EDITORIAL COMMENT

Cardioprotective Effects of an Early Invasive Strategy for Non–ST-Segment Elevation Acute Coronary Syndromes

Are We All Becoming “Interventional” Cardiologists?*

Ravi K. Yarlagadda, MD,†‡
William E. Boden, MD, FACC†‡
Hartford and Farmington, Connecticut

Unstable angina and non–ST-segment elevation myocardial infarction (NSTEMI) comprise a growing percentage of patients with acute coronary syndromes (ACS) and are emerging as a major public health problem worldwide, especially in Western countries, despite significant improvements and refinements in management over the past two decades. In the U.S. alone, nearly 1.5 million people suffer from acute MI each year with more than one million people admitted to coronary care units annually, the great majority of whom now present with NSTE ACS (1). Consequently, much attention has been directed toward optimizing the diagnosis and management of such patients, particularly in light of the continued evolution of catheter-based interventions and newer pharmacologic strategies that afford more complete platelet and thrombin inhibition and which, when used together, appear to have an important synergistic effect in reducing prognostically important ischemic events.

Two distinct approaches have emerged over the past 10 to 15 years in the management of patients with NSTE ACS: 1) a “routine early invasive” strategy consisting of prompt diagnostic coronary angiography within 24 to 48 h in all patients with ACS or NSTEMI followed by myocardial revascularization—generally with percutaneous coronary intervention (PCI) and stenting—if coronary anatomy is amenable to this approach; and 2) a “conservative” or “ischemia-guided” strategy that consists of rapidly intensifying medical therapy with aggressive antplatelet, anti-thrombin, and anti-ischemic therapy for a predefined treatment interval, ranging generally from 24 to 36 h to several days, after which intravenous medications are discontinued and, if the patient remains symptom-free, myocardial perfusion imaging with exercise or vasodilator stress, using either sestamibi or dobutamine stress echocardiography, is undertaken to delineate objective evidence of inducible ischemia. In this strategy, persistence or recurrence of ischemic symptoms, development of heart failure or hemodynamic instability, or a positive stress test leads to prompt cardiac catheterization and a more “selective” approach to intervention.

The central hallmark of both approaches is risk stratification: the delineation of patients into subsets of high, intermediate, or low risk depending on whether this is an “anatomy driven” (based on coronary angiographic findings) or an “ischemia-driven” (based on clinical presentation, electrocardiogram [ECG] findings, serum inflammatory and biomarkers, and the results of functional, non-invasive testing) process. The relative merits of these approaches have been tested in four large randomized trials: Thrombolysis in Myocardial Infarction (TIMI) IIIB, Veterans Affairs Non–Q-Wave Infarction Strategies in-Hospital (VANQWISH), FRAGmin and Fast Revascularization during Instability in Coronary artery disease (FRISC-II), and the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS)-TIMI 18 (2–7) (Table 1).

Given the heterogeneous nature of patients who present with NSTE ACS, the American College of Cardiology and the American Heart Association promulgated joint guidelines in 2000 for the diagnosis, risk stratification, and management of patients with NSTE ACS and endorsed both approaches (8). These guidelines provide a range of options that are amenable to individual physician interpretation and hospital resource availability. However, in light of more recent studies, including newer reports and analyses from the FRISC-II and TACTICS-TIMI 18 trials, among others, there is an intensifying movement to recommend a “routine early invasive strategy” for all patients with NSTE ACS regardless of their initial risk stratum. Based on the results of these studies, is this an appropriate and rational approach?

In the FRISC-II trial, which was published originally in the Lancet, 2,457 patients with unstable coronary disease were randomized after 48 h to an invasive or noninvasive approach (5). The invasive approach included catheterization followed by revascularization within seven days, and the noninvasive group had angiography followed by revascularization for a markedly positive exercise test, refractory or severe angina, or MI. All patients were treated with aspirin, intravenous nitroglycerin, beta-blockers, and low-molecular-weight heparin (dalteparin) for four to six days until revascularization was performed in the invasive group (78% of patients underwent PCI or bypass surgery) or for a similar duration in the noninvasive group, 38% of whom crossed over to revascularization during follow-up. At six months, the rate of death or MI was significantly lower in the invasive group (9.4%) compared with the noninvasive...
Table 1. Conservative Versus Invasive Strategies in ACS—Four Randomized Clinical Trials

<table>
<thead>
<tr>
<th>TIMI IIB</th>
<th>VANQWISH</th>
<th>FRISC-II</th>
<th>TACTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Countries</td>
<td>U.S./Canada</td>
<td>U.S.</td>
<td>Sweden/Denmark/Norway</td>
</tr>
<tr>
<td>Hospitals</td>
<td>Varied</td>
<td>VA</td>
<td>Varied</td>
</tr>
<tr>
<td>Sites</td>
<td>25</td>
<td>15</td>
<td>58</td>
</tr>
<tr>
<td>Patients</td>
<td>1,493</td>
<td>920</td>
<td>2,457</td>
</tr>
<tr>
<td>UA/NSTEMI</td>
<td>68%/32%</td>
<td>0%/100%</td>
<td>41%/59%</td>
</tr>
</tbody>
</table>

ACS = acute coronary syndrome; FRISC-II = Fragmin and Fast Revascularization during Instability in Coronary artery disease; NSTEMI = Non-ST-segment Elevation Myocardial Infarction; TACTICS = Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy; TIMI = Thrombolysis in Myocardial Infarction; UA = unstable angina; VA = Veterans Affairs; VANQWISH = Veterans Affairs Non-Q-Wave Infarction Strategies in-Hospital.

group (12.1%); the difference was primarily due to a lower rate of MI (7.8% vs. 10.1%), while the difference in mortality was not significant. Of note, the greatest benefit was observed in high-risk patients who had signs of necrosis or ischemia (only patients who had initial ST-segment depression [45%] or biochemical markers of myocardial damage [45%] benefited significantly from the invasive strategy). There was a 50% reduction in angina and the need for subsequent readmission with the invasive approach.

Importantly, these beneficial results were maintained at one year of follow-up (6). Compared with the non-invasive strategy, the invasive group had significantly lower rates of mortality (2.2% vs. 3.9%), MI (8.6% vs. 11.6%), readmission (37% vs. 57%), and need for revascularization after the initial admission (7.5% vs. 31%).

In this current issue of the Journal, Lagerqvist et al. (9) report on the important 24-month follow-up of the FRISC II cohort, which showed a consistent reduction and continued separation of the event-curves between the two strategies at two years. The predominant benefit between the two groups, however, was still most apparent within the first 6 to 12 months. For example, during the first 12 months, 27 deaths occurred in the invasive arm compared with 48 in the non-invasive arm, whereas between one and two years there were 18 and 19 deaths, respectively. For each six-month analysis interval beyond the first year (e.g., 13th to 18th month, 19th to 24th month), there were strong trends for reductions in the endpoint of MI and death or MI for the invasive strategy, but the 95% confidence intervals surrounding these individual risk ratios crossed the unity boundary and were not, hence, statistically significant. For the separate two-year end points of need for myocardial revascularization and readmissions, the invasive strategy was superior to the non-invasive strategy, indicating an important salutary effect in reducing cardiac morbidity.

These findings mirrored the results of the TACTICS-TIMI 18 trial, which randomly assigned 2,220 patients with ACS or NSTEMI to an invasive strategy (catheterization within 4 to 48 h and revascularization with PCI/stenting or bypass surgery, if feasible) or a conservative strategy; all patients received aspirin, beta-blockers, heparin, and tirofiban for 48 to 108 h (7). At six months, the primary endpoint (death, MI, rehospitalization for an ACS) was significantly lower with the invasive strategy (15.9%) compared with the conservative strategy (19.4%); the rate of death or nonfatal MI was also reduced (7.3% vs. 9.5%). As in FRISC-II, the majority of benefit for the invasive strategy was observed in patients with NSTE ACS who initially displayed ST-segment depression on the entry ECG (37% of patients) and those who were biomarker-positive (54% of patients); the clinical outcomes of patients who did not have ST-segment depression or abnormal troponin on admission did not differ between the invasive or conservative strategies.

Obviously, differences in clinical outcomes among these four randomized studies can be explained by the fact that the TIMI IIIB and VANQWISH trials were conducted in the pre–glycoprotein (GP) IIb/IIIa inhibitor therapy era and before the advent and widespread use of stents (Table 2), whereas newer adjunctive pharmacotherapies were employed in FRISC-II (dalteparin) and TACTICS (tirofiban), as well as stent usage (65% in FRISC-II and 84% in TACTICS-TIMI 18). Moreover, TIMI-IIIB, VANQWISH, and FRISC-II all showed an increased hazard associated with the “routine early invasive strategy”; namely, there was an approximately 60% excess MI rate within the first two weeks with this approach in

Table 2. Conservative Versus Invasive Strategies in ACS—Four Randomized Clinical Trials

<table>
<thead>
<tr>
<th>TIMI IIB</th>
<th>VANQWISH</th>
<th>FRISC-II</th>
<th>TACTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background medications</td>
<td>ASA, UFH</td>
<td>ASA, UFH</td>
<td>ASA, dalteparin</td>
</tr>
<tr>
<td>Invasive arm—time to cath</td>
<td>1.5 days</td>
<td>2 days</td>
<td>4 days</td>
</tr>
<tr>
<td>Stents</td>
<td>0%</td>
<td>0%</td>
<td>65%</td>
</tr>
<tr>
<td>GP IIb/IIIa</td>
<td>0%</td>
<td>0%</td>
<td>10%</td>
</tr>
<tr>
<td>CONS arm—threshold to cath</td>
<td>Rec sx, + ST Holter or +ETT/TL201</td>
<td>Rec sx, +ETT/TL201</td>
<td>Rec ref sx, + ++ETT (3 mm ST ↓)</td>
</tr>
</tbody>
</table>

+ = positive; +++ = markedly positive; ASA = acetylsalicylic acid; Cath = coronary angiography; CONS = conservative; ETT = exercise stress test; GP = glycoprotein; mibi = mibibi; Rec = recurrence; refl = refractory; sx = symptoms; UFH = unfractionated heparin. Other abbreviations as in Table 1.
patients with NSTE ACS, whereas in TACTICS this early hazard was not observed, suggesting that tirofiban administration mitigated the adverse consequences of distal microembolization and incomplete platelet inhibition associated with early intervention.

Where does all of this leave the clinician in 2002–2003? It now seems abundantly clear that high-risk (and probably intermediate-risk) patients with NSTE ACS benefit from an early invasive strategy and, as the current study suggests, this beneficial effect is maintained during long-term follow-up, although most of the benefit appears to be “front-loaded” within the first year. This is, perhaps, not surprising because one would presume that the major adverse effects of reinfarction and post-infarction angina after an ACS would be more likely to occur in the same vascular bed (either restenosis or progression of native coronary disease) within this time frame rather than a new event in a different vascular bed. Development of new ACS late (1 to 2 years or longer) after an initial intervention would be as—or more—likely attributable to disease progression in a different vascular bed and, hence, would not likely represent “cardio-protection” from catheter-based or surgical intervention of the original culprit stenosis.

Yet, it is also true that risk stratification remains an important part of optimal clinical decision making today because NSTE ACS is heterogeneous, representing a spectrum of risk ranging from low to high. A routine invasive approach with acute revascularization for all patients is not supported by even contemporary randomized trials (5–7) and may not be cost-effective (10) (FRISC-II and TACTICS did not demonstrate clear superiority for patients who were biomarker-negative and those without ST-segment depression (5,7); FRISC-II also did not demonstrate clear benefit for the routine invasive strategy in women patients with unstable coronary disease—a sizeable and growing segment of the population (11). Thus, 45% to 50% of all NSTE ACS patients may fall into a category where either a “routine invasive” or an “ischemia-guided” (or “selective invasive”) approach may be appropriate.

Most important of all, aggressive pharmacologic intervention is indicated in all patients with ACS regardless of one’s approach to the role of mechanical intervention or revascularization. Based on the results of multiple randomized trials, all patients, unless there is a contraindication, should receive aspirin, clopidogrel, unfractionated heparin, or low-molecular-weight heparin (two trials have shown the superiority of enoxaparin compared with unfractionated heparin in these patients (12,13), intravenous nitroglycerin (if hemodynamically stable), a GP IIb/IIIa agent (in intermediate- and high-risk patients, based on several studies utilizing abciximab as part of an early PCI triage strategy (14–17) or tirofiban/epifibatide as “upstream therapy” in ACS patients triaged to an initial non-invasive approach (18–24), a beta-blocker and a statin (based on the results of two recent studies (25,26)—all of which should be used in combination to reduce clinical events. In particular, the results of the recent Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial (27) demonstrate that all subsets of patients with NSTE ACS benefited from clopidogrel regardless of age, gender, presence or absence of ECG ST-segment depression or biomarker positivity, or whether patients were managed with an invasive or non-invasive approach.

Finally, it is important to emphasize that the long-term benefits attributed to the “routine early invasive strategy” or to myocardial revascularization alone, as Lagerqvist’s current study suggests, as well as the TACTICS TIMI–18 trial results, might actually be due, in part, to the aggressive “polypharmacy” of antiplatelet, antithrombin, and anti-ischemic therapy that was used in both trials as a prelude to mechanical intervention or myocardial revascularization. The concept of so-called “plaque passivation” has been advanced as a potential explanation for the improved clinical outcomes that may occur as a consequence of various pharmacologic “interventions” that could reduce oxidative stress, improve endothelial function and vascular homeostasis, and reduce both inflammation and microembolization (28–31).

Neither FRISC-II nor TACTICS evaluated the role of very early mechanical intervention within hours of ACS symptom onset. As noted earlier, all patients received aspirin, heparin, or dalteparin (FRISC–II), tirofiban (TACTICS), and anti-ischemic therapy (intravenous nitroglycerin followed by beta-blockers) for at least 48 h after symptom onset (TACTICS) or during the four to six days (FRISC–II) that preceded revascularization in all subjects. Moreover, one could hardly classify such a four- to six-day pretreatment interval as being “Fast” Revascularization by North American standards, as the “F” in FRISC-II connotes! Thus, one might argue logically that “pharmacologic intervention” as a prelude to “mechanical intervention” or revascularization might be as—if not more—important to facilitating cardioprotection and reducing clinical events in patients with ACS.

Perhaps it is time that we abandon attempts to categorize or label cardiologists as “invasive” versus “non-invasive” or “aggressive” versus “conservative,” because these dichotomous classifications woefully oversimplify clinical decision making and patient management. In reality, perhaps we are all “interventional” cardiologists—some of us perform much needed and highly effective mechanical interventions, while many more of us engage in aggressive pharmacologic intervention with or without mechanical intervention. It is becoming increasingly clear that, if our therapeutic goals of reducing death, recurrent MI, or ischemia and preserving or enhancing quality of life in patients with ACS are to be optimized, the best clinical outcomes can be achieved by coupling mechanical intervention and revascularization with intensive, multifaceted pharmacologic intervention as part of an integrated, two-pronged approach that embodies treatment of coronary culprit stenoses together with systemic multidimensional medical therapy.

In summary, the treatment of patients with ACS remains a difficult moving target for the clinician. Incorporating the
latest advances in pharmacotherapy and catheter-based revascularization into clinical practice, and perhaps more importantly, using a combination of pharmacologic and mechanical interventions in ACS patients at risk for continued morbidity and mortality is of paramount importance to achieving true cardioprotection and prolonging both short- and long-term event-free survival.

Addendum
Since the time this Editorial went to press, the RITA-3 Trial has been published (Lancet 2002;360:743–51) and has shown that an interventional strategy is preferable to a conservative strategy in 1,810 patients with NSTE ACS. The difference was mainly due to a reduction of refractory angina in the interventional group, but there was an increased incidence of early procedural events (MI) and worse outcomes in women patients assigned to the interventional strategy.

Reprint requests and correspondence: Dr. William E. Boden, Hartford Hospital, 80 Seymour Street, Hartford, Connecticut 06102. E-mail: wboden@hartsh.org.

REFERENCES