



## Unstable Angina and Non-ST-Elevation Myocardial Infarction

### Initial Antithrombotic Therapy and Early Invasive Strategy

Christopher P. Cannon, MD; Alexander G.G. Turpie, MD

**C**ase: Presentation: A 59-year-old woman with a history of prior coronary artery bypass surgery 8 years ago presents with ongoing chest discomfort for 45 minutes that has been unrelieved with 3 sublingual nitroglycerin tablets. Past medical history is notable for diabetes controlled with oral medication, longstanding hypertension, and a family history of coronary disease. She has a history of a non-ST-elevation myocardial infarction (NSTEMI) with preserved ejection fraction. Her baseline medications include aspirin, a  $\beta$ -blocker, and an angiotensin-converting enzyme (ACE) inhibitor. In the ambulance, she received additional sublingual nitroglycerin and had resolution of her pain. In the emergency department, an ECG showed 1 mm of ST-segment depression anteriorly. Initial creatinine kinase-MB and troponin measurements were negative (ie, below the upper reference limit).

#### Initial Assessment

The initial evaluation of patients with unstable angina and NSTEMI (UA/NSTEMI) begins with assessment of the likelihood that the presenting

symptoms represent ischemia. According to the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for UA/NSTEMI, several factors are associated with a high likelihood that symptoms represent ischemic acute coronary syndrome. Most important among them are chest or left arm pain or discomfort that reproduces the patient's prior documented angina, a known history of coronary disease or MI, evidence of heart failure on physical examination, ST-segment or T-wave changes on ECG, or elevated cardiac biomarkers.<sup>1</sup> An intermediate likelihood can be predicted by age over 70 years, male sex, and diabetes or by evidence of extracardiac vascular disease on physical examination or ECG abnormalities not documented to be new. Thus, the clinical history is critical in the initial evaluation of patients with possible acute coronary syndromes to discriminate patients with true ischemic symptoms from those with non-cardiac chest pain. In our case, the patient's history is consistent with a very high likelihood that her symptoms—chest discomfort, prior history of coronary disease, and

ECG changes—represent an acute coronary syndrome.

#### Risk Stratification

To determine the intensity of both medical and interventional therapies, the next assessment is for the short-term risk of death or recurrent MI. Factors associated with a high risk of death or nonfatal MI are a history of accelerating symptoms in the prior 48 hours, prolonged (>20 minutes) rest pain, evidence of congestive heart failure, age over 75 years, ST-segment changes, or elevated cardiac biomarkers.<sup>1,2</sup> Low-risk patients present without rest pain,<sup>3</sup> ECG changes, or evidence of heart failure.

The ECG is very useful in risk stratifying patients in that multiple studies have shown that the presence of ST-segment depression or transient elevation is a marker of increased risk.<sup>2,4</sup> T-wave inversion appears to add little risk,<sup>4</sup> but may be useful in differentiating a patient experiencing true myocardial ischemia from one with non-cardiac chest pain.

#### Cardiac Biomarkers

Cardiac biomarkers are a cornerstone for evaluating and targeting therapy in

From the TIMI Study Group, Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Mass (C.P.C.), and McMaster University, Hamilton, Ontario, Canada (A.G.G.T.).

Correspondence to Christopher Cannon, MD, Cardiovascular Division, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115. E-mail [cpcannon@partners.org](mailto:cpcannon@partners.org)

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UA/NSTEMI. Multiple studies have shown that patients with an elevated troponin level are at increased risk.<sup>1,5-7</sup> There appears to be a direct relationship between the degree of troponin elevation and mortality.<sup>5</sup> Interestingly, recurrent MI appears to be very high among patients with low levels of troponin elevation, and thus the rate of death or MI appears to be equally high in patients with either low or high troponin values.<sup>7</sup> The European Society of Cardiology (ESC)/ACC consensus document on MI, as well as multiple trials in UA/NSTEMI, supports a very low cut-point for troponin elevation as a biomarker of adverse outcome in patients presenting with a clear history of ischemic symptoms.<sup>1,5-8</sup> It should be noted however, that in patients without a clear history, troponin elevations in the absence of ischemia have been reported<sup>9,10</sup> and can be caused by congestive heart failure,<sup>11</sup> pulmonary embolism,<sup>12</sup> or technical problems with the assay.<sup>10</sup> Thus, in patients with an unclear history, small troponin elevations may not be diagnostic of acute coronary syndromes (ACS). In contrast, among patients with a clinical history suggestive of myocardial ischemia, troponin elevations have very strong prognostic implications of adverse outcomes.<sup>1,5-7,13-15</sup>

Multiple studies show that troponin can be used to guide antithrombotic and interventional therapies.<sup>6,7,13-15</sup> This was seen in trials with low molecular weight heparin (LMWH).<sup>13,14</sup> In 4 trials of glycoprotein (GP) IIb/IIIa inhibitors, there was a 50% to 70% reduction in death or MI in troponin-positive patients receiving GP IIb/IIIa inhibitors compared with those receiving aspirin and heparin alone.<sup>6,16</sup> In contrast, patients with a negative troponin level had no benefit from LMWH or GP IIb/IIIa inhibition as compared with aspirin and heparin.<sup>6,13,14,16</sup> Similarly, in the Treat angina with Aggrastat and determine Costs of Therapy with Invasive or Conservative Strategies-Thrombolysis in Myocardial Infarction 18 (TACTICS-TIMI 18) study,

an early invasive strategy conferred a 40% reduction in recurrent cardiac events for patients with a positive troponin (troponin T >0.01 or troponin I >0.1 ng/mL), whereas no benefit was seen for patients with a negative troponin.<sup>7,15</sup>

It should be noted that the oral antiplatelet agents appear to have a different pattern: Both aspirin and clopidogrel benefit patients across the range of risk as predicted by baseline characteristics, including those with positive or negative biomarkers.<sup>17,18</sup>

Among numerous other cardiac biomarkers under intensive investigation are C-reactive protein<sup>19</sup> and B-type natriuretic peptide,<sup>20</sup> both of which correlated with increased mortality and recurrent cardiac events in patients presenting with acute coronary syndromes. Further ongoing research will determine if therapies are differentially beneficial in patients with elevated novel markers. A multi-marker strategy is being developed to more fully define the pathophysiologic mechanisms underlying a given patient's presentation and to further risk-stratify the patient across the axes of myocardial necrosis, inflammation, and neurohormonal activation.<sup>21</sup>

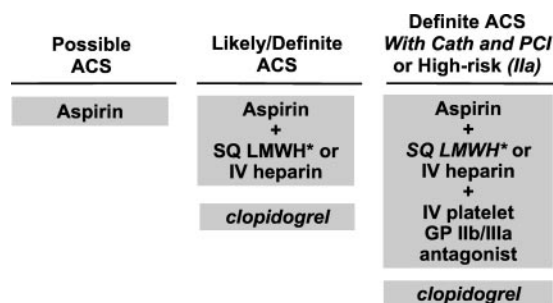
Finally, a comprehensive risk score can be calculated. For example, the TIMI Risk Score for UA/NSTEMI is comprised of 7 factors; an increase in the number of factors correlates with an increase in the rate of recurrent cardiac events.<sup>2</sup> Importantly, use of the

TIMI Risk Score can enable identification of patients who would benefit to a higher degree from the more aggressive antithrombotic and interventional strategies.<sup>2,15,22</sup> Thus, risk stratification is a key and integral part of the initial evaluation and management of patients with acute coronary syndromes.

### Treatment

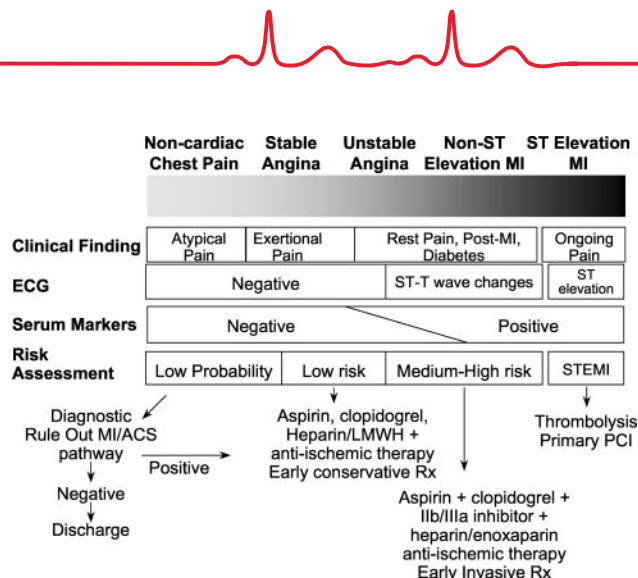
Initial treatment for unstable angina has evolved rapidly, with increasing emphasis on antithrombotic therapy.<sup>1,23</sup> Initial treatment should include aspirin, which reduces events by 50% to 70% as compared with placebo (Figure 1 and Figure 2).<sup>24</sup> On the basis of a demonstrated incremental benefit over aspirin alone,<sup>25-27</sup> unfractionated heparin (UFH) or LMWH should be added to the medical regimen of all patients with UA/NSTEMI. Comparative trials of the LMWH enoxaparin have demonstrated its superiority over UFH in reducing recurrent cardiac events.<sup>28,29</sup> The 2002 Updated ACC/AHA UA/NSTEMI practice guidelines noted with a class IIA recommendation that enoxaparin is the preferred antithrombin over UFH.<sup>23</sup>

Two direct thrombin inhibitors, hirudin and bivalirudin, have been tested in patients with UA/NSTEMI with trends toward benefit, although none of the trials showed a statistically significant reduction in their primary endpoint. Thus, no direct antithrombin has as yet been approved for manage-



\*Class IIA recommendation: Enoxaparin preferred over unfractionated heparin

**Figure 1.** Recommendations for antithrombotic therapy based on the 2002 ACC/AHA Guidelines for UA/NSTEMI Risk Stratification scheme. See text for discussion of timing of clopidogrel and GP IIb/IIIa inhibition. Cath indicates cardiac catheterization; SQ, subcutaneous. The figure is updated by the authors, with changes in italics, from a figure which appeared in the 2000 Guideline (Braunwald E, et al *J Am Coll Cardiol.* 2000;36:970-1056).



**Figure 2.** Algorithm for risk stratification and treatment of patients with UA/NSTEMI. See text for discussion of timing of clopidogrel and GP IIb/IIIa inhibition. DM indicates diabetes mellitus; Rx=treatment. Updated with permission from Braunwald E, Zipes DP, Libby P, eds. *Heart Disease: A Textbook of Cardiovascular Medicine*. 6th ed. Philadelphia, Pa: W.B. Saunders; 2001:1232–1263.

ment of UA/NSTEMI.<sup>30,31</sup> These agents are presently approved for anticoagulation of patients with heparin-induced thrombocytopenia and one for PCI.

In the large Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) trial, clopidogrel in combination with aspirin was shown to confer a 20% reduction in cardiovascular death, MI, or stroke compared with aspirin alone in both low- and high-risk patients with UA/NSTEMI.<sup>18</sup> The benefit was seen as early as 24 hours, with the Kaplan-Meier curves diverging after just 2 hours, thus indicating a very early antithrombotic and clinical effect. Moreover, the benefit continued throughout the trial's 1-year treatment period, consistent with data from the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial showing benefit of clopidogrel alone versus aspirin through 3 years of follow-up in patients with atherosclerotic disease.<sup>32</sup> Benefit of early treatment before percutaneous coronary intervention (PCI) was also seen with a 31% reduction in cardiac events at 30 days and 1 year in patients.<sup>33</sup> Thus, the ACC/AHA guidelines have added clopidogrel to the class I treatment recommendations (Figure 1 and Figure 2).<sup>23</sup>

Although there are no randomized studies in ACS patients using quadruple antithrombotic therapy (aspirin, clopidogrel, heparin or LMWH, and "upstream" GP IIb/IIIa inhibitor) as recommended in the ACC/AHA Guidelines, there are now data available from several PCI trials, including Clopidogrel in Unstable angina to prevent Recurrent ischemic Events in patients undergoing Percutaneous Coronary Intervention (PCI-CURE), do Tirofiban And Reopro Give similar Efficacy outcomes Trial (TARGET), and the Clopidogrel for Recurrent of Events During Observation (CREDO) trial. In CREDO, patients with planned or likely PCI (which included approximately two-thirds of patients with ACS) were randomized to receive a loading dose of clopidogrel (300 mg) or placebo between 3 and 24 hours before PCI. After stenting, all patients received open label clopidogrel for 28 days after stenting; after 28 days, patients in the pretreatment group continued on clopidogrel for 1 year, whereas the non-pretreatment group was treated with matching placebo. This study found no increase in bleeding in patients receiving the clopidogrel versus placebo in addition to aspirin, heparin, and GP IIb/IIIa inhibition. Similar safety observations regarding clopidogrel have been made in PCI-

CURE, TARGET, and the randomized Troponin in Planned PTCA/Stent Implantation With or Without Administration of the Glycoprotein IIb/IIIa Receptor Antagonist Tirofiban (TOPSTAR) trials.<sup>33–35</sup>

The efficacy results from CREDO lend further support to both early and long-term use of clopidogrel in UA/NSTEMI patients. Pretreatment with clopidogrel led to a non-significant 19% risk reduction in events; however, patients given clopidogrel at least 6 hours before PCI had a significant 38.6% relative risk reduction in major events at 28 days ( $P=0.05$ ) compared with no reduction with treatment less than 6 hours before PCI. This finding emphasizes the need to initiate clopidogrel as soon as possible on admission for UA/NSTEMI, before any planned catheterization and followed by possible PCI. Overall, long-term treatment (1 year) with clopidogrel plus aspirin led to a 26.9% relative reduction in death, MI, or stroke compared with post-PCI clopidogrel therapy for one month (8.5% versus 11.5% [placebo],  $P=0.02$ ). This included a further 37.4% relative reduction in major events from day 29 to 1 year with clopidogrel ( $P=0.04$ ). In summary, the results of PCI-CURE and CREDO support preprocedural loading with clopidogrel in those scheduled or expected to undergo PCI, showing significant benefits with or without the concomitant use of GP IIb/IIIa inhibitors. In addition, data from these trials and CURE support long-term treatment with aspirin plus clopidogrel in patients after PCI and in those with ACS.

Intravenous GP IIb/IIIa inhibitors are also beneficial in treating UA/NSTEMI.<sup>36</sup> For "upstream" management (ie, initiating therapy when the patient first presents to the hospital), the small-molecule inhibitors eptifibatid and tirofiban clearly show benefit, whereas abciximab was of no benefit in an unselected UA/NSTEMI patient population,<sup>37</sup> and is in fact contraindicated for patients treated with a noninvasive strategy.<sup>23</sup> Abcix-

imab is strongly beneficial in patients undergoing PCI.<sup>34,38</sup> The benefit of “upstream” GP IIb/IIIa inhibitors is limited to patients at high risk and, notably, to troponin-positive patients,<sup>6,16</sup> whether or not they underwent revascularization.<sup>16</sup> Because of the great benefit of GP IIb/IIIa inhibition during PCI,<sup>39</sup> the ACC/AHA guidelines emphasize using GP IIb/IIIa inhibitors in patients managed with an invasive strategy, whereas it is a class IIa recommendation to use GP IIb/IIIa inhibitors in high-risk patients for whom PCI is not planned.<sup>23</sup> However, an early invasive strategy is recommended for high-risk patients, and thus the new ACC/AHA guidelines link together risk assessment, strategy selection, and then GP IIb/IIIa inhibition for this group of patients. (Figure 2)

As with all of the antithrombotic agents, bleeding is the significant side effect. Thus, patients with a recent history of bleeding must be screened carefully, and fewer antithrombotic agents should be considered for such patients.

Anti-ischemic therapy with nitrates is also recommended for patients with UA/NSTEMI. Intravenous nitrates should be prescribed for ongoing ischemic pain.<sup>1</sup> Although useful for treating angina, oral nitrates do not prevent cardiac events during long-term treatment and thus can be discontinued on successful revascularization.  $\beta$ -Blockade remains a cornerstone of treatment. Intravenous  $\beta$ -blockade followed by oral  $\beta$ -blockade targeted to a heart rate of 50 to 60 is recommended for ongoing pain. Additional medical therapy includes ACE inhibition for long-term secondary prevention.<sup>40</sup> When started early during hospitalization for UA/NSTEMI, statin therapy can be beneficial in reducing recurrent ischemic events.<sup>41</sup> The wealth of data in long-term secondary prevention has elevated statin use to a class I recommendation for those with low-density lipoprotein (LDL) levels  $>130$  and is likely relevant to those with LDL  $>100$ , as per the National Cholesterol Education Program (NCEP) III guide-

lines.<sup>42</sup> New information from the Heart Protection Study shows benefit of simvastatin 40 mg over placebo during long-term secondary prevention regardless of baseline LDL, including patients with a baseline LDL of  $<100$ , thus suggesting that statin therapy may be indicated for patients with any evidence of coronary or vascular disease.<sup>43</sup> Further review of these data and potential revision of the NCEP practice guidelines may be necessary before widespread use of statin therapy is adopted in patients with LDL  $<100$ .

### Invasive Versus Conservative Strategy

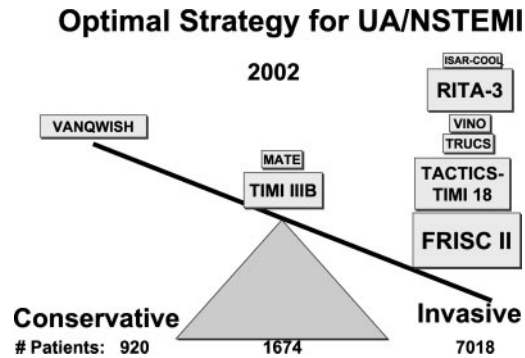
Nine randomized trials have assessed the merits of an invasive strategy involving routine cardiac catheterization, with revascularization if feasible, versus a conservative strategy where angiography and revascularization are reserved for patients who have evidence of recurrent ischemia either at rest or on provocative testing. The first 3 of these trials failed to demonstrate a significant benefit,<sup>44</sup> but the subsequent 6 trials (including the Fragmin and fast Revascularization during Instability in Coronary artery disease [FRISC] II, TACTICS-TIMI 18, and Randomized Intervention Trial of unstable Angina [RITA] trials) have shown a significant benefit (Figure

3).<sup>15,45,46</sup> Preliminary data from the Intracoronary Stenting with Anti-thrombotic Regimen COOLing-off (ISAR-COOL) study found a benefit of an immediate invasive strategy with an average time to catheterization of 2 hours compared with a delayed invasive strategy (average time to catheterization 4 days).<sup>47</sup>

The benefits of the early invasive strategy were seen in intermediate- and high-risk patients, especially in those with ST-segment changes who had a positive troponin on admission.<sup>7,15</sup> Similar findings regarding risk and degree of enhanced benefit were seen in the FRISC II trial.<sup>45,48</sup> Accordingly, the 2002 ACC/AHA guidelines added ST-segment changes and positive troponin to the list of high-risk indicators that would lead to a class I recommendation for an early invasive strategy.<sup>23</sup> An early invasive strategy is very cost-effective, with a cost of \$12 739 per life year saved, even in low-risk patients.<sup>49</sup>

### Summary

The evaluation of patients with UA/NSTEMI begins with the clinical history, ECG testing, and measurement of cardiac biomarkers to assess (1) the likelihood of coronary disease and (2) the patient’s risk of death or recurrent cardiac events (Figure 2). Patients with



**Figure 3.** The “weight of the evidence” showing benefit of an invasive versus conservative strategy in patients with UA/NSTEMI. The size of the boxes for each of the 9 randomized trials corresponds to the number of patients enrolled. VANQWISH indicates Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital; MATE, Medicine versus Angiography in Thrombolytic Therapy; VINO, Value of First Day Angiography/Angioplasty in Evolving Non-ST-Segment Elevation Myocardial Infarction: A Multicenter Randomized Trial; and TRUCS, Treatment of Refractory Unstable angina in geographically isolated areas without Cardiac Surgery: invasive versus conservative strategy. See text for other trial names.


a low likelihood of having UA/NSTEMI should undergo a “diagnostic pathway” evaluation via serial ECGs, cardiac biomarkers, and early stress testing to evaluate for coronary disease. This can frequently be accomplished in an emergency department observation/chest pain unit. Among patients with a clinical history strongly consistent with UA/NSTEMI, those at low risk should be treated with anti-thrombotic therapy with aspirin, clopidogrel, and either heparin or LMWH. An early conservative strategy is adequate in low-risk patients, although an invasive strategy is equally clinically beneficial. For intermediate and high-risk patients (ST-segment changes, positive troponin, TIMI Risk Score  $\geq 3$ ), the above-mentioned medications plus GP IIb/IIIa inhibition (thus, 4 antithrombotic agents) are beneficial, and an early invasive strategy is preferred (Figure 1). Additional studies of the various combinations of treatments are ongoing to define further the safety of these regimens.

### Case Follow-Up

The patient described above presented with ST segment changes and a TIMI risk score of 4, and her guideline-recommended treatment regimen was initiation of aspirin, clopidogrel, enoxaparin, and a small-molecule GP IIb/IIIa inhibitor, in addition to continued  $\beta$ -blocker and ACE inhibitor. On the morning after admission, she was referred for angiography and had a 90% left anterior descending artery stenosis that was successfully stented. She was discharged the next day receiving aspirin, clopidogrel for at least 9 months, a  $\beta$ -blocker, an ACE inhibitor, a statin, and an oral hypoglycemic agent.

### References

- Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guidelines for the management of patients with unstable angina and non-ST segment elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Unstable Angina and Non-ST Segment Elevation Myocardial Infarction). *J Am Coll Cardiol*. 2000;36:970–1056.
- Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA*. 2000;284:835–842.
- Scirica BM, Cannon CP, McCabe CH, et al. Prognosis in the Thrombolysis in Myocardial Ischemia III Registry according to the Braunwald unstable angina pectoris classification. *Am J Cardiol*. In press.
- Cannon CP, McCabe CH, Stone PH, et al. The electrocardiogram predicts one-year outcome of patients with unstable angina and non-Q wave myocardial infarction: results of the TIMI III Registry ECG Ancillary Study. *J Am Coll Cardiol*. 1997;30:133–140.
- Antman EM, Tanasijevic MJ, Thompson B, et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med*. 1996;335:1342–1349.
- Hamm CW, Heeschen C, Goldmann B, et al. Benefit of abciximab in patients with refractory unstable angina in relation to serum troponin T levels. *N Engl J Med*. 1999;340:1623–1629.
- Morrow DA, Cannon CP, Rifai N, et al. Ability of minor elevations of troponin I and T to predict benefit from an early invasive strategy in patients with unstable angina and non-ST elevation myocardial infarction: results from a randomized trial. *JAMA*. 2001;286:2405–2412.
- The Joint European Society of Cardiology/American College of Cardiology committee. Myocardial infarction redefined: a consensus document of the joint European Society of Cardiology/American College of Cardiology committee for the redefinition of myocardial infarction. *Eur Heart J*. 2000;21:1502–1513.
- Wright SA, Sawyer DB, Sacks DB, et al. Elevation of troponin I levels in patients without evidence of myocardial injury. *JAMA*. 1997;278:2144.
- Fleming SM, O’Byrne L, Finn J, et al. False-positive cardiac troponin I in a routine clinical population. *Am J Cardiol*. 2002;89:1212–1215.
- Missov E, Calzolari C, Pau B. Circulating cardiac troponin I in severe congestive heart failure. *Circulation*. 1997;96:2953–2958.
- Giannitsis E, Muller-Bardorff M, Kurowski V, et al. Independent prognostic value of cardiac troponin T in patients with confirmed pulmonary embolism. *Circulation*. 2000;102:211–217.
- Lindahl B, Venge P, Wallentin L, et al. Troponin T identifies patients with unstable coronary artery disease who benefit from long-term antithrombotic protection. *J Am Coll Cardiol*. 1997;29:43–48.
- Morrow DA, Antman EM, Tanasijevic M, et al. Cardiac troponin I for stratification of early outcomes and the efficacy of enoxaparin in unstable angina: a TIMI 11B substudy. *J Am Coll Cardiol*. 2000;36:1812–1817.
- Cannon CP, Weintraub WS, Demopoulos LA, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med*. 2001;344:1879–1887.
- Heeschen C, Hamm CW, Goldmann B, et al. Troponin concentrations for stratification of patients with acute coronary syndromes in relation to therapeutic efficacy of tirofiban. *Lancet*. 1999;354:1757–1762.
- Antithrombotic Trialists’ Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ*. 2002;324:71–86.
- Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001;345:494–502.
- Lindahl B, Toss H, Siegbahn A, et al. Fragmin during instability in coronary artery disease: markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. *N Engl J Med*. 2000;343:1139–1147.
- de Lemos JA, Morrow DA, Bentley JH, et al. The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. *N Engl J Med*. 2001;345:1014–1021.
- Sabatine MS, Morrow DA, de Lemos JA, et al. Multimarker approach to risk stratification in non-ST elevation acute coronary syndromes: simultaneous assessment of troponin I, C-reactive protein, and B-type natriuretic peptide. *Circulation*. 2002;105:1760–1763.
- Morrow DA, Antman EM, Snapinn SM, et al. An integrated clinical approach to predicting the benefit of tirofiban in non-ST elevation acute coronary syndromes: application of the TIMI risk score for UA/NSTEMI in PRISM-PLUS. *Eur Heart J*. 2002;23:223–229.
- Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guideline update for the management of patients with unstable angina and non-ST segment elevation myocardial infarction—2002: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Unstable Angina). *Circulation*. 2002;106:1893–1900.
- Theroux P, Ouimet H, McCans J, et al. Aspirin, heparin or both to treat unstable angina. *N Engl J Med*. 1988;319:1105–1111.
- Oler A, Whooley MA, Oler J, et al. Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina: a meta-analysis. *JAMA*. 1996;276:811–815.
- Klein W, Buchwald A, Hillis SE, et al. Comparison of low-molecular-weight heparin with unfractionated heparin acutely and with placebo for 6 weeks in the management of unstable coronary artery disease: Fragmin in Unstable Coronary Artery Disease Study (FRIC). *Circulation*. 1997;96:61–68.
- Massel D, Cruickshank MK. Enoxaparin in acute coronary syndromes: evidence for

- 
- superiority over placebo or untreated control. *Am Heart J.* 2002;143:748–752.
28. Antman EM, Cohen M, Radley D, et al. Assessment of the treatment effect of enoxaparin for unstable angina/non-Q-wave myocardial infarction: TIMI 11B-ESSENCE meta-analysis. *Circulation.* 1999;100:1602–1608.
  29. Goodman S, Fitchett D, Armstrong PW, et al. Randomized evaluation of the safety and efficacy of enoxaparin versus unfractionated heparin in high risk patients with non-ST-segment elevation acute coronary syndromes receiving the glycoprotein IIb/IIIa inhibitor eptifibatide. *Circulation.* 2003;107:238–244.
  30. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb Investigators. A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. *N Engl J Med.* 1996;335:775–782.
  31. Organisation to Assess Strategies for Ischemic Syndromes (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.
  32. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet.* 1996;348:1329–1339.
  33. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet.* 2001;358:527–533.
  34. Topol EJ, Moliterno DJ, Herrmann HC, et al. Comparison of two platelet glycoprotein IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization. *N Engl J Med.* 2001;344:1888–1894.
  35. Bonz AW, Lengenfelder B, Strotmann J, et al. Effect of additional temporary glycoprotein IIb/IIIa receptor inhibition on troponin release in elective percutaneous coronary interventions after pretreatment with aspirin and clopidogrel (TOPSTAR trial). *J Am Coll Cardiol.* 2002;40:662–668.
  36. Boersma E, Harrington RA, Moliterno DJ, et al. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. *Lancet.* 2002;359:189–198.
  37. 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.
  38. Anderson KM, Califf RM, Stone GW, et al. Long-term mortality benefit with abciximab in patients undergoing percutaneous coronary intervention. *J Am Coll Cardiol.* 2001;37:2059–2065.
  39. Kong DF, Califf RM, Miller DP, et al. Clinical outcomes of therapeutic agents that block the platelet glycoprotein IIb/IIIa integrin in ischemic heart disease. *Circulation.* 1998;98:2829–2835.
  40. Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet.* 2000;355:253–259.
  41. Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA.* 2001;285:1711–1718.
  42. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA.* 2001;285:2486–2497.
  43. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo controlled trial. *Lancet.* 2002;360:7–22.
  44. 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.
  45. FRagmin, and Fast Revascularisation during InStability in Coronary artery disease Investigators. Invasive compared with non-invasive treatment in unstable coronary artery disease: FRISC II prospective randomised multicentre study. *Lancet.* 1999;354:708–715.
  46. Fox KA, Poole-Wilson PA, Henderson RA, et al. Interventional versus conservative treatment for patients with unstable angina on non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. *Lancet.* 2002;360:743–751.
  47. Neumann FJ. Intracoronary Stenting With Antithrombotic Regimen Cooling-Off (ISAR-COOL) Study. Presented at the American Heart Association Scientific Sessions. Chicago, Ill, November 17–20, 2002.
  48. Wallentin L, Lagerqvist B, Husted S, et al. Outcome at 1 year after an invasive compared with a non-invasive strategy in unstable coronary-artery disease: the FRISC II invasive randomised trial. *Lancet.* 2000;356:9–16.
  49. Mahoney EM, Jurkowitz CT, Chu H, et al. Cost and cost-effectiveness of an early invasive versus conservative strategy for the treatment of unstable angina and non-ST elevation myocardial infarction. *JAMA.* 2002;288:1851–1858.