ON-LINE APPENDIX

Sample Search Strategy (MEDLINE via Ovid)

1. Randomized Controlled Trials as Topic/
2. randomized controlled trial/
3. Random Allocation/
4. Double Blind Method/
5. Single Blind Method/
6. clinical trial/
7. clinical trial, phase i.pt.
8. clinical trial, phase ii.pt.
9. clinical trial, phase iii.pt.
10. clinical trial, phase iv.pt.
11. controlled clinical trial.pt.
12. randomized controlled trial.pt.
13. multicenter study.pt.
14. clinical trial.pt.
15. exp Clinical Trials as topic/
16. or/1–15
17. (clinical adj trial$).tw.
18. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
19. PLACEBOS/
20. placebo$.tw.
21. randomly allocated.tw.
22. (allocated adj2 random$).tw.
23. or/17–22
24. 16 or 23
25. case report.mp.
26. letter/
27. historical article/
28. or/25–27
29. 24 not 28
30. exp Tomography, Emission Computed/ or exp Magnetic Resonance Imaging/ or brain imaging.af.
31. (ct or dwi).af.
32. imaging.af.
33. (perfusion or diffusion).af.
34. magnetic resonance imag$.af.
35. mri.af.
36. computed tomograph$.af.
37. pet.af.
38. spect.af.
39. exp Tomography, X-Ray Computed/
40. or/30–39
41. Cerebrovascular disorders/
42. exp Brain ischemia/
43. Carotid artery diseases/ or Carotid artery thrombosis/
44. stroke/ or exp brain infarction/
45. exp Hypoxia-ischemia, brain/
46. Cerebral arterial diseases/ or Intracranial arterial diseases/
47. exp Intracranial embolism/ and thrombosis/
48. (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva or transient isch?emic attack$ or tia$).mp.
49. (brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation).mp.
50. (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$).mp.
51. 49 and 50
52. 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 51
53. 29 and 40 and 52
54. limit 53 to (English language and humans and yr="1995 -Current" and "all adult (19 plus years)")

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On-line Table 1: Studies using imaging eligibility criteria

Author (yr)	Intervention	No. of Participants	Modality	Criterion
Hacke et al (1995)[2]	Alteplase	620	CT	<1/3 MCA territory
Clark et al (1997)[6]	Citicoline	259	CT	No evidence of cerebral edema
De Deyn et al (1997)[7]	Piracetam	927	CT	No mass effect with midline shift
del Zoppo et al (1998)[8]	IA prourokinase	46	CT	No mass effect with midline shift
			DSA	TIMI 0/1 (M1/M2)
Hacke et al (1998)[9]	Alteplase	800	CT	<1/3 MCA territory
Berrouschot et al (1999)[11]	Rheopheresis	33	CT	<1/3 MCA territory
			SPECT	Activity deficit
Clark et al (1999)[12]	Citicoline	394	CT	No brain stem or cerebellar infarction
Clark et al (1999)[13]	Alteplase	613	CT	<1/3 MCA territory
Furlan et al (1999)[14]	IA prourokinase	180	CT	<1/3 MCA territory
			DSA	TIMI 0/1 (M1/M2 MCA)
Ogawa et al (1999)[17]	Ebselen	105	CT	No low attenuation
			DSA	M1 or M2 MCA occlusion
Warach et al (2000)[22]	Citicoline	100	MRI	Requires >1 mL, <66 mL involving gray matter in MCA territory (DWI)
Clark et al (2001)[23]	Citicoline	899	CT	No evidence of cerebral edema
Diener et al (2001)[25]	Certoparin	404	CT	<1/3 MCA territory
Grotta and Trial (2001)[26]	Lubeluzole	89	CT	<1/3 MCA territory
Alexandrov et al (2004)[33]	TCD	126	TCD	TIBI 0–3 (MCA)
AbESTT inv (2005)[35]	Abciximab	400	CT	<1/2 MCA territory
Daffertshofer et al (2005)[36]	TCD	26	MRI	DWI lesion present and exclude if complete MCA infarction
			MRA	Vascular obstruction on MRA
Hacke et al (2005)[39]	Desmoteplase	104	MRI	<1/3 MCA territory (DWI)
			MRA	Exclude ICA occlusion without ipsilateral distal occlusion
			MRP	Diffusion-perfusion mismatch
Singhal et al (2005)[41]	Normobaric oxygen	16	MRP	Diffusion-perfusion mismatch
Els et al (2006)[43]	Hypothermia (patients with HC)	25	MRP	Diffusion-perfusion mismatch
Furlan et al (2006)[44]	Desmoteplase	37	MRP	Diffusion-perfusion mismatch
Hennerici et al (2006)[45]	Ancrod	1222	CT	<1/3 MCA territory
Warach et al (2006)[46]	Gavestinel	106	MRI	Requires >1.5-cm diameter or >5 mL (DWI)
Shin et al (2007)[47]	Albumin	49	MRI	DWI lesion in MCA territory
Vahedi et al (2007)[48]	Hemicraniectomy	38	MRI	Requires >145 mL (DWI)
Wong et al (2007)[49]	Heparin (nadroparin)	353	Carotid duplex/ TCD/MRA	Moderate large-artery occlusive disease
Adams et al (2008)[50]	Abciximab	808	CT	<1/2 MCA territory
Alexandrov et al (2008)[51]	Microspheres (with TCD)	15	TCD	TIBI 0–3 (MCA)
Davis al (2008)[52]	Alteplase	101	CT	<1/3 MCA territory
Hacke et al (2008)[53]	Alteplase	821	CT	<1/3 MCA territory
Ehrenreich et al (2009)[56]	EPO	522	MRI	DWI lesion and FLAIR negative
Hacke et al (2009)[57]	Desmoteplase	193	MRI/CT	<1/3 MCA territory (DWI or CT)
			MRA/CTA	Exclude ICA occlusion
			MRP/CTP	Diffusion-perfusion mismatch
Kidwell et al (2009)[58]	Magnesium	90	MRI	Requires >5 mL, later 3 mL (DWI)
Molina et al (2009)[59]	TCD + microspheres	35	TCD	TIBI 0–3 (MCA/ACA/PCA/ICA/BA)
Sen et al (2009)[60]	IA alteplase	7	CT	<1/3 MCA territory
			CTA	Major vessel occlusion
Teal et al (2009)[61]	Repinotan	681	CT	<1/3 MCA territory
Thijs et al (2009)[62]	Microplasmin	40	CT	<1/3 MCA territory
			MRP	PWI >2 cm diameter
Schäbitz et al (2010)[67]	G-CSF	44	MRI	<2/3 MCA (DWI) and nonlacunar infarct
			MRA	No carotid bifurcation occlusion
			MRP	Diffusion-perfusion mismatch
Bi et al (2011)[68]	Hypothermia	93	MRP	Diffusion-perfusion mismatch
Shuaib et al (2011)[70]	NeuroFlo[a]	515	CT	<1/3 MCA territory
Michel et al (2012)[71]	IV tPA	12	CTP	Favorable CTP profile
			CTA	Occluded extracranial ICA
Parsons et al (2012)[74]	Tenecteplase	75	CT	<1/3 MCA territory
			CTA	Vessel occlusion (ACA/MCA/PCA)
			CTP	Diffusion-perfusion mismatch
Rosso et al (2012)[75]	IV insulin	180	MRI	DWI lesion present
Broderick et al (2013)[77]	Endovascular treatment	656	CTA	M1/ICA/BA occlusion and NIHSS 8–9
Ciccone et al (2013)[78]	Endovascular treatment	362	CT	Acute infarction
Gui et al (2013)[79]	Xueshuantong	64	MRI	DWI lesion <2 cm (lacunar infarct)
Hougaard et al (2014)[84]	Remote ischemic perconditioning	443	MRI	DWI lesion present
Kidwell et al (2013)[81]	Embolectomy	118	MRA/CTA	Target occlusion
Ringelstein et al (2013)[82]	G-CSF	328	MRI	DWI lesion >15 mL
			MRI	<1/3 MCA territory
			MRI	No mass effect with midline shift
			MRI	Nonlacunar infarct
			MRA	No carotid bifurcation occlusion

Note:—IA indicates intra-arterial; EPO, erythropoietin; TIMI, Thrombolysis in Myocardial Infarction score; TIBI, Thrombolysis in Brain Ischemia; ACA, anterior cerebral artery; PCA, posterior cerebral artery; BA, basilar artery; AbESTT inv, Abciximab Emergent Stroke Treatment Trial Investigators; HC, hemicraniectomy; G-CSF, granulocyte colony stimulating factor; MRP, MRI perfusion.

[a] CoAxia, Maple Grove, Minnesota.

On-line Table 2: Studies using imaging to assess outcome

Author (yr)	Intervention	Modality	Measure	Timing	Imaging Result	Prespecified
NINDS (2000)[19]	Alteplase	CT	Lesion volume	3 mo	Neg	No
		CT	Lesion volume	7–10 days	Neg	No
		CT	Lesion volume	24 hr	Pos	No
Alexandrov et al (2004)[33]	TCD	TCD	Recanalization (TIBI 5)	2 hr	Pos	Yes
Berrouschot et al (1999)[11]	Rheopheresis	CT	Lesion volume	5 days	Neg	Yes
		SPECT	Graded SPECT scale	6–8 hr	Neg	Yes
		SPECT	Graded SPECT scale	5 days	Neg	Yes
Chemmanam et al (2010)[63]	Alteplase	MRI	% voxels with DWI reversal	3 mo	Neg	No
Daffertshofer et al (2005)[36]	TCD	MRA	Recanalization rate	6–24 hr	Neg	Yes
		MRP	Perfusion deficit	6 hr	Neg	Yes
		MRI	Lesion volume (DWI)	6 hr	Neg	Yes
Davis et al (2008)[52]	Alteplase	MRI	Geometric mean growth (exponential of mean log relative growth: day 90 T2 ÷ baseline DWI)	3 mo	Neg	Yes
		MRI	Median relative growth (day 90 T2 ÷ baseline DWI)	3 mo	Neg	Yes
		MRI	Median absolute growth (day 90 T2 − baseline DWI)	3 mo	Neg	Yes
		MRI	Mean difference in cube root volumes	3 mo	Neg	Yes
		MRI	Lesion growth >0% (T2 and baseline DWI)	3 mo	Pos	Yes
		MRA	Recanalization (>1 point increase in TIMI)	3 mo	Neg	Yes
		MRP	Reperfusion (>90% of initial deficit, Tmax +2sec)	3 mo	Pos	Yes
De Georgia et al (2004)[34]	Endovascular cooling	MRI	Lesion growth (day 3–5 DWI ÷ baseline DWI)	3–5 days	Neg	Yes
del Zoppo et al (1998)[8]	IA prourokinase	DSA	Recanalization (TIMI 2/3)	2 hr	Pos	Yes
Demchuk et al (2005)[37]	Alteplase	CT	Lesion volume	7–10 days	Neg	No
Diener et al (2001)[25]	Certoparin	CT	No lesion	7–8 days	Neg	Yes
		CT	Lesion volume	7–8 days	Neg	Yes
Ebinger et al (2009)[55]	Alteplase	MRI	Lesion growth (day 3–5 DWI − baseline DWI, median)	3–5 days	Pos	No
		MRI	Lesion growth (day 90 T2 − days 3–5 DWI, median)	90 days	Neg	No
		MRI	Lesion growth (day 90 T2 − baseline DWI, median)	90 days	Pos	No
Ehrenreich et al (2009)[56]	EPO	MRI	Lesion volume (FLAIR)	7–8 days	Neg	Yes
Emsley et al (2005)[38]	Interleukin-1 receptor antagonist	CT	Lesion volume	5–7 days	Neg	Yes
Fogelholm et al (2000)[21]	Nimodipine	CT	Lesion volume	3 weeks to 3 mo (IQR)	Neg	No
Furlan et al (1999)[14]	IA prourokinase	DSA	Recanalization (TIMI 3 or 2/3)	2 hr	Pos	Yes
Furlan et al (2006)[44]	Desmoteplase	MRP/MRA	Reperfusion (>30% reduction in MTT deficit volume) or TIMI 2/3	4–8 hr	Neg	Yes
		MRI	Lesion growth (increase in T2-weighted lesion, median)	1 month	Neg	No
Gui et al (2013)[79]	Xueshuantong	MRP	Change in rCBV	1 month	Neg	Yes
		MRP	Change in rCBF	1 month	Neg	Yes
		MRP	Change in rMTT	1 month	Neg	Yes
Hacke et al (2005)[39]	Desmoteplase	MRP/MRA	Reperfusion (>30% reduction in MTT deficit volume) or TIMI 2/3	4–8 hr	Neg	Yes
		MRI	Lesion growth (day 30 FLAIR − 24 hour DWI)	1 month	Not reported	Yes
Hacke et al (2009)[57]	Desmoteplase	MRI/CT	Lesion growth (day 30 to 24 hour, various)	1 month	Neg	Yes
Hennerici et al (2006)[45]	Ancrod	CT	Lesion volume	7–10 days	Neg	Yes

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On-line Table 2: Continued

Author (yr)	Intervention	Modality	Measure	Timing	Imaging Result	Prespecified
Hougaard et al (2014)[84]	Remote ischemic perconditioning	MRI	Penumbral salvage: (Baseline Tmax 6-sec volume − DWI lesion) − 1-month FLAIR	1 month	Neg	Yes
		MRI	Lesion volume (FLAIR)	1 month	Neg	Yes
		MRI	Infarct growth (1-month FLAIR − baseline DWI)	1 month	Neg	Yes
		MRI	Baseline DWI volume	Presentation	Neg	Yes
		MRI	Baseline PWI volume	Presentation	Neg	Yes
Infeld et al (1996)[3]	Streptokinase	SPECT	Hypoperfusion volume	3 mo	Neg	Yes
		SPECT	Hypoperfusion volume	1 day	Neg	Yes
		SPECT	Early hypoperfusion volume change (24 hr − baseline)	3 mo	Neg	Yes
		SPECT	Late hypoperfusion volume change (3 mo − 24 hr)	3 mo	Neg	Yes
		SPECT	Early hypoperfusion volume change (3 mo − baseline)	3 mo	Neg	Yes
Infeld et al (1999)[15]	Nimodipine	SPECT	Hypoperfusion volume	3 mo	Neg	Yes
		SPECT	Hypoperfusion volume	1 day	Neg	Yes
		SPECT	Early hypoperfusion volume change (24 hr − baseline)	3 mo	Neg	Yes
		SPECT	Late hypoperfusion volume change (3 mo − 24 hr)	3 mo	Neg	Yes
		SPECT	Early hypoperfusion volume change (3 mo − baseline)	3 mo	Neg	Yes
Kasner et al (2013)[80]	Transcranial laser therapy	MRI/CT	Lesion volume	5 days	Neg	No
		MRI/CT	ASPECTS	5 days	Neg	No
		MRI/CT	Cortical ASPECTS	5 days	Neg	No
Kidwell et al (2009)[58]	Magnesium	MRI	Median absolute growth (day 90 FLAIR − baseline DWI)	3 mo	Neg	Yes
		MRI	Median relative growth (day 90 FLAIR − baseline DWI) ÷ baseline DWI	3 mo	Neg	Yes
		MRI	Lesion growth (>0% day 90 FLAIR and baseline DWI)	3 mo	Neg	Yes
Kidwell et al (2013)[81]	Embolectomy	MRI/CT	Infarct volume (day 7)	7 days	Neg	Yes
		MRI/CT	Infarct growth (day 7 − day 1)	7 days	Neg	Yes
		MRI/CT	Reperfusion >90% (day 7)	7 days	Neg	Yes
		MRI/CT	Recanalization (day 7)	7 days	Neg	Yes
NINDS (2005)[40]	Alteplase	CT	Lesion volume	7 days	Neg	No
Lyden et al (2002)[29]	Clomethiazole	CT	Lesion volume	1 month	Neg	Yes
McCormick et al (2010)[65]	Insulin	MRI	Lesion growth (day 7 FLAIR − baseline DWI)	7 days	Neg	Yes
		MRI	Lesion volume (FLAIR)	7 days	Neg	Yes
		MRS	Lactate	3 days	Pos	Yes
		MRS	Lactate	7 days	Neg	Yes
Michel et al (2012)[71]	IV tPA	MRI	Noninfarcted at-risk tissue (day 4)	4 days	Neg	Yes
		CTA	Recanalization (24 hr)	24 hr	Neg	Yes
Molina et al (2009)[59]	TCD + microspheres	TCD	Complete recanalization	2 hr	Neg	Yes
		TCD	Time to complete recanalization	2 hr	Neg	Yes
Nagakane et al (2011)[69]	Alteplase	MRI	Geometric mean lesion growth (day 90 T2 and baseline DWI)	3 mo	Pos	No
		MRI	Median absolute growth (day 90 T2 and baseline DWI)	3 mo	Pos	No
		MRI	Mean difference in cube root volumes (day 90 T2 and baseline DWI)	3 mo	Neg	No
		MRI	Median difference in cube root volumes (day 90 T2 and baseline DWI)	3 mo	Pos	No
		MRI	Growth >0% (day 90 T2 and baseline DWI)	3 mo	Pos	No
		MRP	Reperfusion (>90% of initial deficit, Tmax + 2 sec)	3–5 days	Pos	No
		MRP	Median percentage reperfusion	3–5 days	Pos	No
		MRA	Recanalization (>1 point increase on TIMI)	3–5 days	Neg	No

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On-line Table 2: Continued

Author (yr)	Intervention	Modality	Measure	Timing	Imaging Result	Prespecified
Nichols et al (2008)[54]	Alteplase	CT	Median lesion volume	24 hr	Pos	No
		CT	Recanalization by resolution of HMCAS	24 hr	Pos	No
Ogawa et al (1999)[17]	Ebselen	CT	Lesion volume	1 month	Neg	Yes
Pantano et al (1999)[18]	Alteplase	CT	Lesion growth (day 7 − 24 hour)	7 days	Neg	No
		CT	Presence of any change (as a proportion, day 7 − 24 hour)	7 days	Neg	No
Parsons et al (2012)[74]	Tenecteplase	MRP/CTP	Reperfusion of initial deficit (% volume change of MTT-defined tissue)	24 hr	Pos	Yes
		MRI/CTP	Lesion growth (24 hr DWI − CTP)	24 hr	Pos	Yes
		MRI/CTP	Lesion growth (90-day FLAIR − CTP)	3 mo	Pos	Yes
		MRA	Complete recanalization (TIMI 3)	24 hr	Neg	Yes
		MRA	Complete or partial recanalization (improved TIMI)	24 hr	Pos	Yes
		MRP	Volume reperfusion at 24 hr (MTT)	24 hr	Pos	No
		MRP	Penumbral salvage (24 hr)	24 hr	Pos	No
		MRP	Penumbral salvage (90 days)	3 mo	Pos	No
Patel et al (2001)[27]	Alteplase	CT	Lesion volume	3 mo	Pos	No
Ringelstein et al (2013)[82]	G-CSF	MRI	Lesion volume	1 month	Neg	Yes
Roberts et al (2002)[30]	IA prourokinase	CT	Lesion volume	24 hr	Pos	No
		CT	Lesion volume	7 days	Pos	No
Rosso et al (2012)[75]	IV insulin	MRI	Mean infarct growth	1–3 days	Neg	Yes
Schäbitz et al (2010)[67]	G-CSF	MRI	Lesion volume (unspecified modality)	3 mo	Neg	Yes
Sen et al (2009)[60]	IA alteplase	MRA	Recanalization (TIMI 2/3)	24 hr	Pos	Yes
Shin et al (2007)[47]	Albumin	MRI	Lesion growth ([day 3–4 DWI − baseline DWI] ÷ baseline DWI)	3–4 days	Neg	Yes
Singhal et al (2005)[41]	Normobaric oxygen	MRI	Lesion growth (4-hr DWI ÷ baseline DWI)	4 hr	Pos	No
		MRI	Lesion growth (24-hr DWI ÷ baseline DWI)	24 hr	Neg	No
		MRI	Lesion growth (7-day FLAIR ÷ baseline DWI)	7 days	Neg	No
		MRI	Lesion growth (3-mo FLAIR ÷ baseline DWI)	3 mo	Neg	Yes
		MRP	Penumbral salvage: (baseline MTT volume − DWI volume) ÷ (baseline MTT volume − baseline DWI volume)	4 hr	Pos	Yes
		MRP	Penumbral salvage: (baseline MTT volume − DWI volume) ÷ (baseline MTT volume − baseline DWI volume)	24 hr	Neg	No
		MRP	Penumbral salvage: (baseline MTT volume − DWI volume) ÷ (baseline MTT volume − baseline DWI volume)	7 days	Neg	No
		MRP	Penumbral salvage: (baseline MTT volume − DWI volume) ÷ (baseline MTT volume − baseline DWI volume)	3 mo	Neg	No
		MRI	Temporary and sustained ADC reversal voxels	24 hr	Neg	No
		MRP	rCBV in affected volume	4 hr	Pos	Yes
		MRP	rCBV in affected volume	24 hr	Pos	No
		MRP	rCBF in affected volume	4 hr	Pos	Yes
		MRP	rCBF in affected volume	24 hr	Pos	No
		MRP	rMTT in affected volume	4 hr	Neg	Yes
		MRP	rMTT in affected volume	24 hr	Neg	No

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On-line Table 2: Continued

Author (yr)	Intervention	Modality	Measure	Timing	Imaging Result	Prespecified
Padma Srivastava et al (2012)[73]	Minocycline	MRI	Infarct volume (day 30)	1 mo	Neg	Yes
		MRI	Infarct growth (1 month FLAIR − DWI)	1 mo	Neg	Yes
Thijs et al (2009)[62]	Microplasmin	MRP	Reperfusion (>30% reduction in PWI or absence of PWI if <10 mL)	4–12 hr	Neg	Yes
		MRA	Improvement on MRA scale of 2 points	4–12 hr	Neg	Yes
Warach et al (2000)[22]	Citicoline	MRI	Lesion volume (week 12 T2 − baseline DWI)	3 mo	Neg	Yes
Warach et al (2006)[46]	Gavestinel	MRI	Lesion growth (% change, 3-month DWI B0 and baseline DWI B1000)	3 mo	Neg	Yes
Yesaka et al (1998)[10]	Streptokinase	SPECT	Reperfusion (binary and change in volume of hypoperfused tissue)	24 hr	Neg	Yes
		TCD	Recanalization (operator assessment, no score)	7 days	Neg	Yes

Note:—EIC indicates early ischemic change; HMCAS, hyperdense MCA sign; rMTT, relative MTT; rCBV, relative cerebral blood volume; rCBF, relative cerebral blood flow; NINDS, National Institute of Neurologic Disorders and Stroke; Neg, negative; Pos, positive; IQR, interquartile range; TIMI, Thrombolysis in Myocardial Infarction; TIBI, Thrombolysis in Brain Ischemia; Tmax, time-to-maximum; MRP, MRI perfusion; IA, intra-arterial; G-CSF, granulocyte colony stimulating factor; EPO, erythropoietin.

On-line Table 3: Studies using imaging to define ischemic penumbra as an inclusion criterion for a trial or subgroup

Author	Intervention	No. of Participants	Criterion	Inclusion or Subgroup	Preplanned
Hacke et al (2005)[39]	Desmoteplase	104	20% PWI/DWI mismatch and PWI lesion >2 mL involving gray matter (MTT/TTP)	Inclusion	Yes
Singhal et al (2005)[41]	Normobaric oxygen	16	20% PWI/DWI mismatch (MTT)	Inclusion	Yes
Els et al (2006)[43]	Hypothermia (patients with HC)	25	DWI and PWI <2/3 hemisphere, no mismatch (PWI modality not specified)	Inclusion	Yes
Furlan et al (2006)[44]	Desmoteplase	37	20% PWI/DWI mismatch and PWI lesion >2-cm diameter and involving cortex (MTT)	Inclusion	Yes
Davis et al (2008)[52]	Alteplase	80	20% PWI/DWI mismatch and PWI lesion–DWI lesion >10 mL (Tmax + 2 sec)	Subgroup	Yes
Hacke et al (2009)[57]	Desmoteplase	193	20% PWI/"core" mismatch (CT or MRI)	Inclusion	Yes
Kidwell et al (2009)[58]	Magnesium	44	20% PWI/DWI mismatch (Tmax + 2 sec)	Subgroup	No
		40	20% PWI/DWI mismatch (Tmax + 2 sec) and DWI <3 mL	Subgroup	No
Parsons et al (2010)[66]	Alteplase	85	20% PWI/DWI mismatch (Tmax + 2 sec)	Subgroup	No
		37	PWI lesion <190 mL, DWI lesion <25 mL (Tmax + 2 sec)	Subgroup	No
		30	PWI lesion 20–190 mL, DWI lesion <25 mL (Tmax + 2 sec)	Subgroup	No
		31	PWI lesion <190 mL, DWI lesion <18 mL (Tmax + 2 sec)	Subgroup	No
		24	PWI lesion 20–190 mL, DWI lesion <18 mL (Tmax + 2 sec)	Subgroup	No
		65	20% PWI/DWI mismatch (Tmax + 2 sec), ICA occlusion excluded	Subgroup	No
		40	PWI lesion >20 mL, DWI lesion <25 mL (Tmax + 2 sec), ICA occlusion excluded	Subgroup	No
		32	PWI lesion >20 mL, DWI lesion <18 mL (Tmax + 2 sec)	Subgroup	No
		62	20% PWI/DWI mismatch (Tmax + 8 sec)	Subgroup	No
		52	PWI lesion <150 mL, DWI lesion <25 mL (Tmax + 8 sec)	Subgroup	No
		40	PWI lesion 10–150 mL, DWI lesion <25 mL (Tmax + 8 sec)	Subgroup	No
		43	PWI lesion <150 mL, DWI lesion <18 mL (Tmax + 8 sec)	Subgroup	No
		33	PWI lesion 10–150 mL, DWI lesion <18 mL (Tmax + 8 sec)	Subgroup	No
Schäbitz et al (2010)[67]	G-CSF	44	PWI/DWI mismatch, any size (PWI unspecified)	Inclusion	Yes
Bi et al (2011)[68]	Hypothermia	93	20% PWI/DWI mismatch (TTP/MTT)	Inclusion	Yes
Michel et al (2012)[71]	Alteplase	6	Favorable CTP profile	Inclusion	Yes
Nagakane et al (2011)[69]	Alteplase	80	20% PWI/DWI mismatch and PWI lesion–DWI lesion >10 mL (Tmax + 2 sec, coregistered)	Subgroup	No
Nagakane et al (2012)[72]	Alteplase	62	20% predicted infarct volume/DWI mismatch	Subgroup	No
Parsons et al (2012)[74]	Tenecteplase	75	20% PWI/CT mismatch and >20 mL mismatch volume (CT MTT)	Inclusion	Yes
Warach et al (2012)[76]	Desmoteplase	66	PWI/"core" mismatch >60 mL (CT or MRI)	Subgroup	No
Kidwell et al (2013)[81]	Embolectomy	68	"Core"/PWI <70% "core" <90 mL (CT or MRI)	Subgroup	Yes

Note:—Tmax indicates time-to-maximum; HC, hemicraniectomy; G-CSF, granulocyte colony stimulating factor.

On-line Table 4: Studies using imaging to define subgroups

Author (yr)	Intervention	No. of Participants	Modality	Criterion	Subgroup Size	Results Different from Primary Analysis
MAST-I (1995)[1]	Streptokinase	622	CT	No EIC	519	No
NINDS (1997)[4]	Alteplase	624	CT	No EIC or thrombus identified	513	No
Broderick et al (2013)[77]	Endovascular treatment	656	CT	ASPECTS 0–7	271	No
			CT	ASPECTS 8–10	378	No
			CTA	ICA/M1/BA occlusion	220	No
Chen (1997)[5]	Aspirin	20,655	CT	No EIC	2764	No
Davis et al (2008)[52]	Alteplase	101	MRI	Lesion volume >5 mL (DWI)	69	Yes
			MRP	20% PWI/DWI mismatch and PWI lesion − DWI lesion >10 mL (Tmax + 2 sec)	80	No
De Silva et al (2010)[64]	Alteplase	87	MRA	MCA occlusion	32	Yes
			MRA	TIMI 0–1	49	No
			MRA	TIMI 2–3	38	No
			MRA	TIMI 0–2	54	No
			MRA	TIMI 3	33	No
Demchuk et al (2005)[37]	Alteplase	608	CT	ASPECTS 8–10	402	No
			CT	ASPECTS 0–7	201	Yes (though same trend)
			CT	ASPECTS 3–7	185	No
			CT	ASPECTS <3	16	Yes (though same trend)
Derex et al (2001)[24]	Alteplase	35	DSA	No vessel occlusion	10	Not clear
Dzialowski et al (2006)[42]	Alteplase	788	CT	ASPECTS >7	557	No
			CT	ASPECTS <8	231	No
Gilligan et al (2002)[28]	Streptokinase	270	CT	No EIC	94	No
			CT	Lesion <1/3 of vascular territory	82	No
			CT	Lesion >1/3 vascular territory	94	No
Hacke et al (2009)[57]	Desmoteplase	193	MRA/CTA	TIMI 0–1	53	No
Hill et al (2003)[31]	IA prourokinase	180	CT	ASPECTS 0–7	88	Yes (negative)
Hill et al (2014)[83]	Endovascular treatment	656	CT	ASPECTS 8–10	378	No
			CT	ASPECTS 0–7	278	No
			CT	ASPECTS 0–4	92	No
			CT/angio	ASPECTS 8–10 and ICA/MCA occlusion	144	No
			CT/angio	ASPECTS 0–7 and ICA/MCA occlusion	128	No
			CT/angio	ASPECTS 0–4 and ICA/MCA occlusion	40	No
Kasner et al (2013)[80]	Transcranial laser therapy	640	MRI/CT	Involvement of cortex	463	No
Kidwell et al (2009)[58]	Magnesium	90	MRI	Lacunar stroke (DWI lesion <1.5 mL, deep location)	15	No
			MRI	Baseline DWI >3 mL	73	No
			MRP	20% PWI/DWI mismatch (Tmax + 2 sec)	44	No
			MRP	20% PWI/DWI mismatch (Tmax + 2 sec) and DWI >3 mL	40	No
Kidwell et al (2013)[81]	Embolectomy	118	CTP/MRP	Infarct/PWI <70% and core <90 mL	68	No
			CTP/MRP	Nonpenumbral	50	No
NINDS (2005)[40]	Alteplase	624	CT	Composite of NIHSS <2 and no EIC	28	No
Manelfe et al (1999)[16]	Alteplase	603	CT	HMCAS	107	Yes
McCormick et al (2010)[65]	Insulin	40	MRA	Intracranial vessel occlusion	11	Yes

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On-line Table 4: Continued

Author (yr)	Intervention	No. of Participants	Modality	Criterion	Subgroup Size	Results Different from Primary Analysis
Nagakane et al (2011)[69]	Alteplase	101	MRI	Lesion volume >5 mL (DWI)	69	Yes
			MRP	20% PWI/DWI mismatch and PWI lesion − DWI lesion >10 mL (Tmax + 2 sec, coregistered)	80	Yes
Nagakane et al (2012)[72]	Alteplase	101	MRP	Severity-weighted mismatch	61	No
Nichols et al (2008)[54]	Alteplase	624	CT	HMCAS	79	Not clear
Ogawa et al (1999)[17]	Ebselen	105	DSA	Persistent complete occlusion of M1 after thrombolysis	45	Yes
			DSA	Persistent complete occlusion of M1 or M2 after thrombolysis	70	Yes
			DSA	Recanalization of M1 and M2 after thrombolysis	13	No
Pantano et al (1999)[18]	Alteplase	450	CT at 24 hr	No EIC	87	Not done
			CT at 24 hr	Subcortical lesion	106	Not done
			CT at 24 hr	Cortical lesion	123	Not done
			CT at 24 hr	Mixed lesion	134	Not done
Parsons et al (2010)[66]	Alteplase	98	MRP	20% PWI/DWI mismatch (Tmax + 2 sec)	85	No
			MRP	PWI lesion <190 mL, DWI lesion <25 mL (Tmax + 2 sec)	37	No
			MRP	PWI lesion 20–190 mL, DWI lesion <25 mL (Tmax + 2 sec)	30	Yes
			MRP	PWI lesion <190 mL, DWI lesion <18 mL (Tmax + 2 sec)	31	Yes, using mRS 0–1; no, using mRS 0–2
			MRP	PWI lesion 20–190 mL, DWI lesion <18 mL (Tmax + 2 sec)	24	Yes
			MRP	20% PWI/DWI mismatch (Tmax + sec), ICA occlusion excluded	65	No
			MRA	Lesion volume <25 mL (DWI) and ICA occlusion excluded	47	Yes, using mRS 0–1; no, using mRS 0–2
			MRP	PWI lesion >20 mL, DWI lesion <25 mL (Tmax + 2 sec), ICA occlusion excluded	40	Yes, using mRS 0–1; no, using mRS 0–2
			MRA	Lesion volume <18 mL (DWI) and ICA occlusion excluded	39	Yes, using mRS 0–1; no, using mRS 0–2
			MRP	PWI lesion >20 mL, DWI lesion <18 mL (Tmax + 2 sec)	32	Yes
			MRP	20% PWI/DWI mismatch (Tmax + 8 sec)	62	No
			MRP	PWI lesion <150 mL, DWI lesion <25 mL (Tmax + 8 sec)	52	No
			MRP	PWI lesion 10–150 mL, DWI lesion <25 mL (Tmax + 8 sec)	40	Yes, using mRS 0–1; no, using mRS 0–2
			MRP	PWI lesion <150 mL, DWI lesion <18 mL (Tmax + 8 sec)	43	No
			MRP	PWI lesion 10–150 mL, DWI lesion <18 mL (Tmax + 8 sec)	33	Yes, using mRS 0–1; no, using mRS 0–2
Patel et al (2001)[27]	Alteplase	616	CT	Lesion volume >1/3 MCA	84	Yes
			CT	Lesion volume <1/3 MCA	110	Yes
			CT	No EIC	422	No
Roberts et al (2002)[30]	IA urokinase	162	CT	No EIC	53	No
			CT	Lesion volume <20 mL	77	No
			CT	Lesion volume 20–40 mL	14	No
			CT	Lesion volume 40–60 mL	7	No
			CT	Lesion volume >60 mL	8	No
			DSA	No collaterals	50	No
			DSA	Collaterals	111	Yes
Rosso et al (2012)[75]	IV insulin	180	MRA	Recanalization	70	Yes, negative
			MRA	Partial recanalization	50	Yes, negative
			MRA	No recanalization	34	Yes, negative
Warach et al (2012)[76]	Desmoteplase	122	MRP	Mismatch volume <60 mL	45	No
			MRP	Mismatch volume >60 mL	66	No
Wechsler et al (2003)[32]	IA urokinase	180	CT	Lesion volume >5.25 mL as part of a multimodal risk score	Variable	No
Yasaka et al (1998)[10]	Streptokinase	37	SPECT	Perfusion deficit (12% drop compared to contralateral)	22	No
			TCD	Vessel occlusion	16	No

Note:—Angio indicates angiography; MAST-I, Multicenter Acute Stroke Trial–Italy; TIMI, Thrombolysis in Myocardial Infarction; Tmax, time-to-maximum; MRP, MRI perfusion; IA, intra-arterial; EPO, erythropoietin; HMCAS, hyperdense MCA sign; EIC, early ischemic change; BA, basilar artery.