Acute coronary syndromes are a major public health problem and the leading cause of death in the western world. Acute coronary syndromes consist of unstable angina pectoris, non-ST-segment-elevation myocardial infarction, and ST-segment-elevation myocardial infarction. These diseases represent a continuum of increasing severity and are pathophysiologically linked to intracoronary thrombus formation that is nonocclusive, transiently occlusive, or completely occlusive, respectively. Antplatelet treatment with aspirin is the cornerstone of treatment for all acute coronary syndromes. Newer intravenous antplatelet agents reduce 30-day mortality and myocardial infarction in unstable angina and non–ST-segment-elevation myocardial infarction. Adenosine diphosphate antagonist antplatelet agents have an ill-defined role in the treatment of acute coronary syndromes. Fibrinolytic therapy has been shown to reduce mortality in ST-segment-elevation myocardial infarction but may pose a hazard in other acute coronary syndromes.

(Key words: thrombolytics, antplatelets, acute coronary syndromes)

Acute coronary syndromes are a continuum of heterogeneous and dynamic pathophysiologic states and clinical presentations. The syndromes, in increasing severity, include unstable angina pectoris, non–ST-segment-elevation myocardial infarction (MI), and ST-segment-elevation MI. The severity of disease is dependent on the extent and duration of coronary artery occlusion caused by thrombus formation and the resultant myocardial damage.

Acute coronary syndromes are the leading cause of death in the United States, accounting for more than 500,000 deaths annually. Early intervention is the cornerstone to improving outcomes in these patients as up to one third of patients die before reaching a hospital and up to 15% will suffer reinfarction or death within 30 days of presentation.1

This overview discusses the current state of understanding of acute coronary syndromes as it relates to pathophysiologic, clinical presentation, and the management of intracoronary thrombus.

Pathophysiology
Acute coronary syndromes are the result of arterial plaque disruption or endothelial damage (without plaque rupture) with resultant mural thrombus formation.2 Atherosclerotic plaques may become vulnerable to disruption by extrinsic factors such as emotional stress, increased sympathetic activity, elevated diastolic blood pressure, blood flow shear stress, and circumferential wall stress as well as intrinsic factors related to lipid content, thickness of the fibrous cap, and the extent of inflammatory cells (which may cause endothelial dysfunction, vasoconstriction, and release of procoagulant factors).3 It has been demonstrated that the degree of coronary stenosis is inversely related to an acute event, with up to 70% of culprit lesions having less than 50% stenosis in retrospective angiographic studies.4,5

Within minutes of plaque disruption, thrombus is formed through a complex series of platelet activation and adherence to form a “white” clot, which then serves to stimulate conversion of prothrombin to thrombin. Thrombin in turn mediates the conversion of fibrinogen to fibrin and further stimulates platelet activation and adherence. As thrombus generates, red blood cells accumulate and form “red clot.”

Clinical presentation
Table 1 outlines the clinical presentation of acute coronary syndromes.

Unstable angina pectoris
Unstable angina pectoris is a clinical diagnosis based on a history of chest discomfort typical for coronary artery disease that has changed in frequency or severity, is of new onset, or has occurred at rest, and for which a MI has been excluded by serum enzyme determinations and electrocardiography. Unstable angina pectoris may be the result of nonocclusive thrombus, dynamic obstruction (vasoconstriction), or increased myocardial oxygen demand in the face of a fixed obstruction.

Mortality ranges from 2% to 5% at 30 days and from 4% to 15% at 1 year. This range in mortality at both 30 days and 1 year reflects a continuum in disease severity among patients with unstable angina pectoris and is linked to electrocardiography. Those with normal electrocardiograms have a better prognosis, while those with ST-segment depression and T-wave inversion have a worse prognosis.

Non–ST-segment-elevation myocardial infarction
Non–ST-segment-elevation MI is an acute coronary syndrome whose clinical presentation is similar to unstable angina pectoris but whose outcome is more similar to that in ST-segment-elevation MI.2,6 Patients typically present with anginal chest discomfort that may last up to an hour (because of a transient occlusive thrombus), and myocardial necrosis is subsequently confirmed by serial serum enzyme determinations (creatinine kinase, creatine kinase MB fraction, or troponin I or T). This syndrome represents up to 25% of acute MIs. The 30-day mortality ranges from 5.5% to 9.5%, and 1-year mortality ranges from 11% to 20%. This rate is similar to that for ST-segment-elevation MI.

ST-segment-elevation myocardial infarction
Patients with ST-segment-elevation MI present with prolonged (>1 hour) chest discomfort associated with ST-segment elevation on electrocardiography. In this cohort, complete coronary occlusion by
thrombus (the culmination of platelet aggregation, thrombin generation, and red cell and fibrin activation and accumulation) leads to transmural myocardial necrosis. Serum cardiac enzyme determinations subsequently confirm the diagnosis.

This is the most severe and life threatening of the acute coronary syndromes in both the short and long term. Up to one third of patients may die before reaching a hospital, usually because of sudden cardiac death from ventricular fibrillation.10 In patients who receive reperfusion therapy, 30-day mortality ranges from 4.5% to 19.6% for patients with small inferior to large anterior infarctions, respectively.11 At 1 year, the corresponding death rates are 6.7% and 25.6%, respectively.

Management
The goal in treating all acute coronary syndromes in the acute stages is to relieve the symptoms of angina, preserve myocardium, and reduce the incidence of death. Cornerstones of therapy include supplemental oxygen, analgesia, and β-blockers (and calcium blockers in certain circumstances). Furthermore, thrombolytic agents, oral and intravenous antiplatelet agents, and antithrombin agents may play a major role (Figure).

**Table 1**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unstable angina</th>
<th>Non-ST-segment elevation</th>
<th>ST-segment elevation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of chest pain, h</td>
<td>&lt;1</td>
<td>up to 1</td>
<td>&gt;1</td>
</tr>
<tr>
<td>Thrombus</td>
<td>Nonocclusive occlusion</td>
<td>Transient</td>
<td>Occlusive</td>
</tr>
<tr>
<td>Myocardial necrosis</td>
<td>No</td>
<td>Nontransmural</td>
<td>Transmural</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Death, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 30 days</td>
</tr>
<tr>
<td>At 1 year</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration of chest pain, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
</tr>
<tr>
<td>up to 1</td>
</tr>
<tr>
<td>&gt;1</td>
</tr>
</tbody>
</table>

**Table 2**

<table>
<thead>
<tr>
<th>Agent*</th>
<th>FDA approved</th>
<th>Plasma half-life, min</th>
<th>Fibrin specificity†</th>
<th>Dose</th>
<th>90-Minute infarct-related artery patency</th>
<th>Antigenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steptokinase (SK)</td>
<td>Yes</td>
<td>23 to 29</td>
<td>–</td>
<td>Infusion</td>
<td>++</td>
<td>Yes</td>
</tr>
<tr>
<td>Alteplase (rtPA)</td>
<td>Yes</td>
<td>4 to 8</td>
<td>++</td>
<td>Bolus plus infusion</td>
<td>+++</td>
<td>No</td>
</tr>
<tr>
<td>Tanectoplase (TNK-TPA)</td>
<td>Yes</td>
<td>±20</td>
<td>+++</td>
<td>Single bolus</td>
<td>++++</td>
<td>No</td>
</tr>
<tr>
<td>Retelplase (rPA)</td>
<td>Yes</td>
<td>15</td>
<td>+</td>
<td>Double bolus</td>
<td>++++</td>
<td>No</td>
</tr>
<tr>
<td>Lanetoplase (nPA)</td>
<td>Pending</td>
<td>23</td>
<td>+</td>
<td>Single bolus</td>
<td>++++</td>
<td>No</td>
</tr>
<tr>
<td>Saruplase (scu-PA)</td>
<td>No</td>
<td>9</td>
<td>+</td>
<td>Infusion</td>
<td>++</td>
<td>No</td>
</tr>
<tr>
<td>Staphylokinase (SAK)</td>
<td>No</td>
<td>6</td>
<td>++++</td>
<td>Infusion</td>
<td>++++</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Abbreviation in parentheses.
†none; + minimal; ++ low; +++ intermediate; ++++ high.

Thrombolytic therapy

Table 2 summarizes thrombolytic agents. Fibrinolytic therapy has been extensively examined for the treatment of acute coronary syndromes. No agent has demonstrated a significant benefit in patients with unstable angina or non–ST-segment-elevation MI; in fact, they may be detrimental.12 Fibrinolytic therapy, however, is well accepted as the mainstay of medical treatment for ST-segment-elevation MI. In an overview of randomized clinical trials involving nearly 60,000 patients, the Fibrinolytic Therapy Trialists’ Collaborative Group reported an 18% reduction in 35-day mortality attributable to treatment with thrombolytics (P <.00001), indicating a reduction of 18 deaths per 1000 treated patients12; however, there was an excess stroke rate of 3.9 per 1000 patients treated. Strokes were most likely due to cerebral hemorrhage and were more prone to occur within the first day of treatment (1.2%: day 0 through 1 vs 0.6%: day 2 through 35).

The clinical benefit of thrombolytic therapy (reduced mortality) has been clearly linked to restoration of normal infarct-related artery flow with resultant myocardial salvage.13 This benefit is inversely related to the time from onset of symptoms to treatment, with the majority of benefit occurring when treatment is initi-
ated within the first 2 hours, and more modest (but statistically significant) benefit when patients are treated 2 to 6 hours after onset of symptoms. Alteplase (rtPA) at accelerated dosing has been clearly demonstrated to be the agent of choice; however, even with early administration, less than half the patients achieve sustained normal infarct artery flow. This major limitation and the evolving understanding of the role of microvascular obstruction and reperfusion injury have led to the development of new more fibrin-specific agents, the investigation of low-dose thrombolytic agents in combination with potent systemic antiplatelet agents, and the further study of novel new agents directed toward improving microvascular perfusion and reducing the local myocardial inflammatory response.

**Antiplatelet agents**
Platelets play a central role in triggering and perpetuating acute coronary syndromes. Antiplatelet agents, the prototype being aspirin, have been used for nearly 50 years in the treatment of coronary artery disease. Despite the proven benefits of aspirin in reducing the incidence of death and reinfarction in patients with acute coronary syndromes, it inhibits only one of more than 80 potential pathways of platelet activation. This limitation has led to extensive research and the development of newer oral and intravenous antiplatelet agents (Table 3).

- **Oral antiplatelet agents**—Aspirin irreversibly inhibits platelet aggregation by preventing conversion of arachidonic acid to prostaglandin H$_2$, thus preventing the production of thromboxane A$_2$ (a potent vasoconstrictor and inducer of platelet aggregation). Aspirin has been shown to reduce the incidence of death or infarction by one half in patients with unstable angina and non–ST-segment-elevation MI, and one third in patients with ST-segment-elevation MI. Aspirin is the foundation for all other treatment modalities in acute coronary syndromes.

- Clopidogrel bisulfate and ticlopidine hydrochloride block adenosine diphosphate–mediated platelet aggregation and also appear to inhibit fibrinogen from binding to the glycoprotein IbbIIa receptor. Additionally, ticlopidine may interfere with the binding of von Willebrand’s factor to platelet receptors.

- Ticlopidine has been studied in only one randomized trial in patients with acute coronary syndromes compared with place-
bo administered to a group that did not receive aspirin. In this study of 652 patients, there was a 46% risk reduction from vascular death or nonfatal MI in the group receiving ticlopidine at 6 months compared with the group receiving placebo (7.3% vs 13.6%, respectively; \( P = .009 \)). Ticlopidine has not been studied in conjunction with aspirin.16

In a study of more than 19,000 patients who had a recent MI, a recent ischemic stroke, or symptomatic peripheral vascular disease, clopidogrel was shown to be superior to aspirin in reducing the incidence of vascular death, MI, or ischemic stroke.17 A large, randomized clinical trial is presently under way comparing the combination of aspirin and clopidogrel with aspirin alone in acute coronary syndromes.

The final common pathway in platelet aggregation takes place at the glycoprotein IIb/IIIa receptor site. Despite significant advances in the development of beneficial intravenous agents that act at this site, oral agents have largely been disappointing, and only one agent remains in clinical trials.

### Intravenous antiplatelet agents

All intravenous antiplatelet agents presently in clinical use are glycoprotein IIb/IIIa receptor antagonists. The initial studies of these agents were in patients undergoing coronary intervention. Abciximab, the first agent approved for this indication, has yet to be proven useful in acute coronary syndromes. In pooled analyses of four large clinical trials of eptifibatide, tirofiban, and lamifiban (not yet approved for use) in patients with unstable angina and non-ST-segment-elevation MI, 30-day mortality and MI was reduced by 13%. In the PURSUIT trial 10,948 patients with unstable angina and non–ST-segment-elevation MI were randomly assigned to receive placebo or eptifibatide in addition to standard therapy (to include heparin). Eptifibatide treatment reduced the combined incidence of death or MI at 30 days, 14.2 versus 15.7% (\( P = .04 \)).

Several phase II trials have experimented with varying doses of different glycoprotein IIb/IIIa receptor antagonists and thrombolytic agents in ST-segment-elevation MI with encouraging results. This experimentation has led to large phase III efficacy studies that are now enrolling patients. The role of these agents in patients with ST-segment-elevation MI will become clearer in the year 2001, when the results of these studies are reported.

### Antithrombin agents

Direct (hirudin, hirulog, efegatran, argatroban, and others) and indirect (heparin) thrombin inhibitors have been widely studied in acute coronary syndromes and other hematologic disorders. Currently, the direct thrombin inhibitors have not...
been proven useful in large clinical trials of patients with acute coronary syndromes, although they may have a role in patients with heparin-induced thrombocytopenia. The two indirect agents available for use in acute coronary syndromes are unfractionated heparin and low-molecular-weight heparin (Table 4).

Unfractionated heparin has been proven useful as an adjunct to thrombolytic therapy (rtPA) in ST-segment-elevation MI and as an adjunct to aspirin in non–ST-segment-elevation MI and unstable angina. It appears to be most beneficial to treat patients with a bolus of unfractionated heparin (60 units/kg) followed by an infusion (12 units/kg per hour) to maintain an activated partial thromboplastin time between 50 seconds and 70 seconds. Treatment should be initiated as soon as possible and maintained for 24 to 72 hours in the setting of ST-segment-elevation MI and for 72 hours in the settings of unstable angina and non–ST-segment-elevation MI. Low-molecular-weight heparin has not yet been approved for use in ST-segment-elevation MI, although this use will be examined in a large phase III trial about to be under way. In unstable angina and non–ST-segment-elevation MI, aspirin and dalteparin (a low-molecular-weight heparin preparation) was superior to aspirin alone at 6 and 150 days in reducing the incidence of death, MI, or revascularizations. In patients with acute coronary syndrome treated with aspirin, low-molecular-weight heparin was compared with unfractionated heparin in three large randomized trials and was equal or superior in reducing the incidence of death in all trials.

Low-molecular-weight heparin is a viable (and possibly preferable) treatment of unstable angina and non–ST-segment-elevation MI. It has not been tested in conjunction with glycoprotein IIb/IIIa inhibitors, making its role less clear, particularly in light of the demonstrated efficacy of combination treatment with unfractionated heparin.

Comment

We enter the new century with a much clearer understanding of the pathophysiology underlying acute coronary syndromes and how they correspond to clinical presentation. This understanding has led to unprecedented strides in the development of new modes of therapy and their ability to improve morbidity and mortality.

It is now clear that acute coronary syndromes are a continuum of clinical and pathophysiologic changes. Antiplatelet treatment with aspirin may be the simplest, cheapest, and most efficacious treatment for acute coronary syndromes and the foundation onto which all other modes of therapy will be added. Fibrinolytic therapy with weight-adjusted, accelerated-dosing rtPA is the cornerstone of treatment of ST-segment-elevation MI. Antithrombin therapy with indirect thrombin inhibitors and systemic antiplatelet treatment with glycoprotein IIb/IIIa inhibitors have also staked their claim as standards of treatment through examination in rigorous randomized clinical trials.

Acute coronary syndromes continue to be a major public healthcare problem, and we have a long way to go before we dethrone it as the leading cause of death in the Western World. The perfect agent—dissolves existing clot, prevents new clot formation, and has no bleeding side effects—may be an unattainable dream, but a “cocktail” of medications may bring us closer to this dream. Many additional questions need to be answered:

- How do combination low-molecular-weight heparin and glycoprotein IIb/IIIa inhibitors compare with our current standard of therapy?
- Do glycoprotein IIb/IIIa inhibitors have a role in ST-segment-elevation MI?
- Are multiple oral antiplatelet agents better than one?
- Are there better agents than aspirin for long-term protection after an acute event or even to prevent a first event?

The common thread to improving the care of patients with acute coronary syndromes has been the merging of basic science with clinical care through randomized clinical trials. As we gain a better understanding of the pathophysiology, we are able to tailor our treatment and recognize unprecedented benefits for our patients.

References


