
Access from the University of Nottingham repository: http://eprints.nottingham.ac.uk/544/1/DMC_International_Clin_Practice-1.pdf

Copyright and reuse:

The Nottingham ePrints service makes this work by researchers of the University of Nottingham available open access under the following conditions.

This article is made available under the University of Nottingham End User licence and may be reused according to the conditions of the licence. For more details see: http://eprints.nottingham.ac.uk/end_user_agreement.pdf

A note on versions:

The version presented here may differ from the published version or from the version of record. If you wish to cite this item you are advised to consult the publisher's version. Please see the repository url above for details on accessing the published version and note that access may require a subscription.

For more information, please contact eprints@nottingham.ac.uk
Should Data Monitoring Committees assess efficacy when considering safety in trials in acute stroke?

Philip MW Bath,¹ MD FRCP, Stroke Association Professor of Stroke Medicine
Laura J Gray,¹ MSc, Medical Statistician
Nils-Gunnar Wahlgren,² MD PhD, Associate Professor of Neurology

Institute of Neuroscience,¹ University of Nottingham, Nottingham UK; Department of Neurology,² Karolinska University Hospital, Stockholm, Sweden

Correspondence to:
Professor Philip Bath
Stroke Trials Unit
University of Nottingham
Clinical Sciences Building
City Hospital campus
Nottingham NG7 2UH UK

Tel: 0115 823 1768
Fax: 0115 823 1767
Email: philip.bath@nottingham.ac.uk

Conflicts of interest
No conflicts of interest to declare for Philip Bath, Laura Gray and Nils-Gunnar Wahlgren

Funding
PMWB is Stroke Association Professor of Stroke Medicine. LJG is supported, in part, by The Stroke Association and BUPA Foundation.
ABSTRACT

Background: The primary role of a trial’s Data Monitoring Committee (DMC) is to ensure the safety of enrolled patients. In stroke trials, safety is monitored typically by comparing death and stroke specific events between treatment groups. DMCs may also have the remit for monitoring efficacy depending on the aims of the trial. We hypothesised that functional outcome at end of follow-up, a measure of efficacy, is also a powerful measure of safety and tested this in a systematic review.

Methods: Acute stroke trials with a negative outcome or which were stopped prematurely on the grounds of safety were sought systematically from searches of electronic databases and published reviews. Information on early and late death, impairment, and functional outcome, and the presence of a DMC, were recorded for each trial. The results for each outcome measure were ranked within each trial to determine which was most statistically efficient in detecting hazard.

Results: 14 trials were included. The most efficient outcomes for detecting hazard were: late death or disability, 6 trials; early death, 4 trials (2 of which tested thrombolysis); late death, 3 trials; late death or impairment, 1 trial. Early death was insensitive to hazard in all 6 trials where late death or dependency was most sensitive. Two trials (both phase II) did not report the presence of a DMC.

Conclusions: Functional outcome at end of follow-up can be sensitive to hazard and should be included in all assessments of safety in stroke trials, whether or not efficacy itself is being assessed.
What is the take-home message for clinicians?
All stroke trials should have a Data Monitoring Committee. Functional outcome has been shown to be sensitive to hazard. Data monitoring committees should assess functional outcome alongside safety outcomes in stroke trials.

How did you gather the info you considered in your review?
Non-confounded randomised controlled trials involving patients with acute stroke were identified June 2005 and repeated in March 2006. Trials had to be negative or have stopped prematurely on the grounds of potential or definite hazard.

Key words: stroke; clinical trial; data monitoring committees; functional outcome; efficacy; impairment
INTRODUCTION

The principle role of Data Monitoring Committees (DMC) in clinical trials is to safeguard the interests of study participants.[1] In practice, this means ensuring that patients are not exposed to unnecessary risks. Typically, DMCs will review the trial’s protocol prior to recruitment (and any subsequent protocol amendments), ensure the study’s scientific integrity, and review the primary trial report prior to publication to ensure accuracy.[1, 2] During the study, the DMC will assess unblinded data in the context of ‘safety’; if patients randomised to active therapy fare significantly worse than those in the control group then the DMC will usually recommend to the Trial Steering Committee that the study should be modified or stopped. In many cases, ‘efficacy’ (typically functional outcome in a stroke trial) will also be assessed; differences in outcome in favour of the active treatment group may also lead the DMC to recommend that the trial should stop (or change in design). Finally, in some cases (usually involving commercially-sponsored trials), the DMC will also perform pre-specified futility analyses; these aim to stop the trial early if there is no reasonable chance that it will find a positive treatment effect. The structure, composition and modus operandi of DMCs have been defined recently.[2]

Which events to assess when monitoring safety can vary considerably but those relevant to stroke include death, impairment and deterioration. Intervention-specific safety events will also be monitored, e.g. symptomatic intracranial bleeding in trials of antithrombotic or fibrinolytic agents. Whether DMCs should also review functional outcome (e.g. Barthel Index, modified Rankin Scale) when assessing safety, irrespective of whether efficacy itself is being considered, remains controversial. Safety and efficacy variables overlap considerably and generally run in parallel, i.e. a treatment which increases death may also worsen functional outcome. Nevertheless,
reviewing functional outcome may come at a price if not performed appropriately, e.g. performing formal statistical comparisons will amount to an interim analyses and reduce study power.

We hypothesised that functional outcome measured at the end of follow-up would be sensitive to hazard just as death or impairment are. We performed a systematic review to test this hypothesis by using data from published trials of potential or overtly hazardous interventions in acute stroke.
METHODS

Trial identification
Non-confounded randomised controlled trials involving patients with acute stroke were sought through searches of The Cochrane Library (including systematic reviews, e.g. of neuroprotectants and thrombolysis [3, 4]), PUBMED, the stroke trials register at http://www.strokecenter.org/, and reviews of treatment for acute stroke;[5] searches were performed in June 2005 and repeated in March 2006. (Figure 1)Trials had to be negative (as opposed to positive or neutral) or have stopped prematurely on the grounds of potential or definite hazard; we excluded neutral or positive studies since they would not have tested the hypothesis that functional outcome at end of follow-up is a potential measure of hazard. Identified trials were excluded if data were missing for death, or combined death or disability/dependency. Neutral trials reporting a negative outcome in one or more subgroups were also excluded.

Analyses
Data on conventional measures of safety (death, deterioration, impairment, e.g. based on National Institutes of Health Stroke Scale or Scandinavian Stroke Scale) and efficacy (combined death or disability, e.g. Barthel Index, modified Rankin Scale, Glasgow Outcome Scale) at or shortly after end-of-treatment, and at end-of-follow-up, were obtained from trial publications. Death, impairment and functional outcome were considered to imply hazard if their rate was significantly higher (p<0.05) in the group of patients randomised to active treatment. Data from phase II trials with two or more active treatment groups were merged to increase event rates (as is usually done in systematic reviews); hence, the control group was compared with the aggregated data from the active groups. [6-8] In phase III trials with multiple active
treatment groups, data from the highest dose group were compared with control since hazard/toxicity is usually associated with higher rather than lower doses.[9-11]

The results of statistical analyses were taken from trial publications where available, or calculated using Fisher’s exact test for 2x2 data (http://www.graphpad.com/quickcalcs/index.cfm). The results of significance tests for each outcome were ranked within each trial to determine which outcome was most efficient statistically in detecting hazard. Significance was set at p<0.05 and two-sided tests were performed.
RESULTS

Included trials
Fourteen trials fulfilled the inclusion criteria; event rates for safety and efficacy variables are given in table 1.

Neuroprotection
Aptiganel (CNS-1102, NMDA receptor modulator) was assessed in a phase II/III trial (AASI) of 900 patients with ischaemic stroke.[3] The study was suspended with 628 patients recruited on the advice of the DMC with a trend to a difference in mortality; hazard was apparent in patients receiving high dose aptiganel (table 1).[9] The ASSIST programme assessed selfotel (competitive NMDA receptor antagonist) in patients with acute ischaemic stroke.[12] Two concurrent phase III trials were suspended early on the advice of the DMC because of an imbalance in mortality; overall, 567 patients (of an intended 1,840) had been enrolled when the TSC terminated of the trial.[12] Gavestinel (GV150526, glycine antagonist) was tested in a phase IIb trial;[8] the protocol was changed with DMC involvement when transient asymptomatic reversible elevations in bilirubin were noted. However, hazard was apparent in the form of worse functional outcome although this seems to have been largely explained by an imbalance in stroke severity at baseline. A phase II trial of sipatrigine (BW 919C89, sodium channel blocker, trial 137-104) ran to completion;[3] hazard was present in the form of a worse functional outcome at final follow-up in the patients receiving active treatment.

A phase IIb dose comparison trial of lubeluzole was terminated prematurely (232 patients recruited of 270) on the advice of the DMC due to an imbalance in mortality between the higher dose of lubeluzole versus placebo.[11] The EAST phase III trial of
enlimomab (anti-ICAM monoclonal antibody) in 625 patients with acute ischaemic stroke ran to completion; patients randomised to active treatment had increased impairment and disability.[13] A phase IIa dose-escalation trial (n=95) of a haemoglobin-based oxygen carrier, DCLHb, found that it increased the odds of a poor functional outcome.[6] INWEST was a phase IIb/III trial (n=295) comparing two doses of intravenous nimodipine with placebo;[10] functional outcome was worse in patients randomised to nimodipine and the DMC recommended early closure. Two trials of tirilazad mesylate, a free radical scavenger, are included.[14] STIPAS was a phase IIa dose-escalation trial which ran to completion; however, functional outcome was worse in patients receiving tirilazad.[7] The TESS II phase III trial of tirilazad was stopped early following recommendation by the DMC that hazard was present; by the time the trial actually stopped a few weeks later it was neutral although with a strong negative trend.[14] Overall, a meta-analysis of tirilazad mesylate was negative on two measures (Barthel Index, Glasgow Outcome Scale) of functional outcome.[14]

Thrombolysis
The ATLANTIS A phase III trial of alteplase enrolled patients between 0 and 6 hours after ischaemic stroke; the DMC recommended stopping the trial because of safety concerns (increased severe impairment, symptomatic intracranial haemorrhage, and death) in patients treated in the 5-6 hour group.[15] (The trial was subsequently re-started as ATLANTIS B with recruitment limited to 3-5 hours post stroke onset.[16]) Intravenous streptokinase was tested in three phase III trials. In two of the trials, the DMC alerted the TSCs that potential hazard was present in the form of an increase in early mortality. Recruitment was stopped early, after 310 patients of a planned 600 in MAST-E, and after 340 of 600 in ASK.[17, 18] The result in the third trial, MAST-I, was complicated by its factorial design involving both streptokinase and aspirin; the combination of streptokinase and aspirin was associated with an increase in early
death.[19] The DMC recommended that the TSC should review the trial’s data in the light of ASK and MAST-E; the TSC decided, with some dissent in interpretation of the results,[20] that the trial should stop with 622 patients recruited out of a planned 1,500.

**Excluded trials**

Four trials potentially exhibiting hazard were excluded: (i) a study of ZK200775 (AMPA antagonist) did not report data on functional outcome;[21] (ii) a trial of intravenous nimodipine has only been reported in abstract form;[22] and (iii) a phase II/III trial of trafermin (basic fibroblast growth factor) [5] has not been published at all. A further trial of trafermin was neutral overall and therefore excluded although it had a negative sub-group.[23]

**Death, impairment and disability/dependency**

When ranking the efficiency of outcomes identifying hazard by trial, functional outcome (combined death or disability) at end of follow-up was the most sensitive measure of potential hazard in 6 trials (table 2). The number of trials for the other outcomes were: early death, 4; death at end of follow up, 3; and death or impairment at end of follow up, 1.
DISCUSSION

Whether DMCs should include functional outcome data in their reviews of safety (irrespective of whether efficacy itself is being considered) has been a long-standing question. We hypothesised that measures of efficacy such as the Barthel Index and modified Rankin Scale would provide important information on safety. The results of this systematic review support this hypothesis with six of the 14 included trials finding that functional outcome was the most ‘efficient’ measure of safety (assessed as the smallest ‘p-value’).[3, 6-9, 13] Indeed, a DMC reviewing conventional safety data based on death alone in these six studies would not have identified significant hazard. (Interestingly, functional outcome was also most sensitive to potential hazard in a negative sub-group of the excluded neutral trial, namely those patients treated with trafermin 10 mg within 5 hours of stroke onset.[23])

In 7 of the remaining trials,[11, 12, 14, 15, 17-19] death (early or end of trial) was the more powerful safety measure. Three reasons may explain the discrepancy between these trials and the six above, First, certain interventions such as thrombolytics (as tested in ASK, ATLANTIS A, MAST-E and MAST-I [15, 17-19]) may increase death (through promoting early intracranial haemorrhage) whilst reducing disability.[4] Hence, treatment will move the outcomes of death, and disability, in opposite directions so that the combination of death or dependency may not differ appreciably. Second, some studies analysed functional outcome using dichotomous statistical approaches (with ordinal data collapsed into binary data). We and others have shown that ordinal tests (e.g. ordinal regression, Mann-Whitney U, robust ranks, bootstrapping of the mean) are usually more powerful than dichotomous tests (e.g. Chi-square) when analysing functional data based on the modified Rankin Scale or Barthel Index.[24] Last, reliable functional outcome data relating to end of follow-up...
often lags behind the reporting of end of treatment events such as death so the amount of efficacy data available for assessment by the DMC may be insufficient, especially early on in the life of a trial.

The implication of not assessing efficacy variables such as Barthel Index and modified Rankin Scale when considering safety is that a signal of hazard may be missed. Not only would this situation be detrimental to patients, investigators and sponsors, but the DMC members may lay themselves open to legal action on the grounds of inadequate assessment of the data.

It might be thought that safety measures should only focus on events occurring during treatment, or soon after, rather than later on. The adverse effects of short-term treatment are likely to occur early whilst many events occurring later have little directly to do with the index stroke or its treatment, e.g. falls or myocardial infarction. Nevertheless, early events are few in number relative to those accumulating by 3 months; for example, in control patients early death occurred in up to 18.2% of cases whilst the frequency of combined death or dependency ranged between 7.7% and 81.8% (median 43.5%, table 1). Statistically, maximum power from an analysis based on binary data occurs when the event rate approximates 50% so assessments based on low numbers of events (e.g. death) will be underpowered relative to functional outcome. In reality, it is likely that there will be a balance between the limited power of assessing early mortality, and the delay in collecting end of trial events such as death or disability, at least early on in the trial.

Our study aimed to systematically review the use of efficacy measures as markers of safety in acute stroke trials which were either overtly negative or where they were stopped prematurely on safety grounds. However, identification of such stroke trials using standard literature search criteria was complex, largely because many trialists
describe neutral trials as negative; hence, we may have missed some relevant studies. It is difficult to estimate exactly how many acute stroke trials have been completed in total but those involving putative neuroprotectants or thrombolytics number in excess of 200. From a statistical perspective, we might expect to find 10 negative trials (assuming significance is achieved at 5%) just on the grounds of chance. However, many of the trials we included are likely to reflect true negative studies, in part because hazard was seen across a spectrum of outcomes, and because their statistical significance was considerably smaller than 5% (table 2). An exception to this is the Lub-Int 4 study [11] which was probably falsely negative since the meta-analysis of all lubeluzole trials is neutral.[25] Further complicating the study, the included trials did not all report measures of death and impairment, used different scales for measuring disability, and dichotomised functional outcome scales in different places. Importantly, we used two-sided statistical tests since these allow assessment of benefit as well as hazard. Additionally, we kept the focus of this study on the use of efficacy measures as potential markers of hazard, and have not assessed other potential safety measures, e.g. those based on blood or neuroradiological biomarkers.

Why should DMCs not consider efficacy variables in the context of safety? One explanation may come from the title of committees (or boards) which varies markedly between trials [26] (and even within their publications); commonly used names include data monitoring committee (DMC),[2, 5, 17] data and safety monitoring board (DSMB),[1, 12] data and safety monitoring committee (DSMC),[27] independent data monitoring committee (IDMC),[27] independent data and safety monitoring committee (IDSMC),[9, 28] independent safety monitoring committee (ISMC),[29] international safety committee (ISC),[13] and safety monitoring committee (SMC).[10, 29, 30] The emphasis on ‘safety’ in some titles may explain, in part,
apparent neglect of efficacy measures. It is clear that a short, single and non-restrictive term should be used in future trials, e.g. Data Monitoring Committee.[2, 26]

It is pertinent to ask if there are drawbacks to allowing the DMC to view efficacy data when considering safety. First, the decision-making process for deciding whether a trial will continue, change or stop will increase in complexity as more data are assessed; in theory, this might increase the risk of the DMC making a mistake. Nevertheless, access to efficacy data is likely to improve the ability of the DMC to identify potential hazard so the issue of data complexity is probably of secondary importance. Furthermore, pre-specifying stopping rules for efficacy will reduce the risk that a trial is ended inappropriately early on the grounds of potential hazard. Second, sponsors and trial steering committees (TSC) may be concerned about ‘leakage’ of efficacy data from the DMC to the outside world. Sharing outcome data of any sort from an ongoing trial could introduce several problems, not least damaging centre and patient recruitment, and having effects on a company’s share price. It is vital that DMCs fulfil their responsibility not to share confidential data outside the committee. Last, regulatory authorities may consider that unblinded ‘looks’ at efficacy data constitute interim analyses. This view is inappropriate since DMC reviews of data do not normally, or even have to, involve formal statistical comparisons, unless as part of a planned interim or futility analysis, or if hazard is suspected. In these respects, it is vital that the DMC carries the confidence of the academic or commercial sponsor, TSC, investigators, and regulatory authorities (as relevant).[28]

Three points from this work can be concluded. First, all multicentre phase II and III trials should have a DMC.[26] Second, it is vital that all completed trials are published so we can all learn from their experience. This is particularly relevant where studies
apparently identified hazard, as with nimodipine and trafermin.[5, 22] Last, we believe that DMCs should always review functional outcome data when assessing safety to avoid missing signals of potential hazard. Such efficacy data should include that collected at the end of trial follow-up. TSC and sponsors should support the DMC by providing all necessary efficacy and safety data. The view that DMCs should review both safety and efficacy data is supported by others.[26, 28]
REFERENCES


## TABLE 1

Outcome for nine negative interventions tested in acute stroke. Data given as number (%), mean (standard deviation), or median, and are for active then control treatment groups (%).

<table>
<thead>
<tr>
<th>Trial</th>
<th>Intervention</th>
<th>DMC present</th>
<th>Dead Day 2-10</th>
<th>Dead Day 21-180</th>
<th>Dead/impaired Day 2-10</th>
<th>Dead/impaired Day 21-180</th>
<th>Dead/disabled Day 2-10</th>
<th>Dead/disabled Day 21-180</th>
</tr>
</thead>
<tbody>
<tr>
<td>AASI [9] Aptiganel</td>
<td>Yes</td>
<td></td>
<td></td>
<td>56/214 (26.2)</td>
<td>41/214 (19.2)</td>
<td></td>
<td></td>
<td>mRS (mean) 3.1 (1.9)</td>
</tr>
<tr>
<td>ASK [18] Streptokinase</td>
<td>Yes</td>
<td>31/174 (17.8)</td>
<td>63/174 (36.2)</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td>BI 84/174 (48.3)</td>
</tr>
<tr>
<td>ASSIST [12] Selfotel</td>
<td>Yes</td>
<td>32/280 (11.4)</td>
<td>62/280 (22.1)</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td>BI 109/280 (38.9)</td>
</tr>
<tr>
<td>ATLANTIS A [15] Alteplase</td>
<td>Yes</td>
<td></td>
<td>16/71 (22.5)</td>
<td>NIHSS (mean) 12 (13)</td>
<td>46/71 (65)</td>
<td></td>
<td></td>
<td>mRS (median) 5 v 2</td>
</tr>
<tr>
<td>EAST [13] Enlimomab</td>
<td>Yes</td>
<td>23/315 (7.3)</td>
<td>70/315 (22.2)</td>
<td>NIHSS &gt;6 234/315 (74.3)</td>
<td>NIHSS &gt;6 175/315 (55.6)</td>
<td>mRS 4 v 4</td>
<td></td>
<td>mRS (median) 3 v 3</td>
</tr>
<tr>
<td>GAIN phase II [8] Gavestinel</td>
<td>Yes</td>
<td></td>
<td>15/86 (17.4)</td>
<td>NIHSS &gt;14 18/86 (20.9)</td>
<td>NIHSS &gt;14 72/86 (83.7)</td>
<td>mRS &gt;1</td>
<td>BI &lt;60</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Intervention</td>
<td>No.</td>
<td>Yes</td>
<td>Change in NIHSS (mean)</td>
<td>BI &lt; 75</td>
<td>mRS &gt; 2</td>
<td>mRS</td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>--------------</td>
<td>-----</td>
<td>-----</td>
<td>------------------------</td>
<td>---------</td>
<td>---------</td>
<td>------</td>
<td></td>
</tr>
<tr>
<td>INWEST [10]</td>
<td>Nimodipine</td>
<td>14/94 (14.9)</td>
<td>42/94 (44.7)</td>
<td>33/100 (33.0)</td>
<td>7.5 v 26.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>11/100 (11.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lub-Int 4 [11]</td>
<td>Lubeluzole</td>
<td>-</td>
<td>25/80 (31.2)</td>
<td>-</td>
<td></td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>13/69 (18.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAST-E [17]</td>
<td>Streptokinase</td>
<td>53/156 (34.0)</td>
<td>73/156 (46.8)</td>
<td>59/154 (38.3)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>MAST-I [19, 20]</td>
<td>Streptokinase</td>
<td>83/313 (26.5)</td>
<td>112/313 (35.8)</td>
<td>75/309 (24.3)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Saxena [6]</td>
<td>DCLHb</td>
<td>-</td>
<td>9/40 (22.5)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4/45 (8.9)</td>
<td></td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>137-104 [3]</td>
<td>Sipatrigine</td>
<td>Yes</td>
<td>20/108 (18.5)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7/55 (12.7)</td>
<td></td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STIPAS [7]</td>
<td>Tirilazad</td>
<td>No</td>
<td>4/84 (4.8)</td>
<td>9/84 (10.7)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0/27 (0.0)</td>
<td>1/27 (3.7)</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TESS II [14]</td>
<td>Tirilazad</td>
<td>Yes</td>
<td>19/176 (10.8)</td>
<td>33/174 (19.0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10/172 (5.8)</td>
<td>25/169 (14.8)</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*a* Transformed scores ranging from -100 (maximal worsening) to +100 (maximal improvement)

BI: Barthel Index; DMC: data monitoring committee; GOS: Glasgow Outcome Scale; mRS: modified Rankin Scale; N: no; Y: yes
**TABLE 2**

Significance (2p) for outcome in nine negative interventions tested in acute stroke. Significance calculated using Fisher’s Exact test on outcome data from each publication. Most significant analysis is given in bold.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Death Day 2-10</th>
<th>Death Day 90-180</th>
<th>Dead/impaired Day 2-10</th>
<th>Dead/impaired Day 21-90</th>
<th>Dead/disabled Day 2-10</th>
<th>Dead/disability Day 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>AASI [9] a</td>
<td></td>
<td>0.106</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td><strong>0.040</strong></td>
</tr>
<tr>
<td>ASK [18]</td>
<td>0.089</td>
<td><strong>0.002</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.515</td>
</tr>
<tr>
<td>ASSIST [12] b</td>
<td><strong>0.025</strong></td>
<td>0.140</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.494</td>
</tr>
<tr>
<td>ATLANTIS A [15]</td>
<td>-</td>
<td><strong>0.017</strong></td>
<td>0.36</td>
<td>0.273</td>
<td>-</td>
<td>0.05</td>
</tr>
<tr>
<td>EAST [13]</td>
<td>0.175</td>
<td>0.067</td>
<td>0.009</td>
<td>0.037</td>
<td>0.005</td>
<td><strong>0.004</strong></td>
</tr>
<tr>
<td>GAIN phase II [8]</td>
<td>-</td>
<td>0.297</td>
<td>0.137</td>
<td>0.137</td>
<td>0.235</td>
<td><strong>0.002</strong></td>
</tr>
<tr>
<td>INWEST [10] a</td>
<td>0.521</td>
<td>0.106</td>
<td>-</td>
<td><strong>0.001</strong></td>
<td>-</td>
<td>0.003</td>
</tr>
<tr>
<td>Lub-Int 4 [11]</td>
<td>-</td>
<td><strong>0.093</strong></td>
<td>NS</td>
<td>-</td>
<td>-</td>
<td>0.600</td>
</tr>
<tr>
<td>MAST-E [17]</td>
<td><strong>0.002</strong></td>
<td>0.137</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.667</td>
</tr>
<tr>
<td>MAST-I [19, 20]</td>
<td>&lt;<strong>0.001</strong></td>
<td>0.002</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>Saxena [6]</td>
<td>-</td>
<td>0.130</td>
<td>-</td>
<td>0.034</td>
<td>-</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>137-104 [3]</td>
<td>-</td>
<td>0.383</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td><strong>0.047</strong></td>
</tr>
<tr>
<td>STIPAS [7]</td>
<td>0.570</td>
<td>0.446</td>
<td>-</td>
<td>0.105</td>
<td>-</td>
<td><strong>0.034</strong></td>
</tr>
<tr>
<td>TESS II [14]</td>
<td><strong>0.120</strong></td>
<td>0.317</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.238</td>
</tr>
</tbody>
</table>

* Data from two parallel trials were published in aggregated form

b High dose compared with placebo

NS: Not significant
FIGURE LEGENDS

Figure 1
Flow chart of search strategy

Non stroke n=464,033

Non acute n=7,169

Non 'negative' n=2,208

Excluded Not negative n=14 No data n=4

All trials n=473,442

Stroke trials n=9,409

Acute stroke trials n=2,240

'Negative' trials n=32

Included trials n=14