI Dynamic Registry, 4448 patients were treated at 17 sites from 1997 to 1999. Stent implantation was common (74%), and glycoprotein IIb/IIIa agents were administered in 27%. In this patient group, the observed in-hospital mortality rate was 1.4% (64 deaths) and was statistically similar to the rates predicted by NY State, the Northern New England, and the Cleveland Clinic models. The observed rate was significantly lower than the rate predicted by the current ACC model and slightly but significantly higher than that predicted by the Michigan model.

Variables used in models of PCI outcome must be easily obtained, objective, and have a high degree of observed correlation on repeated measurements, and model fit should be high.$^{12,13}$ Other important considerations include assessment of the validity of the model in patient groups other than those for whom the model was developed and documentation of the relevance of the model when technology used to treat patients involved has changed substantially.

Before this report, external validation of in-hospital mortality models has been evaluated using single-site data. The Northern New England and Cleveland Clinic models were validated using data from 1476 consecutive high-risk PTCA patients$^6$ in whom the in-hospital mortality was 3.4%. Multivariate regression analyses indicated that both models, when fit to the external data set, had excellent discrimination and were quite accurate in predicting in-hospital mortality. The NY state in-hospital model was found to predict procedural mortality accurately in 3761 consecutive patients treated with stents at a single center.$^4$ Again, there was no statistical difference between observed and predicted in-hospital mortality rates, and the model discrimination on the basis of the ROC curve was high.

Although all 5 mortality models$^2,8–12$ incorporated similar demographic, existing comorbidities (cardiogenic shock, renal disease, congestive heart failure), and certain procedural variables, there were some differences. All in-hospital mortality models with the exception of NY State included lesion class and/or complexity variables, which are often subjective and may not have a high degree of correlation on repeated sampling. Specific lesion location, adjunctive therapy (thrombolytics), and modern era device use variables were also integrated into the Northern New England, Cleveland Clinic, and the ACC models. These models were developed using widely different sample sizes, 2 of which had >50 000 procedures, whereas the others ranged between 10 796 and 15 331 procedures. The number of explanatory variables significantly associated with in-hospital mortality and their respective magnitude of effect may be influenced by sample size. For missing data, imput values, most frequently with ejection fraction, were used in model development in the Northern New England, ACC, and Michigan groups, which could have introduced misclassification bias. There was no information available on treatment of missing values for either the NY State or Cleveland Clinic models. The in-hospital mortality rate reported by each study was fairly consistent and ranged between 0.9% (NY State) and 1.6% (Michigan), despite case mix variations, prevalence of risk factors, and type of PCI performed.

We can only speculate as to why the Michigan model$^{12}$ somewhat underestimated and the ACC model$^{10}$ significantly overpredicted in-hospital mortality. The NHLBI Dynamic Registry did not collect data on history of cardiac arrest, a strong risk factor (odds ratio=3.65) in the Michigan model of procedural mortality. Although the prevalence of cardiac arrest may be low, the probability of death based on this model for such patients would actually be higher than the value used in this analysis. Another potential explanation for the underestimation of observed mortality involves creatinine levels, which was also strongly associated with mortality (odds ratio=5.5). We substituted history of renal disease for creatinine $>$1.5 mg/dL; this may have led to the misclassification of patients who did not report a history renal disease but who had a creatinine $>$1.5 mg/dL.

The results generated using the ACC model are more puzzling. This model predicts that patients with no risk factors (those included in their published model) will have a predicted death rate of $\approx$1.1% (Appendix 2). This is a surprisingly high number given that the observed mortality rate among the 100 253 ACC procedures (both low and high risk patients) was 1.4%. Although there are some notable patient differences between the NHLBI and ACC registries with respect to reason for revascularization (unstable angina: NHLBI, 47%; ACC, 62%; acute myocardial infarction: NHLBI, 10%; ACC, 17%), the Northern New England model included a large proportion of patients with unstable angina.

**Table 3.** Odds Ratios and 95% Confidence Intervals for In-Hospital Mortality in the Dynamic Registry for 1-Point Increase in Published Risk Scores ($n=4448$)

<table>
<thead>
<tr>
<th>Model</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>C Statistic</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>NY State</td>
<td>2.93</td>
<td>2.51–3.42</td>
<td>0.89</td>
<td>0.45</td>
</tr>
<tr>
<td>ACC</td>
<td>2.95</td>
<td>2.54–3.44</td>
<td>0.88</td>
<td>0.80</td>
</tr>
<tr>
<td>Northern New England</td>
<td>2.95</td>
<td>2.52–3.45</td>
<td>0.89</td>
<td>0.13</td>
</tr>
<tr>
<td>Cleveland Clinic</td>
<td>2.83</td>
<td>2.42–3.30</td>
<td>0.84</td>
<td>0.32</td>
</tr>
<tr>
<td>Michigan</td>
<td>2.94</td>
<td>2.52–3.44</td>
<td>0.86</td>
<td>0.48</td>
</tr>
</tbody>
</table>

$^*$Hosmer-Lemeshow goodness-of-fit.
(73%), and 13% of PCI patients in Michigan were experiencing an acute myocardial infarction. The baseline model (no risk factors) predicted mortality rate in the Northern New England and Michigan models were 0.05% and 0.07%, respectively. Differences in underlying patient characteristics in the ACC model, therefore, do not seem to account for all of the overprediction. The ACC model will very likely overestimate predicted in-hospital mortality in any population that includes a high proportion of low and medium risk patients, as was seen in the NHLBI Dynamic Registry. Although these results cannot be explained fully, we applied an unpublished in-hospital mortality model developed using a later version of the ACC data (n=78,850 procedures) to the NHLBI Registry, and this new model predicted 51 deaths (1.1%; 95% CI, 0.9% to 1.4%; R. E. Shaw, PhD, unpublished data, October, 2002). Consistent with the published ACC model, the new model included the variables salvage PCI (versus elective) and intra-aortic balloon pump, which were not collected in the NHLBI Registry. Both of these variables were strongly associated with mortality; this could lead to an underestimation of predicted in-hospital mortality using this model.

The present report further extends the validity and relevance of the NY State, the Northern New England, and the Cleveland Clinic models when applied to a multicenter external data source of patients undergoing PCI in the stent era. The NY State and Cleveland Clinic models developed in patients treated with conventional angioplasty remain robust, even though 74% of the NHLBI Dynamic Registry patients received a stent and 27% received a glycoprotein IIb/IIIa receptor inhibitor. The Northern New England model included patients receiving new devices. Despite advances in technology, which introduces the potential to treat successfully more complex lesions and reduce nonfatal complications, the pre- and early stent-era models continue to be applicable in the modern era. Recent technological advances do not seem to improve mortality resulting from underlying comorbid conditions, left ventricular dysfunction, or advanced untreatable disease.

Limitations
The NHLBI Dynamic Registry involves experienced interventional cardiology centers with broad exposure to a wide range of patients. The excellent predictive nature of several in-hospital mortality models using these Dynamic Registry centers may not be completely relevant to other centers, although the NY State and Northern New England models were developed in patients treated at variety of centers. Average risk scores calculated for most of the models (NY State, ACC, Northern New England, and Michigan) might be underestimated in the Dynamic Registry patients because data on several variables were not collected. Finally, imputation of ejection fraction may have led to some misclassification.

Conclusions
The NY State, the Northern New England, and the Cleveland Clinic mortality models, developed in the pre- and early-stent eras of interventional cardiology, remain relevant in the current era of PCI and can be used to predict in-hospital death. Accordingly, they continue to be useful for risk stratification and outcome assessment.

Appendix 1

Model Variables

NY State
- Age
- Female sex
- Prior myocardial infarction and timing
- Shock
- Hemodynamic instability
- Renal failure
- Peripheral vascular disease
- Diabetes mellitus
- Congestive heart failure
- Prior PTCA
- Prior CABG
- Multivessel disease
- Intra-aortic balloon pump
- Left ventricular ejection fraction

ACC
- Acuteness of PCI
- Shock
- Intra-aortic balloon pump
- Age
- Diabetes mellitus
- Left ventricular ejection fraction
- Acute myocardial infarction <24 hours
- Lesion classification based on Society for Cardiac Angiography and Intervention
- Left main disease
- Proximal left anterior descending lesion
- Renal failure
- Chronic lung disease
- Thrombolytic therapy
- No stent device used

Northern New England
- Age
- Therapy for acute myocardial infarction
- Shock
- Urgent PCI
- Emergent PCI
- Left ventricular ejection fraction
- Creatinine ≥2.0 mg/dL
- Peripheral cerebrovascular disease
- Congestive heart failure
- Intra-aortic balloon pump
- Class C lesion attempted

Michigan
- Myocardial infarction within 24 hours
- Shock
- Creatinine >1.5 mg/dL
- Cardiac arrest
- Number of diseased vessels
- Age
- Left ventricular ejection fraction
- Thrombus
- Peripheral vascular disease
- Female sex

Cleveland Clinic Foundation
- Age
- Shock
- Acute myocardial infarction
- Lesion complexity
- Male sex
- Number of diseased vessels
Appendix 2

Hypothetical Example Illustrating the Probability of In-Hospital Mortality in Patients Without Any Identified Risk Factors Based on the NY State and ACC Models

Probability = e^y/(1+e^y), where y is the constant. For the purpose of this example, assume a low-risk patient sample consisting of 50,000 patients. Note that the number of deaths is affected by the sample size but the death rate is not.

NY State Model: 50,000 × (e^{-0.9128})/(1+e^{-0.9128}) ≈ 2.5 patients or 0.005%.
ACC Model: 50,000 × (e^{-4.464})/(1+e^{-4.464}) ≈ 569 patients or 1.1%.

References
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