Progress in the Treatment of Acute Coronary Syndromes
A 50-Year Perspective (1950–2000)

Pierre Théroux, MD; James T. Willerson, MD; Paul W. Armstrong, MD

Early in the past century, skillful physicians observed that prodromal symptoms often precede acute myocardial infarction, an observation that was prospectively validated in mid-century in cohorts of patients presenting with a changing pattern of chest pain. In the 1960s, the new syndrome was in search of a etiology and a natural history and was variously identified by symptoms (crescendo angina, status anginosus, accelerated angina), by presumed pathophysiology (coronary failure, acute coronary insufficiency), or by its prognostic significance (impending myocardial infarction, preinfarction angina). The term unstable angina proposed by Fowler was eventually adopted. The modern era was introduced by an early trial by Paul Wood with an oral antivitamin K prematurely discontinued because of excess events in the absence of treatment, in the 1970s and 1980s and accelerating to the present, by the definition of risk strata and the pioneer works on pathophysiology and treatment (Table 1). Constantinides described fissuring of atherosclerotic plaques leading to coronary artery thrombosis in 1966. Willerson et al, in the late 1970s, postulated that “an alteration in atherosclerotic plaque morphology led to platelet adhesion, thromboxane A2 accumulation, growth of thrombus and dynamic vasoconstriction” and that this sequence of events caused the conversion from a stable to an unstable coronary syndrome. Davies et al and Falk showed at postmortem studies that patients with unstable angina and myocardial infarction almost always have atherosclerotic plaque fissuring or ulceration. The vulnerable plaques have thin fibrous caps, an adjacent lipid core, and a large number of inflammatory cells, primarily monocyte-derived macrophages, activated T cells, and mast cells either immediately beneath the cap or on its surface. The inflammatory cells are attracted, at least in part, by oxidized LDL within the plaque. They release metalloproteinases capable of degrading collagen in the fibrous cap, leading to plaque fissuring or ulceration and thrombosis (Figure 1). Other studies have shown that in addition to thromboxane A2, serotonin, ADP, platelet-activating factor, tissue factor, oxygen-derived free radicals, and endothelin accumulate at sites of endothelial injury leading to thrombosis, dynamic vasoconstriction, and fibroproliferation (Figures 1 and 2). Casscells and Willerson et al have demonstrated angiographically that patients with acute myocardial infarction usually have intracoronary thrombi, and Buja and Willerson confirmed these observations at postmortem examination. Fuster et al documented that the lipid-rich core was the most thrombogenic component of the plaque and that it also expressed intense tissue factor activity. When the thrombosis with its attendant vasoconstriction is transient or not completely occlusive, the patient develops unstable angina, and when it is more prolonged, myocardial infarction occurs.

Recent work by Masera and others has shown that patients with unstable angina and non–ST-segment elevation myocardial infarction who have elevated serum concentrations of selected inflammatory markers, especially C-reactive protein, fibrinogen, the serum amyloid-like protein, and interleukins 1 and 6, often have subsequently complicated clinical courses. T cells and macrophages, the complement system, and nuclear factor-xB are also activated.

The determination of troponin T or troponin I has taken a privileged role in clinical practice during the past decade, first as a sensitive and specific marker of myocyte necrosis, and second as a useful tool for predicting prognosis and determining treatment regimens. Thirty percent to 40% of patients with unstable angina have elevated serum levels of troponin T or troponin I, often with normal creatine kinase (CK)-MB values; these patients have a 5- to 15-fold increase in the risk of a future cardiac ischemic event and profit more from the new antithrombotic therapy, because the elevation of normal CK-MB values suggests an underlying pathophysiology related to an active plaque-shedding thrombotic material and plaque debris more distal in the coronary system that cause microinfarctions.

Casscells and Willerson et al have shown that atherosclerotic plaques with the morphological characteristics that predict risk of plaque ulceration or rupture have temperature heterogeneity. If substantial inflammation exists in the plaque, there is an increased temperature varying from 0.8°C to 4°C. Stefanadis et al confirmed these findings in human coronary arteries in vivo. This has led to efforts to develop catheters and noninvasive imaging systems capable of detecting temperature heterogeneity within the atherosclerotic plaque itself, as well as to identify more specifically the morphology of plaques before their ulceration or fissuring, with the expectation that this will ultimately allow one to prevent the development of unstable angina and myocardial infarction.

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IV-2
TABLE 1. Past Contributions and Future Advances in the Treatment of Acute Coronary Artery Disease Syndromes

<table>
<thead>
<tr>
<th>Past 50 Years</th>
<th>Next 50 Years</th>
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<tr>
<td>1. Clinical recognition of the presence of a premonitory syndrome to acute myocardial infarction</td>
<td>1. Development of increasingly potent and targeted antithrombotic and fibrinolytic medications that can be given parenterally and orally and long-term</td>
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<td>2. Development of blood tests to predict and/or quantify myocardial necrosis (serum CK, CK-MB, troponin I and T, myoglobin)</td>
<td>2. Development of methods to predict vulnerable atherosclerotic plaques and to treat them before they fissure or ulcerate, leading to ACS and cerebrovascular accidents</td>
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<td>4. Insight into the pathogenesis of ACS and recognition of the importance of inflammation and thrombosis</td>
<td>4. Ability to predict individual patients’ risk of developing atherosclerosis and acute coronary events before their occurrence by use of gene screening methods and noninvasive direct mapping of coronary circulation</td>
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<td>5. Emphasis on identifying increases in serum C-reactive protein, fibrinogen, troponin T and/or I, and serum amyloid-like protein as markers of a difficult future prognosis</td>
<td>5. Development of an effective artificial heart</td>
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<tr>
<td>6. Development of coronary bypass surgery</td>
<td>6. Transplantation of engineered animal hearts and tissue/cells that are not rejected by the human heart and use of stem-cell methodologies to regenerate the heart and blood vessels</td>
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<td>7. Development of percutaneous interventional procedures, including angioplasty, stents</td>
<td>7. Development of effective and safe angiogenic therapies</td>
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<td>8. Development and application of the statins</td>
<td>8. Improved interventional therapies that are easy to use and have long-lasting beneficial effects</td>
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<td>9. Recognition of the importance of aspirin and of other potent antiplatelet and antithrombotic medications (including heparins and other thrombin antagonists, ADP antagonists, and inhibitors of platelet GP IIb/IIIa receptors)</td>
<td>9. Development of minimally invasive surgery and surgery done with the help of robotics</td>
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<td>11. Development of left ventricular assist devices and cardiac transplantation</td>
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<td>12. Development of pacemakers and defibrillators, including implantable defibrillators</td>
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infarction. Fuster and colleagues used MRI to identify thin fibrous caps and the lipid core in vulnerable plaques for similar purposes.43 Thus, one may anticipate strong efforts in the future to use measurements of plaque temperature and characterize plaque morphology with various imaging techniques to identify the vulnerable atherosclerotic plaques before they ulcerate or fissure and lead to acute coronary syndromes (ACS) (and probably cerebrovascular accidents as well).

Determinants of progression to myocardial infarction include the duration of the thrombosis,16–18 variables influencing myocardial oxygen consumption,44 presence or absence of coronary collaterals, and the dynamic nature of focal coronary artery occlusion by inappropriate vasoconstriction.19–21 Reimer and Jennings demonstrated that ischemia and infarction begin on the inner wall of the heart and extend outward toward the epicardium.53 Necrosis in the ischemic area at risk grows exponentially within minutes and hours after coronary artery occlusion. Reperfusion halts this process but is associated with a variable amount of cell damage.46 The rapid ion shifts that follow the first few seconds and minutes of reperfusion are particularly disastrous for cell survival, precipitating contraction band necrosis.47–49 In the following hours and days, the inflammation process contributes further to the progression of necrosis.50,51 and a variable amount of apoptosis occurs.52,53 Subsequently, in the following weeks and months, infarct expansion and left ventricular remodeling supervene.54 Incomplete reperfusion with no-reflow at the tissue cell level caused by edema and necrosis of the small arterioles plugged with embolic material and leukocyte accumulation may compromise myocyte function at all these stages.55,55a,55b,56

The past decade has seen a new risk-stratification scheme, based on improved insight into the cellular mechanisms of the disease, and a new therapeutic armamentarium (Table 1). The previous terminology referring to the heterogeneity of the disease has shifted toward a unifying concept encompassing the wide spectrum of manifestations of ACS, subdivided for the purpose of therapeutic considerations into ST-segment elevation myocardial infarction (STEMI), or “Q-wave” myocardial infarction, and non–ST-segment elevation ACS with or without cell necrosis, namely unstable angina (UA) and/or non–Q-wave myocardial infarction (NSTEMI), or “Q-wave” myocardial infarction, and non–ST-segment elevation ACS with or without cell necrosis, namely unstable angina (UA) and/or non–ST-segment elevation MI (NSTEMI), or ST-segment depression or “non–Q-wave” myocardial infarction. A comprehensive definition of unstable angina encompassing the clinical manifestations, the ECG changes, and the blood markers was developed by Braunwald and was recently modified by Braunwald and Hamm57,58 and by the guidelines for management published by the European Cardiac Society59 and by the American College of Cardiology and American Heart Association.60,61
Incidence, Prognosis, and Risk Stratification

The diagnosis of UA/NSTEMI is increasingly recognized and accounts now for the majority of admissions to coronary care units. The prognosis remains serious, and improved risk stratification is associated with selective hospitalization of higher-risk patients. The cumulative risk of an ischemic event during the acute phase and the following 3 months, probably because of the prolonged time required for plaque healing, approaches 50%. This requires specific treatment algorithms to cope cost-effectively with the disease. The possibility of early risk stratification combining clinical features, ST-T changes, troponin T or I, and C-reactive protein plasma levels, and the availability of an increasingly effective antithrombotic therapy and of safer and highly successful

Figure 1. Mechanisms by which atherosclerotic plaques become ulcerated (bottom) or fissured (middle). Top, Inflammation that occurs in selected portions of some atherosclerotic plaques. Plaque fissuring or ulceration appears to be at least sometimes related to metalloprotease release from macrophages present under thin fibrous cap (top) or on its surface (middle). Release of metalloprotease degrades collagen in fibrous cap, causing it to ulcerate or fissure, leading to platelet adhesion, aggregation, and growth of a thrombus (bottom). Typically, atherosclerotic plaque that ulcerates has a thin fibrous cap, a larger number of inflammatory cells immediately beneath that cap, and an adjacent lipid pool (top and bottom). Atherosclerotic plaque that fissures generally has a thicker cap, a smaller number of inflammatory cells on surface of cap, and a smaller adjacent lipid pool (middle). Reproduced with permission from Willerson JT, Cohn J, eds. Cardiovascular Medicine. 2nd ed. New York, NY: Churchill Livingstone and Saunders; 2000.

Figure 2. Mechanisms involved in thrombosis and vasoconstriction at sites of atherosclerotic plaque injury resulting from plaque ulceration or fissuring, interventional therapy with angioplasty or stents, and other injuries to endothelium. With such injury, subendothelium is exposed, platelets adhere and aggregate, there is local accumulation of mediators, largely platelet-derived, including thromboxane A2, serotonin, ADP, thrombin, platelet-activating factor, oxygen-derived free radicals, tissue factor, and endothelin. These mediators promote growth of thrombus, and most are vasoconstrictors. Several mediators are also mitogens promoting fibroproliferation or exuberant scarring that occurs after endothelial injury, i.e., "restenotic lesion." At sites of vascular injury, there are reduced concentrations of normally present endogenous substances that prevent thrombosis, vasoconstriction, and inflammation, including tPA, prostacyclin, and nitric oxide (tPA, PGI2, and EDRF at top right). Loss of these normally present protective substances helps to create a prothrombotic environment and one in which inflammation and fibroproliferation occur after endothelial injury. Reproduced and modified with permission from Willerson JT, Cohn J, eds. Cardiovascular Medicine. 2nd ed. New York, NY: Churchill Livingstone and Saunders; 2000.
reperfusion procedures during the acute phase have rendered possible a fast-track approach to management of UA/NSTEMI, similar to the one developed for the management of patients with ST-segment elevation myocardial infarction.

Treatment

Management of the ACS has become multifactorial as therapies addressing the various steps of the cascade of pathophysiological events involved in UA/NSTEMI, from plaque activation to ischemia and to cell necrosis, have become available.60,61 Restoration of an optimal myocardial blood flow has also gained in importance. In patients with STEMI, prompt reperfusion is mandatory. In patients with UA/NSTEMI, plaque stabilization to prevent progression of the disease and plaque passivation to prevent recurrence of thrombosis and vasoconstriction are required. The demand side is still favorably influenced by drugs acting on heart rate, afterload, inotropic state, and preload to reduce myocardial oxygen consumption. Nitrates, β-blockers, and/or calcium antagonists titrated to the patient’s needs are prescribed liberally for this purpose.60,61 Antiplatelet therapy, however, has become the cornerstone of therapy in ACS following the insights gained into the basic pathophysiological mechanisms and documentation of the benefit of aspirin and heparin in the mid-1980s by Théroux and others (Figure 3).62–93

Antithrombotic Therapy

Aspirin and Heparin

In ISIS-2, the rate of vascular death in patients with STEMI was reduced by 21% with aspirin, a gain of similar magnitude and additive to that of thrombolysis with streptokinase.62 Four controlled trials in UA/NSTEMI showed nearly 50% reduction in the rates of death or MI with very homogeneous results between trials independently of doses of aspirin used, timing of initiation during or after the acute phase, and duration of administration.63–66 The important meta-analysis of the placebo-controlled trials with aspirin by the Antiplatelet Trialists Collaboration showed a >25% reduction in the risk of infarction, stroke, or vascular death among 70 000 high-risk patients.67

Additional benefit was subsequently documented with the addition of heparin to aspirin in patients with UA/NSTEMI (Figure 3).65,66,89,90 This combination reduces the risk of death or MI by 48% compared with aspirin alone, in harmony with the major role of tissue factor as well as platelets and platelet-derived mediators in thrombus formation in human coronary arteries.17,18

The benefits of aspirin are currently explained by its ability to irreversibly inhibit cyclooxygenase-1 activity by acetylation of serine 516 of the enzyme, preventing thromboxane A2 generation and thromboxane A2–induced platelet aggregation, vasoconstriction, and its contribution in promoting endothelial and smooth muscle cell proliferation.16–18 This inhibition is present with low doses of aspirin, 80 to 160 mg/d.68 Other effects of aspirin, as yet not totally defined, could contribute to the benefit provided, such as its anti-inflammation properties.29 Aspirin, however, is a weak antiplatelet drug, and thromboxane A2 is only one of the multiple mediators leading to platelet aggregation.12,16–18 Similarly, heparin has an imperfect pharmacokinetic profile and little access to fibrin-bound thrombin, resulting in incomplete platelet passivation and frequent disease reactivation after its discontinuation.69 These limitations of aspirin and heparin and the recognition that multiple mediators contribute to thrombosis and vasoconstriction in injured coronary arteries (Figure 2)16–18 have forced a continuous search for more effective antithrombotic therapy that has led to the introduction in clinical practice of the ADP receptor blockers and intravenous glycoprotein (GP) IIb/IIIa antagonists as antiplatelet agents and of the low-molecular-weight heparins and direct inhibitors of thrombin as alternatives to heparin.72,75,81–85,90–93

Thromboxane A2 synthase inhibitors and receptor (TP) antagonists provide the theoretical advantages over aspirin of preserving production of prostacyclin, a potent vasodilator and antiplatelet agent, and of blocking the effect of cyclooxygenase-2 (COX-2)–mediated thromboxane A2 production. COX-2 is induced in activated monocytes/macrophages and in endothelial cells in inflammatory states and is poorly inhibited by low doses of aspirin.70 A new generation of agents that block the effects of thromboxane A2 and of other arachidonic acid products on the TP receptor, but not those of prostacyclin, represents promising antiplatelet therapy for the future.71,71a

ADP Receptor Blockers

The thienopyridines ticlopidine and clopidogrel irreversibly block ADP receptors and ADP-induced platelet aggregation. These drugs are useful for the secondary prevention of cerebral and coronary events and of subacute stent occlusion.72–75 Clopidogrel is now preferred over ticlopidine because of a safer hematological side-effect profile with less
leukopenia and thrombotic thrombocytopenia purpura. At present, it is used in the short term in combination with aspirin after stent implantation in patients. This drug combination is now being tested in patients with UA/NSTEMI under the hypothesis that the inhibition of 2 different pathways to platelet aggregation will provide additive clinical benefit. The recent cloning of the P2Y receptor, 1 of the 3 ADP receptors identified and the one responsible for most platelet effects, has made possible the development of more potent and specific blockers with improved pharmacokinetic properties. These drugs directly inhibit the receptor and are active after intravenous as well as oral administration; the inhibition is reversible and dose-related to achieve full inhibition of the P2Y receptor, contrasting with the thienopyridines, which are prodrugs that are active only after oral administration, with a maximum inhibition of 40% achieved.

**GP IIb/IIIa Antagonists**

GP IIb/IIIa receptor antagonists are products of modern biotechnology. From basic research on the congenital platelet defect involved in Glanzmann thrombasthenia and the identification of the mechanisms responsible for fibrinogen binding to GP IIb/IIIa receptors, a chimeric monoclonal antibody was developed by Coller, objectively tested in a randomized double-blind placebo-controlled trial by Topol, Califf, et al, and subsequently approved for clinical use. Shortly thereafter, peptide and nonpeptide compounds mimicking the RGD (arginine-glycine-aspartic acid) or KGD (lysine-glycine-aspartic acid) chain responsible for fibrinogen binding to the receptor were synthesized. These drugs have shown consistent benefit in the management of patients undergoing a percutaneous intervention and in patients hospitalized with UA/NSTEMI. In the EPIC trial, the prototype of the trials performed with a GP IIb/IIIa antagonist, a bolus of abciximab followed by an infusion reduced by 35% the risk of death or MI in the placebo group to 8.3%, P=0.008. These benefits of abciximab have been reproduced in most subsequent trials. In a recent placebo-controlled trial, in patients undergoing stent implantation, the primary end point within the first 30 days occurred in 10.8% of patients in the stent and placebo groups, in 5.3% of patients in the stent plus abciximab group (hazard ratio 0.48, P<0.001) and in 6.9% in the angioplasty plus abciximab group (hazard ratio 0.63, P=0.007). Trials with abciximab, tirofiban (nonpeptide, nonantibody inhibitor of GP IIb/IIIa receptors), andnow are being evaluated in current trials. Trials are still ongoing with the oral GP IIb/IIIa antagonists despite the failure of large-scale studies to document any benefit of the active drug over placebo. The unfavorable trend toward more frequent thrombotic events in these trials with the oral GP IIb/IIIa antagonists have permitted an in-depth investigation of the physiological roles of the GP IIb/IIIa receptors.

**Low-Molecular-Weight Heparins and Direct Thrombin Inhibitors**

Low-molecular-weight heparins are increasingly used in lieu of unfractionated heparin on the basis of results of placebo-controlled trials that have documented their superiority over placebo and of similar or slightly better protection than unfractionated heparin. The low-molecular-weight heparins have a more favorable pharmacokinetic profile than unfractionated heparin in allowing predictable anticoagulation with subcutaneous administration once or twice daily without the need for routine laboratory monitoring.

Hirudin, a potent direct thrombin inhibitor that does not require a cofactor for its effect, has no known endogenous inhibitors, and is effective against thrombin-bound fibrin, has been extensively evaluated in STEMI and in UA/NSTEMI trials. The trials have, in general, shown a superiority of the drug over unfractionated heparin during the period of administration but no statistically significant advantages in the longer term in their primary end points. These results, combined with a narrow margin between efficacy and risks of bleeding, have precluded the routine clinical application of hirudin. Hirudin is now approved for the prophylaxis of deep vein thrombosis and for the management of patients with heparin-induced thrombocytopenia. Argatroban, an arginine derivative that binds thrombin at the apolar-binding site, is also approved for the latter indication, and bivalirudin (Hirulog), a small peptide modeled on the active sites of thrombin, for use with percutaneous coronary angioplasty.

**Newer Antithrombotic Drugs**

The research field on antithrombotic therapy is expanding rapidly as a result of progress in molecular biology and genetic engineering that allows development of drugs acting on highly specific steps of the coagulation cascade and of platelet function. Meanwhile, the methodology of clinical trials has reached a degree of sophistication and an international perspective that permit rapid and objective evaluation of clinical efficacy and hypothesis generation. Thus, drugs acting on tissue factor, factor Vlla, factor X, protein C, and thrombin-activatable fibrinolysis inhibitor (TAFI), as well as orally active heparins and antithrombins and new inhibitors of platelets, are currently being studied.

**Myocardial Cell Protection**

In 1974, an editorial published in *Circulation* by Braunwald and Maroko called for “the reduction of infarct size—an idea whose time (for testing) has come.” Reparfusion therapy was very successfully developed in the following decade, whereas other attempts to prevent cell necrosis pharmacologically aimed primarily at reducing myocardial oxygen con-
sumption have generally failed unless reperfusion was provided. In this era of reperfusion, however, direct cellular protection targeting more fundamental mechanisms responsible for progression of cell ischemia to cell necrosis and reperfusion damage and prevention and correction of no-reflow at the cellular level are new therapeutic targets. Promising interventions during ischemia and very early reperfusion are modifiers of cell acidification and prevention of intracellular proton and calcium accumulation by inhibiting sodium/hydrogen exchange (NHE) with agents, such as cariporide and enaporide, that modulate the contractile state with calcium desensitizers, such as the atrial natriuretic factor, and by uncoupling the cell gap junction to prevent cell-to-cell progression of necrosis. Pharmacological ischemic preconditioning also needs to be explored. Potentially useful interventions at an early stage of clinical investigation are anti-inflammatory agents, such as monoclonal antibodies and low-molecular-weight compounds against the terminal fraction of the complement system and against selectins, integrins, and various cytokines, and antiapoptosis agents. Interventions potentially capable of inhibiting and attenuating remodeling are neurohormones, agents that modulate NHE activity, and matrix metalloproteinase inhibitors. Favorable clinical results have been reported with agonists of the adenosine receptors A1 and A3. The no-reflow phenomenon will most likely be influenced by anti-inflammatory agents and agents that block platelet-leukocyte interactions; in this regard, benefit has already been documented with GP IIb/IIIa receptor inhibition, probably by prevention of distal embolization of platelet aggregates and formation of platelet-leukocyte aggregates that plug small arterioles, as well as inhibition of inappropriate vasoconstriction associated with the platelet-derived mediators (Figure 2). Metabolic interventions that reduce free fatty acid levels and their oxidation and enhance glucose utilization and glycolysis, such as glucose-insulin-potassium infusion and stimulation of pyruvate dehydrogenase activity, may be useful in less severe ischemic states. All these interventions will most likely require reperfusion for optimal benefit.

Reperfusion Procedures
Reperfusion procedures have profoundly influenced the practice of cardiology. With the help of expertise and an improved technology, the indication of coronary artery bypass surgery and of percutaneous intervention to relieve angina was rapidly extended to improve prognosis of patients with UA/NSTEMI and with STEMI. The early trials that have compared bypass surgery with medical management and the more recent trials that have compared an early invasive and an early noninvasive routine management strategy have provided important insight. In the most recent trial, a routine early invasive strategy significantly reduced the rates of death or myocardial infarction. Interventions are frequently the only effective means to control refractory angina. Judicious use of intervention and medical management currently appears to be the optimal approach, whereas an aggressive program for the control of risk factors is emerging as an alternative to mechanical revascularization in stabilized patients.

Closing the Therapeutic Loop
The control of risk factors is associated with plaque stabilization and with some physiological regression of the severity of coronary artery lesions. In one study of selected patients, such therapy was more effective than percutaneous revascularization to prevent the need for a future revascularization procedure. “Endothelial therapy” has become a therapeutic target to control atherosclerosis and plaque activation. One can foresee new pharmacological therapies to control and prevent the causes of the disease and the progression of atherosclerosis and its consequences with such agents as new anti-inflammatory and antithrombotic therapies, as well as anti-infectious therapy and selected forms of gene therapy (Table 1).

Fibrinolytic Therapy
In the 1950s, patients with acute myocardial infarction were admitted for a protracted period to a general medical ward without ECG or physiological monitoring. Those patients who survived received palliative therapy for their symptoms and pharmacological measures directed toward the electrical and functional hemodynamic disturbances that commonly ensued. After the introduction of specialized coronary care units in the early 1960s, anticipation of these problems became more feasible, and the advent of bedside hemodynamic monitoring in the critically ill soon followed. This development provided insight into the various physiological subsets that comprise acute myocardial infarction and not only enhanced clinical and pharmacological management but also circumvented prior detrimental practices, such as overzealous diuresis and inappropriate use of oxygen-wasting catecholamines, etc. By the early 1970s, the determinants of myocardial oxygen consumption were well understood, and it was appreciated that the extent of myocardial necrosis pursuant to acute myocardial infarction directly modulated clinical outcome. Facilitated by ECG, enzymatic, and imaging techniques to quantify both myocardial ischemia and infarction, Braunwald and others led an intense effort to reduce the extent of ischemic injury during the early hours after infarction with the goal of limiting infarct size.

It has been asserted that the inauguration of clot-dissolving therapy began with Tillet and Garner’s original report in 1933 that hemolytic streptococci possess fibrinolytic activity. Purification efforts ensued, and further animal and human volunteer work led finally to the first human studies, in 1958, of intravenous streptokinase in patients with acute myocardial infarction. During this same period of time, discovery of the dynamic nature of the fibrinolytic system occurred with an appreciation of the counterbalancing stimuli for both the formation and dissolution of fibrin. Urokinase isolated from human urine and its precursor, prourokinase, avoided the immunogenic and pyogenic side effects of streptokinase, which affected acceptance of the latter. In addition, urokinase had a shorter half-life and a somewhat better balance between its clot-dissolving and systemic fibrinogenolytic activity. Despite these advances in systemic thrombolysis for myocardial infarction, the view of the Health and Public Policy Committee of the American College of Physicians in 1985 was “... considered investigational and... it cannot yet
be considered uniformly safe or effective. Until studies demonstrate that early thrombolytic therapy can significantly reduce infarct size, morbidity and mortality, widespread use of thrombolytic agents for evolving acute myocardial infarction cannot be recommended as routine therapy.“124 This view was obviously influenced by continuing concern about the introduction of foreign bacterial protein, ie, streptokinase, into humans, the risk of inducing a systemic hemorrhagic state, and the lack of large-scale, well-conducted, randomized, double-blind, placebo-controlled trials on mortality.

However, enthusiasm for this form of therapy had already grown on the basis of several key developments. These included the demonstration by Chazov and colleagues as well as by Rentrop and colleagues in the late 1970s of the efficacy of intracoronary administration of streptokinase in recanalizing occluded coronary arteries in humans with acute myocardial infarction.125,126 At about this time, DeWood and co-workers were evaluating emergency coronary bypass surgery in patients presenting with acute myocardial infarction and were using urgent coronary angiography to confirm the potential of benefit.22 Their studies demonstrated the role of coronary thrombosis in the early hours in patients with acute ST-segment elevation myocardial infarction and that angiography could be accomplished expeditiously and safely in such patients. Intracoronary streptokinase soon became the subject of intense investigation, and randomized trials demonstrated its efficacy. This benefit was ultimately confirmed to enhance clinical outcome, and randomized trials demonstrated its efficacy. This benefit was ultimately confirmed to enhance clinical outcome, and randomized trials demonstrated its efficacy.

Figure 4. Thirty-day mortality in 4 treatment groups. Group receiving accelerated treatment with tPA had a lower mortality than the 2 streptokinase (SK) groups (P=0.001) and each individual treatment group: SK and subcutaneous (SC) heparin (P=0.009), SK and intravenous (IV) heparin (P=0.003), and tPA and SK combined with IV heparin (P=0.04) (left). Right, Coronary flow at 90 minutes in culprit artery demonstrating 54% TIMI II perfusion in tPA group and <40% in other 3 treatment groups (P<0.001). Left, Reproduced with permission of the publisher and Dr Eric Topol for the GUSTO investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med. 1993;329:673-682. Copyright 1993, Massachusetts Medical Society. All rights reserved.

Two randomized megatrials ushered in the current era of contemporary care for patients with acute myocardial infarction and transformed our thinking and practice forever. The GISSI study, published in 1986, was the first of these and consisted of 11 806 patients with ECG changes of either ST elevation or depression, half of whom were randomized to streptokinase within 12 hours of onset of symptoms.129 An 18% relative reduction in 21-day mortality (13% in the controls) was seen, and the benefit accrued was confined to patients with ST-segment elevation and was especially marked in those patients treated early after symptom onset. A second placebo-controlled trial (ISIS-2) also evaluated the effects of intravenous streptokinase on 35-day mortality. This trial of 17 187 patients incorporated a 2×2 factorial design to assess the effects of enteric-coated aspirin separately and together with streptokinase.63 Patients were randomized up to 24 hours after chest pain onset with ECG criteria similar to those of GISSI I. Both streptokinase and aspirin produced impressive reductions in mortality, 28% and 23%, respectively, and together were associated with a 39% reduction in mortality compared with placebo therapy.

Concurrently, a separate line of investigation, spurred by discovery of the biochemical underpinnings of endogenous fibrinolysis, the desire to avoid a systemic prohemorrhagic state, and the notion of fibrin-specific clot dissolution, catalyzed the application of recombinant DNA to technology to this area. Purification of a plasminogen activator from the Bowes melanoma cell line and the appreciation that it had an affinity for fibrin clot and a similarity to the endogenous physiological plasminogen activator in blood led to the discovery of tissue plasminogen activator (tPA). Purification of this substance, establishment of its thrombolytic efficacy in animals and humans, and demonstration of its relative clot-specificity occurred at the same time as cloning and expression of the tPA gene. The production of recombinant tPA was the next step.122 This subsequently spawned the design of several mutants of a deletion or substitution character with different properties. The GUSTO trial, which used a front-loaded rtPA infusion protocol coupled with intravenous heparin, demonstrated that this treatment strategy had a clear survival advantage over streptokinase.130 Importantly, this benefit was mediated by more rapid achievement of effective coronary patency, thereby validating the open-artery hypothesis131 (Figure 4). The major milestones in fibrinolytic therapy over the past 50 years are summarized in Table 2.

Several issues still require resolution to optimize our current approach to acute myocardial infarction. Although the weight of current evidence indicates that timely percutaneous intervention coupled with appropriate pharmacological therapy may yield the best coronary patency, the broad applica-
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<td>Intravenous SK given in patients with AMI</td>
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<td>Intracoronary SK recanalizes coronary arteries in AMI</td>
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<td>Thrombotic coronary occlusion demonstrated early after ST-segment elevation AMI in humans</td>
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SK improves survival, and the combination of aspirin and SK proves to have synergistic benefit in the first 2 cardiovascular megatrials of fibrinolysis. Recombinant tPA proves superior to SK, and the open-artery hypothesis is validated. Primary PTCA and stenting produces superior early reperfusion in selected patients. New third-generation bolus fibrinolytics and combination therapy with intravenous GP IIb/IIIa inhibitors enhances pharmacological reperfusion. AMI indicates acute myocardial infarction; SK, streptokinase.

Thrombotic coronary occlusion is amenable to pharmacological flow. Primary stenting combined with platelet GP IIb/IIIa inhibitors enhances pharmacological reperfusion. Intracoronary SK recanalizes coronary arteries in AMI. Intravenous SK given in patients with AMI. Intracoronary SK recanalizes coronary arteries in AMI. Thrombotic coronary occlusion demonstrated early after ST-segment elevation AMI in humans.

Primary coronary intervention may well become the preferred approach in elderly patients, although the benefit may paradoxically be greatest in patients >75 years old, but this remains to be proven. Time from symptom onset constitutes a key variable at both ends of the treatment window. Delay from symptom onset to hospital arrival remains long and thus far immune to vigorous public education campaigns: hence, moving newer forms of simple-to-administer bolus fibrinolytics into the field appears to be the next most logical step. The longer the delay, the less thrombotic coronary occlusion is amenable to pharmacological therapy, which is presumably related to the presence of fibrin cross-linking. Later administration of fibrinolysis to such patients is also associated with more frequent complications, and in such circumstances, percutaneous intervention may well be preferable, especially if there is active ischemia in a substantial territory at risk. In patients who present with cardiogenic shock, mechanical intervention seems preferable, although the benefit may paradoxically be greatest in patients <75 years old. The global scope of acute myocardial infarction, taking into consideration the epidemic of coronary disease in Eastern Europe and Asia, coupled with a shift to a more aged population, places a high priority on simply administered, cost-effective, and safe reperfusion strategies.

Failure to achieve successful fibrinolysis pharmacologically may reflect multiple factors, including (1) the complexity of the culprit plaque, (2) any associated intramural hemorrhage or hematoma, (3) the magnitude and accessibility of the thrombotic occlusion, (4) the proportion of platelets composing the original thrombus, (5) embolization of various components of the occlusive thrombus and plaque with resultant small-vessel plugging, (6) associated macrovascular and microvascular coronary spasm, and (7) finally, coronary endothelial dysfunction modulated by the ischemic process. Although even the most optimistic Phase II angiographic studies of novel fibrinolytics report an ~60% TIMI 3 patency, Ito and colleagues brought some sobriety to these estimates by demonstrating impaired microcirculatory flow in as many as 23% of patients with excellent TIMI 3 patency.

The emergence of intravenous GP IIb/IIIa inhibitors has had a major impact on the safety and efficacy of percutaneous coronary interventions and the outcomes of patients presenting with acute non–ST-segment elevation coronary disease. Their use in primary angioplasty and stenting for acute ST-segment elevation myocardial infarction and during rescue angioplasty for failed fibrinolysis has been a significant advance. Recently, promising Phase II studies with reduced-dose fibrinolytics combined with intravenous GP IIb/IIIa inhibitors has resulted in earlier and improved coronary patency (Figure 5). Whether this will be associated with reduced intracranial hemorrhage and reinfarction is unknown and is now being evaluated in GUSTO IV and ASSENT 3, 2 large-scale Phase III studies. Future pathways for fibrinolysis offer both opportunity and promise and are depicted in Table 3.

Summary
There has been enormous progress in the care of patients with acute coronary heart disease syndromes during the past 50 years. This progress includes the development of new fibrinolytics, the use of thrombolytic therapy in acute myocardial infarction, and the use of percutaneous coronary intervention. The combination of these therapies has led to improved outcomes and reduced mortality in patients with acute coronary syndromes. However, despite these advances, there are still significant gaps in our understanding of the optimal use of these therapies, and further research is needed to improve patient outcomes.
years. The pathogenesis of ACS has been increasingly well defined, and improved pharmacological and interventional therapies have come from the enhanced mechanistic insight. This progress will continue in the next 50 years, but the focus of future experimental efforts needs to be just as vigorously directed at identifying the genes and gene products involved in leading to premature coronary syndromes and their consequences. From this insight into genes and gene products contributing to development of ACS will come the ability to predict, prevent, and cure coronary heart disease in both its acute and chronic forms. The American Heart Association and Circulation have played major roles in contributing to these developments in the past 50 years, and their contributions will be equally important and just as dedicated in the future.

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