

Letter to the Editor Regarding CADTH Rapid Review: *Systemic Thrombolysis by Alteplase for Acute Ischemic Stroke*

Andrew Micieli, Michal Krawczyk, Gary Hunter, Dylan Blacquiere, Andrew M. Demchuk, on Behalf of the Canadian Stroke Consortium Policy and Advocacy Committee

The Canadian Stroke Consortium read with interest the recent rapid review by CADTH¹ on the evidence of alteplase for acute ischemic stroke. We felt it necessary to reply for several reasons: (1) despite the 27-year history of alteplase since the NINDS publication, the rapid review limits the search to the last 6 years, which does not reflect the totality of the evidence, (2) the process for inclusion of studies was questionable, leading to a strongly biased representation of the existing literature, and (3) important concerns from the single expert reviewer were not adequately addressed prior to publication.

Choice of Included Meta-Analyses

In the hierarchy of evidence-based medicine, an individual patient-level meta-analysis provides the most reliable estimate as it involves the pooling of all available data from each trial. This allows for adjustments for potential confounders and is therefore considered the “gold standard”.² The Stroke Thrombolysis Trialists’ Collaborative Group published a pooled meta-analysis of all double-blind RCTs in 2010³ and in 2014⁴ added the more recent published IST-3 trial.⁵ These meta-analyses provide clear evidence for the improvement in clinical outcomes with alteplase within the 4.5-hour treatment window, with earlier treatment resulting in larger absolute benefits. Additionally, pooled meta-analyses demonstrate benefit with alteplase across the age spectrum, stroke severity, and multiple definitions of good outcome.⁶ The CADTH rapid review excluded these important meta-analyses on the basis that they were without a systematic review. However, Emberson et al.⁴ utilized an updated systematic review by Cochrane and enquiry to various sources to ensure eligible trials were not omitted. Importantly, the CADTH rapid review neglect the advantage of pooling data, which allows for a greater inclusion of major trials compared to study level meta-analyses. As an example, the meta-analysis by Chen et al. (included in the rapid review),⁷ did not have access to 3 major trials in the 0- to 3-hour window, and 8 major trials in the 3- to 4.5-hour window that were included in Emberson et al. Selective exclusion of these important patient level meta-analyses leads to a very biased conclusion of the evidence for alteplase. Furthermore, it is unclear why the rapid review included a meta-analysis by Lan et al., a study focusing solely on minor stroke that included data from non-disabling stroke,⁸ which is not an indication for alteplase as per the Canadian Stroke Best Practice Guidelines.⁹

Efficacy of Alteplase Within 3 Hours of Symptom Onset

In addition to the 2 NINDS trials,¹⁰ prespecified subgroup data from IST-3⁵ and post-hoc data from ECASS 1 and ATLANTIS support the early 0- to 3-hour treatment window. Unsurprisingly, individual patient level³ and study level meta-analyses^{7,11,12} further support the 3-hour window. In a recent study on the cumulative fragility index of studies on alteplase within the 3-hour window confirmed the evidence is highly robust.¹³ The CADTH rapid review suggests “investigating whether there is a need to re-analyze data from other trials,” but this has already been extensively done. An independent committee in 2004⁸ and multiple other re-analyses of the NINDS trials all confirm the findings of benefit.¹⁴⁻¹⁹ A full description of why Hoffman et al. re-analysis is problematic is outlined elsewhere (see Saver et al.).¹⁴

Several problematic trials to imply uncertainty of the benefit of alteplase within the 0- to 3-hour treatment window were included in the rapid review. (1) The PRISMS trial,²⁰ a trial on non-disabling deficits, which as mentioned above is not an indication for alteplase. (2) A NINDS retrospective subgroup analysis²¹ of 58 patients with mild strokes (NIHSS 5 or less). It is highly questionable to use post-hoc subgroup data of the NINDS trials on minor stroke to imply uncertainty within the 0- to 3-hour window when the NINDS trials confirmed efficacy within that time window.

Efficacy of Alteplase Between 3 and 4.5 Hours From Symptom Onset

The ECASS III study closely mirrored the NINDS trials with the important exception that ECASS III enrolled patients in the 3- to 4.5-hour window, demonstrating a statistically significant benefit for alteplase and indirectly validating the findings in NINDS.²² The rapid review selectively included a recent post-hoc re-analysis of ECASS III by Alper et al. that adjusted for baseline imbalances to imply uncertainty in the conclusions of ECASS III.²³ However, a prior re-analysis by Bluhmki et al. in 2009 confirmed the benefit of alteplase was independent of any imbalances.²⁴ The rapid review incorrectly claims that Alper et al. showed little-to-no difference in functional outcome after adjustment for baseline differences.²³ In fact, Alper et al. reconfirmed the adjustments reported in Bluhmki et al., however, when Alper et al. departed from the original study protocol, the results were not statistically significant.²³ Importantly, the results of post-hoc data cannot change the conclusion of an RCT, only the degree of certainty, and individual patient level meta-analyses provide further robust certainty for the benefit of alteplase within this time window, with adjustments for baseline imbalances.^{3,25}

Conclusion

The CADTH rapid review mentions multiple “limitations of the evidence on alteplase;” however, these limitations represent the selective inclusion of studies and a superficial exploration of the literature. As a further example, the rapid review lists the lack of generalizability to the Canadian population as a limitation of the evidence. Alteplase was conditionally licensed in Canada in 1999 based on the results of a prospective registry conducted at 60 centres across Canada that demonstrated a similar favourable efficacy and safety profile of alteplase as compared to clinical trials.²⁶ The question of the benefit of alteplase within 4.5 hours of the onset of symptoms has already been adequately answered, and clinicians across Canada can be reassured that they are delivering a robust treatment with proven benefits to patients. Stroke researchers are now actively involved in future innovations in thrombolysis therapy. The recent evidence demonstrating the benefit of alteplase in wake-up stroke population, beyond 4.5 hours in highly selected patients, and in mobile stroke units, are only a few examples. With the recent publication of

the cross-Canada Act RCT, we likely will be transitioning to tenecteplase very soon.²⁷ We look forward to future publications that review the totality of the evidence when assessing the benefits of thrombolysis and future collaborations with CADTH incorporating a clear and open expert review process with approval of final drafts before publication. This is the best way forward for patient care.

References

1. Darvesh N, Butcher R. Systemic thrombolysis by alteplase for acute ischemic stroke (CADTH rapid review with expert input). *Can J Health Technol.* 2022;2(6).
2. Cochrane methods IPD meta-analysis: about IPD meta-analysis. London (UK): The Cochrane Collaboration; 2022: <https://methods.cochrane.org/ipdma/about-ipd-meta-analyses>. Accessed 2022 Sep 7.
3. Lees KR, Bluhmki E, von Kummer R, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet.* 2010;375(9727):1695-1703.
4. 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(9958):1929-1935.
5. 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(9834):2352-2363.
6. Lees KR, Emberson J, Blackwell L, et al. Effects of alteplase for acute stroke on the distribution of functional outcomes: a pooled analysis of 9 trials. *Stroke.* 2016;47(9):2373-2379.
7. Chen X, Shen Y, Huang C, Geng Y, Yu Y. Intravenous thrombolysis with 0.9 mg/kg alteplase for acute ischaemic stroke: a network meta-analysis of treatment delay. *Postgrad Med J.* 2020;96(1141):680-685.
8. Lan L, Rong X, Li X, et al. Reperfusion therapy for minor stroke: a systematic review and meta-analysis. *Brain Behav.* 2019;9(10):e01398.
9. Acute stroke management: acute ischemic stroke treatment. *Canadian Stroke Best Practice recommendation.* Toronto (ON): Heart and Stroke Foundation of Canada; 2018: <https://www.strokebestpractices.ca/recommendations/acute-stroke-management/acute-ischemic-stroke-treatment>. Accessed 2022 Sep 7.
10. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med.* 1995;333(24):1581-1587.
11. Wardlaw JM, Murray V, Berge E, et al. Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis. *Lancet.* 2012;379(9834):2364-2372.
12. Carpenter CR, Keim SM, Milne WK, Meurer WJ, Barsan WG. Thrombolytic therapy for acute ischemic stroke beyond three hours. *J Emerg Med.* 2011;40(1):82-92.
13. Mun KT, Bonomo JB, Liebeskind DS, Saver JL. Fragility index meta-analysis of randomized controlled trials shows highly robust evidential strength for benefit of <3 hour intravenous alteplase. *Stroke.* 2022;53(6):2069-2074.
14. Saver JL, Gornbein J, Starkman S. Response to: "A graphic reanalysis of the NINDS Trial". *Ann Emerg Med.* 2010;55(2):226-227; author reply 229.
15. Agarwal S, Scher E, Lord A, et al. Redefined measure of early neurological improvement shows treatment benefit of alteplase over placebo. *Stroke.* 2020;51(4):1226-1230.
16. Saver JL, Yafeh B. Confirmation of tPA treatment effect by baseline severity-adjusted end point reanalysis of the NINDS-tPA stroke trials. *Stroke.* 2007;38(2):414-416.
17. Savitz SI, Lew R, Bluhmki E, Hacke W, Fisher M. Shift analysis versus dichotomization of the modified Rankin scale outcome scores in the NINDS and ECASS-II trials. *Stroke.* 2007;38(12):3205-3212.
18. Gladstone D, Hill M, Black S. tPA for acute stroke: balancing baseline imbalances. *CMAJ.* 2002;166(13):1652-1653.
19. Kwiatkowski TG, Libman RB, Frankel M, et al. Effects of tissue plasminogen activator for acute ischemic stroke at one year. National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study Group. *N Engl J Med.* 1999;340(23):1781-1787.

20. 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. *JAMA*. 2018;320(2):156-166.
21. Khatri P, Kleindorfer DO, Yeatts SD, et al. Strokes with minor symptoms: an exploratory analysis of the National Institute of Neurological Disorders and Stroke recombinant tissue plasminogen activator trials. *Stroke*. 2010;41(11):2581-2586.
22. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359(13):1317-1329.
23. Alper BS, Foster G, Thabane L, Rae-Grant A, Malone-Moses M, Manheimer E. Thrombolysis with alteplase 3-4.5 hours after acute ischaemic stroke: trial reanalysis adjusted for baseline imbalances. *BMJ Evid Based Med*. 2020;25(5):168-171.
24. Bluhmki E, Chamorro A, Dávalos A, et al. Stroke treatment with alteplase given 3.0-4.5 h after onset of acute ischaemic stroke (ECASS III): additional outcomes and subgroup analysis of a randomised controlled trial. *Lancet Neurol*. 2009;8(12):1095-1102.
25. Lansberg MG, Bluhmki E, Thijs VN. Efficacy and safety of tissue plasminogen activator 3 to 4.5 hours after acute ischemic stroke: a metaanalysis. *Stroke*. 2009;40(7):2438-2441.
26. Hill MD, Buchan AM. Thrombolysis for acute ischemic stroke: results of the Canadian Alteplase for Stroke Effectiveness Study. *CMAJ*. 2005;172(10):1307-1312.
27. Menon BK, Buck BH, Singh N, et al. Intravenous tenecteplase compared with alteplase for acute ischaemic stroke in Canada (AcT): a pragmatic, multicentre, open-label, registry-linked, randomised, controlled, non-inferiority trial. *Lancet*. 2022;400(10347):161-169.