Thrombolytic therapy in Europe: current status

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Thrombolytic therapy is a practical, effective approach to the management of acute myocardial infarction that is widely used in Europe today. Early European trials demonstrated a clear reduction in mortality in patients who received thrombolytic therapy compared with those given conventional treatment. The findings of experimental studies suggest that early reperfusion of the infarct-related artery reduces myocardial damage, which results in the preservation of left ventricular function and, in turn, may improve survival. Although tissue plasminogen activator (t-PA) has been shown to produce more rapid and complete reperfusion than streptokinase, two large-scale clinical trials in which t-PA was given as a standard 3- or 4-h infusion provided no evidence of a survival advantage with this agent. However, the accelerated t-PA regimen used in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) study was associated with a lower mortality than streptokinase or a combination of t-PA and streptokinase, thus lending support to the 'open artery' theory.

Two recent studies conducted in Europe, the Grampian Region Early Anistreplase Trial (GREAT) and the European Myocardial Infarction Project (EMIP), have demonstrated the feasibility, safety, and efficacy of early thrombolytic therapy before admission to hospital. In GREAT, anistreplase (APSAC) was administered at home by general practitioners. In EMIP, this same agent was given by emergency medical personnel. In both studies, pre-hospital administration reduced the time between the onset of symptoms and initiation of thrombolysis and was associated with a lower mortality rate. Recent data from the European Cooperative Group Study show that the benefits of thrombolytic therapy are maintained for up to 5 years.

The benefits of thrombolytic therapy on survival were first demonstrated in the large controlled GISSI study; an 18% reduction in 21-day mortality was seen in patients with AMI given streptokinase within 12 h of the onset of symptoms and a 23% reduction in those treated within 3 h[6]. Similarly, in ISIS-2, 5-week vascular mortality in patients treated with streptokinase within 24 h of the onset of symptoms was 25% lower than in placebo control[7]; a 35% reduction was achieved in patients treated within 4 h of symptom onset. These findings are corroborated in a recently published analysis of combined data from nine randomized trials involving a total of 58,600 patients that demonstrated an 18% reduction in 35-day mortality associated with the use of streptokinase, anistreplase (APSAC), tissue plasminogen activator (t-PA), or urokinase[8].

Percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass grafting (CABG) represent alternative methods for myocardial reperfusion. Investigators in the Netherlands reported higher coronary artery patency rates, greater salvage of the

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**Introduction**

In Europe, thrombolytic therapy for the dissolution of an occlusive coronary thrombus is a widely accepted approach to the management of acute myocardial infarction (AMI). Surveys conducted by the British Heart Foundation showed that 68% of consultant physicians and cardiologists in the United Kingdom routinely used thrombolysis to treat patients with AMI, and an additional 28% occasionally used such therapy[1]. More recently, the proportion of patients treated with thrombolysis was ≥70% in two large European clinical trials: the third study of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-3)[2] and the fourth International Study of Infarct Survival (ISIS-4)[3]. Reported rates of thrombolysis in the United States during similar periods were much lower, ranging from 18%[4] to about 40%[5].

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jeopardized myocardium, and subsequent lower mortality and reinfarction rates in patients with myocardial infarction treated with immediate PTCA compared with those who received thrombolytic therapy\[^9,10\]. PTCA, however, requires special facilities and a trained, experienced team of medical personnel. In many European countries, fewer than 10% of hospitals are able to meet these requirements\[^11\]. These same factors limit the routine use of emergency CABG in patients with AMI.

Data from the European Cooperative Study Group, which paralleled those of the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) and Thrombolysis in Myocardial Infarction (TIMI) Ila trials in the United States showed that the systematic use of PTCA after thrombolysis was not associated with a better outcome than non-invasive treatment and thus should be avoided\[^12\]. The Should We Intervene Following Thrombolysis? (SWIFT) study failed to support the routine use of intervention in the form of PTCA or CABG several days after thrombolysis\[^13\]. The latter study, which was conducted at 21 district hospitals and regional cardiac centres in Britain and Ireland, involved 800 patients who presented within 3 h of the onset of symptoms of AMI. All received thrombolytic therapy with APSAC. In 397 patients, thrombolytic therapy was followed by early angiography and appropriate intervention in the form of PTCA or CABG. The other 403 patients were randomized to a conservative strategy of angiography and intervention only if clinically indicated. In-hospital mortality was 3.3% (13 deaths) in the intervention group and 2.7% (11 deaths) in the conventional care group. Twelve-month mortality in the two groups was 5.8% (23 deaths) and 5.0% (20 deaths), respectively. Reinfarction rates before hospital discharge and after 12 months of follow-up as well as left ventricular ejection fraction at 3 and 12 months were also similar in the two groups. These findings reflect those of the TIMI II trial, which showed no significant difference in mortality, reinfarction rate, or left ventricular ejection fraction between patients in whom angiography and PTCA were routinely performed within 18 to 48 h after administration of t-PA and those in whom such intervention was performed only in the event of spontaneous or exercise-induced ischaemia\[^14\].

The open artery theory

As long ago as 1941, the relationship between early reperfusion of an obstructed coronary artery and clinical outcome after an AMI was suggested by the results of an experimental study conducted by Blumgart et al\[^15\]. In this investigation, the extent of MI in dogs with transient coronary occlusion was found to be directly proportional to the duration of arterial occlusion. These experimental findings formed the basis of the open artery theory, which holds that early reperfusion of the infarct-related coronary artery reduces myocardial damage, resulting in the preservation of ventricular function and leading to improved survival\[^16\].

The open artery theory triggered a search for new thrombolytic agents capable of providing more rapid and complete myocardial reperfusion than streptokinase; t-PA was a product of this research. A trial conducted by the European Cooperative Study Group for Recombinant Tissue-Type Plasminogen Activator showed that t-PA was superior to streptokinase in achieving early coronary patency\[^17\]. Two large-scale international trials involving more than 60,000 patients, however, failed to demonstrate the improvement in survival that might have been expected to accompany this enhanced patency rate\[^18,19\]. The GISSI International Study group compared t-PA and streptokinase, with and without subcutaneous (s.c.) heparin, in more than 20,000 patients with suspected AMI\[^18\]. The in-hospital mortality rate was 9.0% (929 deaths) in the 10,372 patients treated with t-PA and 8.5% (887 deaths) in the 10,396 patients who received streptokinase. In ISIS-3, 41,299 patients hospitalized within 24 h of the onset of suspected MI were randomly assigned to groups receiving streptokinase, t-PA, or APSAC\[^19\]. Mortality rates during the first 5 weeks postinfarction were similar in the three groups: 10.6% associated with streptokinase, 10.3% with t-PA, and 10.5% with APSAC. Survival after 3–6 months was also nearly identical with the three agents.

In contrast, the results of the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial detected a lower 30-day mortality rate with t-PA plus intravenous (i.v.) heparin (6.3%) than with streptokinase and i.v. heparin (7.4%), streptokinase, and s.c. heparin (7.2%), or the combination of t-PA and streptokinase with i.v. heparin (7.0%) (Fig. 1\[^20\]). These rates represented a statistically significant (P = 0.001) 14% reduction in mortality with t-PA compared with the two streptokinase regimens.

One major difference between the GUSTO study and earlier trials was the method of administration of t-PA. In both ISIS-3\[^19\] and the trial conducted by the GISSI International Study Group\[^18\], t-PA was infused over a period of approximately 3–4 h. In GUSTO\[^20\], an accelerated t-PA dosage regimen was used in which patients received an initial i.v. bolus of 15 mg of t-PA; a 90-min infusion followed, with two thirds of the total dose given within the first 30 min. Previous studies demonstrated a high rate of early patency with such a regimen\[^21,22\]. Thus, more rapid reperfusion of the infarct-related artery achieved with the accelerated t-PA dosing schedule may have accounted for the enhanced survival with t-PA noted in the GUSTO trial.

A subset of 2431 GUSTO participants underwent coronary angiography following thrombolytic therapy\[^23\]. The angiographic data obtained from these patients were used to assess the relationship between the patency rate and such outcome measures as mortality and left ventricular function. At 90 min, the patency rate was higher in patients given the accelerated regimen of t-PA plus i.v. heparin (81%) than in those given streptokinase and s.c. heparin (54%), streptokinase plus i.v.
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Table 1

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Figure 1

Figure 1 Thirty-day mortality in patients with acute myocardial infarction treated with streptokinase plus intravenous (i.v.) heparin, streptokinase plus subcutaneous (s.c.) heparin, accelerated regimen of tissue plasminogen activator (t-PA) plus i.v. heparin, and t-PA with streptokinase and i.v. heparin. (Reproduced from GUSTO Investigators' with permission).

heparin (60%), or the combination of t-PA and streptokinase with i.v. heparin (73%)23. Perfusion was normal (TIMI grade 3) after 90 min in 54% of patients treated with t-PA compared with 29-38% of those treated with the other regimens. Mortality at 30 days was significantly lower (P=0-009) in patients with TIMI grade 3 flow at 90 min (4-4%) than in those with TIMI grade 0 or 1 flow (8-9%); mortality associated with TIMI grade 2 flow was 7-4% (P=0-08 vs TIMI grade 3). Ventricular function also paralleled the rate of patency at 90 min and was best in patients who received the accelerated regimen of t-PA with heparin and in those with normal flow through the infarct-related artery, regardless of the thrombolytic agent administered. Thus, the GUSTO findings appear to support the relationship between early successful myocardial reperfusion and improved survival suggested by the open artery theory.

Review of recent European trials

Importance of early reperfusion

Delivery of thrombolytic therapy as soon as possible before hospitalization for AMI is one strategy for shortening the time from the onset of symptoms to successful myocardial reperfusion. Pre-hospital administration of thrombolytic therapy was evaluated in two European studies completed within the past few years24-26.

Grampian Region Early Anistreplase Trial

The Grampian Region Early Anistreplase Trial (GREAT) assessed the feasibility, safety, and efficacy of domiciliary (at home) administration of APSAC by a general practitioner24. This trial involved 311 patients with suspected AMI seen within 4 h of the onset of symptoms. The 163 patients randomized to thrombolytic therapy at home received a slow i.v. injection of APSAC before being transported to the hospital and placebo injection after hospital admission. In the 148 patients assigned to in-hospital thrombolysis, placebo was injected at home and APSAC was administered in the hospital by the admitting physician. The time from the onset of symptoms to thrombolytic therapy ranged from 25-390 min (median: 105 min) for patients treated at home compared with 80-540 min (median: 240 min) for those treated after hospitalization25 (Fig. 2). Thirteen (8-0%) of the patients treated at home died or were resuscitated from cardiac arrest before or during hospital admission, compared with 24 (16-2%) of those treated in hospital, a statistically significant (P=0-02) difference24.

In the 3 months following thrombolytic therapy, 13 deaths (8-0%) from all causes occurred in patients treated with APSAC at home vs 23 (15-5%) in those treated in hospital, a statistically significant (P=0-04) reduction of 49% with at-home administration. At-home treatment also resulted in a statistically significant (P=0-05) 50% reduction in cardiac death: 11 (6-7%) patients treated at home vs 20 (13-5%) treated in hospital24.

Sixty-five (53-3%) of the 122 confirmed infarctions in patients treated at home were Q wave infarctions, compared with 76 (67-9%) of 112 confirmed infarctions in the in-hospital treated group. This 14-6% difference was also statistically significant (P=0-02). The between-group difference in the incidence of Q wave infarction was especially marked, 20-1%, in patients treated within 2 h of the onset of symptoms24.

'Stroke distance', expressed as a percentage of the age-predicted value, was higher in patients treated at home (87-5%) than in those treated in hospital (84-3%).
The difference reached statistical significance ($P=0.02$) in the subgroup treated within 2 h of symptom onset (87.6% at home, 80.8% in hospital).[24] The survival benefits associated with at-home administration of early thrombolytic therapy persisted at the 1-year follow-up evaluation[25]. At that time, 17 (10.4%) deaths had occurred among patients treated at home, compared with 32 (21.6%) among those treated in hospital, a 52% reduction with domiciliary administration. The difference between the two groups remained statistically significant ($P=0.007$).

**European Myocardial Infarction Project**

The multicentre, double-blind European Myocardial Infarction Project (EMIP) examined the benefits and risks of pre-hospital thrombolytic therapy administered by emergency medical personnel[26]. All participants in this study were seen within 6 h of the onset of symptoms of suspected AMI. Of the 5469 eligible patients, 2750 were randomized to receive APSAC before hospitalization and placebo in hospital. The other 2719 received placebo before admission and APSAC in hospital. The median time from the onset of symptoms to injection of APSAC was 130 min in the pre-hospitalization group compared with 190 min in the hospitalized group. Overall mortality at 30 days was 9.7% (266 deaths) in patients treated before hospitalization vs 11.1% (303 deaths) in those treated in hospital, a 13% reduction with pre-hospital treatment ($P=0.08$).[26] There was no obvious correlation between the reduction in 30-day mortality and the time elapsed between the onset of symptoms and APSAC injection. However, in the subgroup of patients in whom the difference between pre-hospital and hospital treatment exceeded 90 min, treatment before admission was associated with a statistically significant ($P=0.047$) 42% reduction in the risk of 30-day mortality from all causes. Cardiac mortality was 16% lower in the group treated before hospitalization ($P=0.049$).

**Long-term benefits of thrombolytic therapy**

A recent report from the European Cooperative Study Group described long-term survival after thrombolytic therapy with t-PA in participants of two randomized, prospective trials[27]. One of these studies compared t-PA and placebo, while the other assessed the effect of immediate PTCA following thrombolytic therapy with t-PA vs that of t-PA alone. The beneficial effect of t-PA on survival after year one was sustained at 5 years. Five-year actuarial survival was 89% and 86% in the two t-PA groups, compared with 84% in both the placebo group and the group that underwent PTCA following thrombolytic therapy with t-PA (Fig. 3). Enzymatic infarct size, indicators of residual left ventricular function, and the number of diseased vessels were among the factors predictive of mortality at 5 years. In addition, the mortality rate in patients with TIMI grade 2 flow (incomplete perfusion) at the time of discharge was similar to that in patients with TIMI grades 0 and 1 flow. Survival was significantly better ($P=0.01$) in patients with TIMI grade 3 flow (95%) than in those with TIMI flow grades 0 to 2 (84%).

**Evaluation of new thrombolytic regimens**

The evaluation of new thrombolytic regimens has been actively pursued in Europe over the past few years. For
Figure 3 Five-year survival curves in patients with acute myocardial infarction treated with tissue plasminogen activator (t-PA), t-PA followed by immediate percutaneous transluminal coronary angioplasty (PTCA), or placebo. (Reproduced from Lenderink et al. with permission.)

Discussion and conclusions

What is the ideal thrombolytic agent?

The most important characteristic of a thrombolytic agent is the ability to produce rapid recanalization. As previously discussed, early reperfusion is essential for optimal myocardial salvage and a favourable clinical outcome. The ideal thrombolytic drug would establish reperfusion within minutes. Ideally, thrombolytic therapy should also be 100% successful in opening the occluded artery.

Rapid i.v. bolus injection of the entire dose of the active thrombolytic drug is the optimal mode of administration for achieving early reperfusion. Bolus injection is also important for facilitating pre-hospital administration of thrombolytic therapy. Use of a drug with a prolonged half-life is another strategy for shortening the required period of infusion.

Because lysis of haemostatic plugs along with recent thrombi can increase the risk of bleeding, the ideal thrombolytic agent should be selective for recently formed thrombi. Selectivity for thrombi initiated by rupture of atherosclerotic plaque rather than other mechanisms would also decrease the risk of bleeding complications.

Reocclusion is one of the principal factors limiting the full therapeutic potential of thrombolytic therapy. Therefore, the ideal thrombolytic agent should assist in preventing reocclusion and contribute to sustained patency during the period of infarct evolution.

The absence of side effects is another desirable property of the ideal thrombolytic. Such a drug should have little potential for allergic reactions and should not interact adversely with other forms of pharmacological intervention used in patients with AMI. Because several drugs used as adjunctive therapy in patients with AMI (e.g. i.v. nitroglycerin and angiotensin converting enzyme inhibitors) may predispose to systemic hypotension, it is particularly important that a thrombolytic agent have no blood pressure lowering effects. Finally, the ideal thrombolytic agent should be inexpensive.

Do current agents measure up?

None of the agents currently available for clinical use fulfils all the criteria for the ideal thrombolytic drug. Recanalization is achieved more rapidly with fibrin-specific drugs (e.g. t-PA and reteplase) than with agents that produce a systemic fibrinolytic state, such as streptokinase. Nevertheless, 1 h after initiation of infusion, the infarct-related artery remains occluded in approximately half of patients treated with t-PA. Several of the available thrombolytic drugs are associated with 24-h patency rates as high as 80% [29]. None, however, is 100% effective.

An accelerated dosing regimen for t-PA has been found to be more effective in achieving early reperfusion than the standard 3- to 4-h infusion used in the past. However, even this accelerated schedule requires 1.5 h. Streptokinase is generally administered over a 1-h period. APSAC is closer to the ideal in that it is given intravenously over a short time, usually 3–5 min. However, the latter drug is not fully active at the time of administration; it is gradually hydrolysed to its active thrombolytic form after injection.
The decrease in blood viscosity produced by thrombolytic agents induces hypofibrinogenemia, which leads to a reduction in blood pressure. The incidence of hypotension with currently available thrombolytics ranges from about 5% to 10%.[29] Hypotension is most likely to occur with drugs that produce a profound systemic fibrinolytic state. Antigenic reactions may be precipitated by streptokinase, which contains bacterial proteins. The risk of such a reaction is much lower with the use of naturally occurring substances such as t-PA.

Both APSAC and t-PA are much more costly than streptokinase. The recent study by Machecourt et al.[30] showed that the cost of the drug represents only a small part of the total cost of hospitalization. It is probably more appropriate to consider the cost of the entire strategy at the end of hospitalization or, even better, after several years.

Where are we headed?

Research efforts continue toward the development of an ideal thrombolytic agent without the limitations of currently available drugs. Various t-PA mutants are among the substances now being investigated. One recently developed deletion mutant known as retelase has been found to be significantly superior to t-PA in establishing patency of the infarct-related artery in patients with AMI.[31] Another potentially promising new agent is a t-PA homologue isolated from the saliva of the vampire bat (bat t-PA). Studies in animal models suggest that this substance may be more fibrin-selective than human t-PA and, therefore, less likely to cause bleeding.[32] It remains to be tested in man. Hybrid molecules incorporating domains of both t-PA and single-chain urokinase plasminogen activator are also being evaluated. Although results obtained with these chimeric plasminogen activators have been disappointing,[33] at least one of these chimeras has been shown to have a potent thrombolytic effect in animal models.[34]

Shortening the time from the onset of symptoms to the delivery of thrombolytic therapy represents an alternative strategy for improving clinical outcome in AMI. A GISSI study found that the interval between the onset of symptoms and the decision to seek help was primarily responsible for the delay in the initiation of thrombolytic therapy.[35] Educational programmes informing the public of the symptoms of MI and the importance of early intervention may help in reducing this delay. Improvements in the speed and efficiency of emergency care procedures might also be expected to expedite delivery of thrombolytic therapy.

References

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