It has been now 20 years since the publication of the National Institute of Neurological Disorders and Stroke (NINDS) tissue-type plasminogen activator (tPA) trial. This randomized controlled trial initiated a paradigm shift in the management of ischemic stroke. Before 1995, it was standard for patients with stroke to languish in emergency departments with no need to perform urgent brain imaging because it was argued that even the fundamental differentiation of intracerebral hemorrhage and ischemic stroke would not change management. The subsequent licensing of tPA provided an impetus to redesign stroke services to allow rapid assessment and delivery of therapy. One of the keys to the success of the NINDS tPA study was the remarkable number of patients who were able to be treated within 90 minutes of stroke symptom onset, a major logistic achievement that remains challenging for routine practice at many centers even today.

Subsequently, there have been 6 further randomized trials comparing tPA and placebo in various time windows 0 to 6 hours from stroke symptom onset (Figure 1; Table). The latest individual patient meta-analysis published in 2014 emphasized the generalized efficacy of tPA in the 0- to 4.5-hour time window, regardless of baseline stroke severity or age, but again confirming a striking relationship with treatment time. No trial has demonstrated benefit beyond 4.5 hours. Although there remain isolated but vocal opponents of the evidence for tPA, the therapy is no longer controversial among clinicians who treat patients with stroke. It is a pillar of every evidence-based acute stroke guideline around the world. In this review, we will examine the origins and implications of various indications and contraindications for tPA and the importance, 20 years on, of not just giving tPA to all eligible patients but optimizing efficient delivery to maximize the reduction in disability.

Evolution of the Evidence and Trial Design

The NINDS trial, actually 2 interlinked trials reported together, demonstrated a clear reduction in disability with 0.9 mg/kg tPA versus placebo 0 to 3 hours after stroke symptom onset and a neutral effect on mortality. The chosen end points of a 24-point reduction in National Institutes of Health Stroke Scale Score (NIHSS) for part A and a global composite end point for part 2 were, in retrospect, not as efficient as the ordinal analysis of modified Rankin Scale (mRS) favored in contemporary trials. There was also some concern about the potential effect of imbalance in baseline stroke severity favoring the tPA group, but this was comprehensively refuted in a subsequent independent reanalysis. The rate of symptomatic intracerebral hemorrhage (sICH) was reported as 6.4% in the tPA group. The images of these hemorrhages are published, and with the benefit of hindsight, in many cases, the observed clinical deterioration more likely related to the large ischemic stroke than the small region of bleeding. The definition of sICH has evolved over the subsequent 2 decades to require a substantial parenchymal hematoma (blood clot with mass effect occupying >30% of the infarcted tissue) and clinically significant, temporally related deterioration (≥24-point increase in NIHSS within 36 hours). Differences in definitions are marked, as the rate of sICH can vary between 2% and 9% in the same patients, depending on the precise criteria.

The subsequent trials, published between 1995 and 2002, were European Cooperative Acute Stroke Study (ECASS), ECASS II, and Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) A/B. These tested a 0- to 6-hour treatment window and, although technically neutral on the various primary end points chosen, demonstrated clear trends in favor of tPA that were highly significant within 4.5 hours in the first individual patient data meta-analysis. None included a large number of sub-3-hour patients. However, the 0- to 3-hour patients in all subsequent trials have continued to show a magnitude of benefit consistent with the NINDS tPA trial (Table). One of the keys to success in the NINDS trial was a unique recruitment...
rule requiring a sub–90-minute treatment before a 90- to 180-minute patient could be randomized, dramatically enriching participants in the 0- to 90-minute window.

The next stroke thrombolysis trial was ECASS III, designed at the request of European regulators to confirm the benefit between 3.0 and 4.5 hours suggested in meta-analysis of the previous trials. The success of ECASS III, albeit with an important increase in the number need to treat (NNT), and an updated meta-analysis again supported a 0- to 4.5-hour treatment window.16 The IST37 trial ran for over a decade and was based on the uncertainty principle, that is, doctors randomized patients when unsure whether tPA would be of benefit. The areas of uncertainty evolved significantly during the prolonged recruitment period which somewhat complicates interpretation. However, IST3 clearly established that even these patients with a perceived marginal risk-benefit benefited from thrombolysis within 3 hours. Older patients were well represented and had a higher rate of poor outcome (as with any illness). However, the treatment benefit of tPA was at least as great in those aged 80 as in younger patients. Hence, there is no justification for exclusion of otherwise healthy elderly patients from thrombolysis. EPITHET was a smaller phase 2 randomized controlled trial of 100 patients, testing the role of magnetic resonance imaging perfusion–diffusion mismatch in select patients.29 The presence of a hyperdense artery indicates acute thrombus and improves diagnostic confidence.30 Although longer hyperdense thrombi are associated with reduced reperfusion with tPA,30 this is less absolute than initially reported.31

NNTs have been calculated, which vary based on the outcome used (eg, mRS, 0–1; mRS 0–2; or a shift of ≥1 category on the mRS) and the time window examined. A separate number needed to harm has been suggested by some, although this is already factored in to an ordinal NNT and so remains a controversial concept. Within 3 hours, the NNT for an extra mRS 0 to 1 outcome is 8 (or 4 if considering shift in mRS by ≥1 category). In the 3- to 4.5-hour time window, the NNT for mRS 0 to 1 increases to 14 (and 6–7 for shift by ≥1 category).

**What Is Truly a Contraindication to tPA?**

Given the powerful reduction in disability achieved by tPA across such a broad range of patients, it is important to critically analyze reasons for withholding tPA to understand their origins and ensure they withstand scrutiny. Several studies have demonstrated the safety of tPA in patients with ≥1 standard contraindications, but clearly, some factors are more important than others in determining risk.25–27

Table I in the online-only Data Supplement compiles absolute and relative contraindications listed in the major trials, licences, and guidelines from around the world, stratified by origins and ensure they withstand scrutiny. Several studies have demonstrated the safety of tPA in patients with ≥1 standard contraindications, but clearly, some factors are more important than others in determining risk.25–27

**Stroke Severity and Futile Treatment**

The aim of reducing futile treatment may be reasonable to improve power in clinical trials, but given the potential benefits, a high specificity for poor outcome should be required for any exclusion criterion. NIHSS≥25 is one such criterion. Although many patients will have poor outcome, subgroup analysis of the available trial data indicates a persisting treatment effect. At the other end of the spectrum, mild or rapidly improving patients with stroke are a high-risk group as up to a third deemed too mild to treat do not return to independent function.28 Although all the trials discussed were based purely on noncontrast computed tomographic (CT) imaging criteria, the use of additional imaging may well help assess the risk of deterioration (eg, presence of persistent vessel occlusion on CT angiography or perfusion lesion) and provide the necessary confidence to treat such patients.29 The presence of a hyperdense artery indicates acute thrombus and improves diagnostic confidence. Although longer hyperdense thrombi are associated with reduced reperfusion with tPA,30 this is less absolute than initially reported.31
Stroke Mimics

Factors designed to reduce the rate of stroke mimics exposed to treatment were incorporated in trial designs for obvious reasons but rarely apply in current practice—particularly with the ready availability of advanced imaging which can help in differentiating stroke from migraine and seizure with Todd’s paresis through demonstration of a relevant vessel occlusion or perfusion lesion.

Hemorrhage Risk

Reducing the risk of hemorrhagic complications would be an entirely valid basis to exclude patients, provided the risk outweighed potential benefit. The overall rate of sICH using the SITS definition in the latest tPA meta-analysis was 2.7%. However, there was a clear increase in sICH as stroke severity increased: 0.9% when NIHSS was 0–4 to 6.8% for NIHSS>22. The interpretation in the meta-analysis was that the proportional increase was not significantly different across the range of stroke severity, but this is confounded by low and rather random rates of sICH in the placebo group. As acknowledged in that article, the absolute risk does significantly increase with increasing severity—a simple test for trend in proportion is both statistically ($P<0.001$) and, we would argue, clinically significant when weighing the decision to treat as the risk remains proportional to the demonstrated benefit across the severity spectrum.

One factor related to sICH risk that is a universal exclusion in current guidelines is CT hypodensity in an area equivalent to >1/3 of the middle cerebral artery territory. The finding of established hypodensity should prompt confirmation of the last known well time as it is rare within 4.5 hours. However, subtle loss of grey-white differentiation (which also represents irreversible injury) is not listed as a contraindication in current guidelines as it has not been consistently associated with hemorrhage risk and treatment benefit appears preserved. Although some studies have indicated that patients with a large irreversibly injured ischemic core on perfusion imaging have a high probability of poor outcome, there is currently insufficient evidence to exclude patients from thrombolysis on this basis.

Previous intracerebral hemorrhage is generally regarded as a contraindication but some discretion is required, particularly

### Table. Randomized Trials of Alteplase vs Placebo

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Time Window</th>
<th>Mean Age (SD)</th>
<th>Number Age&gt;80</th>
<th>Median NIHSS</th>
<th>Prespecified Primary Outcome</th>
<th>mRS, 0–1 Overall</th>
<th>mRS, 0–2 Overall</th>
<th>Fatal sICH With Alteplase†</th>
</tr>
</thead>
<tbody>
<tr>
<td>NINDS A</td>
<td>291</td>
<td>0–3</td>
<td>67 (11)</td>
<td>54</td>
<td>14</td>
<td>≥4-point reduction in NIHSS or reaching 0 at 24 h</td>
<td>43% vs 27%; OR, 2.0 ($CI_{95}$, 1.5–2.8)‡</td>
<td>50% vs 38%; OR, 1.6 ($CI_{95}$, 1.2–2.2)‡</td>
<td>2.9%</td>
</tr>
<tr>
<td>NINDS B</td>
<td>333</td>
<td>0–3</td>
<td>68 (13)</td>
<td>14.5</td>
<td>11</td>
<td>Composite mRS, Barthel, NIHSS, GOS</td>
<td>36% vs 29%; OR, 1.3 ($CI_{95}$, 1.0–1.9)</td>
<td>45% vs 40%; OR, 1.3 ($CI_{95}$, 0.9–1.7)</td>
<td>6.1%</td>
</tr>
<tr>
<td>ECASS*</td>
<td>620</td>
<td>0–6</td>
<td>65 (12)</td>
<td>0</td>
<td>12.5</td>
<td>Barthel, median mRS</td>
<td>40% vs 24%; OR, 2.2 ($CI_{95}$, 0.9–5.7)</td>
<td>43% vs 34%; OR, 1.4 ($CI_{95}$, 0.6–3.4)</td>
<td>4.4%</td>
</tr>
<tr>
<td>0–3-h subgroup</td>
<td>87</td>
<td>0–3</td>
<td>68</td>
<td>0</td>
<td>11</td>
<td>mRS, 0–1</td>
<td>40% vs 37%; OR, 1.2 ($CI_{95}$, 0.9–1.6)</td>
<td>54% vs 46%; OR, 1.4 ($CI_{95}$, 1.1–1.8)‡</td>
<td>4.4%</td>
</tr>
<tr>
<td>ECASS II</td>
<td>800</td>
<td>0–6</td>
<td>68</td>
<td>0</td>
<td>11</td>
<td>mRS, 0–1</td>
<td>42% vs 38%; OR, 1.2 ($CI_{95}$, 0.6–2.3)</td>
<td>52% vs 43%; OR, 1.4 ($CI_{95}$, 0.8–2.7)</td>
<td>4.4%</td>
</tr>
<tr>
<td>0–3-h subgroup</td>
<td>158</td>
<td>0–3</td>
<td>68</td>
<td>0</td>
<td>11</td>
<td>mRS, 0–1</td>
<td>48% vs 37%; OR, 1.6 ($CI_{95}$, 0.5–4.5)</td>
<td>57% vs 50%; OR, 1.3 ($CI_{95}$, 0.5–3.7)</td>
<td>4.2%</td>
</tr>
<tr>
<td>ATLANTIS A/B, 0–3 h</td>
<td>61</td>
<td>0–3</td>
<td>66 (11)</td>
<td>0</td>
<td>10</td>
<td>mRS, 0–1</td>
<td>41% vs 43%; OR, 0.9 ($CI_{95}$, 0.7–1.3)</td>
<td>46% vs 49%; OR, 0.9 ($CI_{95}$, 0.6–1.2)</td>
<td>0.7%</td>
</tr>
<tr>
<td>ATLANTIS A/B, 3–6 h</td>
<td>691</td>
<td>3–6</td>
<td>65 (12)</td>
<td>0</td>
<td>9.5</td>
<td>mRS, 0–1</td>
<td>52% vs 45%; OR, 1.3 ($CI_{95}$, 1.0–1.8)‡</td>
<td>67% vs 62%; OR, 1.2 ($CI_{95}$, 0.9–1.7)</td>
<td>0.7%</td>
</tr>
<tr>
<td>ECASS III</td>
<td>821</td>
<td>3–4.5</td>
<td>72 (13)</td>
<td>25</td>
<td>13</td>
<td>Infarct growth</td>
<td>35% vs 24%; OR, 1.6 ($CI_{95}$, 0.7–3.8)</td>
<td>67% vs 62%; OR, 1.2 ($CI_{95}$, 0.6–2.7)</td>
<td>7.7%</td>
</tr>
<tr>
<td>EPITHET</td>
<td>100</td>
<td>3–6</td>
<td>81§</td>
<td>1696</td>
<td>11</td>
<td>mRS, 0–2</td>
<td>24% vs 21%; OR, 1.2 ($CI_{95}$, 1.0–1.4)</td>
<td>37% vs 35%; OR, 1.1 ($CI_{95}$, 0.9–1.2)</td>
<td>3.6%</td>
</tr>
<tr>
<td>IST3</td>
<td>3035</td>
<td>0–6</td>
<td>81§</td>
<td>1696</td>
<td>11</td>
<td>mRS, 0–2</td>
<td>19% vs 15%; OR, 1.4 ($CI_{95}$, 0.95–1.9)</td>
<td>31% vs 23%; OR, 1.5 ($CI_{95}$, 1.1–2.0)‡</td>
<td>3.6%</td>
</tr>
</tbody>
</table>

Data extracted from Cochrane systematic review. ATLANTIS indicates Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke; CI, confidence interval; ECASS, European Cooperative Acute Stroke Study; EPITHET, Echoplanar Imaging Thrombolytic Evaluation; GOS, Glasgow outcomes score; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale Score; NINDS, National Institute of Neurological Disorders and Stroke; OR, odds ratio; and sICH, symptomatic intracerebral hemorrhage.

*Alteplase dose 1.1 mg/kg; all other trials 0.9 mg/kg.
†Fatal sICH used as definition of sICH varied markedly between trials.
‡$P<0.05$.
§Only median age reported.
if bleeding occurred in the context of trauma many years earlier. Similarly, commonly listed exclusions for unruptured vascular malformations require discretion, particularly considering the number of patients with unrecognized incidental aneurysms who must have received tPA without incident in the years preceding frequent use of CT angiography.

A recent and enlightened shift in the American Heart Association guidelines has been the recognition that systemic bleeding risk factors, such as recent surgery or gastrointestinal bleeding, are not absolute contraindications and require careful consideration of risk and benefit. The 2-week exclusion after surgery and 3-week exclusion after gastrointestinal/genitourinary tract bleeding were arbitrary intervals adopted from the NINDS tPA trial entry criteria. Given current knowledge of the clear-cut benefits of tPA in reducing disability, a more flexible approach is justified.

Coagulation abnormalities are clearly a concern when administering thrombolysis. However, current guidelines have removed the requirement for coagulation studies and platelet count before tPA unless there is clinical suspicion of an abnormality. This greatly expedites therapy and seems safe. Previous warfarin usage is not a contraindication provided the international normalized ratio is <1.7 based on observational studies. However, the current American Heart Association recommendation for the use of tPA in patients treated with the non–vitamin K oral anticoagulants excludes anyone with abnormalities in the specific coagulation parameters relevant to the particular agent. This reflects conservatism in the absence of experience with these new agents, and no doubt this recommendation will be modified with the passage of time.

Blood pressure >185/110 mmHg, an arbitrary threshold taken from trial exclusion criteria, is associated with worse outcome and increased hemorrhage. Whether this is causative or confounded by poor collaterals, which are associated with both increased blood pressure and poor outcome, is uncertain.

Other Considerations
Some items in product labeling, for example, a past history of previous stroke and diabetes mellitus in the European label have arisen because of unusual post hoc regulatory analyses that have limited clinical validity. Similarly, the addition of extra restrictions to patients in the 3- to 4.5-hour window based on trial inclusion criterion is not necessarily best clinical practice.

What Metrics Should We Use to Judge Our Performance?
The total proportion of patients treated with tPA worldwide remains much lower than is achievable in individual, well organized centers which can treat up to one third of all ischemic stroke and ≈50% of those presenting within 4.5 hours. This implementation problem remains a major challenge and requires a multifaceted approach with telemedicine, engagement of ambulance services, and nonstroke physicians likely to be important components.

Although much of the emphasis during the past 20 years has rightly been on improving the proportion of patients with ischemic stroke treated with tPA, to truly maximize the benefit of thrombolysis, we need to not just give tPA but give it fast. The time is brain mantra has been known for many years based on progressive recruitment of potentially salvageable ischemic penumbra into the irreversibly injured ischemic core. However, recent data have suggested that increased elapsed time from stroke symptom onset may also reduce the ability of tPA to achieve reperfusion.

At a whole system level, our aim must be to reduce onset to reperfusion time. Individual hospitals have control over door to needle time (DNT). Literature describing system changes that reduce DNT has proliferated. The key features are use of prehospital notification to alert the stroke team to meet the patient at the hospital door and proceed direct to CT brain as the rate-limiting step in determining tPA eligibility. The most effective systems have senior staff directly involved in the assessment of the patient in the emergency department with well-rehearsed decision-making pathways.

Efficiencies need to be sought in every step of the process and multiple aspects of care need to run in parallel (Figure 2). Even a 15-minute reduction in DNT can significantly reduce in-hospital mortality, sICH, and discharge to institutional care, and the NNT to achieve an excellent outcome increases by 1 with every 20 minutes elapsed. Routine DNT <20 min is possible, and treatment of mimics or complications are not an inherent accompaniment of faster treatment.

Future Directions
There is still a great deal of room for systems improvement to maximize the benefits of tPA, simply by giving it to more people and giving it faster. However, as DNT is progressively reduced in many centers, prehospital factors and community recognition are contributing proportionately even more to the onset to needle. Public education to recognize stroke and call emergency services immediately and paramedic training to minimize transport delays are critical. Some health systems are exploring CT-in-ambulance technology for diagnosis and prehospital lysis. The 4.5 hour treatment window remains a limitation, particularly for wake-up onset stroke patients. Trials examining more advanced imaging selection in the
extended time window are ongoing (Figure 1).41–43 Trials in mild stroke are also ongoing (eg, A Phase IIIB, Double-Blind, Multicenter Study to Evaluate the Efficacy and Safety of Alteplase in Patients With Mild Stroke: Rapidly Improving Symptoms and Neurologic Deficits [PRISMS] clinicaltrials.gov NCT02072226). This review has focused on tPA. However, the aim of treatment is, of course, to achieve fast and complete reperfusion. Ongoing trials are testing whether alternative lytic agents such as tenecteplase may surpass the reperfusion efficacy of tPA. The recent endovascular therapy trials provide evidence that newer stent retriever devices improve reperfusion and functional outcomes versus tPA alone.44–46 However, tPA in all eligible patients remains the basis on which the efficacy of endovascular therapy has been demonstrated. We should harness the excitement associated with these new treatments to ensure we have solid foundations of stroke unit care and streamlined intravenous thrombolysis on which to build the more resource-intensive endovascular therapies.

Conclusions

The default position for any patient with ischemic stroke presenting within 4.5 hours of stroke symptom onset should be that they will receive tPA unless there is a good reason not to administer the therapy. Potential contraindications need to be carefully weighed against the benefits of reperfusion and the timely availability of alternatives, such as endovascular therapy. Major initiatives to minimize delay to needle times have shown that faster treatment is possible without compromising safety and outcomes. Future measures to potentially administer thrombolysis prehospital and more closely integrate endovascular device and intravenous lytic therapy hold great promise to further improve ischemic stroke outcomes.

Sources of Funding

Dr Campbell was supported by an early career fellowship from the National Health and Medical Research Council of Australia (1035688) cofunded by the National Heart Foundation of Australia and the National Stroke Foundation of Australia.

Disclosures

Dr Meretoja has received honoraria and travel support (modest) from Siemens. Dr Davis has received honoraria and travel support (modest) from Boehringer Ingelheim, BMS-Pfizer, Allergan, EVER Neuropharma, and Covidien(Medtronic) and receives research support from the National Health and Medical Research Council of Australia and the Royal Melbourne Hospital Neuroscience Foundation. The other authors report no conflicts.

References


Key Words: cerebral infarction ▫ computerized tomography ▫ National Institute of Neurological Disorders and Stroke ▫ numbers need to treat ▫ stroke ▫ tissue-type plasminogen activator
Twenty-Year History of the Evolution of Stroke Thrombolysis With Intravenous Alteplase to Reduce Long-Term Disability
Bruce C.V. Campbell, Atte Meretoja, Geoffrey A. Donnan and Stephen M. Davis

Stroke. 2015;46:2341-2346; originally published online July 7, 2015;
doi: 10.1161/STROKEAHA.114.007564
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/46/8/2341

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2015/07/09/STROKEAHA.114.007564.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/
## SUPPLEMENTAL Table I. Evolution of tPA contraindications in trials, licenses, and guidelines

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time from onset to treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;3h</td>
<td>&gt;6h</td>
<td>&gt;6h</td>
<td>&lt;3h or &gt;5h in B, &gt;6h in A</td>
<td>&lt;3h or &gt;4½h</td>
<td>&gt;6h</td>
<td>&gt;3h</td>
<td>&gt;3h</td>
<td>&gt;3h</td>
<td>&gt;4.5h</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18 and &gt;80</td>
<td>&lt;18 and &gt;80</td>
<td>&lt;18 and &gt;80</td>
<td>&lt;18 and &gt;80</td>
<td>&lt;18 (&gt;75)</td>
<td>&lt;18 and &gt;80</td>
<td>&lt;18 [and &gt;80 only if 3-4.5 hours]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SYMPTOM SEVERITY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor neurological deficit</td>
<td>x</td>
<td>50-58 on SSS</td>
<td>51-58 on SSS</td>
<td>NIHSS &lt;4 + normal speech/visual fields</td>
<td>x</td>
<td>(x)</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapidly improving symptoms</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>(x)</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms lasted at least 30 minutes</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Coma, severe stupor, global aphasia, or dense hemiplegia with fixed eye deviation</td>
<td>Coma, severe obtundation, complete hemiplegia, or fixed eye deviation</td>
<td>NIHSS &gt;25</td>
<td>(NIHSS &gt;22)</td>
<td>NIHSS &gt;25</td>
<td>Caution with major deficits</td>
</tr>
<tr>
<td>Presumed vertebrobasilar stroke</td>
<td>x, including isolated hemianopia or isolated ataxia</td>
<td>x, including isolated hemianopia or isolated ataxia</td>
<td>x, including isolated hemianopia or isolated ataxia</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td><strong>POTENTIAL MIMICS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizure at onset</td>
<td>x</td>
<td>Within previous 6 h</td>
<td>Within previous 6 m</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>Unlesse impairments due to stroke and not postictal</td>
<td>(x)</td>
<td></td>
</tr>
<tr>
<td>History of seizure disorder</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;2.7 mmol/L</td>
<td>&lt;2.8 mmol/L</td>
<td>&lt;2.8 mmol/L</td>
<td>&lt;2.8 mmol/L</td>
<td>&lt;3.0 mmol/L</td>
<td>&lt;2.7 mmol/L</td>
<td>&lt;2.7 mmol/L</td>
<td>&lt;2.7 mmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suspected SAH despite</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>normal imaging</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structural lesion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>potentially mimicking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>stroke, e.g. tumor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BLEEDING RISK</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICH on CT</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic changes on CT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hypodensity/sulcal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>effacement &gt;1/3 of MCA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypodensity or swelling</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1/3 of MCA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypodensity, loss of</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>grey-white differentiation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>or sulcal effacement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1/3 of MCA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>stroke involving</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1/3 of MCA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Severe stroke on imaging)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe stroke on MCA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypodensity &gt;1/3 of MCA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypodensity &gt;1/3 of MCA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of intracranial</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hemorrhage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial neoplasm, AVM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>or aneurysm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any AVM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any aneurysm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic neoplasms with</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>increased bleeding risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oesophageal varices</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic aneurysm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacterial endocarditis,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pericarditis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulcerative gastrointestinal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>x (inc colitis)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3m</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3m</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3m</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3m</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjuncts for Platelet Anticoagulants</td>
<td>Adjuncts for Oral Anticoagulants</td>
<td>Adjuncts for Heparin Anticoagulants</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>---------------------------------</td>
<td>-----------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>With ventricular thrombus/aneurysm</td>
<td>With ventricular thrombus/aneurysm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic retinopathy</td>
<td>x</td>
<td>(x)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septic thrombophlebitis or occluded IV cannula at seriously infected site</td>
<td>(x)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location</td>
<td>(x)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Hemostasis</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic diathesis</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets &lt;100</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Packed cell volume &lt;25%</td>
<td>x</td>
<td>(x)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneously elevated INR</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated APTT alone</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral anticoagulation</td>
<td>Any</td>
<td>Any</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heparin with elevated APTT</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NOAC use with abnormal coagulation tests</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe liver disease</td>
<td>x</td>
<td>(x)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe renal disease</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Recent Surgery/Trauma/Bleeding</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major surgery</td>
<td>&lt;14d</td>
<td>&lt;30d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial or spinal surgery</td>
<td>&lt;3m</td>
<td>Any history</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Puncture of a non-compressible blood-vessel</td>
<td>&lt;7d</td>
<td>&lt;10d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organ biopsy</td>
<td>&lt;1m</td>
<td>&lt;30d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Traumatic external heart massage</td>
<td>&lt;10d</td>
<td>&lt;10d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>&lt;3m</td>
<td>&lt;3m</td>
<td>&lt;14d</td>
<td>&lt;3m</td>
<td>&lt;3m</td>
<td>&lt;3m</td>
<td>&lt;3m (any head trauma)</td>
<td>&lt;3m</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-----</td>
<td>-----</td>
<td>------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>------------------------</td>
<td>-----</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious head trauma</td>
<td></td>
<td></td>
<td>&lt;3m</td>
<td></td>
<td></td>
<td></td>
<td>&lt;3m</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Significant trauma</td>
<td></td>
<td>&lt;1m</td>
<td>&lt;30d</td>
<td>&lt;3m</td>
<td>&lt;21d (recent)</td>
<td>&lt;3m</td>
<td>Acute (&lt;14d)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage</td>
<td>&lt;21d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;3m</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract hemorrhage</td>
<td>&lt;21d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;21d (&lt;21d)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent or ongoing severe bleeding</td>
<td>&lt;30d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;30d (active internal)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstetrics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current childbearing potential</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>(x)</td>
<td>(x)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstetric delivery</td>
<td>&lt;30d</td>
<td>&lt;30d</td>
<td>&lt;10d</td>
<td>(recent)</td>
<td>&lt;10d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast feeding</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OTHERS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous stroke and diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x only if 3-4.5h</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No consent from patient or family</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight &gt;100 kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other significant disease with short life expectancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient dependent prior to stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous disabling stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High likelihood of left heart thrombus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(x)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(*)=relative contraindication, special diligence or warning, the risks may be increased and should be weighed against the anticipated benefits.