Acute revascularization in ischemic stroke: Updated Swiss guidelines

Patrik Michel¹, Michael Diepers², Pasquale Mordasini³, Tilman Schubert⁴, David Bervini⁵, Jean-Daniel Rouvé⁶, Yvan Gasche⁷, Guido Schwegler⁸, Christophe Bonvin⁹, Krassen Nedeltchev¹⁰, Emmanuel Carrera¹¹, Georg Kägi¹², Carlo Cereda¹³, Thomas Nyffeler¹⁴, Stephan Wetzel¹⁵, Susanne Wegener¹⁶, Henrik Gensicke¹⁷, Stefan Engelter¹⁷, Marcel Arnold¹⁸, and on behalf of the Swiss Stroke Society.

Abstract

In acute ischemic stroke, intravenous thrombolysis (IVT) and acute endovascular therapy (EVT) have been shown to reduce long-term disability in randomized trials. International guidelines are partially not up to date and may not address situations for which there is limited scientific evidence. The goals of the present guidelines are to summarize the current scientific data for acute revascularization treatments to make sure that all Swiss Centers apply a similar, evidence, or consensus-based treatment standard. A multidisciplinary working group of the Swiss Stroke Society (SSS) searched and reviewed the literature on new randomized controlled trials (RCTs), large case series, meta-analyses, and other guidelines since the previous recommendations in 2009 to elaborate the consensus guidelines. The new RCTs have confirmed the effectiveness of IVT in various populations up to 4.5 h and proven the benefit of acute EVT up to approximately 8 h. For patients with unknown onset (including wake-up stroke), IVT and EVT can be effective up to 24 h after last proof of good health if patients are selected with advanced neuroimaging. Multiple
Background and methods

Randomized controlled trials (RCTs) have shown long-term benefit for acute acetylsalicylic acid, intravenous thrombolysis (IVT), acute endovascular therapy (EVT), neurorehabilitation, and decompressive craniectomy in selected ischemic stroke patients if they are treated in Stroke Units or Stroke Centers. Most of these treatments can be used in combination.

Treatment in Stroke Units and Stroke Centers is effective for all stroke patients, but IVT can only be offered to approximately 20–30% and EVT to 10–20% of patients arriving at the hospital within 24 h.1 This restricted treatment rate for acute revascularization stems from the need to select patients with specific clinical and radiological criteria to obtain the treatment benefit.

The multidisciplinary working group “Acute Stroke Treatment” of the Swiss Stroke Society (SSS) has now updated the previous guidelines from 20092 in face-to-face reunions and by email. Representatives of the Swiss Neurological Society, the Swiss Society of Neuroradiology, the Swiss Society of Neurosurgery, the Swiss Society for Anesthesiology and Intensive Care, and the Swiss Society of Intensive Care Medicine participated actively in their elaboration. The working group performed a literature review in Pubmed/MEDLINE (2008–2020) for the combination of “stroke” and “randomised” or “meta-analysis” with any one of the following: “thrombolysis,” “thrombectomy,” “endovascular treatment,” “endovascular therapy,” and “anesthesia.” In addition to retrieval phase III studies, we also considered large case series combining the latter five search terms with “minor stroke,” “pediatric,” “preexisting disability,” “pregnancy,” “mismatch,” “antithrombotics,” “anticoagulation,” “platelet inhibitor,” “blood pressure,” “hemorrhage,” “bleeding,” and “craniectomy.” Retrieved articles and other national and international guidelines were also scanned to identify further case series, in particular dealing with conditions potentially including the bleeding risk with IVT. The working group then reviewed these new publications to develop the consensus guidelines. The strength of our recommendations was expressed by the wording rather than a classification system.

Since 2014, the SSS maintains the Swiss Stroke Registry3 for quality improvement and research purposes. The registry follows international recommendations for quality control of acute revascularization treatments.4

The goals of the present guidelines are to summarize the current scientific data for acute revascularization treatments in acute ischemic stroke. This should allow all Swiss Stroke Centers to apply a similar, evidence or consensus-based treatment to optimize the benefit–risk ratio for such patients. The author affiliations and potential conflicts of interest are listed in Appendix I, Table IA.

New scientific data

Since the third Swiss guidelines for acute treatment of ischemic stroke in 2009,2 RCTs have

- confirmed the effectiveness of IVT with recombinant tissue plasminogen activator (rtPA) (alteplase, Actilyse®) within the 4.5 h window (up to 5 h in the meta-analysis); Patients over 85 years, with small vessel strokes, and patients with minor disabling and severe strokes seem to have similar benefit as all other patients;6
- shown the effectiveness of EVT, in particular with stent retrievers7–13 and/or aspiration techniques,14,15 in combination with IVT up to about 8 h after stroke onset16;
- confirmed the major prognostic importance of rapid treatment for both IVT and EVT (“time is brain”);5,17
- shown the effectiveness of direct EVT for unknown onset or late-arriving patients between 6 h and 24 h in the presence of certain neuroradiological selection criteria (computed tomography (CT)- or magnetic resonance imaging (MR)-based perfusion imaging or a combination of clinical deficit and radiological core measures)18,19;
- shown the effectiveness of direct IVT for unknown onset or late-arriving patients beyond 4.5 h since last proof of good health if certain neuroradiological selection criteria are present (CT- or MR-based perfusion imaging20–22 or fluid-attenuated inversion recovery diffusion-weighted imaging (FLAIR-DWI) mismatch on magnetic resonance imaging (MRI))23; not shown the equivalence of low-dose IVT (with rtPA 0.6 mg/kg) with the usual dose (0.9 mg/kg), despite reduced bleeding risk with the lower dose;24
- shown the probable ineffectiveness of IVT for patients with non-disabling stroke;25
- shown the ineffectiveness of ultrasound-assisted IVT;26
- shown the probable superiority of IVT with tenecteplase (Metalyse®) 0.25 mg/kg over rtPA 0.9 mg/kg before EVT27,28;
- shown the ineffectiveness of EVT within 8 h for basilar artery occlusion in two RCT.29,30 A secondary on-
EVT within 6 h reduces the long-term disability in one out of four treated patients and completely avoids disability in one out of two patients,16,17 There is no increase in hemorrhage or early mortality, and long-term mortality is probably decreased.16

**General recommendations**

Given its narrow therapeutic window, we recommend that IVT be given in hospitals equipped with Stroke Units or Stroke Centers certified according to Swiss recommendations.52 Similarly, we recommend that EVT is performed only by Stroke Centers mandated by the Intercantonal Agreement on Highly Specialized Medicine,53 which fulfill the Swiss certification criteria.52,54 In remote hospitals without a Stroke Unit, EVT may be offered in direct collaboration with a Stroke Unit or Stroke Center (e.g. via telemedicine) and should be documented in the national stroke registry for quality control.3

IVT based on simple neuroradiological criteria is effective within at least 4.5 h (in the meta-analysis up to about 5 h) after symptom onset5,55–57 and EVT up to about 8 h.17 Thereafter, patients need to be selected by specific neuroradiological criteria (see details below). Figure 1 shows the indications for different types of revascularization treatments in acute ischemic stroke, depending on delays and neuroradiological criteria.

Based on current scientific data, we recommend IVT within 4.5 h than EVT (bridging therapy) for proximal intracranial occlusions unless there are IVT contraindications as mentioned above. Several RCTs are currently studying this recommendation.

The effectiveness of both revascularization methods decreases minute-by-minute with increasing time from symptoms onset.5,17 For this reason, we recommend speedy interventions for treatable patients, independently of prehospital delays. To shorten treatment delays, we recommend

- standardized prehospital and transfer protocols aiming at defining and shortening triage and transport delays (see the simultaneously published guidelines on this topic)59;
- standardized management protocols in all emergency departments of hospitals with Stroke Units and Stroke Centers offering IVT and EVT, integrating neuroradiology and urgent laboratory assessment;
- to initiate IVT in the diagnostic imaging facility while applying clinical and vital sign surveillance.

We recommend that the choice of the revascularization method for a given situation should be based on all available clinical, neuroradiological, and laboratory data while trying to avoid additional delay.

**Specific recommendations**

Indications and contraindications for IVT and EVT are listed in Tables 2–9. We recommend performing an
individualized benefit-risk estimation in the presence of relative contraindications (Table 8); such contraindications can also be regarded as additional outcome modulators.

Stroke onset is defined as the last time point when the patient was in his/her usual state of health, that is, the last proof of being without stroke symptoms. The NIHSS allows quantification of the clinical neurological deficit in stroke patients. We recommend that the NIHSS is used by medical personnel with appropriate instruction, exercise, and experience.

Given that IVT, and probably of EVT, are effective across all severities of a disabling stroke, we do not recommend to limit the treatments to a specific NIHSS window. We do recommend, however, that a disabling deficit (IVT and EVT) and/or a proven arterial occlusion within the ischemic territory (EVT) are present before initiation of treatment. For nondisabling deficits without major occlusions, IVT is may not be effective.25

If a major occlusion is not treated initially because of mild symptoms, in the case of worsening during continuous clinical surveillance, a “rescue” revascularization may be considered.

For patients with basilar artery occlusion, we recommend applying similar revascularization criteria and time windows as for the anterior circulation. MR-based imaging can help determine the “core” and, therefore, subsequent decision-making (see Table 2). However, measurement of the penumbra for decisions in the late time window is not recommended in basilar artery occlusions.

In patients with significant preexisting disability, there is little data on the effect of IVT and EVT60 and safety concerns are the same as in nondisabled patients. In such patients, an individual estimation of the risk–benefit ratio may be used, which also considers the patient’s personal values (if known).

There are no acute revascularization RCTs on children and adolescents up to 18 years. In this population, IVT and/or EVT may be considered along the criteria used in adult patients, if possible after a consensus discussion between neuropediatricians, adult stroke specialists, and parents.61

Pregnancy is a relative contraindication for IVT, and potential treatment effect on the mother should be balanced by the risk of harm to the fetus. Again, we recommend a discussion with all concerned persons if this does not cause significant treatment delay. The risk for the fetus is probably minor, in particular with EVT. The usual radioprotective measures in pregnancy should be applied.62

Neuroradiological selection of late patients
The irreversible ischemia (“core,” in general, defined by diffusion or perfusion imaging) and the reversible ischemia (“penumbra,” in general, defined by perfusion imaging or estimated from the neurological deficit) can be determined with sufficient precision for clinical decision-making. Rapid recanalization becomes more effective with a small “core” and an increasing “mismatch” between “penumbra” and “core.” Another type of “mismatch” is based on acute MRI on the presence of a DWI and absence of a FLAIR lesion; this kind of mismatch indicates the short duration of ischemia (such as <4.5–6 h) and not the direct presence of a penumbra. Different concepts of mismatch are described in Table 1.

There is also potential for a mismatch between the core and neuroradiologically defined (good) collateral circulation, but current RCTs have not yet used this concept.
We can summarize neuroradiological findings in acute ischemia as follows:

- A large core volume increases the risk of a poor outcome and bleeding, independent of whether acute recanalization is achieved or not.
- A larger “mismatch” between penumbra and core leads to more treatment benefit if acute recanalization is achieved rapidly.

Regarding treatment decisions and its benefits, the presence of a mismatch is as follows:

- Of minor importance in the very early time window.
- More important in late time windows and in patients with unknown stroke onset.

We, therefore, recommend that neuroradiological findings are used in late decisions for IVT/EVT; they may also be used in borderline situations in the early time windows.

We recommend following the revascularization criteria described in Tables 2–9 corresponding to inclusion and exclusion criteria used in RCTs, data from case series, other stroke treatment guidelines and the consensus opinion of the authors.

### Additional measures during and after revascularization

Regarding the anesthesiology management during EVT:

- We do not make a recommendation regarding the type of anesthesia (general anesthesia vs. conscious sedation). Arguments in favor of general anesthesia are as follows:
  - Decreased level of consciousness (Glasgow Coma Scale ≤ 8).
  - Difficult communication, agitation, and excessive movements.
  - Cardiac and respiratory instability.
  - Potentially long-lasting or complex interventions.
- We recommend to elaborate institutional standardized operating procedures for anesthesiology management, aiming to
**Table 4. Indications for early EVT.**

Cf. Table 2 and:
- Treatment onset < 8 h.\(^\text{17}\)
- In middle cerebral artery strokes: usually CT-ASPECTS 6 and/or MRI-DWI < 100 ml.
- Acute occlusion of an intracranial artery that is accessible with acceptable risk.
- If arterial imaging not possible: diagnostic cerebral angiography followed, if needed, by EVT, if indirect neuroradiological signs for arterial occlusion,\(^a\) or if a proximal occlusion is clinically likely (stroke severity).
- If near-complete arterial occlusion, or if isolated extracranial occlusion: consider EVT in the presence of a neuroradiological or clinical–neuroradiological mismatch (cf. Table 1).

EVT: endovascular therapy; MRI: magnetic resonance imaging; DWI: diffusion-weighted imaging; CT: computed tomography.

\(^a\)Noncontrast CT: “dense artery sign.” MRI-SWI: “susceptibility vessel sign.”

**Table 5. Indications for EVT for wake-up stroke, unknown stroke onset, or late hospital arrival.**

Cf. Tables 2 and 4 and:
- Treatment onset 8–24 h after last proof of good health maybe even later.\(^\text{18,19}\)
- Additional criteria for supratentorial strokes.
- Core in general <70 ml
- Neuroradiological or clinical–neuroradiological mismatch (cf. Table 1).

EVT: endovascular therapy.

**Table 6. Indications for IVT for wake-up stroke, unknown stroke onset, or late hospital arrival.**

Attention: If criteria for late EVT are fulfilled (Table 5), direct EVT without IVT is recommended.

Cf. Table 2 and:
- Treatment onset beyond 4.5 (or maximally 5) hours, and
- Acute MRI: IVT without upper time limits\(^b\) if
  - DWI-FLAIR mismatch
  - DWI in general <70 ml
- Or acute perfusion imaging on CT or MRI: IVT up to 9 h from the mid-time between last proof of good health and symptoms discovered\(^b\) if
  - Neuroradiological mismatch (cf. Table 1).
  - Core in general <30 ml.
- Attention: demonstration of an arterial occlusion is not needed for late IVT.

IVT: intravenous thrombolysis; EVT: endovascular therapy; MRI: magnetic resonance imaging; FLAIR: fluid-attenuated inversion recovery; DWI: diffusion-weighted imaging; CT: computed tomography.

- reduce preinterventional delays,
- enhance patient safety,
- respect general principles of neuroanesthesia, including pathophysiology-based blood pressure management.

**Table 7. Contraindications for IVT.**

In the presence of contraindications for IVT, the patient should be immediately evaluated for direct EVT according to Tables 3 and 5.

- Acute or subacute intracranial hemorrhage on acute neuroimaging.
- Rapid regression of symptoms to a degree not fulfilling the above indications for acute revascularization treatment.
- Symptoms or signs highly suggestive of a current subarachnoid hemorrhage.
- History of subarachnoid hemorrhage with unknown or incompletely treated bleeding source.
- Intracranial giant aneurysm >25 mm, large arteriovenous malformation with/without meningeal fistula, large cavernoma, any incompletely treated cavernoma with previous hemorrhage, and multiple cavernomas.
- Active malignant intracranial tumors (e.g. glioblastoma and metastasis).
- Intracranial or intraspinal intervention within <14 days (except lumbar puncture).
- Moderate or severe traumatic brain injury within <6 weeks.
- Known INR >1.7 or aPTT >40 s (spontaneously or from anticoagulants).
- Anticoagulation (inform the laboratory about the drug and time since last dose): if plasma levels not immediately available or if levels above the following limits → direct EVT. Otherwise, respect the following upper limits for IVT:
  - Any anticoagulant INR >1.7 and aPTT >40 s.
  - Therapeutic doses of heparin (unfractionated or low molecular): anti-Xa >0.2 units/ml.
  - Apixaban, rivaroxaban, and edoxaban: anti-Xa >100 ng/ml.\(^c\)
- Dabigatran: TT > 80 s or anti-Il'a (=Hemoclot\(^\text{®}\) = dTT) >100 ng/ml → Consider IVT 10 min after Praxbind\(^\text{®}\) 5 mg IV (without rechecking coagulation).
- Endocarditis, pericarditis, and vasculitis of the central nervous system (known or high suspicion).
- Symptomatic aortic aneurysm (unless completely treated).

IVT: intravenous thrombolysis; EVT: endovascular therapy; aPTT: activated partial thromboplastin time; TT: thrombin time.

\(^b\)No recommendation can be made regarding treatment with Andexxa\(^\text{®}\) before IVT in patients with therapeutic levels of anti-Xa oral anticoagulants, because the efficacy and safety of such a pretreatment are not yet known.

Like in all strokes, we recommend that patients with revascularization treatments are admitted and continuously monitored for at least 24 h in a Stroke Unit or Stroke Center.\(^\text{52,54}\) Treatment in intensive care in a hospital with a Stroke Unit or Stroke Center is recommended if admission criteria for intensive care are present.

We recommend that a platelet inhibitor is administered before, during, or immediately after a direct EVT, for example, with acetylsalicylic acid at a loading dose of 250–500 mg. Exceptions are patients who are already fully anticoagulated at the time of stroke. It is recommended to continue preexisting antiplatelet therapy should be continued and adapted, if needed.

We recommend avoiding antithrombotic drugs during the first 12–24 h after IVT, with justified exceptions. Prevention of deep vein thrombosis is recommended with intermittent...
pneumatic compression and with early mobilization of the patient. The latter may start within the first 24 h with intermittent sitting at the edge of the bed or in a chair, if the neurological deficit and collaboration permit.\textsuperscript{64,65}

According to the current evidence, acute blood pressure treatment seems to have little influence on long-term outcome. Still, the following upper blood pressure limits may be used as follows:

**Table 8. Relative contraindications for IVT.**

- In the presence of relative contraindications, IVT may be used after an individualized benefit-risk estimation taking into consideration other information on the patient, discussion among specialists, consideration of other factors that influence the cost-benefit ratio of IVT, and discussion with the patient and their legal representative (if possible). Consider direct EVT.
- Important prestroke disability (such as a modified Rankin score \(\geq 4\)) and/or severe comorbidities.
- Subacute clinical ischemic stroke (< 6 weeks, with or without previous IVT/EVT).
- Silent (purely neuroradiological) subacute ischemic stroke.
- History of hypertensive intracerebral hemorrhage (consider IVT if blood pressure now well controlled).
- History of or current subdural hematoma.
- Asymptomatic intracranial aneurysm of 10–25 mm.
- Small intracranial arteriovenous malformations, meningeal fistula, isolated small cavernoma, and intracranial dissection (discuss with neuroradiologist).
- Large number of asymptomatic microbleeds (risk starts to increase from about 10) or extensive chronic nontraumatic superficial hemosiderosis.
- Malignant intracranial tumor in remission.
- Epileptic seizure at symptom onset (we recommend IVT if simultaneous acute ischemia proven by neuroimaging).
- Glycemia \(<2.7\) or \(>22.2\) mmol/l (we recommend IVT if simultaneous acute ischemia proven by neuroimaging).
- Known thrombocytopoenia \(<100,000/\text{mm}^3\) (we recommend not to delay IVT while awaiting laboratory tests, unless in patients with recent hemorrhages).
- Treatment with ticagrelor or prasugrel in combination with other antithrombotics.
- High blood pressure clearly above 185/110 mmHg at time of intended IVT.
- Important surgical intervention within <14 days (discuss with specialist).
- Ophthalmological intervention within <14 days (discuss with ophthalmologist).
- Diseases with increased bleeding risk (discuss with specialist).
- Internal bleeding (gastrointestinal, urological, active metrorrhagia, etc.) or biopsy of an internal organ within <14 days (discuss with specialist).
- Severe body trauma within <6 weeks (discuss with specialist).
- Pregnancy (balance potential effectiveness for the mother with risk for the fetus).

**Table 9. Not contraindications for IVT.**

- Antiplatelet agents in monotherapy or combination of acetylsalicylic acid and clopidogrel.
- Vitamin-K-antagonists if INR \(\leq 1.7\).
- Direct oral anticoagulants if
  - last dose at \(>48\) h (>24 h if normal kidney function);
  - and/or plasma levels below certain thresholds (e.g. anti-Xa \(\leq 100\) ng/ml or anti-IIa \(\leq 100\) mg/ml);
  - and/or administration of a specific antidote\textsuperscript{a} before IVT.
- History of subarachnoid hemorrhage with known and completely treated bleeding source (e.g. completely treated cerebral aneurysm).
- Preceding transient ischemic attack.
- Hygroma (asymptomatic not caused by subdural hematoma).
- Small number of (asymptomatic) microbleeds (e.g. <10) or (asymptomatic) superficial hemosiderosis.
- Asymptomatic intracranial aneurysm <10 mm.
- Benign intracranial tumors.
- Active extracranial oncological disease (if gastrointestinal participation: discuss with specialist).
- Known asymptomatic aortic aneurysm.
- After small surgical interventions in an easily accessible location.
- After cerebral or coronary angiography or percutaneous coronary revascularization (if taking aggressive antithrombotics: cf. contraindications in Tables 7 and 8).
- After lumbar puncture or arterial puncture (even if a few hours ago).
- History of sufficiently treated and controlled internal bleedings (gastrointestinal, urological, etc.)
- Menstruation.

\textsuperscript{a}The efficacy and safety of IVT after Andexxa\textsuperscript{®} in patients on anti-Xa oral anticoagulants is not yet known.

IVT: intravenous thrombolysis; EVT: endovascular therapy.
During and after IVT: 185/110 mmHg (mean arterial pressure (MAP) 135 mmHg);
- After successful EVT resulting in a Thrombolysis in Cerebral Ischemia Score 2b or 3: 160/90 mmHg (MAP 115 mmHg);
- After successful revascularization of a chronic carotid stenosis during EVT: 140/70 mmHg (MAP 95 mmHg).

Worsening symptoms during blood pressure reduction and internistic comorbidities may also be considered in the acute blood pressure management.

We recommend offering craniectomy for ischemic mass effect after IVT for large hemispheric or cerebellar infarcts according to published criteria of the SSS66 (and may also in selected patients above age 6067) after IVT and/or EVT if the clotting status (including fibrinogen levels) is within normal limits. This intervention may also be offered in the case of hemorrhagic transformation after IVT and/or EVT.

**Patient information and consent for acute revascularization treatments**

In an emergency medical situation in Switzerland, a patient’s consent is not required for acute treatments such as IVT and/or EVT if they are offered within scientifically proven indications. If a clear expression of treatment refusal is known (e.g. in a living will) at the time of treatment decision, we recommend that this decision is honored. Refusal of a scientifically proven therapy can only be considered valid if expressed by a patient with sufficient decisional capacity regarding the intended treatment. In noncompetent patients, we recommend that the next of kin is informed concisely about risks and benefits of the planned intervention (including anesthetic management) if this does not lead to significant time loss. Deliberations should be documented in the medical chart. If a legal representative declines a scientifically proven therapy, we recommend that the treating physician follows this advice if it corresponds to a previously expressed wish or the patient’s presumed will.

**Author’s note**

The guidelines were elaborated and approved by the Swiss Stroke Society, the Swiss Neurological Society, the Swiss Society of Neuroradiology, the Swiss Society of Neurosurgery, the Swiss Society for Anesthesiology and Resuscitation, and the Swiss Society of Intensive Care Medicine. The German version of this guideline is published elsewhere and is the legally binding text.

**Acknowledgment**

The author(s) acknowledge Mrs Melanie Price Hirt, PhD, for English language correction and editing of the text translated by the first author.

**Declaration of conflicting interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Funding**

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by Swiss Stroke Society.

**ORCID iD**

Patrik Michel https://orcid.org/0000-0003-4954-7579
Christophe Bonvin https://orcid.org/0000-0002-9058-8105
Susanne Wegener https://orcid.org/0000-0003-4369-7023

**References**

1. Vanacker P, Lambrou D, Eskandari A, et al. Eligibility and predictors for acute revascularization procedures in a stroke center. *Stroke* 2016; 47: 1844–1849.
2. Michel P, Engelter S, Arnold M, et al. Thrombolyse de l’attaque cérébrale ischémique: recommandations actualisées. *Swiss Med Forum* 2009; 9: 892–894.
3. Bonati LB, Bonvin R, Cereda CH, et al. Das schweizerische hirnschlagregister (Swiss Stroke Registry)—ein werkzeug für die qualitätssicherung und forschung. *Swiss Med Forum* 2016; 16: 168–169.
4. Sacks D, Baxter B, Campbell BCV, et al. Multisociety consensus quality improvement revised consensus statement for endovascular therapy of acute ischemic stroke. *Int J Stroke* 2018; 13: 612–632.
5. Emberson J, Lees KR, Lyden P, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet* 2014; 384: 1929–1935.
6. Sandercock P, Wardlaw JM, Lindley RI, et al. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (The Third International Stroke Trial [IST-3]): a randomised controlled trial. *Lancet* 2012; 379: 2352–2363.
7. Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med* 2015; 372: 11–20.
8. Jovin TG, Chamorro A, Cobo E, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med* 2015; 372: 2296–2306.
9. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med* 2015; 372: 1019–1030.
10. Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med* 2015; 372: 2285–2295.
11. Campbell BC, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med* 2015; 372: 1009–1018.

---

Clinical & Translational Neuroscience
12. Martins SO, Mont’Alverne F, Rebelo LC, et al. Thrombectomy for stroke in the public health care system of Brazil. *N Engl J Med* 2020; 382: 2316–2326.

13. Bracard S, Ducrocq X, Mas JL, et al. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THROMBO): a randomised controlled trial. *Lancet Neurol* 2016; 15: 1138–1147.

14. Lapergue B, Blanc R, Gory B, et al. Effect of endovascular contact aspiration vs stent retriever on revascularization in patients with acute ischemic stroke and large vessel occlusion: the aster randomized clinical trial. *J Am Med Assoc* 2017; 318: 443–452.

15. Turk AS 3rd, Siddiqui A, Fifi JT, et al. Aspiration thrombectomy versus stent retriever thrombectomy as first-line approach for large vessel occlusion (COMPASS): A multicentre, randomised, open label, blinded outcome, non-inferiority trial. *Lancet* 2019; 393: 998–1008.

16. Goyal M, Menon BK, van Zwan WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet* 2016; 387: 1723–1731.

17. Saver JL, Goyal M, van der Lught A, et al. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. *J Am Med Assoc* 2016; 316: 1279–1288.

18. Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy during stroke: a meta-analysis. *Stroke* 2018; 49: 1398–1404.

19. Albers GW, Marks MP, Kemp S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging (DEFUSE-3). *N Engl J Med* 2018; 378: 708–718.

20. Ringleb P, Bendszus M, Bluhmki E, et al. Extending the time window for intravenous thrombolysis in acute ischemic stroke using magnetic resonance imaging-based patient selection. *Int J Stroke* 2019; 14: 483–490.

21. Ma H, Campbell BCV, Parsons MW, et al. Thrombectomy guided by perfusion imaging up to 9 hours after onset of stroke. *N Engl J Med* 2019; 380: 1795–1803.

22. Campbell BCV, Ma H, Ringleb PA, et al. Extending thrombolysis to 4.5-9 h and wake-up stroke using perfusion imaging: a systematic review and meta-analysis of individual patient data. *Lancet* 2019; 394: 139–147.

23. Thomalla G, Simonsen CZ, Boutitie F, et al. MRI-guided thrombolysis for stroke with unknown time of onset (WAKE-UP). *N Engl J Med* 2018; 379: 611–622.

24. Anderson CS, Robinson T, Lindley RI, et al. Low-dose versus standard-dose intravenous alteplase in acute ischemic stroke. *N Engl J Med* 2016; 374: 2313–2323.

25. Khatri P, Kleindorfer DO, Devlin T, et al. Effect of alteplase vs aspirin on functional outcome for patients with acute ischemic stroke and minor nondisabling neurologic deficits: the PRISMS randomized clinical trial. *J Am Med Assoc* 2018; 320: 156–166.

26. Schellinger PD, Alexandrov AV, Barreto AD, et al. Combined lysis of thrombus with ultrasound and systemic tissue plasminogen activator for emergent revascularization in acute ischemic stroke (CLOTBUST-ER): design and methodology of a multinational phase 3 trial. *Int J Stroke* 2015; 10: 1141–1148.
39. Powers WI, Rabinstein AA, Ackerson T, et al. 2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2018; 49: e46–e110.

40. Powers WI, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2019; 50: e344–e418.

41. Turc G, Bhogal P, Fischer U, et al. European Stroke Organisation (ESO)—European Society for Minimally Invasive Neurological Therapy (ESMINT) guidelines on mechanical thrombectomy in acute ischaemic strokeendorsed by Stroke Alliance for Europe (SAFE). *Eur Stroke J* 2019; 4: 6–12.

42. Berge E, Whiteley W, Audebert H, et al. European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. *Eur J Stroke*. Epub ahead of print 19 February 2021. DOI: 10.1177/2396987321989865.

43. Michel P, P., Martins S, Pandian, JD, et al. Alteplase (recombinant tissue Plasminogen Activator, rt-PA) for the treatment of acute ischemic stroke. Application for inclusion of a new individual medicine in the WHO Model List of Essential Medicines, https://www.who.int/seleation_medicines/committees/expert/22/applications/s12.5.2_alteplase.pdf?ua=1 (accessed 15 July 2020).

44. World Health Organization G. Model list of essential medicines. 21st list, https://apps.who.int/iris/bitstream/handle/10665/325771/WHO-MVP-EMP-IAU-2019.06-eng.pdf?ua=1 (accessed 15 July 2020).

45. Mathiesen EB and Berge E. Tenecteplase in Wake-up Ischaemic Stroke Trial (TWIST), https://clinicaltrials.gov (accessed 15 July 2020).

46. Parsons M, Spratt N, Bivard A, et al. A randomized trial of tenecteplase versus alteplase for acute ischemic stroke. *N Engl J Med* 2012; 366: 1099–1107.

47. Huang X, Maclsaac R, Thompson JL, et al. Tenecteplase versus alteplase in stroke thrombolysis: an individual patient data meta-analysis of randomized controlled trials. *Int J Stroke* 2016; 11: 534–543.

48. Huang X, Cheripelli BK, Lloyd SM, et al. Alteplase versus tenecteplase for thrombolysis after ischaemic stroke (ATTEST): a phase 2, randomised, open-label, blinded endpoint study. *Lancet Neurol* 2015; 14: 368–376.

49. Lansberg MG, Schrooten M, Bluhmki E, et al. Treatment-specific number needed to treat estimates for tissue plasminogen activator therapy in acute stroke based on shifts over the entire range of the modified Rankin Scale. *Stroke* 2009; 40: 2079–2084.

50. Wahlgren N, Ahmed N, Davalos A, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *Lancet* 2007; 369: 275–282.

51. Myslimi F, Caparros F, Dequatre-Ponchelle N, et al. Orolinguial angioedema during or after thrombolysis for cerebral ischemia. *Stroke* 2016; 47: 1825–1830.

52. Schweizerische Hirnschlaggesellschaft. Stroke units and stroke centers in der Schweiz: Richtlinien und Anforderungssprof. *Swiss Med Forum* 2012; 12: 918–922.

53. Fachorgan und Beschlusssorgan der Interkantonalen Vereinbarung über die hochspezialisierte Medizin. Reevaluation «Komplexe Behandlung von Hirnschlagen». Erläuternder Bericht für die Leistungszuteilung Schlussbericht. https://www.gdk-cds.ch/fileadmin/docs/public/gdk/themen/hsm/HSM-Bereiche/ BT_Stroke_Re1_Zuteil_SchlussBT_Pub_20180206_def_d.pdf18.01.2018:1-38 (accessed 15 July 2020).

54. Pierot L, Jayaraman MV, Szikora I, et al. Standards of practice in acute ischemic stroke intervention: international recommendations. *J Neurointerv Surg* 2018; 10: 1121–1126.

55. NINDS rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *New Engl J Med* 1995; 333: 1581–1587.

56. Hacke W, Bluhmki E, Steiner T, et al. Dichotomized efficacy end points and global end-point analysis applied to the ECASS intention-to-treat data set: post hoc analysis of ECASS I. *Stroke* 1998; 29: 2073–2075.

57. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke (ECASS-3). *New Engl J Med* 2008; 359: 1317–1329.

58. Ma H, Campbell BCV, Parsons MW, et al. Thrombolysis guided by perfusion imaging up to 9 hours after onset of stroke. *N Engl J Med* 2019; 380: 1795–803.

59. Kägi GSD, Niederhäuser J, De Marchis GM, et al. Swiss guidelines for the pre-hospital phase in suspected acute stroke. *Clin Transl Neurosci* (accepted for publication).

60. Gensicke H, Strbian D, Zinkstok SM, et al. Intravenous thrombolysis in patients dependent on the daily help of others before stroke. *Stroke* 2016; 47: 450–456.

61. Bigi S, Dulcey A, Gralla J, et al. Feasibility, safety, and outcome of recanalization treatment in childhood stroke. *Ann Neurol* 2018; 83: 1125–1132.

62. European Society of Urogenital Radiology (ESUR), www.esur.org/esur-guidelines/.

63. Ringleb P, Bendszus M, Bluhmki E, et al. Extending the time window for intravenous thrombolysis in acute ischemic stroke using magnetic resonance imaging-based patient selection. *Int J Stroke* 2019; 14: 483–90.

64. Bernhardt J, Churilov L, Ellery F, et al. Prespecified dose-response analysis for A Very Early Rehabilitation Trial (AVERT). *Neurology* 2016; 86: 2138–2145.

65. Dennis MCV, Kappelle LJ, Pavlovic A, et al. European Stroke Organisation (ESO) guidelines for prophylaxis for venous thromboembolism in immobile patients with acute ischaemic stroke. *Eur Stroke J* 2016; 1: 6–19.

66. Michel P, Arnold M, Hungerbuhler HJ, et al. Decompressive craniectomy for space occupying hemispheric and cerebellar ischemic strokes: Swiss recommendations. *Int J Stroke* 2009; 4: 218–223.

67. Juttler E, Unterberg A, Woitzik J, et al. Hemicraniectomy in older patients with extensive middle-cerebral-artery stroke. *N Engl J Med* 2014; 370: 1091–1100.
### Table 1A. Author affiliations, and potential past or current conflicts of interest regarding IVT and EVT.

| Name                  | Institution                                                                 | Potential conflicts of interest                                                                 |
|-----------------------|----------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Patrik Michel         | Service de Neurologie, Center Hospitalier Universitaire Vaudois, Lausanne  | Boehringer-Ingelheim, Medtronic, PROMISE steering committee (Penumbra). All payments go to the employer and are used for research and education. |
| Michael Diepers       | Neuroradiologische Abteilung, Kantonsspital Aarau                         | RAPID Medical, Microvention. All payments go to the employer and are used for research and education. |
| Pasquale Mordasini    | Universitätsinstitut für Diagnostische und Interventionelle Neuroradiologie, Inselspital Bern | Medtronic. Honoraria for presentations and courses go directly to the employer and are used for research and education. Steering committee of the SWIFT-DIRECT trial. |
| Thilman Schubert      | Diagnostische und Interventionelle Neuroradiologie Klinik für Radiologie und Nuklearmedizin Universitätsspital Basel | None                                                                                             |
| David Bervini         | Universitätsklinik für Neurochirurgie, Inselspital Bern                    | None. Honoraria for presentations and courses go directly to the employer and are used for research and education. |
| Jean-Daniel Rouvé     | Service d’Anesthésiologie, Center Hospitalier Universitaire Vaudois, Lausanne | None                                                                                             |
| Yvan Gasche           | Département d’Anesthésiologie, Pharmacologie, Soins Intensifs, & Urgences, Faculté de Médecine, Université de Genève | None                                                                                             |
| Guido Schwegler       | Neurologie, Spital Limmattal                                               | None. Boehringer-Ingelheim: honoraria for presentations and advisory boards                      |
| Christophe Bonvin     | Service de Neurologie, Hôpital du Valais, Sion                            | Boehringer-Ingelheim, Medtronic: honoraria for presentations and advisory boards                 |
| Krassen Nedeltchev    | Klinik für Neurologie, Kantonsspital Aarau                                | Boehringer-Ingelheim, Medtronic: honoraria for presentations and advisory boards                 |
| Emmanuel Carrera      | Service de Neurologie, Hôpitaux Universitaires de Genève                   | None                                                                                             |
| Georg Kägi            | Klinik für Neurologie, Stroke Center, Kantonsspital St.Gallen              | Boehringer-Ingelheim, Zambon: honoraria for presentations and advisory boards                     |
| Carlo Cereda          | Servizio di Neurologia, Neurocentro della Svizzera Italiana, Ospedale Civico di Lugano | None                                                                                             |
| Thomas Nyffeler       | Neurozentrum, Luzerner Kantonsspital                                       | None                                                                                             |
| Stephan Wetzel        | Neuroradiologie, Hirslanden Klinik, Zürich                                | None                                                                                             |
| Susanne Wegener       | Klinik für Neurologie, Universitätssspital Zürich und Universität Zürich | Boehringer-Ingelheim: for research projects                                                       |
| Henrik Gensicke       | Klinik für Neurologie und Stroke Center, Universitätsklinik für Neurologie, Stroke Center, Kantonsspital Basel und Universität Basel | None                                                                                             |
| Stefan Engelter       | Klinik für Neurologie und Stroke Center, Universitätsklinik für Neurologie, Stroke Center, Kantonsspital Basel und Universität Basel | None                                                                                             |
| Marcel Arnold         | Universitätsklinik für Neurologie, Inselspital Bern                        | Boehringer-Ingelheim, Covidien, and Medtronic: honoraria for presentations and advisory boards   |

IVT: intravenous thrombolysis; EVT: endovascular therapy.