

# ACUTE ISCHAEMIC STROKE PUBLICATION ALERT NEWSLETTER – 12/2020

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Traditionally, stroke was not treated as an emergency, because there was little that could be done to improve the brain's blood flow. Improvements in imaging and the introduction of alteplase, which should be given as soon as possible after symptom onset according to the product labels, signalled a step change in the treatment of patients with acute ischaemic stroke (AIS). As a result, healthcare systems and clinicians were called on to view stroke as a medical emergency in line with myocardial infarction and head trauma. The prevailing rule of 'time is brain' was then coined. In this current era of stroke care, the importance of this phrase is as relevant as it was over 25 years ago.

A recent study that models the economic and health impacts of delaying endovascular thrombectomy (EVT) in patients with large vessel occlusion (LVO) is highlighted in this issue of the Acute Ischaemic Stroke Publication Alert Newsletter, along with a corresponding Editorial that puts the results into a wider context. Functional outcomes following delayed EVT are quantified down to a timescale of minutes, as are morbidity-related costs on a patient, healthcare, and societal level.

A meta-analysis was performed to compare EVT vs medical treatment in patients subdivided according to stroke severity, using data from randomized controlled trials (RCTs) and observational studies published within the last decade. Real-world evidence was included to obtain more information on outcomes in patients with mild and severe stroke, because these patients are often excluded from RCTs. The results are summarized herein, followed by a synopsis of a novel approach to improving the design of and providing insight on the results of EVT RCTs using computer-based simulations. The final summary outlines a review of thrombolytic therapies for the management of central retinal artery occlusion (CRAO). The authors argue that, because CRAO is a visual analogue of AIS, patients with CRAO should be afforded the same treatment options as those with AIS.

The list of presented publications is as follows:

1. [Kunz WG, Menon BK et al. Public health and cost consequences of time delays to thrombectomy for acute ischemic stroke. \*Neurology\* 2020.](#)
2. [Pollard R et al. No time to delay with large vessel occlusions: Every minute counts. \*Neurology\* 2020.](#)
3. [Zhao Z et al. Is endovascular treatment still good for ischemic stroke in real world?: A meta-analysis of randomized control trial and observational study in the last decade. \*Stroke\* 2020.](#)
4. [Konduri PR et al; INSIST Investigators. In-silico trials for treatment of acute ischemic stroke. \*Front Neurol\* 2020.](#)
5. [Dumitrascu OM et al. Thrombolysis for central retinal artery occlusion in 2020: Time is vision! \*J Neuroophthalmol\* 2020.](#)

## 1. WHAT ARE THE PUBLIC HEALTH AND COST CONSEQUENCES OF EVT TIME DELAYS FOR PATIENTS, HEALTH CARE SYSTEMS, AND SOCIETY?

In the USA, the estimated annual costs for stroke are \$40 billion and are projected to triple by 2030. Although EVT has led to extensive long-term cost-savings for healthcare systems and societies, the speed of treatment delivery remains critical. Significant time delays are still present in today's healthcare systems. Using an economic and health model, the authors of this study sought to define and quantify the public health and cost consequences of delays for patients with stroke, healthcare systems, and society.<sup>1</sup>

### Study details

- Data from seven trials within the HERMES collaboration served as the data source
- Quality-adjusted life-year (QALY) and cost estimations for the USA were performed, adopting the healthcare and societal perspective
- A Markov model was developed to analyse costs and functional outcomes within the initial 90 days after the index stroke

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- Patients entered the model on admission to the hospital for AIS at different times from symptom onset, were EVT eligible or EVT ineligible due to time delays, and then entered one of the seven health states according to the degree of disability as assessed by the modified Rankin Scale (mRS); the reference case analysis was performed for a stroke onset at the age of 65 years
- For 849 patients in the intervention arms of the seven EVT trials, times to expected arterial puncture and 90-day clinical outcomes were available

#### Study results

- Patients with later treatment had higher morbidity-related costs but over a shorter time span due to their shorter life expectancy, resulting in similar lifetime costs as in patients with early treatment
- Every hour of later treatment decreased the healthcare and societal net monetary benefit (NMB) of EVT treatment
  - For early treatment within 60 to 119 min, EVT led to an average NMB of \$425 738 from the healthcare perspective, adding on average more than \$300 000 in care value compared to treatment within 360 to 419 min
- Expediting EVT treatment by 10 min is estimated to gain each individual patient a median of 39 additional days of disability-free life (95% prediction interval 23–53 days) and 106 additional days of life in functional independence (95% prediction interval 64–144 days)
- Faster treatment by 10 min is estimated to increase the NMB of EVT treatment by an average of \$10 593 (95% prediction interval \$5549–14 847) from a healthcare perspective and \$10 915 (95% prediction interval \$5928–15 356) from a societal perspective (**Table**)
- In the USA as a whole, a median 10-min reduction in treatment times is estimated to result in an annual increase of 2440 additional QALYs (95% prediction interval 1464–3316 QALYs) in patients with stroke treated with EVT
- Annually, faster treatment by 10 min would increase the NMB of EVT by an estimated \$242 million (95% prediction interval \$127–339 million) from a healthcare perspective and \$249 million (95% prediction interval \$135–351 million) from a societal perspective (**Table**)

**Table. Estimates of patient- and population-level effects of reduced EVT treatment times in the USA**

INDIVIDUAL PATIENT-LEVEL EFFECTS (MEDIAN ESTIMATES WITH 95% PREDICTION INTERVALS)				
Earlier EVT treatment (min) by	Disability-free life-days gained	Life-days gained with functional independence	Incremental NMB, USD	
			Healthcare perspective, USD	Societal perspective, USD
1	3.90 (2.34–5.30)	10.61 (6.36–14.42)	1059 (555–1485)	1092 (593–1536)
5	20 (12–27)	53 (32–72)	5297 (2775–7424)	5458 (2964–7678)
10	39 (23–53)	106 (64–144)	10 593 (5549–14 847)	10 915 (5928–15 356)
30	117 (70–160)	318 (191–432)	31 779 (16 647–44 541)	32 745 (17 784–46 068)
60	234 (140–318)	637 (382–865)	63 558 (33 294–89 082)	65 490 (35 568–92 136)
ANNUAL POPULATION-LEVEL EFFECTS IN THE USA (MEDIAN ESTIMATES WITH 95% PREDICTION INTERVALS)				
National reduction of times to EVT (min) by	Annual disability-free life-days gained	Annual QALYs gained	Incremental NMB, USD	
			Healthcare perspective, USD, M	Societal perspective, USD, M
1	89K (53–121K)	244 (146–332)	24.2 (12.7–33.9)	24.9 (13.5–35.1)
5	445K (267–605K)	1220 (732–1658)	121 (63–170)	125 (68–175)
10	891K (534–1210K)	2440 (1464–3316)	242 (127–339)	249 (135–351)
30	2.7M (1.6–3.6M)	7320 (4392–9947)	726 (380–1017)	748 (406–1052)
60	5.3M (3.2–7.3M)	14 639 (8783–19 894)	1451 (760–2034)	1495 (812–2104)

K, thousand; M, million; USD, US dollars

#### Study limitations

- The study focused on estimating the health and cost consequences of time delays if patients are treated as per current guidelines with intravenous thrombolysis (IVT, if eligible) followed by EVT; different treatment strategies were not compared

- The results are based on patients included in the HERMES meta-analysis; the effects of triage that occurred before inclusion are therefore not represented
- Population-level estimates reported in this study are extrapolations based on 65-year-old patients with stroke, the average age in recent stroke trials
- The cost calculations were conducted in the USA, and the absolute amount cannot be converted to other currencies
- The cumulative costs reported for the societal perspective are therefore underestimated because they do not account for all items as recommended by current health-economic guidelines

#### *Study conclusions*

- Every treatment delay to EVT reduces QALYs and decreases the NMB of this intervention
- Healthcare policies to implement efficient prehospital triage and accelerate in-hospital workflow are urgently needed to harness the full potential of EVT for patients with stroke who have LVO

**“During the in-hospital period, stroke needs to be given the same priority status as acute coronary syndrome and acute trauma.”<sup>1</sup>**

## **2. QUANTIFYING THE HEALTH AND ECONOMIC CONSEQUENCES OF EVT TREATMENT DELAY HIGHLIGHTS THE IMPORTANCE OF REDUCING UNNECESSARY TIME DELAYS IN STROKE TREATMENT**

Strokes happen very frequently, with estimates of one occurring every 40 seconds in the USA. Stroke remains among the top causes of long-term disability and the cost of stroke to society is substantial. For eligible patients with LVO, the safety and efficacy of EVT are established between 16 and 24 hours from last known well. Within the 6-hour window, multiple studies have found better functional outcomes and lower degrees of disability with earlier intervention. The authors of an editorial in *Neurology*<sup>2</sup> explore the findings of the model to estimate the economic and health impacts of delaying EVT in patients with LVO.<sup>1</sup>

Intervening just 1 minute earlier provides a predicted gain of 3.9 disability-free life-days and 10.6 days of functional independence. However, extended treatment windows may increase the number of patients who qualify for the intervention but with diminishing returns in terms of function and economic impact. In future, further prediction models will be needed to assess the consequences of treatment delays for these late-window patients.

Some of the study’s limitations were discussed. The findings should be taken in the context of the model’s input parameters based on patient data that were limited to thrombectomy-eligible patients who would have been ineligible due to time delays within the 6-hour window. The results cannot be extrapolated to delays beyond the 6-hour window. Ineligibility was estimated at a 3% loss of eligibility for every 30-minute delay based on expert consensus and limited observational data; however, the true decline in treatment eligibility over time may be even greater, thereby increasing the accumulated disability and costs even more dramatically.

The editorial concludes by noting that the study results emphasize the importance of improving prehospital triage of patients with stroke from a functional and financial perspective. When a stroke occurs every 40 seconds, there is no time to delay when both disability and public health costs are at stake.

**“This study reminds us of the age-old truths in stroke: that time is still brain and minutes still matter.”<sup>2</sup>**

## **3. A META-ANALYSIS OF RCT AND OBSERVATIONAL DATA FROM THE LAST DECADE INVESTIGATES EVT VS MEDICAL MANAGEMENT FOR PATIENTS WITH MILD, NORMAL, OR SEVERE STROKE**

Patients with National Institutes of Health Stroke Scale (NIHSS) score <6 or Alberta Stroke Program Early CT Score (ASPECTS) <6 were excluded from the pivotal RCTs on which criteria for EVT eligibility are based. Although the guidelines for management of AIS state that EVT is reasonable for these patients, uncertainty remains regarding the eligibility criteria for EVT use with respect to stroke severity. In this study, the authors examined both RCTs and observational studies (OSs) published in the last decade to compare the therapeutic effect of EVT and medical treatment, including

recombinant tissue plasminogen activator (rt-PA), and the effectiveness of EVT in treating patients with mild or severe stroke.<sup>3</sup>

OSs were categorized based on patients' imaging data on admission: mild stroke group (MSG; NIHSS score <6); severe stroke group (SSG; ASPECTS <6 or ischaemic core under imaging devices ≥50 mL); normal stroke group (NSG; all remaining studies). RCTs were compared to NSG data, and EVT among MSG, SSG, and NSG was evaluated. The primary outcome measure was the proportion of patients with mRS score 0–2 at 90 days after intervention; the secondary outcomes were mortality at 90 days and symptomatic intracranial haemorrhage (sICH) at 24 hours. A total of 15 RCTs reporting data (n=3694) and 37 OSs (n=9090) were included in the meta-analysis.

#### *mRS score 0–2*

- EVT was associated with a higher rate of mRS score 0–2 in RCTs and NSG (RCTs: odds ratio [OR], 1.97 [95% CI: 1.48–2.63];  $I^2=72.8\%$ ; NSG: 1.72 [95% CI: 1.46–2.02];  $I^2=47.7\%$ )
- EVT in OSs and the SSG was associated with higher rates of mRS score 0–2 than medical treatment (OSs: OR, 1.56 [95% CI: 1.32–1.84]; SSG: 5.33 [95% CI: 2.22–12.76];  $I^2=27.85\%$ ); there was no significant difference between EVT and medical treatment in MSG

#### *Mortality*

- EVT was associated with lower mortality than medical treatment in RCTs and NSG (RCTs: OR, 0.82 [95% CI: 0.69–0.99];  $I^2=0.00\%$ ; NSG: 0.71 [95% CI: 0.55–0.92];  $I^2=51.6\%$ )
- EVT was associated with lower mortality rates than medical treatment in OSs and SSG (OSs: OR, 0.77 [95% CI: 0.63–0.95]; SSG: 0.53 [95% CI: 0.34–0.82];  $I^2=0.00$ ) and higher mortality than medical treatment in MSG (2.22 [95% CI: 1.26–3.89];  $I^2=0.00$ )

#### *sICH*

- There was no significant difference in sICH between EVT and medical treatment in RCTs
- EVT was associated with higher sICH than medical treatment in NSG (1.62 [95% CI: 1.30–2.03];  $I^2=0.00$ ) and higher sICH than medical treatment in OSs (OR, 1.58 [95% CI: 1.29–1.93]) and MSG (2.78 [95% CI: 1.24–6.21];  $I^2=37.9\%$ ); no significant difference in sICH between EVT and medical treatment was found in SSG.

Study limitations included variable designs, reporting, and potential publication bias of included studies.

The authors concluded that evidence from both RCTs and OSs support the use of EVT as first-line choice for eligible patients, corresponding to the Level I evidence of the guidelines. Data in this study do not support EVT for patients with NIHSS score <6, which is contrary to the guidelines. For patients with ASPECTS <6, EVT shows significant superiority over medical treatment; however, more clinical trials and large prospective cohort studies are required.

**“Our result in the additional analysis highlighted the inferiority of EVT compared with medical treatment, as there was no significant difference in mRS score of 0 to 2 between EVT and medical treatment, whereas EVT was associated with higher sICH rate and lower mortality than medical treatment in MSG.”<sup>3</sup>**

#### **4. A PLATFORM FOR IN-SILICO TRIALS FOR AIS SEEKS TO GENERATE AND REFINE HYPOTHESES ON THE POTENTIAL SUCCESS OF NEW TREATMENTS AND THE SUITABILITY OF TREATMENTS FOR SPECIFIC PATIENT POPULATIONS**

The benefits of EVT for patients with AIS was demonstrated by multiple RCTs. However, up to 66% of patients have an unfavourable outcome and remain functionally dependent after EVT. New AIS trials are focusing on testing new thrombolytics and stent designs and are testing the effectiveness of EVT in previously understudied patient subgroups. The authors of this white paper describe how in-silico trials (ISTs), computer-based simulations of RCTs, may optimize future AIS trial designs and provide insight of the efficacy of new treatments.<sup>4</sup> A proof-of-concept platform will be developed to investigate the extent to which in-silico modelling can accurately simulate bench testing, animal testing, and RCT results. The approach may generate hypotheses that may be useful in optimizing trial designs. The overall aim of the study is to obtain a deeper understanding of the pathophysiology of AIS and reasons for failure of current treatments. This project by the INSIST investigators aims to show the credibility of ISTs and take a step towards regulatory acceptance of this process for decision-making and pre-market submissions.

Virtual populations of patients with AIS will be generated and in-silico models (ISM) will be developed, based on anonymized data from the MR CLEAN trial, MR CLEAN Registry, and HERMES collaboration. The three ISMs are for

thrombosis and thrombolysis; intra-arterial thrombectomy; and microvascular perfusion, cell death, and recovery of brain tissue after reperfusion. The accuracy of ISTs will be assessed by comparing their results with the findings from ongoing and recently completed RCTs.

The study is limited because basic knowledge of the underlying physiology of brain tissue infarction is lacking, as are sufficiently detailed experimental data that allow for detailed modelling of brain perfusion and metabolism. Therefore, modelling of these processes is very challenging.

**“ISTs have the potential to lead to a more effective human clinical trial design, reduce animal testing, lower development costs, and shorten time to market for new medical products.”<sup>4</sup>**

## 5. A SYSTEMATIC REVIEW INVESTIGATES WHETHER THE SAME THROMBOLYTIC THERAPIES AND TIME WINDOW FOR AIS TREATMENT SHOULD APPLY TO CENTRAL RETINAL ARTERY OCCLUSION

Central retinal artery occlusion (CRAO) is an ophthalmological and neurological emergency, with an incidence that increases with age. Occlusion of the central retinal artery (CRA) leads to acute retinal infarction, which classifies CRAO as an acute carotid circulation ischaemic stroke syndrome. CRAO-related visual morbidity is associated with poor mental health, decreased quality of life, and possibly institutional care.

Despite retinal infarction being clearly recognized as comparable with brain infarction, controversy remains regarding the net benefit of acute reperfusion therapies in CRAO. Patients with isolated visual loss usually present to eyecare providers, and studies show that only about one-third of ophthalmologists transfer patients with acute CRAO to an emergency department for immediate evaluation. It is likely that thrombolytic administration up to 4.5 hours from symptom onset will help retinal reperfusion. Results from recent acute stroke trials for cerebral ischaemia suggest that the treatment window may be longer in patients with ischaemic but not yet infarcted brain tissue, and that selection of stroke patients for reperfusion therapies on the basis of tissue viability rather than time from onset of stroke may result in better outcomes.

The authors review the evidence for thrombolytic treatment for patients with non-arteritic CRAO, with a particular focus on alteplase, and propose practical recommendations for the management of these patients.<sup>5</sup>

### Study details

#### *Intravenous thrombolysis with alteplase*

- A literature search was completed for studies reporting acute intravenous (IV) or intra-arterial (IA) therapy with alteplase or tenecteplase in CRAO; no reports of tenecteplase administration in CRAO were found
- Seven articles on the use of IVT with alteplase were identified; 60/111 patients (54%) received IV rt-PA within 4.5 h of symptom onset; study details, number and age of patients, timing and dosing of IV alteplase, and adverse events are summarized below (Table)
- In the retrospective analysis by Preterre *et al*, one sICH occurred in a patient in whom IV heparin was started just after alteplase administration (which constitutes a protocol violation as per the current guidelines)
- In the only RCT conducted to date, the mean time of IV rt-PA administration was 14.4±6.5 h from symptom onset; only one patient received alteplase at 4.5 h, and one was treated at 6 h. Likely due to delayed alteplase administration, one patient had ICH 45 min after infusion and an mRS score of 2 at discharge
- In terms of visual outcomes, most studies demonstrated benefit of IV rt-PA therapy when administered very early
- None of the 60 patients that received IV alteplase within 4.5 h of symptom onset developed sICH or ocular haemorrhage

**Table. Large studies evaluating IVT in central retinal artery occlusion patients**

Author, Year, Country	Study type	N Age (yrs)	IV alteplase dose	Time of alteplase administration since onset/last known well (h)	Safety reports
Mames <i>et al</i> , 1995, USA	Case reports	2 (74 and 61)	Not mentioned	2.75 and 4	No complications

Kattah <i>et al</i> , 2002, USA	Prospective	12 (range 53–89)	0.9 mg/kg	2–18 (6 within 4.5 h)	No complications
Hattenbach <i>et al</i> , 2008, Germany	Prospective interventional case series	28 (range 30–85)	50 mg over 60 min	1.5–12 (7 within 4.5 h)	No complications
Chen <i>et al</i> , 2011, Australia	Phase II, placebo-controlled RCT	8 (mean 73±8)	0.9 mg/kg	Mean 14.4±6.5 (1 within 4.5 h)	1 ICH; 1 vitreous haemorrhage (CNV)
Nedelmann <i>et al</i> , 2015, Germany	Prospective interventional case series	11 (age range not specified)	0.9 mg/kg	Median 4.25 (range 1.75–10.5) (7 within 4.5 h)	No complications
Preterre <i>et al</i> , 2017, France	Retrospective analysis	30 (mean 62.5±15.1)	0.9 mg/kg	Mean 4.55 ± 1.05 (17 within 4.5 h)	1 symptomatic ICH (alteplase and IV heparin); 2 asymptomatic ICH; 1 haematuria
Schultheiss <i>et al</i> , 2018, Germany	Prospective interventional case series	20 (mean 72.8±10.9)	0.9 mg/kg	Median 3.5 (IQR 2–4) (20 treated within 4.5 h)	1 angioedema 1 bleeding from abdominal aortic aneurysm

CNV, choroidal neovascular membrane; ICH, intracranial haemorrhage; IQR, interquartile range

#### *Intra-arterial thrombolysis (IAT) with alteplase*

- Although IAT initiated within 6 h of stroke onset in carefully selected patients who have contraindications to the use of IV alteplase is a consideration, it is not standard practice according to the current guidelines
- Patients with CRAO are not candidates for mechanical thrombectomy given a distal embolus and low CRA diameter; however, microcatheterization of the ophthalmic artery (OA) or other collateral vessels in cases with difficult direct access to the OA allows for in situ administration of IA thrombolytics
- Six studies that described IA alteplase administration were identified; 18/134 patients (13.4%) were treated within the first 6 h after visual loss
- Overall, minimal safety concerns were reported; no patient had an adverse event with long-term complications
- The duration of alteplase infusion was variable and administered either continuously or in aliquots; the dose varied between 8.8 and 80 mg, with lower doses given when administered using aliquots
- A wide spectrum of times from symptom onset was seen with alteplase injection, with a mean of 8.07 (SD 3.34) h in all case series and 12.7 (SD 5.77) h in the RCT

#### *CRAO thrombolysis through a telestroke encounter*

Telestroke allows for timely alteplase eligibility decision-making and administration and tele-eye stroke code evaluations must include an ophthalmological assessment; if an ophthalmologist is unavailable, an ocular fundus photograph should be obtained. The telestroke provider should then be guided by an eyecare provider to confirm a diagnosis of non-arteritic CRAO before remotely recommending IV alteplase administration or transfer to specialized centres for IAT

#### *Study conclusions*

- As CRAO is an ocular analogue of brain AIS, the same thrombolytic therapies and time window for patients with AIS should apply to patients with CRAO
- Code eye stroke team must include an in-person or virtual eyecare provider to help establish the correct diagnosis and exclude ocular signs that may prohibit thrombolytic therapy
- Future research should focus on developing advanced, feasible, and real-time retinal tissue viability (core vs penumbra) imaging studies to be incorporated into the current time-based thrombolysis decision-making algorithm.
- In the meantime, the education of eyecare providers, emergency medical services, and patients should continue to facilitate patients with acute CRAO reaching emergency departments and facilities able to administer thrombolysis and provide acute stroke care

**“Akin to cerebral infarction, once eye strokes are suspected, fast action is needed.”<sup>4</sup>**

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AIS, acute ischaemic stroke; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; CI, confidence interval; CNV, choroidal neovascular membrane; CRA, central retinal artery; CRAO, central retinal artery occlusion; CT, computed tomography; EVT, endovascular thrombectomy; HERMES, Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials; IA, intra-arterial; IAT, intra-arterial thrombolysis; ICH, intracranial haemorrhage; IQR, interquartile range; ISM, in-silico model; IST, in-silico trials; IV, intravenous; K, thousand; LVO, large vessel occlusion; M, million; MR CLEAN, Multicentre Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands; mRS, modified Rankin Scale; MSG, mild stroke group; NIHSS, National Institute of Health Stroke Scale; NMB, net monetary benefit; NSG, normal stroke group; OA, ophthalmic artery; OR, odds ratio; OS, observational study; QALY, quality-adjusted life-year; RCT, randomized controlled trial; rt-PA, recombinant tissue plasminogen activator; SD, standard deviation; sICH, symptomatic intracranial haemorrhage; SSG, severe stroke group; USD, US dollars.

## References

1. [Kunz WG, Hunink MG, Almekhlafi MA, Menon BK \*et al\*. Public health and cost consequences of time delays to thrombectomy for acute ischemic stroke. \*Neurology\* 2020;95:e2465–75.](#)
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5. [Dumitrascu OM, Newman NJ, Biousse V. Thrombolysis for central retinal artery occlusion in 2020: Time is vision! \*J Neuroophthalmol\* 2020;40:333–45.](#)

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