

## **Methodological Issues Related to Dynamic Modeling**

### **Model Enhancement**

Unlike previous models, the GUSTO-IIb models were enhanced with quantitative measures such as serum cardiac markers and baseline ST depression. These added considerable prognostic information, especially when the CK-MB level was more than double the ULN<sup>1</sup> or when baseline ST depression was >2 mm.<sup>2</sup> We further extended these models to include in-hospital events up to 6 days postadmission, showing that such events and interventions strongly influenced 30-day endpoints. The availability of an independent PURSUIT dataset with similar variable definitions provided a rare opportunity for rapid validation of the initial model.

### **Methodological Issues**

Many baseline historical factors, such as previous MI, heart failure, or angioplasty, became less influential and nonsignificant in the Day 3-30, 5-30, and 7-30 models. These variables would be excluded from the model if treated independently from their postenrollment counterparts. To prevent this, we combined and retained these variables to show that they were no longer significant. If such measures were not taken, prognostic comparisons between baseline and later days for such variables would be distorted. For instance, patients with previous PCI would have a reduced risk at baseline but not at Day 2 if previous PCI were excluded from the Day 3-30 model, so that the prognosis would worsen at Day 2. Care must be taken to construct and interpret prognostic models based on which prognostic assessments are to be made over time.

Several other issues require further deliberation and discussion. First, continuous predictions of 30-day outcome would be enhanced with additional data such as heart rate, blood pressure, rales, and ECG variables to reassess patients at Days 2, 4, and 6. Such indicators of change from baseline to a clinically meaningful “landmark” typically are used in landmark analysis to minimize problems associated with response bias in cancer research.<sup>3</sup> Moreover, additional risk predictors (such as new biomarkers developed since our studies were conducted) likely would enhance predictive capacity and could be readily incorporated into this model. The inclusion of biomarkers beyond CK isoenzymes should be particularly rewarding in future risk models. Both the cardiac troponins and C-reactive protein now are known to be highly significant predictors of future cardiac events, independent of baseline characteristics.<sup>4,5</sup> Several studies also have shown that recurrent ischemia on follow-up ECG adds to the prediction of risk.<sup>6</sup>

Second, the use of 30-day mortality rather than death or (re)MI as the outcome for risk assessment was justified on the grounds that the 2 risk estimates are highly correlated ( $r=0.89$ ) and that the predictive model was superior if based on mortality rather than the composite event. Further research is required to determine the appropriateness of various clinical outcomes, however, including the length of follow-up periods (e.g., 6 months or 1 year), more appropriate biomarkers, ongoing monitoring of key clinical indicators, and predictive modeling based on these outcomes.

Third, some of the estimates obtained in our models may reflect the peculiarity of the GUSTO-

IIB dataset. The extremely low odds ratio of 0.03 in the Day 3-30 model for early PCI highlights this issue. There was only 1 death (0.3%) during Days 3-30 among the 299 patients who had PCI and survived the first 2 hospital days versus 208 deaths (3.0%) among 6933 patients who survived the first 2 hospital days without undergoing early PCI. The comparable figures in PURSUIT were 12 (1.2%) deaths among 979 patients who underwent PCI within 2 days and 284 (3.4%) deaths among 8436 patients who did not. Other predictors, on the other hand, seem to be fairly robust and could be generalized to other NSTEMI ACS populations, although a closer examination of this matter is again warranted.

Fourth, further clinical judgments about risk stratification are required in some applications, such as discharge planning. It is necessary, in particular, to investigate appropriate thresholds for various clinical decision-making, including decisions to admit to or discharge from the ICU/CCU or hospital; our definition of a “low” risk based on a 1% risk of dying within 30 days is for illustrative purposes only and should be further studied and refined.

Finally, there are also a host of issues regarding the development of practical, dynamic prognostication models, chief among them the consistency of simplified risk scores across various models and validity, reliability, and utility of simplified versus full models. These issues are discussed in detail in Technical Appendix 2.

## References

1. Alexander JH, Sparapani RA, Mahaffey KW et al. Association between minor elevations of creatine kinase-MB level and mortality in patients with acute coronary syndromes without ST-segment elevation. *JAMA* 2000;283:347-353.
2. Kaul P, Fu Y, Chang W-C et al. Prognostic value of ST-segment depression in acute coronary syndromes: insights from PARAGON-A applied to GUSTO-IIb. *J Am Coll Cardiol.* 2001;38:64-71.
3. Anderson JR, Cain KC, Celber RD. Analysis of survival by tumor response. *J Clin Oncol.* 1983;1:710-719.
4. The FRISC II Investigators. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. *Lancet.* 1999;354:708-715.
5. The GUSTO IV ACS Investigators. Effect of glycoprotein IIb/IIIa receptor blocker abciximab on outcome in patients with acute coronary syndromes without early coronary revascularisation: the GUSTO IV-ACS randomised trial. *Lancet.* 2001;357:1915-1924.
6. Armstrong PW, Fu Y, Chang W-C et al. Acute coronary syndromes in the GUSTO-IIb trial: prognostic insights and impact of recurrent ischemia. *Circulation.* 1998;98:1860-1868.