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**EDITORIAL**

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# Invasive vs Conservative Management of Acute Coronary Syndromes

## Do the Data Support the Guidelines?

David J. Cohen, MD, MSc

**A**CU TE CORONARY SYNDROMES (ACSS) ACCOUNT FOR approximately 1.4 million hospitalizations each year in the United States alone, and more than 2 million worldwide.<sup>1</sup> Until recently, however, there was no consistent guidance as to how such patients should be optimally managed during the hospital phase. Some clinicians favored an early invasive strategy, with cardiac catheterization during the first 24 to 48 hours of presentation. Others favored a more conservative strategy with initial medical stabilization followed by cardiac catheterization only if the patient demonstrated high-risk features (such as recurrent myocardial ischemia or congestive heart failure) or significant myocardial ischemia on noninvasive testing. Although the invasive strategy offers the ability to identify patients with high-risk coronary anatomy quickly and definitively, several clinical trials suggested that these poten-

tial benefits were offset by the early risks of revascularization procedures in these high-risk subgroups.<sup>2,3</sup>

Recently, however, 2 large-scale randomized clinical trials have demonstrated that advances in percutaneous coronary intervention (PCI) and adjunctive medical therapy have tipped the balance in favor of an early invasive strategy. In the Fragmin and Fast Revascularization during Instability in Coronary Artery Disease (FRISC) II trial, 2457 patients with unstable angina or non-ST-segment elevation myocardial infarction (MI) were initially stabilized with dalteparin (5-7 days) and then were randomly assigned to an early invasive strat-

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egy or to a more conservative management strategy.<sup>4</sup> At 6-month follow-up, there was a substantial reduction in the primary end point of death or nonfatal MI among patients assigned to receive the early invasive strategy (9.4% vs 12.1%, respectively;  $P=.03$ ), which translated into a reduction in overall 1-year mortality (2.2% vs 3.9%, respectively).<sup>5</sup>

In the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS)—Thrombolysis in Myocardial Infarction (TIMI) 18 trial, 2220 patients with unstable angina or non-ST-segment elevation MI were treated with aspirin, heparin, and the platelet glycoprotein (Gp IIb/IIIa) inhibitor, tirofiban, and were randomly assigned to an early invasive strategy (ie, coronary angiography within 48 hours of presentation followed by prompt revascularization) vs a more conservative, watchful waiting approach. The primary end point of death, nonfatal MI, or rehospitalization for ACS at 6 months was reduced by 22% in patients assigned to receive the early invasive strategy (15.9% vs 19.4%, respectively;  $P=.009$ ), and there was also a 26% reduction in the risk of death or nonfatal MI (7.3% vs 9.5%, respectively;  $P<.05$ ).<sup>6</sup> A prespecified subgroup analysis demonstrated that the benefits of the early invasive approach were particularly strong in patients with the highest underlying risk of late adverse events as demonstrated by an elevated serum level of troponin T ( $>0.01$  ng/mL) at the time of presentation.<sup>7</sup>

On the basis of these findings, the American College of Cardiology—American Heart Association (ACC—AHA) Practice Guidelines for management of unstable angina and non-ST-segment elevation MI have recently been updated and now recommend that patients with ACS be managed with an early invasive strategy if they have one or more high-risk features—which include elevated cardiac troponin, new ST-segment depression, decreased left ventricular function, and prior coronary artery bypass graft (CABG) surgery or PCI.<sup>1</sup>

With current emphasis on evidence-based medicine and quality improvement,<sup>8</sup> the promulgation of these guidelines is likely to have an important effect on the management of such patients. Given the current cost of these procedures (approximately \$10 000 for PCI and approximately \$25 000 for CABG surgery per episode of care),<sup>9,10</sup> a shift from a conservative to an early invasive approach for even 25% of patients with ACS could increase initial health care costs by \$3 to \$5 billion annually. Clearly, in the current health care environment such an increase in expenditures demands careful attention; formal evaluations of cost-effectiveness should be considered in the development of such guidelines, particularly when the impact on public health, overall health expenditures, or both is likely to be quite large.

In this issue of THE JOURNAL, Mahoney and colleagues<sup>11</sup> describe the results of a prospective economic study performed in a subgroup of 1722 US—non-Veterans Affairs (VA) patients enrolled in the TACTICS-TIMI 18 trial.<sup>11</sup> Their eco-

omic evaluation involved 2 components: an analysis of medical care costs and formal quantification of health benefits in terms of quality-adjusted years of life gained.<sup>12</sup> Not surprisingly, the authors found that the early invasive strategy increased initial hospital costs by more than \$1600 per patient, reflecting the higher utilization of costly procedures including coronary angiography, PCI, and CABG surgery with this strategy. During the 6-month follow-up period, the early invasive strategy was associated with fewer hospitalizations, and, thus, follow-up costs were approximately \$1000 less per patient than with the conservative strategy. Nonetheless, these savings were insufficient to fully offset the initial cost increment; aggregate 6-month costs remained \$586 per patient higher with the invasive than the conservative strategy. Although the 6-month cost difference between the 2 strategies was not “statistically significant,” it should be kept in mind that most clinical trials (including TACTICS-TIMI 18) are designed with sample sizes sufficient to detect primarily clinical differences. Thus, in the case of TACTICS-TIMI 18, although there is considerable uncertainty surrounding the estimate, the observed cost difference represents the most likely value for the true cost difference.

To determine whether the higher cost of the invasive strategy can be justified, Mahoney and colleagues used a mathematical model to project life expectancy for the substudy population. Based on long-term survival data from similar patients in the Framingham Heart Study and the Duke Cardiovascular Disease Databank, the authors estimated that the 6-month clinical benefits observed in their substudy cohort would increase life expectancy for the population by 0.06 to 0.07 years. Although this difference seems quite small on the individual level ( $<1$  month of increased life expectancy), such degrees of benefit are quite commonly observed in economic analyses.<sup>13</sup> In fact, these benefits do not represent a gain of 3 to 4 weeks of life for each individual in the study but rather more striking gains (on the order of 1 to 2 years) for a much smaller proportion of treated patients. When these projections were combined with the observed 6-month cost differences, the incremental cost-effectiveness ratio for the early invasive strategy compared with the conservative, ischemia-driven strategy was between \$8000 and \$15 000 per year of life gained, depending on the specific life expectancy model chosen. Although no single cost-effectiveness threshold is universally accepted, the general consensus within the US health care system is that ratios of less than \$20 000 per year of life gained are highly attractive, whereas ratios between \$20 000 and \$50 000 per year of life gained are reasonably attractive.<sup>12,14</sup> Thus, based on this comprehensive, prospectively designed study, it appears that the early invasive strategy for management of ACS is highly cost-effective compared with many other accepted medical interventions.

An additional important finding of this study is that the cost-effectiveness of the early invasive strategy is highly de-

pendent on the underlying characteristics of the patient population—in particular markers of active myocardial ischemia or myonecrosis. It is interesting to note that both the in-hospital and 6-month cost differences between the invasive and conservative management strategies were actually higher in the patient subgroups at highest risk. This finding presumably reflects the fact that higher risk patients managed with early coronary angiography were more likely to be identified to have coronary anatomy that warranted revascularization. Nonetheless, in patient subgroups with either ST-segment depression or elevated troponin-T levels at presentation, the absolute clinical benefits (in terms of deaths or MIs prevented or in terms of years of life gained) were greater than in the overall population. Thus, despite the higher incremental costs, the cost-effectiveness ratios for the early invasive strategy remained less than \$30 000 per year of life gained in virtually all of the scenarios tested.

On the other hand, it does not appear that the early invasive strategy is particularly attractive for lower risk patients, at least from an economic perspective. With the exception of nondiabetic patients, the mean cost per patient over the 6-month study period was greater for the early invasive strategy than for the conservative strategy across all of the low-risk subgroups evaluated. Thus, some clinical benefits would be required to justify the increased expense of the invasive strategy for these lower-risk patient groups. Although not reported in this specific study, review of the previously published results for the overall clinical trial demonstrates that in patients without ST-segment depression or elevated troponin levels, the early invasive strategy was not associated with any meaningful reductions in either death or nonfatal MI.<sup>6</sup> Thus, the conservative strategy appears to be economically “dominant” for lower-risk patients, less costly and producing equivalent clinical outcomes. Consequently, the argument that early coronary angiography may be of direct economic value for lower-risk patients by streamlining care pathways is not supported by this study.

It is noteworthy that the findings in the study by Mahoney et al, although not incorporated explicitly in the formulation of the updated ACS guidelines, strongly support the current recommendations for management of patients with ACS.<sup>1</sup> For patients at high risk of ischemic complica-

tions, an early invasive strategy is both clinically beneficial and economically attractive by any contemporary standards. As economic pressures continue to increase on the medical care system, it is likely that such evaluations—if conducted with high-quality methods and in a timely fashion—will play an increasingly important role in development of care guidelines.

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