EDITORIAL COMMENT

Risk Prediction After Myocardial Infarction in the Elderly*

Koon K. Teo, MB, PtD, FACC,†
Diane J. Catellier, DRPH‡
Hamilton, Ontario, Canada, and Chapel Hill, North Carolina

In medical practice, knowledge of the prognosis of the disease being treated is important both for the clinician and the patient. Unlike physicians of old, who depended solely on their own personal knowledge and experience accumulated from careful and systematic observations of their patients, modern physicians are fortunate in having easy access to the large store of common medical knowledge, particularly pathophysiology and therapeutics, in addition to the personal knowledge and experience gained in practice, on which to base their disease prognostication and treatment decisions. Often, however, this knowledge is found to be inadequate or imprecise in helping a physician predict, to a reasonable degree of certainty, a patient's prognosis, and to use this knowledge as a guide in making therapeutic decisions. The convergence of modern databases, statistical methods and computing capabilities, in making possible the analysis of prognostic predictors, would appear to fulfill this need. This in essence combines, quantitatively, the experience of many physicians and their observations on a particular disease. By so doing, the influence of the peculiarities in particular case or cases experienced by any one physician would be diminished; instead, the commonality of many similar cases would be strengthened, resulting in a greater degree of certainty.

Myocardial infarction (MI) is a disease in which the development of more precise estimates of risk and prognosis is desirable. It affects many people. Coronary atherosclerosis, which forms the underlying basis for acute MI, is a chronic disease that can result in serious and fatal outcomes, both in the acute phase and subsequently. It is also a disease for which efficacious therapies have been developed during the last two decades. This further amplifies the need for prognostic prediction on which to form an understanding of future expectations and to base therapeutic and other management decisions so as to reduce the associated short- and long-term morbidity and mortality.

In risk stratification studies, the presence of a variable such as the presence of myocardial ischemia or poor left ventricular function has been usefully employed to guide decisions involving management and interventions to reduce risk for future events (1–4). In the acute phase of MI, studies have identified adverse prognostic variables, and algorithms have been produced using this information in order to aid decision making and improve patient outcomes (5,6). Other studies about survivors of acute MI, based on patients enrolled in clinical trials or on regional or local populations, can provide useful insights into the evolution of the MI and the underlying coronary artery disease and guide practice decisions regarding secondary prevention (7–9). Of the many risk prediction and stratification studies carried out, most were done in a narrowly focused or nonsystematic manner, using information available in a particular data set. This can limit the relevance of such studies to other populations. Also, though the information from these studies can be judged to be generally relevant to all patients with MI, the prognostic predictors reported in most of these studies are more limited in their applicability to special populations, such as the elderly and women.

In this context, the analysis by Krumholz et al. (10) in this issue of the Journal can fill a large information gap on the elderly, focusing on the important co-morbidities and disease severity in elderly survivors of acute MI. The data from the U.S. nationwide Cooperative Cardiovascular Project (CCP), which encompassed a wide range of individuals over a wide geographical distribution, have proven to be extremely useful (6,10). The CCP database, combining both information extracted from individual patient charts and administrative databases, includes data on a large number of individuals age 65 years or older that are included in the Krumholz et al. (10) study. There are a large number of variables, both clinical and laboratory, that can be important for the purpose of this analysis. By using the data from over 100,000 individuals who have survived the hospitalization for the index MI, one can be impressed with the statistical power that this database can confer on the analysis.

The process for arriving at a model for prediction of one-year mortality from a set of variables encompasses three components: selection of predictors, parameter estimation and assessment of model performance. In the present analysis, Cox regression models were appropriately used to identify the variables most predictive of one-year mortality. Although estimation for such models is relatively straightforward using commercially available software, selection of a “best” prediction model and validation of that model are much more subtle tasks. The investigators (10) used an analytical approach in which the data were randomly divided in two subsamples: the first being used for model construction and estimation and the second for assessment of performance of model predictors. To avoid adversely affecting model performance by overfitting or from multi-

*Editorials published in the Journal of the American College of Cardiology reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

From †McMaster University, Hamilton, Ontario, Canada, and ‡University of North Carolina, Chapel Hill, North Carolina.
colinearity, only a limited number of the variables most highly associated with one-year mortality were kept. No appreciable drop in the predictability (as measured by the area under the receiver-operating characteristic curve) was found when this set of “optimal” predictors was included in a model constructed from the validation sample.

The analysis largely ignores errors arising from uncertainty regarding the model specification. The multitude of strong associations with mortality in the CCP dataset allows for construction of numerous highly predictive models. Although a single prediction model was selected, other model specifications may be virtually indistinguishable in terms of their predictability. Whether a model is specified on subject-matter grounds or fitted in an iterative way (as was done here), error due to this model uncertainty is likely to be far worse than that arising from estimation of regression coefficients (which the present validation method found to be minimal).

A simple way of addressing the issue of model uncertainty is to determine to what extent the performance of the “best” model reported here is superior (in terms of predictability) to some “reference” prediction model that contains only the traditional risk factors for mortality. For example, it would be of considerable interest if the discriminatory ability of the proposed model for coronary heart disease (CHD) is considerably greater than that of the model for CHD prediction derived from the Framingham Study data, which include age, gender, blood pressure, total cholesterol, high density lipoprotein cholesterol, smoking and diabetes (11), although it should be noted that the Framingham data did not deal exclusively with elderly survivors of MI. In theory, use of prediction models should be restricted to individuals who resemble the population from which the models were derived. However, reasonable accuracy in prediction has been demonstrated in the past when the Framingham CHD prediction equations were applied to diverse population samples. With this in mind, the merit of the proposed prediction model for risk stratification, although clearly demonstrated in this analysis, may not represent a significant improvement over prediction based on traditional risk factors. Further analyses may settle this issue.

There are three findings of interest to the clinician: 1) identification of prognostic predictors of mortality at one year; 2) demonstration that the prediction model built on the analysis has performed well; and 3) derivation of a risk score and categorization of individuals into different levels of risk. Because of the large sample size, bivariate analyses have identified a large number of variables that have reached nominal statistical significance. For the analytic and statistical reasons outlined above, the investigators have wisely set critical levels of significance. One may ask whether or not these interventions had conferred a worthwhile benefit in reducing the risk of dying within one year in these individuals. Examination of the bivariate comparisons shows that these interventions were individually associated with a significant survival advantage, but the influence of patient selection bias for these interventions is likely to be very strong. It is probable that the individuals who were more likely to survive due to the absence of the physical frailty and other co-morbidities were those more likely to receive these interventions.

Furthermore, the influence of competing risk from the systemic co-morbidities is particularly strong in this population. For example, the in-hospital use of angiotensin-converting enzyme inhibitors was found to be associated with excess mortality, suggesting that these agents may have been prescribed preferentially to those with heart failure, which itself has a much greater negative impact on eventual survival in this population than the positive beneficial effects of the medication.

It is reassuring to find that the logistic regression model has good model discrimination and that the performance of the validation model was similar to the original prediction model. Subject to the methodological concerns discussed above, regarding errors arising from uncertainty in the model specifications, it would appear that extrapolation of the findings to a similar population would be appropriate and valid. Given that the study sample is derived from a large nationwide cohort of elderly subjects, all with a diagnosis of acute MI, the relevance of extrapolating this model to similar patients would be much greater than the corresponding models in many other studies.

A risk score, ranging from 0 to 13, was formulated based on the final prediction Cox regression model, and weights were assigned to each risk factor according to the magnitude of the risk ratios derived from the Cox regression analysis. By calculating the scores for individual patients and assigning them into risk categories, the model was able to identify a low-risk group with a 7%, a medium-risk group with a 24% and a high-risk group with a 49% one-year mortality. Similar useful risk stratification findings were also obtained for the combined end points of death plus rehospitalization and death from acute MI plus rehospitalization. The usefulness of such a score is obvious and may prove to be the major contribution of this study to clinical practice.

Many studies have reported on risk stratification of patients with MI. An example is a comprehensive review of risk stratification of hospitalized acute MI patients by Peterson et al. (5). A timely and ongoing process of risk stratification of the patient immediately at presentation to the hospital with suspected MI is logical in order that reperfusion therapy and other emergency care can be given...
without delay. Patients identified at high risk can be further triaged to receive early angiography and other appropriate interventions, whereas those at low risk for recurrent events may be evaluated with noninvasive stress testing for further risk stratification. Other studies have focused on elements of risk stratification by using various noninvasive techniques (1–3). Yet other studies attempted to identify risk factors associated with long-term morbidity and mortality of survivors of acute MI (7–9). It might not be surprising that results of these studies do not always agree, because of differences in patient characteristics, choice and definition of study end points, inclusion of various identified risk factors, statistical power and other variables in the analyses (12).

This study by Krumholz et al. (10) is unique in several respects. In addition to dealing exclusively with an elderly population using a large sample size obtained on a nationwide scale, this study placed a greater emphasis on clinical variables and identified a number of variables not usually included in other studies, but it did not deal with issues directly related to the early phase of the index MI. The variables selected in such a geriatric population appropriately included those on indices of frailty such as decreased functional status and low body mass index, which have been known in geriatric medicine as indicators of increased mortality risk. By combining these clinical markers of risk with a measure of cardiac function (left ventricular ejection fraction [LVEF]) and the presence or absence of other systemic co-morbidities, which are much more specific to this elderly population, the presence or absence of other systematic diseases, which can have a large influence on outcomes, the investigators have formulated what appears to be a useful and practical risk prediction model. This is a model that clinicians would be able to apply to their patients without having to resort to sophisticated equipment and tests for risk stratification.

However, the fact that this study did not include the commonly used indices of subsequent cardiac risks, and that the use of interventions such as beta-blockers, aspirin and cardiac procedures did not materially affect the statistical levels of significance may be causes for concern. Other than including LVEF, this study has not included such conventional predictors of risk as infarct characteristics, extent of coronary disease, myocardium at risk for recurrent ischemia, and electrocardiographic and other noninvasive markers of ischemia. Thus, it is not clear whether inclusion of these variables would improve upon the predictive utility of the variables already included in this study.

On the one hand, it can be argued that this noninclusion is a major flaw of this study and that inclusion of tests results on these variables would clearly improve the study. On the other hand, it may well be that, similar to the effects of interventions such as beta-blockers, aspirin and cardiac procedures, inclusion of these test results might not materially change the statistical significance, given the predominant influence of the competing risks from the other systemic co-morbidities commonly found in this population. It is possible that both the impact of the conventional risk predictors of cardiac function and myocardial ischemia and the use of proven efficacious therapies, which have not been addressed in this study, are of lesser importance in this population. However, the usefulness of these diagnostic and therapeutic strategies has been shown in the general population, and there is no plausible reason that the elderly population would not benefit from similar and appropriate approaches to treatment. Thus, the generally accepted management strategies for postinfarction patients should be applied appropriately, taking into account the individual patient’s potential to benefit or not to benefit from these strategies. What this study emphasizes, however, is that other information, particularly that on other noncardiac co-morbidities, which are much more specific to this elderly population, should be included in the decision-making process.

As with all retrospective database analyses, the Krumholz et al. (10) study suffers from the problem of missing data. The most conspicuous of the missing data are LVEF (30%), albumin (27%) and body mass index (15%). Left ventricular ejection fraction and body mass index have been found to be important independent risk predictors in this analysis, and there is always a concern that the absence of these variables in so many patients may affect the final results. It is quite possible that the missing data were not random and that these measurements were preferentially not obtained in much sicker and frail patients. If this is the case, the impact of the missing data might have important implications as to the precision of the estimates. The investigators have tried to overcome some of the deficiencies by using accepted statistical methods. It is also reassuring to find that, in the evaluation of performance of the prediction regression model, analysis of outcomes on only those patients with known ejection fractions showed the same high degree of model discrimination.

Thus, the inclusion of predictive variables consisting mainly of clinical and routine laboratory variables (and minimum need for sophisticated assessment of cardiac function and myocardial ischemia) in a large nationwide population makes the extrapolation of these results practical and useful in a widespread variety of clinical and health care settings. By applying the risk score and risk categorization to individual patients, clinicians can get a sense of the risk level of subsequent one-year mortality and morbidity in their patients and use this information as a basis for making further diagnostic and therapeutic decisions. By including the presence or absence of other systemic co-morbidities into the consideration of risk quantitatively, a more realistic expectation of treatment and outcomes can be obtained.

Reprint requests and correspondence: Dr. Koon K. Teo, Room 3U4, McMaster University Medical Centre, 1200 Main St. West, Hamilton, Ontario, Canada L8N 3Z5. E-mail: teok@mcmaster.ca.
REFERENCES