The role of thrombolytic drugs in the management of myocardial infarction

Comparative clinical trials

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Optimal thrombolytic therapy in acute myocardial infarction must aim to achieve early and complete reperfusion of the infarct related coronary artery. Establishment of normal coronary flow (Thrombolysis in Myocardial Infarction [TIMI] grade 3) is the key correlate of improved survival. Three large-scale clinical trials, the Reteplase Angiographic Phase II International Dose-finding Study (RAPID 1), the Reteplase vs Alteplase Patency Investigation During Acute Myocardial Infarction Study (RAPID 2), and the International Joint Comparison of Thrombolytics Study (INJECT), have evaluated the comparative efficacy and safety of reteplase, a new, rapid-acting thrombolytic agent that offers the practical clinical convenience of bolus dosing. RAPID 1 and 2 demonstrated that reteplase was associated with superior early coronary artery patency rates compared with alteplase, whether alteplase was infused over 3 h or over 90 min. Further, the TIMI 3 flow rates achieved in reteplase-treated patients at 60 min were comparable to those achieved at 90 min with the accelerated alteplase dosing regimen. The INJECT trial showed that reteplase resulted in comparable mortality and clinical benefits to those achieved with streptokinase. All three studies demonstrated that reteplase therapy was not associated with an increase in bleeding complications or other adverse clinical events. The simple double-bolus regimen of reteplase administration may permit earlier initiation of thrombolysis with fewer dosing errors than with continuous infusion regimens and thus afford a reduction in the morbidity and mortality risks in patients with acute myocardial infarction.

Key Words: Acute myocardial infarction, thrombolytics, tissue plasminogen activator, reteplase

Introduction

The therapeutic goals in acute myocardial infarction (AMI) are to retard coagulation and platelet function, open the affected coronary artery and achieve the greatest degree of myocardial reperfusion in the shortest possible time. Clinical approaches usually include some combination of thrombolysis, angioplasty, anticoagulation, platelet inhibition and β-adrenergic blockade. As access to primary angioplasty is often limited, thrombolytic drugs are the most powerful agents currently available for reversing coronary arterial occlusion in the majority of patients. But which thrombolytic drug provides the most optimal therapy remains controversial.

Evidence from many clinical trials now indicates that two characteristics of a thrombolytic drug determine its efficacy: (1) the ability to achieve early and complete reperfusion (2) the ease of administration to ensure the earliest institution of treatment. This review examines the efficacy and safety of a new thrombolytic agent, reteplase, in this role. Reteplase is a protein consisting of the kringle-2 and protease domains of tissue-type plasminogen activator (t-PA). The structural modifications to the naturally occurring t-PA molecules result in the improved ability of reteplase to re-open infarct related coronary arteries rapidly and completely. Clinical trials with reteplase show that it achieves early and complete reperfusion with TIMI 3 coronary artery flow rates at 60 min comparable to those achieved at 90 min with accelerated alteplase dosing and without any increase in bleeding complications or other adverse clinical events.

Importance of early and complete reperfusion

In 1980, it was demonstrated that occluding thrombosis of a coronary artery is the most frequent cause
of AMI[12]. Since then, a number of authors have hypothesized that early reperfusion of the infarct related coronary artery may potentially limit infarct size, preserve left ventricular function and ultimately reduce morbidity and mortality[13-19]. During the mid-1980s, angiographic studies demonstrated that alteplase (recombinant t-PA) was superior to streptokinase in restoring early coronary flow[20,21]. However, two clinical trials with more than 46,000 patients enrolled—the International Study Group of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2/International)[22] and the Third International Study of Infarct Survival (ISIS-3)[23]—failed to show a difference in patient survival rates between these two thrombolytic treatments.

In 1993, the results of the Global Utilisation of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) trial convincingly established that early and complete reperfusion, as assessed 90 min after initiation of thrombolytic therapy, was the most important treatment correlate with the clinical outcome[2,10]. There were two significant differences in the methodology of the GUSTO trial compared with the earlier trials. First, t-PA was administered in an accelerated dosing regimen which had been shown to facilitate early patency[39]. Second, intravenous heparin was started at the time of thrombolysis to reduce the risk of coronary artery reocclusion[30]. In addition, the GUSTO trial included a substudy utilizing cardiac angiography to assess the rate of patency of the infarct related artery in 2431 patients at 90 min, 180 min, 24 h, and 5-7 days[109]. This angiographic substudy provided new information about the mechanism underlying these results; t-PA induced significantly greater reperfusion at 90 min than streptokinase (51% vs 31%). In turn, this more rapid patency correlated with improved left ventricular function and a reduction in 24-h mortality. In the 1210 patients randomized to angiography at 90 min, predicted and observed rates of mortality were similar and the high proportion of squared error (R²=0.92) suggests that 92% of the variation in mortality amongst the four drug treatments was related to differences in coronary flow achieved at 90 min[25]. However, by 180 min after initiation of therapy, coronary artery patency rates were similar between t-PA and streptokinase, suggesting that the improvement in survival was primarily related to the ability to achieve earlier reperfusion of the infarct related coronary artery[19]. The GUSTO study also demonstrated that the goal of early and complete reperfusion was achieved in only slightly more than half the patients (54%), even with the most aggressive strategy tested, indicating that significant room still remains for improvement in thrombolytic therapy. Other more recent studies confirmed that an optimal outcome result is dependent upon the restoration of normal coronary artery flow (TIMI grade 3); establishment of TIMI grade 2 flow alone is not associated with a favourable clinical outcome[25-27].

Figure 1 Molecular structure of reteplase. K₂ is the kringle domain; P is the protease domain. Reteplase lacks the finger, epidermal growth factor, and kringle 1 domains seen in wild-type tissue plasminogen activator.

Table 1 Structure—function relationships of tissue plasminogen activator (t-PA) domains

<table>
<thead>
<tr>
<th>Structure</th>
<th>Function</th>
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<tbody>
<tr>
<td>Finger domain</td>
<td>High-affinity fibrin binding</td>
</tr>
<tr>
<td>Epidermal growth factor domain</td>
<td>Hepatic receptor binding</td>
</tr>
<tr>
<td>Kringle 1 domain</td>
<td>Possible hepatic receptor binding</td>
</tr>
<tr>
<td>Kringle 2 domain</td>
<td>Possible fibrin binding</td>
</tr>
<tr>
<td>Protease domains</td>
<td>Low-affinity interaction with fibrin</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>Plasminogen-specific enzymatic activity</td>
</tr>
</tbody>
</table>

Reteplase: a new thrombolytic agent

Molecular structures of reteplase and alteplase

Utilizing selected domains from the native t-PA molecule, reteplase is the first ‘third generation’ thrombolytic[28]. Reteplase differs from wild-type t-PA in the lack of three domains (finger, epidermal growth factor and kringle-1) and because it is produced in Escherichia coli cells, reteplase also lacks carbohydrate side chains[29] (Fig. 1). These differences in molecular structure between reteplase and alteplase account for their different pharmacological profiles (Table 1).

A major difference between reteplase and alteplase, is the deletion of the kringle-1 and epidermal growth factor domains in reteplase. These domains facilitate binding to receptors in the liver and enhance...
The RAPID 1 study was a dose-ranging study designed to evaluate three dosage regimens of reteplase (15 MU). The clinical efficacy and safety profile of reteplase have been studied in three large, controlled clinical trials in patients with AMI. Although fibrin specificity is desirable to minimize occurrence of the plasminemia which occurs with streptokinase, very high-affinity fibrin binding may cause high concentrations of t-PA to accumulate at surface receptors on the fibrin clot. As a result, fibrinolysis may occur more slowly, since the fibrinolytic activity must progress from the surface to the interior of the clot. The lower fibrin affinity of reteplase may allow for more efficient clot penetration and lysis.

The concentration-dependent lysis of plasma clots by reteplase and alteplase, as indicated by the percentage of radioactivity released from radiolabelled plasma clots after 4 h of incubation, has shown that reteplase has the same maximal lytic efficacy as alteplase at equipotent concentrations. However, reteplase has less lytic efficacy in platelet-rich plasma clots and aged clots, suggesting that reteplase preserves haemostatic plugs and may thus produce fewer bleeding complications than does alteplase.

**Clinical pharmacology**

In humans, following i.v. bolus doses of reteplase (0.11–5.5 MU), plasma fibrinogen concentrations remain unchanged except at higher doses; however, α-antiplasmin and fibrin-D dimer levels exhibited dose-related decreases. In patients with AMI, reteplase results in significantly decreased levels of fibrinogen, plasminogen, α-antiplasmin, fibrinogen degradation products, and fibrin D-dimers.

Reteplase has been shown to have low antigenic activity; antibodies to reteplase have not been observed in any of 2400 patients tested for antibody formation. This property has a clinically significant advantage over streptokinase and its derivatives.

**Clinical trials with reteplase**

The clinical efficacy and safety profile of reteplase have been studied in three large, controlled clinical trials in patients with AMI.

**Rapid 1: reteplase vs standard dose alteplase**

The RAPID 1 study was a dose-ranging study designed to evaluate three dosage regimens of reteplase (15 MU single bolus, 10 MU + 5 MU double bolus, and 10 MU + 10 MU double bolus) vs standard dose alteplase (100 mg infused over 3 h).

**Table 2** RAPID 1: TIMI 2 and 3 flow at 90 min after initiation of thrombolysis and at hospital discharge (5–14 days)

<table>
<thead>
<tr>
<th>Perfusion grade</th>
<th>t-PA (15 MU)</th>
<th>r-PA (10+5 MU)</th>
<th>r-PA (10+10 MU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI 2 90 min</td>
<td>77.2</td>
<td>62.8†</td>
<td>66.7</td>
</tr>
<tr>
<td>Hospital discharge</td>
<td>87.8</td>
<td>85.5</td>
<td>80.5</td>
</tr>
<tr>
<td>TIMI 3 90 min</td>
<td>49.0</td>
<td>40.9</td>
<td>45.7</td>
</tr>
<tr>
<td>Hospital discharge</td>
<td>70.7</td>
<td>71.0</td>
<td>73.2</td>
</tr>
</tbody>
</table>

*P<0.05, †P<0.01, ‡P<0.001 compared with t-PA. r-PA = recombinant t-PA (reteplase); t-PA = tissue plasminogen activator.

RAPID 1 = Reteplase Angiographic Phase II International Dose-finding Study; TIMI = Thrombolysis in Myocardial Infarction. (Adapted from with permission.)

**Study design**

Six hundred and six patients, aged 18–75 years, who presented within 6 h with at least 30 min of typical chest pain unresolved by nitroglycerin and accompanied by ECG ST-segment elevation were enrolled. The primary outcome measure was TIMI grade 2–3 patency at coronary angiography 90 min after initiation of thrombolytic therapy. Secondary end-points included TIMI 2–3 patency at 30 min, 60 min and 5–14 days as well as global (ejection fraction) and regional (infarct zone) function at hospital admission and discharge. The incidence of stroke, reinfarction, heart failure and angina were also monitored for differences between groups, as was the need for angioplasty, bypass surgery or intra-coronary thrombolysis. Adjunctive therapy consisted of soluble aspirin and heparin in standard conventional doses.

**Results**

The reteplase double-bolus 10 MU + 10 MU dosage regimen was the most effective of the regimens tested (Table 2). This regimen of reteplase administration resulted in comparable coronary artery patency rates at 90 min to alteplase (85% vs 78%, respectively) and significantly higher patency rates at hospital discharge than alteplase (95% vs 88%, respectively). TIMI 3 flow was significantly higher in the double-bolus reteplase recipients than patients receiving alteplase at 60 min (51% vs 33%, P=0.009), 90 min (63% vs 49%, P=0.019), and at hospital discharge (88% vs 71%, P<0.001) (Fig. 2). The 10 MU + 10 MU reteplase double-bolus dosing regimen produced the highest 60 and 90 min patency rates of all the treatment regimens. Importantly, the improved coronary artery patency with reteplase was not associated with an increased risk of bleeding or adverse clinical outcomes (Table 3).
Figure 2  TIMI 3 (Thrombolysis in Myocardial Infarction perfusion grade) patency in the infarct related artery after initiation of therapy with alteplase (■) or reteplase (□) in the Reteplase Angiographic Phase II International Dose-finding Study (RAPID 1). Significant differences were observed at 60 min, at 90 min, and at hospital discharge (5–14 days). *P<0.05, †P<0.01, ‡P<0.001 compared to alteplase. (Data from [9].)

Table 3  RAPID 1: Incidence of bleeding complications and adverse clinical outcomes within 30 days

<table>
<thead>
<tr>
<th></th>
<th>r-PA (n=154)</th>
<th>r-PA, 10+10 MU (n=154)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bleeding complications, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>4 (2-6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Transfusions (excluding surgical transfusion)</td>
<td>14 (9-11)</td>
<td>21 (13-6)</td>
</tr>
<tr>
<td>Transfusions (excluding surgical patients and catheter site bleeding)</td>
<td>7 (4-5)</td>
<td>6 (3-9)</td>
</tr>
<tr>
<td><strong>Adverse clinical outcomes, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>6 (3-9)</td>
<td>3 (1-9)</td>
</tr>
<tr>
<td>Stroke</td>
<td>6 (3-9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Disabling</td>
<td>3 (1-9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Reinfarction</td>
<td>7 (4-5)</td>
<td>4 (2-6)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>9 (5-8)</td>
<td>9 (5-8)</td>
</tr>
</tbody>
</table>

Abbreviations from Table 2.
(Adapted from [8] with permission.)

Conclusions
The bolus administration of 10 MU of reteplase followed by an additional 10 MU bolus 30 min later resulted in TIMI 3 flow rates, both early and at hospital discharge, superior to those obtained with standard dose alteplase. Additionally, TIMI 3 flow may occur earlier after bolus administration of reteplase than after initiation of alteplase.

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Rapid 2: reteplase vs accelerated alteplase

This study was designed to compare coronary perfusion rates and the need for acute coronary intervention in AMI patients treated with a double bolus (10 MU + 10 MU) of reteplase or 'accelerated' alteplase (15 mg bolus, 0.75 mg kg⁻¹ infused over 30 min, followed by 0.5 mg kg⁻¹ infused over 60 min) [10]. One hundred and sixty nine patients were randomized to receive reteplase and 155 to receive alteplase.

Study design
Patients enrolled were older than 18 years, presented within 12 h of the onset of at least 30 min of typical chest pain not relieved by nitroglycerin and accompanied by ECG ST-segment elevation. The primary outcome measure was coronary artery patency as assessed by TIMI flow grade at coronary angiography 90 min after initiation of thrombolytic therapy. Secondary endpoints included TIMI 2–3 patency at 30 min, 60 min and 5–14 days after thrombolysis; reocclusion at 5–14 days after therapy; and global (ejection fraction) and regional (infarct zone) left ventricular function at 90 min and 5–14 days after therapy. TIMI 2–3 patency and TIMI 3 flow rate were determined by a core laboratory blinded to treatment assignment. Whereas TIMI 3 flow rate can vary as much as 15% between laboratories, patency varies within 1–2%. The incidence of stroke, reinfarction, heart failure and angina were also monitored as was the need for angioplasty, bypass surgery, intracoronary thrombolysis, atherectomy, rotablation, within 35 days. Bleeding episodes were also documented. Adjunctive therapy consisted of aspirin and heparin in standard conventional doses.

Results
At both the 60 and 90 min angiographic evaluations, significantly higher rates of TIMI 3 and combined TIMI 2–3 patency were demonstrated with reteplase than with accelerated alteplase (Fig. 3). Total TIMI 2–3 patency was achieved with reteplase in 82% of patients at 60 min compared to 66% of patients who received accelerated alteplase. At the primary end-point of 90 min, the patency rate was higher (83% vs 73%) and the incidence of normal flow (TIMI 3) higher (60% vs 45%) in the reteplase group than in the accelerated alteplase group (P=0.011). The TIMI 2–3 patency and TIMI grade 3 flow rates in the reteplase group at 60 min were similar to the corresponding 90 min results in the accelerated alteplase group. In addition, significantly fewer reteplase-treated patients required additional interventions during the first 6 h post-treatment than did alteplase-treated patients (14% vs 27%, P=0.004) (Fig. 4).

There was a lower potential for serious bleeding complications in both groups: the incidence of intracranial bleeding was 1.2% in the 169 reteplase-treated patients and 1.9% in the 155 alteplase-treated group. Mortality was 4.2% in the reteplase patients compared with 8.4% in the accelerated alteplase group, a difference
Thrombolytic drugs in AMI

Figure 3  TIMI 2 (○) and 3 (■) flow rates in the infarct related artery in the Reteplase vs Alteplase Patency Investigation During Acute Myocardial Infarction Study (RAPID 2). Significantly more patients demonstrated greater patency with reteplase at 60 and 90 min after initiation of thrombolysis. The differences in patency at 30 min and at hospital discharge (5-14) days were not significant. *P<0.01, †P<0.05 compared to alteplase. Abbreviations as in Fig. 2. (Adapted from [10] with permission.)

Figure 4  Coronary artery interventions performed within 6 h after thrombolytic therapy in RAPID 2. Significantly fewer patients who received reteplase required such procedures as angioplasty, atherectomy, and bypass surgery. *P<0.01 compared to alteplase. Abbreviations as in Fig. 3. (Adapted from [10] with permission.)

that was not statistically significant. However, there was a significant inverse correlation between 35-day mortality and TIMI flow grade, underscoring the importance of early and complete restoration of patency. Regardless of the thrombolytic drug administered, 12.2% of patients with TIMI flow grade 0–1 were dead by 35 days; in contrast, only 3.5% of patients with TIMI grade 2 flow and 4.2% of patients with TIMI grade 3 flow at 90 min died within the same period (P<0.05).

Conclusions
These findings confirm the efficacy, safety and ease of administration of reteplase given as two 10 MU boluses 30 min apart in patients with AMI. Reteplase achieved significantly higher rates of early reperfusion of the infarct related coronary artery than did accelerated alteplase therapy and significantly fewer acute coronary interventions were required in patients who received reteplase therapy. There was no significant difference in the incidence of bleeding or the 35 day mortality rate between the two thrombolytic regimens. Further, the relatively simple double-bolus administration of reteplase facilitated its administration compared to the relatively complex dosing infusion of alteplase.

Inject: evaluating equivalency of reteplase and streptokinase

This study compared reteplase double-bolus administration with standard dose of streptokinase in 6010 patients with AMI. It was designed as a randomized, double-blind trial to show that reteplase had equivalent efficacy to that of streptokinase; it did not have the statistical power to detect possible superiority of one or other treatment regimen in reducing mortality risk. A total of 2965 patients received the double-bolus of reteplase (10 MU+10 MU), and 2971 patients received 1.5 MU infusion of streptokinase over 60 min. Patients also received standard doses of aspirin and heparin.

The trial established that reteplase was as effective as streptokinase in terms of reducing mortality risk; although reteplase was associated with a positive trend toward improvement in mortality rates this was not statistically significant (Fig. 5). Patients in the reteplase group had a significantly lower incidence of atrial fibrillation, asystole, cardiogenic shock, congestive heart failure, hypotension and all allergic reactions than patients receiving streptokinase. The incidences of stroke and bleeding were similar in the two study groups. In a substudy, 1909 patients, early resolution of the elevated ST-segment was found to be the most powerful predictor of 35 day mortality. Complete
resolution of the ECG ST-segment elevation was found in a significantly larger proportion of patients treated with reteplase than in patients treated with streptokinase. Mortality rates were 5% in the reteplase-treated group and 7% in the streptokinase-treated group, but this difference was not statistically significant.

Summary

There is now substantial evidence that shortening the interval from presentation to attainment of patency of the infarct-related coronary artery can lower mortality and morbidity risks in patients with AMI. Two large-scale, controlled clinical trials, RAPID 1 and 2 have demonstrated that reteplase provided earlier patency rates, including restoration of TIMI grade 3 flow, than did alteplase. A third trial, the INJECT Study, also demonstrated that reteplase was at least as effective as streptokinase in reducing mortality after AMI. Compared with other thrombolytic drugs, reteplase was not associated with an increased incidence of adverse events, including bleeding complications. The results of these three trials clearly support the efficacy and safety of reteplase in the treatment of patients with AMI and the simplicity of its double-bolus administration greatly enhances its clinical applicability.

References


