A randomized trial comparing axillary versus innominate artery cannulation for aortic arch surgery

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ABSTRACT

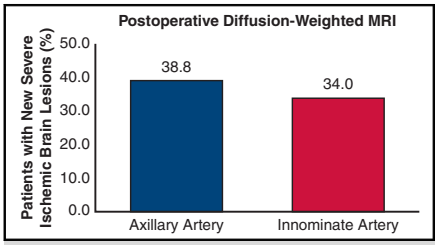
Background: Cerebral protection remains the cornerstone of successful aortic surgery; however, there is no consensus as to the optimal strategy.

Objective: To compare the safety and efficacy of innominate to axillary artery cannulation for delivering antegrade cerebral protection during proximal aortic arch surgery.

Methods: This randomized controlled trial (The Aortic Surgery Cerebral Protection Evaluation CardioLink-3 Trial, ClinicalTrials.gov Identifier: NCT02554032), conducted across 6 Canadian centers between January 2015 and June 2018, allocated 111 individuals to innominate or axillary artery cannulation. The primary safety outcome was neuroprotection per the appearance of new severe ischemic lesions on the postoperative diffusion-weighted-magnetic resonance imaging. The primary efficacy outcome was the difference in total operative time. Secondary outcomes included 30-day all-cause mortality and postoperative stroke.

Results: One hundred two individuals (mean age, 63 ± 11 years) were in the primary safety per-protocol analysis. Baseline characteristics between the groups were similar. New severe ischemic lesions occurred in 19 participants (38.8%) in the axillary versus 18 (34%) in the innominate group (P for noninferiority = .0009). Total operative times were comparable (median, 293 minutes; interquartile range, 222-411 minutes) for axillary versus (298 minutes; interquartile range, 231-368 minutes) for innominate (P for superiority = .47). Stroke/transient ischemic attack occurred in 4 (7.1%) participants in the axillary versus 2 (3.6%) in the innominate group (P = .43). Thirty-day mortality, seizures, delirium, and duration of mechanical ventilation were similar in both groups.

Conclusions: diffusion-weighted magnetic resonance imaging assessments indicate that antegrade cerebral protection with innominate cannulation is safe and affords similar neuroprotection to axillary cannulation during aortic surgery, although the burden of new neurological lesions is high in both groups. (J Thorac Cardiovasc Surg 2022;164:1426-38)



Patients with new severe ischemic brain lesions postantegrade cerebral perfusion.

CENTRAL MESSAGE

In patients undergoing proximal aortic arch surgery, innominate artery cannulation is a safe option for establishing antegrade cerebral perfusion for neuroprotection.

PERSPECTIVE

Large multicenter randomized controlled trials comparing the full spectrum of cerebral protection strategies employed during proximal aortic arch operations are necessary to determine the optimal cerebral protection strategy to further reduce the burden of postoperative neurological injury.

See Commentaries on pages 1439, 1440, and 1442.

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Abbreviations and Acronyms

ACE CardioLink-3 = Aortic Surgery Cerebral Protection Evaluation CardioLink-3
ACP = antegrade cerebral protection
CPB = cardiopulmonary bypass
DW-MRI = diffusion-weighted magnetic resonance imaging
HCA = hypothermic circulatory arrest
MRS = Modified Rankin Scale
NSE = neuron-specific enolase
RCTs = randomized controlled trials
S100β = S100 calcium-binding protein β
TIA = transient ischemic attack

Scanning this QR code will take you to the table of contents to access supplementary information.

Aneurysms of the aortic root, ascending aortic arch, and proximal aortic arch are potentially fatal and rank consistently in the top-20 causes of death worldwide.[1-4] Despite significant advances in endovascular repair strategies for descending and abdominal aortic aneurysms, open surgical reconstruction with a woven polyester graft is essential for definitive repair of the proximal aorta.[4-6] Complete ascending and proximal arch replacements require cardiopulmonary bypass (CPB) and a period of hypothermic circulatory arrest (HCA) to enable surgical reconstruction. Current trends suggest that antegrade cerebral perfusion (ACP) techniques are increasingly being used for brain protection with less reliance on hypothermia alone.

Contemporary studies that have focused on clinically defined strokes have consistently demonstrated a relatively low incidence of stroke (between 2% and 8%) following aortic surgery with HCA.[7,8] However, in instances when neuroimaging was obtained postaortic surgery, new lesions were frequently observed.[9,10] Although defining the overall burden of neurological injury can be challenging, these silent ischemic brain lesions may have substantial clinical relevance because they can result in cognitive or neuropsychological deficits and accelerate vascular dementia.[11] Previous studies have demonstrated that neurological injury following aortic surgery increases both the risk of death and morbidity, including prolonged mechanical ventilation, and extended intensive care unit and hospital stay.[12]

Over the past 2 decades, cerebral protection techniques employed during aortic surgeries that rely on circulatory arrest have evolved from reliance on deep hypothermia alone to moderate hypothermia plus ACP delivered via the right axillary artery.[13] Although deep HCA with or without retrograde cerebral perfusion is still practiced, particularly during emergency aortic operations where simplicity and speed are priorities, ACP delivered via the axillary has been associated with better neurological outcomes and survival.[7,13-21] ACP via the axillary artery is relatively straightforward; however, it is time consuming and is associated with local complications, including brachial plexus injury and seroma.[22-25]

We previously reported our method of innominate artery cannulation to overcome some of the limitations associated with axillary delivered ACP while allowing for simple, practical, and efficient perfusion of the brain.[26] Notably, several retrospective analyses have suggested that ACP achieved via the innominate is associated with low rates of neurological injury and good survival.[26-32] Based on these observations, innominate cannulation for ACP has emerged as an attractive option for surgeons who perform proximal aortic arch operations. However, there are no data from robust randomized controlled trials (RCTs) comparing the neurological safety of ACP via innominate cannulation to the axillary approach.

We therefore sought to evaluate the safety and efficacy of innominate cannulation against axillary cannulation for establishing ACP in an RCT of patients undergoing proximal aortic arch surgery with HCA. This article describes the results of the prospective Aortic Surgery Cerebral Protection Evaluation (ACE) CardioLink-3 trial.

METHODS

Study Design

The study design and protocol of the ACE CardioLink-3 trial have been described.[33] In brief, this 6-center, 2-arm, noninferiority RCT compared innominate to traditional axillary cannulation for providing ACP in adults undergoing elective repair of the ascending aorta and proximal arch requiring HCA and an open distal anastomosis. Individuals requiring urgent or emergent operations, total aortic arch replacements, or surgery for aortic dissection were excluded. Additionally, preoperative computed tomography imaging for each potential subject was reviewed by the primary surgeon before approaching for consent, to ensure either cannulation technique could be performed safely. Excessive calcification, tortuosity, or atheroma in the innominate artery was considered a relative contraindication to innominate cannulation. ACP was delivered unilaterally because the method is simple, efficient, and has been shown to provide similar adjunct benefits to bilateral ACP.[34] Neuromonitoring was standardized across study sites, with the use of bilateral noninvasive near infrared spectroscopy to measure cerebral oximetry for the duration of surgery. There was a set target of right brachial pressure of 50 to 70 mm Hg. The trial was coordinated, and the data collected and analyzed by the Applied Health Research Center at the Li Ka Shing Knowledge Institute of St Michael's Hospital in Toronto, Ontario, Canada. The protocol and consent were approved at the lead site and subsequently by local research ethics boards. The primary outcome was independently adjudicated by a central committee that was

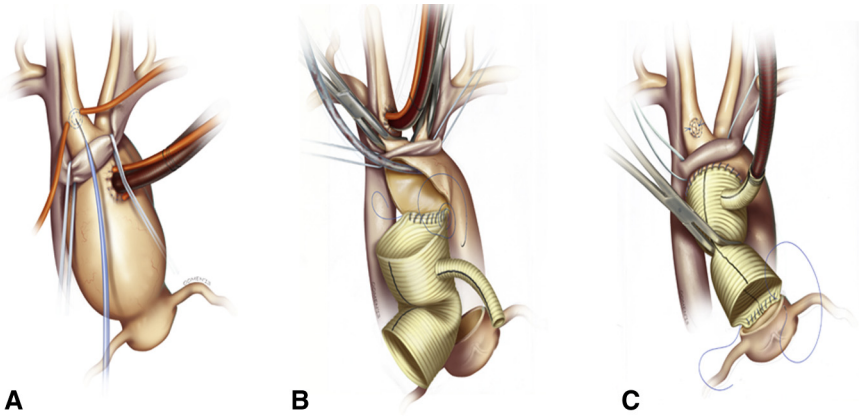


FIGURE 1. Surgical technique used in innominate artery cannulation.[26] A, The distal aneurysmal ascending aorta is cannulated using a standard 7 to 8 mm arterial cannula before cardiopulmonary bypass and cooling are initiated. The base of the innominate artery is mobilized after exposure with vessel loop control. Two purse string sutures are placed on the anterior wall of the proximal innominate artery, followed by sequential dilators and the 14Fr pediatric venous cannula, inserted using the Seldinger technique over a guidewire. B, The base of the innominate artery is clamped, and antegrade cerebral perfusion (ACP) is initiated as the afferent limb of the cardiopulmonary bypass (CPB) circuit is connected to the 14Fr pediatric venous cannula. Distal reconstruction is underway. C, The distal anastomosis is complete. ACP has been discontinued as the aortic line is connected to the 8-mm side limb of the Dacron (Du Pont, Wilmington, Del) graft. Full CPB is resumed and the graft is clamped distally to allow for completion of the proximal reconstruction.

blinded to group assignments, with the use of standard criteria.[35] The ACE CardioLink-3 trial is registered at ClinicalTrials.gov (Identifier: NCT02554032).

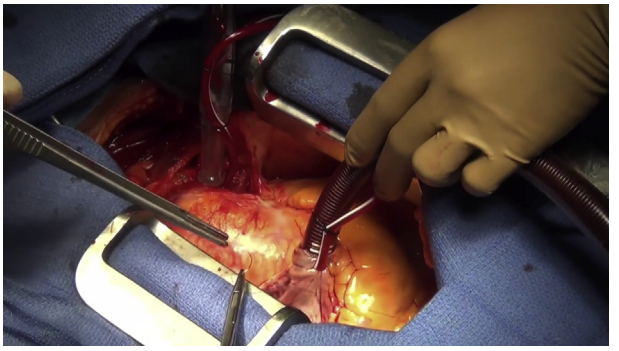
Surgical Strategies

The surgical strategies using the innominate (Figure 1) and axillary artery approaches have been described[21,26] and were standardized before randomization of the first participant. Details of each cannulation technique are in Video 1. The majority of patients requiring elective aortic operations with a hemiarch or open distal anastomosis, qualified anatomically for either innominate or axillary cannulation. We excluded, by design, patients presenting with acute type A aortic dissection or intramural hematoma, contained rupture, reoperative cardiac surgery with moderate to high risk sternal re-entry, or planned total arch replacement because most of the study authors continue to preferentially employ axillary cannulation for this select group of patients.

Outcomes

The primary safety outcome was the proportion of participants with new severe ischemic lesions as evidenced by comparing preoperative and postoperative diffusion-weighted magnetic resonance imaging (DW-MRIs).[33] The prespecified MRI protocol adhered to American College of Radiology standards for performance and interpretation of MRI of the brain, and required DW-MRI, apparent diffusion coefficient, fluid-attenuated inversion recovery, and T1-weighted images.[36] Severe ischemic lesions were defined as severe white matter injury; an infarction involving the basal ganglia, thalamus, or internal capsule; or a large hemispheric infarction present on the postoperative DW-MRI when compared with preoperative DW-MRI.[33] Severe white matter injuries involved 6 or more punctate lesions (<4 mm), or 2 or more lesions that were 4 mm or larger, consistent with recent infarcts in the white matter. A large hemispheric DW-MRI positive lesion was defined as >15 mm or involving most (>50%) of the territory of a circle of Willis branch or the major divisions, including middle cerebral artery, anterior cerebral artery, posterior cerebral artery, anterior inferior cerebellar artery, posterior inferior cerebellar artery, or the superior cerebellar artery. All DW-MRIs were processed and read at the central core imaging laboratory at the University of Calgary by 2 independent neuroradiologists blinded to treatment assignment. All discrepancies were identified in the central database and sent to the core imaging lab for further adjudication. These images were reviewed by a third neuroradiologist, also blinded to treatment allocation, who made the final decision. MRI data acquisition, handling, and review were defined in an imaging charter document, adhering to existent draft guidance from the US Food and Drug Administration for clinical trial imaging end point process standards.[37]

The primary efficacy outcome was the difference in total operative time between the 2 study groups. Important secondary postoperative outcomes included 30-day all-cause mortality, in hospital stroke or transient ischemic



VIDEO 1. Innominate artery cannulation technique. The video demonstrates the simplicity of cannulating the innominate artery, using a 14Fr cannula. Importantly, the video demonstrates how innominate cannulation streamlines the flow of the operation: we open the chest, establish cardiopulmonary bypass by cannulating the ascending aorta with a standard cannula, begin cooling, then we isolate the base of the innominate artery, place 2 purse string sutures on the anterior wall, and cannulate over a wire after gentle dilatation through the purse strings. Once the target systemic temperature is achieved, flow is initiated via the innominate artery to the brain, while the ascending cannula is removed. The open distal or hemiarch anastomosis is constructed, then full bypass is resumed via an anteflo (Gelweave; Terumo Corporation, Tokyo, Japan) limb on the graft. We then immediately remove the innominate cannula and tie down the purse string sutures, begin systemic rewarming and complete the proximal work. Video available at: https://www.jtcvs.org/article/S0022-5223(20)33143-3/fulltext.

attack (TIA), and cognitive dysfunction at 4 days (evaluated with the Montreal Cognitive Assessment and Mini-Mental State Examination). MRI indices such as total lesion volume, levels of S100 calcium-binding protein β (S100β) and neuron specific enolase (NSE) were measured at 24 hours postoperatively with commercially available enzyme-linked immunosorbent assay kits. Complications including sepsis, delirium, myocardial infarction, and local brachial plexus injury and seroma were also recorded.

Randomization and Follow-up

On the day of the scheduled operation central randomization via a concealed, locked, web-based electronic data capturing system, allocated participants in a 1:1 ratio to innominate or axillary artery cannulation. The sequence was computer-generated, blocked with random permuted blocks of sizes 2 and 4 and stratified by surgical center. In-hospital follow-up occurred daily during the postoperative course and involved DW-MRI procedures and Modified Rankin Scale (MRS) interviews for stroke, and Montreal Cognitive Assessment/Mini-Mental State Exam for neurocognitive assessment. A telephone follow-up occurred 30 days postsurgery to assess for vital status and new stroke using MRS.

Interim Analysis and Data Monitoring

An independent data safety and monitoring board, composed of experts in cardiac surgery, neuroimaging, and perioperative care, reviewed the clinical and safety data that included all adverse events listed as primary and secondary outcomes during the trial.

Statistical Analysis

Sample size calculations were based on prior literature that reported that approximately 50% of those assigned to the axillary cannulation group would develop new lesions.[6] An acceptable noninferiority margin of an absolute risk difference of 25% was determined via consensus of investigators from cardiac surgery, anesthesia, critical care, and radiology. A final sample size of 110 participants (55 in each group) would provide 80% power to detect noninferiority of the primary safety outcome at this margin with a 1-sided alpha of 0.05 while allowing for 10% attrition. This sample size also gave >80% power to detect a difference of 45 minutes in the superiority analysis of the primary efficacy outcome of total operative time at a 2-sided alpha of 0.05 assuming a standard deviation of 80 minutes.

Because the primary safety outcome was a noninferiority comparison, we used a per-protocol analysis to avoid bias toward noninferiority, which is inherent with intention-to-treat analyses. The observed difference was compared against the noninferiority margin using a 1-sided z test. Differences in proportions are reported with 90% confidence intervals (CIs) to reflect the 1-sided test. The primary efficacy analysis was an intention-to-treat superiority comparison of total operative time between groups using a 2-sample t test with $\alpha = 0.05$. To control the familywise type I error rate, stepwise testing of primary outcomes was performed, allowing for superiority testing of the primary efficacy outcome only if noninferiority could be established for the primary safety outcome. Binary outcomes (ie, 30-day mortality, stroke/TIA, delirium, seizure, encephalopathy, adverse events, and local complications) were compared using a χ^2 test or Fisher exact test if expected counts were <5. For each outcome, the absolute risk difference and 95% CI were reported. Continuous outcomes were analyzed using t tests or analysis of covariance adjusted for baseline scores, as appropriate. Analyses were performed using the R statistical package version 3.4.3 (R Foundation for Statistical Computing, Vienna Austria).

RESULTS

Study Population and Participant Characteristics

A total of 111 participants from 6 Canadian centers (Appendix E1) underwent randomization from January 2015 through June 2018. Of these, 102 were included in the primary safety per-protocol analysis (Figure 2). The baseline clinical characteristics between the groups were well balanced (Table 1). More than one-third underwent a Bentall plus hemiarch procedure, the remaining had either supra-coronary replacement of the ascending aorta with or without concomitant hemiarch or aortic valve replacement (Table 2). Total HCA duration, ACP duration, CPB time, and nadir nasopharyngeal temperatures were similar between the groups (Table 2).

Clinical and Biomarker Outcomes

New severe ischemic lesions occurred in 19 (38.8%) patients from the axillary cannulation group and in 18 (34.0%) patients from the innominate cannulation group (absolute risk difference, –4.8 percentage points; 90% CI, –20.4 to 10.9; odds ratio, 0.81; 90% CI, 0.41 to 1.60) (Figure 3, *A*). The upper limit of the 90% CI for the risk difference was within the prespecified noninferiority margin ($P = .0009$). The median number of any ischemic lesion on DW-MRI was 1 (interquartile range [IQR], 0-5) lesion per patient in the axillary group versus 2 (IQR, 0-5.5) lesions per patient in the innominate group ($P = .46$). Twenty-three (41%) patients in the axillary group had no new lesions versus 17 (31%) in the innominate group ($P = .32$).

Total lesion volume in the 2 groups was comparable (Figure 3, *B*). The primary efficacy analysis demonstrated no significant difference in the median total operative time, 293 minutes (IQR, 222-411 minutes) for axillary versus 298 minutes (IQR, 231-368 minutes) for the innominate group (P value for superiority = .47) (Figure 3, *C*).

Table 3 summarizes the occurrences of new severe ischemic lesions, defined as type 1 through 4. There was no significant difference in the number of small or larger lesions in the white matter, basal ganglia, thalamus, or internal capsule, or large hemispheric lesions between the 2 groups.

Neurocognitive outcomes were similar between the 2 groups pre- and postoperatively as were other secondary safety outcomes (Table 4). The 30-day all-cause mortality was 3.9% in the axillary group versus 3.7% in the innominate group ($P = 1.0$). The percentage of participants who experienced seizures, delirium, and encephalopathy were similar across the groups. Stroke/TIA occurred in 4 (7.1%) patients in the axillary group and in 2 (3.6%) allocated to the innominate group ($P = .43$). Duration of mechanical ventilation, length of intensive care unit and hospital stays were all similar. Biomarkers of neuronal injury (NSE and S100β) were not significantly different between the groups both pre- and postoperatively. Adjusted for preoperative levels, the postoperative NSE level was 1.2 ng/mL (95% CI, –0.9 to 3.4; $P = .27$) higher in the innominate versus axillary group, whereas the S100β postoperative level was 25.4 pg/mL (95% CI, –74.2 to 23.5;

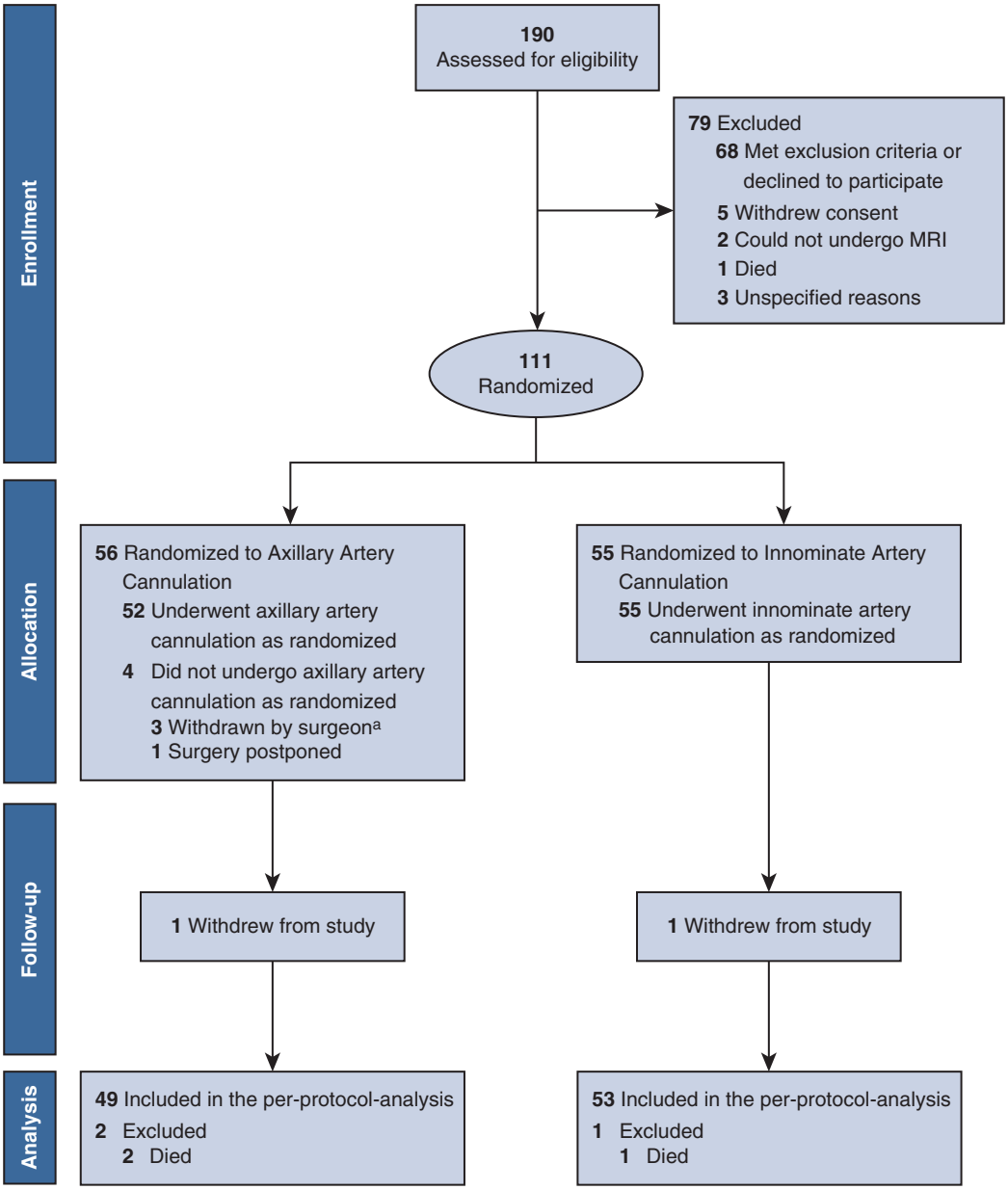


FIGURE 2. Consolidated standards of reporting trials diagram. [a]Withdrawn by surgeon before cannulation for safety reasons.

$P = .31$) lower in the innominate versus axillary group. Efficacy of ACP, as assessed by cerebral oxygen saturation monitoring, was similar in both groups (Figure E1).

DISCUSSION

The ACE CardioLink-3 trial used pre- and early postoperative DW-MRI results as the primary outcome measure to provide the first rigorously conducted, randomized comparison of innominate versus axillary artery cannulation with respect to delivery of cerebral protection in adults undergoing aortic surgery. We report noninferiority for the primary safety outcome of new severe ischemic brain lesions and key secondary cerebral outcomes between both techniques, and no significant difference between innominate versus axillary artery cannulation with respect to total operative time. New and clinically silent brain lesions were detected by DW-MRI following aortic surgery far more frequently than observed clinical end points of neurological injury, such as stroke and TIA.

Aortic surgery, in many instances, necessitates HCA to allow complete resection of the ascending aorta and proximal aortic arch. Cerebral protection during such periods remains the most important consideration for favorable patient outcomes. There are several approaches that are

TABLE 1. Baseline characteristics of the Aortic Surgery Cerebral Protection Evaluation CardioLink-3 cohort

Variable	Axillary artery cannulation (n = 56)	Innominate artery cannulation (n = 55)
Age (y)	61.5 ± 12.8	64.8 ± 10.5
Women	14 (25.5)	12 (21.8)
Body surface area (m^2)	2.1 ± 0.3	2.1 ± 0.3
Hypertension	38 (71.7)	35 (63.6)
Diabetes mellitus	8 (15.1)	6 (10.9)
Requiring insulin*	1 (12.5)	0 (0.0)
Dyslipidemia	25 (47.2)	30 (54.5)
History of heart failure	6 (11.3)	12 (21.8)
Left ventricular ejection fraction (%)	60.8 ± 12.0	50.2 ± 13.3
NYHA class†		
I	5 (83.3)	8 (66.7)
II	1 (16.7)	2 (16.7)
III	0 (0.0)	1 (8.3)
IV	0 (0.0)	1 (8.3)
Stroke	3 (5.7)	3 (5.5)
Transient ischemic attack	2 (3.8)	2 (3.6)
Chronic kidney disease	2 (3.8)	3 (5.5)
Coronary artery disease	11 (20.8)	10 (18.2)
Previous percutaneous coronary intervention	1 (1.9)	4 (7.3)
Chronic obstructive pulmonary disease	6 (11.3)	4 (7.3)
Past/current smoker	28 (52.8)	22 (40.0)
Pulmonary hypertension	4 (7.5)	5 (9.1)
Congenital aortic disease	21 (39.6)	8 (14.5)
Previous cardiac surgery	4 (7.5)	2 (3.6)
History of atrial fibrillation	5 (9.4)	8 (14.5)
Aortic root diameter (mm)	41.3 ± 8.1	43.4 ± 8.1
Aortic valve involvement with aortic aneurysm	35 (66.0)	39 (70.9)
Ascending aorta diameter (mm)	49.8 ± 8.6	51.2 ± 7.9
Patent foramen ovale	1 (1.9)	0 (0.0)

Values are presented as mean ± standard deviation or n (%). *NYHA*, New York Heart Association. *Only applicable to those who have diabetes mellitus. †Only applicable to patients with a history for heart failure.

commonly used to achieve cerebral protection, amongst which are deep hypothermia (<20°C) without brain perfusion and variations of hypothermic temperatures with either retrograde or ACP.[38-43] Although deep HCA without adjunctive brain perfusion is still used, it has been associated with greater morbidity, including a higher risk of stroke and neurological dysfunction and in some studies, an increased risk of death with prolonged periods of circulatory arrest.[44-46] In the contemporary era, hypothermic arrest with cerebral perfusion, delivered in an antegrade fashion via the right axillary artery, is a common strategy for brain protection during periods of circulatory arrest in many high volume aortic centers.[44-47]

There interest in establishing ACP via the innominate artery obviating the need for an additional axillary incision, and therefore preventing associated complications while simplifying the ACP delivery strategy and reducing operative time.[21] Innominate cannulation is widely applicable because most patients are anatomically suitable, and complications related to the technique, such as arterial perforation and dissection, are very low.[40,48-50] Despite the increased adoption of innominate artery cannulation as an

TABLE 2. Types of aortic surgical procedures and key operative variables

Procedure or variable	Axillary artery cannulation (n = 56)	Innominate artery cannulation (n = 55)
Aortic surgical procedures		
RAA + hemiarch	13 (25.5)	5 (9.1)
Bentall + hemiarch	18 (35.3)	20 (37.0)
RAA + hemiarch + AVR	11 (21.6)	19 (35.2)
Key operative variables		
Total HCA duration (min)	20.4 ± 7.6	21.6 ± 9.3
Total CPB duration (min)	164.2 ± 68.5	179.2 ± 68.3
Total crossclamp duration (min)	134.5 ± 58.3	149.1 ± 59.5
Total ACP time (min)	22.3 ± 15.4	22.2 ± 13.6
Cooling time (min)	36.1 ± 21.7	31.6 ± 19.2
Rewarming time (min)	70.2 ± 37.6	69.3 ± 41.2
Nadir nasopharyngeal temperature (°C)	25.8 ± 3.7	25.6 ± 3.9

Values are presented as n (%) or mean ± standard deviation. *RAA*, Replacement of the ascending aorta; *AVR*, aortic valve replacement; *HCA*, hypothermic circulatory arrest; *CPB*, cardiopulmonary bypass; *ACP*, antegrade cerebral perfusion.

alternative to axillary cannulation, there have been no well-designed trials with rigorous comparative data to evaluate the safety and efficacy of these techniques.

Clinical markers of neurological injury, such as stroke/TIA and delirium, are relatively infrequent and thus not sufficiently sensitive to detect the true burden of brain injury. Although postoperative neurological injury is often noted anecdotally, with patients describing inability to concentrate or increased forgetfulness, defining the mechanism and the true incidence has been a challenge. Additionally, the exact incidence of brain injury is likely much higher than is appreciated clinically. Studies after transcatheter aortic valve implantation, using sensitive imaging modalities such as DW-MRI, demonstrate new ischemic lesions in up to 70% to 80%,[51,52] whereas studies with patients undergoing surgical valve replacement or coronary artery bypass grafting have observed new lesions in up to half of all patients.[53]

This trial is among very few RCTs to utilize DW-MRI both preoperative and early postoperatively to accurately document new ischemic lesions that occurred following aortic replacement. Our study revealed new severe ischemic lesions in 38.8% of participants in the axillary cannulation group and 34.0% in the innominate. These results are consistent with and add to the growing literature showing that the rate of new ischemic brain lesions on DW-MRI after aortic surgery in adults ranges from 40% to 60%.[6,54,55]

Although the prognostic significance of these silent ischemic lesions remains poorly understood, some studies indicate a potentially increased risk of cognitive decline and a 2-fold increase risk of dementia.[56,57] Barber and colleagues[54] demonstrated a correlation between the presence of these lesions and neurocognitive dysfunction following cardiac surgery. Despite a significant number of patients having new severe ischemic lesions found on postoperative DW-MRI in this study, the rates of clinically relevant neurological or neurocognitive deficits does not appear clinically significant in the short-term, at least as judged by the battery of neurocognitive tests used in this study. It is possible, that more detailed neurocognitive assessment would have revealed more subtle impairment. More extensive studies focused on understanding both the immediate, as well as the long-term influence on brain function are needed.

The total size of the new ischemic lesions is a prognostically significant measure[11,58,59] and served as the impetus for prespecifying total lesion volume as a key secondary outcome. In previous studies, total lesion volume was found to be the most reproducible measurement and a better method of assessing overall burden of ischemic injury.[11,58] Furthermore, total lesion volume determined by DW-MRI was shown to be an independent predictor of ischemic as well as functional outcomes.[59] Our study did not uncover any difference in total lesion volume between the axillary and innominate artery cannulation groups.

DW-MRI is an excellent tool for detecting brain injury in postsurgical settings with 92% sensitivity and 97% specificity.[11] Although the ACE CardioLink-3 Trial is not the first to explore MRI outcomes in adults undergoing aortic surgery, it is the most rigorously conducted RCT to date to incorporate DW-MRI as a means of uncovering neurological injury. A small pilot RCT of 20 patients randomized to DHCA plus retrograde cerebral perfusion versus moderate HCA plus ACP examining neurologic injury with DW-MRI in patients undergoing aortic arch surgery was recently published.[60] However, the limited patient enrollment leaves the study insufficiently powered to detect clinically or statistically meaningful differences, in addition to the lack of a preoperative DW-MRI. Furthermore, all subjects

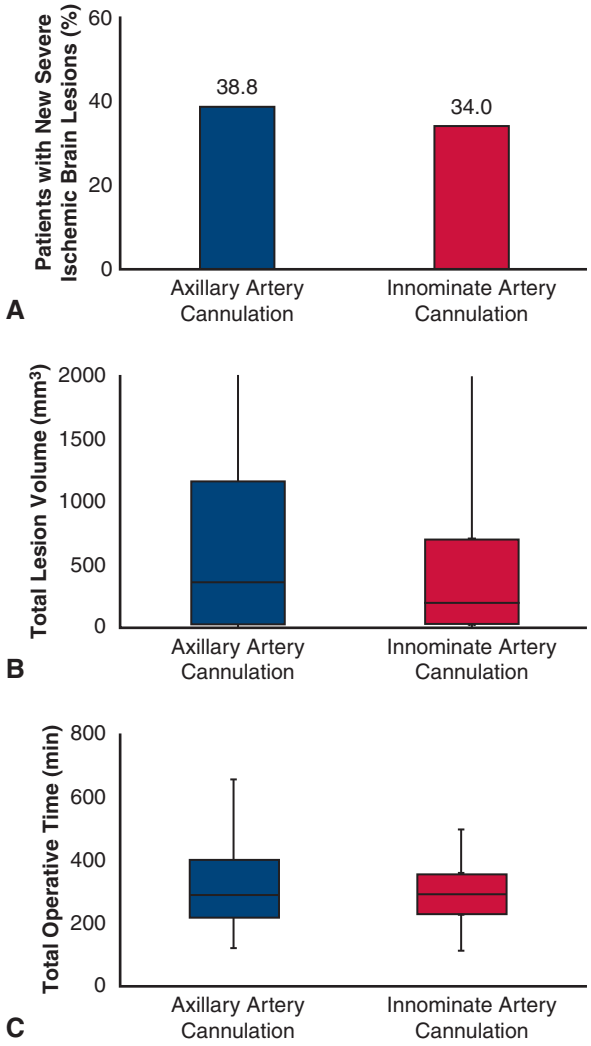


FIGURE 3. Primary safety and efficacy outcomes. A, Percentage of patients with new severe ischemic brain lesions following antegrade cerebral perfusion (ACP). B, Total volume of new ischemic brain lesions following ACP. The *upper* and *lower borders* of the *box* represent the upper and lower quartiles. The *middle horizontal line* represents the median. Sample size was 49 for the axillary artery cannulation group and 53 for the innominate artery cannulation group. C, Total operative times for the 2 study arms of the The Aortic Surgery Cerebral Protection Evaluation CardioLink-3 Trial cohort. The *upper* and *lower borders* of the *box* represent the upper and lower quartiles. The *middle horizontal line* represents the median. Sample size was 49 for the axillary artery cannulation group and 53 for the innominate artery cannulation group.

randomized to ACP plus moderate HCA were cannulated via the right axillary artery, further limiting the study. Accordingly, the ACE CardioLink-3 trial extends the literature by providing cogent and robust data to support noninferiority of the innominate ACP strategy during HCA.

In a previous retrospective analysis of data from 97 patients undergoing hemiarch reconstruction with moderate hypothermia and ACP, there was a statistically significant

TABLE 3. Presentation of lesions (stratified by severity)*

Lesion type and their characteristics	Axillary artery cannulation	Innominate artery cannulation
Type 1: ≥6 punctate (<4 mm) DW-MRI-positive lesions in the white matter	4/56	4/55
Type 2: ≥2 large (>4 mm) DW-MRI-positive lesions in the white matter	8/56	9/55
Type 3: ≥1 DW-MRI-positive lesions in the basal ganglia, thalamus, or internal capsule	6/56	12/55
Type 4: ≥1 large hemispheric DW-MRI-positive lesion	5/56	4/55

Values are presented as n/N. *DW-MRI*, Diffusion-weighted magnetic resonance imaging. *Categories of lesion types are not mutually exclusive.

difference in total operative time in favor of the innominate strategy.[21] These results informed our primary efficacy outcome that sought superiority of the innominate artery cannulation technique with regard to total operative time. In experienced hands, the total time taken to prepare for ACP delivery via the innominate artery, is routinely under 5 minutes, including the time required to mobilize the innominate vein and the base of the innominate artery, place the purse strings on the innominate artery, and cannulate the innominate artery with a small cannula over a wire and Y the line into the arterial circuit. The key advantage to this particular method of innominate cannulation is that it is very simple, almost universally applicable to a wide variety of innominate artery anatomies and can be used in both small and large innominate arteries, and has a very low risk of arterial injury. Additionally, the innominate cannulation strategy described herein saves time because it can be implemented once the patient is already on CPB and actively cooling, by establishing CPB in a standard manner with a central aortic cannula, whereas the axillary artery is cannulated at the start of the case, requires a separate incision, adding a minimum of 20 to 30 minutes to the start of the case and additional time to close the site.

Although we demonstrated shorter operative times in the innominate versus axillary artery group, this difference was not significantly different in the study. It is possible that the time savings with innominate cannulation was diluted by the increased root complexity performed by the surgeons in our trial with approximately 35% of patients undergoing a complex root operation in the innominate arm versus 21% in the axillary group (Table 2). In an exploratory analysis of patients who underwent isolated Bentall and hemiarch reconstruction, the operative time difference was 59.5 minutes, favoring the innominate cannulation group ($P = .115$);

ADULT

TABLE 4. Key secondary outcomes and adverse events

Outcome	Axillary artery cannulation (n = 56)	Innominate artery cannulation (n = 55)	*P* value
Postoperative clinical outcome			
Any adverse event*	31 (59.6)	30 (55.6)	.82
30-d mortality	2 (3.9)	2 (3.7)	1.0
Stroke/TIA	4 (7.7)	2 (3.7)	.43
Seizure	1 (1.9)	1 (1.9)	1.0
Delirium	4 (7.7)	4 (7.5)	1.0
Encephalopathy	3 (5.8)	1 (1.9)	.36
Atrial fibrillation	18 (34.6)	19 (35.2)	
Myocardial infarction	0 (0.0)	2 (3.7)	
Sepsis	0 (0.0)	0 (0.0)	
Pulmonary complication	3 (5.8)	5 (9.3)	
Right arm pain	1 (1.9)	0 (0.0)	
Infraclavicular seroma	0 (0.0)	0 (0.0)	
Right arm vascular injury	0 (0.0)	0 (0.0)	
Right arm neurological injury	1 (1.9)	1 (1.9)	
Local complication†	2 (3.8)	1 (1.9)	.61
New dialysis	1 (1.9)	0 (0.0)	
Need for reoperation	2 (3.8)	3 (5.6)	
Duration of mechanical ventilation (h)	11.4 (8.0-18.0)	12.0 (8.0-16.0)	
Length of ICU stay (h)	25.2 (23.8-47.5)	26.6 (24.0-68.3)	
Length of hospital stay (h)	6.0 (5.0-9.0)	6.0 (5.0-8.0)	
Neurocognitive outcome			
Preoperative MoCA	26.0 (3.2)	25.9 (2.3)	
Postoperative MoCA	25.0 (3.9)	25.5 (2.9)	
Decrease in MoCA > 1 point (pre vs post)	16 (34.8)	16 (32.7)	.96
Preoperative MMSE	28.6 (1.9)	28.9 (1.5)	
Postoperative MMSE	27.5 (3.2)	28.6 (2.0)	
Decrease in MMSE > 1 point (pre vs post)	14 (30.4)	10 (20.4)	.35

Values are presented as n (%) or median (interquartile range). *TIA*, Transient ischemic attack; *ICU*, intensive care unit; *MoCA*, Montreal Cognitive Assessment; *MMSE*, Mini-Mental State Exam. *Any of mortality, stroke/TIA, dialysis, reoperation, red blood cell transfusion, encephalopathy, seizure, atrial fibrillation, delirium, myocardial infarction, sepsis, pulmonary complications, infraclavicular seroma, right arm pain/vascular injury and right arm/shoulder neurological injury. †Any of infraclavicular seroma, right arm pain/vascular injury, and right arm/shoulder neurological injury.

however, the trial was underpowered to detect a significant difference in this subgroup.

There were no cases of seroma or right arm vascular injury, and 1 individual (2.0%) in each group suffered a right arm neurological injury. Furthermore, the incidences of local complications in the 2 study groups were comparable: 3.8% in the axillary group and 2.0% in the innominate group. These are consistent with earlier studies that reported local complication rates of approximately 0% to 5% in patients undergoing axillary artery cannulation for aortic surgery.[17,20,23,61] Given that the innominate artery is as efficacious at providing ACP as axillary cannulation, avoids an additional incision, potentially saves time, and overall streamlines the operation, there is likely a net benefit in favor of using the innominate artery strategy for proximal or hemiarch operations. Although utilizing wire-based innominate cannulation for total arch reconstruction is technically feasible, we continue to preferentially employ axillary cannulation for total arch reconstructions for 3 main reasons: the innominate artery is free and unencumbered for a branch graft anastomosis; as the arch is progressively reconstructed with a trifurcated graft, we increase the flow to the upper body, after reimplantation of the innominate, left common carotid, and the left subclavian artery, while we finish either the conventional or frozen elephant trunk, and the 14Fr innominate cannula is limited when trying to increase the flow beyond 1 L/min; and we can utilize the axillary cannula when reinitiating CPB for the rewarming phase, without the need for an anteflo (Terumo Corporation, Tokyo, Japan) limb on the arch graft. Additionally, we also preferentially cannulate the axillary artery during acute type A dissections, to avoid cannulating or placing a wire into a potentially dissected and friable innominate artery.

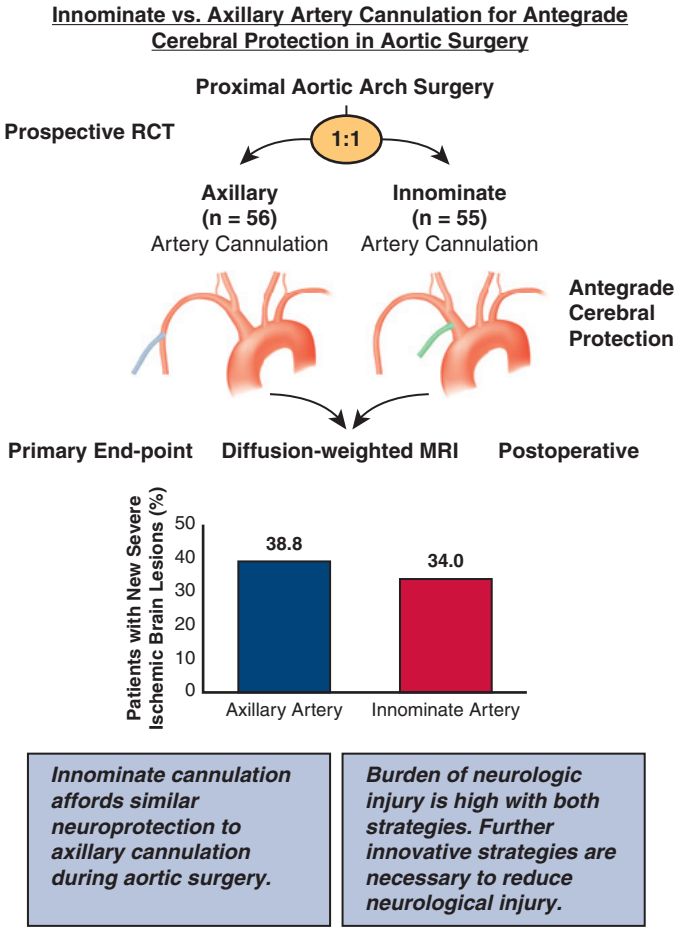


FIGURE 4. A prospective, randomized trial allocated 111 individuals to axillary or innominate artery cannulation for delivery of antegrade cerebral protection during proximal aortic surgery requiring a hemiarch or open distal anastomosis. The primary safety outcome for neuroprotection was the proportion of new severe ischemic lesions on the postoperative diffusion-weighted magnetic resonance imaging (P = not significant).

The ACE CardioLink-3 Trial provides novel and important insight regarding the safety and efficacy of both neuroprotection strategies. However, the trial does have limitations. First, because this was a surgical intervention trial, complete blinding was not possible. Additionally, neurologic outcome assessments were not adjudicated by a neurologist. To prevent bias, our protocol mandated that the outcomes be adjudicated and assessed by individuals blinded to the surgical assignment with the use of standard Valve Academic Research Consortium stroke definitions and the MRS, and our main safety outcome was an independent, objective measure of tissue infarction. Second, a more detailed neurocognitive assessment may have detected more subtle neurocognitive impairment. Third, the variation in operative time was larger than assumed in the sample size consideration, and therefore our trial was underpowered to detect a clinically relevant difference in operative time. In addition, although the overall primary event rate was lower than anticipated, it was sufficiently close and directionally appropriate to support the noninferiority conclusion. Finally, because the end-of-study follow-up took place 30-days postoperatively, our study does not allow for the determination of longer-term safety outcomes or the long-term neurological sequalae of patients with newly observed severe ischemic lesions.

This study validates the safety of innominate artery cannulation for delivering ACP during proximal aortic arch surgery, and given the simplicity and ease of use, we will continue to employ it as our default strategy.

CONCLUSIONS

The ACE CardioLink-3 study is the first RCT to demonstrate that ACP delivered via innominate cannulation is noninferior to axillary cannulation with regard to neurological safety in patients undergoing aortic surgery with HCA. This randomized study introduces high quality data to help guide the safe use of innominate artery cannulation as an alternative to axillary artery cannulation in patients undergoing aortic surgery. Brain protection is an important adjunct to modern aortic surgery; however, silent ischemic

lesions are detectable in more than one-third of patients, mandating further study of the long-term sequalae of these lesions and the development of new strategies to further mitigate brain injury (Figure 4).

Conflict of Interest Statement

Dr Mazer has received honoraria and/or research grants to the institution from Amgen and Boehringer Ingelheim. Dr Chu has received honoraria and/or research grants from Abbott Vascular, Boston Scientific, Cryolife, LivaNova, Medtronic, and Terumo Aortic. Dr Jüni has received research grants to the institution from AstraZeneca, Biosensors International, Biotronik, Eli Lilly, and The Medicines Company, and serves as an unpaid member of the steering group of trials funded by AstraZeneca, Biosensors International, Biotronik, St. Jude Medical, and The Medicines Company. Dr Bhaat is a member of the advisory board for Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; on the board of directors for Boston VA Research Institute, and Society of Cardiovascular Patient Care; chair of the American Heart Association Quality Oversight Committee; a member of the data monitoring committees of Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute), Cleveland Clinic, Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine, Population Health Research Institute; has received honoraria from American College of Cardiology, Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim), Belvoir Publications, Duke Clinical Research Institute (clinical trial steering committees), HMP Global, *Journal of the American College of Cardiology*, Population Health Research Institute (clinical trial steering committee), Slack Publications, Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees), *Clinical Cardiology*, NCDR-ACTION Registry Steering Committee, VA CART Research and Publications Committee; and received research funding from Abbott, Amarin, Amgen, AstraZeneca, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Idorsia, Ironwood, Ischemix, Lilly, Medtronic, PhaseBio, Pfizer, Regeneron, Roche, sanofi-aventis, Synaptic, and The Medicines Company; received royalties from Elsevier; is a site coinvestigator for Biotronik, Boston Scientific, St Jude Medical (now Abbott), and Svelte; has served as a trustee for the American College of Cardiology; and conducted unfunded research for FlowCo, Merck, PLx Pharma, and Takeda. Dr Teoh reports receiving honorarium from Boehringer Ingelheim and writing fees for unrelated manuscripts from Merck Canada Inc and Servier. Mr Smith has received research service contracts from St Michael's Hospital (Toronto), McMaster University, and the Ottawa Heart Institute; consulting fees from Portola; and writing fees from Up-to-Date. Dr Verma reports receiving research grants and/or speaking honoraria from Amgen, AstraZeneca, Bayer HealthCare, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Janssen, Merck, Novartis, Novo Nordisk, and Sanofi and is president of the Canadian Medical and Surgical Knowledge Translation Research Group. All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: antegrade cerebral protection, axillary artery cannulation, innominate artery cannulation, new ischemic brain lesions, transient ischemic attack, cardiopulmonary bypass, deep hypothermic circulatory arrest, replacement of the ascending aorta, diffusion-weighted magnetic resonance imaging

APPENDIX E1. LIST OF SITES, INVESTIGATORS, AND RESEARCH COORDINATORS WHO RECRUITED AT LEAST 1 PARTICIPANT

- St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada: Dr Mark D. Peterson, Dr C. David Mazer, Dr Subodh Verma, Shira Brodutch, Charmagne Crescini, Kaho Han, Anna Slabiak, and Sanjay Yagnik.
- Lawson Health Research Institute, Western University, London, Ontario, Canada: Dr Michael W. A. Chu, Stephen Mardell, and Stephanie Fox.
- Royal Jubilee Hospital, University of British Columbia, Vancouver, British Columbia, Canada: Dr John Bozinovski.
- Institut universitaire de cardiologie et de pneumologie de Québec, Université Laval, Québec City, Québec, Canada: Dr François Dagenais, Hugo Tremblay, Nathalie Gagné, and Valérie Lafrenière Bessi.
- Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, Alberta, Canada: Dr Roderick G. G. MacArthur, Dr Michael C. Moon, and Lyne Bourassa.
- University Health Network, University of Toronto, Toronto, Ontario, Canada: Dr Maral Ouzounian, Shakira Christie, Megan McKeever, Linda Wright.

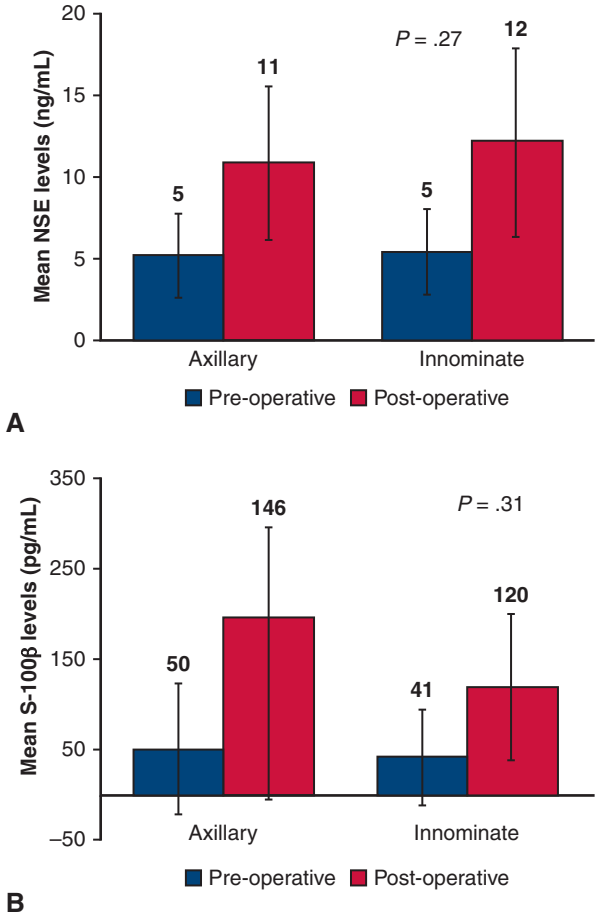

FIGURE E1. Preoperative and postoperative biomarkers of neuronal injury. A, Neuron-specific enolase (*NSE*). B, S100 calcium-binding protein *β* (*S-100β*).