Supplementary (Online only) material

Supplementary Table 1. Ideal design of an MRI study to investigate whether the presence of cerebral microbleeds on pre-thrombolysis MRI scans is associated with an increased risk of intracerebral haemorrhage.

Study population:
- Clearly defined clinical characteristics and selection criteria
- Representative of the population of patients with acute ischaemic stroke (ideally consecutive cases in centres using MRI routinely for acute stroke assessment)
- Report of number and characteristics of patients excluded
- Adequate sample size to detect an effect of CMBs based on power calculations:
  e.g. If it is assumed that 20% of patients have baseline CMBs, then to have power 0.8 (α=0.05) to detect the difference in thrombolysis-related ICH rate between CMB(+) and CMB(-) groups, with a relative risk of ICH attributable to the presence of CMBs of 2.0, a sample of ***3132*** *patients would be needed. (calculations performed using Stata 11.2).* Realistically this will require large collaborative multicentre studies.

Detection and rating of CMBs:
- Standardized MRI parameters for T2*-GRE or susceptibility-weighted imaging (field strength, echo time, slice thickness, gap, etc.)
- Clear definition of CMBs and mimics
- Use of a standardized CMB rating instrument with clearly defined anatomical regions
- Rating instrument demonstrated to have good inter- and intra-rater reliability
- Trained observers (ideally a single observer for all analysis in a study).
- Classification of CMB distribution (deep versus lobar) and number

Definition of outcome:
- Post-thrombolysis ICH definition criteria and methods and timing of assessment clearly defined
- Clinically relevant definition of post-thrombolysis ICH (e.g. associated with significant clinical deterioration)

Reporting and analysis:
- Results adjusted for confounding from other baseline risk factors known to be associated with thrombolysis-related ICH and CMBs (including age, leukoaraiosis, etc.)
- Results presented according to number and anatomical distribution of CMBs

CMBs= cerebral microbleeds; ICH= Intracerebral haemorrhage

Study	Study size	Clear definition of study population	Standardised MRI parameters	CMB criteria clearly defined	ICH criteria clearly defined	Awareness of >2 CMB mimics	Standardised rating scale or trained observer agreement reported (inter/intra-rater)	Classification of CMB distribution	Results adjusted for other baseline risk factors	No. of quality indicators fulfilled
Fiehler 2007	570	✓	x	✓	✓	✓	✓	x	x	6/9
Kim 2006	65	✓	✓	✓	x	✓	✓	✓	✓	8/9
Kakuda 2005	70	✓	✓	✓	✓	✓	✓	x	x	7/9
Derex 2004	44	✓	✓	✓	✓	✓	✓	x	✓	8/9
Kidwell 2002	41	✓	✓	✓	✓	✓	✓	x	✓	8/9

Supplementary Table 2. Summary of study quality indicators.

CMB= cerebral microbleeds; ICH= intracerebral haemorrhage.

Supplementary Table 3. Details of the thrombolysis treatment protocols of included studies.

Study	Thrombolysis
Fiehler 2007	IV tPA dosage: 0.9 mg/kg bodyweight; maximum dose: 90 mg
Kim 2006	IV tPA within 3 hr of symptom onset (n=12), intraarterial urokinase within 6 hr of symptom onset (n=53). IV tPA dosage: 0.9 mg/kg. Intraarterial urokinase (up to a maximum of 1 million U) was infused at the site of the clot at angiography until recanalization was achieved or the maximum dose was reached.
Kakuda 2005	IV tPA therapy administered to selected ischemic stroke patients within 3 to 6 hours after symptom onset. All patients were treated with 0.9 mg/kg of IV tPA (10% bolus over 1 minute, followed by continuous infusion of the remaining dose over 60 minutes) as quickly as possible following their initial MRI scan, but no later than 6 hours from the onset of their stroke symptoms.
Derex 2004	Intravenous recombinant tPA (alteplase) was given after MRI within 7 h of stroke onset. Patients were randomly assigned either to receive tPA at a dose of 0.9 mg/kg body weight as a constant intravenous infusion over a period of 60 min or tPA at a dose of 0.8 mg/kg body weight as a constant intravenous infusion over a period of 90 min.
Kidwell 2002	Combined intravenous/intra-arterial tPA within 3 hours of symptom onset, or with only intra-arterial thrombolytics within 6 hours from symptom onset for patients with anterior circulation ischemia or 12 hours from symptom onset for patients with posterior circulation ischemia: Combined intravenous/intra-arterial tPA was administered at a dose of 0.6 mg/kg IV, 10% bolus over 1 minute, remaining dose infused over 30 minutes, followed by a 10 mg/h intra-arterial infusion until recanalization was achieved or a maximum intra-arterial dose of 22 mg was reached.7 Pure intra-arterial thrombolysis was administered with either urokinase (up to a maximum of 1 000 000 U) or tPA (generally up to a maximum dose of 22 mg) infused at the site of the clot at the time of angiography until recanalization was achieved or until maximum dose was reached. Gentle mechanical clot disruption was also allowed at the time of the intra-arterial thrombolytic infusion.

IV: intravenous; tPA: tissue plasminogen activator

Supplementary Figure 1. Funnel plot of included studies.