

# **ONLINE SUPPLEMENT**

## **Applicability of Clinical Trials in an Unselected Cohort of Patients with Intracerebral Hemorrhage**

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## Supplemental Methods

### Comments on variable assessment

Eligibility criteria from the original publications were used for completed trials and eligibility criteria from the three online databases for clinical trial registration, ClinicalTrials.gov ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)), ISRCTN registry ([www.isrctn.com](http://www.isrctn.com)), and the Stroke Trials Registry ([www.strokecenter.org](http://www.strokecenter.org)), were used for remaining, ongoing trials.

Due to the large number of patients assessed from Lund Stroke Register (LSR) and the many different selection criteria in the trials, we conducted the variable assessment in two steps. First potential eligibility was assessed using a basic set of variables (including time from stroke onset to diagnostic CT, age, ICH volume, and ICH location) with trial specific cut-offs. Second, the remaining trial specific variables were gathered for patients deemed potentially eligible in the first step. Hence, all patients do not have information about results for all individual variables.

If exact time between ICH onset and CT was missing we used the last time the patient was known to be well to determine eligibility with regard to the inclusion time of each trial. If time to CT was not possible to determine from medical reports the patients were regarded as non-eligible (see supplemental Figure II). Patients with missing data for any other eligibility criteria were regarded as potentially eligible for respective trial.

We assumed that consent to participate was possible to obtain for all patients. Two surgical trials (STICH-I and -II) used the clinical equipoise-concept for patient-selection, this criteria was not considered in the present analysis unless surgical removal of ICH was conducted in LSR-patients as described below. The clot stability-criteria used in three trials (MISTIE-III, CLEAR-III, and SWITCH, see below) was not considered in the present analysis due to lack of standardized acute-phase radiological follow-up in LSR patients.

### Description of included trials and definitions of their eligibility criteria

References (trial-id or original article) are stated after each study-headline. Explanation of trial acronyms are provided in the main text (Table 1). Number of screened patients is included if the trial is completed and screening numbers have been presented. Some combined eligibility criteria have been subdivided and some criteria have been shortened and modified for clarity.

*[Text in Italics below describes adaptation/interpretation of eligibility criteria performed in our study]*

## 1. STICH-I

**Reference:** Mendelow AD, et al. 2005<sup>1</sup>

**Study status as of June 2016:** Completed

**Recruitment period:** 1995-2003

**Intervention:** Surgery

**Study size:** 1033 (N=503 intervention, N=530 control)

**Screened patients:** Unknown

### **Inclusion criteria:**

1.1 CT evidence of spontaneous supratentorial ICH

1.2 Within 72 h of ICH onset

1.3 The responsible neurosurgeon was uncertain about the benefits of either treatment (the clinical uncertainty principle) [*since current European guidelines<sup>2</sup> express uncertainty of when to operate, LSR patients were only regarded as non-eligible if undergoing ICH evacuation and no uncertainty to operate was expressed in the preoperative assessment*]

1.4 Minimum hematoma diameter of 2 cm

1.5 Glasgow coma score (GCS)  $\geq 5$

### **Exclusion criteria:**

1.6 ICH probably due to an aneurysm or an angiographically proven arteriovenous malformation (AVM) or secondary to a tumor or trauma

1.7 Cerebellar ICH or extension of a supratentorial ICH into the brainstem

1.8 Severe pre-existing physical disability that might interfere with the assessment of outcome [*defined as pre-stroke mRS 4-5*]

1.9 Severe pre-existing mental disability that might interfere with the assessment of outcome

1.10 Severe comorbidity that might interfere with the assessment of outcome [*Charlson Comorbidity Index (CCI)<sup>3</sup>  $\geq 3$* ]

1.11 Surgery could not be undertaken within 24 h of randomization [*assumed to be possible for all patients*]

## 2. INTERACT-2

**Reference:** Anderson CS, et al. 2013<sup>4</sup>

**Study status as of June 2016:** Completed

**Recruitment period:** 2008-2012

**Intervention:** Medical

**Study size:** 2839 (N=1403 intervention, N=1436 control)

**Screened patients (estimated):** 28 829 (10% estimated screening to enrollment ratio)

### **Inclusion criteria:**

2.1 Age  $\geq 18$  years

2.2 Patients with CT-confirmed spontaneous ICH

2.3 Two systolic blood pressure (SBP) measurements of  $\geq 150$  and  $\leq 220$  mmHg, recorded  $\geq 2$  minutes apart. Patients with initial SBP levels outside of this range ( $< 150$  or  $> 220$  mmHg) may be randomized should the BP levels fulfil entry criteria on rechecking up to 6 hours after the onset of ICH. Patients with an initial SBP  $> 220$  mmHg may receive initial BP lowering and then be randomized, provided that the SBP is  $\leq 220$  mmHg within 6 hours of symptom onset [*SBP at admission used because no standardized recheck of SBP was available*]

2.4 Treatment possible to commence  $< 6$  hours of ICH onset

2.5 Active treatment and care will be provided to the patient in a suitable monitored facility even if they are assigned with 'Not For Resuscitation (NFR)' or 'Do Not Resuscitate' (DNR) orders [*assumed possible for all*]

2.6 Written informed consent obtained from the patient, or an appropriate surrogate [*not used*]

**Exclusion criteria:**

2.7 Known definite contraindication to intensive BP lowering (e.g. known severe carotid, vertebral or cerebral arterial stenosis, Moya Moya disease or Takayasu's arteritis, high grade stenotic valvular heart disease, or severe renal failure)

2.8 Known definite indication to intensive BP lowering (e.g. SBP >220 mmHg, hypertensive encephalopathy, or aortic dissection) [*additionally, patients with a baseline mean arterial pressure >150 mmHg as defined by American Heart Association's guidelines 2010<sup>5</sup> were regarded as non-eligible*]

2.9 Evidence of ICH secondary to a structural abnormality (e.g. AVM, intracranial aneurysm, tumor, or trauma)

2.10 Cerebral infarction within the last 30 days [*only first-ever stroke patients are included in LSR*]

2.11 Thrombolysis prior to ICH

2.12 A high likelihood that the patient will die within the next 24 hours on the basis of clinical and/or radiological criteria (e.g. massive hematoma with mid-line shift of a hemisphere or deep coma on presentation, defined by GCS 3-5) [*we instead used withdrawal of care <6 h of ICH onset and GCS 3-5 at admission to minimize subjectivity regarding what constitutes as "massive hematoma with mid-line shift of a hemisphere"*]

2.13 Known existing dementia

2.14 Known pre-stroke disability (e.g. score 3-5 on the modified Rankin scale) [*pre-stroke dependence, mRS 3-5*]

2.15 Concomitant medical illness that would interfere with the outcome assessments and/or follow-up (e.g. advanced cancer or respiratory disease) [*defined as CCI ≥6*]

2.16 Patients considered for early surgical evacuation of ICH [*ICH evacuation within the study specific time from ICH onset to randomization*]

2.17 Participation in INTERACT-2 or another clinical trial [*not used*]

2.18 Patients who are considered to have a high likelihood of not adhering to the study treatment or the follow-up regimen [*only applied if known illicit substance abuse was described*]

**3. TICH-2**

**Reference:** Trial-ID ISRCTN registry: ISRCTN93732214. First accessed March 1, 2015 and remained unchanged at control June 1, 2016

**Study status as of June 2016:** Ongoing

**Recruitment period:** 2013-2017

**Intervention:** Medical

**Study size (planned):** 2000 (N=1000 intervention, N=1000 control)

**Inclusion criteria:**

3.1 Age ≥18 years

3.2 Either sex

3.3 Primary ICH [*excluding traumatic ICH*]

3.4 Within 8 hours of stroke onset

**Exclusion criteria:**

- 3.5 ICH secondary to anticoagulation or thrombolysis
- 3.6 ICH due to known underlying structural abnormality such as AVM, aneurysm, tumor, venous thrombosis
- 3.7 Patients for whom tranexamic acid is contraindicated [*contraindication for iv tranexamic acid (TA) according to the official Swedish Medicines Compendium for physicians: acute thrombosis, disseminated intravascular coagulation (DIC), gravely decreased kidney function, or convulsions in medical history*<sup>6</sup>]
- 3.8 Premorbid dependency (mRS >4)
- 3.9 Participation in another drug trial concurrently [*not used*]
- 3.10 Pre-stroke life expectancy <3 months (e.g. advanced metastatic cancer) [*see criterium 2.15*]
- 3.11 GCS <5

**4. CHANT**

**Reference:** Lyden PD, et al. 2007<sup>7</sup>

**Study status as of June 2016:** Completed

**Recruitment period:** 2004-2005

**Intervention:** Medical

**Study size:** 607 (N=305 intervention, N=302 control)

**Screened patients:** Unknown

**Inclusion criteria:**

- 4.1 Written informed consent from the patient or legally acceptable representative [*not used*]
- 4.2 Either sex
- 4.3 Age  $\geq 18$  years
- 4.4 Clinical diagnosis of acute stroke with limb weakness
- 4.5 ICH on CT or MRI
- 4.6 The sum of scores on items 5 and 6 on the NIHSS were  $\geq 2$  at baseline and the total score (items 1–11) was  $\geq 6$
- 4.7 Therapy initiated <6 hours of ictus
- 4.8 Premorbid mRS 0-1

**Exclusion criteria:**

- 4.9 Acute ischemic stroke, an epidural, subdural or subarachnoid hemorrhage, tumor, encephalitis, or any diagnosis other than acute ICH. Small areas of epidural, subdural, or subarachnoid hemorrhage associated with large primary ICH were allowed
- 4.10 ICH attributable to trauma. Patients who suffered minimal head trauma following the onset of a primary ICH were allowed
- 4.11 Unconsciousness (i.e., 3 points on item 1a. of the NIHSS) [*GCS<9 at admission used*]
- 4.12 Severe concurrent illness with life expectancy less than 6 months [*see criterium 2.15*]
- 4.13 Planned surgical removal of the ICH. EVD or intracranial pressure monitor allowed [*see criterium 2.16*]
- 4.14 Unlikely to complete the 72-hour infusion of investigational product because of a severe clinical condition at baseline [*defined as withdrawal of care <6 h of ICH*]
- 4.15 Known severe renal disorder (creatinine clearance of <30 mL/min using the Jaffe method or <35 mL/min using the modified Jaffe or enzymatic method) [*eGFR<35 according to the LM-method, accounting for creatinine, age and sex*<sup>8</sup>]
- 4.16 Known alcohol or illicit drug abuse or dependence

- 4.17 Pregnancy or breast-feeding. Women of childbearing potential were excluded unless a negative test for pregnancy has been obtained before randomization [*cause for exclusion only if known pregnancy is explicitly mentioned in medical files*]
- 4.18 Treatment since onset of stroke symptoms with experimental (i.e., drugs in clinical studies) or empirical treatments for stroke with the exception of mannitol, glycerol, and steroids for the treatment of ICP [*not used*]
- 4.19 Treatment with acetazolamide and methotrexate during the 72-hour infusion [*all patients with these treatments 2 days prior to ICH are regarded as non-eligible*]
- 4.20 Previous inclusion in CHANT or concurrent inclusion in another clinical study [*not used*]

## 5. RESTART

**Reference:** Trial-ID ISRCTN registry: ISRCTN71907627. First accessed March 1, 2015 and remained unchanged at control June 1, 2016

**Study status as of June 2016:** Ongoing

**Recruitment period:** 2013-2018

**Intervention:** Medical

**Study size (planned):** 720 (N=360 intervention, N=360 control)

### **Inclusion criteria:**

5.1 Age  $\geq$ 18 years

5.2 Either sex

5.3 Spontaneous ICH on the basis of:

5.3.1 Symptom onset without preceding head trauma, head trauma occurring subsequent to ICH symptom onset is permissible

5.3.2. Brain imaging consistent with spontaneous ICH

5.3.3 Either 'secondary' to an underlying structural cause (e.g. aneurysm, tumor, AVM, or intracranial venous thrombosis), or 'primary' (no suspicion of underlying structural cause, or it is not detected by further radiographic investigation)

5.4 Patient had taken an antithrombotic (i.e. anticoagulant or antiplatelet) drug for the prevention of vaso-occlusive disease before ICH onset [*patient not eligible if e.g. acetylsalicylic acid was taken for pain or fever prior to ICH*]

5.5 At least >24 hours after ICH symptom onset [*patients who died <24 h of ICH are not eligible*]

5.6 Patient and their doctor are both uncertain about whether to start or avoid antiplatelet drugs [*Patients who had care withdrawn within hospital stay were not considered to be eligible. In all remaining cases we assumed that there was an uncertainty whether to start or avoid antiplatelet therapy*]

5.7 Patient is registered with a general practitioner (GP) [*not used as all patients are listed with a GP as a part of Sweden's universal health care*]

5.8 The brain imaging study where ICH was diagnosed is available

5.9 Consent to randomization from the patient or representative if the patient does not have mental capacity [*not used*]

### **Exclusion criteria:**

5.10 ICH due to traumatic brain injury

5.11 ICH due to hemorrhagic transformation of an ischemic stroke

5.12 Anticoagulant drug use following ICH [*including warfarin, heparin, or low-molecular-weight heparins*]

5.13 Patient is pregnant, breastfeeding, or of childbearing age and not taking contraception [*see criterium 4.17*]

5.14 Patient is being treated or followed up in another clinical trial of an investigational medicinal product [*not used*]

5.15 Patient and carer unable to understand spoken or written English [*not used*]

## 6. FAST

**Reference:** Mayer SA, et al. 2008<sup>9</sup>

**Study status as of June 2016:** Completed

**Recruitment time:** 2005-2007

**Intervention:** Medical

**Study size:** 841 (N=573 intervention, N=268 control)

**Screened patients:** 8886 (9% screening to enrollment ratio)

### **Inclusion criteria:**

6.1 Age  $\geq 18$  years

6.2 Spontaneous ICH

6.3 CT scan  $< 3$  hours after symptom onset

### **Exclusion criteria:**

6.4 GCS score  $\leq 5$

6.5 Surgical evacuation of hematoma planned  $< 24$  hours

6.6 Secondary ICH resulting from trauma, AVM, or other causes

6.7 Known use of oral anticoagulant therapy

6.8 Thrombocytopenia or coagulopathy [*platelet count  $< 100,000$  / $\mu$ L or INR  $\leq 1.2$ . Patient eligible even if INR is elevated at admission if it is assessed that INR could have been normalized within the time-window for randomization*]

6.9 Acute sepsis, crush injury, or DIC [*sepsis as defined by Annane D et al.<sup>10</sup>*]

6.10 Pregnancy [*see criterium 4.17*]

6.11 Prestroke modified Rankin scale score  $> 2$

6.12 Known recent ( $< 30$  days before enrollment) thromboembolic disease (angina, claudication, deep-vein thrombosis, cerebral infarction, or myocardial infarction) [*angina pectoris and claudication only causes for exclusion if patients have had manifestations of disease  $< 30$  days of ICH i.e. patients with long-term symptomatic treatment that are symptom free are included*]

## 7. ATACH-II

**Reference:** The ATACH-II trial results was published during the preparation of this manuscript. Trial criteria are therefore from ClinicalTrials.gov (trial-ID: NCT01176565, first accessed March 1, 2015, remained unchanged at control June 1, 2016), and study information from Qureshi AI et al. 2016<sup>11</sup>

**Study status as of June 2016:** Completed

**Recruitment time:** 2011-2015

**Intervention:** Medical

**Study size:** 1000 (N=500 intervention, N=500 control)

**Screened patients:** 8532 (12% screening to enrollment rate)

**Inclusion Criteria:**

- 7.1 Age  $\geq 18$  years
- 7.2 Therapy can be initiated within 4.5 hours of symptom onset
- 7.3 Clinical signs consistent with stroke
- 7.4 GCS score  $\geq 5$
- 7.5 INR  $< 1.5$  [*see criterium 6.8*]
- 7.6 Intraparenchymal hematoma  $< 60$  mL [*ICH-volume measured by the ABC/2 method<sup>12</sup>*]
- 7.7 SBP  $> 180$  mmHg [*SBP at admission used*]
- 7.8 For randomization after IV antihypertensive administration: SBP  $> 180$  mmHg prior to IV antihypertensive treatment without SBP reduction to below 140 mmHg at the time of randomization [*SBP at admission used*]
- 7.9 Informed consent obtained by subject or representative [*not used*]

**Exclusion Criteria:**

- 7.10 ICH is due to previously known neoplasms, AVM, or aneurysm
- 7.11 ICH related to trauma
- 7.12 Infratentorial ICH
- 7.13 Intraventricular hemorrhage (IVH) associated with intraparenchymal hemorrhage and blood completely fills one lateral ventricle or more than half of both ventricles [*defined as  $\geq 2$  modified Graeb scale (mGS)<sup>13</sup> score in the main body of both lateral ventricles or a mGS score of 4 in the main body of one lateral ventricle*]
- 7.14 Patient to receive immediate surgical evacuation [*see criterium 2.16*]
- 7.15 Pregnancy, parturition within previous 30 days, or active lactation [*see criterium 4.17*]
- 7.16 Use of dabigatran within the last 48 hours [*dabigatran was not in use when the LSR-patients were registered*]
- 7.17 Platelet count  $< 50,000$  / $\mu$ L
- 7.18 Known sensitivity to Nicardipine
- 7.19 Pre-morbid disability requiring assistance in ambulation or activities of daily living [*prestroke mRS  $> 2$* ]
- 7.20 Subject's living will precludes aggressive ICU management [*exclusion if medical files state that the patient expressed a wish to withhold ICU care*]
- 7.21 Subject is currently participating in another interventional clinical trial [*not used*]

**8. STICH-II**

**Reference:** Mendelow AD, et al. 2013<sup>14</sup>

**Study status as of June 2016:** Completed

**Recruitment time:** 2007-2012

**Intervention:** Surgical

**Study size:** 601 (N=307 surgery, N=294 conservative)

**Screened patients (sample):** 3984 of whom 313 (8%) were eligible

**Inclusion criteria:**

- 8.1 Spontaneous lobar ICH on CT ( $\leq 1$  cm from the cortex surface of the brain)
- 8.2 Patient  $< 48$  h of ictus
- 8.3 Best motor score on GCS of 5 or 6 and best eye score on the GCS of 2 or more
- 8.4 ICH volume between 10-100 mL, calculated using the ABC/2-method



8.5 Only patients for whom the treating neurosurgeon is in equipoise about the benefits of early craniotomy compared to initial conservative treatment are eligible for the trial [*see criterium 1.3*]

**Exclusion criteria:**

8.6 Clear evidence that the hemorrhage is due to an aneurysm or angiographically proven AVM or secondary to tumor or trauma

8.7 Intraventricular hemorrhage

8.8 Basal ganglia, thalamic, cerebellar or brainstem hemorrhage or extension of a lobar hemorrhage into any of these regions

8.9 Severe pre-existing physical disability which might interfere with assessment of outcome [*see criterium 1.8*]

8.10 Severe pre-existing mental disability which might interfere with assessment of outcome

8.11 Severe co-morbidity which might interfere with assessment of outcome [*see criterium 1.10*]

8.12 Surgery cannot be performed <12 hours [*see criterium 1.11*]

**9. CLEAR-III**

**Reference:** Ziai WC, et al. 2014<sup>15</sup>

**Study status as of June 2016:** Completed (results presented at the International Stroke Conference February 2016)

**Recruitment time:** 2009-2015

**Intervention:** Surgical

**Study size:** 500 (N=250 intervention, N=250 standard care)

**Screened patients:** 10 278 (5% screening to enrollment ratio)

**Inclusion criteria:**

9.1 Age 18-80 years

9.2 Symptom onset <24 hours prior to diagnostic CT scan (dCT) [*as described by Ziai WC et al. "The primary aim of this study is to test the hypothesis that IVH patients (...) will have better clinical outcomes when treated with intraventricular rtPA (...) relative to those receiving placebo within 72 h of onset". We therefore used the 72 hours from ictus to dCT as the upper time limit*]

9.3 Spontaneous ICH  $\leq$ 30 mL [*including primary IVH, excluding ICH second to trauma*]

9.4 IVH obstructing 3rd and/or 4th ventricles [*patient eligible if 4 mGS points for the IIIrd and/or IVth ventricle*]

9.5 An EVD must be in place and stable at the time of randomization [*not used as there is no uniform evidence based consensus regarding when EVD should be placed<sup>2</sup>*]

9.6 SBP <200 mmHg sustained for the six hours before drug administration (closest to randomization) [*assumed to be possible for all patients without contraindications for rapid BP-lowering as defined by criterium 2.7*]

9.7 Able to randomize within 72 hours of dCT [*see criterium 9.2*]

9.8 Pre-stroke mRS of 0-1

9.9 No test article may be administered until at least 12 hours after symptom onset [*patient not eligible if withdrawal of care or death <12 hours of ICH onset*]

9.10 ICH <35 mL on subsequent stability scans performed six hours or more after EVD placement [*see the general section "Comments on variable assessment", above*]

9.11 Hematoma stability is assessed by comparison with the most recent previous CT scan and is defined by: (1) ICH size difference is  $\leq$ 5 mL; (2) the width difference of the lateral

ventricle most compromised by IVH is  $<2$  mm; (3) catheter tract bleeding  $\leq 5$  mL or mm. Investigator may continue to screen for the initial bleeding to stabilize, if the patient can be randomized  $<72$  h from time of dCT. If clot sizes stabilize between two sequential CT scans at least 12 h apart, the patient is eligible [*see criterium 9.10*]

**Exclusion criteria:**

9.12 Suspected or untreated ruptured cerebral aneurysm, AVM, choroid plexus malformation, Moyamoya disease or tumor [*all patients with concomitant subarachnoid hemorrhage were regarded as having a suspected cerebral aneurysm and therefore non-eligible*]

9.13 Clotting disorders (reversing anticoagulation will be permitted where long-term anticoagulation is not required) [*defined as ICD-10 codes D65-D69*]

9.14 Platelet count  $<100,000$  / $\mu$ L, INR  $>1.4$  [*see criterium 6.8*]

9.15 Pregnancy [*see criterium 4.17*]

9.16 Infratentorial hemorrhage

9.17 ICH/IVH enlargement that cannot be stabilized in the treatment time window [*see criterium 9.10*]

9.18 Ongoing internal bleeding involving retroperitoneal sites, or the gastrointestinal, genitourinary, or respiratory tracts

9.19 Multifocal, superficial bleeding observed at multiple vascular puncture and access sites (e.g. venous cutdowns, arterial punctures) or site of recent surgical intervention

9.20 Prior enrollment in the study [*not used*]

9.21 Any other condition that the investigator believes would pose a significant hazard to the subject if the investigational therapy were initiated [*not used, however criteria 9.9, 9.22, and 9.23 cover this to some extent*]

9.22 Not expected to survive to the day 180 visit because of comorbidities [*see criterium 2.15*]

9.23 Do not resuscitate/do not intubate (DNR/DNI) status prior to randomization [*in addition to criterium 9.9 patients with DNR/DNI status  $<6$  hours of dCT, the minimum time required from EVD placement to new CT for assess hematoma stability, were regarded as non-eligible*]

9.24 Planned or simultaneous participation in another interventional medical investigation or clinical trial [*not used*]

**10. MISTIE-III**

**Reference:** Trial-ID ClinicalTrials.gov: NCT01827046. First accessed March 1, 2015. Due to minor changes at control June 1, 2016 the new up-dated criteria were used

**Study status as of June 2016:** Ongoing

**Recruitment time:** 2013-2018

**Intervention:** Surgical

**Study size (planned):** 500 (N=250 surgery, N=250 conservative)

**Inclusion Criteria:**

10.1 Spontaneous ICH  $\geq 30$  mL [*excluding traumatic ICH*]

10.2 GCS  $\leq 14$  or NIHSS  $\geq 6$

10.3 Six-hour clot size equal to the most previous clot size (within 5 mL) as determined by additional CT scans at least 6 hours apart [*see criterium 9.10*]

10.4 Symptoms  $<24$  hours prior to dCT (an unknown time of onset is exclusionary) [*the maximum time window for MISTIE-III is 96 h from ICH onset to randomization (maximum 24*

*h from ictus to dCT +72 h from dCT to randomization, see below). To better reflect this we used a 72 h time limit from ICH onset to dCT*

10.5 Ability to randomize between 12 and 72 hours after dCT [*see criterium 10.4*]

10.6 SBP <180 mmHg sustained for six hours recorded closest to the time of randomization [*see criterium 9.6*]

10.7 Historical Rankin score of 0-1 [*mRS 0-1 used*]

10.8 Age  $\geq$ 18 years

#### **Exclusion Criteria:**

10.9 Infratentorial hemorrhage

10.10 IVH requiring treatment for IVH-related mass effect or shift due to trapped ventricle [*patient not eligible if 4 mGS points for the IIIrd, IVth ventricle*]

10.11 Thalamic bleeds with apparent midbrain extension with third nerve palsy or dilated and non-reactive pupils

10.12 Irreversible impaired brain stem function (bilateral fixed, dilated pupils and extensor motor posturing), GCS  $\leq$  4

10.13 Ruptured aneurysm, AVM, vascular anomaly, Moyamoya disease, hemorrhagic conversion of an ischemic infarct, or recurrence of a recent (< 1 year) hemorrhage

10.14 Patients with unstable mass or evolving intracranial compartment syndrome [*defined as: rapid deterioration in GCS, sudden pupil dilatation, or midline deviation >1.5 cm (arbitrarily chosen limit)*]

10.15 Platelet count <100,000 / $\mu$ L, INR >1.4, or an elevated prothrombin time (PT) or activated partial thromboplastin time (aPTT) [*see criterium 6.8*]

10.16 Any irreversible coagulopathy or known clotting disorder [*see criterium 9.13*]

10.17 Inability to sustain INR  $\leq$ 1.4 using short- and long-active procoagulants [*assumed possible for all*]

10.18 Subjects requiring long-term anti-coagulation. Reversal of anti-coagulation is permitted for medically stable patients who can realistically tolerate the short term risk of reversal [*assumed possible for all except patients excluded by criteria 10.30 and 10.31*]

10.19 Patient must not require Coumadin (anticoagulation) during the first 30 days, and normalized coagulation parameters must be demonstrated, monitored closely and maintained during the period of brain instrumentation [*see criterium 6.8 and 10.18*]

10.20 Use of dabigatran, apixaban, and/or rivaroxaban prior to ICH [*these drugs were not in use when the LSR-patients where registered*]

10.21 Internal bleeding, involving retroperitoneal sites, or the gastrointestinal, genitourinary, or respiratory tracts

10.22 Superficial or surface bleeding, observed mainly at vascular puncture and access sites (e.g., venous cutdowns, arterial punctures, etc.) or site of recent surgical intervention

10.23 Pregnancy [*see criterium 4.17*]

10.24 Allergy/sensitivity to rt-PA [*not used*]

10.25 Prior enrollment in the study [*not used*]

10.26 Participation in a concurrent interventional medical investigation or clinical trial [*not used*]

10.27 Not expected to survive to the day 365 visit due to co-morbidities [*see criterium 2.15*]

10.28 DNR/DNI status prior to randomization [*defined as withdrawal of care or DNR/DNI status within 12 h of dCT as this is the earliest time for randomization (see criterium 10.5)*]

10.29 Any concurrent serious illness that would interfere with the safety assessments including hepatic, renal, gastroenterologic, respiratory, cardiovascular, endocrinologic, immunologic, and hematologic disease [*not used, covered by criterium 10.27*]

10.30 Mechanical heart valve

- 10.31 Known risk for embolization, including history of left heart thrombus, mitral stenosis with atrial fibrillation, acute pericarditis, or subacute bacterial endocarditis
- 10.32 Any other condition that the investigator believes would pose a significant hazard to the subject if the investigational therapy were initiated [*not used, however criteria 10.27 and 10.28 cover this to some extent*]
- 10.33 Active drug or alcohol use or dependence that would interfere with adherence to study requirements [*all active drug or alcohol dependence is regarded as cause for exclusion*]
- 10.34 Unstable patient that would benefit from a specific intervention rather than supportive care plus or minus MIS+rt-PA removal of the ICH [*see criteria 10.14 and 10.28*]
- 10.35 Inability or unwillingness of subject or legal guardian/representative to give written informed consent [*not used*]

## 11. SWITCH

**Reference:** Trial-ID ClinicalTrials.gov: NCT02258919. First accessed March 1, 2015 and remained unchanged at control June 1, 2016

**Study status as of June 2016:** Ongoing

**Recruitment time:** 2014-2017

**Intervention:** Surgical

**Study size (planned):** 300 (N=150 surgery, N=150 conservative)

### Inclusion Criteria:

- 11.1 Written informed consent of the patient or next of kin plus consent of an independent physician if patient is unable to consent before randomization [*not used*]
- 11.2 Spontaneous ICH
- 11.3 ICH in the basal ganglia and/or thalamus that may extend into the ventricles and into the cerebral lobes, and into the subarachnoid space
- 11.4 Age  $\geq 18$  to  $\leq 75$  years
- 11.5 GCS  $< 14$  and  $> 7$
- 11.6 NIHSS score of  $\geq 10$  and  $\leq 30$
- 11.7 Able to be randomly assigned to surgical treatment  $< 66$  hours of ictus
- 11.8 Surgery performed  $< 6$  hours of randomization [*see criterium 1.11*]
- 11.9 ICH volume  $\geq 30$  mL and  $\leq 100$  mL
- 11.10 Stable clot volume [*see criterium 9.10*]
- 11.11 INR  $< 1.5$ , thrombocytes  $> 100,000/\mu\text{L}$  [*see criterium 6.8*]

### Exclusion Criteria

- 11.12 ICH due to structural abnormality in the brain (e.g., intracranial aneurysm, AVM, brain tumor) or brain trauma
- 11.13 ICH due to previous stroke [*see criterium 2.10*]
- 11.14 ICH due to thrombolysis
- 11.15 Infratentorial ICH
- 11.16 Exclusive lobar ICH
- 11.17 Known advanced dementia [*unclear what classifies as "advanced", therefore any known dementia was regarded as cause for exclusion*]
- 11.18 Significant pre-stroke disability [*see criterium 2.14*]
- 11.19 Concomitant medical illness that would interfere with outcome assessment and follow-up [*see criterium 1.10*]
- 11.20 Pregnancy [*see criterium 4.17*]
- 11.21 Prior major brain surgery within  $< 6$  month or prior decompressive craniectomy

- 11.22 Foreseeable difficulties in follow-up due to geographic reasons [*not used*]
- 11.23 Known definite contraindication for a surgical procedure
- 11.24 A very high likelihood that the patient will die within the next 24 hours on the basis of clinical and/or radiological criteria [*defined as withdrawal of care within 24 h of ICH onset*]
- 11.25 Previous participation in this trial or in another ongoing investigational trial [*Not used*]
- 11.26 Prior ICH [*see criterium 2.10*]
- 11.27 Bilateral areactive pupils

## Supplemental Table

**Table I.** Baseline characteristics for eligible and non-eligible ICH-patients

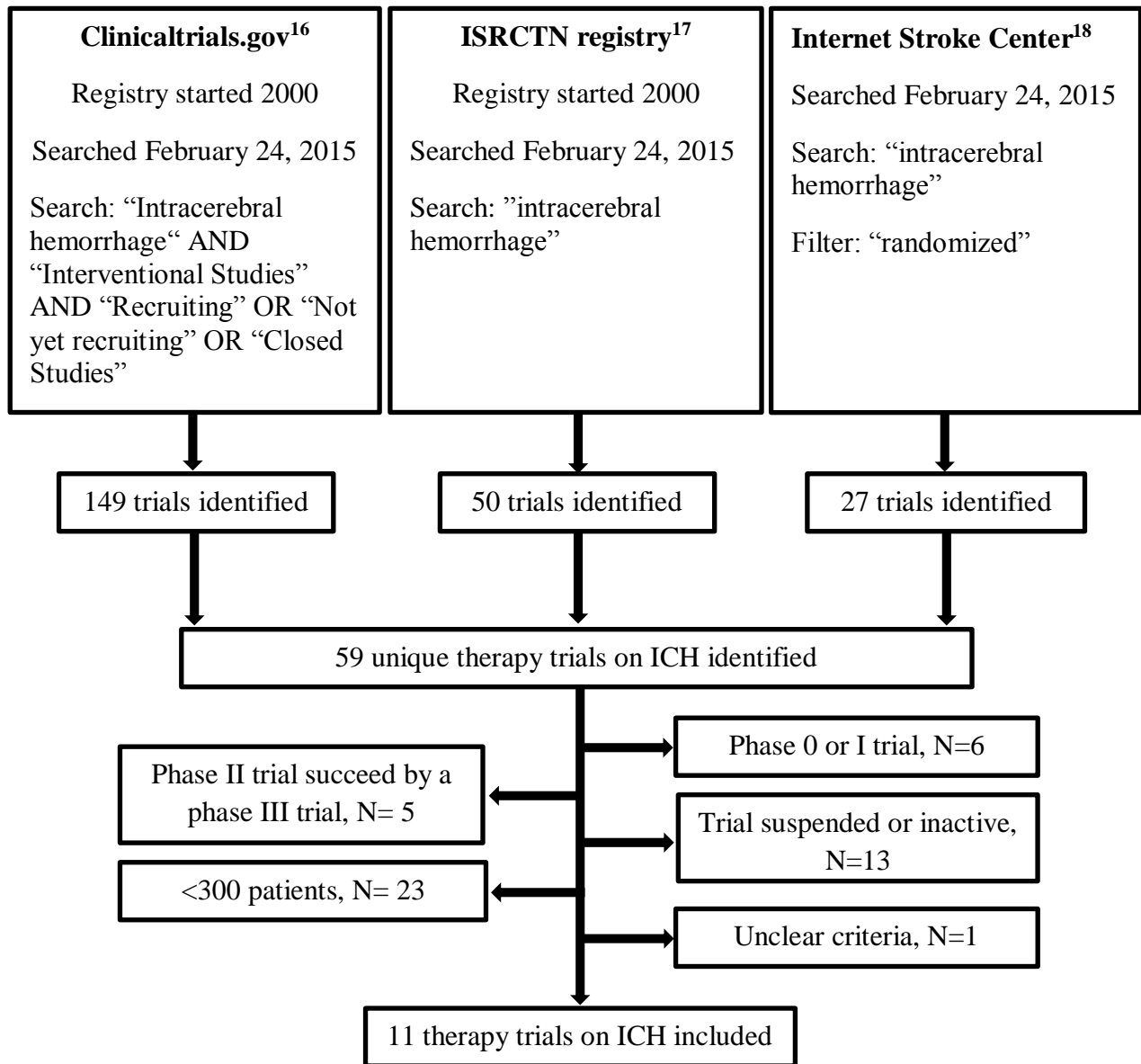
	<b>Total</b>	<b>Eligible</b>	<b>Non-eligible*</b>	<b>p-value</b>	<b>Missing (n)</b>
Total, n (%)	253 (100%)	157 (62%)	96 (38%)	-	-
Female, n (%)	116 (46%)	71 (45%)	45 (47%)	0.798†	0
Age, years, median (IQR)	74 (63-81)	73 (62-80)	75 (66-82)	0.229‡	0
ICH-volume, mL, median (IQR)	15 (5-43)	15 (5-31)	14 (4-62)	0.476‡	0
Intraventricular hemorrhage	115 (45%)	60 (38%)	55 (57%)	0.003†	0
mGS, median (IQR)	0 (0-10)	0 (0-6.5)	4.5 (0-13)	0.001‡	1
GCS, median (IQR)	14 (10-15)	15 (13.5-15)	8 (4-15)	<0.001‡	7
ICH-location, n (%)				<0.001†	0
Lobar	68 (27%)	54 (34%)	14 (15%)	§	-
Deep	131 (52%)	81 (52%)	50 (52%)		-
Mixed	5 (2%)	1 (1%)	4 (4%)		-
Cerebellar	31 (12%)	13 (8%)	18 (19%)	§	-
Brainstem	18 (7%)	8 (5%)	10 (10%)		-

\*Patients not eligible for inclusion in any of the 11 trials studied; †Pearson's  $\chi^2$ -test; ‡Mann-Whitney

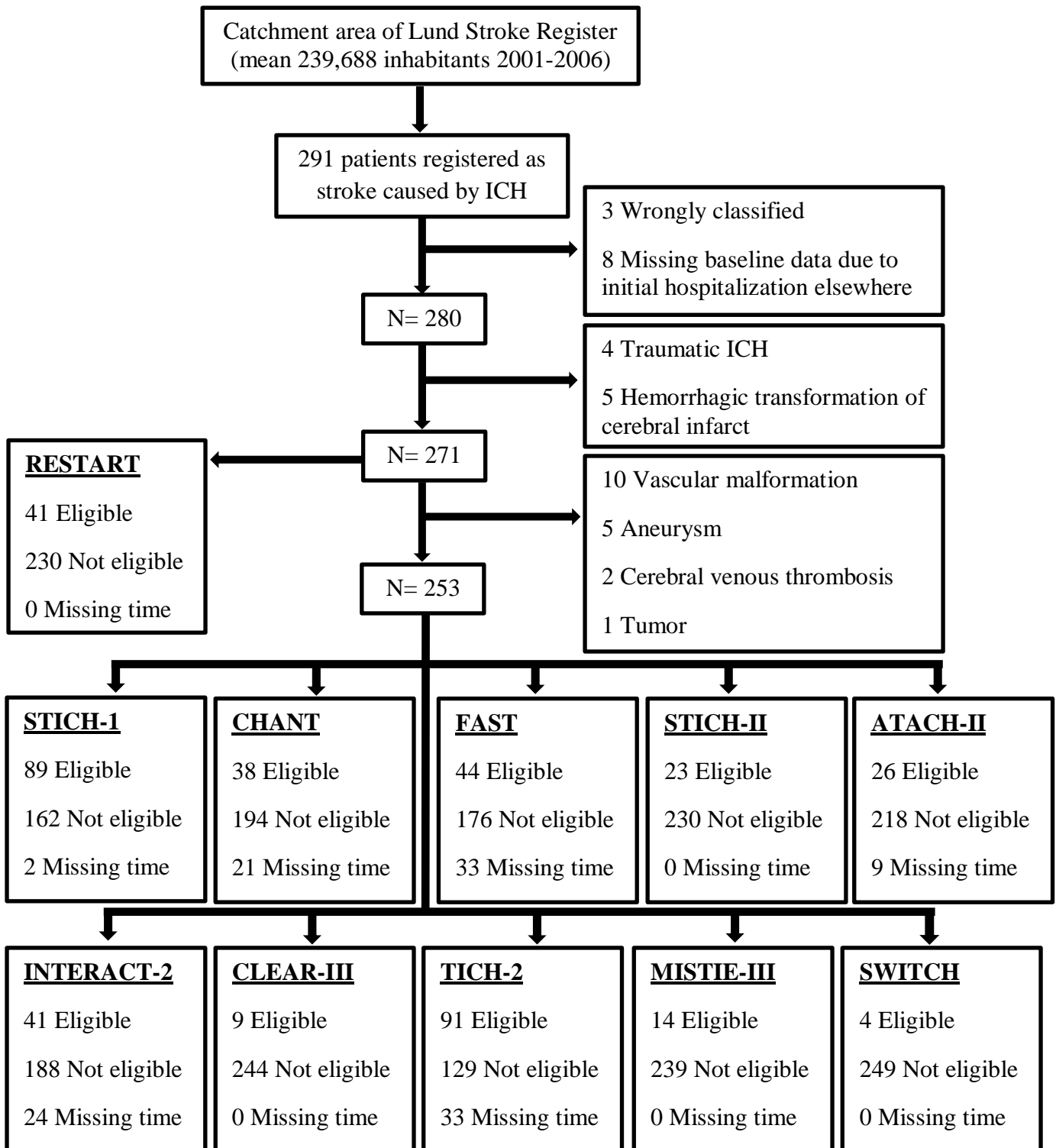
U-test; §Significant differences ( $p<0.05$ ); IQR=Interquartile range; mGS=modified Graeb Scale;

GCS=Glasgow Coma Scale

**Supplemental Figures**

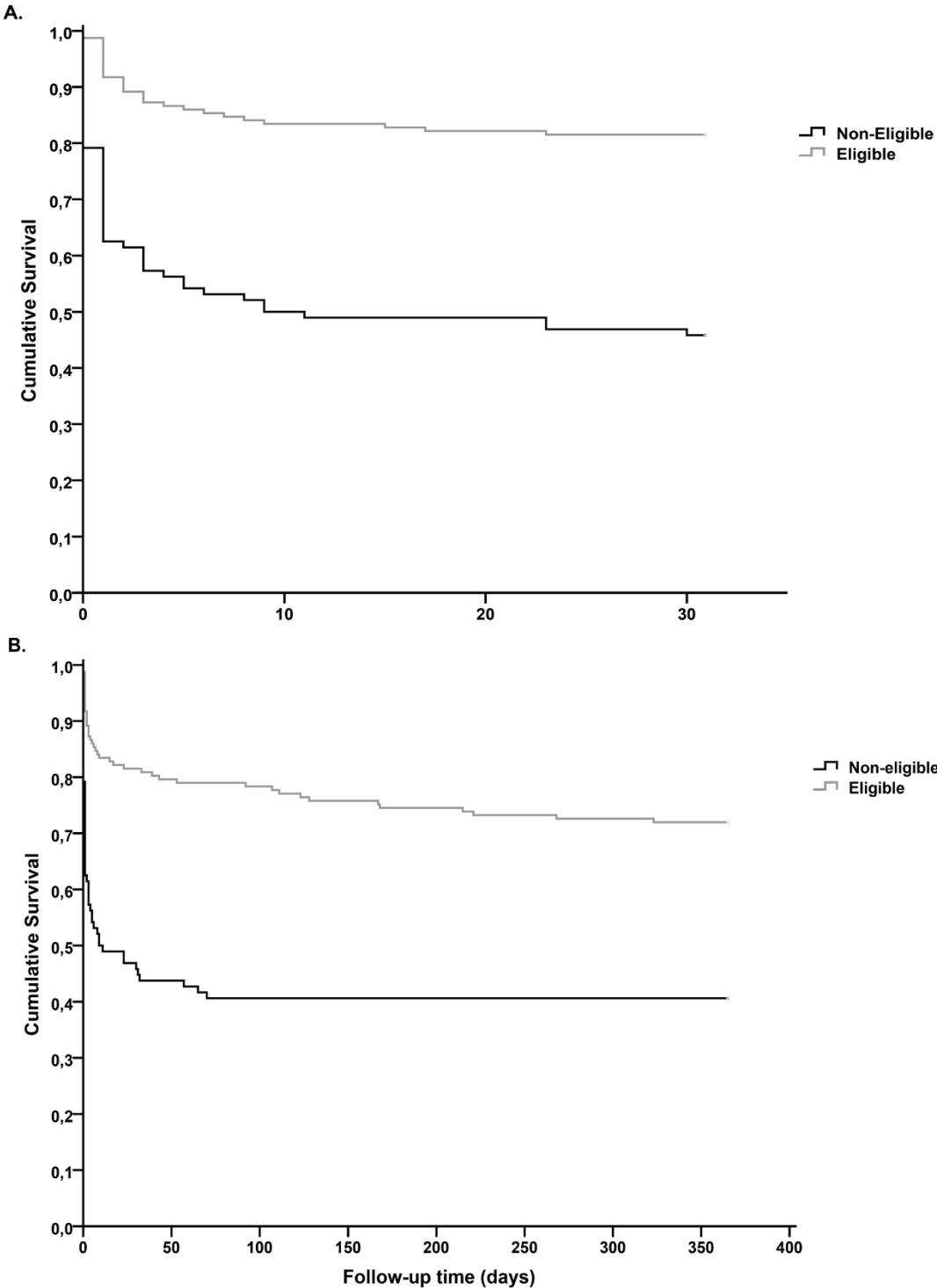


**Supplemental Figure I.** Trial selection, flow-chart. We did not actively restrict the search to a specific time-span but the search was limited by when the registers started. Both clinicaltrials.gov and the ISRCTN registry started in 2000, start time for the Internet Stroke Center was not available.



**Supplemental Figure II.** Patient selection for the 11 included trials. Missing time indicate that time from ictus to CT was not available and the numbers of patient missing due to this differ between trials with identical inclusion times because patients were excluded due to other causes.





**Supplemental Figure III.** Kaplan-Meier survival tables for 30-day (A) and

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