“Ischemia-Guided” Versus “Early Invasive” Strategies in the Management of Acute Coronary Syndrome/Non–ST-Segment Elevation Myocardial Infarction
The Interventionalist’s Perspective
Raymond G. McKay, MD, FACC
Hartford, Connecticut

Conventional therapy for non–ST-segment elevation acute coronary syndrome (ACS) has traditionally employed an “ischemia-guided” strategy. In this approach, diagnostic cardiac catheterization and revascularization are only used in patients with objective evidence of myocardial ischemia as identified by recurrent symptoms or provocative stress testing. More recent studies, however, have demonstrated improved clinical outcomes with the use of an “early invasive” approach, employing routine coronary angiography early in the patient’s hospital course, followed by percutaneous intervention or bypass surgery where appropriate. Improved clinical outcomes associated with an “early invasive” strategy may have evolved as a consequence of recent advances in both adjunctive pharmacotherapy and revascularization technique. In particular, use of glycoprotein IIb/IIIa inhibitors and/or low-molecular-weight heparin before catheterization have been shown to reduce clinical events in patients with ACS, and may reduce the risk of an invasive approach by plaque passivation before interventional therapy. Perhaps more importantly, the combined use of glycoprotein IIb/IIIa inhibitors and intracoronary stenting may reduce the potential early hazard of an invasive approach by specifically decreasing the incidence of death and nonfatal myocardial infarction associated with percutaneous intervention. In spite of the benefits of this synergistic combination of pharmacology and mechanical revascularization, risk stratification remains important in identifying high-risk individuals most likely to benefit from an “early invasive” approach. In addition, angiography with possible percutaneous coronary intervention of “culprit” lesions should always be used in combination with aggressive medical therapy to treat the widespread coronary atherosclerosis commonly seen in patients with ACS. (J Am Coll Cardiol 2003;41:96S–102S) © 2003 by the American College of Cardiology Foundation

Two general approaches have evolved for patients with unstable angina and non–ST-segment elevation myocardial infarction (NSTEMI). Conventional therapy of NSTEMI acute coronary syndrome (ACS) has mainly involved the rapid initiation of intensive medical management, followed by noninvasive risk stratification to identify those who need catheterization and possible revascularization versus those who can continue with medical therapy alone. This “ischemia-guided” approach differs from an “early invasive” approach in which noninvasive testing is deferred, and all patients with suspected ACS are referred for coronary angiography and possible revascularization early in their hospital course. The debate over the relative superiority of these two treatment strategies has been longstanding and has been further fueled by the results of several recent clinical trials.

Proponents of the “ischemia-guided” approach argue that intensive medical therapy, particularly in patients who have not been previously treated with aggressive antiplatelet, antithrombotic, anti-ischemic and lipid-lowering agents, may result in rapid clinical stabilization. Exercise stress testing in its various forms (i.e., treadmill exercise or pharmacologic vasodilator stress testing with myocardial perfusion imaging) may then reliably identify those patients at risk for future events who need to undertake the risk of cardiac catheterization and subsequent revascularization. This approach—tailoring therapy to risk—optimizes clinical efficacy and cost-effectiveness because high-risk patients are identified and treated, while low-risk patients avoid costly invasive procedures that are unlikely to confer clinical benefit and may actually cause harm.

Alternatively, it has been argued that an “early invasive” approach can accurately determine coronary anatomy early in the patient’s hospital course, thus avoiding lengthy delays and possible ambiguities sometimes associated with noninvasive testing. Specific anatomical subgroups can be expeditiously identified and treated. These include patients with normal coronary arteries and minimal disease who can be discharged home, and also patients with left main stenoses, three-vessel disease, or multivessel disease with decreased left ventricular function who would benefit from bypass surgery. The remaining patients can be risk-stratified and treated according to their angiographic findings, with ap-
appropriate use of percutaneous coronary intervention (PCI) as indicated by angiography, intravascular ultrasound, and/or Doppler blood flow and pressure measurements.

Over the last seven years, four major randomized studies have examined the relative benefits of an “ischemia-guided” versus “early invasive” approach. These include: the Thrombolysis In Myocardial Infarction (TIMI)-IIIB (1); the Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) (2); the Fragmin and fast Revascularization during InStability in Coronary artery disease (FRISC) II (3); and the Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS) TIMI-18 (4) trials. Conclusions derived from TIMI-IIIB and VANQWISH have been the primary basis for the current use of “ischemia-guided” therapy. In contrast, FRISC II and TACTICS have, more recently, identified possible advantages of an “early invasive” approach. Differing conclusions reached by these studies may have been a natural consequence of the recent rapid advances in both adjunctive pharmacotherapy and revascularization techniques.

The TIMI-IIIB trial. Published in 1994, the TIMI-IIIB trial (1) was designed to evaluate the effect of a fibrinolytic agent added to conventional medical therapies and to compare an early invasive with an early conservative approach in the management of patients with unstable angina or non-Q-wave MI. Using a 2 × 2 factorial design, 1,425 patients were randomized to receive either tissue-plasminogen activator or placebo and either an early invasive strategy or an early conservative therapy. Patients randomized to the early invasive strategy underwent routine coronary angiography 18 to 48 h after randomization, with use of percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG) surgery depending upon coronary anatomy. Patients randomized to conservative therapy were treated with initial medical therapy, with subsequent angiography and revascularization only for recurrent rest ischemia (defined by chest pain, electrocardiogram [ECG] changes, or ST-segment depression on Holter monitoring), or for ischemia on a predischarge thallium stress test. All patients were treated with intravenous heparin, aspirin, beta-blockers, nitrates, and calcium antagonists, as clinically indicated.

In the early invasive strategy, coronary angiography was performed in 98% of patients, with revascularization in 61% of patients within 6 weeks (PTCA in 38% and CABG in 25%). In the conservative strategy arm, angiography was performed in 64% of patients, with revascularization in 49% by 6 weeks, including PTCA in 26% and CABG in 24%. By 1 year, the difference in the rates of revascularization became even smaller, with 64% in the early invasive strategy and 58% in the conservative strategy. This small difference was primarily due to differences in the use of PTCA (39% invasive vs. 32% conservative, p < 0.001), with no significant differences in the use of bypass surgery (30% in each group).

At six weeks there was no significant difference in the primary end point—defined as the composite incidence of death, postrandomization nonfatal MI, or a positive stress test—between conservative or invasive strategies (18.1% for the conservative therapy vs. 16.2% for the early invasive strategy, p = NS). The overall incidence of death (2.4%) and MI (6.3%) were low, with no significant differences between the two strategies. Patients in the early invasive therapy had a shorter initial hospitalization, less frequent rehospitalization, fewer days of rehospitalization, and required less antianginal medications at their six-week evaluation.

At 1 year the incidence of mortality for all patients increased to 4.3% while nonfatal MI increased to 8.8%. Again, there was no significant difference in the combined incidence of death and nonfatal MI between the two strategies (10.8% in the early invasive group vs. 12.2% in the early conservative group, p = NS). However, a prespecified subgroup analysis did show a benefit for the invasive approach in higher-risk patients (including patients with ECG changes, elevated cardiac enzymes, female gender, and age >65 years). Also, patients in the early invasive arm required less hospitalization.

Based on these results, the TIMI-IIIB authors concluded that an early invasive strategy provided more rapid and effective relief of angina in patients with non-ST-segment elevation ACS than a conservative strategy, but that equivalent early and late outcomes were achieved with the two approaches with respect to death and MI. Given the similar outcomes with the two different strategies, patients could be managed individually depending upon the severity of their presentation, cardiac risk factors, left ventricular function, and response to medical therapy.

The VANQWISH trial. Published in 1997, the VANQWISH trial randomized 920 non-Q-wave MI patients from 17 Veterans Affairs medical centers to an early invasive or an early conservative strategy between April 1993 and December 1995 (2). Patients in the early invasive arm underwent coronary angiography within one to three days after hospital admission, while patients in the conservative arm were treated with medical therapy and underwent...
catheterization only for spontaneous post-MI angina or for an abnormal predischarge thallium stress test. Of note, the early invasive strategy did not require myocardial revascularization. All patients were treated with aspirin and diltiazem, with use of heparin, nitrates, beta-blockers, and angiotensin-converting enzyme (ACE) inhibitors as clinically indicated.

In the early invasive strategy, coronary angiography was performed in 96% of patients. Revascularization was done in 44%, including PTCA in 48%, CABG in 47%, and both in 5%. In the conservative strategy arm, angiography was performed in 48% of patients, with revascularization in 33%, including PTCA in 36%, CABG in 57%, and both in 7%.

The primary end point of the study was the combination of mortality and nonfatal MI during at least 12 months follow-up. At the time of hospital discharge, at one month and at one year, clinical outcomes were significantly better in the early conservative arm compared with the early invasive arm. There was a 1.3% mortality risk in the conservatively managed patients compared with 4.5% in the invasive group at hospital discharge (p = 0.007), 1.9% versus 4.9% at 1 month (p = 0.02), and 7.8% versus 12.5% at 1 year (p = 0.025), respectively. Similarly, for combined mortality and nonfatal MI, conservative compared with invasive results were 3.3% versus 7.7% at hospital discharge (p = 0.004), 5.6% versus 10.3% at 1 month (p = 0.012), and 18.5% versus 24.0% at 1 year (p = 0.05). The increase in mortality in the early invasive arms was primarily attributed to a high rate of in-hospital mortality for bypass surgery (30-day mortality after CABG surgery was 7.7%). After hospital discharge there was no significant difference in the death or reinfarction rates between the two revascularization modalities. Moreover, by 23 months of follow-up, there was no significant difference in the combined end point of death and MI between the two groups: 29.9% in the early invasive group versus 26.9% in the conservative treatment group.

Based on these results, the VANQWISH investigators concluded that the early conservative approach was the preferred treatment strategy for patients with non-Q-wave MI. The authors did not comment upon the effect of the two therapies on the extent of symptom relief.

The FRISC II trial. The FRISC II trial randomized 2,457 patients with unstable angina and NSTEMI in 58 Scandinavian hospitals to an early invasive strategy or to an ischemia-guided approach, with placebo-controlled long-term low-molecular-weight heparin (dalteparin) for 3 months. Patients in the early invasive group underwent catheterization followed by revascularization within seven days, while ischemia-guided patients underwent angiography only if they had recurrent angina or severe ischemia on a symptom-limited exercise tolerance test. Patients in the invasive arm were treated with dalteparin until revascularization, while patients in the ischemia-guided arm received the drug for at least five days. The NSTEMI was diagnosed by elevated troponin T (≥0.1 μg/l) in 57% of patients in the early invasive group and 58% of patients in the ischemia-guided group.

In the early invasive arm, 98% of patients underwent coronary angiography, with subsequent revascularization in 78%, including PCI in 44% and CABG in 34%. In the ischemia-guided arm, 38% underwent angiography, followed by revascularization in 37%, including PCI in 18% and CABG in 19%. Most of these procedures (80%) were performed within 10 days in the early invasive group, while only a minority (20%) of patients in the ischemia-guided group had CABG or PCI within 10 days of randomization. Stenting was used in 61% of the PCI procedures in the invasive group and in 70% of the PCI procedures in the ischemia-guided group. About 10% of patients in both groups were treated with abciximab.

The primary end point of the study was the combination of death and nonfatal MI. At 6 months the rate of death or MI was 9.4% in the early invasive group and 12.1% in the ischemia-guided patients (relative risk [RR], 0.78; 95% confidence interval [CI], 0.62 to 0.98). For death alone, the difference between the groups was less impressive, but still favored an early invasive approach (1.9% vs. 2.9%; RR, 0.65; 95% CI, 0.39 to 1.09).

Subset analysis showed no evidence of a beneficial effect of an early invasive strategy in women, while the invasive strategy resulted in a highly significant 34% reduction in the combined end point (p = 0.002) and a significant 52% reduction in mortality from 3.2% to 1.5% (p = 0.03) in men. For both men and women, the early invasive strategy provided a 50% relative reduction in symptoms of angina and need for hospital readmission during the 6-month follow-up.

The TACTICS TIMI-18 trial. The TACTICS TIMI-18 trial was designed to evaluate the upstream use of tirofiban in NSTE ACS patients combined with an “early invasive” approach using diagnostic catheterization and PCI (4). The trial included 2,220 patients with unstable angina or NSTEMI who had either ECG changes, elevated cardiac markers, and/or a prior history of coronary artery disease. All patients were initially treated with aspirin, heparin, and tirofiban. They were then randomized to either early diagnostic catheterization (within 4 to 48 h) and revascularization as indicated, or to a more conservative approach with invasive procedures performed only if the patient had objective evidence of residual ischemia with recurrent angina or a positive stress test. Electrocardiographic changes were present in 48% of patients, while 54% of the study group had elevated troponin T levels.

In the early invasive strategy group, coronary angiography was carried out in 97% of patients, with revascularization performed in 61%, including PTCA in 41% and CABG in 20%. In the conservative strategy arm, angiography was performed in 51% of patients, with revascularization in 37%, including PTCA in 24% and CABG in 13%. Coronary stents were used during PCI procedures in 83% of the early
invasive group and in 85% of the conservative treatment patients.

The primary end point of the study was a composite of death, nonfatal MI, or rehospitalization for an ACS at six months. This end point was reduced from 19.4% with the conservative approach to 15.9% with the early invasive strategy (p = 0.025), with similar significant reductions in death or MI from 9.5% to 7.3% (p = 0.0498). This benefit of an early invasive approach was largely confined to patients who were troponin-positive or who had ST-segment depression on their admission ECG.

**Understanding the differences between trials.** Compared with TIMI-IIIB and VANQWISH, the FRISC II and TACTICS trials showed, for the first time, a significantly lower cardiac event rate in NSTE ACS patients referred for an early invasive approach compared with an ischemia-guided strategy. Both studies clearly demonstrated a significant reduction in the composite incidence of death and nonfatal MI at six months in early invasive patients compared with their ischemia-guided counterparts. These results differ sharply from the TIMI-IIIB results in which there were no significant differences in strategy outcomes, and from VANQWISH, in which ischemia-guided therapy was clearly favored.

Differences in outcomes for these four studies may be related, in part, to specific aspects of trial design or to deficiencies in study implementation. For example, in the TIMI-IIIB trial, the study’s outcomes may have been adversely affected by the administration of fibrinolytic therapy in 50% of patients, potentially resulting in lysis-induced platelet activation, which raised the risk for PCI. Similarly, proponents of the early invasive approach cite the high surgical mortality in the early invasive arm of the VANQWISH trial as an outlying factor that is the principal cause for the study’s conclusions. Finally, proponents of the ischemia-guided strategy are critical of the noninvasive arm of the FRISC II trial because the study design used strict criteria on standard exercise testing rather than myocardial perfusion imaging to identify patients who required catheterization and possible revascularization.

In addition to these trial-specific criticisms, another possible basis for the different trial outcomes relates to the absolute revascularization rates among patients. Comparing ischemia-guided to early invasive groups, the revascularization rates were 49% versus 61% in TIMI-IIIB, 33% versus 44% in VANQWISH, 37% versus 78% in FRISC II, and 37% versus 61% in TACTICS. It is clear that the differences in absolute revascularization rates were smaller in TIMI-IIIB and VANQWISH, raising the possibility that these two studies were insufficiently powered to detect significant differences between ischemia-guided and early invasive strategies.

Apart from the considerations described in the preceding text, perhaps the most important differences between earlier and more recent studies is that FRISC II and TACTICS have incorporated improvements in both adjunctive pharmacotherapy and revascularization technique that may have made an “early invasive” approach safer and more effective. These include the use of low-molecular-weight heparin, glycoprotein (GP) IIb/IIIa inhibitors, and intracoronary stents, as well as improvements in anesthesiology and CABG techniques. Low-molecular-weight heparin, GP IIb/IIIa inhibitors, and intracoronary stents were not available in the TIMI-IIIB and VANQWISH trials because enrollment was completed before 1995.

**Decreasing the hazards of PCI.** The presence of unstable angina has long been recognized as a risk factor for PCI in the cardiac catheterization laboratory. Previous studies involving conventional balloon angioplasty have clearly documented an increased risk of major complications in patients with unstable versus stable angina, including an increased risk of Q-wave MI, emergency CABG surgery, and death (5–7). Based on this increased complication rate, a specific “early hazard of intervention” has been defined for PCI in the ACS patient. Proposed pathophysiologic causes include plaque rupture within an epicardial vessel with variable amounts of thrombus that may propagate or embolize to the distal vasculature, as well as the inherent deficiencies of conventional balloon angioplasty in achieving stable lumen enlargement.

Theoretically, the risk of an early invasive approach in NSTE ACS might be reduced by both preprocedure plaque passivation to reduce thrombus and by specific procedural measures to reduce the incidence of complications in the catheterization laboratory. In this regard, newer antithrombotic and antiplatelet agents given “upstream” before and during cardiac catheterization, as well as use of newer mechanical revascularization techniques at the time of intervention, may be expected to affect outcomes.

Based on the TIMI-IIIB (8) and the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events (ESSENCE) (9) trials, low-molecular-weight heparin has clearly been shown to provide clinical benefit as “upstream” therapy for patients with NSTE ACS. In a meta-analysis of ACS patient data from these two trials (10), enoxaparin was shown to result in a 20% reduction in death or serious cardiac ischemic events compared with unfractionated heparin. This clinical benefit was evident within the first few days of treatment and persisted for 43 days after enrollment. A similar potential benefit of dalteparin was evident in the FRISC II trial. In terms of the effect of dalteparin during three months of double-blind treatment, there was a significant decrease in the composite end point of death and MI in favor of dalteparin over placebo (6.7% vs. 8.0%). While this benefit is conveyed to all ACS patients, it may have specifically improved outcomes in “early” invasive patients by improving plaque passivation before PCI, leading to less serious clinical events.

More convincing data are evident with respect to the GP IIb/IIIa inhibitors. The clinical benefit of GP IIb/IIIa inhibitors has been incontrovertibly tested over the last
decade, both in unstable angina patients before intervention and during PCI (11–14). Based upon data from over 24,000 patients, clinical trials have demonstrated that treatment of NSTE ACS patients with GP IIb/IIIa agents results in an approximate 12% RR reduction for the incidence of death or MI at 30 days (15,16). More importantly, based upon the Platelet glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT), the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS), and the Platelet IIb/IIIa Antagonist for the Reduction of Acute coronary syndrome events in a Global Organization Network (PARAGON) B trials, the benefits of GP IIb/IIIa agents also appear to be magnified in NSTE ACS patients referred for early cardiac catheterization and PCI. Comparing the composite outcome of 30-day death or MI among patients referred for PCI versus those who did not undergo intervention, the RR reduction with GP IIb/IIIa use was 31% versus 6% for PURSUIT, 42% versus 12% for PRISM-PLUS, and 35% versus 7% for PARAGON B (16).

Apart from antithrombotic and antiplatelet advances, improvements in mechanical revascularization may account for improved outcomes in the FRISC II and TACTICS trials. In particular, stenting has emerged as the preferred PCI approach, with reductions in repeat target vessel revascularization and angiographic restenosis (17), and with a synergistic improvement in clinical outcomes when combined with GP IIb/IIIa inhibition (18). The specific advantage of stenting versus PTCA in patients with unstable angina was recently examined at the Mayo Clinic. In this retrospective study of over 7,600 patients, significant decreases in in-hospital mortality and emergency CABG were found, as well significant reductions in Q-wave MI, CABG surgery, and recurrent angina at one year (19). In addition to stenting, other revascularization techniques are currently being investigated that may have an impact on outcomes. These include percutaneous thrombectomy catheters and embolic protection devices.

The benefits from new advances in pharmacotherapy and revascularization techniques for the early invasive approach are most apparent in the TACTICS TIMI-18 trial. Using GP IIb/IIIa inhibition in all patients and intracoronary stenting in most, an extremely low (4.7%) absolute rate of death or nonfatal MI at 30 days was found in the early invasive patients. As noted by the study’s authors, this represents the lowest rate in any ACS trial reported to date. Most importantly, compared with the TIMI-IIIb, VANQWISH, and FRISC II trials (each of which showed an increased incidence of MI and combined death/MI within the first seven days in the “early invasive” group), there was no “early hazard” observed with PCI in the TACTICS TIMI-18 patients. Tirosiban treatment may have mitigated the consequences of incomplete platelet inhibition that led to excess in-hospital events observed in earlier studies, while intracoronary stenting probably provided for a more stable angiographic result.

**Continued need for risk stratification.** While TACTICS and FRISC II provide growing impetus for a combined pharmacologic and interventional approach, these studies underscore previous conclusions from TIMI-IIIb and VANQWISH regarding the value of risk stratification in delineating subgroups most likely (or unlikely) to benefit from early intervention. For example, both FRISC-II and TACTICS TIMI-18 demonstrate a concordance of benefit with the “early invasive” strategy in high-risk, troponin-positive patients, with a neutral effect among troponin-negative subjects, and little benefit in lower-risk patients. Similarly, “early invasive” benefits were largely confined to patients with ST-segment depression on the admission ECG. With the advent of “point-of-care” troponin testing in the emergency department, together with routine ECG, rapid identification of those high-risk patients most likely to benefit from an “early invasive” approach is readily feasible.

**Continued need for aggressive medical therapy.** In addition to recognizing the importance of risk stratification, an early invasive approach should not be considered as an alternative to complementary aggressive medical therapy. Such therapy should be administered to all ACS patients and should include aspirin (with or without clopidogrel), beta-blockade, anti-thrombotic therapy with unfractionated or low-molecular-weight heparin, nitrates, GP IIb/IIIa inhibitors, statins, and ACE inhibitors.

Most patients with ACS have diffuse systemic atherosclerosis that involves the entire coronary vascular system. Angiography is only capable of measuring cross-sectional anatomy from a simple planar two-dimensional silhouette of the contrast-filled lumen and, therefore, may grossly underestimate plaque burden and the true extent of atherosclerosis (20–22). Individual lesion assessment may be particularly difficult if adjacent “normal” arterial segments are diffusely diseased, or if there has been significant coronary remodeling with the development of “extraluminal” plaques.

In addition to underestimating disease severity, angiography is similarly incapable of assessing plaque vulnerability and the subsequent risk for plaque rupture. Previous studies have clearly demonstrated that most coronary occlusions and Mls occur at sites where angiography has previously identified mild or moderate stenoses, with few acute syndromes evolving from high-grade lesions (23). Perhaps more importantly, more recent studies have suggested that ACS patients may have multiple sites of plaque ulceration that may subsequently result in plaque rupture (24,25).

Given the diffuse nature of coronary atherosclerosis and the limitations of angiography in identifying plaque burden and lesions prone to plaque rupture, it follows that all ACS patients should be treated with aggressive medical therapy, whether or not cardiac catheterization and PCI is used. The theoretical benefit of such therapy, particularly with statins, beta-blockers, and ACE inhibitors, is that there may be
underlying stabilization of atherosclerotic plaque throughout the coronary vasculature (26,27).

**Conclusions.** While the debate over the relative superiority of an ischemia-guided versus an early invasive approach remains unsettled, it is clear that recent studies, including FRISC II and TACTICS TIMI-18, have demonstrated improved clinical outcomes in NSTE ACS patients with routine use of diagnostic catheterization and revascularization as indicated. Apart from the fact that these recent studies have been appropriately powered to determine potential differences between the two treatment strategies, an important component of their findings has been their incorporation of newer antiplatelet and antithrombotic agents and intracoronary stenting into study protocols. Use of these newer modalities has improved clinical outcomes before catheterization and during PCI.

In spite of the benefits of an early invasive approach observed in FRISC II and TACTICS TIMI-18, both studies clearly demonstrated the continued need for risk stratification. In particular, using point-of-care testing, such stratification can identify high-risk patients most likely to benefit from an invasive approach. These high-risk attributes include a history of chest pain at rest, ST-segment depression on the ECG, positive cardiac markers of ischemic injury (e.g., creatine kinase myocardial band isoenzyme, troponin, myoglobin), evidence of hemodynamic instability or ventricular dysfunction, and a prior history of PCI or bypass surgery.

The debate over the routine use of coronary angiography, however, continues for patients who are considered low- or intermediate-risk, including for those with normal ECG or nonspecific ECG changes and for those without biomarker positivity. In spite of FRISC II and TACTICS, an “early invasive” approach does not appear to be warranted in this subclass of patients. Optimal therapy continues to involve noninvasive testing for risk stratification, which minimizes the early hazard of revascularization in patients without significant myocardium at risk or recurrent symptoms. Alternatively, it is also important to make the distinction in the “early invasive” strategy between coronary angiography per se and angiography leading to percutaneous intervention. While there was no apparent advantage to an invasive approach in the troponin-negative, non–ST-segment depression group in TACTICS TIMI-18, there was also no added harm. Angiography alone, despite its limitations, can serve as a powerful risk-stratification technique to obtain useful anatomic information in a wide range of difficult patient subsets, ranging from low-risk patients with unremitting symptoms and inconclusive noninvasive tests to higher-risk patients (i.e., diabetics) with atypical presentations.

Finally, regardless of the use of cardiac catheterization and possible PCI, all clinicians certainly agree that suspected ACS patients should be treated aggressively with medical therapy as clinically indicated. The diffuse nature of coronary atherosclerosis and the inherent limitations of coronary angiography in determining plaque burden and vulnerability necessitate the appropriate use of such therapy to decrease the incidence of MI and death in the ACS setting.

**Reprint requests and correspondence:** Dr. Raymond G. McKay, Hartford Hospital, University of Connecticut, 80 Seymour Street, Hartford, Connecticut 06102. E-mail: rmckay@harthosp.org.

**REFERENCES**


