Table S1: In- and exclusion criteria

Inclusion criteria

- Patients presenting with acute ischemic stroke
- Patient, family member or legally responsible person depending on local ethics requirements has given informed consent
- Patient's age is ≥18 years
- Treatment onset within ≥ 4.5 – 9 hours after stroke onset

Patients who wake with stroke may be included if neurological and other exclusion criteria are satisfied. These 'wake up' strokes are defined as having no symptoms at sleep onset, but stroke symptoms on waking

- NIHSS score of 4 to 26 with clinical signs of hemispheric infarction
- Penumbral imaging with a perfusion volume (PWI) to infarct core (DWI) ratio of 1.2, and a perfusion lesion minimum volume of 20 ml

Exclusion criteria

- Intracranial hemorrhage (ICH) identified by CT or MRI
- Rapidly improving symptoms, particularly if in the judgment of the managing clinician the improvement is likely to result in the patient having an NIHSS score of < 4 at randomization
- Pre-stroke mRS score of more than 1 (indicating previous disability)
- Contra indication to imaging with MR
- Infarct core >1/3 MCA territory qualitatively or >100 ml quantitatively (determined by DWI lesion on MRI).
- Participation in any investigational study in the previous 30 days
- A life expectancy of less than 3 months
- Any condition that could impose hazards to the patient if study therapy is initiated or affect the participation of the patient in the study (this applies to patients with severe microangiopathy such as hemolytic uremic syndrome or thrombotic thrombocytopenic purpura). The judgment is left to the discretion of the investigator
- Pregnant women (clinically evident) or breastfeeding women
- Previous stroke within last three months
- Recent past history or clinical presentation of ICH, subarachnoid hemorrhage (SAH), arterio-venous (AV) malformation, aneurysm, or cerebral neoplasm. The judgment is left to the discretion of the investigator
- Use of oral anticoagulants within 48 hours prior to randomization (including, but not limited to Rivaroxaban, Apixaban, or Edoxaban) or a prolonged prothrombin time (INR > 1.6) or any activated partial thromboplastin (aPTT) time exceeding 1.5 times the normal range or prolonged Thrombin-Time (TT), indicating the potential use of Dabigatran-Etexilate
- Use of heparin, except for low dose subcutaneous heparin, in the previous 48 hours
- Use of glycoprotein IIb-IIIa inhibitors within the past 72 hours
- Platelet count <100.000/µl (<100G/l)
- Blood glucose <50mg/dl (2.8 mmol/l) or >400mg/dl (22.2 mmol/l)
- Uncontrolled hypertension defined by a blood pressure > 185 mmHg systolic or >110 mmHg diastolic on at least 2 separate occasions at least 10 minutes apart, or requiring aggressive treatment to reduce the blood pressure to within these limits. The definition of "aggressive treatment" is left to the discretion of the responsible Investigator
- Hereditary or acquired hemorrhagic diathesis
- Gastrointestinal or urinary bleeding within the preceding 21 days
- Manifest or recent acute pancreatitis
- Manifest severe liver disease including hepatic failure, cirrhosis, portal hypertension and active hepatitis
- Major surgery within 14 days prior to randomization which poses a risk in the opinion of the investigator
- Recent (within 10 days) traumatic external heart massage, obstetrical delivery, recent puncture of a non-compressible blood-vessel
- Exposure to a thrombolytic agent within the previous 72 hours

Table S2: Baseline characteristics

	rt-PA (n=61)	Placebo (n=58)
Age [Median (IQR)]	76 (65-83) y	79 (67-84) y
Female [n (%)]	25 (41.0%)	27 (46.6%)
Caucasian [n (%)]	61 (100%)	58 (100%)
pRS 0 [n (%)]	48 (78.7%)	46 (79.3%)
$NIHSS_0$ [Median (IQR)]	10 (9)	9 (10)
Time strata (<6 | 6-9 | wake up)	4 | 15 | 42	5 | 13 | 40
Time-Window* [Median (IQR)]	7.7 (1.5) hrs	7.3 (1.9) hrs
Atrial fibrillation [n (%)]	14 (23.0%)	16 (27.6%)
Ischemic heart disease [n (%)]	9 (14.8%)	11 (19.0%)
Previous stroke [n (%)]	12 (19.7%)	16 (27.6%)
Hypertension [n (%)]	42 (68.9%)	42 (72.4%)
Diabetes [n (%)]	16 (26.2%)	12 (20.7%)
Lipid disorder [n (%)]	31 (50.8%)	24 (41.4%)
Smoker [n (%)]	3 (4.9%)	3 (5.2%)
Peripheral artery disease [n (%)]	3 (4.9%)	3 (5.2%)
DWI [Mean (SD)]	17.1 (17.5) ml	22.9 (25.3) ml
PI [Mean (SD)]	93.6 (76.6) ml	112.4 (107.1) ml
DWI/PI-Ratio [Mean (SD)]	29.3 (79.3)	16.7 (40.2)

*: Time of stroke onset was taken as the mid-point between sleep onset and time of waking

pRS: premorbid Rankin Score; DWI: diffusion weighted imaging; PI: perfusion imaging