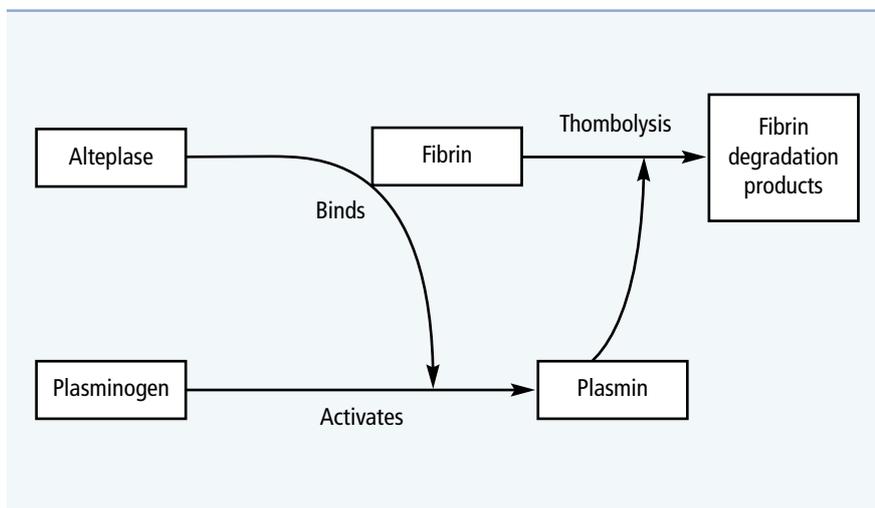


# Alteplase



**Figure 1.** Alteplase binds to fibrin within a thrombus, converts plasminogen to plasmin and thereby initiates fibrinolysis

## Introduction

Stroke is the second most common cause of worldwide mortality and remains the leading cause of adult disability. Approximately 85% of strokes are ischaemic in nature and predominantly secondary to thromboembolic disease. The emergence of percutaneous coronary intervention (PCI) means that the major use of thrombolysis is now in acute ischaemic stroke.

Alteplase became available in the 1990s and currently remains the only licensed thrombolytic treatment for this indication. It can be used in ischaemic strokes within 4.5 hours of onset of symptoms, but due to its potential bleeding complications, in particular intracerebral haemorrhage, patients are selected carefully on the basis of their eligibility.

## Pharmacology

Figure 1 outlines the pharmacological action of alteplase. It is manufactured by recombinant DNA technology using the naturally occurring enzyme tissue plasminogen activator (t-PA). This is located on endothelial cells, and catalyses the conversion of plasminogen to plasmin. Alteplase binds to fibrin within a thrombus, converts plasminogen to plasmin and thereby initiates fibrinolysis. It produces

limited conversion of plasminogen in the absence of fibrin.

It is given at a dose of 0.9mg/kg (maximum of 90mg), with a 10% bolus over 1 minute and the remainder over 1 hour via continuous infusion and reaches its peak plasma concentration within 20–40 minutes. Half life is less than 5 minutes, and plasma clearance rate is 380–570ml/min via the liver, with excretion in urine.

## Trials of safety and efficacy

The National Institute of Neurological Disorders and Stroke (NINDS) was the first, in 1995, to demonstrate benefit from thrombolysis therapy when used within 3 hours of symptom onset.<sup>1</sup> This randomised, double-blind trial of intravenous recombinant tissue plasminogen activator (t-PA) for ischaemic stroke was done in two parts looking at immediate outcomes and at three months (291 and 333 patients enrolled respectively) in terms of disability using a combination of scoring systems (Barthel index, NIHSS score, modified Rankin scale and Glasgow outcome scale). There was no difference in immediate benefit but the odds ratio for a favourable outcome in the t-PA group at three months was 1.7 (95% confidence interval [CI] 1.2 to 2.6;  $p=0.008$ ).

### Natalie Rennie

MRCP(UK), Specialty Trainee in Acute Medicine, Queen Elizabeth University Hospital, Glasgow, UK

### Miles Fisher

MD, FRCP, Consultant Physician, Glasgow Royal Infirmary, UK

### Gerry McKay

BSc (Hons), FRCP, Consultant Physician, Glasgow Royal Infirmary, Glasgow, UK

### Correspondence to:

Professor Gerry McKay, Wards 3, 4 & 5, Glasgow Royal Infirmary, Glasgow G4 0SF, UK; email: gerard.mckay@ggc.scot.nhs.uk

The third European-Australasian Cooperative Acute Stroke Study (ECASS-3) demonstrated efficacy beyond this to extend the time to treatment to 4.5 hours.<sup>2</sup> A total of 821 patients were randomised in a 1:1 ratio with the primary endpoint being major disability at 90 days using the modified Rankin scale. More patients had a favourable outcome with alteplase than with placebo (52.4% vs 45.2%; odds ratio 1.34; 95% CI 1.02 to 1.76;  $p=0.04$ ). In a predefined secondary outcome using combined disability outcome scores, alteplase was superior to placebo (odds ratio 1.28; 95% CI 1.00 to 1.65;  $p<0.05$ ). The incidence of intracranial haemorrhage was higher with alteplase than with placebo (for any intracranial haemorrhage, 27.0% vs 17.6%;  $p=0.001$ ; for symptomatic intracranial haemorrhage, 2.4% vs 0.2%;  $p=0.008$ ), but mortality did not differ significantly (7.7% and 8.4%, respectively;  $p=0.68$ ).

The third International Stroke Trial (IST-3) incorporated patients of different ages and severity of stroke, and concluded that age should be no barrier to thrombolysis and studies looking at thrombolysis use beyond 4.5 hours are required.<sup>3</sup>

In terms of monitoring safety the Safe Implementation of Treatments in Stroke (SITS) registry is a non-profit, research driven, independent and international collaboration, initiated by the medical profession to assure excellence in acute and secondary prevention stroke treatment and to facilitate clinical trials.<sup>4</sup> It includes specific data and studies on the safety of alteplase. The SITS network now includes over 1400 stroke centres in more than 65 countries on five continents. Figures to date include over 135 000 recruited patients.

Although there are strict criteria in the US for use of thrombolysis beyond the 3-hour window, guidelines in the UK and Europe, including those of the Scottish Intercollegiate Guideline Network (SIGN), the National Institute for Health and Care Excellence (NICE), and the European Stroke Organisation (ESO), all recommend thrombolysis treatment up to 4.5 hours which is considered to be cost effective.

### Specific evidence for use in diabetes

Diabetes is an independent risk factor for stroke disease. Diabetes and admission hyperglycaemia are predictors for poor outcome after thrombolysis, in addition to increasing the risk of symptomatic intracerebral haemorrhages. Despite the poorer outcomes, stroke patients with diabetes have better outcomes after thrombolysis than those not thrombolysed, and therefore they should not be excluded from thrombolytic treatment.

This benefit has been clearly demonstrated in a study using a large risk registry of over 4000 patients.<sup>5</sup> Functional outcome (modified Rankin scale) was significantly better in thrombolysed versus non-thrombolysed patients with diabetes at discharge from the stroke unit ( $p<0.001$ ) and three months later ( $p=0.006$ ), with no significant difference in symptomatic intracerebral haemorrhage (4.9% and 3.5%, respectively).

Hypoglycaemia (blood glucose  $<2.8$ mmol/L) is a contraindication to thrombolysis due to its potential to mimic the presentation of acute ischaemic stroke. Within the guidelines for use of alteplase, glucose levels  $<2.8$ mmol/L or  $>22.2$ mmol/L are contraindications.

Pending results from ongoing trials, there is no evidence to support the use of insulin regimens to control blood glucose in acute ischaemic strokes.

### Discussion

Thrombolysis with alteplase is a proven and effective treatment for ischaemic stroke, but it is critically time dependent. It is known that there is an association with diabetes/hyperglycaemia and less favourable outcomes compared to those without diabetes. Hyperglycaemia is thought to hinder the fibrinolytic effect of alteplase, as well as increase the concentrations of blood plasminogen activator inhibitor, which may cause a delay in the reperfusion of the ischaemic penumbra. It also increases the risks of intracerebral haemorrhage. This increased risk of haemorrhage is considered to be secondary to microvascular damage directly from

### Key points

- Alteplase is licensed for the treatment of acute ischaemic stroke up to 4.5 hours
- Diabetes and hyperglycaemia are associated with poorer outcomes in acute ischaemic stroke even in those thrombolysed
- Patients with diabetes with acute ischaemic stroke have better functional outcomes when thrombolysed compared to those not thrombolysed

the biochemical effect the hyperglycaemia has on the vascular endothelial cells. It is also thought that stroke patients with diabetes have a higher prevalence of large vessel atherothrombotic disease, and thrombolysis is less efficacious in this stroke subtype, due to failed recanalisation rates. However, diabetes or hyperglycaemia should not be considered to be a reason for withholding treatment with thrombolysis for those with an acute ischaemic stroke as the evidence for benefit, while less than for those without diabetes, is still statistically and potentially for the patient clinically significant.

### Declaration of interests

Professor McKay has received honoraria for talks, advisory boards and support for attendance at conferences from Boehringer Ingelheim. Professor Fisher has received honoraria for talks and advisory boards from Boehringer Ingelheim.

### References

1. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischaemic stroke. *N Engl J Med* 1995;333:1581–8.
2. Hacke W, et al.; ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischaemic stroke. *N Engl J Med* 2008;359:1317–29.
3. The IST-3 collaborative group. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial (IST-3): a randomised controlled trial. *Lancet* 2012;379:2352–63.
4. <https://sitsinternational.org/> [accessed 23 September 2015].
5. Reiter M, et al.; Austrian Stroke Unit Registry Collaborators. Diabetes and thrombolysis for acute stroke: a clear benefit for diabetics. *Eur J Neurol* 2014;21:5–10.