Thrombolytic Therapy for Acute Coronary Obstruction: Status in 1986

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The effect of thrombolysis in acute myocardial infarction on enzymatic infarct size, left ventricular function, and early mortality was studied in subsets of patients in a randomized trial at The Netherlands Interuniversity Cardiological Institute during a 5-year period. Early thrombolytic therapy with intracoronary streptokinase (152 patients) or with intracoronary streptokinase preceded by intravenous streptokinase (117 patients) was compared to conventional treatment (264 patients). All 533 patients were admitted to the coronary care unit within 4 hours after onset of symptoms indicative of acute myocardial infarction. There were 488 patients eligible for this detailed analysis, of whom 245 were allocated for thrombolytic therapy. Early angiography was performed in 212 of the 245 patients. Patency of the infarct-related artery was achieved in 181 patients (85%). Enzymatic infarct size measured from cumulative alpha HBDH release was smaller in patients allocated to thrombolytic therapy (median 760 U/l vs. 1179 U/l in controls, $p = 0.0001$). LVEF measured by radionuclide angiography before discharge was higher after thrombolytic therapy (median 50% vs. 43% in controls, $p = 0.0001$). The 12-month mortality was lower in patients allocated to thrombolytic therapy (8% vs. 16% in the control group, $p < 0.01$). In multivariate regression analysis, infarct size limitation, improvement of LVEF, and a 3-month mortality were predicted by ST, time from onset of symptoms to admission, and Killip class at admission. Thrombolysis was most useful in patients admitted within 2 hours after onset of symptoms and in patients with ST of 1.2 mV or more. On the other hand, no beneficial effects of streptokinase on enzymatic infarct size, left ventricular function, or mortality were observed in the subset of patients with ST less than 1.2 mV admitted 2 to 4 hours after onset of symptoms.

In the long term, improved survival and enhanced quality of life are most evident after thrombolytic therapy in patients with larger anterior wall infarction, and less pronounced in patients with smaller inferior wall infarction. ***(Texas Heart Institute Journal 1986; 13:433-445)***

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IN THE LAST TWO decades, coronary care units (CCU) have made it possible to recognize and expeditiously treat previously fatal arrhythmias during the acute stage of myocardial infarction. This has reduced the in-hospital mortality rate from ± 30% to < 15%. At the same time it has become evident that pump failure, arising from such factors as ventricular dysfunction and acute cardiogenic shock, is now the leading cause of death. Efforts at temporary mechanical or pharmacological support of the heart have been largely unsuccessful, so attention is now directed towards prevention of ventricular failure and limitation of the myocardial infarct size, or even towards outright prevention of infarction itself. Although data from experimentation with a variety of pharmacologic agents seemed promising, recent large-scale clinical trials with the early administration of beta blockers[1,2] and calcium antagonists[3-6] have shown no major reduction in mortality, and this has helped to refocus attention on earlier reperfusion efforts with streptokinase, a powerful thrombolytic agent. The relevance of attempts to improve left ventricular funtion by reducing the amount of tissue lost to infarction is evident when one considers the general relationship between post-infarction left-ventricular ejection fraction, a general expression of left-ventricular function, and one-year mortality. It also shows the benefits that may be expected if ventricular function can be maintained or improved.

The causal thrombosis in acute myocardial infarction has for a long time been a matter for debate. Although it had been assumed since Herrick's days that thrombosis was always the cause of an infarction, careful postmortem studies in the sixties cast doubt on this theory because many patients showed infarction without complete obstruction. Some researchers postulated, therefore, that thrombosis was the sequel of infarction. Such theories, based on postmortem examination, were corrected through the detailed anatomic studies of Fulton et al[7] and were corroborated by DeWood et al,[8] who showed by coronary arteriography that, in the first few hours after myocardial infarction, thrombosis was present in nearly all cases. In 517 patients studied within 4 hours after onset of symptoms, they found a complete obstruction in 86%. These data were confirmed in the recent large trial carried out by the Netherlands Interuniversity Cardiological Institute,[9] a trial that indicated complete obstruction in 84% of 264 patients who were randomized to early angiography and intracoronary thrombolysis (Table I). Similar data were found by others.[10-15]

These observations, therefore, bring three fundamental concepts into focus: first, angiography can be carried out in acute myocardial infarction without major risks; second, thrombosis is present in the majority of patients when they are studied within the first few hours after symptoms; and third, the prevalence of complete obstruction declines as the time after the onset of symptoms lengthens. Indeed, obstruction was found in only 60% of patients when the interval after onset of symptoms exceeded 6 hours, corresponding to the observations of the pathologists who had found, on average, complete obstruction in only half of all cases, which were usually studied at 6 to 24 hours after onset of symptoms or death. It is therefore likely that only in those patients who present at an early stage of acute myocardial infarction can infarct size be limited by an approach aimed at desobstruction. Furthermore, from the experiments carried out by Sobel's group, [15] it is evident that early reperfusion not only limits the ultimate infarct size but also achieves a return to normal cardiac function and metabolism. Thus all available evidence points towards the need for early desobstruction.

The feasibility of rapid dissolution of intracoronary thrombi by systemic or selective infusion of thrombolytic substances has been convincingly demonstrated in experimental series and in clinical pilot studies for the past quarter-century.[16-21] This has led to widespread trials using streptokinase, which was given intravenously in varying doses and at varying time intervals, mostly with disappointing or insignificant results. This initial failure of streptokinase can now be explained by the facts that the series were too small, the patient selection and evaluation techniques were flawed, and the statistical design was old-fashioned, but mainly by the fact that streptokinase was administered too late. In particular, no attempts were made to prove patency of the infarct-related artery by angiography nor to measure infarct size. The older experience should therefore be eliminated from current

TABLE I. Data from the Netherlands Trial, Showing Clinical Course in Hospital

	302 Patients Randomized to		231 Patients Randomized to		533 Patients Total		
	Controls *or*	Intracoronary Thrombolysis	Controls *or*	Intravenous + Intracoronary Thrombolysis	Total Controls	All Thrombolysis	p
Number of patients	150	152	114	117	264	269	
Severe heart failure CCU	8	4	4	6	12	10	
Cardiogenic shock	12	4	12	9	24	13	
Heart failure during convalescence	23	17	30	20	53	37	0.05
Ventricular fibrillation	31	20	30	18	61	38	0.01
Pericarditis	23	6	23	13	46	19	0.0004
Bleeding	2	24	5	29	7	53	0.0001
Angina	38	34	17	23	55	57	
Recurrent infarction	3	5	6	7	9	12	
Mortality (14 days)	12	9	14	5	26	14	0.05

Combined data (p-values < 0.05, two-sided) from CCU, catheterization laboratory, and cardiology ward are reported (Fisher exact test). Reproduced with permission of the Netherlands Interuniversity Cardiology Institute Trial.

considerations, although Yusuf et al[22] conclude from a pooled analysis of some 6,000 patients in 24 randomized trials with intravenous streptokinase that a reduction in the odds of death by 22 ± 5% can be deduced.

This entire field has now been changed radically by the data from the GISSI-trial,[23] an all-Italian study, which has shown a highly significant reduction in mortality in those patients who were treated within the first 3 hours after onset of symptoms (Table II). Because of the large numbers involved in this trial, these mortality statistics are convincing.

It was not, however, until 1979 that the systematic effort at restoration of anterograde flow after intracoronary streptokinase administration was introduced into clinical practice by Rentrop and other workers in Germany.[21,24,25] Since then, we have witnessed a dramatic increase in the number of patients with acute ischemic cardiac disorders who have been treated by intracoronary streptokinase infusion,[22,25-27] and the results have given new color to the cheeks of those who advocated the intravenous route prior to GISSI. A more widespread and thoroughgoing application of the new technique—combining the advantages of early intravenous administration with intracoronary clot lysis and the follow-up treatment of residual coronary artery obstruction (with PTCA or bypass surgery)—now appears to be justified in medical centers capable of executing it. Benefits and risks have recently, and adequately, been investigated. Furthermore, the technique is entirely consistent with experimental evidence.[26,28,29]

In a 1982 editorial reviewing the literature up to that year, Rentrop and I urged caution against too much early enthusiasm. We pointed to the main factors that could influence the ultimate outcome: the need to know the time interval between onset of symptoms and desobstruction; the extent of restoration of myocardial function in the region perfused by that artery; the availability of functional collateral flow; the best route for and the optimal amount of thrombolytic agents; the best agent; agents' side effects; and the degree to which the usual sequelae of myocardial infarction, such as subsequent angina, reinfarction and death, can be reduced when

TABLE II. Data from the GLISSI Trial Involving 11,483 Patients, Oct. 1985 (Tognoni)

Hospital mortality	IV SK 5,756	Controls 5,727	Difference p-value
≤1 hr	8.1%	15.3%	<0.002
≤3 hrs	8.5%	11.9%	<0.001
3-6 hrs	11.3%	12.9%	N.S.
12 hrs	10.6%	12.9%	<0.02
First MI	9.7%	12.0%	<0.01
Re-infarction	180	92	<0.001
Pericarditis	325	565	<0.001
LV failure	583	671	N.S.

streptokinase recipients are compared to a control group randomly assigned to conventional treatment. These arguments have recently been repeated by Yusuf et al,[22] although their conclusion regarding the need for giant trials with thousands of patients to answer these questions is debatable. So long as the true pathophysiological basis for treatment has not been sufficiently clarified, and in fact grows less clear as the ischemia evolves (a function of the available collateral supply, among other factors), it would seem unwise to lump together patient groups with widely varying characteristics in an effort to reach some form of statistical significance. Rather, we should direct our efforts at therapeutic intervention for specific derangements. Returning to the editorial question (quo vadis?),[30] what *have* we learned from the smaller series and from incidental observations in the years since 1980?

Most importantly, recanalization, whether by guidewire alone[30,31] or by clot lysis with streptokinase,[9,15,26,32,33] urokinase[34] or recombinant tissue plasminogen activator,[12,15,35-37] has now been shown to limit infarct size, provided it is carried out within the first few hours after onset of occlusion. On the other hand, Reimer et al[38] and others have confirmed in many animal models that after 6 hours of complete ischemia, the amount of salvageable myocardium is insignificant. Bergmann et al[39] have confirmed these findings in closed-chest dogs, employing positron emission tomography to assess[11] C-palmitate uptake reperfused myocardium. Salvageable

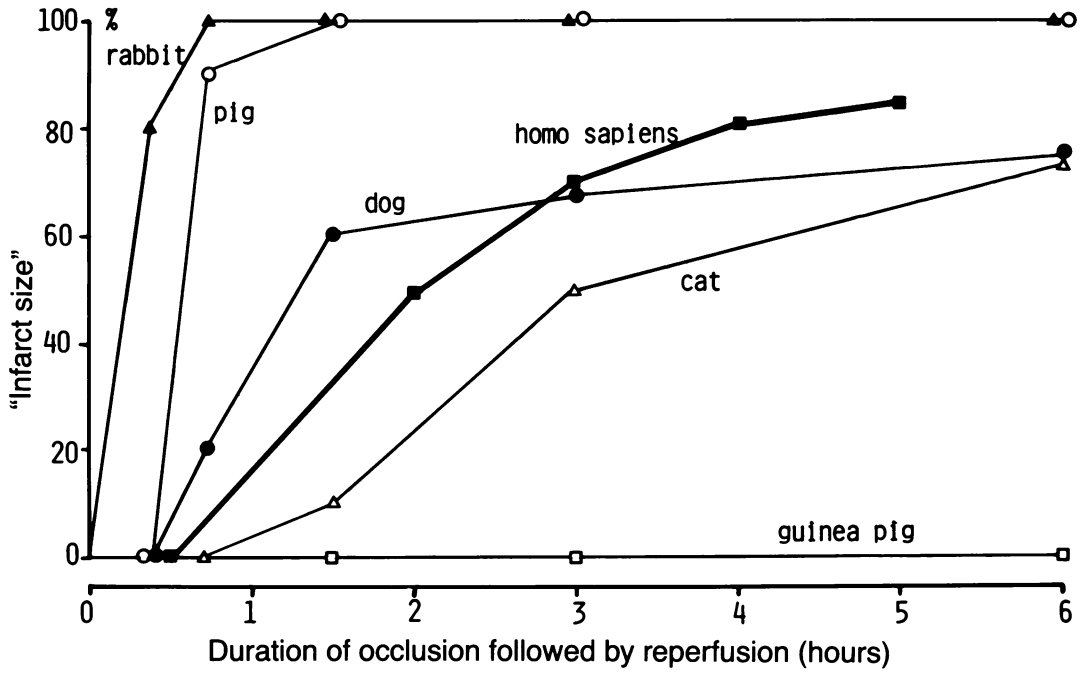
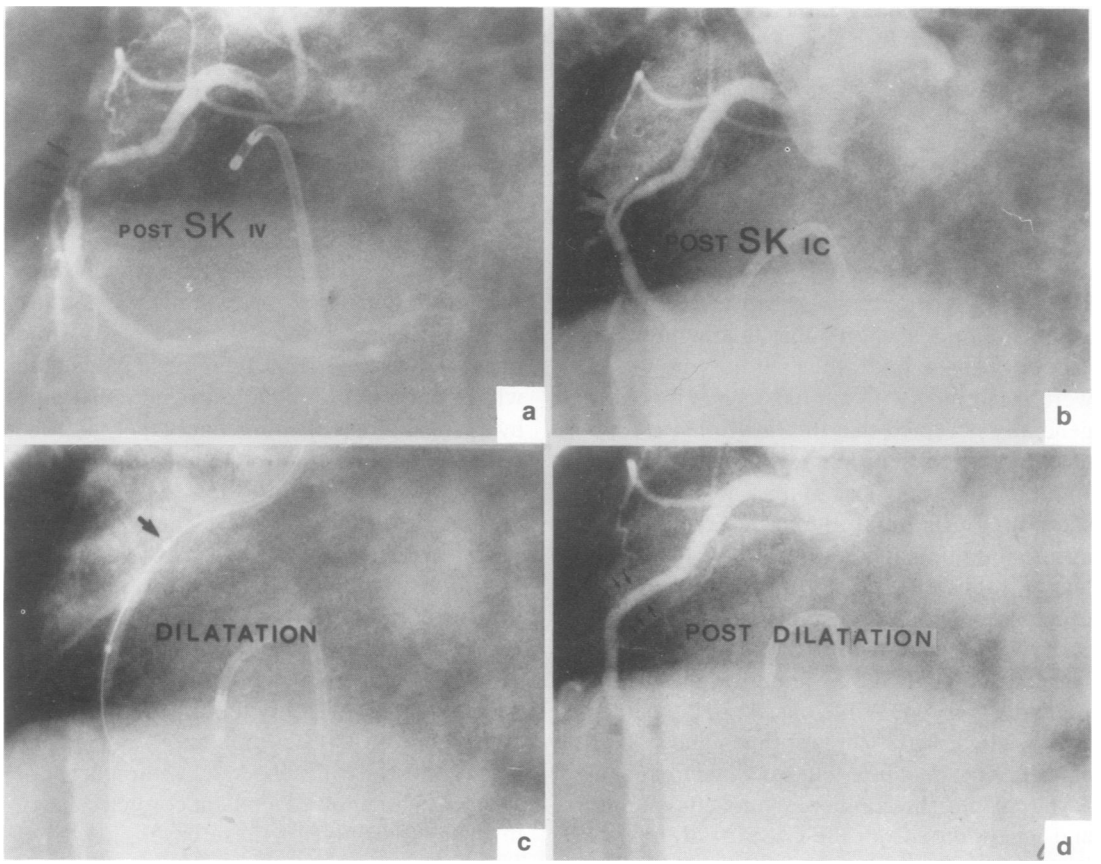


Fig. 1 Development of infarct size as percentage of the "infarct size" that would occur when the coronary artery is permanently occluded. Schaper[29] has shown that in various animal species infarct size varies greatly despite similar occlusion periods. Enzymatic estimation of infarct size in patients after thrombolytic therapy shows that occlusions of less than 30 minutes usually do not lead to substantial loss of myocardial tissue. Occlusions of 2 hours lead to approximately 50% of the ultimate infarct size, while occlusions up to 4 hours result in 80% of the ultimate infarct size. If we suppose that thrombolysis will occur 30 minutes earlier, when streptokinase or rt-PA is given in the ambulance, approximately one-eighth of the ultimate infarct size will be prevented, in addition to that demonstrated in the studies of the Interuniversity Cardiological Institute in the Netherlands.[9]

myocardium increased by 76%, as opposed to 15%, when reperfusion was carried out within 2 hours after occlusion rather than within 2 to 4 hours. These and other studies, however, were performed with animals; since it is now generally accepted that the functional characteristics of their coronary circulations differ significantly from those of man, it has become clear that no animal model can completely mimic the human situation.[29,39,40] Nevertheless, all these data support the concept that reperfusion must be established soon after occlusion, for no major beneficial effects can be expected beyond 3 to 4 hours after onset of ischemia (Fig. 1). While data from the pooled analysis by Yusuf[22] suggest that some statistical benefit cannot be excluded when treatment is started late, the numbers are not convincing, and recent data from the GISSI trial indicate actual damage by late therapy[23] (Table II). Rentrop et al,[41] Schwarz et al,[42] and Schröder et al[43] have also found that while the extent of salvage is less when therapy is started beyond the fourth hour after onset of symptoms, late recanalization may still result in some improvement, particularly in those patients in whom collateral circulation is demonstrable by acute angiography. It is likely that, in these patients, the evolution of myocardial necrosis ("stuttering necrosis") is slowed when collateral flow is enhanced early. The Netherlands data have shown the best improvement in cardiac function, smallest infarct size and lowest mortality in the subset of 117 patients in whom intracoronary clot lysis was preceded by intravenous streptokinase. In these patients, lysis was begun at a median of 3 hours after onset of symptoms. Angiography before the start of subsequent intracoronary streptokinase showed a patent coronary artery in fewer than half of these cases, however. This finding therefore supports the notion that lytic therapy works not only through desobstruction of the main infarct-related vessel but

also through improved rheology and reduced viscosity, benefiting the collateral bed. In keeping with this is the fact that enzyme washout was highest in those patients who were treated earliest, but also occurred in those in whom the infarct-related vessel remained closed. The GISSI data,[23] which show a significant mortality reduction after intravenous administration only within 3 hours of symptom onset, together with the Netherlands data that show a drastic reduction in mortality for the intravenous plus intracoronary streptokinase group, confirm for the first time the thesis recently proposed by Verstraete[44] that intravenous administration is "the only way." There is, however, one essential condition: intravenous thrombolysis within 1 to 3 hours will not alone "fill the bill" when signs of ischemia persist or return. This will be the case in many, if not half, the cases because of the underlying atheromatous lesion. So the "only way" has to be modified (Fig. 2).

To clarify these issues, a large-scale investigation into the relevance of intracoronary administration of streptokinase was begun in 1980 at the Thoraxcenter in Rotterdam and expanded to three other centers, so that by March 15, 1985, we were able to include 533 patients in a randomized study.[9] This figure excludes our earlier pilot trial of 82 patients, whose results in fact mimic those of the randomized trial. Half of the patients (264 of the Netherlands Interuniversity Institute Trial) were allocated to conventional treatment in the CCU and the other half (269) to an attempt at reperfusion. Of these 269 patients, 152 were



Figs. 2a, b, c, d A case where everything went according to plan (optimal reperfusion within 4 hours after onset of symptoms). Figures show sequence of events.

assigned to streptokinase therapy by the intracoronary route only, with 117 receiving 500,000 units of streptokinase intravenously, an average of 100 minutes prior to intracoronary administration. This second group was so treated when experience showed us that a significant delay persisted during preparation of the catheterization laboratory and before introduction of catheters. In more than 80% of the total trial group, therapy was begun within 3 hours after onset of symptoms. It was shown that mortality at 14 days was 5% in the group assigned to thrombolysis (14 out of 269) versus 9% in the group assigned conventional therapy (25 out of 264), and that at a median of 8 months, mortality was 9% versus 16%, a highly significant reduction ($p < 0.01$) (Table I). As stated earlier, the mortality in the intravenous plus intracoronary group was even lower than in the overall group of reperfused patients. Best results were achieved when spontaneous lysis cases were added to those with lysis and PTCA—one death out of 98 cases in one year, an observation strongly supporting the hypothesis that early and complete revascularization by whatever means is essential. Furthermore, cardiogenic shock, CHF, ventricular fibrillation, and pericarditis were half as frequent in the group assigned to thrombolysis (Table I) (Fig. 2).

In addition, enzyme (alpha HBDH) release was 30% lower in the treated group, indicating a smaller size of the ultimate infarct. Smaller infarct size was also indicated by a marked improvement in left ventricular ejection fraction, which was significantly higher in the treated group than in the control group (53% versus 46%). In the latter group, furthermore, end-diastolic and end-systolic volumes were normal. In addition, experience throughout the study was gained with percutaneous transluminal angioplasty (PTCA), which was carried out in those patients who, after initial reperfusion, showed significant residual coronary artery obstruction or reocclusion while still in the catheterization laboratory. In this subgroup of patients, further reduction of the one-year mortality rate was achieved. It is of interest to look at other data collected during the same time span at the Thoraxcenter in patients with unstable angina, a condition that may be considered to be a precursor of acute myocardial infarction. In 136 patients who had been refractory to intense, often triple, pharmacological treatment, aggressive treatment with PTCA reduced one-year mortality to a low 1%, with low recurrence of angina or infarction. This indicates the desirability of "cleaning up" the obstruction when symptoms of ischemia persist, regardless of whether prior treatment was vasodilating or thrombolytic. It is the underlying atheromatous obstruction that must be reduced. In this regard we emphasize the comments by Verstraete[44] that "critical narrowing continues to be a threat to the patient, even after early reestablishment of anterograde flow." The results in the 533 Dutch patients demonstrate that a strategy aimed at early recanalization of the infarct-related artery by both intravenous and intracoronary administration of streptokinase can indeed improve both clinical course and survival rate in the first year after myocardial infarction.

While earlier analysis of pooled data from randomized trials of intracoronary streptokinase (including preliminary data from the now completed Netherlands study) indicated no major beneficial effects on survival,[22] the current Netherlands data,[9] and the GISSI data,[23] show convincing evidence that thrombolysis by streptokinase can result in a striking reduction of mortality in acute myocardial infarction, as a result of smaller infarct size and better residual left ventricular function, provided such therapy is initiated early, i.e., within 4 hours after the onset of symptoms.

Since the Italian and Dutch trial results are all based on the "intention-to-treat principle" and on a random assignment procedure, early reperfusion of the obstructed coronary artery in acute myocardial infarction can now be recommended in health care systems where the conditions outlined above can be met. In Western Germany 66% of the population[45] now have access to such facilities, while in the Netherlands at least 75% have similar access, provided adequate referral arrangements are made. Furthermore, subset analysis of the Western Washington trial,[14] the only other large-scale randomized trial, has indicated that patients treated early benefit from similar reductions in mortality rates. Added to these trials are non-randomized studies such as those

carried out in Germany (Aachen, 461 patients;[46] Mainz and Heidelberg, ± 700 patients taken together;[46] and Hamburg and Berlin, over 1,000 taken together[47]) and by the French collaborative group (± 1,000 patients[48]), all of which indicate that a marked reduction in mortality, with improvement in ventricular function, can be demonstrated in those patients in whom early reperfusion was achieved, particularly when compared to early efforts at "permanent" recanalization.

The entire field has been enormously stimulated by the development of still better agents to lyse the thrombus. In his 1979 Edward Kowalski memorial lecture,[49] Collen presented evidence that plasminogen activation could occur in several different pathways. Shortly afterwards, Collen and Verstraete[50] argued in favor of tissue-type plasminogen activator for systemic thrombolytic therapy.

This in turn led to several trials, one of which was published in 1985 by Verstraete et al,[35] who reported from the European Cooperative Study Group that in 64 patients treated with recombinant tissue plasminogen activator (rt-PA) the frequency of coronary patency was found to be higher (72%) than after intravenous streptokinase (55%). A second study just published shows that when rt-PA is compared to placebo by angiographic documentation, the former achieves patency in 38 out of 62 patients (61%), versus the placebo in 13 out of 62 (21%), although there was a 6-hour delay in onset of therapy.

These and trials currently in progress indicate that all inferences based on current evidence from "the best" intravenous streptokinase trials (Yusuf et al[16]) can be expected to be even more promising with infusion of rt-PA. The earlier thesis, amended by Verstraete[44] — that the intravenous route of early drug administration is the only realistic one, but will require in a certain subset further therapy of "critical narrowing"—appears therefore to be confirmed, although still more recent evidence indicates that the rapid activity of rt-PA may lead to higher reocclusion rates after initial success. In 20 patients treated with rt-PA, Gold et al[51] found early reflow in 80%, but reocclusion despite heparinization in 37%, one hour after cessation of rt-PA infusion. This, in turn, strengthens our previous arguments[9,52] that if relief of ischemic signs is not complete within 2-4 hours after intravenous rt-PA, or for that matter after administration of any other agent, intracoronary manipulations remain mandatory, since myocardium is jeopardized from the first few minutes of ischemia-on.[53,54] The short duration of rt-PA action is an advantage, not only because of the limited suppression of systemic fibrinolysis, but also because of the increased chance this affords for surgical intervention when obstruction persists on the basis of the underlying residual atheromatous lesion.

CONCLUSIONS

1. Thrombus formation is present in ± 85% of all patients who present within the first four hours after the onset of acute myocardial infarction. It is the cause of infarction.
2. While the thrombus may lyse spontaneously, this usually occurs after the fourth hour, by which time the interruption of blood supply most often has led to permanent damage of myocardial tissue.
3. Coronary angiography and intracoronary manipulations can be carried out without undue complications, provided that trained personnel and suitable facilities are available.
4. Intracoronary streptokinase, preferably preceded by intravenous streptokinase, is currently the most effective method to lyse a thrombus, provided it is administered early after the onset of symptoms. It has halved the one-year mortality rate from 15.9 to 8.5% in the recent Netherlands trials.
5. Intravenous streptokinase given within 0-3 hours of onset of symptoms can achieve similiar results (GISSI trial).
6. Intracoronary adminstration must therefore be considered a sequel to intravenous therapy, when recanalization by the intravenous route (achieved on average in only 50-55% of cases) has not alleviated ischemia. Although rheologic factors (opening of collaterals, decreased viscosity) may already be beneficial, even when the main obstruction has not yet been resolved, they are of secondary importance.

7. It has been shown that when residual stenosis is detected by clinical signs (such as recurrence of pain, ST-segment elevation or increases in CPK release) early PTCA or CABG can achieve optimal recanalization, ultimately reducing one-year mortality to a few percent.
8. Early reperfusion will lead to smaller infarct sizes[55,56] and maintained left ventricular function,[57] thus explaining the much improved prognosis and survival rates.[9]
9. Thus far the reported data from rt-PA indicate it to be superior to intravenous streptokinase. Although reocclusion rates are higher than with streptokinase,[51] early PTCA has been advocated and has proved successful.[58] It may well be the agent of the future.
10. Early PTCA and bypass surgery without prior pharmacological lysis has shown similar benefits in selected centers, but is costly.
11. Determining whether the full benefits of these new strategies can be given to the majority of patients with acute infarction will be more a matter of improving existing coronary care facilities to permit rapid detection, referral, and admission, than of finding the optimal reperfusion therapy.

While these conclusions indicate that early reperfusion must be recommended in all patients with suspected acute myocardial infarction for the desired reduction in unnecessary death, many practiced restrictions remain.[30,59,60] The need for cardiac catheterization in perhaps more than 50% of cases, in order to verify the quality and the extent of recanalization, particularly in those patients where residual signs of ischemia persist, can be met only in appropriately equipped centers.[61] Furthermore, the inevitable delays in recognition of symptoms, the need to call the appropriate authority or the physician, the delay in transport, the limited availability of catheterization laboratories or operating rooms on permanent standby, all will influence the effectiveness of such an approach. Therefore, if a simple intravenous thrombolytic agent were available—currently human tissue rt-PA is a leading candidate—or if an improved streptokinase derivative (BRL.26922) were to be proved effective, together with aggressive anti-ischemic therapy such as the administration of an effective beta blocker in combination with a calcium antagonist (atenolol in combination with nifedipine would on theoretical grounds be the leading contender)[62,63] or with an afterload-reducing agent such as captopril, then the scheme discussed above will gain attractiveness. If rt-PA, which is a natural activator of the fibrinolytic system presently reproduced by a recombinant DNA technique, were to become available on a large scale and if the early data[12,35] that indicate up to 7% reperfusion within 1 to 4 hours after intravenous administration of rt-PA were to be confirmed, these developments would certainly revolutionize the treatment of acute myocardial infarction. A European trial with rt-PA is now proposed to judge its efficacy on patients given one of three alternative treatments for acute myocardial infarction: 1) conventional treatment with intravenous rt-PA; 2) intravenous rt-PA followed by coronary angiography and, where needed, by PTCA; or 3) conventional CCU treatment with placebo. Results to be studied are ventricular function, infarct size, and mortality. If these are positive, we can conceive a future in which this plasminogen activator, combined with cardioprotective agents, will be widely administered by general practitioners and ambulance services within the first few hours after the onset of acute myocardial infarction (Fig. 3). Upon admission to the CCU within 4-6 hours, those patients with residual ischemic signs would be catheterized with the aim of permanent recanalization by PTCA or bypass surgery. The other ("cooled off") cases would not need any urgent intervention. Proof of the efficacy of such a strategy lies in application of this scheme to all patients suffering from acute myocardial infarction in a given health region. For example, such a large-scale approach could be applied to cities the size of Seattle or Rotterdam, with "modest" populations of 600,000. Well organized transport systems and properly distributed health care centers that have already proved their value in reducing sudden death in these cities could serve as the underlying support.

Accordingly, a Rotterdam study has now been proposed to investigate whether such a

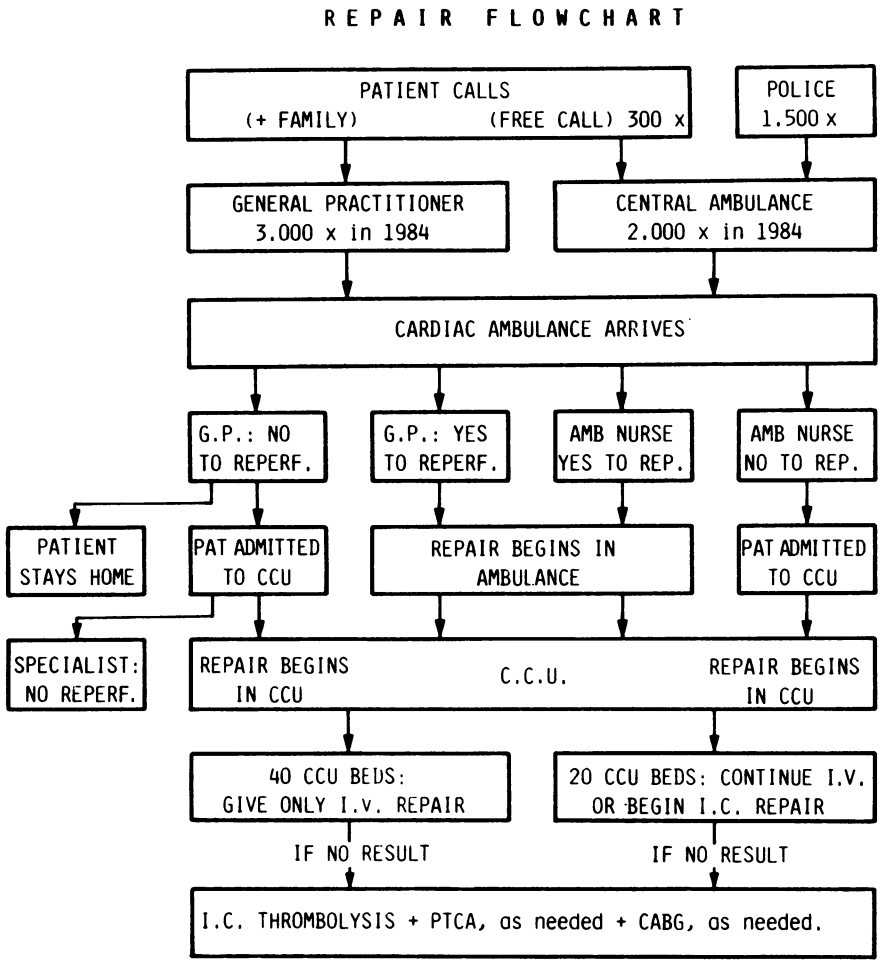


Fig. 3 Flowchart of potential study to be carried out world wide. Based on 1984 transport and referral data. It is estimated that up to 3,000 patients would arrive in the system on time to begin REPAIR (Reperfusion Acute Infarction Rotterdam).

large-scale attack on acute myocardial infarction is possible on the basis of currently existing facilities (Fig. 3). It will require the participation of all general practitioners (280 for ± 600,000 inhabitants), of the centralized ambulance service, and of existing hospital facilities. From an economic viewpoint, the ultimate hope is that if myocardial infarction can be limited in size or avoided altogether, with a consequential halving of the death rate, the cost savings from avoiding expensive post-myocardial infarction intervention measures alone, such as treatment of cardiogenic shock or CHF, could easily outweigh the modest increase in initial costs required by early treatment.[64] If this proves correct, both the quality and the duration of life after infarction can be improved at acceptable cost.

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