Authors' objectives
To explore disagreements between meta-analyses of phase 2 (small) and phase 3 (large) randomised controlled trials comparing the efficacy of bolus thrombolytic therapy with infusion for acute myocardial infarction, with regards to serious adverse safety (intracranial haemorrhage) and efficacy outcomes.

Searching
MEDLINE and the Cochrane Controlled Trials Register were searched from January 1980 to December 1999. The search terms were 'thrombolysis', 'thrombolytic therapy' and 'myocardial infarction'. Conference proceedings and reference lists were searched manually.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials.

Specific interventions included in the review
Studies comparing thrombolytic therapy administered by bolus injection (each bolus given over at most 5 minutes) with that administered by infusion (at least 30 minutes) were included. Studies evaluating the use of bolus anistreplase were excluded. The bolus therapies (number of boluses shown in brackets) included: reteplase, 5 to 15 MU (1 or 2); E6010, 0.22 mg/kg; staphylokinase, 15 mg (2); saruplase, 40 to 80 mg (1 or 2); alteplase 40 to 50 mg (2); lanoteplase, 15 to 120 KU/kg (1); tenecteplase, 30 to 50 mg (1); and urokinase, up to 1.5 MU (2). The infusion therapies included: alteplase; tisokinase, 14.4 MU; saruplase, 80 mg; and streptokinase, 1.5 MU.

Participants included in the review
Patients with acute myocardial infarction.

Outcomes assessed in the review
To be included in the review, the studies had to provide objective confirmation of the diagnosis of intracranial haemorrhage (ICH), based on the result of cranial computed tomography or a magnetic resonance imaging scan. The primary outcome was ICH. The other outcomes of interest were other causes of stroke, total mortality, and reinfarction.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The studies were assessed on the basis of the following: concealment of randomisation; blinding of the patient and investigator to the intervention; completeness of follow-up (greater than 95%); and the use of an intention to treat analysis. The authors do not state how the papers were assessed for validity, or how many of the reviewers performed the validity assessment.

Data extraction
Data on ICH, other causes of stroke, total mortality, and reinfarction were independently extracted from each study by two observers. The other data extracted were the trial, year of trial, the number of participants, their age, the
interventions, and the primary outcome.

Methods of synthesis
How were the studies combined?
The results for each outcome were pooled separately for phase 2 and phase 3 trials. Phase 2 trials (pilot studies with generally less than 1,000 patients) were designed to assess the effectiveness and safety of a drug based on a surrogate outcome, whereas phase 3 trials (generally greater than 1,000 patients) were designed to assess these factors on the basis of clinical outcomes. The studies were pooled using the Mantel-Haenszel fixed-effect model. The results were presented as odds ratios (ORs) together with their 95% confidence intervals (CIs). ORs less than 1.0 show results favouring bolus therapy, whereas ORs greater than 1 favour infusion. Publication bias was explored with a funnel plot of effect size (the OR of ICH) versus study precision. Formal tests for publication bias were performed.

How were differences between studies investigated?
The authors did not report a method for assessing heterogeneity, although p-values for the presence of heterogeneity were presented. Subgroup analyses were performed, comparing phase 2 and phase 3 trials and subgroups of trials, according to their baseline patient characteristics, fibrin-specificity of the bolus thrombolytic agent, and indicators of study quality.

Results of the review
Nine phase 2 trials (n=4,013) and six phase 3 studies (n=62,673) were included.

ICH.

Phase 2 trials: the pooled OR was 0.53 (95% CI: 0.27, 1.01; heterogeneity, p=0.21).
Phase 3 trials: the pooled OR was 1.25 (95% CI: 1.06, 1.49; heterogeneity, p=0.12).
All trials combined: the pooled OR was 1.19 (95% CI: 1.01, 1.41; heterogeneity, p=0.03).

There was significant heterogeneity between the phase 2 and phase 3 trials (p=0.01).

The funnel plot suggested that there was a disproportionately greater number of trials with point estimates for ICH lower than the overall summary point estimate. A relative paucity of trials demonstrated an increased risk of ICH with bolus therapy. Formal tests for publication bias were not significant.

Stroke.

Phase 2 trials: the pooled OR was 0.60 (95% CI: 0.24, 1.48).
Phase 3 trials: the pooled OR was 0.96 (95% CI: 0.80, 1.15).
All trials combined: the pooled OR was 0.93 (95% CI: 0.78, 1.12).

There was no evidence of heterogeneity between the phase 2 and phase 3 trials.

Death.

Phase 2 trials: the pooled OR was 0.95 (95% CI: 0.69, 1.30).
Phase 3 trials: the pooled OR was 1.01 (95% CI: 0.95, 1.08).
All trials combined: the pooled OR was 1.01 (95% CI: 0.95, 1.07). There was no evidence of heterogeneity between the phase 2 and phase 3 trials.

Reinfarction.
Phase 2 trials: the pooled OR was 0.78 (95% CI: 0.57, 1.07).

Phase 3 trials: the pooled OR was 0.99 (95% CI: 0.92, 1.07).

All trials combined: the pooled OR was 0.98 (95% CI: 0.91, 1.06). There was no evidence of heterogeneity between the phase 2 and phase 3 trials.

**Authors' conclusions**
The results suggested that when therapeutic interventions are associated with a potential for uncommon but serious adverse safety outcomes, there may be differences between small phase 2 and large phase 3 trials that results in their disagreement for safety, but not necessarily efficacy, outcomes.

**CRD commentary**
This was a good review of the area. A reasonable literature search was conducted although this could have been expanded to include additional databases. Both unpublished and published studies were included and publication bias was investigated.

The inclusion criteria were clearly stated and relevant study details were presented in the results section. Quality was formally assessed, and there was a limited discussion of the quality of the included studies in the results section. The pooling was appropriate given the nature of the results, Heterogeneity was formally investigated, although the exact test used was not reported.

The authors' conclusions are supported by the results presented.

**Implications of the review for practice and research**
Practice: The authors did not state any implications for practice.

Research: The authors state that 'Further investigation of the frequency and causes of disagreement between small and large trials for safety outcomes is warranted'.

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