ACUTE ISCHAEMIC STROKE PUBLICATION ALERT NEWSLETTER (04/2021)

Please be aware that the purpose of this Newsletter is to make you familiar with the most recent scientific publications, and you must keep in mind that all aspects may not be covered by the label. Please always refer to the current prescribing information as in force in your country.

The recent publication of the updated European Stroke Organisation guidelines on intravenous thrombolysis (IVT) for acute ischaemic stroke (AIS) provide evidence-based recommendations to aid clinical decision-making in this setting. The guidelines strengthen the cornerstone position of IVT for AIS within the approved time window of 4.5 hours, with no upper age limitation. Guidance is also provided on IVT treatment outside the 4.5-hour time window and in patients eligible for endovascular thrombectomy (EVT), and the use of tenecteplase.

In this issue of the Acute Ischaemic Stroke Publication Alert Newsletter, results are reported from a registry-based study on long-term follow-up of patients analysed according to time to IVT. A retrospective analysis of the EXTEND trial is summarized, which investigated whether IVT administration within 4.5–9 hours versus placebo increases the risk of distal clot migration. The question of whether to replace alteplase with tenecteplase ahead of regulatory approval is discussed in a *Stroke* Editorial, which highlights potential consequences of such a shift in clinical practice. Finally, to address the lack of evidence-based treatment strategies for central retinal artery occlusion (CRAO), management of CRAO is outlined in a scientific statement from the American Heart Association (AHA).

The list of presented publications is as follows:

1. Yafasova A *et al*. Time to thrombolysis and long-term outcomes in patients with acute ischemic stroke: a nationwide study. *Stroke* 2021.
2. Lim JC *et al*. Does intravenous thrombolysis within 4.5 to 9 hours increase clot migration leading to endovascular inaccessibility? *Stroke* 2021.
3. Muir KW. Should tenecteplase replace alteplase for acute thrombolysis? *Stroke* 2021.
4. Mac Grory B *et al*; American Heart Association Stroke Council; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Hypertension; and Council on Peripheral Vascular Disease. Management of central retinal artery occlusion: a scientific statement from the American Heart Association. *Stroke* 2021.

1. TO WHAT EXTENT DOES INCREASED TIME TO THROMBOLYSIS TREATMENT AFFECT LONG-TERM PATIENT OUTCOMES?

SUMMARY

- A Danish, nationwide, registry-based study examined long-term outcomes according to time to thrombolysis in patients with first-time AIS
- Time to thrombolysis >90 min vs <90 min was significantly associated with a higher rate of the composite outcome (post-discharge death and recurrent ischaemic stroke); this levelled off after 138 min
- Continuing focus on decreasing the time delay from symptom onset to thrombolysis is warranted

It is well-established that increasing treatment delay reduces the benefits of IV recombinant tissue plasminogen activator (rt-PA) in patients with AIS. However, most randomized controlled trials (RCT) and real-world studies have focused only on short-term outcomes. Because post-stroke survival is improving in the developed world, data on time to thrombolysis and subsequent long-term outcomes are warranted. Such studies could provide further insight into the importance of time to treatment and contribute to evidence for structuring emergency care settings to minimize system delay. In addition, further factors could be identified that are associated with long-term outcomes, thus facilitating the identification of potentially at-risk patients.

The authors of this paper conducted a nationwide registry-based study to examine the long-term rate of post-discharge death and recurrent ischaemic stroke. Data were analysed according to time to thrombolysis in patients with first-time AIS treated with IVT.[1]

Study details

- The study population included all Danish individuals (N=6252) admitted with ischaemic stroke and treated with IVT between 1 January 2011 and 30 June 2017
    - Patients were excluded if they received thrombolysis >270 min after symptom onset, had a history of previous stroke, or died during admission
- The primary outcome was a composite of post-discharge, all-cause mortality and recurrent ischaemic stroke; secondary outcomes were post-discharge death and recurrent ischaemic stroke
- Patients were followed up for a median of 2.5 years for the primary outcome
- The median age of the study population was 69 years (25th–75th percentile 60–78), and 60% were men. The median National Institute of Health Stroke Scale (NIHSS) score at presentation was 5

Study results

- The median time to thrombolysis was 138 min (25–75th percentile: 101–185)
- Compared with the 91–180- and 181–270-min groups, patients in the 0–90-min group were characterized by a lower prevalence of ischaemic heart disease, diabetes, and use of antiplatelets before admission; a higher prevalence of atrial fibrillation (AF); a higher NIHSS at presentation; and were more often concomitantly treated with EVT
- Time to thrombolysis in the 91–180- and 181–270-min groups was significantly associated with a higher rate of the composite outcome compared with time to thrombolysis between 0 and 90 min (**Figure 1**)
    - HR: 1.25 (95% CI: 1.06–1.48) and 1.35 (95% CI: 1.12–1.61), respectively
- In a restricted cubic spline analysis, the rate of the composite outcome increased with increasing time to thrombolysis and levelled off after 138 min (**Figure 2**)
- Time to thrombolysis of 91–180 and 181–270 min compared with 0–90 min was significantly associated with:
    - higher post-discharge death rate (HR: 1.27 [95% CI: 1.03–1.56] and 1.38 [95% CI: 1.10–1.73], respectively)
    - higher rate of recurrent ischaemic stroke (HR: 1.16 [95% CI: 0.90–1.48] and 1.13 [95% CI: 0.86–1.49], respectively)
- Increasing stroke severity, advanced age, male sex, living alone, and a medical history of heart failure, AF, hypertension, cancer, chronic obstructive pulmonary disease, or carotid disease were associated with a higher rate of the composite outcome, while EVT was associated with a lower rate

Figure 1. Unadjusted absolute risks of the composite outcome (post-discharge death and recurrent ischaemic stroke) according to time to thrombolysis

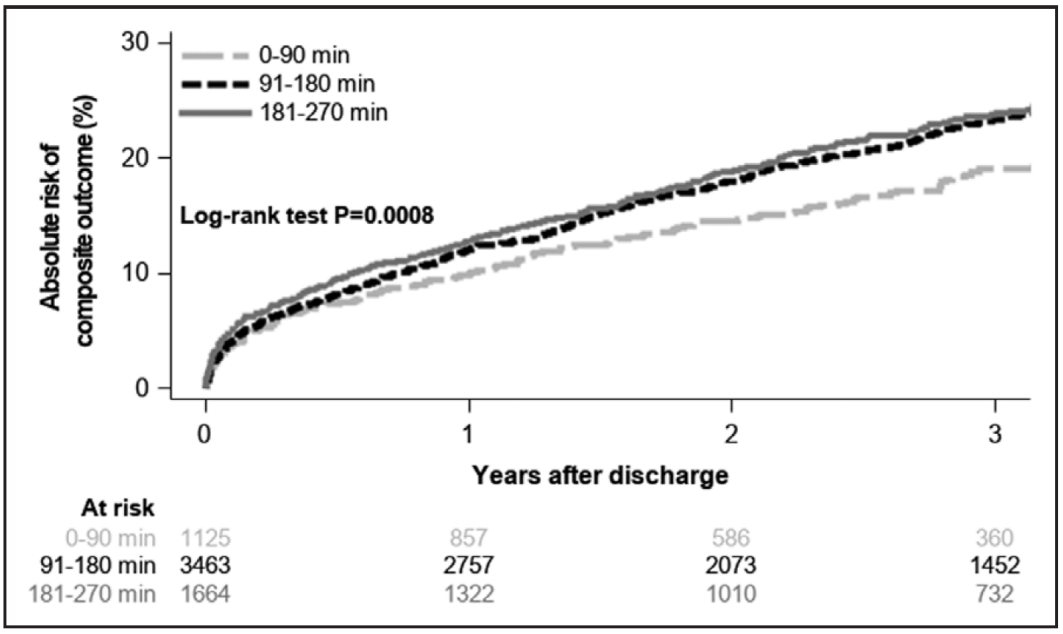
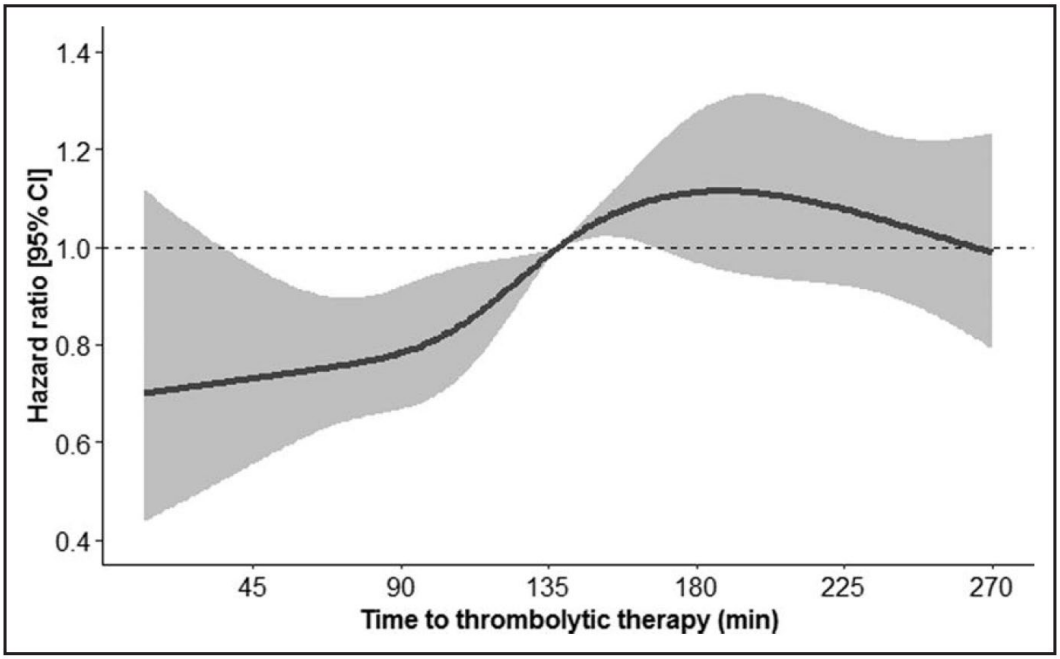


Figure 2. Restricted cubic spline of the association between the composite outcome (post-discharge death and recurrent ischaemic stroke) and time to thrombolysis



The model was adjusted for sex, age, stroke severity, and EVT. The median time to thrombolysis (138 min) served as the reference. Grey lines indicate 95% CIs

Study limitations

- This study is based on the Danish healthcare system, a primarily tax-financed universal healthcare system with free access for all residents. Caution is needed when translating these findings to countries with different welfare systems
- Despite multivariable adjustment for several potential confounders, the possibility of residual confounding cannot be excluded due to the observational nature of the study
- Information on functional independence measures, including modified Rankin Scale, was not available

Study conclusions

- Time to thrombolysis >90 min was associated with a higher long-term rate of a composite of post-discharge death and recurrent ischaemic stroke, as well as higher long-term all-cause mortality compared with thrombolysis <90 min
- The increasing rate of the composite outcome with increasing time to thrombolysis levelled off after 138 min

"Continuing focus on decreasing the time delay from symptom onset to thrombolysis is warranted. This includes efforts to raise public awareness of stroke symptoms and immediate contact to emergency medical services to ensure fast hospital presentation and administration of thrombolytic and/or endovascular therapy in eligible patients."[1]

2. DOES IVT WITHIN 4.5 TO 9 HOURS INCREASE CLOT MIGRATION LEADING TO EVT INACCESSIBILITY?

SUMMARY

- A retrospective analysis of the EXTEND trial investigated the association between IVT, received between 4.5 and 9.0 h after stroke onset, and clot migration leading to irretrievability
- There was no significant difference in the incidence of clot migration leading to inaccessibility (change from baseline retrievable to non-retrievable clot location on follow-up imaging) between placebo and IVT groups
- The use of IVT before EVT is further supported

In patients presenting with AIS caused by large vessel occlusion (LVO), current treatment guidelines recommend bridging IVT for all patients receiving EVT within the 4.5-hour time window. EVT is also recommended in selected patients up to 24 hours post-onset of symptoms, but it remains unclear whether IVT pretreatment should be administered in this setting.

Distal clot migration, a potential issue following IVT administration, may prevent successful thrombectomy. To investigate the association between IVT and clot migration leading to clot irretrievability, the authors of this study performed a retrospective analysis of the EXTEND trial, a prospective, randomized, double-blinded, placebo-controlled, multicentre trial of patients treated with IVT between 4.5 and 9.0 hours after stroke onset.[2]

Eligible patients presenting with AIS were randomly assigned to receive IVT (alteplase, 0.9 mg/kg) or matching placebo. Baseline imaging (computed tomography or magnetic resonance angiogram) was performed before randomization, and follow-up imaging was performed 12–24 hours later to assess vessel recanalization (median time to follow-up, 22 hours; interquartile range, 17–25 hours). Clot migration leading to inaccessibility was defined as a change from retrievable to non-retrievable clot location between baseline and follow-up imaging. Clot resolution was defined as absence of clot on follow-up imaging.

Out of 220 patients (n=109 in the placebo group and n=111 in the IVT group), 77 (68.8%) in the placebo group and 69 (61.0%; *p*=0.436) in the IVT group had retrievable clot on baseline imaging. Clot resolution occurred in 31 patients (28.4%) in the placebo group and 56 patients (50.5%; *p*=0.003) in the IVT group.

No significant difference was observed in the incidence of clot migration leading to inaccessibility, which occurred in 21 (19.3%) and 16 patients (14.4%) in the placebo and IVT groups, respectively (odds ratio: 0.70; 95% CI: 0.35–1.44]; *p*=0.336).

This study has limitations. Only clot migration from a retrievable to non-retrievable location was assessed and so the true clot migration frequency could be higher. There was a 12- to 24-hour time frame between baseline and follow-up imaging, unlike prior studies that compared baseline imaging to digital subtraction angiography performed immediately after IVT. Therefore, clinically important clot migration or recanalization in the hyperacute phase may not have been detected.

These results provide further support for the use of IVT as a pretreatment before EVT. In addition, the results are relevant to ongoing trials investigating the removal of IVT pretreatment within the 4.5-hour time window in thrombectomy patients (DIRECT-SAFE, MR CLEAN-NO IV, SWIFT DIRECT) and will be useful in future trial designs incorporating the extended time window.

"This is the first randomized controlled study to assess the effect of IVT on clot migration and accessibility in an extended time window."[2]

3. AN EDITORIAL ADDRESSES POTENTIAL IMPLICATIONS OF REPLACING ALTEPLASE WITH TENECTEPLASE FOR ACUTE THROMBOLYSIS

SUMMARY

- Possible consequences of a global replacement of alteplase with tenecteplase before potential regulatory approval are discussed by Professor Keith Muir
- Phase II tenecteplase data are insufficient to draw conclusions on whether tenecteplase's safety profile is comparable to that of alteplase in a broad range of patients
- The significant caveats around tenecteplase data are reflected in the low grade of evidence and limited scope of use recommended in recent guidelines; ongoing Phase III randomized controlled trial (RCT) data are needed before regulatory agencies can support tenecteplase approval

Tenecteplase has several hypothetical advantages over alteplase, including longer half-life, greater fibrin specificity, and lesser likelihood of fibrinogen depletion. In addition, it is administered as a single bolus, which is particularly advantageous in the setting of patient transfer between hospitals. To date, data on tenecteplase have prompted recent proposals to shift routine practice in favour of unlicensed use of tenecteplase. However, there are significant caveats around the data currently available for tenecteplase; these are reflected in the low grade of evidence and limited scope of use for tenecteplase recommended in recent guidelines. In this *Stroke* Editorial, Professor Keith Muir discusses the

potential consequences of a global replacement of alteplase with tenecteplase before regulatory approval may be obtained in due course.[3]

Completed tenecteplase RCTs

A pooled analysis of 291 patients from three Phase II trials found no significant differences in clinical or safety outcomes between tenecteplase and alteplase. However, the analysis suggested better early neurological improvement with the 0.25 mg/kg tenecteplase dose that was most commonly used.

Two additional Phase II RCTs comparing tenecteplase with alteplase had larger patient populations (EXTEND-IA TNK [N=202] and NOR-TEST [N=1100]). However, their interpretation is compromised. The EXTEND-IA TNK population was restricted to patients with M1 occlusions and a favourable perfusion profile. NOR-TEST investigated an atypically mild population (17% were stroke mimics and the median NIHSS score was 4) and patients were treated with a higher tenecteplase dose (0.4 mg/kg) than that considered equivalent to alteplase 0.9 mg/kg.

In summary, Professor Muir notes that Phase II data are insufficient to draw reliable conclusions.

Ongoing tenecteplase RCTs

ATTEST 2 and AcT are comparing alteplase with tenecteplase within 4.5 hours of symptom onset in thrombolysis-eligible patients within a general population. The TASTE trial targets M1 occlusion patients with favourable perfusion characteristics. Extended indications for thrombolysis are also being explored, including wake-up strokes (TWIST), minor stroke and transient ischaemic attack with intracranial vessel occlusion (TEMPO-2), or late time windows (TIMELESS). All these trials use tenecteplase 0.25 mg/kg.

Potential disadvantages of switching to tenecteplase ahead of potential regulatory approval for AIS

Because the data in the 4.5-hour time window are challenging to generalize, treatment decisions for those outside the trial populations are much less informed than those for alteplase. It is currently unclear whether the 0.4 and 0.25 mg/kg tenecteplase doses have non-inferior safety and efficacy outcomes compared with alteplase, or if the efficacy and safety profiles of the different doses differ.

In most countries tenecteplase lacks regulatory approval for stroke and the tenecteplase packaging and dose instructions reflect the myocardial infarction indication; therefore, there is a risk of significant dose errors. In addition, increased off-label use of tenecteplase in stroke may compromise the availability of the drug for the licensed acute myocardial infarction indication.

"Sufficient data to support regulatory approval of tenecteplase as a global replacement for alteplase in acute stroke will come only from the ongoing RCTs: while some regions might opt to make the switch to tenecteplase ahead of regulatory approval, there are clear risks in doing so."[3]

4. A SCIENTIFIC STATEMENT FROM THE AHA PROVIDES A FRAMEWORK FOR ACUTE TREATMENT AND SECONDARY PREVENTION OF CENTRAL RETINAL ARTERY OCCLUSION

SUMMARY

- An AHA scientific statement discusses management of central retinal artery occlusion
- Current data suggest rt-PA may be an effective treatment; however, no RCTs have been conducted in this setting
- Systems of care for urgent recognition, triage, and management, similar to those for cerebral ischaemic stroke, are needed

Central retinal artery occlusion (CRAO) is a form of AIS defined as 'interruption of blood flow through the central retinal artery by thromboembolism or vasospasm with or without retinal ischemia'. Fewer than 20% of affected patients regain functional visual acuity in the affected eye. Analogous to cerebral ischaemic stroke, CRAO is associated with a risk of recurrent vascular events. Despite the serious consequences of CRAO, it has no effective evidence-based forms of therapy. To this end, the authors of an AHA scientific statement discuss the management of CRAO with particular reference to acute therapy and cardiovascular secondary prevention strategies.[4]

Epidemiology, risk factors, and pathophysiology

The age- and sex-adjusted incidence of CRAO is 1.8, 1.9, and 2.5 per 100 000 person-years in South Korea, the USA and Japan, respectively. Elderly people (aged >80 years) have a higher incidence (10.1 per 100 000 person-years) than the general population and CRAO is more common in men compared with women.

CRAO is strongly associated with an ipsilateral internal carotid artery stenosis. Patients with CRAO are more likely to have AF than age- and sex-matched controls, and there is a high risk of recurrent stroke in patients with CRAO and AF.

The most important determinant of retinal damage and final visual outcome is the duration of occlusion of the central retinal artery. Typically, CRAO presents as sudden, painless monocular loss of visual acuity and peripheral vision.

Acute treatment of CRAO

Due to the narrow time window for effective CRAO treatment, immediate triage to an emergency department is necessary. Stroke centres should develop relationships with community ophthalmologists and optometrists to promote efficient pathways for transfer of patients with CRAO; this may allow more patients to reach the emergency department within the window for rt-PA.

In the USA, rt-PA is currently administered in 5.8% of patients with CRAO. Results from a patient-level meta-analysis showed treatment of acute CRAO with any lytic drug within 4.5 hours of onset exhibited a 50% rate of clinical recovery (improvement in both visual acuity and functional clinical outcomes). To date, no adequate RCTs of IV rt-PA in patients with CRAO have been completed due to difficulty with patient enrolment. However, three European RCTs are currently underway to compare IVT with placebo in eligible patients (THEIA and REVISION: rt-PA vs placebo; Ten-CRAOS: tenecteplase vs placebo). Until full RCT results are available, the decision to use IV rt-PA for CRAO rests jointly with the treating specialist and affected patient, following thorough discussion of the benefits and risks of treatment. Because of a 30% incidence of concurrent cerebral ischaemic stroke and a reduced efficacy signal in the 4.5- to 6-hour time window, treatment beyond 4.5 hours requires further study.

In EVT centres, intra-arterial rt-PA (IAT) may be considered in patients with disabling visual deficits at early time points, especially if they are not candidates for IV rt-PA. However, IAT is currently an unproven therapy and should be considered only in light of the devastating visual outcome associated with CRAO.

Given the size of the affected vessels (the diameter of the central retinal artery is 160 µm at its terminus), EVT is not possible with the existing technology.

Secondary prevention

Treatment of comorbidities, e.g. hypertension and diabetes; smoking cessation; implementation of a plant-based diet; and regular physical activity are critical for secondary prevention after CRAO and should follow established professional guidelines for cerebral ischaemic stroke. For those without an indication for anticoagulation or surgery, an antithrombotic therapy regimen paralleling that seen in cryptogenic ischaemic stroke is reasonable.

Conclusions and future directions

CRAO and cerebral ischaemic stroke share the same underlying mechanisms and therapeutic approaches. At present, there is no widely accepted therapy, and practitioners vary in their management of this condition. There is an unmet need for an RCT comparing IV rt-PA with placebo at early time points in patients with CRAO. Systems of care need to be developed for the urgent recognition, triage, and management of CRAO in a manner similar to cerebral ischaemic stroke.

"Future research should be directed toward the development of novel biomarkers of retinal tissue viability that can be deployed in real time and complement existing time-based decision-making algorithms, potentially allowing the use of rt-PA at delayed time points in selected patients."[4]

AcT, Alteplase Compared to Tenecteplase in Patients With Acute Ischemic Stroke; AF, atrial fibrillation; AHA, American Heart Association; AIS, acute ischaemic stroke; ATTEST 2, Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis; CI, confidence interval; CRAO, central retinal artery occlusion; EXTEND, Extending the Time for Thrombolysis in Emergency Neurological Deficits; DIRECT-SAFE, A Randomized Controlled Trial of DIRECT Endovascular Clot Retrieval Versus Standard Bridging Thrombolysis With Endovascular Clot Retrieval Within 4.5 Hours of Stroke Onset; EXTEND-IA TNK, Tenecteplase Versus Alteplase Before Endovascular Therapy for Ischemic Stroke; EVT, endovascular thrombectomy; HR, hazard ratio; IAT, intra-arterial thrombolysis; IV, intravenous; IVT, intravenous thrombolysis; LVO, large vessel occlusion; MR CLEAN-NO IV, Multicentre Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands No IV; NIHSS, National Institute of Health Stroke Scale; NOR-TEST, Norwegian Tenecteplase Stroke Trial; RCT, randomized controlled trial; REVISION, Early Reperfusion Therapy with Intravenous Alteplase for Recovery of Vision in Acute Central Retinal Artery Occlusion; rt-PA, recombinant tissue plasminogen activator; SWIFT DIRECT, Bridging Thrombolysis Versus Direct Mechanical Thrombectomy in Acute Ischemic Stroke; TASTE, Tenecteplase Versus Alteplase for Stroke Thrombolysis Evaluation; TEMPO-2, TNK–Tissue-Type Plasminogen Activator Evaluation for Minor Ischemic Stroke With Proven Occlusion; Ten-CRAOS, Tenecteplase in Central Retinal Artery Occlusion Study; THEIA, A Phase III Randomized, Blind, Double Dummy, Multicenter Study Assessing the Efficacy and Safety of IV THrombolysis (Alteplase) in Patients With acutE Central retInal Artery Occlusion; TIMELESS, Thrombolysis in Imaging-Eligible, Late-Window Patients to Assess the Efficacy and Safety of Tenecteplase; TWIST, Tenecteplase in Wake-Up Ischaemic Stroke Trial.

References

1. Yafasova A, Fosbøl EL, Johnsen SP *et al*. Time to thrombolysis and long-term outcomes in patients with acute ischemic stroke: a nationwide study. *Stroke* 2021; doi: 10.1161/STROKEAHA.120.032837 [Epub ahead of print].
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