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SYMPOSIUM ON MODERN THROMBOLYTIC THERAPY

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Introduction

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It has been widely appreciated for more than a century that thromboses in the arterial and venous beds and in the heart are major causes and important complications of many forms of cardiovascular disease. Whereas early observers considered thrombosis to be the primary cause of transmural myocardial infarction, later investigators seriously questioned this concept because of the frequent absence of thrombosis in the infarct-related artery at postmortem examination. Streptokinase and urokinase, the so-called *first generation* thrombolytic agents, became available for clinical use in the 1960s and, although employed in a number of clinical trials initially, were not widely used in the treatment of acute myocardial infarction.

The situation changed radically and rapidly at the beginning of this decade when coronary arteriography, carried out during the first few hours of myocardial infarction, revealed that coronary thrombosis indeed is the proximate cause of transmural myocardial infarction in a large majority of patients. This observation sparked enormous interest in the thrombolytic therapy of acute myocardial infarction. At first this involved the infusion of streptokinase directly into the occluded coronary vessel. Soon thereafter the field expanded in two important directions: 1) Streptokinase (and then other thrombolytic agents) were administered by the intravenous rather than the intracoronary route to make thrombolytic therapy available to patients in settings in which a fully staffed cardiac catheterization laboratory is not available and to shorten the time interval between the onset of symptoms and successful reperfusion; and 2) the development of so-called *second generation* thrombolytic agents that are more fibrin specific and effective than streptokinase and urokinase.

Few times in the history of cardiology has a new therapeutic development generated more excitement and interest and few times has clinical research to assess its efficacy moved more swiftly. In contrast to some earlier therapeutic advances, many investigations of thrombolytic therapy have been carefully designed prospectively, with clearly defined end points and appropriate attention to sample size and to other statistical considerations.

In an effort to keep cardiologists and internists current in this rapidly advancing field, the Department of Continuing Education of the Harvard Medical School conducted a postgraduate course on Modern Thrombolytic Therapy in association with the Annual Meeting of the American College of Cardiology in March 1987. The presentations at this course have been updated and are now available to the readers of the *Journal of the American College of Cardiology* in this supplement.

The first four articles deal with a description of the various thrombolytic agents. Verstraete provides a helpful historical perspective and summarizes the pharmacology of a large number of these drugs, commencing with streptokinase and urokinase and ending with thrombolytic agents still under development. Collen then summarizes the known and postulated molecular mechanisms of action of the relatively new fibrin-specific thrombolytic agents, particularly the *second generation* drugs, that is, recombinant tissue-type plasminogen activator (rt-PA) and single chain urokinase plasminogen activator (scu-PA or pro-urokinase). He describes an interesting synergism between these two agents, and discusses the development of mutants of rt-PA and scu-PA, drugs that might be termed *third generation* thrombolytic agents, some of which may possess greater fibrin affinities and have a longer half-life than the second generation drugs. Even more exciting is the early work on molecules that are hybrids of rt-PA and scu-PA; perhaps these will become the *fourth generation* thrombolytic agents. From Verstraete's and Collen's papers it is evident that we are still in the early stages of development of thrombolytic agents and can anticipate even more effective and more specific agents with more favorable pharmacokinetic properties.

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Gurewich presents early clinical experience with prourokinase, and discusses further the synergism between this drug and both rt-PA and urokinase. Another new thrombolytic agent, anisoylated plasminogen streptokinase activator complex (APSAC), has been designed to improve the kinetic properties of the streptokinase-plasminogen complex; it is inactive on injection, but is activated by hydrolysis in a controlled fashion. Anderson reviews the pharmacology of this interesting drug and the clinical experiences with its use. APSAC can be administered as a bolus and is at least as effective as the parent compound, streptokinase; it is not yet clear whether or not it is more fibrin specific.

There has now been considerable clinical experience with the use of both intracoronary and intravenous streptokinase in the treatment of acute myocardial infarction. Kennedy reviews the results of clinical trials with this agent (seven trials with intracoronary and three with intravenous administration), an overview that indicates that this therapy improves survival in some groups of patients with acute myocardial infarction. The GISSI trial of intravenous streptokinase, carried out on almost 12,000 patients in Italy and reported in 1986, was a watershed study because it showed quite clearly that improvement in survival during the hospital phase of acute myocardial infarction can indeed be obtained with intravenous streptokinase, particularly if it is administered during the first 3 hours after the onset of myocardial infarction. In the initial report it was not clear whether this early improvement in survival would be sustained after hospital discharge. Tognoni and Franzosi report in this supplement that this improvement in survival is indeed sustained, at least for 1 year. This follow-up of patients entered into the GISSI trial is especially meaningful because of the very low rates of mechanical revascularization—percutaneous transluminal coronary angioplasty and coronary artery bypass grafting—that were utilized in Italy during the course of the trial and that might have obscured the results of thrombolytic therapy itself.

Substantial clinical experience has now been obtained with the use of intravenously injected tissue plasminogen activator produced by recombinant techniques (rt-PA) in the early treatment of myocardial infarction. In two randomized, double-blind controlled trials it has been found to be superior to intravenous streptokinase in reestablishing coronary patency. Further experiences with rt-PA are reviewed in the next five articles. The first three of these come from the National Heart, Lung, and Blood Institute's Thrombolysis in Myocardial Infarction (TIMI) trial. First, Sobel reviews the overall experience with rt-PA in the TIMI trial, focusing on both efficacy and adverse effects. Although this drug appears to open occluded coronary arteries more frequently while causing less biochemical perturbation of the coagulation system than does streptokinase, in large doses rt-PA can cause intracranial bleeding. Fortunately, moderate doses appear to be quite effective in establishing coronary patency and rarely cause intracranial hemorrhage.

After successful thrombolysis many patients with evolving myocardial infarction are left with critically narrowed coronary arteries. These vessels may reocclude promptly and, even if they remain patent, these markedly narrowed vessels could be responsible for demand-induced ischemia. Coronary angioplasty is potentially useful in sustaining the benefits of reperfusion in such patients. Williams et al. describe the initial experience of the TIMI investigators with this technique. In a sizable fraction of patients who had received intravenous rt-PA 18 to 48 hours earlier, coronary angioplasty either was found to be unnecessary because of less than critical obstruction of the infarct-related artery, or was not feasible, because of complex coronary anatomy. However, despite the somewhat limited applicability of angioplasty in this setting, thrombolysis followed by angioplasty was successful in almost all patients in whom it was indicated and attempted.

Passamani et al. then describe the TIMI II trial, an ongoing study designed to determine whether coronary angioplasty (if the latter is found to be feasible and indicated) should be carried out routinely after thrombolytic therapy or, alternatively, if the more conservative strategy of "watchful waiting" should be pursued, subjecting the patient to coronary arteriography followed by mechanical revascularization only if recurrent ischemia becomes manifest. Before this large, complex trial was initiated, an open pilot study was carried out to test the protocol. Analysis of the pilot study revealed that a moderately aggressive approach to reperfusion therapy, that is, intravenous administration of rt-PA within 4 hours of acute myocardial infarction followed 18 to 48 hours later by coronary arteriography and, when feasible and indicated, by coronary angioplasty, can result in the remarkably low early mortality rate of 4% and patent infarct-related coronary arteries without critical obstruction in approximately two-thirds of patients. The results of the ongoing trial are necessary to determine how this moderately aggressive strategy compares with a less aggressive regimen, rt-PA followed by watchful waiting, or by a more aggressive approach, rt-PA followed by *immediate* coronary angiography and coronary angioplasty. What appears to be clear at this point is that the intermediate course provides excellent results in terms of survival and patency of the infarct-related coronary artery.

Topol and Califf then report on the results of the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) trial, which suggest that the very aggressive approach to the treatment of acute myocardial infarction, emergency coronary arteriography during rt-PA infusion followed by mechanical revascularization, may be most appropriate for high risk patients, whereas patients at lower risk may be best managed by intravenous rt-PA with later treatment determined by predischarge exercise testing or coronary arteriography, or both.

The role of rt-PA in the management of acute myocardial infarction is being studied with equal vigor on both sides

of the Atlantic. de Bono summarizes the results of the European clinical trials with this agent. The comparisons between intravenous rt-PA and streptokinase were similar in the European and the American (TIMI) trials. de Bono also whets our appetite by describing the design of the ongoing trials with rt-PA in acute myocardial infarction in Europe; their results are awaited with great interest.

Altering the strategy of treatment of acute myocardial infarction by means of early reperfusion will surely affect the costs of care of this condition and, given the high incidence of myocardial infarction, the economic consequence of such alterations may be quite substantial. Laffel et al. consider this important problem and demonstrate that the incremental costs and benefits of thrombolytic therapy depend principally on the quantity of myocardium undergoing infarction, the time after the onset of the event at which reperfusion occurs and the degree of aggressiveness of postthrombolytic therapy. Estimates of the costs of a life saved by thrombolytic therapy in patients experiencing a large infarction early in their course are within the range of commonly accepted procedures but, as might be anticipated, these costs are much higher in patients with a small infarction (in whom survival is excellent regardless of therapy), patients who receive thrombolytic therapy relatively late in their course (in whom little myocardium can be salvaged) and patients who are subjected to aggressive postthrombolytic mechanical reperfusion therapy. The *routine* use of postthrombolytic coronary arteriography and mechanical reperfusion, that is, coronary angioplasty and, if necessary, coronary artery bypass grafting, adds greatly to the cost of thrombolytic therapy. Therefore, the results of the ongoing TIMI and European trials designed to assess the efficacy and to define the role of mechanical reperfusion therapy after thrombolysis are significant not only from a medical but also from an economic viewpoint.

The two last articles deal with thrombolytic therapy of conditions other than acute myocardial infarction. Gold et al. describe the use of the prolonged infusion of rt-PA in patients with unstable angina who, like patients with acute infarction, often have coronary thrombi. Although this regimen appears to be effective in lysing such thrombi, it may also cause excessive bleeding. When the details of dosage and duration of administration have been optimized it is likely that intravenous thrombolytic therapy will play a significant role in the management of unstable angina. Finally, Goldhaber et al. present the favorable results of rt-PA infusion in the lysis of pulmonary emboli. However, the *clinical* value of thrombolysis in the management of this condition remains to be defined.

I believe that these 15 articles, when considered collectively, demonstrate clearly that we have entered a new era in the treatment of acute myocardial infarction and perhaps of related conditions such as unstable angina and pulmonary embolism. My task in editing this supplement was facilitated by the contributors who provided excellent manuscripts in a timely manner. The Genentech Corporation provided an educational grant to support publication of the supplement as well as total freedom in selecting both the subjects and contributors. Patricia DeLosh and Carolyn Farley in my office provided expert editorial and secretarial support.