Randomized controlled trials in emergency settings: Taking a HEADSTART on acute type A aortic dissection trials

Dominique Vervoort, MD, MPH, MBA,[a,b] Munir Boodhwani, MD, MMSc,[c] Michael W. A. Chu, MD,[d] Jennifer C. Y. Chung, MD, MSc,[a,e] Jehangir J. Appoo, MD,[f] *and* Maral Ouzounian, MD, PhD,[a,e] *Toronto, Ottawa, and London, Ontario, and Calgary, Alberta, Canada*

Keywords: Acute type A aortic dissection; Randomized controlled trial; Thoracic aortic surgery

Emergency operations comprise ≤50% of surgical practice across specialties, yet only 9.4% of surgical trials are related to emergency surgery settings.[1] In vascular surgery, nascent experiences arose from the IMPROVE (immediate management of patients with rupture: open versus endovascular repair) trial for ruptured abdominal aortic aneurysms (AAAs), which randomized patients to either open or endovascular surgical repair. In emergency thoracic aortic surgery, the DARTS (dissected aorta repair through stent implantation) and Evaluation of the GORE ascending stent graft in the treatment of lesions of the ascending aorta trials provided nonrandomized insights; however, no randomized trials have been conducted in the acute setting to date. Acute type A aortic dissections (ATAADs), however, remain associated with considerable morbidity and mortality, with ≤25% of patients dying before reaching the hospital, and operative mortality remains as high as 20% to 25%.[2,3] Although the burden of ATAAD is proportionally lower than that of AAAs and ruptured AAAs, the known incidence and prevalence rates are increasing across countries due to improved diagnostics and referral, aging populations, and increasing rates of hypertension. Conversely, prehospital and preoperative mortality rates have decreased due to faster referral and emergency care networks and reduced times to intervention, and operative mortality has decreased due to improved perioperative care practices and surgical techniques. Nevertheless, practice variation persists. In the United States, the center volumes for ATAAD repair range from a few procedures per year to high-volume referral centers.[4]

Surgery for ATAAD involves either the standard hemiarch repair or extended arch repair techniques. Hemiarch repair is in the skillset of every cardiac surgeon and involves a more conservative approach to quickly manage the dissection. Extended arch repair techniques require specialized aortic expertise to perform more extensive distal repairs but are associated with improved false lumen thrombosis and lower rates of reintervention. In patients without an intimal tear in the aortic arch or additional arch aneurysm, hemiarch repair is recommended. However, for patients with malperfusion, societal guidelines encourage the consideration of extended arch repair techniques.[5] However, for patients eligible for both procedures, clinical equipoise remains based on expert consensus and meta-analyses based on purely observational evidence. As a result, the rates of extended arch repair vary substantially between countries (eg, higher rates in Europe and Asia compared with North America) and within countries (eg, across Canada).[6,7] Randomized evidence is, thus, urgently needed to best inform patients and guide the training and practice of future cardio-aortic surgeons. The Treatment in Thoracic Aortic Aneurysm: Hemiarch vs Extended Arch in Aortic Dissection—a SystemaTic Analysis by Randomized Trial (TITAN:HEADSTART; ClinicalTrials.gov identifier, NCT03885635) will seek to randomize patients with ATAAD eligible for both hemiarch and extended arch repair procedures to either intervention with deferred consent. The trial will comprise a pilot trial (n = 50) to determine the feasibility of randomizing patients in an emergency surgery setting and, if successful, a full trial (n = 296) to

From the Division of Cardiac Surgery,[a] and Institute of Health Policy, Management and Evaluation,[b] University of Toronto, Toronto; the University of Ottawa Heart Institute, University of Ottawa, Ottawa[c]; the Division of Cardiac Surgery, University of Western Ontario, London[d]; the Division of Cardiovascular Surgery, Peter Munk Cardiac Centre, Toronto General Hospital, University of Toronto, Toronto[e]; and the Libin Cardiovascular Institute, University of Calgary, Calgary.[f]

The TITAN:HEADSTART trial is funded by a grant by the Heart and Stroke Foundation.

Correspondence: Maral Ouzounian, MD, PhD, FRCSC, Division of Cardiovascular Surgery, Peter Munk Cardiac Centre, Toronto General Hospital, University of Toronto, 200 Elizabeth St, 4N-464, Toronto, ON M5G2C4, Canada (e-mail: maral.ouzounian@uhn.ca).

The editors and reviewers of this article have no relevant financial relationships to disclose per the Journal policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

J Vasc Surg Cases Innov Tech 2024;10:101457

2468-4287

https://doi.org/10.1016/j.jvscit.2024.101457

comparatively evaluate both procedures with 3-year outcomes. The outcomes will include detailed neurologic and imaging end points with a core computed tomography laboratory. The trial has surgeon and center expertise criteria that are manageable for most cardiac centers to minimize confounding in procedural outcomes. The trial will operate under the TITAN trial umbrella, alongside other successful (but nonemergency) trials of thoracic aortic surgery, such as the Treatment in Thoracic Aortic Aneurysm: Surgery versus Surveillance (TITAN:SvS; ClinicalTrials.gov identifier, NCT03536312) trial[8] and the Comparing Hypothermic Temperatures During Hemiarch Surgery (TITAN:COMMENCE; ClinicalTrials.gov identifier, NCT02860364) trial. It has further obtained competitive grant funding and laid the foundation among participating pilot sites across Canada.

Despite the initial successes of TITAN:HEADSTART, several challenges are anticipated. First, the heterogeneity in extended arch procedures (eg, total arch replacement, frozen elephant trunk, Ascyrus Medical dissection stent) requires a balance between matching variability in clinical practice and ensuring statistical power for trial analysis and subsequent generalizability of findings.[9] To overcome this, the pilot trial will compare hemiarch repair with total arch and frozen elephant trunk repair, excluding other techniques, such as the Ascyrus Medical dissection stent. Depending on the success of the pilot trial and experience of the participating sites, the full trial might follow the same protocol or expand the scope of extended arch procedures as an adaptive trial. Second, expertise plays an important role in the performance of extended arch repair, which raises the question of whether regionalization and/or the establishment of centers of excellence for extended arch procedures is necessary.[10] The expertise criterion for participation is introduced to standardize outcomes, because randomization among surgeons uncomfortable performing extended arch procedures would not be justifiable. Whether the findings will be generalizable to smaller centers or all surgeons can thus be debated. Third, quality of life and patient preference must be evaluated, because ATAADs, rehabilitation after surgery, and potential reinterventions substantially affect patients' and families' lives. The trial incorporates a range of patient-reported outcome measures to accompany the clinical outcomes.

Encouragingly, we foresee several opportunities to take a head start on trials for ATAADs. The TITAN:HEADSTART trial will be the first randomized controlled trial for ATAADs, opening the door for other aortic and nonaortic cardiac trials in the emergency setting. In so doing, the trial will be a learning opportunity for the cardiovascular surgical community as it relates to setting up the "ideal" trial for ATAAD surgery, both for TITAN:HEADSTART and for future trials. Adaptive trial designs might become the norm, particularly in increasingly complex, personalized, and specialized domains such as thoracic aortic surgery, in which flexibility and sustained methodologic rigor will be paramount. Furthermore, deferred consent and neurologic and imaging end points with a core laboratory will provide novel insights into their application for thoracic aortic surgical trials. In particular, deferred consent can enable recruitment for randomized controlled trials even in emergency settings, where the acuity, severity, and emotional load would otherwise not facilitate standard trial consent practices. Finally, the trial actively incorporates room for qualitative and mixed-methods research to inform future center participation, patient recruitment, deferred consent, imaging, and funding.

DISCLOSURES

D.V. is supported by the Canadian Institutes of Health Research Vanier Canada Graduate Scholarship. M.O. is partially supported by the Munk Chair in Advanced Therapeutics and the Antonio & Helga DeGasperis Chair in Clinical Trials and Outcomes Research. M.W.A.C. is supported by the Ray and Margaret Elliott Chair in Surgical Innovation and has received speakers' honoraria from Medtronic, Edwards Lifesciences, Terumo Aortic, and Artivion.

REFERENCES

1. Morley RL, Edmondson MJ, Rowlands C, Blazeby JM, Hinchliffe RJ. Registration and publication of emergency and elective randomised controlled trials in surgery: a cohort study from trial registries. *BMJ Open*. 2018;8:e021700.
2. Hagan PG, Nienaber CA, Isselbacher EM, et al. The international registry of acute aortic dissection (IRAD): new insights into an old disease. *JAMA*. 2000;283:897–903.
3. LeMaire SA, Russell L. Epidemiology of thoracic aortic dissection. *Nat Rev Cardiol*. 2011;8:103–113.
4. Bowdish ME, D'Agostino RS, Thourani VH, et al. STS Adult Cardiac Surgery Database: 2021 update on outcomes, quality, and research. *Ann Thorac Surg*. 2021;111:1770–1780.
5. Isselbacher EM, Preventza O, Hamilton Black J 3rd, et al. 2022 ACC/AHA guideline for the diagnosis and management of Aortic Disease: a report of the American heart association/American college of cardiology joint committee on clinical practice guidelines. *Circulation*. 2022;146:e334–e482.
6. Elbatarny M, Stevens LM, Dagenais F, et al. Hemiarch versus extended arch repair for acute type A dissection: results from a multicenter national registry. *J Thorac Cardiovasc Surg*. 2023;167:935–943.e5.
7. Ouzounian M, Hage A, Chung J, et al. Hybrid arch frozen elephant trunk repair: evidence from the Canadian Thoracic Aortic Collaborative. *Ann Cardiothorac Surg*. 2020;9:189–196.
8. Guo MH, Appoo JJ, Wells GA, et al. Protocol for a randomised controlled trial for treatment in thoracic aortic aneurysm: surgery versus surveillance (TITAN: SvS). *BMJ Open*. 2021;11:e052070.
9. Smith HN, Boodhwani M, Ouzounian M, et al. Classification and outcomes of extended arch repair for acute Type A aortic dissection: a systematic review and meta-analysis. *Interact Cardiovasc Thorac Surg*. 2017;24:450–459.
10. Dobaria V, Kwon OJ, Hadaya J, et al. Impact of center volume on outcomes of surgical repair for type A acute aortic dissections. *Surgery*. 2020;168:185–192.

Submitted Feb 1, 2024; accepted Feb 13, 2024.