Targeting new thrombolytic regimens at specific patient groups: implications for research and cost-containment

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Fibrinolytic drugs and aspirin, compared with placebo, have reduced the 35-day mortality of patients with acute myocardial infarction from approximately 12% to about 8%. The mortality reduction with active treatment is most evident in high risk groups of patients. Moreover, mortality with a fully patent infarct-related artery at 90 min from the start of thrombolytic treatment is half that found with an occluded artery. Yet more than 50% of acute infarct patients receiving thrombolysis fail to achieve complete early coronary patency or develop re-occlusion.

Although thrombolytic strategies are continually evolving to try to further reduce early mortality and increase coronary reperfusion rates, new regimens, when tested in unselected patients against successful active treatments, such as streptokinase and aspirin, are likely to show no, or only small, average benefits, even when applied to tens of thousands of patients. In contrast, the effect of a new thrombolytic regimen is likely to be most evident in selected patients showing large areas of potentially salvageable ischaemic myocardium, as these patients have a higher absolute risk of premature death than patients with smaller infarcts and therefore should gain greater benefit from successful reperfusion. Since the effect of the new treatment, if present, would be greatest in this group, a smaller number of patients would be needed to show an effect; moreover, the risk of the new treatment would be justified against the larger potential benefit to be gained.

We propose to target future thrombolytic regimens, in the first instance, at homogenous groups of high-risk patients; for example, those with large areas of potentially salvageable myocardium. This approach seems a rational and cost-effective way to invest limited amounts of medical resources and offers patients the greatest potential benefit of the new therapy, while restricting possible complications to a smaller number. Continued clinical research aimed at identifying possibly different causes of coronary occlusion and the reasons for worse outcomes is also essential to assign the most appropriate treatments to selected groups of patients.

Key Words: Thrombolysis, acute myocardial infarction, patient selection, new approach.

Introduction

The GISSI-1 and ISIS-2 trials showed that patients with acute myocardial infarction (MI) receiving streptokinase (SK) had a better short-term survival than patients randomized to conventional therapy or placebo. In the month following acute MI, approximately 30 lives were saved per 1000 patients receiving active treatment. This opened the way to the widespread application of thrombolysis in acute MI.

From the subsequent large randomized trials comparing the effects of different thrombolytic agents, it became evident that in unselected (and therefore probably heterogeneous) patients, it was difficult to prove that new interventions could lead to a further statistically significant average reduction in short-term mortality below the levels already achieved by previous treatments.

We propose to target new forms of therapy at homogeneous sub-groups of high-risk patients who share similar pathogenetic components. This approach, if vigorously pursued, could eventually improve patient management and the economics of health care.

Lessons from the megatrials on thrombolysis

A number of lessons from the megatrials on thrombolysis support the application of new treatment regimens to specific groups of patients with acute MI and...
highlight the need to expand our understanding of the disease. The following examples should reinforce these points.

1. The more salvageable myocardium, the greater the benefit from thrombolysis

The first megatrials on thrombolysis indicated that the benefit of treatment is proportional to the amount of salvageable myocardium. This in turn depends on the area of myocardium perfused by the infarct-related artery (IRA) and on the speed with which reperfusion is achieved.

**Benefit of treating patients with large infarcts**

Both the GISSI-1 and the ISIS-2 studies indicated that thrombolytic therapy saved more patients with anterior infarctions than patients with inferior infarcts. Anterior infarcts on average are larger and confer a higher baseline absolute risk of premature death than inferior infarcts. Thus, a greater benefit is to be expected from thrombolysis in patients with large areas of potentially salvageable myocardium.

**Benefit of early treatment**

Patients in the GISSI-1 study treated with SK within 1 h of the onset of symptoms had a 47% reduction in 21-day mortality, compared with the control group enrolled at equivalent times (8.2% died with SK vs 15.4% with conventional treatment). Early mortality was reduced by 23% in patients treated within 3 h and by 17% in those treated between 3 and 6 h. For every 1000 patients treated, about 70 lives were saved when treatment was started within 1 h, but only about 20 lives were saved when it was started after 3 h. Therefore, the earlier the thrombolysis, the more lives saved from early death, presumably because of the larger amount of salvaged myocardium. Such an exponential fall in early survival benefit with increasing time to thrombolytic therapy has been confirmed by a recent meta-analysis of 22 randomized trials. It has also been shown that very early thrombolytic therapy can totally prevent myocardial infarction.

2. The greater the benefit of treatment, the smaller the number of patients needed to show benefit

In the GISSI-1 study, it was sufficient to randomize 1277 patients within 1 h of symptom onset to either SK or conventional therapy to achieve a highly statistically significant result in favour of SK ($P=0.0001$). The benefit of treatment at this time was more than 2-fold greater than at later times. The randomization of 3649 patients between 3 h and 6 h still favoured SK, but with a $P=0.03$. No significant reduction in early mortality was demonstrated with SK in patients treated between 6 h and 12 h, as the benefit of treatment at this time was smaller than at earlier times, and the number of randomized patients (2286) too small. Thus, the more lives saved by the new treatment, the fewer the patients needed to demonstrate statistically significant survival benefits.

3. Why are further reductions in average mortality so difficult to achieve with new thrombolytics?

The GISSI-2 and ISIS-3 studies enrolled, respectively, a total of 12,490 and 41,299 unselected acute MI patients. These trials failed to show a further significant reduction in early mortality in patients randomized to recombinant t-PA (rt-PA) administered over 3 or 4 h, compared to SK or anistreplase, even though a substantial improvement had been anticipated on the basis of the more favourable pharmacological characteristics of rt-PA and of several studies using surrogate endpoints.

Similarly, the GUSTO I trial randomized a total of 41,021 unselected acute MI patients to four different treatments. The study showed that in the month following infarction, about 1 life was saved per 100 patients treated with recombinant t-PA given over 90 min, in comparison with 2 SK regimens, but not in comparison with the combination of rt-PA and SK given over 60 min. Average left ventricular ejection fraction at 90 min and at 5–7 days post-thrombolysis was 59% in the group treated with accelerated rt-PA vs approximately 58% in the other treatment groups. Hence, on average, the patients who met the broad GUSTO I inclusion criteria (significant ST-segment elevation in two adjacent ECG leads and symptom duration of less than 6 h, with a mean treatment delay of 2.8 h) developed rather small infarctions, irrespective of the drug regimen used. The mean left ventricular ejection fraction was well above 50%, placing these patients in a low-risk group. In such unselected patients, it may be difficult to demonstrate a further statistically significant reduction of average mortality over the following months or years by potentially more effective new thrombolytic regimens.

4. Importance of — and failure to achieve — early, complete and lasting reperfusion of the IRA

The angiographic arm of the GUSTO I study reported a 30-day mortality of about 4% in patients who showed normal perfusion of the IRA (TIMI grade 3) after 90 min from the start of thrombolysis. Early mortality
rose to 9% when the IRA showed a TIMI perfusion grade of 0–1 at 90 min (P=0.009)\textsuperscript{[13]}. These patients also had an accelerated mortality rate at 1 year\textsuperscript{[14]} Even with the most effective thrombolytic regimens, however, only 50–60% of the IRAs achieve complete reperfusion (TIMI 3 flow) by 90 min\textsuperscript{[13,15]}, and approximately 10% of successfully recanalized arteries re-occlude during the following weeks\textsuperscript{[13,16]}, with an associated doubling of early mortality\textsuperscript{[17,18]}. Therefore, continued efforts should go toward understanding the mechanisms that prevent effective thrombolysis and identifying poor responders who may require different or additional treatment strategies.

5. Value of adjunctive treatment

The ISIS-2 study showed that aspirin compared with placebo produced a marked reduction in 35-day vascular mortality (25 lives saved per 1000 treated patients), similar to that produced by SK alone (28 lives saved per 1000 treated patients). The beneficial effect of aspirin was additive to that of SK, with a total of 52 lives saved per 1000 patients on the combined treatment compared to placebo\textsuperscript{[2]}. This striking result suggests that adjunctive therapy acting on a different component of the disease (e.g., platelet inhibition as opposed to fibrin dissolution) can produce a significant improvement in overall outcome, even in unselected patients. Future strategies, therefore, should focus on a better understanding of the underlying mechanisms of disease in order to act on possibly untackled pathogenetic components of acute MI.

6. Benefit of late thrombolysis

Sub-group analyses of the ISIS-2 study indicated that thrombolytic therapy applied between 5 h and 24 h of the onset of symptoms could still reduce early mortality compared with placebo\textsuperscript{[3]}. The LATE study confirmed these results. It showed that, compared to placebo, thrombolytic therapy between 6 h and 12 h could save 31 lives per 1000 treated patients in the first 35 days after MI\textsuperscript{[19]}. A total of 5711 patients (2075 between 6 h and 12 h) were randomized in order to show a statistically significant benefit (P=0.02). These findings proved that thrombolysis could improve survival in some patients even after 6 h from symptom onset, mainly by reperfusion of not yet irreversibly damaged myocardium. However, patients in whom the necrotic process had already been completed may have derived no benefit or even suffered harm as a result of treatment.

7. How to tackle unsolved issues

From this partial review of the megatrials on thrombolysis, two important objectives emerge: (1) to increase the rate of prompt and complete coronary recanalisation (TIMI 3 flow) by shortening the time to thrombolysis and by using more appropriate thrombolytic strategies without increasing complication rates; (2) to identify those patients who present late, but in whom reperfusion of the IRA may still limit infarct size and improve the probability of survival. Additional unsolved issues are the possible benefits of treating patients with ST segment depression and patients with unstable angina, and reducing re-occlusion rates of recanalised IRAs.

Because health resources are limited, it is important to identify the best strategies for solving these issues. A rational plan of patient management and an efficient use of resources would warrant initial testing of the effects of new treatments on those patient groups in whom the effect is expected to be greatest (for instance, those presenting early with large areas of potentially salvageable myocardium at risk), allowing the enrollment of a smaller number of patients.

‘Good for all’ vs ‘targeted’ treatment

1. Pros and cons of a ‘good-for-all’ approach

To date, research has focused on the development of more effective and safer thrombolytic regimens to be applied indiscriminately to all patients, provided the patients meet rather broad eligibility criteria for treatment. Up to now, this good-for-all strategy has seemed the most appealing, as it simplified and speeded up patient recruitment\textsuperscript{[9]}.

When applied to the placebo-controlled trials on thrombolysis, this approach has achieved a remarkable average success rate, so that less room is probably left for further average improvements. As a result, the good-for-all approach is now being tailored to smaller randomized trials, aimed at showing equivalent rather than superior effects of a new treatment on outcome\textsuperscript{[20]}. In order to show significant treatment effects in future trials, it may be necessary and ultimately more advantageous to target new thrombolytic regimens to specific sub-groups of patients.

2. Principles of ‘targeted’ treatment

The basic principle of a targeted strategy is the selective application of new, potentially more effective treatments to patients who: (1) are likely to gain little or no benefit from the therapeutic regimens already available; and (2) are likely to derive a benefit that surpasses the anticipated risk associated with the treatment.

In contrast to the good-for-all strategy, which still dominates clinical trials, a targeted approach would mean treating patients more selectively and
using limited research and health care resources more cost-effectively. For some issues, however, such an approach still requires preliminary breakthroughs in the understanding of the disease process.

Some examples will show how targeted treatment might be introduced in clinical trials of patients with acute MI.

3. Good-for-all vs targeted treatment for testing earlier and more effective thrombolysis

Good-for-all early thrombolysis
Prehospital thrombolysis can shorten the average time to treatment and has been shown to be safe, feasible and effective in reducing long-term mortality.[21-23] However, a number of difficulties in reaching an accurate out-of-hospital diagnosis have produced considerable scepticism about this practice, with limited resources made available for its widespread application.

Targeted early thrombolysis
The potential benefits of prehospital, compared to in-hospital, thrombolysis vary widely, mainly as a function of two factors: (1) the area of ischaemic myocardium potentially salvageable by prompt thrombolysis; and (2) the delay in coronary reperfusion that would be caused by deferring treatment until after admission to hospital. In turn, the amount of potentially salvageable myocardium depends on the size of the area at risk and on the extent to which irreversible cell damage has already occurred. At one extreme, the burden and risk of prehospital thrombolysis would be justified in patients with recent onset of symptoms and with large injury waves in multiple ECG leads without or with minimal pathological Q waves and in whom admission to the nearest hospital would take more than 2 h. At the other extreme, the burden and risk of prehospital thrombolysis would not be justified in patients with minimal ST segment elevation involving a few ECG leads or with extensive pathological Q waves and in whom admission to hospital would take less than 1 h.

Similarly, the advantage of a possible faster-acting thrombolytic regimen would likely be much more evident in the first group of patients, with a large area of myocardium at risk still spared from necrosis, than in the second. In the first group, the increased risks (for instance, of bleeding) would be justified by the large potential benefit to be gained from more effective thrombolysis.

The enrollment of these two extreme groups of patients into a single clinical study, by adopting as inclusion criteria only the diagnosis of acute MI and the duration of symptoms, could produce meaningless average results influenced by the relative prevalence of the two types of patients.

4. Good-for-all vs targeted treatment for testing adjunctive therapy

Good-for-all treatment
Aspirin compared to placebo, added to SK, produced very rewarding results in unselected patients with acute MI.[9] However, more recent adjunctive therapies (such as the specific thrombin inhibitor hirudin, tested against another anticoagulant drug) have been less successful. The recent TIMI 9B and GUSTO IIB trials randomized, respectively, 3002 and 4131 unselected acute MI patients to either intravenous hirudin or heparin for 72-120 h.[24,25] Both studies failed to show a statistically significant difference between the two treatments in the rates of death and recurrent infarction after 30 days. Trials investigating the effect of adding inhibitors of the platelet glycoprotein receptor Ilb/IIIa to thrombolytics and aspirin are under way.

Targeted treatment
The indiscriminate application of new regimens to all patients meeting the traditional inclusion criteria implies treating also those patients who would have responded to simpler, less expensive and perhaps less risky regimens. As long as there is no certain way of predicting which patients will respond promptly to standard thrombolytic therapy,[26] it seems reasonable to reserve more aggressive reperfusion regimens, likely to be associated with a greater risk of bleeding, to groups of high-risk patients with extensive ST-segment elevation on the 12-lead ECG and with clinical or echocardiographic evidence of ventricular dysfunction.

5. Good-for-all vs targeted treatment for testing late thrombolysis

Good-for-all late thrombolysis
The short-term mortality of unselected acute MI patients is clearly reduced by thrombolytic therapy administered up to 12 h after the onset of symptoms.[3,19] The benefit of treating patients presenting between 12 h and 24 h after symptom onset has been suggested by at least two large trials[5,19] but is still disputed, so that in clinical practice such patients usually do not receive thrombolytic therapy.

Targeted late thrombolysis
The average results of trials of late thrombolysis may be the consequence of a beneficial effect of treatment in patients with large areas of ischaemic myocardium not yet fully necrosed and of a detrimental effect of thrombolysis in patients in whom the necrotic process is already completed. At one extreme, patients with low myocardial oxygen demand, good collateral blood flow, or intermittent coronary occlusion may have obvious injury waves and only small pathological Q waves on the ECG even late after the onset of symptoms. Such patients are more likely to benefit from thrombolysis.
than are those who, at a comparable time after symptom onset, have a widespread loss of R waves and pathological Q waves. Indeed, this latter group may be harmed by thrombolytic therapy because of an increased incidence of intramyocardial haemorrhage and cardiac rupture\cite{27-29}. A clinical trial enrolling patients only on the basis of time from the onset of symptoms would include both groups. In the LATE study, for instance, only 55% of the enrolled patients had injury waves on the ECG at the time of randomization, while 45% had ST segment depression or T wave abnormalities or pathological Q waves\cite{19}. Clearly, the average results will be strongly influenced by the relative prevalence of these heterogeneous types of patients and may well be deprived of any practical value. We propose, instead, to target late thrombolyis at patients with ECG evidence of extensive incomplete myocardial infarction.

6. Good-for-all vs targeted treatment for testing thrombolysis in patients with ST segment depression or unstable angina

Good-for-all thrombolysis

Thrombolytic therapy in patients with persistent ST segment depression and in those with unstable angina has failed to show benefit\cite{2,30-32}. However, the composition of both groups of patients is likely to be heterogeneous, with certain sub-groups deriving benefit and others harm from thrombolytic treatment.

Targeted thrombolysis

Some patients with ST segment depression may have complete coronary occlusion caused by a fresh thrombus but, because of collateral perfusion distal to the occlusion, ischaemia remains confined to the subendocardium rather than extending transmurally. In such patients, thrombolysis may improve prognosis. In others, the ST segment depression may not be caused by a fresh thrombus; in these, thrombolysis may be ineffective. In unstable patients, the lysis of a thrombus that acutely impairs blood flow may improve prognosis as long as the thrombotic stimuli do not recur, but may be ineffective if they do recur.

Benefits to be gained from a better understanding of the disease process

1. Identifying possible distinct pathogenetic mechanisms of MI

The case of anaemias illustrates the importance of identifying possible different causes of a single disorder. Although acute anaemias are best treated by the indiscriminate use of blood transfusions, the long-term effective cure of anaemias nowadays has become highly differentiated, as a consequence of the advances made in recognizing their different forms and multiple causes. Such cures range from bone marrow transplantation for certain severe aplastic forms, or surgical removal of a bleeding organ, to iron, vitamin B12, folate or erythropoietin supplementation in cases of deficiency anaemias, or immunosuppressive treatment for certain autoimmune forms. Before starting treatment, it is essential to determine which type of anaemia is present, as iron overload, for instance, would be harmful to patients with anaemias not caused by iron deficiency. A simple blood test measuring red cell size and haemoglobin concentration can distinguish an anaemia caused by lack of iron from one caused by vitamin B12 deficiency.

Similarly, the stimuli that initiate coronary thrombosis and the mechanisms that lead to complete, persistent vessel occlusion are probably multiple and not necessarily the same in all patients (Fig. 1)\cite{33}. The type, intensity, and duration of the thrombogenic stimuli may vary, as may the thrombotic and fibrinolytic response to such stimuli. Vasoconstriction of proximal and distal coronary vessels may contribute to blood flow stasis and to the intermittence of occlusion\cite{34}. It would be useful to discover not only the possible different causes of coronary occlusion, but also the reasons for spontaneous intermittent coronary recanalisation\cite{35}, as this may
more costly and possibly hazardous drugs would not be required. Potentially more effective, but also more expensive and potentially harmful, newer treatments could be reserved for those not responding to the simpler therapies. A better understanding of the factors influencing outcome could be obtained, in the first instance, by a simple but rigorous systematic clinical and laboratory characterization of patients who do or do not recanalize the IRA (identified, for instance, non-invasively by recording the reduction of maximal ST segment elevation at 2-4 h after the start of thrombolysis\cite{36-38} and of patients who survive or who die prematurely\cite{39}.

Preliminary data indicate that the plasma concentrations of the prothrombin fragment 1 + 2 (a marker of thrombin generation), measured before the start of thrombolysis, can identify approximately one third of patients with coronary occlusion refractory to thrombolysis (Fig. 2)\cite{40}. Clinical data also suggest that acute MI patients with a recent history of unstable angina have more rapid reperfusion of the IRA in response to recombinant t-PA than do patients with unheralded infarction\cite{41}. The explanation of these findings might provide clues for identifying different pathogenetic components of coronary occlusion and for developing new thrombolytic strategies. It is possible, for instance, that inflammatory mechanisms active in patients with pre-infarction unstable angina\cite{42}, or mediators such as adenosine released during pre-infarction ischaemic episodes\cite{43}, may favour coronary thrombolysis. Because at present there is no simple, rapid way to predict with certainty which patients will not respond to standard thrombolytic therapy\cite{26}, we propose to reserve the most aggressive reperfusion regimens for those patients with greater areas of salvageable myocardium.

Finally, it would be desirable to find out which patients are at risk of coronary re-occlusion and re-infarction and why\cite{16}. The rate of coronary re-occlusion is scarcely correlated to that of re-infarction\cite{16,44}, and it is not known how often re-occlusion and re-infarction are associated with, or preceded by, post-infarction angina. Similarly, it would be important to establish why, when and in whom an open IRA confers a better prognosis.

Only intensive clinical research in these areas will allow the development of new and effective targeted interventions.

2. Predicting adverse outcome

If we could predict which patients respond to the simplest forms of current therapy, treatment with other

References


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Targeting new thrombolytic regimens


