

# Avoidance of Routine Revascularization in the Management of Patients with Non-ST-Segment Elevation Acute Coronary Syndromes

William E. Boden, MD

A debate continues over whether a routine invasive or a conservative strategy is the best treatment approach for patients with non-ST-segment elevation acute coronary syndrome. The fundamental question underlying this debate is whether risk stratification should be an anatomy-driven or an ischemia-driven process. An early routine invasive or "drive-through" strategy, which consists of cardiac catheterization followed by percutaneous coronary intervention within 24 hours of the onset of angina, has not been shown to result in improved outcomes. In fact, investigators in the Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) trial found that aggressively treated patients had significantly worse outcomes during the first year of follow-up than did those treated with a conservative strategy. In this overview, a conservative (ischemia-guided) strategy

with aggressive medical therapy is recommended for patients with non-ST-segment elevation acute coronary syndrome. This conservative treatment includes intensive antiplatelet, antithrombotic, and anti-ischemic therapy combined with careful clinical assessment and provocative testing. Patients undergo catheterization and revascularization only if spontaneous angina occurs or there is objective evidence of stress-induced myocardial ischemia. In the future, it may be revealed that only patients at high risk have real benefit from early aggressive therapy, but the same approach may result in harm to patients at low risk. Tailoring therapy to the level of risk is essential to optimizing efficacy and clinical outcomes. ©2000 by Excerpta Medica, Inc.

Am J Cardiol 2000;86(suppl):42M-47M

An interesting paradigm exists in the treatment of acute coronary syndromes: the higher the initial clinical risk, the greater the proportional benefit of therapy. Many examples support this, including use of thrombolytic therapy in the elderly,<sup>1</sup>  $\beta$  blockers in patients with advanced heart failure,<sup>2,3</sup> implantable cardiac defibrillators (ICDs) for sudden cardiac death,<sup>4</sup> and primary angioplasty in cases of cardiogenic shock.<sup>5,6</sup> In the United States, however, the proportion of low-risk patients with acute coronary syndromes who undergo invasive cardiac procedures exceeds that of high-risk patients. Whereas higher rates of invasive and revascularization procedures are associated with lower rates for refractory angina and readmission for unstable angina, it is also true that the higher rates of angiography and revascularization are not associated with lower rates of cardiovascular death or recurrent myocardial infarction (MI). Moreover, complications of increased stroke and major bleeding may negate the marginal benefit of percutaneous cor-

onary intervention in low-risk or asymptomatic patients with acute coronary syndromes.

In the management of patients with acute coronary syndromes, particularly those with non-ST-segment elevation MI, a fundamental question underlies the debate on invasive versus conservative strategies: Should risk stratification be an anatomy-driven or an ischemia-driven process? During the past 2 decades, percutaneous transluminal coronary angioplasty (PTCA) has become a standard treatment option for patients with coronary heart disease. Following widespread acceptance of the procedure has been the emergence of the aggressive ("drive-through") approach to coronary angioplasty for many patients presenting with an acute MI. The routine early invasive strategy is typically defined as cardiac catheterization followed by percutaneous coronary intervention in all patients without a clinical contraindication within the first 24 hours of presentation. Those who favor this strategy believe it is appropriate for all patients presenting with acute coronary syndromes, including those with non-ST-segment elevation MI. Clinicians who favor the more invasive approach to treatment tend to argue that any form of risk stratification should be abandoned. The rationale behind this concept is that once angiography is performed, the cardiologist can tailor therapy more appropriately to the findings of coronary angiography. Whether improved clinical outcomes can be demonstrated with an aggressive early revascularization approach in all subsets of patients remains to be determined, however. In the final analysis, with regard to an early invasive approach, there may be a differ-

From the University of Connecticut School of Medicine and Hartford Hospital, Hartford, Connecticut, USA.

The treatment approach presented herein was developed in an educational debate format designed to explore possible strategies for management of acute coronary syndromes. The text represents a defense of 1 of 5 propositions, but not necessarily the author's personal recommendation or endorsement of this particular treatment strategy.

Address for reprints: William E. Boden, MD, Hartford Hospital, 80 Seymour Street, Jefferson Building 722, Hartford, Connecticut 06102.

ential effect—a real benefit if the initial risk is high, and potential harm if the initial risk is low.

In this overview, the more conservative approach will be recommended for routine management of uncomplicated patients with non-ST-segment elevation acute coronary syndrome, that is, an ischemia-guided strategy with aggressive medical therapy. Randomized clinical trials focused on the various treatment approaches will be reviewed. A conservative strategy includes intensive antiplatelet, antithrombotic, and anti-ischemic therapy combined with careful clinical assessment and provocative testing (e.g., myocardial perfusion imaging with use of treadmill exercise or pharmacologic vasodilator stress testing). Selective catheterization and, if necessary, revascularization are performed only if spontaneous angina occurs or there is objective evidence of stress-induced myocardial ischemia.

## INVASIVE VERSUS CONSERVATIVE STRATEGIES IN CLINICAL TRIALS

### The Thrombolysis in Myocardial Infarction IIIB trial:

No significant differences in outcome between the invasive and conservative strategies for treating patients with unstable angina and non-Q-wave MI were shown in the Thrombolysis in Myocardial Infarction (TIMI) IIIB trial, which was published in 1994.<sup>7</sup> In the trial, 1,473 patients who were considered to have unstable angina or non-Q-wave MI were randomly assigned to receive (1) tissue plasminogen activator (tPA) versus placebo as initial therapy; and (2) an early invasive strategy (cardiac catheterization, left ventricular angiography, and coronary arteriography 18–48 hours after randomization) versus an early conservative strategy (catheterization and angiography only after failure of initial therapy). The composite endpoint for the comparison of the 2 strategies of death, MI, or an unsatisfactory exercise stress test at 6 weeks occurred in 18.1% of patients assigned to the early strategy and 16.2% of those assigned to the invasive strategy (Table 1). Although the early invasive strategy indicated more rapid relief of angina than the conservative approach, by 6 weeks anginal status was similar between patients, as was the major clinical outcome of death or MI.

**The Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital trial:** In the Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) trial,<sup>8</sup> which was also conducted during the early 1990s, an unexpected difference was found in outcomes between the 2 approaches. The study compared early and late clinical outcomes (death or recurrent MI) in 462 patients randomly assigned to the early invasive strategy with 458 patients who received the early conservative treatment. Patients treated with the routine, early invasive strategy (heart catheterization followed by revascularization) had significantly worse clinical outcomes during the first year of follow-up than did those treated with a conservative strategy (intervention guided by rigorous ischemia management, noninvasive stress testing, and medical therapy). VANQWISH is the largest trial of its kind to test

**TABLE 1** Invasive Versus Conservative Strategies in Patients with Non-ST-Segment Elevation Myocardial Infarction (MI): Outcomes at 6 Weeks in the Thrombolysis in Myocardial Infarction (TIMI) IIIB Trial

	n (%)		p
	Invasive Strategy (n = 740)	Conservative Strategy (n = 733)	
Death	18 (2.4)	18 (2.5)	NS
MI	38 (5.1)	42 (5.7)	NS
Positive 6-wk ETT	64 (8.6)	73 (10.0)	NS
Combined	120 (16.2)	133 (18.1)	NS

ETT = exercise tolerance test; NS = not significant.  
Adapted from *Circulation*.<sup>7</sup>

**TABLE 2** Clinical Outcomes of Patients Who Underwent Coronary Angiography Versus No Angiography (No Revascularization): Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial

	Invasive Strategy* (With Angiography), n = 238 (52%)	Conservative Strategy† (Without Angiography), n = 236 (52%)
30-Day event rate		
Cardiac event	18 (8%)	3 (1%)
Death	12 (5%)	2 (1%)
1-Yr event rate		
Cardiac event	56 (24%)	26 (11%)
Death	31 (13%)	15 (6%)

\*After angiography.

†After randomization.

Modified from *N Engl J Med*.<sup>8</sup>

the efficacy of long-term management strategies in patients recovering from non-Q-wave MI. The number of patients who had one of the components of the primary endpoint and the number of patients who died were significantly higher in the invasive-strategy group at hospital discharge ( $p = 0.004$ ), at 1 month ( $p = 0.012$ ), and at 1 year ( $p = 0.052$ ).

An overlooked feature of the VANQWISH trial is that patients who remained in the conservative treatment arm and did not cross over to cardiac catheterization in the 44 months of follow-up had a remarkably low cardiac event rate: 2 patients died, and 3 patients had experienced a clinical event at 30-day follow-up (Table 2). There was a significant increase in the number of events documented between 1 month and 1 year of follow-up, but that increase was reflective of a subset of patients. In this case, 52% of the patients in the VANQWISH trial had an acceptable low rate of events, despite the fact that they had high clinical comorbidity and an almost 80% incidence of triple-vessel and left main coronary disease. Kaplan-Meier curves (Figure 1) for 1-year combined event rates of death and MI favored the ischemia-guided conservative strategy.

An interaction analysis to determine whether any subset of patients benefited with the invasive strategy revealed no evidence of an interaction that supported

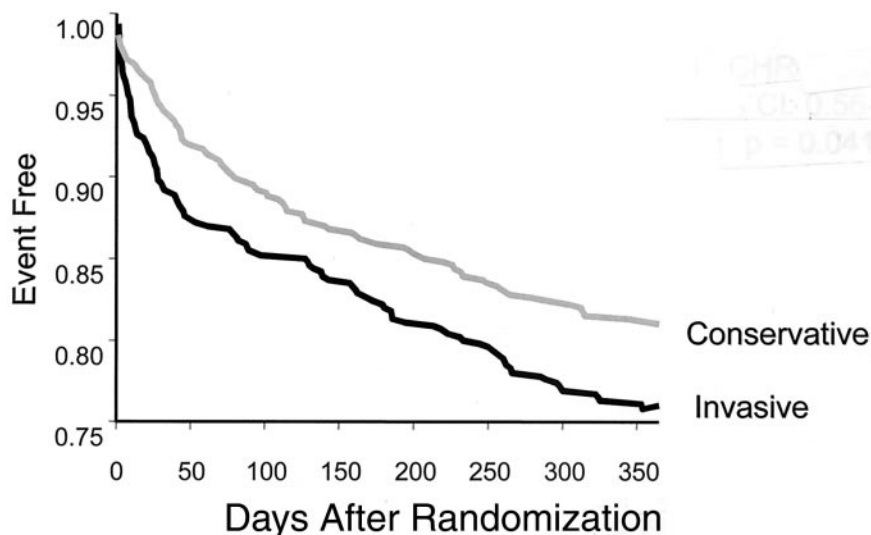


FIGURE 1. From the Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VAN-QWISH) trial, Kaplan-Meier analysis of the probability of event-free survival according to strategy group during 1 year of follow-up. Events included in the analysis were death and nonfatal myocardial infarction (the composite endpoint). The Cox proportional hazards ratio (CHR) for the conservative versus the invasive strategy was 0.74 (95% confidence interval = 0.56–0.99;  $p = 0.041$ ).

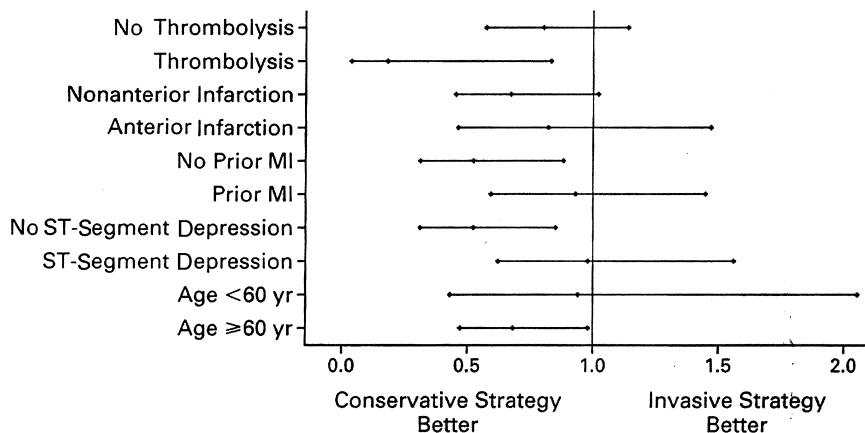
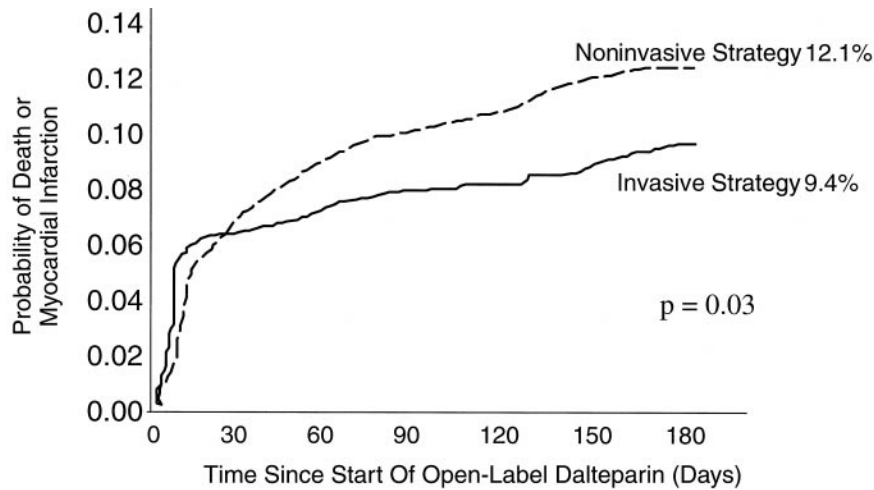


FIGURE 2. From the Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) trial, hazard ratios for death in the 2 strategy groups with stratification according to 5 specified variables. The interaction analysis was conducted for time to death in subgroups, using the Cox proportional-hazards model, to determine whether the main results were consistent among subgroups. Hazard ratios are shown with 95% confidence intervals. Hazard ratios that are  $<1.0$  with confidence intervals that do not cross the unity boundary favor conservative management, and ratios  $>1.0$  favor invasive management. MI = myocardial infarction. (Reprinted with permission from *N Engl J Med*.<sup>8</sup> Copyright© 1998 Massachusetts Medical Society. All rights reserved.

improved outcomes in the patients with the invasive strategy (Figure 2).<sup>8</sup> In contrast, the ischemia-guided strategy benefited 4 of 10 prespecified subsets of patients.

Whether the results of TIMI IIIB and VANQWISH are really relevant to the contemporary practice of managing patients with non-ST-segment elevation MI remains unclear. On the one hand, the results are not relevant in the sense that both trials were conducted before the advent of stents and the newer catheter-based techniques that have proliferated during the past

2–3 years. Since these trials were undertaken, glycoprotein IIb/IIIa receptor antagonists have exploded onto the scene with a variety of well-documented secondary prevention trials.<sup>9–12</sup> The benefits of low-molecular-weight heparins, particularly enoxaparin, have been convincingly demonstrated.<sup>13–15</sup> Evidence from the Organisation to Assess Strategies for Ischemic Syndromes (OASIS-2) trial revealed that hirudin (lepirudin), a direct thrombin inhibitor, may have benefit, especially in those patients who are biochemical marker (troponin or creatine kinase-myocardial



**FIGURE 3.** From the Fragmin and Fast Revascularisation during InStability in Coronary artery disease (FRISC II) study, probability of death or myocardial infarction in the invasive and non-invasive groups. (Reprinted with permission from *Lancet*.<sup>18</sup>) Copyright by The Lancet Ltd, 1999.

ST-T Changes	n	Primary Endpoint (%)		Invasive vs. noninvasive
		Noninvasive	Invasive	RR (95% CI)
None	418	9.0	9.6	1.07 (0.59–1.95)
Inverted T only	866	8.5	7.7	0.90 (0.57–1.41)
ST depression	1,100	14.9	10.3	0.69 (0.50–0.95)
All patients	2,457	12.0	9.2	0.77 (0.61–0.97)

CI = confidence interval; RR = relative risk.  
Reprinted with permission from *Circulation*.<sup>20</sup>

band) positive and/or those with ST-segment depression.<sup>16</sup> The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial<sup>17</sup> showed clopidogrel, a thienopyridine derivative similar to ticlopidine, to be an important adjunctive treatment in the management of patients with acute coronary syndromes.

On the other hand, the TIMI IIIB<sup>7</sup> and VANQWISH<sup>8</sup> trials are relevant to risk stratification because they reveal that both high- and low-risk subsets can be identified. In the VANQWISH trial, only 9% of patients were excluded during the first 48–72 hours for symptoms of refractory angina, persistent ischemia, heart failure, or significant ventricular tachyarrhythmia or fibrillation. As shown earlier, the 30-day event rate of death and MI was remarkably low (1%) with the conservative strategy, despite the high prevalence of clinical comorbidity and angiographic morbidity.

**The Fragmin and Fast Revascularisation during InStability in Coronary artery disease trial:** The Fragmin and Fast Revascularisation during InStability in Coronary artery disease (FRISC-II) invasive trial<sup>18</sup> showed for the first time, in a subset of patients with unstable angina and non-Q wave infarction, a significant event rate reduction favoring the invasive over the noninva-

sive strategy at 6 months (Figure 3). In the trial, 2,457 patients in 58 Scandinavian hospitals were assigned an early invasive (1,222 patients) or noninvasive treatment strategy (1,235 patients) with placebo-controlled long-term low-molecular-weight heparin (dalteparin) for 3 months. In the invasive group, 96% of patients received angiography within 7 days; of those, 71% underwent revascularization within 10 days. For the noninvasive group, 10% received angiography within 7 days; of those, 9% went on to undergo revascularization procedures. At 6 months, the rate of death, MI, or both, was 9.4% in the invasive group (113 of 1,207 patients) and 12.1% in the noninvasive group (148 of 1,226 patients) (risk ratio [RR] = 0.78, 95% confidence interval [CI] = 0.62–0.98; p = 0.031).

The results favoring the invasive strategy were not uniformly shown among patient subsets in FRISC-II, however. In a substudy examining the influence of troponin levels in study patients, plasma samples for central analyses of troponin T levels were available in 2,230 patients; of those, 42% had troponin-negative levels (<0.1 ug/L).<sup>19</sup> The 6-month rate of death or MI was 8.3% in patients assigned to an invasive strategy versus 10.3% in those assigned to a conservative strategy. Although there was a trend toward improvement with the invasive strategy, the difference between

groups was not statistically significant (RR = 0.80; 95% CI = 0.054–1.19).

Similarly, in the evaluation of patients who had ST-segment deviations on the admission electrocardiogram in FRISC II, 418 patients had no demonstrable ST-T wave changes (Table 3).<sup>20</sup> The relative risk of an unfavorable outcome—death or MI at 6 months—was actually slightly higher for patients in the invasive group (RR = 1.07; 95% CI = 0.59–1.95). No significant benefit was shown with the invasive strategy in patients who had isolated T wave inversion only. The early invasive strategy was not shown to be beneficial in fully 52% of patients who had either no electrocardiographic changes or T wave inversion only. The true benefit of early invasive treatment, when evaluated by electrocardiography, was derived only from the subset of patients with ST-segment depression MI (RR = 0.77; 95% CI = 0.61–0.97).

Several factors account for the improved clinical outcomes in FRISC II: the high rate of revascularization (78% in the invasive arm), or aggressive multifaceted medical therapy with aspirin, intravenous nitroglycerin,  $\beta$  blockers, and dalteparin for 4–6 days, which induced plaque passivation and optimized the benefit of revascularization. The noninvasive strategy was likewise doomed to failure in FRISC II because only standard exercise testing was used to detect ischemia, and treadmill exercise testing is far less sensitive than thallium perfusion scintigraphy or myocardial perfusion imaging. In FRISC II, patients could undergo angiography and revascularization only after a markedly positive exercise stress test with abnormal or positive findings of hypotension, exercise-induced ST elevation,  $\geq 3$  mm ST depression, or ischemia during the first stage of exercise. Therefore, too few patients with moderate-to-severe ischemia in the noninvasive arm underwent myocardial revascularization (25% at 1 month and 38% at 6 months). In other words, the requirements were too rigid for triggering appropriate crossovers to the invasive strategy, thus excluding patients with significant inducible ischemia who might have benefited from revascularization.

Finally, patients who were troponin-negative and those who had no ST-T wave changes or only isolated T wave inversions (>50% of all patients) did not benefit from an invasive strategy. There are only observational data and registry data available to show a reduction of death or MI, or refractory ischemia, in non-ST-segment elevation MI patients who underwent percutaneous coronary intervention within 24 hours of presentation. Thus, much remains to be proven about the overall benefit of applying an early aggressive invasive strategy in such patients.

## RISK STRATIFICATION

**High-risk patients:** High-risk patients with non-ST-segment elevation acute coronary syndromes who clearly warrant catheterization and early revascularization include those with rest angina with ST-segment depression and/or elevated serum concentrations of cardiac markers of ischemic injury (creatinine kinase–

myocardial band isoenzyme, troponin, myoglobin). Those who have rest angina with hemodynamic instability, heart failure, or an ejection fraction <0.40, and those with rest angina and prior revascularization (percutaneous coronary interventions or coronary artery bypass grafting) should be sent to the catheterization laboratory and undergo revascularization as indicated.

**Intermediate-risk patients:** Patients with non-ST-segment elevation acute coronary syndromes at an intermediate level of risk for future cardiac events may benefit from catheterization and early revascularization. This subset includes patients with Canadian Cardiovascular Society (CCS) class III or IV angina within the past 2 weeks, those with diabetes mellitus, and those who have deep T wave inversions in >5 leads with chest discomfort or pain.

**Low-risk patients:** Patients with non-ST-segment elevation who are not likely to benefit from catheterization or early revascularization include those with CCS I or II angina, normal or nonspecific electrocardiographic changes, T wave inversion without ST-segment depression, and biochemical markers that are negative for creatine kinase–myocardial band or troponin levels.

## CONCLUSIONS

Risk stratification makes as much sense in 2000 as it did 30 years ago because non-ST-segment elevation acute coronary syndrome is largely a heterogeneous syndrome with a spectrum of risk ranging from low to high. Patients with non-ST-segment elevation who are at high risk comprise 25–50% of all patients. In the more uncomplicated cases, there will not be a flow-limiting stenosis at coronary angiography. The early aggressive or drive-through approach to angioplasty will inevitably subject low-risk or asymptomatic patients to procedures that may not confer clinical benefit. Since the VANQWISH trial demonstrated that 50% of non-Q-wave MI patients randomized to the ischemia-guided strategy had a very acceptable low 30-day event rate (1%), a routine invasive approach with acute revascularization for all patients may not be clinically effective or cost-effective. Finally, a routine interventional approach in all patients will likely result in unnecessary complications such as restenosis, need for revascularization, and risk of stroke, which could be avoided with risk stratification and the selective use of angiography and percutaneous coronary intervention. Powerful antiplatelet and antithrombin therapies are presently available, which, if used intensively with anti-ischemic invasive dilator therapy, can result in significant cardiac event–rate reduction, even in the absence of catheter-based intervention.

Currently, there are no randomized clinical trial data to support drive-through angioplasty for all MI patients. The approach of watchful waiting with medical therapy and no percutaneous coronary intervention, although advocated in the United Kingdom and other parts of Europe, has little basis for support. Between those 2 approaches are the VANQWISH approach of intensive medical therapy with noninvasive risk stratification at 2–3 days and with percuta-

neous coronary intervention for inducible ischemia, and the FRISC-II approach, which advocates a period of intensive medical therapy for 2–3 days to allow plaque passivation, followed by the selective use of percutaneous coronary intervention.

The balanced approach to managing such patients is catheterization and revascularization *only* for high-risk patients. Subjecting low-risk patients to routine intervention will increase marginal risk at the expense of marginal benefit. Aggressive pharmacologic therapy is indicated in all patients, with use of aspirin, with or without clopidogrel; glycoprotein IIb/IIIa receptor antagonists; low-molecular-weight heparin, especially enoxaparin; intravenous nitroglycerin;  $\beta$  blockers; 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins); and angiotensin-converting enzyme inhibitors, as indicated.

Stress myocardial perfusion imaging, preferably symptom-limited exercise-induced imaging with gated single-photon emission computed tomography sestamibi, will clearly delineate intermediate- and high-risk patients at 2–3 days in those patients who are otherwise stable at the time of transfer to the coronary care unit. Selective use of coronary intervention after several days of plaque passivation should improve clinical outcomes in patients most likely to derive clinical benefit. Most importantly, tailoring therapy to the level of risk is essential for optimizing efficacy and cost-effectiveness.

1. Woods KL, Ketley D. Utilisation of thrombolytic therapy in older patients with myocardial infarction. *Drugs Aging* 1998;13:435–441.
2. Pamboukian SV, Aminbaksh A, Thompson CR, Amin H, Mortimer S, D'yachkove Y, Ignaszewski AP. Carvedilol improves functional class in patients with severe left ventricular dysfunction referred for heart transplantation. *Clin Transplant* 1999;13:426–431.
3. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomized trial. *Lancet* 1999;353:9–13.
4. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease: Multicenter Unsustained Tachycardia Trial Investigators. *N Engl J Med* 1999;16:341:1882–1890.
5. American College of Emergency Physicians. The role of primary angioplasty in patients presenting with acute myocardial infarction. *Ann Emerg Med* 2000; 35:532–533.
6. Hochman JS, Sleeper LA, Webb JG, Sanborn TA, White HD, Talley JD, Buller CE, Jacobs AK, Slater JN, Col J, McKinlay SM, LeJemtel TH. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should we emergently revascularize occluded coronaries for cardiogenic shock? *N Engl J Med* 1999;341:625–634.

7. The TIMI IIIB Investigators. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction: results of the TIMI IIIB Trial. *Circulation* 1994;89:1545–1556.
8. Boden WE, O'Rourke RA, Crawford MH, Blaustein AS, Deedwania PC, Zoble RG, Wexler LF, Kleiger RE, Pepine CJ, Ferry DR, Chow BK, Lavori PW, for the Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial Investigators. Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. *N Engl J Med* 1998;338:1785–1792.
9. The Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. *N Engl J Med* 1998;338:1498–1505.
10. The Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. Inhibition of the Platelet Glycoprotein IIb/IIIa Receptor with Tirofiban in Unstable Angina and Non-Q-wave Myocardial Infarction. *N Engl J Med* 1998; 338:1488–1497.
11. The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatid in patients with acute coronary syndromes. *N Engl J Med* 1998;339:436–443.
12. The RESTORE Investigators. Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty: Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis. *Circulation* 1997;96: 1445–1453.
13. Cohen M, Demers C, Gurfinkel EP, Turpie AGG, Fromell GJ, Goodman S, Langer A, Califf RM, Fox KAA, Premeureur J, Bigonzi F, for the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events Study. *N Engl J Med* 1997;337:447–452.
14. Antman EM, McCabe CH, Gurfinkel EP, Turpie AGG, Bernink PJLM, Salein D, de Luna AB, Fox K, Lablanche J-M, Radley D, Premeureur J, Braunwald E, for the TIMI IIIB Investigators. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI) IIIB Trial. *Circulation* 1999;100: 1593–1601.
15. Fragmin and Fast Revascularisation during InStability in Coronary artery disease (FRISC II) Investigators. Long-term low-molecular-mass heparin in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. *Lancet* 1999;354:701–707.
16. The OASIS-2 Investigators. Effects of recombinant hirudin (lepirudin) compared with heparin on death, myocardial infarction, refractory angina, and revascularisation procedures in patients with acute myocardial ischaemia without ST elevation: a randomised trial. *Lancet* 1999;353:429–438.
17. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996; 348:1329–1339.
18. Fragmin and Fast Revascularisation during InStability in Coronary artery disease (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.
19. Lagerqvist B, Diderholm E, Lindahl B, Husted S, Kontny F, Stahle E, Swahn E, Wallentin L. An early invasive treatment strategy reduces cardiac events regardless of troponin levels in unstable coronary artery (UCAD) with and without troponin-elevation: a FRISC II substudy. (Abstr.) *Circulation* 1999; (suppl I):100:I-497.
20. Diderholm E, Andren B, Frostfeldt G, Gengerg M, Jernberg T, Lagerqvist B, Lindahl B, Wallentin L. ST depression in electrocardiogram at entry identifies patients who benefit most from early revascularisation in unstable coronary artery disease: a FRISC II substudy. (Abstr.) *Circulation* 1999;(suppl I):100:I-497.