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Comparative efficacy of thrombolytics in acute myocardial infarction: a systematic review

Y. DUNDAR, R. HILL, R. DICKSON and T. WALLEY

From the Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool, UK

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Summary

Background: The comparative clinical effectiveness of new (reteplase, tenecteplase) vs. older (alteplase, streptokinase) thrombolytic agents in the treatment of acute myocardial infarction is uncertain.
Aim: To examine 30–35 day mortality and major adverse effects of thrombolytic agents in the treatment of acute myocardial infarction.
Design: Systematic review of randomized controlled trials comparing the clinical efficacy of included drug regimens.
Methods: We searched MEDLINE, EMBASE, Science Citation Index/Web of Science from 1980 to December 2001, and the Cochrane Library (2001, Issue 4). Reference lists of included studies and a number of medical journals were hand searched. Randomized controlled trials that compared any two of the included drugs provided to patients in the early stages of acute myocardial infarction, were included. Outcome measures included: mortality, bleeding, stroke, reinfarction, allergy and anaphylaxis.
Results: We found 14 studies, total study population 142 907. For available comparisons (all alteplase vs. streptokinase, reteplase vs. streptokinase or alteplase, tenecteplase vs. alteplase), meta-analysis showed no significant differences in mortality at 30–35 days. The GUSTO-I study showed an apparent benefit of accelerated alteplase over streptokinase, but its inclusion or exclusion made little difference. Total stroke and haemorrhagic stroke rates were lower for streptokinase than for all alteplase combined (total stroke, OR 1.29, 95%CI 1.13–1.46; haemorrhagic stroke OR 1.83, 95%CI 1.14–2.93).
Discussion: All thrombolytic drugs appear to be of similar efficacy in reducing mortality, and the apparent benefits of accelerated alteplase in GUSTO-I are consistent with this. Whether accelerated alteplase is sufficiently different from other regimens of administering alteplase to be excluded from a meta-analysis, and whether more weight should be placed on a meta-analysis than on a single trial, are matters for debate.

Introduction

The benefits of thrombolytic therapy in patients with acute myocardial infarction are well established, in the meta-analyses by Yusuf *et al.*[1] and by the Fibrinolytic Therapy Trialists (FTT) Collaborative Group who showed that thrombolytic therapy decreases mortality at 35 days by 1.9%.[2] Later trials compared the effectiveness of a variety of agents, but especially streptokinase and alteplase.

Address correspondence to Professor T. Walley, Department of Pharmacology and Therapeutics, University of Liverpool, 70 Pembroke Place, Liverpool L69 3GF. e-mail: twalley@liv.ac.uk

The 'first generation' thrombolytics had clinical disadvantages such as low specificity for fibrin, increased risk of allergic reactions (in particular with streptokinase) and short half-life. Newer thrombolytic agents such as reteplase and tenecteplase have been developed with potential advantages that include: prolonged half-life, increased fibrin specificity and increased resistance to inhibition by plasminogen activators. However, these laboratory-measured advantages may not translate into measurable clinical benefits. For instance, the new thrombolytic drug lanoteplase was withdrawn from development as a result of in an increased incidence of intracranial haemorrhage.[3,4]

We therefore conducted a systematic review to examine the comparative effectiveness of older and newer agents used for early thrombolysis, so as to allow recommendations to be made to service users. If there were appropriate head-to-head comparisons between all thrombolytic drugs, then drawing conclusions from such a review would be simple. However, such direct comparisons do not exist, and therefore indirect comparisons were required to inform clinical guidance. This required a two-stage process: the first evaluating and comparing the evidence from clinical trials, and the second an indirect and therefore more speculative comparison where interpretation of data was more difficult.

This paper presents the results of the systematic review, the first of these two processes; the second is described in the accompanying commentary.[5]

Methods

The review was restricted to those drugs currently available in the UK, i.e. streptokinase, alteplase, reteplase and tenecteplase. Two other drugs, anistreplase and urokinase, are licensed in the UK but are not available for commercial reasons.

Searching

The search strategy covered the period from 1980 to December 2001, and included the following electronic databases: MEDLINE, EMBASE, Science Citation Index/Web of Science and The Cochrane Library (2001, Issue 4). Search terms used were 'myocardial infarction', 'heart infarction' and 'thrombolysis' combined with drug terms (e.g. alteplase (t-PA) reteplase, streptokinase and tenecteplase). In addition, reference lists of included studies were examined and a number of medical journals were hand-searched to identify other potentially relevant papers.

Selection of studies

Studies included in the review were randomized controlled trials that compared the effectiveness of any two of the studied thrombolytic agents used in patients experiencing acute myocardial infarction. The review focused on clinical outcomes, and included mortality, bleeding, stroke, re-infarction, allergy and anaphylaxis.

Quality assessment

Two reviewers assessed the methodological quality of included studies independently using the criteria based on the NHS Centre for Reviews and Dissemination (CRD) Report No. 4.[6] Components of study quality included in this tool are: study randomization, baseline comparability, eligibility criteria, blinding, number of and reasons for withdrawals, and whether an intention-to-treat analysis was used.

Data extraction

Data were independently extracted by one reviewer and checked by a second.

Meta-analysis

Meta-analysis used RevMan 4.1.1 (Cochrane collaboration). Treatment effects are presented using odds ratios (OR) with corresponding 95%CIs, using a random effects model. Analysis of data included mortality (30–35 day), stroke (total and haemorrhagic), major bleed and reinfarction.

Results

A total of 162 references were identified, of which 20 studies (reported in 50 publications) met the inclusion criteria. Of these, four were dose-ranging trials and two were comparisons of the same drug. The review therefore includes 14 studies,[7–21] involving a total study population of 142 907 participants. Two studies (ISG and GISSI-2) provided combined data and this combination of data was maintained in the review. All the studies were conducted in hospital settings.

Table 1 Characteristics of studies

Study	Interventions	*n*	Location	Primary endpoint	Other outcomes	Adjunct treatment(s)
Alteplase/streptokinase						
GUSTO I*	Acc t-PA SK SK+ t-PA SK 1.0 MU/1 hour, t-PA 1.0 mg/kg/one hour	10 396 20 251 10 374	International 1081 hospitals 15 countries	Mortality 30-day	Combined 30-day mortality or non-fatal stroke or non-fatal haemorrhagic stroke Combined 30-day, mortality or non-fatal disabling stroke	Aspirin Heparin
Central Illinois	t-PA 10 mg bolus, followed by 50 mg in the first hour, and 20 mg/hour for the next 2 hours SK 375 000 IU bolus, followed by 1 125 000 IU/1 h	123 130	USA 30 hospitals	Not stated	LVF Mortality Bleeding Stroke Allergic reactions	Aspirin IV heparin
Cherng	t-PA SK	59 63	Taiwan	Unclear	Patency LVF Bleeding Mortality	Aspirin IV nitroglycerin IV heparin
ECSG	t-PA 0.75 mg/kg 90 min SK	64 65	Europe 7 hospitals	Not stated	Patency Mortality Adverse events—used their own criteria	IV heparin SK group also got aspirin
GISSI-2/ISG	t-PA SK 1.5 MU/30–60 min	10 372 10 396	International 14 countries	Mortality in-hospital	Mortality (discharge + 6 months) Major adverse events	Aspirin Heparin (50%)
Alteplase/streptokinase						
ISIS-3	t-PA SK APSAC 30 units over 3 minutes	13 746 13 780 13 773	International 914 hospitals 17 countries	Mortality 35-day	Allergy ↓BP Stroke Shock PE VF Cardiac arrest Reinfarction	Aspirin (all patients) Heparin (half of patients)
PAIMS	t-PA SK	86 85	Italy 8 hospitals	Thrombolytic efficacy and effects on LVF	Time to reperfusion ECG output Intensity of chest pain Adverse events	Heparin NTG

Table 1 continued

Study	Interventions	*n*	Location	Primary endpoint	Other outcomes	Adjunct treatment(s)
TIMI-1	t-PA	157	USA 13 hospitals	Recanalization at 90 min	LVF	IV heparin
	SK	159			EF	IC nitroglycerin
					Adverse events	
White	t-PA	135	New Zealand	LVF	Patency rates at 3 weeks	Aspirin
	SK 1.5 MU/30 min	135	4 hospitals		Reinfarction	IV heparin
					Adverse events	
					Mortality	
Alteplase/alteplase and streptokinase						
KAMIT	t-PA	107	USA	Patency at 90 min	In-hospital reocclusion	Aspirin
	t-PA (half dose—10 mg bolus the 40 mg/l h) + SK (1.5 MU)	109			LVF	Heparin
					Bleeding	
					Recurrent ischaemic events	
Alteplase/tenecteplase						
ASSENT-2 $^{+}$	Acc t-PA	8488	International	Mortality 30-day	Non-fatal stroke	Aspirin
	TNK 30–50 mg, single bolus, weight-adjusted	8461	29 countries 1021 hospitals		Major non-fatal cardiac events	IV heparin
					Stroke	
Alteplase/reteplase						
GUSTO III*	Acc t-PA	4921	International	Mortality 30-day	Net clinical benefit (freedom from death or disabling stroke)	Aspirin
	r-PA	10 138	20 countries 807 hospitals			Heparin
					Death or stroke	
					Adverse events	
RAPID 2*	Acc t-PA	155	USA 20 Germany	Patency at 90 min	Patency rates	Aspirin
	r-PA	169	5 hospitals		Left ventricular function	IV heparin
					Stroke	
					Reinfarction	
					Bleeding	
					Death	
Streptokinase/reteplase						
INJECT	SK	3006	Europe 9 countries	Mortality 35-day	Intracerebral events	Aspirin
	r-PA	3004	208 hospitals		Bleeding	IV heparin
					Cerebrovascular events	
					Allergic reactions	
					Reinfarction	

*Involved accelerated alteplase. t-PA, alteplase; SK, streptokinase; TNK, tenecteplase; r-PA, reteplase.

Study characteristics

Studies are summarized in Table 1 and ranged in size from 122 to 41 299 patients. Ten studies compared alteplase and streptokinase. Of these, one[7] used accelerated administration of alteplase, which includes a bolus dose, followed by infusion over 90 min. One study compared alteplase to tenecteplase, two studies compared accelerated alteplase with reteplase, and one study compared streptokinase with reteplase. No study provided a direct comparison of reteplase and tenecteplase.

Meta-analysis

A formal meta-analysis was performed for those comparisons where there was more than one relevant trial. The inclusion of GUSTO I in such a meta-analysis is controversial, since it is argued the accelerated regimen is sufficiently different from the older regimen used in most trials. Therefore, data comparing streptokinase and alteplase are presented in two analyses, one including and one excluding the GUSTO I study. There is no statistical evidence for heterogeneity between studies in either analysis. An inability to confidently extract data related to bleeding events from GUSTO I precluded its inclusion in the analysis.

The main results of the meta-analysis were as follows:

All alteplase vs. streptokinase (Figure 1)

No difference in mortality or reinfarction. Total stroke and haemorrhagic stroke rates were lower in streptokinase group.

Alteplase excluding accelerated alteplase vs. streptokinase (Figure 2)

No difference in mortality. In the streptokinase group, there was a lower incidence of total stroke and haemorrhagic stroke. Major bleed and reinfarction rates were lower in the alteplase group.

Accelerated alteplase vs. reteplase (Figure 3)

No differences in mortality, total stroke, haemorrhagic stroke, major bleeds or reinfarction. Data on haemorrhagic stroke, major bleeds or reinfarction were only available for GUSTO-III, but this accounts for 98% of the patients studied.

For the following two comparisons, there was only one study reported: these are summarized in Table 2.

Accelerated alteplase vs. tenecteplase

No differences in mortality, total stroke, haemorrhagic stroke or reinfarction. Fewer major bleeds with tenecteplase.

Reteplase vs. streptokinase

No differences in mortality, total stroke, major bleeds. There was a lower incidence of haemorrhagic strokes in the streptokinase group.

Adverse events

There are substantial differences in the definition of bleeding events reported in the studies. Therefore, as would be expected, the reported rates for a 'major bleed' varied between 0%[17] and 18% for streptokinase.[8] We found a slightly higher risk of major bleed associated with the use of streptokinase than with alteplase (Figure 1).

There was a significantly higher risk of stroke, largely accounted for by an increase in the incidence of haemorrhagic stroke, associated with the use of alteplase compared to streptokinase. This difference was statistically significant in both meta-analyses (Figures 1 and 2) and in GUSTO I (alteplase 0.72%, streptokinase 0.52%). Reteplase was also associated with an increased tendency to stroke and a significant increase in haemorrhagic stroke when compared to streptokinase (Table 2). No differences were found between alteplase and reteplase in GUSTO III or between alteplase and tenecteplase in ASSENT-2.

When compared with other thrombolytic drugs, streptokinase was associated with a higher incidence of allergic reactions, which also included anaphylaxis.

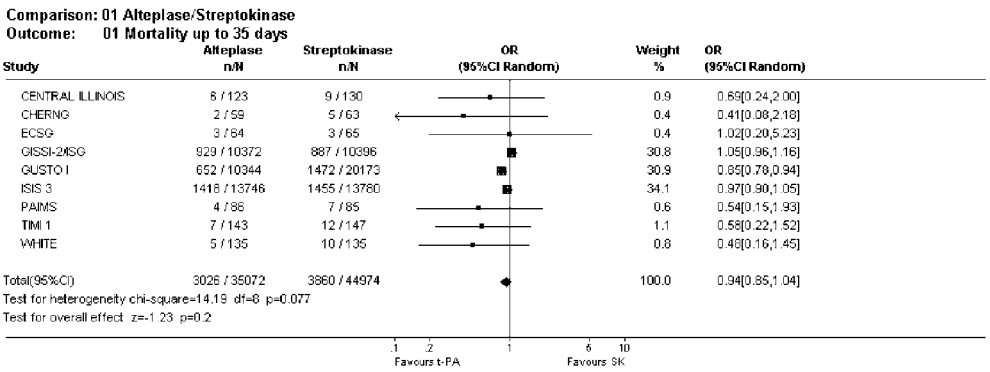
There was no significant difference between any of the drugs with regard to reinfarction rates.

Subgroups

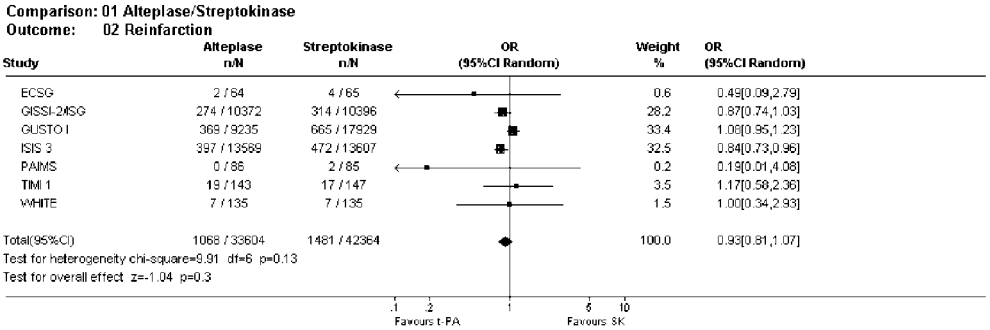
Six studies[7,11–13,18,19,21] conducted subgroup analyses of mortality at 30–35 days, which were based on the three most common subgroups of patients including age, infarct location and time from symptom onset.

There were no consistent differences with respect to drugs in these subgroups. There were some apparent differences between reteplase and alteplase in GUSTO III (better mortality benefit in late-treated patients with alteplase) and between tenecteplase and alteplase in ASSENT-2 (absolute difference of 2% in 30-day mortality favouring tenecteplase in patients treated within 4 h of symptom onset).

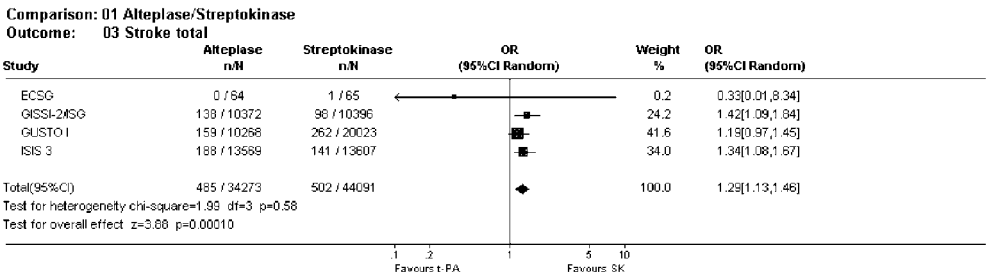
i. Mortality



ii. Reinfarction



iii. Total stroke



iv. Haemorrhagic stroke

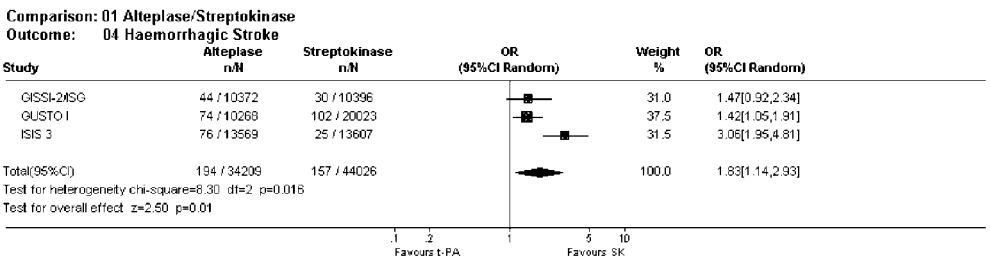
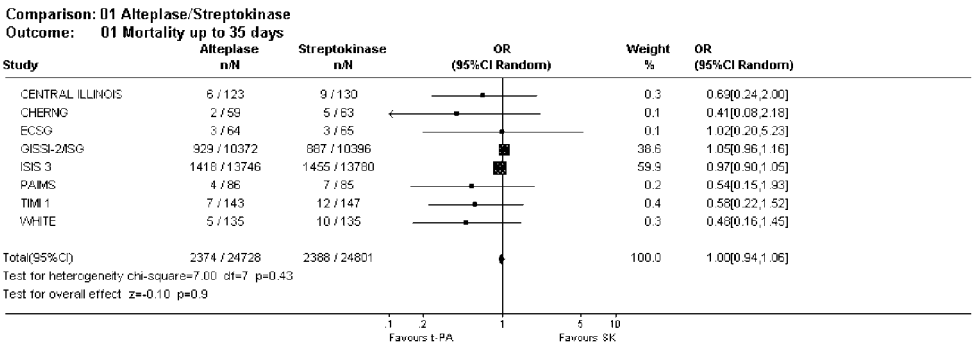
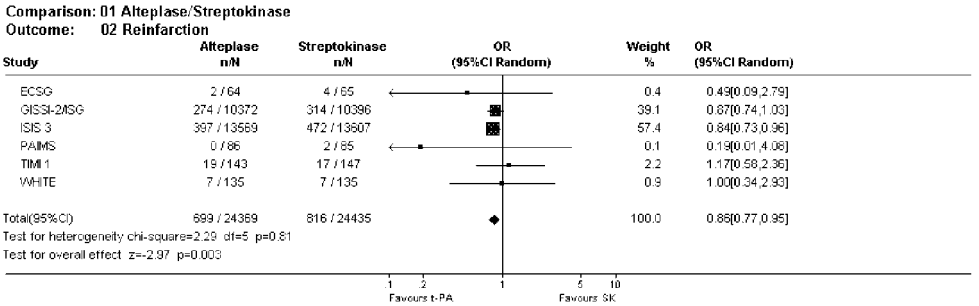


Figure 1. Meta-analyses: all alteplase (including accelerated and non-accelerated alteplase regiments) vs. streptokinase. t-PA, alteplase; SK, streptokinase.

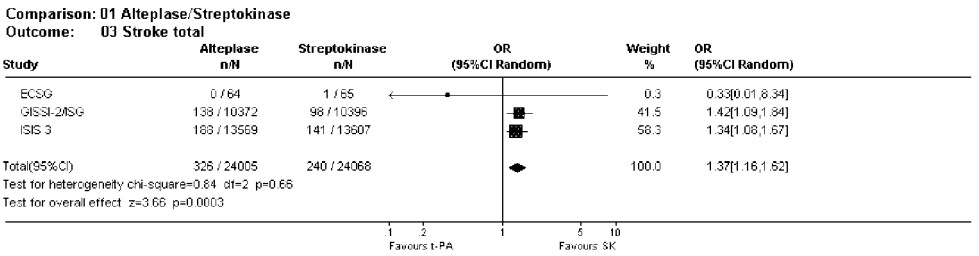
i. Mortality



ii. Reinfarction



iii. Total stroke



iv. Haemorrhagic stroke

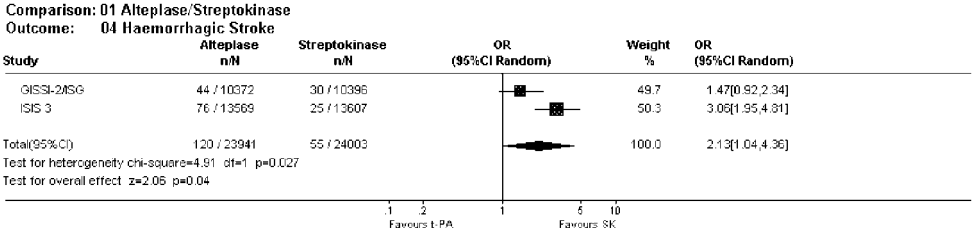


Figure 2. Meta-analyses: alteplase excluding accelerated alteplase (no GUSTO I) vs. streptokinase. t-PA, alteplase; SK, streptokinase.

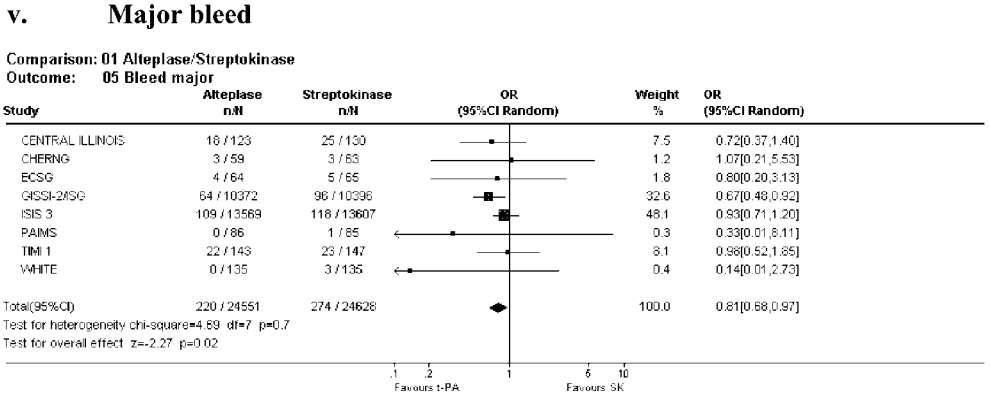


Figure 3. Meta-analyses: accelerated alteplase vs. reteplase. t-PA, alteplase; r-PA, reteplase.

Table 2 Meta-analyses: single study comparisons

a. Accelerated alteplase/tenecteplase—ASSENT-2

Outcome	Acc Alteplase	Tenecteplase	OR random effect (95%CI)
Mortality-up to 35 days	522/8488	523/8461	0.99 (0.88–1.13)
Reinfarction	323/8488	347/8461	0.93 (0.79–1.08)
Stroke	141/8488	151/8461	0.93 (0.74–1.17)
Hemorrhagic stroke	80/8488	79/8461	1.01 (0.74–1.38)
Major bleed	504/8488	394/8461	[a]*1.29 (1.13–1.48)

b. Reteplase/streptokinase—INJECT

Outcome	Reteplase	Streptokinase	OR random effect (95%CI)
Mortality-up to 35 days	270/2994	285/2992	0.94 (0.79–1.12)
Stroke (total)	37/2994	30/2992	1.24 (0.76–2.00)
Hemorrhagic stroke	23/2994	11/2992	[b]*2.10 (1.02–4.31)
Major bleed	138/2994	141/2992	0.98 (0.77–1.24)

*OR (odds ratios) statistically significant ([a]$p = 0.0002$; [b]$p = 0.04$).

Discussion

There has been no previous systematic comparison of thrombolytic agents, although a Cochrane review is underway (Bijsterveld NR, personal communication, 2002). Organisations such as the American College of Chest Physicians (ACCP)[22] and the American Heart Association[23] provide regular updates of guidelines for care in this area. Their method of reviewing evidence has evolved, but their methods of identification, quality assessment and data extraction and analysis do not follow the current gold standard as set out by such groups as the Cochrane Collaboration.

The conclusions from our review may seem simple—i.e. that no one drug is more effective than any other—but are potentially confusing and require interpretation. In this Discussion section, we address the controversies surrounding the use of meta-analysis in this area, and the weaknesses of our work. The accompanying Commentary[5] uses the results of this review to expand the evidence-based comparisons into areas where direct head-to-head comparisons of treatments are not available. It also deals with issues related to what constitutes equivalence in thrombolytic therapy.

Meta-analysis is often conducted as part of systematic reviewing, but has been controversial in

cardiology. An example often used by the proponents of meta-analysis is that unequivocal evidence of the effectiveness of thrombolysis for acute myocardial infarction was available from research by 1971.[24,25] However it took almost 20 years before the treatment was approved by the FDA. Even then, implementation into clinical practice was driven not by meta-analysis but by the publication of two large trials, GISSI[26] and ISIS-2.[27]

Conversely, the opponents of meta-analysis point out its flawed use in areas such as use of magnesium in acute myocardial infarction. In this instance, a meta-analysis supported its use,[28] but a single large trial reversed this conclusion.[29] In retrospect, the meta-analysis was flawed, probably by failure to identify all relevant studies; this in turn arose from publication bias affecting unfavourable trials,[30] at a time when the limitations of the technique were less well understood. Thus the role of meta-analysis versus a single large trial has been heatedly debated.

Cardiology, in contrast to other areas of medicine, has an established tradition of very large well-focused, clinical trials designed to provide definitive answers to questions.[31] Such trials have other advantages—their size allows precision in defining the size of any benefit, and to some extent guarantees generalizability. Meta-analysis may therefore seem less important or useful. This is reflected in our review where the meta-analyses, with the exception of the comparison of alteplase and streptokinase, are all dominated by one large trial. It might be argued that accelerated alteplase is quite different in effect from standard alteplase, and should not be included in this meta-analysis which dilutes the evidence of its particular benefits: this is considered more fully in the accompanying Commentary.[5]

The benefits and limitations of meta-analysis have been extensively discussed.[32,33] This review highlights the limitations in two areas. The first is that the primary focus is placed on the impact of treatment on mortality, well reported in all trials, and may exclude the assessment of adverse events such as stroke and major bleeding events, which are variably reported. Second, a meta-analysis may mislead if it groups disparate trials together inappropriately. Conversely, an excessive focus on a single trial such as GUSTO-I may mislead if it excludes other relevant studies and does not consider the totality of the evidence available.[34] This is well illustrated in our results, where the GUSTO-I study shows an apparent benefit of accelerated alteplase over streptokinase, but the meta-analysis shows no benefit and no heterogeneity (although the ability to detect heterogenetity in such analyses is limited).

In conclusion, this systematic review suggests that all thrombolytic drugs are of similar efficacy in reducing mortality, and that the apparent benefits of accelerated alteplase in one trial are still consistent with this. There are differences in rates of stroke, favouring streptokinase over newer drugs. The key questions remaining are whether accelerated alteplase is sufficiently different from other regimens of administering alteplase to be excluded from a meta-analysis, and whether we should place more weight on a meta-analysis rather than on a single trial. This is a matter for judgment and debate, and the implications of these are considered in the accompanying Commentary.[5]

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References

1. Yusuf S, Collins R, Peto R, *et al*. Intravenous and intracoronary fibrinolytic therapy in acute myocardial infarction: overview of results on mortality, reinfarction and side-effects from 33 randomized controlled trials. *Eur Heart J* 1985; **6**:556–85.
2. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet* 1994; **343**:311–22.
3. Llevadot J, Giugliano R, Antman E. Bolus fibrinolytic therapy in acute myocardial infarction. *JAMA* 2001; **286**:442–9.
4. Wilcox RG. Clinical trials in thrombolytic therapy: what do they tell us? INJECT 6-month outcomes data. *Am J Cardiol* 1996; **78**:20–3.
5. Walley T, Dundar Y, Dickson R, Hill R. Superiority and equivalence in thrombolytic drugs: an interpretation. *Q J Med* 2003; **96**:155–60.

6. Khan K, Ter Riet G, Glanville J, Sowdon A, Kleijnen J. Undertaking systematic reviews of research on effectiveness. *CRD guidance for carrying out or commissioning reviews*, 2nd edn. CRD Report 4. York, NHS Centre for Reviews and Dissemination (CRD), University of York, 2000.
7. GUSTO. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. The GUSTO investigators. *N Engl J Med* 1993; **329**:673–82.
8. Taylor GJ, Moses HW, Koester D, Colliver JA, Katholi RE, Dove JT, *et al*. A difference between front-loaded streptokinase and standard-dose recombinant tissue-type plasminogen activator in preserving left ventricular function after acute myocardial infarction (the Central Illinois Thrombolytic Therapy Study). *Am J Cardiol* 1993; **72**:1010–14.
9. Cherng WJ, Chiang CW, Kuo CT, Lee CP, Lee YS. A comparison between intravenous streptokinase and tissue plasminogen activator with early intravenous heparin in acute myocardial infarction. *Am Heart J* 1992; **123**:841–6.
10. Verstraete M, Bernard R, Bory M, Brower RW, Collen D, de Bono DP, *et al*. Randomised trial of intravenous recombinant tissue-type plasminogen activator versus intravenous streptokinase in acute myocardial infarction. Report from the European Cooperative Study Group for Recombinant Tissue-type Plasminogen Activator. *Lancet* 1985; **1**:842–7.
11. Feruglio GA, Lotto A, Rovelli F, Solinas P, Tavazzi L, Tognoni G, *et al*. GISSI-2: A factorial randomised trial of alteplase versus streptokinase and heparin versus no heparin among 12,490 patients with acute myocardial infarction. *Lancet* 1990; **336**:65–71.
12. Van de Werf F, Wilcox RG, Barbash GI, Diaz R, Franzosi MG, Hampton JR, *et al*. In-hospital mortality and clinical course of 20,891 patients with suspected acute myocardial infarction randomised between alteplase and streptokinase with or without heparin. *Lancet* 1990; **336**:71–5.
13. Hunt D, Varigos J, Dienstl F, Lechleitner P, Mauel C, Dienstl A, *et al*. ISIS-3: A randomised comparison of streptokinase vs tissue plasminogen activator vs anistreplase and of aspirin plus heparin vs. aspirin alone among 41,299 cases of suspected acute myocardial infarction. *Lancet* 1992; **339**:753–770.
14. Grines CL, Nissen SE, Booth DC, Gurley JC, Chelliah N, Wolf R, *et al*. A prospective, randomized trial comparing combination half-dose tissue-type plasminogen activator and streptokinase with full-dose tissue-type plasminogen activator. *Circulation* 1991; **84**:540–9.
15. Magnani B. Plasminogen Activator Italian Multicenter Study (PAIMS): comparison of intravenous recombinant single-chain human tissue-type plasminogen activator (rt-PA) with intravenous streptokinase in acute myocardial infarction. *J Am Coll Cardiol* 1989; **13**:19–26.
16. Chesebro JH, Knatterud G, Roberts R, Borer J, Cohen LS, Dalen J, *et al*. Thrombolysis in Myocardial Infarction (TIMI) Trial, Phase I: A comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. *Circulation* 1987; **76**:142–54.
17. White HD, Rivers JT, Maslowski AH, Ormiston JA, Takayama M, Hart HH, *et al*. Effect of intravenous streptokinase as compared with that of tissue plasminogen activator on left ventricular function after first myocardial infarction. *N Engl J Med* 1989; **320**:817–21.
18. Van de Werf F, Adgey J, Ardissino D, Armstrong PW, Aylward P, Barbash G, *et al*. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. *Lancet* 1999; **354**:716–22.
19. Topol EJ, Califf R, Ohman E, Skene A, Wilcox R, Grinfeld L, *et al*. A comparison of reteplase with alteplase for acute myocardial infarction. *N Engl J Med* 1997; **337**:1118–23.
20. Bode C, Smalling RW, Berg G, Burnett C, Lorch G, Kalbfleisch JM, *et al*. Randomized comparison of coronary thrombolysis achieved with double- bolus reteplase (recombinant plasminogen activator) and front-loaded, accelerated alteplase (recombinant tissue plasminogen activator) in patients with acute myocardial infarction. *Circulation* 1996; **94**:891–8.
21. Hampton JR, Schroder R, Wilcox RG, Skene AM, Meyer-Sabellek W, Heikkila J, *et al*. Randomised, double-blind comparison of reteplase double-bolus administration with streptokinase in acute myocardial infarction (INJECT): trial to investigate equivalence. *Lancet* 1995; **346**:329–36.
22. Ohman E, Harrington R, Cannon CP, Agnelli G, Cairns J, Kennedy JW. Intravenous thrombolysis in acute myocardial infarction. *Chest* 2001; **119(Suppl.)**:253–77S.
23. Ryan TJ, Antman EM, Brooks NH, Califf RM, Hillis LD, Hiratzka LF, *et al*. *ACC/AHA guidelines for the management of patients with acute myocardial infarction: update—a report*. American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction), 1999; available at www.acc.org.
24. Mulrow C. Rationale for systematic reviews. In: Chalmers I, Altman D, eds. *Systematic Reviews*. London, BMJ1995.
25. Lau J, Antman E, Jiimenez-Silva J, Kupelnick B, Mosteller F, Chambers T. Cumulative meta-analysis of therapeutic trials for myocardial infarction. *N Engl J Med* 1992; **327**:248–54.
26. GISSI. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). *Lancet* 1986; **1**:397–402.
27. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomized Trial of intravenous streptokinase, oral aspirin, both or neither among 17,187 cases of suspected acute myocardial infarction: ISIS2. *J Am Coll Cardiol* 1988; **12**:3–13A.
28. Teo K, Yusef S, Collins R, Held P, Peto R. Effects of intravenous magnesium in suspected acute myocardial infarction: overview of randomised trials. *Br Med J* 1991; **303**:1499–505.
29. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate and intravenous magnesium sulphate in 58050 patients with suspected acute myocardial infarction. *Lancet* 1995; **345**:669–85.
30. Yusuf S, Flather M. Magnesium in acute myocardial infarction. *Br Med J* 1995; **310**:751–2.
31. Yusuf S, Collins R, Peto R. Why do we need some large, simple randomized trials? *Stat Med* 1984; **3**:409–22.

32. Thompson S, Pocock S. Can meta-analyses be trusted? *Lancet* 1991; **338**:1127–30.

33. Egger M, Smith G, Sterne J. Uses and abuses of meta-analysis. *Clin Med* 2001; **1**:478–84.

34. Collins R, Peto R, Parish S, Sleight P. ISIS-3 and GISSI-2: no survival advantage with tissue plasminogen activator over streptokinase, but a significant excess of strokes with tissue plasminogen activator in both trials. *Am J Cardiol* 1993; **71**:1127–30.