

# Calming the Plaque to Delay Intervention for 24 Hours in Acute Coronary Syndromes

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One approach to management of patients with acute coronary syndromes involves use of pharmacologic therapy to passivate plaque for at least 24 hours before interventional procedures are undertaken. This approach is supported by the view that whatever subsequent treatment the patient receives will less likely be complicated. An important factor in revolutionizing treatment for acute coronary syndromes in recent years has been the introduction of potent new antithrombotic and antiplatelet pharmacologic therapies such as low-molecular-weight heparins and glycoprotein IIb/IIIa in-

hibitors. Incorporation of these newer agents into clinical practice, along with a better understanding of the pathophysiology underlying acute coronary syndromes, has contributed greatly to improved outcomes in these patients. Although the optimal methods for integrating the newer therapies remains to be determined, thus far, they have been shown to lower the risk of acute complications, as well as improve long-term results. ©2000 by Excerpta Medica, Inc.

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Several recent studies support the concept that patients with acute coronary syndromes will have improved outcomes if they are pretreated with medical therapy before interventional procedures are undertaken.<sup>1-5</sup> The approach of stabilizing the patient with pharmacologic therapy for at least 24 hours before performing a percutaneous coronary intervention, or even coronary bypass grafting, is supported by the view that whatever subsequent treatment the patient receives will less likely be complicated. Early trials, such as the Thrombolysis in Myocardial Ischemia (TIMI IIIB) trial<sup>6</sup> and the Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) trial,<sup>7</sup> focused on invasive therapy versus chronic medical therapy. Investigators for the VANQWISH trial clearly recommended a conservative, ischemia-guided initial approach for patients with non-Q-wave myocardial infarction (MI).<sup>7</sup>

Along with a better understanding of the pathophysiology of acute coronary syndromes achieved in recent years has been the introduction of novel antithrombotic agents and potent antiplatelet inhibitors. Now, clinicians have greater choices for management of patients with acute coronary syndromes, but the best way of integrating these newer treatments into the overall treatment approach remains to be determined. Incorporation of antithrombin and antiplatelet agents into the pharmacologic regimen, both before and after

interventional procedures, appears to lower the risk of acute complications, as well as improve long-term outcomes.<sup>8</sup> A combination of anticoagulant agents may prove to be more beneficial than single-agent therapy. Thus far, both approaches have been shown to reduce cardiac event rates.<sup>1,4-5</sup>

## PATHOPHYSIOLOGY OF ACUTE CORONARY SYNDROMES

Although the problem is far from simple, many clinicians approach patients with acute coronary syndromes with the idea that they are dealing with a straightforward mechanical configuration. They operate under the premise that there is a mechanical obstruction and, therefore, the solution is mechanical. The basic biology of coronary atherosclerosis, however, cannot be addressed by surgical or percutaneous revascularization. Atherosclerosis is an inflammatory disease<sup>9</sup> and, as is well known in the field of rheumatology, there are few mechanical solutions to inflammatory disease.

Ross, among others,<sup>9-13</sup> revealed the complexity of the clinical situation for patients with the acute coronary syndrome. In the response-to-injury hypothesis of atherosclerosis, the inflammatory response is followed by a fibroproliferative response that begins as a protective mechanism, but with time may become excessive. If allowed to continue, the injury in its excess becomes the disease itself.<sup>9</sup>

Continued plaque growth is a causative factor in the clinical symptoms of coronary heart disease; however, most clinical symptoms, including angina, MI, and death, occur as a result of thrombus formation that is large enough to protrude into the vessel lumen and acutely decrease blood flow. Acute thrombosis primarily results from plaque rupture or from erosion of a fibrous atherosclerotic plaque.<sup>14,15</sup> Plaque instability is closely related to the degree of inflammation. The likelihood of a clinical ischemic event is related to the number of vulnerable lesions present; but one single

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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.

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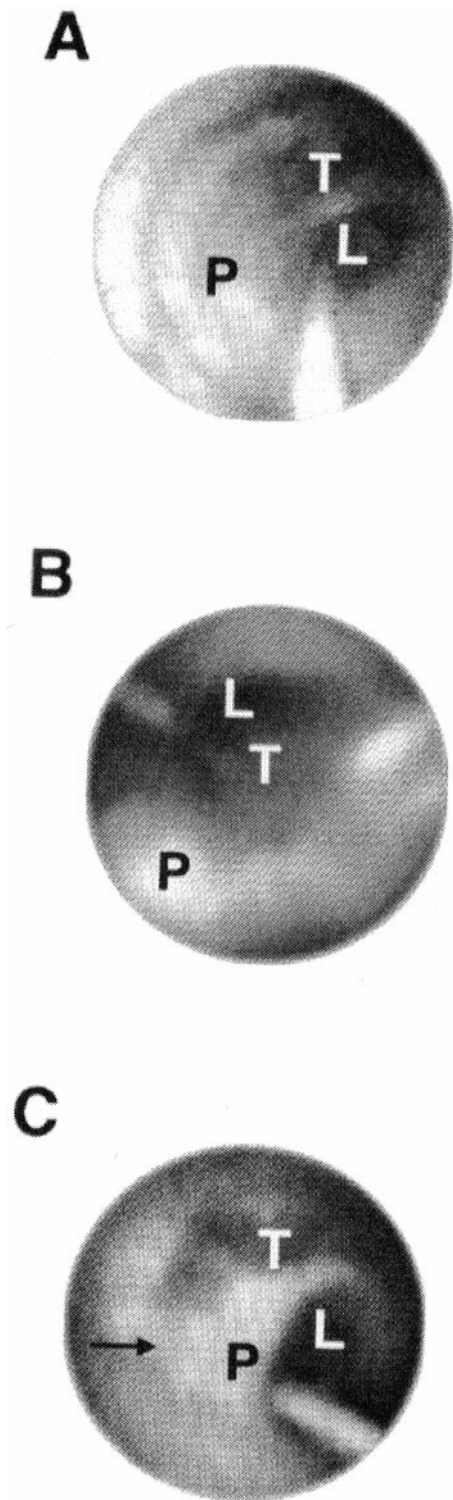
rupture-prone lesion can lead to death. Most ischemic events result from lesions causing only mild or moderate stenosis because those lesions are more numerous in the arterial tree than those causing severe obstruction.

The appearance of culprit lesions on angiography and angioscopy is often very complex.<sup>16,17</sup> The work of Van Belle et al<sup>18</sup> reminds us that, in patients with acute coronary syndromes, the results after thrombolysis are still less than optimal. These investigators used angioscopy to observe the morphologic characteristics of infarct-related lesions in 56 patients, 40 of whom had initially received a thrombolytic agent. Angioscopy was performed between 24 hours and 4 weeks after an acute MI and before any mechanical revascularization procedure. Angioscopic evaluation included assessment of the shape of the narrowing, plaque color, and presence of thrombus (Figure 1). Use of a thrombolytic agent at the onset of MI was associated with a reduction in thrombus size, but not with a decreased frequency of plaque containing thrombi. Interestingly, more frequently ulcerated plaques were seen with use of a thrombolytic agent (45% vs 16%,  $p = 0.06$ ). Characteristics of plaque instability seen on angioscopy lasted for 1 month, even in asymptomatic patients and in those treated with thrombolysis. This persistence of plaque instability may explain the high rate of restenosis and reocclusion with angioplasty for recent infarct-related lesions, as well as late vessel reocclusion after successful thrombolysis.

## MEDICAL THERAPY

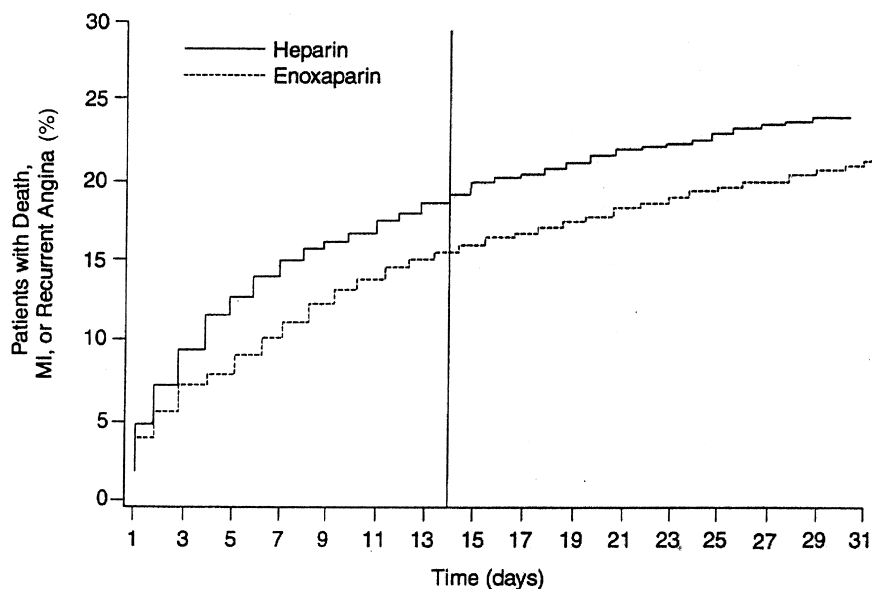
**Heparin:** Heparin has long been recommended in the management of patients with unstable angina and non-Q-wave MI.<sup>19</sup> Despite its widespread use, unfractionated heparin has several important disadvantages, such as an inability to inhibit clot-bound thrombin and a variable anticoagulant effect, which necessitates frequent monitoring and adjustment of dosage schedules. Because of low and variable bioavailability, heparin is usually delivered intravenously instead of subcutaneously. It is sensitive to the inhibitory effects of platelet factor 4 and also has an associated risk of thrombocytopenia and thrombosis.<sup>20–22</sup>

**Low-molecular-weight heparins:** Low-molecular-weight heparins have the advantage of a predictable anticoagulant response to a given dosage and thus may be administered through a subcutaneous route. Several clinical trials have been conducted in recent years to compare standard heparin given over 3–8 days with low-molecular-weight heparin given subcutaneously twice a day. In the Fragmin during Instability in Coronary artery disease (FRIC) and FRAXiparine in Ischaemic Syndrome (FRAXIS) trials,<sup>23,24</sup> the 2 regimens had similar effectiveness. Low-molecular-weight heparins have been shown to be superior to unfractionated heparins in the management of unstable angina and non-Q-wave MI in 2 other trials: the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE)<sup>1</sup> and Thrombolysis in Myocardial Infarction (TIMI) 11B.<sup>2</sup>



**FIGURE 1.** Coronary angioscopic findings. A, Plaque (P) with a lining thrombus (T). B, Plaque (P) with a large protruding thrombus (T). C, Predominantly white plaque (P) with a localized yellow area (arrow) and an adjacent lining thrombus (T). L indicates lumen. (Reprinted with permission from *Circulation*.<sup>18</sup>)

The ESSENCE trial<sup>1</sup> underscored the value of the newer antithrombotic regimens in helping stabilize patients until the medications reached their full effect. This trial showed that treatment with enoxaparin, a



**FIGURE 2.** From the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events (ESSENCE) trial, Kaplan-Meier plots of time to a first event during a period of 30 days of heparin or enoxaparin treatment with regard to the composite endpoint of death, myocardial infarction (MI), or recurrent angina. (Reprinted with permission from *Am J Cardiol*.<sup>35</sup>)

low-molecular-weight heparin, had superiority over unfractionated heparin with a treatment effect that was durable over time. The simple medical therapy of aspirin and enoxaparin, administered for an average of 2½ days, resulted in a significant reduction in the need for revascularization altogether by effectively reducing the number of patients with recurrent or refractory chest pain. The study was a double-blind, placebo-controlled study in which 3,171 patients with angina at rest or non-Q-wave myocardial MI were assigned to receive either enoxaparin (1 mg/kg, every 12 hours, subcutaneously) or continuous intravenous unfractionated heparin (bolus of 5,000 U, followed by continuous infusion at dosages adjusted to the activated partial thromboplastin time). Therapy was administered for at least 48 hours to a maximum of 8 days. Important coronary endpoints were recorded for 30 days. The incidence of the primary composite endpoint of MI, death, or recurrent angina decreased from 19.8% with unfractionated heparin to 16.6% with enoxaparin ( $p = 0.019$ ) after 14 days. The risk of the composite endpoint remained significantly lower at 30 days (23.3% with unfractionated heparin vs 19.8% with enoxaparin;  $p = 0.016$ ; Figure 2) and at 1 year (35.7% vs 32.0%;  $p = 0.022$ ).<sup>1,25</sup> The rate of revascularization procedures was significantly lower with enoxaparin (27.1%) compared with unfractionated heparin (32.2%;  $p = 0.001$ ).

Montalescot et al<sup>26</sup> in France conducted a substudy of the ESSENCE trial in which they provided further evidence of what could be accomplished with adequate antithrombotic therapy. This group looked at the predictive value of 5 biologic indicators of inflammation, thrombogenesis, vasoconstriction, and myocar-

dial necrosis. The markers, C-reactive protein, fibrinogen, von Willebrand factor antigen, endothelin-1, and troponin I, were measured on admission and 48 hours later. The effects of enoxaparin and unfractionated heparin on those markers were examined 48 hours after treatment. The increase of von Willebrand factor, a marker of the degree of activation of platelets, over the 48-hour period was a significant and independent predictor of the composite endpoint of death, MI, recurrent angina, or revascularization both at 14 days and 30 days. Baseline levels of von Willebrand factor that increased over the 48 hours after admission revealed the presence of an ongoing inflammatory response. The study confirmed that there is a significant acute-phase response occurring in the initial hours of evolving unstable coronary disease. The antithrombotic therapy of aspirin and enoxaparin could effect passivation of the platelets, however, by minimizing the likelihood that activated platelets would continue to release von Willebrand factor as they did in the heparin-treated patients. In the patients randomized to receive unfractionated heparin, the von Willebrand factor plasma levels increased dramatically over 48 hours, whereas the response appeared to be blunted in patients receiving enoxaparin (Figure 3).

The value of the newer medical therapies can be appreciated without a long waiting period. Results from the TIMI 11B study showed a significant, meaningful reduction in clinical events after enoxaparin administration within 48 hours of treatment in patients with unstable angina and non-Q-wave MI.<sup>2</sup> Enoxaparin was shown to be superior to unfractionated heparin in reducing the composite endpoint of death and serious cardiac ischemic events (Figure 4).<sup>2</sup> In the trial,

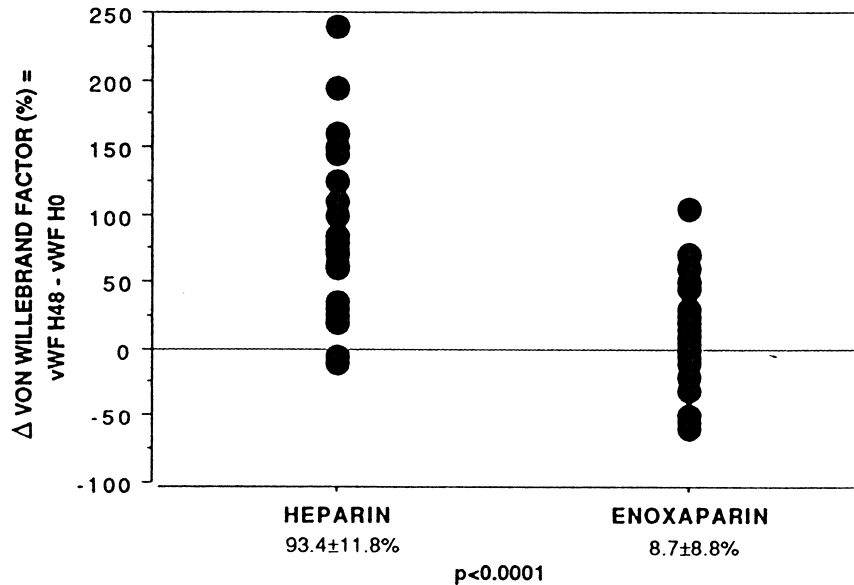


FIGURE 3. Absolute changes of von Willebrand factors (vWF) levels (%) over 48 hours (vWF level at 48 hours [%]) in patients randomly assigned to receive unfractionated heparin or enoxaparin in the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events (ESSENCE) trial. (Reprinted with permission from *Circulation*.<sup>26</sup>)

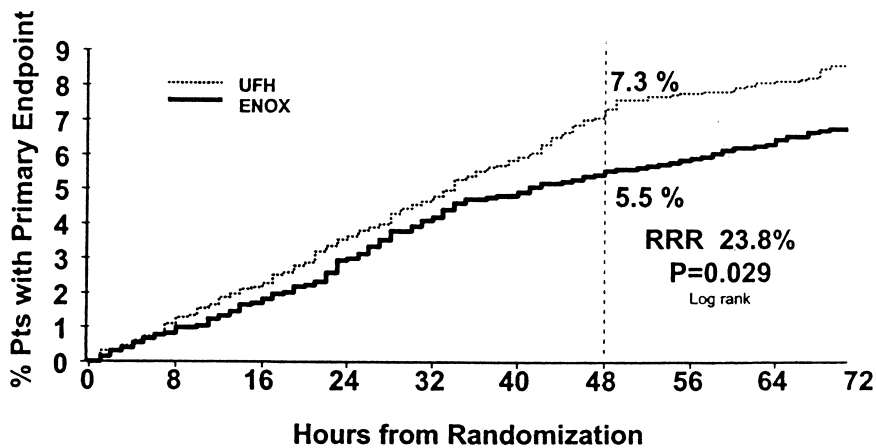


FIGURE 4. Kaplan-Meier plots of time to first event of primary endpoint of death, myocardial infarction (MI), or urgent revascularization over early days of treatment, from the TIMI 11B trial. Direct comparison of intravenous unfractionated heparin (UFH) and subcutaneous enoxaparin (ENOX) is shown. Pts = patients; RRR = relative risk reduction. (Reprinted with permission from *Circulation*.<sup>2</sup>)

3,910 patients were randomized to receive intravenous unfractionated heparin for  $\geq 72$  hours followed by subcutaneous placebo injections, or uninterrupted antithrombin therapy with enoxaparin during both the acute and outpatient phases of treatment. With regard to the outpatient phase, there was a durable treatment effect in that the initial treatment benefit seen with enoxaparin was sustained through 43 days (Figure 5).

Neither the ESSENCE nor the TIMI 11B trial was designed with sufficient power to show statistically significant treatment effects of enoxaparin on endpoints other than the composite ones used in the individual trials. Therefore a meta-analysis of the 2

trials was done by Antman et al<sup>27</sup> to provide a stronger statistical conclusion on the treatment effects, particularly the incidence of death and nonfatal MI, as well as major hemorrhage. Treatment effects at days 2, 8, 14, and 43 were expressed as the odds ratios (OR) and 95% confidence intervals (CI) for enoxaparin versus unfractionated heparin. In the meta-analysis, compared with unfractionated heparin, enoxaparin was associated with a 20% relative reduction in rates of death and MI during the first 7–14 days. The treatment benefit of enoxaparin occurred within 48 hours and was persistent; the treatment effect was similar at day 2 and day 43 (Figures 6 and 7). Although there was no

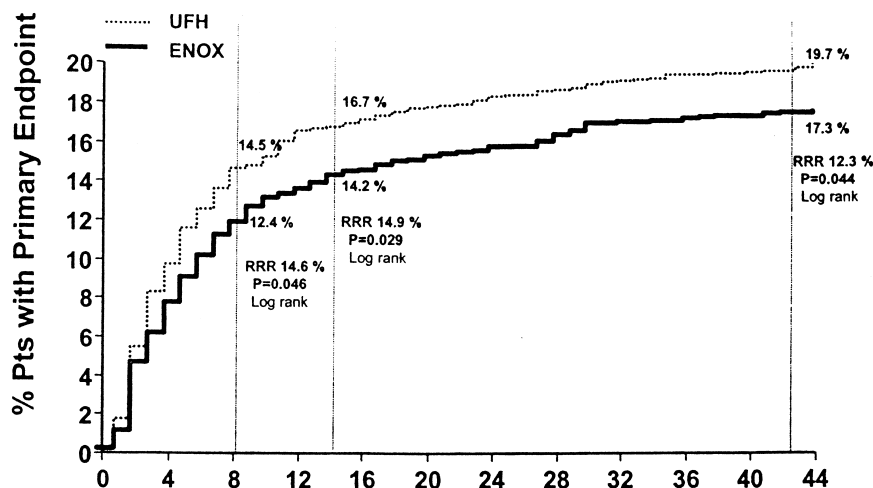


FIGURE 5. Kaplan-Meier plots of time to first event of primary endpoint through 43 days, from the Thrombolysis in Myocardial Ischemia (TIMI) 11B trial. Vertical dashed lines indicate comparisons at day 8 (end of acute phase), day 14 (for comparison with primary endpoint of the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events [ESSENCE] trial), and day 43 (end of chronic phase). Abbreviations as in Figure 4. (Reprinted with permission from *Circulation*.<sup>2</sup>)

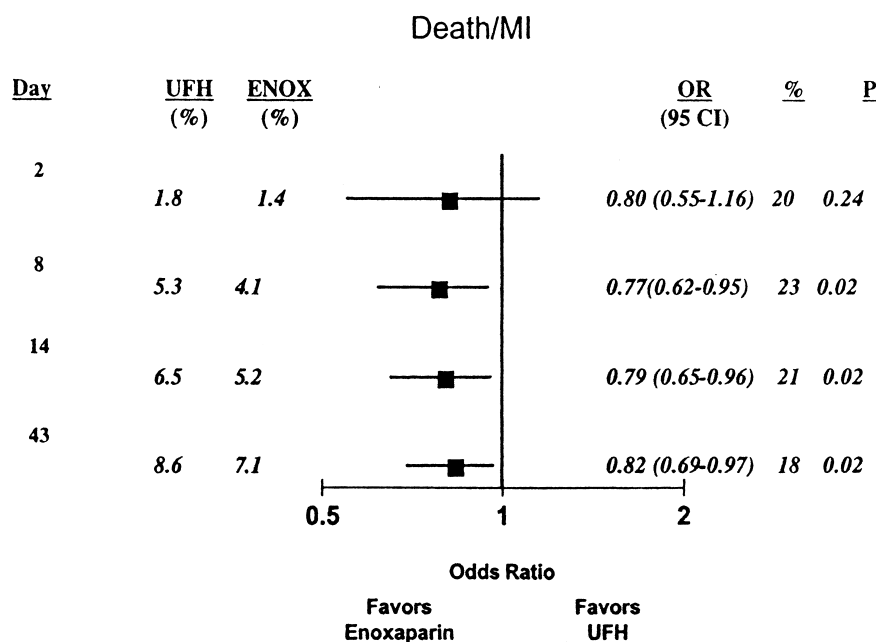


FIGURE 6. Meta-analysis of the treatment effect of enoxaparin (ENOX) versus unfractionated heparin (UFH) on death and nonfatal myocardial infarction at time points shown. Point estimates of odds ratios (OR) for treatment effect are shown as squares, and 95% confidence intervals (CI) are represented by width of horizontal lines. (Reprinted with permission from *Circulation*.<sup>27</sup>)

increase in major hemorrhage in the early phase, minor hemorrhaging did increase significantly during that period.

**Glycoprotein IIb/IIIa receptor blockade:** The glycoprotein IIb/IIIa receptor blockers also provide early protection against life-threatening cardiac complications in patients with acute coronary syndromes without ST-segment elevation. Regardless of the respon-

sible stimulus for platelet activation and aggregation, platelet glycoprotein IIb/IIIa receptor activation is the key factor in thrombus formation. The role of platelet inhibitors for suppressing adverse cardiac events in the period before percutaneous coronary intervention has been highlighted in 3 trials; each used triple anti-thrombotic treatment, adding a glycoprotein IIb/IIIa inhibitor to aspirin and heparin.<sup>3-5</sup> The Chimeric 7E3

## Death/MI/Urgent Revascularization

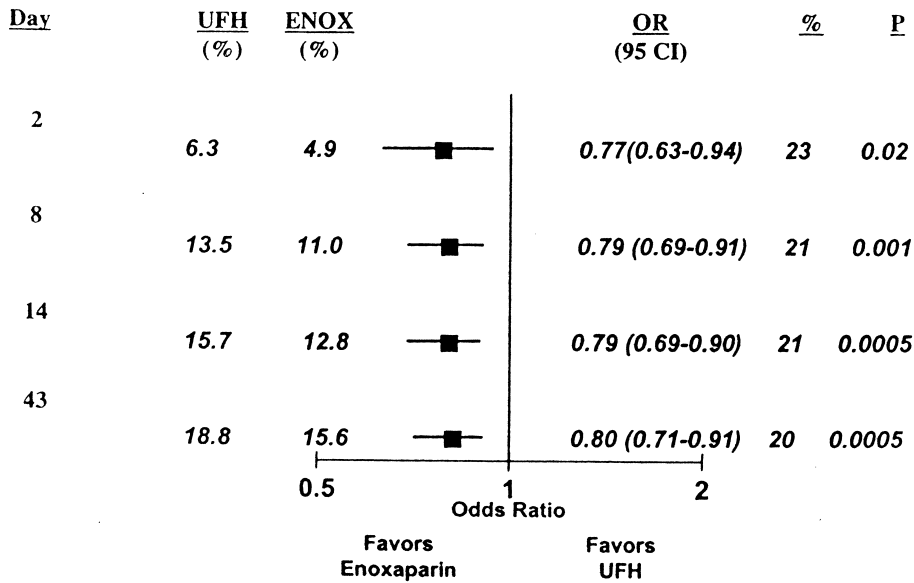


FIGURE 7. Meta-analysis of treatment effect of enoxaparin (ENOX) versus unfractionated heparin (UFH) on composite endpoint of death/myocardial infarction (MI)/urgent revascularization at time points shown. Arrangement of data as in Figure 6. CI = confidence interval; OR = odds ratio. (Reprinted with permission from *Circulation*.<sup>27</sup>)

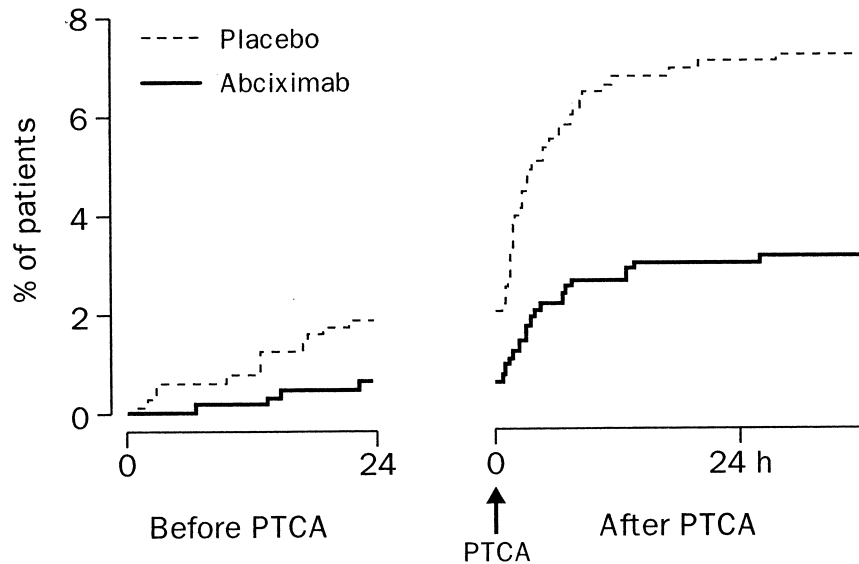
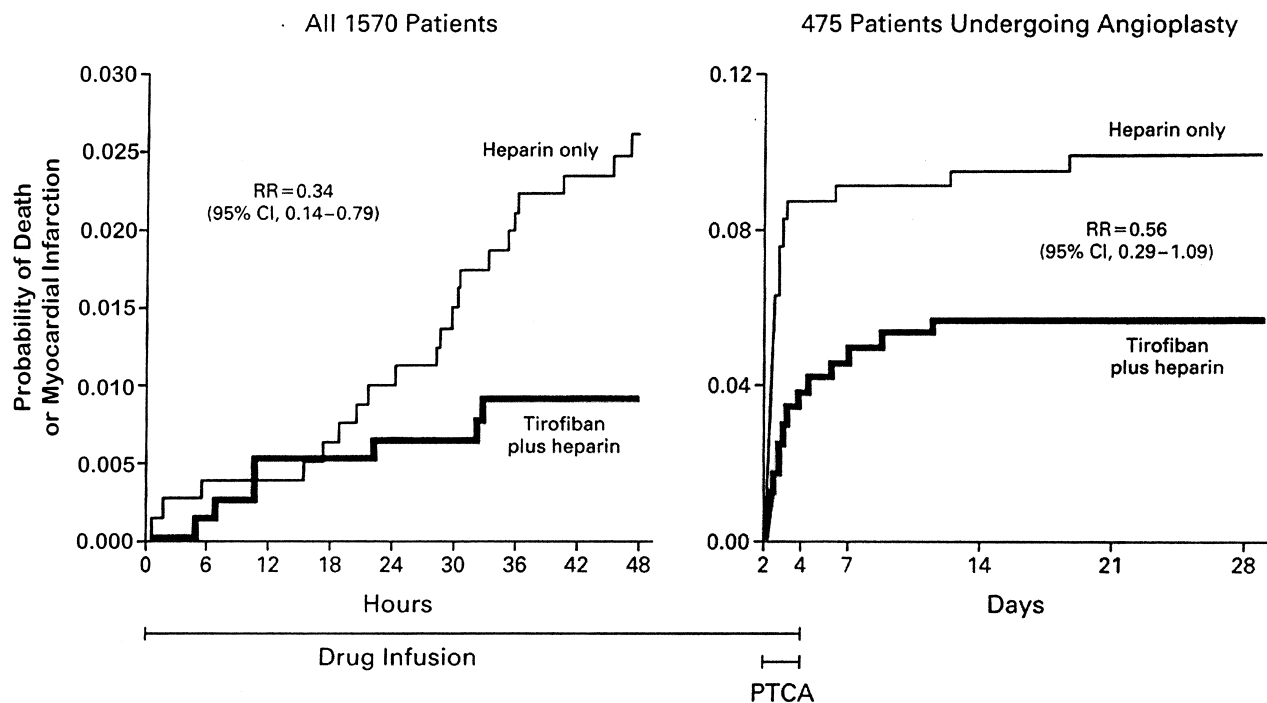


FIGURE 8. From the Chimeric 7E3 AntiPlatlet in Unstable Angina Refractory to standard treatment (CAPTURE) study, development of myocardial infarction (MI) during treatment with abciximab or placebo, before and in association with percutaneous transluminal coronary angioplasty (PTCA). (Reprinted with permission from *Lancet*.<sup>3</sup> Copyright © by the Lancet Ltd., 1997.)

AntiPlatlet in Unstable Angina Refractory to standard treatment (CAPTURE) trial<sup>3</sup> was the first to highlight the potential beneficial effect of treatment for 18–24 hours with the glycoprotein IIb/IIIa receptor antagonist abciximab before percutaneous transluminal coronary angioplasty (PTCA) in patients with refractory unstable angina. CAPTURE was a multicenter, randomized placebo-controlled trial that en-

rolled 1,266 patients. Although at the end of the 24-hour pretreatment period, the difference did not reach statistical significance, the abciximab-treated group demonstrated a strong trend toward a lower event rate before intervention. Figure 8 shows the percentages of patients in each group who developed MI before and in association with PTCA. As seen in Figure 8, there is an early separation between the 2



**FIGURE 9.** From the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) study, Kaplan-Meier curves showing cumulative incidence of death or myocardial infarction (MI) among patients randomly assigned to heparin or to tirofiban plus heparin. The left panel shows events during the initial 48 hours of medical treatment among all 1,570 patients in the 2 groups. The right-hand panel shows the cumulative incidence of death or MI from the time of the procedure to 30 days after randomization among 475 patients who underwent percutaneous transluminal coronary angioplasty (PTCA). CI = confidence interval; RR = risk ratio. (Reprinted with permission from *N Engl J Med*.<sup>4</sup> Copyright© Massachusetts Medical Society. All rights reserved.)

curves, underscoring the fact that suppression of ischemic events can be achieved before the use of mechanical intervention.

In the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and symptoms (PRISM-PLUS)<sup>4</sup> trial, investigators identified a clear and significant difference in outcome in the 48 hours before percutaneous coronary intervention, as well as in the several days before coronary bypass surgery in patients treated with the glycoprotein IIb/IIIa receptor tirofiban.<sup>4</sup> PRISM-PLUS was a double-blind study in which 1,915 patients were randomly assigned to receive tirofiban, heparin, or tirofiban plus heparin. Patients could receive aspirin if its use was not contraindicated. Study drugs were infused for a mean ( $\pm$  SD) of  $71.3 \pm 20$  hours; angiography and coronary angioplasty were performed when indicated after 48 hours. The composite primary endpoint was death, MI, or refractory ischemia within 7 days after randomization. The patients treated with triple therapy demonstrated a significantly lower event rate after 48 hours, but before coronary intervention. The risk reduction for death or MI at the end of the pretreatment phase was 34%. Triple therapy with aspirin, unfractionated heparin, and tirofiban after 48 hours afforded an impressive reduction in clinical events before any mechanical intervention, and there was a very dramatic blunting of recurrent ischemic events (Figure 9).

Apart from the general clinical outcome of the

PRISM-PLUS trial, monitoring troponin levels in the patients treated with triple therapy revealed a blunted increase in their troponin level.<sup>28</sup> Heesch et al<sup>28</sup> measured serial troponin I levels over a 24-hour period after trial enrollment in PRISM-PLUS patients. Whereas baseline troponin I levels were similar between the 2 groups, the peak troponin I level was significantly higher in the heparin group ( $15.5 \pm 29.1$  ng/mL) than in the group receiving combination therapy ( $5.2 \pm 8.3$  ng/mL,  $p = 0.017$ ). Mean troponin I levels over the initial 24-hour period were  $8.5 \pm 14.8$  for the heparin group versus  $3.2 \pm 5.0$  ng/mL for the combination group ( $p = 0.016$ ). Myocardial infarction was essentially avoided in the patients receiving combination therapy; at least, there was only small myonecrosis. In the patients treated with conventional therapy, however, there was no appreciable benefit.

In a landmark angiographic study from the PRISM-PLUS trial, Zhao et al<sup>29</sup> sought to characterize the effects of glycoprotein IIb/IIIa blockade on culprit lesions in patients with unstable angina or non-Q-wave MI. This is the largest prospective study undertaken to examine the angiographic characteristics of culprit lesions and their prognostic significance. The intraluminal morphology and the intraluminal thrombus load in the culprit vessels were examined in 1,491 patients enrolled in the trial. Each of those patients had a readable film obtained a median of 65 hours after randomization. The combination of tirofiban plus heparin compared with heparin alone resulted in sig-

nificant reduction of the intracoronary thrombus burden of the culprit lesions (OR = 0.77,  $p = 0.022$ ). In addition, the combination therapy improved the perfusion grade (OR = 0.65,  $p = 0.002$ ) and decreased the severity of the obstruction ( $p = 0.037$ ). However, it did not influence the severity of the underlying plaque.

Earlier, the CAPTURE investigators<sup>3</sup> suggested some intraluminal improvement after treatment with abciximab. The patients treated with triple therapy had a significantly lower rate of large or moderate intraluminal thrombus compared with the patients treated for 48 hours with conventional aspirin and unfractionated heparin. Clearly, this reveals that a newer medical therapy is enhancing endogenous thrombolysis, without mechanical intervention or a lytic agent that may be associated with intracerebral hemorrhage.

In the Platelet IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) study,<sup>5</sup> the glycoprotein IIb/IIIa receptor eptifibatid was also shown to have a beneficial effect in patients during the pretreatment phase (0–72 hours) before a coronary intervention. The PURSUIT trial, a multicenter study with enrollment of 10,948 patients, was undertaken to determine whether eptifibatid would be superior to heparin plus aspirin in reducing the frequency of adverse outcomes in patients without persistent ST-segment elevation MI. The primary endpoint was a composite of death and nonfatal MI up to 30 days after the index event. Data from the trial underscore the idea that passivation can take place either at shorter time intervals or longer time intervals, but when this is done, agents must be used that provide value beyond that of aspirin and unfractionated heparin. In the PURSUIT trial, the triple therapy afforded a benefit, irrespective of how long it was given. Benefit was shown within 4–7 hours of initiation of therapy. Addition of the glycoprotein IIb/IIIa inhibitor eptifibatid to the regimen produced a 15–20% relative reduction in death and MI.

**Hydroxy-methylglutaryl coenzyme A reductase inhibitors:** Another approach that may offer value in the context of acute administration of novel medical treatments for acute coronary syndromes is the administration of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors, or “statins.” These agents have proven benefits in lowering low-density lipoprotein (LDL) cholesterol, but also have been shown to exhibit pleiotropic effects on many components of atherosclerosis, including plaque thrombogenicity, cellular migration, endothelial function, and thrombotic tendency.<sup>30</sup> The mechanisms behind the benefit of statin therapy on endothelial dysfunction induced by hypercholesterolemia are still unclear, but one explanation centers on nitric-oxide-dependent mechanisms.<sup>30,31</sup>

One recent study showed improvement in endothelial function in patients with acute coronary syndromes who were given pravastatin therapy for 6 weeks.<sup>32</sup> In another study, preoperative lipid control with simvastatin was shown to reduce thrombocytosis

and thrombotic complications after coronary artery bypass surgery.<sup>33</sup>

Further research may indeed establish a role for statin therapy in the treatment of acute coronary syndromes. One trial currently underway, the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial, will evaluate the effect of pharmacologic cholesterol lowering on early recurrent ischemic events.<sup>34</sup> Within 1–4 days after patients present with unstable angina and non-Q-wave MI, they will be randomly assigned to receive atorvastatin, 80 mg/day, or placebo in a double-blind fashion. During a 16-week follow-up period, the primary outcome measure will be time to occurrence of an ischemic event: death, nonfatal acute MI, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischemia requiring emergency hospitalization. Results of this study will help determine the usefulness of early intervention with cholesterol lowering in acute coronary syndromes. Additional trials with simvastatin (Aggrastat to Zocor; A to Z) and cervistatin are underway.

## CONCLUSION

Both the low-molecular-weight heparin enoxaparin and glycoprotein IIb/IIIa receptor inhibitors have shown the potential for calming the plaque before percutaneous coronary intervention or other revascularization procedures are undertaken in patients with acute coronary syndromes. Statin therapy may also have an important role in combination therapy in the future. If clinicians choose the approach of early intervention, they should consider use of the newer, stronger antithrombotic agents—not traditional therapies. There is a whole host of newer agents that may be administered in adjunctive capacities early in the process of evolving acute coronary syndromes to allow passivation of the plaque and, importantly, prevent serious clinical events.

1. 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 Group. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. *N Engl J Med* 1997;337:447–452.

2. 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 11B Investigators. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI) 11B Trial. *Circulation* 1999;100:1593–1601.

3. The CAPTURE Investigators. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE study. *Lancet* 1997;349:1429–1435.

4. 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.

5. 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.

6. 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.

7. 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.

- Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy: Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial Investigators. *N Engl J Med* 1998;338:1785-1792.
8. Deutsch E. The emerging role of low-molecular-weight heparin and antiplatelet therapies in the cardiac catheterization laboratory. *Am Heart J* 1999;138:S577-S585.
  9. Ross R. Atherosclerosis: an inflammatory disease. *N Engl J Med* 1999;340:115-126.
  10. Davies MJ. Pathology of coronary atherosclerosis. In: Alexander RW, Schlant RC, Fuster V, eds. *Hurst's The Heart, Arteries and Veins*, ed. 9, vol. 1. New York: McGraw-Hill, 1998:1161-1173.
  11. Libby P. Molecular bases of the acute coronary syndromes. *Circulation* 1995;91:2844-2850.
  12. Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. *Nature* 1993;362:801-809.
  13. Ross R. Rous-Whipple Award Lecture. Atherosclerosis: a defense mechanism gone awry. *Am J Pathol* 1993;143:987-1002.
  14. Fuster V, Badimon J, Badimon L. Clinical-pathological correlations of coronary artery disease and the acute coronary syndromes. *Circulation* 1992;86(suppl III):III-1-III-11.
  15. Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes (part 2). *N Engl J Med* 1992;326:310-318.
  16. Mizuno K, Satumora K, Miyamoto A. Angiographic evaluation of coronary artery thrombi in acute coronary syndromes. *N Engl J Med* 1992;326:287-291.
  17. The TIMI IIIA Investigators. Early effects of tissue-type plasminogen activator added to conventional therapy on the culprit coronary lesion in patients presenting with ischemic cardiac pain at rest: results of the Thrombolysis in Myocardial Ischemia (TIMI) Trial. *Circulation* 1993;87:38-52.
  18. Van Belle E, Lablanche J-M, Bauters C, Renaud N, McFadden EP, Bertrand ME. Coronary angiographic findings in the infarct-related vessel within 1 month of acute myocardial infarction: natural history and effect of thrombolysis. *Circulation* 1998;97:26-33.
  19. Braunwald E, Mark DB, Jones RH, Cheitlin MD, Fuster V, McCauley KM, Edwards C, Green LA, Mushlin AI, Swain JA, et al. Unstable Angina: Diagnosis and Management. Rockville, MD: Agency for Health Care Policy and Research and the National Heart, Lung, and Blood Institute, Public Health Service, US Dept of Health and Human Services; 1994. Clinical Practice Guideline Number 10.
  20. Weitz JI. Low-molecular-weight heparins. *N Engl J Med* 1997;337:688-698.
  21. Antman EM, Cohen M. New antithrombin agents in acute coronary syndromes. *Am Heart J* 1999;138:S563-S569.
  22. Theroux P, Waters D, Lam J, Juneau M, McCans J. Reactivation of unstable angina after the discontinuation of heparin. *N Engl J Med* 1992;327:141-145.
  23. Klein W, Buchwald A, Hillis SE, Monrad S, Sanz G, Turpie AGG, van der Meer J, Olaisson E, Undeland S, Ludwig K, for the FRIC Investigators. 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.
  24. FRAXIS Study Group. Comparison of two treatment durations (6 days and 14 days) of a low molecular weight heparin with a 6-day treatment of unfractionated heparin in the initial management of unstable angina or non-Q-wave myocardial infarction: FRAXIS: (Fraxiparine in Ischaemic Syndrome). *Eur Heart J* 1999;20:1553-1562.
  25. Goodman S, Cohen M, Bigonzi F, Le Louer V, Radley D, Fromell GJ, Demers C, Gurfinkel EP, Turpie AGG, Langer A, Califf RM, Fox KAA, for the ESSENCE study group. Randomized trial of low molecular weight heparin (enoxaparin) versus heparin for unstable coronary disease: one year results of the ESSENCE Study. *J Am Coll Cardiol* 2000;36:693-698.
  26. Montalescot G, Phillippe F, Ankri A, Vicaut E, Bearez E, Carrie D, Flammang D, Dutoit A, Carayon A, et al, for the French Investigators of the ESSENCE trial. Early increase of von Willebrand factor predicts adverse outcome in unstable coronary artery disease: beneficial effects of enoxaparin. French Investigators of the ESSENCE Trial. *Circulation* 1998;98:294-299.
  27. Antman EM, Cohen M, Radley D, McCabe C, Rush J, Premmereur J, Braunwald E, for the TIMI 11B (Thrombolysis in Myocardial Infarction) and ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events) Investigators. 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.
  28. Heesch C, Hamm CW, Goldmann B, Deu A, Langenbrink L, White HD. Troponin concentrations for stratification of patients with acute coronary syndromes in relation to therapeutic efficacy of tirofiban. PRISM Study Investigators. Platelet Receptor Inhibition in Ischemic Syndrome Management. *Lancet* 1999;354:1757-1762.
  29. Zhao X-Q, Theroux P, Snapinn SM, Sax FL, for the PRISM-PLUS Investigators. Intracoronary thrombus and platelet glycoprotein IIb/IIIa receptor blockade with tirofiban in unstable angina or non-Q-wave myocardial infarction: angiographic results from the PRISM-PLUS Trial (Platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms). *Circulation* 1999;100:1609-1615.
  30. Vaughn CJ, Gotto AM Jr, Basson CT. The evolving role of statins in the management of atherosclerosis. *J Am Coll Cardiol* 2000;35:1-10.
  31. Aengevaeren WR. Beyond lipids: the role of the endothelium in coronary artery disease. *Atherosclerosis* 1999;147(suppl 1):S11-S16.
  32. Dupuis J, Tardif JC, Cernacek P, Theroux P. Cholesterol reduction rapidly improved endothelial function after acute coronary syndromes: the RECIFE (reduction of cholesterol in ischemia and function of the endothelium) trial. *Circulation* 1999;99:3227-3233.
  33. Christenson JT. Preoperative lipid-control with simvastatin reduces the risk of postoperative thrombocytosis and thrombotic complications following CABG. *Eur J Cardiothorac Surg* 1999;15:394-399.
  34. Schwartz GG, Oliver MF, Ezekowitz MD, Ganz P, Waters D, Kane JP, Texter M, Pressler ML, Black D, Chaitman BR, Olsson AG. Rationale and design of the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study that evaluates atorvastatin in unstable angina pectoris and in non-Q-wave acute myocardial infarction. *Am J Cardiol* 1998;81:578-581.
  35. Fox KAA. Implications of the Organization to Assess Strategies for Ischemic Syndromes-2 (OASIS-2) study and the results in the context of other trials. *Am J Cardiol* 1999;84(suppl):26M-31M.