Optimizing endovascular thrombectomy timing and thrombolysis use for ischemic stroke: insights from the SELECT2 and TIMELESS trials

Gauthier Nendumba[1], Julien Moury[1], Michael Van Nieuwenhove[1], Arnaud Robert[1], Benedicte Hauqiert[1], Ovidiu Vornicu[1,2], Sydney Blackman[3], Emily Perriens[4], Ryma Ghorayeb[4], Sofia Belhoussine Drissi[4], Patrick El Nawar[4], Alexis Philippot[4], Anne-Sophie Dincq[1,2], Patrick Evrard[1], Pierre Bulpa[1], Isabelle Michaux[1], Patrick M. Honore[1]^

[1]ICU, CHU UCL Godinne Namur, UCL Louvain Medical School, Yvoir, Belgium; [2]ICU and Anesthesiology Departments, CHU UCL Godinne Namur, UCL Louvain Medical School, Yvoir, Belgium; [3]ULB University Centre Hospitalier Universitaire Brugmann, Brussels, Belgium; [4]ULB University, Brussels, Belgium

Correspondence to: Prof. Patrick M. Honore, MD, PhD, FCCM. ICU, CHU UCL Godinne Namur, UCL Louvain Medical School, Campus Godinne, Avenue G Thérasse 1, 5530 Yvoir, Belgium. Email: patrick.honore@chuuclnamur.uclouvain.be.

Comment on: Sarraj A, Abraham MG, Hassan AE, *et al.* Endovascular thrombectomy plus medical care versus medical care alone for large ischaemic stroke: 1-year outcomes of the SELECT2 trial. Lancet 2024;403:731-40.

Keywords: Thrombectomy; thrombolysis; stroke; ischemic stroke

Submitted Mar 29, 2024. Accepted for publication Aug 21, 2024. Published online Aug 30, 2024.
doi: 10.21037/atm-24-64
View this article at: https://dx.doi.org/10.21037/atm-24-64

Introduction

The SELECT2 trial was designed to assess the long-term functional status of patients with large ischemic strokes at 1-year post-endovascular thrombectomy, as opposed to the established 3-month period during which improved functional status has already been established (1). Nine years ago, randomized controlled studies demonstrated the superiority of endobacterial thrombectomy over classical treatment in patients with cerebral vascular accident induced by vascular thrombosis in the bilateral internal carotid arteries (ICAs) and supplies blood to the majority of the cerebral hemispheres, including the frontal lobes, parietal lobes, lateral temporal lobes and anterior part of deep cerebral hemispheres. Nevertheless, the authors expressed concerns about the clinical outcomes of patients with large-core strokes following reperfusion. They observed that the number of sick persons achieving self-reliance and the ability to walk freely in those studies was significantly reduced compared to early studies of removal of a blood clot for sick persons with favorable scanners and limited ischemic modifications (2). Therefore, for large ischemic strokes, there was uncertainty about whether endovascular thrombectomy yielded superior long-term functional outcomes compared to thrombolysis alone (3,4).

The TIMELESS study addresses another area of medical uncertainty. Its aim was to with thrombolysis improve better recovery in sick patients with cerebral vascular accidents due to blood clots who were admitted later than 4.5 hours but within 24 hours after symptom onset. In these patients, thrombectomy is utilized if indicated.

What did the SELECT2 trial results reveal?

Patients eligible for inclusion were those within 24 hours of ischemic stroke onset and last known to be well. They were randomly assigned to thrombectomy (178 patients), with 21% receiving thrombolysis, or to medical care only

^ ORCID: 0000-0002-6697-4890.

(174 patients), with functional outcome as the primary endpoint (5).

Clot mechanical removal ameliorates with the significance of a specific scoring system after 12 months (modified ranking scale) compared to controls. A specific statistical analysis did show an important neurological gain with a P value of 0.0019. After 12 months 45% with clot mechanical removal passed away and 52% in the control group. This was not significant (1). These findings are reassuring as they confirm the results of another recent trial published by Sarraj *et al.*, which compared thrombectomy with medical treatment to medical treatment alone for large ischemic strokes (6). Indeed, in Sarraj study after 3 months using the same specific statistical analysis did show an important neurological gain as well with a P value of 0.001.

What did the TIMELESS trial results reveal?

In the TIMELESS trial, Albers *et al.* (7) conducted a comparative analysis of tenecteplase versus placebo, both administered with thrombectomy if indicated. This treatment was given within 4 to 24 hours after the sick person was still in good neurological shape among individuals exhibiting indications of salvageable tissue on perfusion imaging. In this study, the data obtained using the same specific statistical analysis did not show an important neurological gain for thrombolysis versus control arm.

In summary, tenecteplase therapy started at four and a half up to 24 hours after cerebral vascular accident was not associated with a neurological improvement as compared to placebo.

Comparison of data versus TIMELESS trial

Conversely, within the SELECT2 trial, 21% of the thrombectomy cohort also received thrombolysis. However, the specific timing of thrombolytic administration remains ambiguous, described as occurring within 24 hours of stroke onset without specifying the starting hour. This ambiguity prompts inquiry into whether the administration occurred before the 4.5-hour mark or later, between 4.5 and 24 hours. The distinction highlights a critical aspect of the TIMELESS trial, where the administration of thrombolysis within the window of 4.5 to 24 hours did not correlate with an elevated incidence of brain bleeding.

Another notable disparity lies in the primary endpoints of each study. In the TIMELESS trial, the primary endpoint evidently centered on functional improvement at 3 months, while the SELECT2 trial sought to evaluate functional improvement at one year. It can be posited that these two studies complement each other effectively, as they both shed light on how the combination of thrombolysis with thrombectomy in the management of large-core strokes appears to preserve brain function without increasing bleeding. Moreover, the pioneering approach of recruiting patients up to 24 hours after symptom onset represents a potentially advantageous strategy, particularly for patients who must traverse significant distances to access medical care.

Are these results applicable to a clinical setting?

The lessons after following those patients at 1 year look impressive and are somewhat confirmatory of the previous studies affirming the value of clot mechanical elimination in acute vascular cerebral events (7). This particular subgroup presents a distinct challenge for treatment indication, with only 3-month follow-up data currently available regarding functional benefits. The consistency of positive clinical outcomes observed at 1 year underscores the lasting benefit of clot mechanical elimination in large acute vascular cerebral events. However, it is noteworthy that the SELECT2 trial included only patients with an early computed tomography (CT) scanner in acute vascular ischemic events from three up to five, thereby limiting the generalizability of the findings. Furthermore, these patients exhibited a superior quality of life compared to those who were in the control arm.

While favorable results in the long run looking at clot mechanical elimination that sometimes ago elicited in the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) (following the sick people for 2 years) (8) together with REVASCAT trials, it is essential to acknowledge that those studies were not taking sick people with large acute vascular ischemic events (9,10). Another pertinent issue pertains to the North American cardiologic and brain recommendations for the first hour of taking care of an acute vascular ischemic event. According to these guidelines, endovascular therapy is indicated for stroke cases when administered within a time frame of 0 to 6 hours after onset. However, there is ongoing debate about whether this specific patient cohort could be treated by avoiding tissue plasminogen activator at the beginning, given the potential increased risk of bleeding associated with thrombectomy (10).

In the end, TIMELESS did not show a significant difference in outcomes when combining thrombectomy

and thrombolysis for strokes occurring 4.5 to 24 hours after onset. These results align with the recent multicenter retrospective CLEAR study, which compared the clinical outcomes and safety of bridging intravenous thrombolysis (IVT) in sick people undergoing acute vascular ischemic events in the bilateral ICAs and supply blood to the majority of the cerebral hemispheres, including the frontal lobes, parietal lobes, lateral temporal lobes and anterior part of deep cerebral hemispheres. Large vessel thrombosis who underwent IVT 6 up to 24 hours after the sick person was still in good neurological shape. There was no difference in functional outcomes at 3 months (adjusted common odds ratio for modified Rankin Scale shift, with a P value of 0.72 (11).

Summary

Based on the findings from both the SELECT2 and TIMELESS trials, there is evidence supporting the successful implementation of thrombectomy up to 24 hours after the onset of symptoms for large ischemic strokes, particularly in patients with viable brain tissue. However, a crucial unresolved issue pertains to the optimal timing and concomitant use of thrombolysis alongside thrombectomy for large ischemic strokes. Specifically, further investigation is warranted to determine whether thrombolysis should be administered concurrently with thrombectomy, and, if so, whether it is most beneficial within the initial 4.5 hours or within the extended 24-hour timeframe. This critical question underscores the need for ongoing research to refine treatment protocols and optimize outcomes for stroke patients.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was a standard submission to the journal. The article has undergone external peer review.

Peer Review File: Available at https://atm.amegroups.com/article/view/10.21037/atm-24-64/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-24-64/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Nendumba G, Moury J, Van Nieuwenhove M, Robert A, Hauqiert B, Vornicu O, Blackman S, Perriens E, Ghorayeb R, Belhoussine Drissi S, El Nawar P, Philippot A, Dincq AS, Evrard P, Bulpa P, Michaux I, Honore PM. Optimizing endovascular thrombectomy timing and thrombolysis use for ischemic stroke: insights from the SELECT2 and TIMELESS trials. Ann Transl Med 2024;12(5):100. doi: 10.21037/atm-24-64