Thrombolytic Therapy in Acute Myocardial Infarction

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The following review summarizes one of the early randomized controlled trials of the use of thrombolytic therapy for acute myocardial infarction. The results of this and other smaller trials carried out in the early 1980s redirected the therapy of acute myocardial infarction from a strategy of reducing myocardial work and arrhythmia suppression to one of early reperfusion of the infarcting myocardium. The reduction in morbidity and mortality that have resulted from this shift in management can be compared in importance to the introduction and development of coronary artery bypass surgery and coronary artery angioplasty.

Early Thrombolysis in Acute Myocardial Infarction: Limitation of Infarct Size and Improved Survival

ABSTRACT
The effect of thrombolysis in acute myocardial infarction on infarct size, left ventricular function, clinical course and patient survival was studied in a randomized trial comparing thrombolysis (269 patients) with conventional treatment (264 control patients). All 533 patients were admitted to the coronary care unit within 4 hours after the onset of symptoms related to the infarction. Baseline characteristics were similar in both groups. Informed consent was requested only of patients allocated to thrombolysis; no angiography was performed in 35. The infarct-related artery was patent in 65 patients and occluded in 169. Recanalization was achieved in 133 patients. The median time to angiographic documentation of vessel patency was 200 minutes after the onset of symptoms.

The clinical course in the coronary care unit was more favorable after thrombolysis. Infarct size, estimated from myocardial enzyme release, was 30% lower after thrombolysis. In patients admitted within 1 hour after the onset of symptoms the reduction of infarct size was 51%, in those admitted between 1 and 2 hours it was 31% and in those admitted later than 2 hours it was 13%. Left ventricular function measured by radionuclide angiography before hospital discharge was better after thrombolysis (ejection fraction 48 ± 15%) than in control patients (44 ± 15%). Similar improvement was observed in patients with a first infarct only (thrombolysis 50 ± 14%, control subjects 46 ± 15%), in patients with anterior infarction...
(thrombolysis 44 ± 16%, control subjects 35 ± 14%) and in those with inferior infarction (thrombolysis 52 ± 12%, control subjects 49 ± 12%). Similar results were obtained by contrast angiography.

Mortality was lower after thrombolysis. After 28 days 16 patients allocated to thrombolysis and 31 control patients had died. One year survival rates were 91 and 84%, respectively. On the other hand, nonfatal reinfarction occurred more frequently after thrombolysis (36 patients) than in control subjects (16 patients). Early thrombolysis by intracoronary streptokinase leads to a smaller infarct size estimated by enzyme release, preserves left ventricular function at the second week and leads to improved 1 year survival.

Originally published in the *Journal of the American College of Cardiology*, April 1986.

**Review**

**Historical Background.** Before 1980, the management of patients with acute myocardial infarction (AMI) was centered around pharmacologic therapy directed toward managing arrhythmias and attempting to limit the size of the evolving infarct. Although these efforts were partially effective, the morbidity and mortality from AMI remained high.

In the mid 1970s, a group of cardiologists and cardiac surgeons in private practice in Spokane, Washington, began a program of urgent coronary angiography on patients presenting to the emergency department with evolving myocardial infarctions to select those who might benefit from emergency coronary bypass surgery. From this experience, later reported by DeWood et al. (2), they demonstrated that emergency angiography could be performed safely in this group of patients. They also observed that in most patients presenting with ST elevation on the electrocardiogram, immediate coronary angiography identified a thrombotic occlusion of the infarct–related artery. Although urgent bypass surgery never became widely accepted as a primary therapy for AMI, these observations provided critical background information for the later development of both thrombolytic therapy and primary angioplasty for the management of AMI.

In 1979, two European investigators reported new approaches to the management of coronary artery disease in U.S. publications. Rentrop et al. reported the successful use of intracoronary streptokinase (ICSK) for reperfusion of patients with AMI, and Gruentzig et al. described the development of percutaneous transluminal coronary angioplasty (3,4). Although angioplasty, early in its development, was not yet suitable for use in the setting of acute infarction, ICSK therapy could be performed in any catheterization laboratory without special equipment or training. For this reason, ICSK therapy was rapidly introduced into clinical practice by cardiologists in Europe and North America; academic medical centers in Detroit, Salt Lake City, Seattle, Auckland, New Zealand, and Simoons’s group in the Netherlands initiated randomized controlled trials of this new therapy.

The working group on thrombolytic therapy in AMI of the Netherlands Interuniversity Cardiology Institute began their randomized controlled trial in May 1981, and their early results were published in April 1986 (1). These investigators randomized 533 patients to either ICSK or conventional management in a coronary care unit. The initial protocol required patients in whom an occluded infarct-related artery was identified and who were in the active treatment arm to undergo coronary angiography followed by ICSK. Later in the trial, patients allocated to thrombolytic therapy received an initial intravenous dose of 500 mg of streptokinase before cardiac catheterization to reduce the time from diagnosis to initiating thrombolytic therapy. In addition, when angioplasty became available, 35 patients who had an unsatisfactory result from ICSK underwent immediate angioplasty of the infarct-related lesion. Thus, the Netherlands investigators tested a strategy of early reperfusion therapy for AMI that utilized a combination of immediate coronary angiography followed by ICSK, intravenous streptokinase followed by coronary angiography and ICSK and, later in the trial, angioplasty when thrombolytic therapy failed. By changing the treatment protocol as new methods became available, these investigators attempted to achieve coronary artery reperfusion as early and as completely as possible with the drugs and techniques available to them at that time.

**Early results of thrombolytic therapy.** In the Netherlands trial, the cumulative distribution of infarct size as estimated by serial enzyme measurements averaged 30% smaller in the treatment patients as compared with the control subjects (p = 0.0001). The left ventricular ejection fraction (EF) was measured by radionuclide angiography 10 to 20 days after infarction and was 4% higher in the lytic patients as compared with the control subjects (p = 0.05). At 28 days of mean follow-up, total mortality rate was reduced by 50% in the treatment patients as compared with the control subjects (5.9% vs. 11.7%). At the time of intermediate follow-up, which varied from 1 to 48 months, there continued to be a 45% reduction in mortality in the treatment group as compared with the control subjects. There were 35 patients who were allocated to thrombolytic therapy who did not undergo angiography or receive streptokinase. As required by the Zellen technique of randomization used in this trial, these patients were included in the data analysis as being in the treatment group. In this group, there was a high early mortality of 14.3%. In comparison, patients who had an open vessel at the time of initial diagnostic angiography or after successful reperfusion with ICSK had a remarkably low mortality of 4.5%. Among the 36 patients who failed to reperfuse with ICSK, nine (25%) died. These results demonstrated the profound beneficial effect of early coronary artery reperfusion on mortality in patients with AMI. These results also confirmed those of the smaller 250-patient
and 40 days after admission into the trial in whom an angiographic follow-up angiogram between 10 and 21 days was performed in 422 patients with a follow-up angiogram between 10 and 21 days. The shape of the survival curve demonstrates that the benefits of thrombolytic therapy occur during the first few months after AMI, and after that period of time the survival of the two groups is similar. Both the ISIS-2 and GISSI-1 trials demonstrated the same pattern of survival over 10 years of follow-up (9,10).

Long-term follow-up of thrombolytic trials. Long-term follow-up has been published from the Netherlands trial, the combined results of three Western Washington trials and the two early mega-trials of intravenous streptokinase therapy ISIS-2 and GISSI-1 (7–10). The Netherlands investigators were the first to publish their long-term follow-up. They reported a sustained benefit of thrombolytic therapy over three to seven years. The survival curve for the treatment and control patients is shown in Figure 1. After three years, the mean survival of the lytic patients was 87% versus 79% for the control subjects, and the five-year survival had a similar benefit in favor of thrombolytic therapy (81% vs. 71%). The overall reduction in five-year mortality for the treatment patients was 39% compared with the control subjects. The shape of the survival curve demonstrates that the benefits of thrombolytic therapy occur during the first few months after AMI, and after that period of time the survival of the two groups is similar. Both the ISIS-2 and GISSI-1 trials demonstrated the same pattern of survival over 10 years of follow-up (9,10).

Follow-up angiographic findings predict long-term outcome. During the first three years of follow-up in the Netherlands trial, reinfarction was more common in the lytic patients than in the control subjects. This occurred most often in those with initial inferior infarctions. There were 422 patients with a follow-up angiogram between 10 and 40 days after admission into the trial in whom an angiographic ejection fraction could be determined. Among these patients, the five-year survival for those with an EF >40% was similar in the treatment and control patients, being 83% and 86%, respectively. For those with an EF of <40%, the lytic patients had improved long-term survival (65% vs. 57%). The severity of the residual stenosis in the infarct-related coronary artery on follow-up angiography was also an important predictor of long-term outcome. In patients with a residual stenosis <90%, the five-year survival was 94% for treatment patients and 80% for control patients. For those with a residual stenosis >90%, lytic therapy did not improve five-year survival, which was 78% in both groups. Thus, in patients in this trial who survived to have a follow-up angiogram, those with good residual left ventricular function had excellent long-term survival regardless of whether or not they had received thrombolytic therapy. When thrombolytic therapy was unsuccessful or when a high grade stenosis persisted after lytic therapy, the outcome was less favorable. As has been apparent for several years, left ventricular ejection fraction is an important predictor of long-term outcome after myocardial infarction (MI) independent of the form of therapy provided to the patient. This trial helped establish this fact and the additional importance of the severity of the residual stenosis in the infarct-related vessel after therapy for patients’ long-term survival.

CONCLUSIONS

Early reperfusion of the infarct-related coronary artery is the cornerstone of the current management of AMI. The Netherlands trial provided one of the important steps in the development of this therapy. Although it is traditional for clinical trials to maintain a rigid protocol for the duration of the study, the Netherlands investigators chose to change their strategy of reperfusion as new forms of therapy became available. Because these researchers adopted an unorthodox approach to clinical investigation, the results of this study contributed to the rapid evolution of reperfusion therapy. The best way to accomplish reperfusion in patients with evolving MI continues to be debated, although there is strong agreement that very early reperfusion must be accomplished to preserve myocardium. In addition, normal or nearly normal flow (Thrombolysis in Myocardial Infarction grade 3) must be established in the infarct-related vessel to provide optimal reduction in morbidity and mortality (11,12). The early and long-term results of primary PTCA have been demonstrated to be excellent when carried out in an experienced laboratory by expert interventionists (13). Intravenous thrombolytic therapy, when applied in the first 1 to 2 h after the onset of AMI, also yields good results, but despite the development of many new thrombolytic agents, there remains a relatively high incidence of intracranial hemorrhage. It now appears that a combination of platelet glycoprotein IIIb/IIIa inhibitors and a lower dose of thrombolytic agents may be superior to any of the pharmacologic revascularization strategies currently in use (14). There is now at least a reasonable hope that in the near future...
pharmacologic therapy that is the equal of primary angioplasty will be available in every community hospital in the U.S. If this occurs, we can anticipate a further important reduction in the morbidity and mortality that result from MI.

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REFERENCES