



**EDUCATIONAL OBJECTIVE:** Readers will manage acute coronary syndromes according to evidence gained from clinical trials

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# Managing acute coronary syndromes: Decades of progress

## ABSTRACT

In managing acute coronary syndromes, physicians can draw on a large body of evidence from clinical trials. This article reviews clinical trials that inform current standards of practice regarding reperfusion, aggressive vs conservative initial approaches, and the appropriate use of aspirin, dual antiplatelet therapy, glycoprotein IIb/IIIa antagonists, anticoagulants, and statins.

## KEY POINTS

For acute ST-elevation myocardial infarction, primary percutaneous coronary intervention is preferred over fibrinolytic therapy if it is available within 90 minutes of first medical contact.

For non-ST-elevation acute coronary syndromes, either an early invasive or conservative strategy is recommended depending on patient risk and whether intensive medical therapy is available and appropriate.

Daily aspirin therapy is indicated for all patients with acute coronary syndromes unless they have a true aspirin allergy.

Adenosine diphosphate receptor inhibitors—clopidogrel, prasugrel, and ticagrelor—reduce ischemic events but increase bleeding risk and should be used only for patients with no history of stroke or transient ischemic attack.

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**M**OST DECISIONS for managing acute coronary syndromes can be based on ample data from large randomized trials with hard clinical end points, so there is little reason to provide care that is not evidence-based.

This article reviews some of the trials that provide guidance on diagnosing and managing acute coronary syndromes, including the timing of reperfusion and adjunctive therapies in different situations.

## ■ MOST ACUTE CORONARY SYNDROMES ARE NON-ST-ELEVATION CONDITIONS

Acute coronary syndromes range from unstable angina and non-ST-elevation myocardial infarction (NSTEMI) to ST-elevation MI (STEMI), reflecting a continuum of severity of coronary stenosis. The degree of coronary occlusion may ultimately determine whether a patient has unstable angina or MI with or without ST elevation.<sup>1</sup>

The substrate for all of these is vulnerable plaque. Angiographic studies have indicated that in many cases medium-size plaques (30%–40% stenosis) are more likely to rupture than larger, more obstructive ones. Moderate plaques may be vulnerable because they are less mature, with a large lipid core and a thin cap prone to rupture or erode, exposing the thrombogenic subendothelial components.<sup>2</sup>

Because the vulnerability of a coronary plaque may not correlate with the severity of stenosis before the plaque ruptures, stress tests and symptoms may not predict the risk of MI. The key role of thrombosis in the pathogenesis also highlights the importance of antithrombotic therapy in the acute phases of acute coronary syndromes, which can significantly reduce mortality and morbidity rates.

Perhaps because of the widespread use of

aspirin and statins, most patients who currently present with an acute coronary syndrome have either unstable angina or NSTEMI: of about 1.57 million hospital admissions in 2004 for acute coronary syndromes, for example, only 330,000 (21%) were for STEMI.<sup>3</sup>

### ■ DIAGNOSING ACUTE CORONARY SYNDROME

#### Symptoms may not be classic

The classic symptoms of acute coronary syndromes are intense, oppressive chest pressure radiating to the left arm, but nearly any discomfort “between the nose and navel” (eg, including the jaw, arm, and epigastric and abdominal areas) may be an acute coronary syndrome. Associated symptoms may include chest heaviness or burning, radiation to the jaw, neck, shoulder, back, or arms, and dyspnea.

Particularly in older, female, postoperative, or diabetic patients, the presentation may be atypical or “silent,” including nausea or vomiting; breathlessness; sweating; arrhythmias; or lightheadedness. Especially in these groups, symptoms may be mild or subtle, and acute coronary syndrome may manifest only as “not feeling well.”

The differential diagnosis of acute coronary syndromes is broad. Most important to immediately consider are pulmonary embolism and aortic dissection, as they are life-threatening and are treated differently from acute coronary syndromes. Otherwise, it is best to err on the side of caution and treat for an acute coronary syndrome until it is proven otherwise.

#### Electrocardiography is critical

Electrocardiography (ECG) gives valuable information about the location, extent, and prognosis of infarction, and it is critically important for distinguishing STEMI from NSTEMI, with ST elevation classically diagnostic of complete coronary occlusion. Q waves can occur early and do not necessarily signify completed infarction, as traditionally thought. ST depression or T inversion indicates that total coronary occlusion is unlikely unless they are in a pattern of circumflex infarct associated with an enlarging R wave in lead V<sub>1</sub>. An ST elevation in RV<sub>4</sub> indicates right ventricular infarction.

The appearance on ECG may evolve over time, so a patient with atypical symptoms and a nonspecific electrocardiogram should be ob-

served for 24 hours or until more specific criteria develop.

#### Biomarkers in NSTEMI

In MI, cardiac troponin levels begin to rise about 3 hours after the onset of chest pain, and elevations can last for up to 14 days. Levels can also be mildly elevated chronically in patients with renal dysfunction, so positive biomarker tests in that population should be interpreted cautiously.

For STEMI, the opportunity to reperfuse is lost if one waits for cardiac biomarkers to become elevated. But for NSTEMI, they are highly sensitive and specific for identifying patients at high risk and determining who should be treated aggressively. Patients who are biomarker-negative have a better prognosis than patients with identical symptoms and electrocardiograms who are biomarker-positive.

MI is currently defined as a rise in any biomarker (usually troponin) above the 99th percentile for a reference population, with at least one of the following:

- Ischemic symptoms
- New ST/T changes or left bundle branch block
- Pathologic Q waves
- Loss of myocardium or abnormal wall motion seen by imaging
- Intracoronary thrombus.

### ■ REPERFUSION FOR ACUTE STEMI

Because acute coronary syndromes have a common pathophysiology, for the most part, lessons from clinical trials in one syndrome are relevant to the others. However, important differences exist regarding the need for immediate reperfusion in STEMI, since in most cases these patients have total rather than partial occlusion.

#### Fibrinolysis has limitations

The standard of management for STEMI is immediate reperfusion. The goal is to interrupt the wave front of myocardial necrosis, salvage threatened myocardium, and ultimately improve survival.

Five placebo-controlled trials showed a 30% reduction in the death rate in patients who received fibrinolytic therapy within 6 to 12 hours of presentation.<sup>4</sup>

Nearly any symptoms between the nose and the navel can be an acute coronary syndrome

Patients with ST elevation or with new bundle branch block benefit most from fibrinolytic therapy. Those with ST depression, T inversion, or nonspecific changes on ECG do not benefit; they probably do not have complete coronary occlusion, so the prothrombotic or platelet-activating effects of fibrinolytic therapy may make them worse.<sup>5</sup> Further, fibrinolytic therapy poses the risk of intracranial hemorrhage, which, although rare (occurring in up to 1% of cases depending on the drug regimen), is a devastating complication.

In general, absolute contraindications to fibrinolysis include intracranial abnormalities, hemorrhage, and head trauma. An important relative contraindication is uncontrolled blood pressure (> 180/110 mm Hg at any point during hospitalization, including during the immediate presentation). Studies show that even if blood pressure can be controlled, the risk of intracranial hemorrhage is substantially higher, although the risk may not outweigh the benefit of reperfusion, particularly for large infarctions when percutaneous coronary intervention (PCI) is not available as an alternative to fibrinolysis.

### Prompt PCI is preferable to fibrinolysis

If PCI is available on site, there is nearly no role for fibrinolytic therapy. PCI is better than fibrinolytic therapy in terms of the degree of reperfusion, reocclusion, MI recurrence, and mortality rate, and it poses little or no risk of intracranial hemorrhage.<sup>6</sup>

For either fibrinolytic therapy or percutaneous therapy, “time is muscle”: the longer the ischemic time, the higher the mortality rate (relative risk = 1.075 for every 30 minutes of delay,  $P = .041$ ).<sup>7</sup>

At centers that do not have PCI on site, studies (mainly from Europe) have shown that it is better to transport the patient for PCI than to give immediate fibrinolytic therapy.<sup>7,8</sup> But because the centers studied tended to have short transport times (usually 40 minutes or less), it is uncertain whether the results are applicable throughout the United States.

The delay between symptom onset and presentation is also relevant. Reperfusion within the first 1 to 2 hours after the onset of symptoms provides the greatest degree of myocardial salvage and of reduction in the risk of death; the extent of benefit thereafter is substantially

### Studies discussed in this article

**ACUITY**—Acute Catheterization and Urgent Intervention Triage Strategy trial<sup>31</sup>

**CAPRICORN**—Carvedilol Post-infarct Survival Control in Left Ventricular Dysfunction<sup>43</sup>

**COMMIT**—Clopidogrel and Metoprolol in Myocardial Infarction Trial<sup>23,42</sup>

**CURE**—Clopidogrel in Unstable Angina to Prevent Recurrent Events<sup>22</sup>

**CURRENT-OASIS 7**—Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events—Seventh Organization to Assess Strategies in Ischemic Syndromes<sup>21</sup>

**EARLY ACS**—Early vs Delayed, Provisional Eptifibatide in Acute Coronary Syndromes<sup>32</sup>

**EXTRACT-TIMI 25**—Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment—Thrombolysis in Myocardial Infarction 25<sup>35</sup>

**FINESSE**—Facilitated Intervention With Enhanced Reperfusion Speed to Stop Events<sup>33</sup>

**ICTUS**—Invasive Versus Conservative Treatment in Unstable Coronary Syndromes<sup>14</sup>

**ISIS-2**—second International Study of Infarct Survival<sup>20</sup>

**OASIS-5**—fifth Organization to Assess Strategies in Acute Ischemic Syndromes<sup>36,37</sup>

**PLATO**—Platelet Inhibition and Patient Outcomes<sup>28</sup>

**PROVE-IT TIMI 22**—Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22<sup>45</sup>

**SYNERGY**—Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa Inhibitors<sup>34</sup>

**TACTICS**—Treat Angina With Aggrastat and Determine Cost of Therapy With an Invasive or Conservative Strategy<sup>13</sup>

**TIMACS**—Early Versus Delayed Timing of Intervention in Patients With Acute Coronary Syndromes<sup>17</sup>

**TRITON-TIMI 38**—Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel—Thrombolysis in Myocardial Infarction 38<sup>27</sup>

less. As a result, patients who present very early after symptom onset have the most to lose if their reperfusion is delayed by even a few more hours, whereas patients who have already experienced several hours of pain are affected less by additional delay.<sup>9</sup> Thus, patients presenting within the “golden” 1 or 2 hours after symptoms begin should be considered for fibrinolytic therapy if transfer for PCI cannot be done expeditiously. It is important for hospitals without PCI available on site to have a

system in place for rapid transport of patients when needed.

Guidelines advise that patients with STEMI should undergo PCI rather than receive fibrinolytic therapy as long as PCI is available within 90 minutes of first medical contact. Otherwise, fibrinolysis should be started within 30 minutes.<sup>10</sup> For patients who present several hours after symptom onset, PCI may still be preferable even if the transport time is somewhat longer.

**PCI after fibrinolytic therapy**

In prior decades, PCI immediately after fibrinolytic therapy was associated with an increased risk of bleeding complications and reinfarction. That has changed with improvements in equipment and antithrombotic therapy.

Two large trials conclusively found that routinely transferring high-risk patients for PCI immediately after receiving fibrinolytic therapy (combined half-dose reteplase [Retavase] and abciximab [ReoPro]<sup>11</sup> or full-dose tenecteplase [TNKase]<sup>12</sup>) resulted in much lower rates of ischemic end points without an increase in bleeding complications compared with transferring patients only for rescue PCI after fibrinolytic therapy.

Routine transfer is now the standard of care for high-risk patients after fibrinolytic therapy and probably is best for all patients after an MI.

■ **MANAGING NSTEMI AND UNSTABLE ANGINA**

For patients with NSTEMI, immediate reperfusion is usually not required, although initial triage for “early invasive” vs “initial conservative” management must be done early in the hospital course. Randomized trials have evaluated these two approaches, with most studies in the contemporary era reporting improved outcomes with an early invasive approach.

The **TACTICS trial**,<sup>13</sup> the most important of these, enrolled more than 2,200 patients with unstable angina or NSTEMI and randomized them to an early invasive strategy or a conservative strategy. Overall, results were better with the early invasive strategy.

The **ICTUS trial**.<sup>14</sup> Although several studies showed that an early invasive approach was better, the most recent study using the most

modern practices—the **ICTUS trial**—did not find that it reduced death rates. Most patients eventually underwent angiography and revascularization, but not early on. However, all studies showed that rates of recurrent unstable angina and hospitalization were reduced by an early invasive approach, so revascularization does have a role in stabilizing the patient. But in situations of aggressive medical management with antithrombotic and other therapies, an early conservative approach may be an appropriate alternative for many patients.<sup>15</sup>

The selection of an invasive vs a conservative approach should include a consideration of risk, which can be estimated using a number of criteria, including the Thrombolysis in Myocardial Infarction (TIMI) or the GRACE risk score. When risk was stratified using the TIMI risk score,<sup>16</sup> in the **TACTICS trial**, the higher the risk score, the more likely patients were to benefit from early revascularization.

When an invasive approach is chosen, it does not appear necessary to take patients to catheterization immediately (within 2–24 hours) compared with later during the hospital course.

The **TIMACS trial**,<sup>17</sup> with more than 3,000 patients, tested the benefits of very early vs later revascularization for patients with NSTEMI and unstable angina. Early intervention did not significantly improve outcomes for the primary composite end point of death, MI, and stroke in the overall population enrolled in the trial, but when the secondary end point of refractory ischemia was added in, early intervention was found to be beneficial overall. Moreover, when stratified by risk, high-risk patients significantly benefited from early intervention for the primary end point.

**Guidelines** for NSTEMI and unstable angina continue to prefer an early invasive strategy, particularly for high-risk patients, although a conservative strategy is considered acceptable if patients receive intensive evidence-based medical therapy and remain clinically stable.<sup>18</sup>

■ **ANTITHROMBOTIC THERAPIES**

Once a revascularization strategy has been chosen, adjunctive therapies should be considered. The most important are the antithrombotic therapies.

**In STEMI, the opportunity to reperfuse is lost if one waits for biomarkers to become elevated**

Many drugs target platelet activity. Most important are the thromboxane inhibitor aspirin, the adenosine diphosphate (ADP) receptor antagonists clopidogrel (Plavix), prasugrel (Effient), and ticagrelor (Brilinta), and the glycoprotein (GP) IIb/IIIa antagonists abciximab and eptifibatid (Integrilin). Others, such as thrombin receptor antagonists, are under investigation.<sup>19</sup>

### Aspirin for secondary prevention

Evidence is unequivocal for the benefit of aspirin therapy in patients with established or suspected vascular disease.

The **ISIS-2 trial**<sup>20</sup> compared 35-day mortality rates in 16,000 patients with STEMI who were given aspirin, streptokinase, combined streptokinase and aspirin, or placebo. Mortality rates were reduced by aspirin compared with placebo by an extent similar to that achieved with streptokinase, with a further reduction when aspirin and streptokinase were given together.

Therefore, patients with STEMI should be given aspirin daily indefinitely unless they have true aspirin allergy. The dose is 165 to 325 mg initially and 75 to 162 mg daily thereafter.

For NSTEMI and even for secondary prevention in less-acute situations, a number of smaller trials also provide clear evidence of benefit from aspirin therapy.

The **CURRENT-OASIS 7 trial**<sup>21</sup> showed that low maintenance dosages of aspirin (75–100 mg per day) resulted in the same incidence of ischemic end points (cardiovascular death, MI, or stroke) as higher dosages. Although rates of major bleeding events did not differ, a higher rate of gastrointestinal bleeding was evident at just 30 days in patients taking the higher doses. This large trial clearly established that there is no advantage to daily aspirin doses of more than 100 mg.

### ■ DUAL ANTIPLATELET THERAPY IS STANDARD

Standard practice now is to use aspirin plus another antiplatelet agent that acts by inhibiting either the ADP receptor (for which there is the most evidence) or the GP IIb/IIIa receptor (which is becoming less used). Dual therapy should begin early in patients with acute coronary syndrome.

### Clopidogrel: Well studied with aspirin

The most commonly used ADP antagonist is clopidogrel, a thienopyridine. Much evidence exists for its benefit.

The **CURE trial**<sup>22</sup> randomized more than 12,000 patients with NSTEMI or unstable angina to aspirin plus either clopidogrel or placebo. The incidence of the combined end point of MI, stroke, and cardiovascular death was 20% lower in the clopidogrel group than in the placebo group over 12 months of follow-up. The benefit of clopidogrel began to occur within the first 24 hours after randomization, with a 33% relative risk reduction in the combined end point of cardiovascular death, MI, stroke, and severe ischemia, demonstrating the importance of starting this agent early in the hospital course.

**COMMIT**<sup>23</sup> found a benefit in adding clopidogrel to aspirin in patients with acute STEMI. Although it was only a 30-day trial, significant risk reduction was found in the dual-therapy group for combined death, stroke, or reinfarction. The results of this brief trial were less definitive, but the pathophysiology was similar to non-ST-elevation acute coronary syndromes, so it is reasonable to extrapolate the long-term findings to this setting.

The **CURRENT-OASIS 7 trial**<sup>21</sup> randomized more than 25,000 patients to either clopidogrel in a double dosage (600 mg load, 150 mg/day for 6 days, then 75 mg/day) or standard dosage (300 mg load, 75 mg/day thereafter). Although no overall benefit was found for the higher dosage, a subgroup of more than 17,000 patients who underwent PCI after randomization had a lower risk of developing stent thrombosis. On the other hand, higher doses of clopidogrel caused more major bleeding events.

### Ticagrelor and prasugrel: New alternatives to clopidogrel

The principal limitation of clopidogrel is its metabolism. It is a prodrug, ie, it is not active as taken and must be converted to its active state by cytochrome P450 enzymes in the liver. Patients who bear certain polymorphisms in the genes for these enzymes or who are taking other medications that affect this enzymatic pathway may derive less platelet inhi-

**Nearly no role exists for fibrinolytic therapy if PCI is available on site**

bition from the drug, leading to considerable patient-to-patient variability in the degree of antiplatelet effect.

Alternatives to clopidogrel have been developed that inhibit platelets more intensely, are activated more rapidly, and have less interpatient variability. Available now are ticagrelor and prasugrel.<sup>24</sup> Like clopidogrel, prasugrel is absorbed as an inactive prodrug, but it is efficiently metabolized by esterases to an active form, and then by a simpler step within the liver to its fully active metabolite.<sup>25</sup> Ticagrelor is active as absorbed.<sup>26</sup>

Pharmacodynamically, the two drugs perform almost identically and much faster than clopidogrel, with equilibrium platelet inhibition reached in less than 1 hour. The degree of platelet inhibition is also more—sometimes twice as much—with the new drugs compared with clopidogrel, and the effect is much more consistent between patients.

Both clopidogrel and prasugrel permanently inhibit the platelet ADP receptor, and 3 to 7 days are therefore required for their antiplatelet effects to completely wear off. In contrast, ticagrelor is a reversible inhibitor and its effects wear off more rapidly. Despite achieving a much higher level of platelet inhibition than clopidogrel, ticagrelor's activity falls below that of clopidogrel's by 48 hours of discontinuing the drugs.

**Trial of prasugrel vs clopidogrel**

The TRITON-TIMI 38 trial<sup>27</sup> enrolled more than 13,000 patients with acute coronary syndromes, randomized to receive, either prasugrel or clopidogrel, in addition to aspirin. The patients were all undergoing PCI, so the findings do not apply to patients treated medically with an early conservative approach. The study drug was given only after the decision was made to perform PCI in patients with non-ST-elevation acute coronary syndrome (but given immediately for patients with STEMI, because nearly all those patients undergo PCI).

Prasugrel was clearly beneficial, with a significant 20% lower rate of the combined end point of cardiovascular death, MI, and stroke at 15 months. However, bleeding risk was higher with prasugrel (2.4% vs 1.8%, hazard ratio 1.32, 95% confidence interval 1.02–1.68, *P* = .03). Looking at individual end points,

the advantages of prasugrel were primarily in reducing rates of stent thrombosis and nonfatal MI. Death rates with the two drugs were equivalent, possibly because of the higher risk of bleeding with prasugrel. Bleeding in the prasugrel group was particularly increased in patients who underwent bypass surgery; more patients also needed transfusion.

Subgroup analysis showed that patients with a history of stroke or transient ischemic attack had higher rates of ischemic and bleeding events with prasugrel than with clopidogrel, leading to these being labeled as absolute contraindications to prasugrel. Patients over age 75 or who weighed less than 60 kg experienced excess bleeding risk that closely matched the reduction in ischemic event rates and thus did not have a net benefit with prasugrel.

**Trial of ticagrelor vs clopidogrel**

The PLATO trial<sup>28</sup> included 18,000 patients, of whom 65% underwent revascularization and 35% were treated medically. The drug—clopidogrel or ticagrelor—was given in addition to aspirin at randomization (within 24 hours of symptom onset); this more closely follows clinical practice, in which dual antiplatelet therapy is started as soon as possible. This difference makes the PLATO study more relevant to practice for patients with non-ST-elevation acute coronary syndrome. Also, because they gave the drugs to all patients regardless of whether they were to undergo PCI, this study likely had a higher-risk population, which may be reflected in the higher mortality rate at 30 days (5.9% in the clopidogrel group in the PLATO study vs 3.2% in the clopidogrel group in the TRITON study).

Another important difference between the trials testing prasugrel and ticagrelor is that patients who had already received a thienopyridine were excluded from the prasugrel trial but not from the ticagrelor trial. Nearly half the patients in the ticagrelor group were already taking clopidogrel. The clinical implication is that for patients who arrive from another facility and already have been given clopidogrel, it is safe to give ticagrelor. There is limited information about whether that is also true for prasugrel, although there is no known reason why the safety of adding prasugrel to clopidogrel should be different from that of ticagrelor.

**Other than initially, high doses of aspirin confer no benefit over low doses**

The rate of ischemic events was 20% lower in the ticagrelor group than in the clopidogrel group, importantly including reductions in the incidence of death, MI, and stent thrombosis. There was no increase with ticagrelor compared with clopidogrel in bleeding associated with coronary artery bypass graft surgery, likely because of the more rapid washout of the ticagrelor effect, or in the need for blood transfusions. However, the rate of bleeding unrelated to coronary artery bypass was about 20% higher with ticagrelor.

In summary, more intense platelet inhibition reduces the risk of ischemic events, but, particularly for the irreversible inhibitor prasugrel, at the cost of a higher risk of bleeding. In general, the net benefit of these agents in preventing the irreversible complications of MI and (in the case of ticagrelor) death favor the use of the more intense ADP inhibitors in appropriate patients. Ticagrelor is indicated in patients with acute coronary syndromes undergoing invasive or conservative management; prasugrel is indicated in patients undergoing PCI, but contraindicated in patients with a previous stroke or transient ischemic event. Neither drug is indicated in patients undergoing elective PCI outside the setting of acute coronary syndromes, although these agents may be appropriate in patients with intolerance or allergy to clopidogrel.

### Glycoprotein IIb/IIIa antagonists for select cases only

GP IIb/IIIa antagonists such as abciximab were previously used more commonly than they are today. Now, with routine pretreatment using thienopyridines, their role in acute coronary syndromes is less clear. They still play a role when routine dual antiplatelet therapy is not used, when prasugrel or ticagrelor is not used, and when heparin rather than an alternative antithrombin agent is used.

A meta-analysis<sup>29</sup> of 3,755 patients showed a clear reduction in ischemic complications with abciximab as an adjunct to primary PCI for STEMI in patients treated with heparin.

Kastrati et al<sup>30</sup> found that patients with non-ST-elevation acute coronary syndromes benefited from abciximab at the time of PCI with heparin, even though they had been routinely pretreated with clopidogrel. However, benefits were seen only in high-risk patients who had presented with elevated troponins.

On the other hand, the role of GP IIb/IIIa blockade for “upstream” medical management in patients with acute coronary syndromes has been eroded by several studies.

The **ACUITY trial**<sup>31</sup> randomized more than 9,000 patients to receive either routine treatment with a GP IIb/IIIa inhibitor before angiography or deferred selective use in the catheterization laboratory only for patients undergoing PCI. No significant differences were found in rates of MI and death.

The **Early ACS trial**<sup>32</sup> compared early routine eptifibatid vs delayed, provisional eptifibatid in 9,492 patients with acute coronary syndromes without ST elevation and who were assigned to an invasive strategy. The early-eptifibatid group received two boluses and an infusion of eptifibatid before angiography; the others received a placebo infusion, with provisional eptifibatid after angiography if the patient underwent PCI and was deemed at high risk. No significant difference in rates of death or MI were noted, and the early-eptifibatid group had significantly higher rates of bleeding and need for transfusion.

The **FINESSE trial**<sup>33</sup> also discredited “facilitating” PCI by giving GP IIb/IIIa antagonists in patients with STEMI before arrival in the catheterization laboratory, with no benefit to giving abciximab ahead of time vs in the catheterization laboratory, and with an increased risk of bleeding complications.

These studies have helped narrow the use of GP IIb/IIIa inhibitors to the catheterization laboratory in conjunction with heparin anticoagulation (as compared with bivalirudin [Angiomax]; see below) and only in select or high-risk cases. These drugs are indicated in the medical phase of management only if patients cannot be stabilized by aspirin or ADP inhibition.

### NEWER ANTITHROMBOTICS: ADVANTAGES UNCLEAR

The complex coagulation cascade has a number of components, but only a few are targeted by drugs that are approved and recommended: fondaparinux (Arixtra) and oral factor Xa inhibitors affect the prothrombinase complex (including factor X); bivalirudin and oral factor IIa inhibitors affect thrombin; and heparin

**More platelet inhibition reduces ischemic events but increases bleeding risk**

and the low-molecular-weight heparins inhibit both targets.

### Low-molecular-weight heparins

The SYNERGY trial<sup>34</sup> randomized nearly 10,000 patients with non-ST-elevation acute coronary syndromes at high risk for ischemic cardiac complications managed with an invasive approach to either the low-molecular-weight heparin enoxaparin (Lovenox) or intravenous unfractionated heparin immediately after enrollment. Most patients underwent catheterization and revascularization. No clinical advantage was found for enoxaparin, and bleeding complications were increased.

The EXTRACT-TIMI 25 trial<sup>35</sup> randomized more than 20,000 patients with STEMI who were about to undergo fibrinolysis to receive either enoxaparin throughout hospitalization (average of 8 days) or unfractionated heparin for at least 48 hours. The enoxaparin group had a lower rate of recurrent MI, but it was unclear if the difference was in part attributable to the longer therapy time. The enoxaparin group also had more bleeding.

### Fondaparinux

The OASIS-5 trial<sup>36,37</sup> compared enoxaparin and fondaparinux, an exclusive factor Xa inhibitor, in more than 20,000 patients with unstable angina or NSTEMI. Fondaparinux was associated with a lower risk of death and reinfarction as well as fewer bleeding events. However, the benefits were almost exclusively in patients treated medically. In those undergoing PCI within the first 8 days, no benefit was found, although there was still a significant reduction in major bleeding events. Catheter thrombosis was also increased in patients taking fondaparinux, but only in those who did not receive adequate unfractionated heparin treatment before PCI.

### Bivalirudin superior at time of catheterization

The most significant advance in antithrombotic therapy for patients with acute coronary syndromes is bivalirudin. This drug has a clear role only in the catheterization laboratory, where patients can be switched to it from heparin, low-molecular-weight heparin, or fondaparinux.

Three trials<sup>38-40</sup> evaluated the drug in a total of more than 20,000 patients receiving invasive management of coronary artery disease undergoing PCI for elective indications, NSTEMI, or STEMI.

Results were remarkably similar across the three trials. Patients who were treated with bivalirudin alone had the same rate of ischemic end points at 30 days as those receiving heparin plus a GP IIb/IIIa inhibitor, but bivalirudin was associated with a consistent and significant 40% to 50% lower bleeding risk. For the highest-risk patients, those with STEMI, the bivalirudin group also had a significantly lower risk of death at 1 year.<sup>41</sup>

### OTHER DRUGS: EARLY TREATMENT NO LONGER ROUTINE

Most data for the use of therapies aside from antithrombotics are from studies of patients with STEMI, but findings can logically be extrapolated to those with non-ST-elevation acute coronary syndromes.

### Beta-blockers: Cardiogenic shock a risk

For beta-blockers, many historical trials were done in stable coronary disease, but there are no large trials in the setting of NSTEMI or unstable angina, and only recently have there been large trials for STEMI. Before the availability of recent evidence, standard practice was to treat STEMI routinely with intravenous metoprolol (Lopressor) and then oral metoprolol.

When large studies were finally conducted, the results were sobering.

**COMMIT.**<sup>42</sup> Nearly 46,000 patients with suspected acute MI were randomized to receive either metoprolol (up to 15 mg intravenously, then 200 mg by mouth daily until discharge or for up to 4 weeks in the hospital) or placebo. Surprisingly, although rates of reinfarction and ventricular fibrillation were lower with metoprolol, a higher risk of cardiogenic shock with early beta-blockade offset these benefits and the net mortality rate was not reduced. This study led to a reduction in the early use of beta-blockers in patients with STEMI.

The standard of care has now shifted from beta-blockers in everyone as early as possible after MI to being more cautious in patients with contraindications, including signs of

**Bivalirudin has a clear role only in the catheterization laboratory**

heart failure or a low-output state, or even in those of advanced age or with borderline low blood pressure or a high heart rate. Patients who present late and therefore may have a larger infarct are also at higher risk.

Although the goal should be to ultimately discharge patients on beta-blocker therapy after an MI, there should be no rush to start one early.

### Carvedilol now preferred after STEMI

The CAPRICORN trial<sup>43</sup> randomized nearly 2,000 patients following MI with left ventricular dysfunction (an ejection fraction of 40% or below) to either placebo or the beta-blocker carvedilol (Coreg). Patients taking the drug had a clear reduction in rates of death and reinfarction, leading to this drug becoming the beta-blocker of choice in patients with ventricular dysfunction after STEMI.

### Angiotensin-converting enzyme inhibitors: Early risk of cardiogenic shock

The use of angiotensin-converting enzyme (ACE) inhibitors after MI is also supported by several studies.<sup>44</sup> Two very large studies, one of nearly 60,000 patients and one of nearly 20,000, showed a clear reduction in the mortality rate in those who received an ACE inhibitor. Most of the benefit was in patients with an ejection fraction of less than 40%. On the basis of these trials, ACE inhibitors are indicated for all patients for the first 30 days after MI and then indefinitely for those with left ventricular dysfunction. However, the trial in which an ACE inhibitor was given

intravenously early on had to be stopped prematurely because of worse outcomes owing to cardiogenic shock.

These studies highlight again that for patients who are unstable in the first few days of an acute coronary syndrome, it is best to wait until their condition stabilizes and to start these therapies before hospital discharge.

### Intensive statin therapy

In the last 20 years, unequivocal evidence has emerged to support the beneficial role of statins for secondary prevention in patients with established coronary artery disease. More-recent trials have also shown that intensive statin therapy (a high dose of a potent statin) improves outcomes better than lower doses.

The PROVE-IT TIMI 22 trial<sup>45</sup> randomized patients after an acute coronary syndrome to receive either standard therapy (pravastatin [Pravachol] 40 mg) or intensive therapy (atorvastatin [Lipitor] 80 mg). The intensive-therapy group had a significantly lower rate of major cardiovascular events, and the difference persisted and grew over 30 months of follow-up.

A number of studies confirmed this and broadened the patient population to those with unstable or stable coronary disease. Regardless of the risk profile, the effects were consistent and showed that high-dose statins were better in preventing coronary death and MI.<sup>46</sup>

Guidelines are evolving toward recommendation of highest doses of statins independently of the target level of low-density lipoprotein cholesterol. ■

**Carvedilol is the beta-blocker of choice for ventricular dysfunction after STEMI**

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