

# Thrombolysis in Myocardial Infarction

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## 1. Introduction

Worldwide around 7 million people suffer myocardial infarctions per year according to White et al. (2008). Around one third of these patients having acute myocardial infarction die within the first hour of having symptoms usually due to fatal arrhythmia. Characteristic ST segment elevation in the 12 lead electrocardiogram (ECG) accompanied by clinical symptoms of chest pain provide the most rapid way to diagnose those patients who should receive thrombolysis to help dissolve thrombus and restore blood flow. In fact, since the early 1980s, thrombolysis has been the cornerstone of treatment for patients having ST segment elevation myocardial infarctions (STEMI) by improving outcomes and preserving left ventricular function. There are in fact many large randomised clinical trials which support early thrombolysis and these can be found in the Fibrinolytic Therapy Trialists' (FTT) Collaborative Group publication from 1994. This document reinforces the importance of early reperfusion with 30 lives per 10000 being saved by thrombolysis given within 6 hours of presentation and 20 lives per 1000 saved if initiation is between 6 and 12 hours.

## 2. Pathophysiology of myocardial infarction

Acute myocardial infarction which is commonly known as a heart attack is the interruption of blood supply and therefore oxygen to heart muscle thereby potentially causing cell death or necrosis. This is usually due to the occlusion of the coronary artery lumen by clot called thrombus. This thrombus is formed by the rupture of unstable arteriosclerotic plaque which consists of white blood cells (mainly macrophages) which engulf lipids to form foam cells covered with a fibrous cap in the arterial wall. The plaque can rupture as a result of many factors including the mechanical shear stress from blood flow and flexion and tension of the fibrous causing it to be injured and thinned. Rupture exposes adhesion molecules in the sub-endothelium which form thrombus when exposed to flowing blood. This allows primary haemostasis to occur, resulting in platelet adhesion, platelet activation and aggregation forming thrombus. Thrombolytic drugs break down this thrombus thereby restoring blood flow and preventing further damage to myocardium. It is therefore obvious to see that the sooner myocardial infarction is diagnosed and the earlier thrombolysis can be given the greater the myocardial salvage.

### 3. Clinical indications

The indications for thrombolysis in myocardial infarction rely on eliciting a history of typical clinical symptoms (mainly but not exclusively chest pain) and diagnosing characteristic changes in the 12-lead electrocardiogram (ECG) which is a non-invasive means of recording the electrical activity of the heart over seconds using transthoracic electrodes. The prompt recognition of the characteristic symptoms and ECG changes are required to institute rapid reperfusion therapy through thrombolysis.

The main clinical symptom of acute myocardial infarction is central or left-sided chest pain which can be described as dull, squeezing or tightness. This is called angina pectoris. The pain most commonly radiates to the left arm but can radiate to the neck, jaw, epigastrium, back and the right side of the chest. The management of myocardial infarction also requires prompt relief of the ischaemic pain with oxygen, opiates and sublingual or intravenous nitrates which act through vasodilatation. Other symptoms are shortness of breath from left ventricular dysfunction and resultant pulmonary oedema due to myocardial ischaemia. The remaining symptoms are due to surges of catecholamines from sympathetic overdrive such as palpitations, nausea, vomiting, light-headedness, weakness, anxiety and excessive sweating termed diaphoresis. Loss of consciousness may also occur and is usually due to arrhythmia as a consequence of ischaemia or cerebral hypoperfusion due to poor left ventricular output and cardiogenic shock. Notably women tend to report more atypical symptoms and so when making a diagnosis clinicians should bare this in mind. To complicate matters further around one quarter of patients suffering an acute myocardial infarction do not have any symptoms at all. These 'silent' myocardial infarctions most commonly occur in the elderly and diabetic patients. This can cause problems when selecting out patients that are suitable for thrombolysis as the clinician would have to rely on the ECG criterion and any other relevant history that is available at that time.

Other scenarios where a history may be difficult to obtain are patients that are acutely breathless from pulmonary oedema or those that have been successfully resuscitated or are being resuscitated from cardiac arrest. In these situations if the ECG shows characteristic changes and the bleeding risk from chest compressions is felt to be low then an experienced clinician can make the decision to proceed with thrombolysis. In cardiac arrests with refractory ventricular fibrillation and a prior history of chest pain or ischaemic heart disease then also in these cases a decision may be taken to give thrombolysis.

### 4. Electrocardiogram criterion

The ECG criterion for thrombolysis are well validated and need to be met before initiation of therapy. As mentioned earlier the ECG is a recording of electrical activity as it spreads through the heart muscle. The ECG can be daunting in its interpretation and in itself a massive topic but here we focus specifically on the parts of the ECG that are relevant for diagnosing acute myocardial infarction suitable for thrombolysis.

Ventricular depolarisation and contraction are represented on the ECG by a waveform termed the QRS complex which is later followed by a smaller deflection termed the T wave which constitutes ventricular repolarisation and relaxation. In fact, repolarisation begins with the ST segment which connects the QRS complex to the T wave. The beginning of the ST segment is termed the J point.

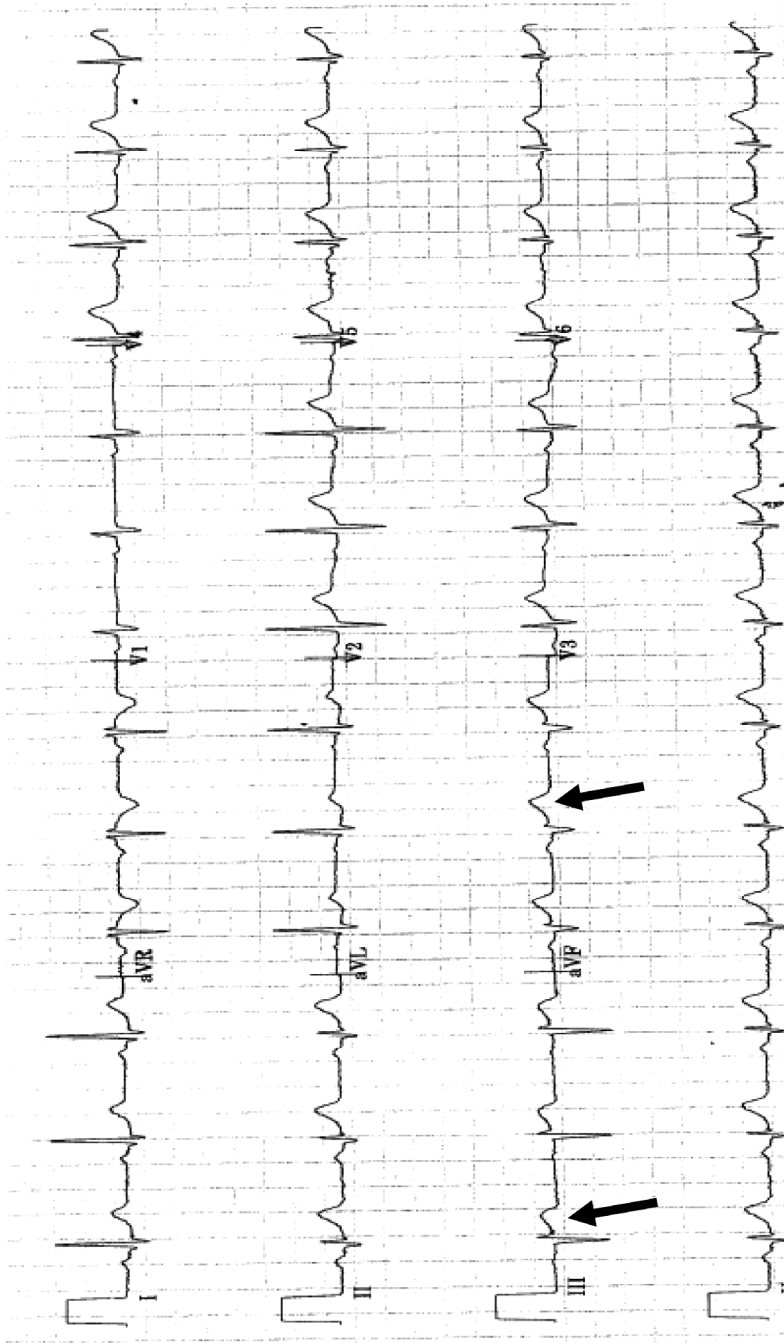


Fig. 1. An electrocardiogram showing ST elevation in leads III and AVF.

The criterion for thrombolysis refer to the QRS complex and ST segments and are as follows:

1. 1mm of ST segment elevation from the J point in at least 2 contiguous limb leads (I, II,III, AVF and AVL)
2. 2mm of ST segment elevation from the J point in at least 2 contiguous chest leads (any two of V1 to V6)

New onset left bundle branch block. This is recognised as characteristic deflections of the QRS complex and an increased width of greater than 120 milliseconds which is 3 small squares on the ECG when the recording speed is set to the usual 25mm/second.

The various limb leads and chest leads pick up electrical signals by literally overlying and 'pointing' towards various parts of the heart. Therefore ECG changes in certain leads represent ischaemia affecting certain territories or areas of heart muscle. ECG changes in leads I and AVR represent ischaemia in the anterior wall of the left ventricle while II, III, and aVF represent the inferior aspect of the heart. The V leads or chest leads show if the anterior-septal area is affected (V1-V4) and the late V leads signify infarction of the lateral wall of the ventricle. Leads I and AVL also represent the lateral territory of the heart. The criterion requires that these changes are in at least two contiguous leads because this is more likely to represent a significant area or 'territory' of myocardium. ST segment changes in a single lead are more likely to be due to other causes the most likely being normal variant due to an earlier repolarisation of the myocardium. Clinicians also need to bear in mind alternative diagnoses which could present with ST elevation by ECG. Acute pericarditis, which is a usually benign condition of pericardial inflammation, can present with ST elevation but typically the ST segment has a saddle-shaped appearance. The clinical symptoms may also mimic myocardial infarction but the classical description is of pain is different in that it is sharp and stabbing which varies with respiration and is also positional. Clinically the patient may also have an audible rub on auscultation using a stethoscope. This is a scratchy noise caused by the inflamed layers of pericardium rubbing against each other. The other condition in which ST elevation may be present is when the patient has an outpouching of the left ventricle termed an aneurysm. Again the ECG can have a more characteristic Clinicians should keep the possibility of these alternative diagnoses at the forefront of their minds to avoid misdiagnosis and therefore inappropriate administration of thrombolysis.

Other ECG changes that accompany ST elevation may also be present and aid the diagnosis of acute ST elevation myocardial infarction. The T waves may become hyperacute and lose their normal concavity. There may also be the presence of a pathological Q wave at the start of the QRS complex which is represented by a negative deflection of at least 1 small square on the ECG (40 milliseconds). This is said to represent infarcted non-viable myocardium. The other common abnormality which can accompany ST elevation is ST depression in reciprocal leads. Essentially, this means that leads looking at the opposite aspect of the heart show a mirror image of the leads showing ST elevation.

## 5. Contraindications for thrombolysis

Contraindications to thrombolysis in myocardial infarction can be separated into absolute and relative ones. Absolute contraindications are suspected dissecting aortic aneurysm, ischaemic stroke within 3 months (except if acute and within 3 hours of symptom onset when it is a treatment), intracranial neoplasm or arterio-venous malformation, active

bleeding diathesis, uncontrolled hypertension (systolic >180mmHg or diastolic >100mmHg), significant closed-head trauma or facial trauma within 3 months.

Rigorous cardiopulmonary resuscitation or compressions of greater than 10 minutes duration is a relative contraindication to thrombolysis. Other scenarios which require precaution include active peptic ulceration, therapeutic anticoagulation with warfarin therapy, active menstruation, pregnancy, recent streptococcal infection of less than five days, controlled severe hypertension, haemorrhagic or diabetic retinopathy and invasive or surgical procedure in the preceding three weeks.

## **6. Evidence base for thrombolysis and alternative strategies**

Initially, streptokinase infusion produced conflicting results until the (GISSI) trial in 1986, which validated streptokinase as an effective therapy and established a fixed regime for its use in acute myocardial infarction. As mentioned earlier the evidence supporting thrombolysis as opposed to not giving thrombolysis is outlined in the Fibrinolytic Therapy Trialists' (FTT) Collaborative Group publication from 1994. This combined the data from 9 trials and included a total of 58,600 patients. Here, the obvious survival advantage of thrombolysis in ST segment elevation in myocardial infarction and left bundle branch block was established. However, excess deaths were noted in the elderly and those thrombolysed after 12 hours of symptom onset. Most notably, it was clearly seen that the earlier thrombolysis was given the greater the benefit. The reason being that the earlier reperfusion is achieved the smaller the infarct size and the greater the myocardial salvage, which in turn has a significant impact on morbidity and mortality. This has led to targets for thrombolysis to be initiated within 20 to 30 minutes of arrival at hospital ("door to needle" time) and within 60 minutes of calling for help ("call to needle" time) across the UK and in Europe.

Primary percutaneous coronary intervention (PPCI) has evolved as an alternative emergency treatment for patients with STEMI. This is an invasive keyhole procedure which involves the passing of thin catheters from the femoral or radial arteries in to the aorta and then in to the openings of the coronary arteries to act as a conduit for various specialized equipment that can be used to treat the acute thrombus. The equipment used for this purpose are primarily clot extraction catheters termed extraction catheters, inflatable balloons and metal stents which act as a scaffold for keeping the arteries open. Although the number of patients receiving this treatment is steadily increasing because of the potential benefits, not all hospitals have the facilities to provide this therapy and so most patients in Europe still receive thrombolysis as initial management.

Once thrombolysis was established as a mode of treatment it was initially given in hospital by clinicians but with the extensive data that early thrombolysis yielded better outcomes there was a move towards pre-hospital thrombolysis (PHT). This involved emergency services giving thrombolysis at the scene on arrival to the patient.

Meta-analyses of RCTs show that PHT is superior to in-hospital thrombolysis (IHT) as it saves on average 30 minutes to 1 hour from the time between calling for medical help and initiation of thrombolysis. The time benefit is even more apparent where ambulance transport times are long. For this reason IHT is only reserved for those places that do not offer PHT or PPCI. When PPCI is not available or offered around the clock then PHT becomes the treatment modality of choice to ensure the maximal myocardial salvage.

Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction (CAPTIM) compared PHT directly against PPCI. This showed that if thrombolysis was administered within 2 hours of symptom onset mortality data at 30 days strongly favoured this treatment over PPCI. However, after 2 hours the trend of outcomes reversed and PPCI became the treatment of choice. This was mirrored in the PRAGUE-2 trial which showed the benefits of IHT up to 3 hours.

In contrast to this the Primary Coronary Angioplasty vs. Thrombolysis (PCAT)-2 Trialists Collaborative Group meta-analysis looked at IHT versus an invasive strategy and showed that PPCI was superior to thrombolysis with lower mortality rates and risk of re-infarction. In the USA, guidelines favour the data on PHT over PPCI but also focus on the time factor with regards to reperfusion. They recommend that PHT should be given within 30 minutes after the arrival of emergency services at the scene and if this is not available and the patient is transferred to a hospital without PPCI facility then IHT should be given within 30 minutes of arrival at the centre (this is termed to door-to-needle time). If PPCI is offered in the hospital then actual disruption of the acute thrombus in the coronary artery should take place within 90 minutes (termed door-to-balloon time). European guidelines differ in that they prefer PPCI as the primary mode for reperfusion but with the several caveats. They stipulate that the procedure should be performed by a skilled operator in a high volume centre (operator performing more than 75 PCIs a year and the centre performing more than 200 PCIs) within 120 minutes of the first medical contact or within 90 minutes in patients receiving medical help within 2 hours from the onset of symptoms. If PPCI is not available then thrombolysis should be given within 3 hours of symptom onset with preference given to PHT over IHT.

## **7. Rescue PCI, routine PCI and facilitated PCI**

When thrombolysis fails then rescue PCI should be considered. In the REACT trial patients that had not been successfully treated by thrombolysis after 90 minutes from initiating therapy (signified by less than 50% resolution of ST segment resolution by ECG) were randomized between conservative management, repeat thrombolysis and rescue PCI. This trial showed a clear benefit of the latter in all outcome data including 6 month mortality. Rescue PCI should therefore be offered to all patients within 12 hours of symptom onset. This may therefore involve patient transfer to a centre that offers a PCI service if not available at the hospital where the patient was thrombolysed or where they were taken after PHT. The exact definition of failed thrombolysis is controversial but the absence of chest pain is considered as misleading as opiates, analgesics and vasodilators may contribute to this. Generally accepted markers are taken as ST segment resolution of less than 50-70% and the time taken to assess whether thrombolysis has taken effect is between 45 and 90 minutes.

All patients should receive PCI subsequent to this, ideally within a period of 24 hours, but a benefit is even seen up to 30 days as evidenced by the CAPTIM trial. GRACIA-1, CARESS-in-AMI and the WEST trials all looked at PCI within a quicker time frame after thrombolysis and the overall results showed that this was comparable to PPCI outcomes when the post-thrombolysis PCI was performed within 24 hours. The very recent TRANSFER-AMI trial reinforced the benefits of a pharmaco-invasive strategy which compared PCI at 6 hours after thrombolysis with 'standard treatment' which involved thrombolysis with delayed angiography and PCI (after 24 hours). There was a statistically significant reduction in the

primary endpoint of combined incidence of death, reinfarction, recurrent ischemia, new or worsening heart failure, or cardiogenic shock at 30 days for the pharmaco-invasive strategy (11% in the pharmaco-invasive arm vs. 17.2% in the standard treatment arm). There was also less recurrent ischaemia (0.2% vs. 2.1%) and reinfarction (3.4% vs. 5.7%) in the pharmaco-invasive strategy and fewer congestive heart failure (3.0% vs. 5.6%). On the other hand, there were more deaths and more patients experiencing cardiogenic shock in the pharmaco-invasive arm but these differences were not statistically significant. There were significantly more minor bleeding episodes in the combined strategy arm when compared to standard treatment but there was no difference in major bleeding. It is important to note that this pharmaco-invasive strategy is very different to thrombolysis followed by *immediate* PCI. This is called facilitated PCI and in fact has failed to show clinical benefit and may in fact be harmful. The reason for this being that if PCI is performed too early then the thrombolytic administered is still active causing increased bleeding risk as well as resulting in more acute stent thrombosis (the potentially catastrophic blocking of a stent by thrombus within 24 hours of it being deployed) which is caused by the increased platelet activation and aggregation which accompanies thrombolytics.

The ideal setting for PHT in the USA involves an experienced physician being available to interpret the ECG by either being part of the Emergency Medical service team on the ambulance or being available to review a copy of a transmitted ECG. This has proved harder to achieve in Europe where more frequently, trained paramedics decide on whether the ECG meets criterion. Some UK studies have shown that this is safe and sometimes even better than the physician-assisted model due to technological issues when transmitting the ECG or failure of mobile phones when trying to communicate to doctors from remote areas. However, in contrast a study in Finland has shown that having physicians on site for PHT is superior to paramedics alone. A checklist of contraindications should also be gone through prior to administration to ensure that the patient is not placed at increased risk of catastrophic bleeding. Therefore, this can also be used as a means of identifying those patients that are more suitable for PPCI.

## 8. Adjunctive therapies for thrombolysis

Aspirin is well established as an adjunctive therapy to thrombolysis and it is recommended that 150 to 325mg of chewable aspirin be given to the patient with thrombolysis. Clopidogrel is an oral, thienopyridine class antiplatelet agent which when given at a dose of 300 mg also provides prognostic benefit. The COMMIT-CCS-2 and CLARITY-TIMI 28 trials provided this evidence for adding clopidogrel to aspirin in patients undergoing fibrinolytic therapy.

It is recommended that unfractionated heparin, an intravenous anticoagulant is given intravenously with all of the thrombolytics to enhance clot dissolution and decrease the risk of re-occlusion. In vitro studies and animal models show discordant results regarding concomitant administration of heparin with thrombolysis suggesting that it may enhance, inhibit or have no effect. Hsia J et al.(1990) have shown that thrombolysis achieves faster lysis with greater vessel patency in combination with heparin (between 7 and 24 hours a patent vessel was found in 88% of those receiving thrombolysis with heparin and aspirin vs. 52% in those treated with thrombolysis and aspirin alone). Unfortunately this does not translate into clinical outcome with a meta-analysis of the six trials by Muhaffey KW et al.

(1996) showing that there were similar rates of mortality and re-infarction before discharge. Despite this the general consensus from expert opinion is that heparin is beneficial in preventing re-occlusion and that it should be given as a bolus with all thrombolytics other than Streptokinase and then be given as a continuous IV infusion. With the advent of low molecular weight heparins (LMWHs) which only need once or twice daily subcutaneous administration without regular blood monitoring the continuous IV infusion of unfractionated heparin has been superseded by these newer anticoagulants. In fact there is evidence that the LMWH, Enoxaparin, appears superior to UFH in the EXTRACT-TIMI 25 trial when given during thrombolysis. In fact, patients under the age of 75 years can be given a 30 mg intravenous bolus followed by the subcutaneous dose every 12 hours. In practice this intravenous preparation LMWH is less widely available and UFH is more commonly given.

## **9. Thrombolytics used in clinical practice**

### **9.1 Streptokinase**

This was the first thrombolytic used in the treatment of STEMI and remains the cheapest and most commonly used. Two large trials were pivotal in demonstrating the efficacy of Streptokinase as a thrombolytic in myocardial infarction which reduces mortality when compared against placebo. The first of these was the GISSI trial mentioned earlier, published in 1986 and included 11,712 patients. This trial showed that at 21 days the mortality for patients treated with Streptokinase was 10.7% vs 13% for the placebo group which represented a statistically significant absolute reduction of 2.3% (risk ratio 0.81; 95% confidence ratio [CI] 0.72 to 0.9). The second trial, ISIS-2 trial included 17,187 patients and was published 2 years after GISSI in 1988. In this study, vascular mortality at 5 weeks was 9.2% in the streptokinase group and 12% in those treated with placebo which represented a statistically significant absolute reduction of 2.8%. Streptokinase is administered as an IV infusion over 1 hour. Streptokinase has a few side-effects which are namely low blood pressure termed hypotension, infrequent allergic reactions and sometimes although not commonly, anaphylaxis. Patients treated with streptokinase develop anti-streptococcal antibodies, which is why patients should only ever receive this drug once in a lifetime.

### **9.2 Alteplase**

A meta-analysis of eight trials which compared alteplase with streptokinase found that there was no significant difference between the two drugs in terms of mortality up to 35 days. However, re-infarction rates were found to be in favour of alteplase but this was offset by a doubling in the risk of haemorrhagic stroke (odds ratio 2.13; 95% CI 1.04 to 4.36). In contrast to this, streptokinase was associated with a statistically significant higher risk of major bleeds than alteplase. However, the definitions of major bleeding varied between the trials and so it is difficult to judge the clinical significance of these findings.

### **9.3 Alteplase**

Alteplase which is also known as recombinant human tissue plasminogen activator or rtPA can be delivered in a standard or accelerated regimen. The accelerated regimen, which is much more commonly used especially in PHT because of its ease of administration as it is



delivered by an initial IV bolus injection. This is followed by only two IV infusions at 30 minutes and 60 minutes. The GUSTO-I trial was the only study in the meta-analysis mentioned above which looked at the more commonly used accelerated regimen rather than the standard regimen. This trial which included over 40000 patients was also the only trial to demonstrate superiority over different thrombolytics with an absolute reduction in mortality at 30 days of 1.0% (6.3% versus 7.3%; 95% CI 0.4% to 1.6%) in favour of accelerated alteplase when compared to streptokinase. However, this benefit was balanced by a statistically significantly higher incidence of haemorrhagic stroke (odds ratio 1.42; 95% CI 1.05 to 1.91). Using a combined outcome measure of mortality and disabling stroke, there was in fact a statistically significant absolute advantage of streptokinase over alteplase of 0.9%;  $p = 0.006$ ). Interestingly, statistically significant rates of moderate bleeding or worse were lower in the alteplase group. Alteplase also fared better with regards to the common side effects experienced by streptokinase namely causing less allergic reactions, anaphylaxis, and sustained hypotension and these were also statistically significantly lower. Despite this a further meta-analysis of nine trials comparing standard alteplase with streptokinase, including the findings of GUSTO-I (i.e. accelerated alteplase), found no significant difference between the two drugs in terms of mortality up to 35 days (odds ratio 0.94; 95% CI 0.85 to 1.04).

#### 9.4 Reteplase

This is the third most commonly used thrombolytic and one of the easiest to administer as it only involves two IV boluses administered 30 minutes apart. The INJECT study involving nearly 6000 patients compared reteplase to streptokinase. This study found an absolute difference in 35 day mortality of 0.5% (95% CI -1.98% to 0.96%) in favour of reteplase but this was not deemed as statistically significant. Similarly to alteplase, when a combined outcome measure using overall effects on mortality and disabling stroke is applied to the trial data then reteplase may in fact be inferior to streptokinase, as the trial also found a statistically significantly lower risk of haemorrhagic stroke in the streptokinase group (odds ratio 2.1; 95% CI 1.02 to 4.31). However, the trial also found that the in the reteplase group the rates of heart failure (23.6% vs 26.3%,  $p < 0.05$ ) and allergic reactions (1.1% vs 1.8%,  $p < 0.05$ ) were significantly lower. In one small study of 324 patients (RAPID-2), reteplase was compared to alteplase and this found that better vessel patency was achieved when coronary angiography was the endpoint. Subsequent to this the large GUSTO-III trial involving 15,059 was designed to test the clinical superiority of reteplase over accelerated alteplase. However, GUSTO-III found no statistically significant difference between the two drugs, in terms of survival or adverse effects but at 30 days mortality was 7.5% in the reteplase group and 7.2% in the accelerated alteplase group giving an absolute risk reduction of 0.23% in favour of accelerated alteplase (95% CI -1.10% to 0.66%). Therefore, reteplase cannot be considered as equivalent to accelerated alteplase.

#### 9.5 Tenecteplase

This is the easiest of the thrombolytics to administer and only involves a single bolus. ASSENT-2 enrolled over 16,000 patients to compare tenecteplase and accelerated alteplase and found that 30-day mortality was the same in the tenecteplase group and the accelerated alteplase at 6.2% each, thereby showing equivalence in outcomes. In fact there was an

absolute difference of 0.03% in favour of accelerated alteplase but this was not statistically significant (95% CI -0.55% to 0.61%). However, there was a small but statistically significant reduction in the incidence of bleeding with tenecteplase of 26.4% compared with 28.9% in the accelerated alteplase group. This resulted in fewer blood transfusions in the tenecteplase group (4.3% of patients compared with 5.5% in the accelerated alteplase group).

In summary, with regards to clinical effectiveness and mortality, standard alteplase and reteplase are as effective as streptokinase, and tenecteplase is as effective as accelerated alteplase. According to GUSTO-I, accelerated alteplase is believed to be superior to streptokinase and if this is the case then indirectly tenecteplase would also be considered to be superior to streptokinase (as tenecteplase was superior to accelerated alteplase in ASSENT-2). In practice, cost and availability is a significant issue with regards to what is ultimately used and also use may also go unchanged for long periods purely because of a specific thrombolytic having historical use in a certain area.

### 9.6 Other considerations

In the elderly, evidence suggests that thrombolysis provides a mortality benefit but that there is increased risk of adverse events and poor outcomes in those with advancing age. The main risk in the older age group is of intracerebral haemorrhage and this is why a clear benefit is seen for PPCI in patients above the age of 75 and in fact the benefit is maintained even when there are longer door-to-balloon times. Low body weight has also been found to be independently associated with increased mortality and morbidity. With regards to sex, it is accepted that there is no difference with regards to efficacy but studies have shown that for unknown reasons women are less likely to receive any type of reperfusion (thrombolysis or PPCI) than men. Anterior infarcts also seem to show an increased benefit with thrombolysis over other territories but this may simply reflect the increased baseline risk in this group. Overall, when clinicians are deciding who would benefit from thrombolysis it appears that patient selection is key and benefits should be balanced against any potential risks.

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