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SYSTEMATIC REVIEW OF INTRAVENOUS THROMBOLYSIS IN ACUTE ISCHAEMIC STROKE

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Acknowledgements

An Expert Advisory Panel provided guidance on the scope, methodology and clinical context of this evaluation:

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- Prof George Braitberg, Director of Emergency Medicine, The Royal Melbourne Hospital
- Prof Arduino Mangoni, Clinical Pharmacologist and General Physician, Flinders University and Flinders Medical Centre
- Dr Tapuwa Musuka, Neurologist, Fiona Stanley Hospital, Royal Perth Hospital
- Dr Yusuf Nagree, Emergency Physician, Fiona Stanley Hospital
- Dr Christopher Staples, Adult Neurologist, Mater Hospital, Brisbane

Project support was provided by the Australasian College for Emergency Medicine, Department of Policy & Research:

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LIST OF ABBREVIATIONS

ACEM	Australasian College for Emergency Medicine
ACS	Anterior circulation stroke
AF	Atrial fibrillation
AIS	Acute ischaemic stroke
AMSTAR	Assessing the methodological quality of systematic reviews
ATLANTIS	Alteplase Thrombolysis for Acute Noninterventional Therapy in Stroke
BP	Blood Pressure
ECASS	European Co-operative Acute Stroke Study
GOS	Glasgow outcome Scale
ICA	Internal carotid artery
ICH	Intracranial haemorrhage
IST-3	Third International Stroke Trial
IVT	Intravenous thrombolysis
ITT	Intention to treat
LVO	Large vessel occlusion
MI	Myocardial infarction
mRS	Modified Rankin Score
NHISS	National Institutes of Health Stroke Scale
NINDS	National Institute of Neurological Disorders and Stroke
NNT	Numbers needed to treat
NNTB	Numbers needed to treat to benefit
NNTH	Numbers needed to treat to harm
OR	Odds Ratio
OTT	Onset to treatment time
PCS	Posterior circulation stroke
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
RCT	Randomised control trial
rtPA	Recombinant tissue plasminogen activator
sICH	Symptomatic intracranial haemorrhage
SITS-ISTR	Safe Implementation of Thrombolysis in Stroke International Stroke Thrombolysis Register
SITS-MOST	Safe Implementation of Thrombolysis in Stroke Monitoring Study

STEMO	Stroke emergency mobile
TESPI	Thrombolysis in Elderly Stroke Patients in Italy
TIA	Transient Ischemic Attack
VISTA	Virtual International Stroke Trials Archive

GLOSSARY OF TERMS

AMSTAR is a checklist used for reviewing the methodological quality of systematic reviews. The list consists of 11 items each with a Yes, No, Can't Answer or Not Applicable option. Checks for features such as an a priori design; duplicate study selection and data extraction; the use of status of publication as an inclusion criteria; assessment of methodological quality and bias of included studies. Has good inter-rater agreement, test-retest reliability, face and construct validity.

Barthel Index is a scale used to evaluate a person's mobility and ability to carry out the activities of daily living. It assesses topics including incontinence, whether or not help is needed with activities such as personal care, walking, climbing stairs, feeding, dressing and so on.

Glasgow Outcomes Scale (GOS) provides a very general assessment of the physical functioning of a person who has experienced traumatic brain injury such as stroke. It consists of five categories: death, persistent vegetative state, severe disability, moderate disability, and good recovery.

The modified Rankin Scale (mRS) measures the degree of disability or dependence in the daily activities of people who have suffered a stroke. Scores range from 0-6, with 0 indicating total independence and no symptoms, and 6 representing death. There is no consistency in the literature with regard to how each end point score is defined; for example Hacke et al (2008) refer to a score of 0-1 as a favourable outcome, whilst Norby et al (2013) use the same description for a score of 0-3. Thus, for the purpose of this review, a score of 0-1 indicates a return to functional independence and a score of 0-2 as a good outcome. At the other end of the scale, a score of 4-5 indicates moderately severe or severe disability.

The National Institutes of Health Stroke Scale (NIHSS) quantifies the impairment caused by a stroke. The NIHSS is composed of 11 items, each of which scores a person's performance on a specific ability between 0 and 4, with higher scores indicating impairment. Abilities assessed include level of consciousness, facial palsy, limb motor function and ataxia, language, speech and sensory functioning.

Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement aims to help authors improve the reporting of systematic reviews and meta-analyses. It does this by providing a 27 item checklist and a flow diagram that shows the different phases of a systematic review. PRISMA can be used as a basis for reporting systematic reviews of RCTS, evaluations of interventions and so on. PRISMA may also be useful for critical appraisal of published systematic reviews, although it should be noted that the PRISMA checklist is not a quality assessment instrument for judging systematic reviews.

ABSTRACT

Background

The Australasian College for Emergency Medicine (ACEM) recognises intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (rtPA) as a potentially beneficial intervention for acute ischaemic stroke (AIS). However, there is conflicting evidence regarding the impact of using IVT for AIS meaning it cannot currently be considered a standard of care. An evidence review was therefore undertaken to inform revision of the ACEM guidelines on the use of rtPA in AIS.

Objectives

To evaluate the consequence of administering intravenous standard dose rtPA (Alteplase) within 4.5 hours of acute ischaemic stroke onset in order to clarify the risk of harm and potential benefits for patients.

Search methods

MEDLINE, EMBASE, CDSR and CENTRAL were searched. Key conference proceedings and reference lists of included papers were also hand searched.

Selection criteria

Randomised control trials comparing intravenous (IV) administration of Alteplase with control within 4.5 hours of onset of ischaemic stroke were selected for inclusion in a meta-analysis. In addition a narrative review of well-designed prospective and retrospective studies (cohort, case control and case series) was undertaken.

Data collection and analysis

Studies were screened and outcome data extracted using a standardised data extraction form by one researcher and independently checked by a second. Any disagreements were resolved through discussion, with involvement of a third reviewer when necessary.

Main results

Six trials, involving 2,221 participants – 1,105 who received rtPA and 1,116 controls – were included in the review. All trials fulfilled the criteria for effective concealment and in four of the six there were few losses to follow-up for the main outcomes. All studies were drug-company funded, with half of the studies rated as high risk for potential conflict of interest.

Included studies were all Phase 3 trials comparing rtPA at a dose of 0.9mg/kg (max 90mg) to placebo. Three studies (ECASS III, NINDS 1 & 2) had a treatment window within the 0-4.5 hour timeframe, whilst the remaining studies (ATLANTIS A & B, ECASS II) all provided sufficient information to allow the extraction of relevant data from within this timeframe. The largest single trial to date IST-3 was not included in the meta-analysis as did not fit the inclusion criteria (i.e. it was open label, used different eligibility criteria, and had a treatment timeframe outside of 4.5 hours).

Thrombolytic therapy, administered within 4.5 hours after ischaemic stroke, increased the odds that participants were independent (modified Rankin Scale (mRS) score of 0-1) at 90 days after stroke (odds ratio (OR) 1.58, 95% confidence interval (CI) 1.26 to 1.99).

Evidence from the NINDS studies indicates that this benefit is sustained in the longer term (12 months after treatment) - (OR = 1.7, 95% CI = 1.2 to 2.3). A statistical difference in the proportion of patients with good outcome was also indicated (mRS 0-2 (OR = 1.44, 95% CI = 1.15 to 1.79).

Treatment with Alteplase significantly increased the odds of symptomatic intracranial haemorrhage (sICH) during the first week to 10 days following treatment (OR = 6.90, 95% CI = 2.21 to 21.50) and early death from intracranial haemorrhage (ICH) (OR = 7.39, 95% CI = 1.93 to 28.29). Treatment with Alteplase did not significantly affect all-cause mortality by day 30 (OR = 1.48, 95% CI = 0.46 to 4.81) or day 90 (OR = 0.89, 95% CI = 0.60 to 1.34). However, heterogeneity in the safety data suggests caution should be applied in the interpretation of these results.

Treatment within three hours of stroke (OR = 1.85, 95% CI = 1.38 to 2.47), provided a greater advantage for a return to independence (mRS 0-1) than treatment between 3-4.5 hours (OR = 1.27, 95% CI = 1.01 to 1.60). Timing had little impact on mortality rates, although there was heterogeneity between studies with regard to the safety data.

Consideration of numbers needed to treat (NNT) to achieve functional benefits as measured by mRS ranged from 10 patients (95% CI = 19 to 6) needing to be treated for one to achieve a return to independence (mRS 0-1), to 13 (95% CI = 29 to 8) needing to be treated for one to achieve a good outcome (mRS 0-2). Timing of administration alters numbers needed to treat to benefit (NNTB), with around half the number of patients needing to be treated for one to benefit at 3 hours (NNTB = 7, 95% CI = 14 to 5), compared to treatment at 3-4.5 hours (NNTB = 18, 95% CI = 419 to 9). In terms of adverse outcome, approximately 42 patients (95% CI = 119 to 13) would need to be treated for one to experience sICH, and 122 (95% CI = 830 to 30) would need to be treated for one patient to die from ICH. The large confidence intervals around these figures should be considered when interpreting the NNT.

The narrative review supported the advantage of early treatment suggesting that administration of IV rtPA within the first two hours after symptom onset is associated with more favourable outcomes and reduced risk. Characteristics such as age and biological sex appeared to be less important than clinical factors such as stroke severity and the presence of co-morbidities such as hypertension, diabetes and atrial fibrillation for determining the effectiveness of IV rtPA. Poorer outcomes following thrombolysis were most clearly associated with greater stroke severity.

The evidence also indicated that the use of telemedicine to support the administration of IV rtPA to patients in community hospitals, and the use of mobile stroke units, provides outcomes comparable to treatment in a specialist stroke unit. Poorer outcomes in non-specialist units are usually associated with clinician inexperience.

Finally, patient preference studies indicate that patients most likely to consent to thrombolysis are male (79% vs. 86%, P=0.014), have poorer health status and a higher level of education. However, clinician uncertainty around treatment outcomes results in practice variation, some of which may be potentially confusing for patients, in particular the use of ‘elastic terminology’ and inconsistency in level of risk or benefit portrayed.

Conclusions

Current evidence shows that intravenous thrombolysis with rtPA, particularly within three hours of symptom onset, increases the odds of a better functional outcome, but also increases the risk of intracranial haemorrhage and related death.

INTRODUCTION

Rationale

The Australasian College for Emergency Medicine (ACEM) recognises intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (rtPA) as a potentially beneficial intervention for acute ischaemic stroke (AIS). There is, however, conflicting evidence regarding the impact of using IVT for AIS, with some trials indicating clear patient benefits and others having been stopped early due to harm. Furthermore, despite a number of systematic reviews having been conducted, there continue to be questions over the interpretation of the evidence, including the appropriateness of pooling estimates of effect in clinical heterogeneous samples and the effect of potential and actual conflicts of interest. Thus the administration of stroke thrombolysis by Emergency Department staff remains a controversial area and cannot currently be considered a 'standard of care.'[1] The aim of this review is therefore to inform revision of the ACEM guidelines on the use of rtPA in AIS. The review focused specifically on the use of Alteplase as it is currently the only form of rtPA licensed for stroke management in Australia.

Objectives

Evaluate the consequence of administering intravenous standard dose rtPA (0.9mg/kg to a max of 90mg) within 4.5 hours of acute ischaemic stroke onset in order to clarify the risk of harm and potential benefits for patients.

Specifically the review aimed to address the following research questions:

1. Does rtPA thrombolysis impact upon patient functional outcomes:
    a. As assessed by the modified Rankin Scale (mRS) at:
        i. 30 days
        ii. 90 days
        iii. In the longer term (12-18 months, 24 months)
2. Does rtPA thrombolysis alter the risk of death from:
    a. Intracranial haemorrhage:
        i. Within the first 7 days following treatment
        ii. Within the first 30 days following treatment
        iii. 3-6 months post treatment
    b. Other causes
        i. Within the first 7 days following treatment
        ii. Within the first 30 days following treatment
        iii. 3-6 months post treatment
3. Does rtPA thrombolysis alter the risk of symptomatic intracranial haemorrhage (sICH[2]):
    a. Within the first 24 hours following treatment
    b. Within the first 7 days following treatment
4. How does the risk of mortality, or neurological and/or functional outcomes alter depending on:

[1] ACEM (2014) STATEMENT ON INTRAVENOUS THROMBOLYSIS FOR ISCHAEMIC STROKE (S126) https://www.acem.org.au/getattachment/1636cfd5-3829-4fc6-9eb2-91742f3d250b/Statement-on-Intravenous-Thrombolysis-for-Ischaemi.aspx

[2] As defined by ECASSIII

a. Timing of administration (less than 90 minutes, 90 minutes to 3 hours, 3 hours to 4.5 hours) of rtPA after the ischaemic event
b. Patient's age (<65, 65-75, >75)
c. Patient's weight
d. Other patient demographics
e. Patient's smoking history
f. Patient's alcohol consumption
g. Baseline systolic and diastolic blood pressure
h. Co-morbidities (previous stroke/TIA, heart disease including previous myocardial infarction, hypertension, diabetes, chronic atrial fibrillation)
i. Stroke severity on presentation (NIHSS score groupings[3])
j. Stroke aetiology or location (e.g. cardioembolic, atherothrombotic, lacunar/small vessel disease, other)
k. Patients currently or previously receiving anticoagulant therapy
l. Patients currently or previously receiving antiplatelet therapy
m. Treatment centre specifics:
    i. Stroke Service
    ii. Stroke Ward
    iii. Allied Health available 24/7
    iv. Presented to Stroke Centre or interhospital transfer to one
    v. Telemedicine

METHODS

Eligibility criteria

Only studies evaluating intravenous (as opposed to intra-arterial) thrombolysis using Alteplase for adults (aged 18 years and over) were included in the review. Animal studies were excluded.

The search included studies published in any language in order to determine the extent of the evidence worldwide. However, it was agreed that due to time constraints only those published in English were to be included in the final review, unless addition of the trials published in non-English journals would significantly boost the sample size available for the analysis.

Studies were included if they were either comparative (randomized or non-randomized) or single-arm studies; patients had been treated with IV rtPA at a dose of 0.9mg/kg to a

3

Score	Stroke Severity
0	No Stroke Symptoms
0-4	Minor Stroke
5-15	Moderate Stroke
16-20	Moderate to Severe Stroke
21-42	Severe Stroke

maximum of 90mg within 4.5 hours; at least one of following outcomes was reported: functional outcome, mortality, or sICH.

Information sources

The following electronic sources were searched:

- MEDLINE
- MEDLINE In-Process & Other Non-Indexed Citations
- EMBASE
- CDSR
- CENTRAL (via the Cochrane Library).

Other sources:

- Key conference proceedings and reference lists of included papers were hand searched.

Search

The search strategy focused on the intravenous administration of thrombolysis in acute ischaemic stroke and its effect on mortality and morbidity (specifically neurological outcomes). Search terms included:

- Brain ischaemia OR cerebrovascular accident OR acute ischaemic stroke

AND

- Systemic thrombolysis OR thrombolytic therapy OR rtPA OR Alteplase OR fibrinolytic agent/therapy OR plasmin/plasminogen.

Study Selection

One reviewer independently screened the titles and abstracts of every record. The full articles were obtained when the information given in the title or abstracts conformed to the selection criteria outlined previously.

Types of study included

RCTs were included in the main analysis; in addition a narrative analysis was undertaken which included high quality:

- Systematic reviews
- Prospective cohort studies
- Single-arm studies
- Retrospective reviews of medical records
- Case series
- Registry studies
- Patient or clinician surveys.

Judgements about the quality of the individual studies were based on factors such as the clarity of the research question, the study design, sample size and analysis approach. Existing systematic reviews were excluded from the main analysis, but were assessed for quality and included in the narrative review. In addition recent evidence around factors such as clinical decision-making, patient preference, and reasons for patient non-consent to inclusion in trials of thrombolysis in stroke were sought. These findings provide additional,

and alternative insight into the effectiveness of the intervention and help inform the report recommendations.

Data collection process

Studies were screened and outcome data extracted using a standardised data extraction form by one researcher and independently checked by a second. Any disagreements were resolved through discussion, with involvement of a third reviewer when necessary.

Data items

The data extraction form included contents as follows: (1) general characteristics of studies and patients, (2) sample size, (3) outcome measurements (e.g. functioning, mortality, sICH).

Outcomes

Mortality (+ cause) rate
Rate of symptomatic intracranial haemorrhage
Functional outcome:

- mRS scores, grouped as follows:
    - 0-1, 2-3,4-5
    - 0-2,3,4-5

Other outcome measures:

- Barthel Index scores
- Glasgow Outcome Scale
- NIHSS score groupings
- Where available information on
    - Proportion returning to employment in under 65s
    - Proportion returning to same accommodation type (e.g. own home, low level aged care facility) compared with returning to higher level care
    - Factors such as communication/speech, perception, memory, or concentration

Risk of bias in individual studies

All included studies were critically appraised for risk of bias using an appropriate tool, depending on the design of the original study:

- RCT - Cochrane risk of bias (Higgins & Green, 2008);
- Single-arm studies - National Institute for Health and Clinical Excellence Methodology Checklist: Prognostic Studies (NICE, 2009);
- Systematic reviews - AMSTAR tool (Shea et al, 2009).

Adherence of systematic reviews to PRISMA guidelines (Moher et al., 2009) was also gauged. Finally any risk of bias arising from potential conflict of interest for authors was assessed and documented using the Institute of Medicine (USA) Guidelines (Field & Lo, 2009).

Summary of measures

Odds ratio for dichotomous variables (mortality, sICH).

Synthesis of results

Synthesis was attempted where there was deemed to be sufficient clinical (population characteristics, outcome measures) and methodological (study design) homogeneity of

studies. Data from RCTs was combined (using random effects meta-analysis) to provide comparative estimates of treatment efficacy. In line with CONSORT (Moher et al., 2001) statement recommendations analyses used Intention to Treat (ITT) population data.

Risk of bias across studies

Factors such as incomplete data and how this might affect study outcomes were assessed. Where bias was high for a particular outcome, data was excluded from analysis; where it was uncertain for a particular outcome, analysis was conducted including and excluding that data to explore its impact on analysis outcomes. I^2 was used as a measure of consistency of results between trials, with heterogeneity classified as low (<25%), moderate (25-50%) or high (>50%) (Higgins et al., 2003).

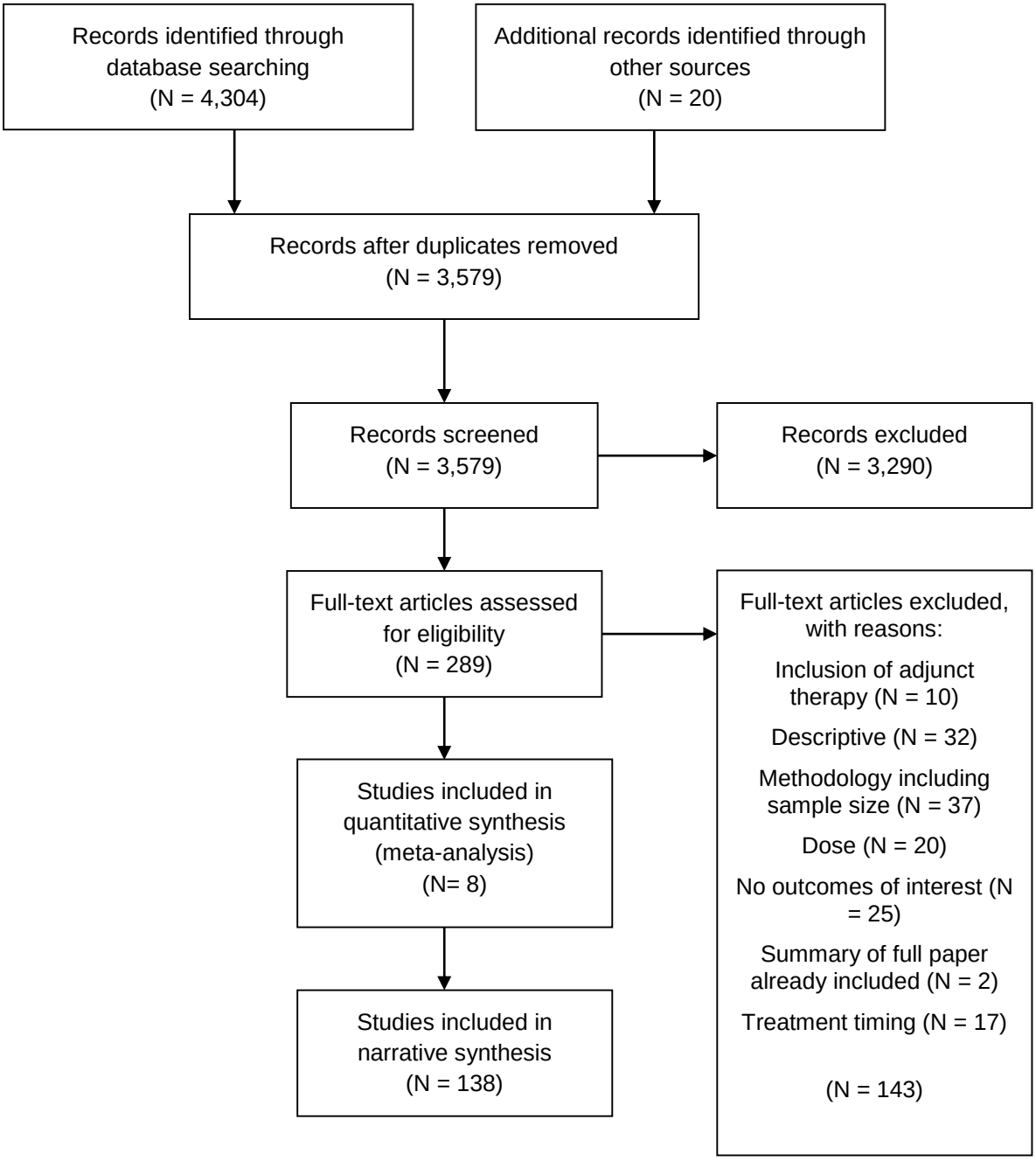
Analysis of subgroups or subsets

Sub group analysis included:

- Timing of administration of rtPA (0-3 and 3-4.5 hours)
- Improvement in NHISS scores.

RESULTS

Study selection



Study Characteristics

Six trials (reported in 8 papers – Albers et al., 2002; Bluhmki et al., 2009; Clark et al.,1999; Clarke et al., 2000; Hacke et al 1998; Hacke et al., 2008; Kwiatkowski et al., 1999; NINDS Study Group, 1995) fitted the criteria and were deemed sufficiently similar in approach for initial synthesis. The key characteristics of these six trials are summarised in Table 1. All were Phase 3 trials comparing rtPA at a dose of 0.9mg/kg (max 90mg) to placebo. Three studies (ECASS III, NINDS 1 & 2) had a treatment window that was within the 0-4.5 hour timeframe, whilst the remaining studies (ATLANTIS A & B, ECASS II) all provided sufficient information to allow the extraction of relevant data from within this timeframe. In addition, all trials used mRS as a functional outcome measure, thereby allowing comparison across trials. The largest single trial to date IST-3 was not included in the meta-analysis as it was open label, used different eligibility criteria, and differed in terms of the main outcome measure. Furthermore, the principal aim of IST-3 was to determine whether using thrombolysis up to 6 hours post stroke was beneficial, and the extraction of data for the 4.5 hour cut-off was not possible.

Table 2 demonstrates the risk of bias within each study, according to Cochrane Guidelines. Risk of bias was generally low in relation to trial design and procedures. However, attrition bias was unclear for the ATLANTIS trials, particularly as some outcomes had not been collected in the first ATLANTIS trial. Thus outcomes for mRS and the Glasgow Outcome Scale (GOS) in this study should be treated with caution. Reporting bias was unclear for all studies: ECASS II failed to explain how missing data had been dealt with, whilst the remaining studies all demonstrated differences between intervention and control groups in at least one baseline characteristic that may have had an impact on study outcomes. Finally it was noted that all studies were pharmaceutical company funded. Whilst this in itself is not necessarily cause for concern, the lack of information concerning the drug company involvement in one study (ECASS II), and the direct involvement of the drug companies in data management and analysis in the remaining five trials meant that the risk was unclear.

This table also presents any conflict of interest for study authors. Reports of the oldest studies – NINDS 1 & 2, ECASS II – provided very little information regarding conflict of interest. This may be due to the age of the paper and changes in journal reporting requirements. However, the lack of information meant that it was not possible to give other than a rating of ‘unclear risk’. Conflict of interest was rated high risk for the remaining trials – ECASS III, ATLANTIS A & B – as study authors either were or had been employed by the trial sponsor, or were in receipt of financial support from the sponsors, either through grants, honoraria, or paid consultation.

Table 1: Study characteristics (RCTs)

Trial	Study dates	ITT (rtPA/cont)	Known protocol violations (rtPA/cont)	Age eligibility (yrs)	Mean age (rtPA/cont)	% male (rtPA/cont)	Treatment window (hrs)	Mean OTT (mins)	Baseline NIHSS (M)	Functional outcome measure
ATLANTIS A & B 0-3 hour cohort *	1991-1998	23/38	Not Reported	18-79	66/66	82.6/57.9	0-3	161/144	12/12	NIHSS mRS 0/1 BI
ECASS II*	1996–1998	409/391 (81/77)	34/38	18-80	68/68	60.6/56.5	0-6 (0-3)	Not Reported	11/11**	mRS
ECASS III	2003–2007	418/403	43/48	18-80	65.6/64.9	63.2/57.3	3-4.5	239/238	9/10**	mRS mRS/BI combined GOS
NINDS 1	1991-1992	144/147	10/8%	18+	67/66	58/60	0-3	Not Reported	14/14	NIHSS GOS BI mRS
NINDS 2	1992-1994	168/165	7/7%	18+	69/66	57/58	0-3	Reported	14/15	NIHSS GOS BI mRS

*We were also able to extract minimal data (mortality and mRS 0-1 at day 90) for the 3-4.5 hour cohorts **Median values

Table 2: Risk of bias within studies

	ECASS II	ECASS III	ATLANTIS A & B	NINDS 1 & 2
Selection bias *Random sequence generation*	LOW RISK: Randomisation by computer programme.	LOW RISK: Randomisation by computer programme.	LOW RISK: Randomisation by computer programme.	LOW RISK: Randomisation by computer programme.
Selection bias *Allocation concealment*	LOW RISK: Allocation adequately concealed.	LOW RISK: Allocation adequately concealed.	LOW RISK: Allocation adequately concealed.	LOW RISK: Allocation adequately concealed.
Performance bias *Blinding of participants and personnel*	LOW RISK: Patients and personnel blind to allocation.	LOW RISK: Patients and personnel blind to allocation.	LOW RISK: Patients and personnel blind to allocation.	LOW RISK: Patients and personnel blind to allocation.
Detection bias *Blinding of outcome assessment*	LOW RISK: Outcome assessments undertaken by personnel blind to allocation.	LOW RISK: Outcome assessments undertaken by personnel blind to allocation	LOW RISK: Outcome assessments undertaken by personnel blind to allocation.	LOW RISK: Outcome assessments undertaken by personnel blind to allocation.
Attrition bias *Incomplete outcome data*	LOW RISK: ITT analysis. Attrition for primary endpoints low and similar between groups. Secondary endpoints hospital stay and SF-36 higher attrition.	LOW RISK: ITT and per-protocol analyses both reported.	UNCLEAR RISK: ITT analysis. No loss to follow up reported; however, not all patients had mRS or GOS scores as these outcomes were not collected through Part A and N missing were provided.	LOW RISK: ITT analysis. Missing data minimal and replaced following acceptable standard approach.
Reporting bias *Selective reporting*	UNCLEAR RISK: Predefined outcomes used in almost all cases. But no information on how missing data dealt with.	UNCLEAR RISK: All predefined outcomes reported. However, significant differences between groups (before adjustment for multiple comparisons) with respect to initial stroke severity and history.	UNCLEAR RISK: All predefined outcomes reported. However, significant differences between the groups with respect to sex, OTT, and distribution of presenting NIHSS scores also differed.	UNCLEAR RISK: All predefined outcomes reported, and groups looked similar at baseline, although in a significant difference in aspirin use was reported for Part 2.
Other bias	UNCLEAR RISK: Drug company funded (Boehringer). No direct involvement reported and independent auditing was conducted at individual study sites, Boehringer Ingelheim operative units, and the independent data-management centre.	UNCLEAR RISK: Drug company funded (Boehringer). Sponsor undertook monitoring, data management and analysis. However, analyses were also performed simultaneously by an independent external statistician.	UNCLEAR RISK: Drug company funded (Genentech). Sponsor conducted data management and analysis but was blinded to study drug codes.	UNCLEAR RISK: Drug company provided study drug and carried out study monitoring.
Conflict of interest *Likelihood of undue influence and seriousness of possible harm*	UNCLEAR RISK: Limited detail given re involvement of sponsor or any relationship between sponsor and authors.	HIGH RISK: Ten authors of the study served as paid consultants to Boehringer, received financial honoraria or grant funding from Boehringer. Three other study authors were directly employed by Boehringer.	HIGH RISK: Two authors received financial honoraria from Genentech and one author was previously employed by Genentech.	UNCLEAR RISK: Limited detail given re involvement of sponsor or any relationship between sponsor and authors.

Table 3 provides key outcomes for the included studies. Early all-cause mortality rate was only reported by one trial, ECASS III, and differences were statistically non-significant. Differences in all-cause mortality rates were non-significant in all trials at 30 and 90 days, despite being higher in rtPA treated patients in ATLANTIS and ECASS II. Rates of ICH were higher in the treatment group for all trials, and this was significant in all trials except ECASS II and III. Functional dependency, as measured by mRS scores of 4-5, was only reported by two trials (ECASS III and NINDS II) and whilst the rate was higher for survivors who did not receive rtPA, the difference was non-significant. Rates of independence, as measured by mRS scores of 0-1, were higher for individuals treated with rtPA, both as a function of all trial patients and when considering survivors only. However, rates of independence in all trial patients were only statistically significant in two trials (NINDS 1 and 2) whilst rates of independence in survivors were statistically significant in ECASS III as well as NINDS 1 and 2.

Table 3: Rates of mortality, ICH and functional outcome

	ATLANTIS (% Int/cont)	ECASS II (% Int/cont)	ECASS III (% Int/cont)	NINDS 1 (% Int/cont)	NINDS 2 (% Int/cont)
Mortality rate at 7-10 days	Not reported	Not reported	2.9/3.2	Not reported	Not reported
Mortality rate at 30 days	17.4/5.3	Not reported	5.3/5.2	Not reported	Not reported
Mortality rate at 90 days	17.4/5.3	13.6/7.8	6.7/7.7	17.4/19.7	17.3/21.2
ICH rate at 10 days	13/0*	48.4/40.2	2.4/0.3	5.6/0***	7.1/1.2*
Dependency 90 days (mRS 4-5, all patients)	Not reported	Not reported	17.4/18.9	Not reported	23.2/27.3
Dependency rate at 90 days (mRS 4-5, survivors)	Not reported	Not reported	19.5/19.7	Not reported	28.1/34.6
Independence rate at 90 days mRS 0-1, all patients)	47.8/39.5	41.9/37.7	52.4/45.2	57.2/27.2***	39.3/26.1**
Independence rate at 90 days (mRS 0-1, survivors)	57.9/41.7	48.6/40.8	59.2/46.7***	57.1/33.9***	47.5/33.1*

*Significant at p<0.05 ** Significant at p<0.01 ***Significant at p<0.001

Efficacy – functional outcomes

Does rtPA thrombolysis impact upon patient functional outcomes as assessed by mRS at 30 days?

Only one study (ECASS III) reported 30 day mRS scores, providing an OR of 1.42 (95% CI = 1.09 to1.96) for mRS scores of 0-1 and an OR of 1.32 (95% CI = 0.98 to 1.77) for mRS scores of 0-2. This shows a functional advantage at 30 days for patients treated with rtPA.

Does rtPA thrombolysis impact upon patient functional outcomes as assessed by mRS at 90 days? Specifically:

a) *Does thrombolytic therapy impact on patient functional outcome by altering the proportion of surviving patients who are able to return to independent living after treatment (i.e. no/mild disability as assessed by mRs 0-1)?*

Figure 1: Forest Plot showing ORs for individual studies and overall meta-analysis of effects of treatment with rtPA on return to functional independence (survivors)

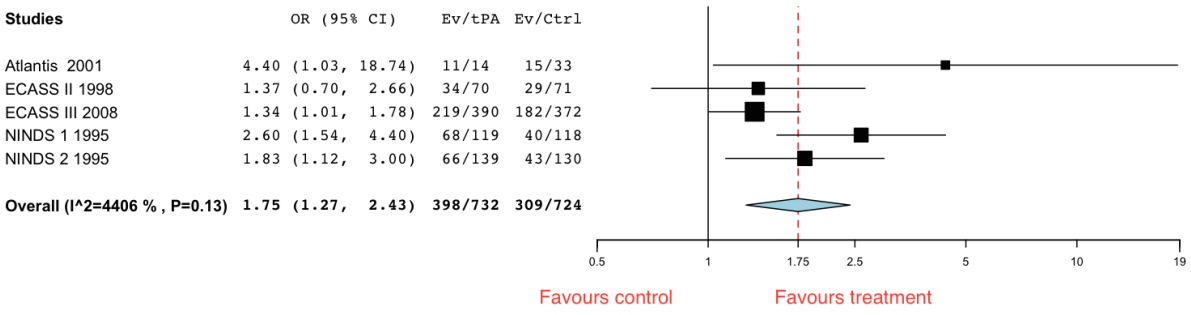
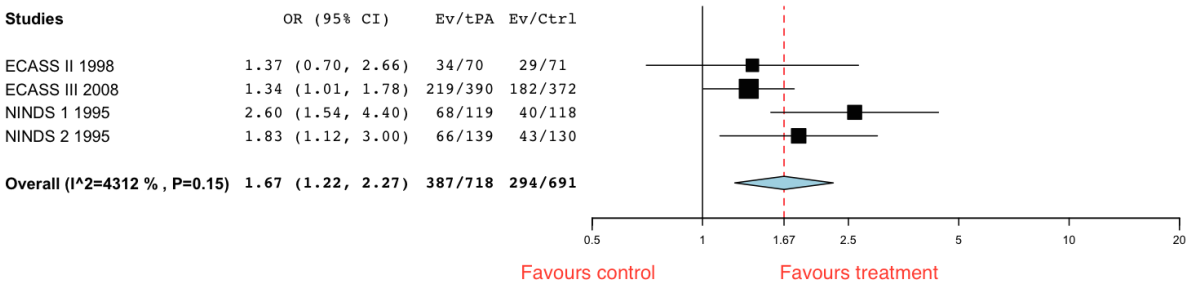


Figure 1 shows a benefit for survivors of having been treated with rtPA (OR = 1.75, 95% CI = 1.27 to 2.43). I^2 = 44.06%, suggesting moderate heterogeneity. The analysis was therefore rerun omitting the ATLANTIS data (Figure 2). This removed the heterogeneity but retained the advantage for survivors (OR = 1.67, 95% CI = 1.22 to 2.27).

Figure 2: Forest Plot showing ORs for individual studies except ATLANTIS and overall meta-analysis of effects of treatment with rtPA on return to functional independence (survivors)



This same analysis was run with additional data provided by the Cochrane review for ATLANTIS and ECASS II 3-4.5 hour treatment window. As details on survivors were not available for these data sets, the analysis was run using all trial patients as the denominator. As figure 3 demonstrates, this also shows an advantage in patients treated with rtPA (OR = 1.48, 95% CI = 1.18 to 1.86). Once again the heterogeneity was moderate so the analysis was rerun without the ATLANTIS data (figure 4). This reduced the heterogeneity to acceptable levels (<25%) and increased the advantage to patients treated with rtPA by 0.10 (OR = 1.58, 95% CI = 1.26 to 1.99).

Figure 3: Forest Plot showing ORs for individual studies and overall meta-analysis of effects of treatment with rtPA on return to functional independence (all patients)

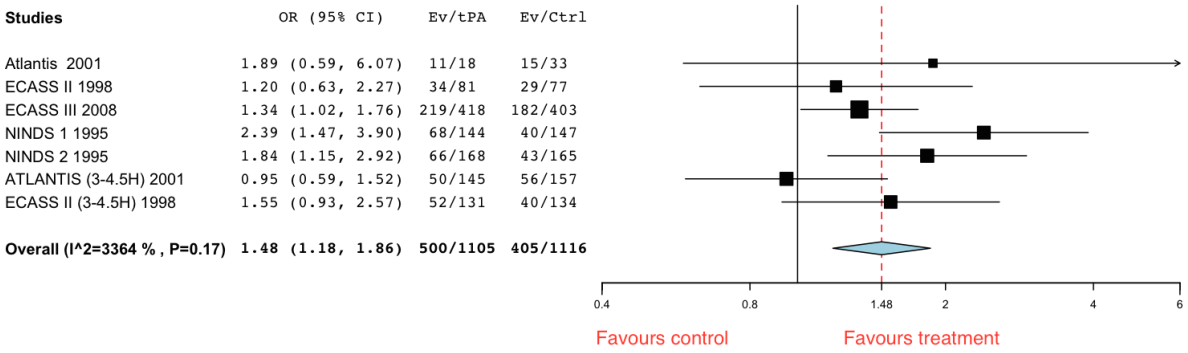
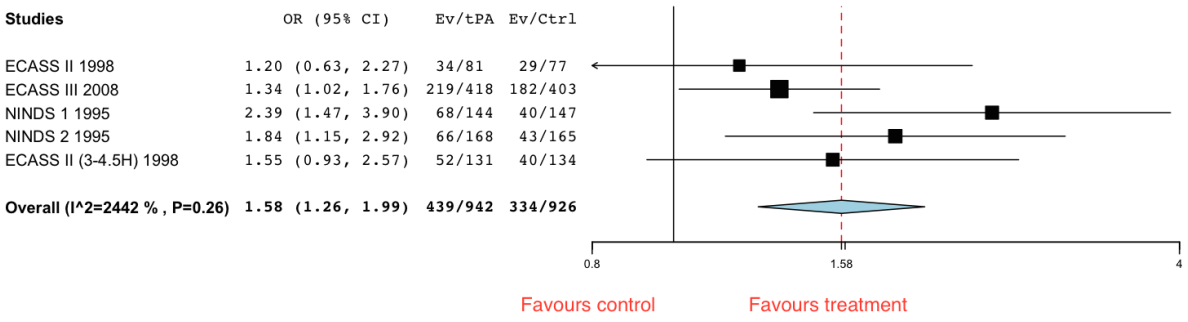


Figure 4: Forest Plot showing ORs for individual studies except ATLANTIS and overall meta-analysis of effects of treatment with rtPA on return to functional independence (all patients)



b) *Does thrombolytic therapy impact on patient functional outcome by altering the proportion of surviving patients who have a good outcome after treatment (i.e. mRs 0-2)?*

Only ECASS III provided data on rates of mRS 0-2 scores (usually referred to as a 'good outcome'); however, this data was extracted from the most recent Cochrane review for ATLANTIS, ECASS II and NINDS. Once again, patients who received rtPA had an advantage (OR = 1.53, 95% CI = 1.11 to 2.10) as shown in Figure 5. I^2 = 36.97%,

suggesting moderate heterogeneity. The analysis was therefore rerun omitting the ATLANTIS data (Figure 6). This removed the heterogeneity and retained a statistically significant advantage for survivors (OR = 1.44, 95% CI = 1.15 to 1.79).

Figure 5: Forest Plot showing ORs for individual studies and overall meta-analysis of effects of treatment with rtPA on good outcomes (survivors only)

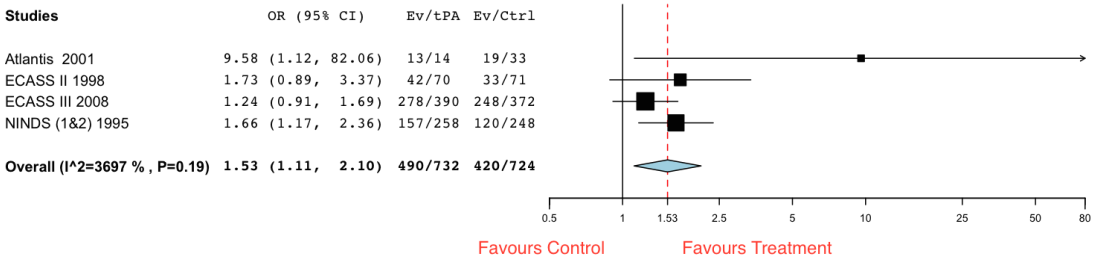
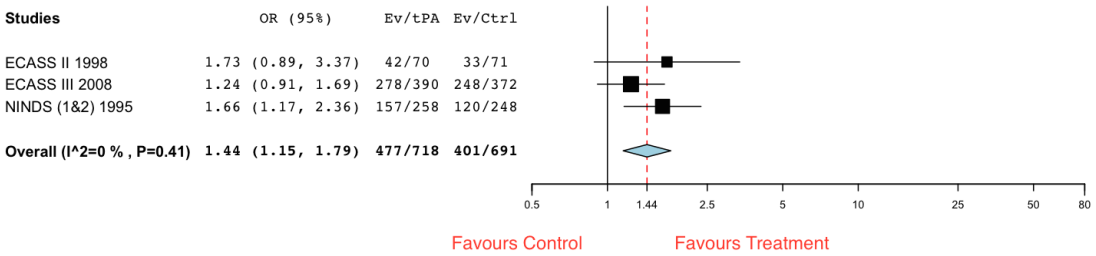


Figure 6: Forest Plot showing ORs for individual studies except ATLANTIS and overall meta-analysis of effects of treatment with rtPA on good outcomes (survivors only)



c) Does thrombolytic therapy alter the proportion of surviving patients who are dependent on others for some or all of their activities of daily living (i.e. moderately severe or severe disability as assessed by mRs, score of 4-5)?

Only two studies (ECASS III and NINDS 2) reported this data. As Figure 7 demonstrates, there is a non-significant (at the 0.05 level) advantage for patients treated with rtPA (OR = 0.84, 95% CI = 0.63 to 1.13).

Figure 7: Forest Plot showing ORs for individual studies and overall meta-analysis of effects of treatment with rtPA on functional dependency

Does rtPA thrombolysis impact upon patient functional outcomes as assessed by mRS In the longer term (12-18 months, 24 months)?

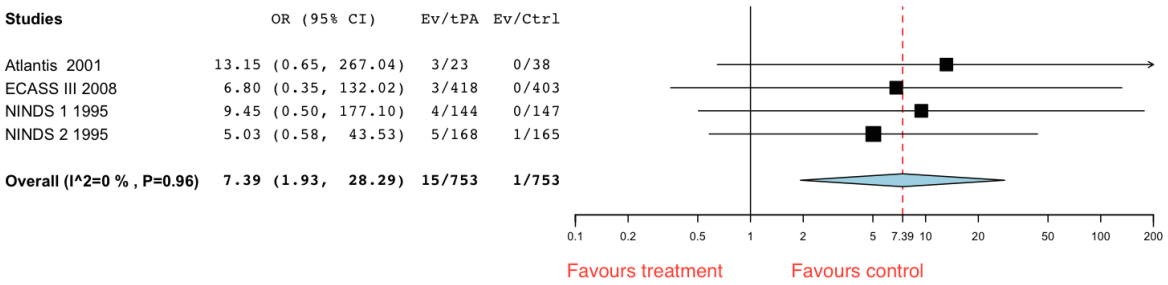
Only one study (NINDS) reported long-term outcomes (Kwiatkowski et al.,1999). This data shows a sustained benefit for patients treated with rtPA at 12 months; good outcomes (mRS 0-1) were more likely to be seen in rtPA treated patients (OR = 1.7, 95% CI = 1.2 to 2.3).

Safety – ICH and mortality

Does rtPA thrombolysis alter the risk of death from intracranial haemorrhage?

Studies provided data on deaths due to ICH as an overall figure within the study period. It was therefore not possible to consider whether death by ICH was greater during the first 7, 30 or 90 days following treatment. Whilst it was not possible to extract this data accurately, it should be noted that all studies advised that either all, or the majority of deaths by ICH occurred within the first few hours or days following treatment. Figure 8 demonstrates that treatment with rtPA increases the odds of death from ICH (OR = 7.39, 95% CI = 1.93 to 28.29). However, the large confidence interval indicates a low level of precision for this result.

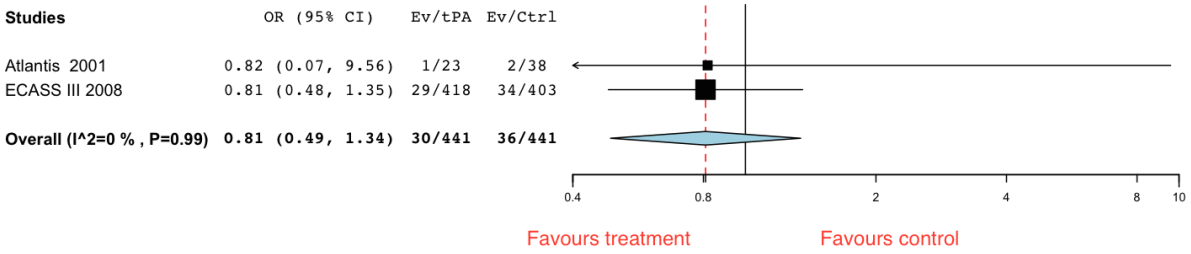
Figure 8: Forest Plot showing ORs for individual studies and overall meta-analysis of effects of treatment with rtPA on death by ICH



Does rtPA thrombolysis alter the risk of death from other causes?

This data was only provided by two studies (ATLANTIS and ECASS III) and once again data was presented as an overall figure, rather than by different time frames. Although limited by small numbers, this suggests that treatment with rtPA does not influence the risk of death by other causes (OR = 0.81, 95% CI = 0.49 to 1.34) as Figure 9 demonstrates.

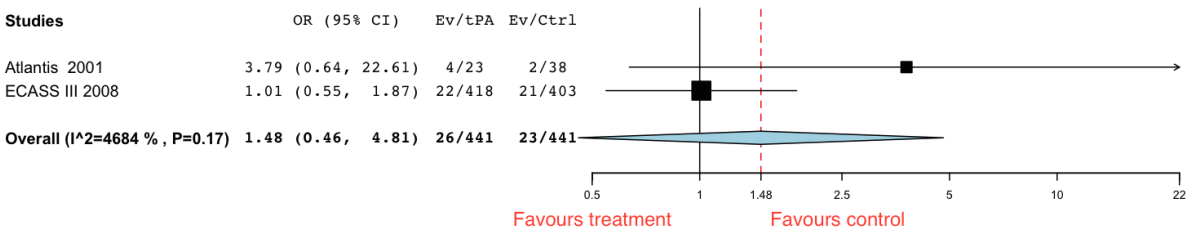
Figure 9: Forest Plot showing ORs for individual studies and overall meta-analysis of effects of treatment with rtPA on death by causes other than ICH



Does rtPA thrombolysis alter the overall risk of death by day 30?

Only two studies provided mortality data for day 30. Overall, these figures suggest treatment does not affect mortality at day 30 (OR = 1.48, 95% CI = 0.46 to 4.81). As shown in figure 10, there are substantial differences in the ORs presented for the two studies; ATLANTIS implies that treatment with rtPA is associated with a trend towards increased overall mortality by day 30, whilst the ECASS III data suggests that mortality was not affected by treatment. Furthermore I^2 suggests moderate heterogeneity in the data (46.84%). Thus caution should be applied in the interpretation of this result.

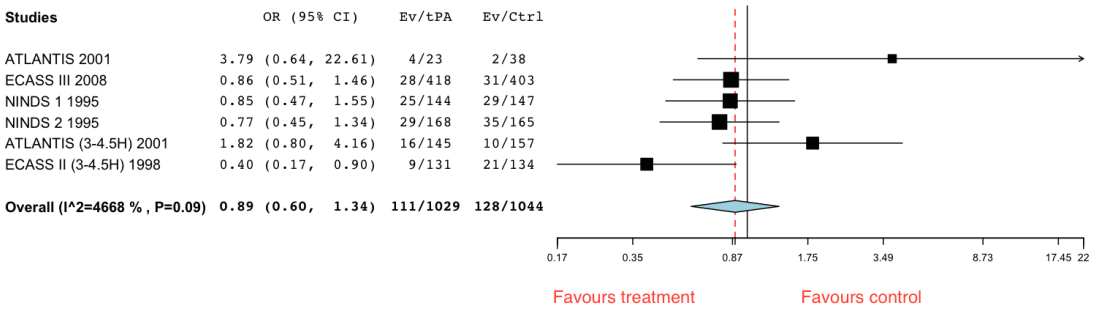
Figure 10: Forest Plot showing ORs for individual studies and overall meta-analysis of effects of treatment with rtPA on death by all causes at day 30



Does rtPA thrombolysis alter the overall risk of death by day 90?

Mortality rates for day 90 were available from most studies. ECASS II (0-3 hours) reported deaths at day 102 so were not included in this analysis. Overall, treatment with rtPA does not influence mortality by day 90 (OR = 0.89, 95% CI = 0.60 to 1.34) as shown in Figure 11. Furthermore moderate heterogeneity is shown for this analysis (I^2 = 46.68) suggesting that caution should be applied in the interpretation of this result.

Figure 11: Forest Plot showing ORs for individual studies and overall meta-analysis of effects of treatment with rtPA on death by all causes at day 90



Does rtPA thrombolysis alter the risk of symptomatic intracranial haemorrhage (sICH[4])?

Studies have used various definitions of sICH (see Table 4), which results in high heterogeneity. The ECASS III definition was therefore applied, using the conversion factors provided by Seet & Rabinstein (2012). This meant that data were available from three studies, all of which provided sICH rates for the first 7-10 days following treatment (Figure 12). This analysis suggests that treatment with rtPA does increase the risk of sICH during the first week to 10 days following treatment (OR = 6.90, 95% CI = 2.21 to 21.50). However, the large confidence interval indicates a low level of precision for this result.

[4] As defined by ECASSIII

Figure 12: Forest Plot showing ORs for individual studies and overall meta-analysis of effects of treatment with rtPA on sICH by day 10.

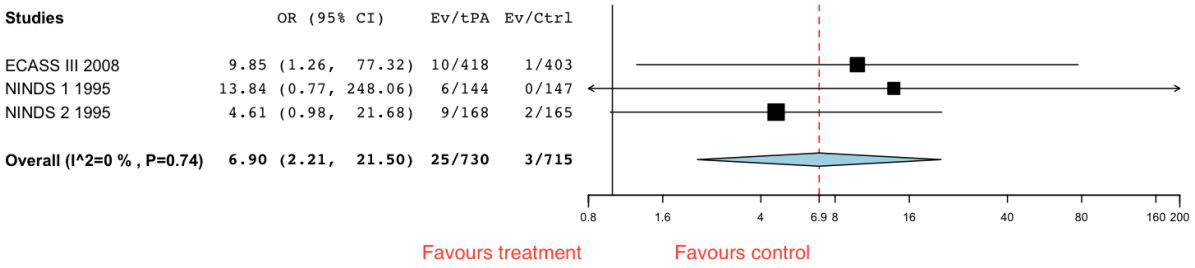


Table 4 : Definitions of symptomatic intracranial haemorrhage used in the included studies

Study	Definitions
ATLANTIS	The presence of any blood seen on a brain CT scan
ECASS II	The presence of blood at any site in the brain on the CT scan, documentation by the investigator of clinical deterioration or adverse events indicating clinical worsening or causing ≥4 point increment in the NIHSS, up to 7 days or leading to death. ECASS III requires a causal relationship between haemorrhage and clinical deterioration.
ECASS III	As for ECASS II, with the addition that ECASS III requires a causal relationship between haemorrhage and clinical deterioration.
NINDS	A haemorrhage is considered symptomatic if it was not seen on a previous CT scan and there had subsequently been either a suspicion of haemorrhage or any decline in neurologic status. Although patients in the NINDS study were followed for up to 10 days, haemorrhages that occur <36 hours are considered to be significant in primary analysis.

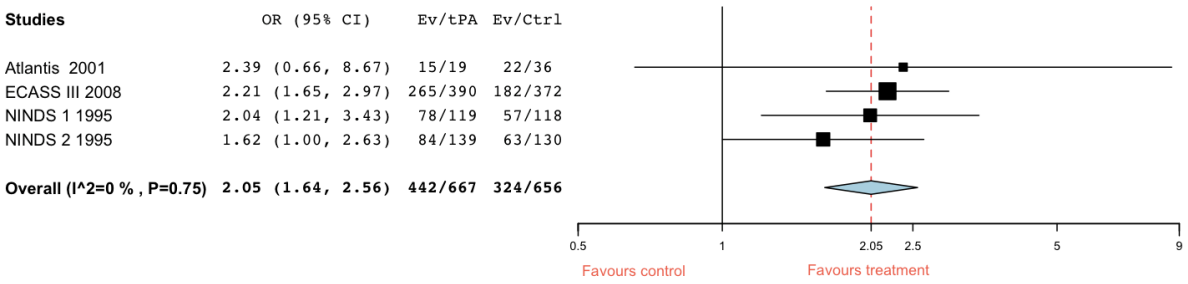
Additional analysis: other outcome measures

No information was available regarding outcomes such as return to employment, return to accommodation type, or cognitive functioning (communication, perception etc.), but was available for Barthel Index, GOS and NIHSS Scores.

Does rtPA thrombolysis impact upon patient functional outcomes as assessed by Barthel Index score of > 95 at 90 days?

Barthel Index scores at day 90 were provided by four studies. Figure 13 shows a benefit for survivors of having been treated with rtPA (OR = 2.05, 95% CI = 1.64 to 2.56).

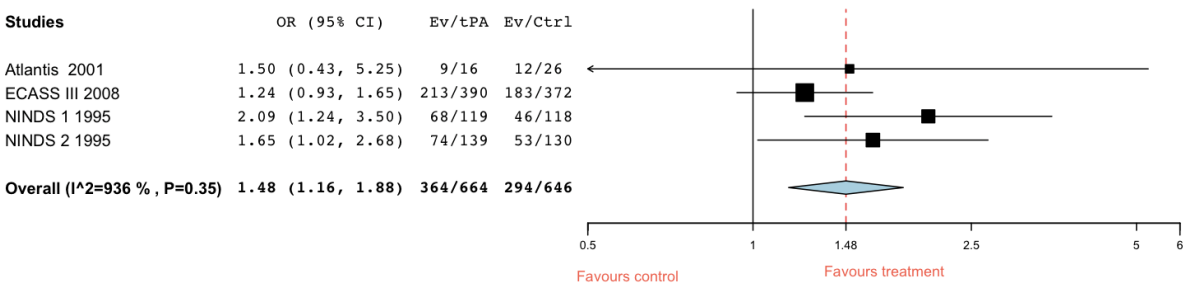
Figure 13: Forest Plot showing ORs for individual studies and overall meta-analysis of effects of treatment with rtPA on Barthel Index at 90 days (survivors only).



Does rtPA thrombolysis impact upon patient functional outcomes as assessed by a GOS score of 1 at 90 days?

GOS scores at day 90 were provided by four studies. Figure 14 shows a benefit for survivors of having been treated with rtPA (OR = 1.48, 95% CI = 1.16 to 1.88). I^2 = 9.36%, suggesting some heterogeneity, although this is low.

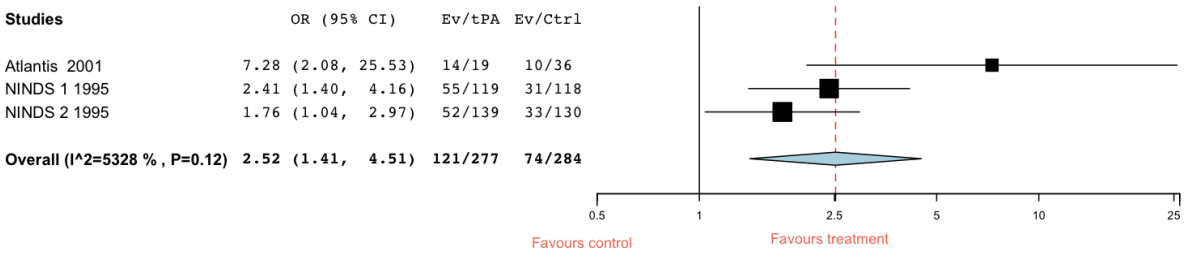
Figure 14: Forest Plot showing ORs for individual studies and overall meta-analysis of effects of treatment with rtPA on GOS scores at 90 day (survivors only).



Does rtPA thrombolysis impact upon patient stroke severity outcomes as assessed by NIHSS scores of 0 or 1 at 90 days?

NIHSS scores at day 90 were provided by three studies. Figure 15 suggests a benefit for survivors of having been treated with rtPA (OR = 2.52, 95% CI = 1.41 to 4.51). However, I^2 = 53.28%, suggesting some significant heterogeneity.

Figure 15: Forest Plot showing ORs for individual studies and overall meta-analysis of effects of treatment with rtPA on NIHSS scores at 90 days (survivors only).



Analysis of subgroups

Sufficient information was available to allow separate analysis to be carried out for:

- Timing of administration of rtPA (0-3 and 3-4.5 hours)
- Improvement in NHISS scores

All calculations have used total patients as the denominators as survivorship numbers were not available for this data.

How does timing of administration affect the impact of rtPA on functional outcomes?

Figures 16 and 17 shows that the administration of rtPA is advantageous for return to functional independence whether administered within 3 hours (OR = 1.85, 95% CI = 1.38 to 2.47), or between 3-4.5 hours (OR = 1.27, 95% CI = 1.01 to 1.60). However, the advantage appears to slightly greater when administration is earlier. I^2 = 7.35% for administration of rtPA between 3-4.5 hours suggesting some heterogeneity, although this is low.

Figure 16: Forest Plot showing ORs for individual studies and overall meta-analysis of effects of treatment with rtPA on return to functional independence (mRS 0-1at 90 days), administration of rtPA within 3 hours

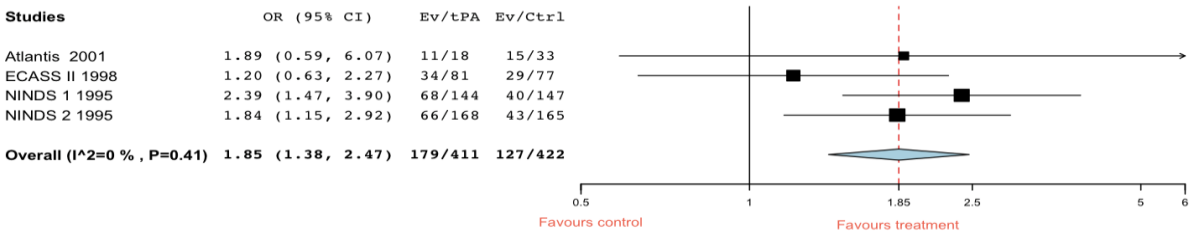
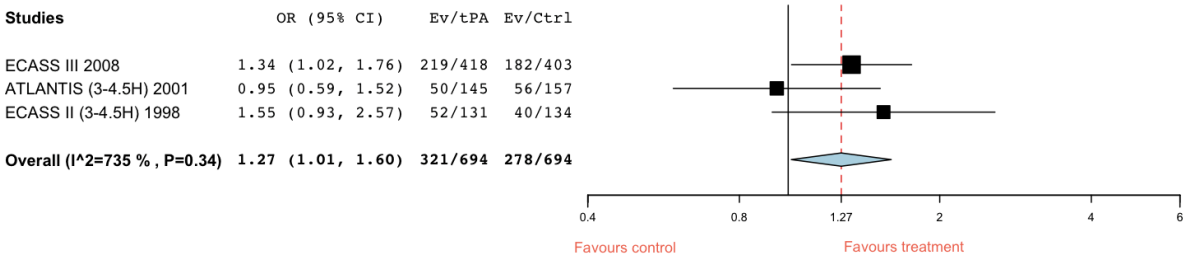


Figure 17: Forest Plot showing ORs for individual studies and overall meta-analysis of effects of treatment with rtPA on return to functional independence (mRS 0-1at 90 days), administration of rtPA between 3-4.5 hours



How does timing of administration affect the impact of rtPA on mortality rates?

Figures 18 and 19 suggest little difference of timing of rtPA administration on mortality rates. However, it should be noted that heterogeneity is moderate for administration of rtPA within 3 hours (I^2 = 28.12%) and high for administration between 3-4.5 hours (I^2 = 69.65%). Furthermore in both sets of analysis the confidence interval crosses the null, indicating that the results are statistically non-significant at the 0.05 level. Caution should be applied in the interpretation of these results.

Figure 18: Forest Plot showing ORs for individual studies and overall meta-analysis of effects of treatment with rtPA on mortality, administration of rtPA within 3 hours

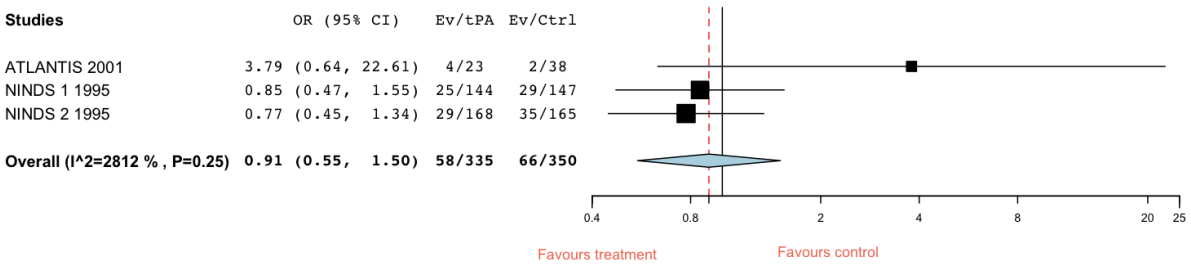
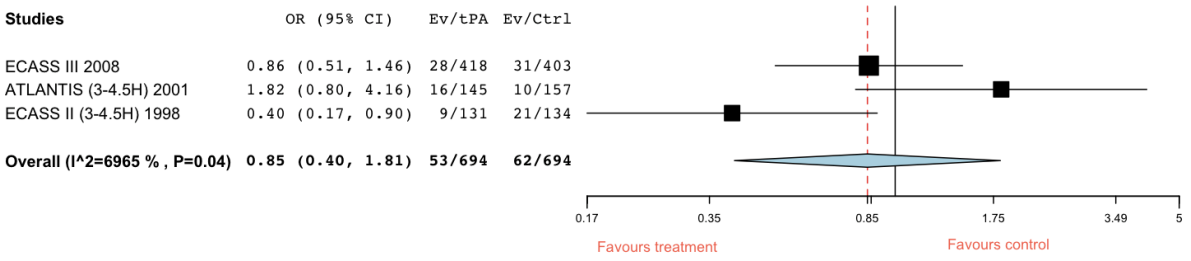


Figure 19: Forest Plot showing ORs for individual studies and overall meta-analysis of effects of treatment with rtPA on mortality, administration of rtPA between 3-4.5 hours



How does stroke severity on presentation, as measured by NIHSS affect the impact of rtPA on NIHSS scores at day 90?

Figures 20 and 21 suggest that treatment with rtPA has a positive impact on NIHSS scores at day 90, whether the presenting NIHSS score is more than or less than 10. However, both sets of results are statistically non-significant at the 0.05 level. Furthermore, Figure 21 shows high heterogeneity (I^2 = 75.31%) and very large confidence intervals, limiting our certainty in the results for outcomes when the presenting NIHSS score was over 10.

Figure 20: Forest Plot showing ORs for individual studies and overall meta-analysis of effects of treatment with rtPA on improvement of NIHSS scores from >10 to complete recovery (NIHSS 0-1)

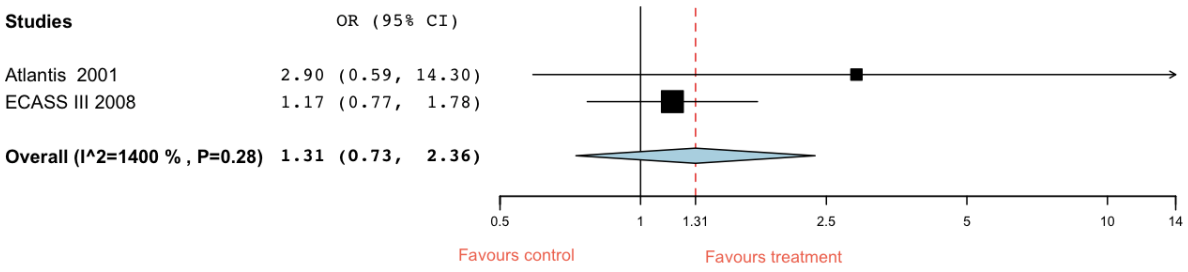
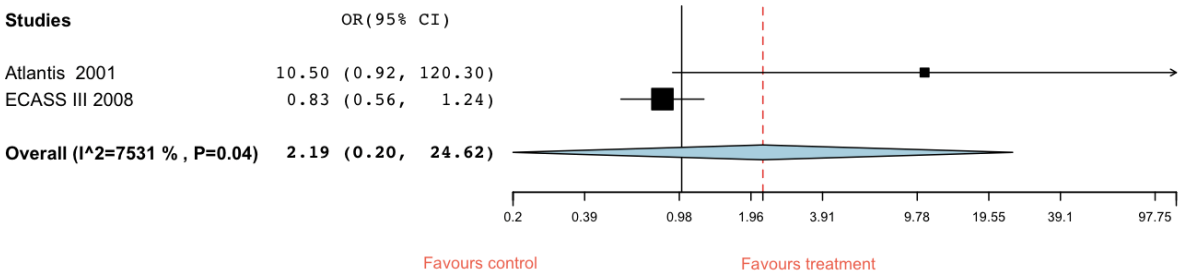


Figure 21: Forest Plot showing ORs for individual studies and overall meta-analysis of effects of treatment with rtPA on improvement of NIHSS scores from >10 to complete recovery (NIHSS 0-1)



Numbers needed to treat (NNT)

An alternative way of looking at the data presented is to calculate the number of patients who need to be treated for one person to have a good outcome (number needed to benefit or NNTB) and the number who would need to be treated for one person to be harmed (NNTBH). NNT was calculated using Cates (2002) method for estimating numbers using ORs. Calculations are provided for the main outcome measures where the benefits or risks to patients were significantly different between treatment and control groups:

Efficacy (functional outcomes)

Does thrombolytic therapy impact on patient functional outcome by altering the proportion of patients at 90 days who are able to return to independent living after treatment (i.e. no/mild disability as assessed by mRs 0-1)?

In the control group 64 people out of 100 were disabled or dead by 90 days, compared to 53 (95% CI = 58 to 47) out of 100 for the active treatment group. **NNTB = 10 (95% CI = 19 to 6).**

Does thrombolytic therapy impact on patient functional outcome by altering the proportion of patients who have a good outcome after treatment (i.e. mRs 0-2)?

In the control group 49 people out of 100 were disabled or dead by 90 days, compared to 41 (95% CI = 46 to 36) out of 100 for the active treatment group. **NNTB = 13 (95% CI = 29 to 8).**

How does timing of administration at 3 hours affect the impact of rtPA on functional outcomes?

In the control group 69 people out of 100 had disability (mRS >1) over 90 days, compared to 55 (95% CI = 62 to 48) out of 100 for the active treatment group. **NNTB = 7 (95% CI = 14 to 5).**

How does timing of administration at 3-4.5 hours affect the impact of rtPA on functional outcomes?

In the control group 60 people out of 100 had disability (mRS >1) over 90 days, compared to 54 (95% CI = 60 to 48) out of 100 for the active treatment group. **NNTB = 18 (95% CI = 419 to 9).**

Safety Outcomes

Does rtPA thrombolysis alter the risk of death from intracranial haemorrhage?

In the control group 0 people out of 100 had death from ICH over 90 days, compared to 1 (95% = CI 0 to 4) out of 100 for the active treatment group. **NNTH = 122 (95% CI** = 830 to 30).

Does rtPA thrombolysis alter the risk of symptomatic intracranial haemorrhage (sICH)?

In the control group 0 people out of 100 had sICH over 7-10 days, compared to 3 (95% = CI 1 to 8) out of 100 for the active treatment group. **NNTH = 42 (95% CI = 199 to 13).**

Additional analysis (Narrative review)

How does the risk of mortality or neurological and/or functional outcomes alter depending on:

Timing of administration (less than 90 minutes, 90 minutes to 3 hours, 3 hours to 4.5 hours) of rtPA after the ischemic event

Randomized clinical trials suggest the benefit of intravenous rtPA in acute ischemic stroke is time dependent. Thrombolysis for stroke is licensed for use within 4.5 hours and amongst stroke neurologists it is widely accepted that administration of rtPA is more beneficial and less harmful if carried out earlier within this timeframe, although there is some debate regarding this in the literature. Beyond this time there appear to be fewer benefits and much greater risk of harm (Ahmed et al., 2013; Maiser et al., 2011). A recent meta-analysis of individual patient data (Emberson et al., 2015) demonstrated a trend towards a larger relative increase in 90-day mortality with increasing treatment delay. This was not statistically significant, however, as Emberson et al. note, the statistical power to detect any true trend was limited by the number of deaths.

In hospital, mortality rates may increase with increasing onset to treatment time (OTT) (Saver et al., 2013), although this seems to pose only a small risk, if any (OR, 0.96, 95% CI, 0.95-0.98); other studies have found no difference in mortality rates within the first 4.5 hours (Gumbinger et al., 2014; Tong et al., 2014). In contrast, a time dependent pattern for better functional outcomes (mRS 0-2) has been confirmed in retrospective registry studies (Gumbinger et al., 2014) and prospective data sets (Saver et al., 2013), although it is not clear whether the greatest advantage relates to treatment within 90 minutes (Gumbinger et al., 2014) or 120 minutes (Muchada et al., 2014). However, according to one analysis (Saver et al., 2013) faster OTT, measured in 15-minute increments, was associated with slightly reduced risks (OR = 0.96, 95% CI = 0.95-0.98 for mortality and sICH) and an increased chance of independent ambulation at discharge (OR = 1.04, 95% CI =1.03-1.05), and of discharge to home (OR = 1.03, 95% CI = 1.02-1.04).

In fact, few studies stratify outcomes by such short timeframes, preferring to compare treatment within 3 hours to treatment between 3-4.5 hours. This may be because only a minority of patients can be treated within the 90-minute time frame, with the majority (77.2%) being treated within 91-180 minutes (Saver et al., 2013). These studies find no greater advantage for functional outcome or risk to safety (sICH and mortality) for earlier or later treatment (Wahlgren et al., 2008; Ahmed et al., 2010; Sarikaya et al., 2011d; Cronin et al., 2013). It has, however, been suggested that the impact of OTT on favourable outcome may vary depending on baseline stroke severity; in particular moderate stroke is thought to be affected by OTT, with favourable outcomes (mRS 0-2) more likely when treatment is given within the first 120 minutes (Muchada et al., 2014).

A number of factors have been found to be associated with shorter OTT. These include greater stroke severity (Saver et al., 2013; Sarikaya et al., 2011d), older age (Cronin et al., 2013), arrival by ambulance, and arrival during regular hours (Saver et al., 2013). This may of course reflect a reluctance of medical staff to thrombolyse patients who are seen to be more ‘at risk’ when OTT is greater than three hours. Thus whilst there is some evidence that early treatment may be associated with more favourable outcomes in daily clinical practice, it

is difficult to be certain that this does not simply reflect differences in clinical decision making depending on a presenting patient's time since onset.

Patient's age (<65, 65-75, >75)

Older age (80 years and over) is known to be a risk factor for stroke. Thrombolysis licencing continues to exclude use in older patients. There is some evidence that clinicians are less likely to offer rtPA to older patients, with reasons often listed as 'other', rather than guideline exclusion criteria (Zeevi et al., 2007). Studies in this area often have small numbers and therefore low power, particularly when considering patients over the age of 80 years. Most trials have excluded those over the age of 80 years; of the trials included in this systematic review, only NINDS 1 and 2 included patients over the age of 80 years. However, patients in this age group comprised only 12.8% (N = 40) of those allocated to rtPA treatment and 9.3% (N = 29) of those allocated to placebo. At 90 days, patients aged less than 80 years who had been treated with rtPA were more likely to have a better outcome defined as mRS of 0-2 (OR = 1.7, 95% CI = 1.2 to 2.4), than patients aged over 80 years (OR = 1.4, 95% CI = 0.45 to 4.0). Thus given the small sample size and the overlap between the data sets it is difficult to be certain that this is a significant difference.

One trial that did include a large number of older patients was IST-3 (Sandercock et al., 2012). This study suggested that older patients treated within 6 hours benefitted more than younger patients, as assessed by the primary outcome - alive and independent at 6 months (defined as Oxford Handicap Scale (OHS) 0-2). However, these results are confounded by the fact that older patients were most likely to have been treated within 3 hours than younger patients. Unfortunately, the study did not have sufficient power to allow further analysis that would establish the interaction between age and time. It should also be noted that the OHS was posted out to patients along with a quality of life measure (EQ-5D) for self-completion, either by the patient themselves or their carer. Whilst this is the usual method of administration for EQ-5D, this is not typically the approach used for the OHS, which is an alternative modification of the Rankin Scale. As the OHS was not developed for self-report, the reliability and validity of the reported outcomes cannot be assumed. Furthermore, it is likely that proxy-reported measures will differ from patient reports, and should not be substituted for these unless concordance is known to be acceptable for the chosen measure (Upton & Upton, 2007). Caution in the interpretation of these results is therefore warranted.

The majority of larger scale, more robust studies tend to be retrospective reviews of cases, and in the main demonstrate that older patients have more co-morbidities, such as atrial fibrillation and hypertension, and more severe strokes both in terms of NIHSS scores and stroke location (e.g. large artery atherosclerosis/cardio-embolism stroke subtypes) than their younger counterparts (Simon et al., 2004; Boulouis et al., 2012; Costello et al., 2012; Tanne et al., 2000; Ford et al., 2010; Dharmasaroja, Muengtaweepongsa & Dharmasaroja, 2013; Mateen et al., 2009; Sylaja et al., 2006). Furthermore, older stroke patients are less likely to be functionally independent before their stroke (Bray et al., 2013; Boulouis et al., 2012).

It is therefore not surprising that older patients have poorer outcomes irrespective of the treatment they are given (Simon et al., 2004; Bray et al., 2013; Mateen et al., 2009; Ford et al., 2010). Moreover, mortality, ICH and morbidity from stroke all increase with age (Dharmasaroja, Muengtaweepongsa & Dharmasaroja 2013), with the highest rates of poor outcome seen in patients aged over 90 years (Sarikaya et al., 2011b). The higher mortality

and the poorer functional outcome seen in older patients treated with rtPA are therefore argued to be consistent with the overall worse prognosis seen in the natural history of this age group, and simply reflect aged-related clinical characteristics (Ford et al., 2010; Sylaja et al., 2006).

In general, studies therefore agree that older patients should not be excluded from rtPA treatment on the basis of age alone (Tanne et al., 2000; Bray et al., 2013; Simon et al., 2004). A good outcome for these patients will depend upon careful selection for treatment, so as to minimise the impact of confounding problems such as co-morbidities (Sarikaya et al., 2011b; Sylaja et al., 2006). For example, both Ford et al. (2010) and Sylaja et al. (2006) found that in selected stroke patients aged over 80 years of age there was a similar rate of sICH compared with younger patients, making them appropriate candidates for thrombolysis. This is further supported by a combined analysis of SITS and VISTA data (Mishra et al., 2010), which demonstrated similar outcomes for older and younger patients.

In 2012 a novel three-year trial focusing specifically on the administration of rtPA to individuals over the age of 80 years of age (TESPI) commenced. It is anticipated that the results of this trial will provide better answers to questions regarding the use of rtPA in older age (Lorenzano et al., 2012).

Patient's weight

The prevalence of obesity among stroke patients is reported to be as high as 74% (Hassan et al., 2013). Given that obesity is known risk factor for stroke (Sarikaya et al., 2011c), this is perhaps not surprising. Patient obesity may also have treatment implications, since the maximum dose of tPA (90g) might result in underdosing in these patients, which could in turn impact on outcome. Furthermore, obese patients have been found to have elevated circulating concentrations of the endogenous plasminogen activator inhibitor (PAI-1), resulting in impaired fibrinolysis, which may further augment the consequences of underdosing of IV rtPA in these patients. However, an obesity paradox has been noted, with obese stroke patients reported to be less likely to experience haemorrhagic transformation, with or without thrombolysis (Kim et al., 2013). In addition, these patients are reported to have significantly better early and long-term survival rates compared to those with normal BMI.

Three papers looked specifically at the impact of weight on outcomes following intravenous thrombolysis (Hassan et al., 2013, Sarikaya et al., 2011c, Seet et al., 2014). A retrospective review of all patients treated in US hospitals 2002-2009 (Hassan et al., 2013) found better outcomes for obese patients in terms of lower intracerebral haemorrhage rates, lower mortality rates and a greater chance of being discharged with minor disability. However, obese patients were more likely to be younger, female and have hypertension and diabetes, and the difference in outcomes disappeared once adjustment was made for these factors. Thus whilst higher survival rates for obese patients are most likely to be related to a decreased rate of ICH (due either to underdosing of rtPA or poor fibrolysis), outcomes in terms of functional ability are not necessarily better. Similar outcomes were noted by Seet et al. (2014) whose retrospective single centre cohort study established that risk of poor functional recovery increased with the number of metabolic risk components. In contrast, Sarikaya et al. (2011c) found that although obese patients presented more often with diabetes and hypertension, obesity was an independent predictor of unfavourable outcome and mortality in acute ischaemic stroke treated with intravenous thrombolysis.

Finally, given that obesity increases the risk of stroke, describing it as having survival benefits is dubious. The perceived paradox reported in the literature may be explained by differences in demographic and clinical characteristics such as age and stroke severity in overweight and obese patients.

Other patient demographics

(a) Gender

The effect of biological sex on various aspects of stroke, including response to treatment, has been widely investigated (Reeves et al., 2008). As noted already, stroke incidence increases with age. Thus it is perhaps not surprising that, given their longer life expectancy, women are more likely to experience stroke than men. Women are also more likely to be older than men when they have their first stroke (Lasek-Bal, Puz & Kazibutowska, 2014). In addition, studies have demonstrated that the natural course and outcomes of stroke are worse in women, with a higher probability of functional dependency and institutionalisation (Reeves et al., 2008). Again, it seems likely that this is related to older age of onset. Although it should also be noted that women tend to present with atypical stroke syndromes (Kapral et al., 2006), it has also been found that women present with higher initial neurological deficit, and a higher prevalence of atrial fibrillation and a cardioembolism as an etiologic subtype of stroke (Jovanovic et al., 2009; Forster et al., 2009).

Sex based differences in coagulation and fibrinolysis markers in individuals with acute stroke have also been noted (Kain et al., 2003), although the implications of this are not clear. Whilst the evidence for sex disparity in response to thrombolysis for acute stroke treatment is deemed inconclusive by some (e.g. European Stroke Organisation, 2008), a biological basis for a difference in response to rtPA cannot be ruled out at present. Early studies such as NINDS identified no sex differences in response to treatment, whilst later studies using larger (pooled) data sets suggested that women benefited more from thrombolysis than men (Kent et al., 2005). This led to the suggestion that intravenous rtPA may modify the survival and recovery advantage observed for men in the natural course of an ischemic stroke. More recently this benefit for women has been replicated in both small (Jovanovic et al., 2009; Lasek-Bal, Puz & Kazibutowska, 2014**)** and large registry studies (Lorenzano et al., 2013). However, Lorenzano also demonstrated that once confounding variables were controlled for, there was no sex difference in functional outcome at 3 months, whilst conversely sICH and mortality risk increased for men (Lorenzano et al., 2013).

Finally, it has also been suggested that women may experience differences in stroke management including less intense diagnostic evaluations and less frequent use of anti-platelets and rtPA (Elkind et al., 2007). This difference may of course link to patient preference, which is discussed later.

(b) Ethnicity

Studies have suggested a difference in response to IV rtPA depending on ethnicity. It has been proposed that this is in part due to biologically based differences in fibrinolysis (Chao et al., 2010). A major criticism of the large Alteplase trials is the predominance of participants who are White and it has been suggested that the evidence from these trials should not be generalized to individuals from other ethnic backgrounds. In particular, it is claimed that

Asian individuals have a heightened response to intravenous rtPA and this has led to trials in China (Chen, 2002) and Japan (Yamaguchi et al., 2006) that use lower doses of rtPA (e.g. 0.6mg/kg), or a lower maximum dose (0.9mg/kg to a max of 50mg).

Many of the studies considering the impact of the standard dose of rtPA on individuals from different ethnic backgrounds use retrospective data; in the main these studies have found no major difference in response to rtPA in different ethnic groups. Thus standard-dose intravenous rtPA (0.9mg/kg) has been found to result in better clinical outcomes and similar death rates, compared to other studies reporting Asian cohorts receiving lower dose intravenous rtPA in Thai (Dharmasaroja, Dharmasaroja & Muengtaweepongsa, 2011) and Chinese patient cohorts (Zhou et al., 2010). Overall, patient outcomes appear to be similar to those seen in trials with predominantly White participants. Thus patients with good outcomes at 3 months tended to be significantly younger, and had less severe strokes and fewer complications. Patients who died within 3 months were significantly older and had more severe stroke aetiologies (Dharmasaroja, Dharmasaroja & Muengtaweepongsa, 2011; Liao et al., 2013; Xu et al., 2014).

This seems to confirm the findings of a prospective Taiwanese study (Chao et al., 2010), which found that for patients aged over 70 years, there were no statistical differences in any of the safety and efficacy parameters between standard-dose and lower-dose groups. Higher rates of sICH and mortality within 3 months were seen for the higher dose in older patients, but this is similar to studies reviewed above regarding age, and does not necessarily indicate a difference for older Chinese patients. It should be noted that patients in this study were not randomized to low or high dose; dose differences were a form of protocol violation since some neurologists in Taiwan chose to reduce the dose of rtPA for safety concerns based on studies recommending lower dose anticoagulants (e.g. Miao et al., 2007) and rtPA for heart attack (Ross et al., 2001). It is difficult to know, therefore, if there is any bias regarding who received the lower dose.

In contrast a large retrospective study in the USA (Nasr et al., 2013) found that when differences in demographics and co-morbidities were controlled for, Asians and Pacific Islanders had significantly higher rates of mortality and ICH compared with Whites, whilst Hispanic patients had a lower risk of morbidity. These outcomes may be explained in part by differences in baseline characteristics between ethnic groups; for example, Asian/Pacific Islander patients had a higher rate of atrial fibrillation than their White counterparts, which has been linked to poorer outcomes following stroke, and following treatment with rtPA. However, it is also possible that the categorisation of patients by ethnic groups based on social rather than biological constructs produces differences based on factors other than genetic difference.

Patient's smoking history

The so-called smoking-thrombolysis paradox of an improved outcome after thrombolysis for smokers was first described in smokers with myocardial infarction. It has been suggested that smoking produces biological changes that increase the risk of thrombosis and thus increase sensitivity to rtPA and protect against haemorrhagic transformation (Moulin et al., 2012). However, the evidence in support of this position is limited; one study (Kufner et al., 2013) has identified a possible link between smoking and recanalization and reperfusion, indicating that thrombolytic therapy acts more effectively in smokers. Unfortunately study numbers were small and as Kufner notes the smokers' better functional outcome 3 months

post stroke was most likely due to their low clinical risk profiles and low NIHSS scores on admission.

As with the obesity paradox, the role of smoking as a risk factor for stroke should not be forgotten; stroke occurs more than 10 years earlier in smokers than in non-smokers (Aries et al., 2009a). Furthermore, on current evidence it seems most likely that any differences in treatment outcomes are explained by confounding variables such as patient age (smokers tend to be younger) and stroke severity, which tends to be milder in these younger smoking patients. Indeed recent studies have found that better outcomes for smokers disappear once age and stroke severity are adjusted for (Moulin et al., 2012, Aries et al., 2009a).

Patient's alcohol consumption

It has been suggested that light to moderate alcohol consumption can be protective against cardiovascular disease and associated problems such as stroke, whilst heavy consumption increases this risk. Studies suggest that this may be explained by an association between lower concentrations of coagulation factors and moderate alcohol intake whilst in heavier drinkers higher intake is associated with impaired fibrinolytic potential which may predispose individuals to thrombosis (Mukamal et al., 2001). Animal studies have also suggested that heavy drinking may increase stroke severity, and reduce the effectiveness of treatment with rtPA; this review was unable to locate any studies considering this topic in humans.

Baseline systolic and diastolic blood pressure

Patients with acute ischaemic stroke often have elevated blood pressure (BP). Australian (National Stroke Foundation, 2010) and American (Jauch et al., 2013) Stroke Management Guidelines, suggest that if blood pressure can be safely lowered prior to less than 185/110 mmHg using antihypertensive agents, then IV rtPA can be administered. However, rapid and/or steep reductions in BP are cautioned against due to concerns that this may cause neurological worsening.

Studies indicate that high systolic, but not diastolic BP, both before and after thrombolysis is associated with poor outcome (Idicula et al., 2008; Ahmed et al., 2009). For example, a prospective study (Idicula et al., 2008) found that lower systolic BP was associated with better functional outcome at three months (mRS 0-2) although this advantage was only modest (OR = 1.27, 95% CI = 1.03 to 1.52).

The risk of poorer outcome for those with higher pre-treatment systolic BP levels, may be related to a reduced ability to recanalyse; Tsivgoulis et al., (2007) found an association between high systolic BP, poorer recanalization and poorer functional outcomes at 3 months as measured by mRS. However, clinical and demographic factors such as age, baseline NIHSS score and time to treatment were independent predictors of outcome, whilst elevated systolic BP was not, suggesting raised BP may be a marker for other clinical factors. This is given further support by studies demonstrating that patients requiring BP lowering medication had other indicators of poor outcome, including more severe strokes, higher serum glucose concentration and a history of hypertension (Martin-Schild et al., 2008). Thus, although rates of adverse events such as sICH and mortality may be higher in those receiving BP-lowering agents, it is not clear if this is a result of the elevated BP, the pharmaceutical intervention or other factors. The finding that there were no differences in outcomes between patients receiving labetalol monotherapy or more aggressive BP lowering treatment (defined as the use of nicardipine treatment, either alone or in addition to labetalol)

are strongly supportive of the role of other clinical factors for poor outcomes in these patients (Martin-Schild et al., 2008).

It should also be noted that in an analysis of SITS-MOST data, patients with elevated systolic BP post-treatment who were treated with antihypertensive therapy within 7 days after thrombolysis and who did not have a history of hypertension previously, had outcomes comparable to those without elevated BP post-treatment (Ahmed et al., 2009). This analysis also found that withholding antihypertensive therapy in patients with raised BP and a history of hypertension was associated with higher mortality, sICH rate, and poorer functional independence. Overall this supports the early use of antihypertensive therapy in patients with raised BP following thrombolysis (Ahmed et al., 2009).

Co-morbidities

A number of co-morbidities have been identified as contraindications to intravenous thrombolysis, including a history of previous stroke or TIA, previous MI, existing hypertension, diabetes or chronic atrial fibrillation. However, the extent to which risk is increased, and the chance of better outcomes are reduced in these patients continues to be debated.

Previous stroke

It is recommended that stroke patients who have experienced either a previous stroke or TIA within three months are not thrombolysed due to an increase risk of bleeding. The data is therefore limited regarding the use of intravenous thrombolysis with this group, relying most often on case studies of patients thrombolysed unintentionally – i.e. where symptoms were unknown at the time of treatment (e.g. Alhazzaa et al., 2013). Observational registry reviews (Fuentes et al., 2012; Lecinana et al., 2012) have found no difference in safety or functional outcomes at 3 months for patients with previous stroke or TIA when compared to those without. Despite these studies recruiting reasonably large numbers over all (1,475 and 877 respectively), the number of patients with prior stroke or TIA thrombolysed was relatively small (153 and 60 patients respectively).

Further support for the use of intravenous rtPA with patients who have had TIA comes from a recent prospective international study in which 25 consecutive patients who had been hospitalised for TIA were treated with intravenous thrombolysis when they developed acute ischemic stroke symptoms (Tsivgoulis et al., 2014). No sICH was documented, and the majority of patients (84%) achieved functional independence at three months, with this being higher in patients treated within 90 mins from symptom onset. Whilst limited by sample size and the lack of comparison to outcomes for patients without TIA, this prospective pilot study does suggested that thrombolysis for patients with prior TIA may not pose a safety issue, and that further investigation into this issue is merited.

Myocardial Infarction

There is some concern that outcomes for patients with previous myocardial infarction (MI) may be poorer following intravenous thrombolysis for stroke. American guidelines regard patients who have had MI within the past three months as a relative contraindication for IV thrombolysis, whilst European guidelines note that stroke and MI often co-exist, and emphasise the importance of monitoring cardiac functioning. Thus in the European context, the focus is on MI as a potential complicating factor in stroke outcomes, but not a reason for exclusion from treatment.

A recent review supports the European approach. De Silva et al. (2011) found that only 5 stroke patients with recent MI (past three months) had cardiac tamponade following treatment with rtPA. Furthermore, they note that since pathological studies show MI healing is completed by 7 weeks, the three-month time window for MI as a contraindication for IV stroke thrombolysis could be reduced.

Chronic heart disease

A recent analysis of VISTA data (Abdul-Rahim et al., 2015) suggested that chronic heart failure was associated with a worse outcome (increased mortality and poorer mRS scores) with or without thrombolysis. Furthermore ischaemic heart disease is associated with a number of other clinical and demographic features indicated in worse outcomes for thrombolysed patients including older age, hypertension, and atrial fibrillation. It has been suggested that whilst a history of congestive heart failure is associated with an increase in the occurrence of sICH following IVT, it does not reverse the overall benefit of treatment (Lansberg, Albers & Wijman, 2007).

Chronic Atrial Fibrillation

Atrial fibrillation (AF) increases the risk of stroke and is associated with poor stroke outcomes. Small single–centre studies (Awadh et al., 2010) and larger registry studies (Saposnik et al., 2013) have demonstrated an association between AF and increased mortality and sICH. Furthermore, even after adjustment for confounding factors (age, gender and stroke severity), thrombolysis was not associated with a favourable functional outcome (mRS 0-2) for patients with AF (Saposnik et al., 2013). However, Saposnik did identify a trend for a clinical response to rtPA which was similar in those with and without AF, suggesting that the lack of a significant treatment effect reflected the small sample size of patients with AF (N = 316), compared to those without (N = 1,373).

This is given some support by Zhang et al., (2010) who found that patients with AF treated with rtPA within 4.5 hours had better outcomes than those with AF not treated with rtPA (OR = 2·67, 95% CI = 1·06 to 6·74). Outcomes were poorer than for rtPA treated patients without AF, however, patients with AF tended to have more severe strokes than those without.

Diabetes

Hyperglycaemia, like elevated blood pressure, is a frequent finding in stroke patients even in the absence of a history of diabetes. This has led to suggestions that it represents a stress response, although analysis of data from VISTA indicates that this may not be the cause (Kerr et al., 2012). It has been claimed that hyperglycaemia or a history of diabetes increases ischaemic injury, and is associated with haemorrhagic transformation in thrombolysed patients, resulting in poorer outcomes (Demchuk et al., 1999, Paciaroni et al., 2009), although findings in this area are mixed. Fuentes et al., (2012) found no difference in safety or functional outcomes at 3 months for patients with diabetes when compared to those without, whilst Demchuk et al., (1999) demonstrated an independent association between diabetes or baseline hyperglycaemia and increased ICH after thrombolysis. However, it has also been suggested that post treatment hyperglycaemia may be a better predictor of poor outcomes than hyperglycaemia on admission; a retrospective study of blood glucose levels before and after treatment (Yoo et al., 2014) detected an association between post-treatment hyperglycaemia, increased mortality rates, and reduced mRS (>2) at 3 months, even after adjustment for confounders (age, NIHSS, and atrial fibrillation).

Nevertheless, it should be noted that persistent hyperglycaemia is also associated with older age and co-morbidities such as hypertension and heart disease as well as diabetes (Putaala et al., 2011).

Stroke severity on presentation (NIHSS score groupings)

Patients with 'mild' stroke (NIHSS <4), or rapidly resolving symptoms are not routinely offered rtPA. Generally, outcomes for these patients are good, although it has been suggested that up to a third of the patients initially deemed too healthy to be treated with rtPA show later neurological worsening and in some cases disability (Smith et al., 2005). Such figures are based on small numbers. In instances where patients with minor deficit have been treated, rates of sICH, mortality and clinical outcomes have been similar to those of treated patients with more severe stroke (Breuer et al., 2011). However, 90-day outcomes for patients with mild stroke not treated with rtPA are similar to those who are treated (Huisa et al., 2012).

In contrast, other studies have found lower baseline NIHSS scores on presentation to be associated with better overall outcomes following thrombolysis (Schlegel et al., 2004; Strbain et al., 2010; Logallo et al., 2014; Greisenegger et al., 2014). One international multi-centre study found that NIHSS score on admission was able to predict discharge to rehabilitation or nursing facilities (Schlegel et al., 2004). Thus patients whose baseline score was 6 to 15 were significantly more likely to go to rehabilitation, but not nursing homes. Patients with NIHSS scores greater than 15 were significantly more likely to need rehabilitation and nursing home care. However, it should be noted that patients reaching an early remission tended to be younger (Strbain et al., 2010), whilst increasing age (particularly over 65 years) was associated with needing nursing home care (Schlegel et al., 2004). Excellent outcomes at day 7 (mRS 0) have been found to be better for patients with mild stroke who were treated with rtPA than those who were not (OR = 1.48, 95% CI = 1.04 to 2.10; Logallo et al., 2014).

Finally, Ifejika-Jones et al. (2011) found lower baseline NIHSS scores to have better outcomes irrespective of treatment. They also noted that patients who received rtPA, who tended to have higher NIHSS on arrival than the non-treatment group, were also more likely to be discharged home than those not treated (OR = 1.95, 95% CI = 1.54 to 2.46). However, the finding that those receiving thrombolysis were younger, and had fewer risk factors such as prior history of stroke than those not treated, confounds this result.

Stroke aetiology or location (e.g. cardioembolic, atherothrombotic, lacunar/small vessel disease, other)

Information concerning the impact of intravenous rtPA dependent on stroke type is often limited by its retrospective nature. Only one trial (NINDS) considered this detail, suggesting that all stroke types had better outcomes (mRS 0-1) when treated with rtPA, but that outcomes were best for a higher proportion of patients with small vessel occlusion (63%) when compared to those with large vessel occlusion (40%) or cardioembolic (38%). Unfortunately this data on subtype was rated invalid by a blue ribbon review (Ingall et al., 2004).

However, retrospective reviews (Chang et al., 2013; Mustanoja et al., 2011) have also identified poorer outcomes for cardioembolic patients. These patients had the worst outcomes, being less likely to have mRS 0-2 either at discharge (Chang et al., 2013) or at 90 days (Mustanoja et al., 2011). In comparison, paradoxical strokes had the best outcomes at

discharge (Chang et al., 2013), whilst small-vessel disease strokes had the best outcomes at 90 days (Mustanoja et al., 2011). However, both Chang et al. (2013) and Mustanoja et al. (2011) noted a number of confounders including lower initial stroke severity in those stroke types with better outcomes. Regression analysis suggested that younger age and milder stroke severity on presentation were better predictors of discharge outcome than stroke type when comparing cardioembolic stroke to paradoxical stroke (Chang et al., 2013). In contrast, Mustanoja et al. (2011) found that patients with small vessel disease still had had a better outcome even after adjusting for baseline stroke severity, glucose level, age, and hyperdense artery sign (OR = 1.81, 95% CI = 1.01 to 3.23). This is particularly notable since the presence of a hyperdense middle cerebral artery sign on baseline brain CT has previously been associated with poor functional outcome (Aries et al., 2009b).

Retrospective observational studies (Lahoti et al., 2014; Griebe et al., 2014) have also compared lacunar and non-lacunar strokes treated with rtPA, finding that lacunar strokes have a similar safety profile to non-lacunar strokes, but have better functional outcomes (mRS 0). However, non-lacunar stroke without internal carotid artery (ICA) occlusion have better outcomes (mRS 0–1) than those with occlusion (Zivanovic et al., 2014). Safety profiles were also similar. It should be noted that in this study patients with ICA occlusion also had more severe stroke scores.

Stroke severity was also an important factor in a retrospective study of large vessel occlusion (LVO), which included middle cerebral, anterior cerebral, posterior cerebral, basilar, or vertebral artery occlusion in addition to ICA occlusion (Zhu et al., 2014). Whilst an association with worse functional outcome (mRS >1) was found for LVO in severe and mild (NIHSS 0-6) stroke, this was only significant for severe strokes. An increase in mortality for those with LVO and a severe stroke was also noted. An analysis of SITS-ISTR (Paciaroni et al., 2012a) identified similar associations between extra cranial ICA occlusion and poor outcomes, with severity acting as an independent predictor of poorer outcomes; however, it should be noted that mean baseline NIHSS scores were higher in this study for patients with extra cranial ICA occlusion.

Better outcomes have also been found for patients with ICA occlusion who had rtPA when compared to those who did not have this treatment, although higher rates of sICH and mortality were also noted (Paciaroni et al., 2012b). However, controls in this study were patients arriving after the 4.5 cut off or for whom onset time was uncertain (wake up stroke), which may have introduced an element of bias.

A prospective comparison of outcomes for anterior (ACS) and posterior (PCS) circulation strokes following treatment with rtPA (Sarikaya et al., 2011a) found that patients with PCS were less likely to experience sICH (0% versus 5%, $P = 0.026$) and were more likely to have a favourable outcome (mRS 0-1; 66% versus 47%, $P = 0.001$). However, after adjustment for age and stroke severity (patients with PCS were younger and had a lower mean baseline NIHSS score) PCS was an independent predictor of lower incidence of sICH ($P = 0.001$), but not favourable outcome or mortality rates.

Finally, in patients treated with rtPA, the presence of arterial dissection has been found to be associated with poorer functional outcomes (mRS >2) in comparison to patients without dissection, but not sICH (Qureshi et al., 2011, Engelter et al., 2009). This remained true after adjustment for confounding factors such as age, sex, initial stroke severity and co-

morbidities. Unfortunately no comparison to patients not treated with rtPA was provided by either study.

Patients currently or previously receiving anticoagulant therapy

The safety of intravenous thrombolysis after ischaemic stroke in this patient population remains controversial; patients with abnormal baseline coagulation or taking warfarin were excluded from large randomized trials, whilst clinical studies in this area often have limited numbers due to the restrictions of European and American licencing for patients on anti-coagulants.

Patients taking anticoagulants are often older, have more comorbidities, and experience more severe strokes compared to other patients (Xian et al., 2012; Mazya et al., 2013). A number of studies (including an analysis of SITS data) have found no significant differences in sICH rates and mortality between patients on anticoagulant therapy and those not, once adjustment is made for these confounders (Schmulling et al., 2003; Xian et al., 2012; Mazya et al., 2013). In contrast, Seet et al. (2011) found a trend for poorer stroke recovery and increased mortality in warfarin-treated patients on univariate, but not on multivariate analyses, although numbers were small (14 of 212 patients had prior warfarin use).

Patients currently or previously receiving antiplatelet therapy

Antiplatelet therapy is also seen as a contraindication to intravenous thrombolysis. As with anticoagulant therapy, patients taking medications such as aspirin tend to be older and have a higher prevalence of vascular risk factors. Likewise, studies are often limited by small numbers in the target population (e.g. Dorado et al., 2010). Pre-treatment with antiplatelet treatment has been found to raise the risk of sICH in both small (Bravo et al., 2008) and larger studies (Meurer et al., 2013; Uyttenboogaart et al., 2008). However, this difference is not statistically significant, particularly in studies where the sample size is large enough to allow for adjustment of confounders (Meurer et al., 2013). Furthermore, Uyttenboogaart et al. (2008) found that patients who had prior antiplatelet therapy had a better chance of mRS score of 0-2 at 3 months than those who had not (OR = 5.96, 95% CI = 2.01 to 17.11). This advantage almost doubled if rtPA was administered within 3 hours of stroke onset (OR = 10.89, 95% CI = 2.40 to 49.34). In contrast a randomised trial of antiplatelet given in combination with rtPA thrombolysis (ARTIS) showed no advantage for concomitant intravenous administration of aspirin (Zinkstok et al., 2012, 2014).

A recent meta-analysis of this topic (Pan et al., 2015) confirmed the increased risk of sICH in thromboysed patients taking antiplatelet medication, but suggested no advantage for prior antiplatelet users. The conclusions of this meta-analysis are limited by the moderate heterogeneity between the pooled studies (I^2 = 42%). Thus whilst it is clear that prior antiplatelet treatment raises the risk of sICH, the impact on long-term functional outcomes is unclear.

Treatment centre specifics

Widespread adoption of IVT as a first line treatment has led to development of new protocols with the aim of increasing access to treatment, particularly in rural and remote communities. These include the so-called ‘ship and drip’ protocols in which a patient is thrombolysed in a local centre before being sent to a stroke unit. Well-organized hierarchic systems of acute stroke care have also been proposed to link community hospitals to specialised stroke centres. This has led to the development of ‘hub and spoke’ models, in which a stroke centre

(the hub) provides advice to 'spoke' hospitals without a neurologist, either by telephone or video link (telemedicine). Unfortunately, many studies are small, indicating a potential bias in which patients are actually thrombolysed; there is some indication that clinicians will err on side of caution if there is no neurologist present, which may in turn explain the exceptionally good outcomes shown in some of these studies, particularly where safety and efficacy is better in the inexperienced spoke hospitals than it is in the more specialised hub hospitals (e.g. Chowdhury et al., 2012).

Despite these limitations a number of retrospective studies have shown similar safety profiles and good outcomes (mRS 0-2) for patients treated following remote assessment in community hospitals compared to treatment after face-to-face assessment in a specialist hub (Rudd et al., 2012; Ionita et al., 2009; LaMonte et al., 2008; Martin Schild et al., 2011; Audebert et al., 2005 & 2006). Similar outcomes to those found in the NINDS trial have also been noted in these hospitals (Akins et al., 2000; Vaishnav, Pettigrew & Ryan, 2008). Not surprisingly, OTT may be longer in spoke hospitals (Martin-Schild et al., 2011; Perez et al., 2009). There also remains some debate concerning the superiority of telephone versus video link assessment; on the one hand a retrospective review of outcomes in spoke hospitals found no difference in effectiveness (Pervez et al., 2010), whilst a randomised, blinded, prospective study determined that decision-making using telephone alone was poorer than with a video-link assessment (Meyer et al., 2008).

Not all studies have found positive outcomes for patients treated in non-specialist centres. There is some suggestion that in hospitals with limited experience of rtPA treatment in routine clinical practice there is an increased in-hospital mortality rate (Heuschmann et al., 2003) or a reduction in the chance of a good functional outcome (mRS 0-2) at 90 days (Perez et al., 2009). This may well be explained by physician experience rather than the setting per se; Akins et al. (2000) found that despite outcomes similar to NINDs, the number of protocol violations such as dosing errors or not treating elevated BP were greater when the emergency doctor, rather than the experienced neurologist, administered rtPA. In this case, increasing educational opportunities at less specialised hospitals may be more effective than limiting the use of rtPA to specialist centres.

Recently attempts to increase the reach and early administration of IVT have used ambulance-based thrombolysis (Ebdinger et al., 2014). A recent RCT (Prehospital Acute Neurological Treatment and Optimization of Medical care in Stroke Study or PHANTOM-S), compared safety outcomes when IV tPA was started in a specially equipped ambulance or Stroke Emergency Mobile (STEMO) versus usual care (no STEMO deployment; infusion commenced on arrival in hospital). During intervention weeks STEMO were deployed based on a stroke identification algorithm used by dispatchers, and acted as mobile stroke units, being manned by an experienced stroke team, which included a neurologist, a paramedic, and a radiology technician. On-board equipment included a CT scanner, a point-of-care laboratory, and a telemedicine connection to allow for immediate assessment of patient eligibility for IV rtPA. The study found a lower proportion of patients experienced ICH when receiving ambulance based thrombolysis rather than standard care (3.5% v 6.4%), although this was non-significant. Mortality rate at day seven was 4.5% in both control and intervention settings. These good outcomes seem to relate at least in part to the shortened OTT afforded by the deployment of STEMO – median OTT was significantly reduced for intervention patients (minutes to treatment = 48, 95% CI = 39 to 56) compared to control patients (minutes to treatment = 72, 95% CI = 62 to 85). However, the expertise and

experience of the STEMO personnel may also be crucial to these outcomes. Further studies investigating the efficacy and cost effectiveness of this approach to IVT will be important in establishing the feasibility of a more widespread use of mobile stroke units (e.g. Rajan et al., 2015).

Patient preference

The decision to thrombolyse a stroke patient must be taken relatively quickly, given the limited treatment window, and the advantage provided by earlier intervention. Gaining consent from stroke patients to instigate thrombolysis can be challenging, given that the neurological impact of the stroke may cause a reduced capacity to consent. In other life threatening emergencies where the patient is unable to consent and no proxy is available, the presumption to consent is often applied; for example the presumption of consent is generally accepted for CPR in the case of a heart attack. Conversely, presumption of consent for less established treatments such as thrombolysis for stroke remains somewhat controversial. Studies of patient preference can therefore help inform emergency room decision-making, indicating what if any circumstances support presumption of consent, the use of proxy consent, or if other approaches are warranted.

According to Chiong et al. (2014b), there is empirical support for presuming consent to IVT when an incapacitated older patient's treatment preferences are unknown and surrogate decision makers are unavailable. In a survey of 2,154 US adults aged 50 and over Chiong et al. (2014a) found that older adults were as likely to want stroke thrombolysis when unable to consent (78.1%) as when asked directly (76.2%). Greater confidence in the medical system and reliance on statistical information in decision making were both associated with desiring thrombolysis.

A sex difference in patient preference for intravenous thrombolysis has also been noted. Kapral et al. (2006) found that women were less likely than men to accept thrombolysis (79% vs. 86%, P = 0.014), even after adjustment for other factors (OR = 0.58, 95% CI = 0.37 to 0.92). Women were less confident in their decisions, were more risk averse, and would have preferred more information to assist them in their decision-making. Chiong et al. (2014a, 2014b) also found that women were more likely to say they would refuse intravenous thrombolysis for stroke. This may explain at least partially, the sex difference in stroke treatment noted earlier.

Personal experience may also influence decision making. A cross-sectional survey of patients attending geriatric and stroke services (N = 121) found that patients who had already experienced either TIA or stroke were more likely to opt for thrombolysis when told of the risks and benefits of treatment (Flatharta et al., 2015). This is supported by an in-depth qualitative study of stroke patients in Norway who had recently been through the process of deciding whether or not to have IV tPA, which found that patients with a longer history of health problems were more willing to take risks than those for whom the stroke was their first dramatic health event (Mangset et al., 2009).

Higher education level has also been found to be associated with an increased likelihood of consenting to intravenous thrombolysis. A survey with stroke patients and their proxies (N = 658) undertaken in Italy before intravenous thrombolysis was licenced (Ciccone et al. 2001), found that 62% of patients would chose the risk of death over severe disability by opting for thrombolysis, but only 39% of these patients would consent to intravenous thrombolysis if

making the decision as a proxy. Likewise 55% of the patients' proxies said they would choose intravenous thrombolysis for themselves, but only 43% would consent on behalf of another person.

This difference in consent rates between patients and proxies is important, given that a retrospective review of case notes by Rosenbaum et al. (2004) found that 16% (N = 10/63) of patients who received thrombolysis during 1996-1998 in 10 Connecticut hospitals had no consent documented, whilst in 63% (N = 5/8) of cases surrogates provided consent when the patients had capacity and 18% (7/38) of patients with diminished capacity provided their own consent. Unfortunately, numbers in this study were small (N = 63). However, whilst the use of thrombolysis for stroke remains controversial, inappropriate consent practices involving intravenous rtPA, particularly involving the overuse of surrogate decision makers, suggests that better consent guidelines and improved capacity assessment are required.

One solution to this problem may be to determine advanced preference in individuals at risk of stroke. Flatharta et al. (2015) found that 89.9% of patients provided information concerning the risks and benefits of thrombolysis, said they would opt for treatment within three hours, whilst 82.6% said they would still be prepared to be treated within 3-4.5 hours. Individuals opting for thrombolysis were significantly more likely to agree to their preferences being recorded (88.8%) than those who said they would refuse thrombolysis (30.4%).

Whilst patient understanding of risk is clearly influenced by individual features such as sex, education and health status, other more extrinsic factors such as the way in which a clinician communicates risk may also be important. A recent qualitative study in the UK (Lie et al. 2014) undertook interviews with doctors (N = 13) and found clear variation in the way that risk is communicated to patients. These differences related both to practice context (telemedicine or stroke unit) and individual clinician communication style. For example, risk and benefit were often, but not always, expressed numerically. However, even this numerical approach was not consistent with absolute numbers, percentages, fractions or ratios all being used by clinicians. Furthermore, figures cited differed between clinicians, even in the same unit. Other explanations did not rely on figures at all, describing risk and benefit instead in terms of relative outcomes, and using 'elastic terminology' such as 'improving the survival a little bit' or being 'less disabled' (Lie et al. 2014). As Lie notes, uncertainty around treatment outcomes results in practice variation, some of which may be potentially confusing for patients.

Clinical decisions

It has been suggested that the main factor influencing whether or not eligible patients are thrombolysed, is not getting the patient to hospital in time (Barber et al. 2001). Indeed it is this factor which has influenced the development of protocols to decrease 'door to needle' times such as the 'ship and drip' approach, the aim of which is to improve patient outcomes by increasing access to intravenous rtPA. It has also been proposed that clinical decision making regarding whether or not to thrombolyse is also influenced by other factors such as time of day, day of the week and physician experience. However, studies rarely link these factors in clinical decision making to patient outcomes such as mortality or functioning, focusing instead on the impact on numbers treated. One registry study that did consider the impact of such factors on patient outcomes found no significant difference in clinical outcomes or door to needle times at different times of day, week or year (Curtze et al., 2012). Less clinician experience was also not associated with poorer outcomes as assessed

by mRS but was associated with longer time to treatment, presumably because inexperienced staff took longer to make the decision to thrombolyse. Data from the SITS-MOST observational study (Wahlgren et al., 2007) and a more recent observational study in France (Tuffal et al., 2015) support the notion that clinical inexperience does not necessarily increase safety issues. Comparison of outcomes at centres experienced in the administration of IVT to those who were new to IVT for stroke, demonstrated similar safety (sICH and mortality rates) and efficacy (mRS 0-2) outcomes (Wahlgren et al., 2007). Furthermore, these outcomes were comparable to pooled trial data. Likewise Tuffal et al. (2015) found no association between clinical experience and safety outcomes such as sICH and mortality. However, patients were more likely to be independent (mRS 0-1) or have a good outcome (mRS 0-2) if treated by a more experienced neurologist (>35 patients previously treated). It is notable that in this study patients treated by more experienced neurologists were more likely to be older and have a pre-existing handicap, or to have experienced 'wake-up stroke' meaning time of onset was unknown. This may reflect the greater reluctance of less experienced staff to treat more 'risky' cases.

In a recent survey of rural health care providers (Williams et al., 2013) physicians reported the strongest barriers to the use of rtPA in acute stroke as pre-hospital delays (91%), risk of ICH (73%) and clinical diagnostic uncertainty (60%).

Longitudinal data

Very few studies provide follow up data past 90 days after treatment for stroke. As already noted, longitudinal follow up data suggests a sustained benefit for NINDS participants treated with rtPA at 12 months. No significant difference was noted in mortality rates at 12 months and for both groups cause of death was clearly not stroke related in 32% of cases. However, mortality causes for patients with definite stroke related death were more commonly linked to ICH in patients who had been treated with rtPA (28% v 6%), whilst severe recurrent stroke explained the majority of deaths in patients not treated (94% v 72%). In addition, further follow up of rtPA treated patients who experienced ICH soon after thrombolysis found favourable outcomes (defined in the paper as mRS 0-3) at 12 months for 30% of patients; however, numbers in this analysis are small and there is no comparison group (Norby et al., 2013).

Similar outcomes to those described by NINDS data for patients treated with tPA have also been demonstrated in clinical practice (Schmulling et al., 2000). Thus NINDS follow up data (Kwiatkowski et al., 1999) demonstrated independence (mRS 0-1) for 41% of rtPA treated patients (compared to 28% of controls) and a mortality rate of 24% (compared to 28% of controls). Schmulling et al. (2000) also found that 41% of thrombolysed patients achieved functional independence, however, mortality rates were lower at 15%. In both studies patients who were younger, had lower NIHSS scores at base line, or did not have diabetes had a higher rate of survival at 12 months following treatment with rtPA.

Follow up data (18 months) is also available for IST-3 (IST-3 Collaborative Group, 2013; Whiteley et al., 2014). This data suggests better long-term outcomes for patients treated with rtPA both in terms of independence as measured by the OHS (score of 0-2) and quality of life (EQ-5D) for patients treated within 6 hours (IST-3 Collaborative Group, 2013). As with the 6 month follow up these measures were posted out for self-completion by patients or carers. Thus the same cautions apply to interpretation of the longitudinal data that were noted with regard to age-related outcomes at 6 months post treatment.

Separate data on functional or quality of life outcomes is not available for IST-3 patients treated within 4.5 hours. However, Whiteley et al (2014) demonstrate lower mortality at 18 months for patients treated with rtPA, particularly if treated within either three or 4.5 hours of stroke, compared to those treated later.

Systematic reviews

Fifteen systematic reviews of studies examining thrombolysis for acute ischaemic stroke were identified in the literature and are summarised in Table 5. The systematic reviews varied widely in aims, number and type of studies reviewed, and quality (as assessed by the AMSTAR rating tool and adherence to PRISMA guidelines). The 2014 Cochrane review (Wardlaw, Murray & Berge, 2014) provides the highest quality and most comprehensive review of previous literature, and concluded that thrombolytic drugs reduce all cause death and dependency rates, but increase the risk of intracranial haemorrhage, and that administration of dose before 3 hours provides more positive outcomes (see Table 5 for further details). Wardlaw, Koumellis & Liu (2013) examined dosage, concluding that higher doses of thrombolytic drugs overall are associated with higher rates of ICH, but that further data is needed to draw conclusions about benefits on the basis of dosage. Other reviews of note include two reviews conducted examining the effect of rtPA for patients with mild stroke (Yeo et al., 2014; Shi, et al., 2014), which concluded that treatment with rtPA was not associated with differential negative outcomes for this group. The Yeo et al. (2014) review also suggested a small significant benefit in outcomes on the basis of administration of rtPA, although the Shi et al. (2014) review reported no significant difference in death and dependency rates.

Table 5 : Key features of systematic reviews of thrombolysis for acute ischaemic stroke

Authors	Topic	Summary of findings	Quality rating (AMSTAR)	PRISM checklist
Bhatnagar, Sinha, Parker, Guyler & O'Brien 2011	Decision making in patients over 80 years of age	13 trials rtPA >= 80 vs. < 80yrs death OR 2.77; positive outcomes 0.49; haemorrhage no diff. Bias in trials.	7	24
Carpenter, Keim, Milne, Meurer & Barsan 2011	Thrombolytic therapy for acute ischemic stroke beyond three hours	4 trials; 1 meta-analysis [Refer to Lansberg et al., 2009 for meta-analysis findings]	1	10
Dharmasaroja & Pattaraarchachai 2011	Low vs. standard dose of recombinant tissue plasminogen activator in treating East Asian patients	6 trials; 2 trials compared rtPA standard vs. low dose positive outcomes @3mths; haemorrhage/death no diff.. Baseline characteristics not comparable.	2	14
Emberson, Lees, Lyden, Blackwell, Albers, et al. 2014	Effect of treatment delay, age, and stroke severity	9 trials; *N* = 6,756 rtPA <3hrs vs. placebo/control no sig disability@3-6mths OR 1.75; 3-4.5hrs OR 1.26; >4.5hrs no diff. No diff in outcomes for age or stroke severity. rtPA symptomatic haemorrhage OR 5.55/6.67. Fatal haemorrhage w/n 7 days OR 7.14. No diff in outcomes for age, time administered, or stroke severity.	3	19
Etgen, Steinich & Gsottschneider 2014	Patients with brain tumours	Review of case reports; *N* = 12 Haemorrhage in 1 patient with glioblastoma. No other adverse events.	1	8
Johansson & Wild 2010	Telemedicine	18 studies; *N* = 739 Outcomes comparing telemedicine vs. control reported. No comparisons rtPA vs. control/placebo.	3	15
Lansberg, Bluhmki & Thijs 2009	Efficacy and safety of tissue plasminogen activator 3 to	4 trials; *N* = 1,622	1	14

	4.5 hours after acute ischemic stroke	rtPA 3-4.5hrs vs. placebo positive outcome OR 1.21, death no diff.		
Maiser, Georgiadis, Suri, Vazquez, Lakshminarayan & Qureshi 2011	3 h following onset of ischaemic stroke	4 trials; *N* = 2,104 rtPA 3-6 hrs vs. placebo positive outcomes OR 1.24; 3-4.5 hrs positive outcomes OR 1.27; 4.5-6 hrs no diff. rtPA symptomatic haemorrhage OR 3.01. No impact of rtPA 3-6 hrs or time administered on death at follow-up.	5	23
Shi, Zhang, Liu, Song, Song, Song & Xu 2014	Mild stroke	14 trials; *N* = 1,906 Mild stroke: rtPA positive outcome no difference. Similar rate haemorrhage.	6	19
Wardlaw, Sandercock, Warlow & Lindley 2000	Choice of primary outcome measure	12 trials; *N* = 4,342 Comparison of two outcome definitions [good vs. poor] based on data from Wardlaw, del Zoppo, Yamaguchi (1999). No change in ORs.	Rating incomplete due to limited access to original 1999 Cochrane review	
Wardlaw & Warlow 1992	General review	60 studies (incl. trials, case reports etc.); 6 randomised trials. Randomised trials meta-analysis sig. reduction in death/deterioration.	1	10
Wardlaw, Koumellis & Liu 2013	Different doses, routes of administration and agents (Cochrane)	20 trials; *N* = 2,527 (subsets used for different analyses) Higher vs. lower dose haemorrhage OR 2.71; no diff in death/dependent @ follow up. Higher vs. lower dose desmoteplase death @ follow up OR 3.21. No diff intra-arterial vs. intravenous. Heterogeneity in trial methodology and reporting.	10	27
Wardlaw, Murray & Berge 2014	Cochrane	27 trials; *N* = 10,187	11	27

		rtPA+others <6hrs vs. placebo death/dependent @3-6mths OR 0.85. Intracranial haemorrhage OR 3.75. Early death OR 1.69. Death @3-6mths OR 1.18. rtPA+others <3hrs vs. placebo death/dependent OR 0.66 + no change in death. rtPA <6hrs vs. placebo death/dependent @3-6mths OR 0.84. rtPA <3hrs vs. placebo death/dependent @3-6mths OR 0.65. No difference in outcomes < > 80 yrs. Additional aspirin use > poorer outcomes. Heterogeneity in trial outcomes.		
Yayan 2013	Orolingual angioedema	19 articles; *N* = 41 case studies. OA one possible complication of rtPA, higher risk if ACE inhibitors, no effect of age or stroke severity.	1	16
Yeo, Ho, Paliwal, Rathakrishnan & Sharma 2014	Mild stroke	8 studies; *N* = 1,205 Mild stroke: rtPA vs. control good outcomes @ 3mths OR 1.319. Death no diff. Age a moderator.	7	24

DISCUSSION

Summary of evidence

The evidence from this meta-analysis of six trials indicates a benefit for patients treated with IV rtPA in terms of a return to functional independence (mRS 0-1), particularly if treated within three hours of symptom onset. The odds of a favourable outcome measured either by mRS (0-2), Barthel Index (>95), GOS (1) or NIHSS (0-1) are also increased by the administration of IV rtPA, whilst the odds of dependency for survivors are reduced. There is limited evidence from one trial that these benefits are sustained over the longer term (12 months). However, there is an increase in the odds of sICH and ICH related death following IV thrombolysis.

NNT needed to achieve functional benefits as measured by mRS range from 10 (95% CI = 19 to 6) for a return to independence to 13 (95% CI = 29 to 8) for a good outcome. However, timing of administration alters the NNTB, with around half the number of patients needing to be treated for one to benefit at 3 hours (NNTB = 7, 95% CI = 14 to 5), compared to treatment at 3-4.5 hours (NNTB = 18, 95% CI = 419 to 9). NNTH were much higher than NNTB: for sICH NNTH = 42 (95% CI = 119 to 13) and for risk of death following ICH NNTH = 122 (95% CI = 830 to 30). The large confidence intervals around these figures should be borne in mind when interpreting the NNT.

The advantage of early treatment is partially supported by the narrative review, which suggests that administering IV rtPA within the first two hours after symptom onset is associated with more favourable outcomes and reduced risk. However, whilst no clear difference between administration within the broader timeframe of three hours, compared to 4.5 hours, has been established in the literature, it is generally accepted amongst stroke neurologists that administration of rtPA is more effective and less harmful if carried out earlier. It should be noted that the majority of patients (around three quarters) are treated between one and a half to three hours after onset.

The evidence concerning which, if any, demographic factors are associated with better outcomes following rtPA treatment is somewhat equivocal. In stroke patients, characteristics such as age and biological sex are heavily confounded by clinical factors such as stroke severity and the presence of co-morbidities such as hypertension, diabetes and AF. Based on the evidence reviewed it would appear that:

- Older patients are more likely to have a severe stroke when compared to younger patients;
- Older patients have poorer outcomes than younger patients irrespective of the treatment they are given;
- The evidence for biologically based differences in fibrinolysis related either to sex or ethnicity is inconclusive;
- A majority of studies find that once confounding variables are controlled for, differences in treatment response based on age, sex or ethnicity are either reduced or removed;
- Clinical factors are more important in determining outcomes than age, sex or ethnicity.

Likewise, any survival benefits which have been described for either overweight patients or smokers are better explained by differences in baseline characteristics such as age and stroke severity, as these patients tend to be younger and experience less severe strokes.

Clinical features associated with poorer outcomes include high BP, the presence of co-morbidities and stroke severity/ location. Once again the evidence is not clear-cut, with many of these factors co-existing. Determining the relative contribution of each clinical factor is challenging, however, based on the studies reviewed it appears that:

- High systolic BP may be a marker for other clinical factors (such as stroke severity, history of hypertension) which explain the poor outcomes in these patients;
- There is some evidence that the early use of antihypertensive therapy in patients with raised BP following thrombolysis improves outcomes;
- Co-morbidities such as previous stroke or TIA, chronic AF, previous myocardial infarction and diabetes are associated with greater stroke severity and poorer outcome irrespective of treatment given;
- Patients presenting with lower baseline NIHSS tend to be younger and have fewer risk factors and whilst IV rtPA may provide some initial benefit for functional outcomes, by 90 day outcomes are similar for patients not treated with rtPA;
- Poorer functional outcomes have been noted for stroke types including cardioembolic, LVO, lacunar and PCS following IV rtPA with better outcomes seen in paradoxical strokes and small-vessel disease, although patients with better outcomes also tend to be younger and have lower initial stroke severity;
- Data is limited on patients taking antiplatelet and anticoagulation medication who have experienced IV thrombolysis however, these patients are also often older, have more comorbidities, and have more severe strokes compared to other patients which may also impact on treatment outcomes.

In terms of treatment location, the evidence indicates that the use of telemedicine to support the administration of IV rtPA to patients in community hospitals can provide outcomes comparable to treatment in a specialist stroke unit. Furthermore the use of mobile stroke units can also be effective. Where poorer outcomes in non-specialist units do occur, this appears to be associated with clinician inexperience rather than location per se. It also seems that:

- Clinical diagnostic uncertainty is a major barrier to the administration of rtPA;
- Less experienced clinicians may take longer to reach the decision to thrombolyse, thereby increasing OTT time;
- Less experienced staff may also be more reluctant to treat more ‘risky’ cases;
- Clinicians may be less likely to treat older patients (possibly due to perceived risk).

Finally patient preference studies indicate that consent to IV rtPA treatment is influenced by sex, education, health status, and clinician communication such that:

- Women are risk averse and so are less likely than men to consent to thrombolysis;
- Patients with poorer health status are more likely to consent to treatment;
- A higher level of education is associated with consent to treatment;
- Proxies are likely to be more equivocal about consenting to IV rtPA for someone else;

- Clinician uncertainty around treatment outcomes results in practice variation, some of which may be potentially confusing for patients, in particular the use of 'elastic terminology' and inconsistency in level of risk or benefit portrayed.

Limitations

In general the design and procedures of the studies reviewed were of a good quality. However, the meta-analysis is limited by small participant numbers in the included studies and moderate to high heterogeneity for some outcomes. Of particular concern is the ATLANTIS data, which was removed from a number of analyses to increase homogeneity. This may relate to the lack of clarity around attrition bias noted for this study.

A further limitation concerns a lack of data from the RCTs that would have allowed sub-analysis of potentially relevant factors such as age, sex, stroke type and severity, recent antiplatelet or anticoagulant use and so on.

The tendency to report only dichotomised values for functional outcomes such as mRS is a further limitation. Whilst this categorisation of a continuous variable may appear to provide an easy to interpret set of results, this simplification comes at a cost (Altman and Royston 2006). There is a loss of information, which in turn reduces the power of the analysis to detect differences between groups. This may result in underestimation of either risk or benefit.

The potential risk of bias in the studies included in the meta-analysis should also be acknowledged. For example, the unclear risk for attrition bias for the ATLANTIS trials, may explain some of the differences between outcomes seen in this study and others. However, the biggest potential risk for all studies relates to study funding and possible conflict of interest for study authors. All studies were drug company funded, which, whilst not automatically problematic, does raise doubt around the objectivity of the published work, particularly when there is either limited information concerning the role of the drug company, or clear indication of direct involvement in data management and analysis. Concerns related to the integrity of RCT study data have been raised previously in the US (Lenzer, 2002; Radecki, 2011) and more recently in the UK (Shinton, 2014). These concerns include the unbalanced randomisation in NINDS and the involvement of nurses representing the sponsoring drug company in pharmacological monitoring of patients in this study. The possibility that the observers monitoring outcomes potentially had knowledge of events around randomization in the remaining drug company funded studies is also raised. Finally, Radecki (2011) has noted that the most influential literature in this area is susceptible to sponsorship bias, indicating the need for independent, placebo-controlled studies.

Whilst the narrative review has provided additional evidence regarding a range of clinical and demographic factors potentially related to outcomes following IV rtPA, the nature of this literature, comprising as it does retrospective, single arm and case-control studies should also be acknowledged.

Conclusions

Current evidence shows that intravenous thrombolysis with rtPA, particularly within three hours of symptom onset, increases the odds of a better functional outcome, but also increases the risk of sICH and early death by ICH.

FUNDING

This review was funded by the Australasian College for Emergency Medicine (ACEM)

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