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Complete List of Authors:	Garg, Vinay; University of Toronto, Internal Medicine Peterson, Mark; St Michael's Hospital Chu, Michael; Western University Schulich School of Medicine and Dentistry Ouzounian, Maral; University Health Network Macarthur, Roderick; University of Alberta Hospital Bozinovski, John; University of British Columbia El-Hamamsy, Ismail ; Universite de Montreal Faculte de medecine Chu, F Victor; McMaster University Garg, Ankit; University of Toronto Hall, Judith; St Michael's Hospital Thorpe, Kevin; University of Toronto Dhingra, Natasha; St Michael's Hospital Teoh, Hwee; St Michael's Hospital Marotta, Thomas; St Michael's Hospital Latter, David; St Michael's Hospital Quan, Adrian; St Michael's Hospital Mamdani, Muhammad; St. Michael's Hospital, Applied Health Research Centre, Li Ka Shing Knowledge Institute Jüni, Peter Mazer, David; St. Michael's Hospital, Shuter Wing, Room 1-028e, 30 Bond Street, Toronto, Department of Anesthesia Verma, Subodh; Division of Cardiac Surgery
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Axillary versus Innominate Artery Cannulation for Antegrade Cerebral Perfusion in Aortic Surgery: Design of the Aortic Surgery Cerebral Protection Evaluation (ACE) CardioLink-3 Randomised Trial

Vinay Garg,[1] Mark D Peterson,[2,3] Michael W A Chu,[4] Maral Ouzounian,[3,5] Roderick G G MacArthur,[6] John Bozinovski,[7] Ismail El-Hamamsy,[8] F Victor Chu,[9] Ankit Garg,[1] Judith Hall,[10] Kevin E Thorpe,[10,11] Natasha Dhingra,[2] Hwee Teoh,[12,13] Thomas R Marotta,[14,15] David A Latter,[2,3] Adrian Quan,[12] Muhammad Mamdani,[15-19] Peter Juni,[10,16] C David Mazer,[20,21] Subodh Verma[3,12,22]

[1]Department of Internal Medicine, University of Toronto, Toronto, ON, Canada
[2]Division of Cardiac Surgery, Li Ka Shing Knowledge Institute of St Michael's Hospital, Toronto, ON, Canada
[3]Department of Surgery, University of Toronto, Toronto, ON, Canada
[4]Division of Cardiac Surgery, London Health Sciences Center, University of Western Ontario, London, ON, Canada
[5]Division of Cardiovascular Surgery, Peter Munk Cardiac Centre, University Health Network, Toronto, ON, Canada
[6]Division of Cardiac Surgery, University of Alberta Hospital, University of Alberta, Edmonton, AB, Canada
[7]Division of Cardiac Surgery, Royal Jubilee Hospital, University of British Columbia, Victoria, BC, Canada
[8]Division of Cardiac Surgery, Montreal Heart Institute, Université de Montréal, Montreal, QC, Canada
[9]Division of Cardiac Surgery, Department of Surgery, Hamilton General Hospital, McMaster University, Hamilton, ON, Canada
[10]Applied Health Research Centre, Li Ka Shing Knowledge Institute of St Michael's Hospital, Toronto, ON, Canada
[11]Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada
[12]Division of Cardiac Surgery, Keenan Research Centre for Biomedical Science and Li Ka Shing Knowledge Institute of St Michael's Hospital, Toronto, ON, Canada
[13]Division of Endocrinology & Metabolism, Li Ka Shing Knowledge Institute of St Michael's Hospital, Toronto, ON, Canada
[14]Department of Diagnostic and Therapeutic Neuroradiology, Keenan Research Centre for Biomedical Science of St Michael's Hospital, University of Toronto, Toronto, ON, Canada
[15]Department of Medicine, University of Toronto, Toronto, ON, Canada
[16]Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada
[17]Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada
[18]Institute for Clinical Evaluative Sciences UofT, Toronto, ON, Canada
[19]Li Ka Shing Centre for Healthcare Analytics Research and Training (LKS-CHART), St. Michael's Hospital, Toronto, ON, Canada
[20]Department of Anesthesia, Li Ka Shing Knowledge Institute of St Michael's Hospital, Toronto, ON, Canada
[21]Department of Anesthesia, University of Toronto, Toronto, ON, Canada
[22]Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada

Correspondence to:

Dr C David Mazer, Department of Anesthesia, St Michael's Hospital, Suite 1-028e, Shuter Wing, 30 Bond Street, Toronto, Ontario, Canada, M5B 1W8. Phone: 416-864-5825; Fax: 416-864-6014. Email: mazerd@smh.ca *OR* Dr Subodh Verma, Division of Cardiac Surgery, St Michael's Hospital, 8th Floor, Bond Wing, 30 Bond Street, Toronto, Ontario, Canada, M5B 1W8. Phone: 416-864-5997; Fax: 416-864-5881. Email: vermasu@smh.ca

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ABSTRACT

Introduction: Neurological injury remains the major cause of morbidity and mortality following open aortic arch repair. Systemic hypothermia along with antegrade cerebral perfusion (ACP) is the accepted cerebral protection approach, with axillary artery cannulation being the most common technique used to establish ACP. More recently, innominate artery cannulation has been shown to be a safe and efficacious method for establishing ACP. Inasmuch as there is a lack of high quality data comparing axillary and innominate artery ACP, we have designed a randomised, clinical trial to compare both cerebral perfusion strategies with regards to brain morphologic injury using diffusion weighted MRI (DW-MRI).

Methods and analysis: 110 patients undergoing elective aortic surgery with repair of the proximal arch requiring an open distal anastamosis will be randomised to either the innominate artery or the axillary artery cannulation strategy for establishing ACP during systemic circulatory arrest with moderate levels of hypothermia. The primary safety endpoint of this trial is the proportion of patients with new severe ischaemic lesions found on post-operative DW-MRI compared with pre-operative DW-MRI. The primary efficacy endpoint of this trial is the difference in total operative time between the innominate artery and the axillary artery cannulation group.

Ethics and dissemination: The study protocol and consent forms have been approved by the participating local research ethics boards. If this study shows that the innominate artery cannulation technique is non-inferior to the axillary artery cannulation technique with regards to brain morphologic injury, it will establish the innominate artery cannulation technique as a safe and potentially more efficient method of antegrade cerebral perfusion in aortic surgery.

Trial registration number: The trial is registered at clinicaltrials.gov Identifier: NCT02554032.

Strengths

- Multicenter randomised controlled trial
- Rigorous design to address an important unanswered question with clinically relevant primary and secondary outcomes
- Strong research team with experts in thoracic aortic surgery and cerebral perfusion techniques

Limitations

- Study population limited to elective procedures of the ascending aorta and proximal arch, excluding aortic dissections and emergency operations
- Patient outcomes only followed to 3 months
- Study requires surgeons skilled in both cannulation techniques

INTRODUCTION

Thoracic aortic aneurysms are associated with substantial morbidity and mortality, Accordingly, aortic surgery is common, with approximately 200,000 surgical cases annually worldwide.[1-3] The natural history of unrepaired aortic aneurysms is poor, with a high incidence of aortic dissection, rupture and death.[1 2 4]

Surgery involving the ascending aorta and aortic arch is complex and several techniques have been developed to safely interrupt or modify the circulation to the brain. Despite advances in cannulation, cerebral perfusion, and temperature management, neurological injury remains the most dreaded complication of aortic arch surgery.[3 5] Manifestations of such injury may range from fatal, or severe/irreversible injury to milder transient ischaemic attack (TIA), or neurocognitive injury.[2 3 5 6]

Current practice for proximal aortic arch surgery with regards to neuro-protection strategies include deep hypothermic circulatory arrest (DHCA) alone, retrograde cerebral perfusion (RCP) with DHCA, antegrade cerebral perfusion (ACP) with DHCA, and moderate hypothermic circulatory arrest with ACP.[6 7] In addition to moderate hypothermia, ACP via right axillary artery cannulation has become a preferred approach for cerebral protection during aortic surgery.[7] Although ACP via the axillary artery has been shown to improve survival and neurologic outcomes after aortic aneurysm repair compared to retrograde cerebral perfusion, there are several associated risks.[6-14] The axillary approach increases the risk of brachial plexus injury, seromas, arm hyper-perfusion and limb ischaemia and it requires additional surgical dissection, increasing the total operative time required, particularly in patients with obesity or challenging anatomy.[10 15] A novel approach for delivering ACP via cannulation of the innominate artery has recently emerged (Figure 1).[16] First devised by Banbury and colleagues in 2000, several retrospective studies and case series have shown innominate artery cannulation to be relatively safe with a low rate of surgical mortality and neurological injury.[10 16-22] A retrospective

analysis comparing innominate artery cannulation with axillary artery cannulation showed no significant differences in neurological complications.[15] However, data evaluating innominate artery cannulation is confounded by potential selection bias with respect to the complexity of patients chosen for each strategy. Although worldwide many surgeons have adopted the innominate artery cannulation strategy in favor of the axillary artery strategy, there are no randomised trial data to help objectively evaluate safety and efficacy of this technique. Given the grave consequences of inappropriate and/or inadequate cerebral protection, a randomised trial to compare each surgical strategy is needed. We describe herein the protocol for the prospective Aortic Surgery Cerebral Protection Evaluation (ACE) CardioLink-3 Randomised Trial that has been designed to establish the efficacy and safety of innominate artery cannulation versus axillary artery cannulation for ACP in patients undergoing proximal aortic arch surgery with hypothermic circulatory arrest.

Study Purpose

The purpose of this trial is to compare innominate artery cannulation to axillary artery cannulation as a means of cerebral protection during hypothermic circulatory arrest in subjects undergoing surgery for aneurysms of the ascending aorta and proximal arch. The primary safety objective of this study is to determine whether the innominate artery cannulation technique is non-inferior to the axillary artery cannulation technique for establishing ACP with regards to brain morphologic injury on diffusion weighted magnetic resonance imaging (DW-MRI). The primary efficacy objective is to determine if the innominate artery technique is superior to the axillary artery technique with respect to surgical operative time.

The secondary objectives are to determine whether innominate artery cannulation for ACP is non-inferior to axillary artery cannulation with regards to post-operative 30-day mortality, and clinical and biomarker evidence of neurological injury and cognitive dysfunction.

METHODS

Study Design Summary

This is a multi-centre, two-arm randomised controlled, non-inferiority trial comparing a novel strategy for establishing ACP via innominate artery cannulation versus traditional axillary artery cannulation, in patients 18 years and older, undergoing elective repair of the ascending aorta and proximal arch requiring hypothermic circulatory arrest and an open distal anastomosis. Patients undergoing surgery for aortic dissection, emergent or urgent operations, and total arch repair will be excluded. Furthermore, patients who cannot undergo MRI, or are using an investigational drug/device at the time of enrolment, or are a part of another clinical trial will also be excluded. Patients will be eligible for randomisation regardless of the proximal extent of the aortic repair (i.e. root replacement vs. valve repair/replacement vs. supracoronary aortic repair). The patient will only remain in the study if the surgeon confirms the technical acceptability of either technique, as to allow for safe randomisation. Patients will then be randomly allocated 1:1 to undergo either the innominate or axillary cannulation strategy (Figure 2). The trial has been registered at clinicaltrials.gov (Identifier: NCT02554032).

Randomisation

Patients will be randomised in a 1:1 ratio, stratified by surgical center, on the day of the scheduled ascending aorta operation to either the innominate artery cannulation strategy or the axillary artery cannulation strategy for establishing ACP during hypothermic circulatory arrest. The randomised assignments will be generated on a computer by a study statistician and will employ random permuted blocks of varying sizes. Randomisation will be centralised, web-based, and generated by the Applied Health Research Center at the Li Ka Shing Knowledge Institute of St Michael's Hospital.

Surgical Strategy

The surgical strategy will be standardised amongst the enrolling aortic surgeons/centers.

Innominate artery cannulation

After median sternotomy and systemic heparinisation, the distal aneurysmal ascending aorta will be cannulated using a standard 7 or 8 mm arterial cannula. Standard central venous cannulation is employed and cardioplegia management is left at the discretion of the individual surgeons; cardio-pulmonary bypass (CPB) and systemic cooling will be initiated. During the cooling phase, the ascending aorta and proximal arch will be mobilised, the innominate vein will be isolated and gently dissected, and the base of the innominate artery will be exposed. Two purse string sutures of 4-0 polypropylene will be placed on the anterior wall of the proximal innominate artery. Once the nasopharyngeal temperature is approximately 26°C the innominate artery will be cannulated with a 0.035-in. J wire, and sequentially dilated using 8/10F and 12/14F dilators. A 14F or 16F cannula with side perforations for gentle dispersion of the perfusate will then be inserted over a guidewire. The period of circulatory arrest with ACP will be initiated by clamping the base of the innominate artery and connecting the afferent limb of the cardiopulmonary bypass (CPB) circuit to the cannula using a 3/8 to 1/4 connector. Cold blood (24-26°C) will be delivered at a flow rate of 10-12 mL/kg/min to achieve a right brachial pressure of 50-70 mmHg. The distal anastamosis will be performed as either a beveled hemiarch or an end-to-end anastamosis using a woven polyester graft with an 8 mm side limb. Once the distal anastamosis is complete the aortic line will be connected to the side limb of the graft, air will be flushed from the graft, the graft clamped and full CPB will be resumed. At that time, ACP will be discontinued. Following five minutes at 26°C, re-warming will resume and the proximal reconstruction will be completed.[16]

Axillary artery cannulation

Patients randomised to the control group will undergo axillary artery cannulation as routinely performed. The details of this operation have been previously described.[15]

Outcomes

Primary outcome

The primary safety endpoint of this trial is the proportion of patients with new severe ischaemic lesions. Two independent neuroradiologists who are blinded to treatment assignment will adjudicate this primary endpoint. New severe ischaemic lesions will be defined as severe white matter injury or an infarction involving the basal ganglia, thalamus or internal capsule or a large hemispheric infarction present on the post-operative DW-MRI. Each patient will have a preoperative DW-MRI to serve as the baseline study for comparison, to ensure the highest quality data. Severe white matter injury will be defined as 6 or more punctate lesions, or 2 or more lesions of 4 mm or larger size.[5] We have included the size of the ischaemic lesions as a defining criterion for severity as the volume of ischaemic lesions is a known independent predictor of stroke outcome.[23 24] Furthermore, it has been shown that the number of DW-MRI lesions is only likely to be clinically relevant if the individual lesion is large. [5 25 26]

The primary efficacy endpoint of this trial is the difference in total operative time between the innominate artery cannulation group and the axillary artery cannulation group.

Secondary Outcomes

Differences in the following secondary outcomes between both surgical strategies will be assessed:

1. 30-day all-cause post-operative mortality.
2. Post-operative stroke or TIA in hospital and at 30 days.

3. Neurocognitive dysfunction at post-operative day 4 and at 3 month follow up as assessed by the MMSE and MOCA tests. Both the MOCA and MMSE have been validated for cognitive screening in patients with cerebrovascular disease.[27-29]
4. DW-MRI parameters including number of total ischaemic lesions, total ischaemic volume of lesions, single lesion volume, watershed injury, intraparenchymal haemorrhage, cerebral haemorrhage, intraventricular haemorrhage, subdural haemorrhage, subarachnoid haemorrhage, partial cerebral sinovenous thrombosis.
5. Pre-operative and post-operative serum levels of circulating biomarkers of neuronal injury (S-100β and neuron specific enolase)
6. Post-operative sepsis, delirium, seizure, encephalopathy, atrial fibrillation, post-operative MI, re-operations.
7. Total length of ICU stay, and number of hours of required intubation and ventilation
8. Seroma, brachial plexus injury, reduced arm mobility and pain, arm ischaemia
9. Total CPB time, total cross-clamp time, total systemic circulatory arrest time, total ACP time, total cooling time (minutes), re-warming time, nadir nasopharyngeal temperature (degrees C), post-operative haemoglobin, peri-operative RBC transfusion, peri-operative inotrope or vasopressor use.
10. Cerebral oximetry will be monitored intraoperatively using bilateral non-invasive near-infrared spectroscopy. The following data will be evaluated: baseline O_2 saturation while awake, total number of desaturations i.e. < 20% of baseline, the total area under the curve of % saturation over time below 20% of baseline, minimal value reached and the maximum change from baseline values.

Data Collection

Preoperative

The screening visit will occur at the time of the initial appointment where the patient will be seen by the cardiac surgeon for evaluation and consideration of aortic surgery. Patients who are booked for elective ascending aortic surgery with a planned open distal anastamosis and hypothermic circulatory arrest will be assessed for eligibility in the clinical trial. Study co-ordinators will review the study with potential participants and upon agreement to participate, obtain informed written consent.

The following baseline information will then be collected at either this initial visit, or at the time of the pre-operative anaesthesia clinic visit:

Clinical information

Demographics (age, sex), medical history including hypertension, diabetes mellitus, dyslipidemia, heart failure or LV dysfunction (latest ECHO or cardiac catheterisation), NYHA class, previous history of stroke, TIA, or systemic embolism, renal disease, peripheral vascular disease, coronary artery disease, previous coronary angioplasty with or without stent, COPD, smoking history, pulmonary hypertension (from latest ECHO or cardiac catheterisation), congenital aortic disease, previous cardiac surgery, history of atrial fibrillation, EuroSCORE II.

Physical examination information

Height (cm), weight (kg), body surface area.

Laboratory/tests

We will obtain baseline haemoglobin (g/L), creatinine (μmol/L), baseline biomarkers of neuronal injury (S-100β and neuron specific enolase), and a 12-lead ECG.

Imaging

DW-MRI will be completed prior to the surgical date.

Neurocognitive tests

MMSE and MOCA will be carried out pre-operatively.

Intraoperative

Intra-operative data collection will include total operative time (from skin incision, to closure of the skin), total CPB time, total cross-clamp time, total hypothermic circulatory arrest time, total ACP time, total cooling time, re-warming duration, nadir nasopharyngeal temperature, mean arterial systolic and diastolic blood pressure, nadir haemoglobin concentration (g/L), intra-operative RBC transfusion (units) and intra-operative inotrope or vasopressor use.

Post-operative

Post-operative data will include total ICU stay, total ventilation time, post-operative hospital stay, in-hospital mortality, delirium, re-operations, post-operative MI, inotropic support, seizure, development of renal failure, atrial fibrillation, post-operative stroke, transfusion, sepsis, and pulmonary complications. Serum S-100β and NSE levels will be drawn post-operatively at 24-48 hours. At post-op day 4 (±3 days), the patient will undergo post-operative DW-MRI. On the day of discharge, the patient will undergo testing for stroke/TIA using the Modified Rankin Scale in addition to repeat neurological physical examination. Neurocognitive testing will also be carried out on the day of discharge, and at the surgical follow up visit conducted at 1 to 3 months post-operatively, using MOCA and MMSE tests.

Study Follow-up

Subjects will be followed daily during their post-operative course in hospital. A phone call at

post-operative day 30 will be conducted to assess for vital status, stroke and TIA, In addition, there will be a follow up visit in 1 to 3 months post-operatively to reassess neurocognitive status.

Study Sample Size and Power

In this trial, the primary endpoint is the number of patients with new severe ischaemic brain lesions on DW-MRI, comparing pre-operative and post-operative imaging. In accordance with previous literature, we anticipate that about 50% of patients will develop new, severe ischaemic lesions in the axillary cannulation group (control group).[5] Based on a consensus of investigators from surgery, anaesthesia and critical care, we have determined that an absolute difference of 25% is an acceptable non-inferiority margin. Finally, we have set the power of this trial at 80% (for the 25% margin) and a one-sided Type I error of 5% (non-inferiority comparisons are one sided by definition). Under these assumptions and conditions, a sample size of 100 subjects (50 per group) is required. Finally, we factor in a 10% attrition rate to arrive at a final sample size of 110. This sample size also gives us greater than 80% power to detect a difference of 45 minutes in total operative time between the axillary artery and innominate artery cannulation strategies.

Data Analysis

The primary analysis is a non-inferiority comparison of the proportion of patients acquiring new severe brain lesions. The observed difference will be compared against the non-inferiority margin of 25% using a one-sided z-test. Since the intention-to-treat approach employed in superiority trials biases towards no difference, it is inappropriate in the non-inferiority trial where lack of difference is the goal. Therefore, the primary analysis will be a per-protocol analysis. The difference in proportions and 90% confidence intervals (corresponds more closely to the one sided test being used) will be reported.

The total operative time will be compared with a t-test and the mean difference and 95% confidence interval will be reported.

Binary outcomes (30-day mortality, stroke/TIA, neurocognitive dysfunction, delirium, seizures, encephalopathy, adverse events, local complications) will be compared using a chi-square test or Fisher's Exact test if expected counts are less than 5. For each outcome the absolute risk difference and 95% CI will be reported. The quantitative DW-MRI parameters will be compared by t-tests and mean differences with 95% CIs will be reported. Whether or not patients experienced none, a single or multiple new lesions will be compared by a chi-square test. The mean levels of post-operative biomarkers (S-100β and NSE) will be compared. The adjusted mean difference and 95% CI will be reported for each biomarker. Intraoperative characteristics will be compare with t-tests and mean differences with 95% CIs will be reported.

DISCUSSION

Axillary artery cannulation for achieving ACP with moderate levels of hypothermia is the currently preferred approach for establishing cerebral perfusion during aortic surgery. We describe the first prospective, randomised controlled trial evaluating the safety and efficacy profile of ACP via cannulation of the innominate artery in comparison to axillary artery cannulation.

We selected new severe ischaemic brain lesions as defined by DW-MRI as our primary safety end-point. DW-MRI has a sensitivity and specificity of 92% and 97% respectively in detecting new ischaemic lesions. Identification of restriction in diffusion of water molecules suggests cerebral ischaemia. Normal tissue appears gray on DW-MRI due to the Brownian motion and diffusion of water molecules. Ischaemic tissue however, due to the prevention of normal loss of MRI signal by restricted diffusion, appears bright white. These differences are apparent within 5 days of injury.[25]

DW-MRI as a modality to assess neurologic injury has been validated in the transcatheter aortic valve implantation (TAVI) population, and more recently in aortic surgery

studies and trials. These studies have demonstrated that the number of new ischaemic lesions, in addition to the size of these lesions together is the most prognostically significant measure.[23-25] Recent literature shows that the rate of new ischaemic brain lesions on DW-MRI after aortic surgery ranges from 40 to 60%.[5 30 31] A recent clinical trial in neonatal aortic arch surgery also employed DW-MRI as a surrogate of neuronal injury comparing ACP to DHCA. This non-inferiority trial used location, number of lesions and size of lesions to characterise severity of injury.[5] We used these data to inform our primary end point.

By comparing DW-MRI pre-operatively and post-operatively, we will be able to effectively quantify new, significant ischaemic brain lesions. Furthermore, given that DW-MRI is highly sensitive for ischaemic brain lesions, it also has an ability to detect “silent” brain injury. Silent brain injury has been shown to be a risk factor for delayed neurological decline. [25 32 33] Retrospective studies evaluating innominate or axillary artery cannulation have primarily assessed clinical end-points such as stroke or temporary neurological deficits. As such events are relatively rare, it is difficult to assess for true differences in outcomes between treatment modalities with the sample sizes available for aortic surgery. Thus, new, severe ischaemic brain lesions found on DW-MRI serves as a useful surrogate marker for risk of neurological injury. The high incidence of new ischaemic brain lesions post-aortic surgery allows us to efficiently assess our outcome with a relatively small sample size of 110 subjects.

In addition to imaging, this trial aims to assess neurological injury by comparing pre-operative and post-operative levels of circulating biomarkers of neuronal injury, specifically, NSE and S-100β. There is extensive literature that shows that proteins that are synthesised by astroglial cells or neurons, and that cross the blood brain barrier can be correlated in peripheral blood with brain injury.[34-37] S-100β is a small dimeric cytosolic protein that exists in multiple forms, with the beta form noted to be highly specific for the central nervous system.[34] NSE is a dimer found in neurons, and belongs to a group of hydrolytic enzymes. It is also present in

erythrocytes, platelets, plasmatic cells, and lymphocytes, which is why it is present in peripheral blood at very low physiologic concentrations.[34]

Given that these biomarkers are present at levels from nil to very low physiologic concentrations at baseline, and S-100β especially is very sensitive for detection of intracranial pathology, elevations in these markers post-operatively will suggest neuronal injury secondary to the procedure. Collecting pre-operative and post-operative samples will allow us to correlate serum levels with neuronal injury secondary to the aortic surgery specifically.

Furthermore, we will use two neurocognitive tests to detect neurocognitive decline post-operatively, and will assess for differences between both cannulation strategies. Studies evaluating neuronal injury post aortic surgery or TAVI have shown that neuronal injury does not always manifest overtly as stroke, but rather can present more subtly as neurocognitive decline. These features are often most prominent in those that have pre-existing neurologic disease or vascular dementia.[38] As a part of our neurocognitive testing, we have chosen to use both the MMSE and MOCA. These are commonly used cognitive screening tools in clinical practice. The MMSE is designed to assess language and memory while the MOCA is designed to detect mild to moderate cognitive impairment. It has been found to have high sensitivity and specificity for detecting mild cognitive impairment. Although more sophisticated neurocognitive testing does exist, due to time constraints of performing such testing, and the lack of generalisability with such tests, the MOCA and MMSE were chosen for ease of administration, and reproducibility of results. Furthermore, MOCA and MMSE have been employed in a number of cardiac surgery studies evaluating neurocognitive decline.[27-29 38]

It is important to recognise that there are important limitations of this trial. We have limited this randomised controlled trial to elective procedures on the ascending aorta and proximal arch. Patients planned for total arch replacement are excluded. Secondarily, we are not studying patients undergoing aortic dissection or urgent/emergent operations. Emergency operations such as for aortic dissection would introduce many confounding variables and

significantly impact the ability to accurately assess the safety and efficacy of innominate artery cannulation in comparison to axillary artery cannulation. In addition, our follow-up period ends at 1 to 3 months post-operatively; therefore the long-term outcomes of the different antegrade cerebral perfusion strategies will not be assessed. However, the catastrophic consequences of inadequate cerebral perfusion are usually apparent soon after surgery. Furthermore, our trial assumes competency of the operating aortic surgeon for establishing both cerebral protection strategies. Poor outcomes that may be linked to techniques by surgeons less familiar with either the innominate or axillary artery cannulation technique will not be known since only surgeons who routinely practice aortic surgery are participating in this study.

ETHICS AND DISSEMINATION

The protocol and consent forms have been approved by the participating local research ethics boards. This study is being carried out in accordance with the current International Conference on Harmonization Guideline for Good Clinical Practice, Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans and applicable local laws and regulations.

Patient Safety

All subject related information including case report forms, evaluation forms, reports, etc. will be kept strictly confidential. All records will be kept in a secure, locked location and only research staff will have access to the records. Subjects will be identified only by means of a coded number specific to each subject. All computerised databases will identify subjects by numeric codes only, and will be password protected.

An independent Data Safety and Monitoring Board (DSMB) composed of experts in cardiac surgery and peri-operative care will be assembled to ensure patient safety, receive safety reports, provide feedback to the trial steering committee, and ensure the study follows the

highest ethical standards. The DSMB will be provided data on safety after enrollment of 1/3 and 2/3 of patients. The safety data will include all adverse events listed as primary and secondary outcomes. The DSMB will consider clinical and statistical significance, consistency of data over time, consistency of the direction of risk and benefit-risk ratios if there is consideration for recommendation for early trial discontinuation. In addition to receiving regular safety data reports, the DSMB will have the ability to request additional safety analyses or additional interim analyses and make any further recommendations to the steering committee about the safe conduct of the trial after considering all the available data and any new external data from relevant studies.

CONCLUSION

This randomised controlled trial is essential to definitively determine adequate brain protection strategies for patients undergoing aortic surgery on the ascending aorta and proximal arch with the use of moderate hypothermia and unilateral antegrade cerebral perfusion. Innominate artery cannulation is rapidly gaining interest as an alternative to axillary artery cannulation, however, there are no high quality prospective data to inform whether or not the two strategies are similar with respect to cerebral protection. Innominate artery cannulation has the potential to decrease surgical times, and reduce complications associated with an axillary approach such as brachial plexus injury, seroma formation, and limb ischaemia. Decreased surgical times could lead to significant cost savings. The ACE CardioLink-3 trial will be the first randomised controlled trial designed to prospectively assess and compare the safety and efficacy of the innominate artery cannulation technique with the current standard of practice, axillary artery cannulation, for establishing ACP for patients having proximal aortic surgery. These data should aid surgeons in informed surgical decision making when considering cannulation techniques for aortic surgery.

Contributors VG, MDP, CDM and SV conceived the study and designed the study protocol. VG, MDP, CDM and SV significantly contributed to the planning of analyses of the data. VG, MDP, AG, CDM and SV drafted the manuscript. VG, MDP, MWAC, MO, RGGM, JB, IH, FVC, AG, JH, KET, ND, HT, TRM, DAL, AQ, MM, PJ, CDM, SV critically revised the manuscript for important intellectual content; reviewed and approved the final manuscript and agree to be accountable for all aspects of the work.

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Figure Legends

Figure 1 Surgical technique used in innominate artery cannulation (with permission from Garg et al.).[16]

A: The innominate vein is isolated, retracted and the base of the innominate artery mobilised. Two purse string sutures are placed on the anterior wall of the proximal innominate artery before dilators and the cannula are inserted over a guidewire. **B:** Antegrade cerebral protection is initiated by clamping the base of the innominate artery and connecting the afferent limb of the cardiopulmonary bypass circuit to the 14 or 16 Fr cannula. **C:** After the distal anastamosis is completed, antegrade cerebral protection is discontinued, and the aortic line is connected to the 8 mm side limb. The graft is clamped distally and full cardiopulmonary bypass is resumed. Proximal reconstruction is performed.

Figure 2 Study schematic of the ACE CardioLink-3 randomised trial.

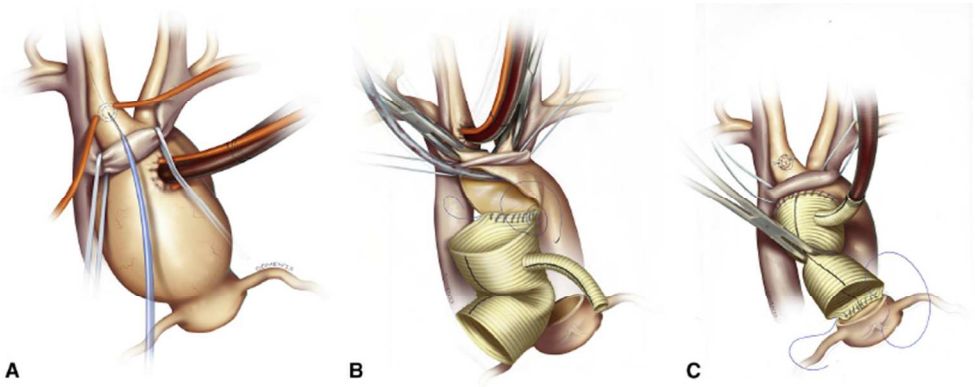

Figure 1 Surgical technique used in innominate artery cannulation (with permission from Garg et al.).16 A: The innominate vein is isolated, retracted and the base of the innominate artery mobilised. Two purse string sutures are placed on the anterior wall of the proximal innominate artery before dilators and the cannula are inserted over a guidewire. B: Antegrade cerebral protection is initiated by clamping the base of the innominate artery and connecting the afferent limb of the cardiopulmonary bypass circuit to the 14 or 16 Fr cannula. C: After the distal anastamosis is completed, antegrade cerebral protection is discontinued, and the aortic line is connected to the 8 mm side limb. The graft is clamped distally and full cardiopulmonary bypass is resumed. Proximal reconstruction is performed.

295x115mm (72 x 72 DPI)

Figure 2

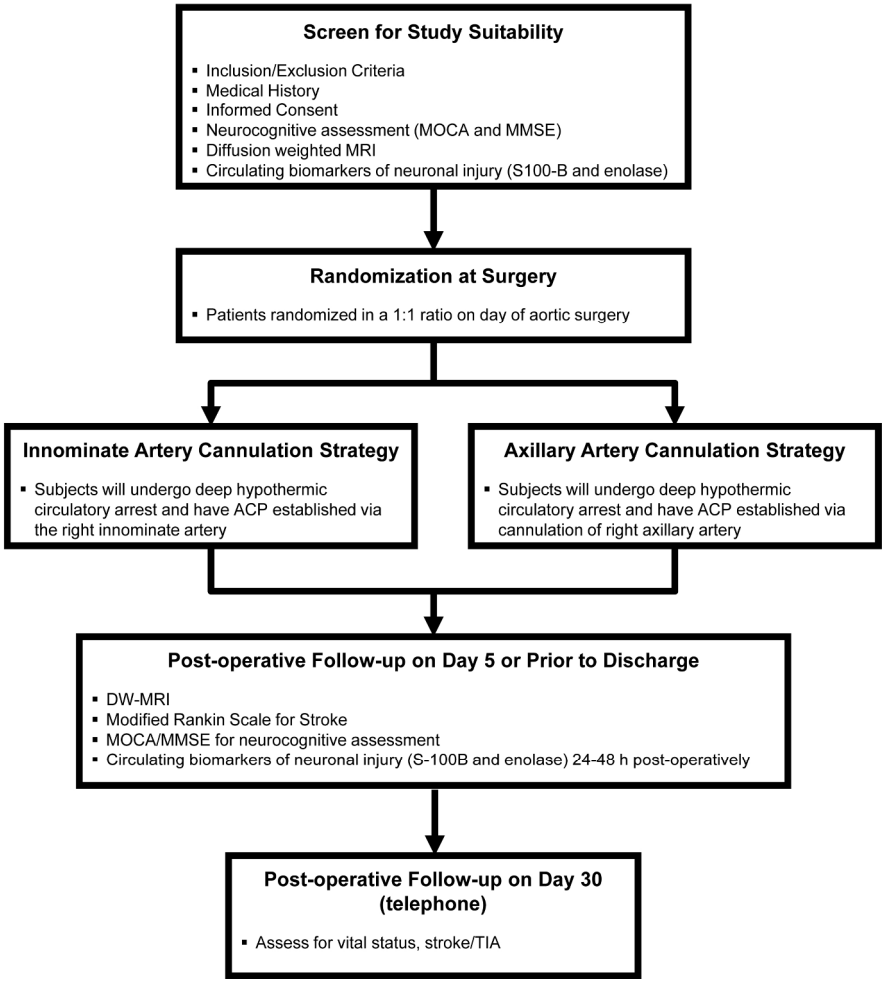

Figure 2 Study schematic of the ACE CardioLink-3 randomised trial.

199x254mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1,5
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2,6
	2b	All items from the World Health Organization Trial Registration Data Set	1, 6 to 9, 12,13,18
Protocol version	3	Date and version identifier	Protocol v.1.3; 26-Aug-2016
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	18
	5b	Name and contact information for the trial sponsor	18
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16,17

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4,5
	6b	Explanation for choice of comparators	4,5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7,8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Not applicable
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Not applicable
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Not applicable
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8,9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10 to 12, Figure 2

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not applicable
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10,11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Not applicable

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10 to 13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12,13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12,13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12,13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16,17
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Not applicable
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8 to 12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Not applicable
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	16

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not applicable
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Not applicable
	31b	Authorship eligibility guidelines and any intended use of professional writers	18
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Not applicable
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Axillary versus Innominate Artery Cannulation for Antegrade Cerebral Perfusion in Aortic Surgery: Design of the Aortic Surgery Cerebral Protection Evaluation (ACE) CardioLink-3 Randomised Trial

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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Evidence based practice, Patient-centred medicine, Surgery
Keywords:	Stroke < NEUROLOGY, Cardiothoracic surgery < SURGERY, Hypertension < CARDIOLOGY

Axillary versus Innominate Artery Cannulation for Antegrade Cerebral Perfusion in Aortic Surgery: Design of the Aortic Surgery Cerebral Protection Evaluation (ACE) CardioLink-3 Randomised Trial

Vinay Garg,[1] Mark D Peterson,[2,3] Michael W A Chu,[4] Maral Ouzounian,[3,5] Roderick G G MacArthur,[6] John Bozinovski,[7] Ismail El-Hamamsy,[8] F Victor Chu,[9] Ankit Garg,[1] Judith Hall,[10] Kevin E Thorpe,[10,11] Natasha Dhingra,[2] Hwee Teoh,[12,13] Thomas R Marotta,[14,15] David A Latter,[2,3] Adrian Quan,[12] Muhammad Mamdani,[15-19] Peter Juni,[10,16] C David Mazer,[20,21] Subodh Verma[3,12,22]

[1]Department of Internal Medicine, University of Toronto, Toronto, ON, Canada
[2]Division of Cardiac Surgery, Li Ka Shing Knowledge Institute of St Michael's Hospital, Toronto, ON, Canada
[3]Department of Surgery, University of Toronto, Toronto, ON, Canada
[4]Division of Cardiac Surgery, London Health Sciences Center, University of Western Ontario, London, ON, Canada
[5]Division of Cardiovascular Surgery, Peter Munk Cardiac Centre, University Health Network, Toronto, ON, Canada
[6]Division of Cardiac Surgery, University of Alberta Hospital, University of Alberta, Edmonton, AB, Canada
[7]Division of Cardiac Surgery, Royal Jubilee Hospital, University of British Columbia, Victoria, BC, Canada
[8]Division of Cardiac Surgery, Montreal Heart Institute, Université de Montréal, Montreal, QC, Canada
[9]Division of Cardiac Surgery, Department of Surgery, Hamilton General Hospital, McMaster University, Hamilton, ON, Canada
[10]Applied Health Research Centre, Li Ka Shing Knowledge Institute of St Michael's Hospital, Toronto, ON, Canada
[11]Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada
[12]Division of Cardiac Surgery, Keenan Research Centre for Biomedical Science and Li Ka Shing Knowledge Institute of St Michael's Hospital, Toronto, ON, Canada
[13]Division of Endocrinology & Metabolism, Li Ka Shing Knowledge Institute of St Michael's Hospital, Toronto, ON, Canada
[14]Department of Diagnostic and Therapeutic Neuroradiology, Keenan Research Centre for Biomedical Science of St Michael's Hospital, University of Toronto, Toronto, ON, Canada
[15]Department of Medicine, University of Toronto, Toronto, ON, Canada
[16]Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada
[17]Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada
[18]Institute for Clinical Evaluative Sciences UofT, Toronto, ON, Canada
[19]Li Ka Shing Centre for Healthcare Analytics Research and Training (LKS-CHART), St. Michael's Hospital, Toronto, ON, Canada
[20]Department of Anesthesia, Li Ka Shing Knowledge Institute of St Michael's Hospital, Toronto, ON, Canada
[21]Department of Anesthesia, University of Toronto, Toronto, ON, Canada
[22]Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada

Correspondence to:
Dr C David Mazer, Department of Anesthesia, St Michael's Hospital, Suite 1-028e, Shuter Wing, 30 Bond Street, Toronto, Ontario, Canada, M5B 1W8. Phone: 416-864-5825; Fax: 416-864-6014. Email: mazerd@smh.ca *OR* Dr Subodh Verma, Division of Cardiac Surgery, St Michael's Hospital, 8th Floor, Bond Wing, 30 Bond Street, Toronto, Ontario, Canada, M5B 1W8. Phone: 416-864-5997; Fax: 416-864-5881. Email: vermasu@smh.ca

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Keywords: innominate artery, axillary artery, antegrade cerebral perfusion, randomised trial, moderate hypothermia

ABSTRACT

Introduction: Neurological injury remains the major cause of morbidity and mortality following open aortic arch repair. Systemic hypothermia along with antegrade cerebral perfusion (ACP) is the accepted cerebral protection approach, with axillary artery cannulation being the most common technique used to establish ACP. More recently, innominate artery cannulation has been shown to be a safe and efficacious method for establishing ACP. Inasmuch as there is a lack of high quality data comparing axillary and innominate artery ACP, we have designed a randomised, multicentre clinical trial to compare both cerebral perfusion strategies with regards to brain morphologic injury using diffusion weighted MRI (DW-MRI).

Methods and analysis: 110 patients undergoing elective aortic surgery with repair of the proximal arch requiring an open distal anastamosis will be randomised to either the innominate artery or the axillary artery cannulation strategy for establishing unilateral ACP during systemic circulatory arrest with moderate levels of hypothermia. The primary safety endpoint of this trial is the proportion of patients with new severe ischaemic lesions found on post-operative DW-MRI compared with pre-operative DW-MRI. The primary efficacy endpoint of this trial is the difference in total operative time between the innominate artery and the axillary artery cannulation group.

Ethics and dissemination: The study protocol and consent forms have been approved by the participating local research ethics boards. Publication of the study results is anticipated in 2018/2019. If this study shows that the innominate artery cannulation technique is non-inferior to the axillary artery cannulation technique with regards to brain morphologic injury, it will establish the innominate artery cannulation technique as a safe and potentially more efficient method of antegrade cerebral perfusion in aortic surgery.

Trial registration number: The trial is registered at clinicaltrials.gov Identifier: NCT02554032.

Strengths

- Multicenter randomised controlled trial
- Rigorous design to address an important unanswered question with clinically relevant primary and secondary outcomes
- Strong research team with experts in thoracic aortic surgery and cerebral perfusion techniques

Limitations

- Study population limited to elective procedures of the ascending aorta and proximal arch, excluding aortic dissections and emergency operations
- Patient outcomes only followed to 3 months
- Study requires surgeons skilled in both cannulation techniques

INTRODUCTION

Thoracic aortic aneurysms are associated with substantial morbidity and mortality, Accordingly, aortic surgery is common, with approximately 200,000 surgical cases annually worldwide.[1-3] The natural history of unrepaired aortic aneurysms is poor, with a high incidence of aortic dissection, rupture and death.[1 2 4]

Surgery involving the ascending aorta and aortic arch is complex and several techniques have been developed to safely interrupt or modify the circulation to the brain. Despite advances in cannulation, cerebral perfusion, and temperature management, neurological injury remains the most dreaded complication of aortic arch surgery.[3 5] Manifestations of such injury may range from fatal, or severe/irreversible injury to milder transient ischaemic attack (TIA), or neurocognitive injury.[2 3 5 6]

Current practice for proximal aortic arch surgery with regards to neuro-protection strategies include deep hypothermic circulatory arrest (DHCA) alone, retrograde cerebral perfusion (RCP) with DHCA, antegrade cerebral perfusion (ACP) with DHCA, and moderate hypothermic circulatory arrest with ACP.[6 7] In addition to moderate hypothermia, ACP via right axillary artery cannulation has become a preferred approach for cerebral protection during aortic surgery.[7] Although ACP via the axillary artery has been shown to improve survival and neurologic outcomes after aortic aneurysm repair compared to retrograde cerebral perfusion, there are several associated risks.[6-14] The axillary approach increases the risk of brachial plexus injury, seromas, arm hyper-perfusion and limb ischaemia and it requires additional surgical dissection, increasing the total operative time required, particularly in patients with obesity or challenging anatomy.[10 15] A novel approach for delivering ACP via cannulation of the innominate artery has recently emerged (Figure 1).[16] First devised by Banbury and colleagues in 2000, several retrospective studies and case series have shown innominate artery cannulation to be relatively safe with a low rate of surgical mortality and neurological injury.[10 16-22] A retrospective

analysis comparing innominate artery cannulation with axillary artery cannulation showed no significant differences in neurological complications.[15] However, data evaluating innominate artery cannulation is confounded by potential selection bias with respect to the complexity of patients chosen for each strategy. Although worldwide many surgeons have adopted the innominate artery cannulation strategy in favor of the axillary artery strategy, there are no randomised trial data to help objectively evaluate safety and efficacy of this technique. Given the grave consequences of inappropriate and/or inadequate cerebral protection, a randomised trial to compare each surgical strategy is needed. We describe herein the protocol for the prospective Aortic Surgery Cerebral Protection Evaluation (ACE) CardioLink-3 Randomised Trial that has been designed to establish the efficacy and safety of innominate artery cannulation versus axillary artery cannulation for ACP in patients undergoing proximal aortic arch surgery with hypothermic circulatory arrest.

Study Purpose

The purpose of this trial is to compare innominate artery cannulation to axillary artery cannulation as a means of cerebral protection during moderate hypothermic circulatory arrest in subjects undergoing surgery for aneurysms of the ascending aorta and proximal arch. The primary safety objective of this study is to determine whether the innominate artery cannulation technique is non-inferior to the axillary artery cannulation technique for establishing ACP with regards to brain morphologic injury on diffusion weighted magnetic resonance imaging (DW-MRI). The primary efficacy objective is to determine if the innominate artery technique is superior to the axillary artery technique with respect to surgical operative time.

The secondary objectives are to determine whether innominate artery cannulation for ACP is non-inferior to axillary artery cannulation with regards to post-operative 30-day mortality, and clinical and biomarker evidence of neurological injury and cognitive dysfunction.

METHODS

Study Design Summary

This is a multi-centre, two-arm randomised controlled, non-inferiority trial comparing a novel strategy for establishing ACP via innominate artery cannulation versus traditional axillary artery cannulation, in patients 18 years and older, undergoing elective repair of the ascending aorta and proximal arch requiring moderate hypothermic circulatory arrest and an open distal anastomosis. A list of the currently active sites is provided in the Appendix. Patients undergoing surgery for aortic dissection, emergent or urgent operations, and total arch repair will be excluded. Furthermore, patients who cannot undergo MRI, or are using an investigational drug/device at the time of enrolment, or are a part of another clinical trial will also be excluded. Patients will be eligible for randomisation regardless of the proximal extent of the aortic repair (i.e. root replacement vs. valve repair/replacement vs. supracoronary aortic repair). The patient will only remain in the study if the surgeon confirms the technical acceptability of either technique, as to allow for safe randomisation. Patients will then be randomly allocated 1:1 to undergo either the innominate or axillary cannulation strategy (Figure 2). All participating centers are academic hospitals within Canada that have expertise in cardiac surgery. The trial has been registered at clinicaltrials.gov (Identifier: NCT02554032).

Randomisation

Patients will be randomised in a 1:1 ratio, stratified by surgical center, on the day of the scheduled ascending aorta operation to either the innominate artery cannulation strategy or the axillary artery cannulation strategy for establishing ACP during moderate hypothermic circulatory arrest. The randomised assignments will be generated on a computer by a study statistician and will employ random permuted blocks of varying sizes. Randomisation will be centralised, web-

based, and generated by the Applied Health Research Center at the Li Ka Shing Knowledge Institute of St Michael's Hospital.

Surgical Strategy

The surgical strategy will be standardised amongst the enrolling aortic surgeons/centers.

Innominate artery cannulation

After median sternotomy and systemic heparinisation, the distal aneurysmal ascending aorta will be cannulated using a standard 7 or 8 mm arterial cannula. Standard central venous cannulation is employed and cardioplegia management is left at the discretion of the individual surgeons; cardio-pulmonary bypass (CPB) and systemic cooling will be initiated. During the cooling phase, the ascending aorta and proximal arch will be mobilised, the innominate vein will be isolated and gently dissected, and the base of the innominate artery will be exposed. Two purse string sutures of 4-0 polypropylene will be placed on the anterior wall of the proximal innominate artery. Once the nasopharyngeal temperature is approximately 26°C the innominate artery will be cannulated with a 0.035-in. J wire, and sequentially dilated using 8/10F and 12/14F dilators. A 14F or 16F cannula with side perforations for gentle dispersion of the perfusate will then be inserted over a guidewire. The period of circulatory arrest with ACP will be initiated by clamping the base of the innominate artery and connecting the afferent limb of the cardiopulmonary bypass (CPB) circuit to the cannula using a 3/8 to 1⁄4 connector. Moderately cold blood (24-26°C) will be delivered at a flow rate of 10-12 mL/kg/min to achieve a right brachial pressure of 50-70 mmHg. The distal anastamosis will be performed as either a beveled hemiarch or an end-to-end anastamosis using a woven polyester graft with an 8 mm side limb. Once the distal anastamosis is complete the aortic line will be connected to the side limb of the graft, air will be flushed from the graft, the graft clamped and full CPB will be resumed. At that time, ACP will be

discontinued. Following five minutes at 26°C, re-warming will resume and the proximal reconstruction will be completed.[16]

Axillary artery cannulation

Patients randomised to the control group will undergo axillary artery cannulation as routinely performed. The details of this operation have been previously described.[15]

Outcomes

Primary outcome

The primary safety endpoint of this trial is the proportion of patients with new severe ischaemic lesions. Two independent neuroradiologists who are blinded to treatment assignment will adjudicate this primary endpoint. New severe ischaemic lesions will be defined as severe white matter injury or an infarction involving the basal ganglia, thalamus or internal capsule or a large hemispheric infarction present on the post-operative DW-MRI. Each patient will have a preoperative DW-MRI to serve as the baseline study for comparison, to ensure the highest quality data. Severe white matter injury will be defined as 6 or more punctate lesions, or 2 or more lesions of 4 mm or larger size.[5] We have included the size of the ischaemic lesions as a defining criterion for severity as the volume of ischaemic lesions is a known independent predictor of stroke outcome.[23 24] Furthermore, it has been shown that the number of DW-MRI lesions is only likely to be clinically relevant if the individual lesion is large. [5 25 26]

The primary efficacy endpoint of this trial is the difference in total operative time between the innominate artery cannulation group and the axillary artery cannulation group.

Secondary Outcomes

Differences in the following secondary outcomes between both surgical strategies will be assessed:

1. 30-day all-cause post-operative mortality.
2. Post-operative stroke or TIA in hospital and at 30 days.
3. Neurocognitive dysfunction at post-operative day 4 and at 3 month follow up as assessed by the MMSE and MOCA tests. Both the MOCA and MMSE have been validated for cognitive screening in patients with cerebrovascular disease.[27-29]
4. DW-MRI parameters including number of total ischaemic lesions, total ischaemic volume of lesions, single lesion volume, watershed injury, intraparenchymal haemorrhage, cerebral haemorrhage, intraventricular haemorrhage, subdural haemorrhage, subarachnoid haemorrhage, partial cerebral sinovenous thrombosis.
5. Pre-operative and post-operative serum levels of circulating biomarkers of neuronal injury (S-100β and neuron specific enolase)
6. Post-operative sepsis, delirium, seizure, encephalopathy, atrial fibrillation, post-operative MI, re-operations.
7. Total length of ICU stay, and number of hours of required intubation and ventilation
8. Seroma, brachial plexus injury, reduced arm mobility and pain, arm ischaemia
9. Total CPB time, total cross-clamp time, total systemic circulatory arrest time, total ACP time, total cooling time (minutes), re-warming time, nadir nasopharyngeal temperature (degrees C), post-operative haemoglobin, peri-operative RBC transfusion, peri-operative inotrope or vasopressor use.
10. Cerebral oximetry will be monitored intraoperatively using bilateral non-invasive near-infrared spectroscopy. The following data will be evaluated: baseline O_2 saturation while awake, total number of desaturations i.e. < 20% of baseline, the total area under the curve of % saturation over time below 20% of baseline, minimal value reached and the maximum change from baseline values.

Data Collection

Preoperative

The screening visit will occur at the time of the initial appointment where the patient will be seen by the cardiac surgeon for evaluation and consideration of aortic surgery. Patients who are booked for elective ascending aortic surgery with a planned open distal anastamosis and moderate hypothermic circulatory arrest will be assessed for eligibility in the clinical trial. Study co-ordinators will review the study with potential participants and upon agreement to participate, obtain informed written consent.

The following baseline information will then be collected at either this initial visit, or at the time of the pre-operative anaesthesia clinic visit:

Clinical information

Demographics (age, sex), medical history including hypertension, diabetes mellitus, dyslipidemia, heart failure or LV dysfunction (latest ECHO or cardiac catheterisation), NYHA class, previous history of stroke, TIA, or systemic embolism, renal disease, peripheral vascular disease, coronary artery disease, previous coronary angioplasty with or without stent, COPD, smoking history, pulmonary hypertension (from latest ECHO or cardiac catheterisation), congenital aortic disease, previous cardiac surgery, history of atrial fibrillation, EuroSCORE II.

Physical examination information

Height (cm), weight (kg), body surface area.

Laboratory/tests

We will obtain baseline haemoglobin (g/L), creatinine (μmol/L), baseline biomarkers of neuronal injury (S-100β and neuron specific enolase), and a 12-lead ECG.

Imaging

DW-MRI will be completed prior to the surgical date.

Neurocognitive tests

MMSE and MOCA will be carried out pre-operatively.

Intraoperative

Intra-operative data collection will include total operative time (from skin incision, to closure of the skin), total CPB time, total cross-clamp time, total circulatory arrest time, total ACP time, total cooling time, re-warming duration, nadir nasopharyngeal temperature, mean arterial systolic and diastolic blood pressure, nadir haemoglobin concentration (g/L), intra-operative RBC transfusion (units) and intra-operative inotrope or vasopressor use.

Post-operative

Post-operative data will include total ICU stay, total ventilation time, post-operative hospital stay, in-hospital mortality, delirium, re-operations, post-operative MI, inotropic support, seizure, development of renal failure, atrial fibrillation, post-operative stroke, transfusion, sepsis, and pulmonary complications. Serum S-100β and NSE levels will be drawn post-operatively at 24-48 hours. At post-op day 4 (±3 days), the patient will undergo post-operative DW-MRI. On the day of discharge, the patient will undergo testing for stroke/TIA using the Modified Rankin Scale in addition to repeat neurological physical examination. Neurocognitive testing will also be carried out on the day of discharge, and at the surgical follow up visit conducted at 1 to 3 months post-operatively, using MOCA and MMSE tests.

Study Follow-up

Subjects will be followed daily during their post-operative course in hospital. A phone call at

post-operative day 30 will be conducted to assess for vital status, stroke and TIA, In addition, there will be a follow up visit in 1 to 3 months post-operatively to reassess neurocognitive status.

Study Sample Size and Power

In this trial, the primary endpoint is the number of patients with new severe ischaemic brain lesions on DW-MRI, comparing pre-operative and post-operative imaging. In accordance with previous literature, we anticipate that about 50% of patients will develop new, severe ischaemic lesions in the axillary cannulation group (control group).[5] Based on a consensus of investigators from surgery, anaesthesia, neuroradiology and critical care, we have determined that an absolute difference of 25% is an acceptable non-inferiority margin. Finally, we have set the power of this trial at 80% (for the 25% margin) and a one-sided Type I error of 5% (non-inferiority comparisons are one sided by definition). Under these assumptions and conditions, a sample size of 100 subjects (50 per group) is required. Finally, we factor in a 10% attrition rate to arrive at a final sample size of 110. This sample size also gives us greater than 80% power to detect a difference of 45 minutes in total operative time between the axillary artery and innominate artery cannulation strategies.

Data Analysis

The primary analysis is a non-inferiority comparison of the proportion of patients acquiring new severe brain lesions. The observed difference will be compared against the non-inferiority margin of 25% using a one-sided z-test. Since the intention-to-treat approach employed in superiority trials biases towards no difference, it is inappropriate in the non-inferiority trial where lack of difference is the goal. Therefore, the primary analysis will be a per-protocol analysis. The difference in proportions and 90% confidence intervals (corresponds more closely to the one sided test being used) will be reported.

Our primary efficacy endpoint, total operative time, is powered for superiority. Thus the

total operative time will be compared with a t-test and the mean difference and 95% confidence interval will be reported.

Binary outcomes (30-day mortality, stroke/TIA, neurocognitive dysfunction, delirium, seizures, encephalopathy, adverse events, local complications) will be compared using a chi-square test or Fisher's Exact test if expected counts are less than 5. For each outcome the absolute risk difference and 95% CI will be reported. The quantitative DW-MRI parameters will be compared by t-tests and mean differences with 95% CIs will be reported. Whether or not patients experienced none, a single or multiple new lesions will be compared by a chi-square test. The mean levels of post-operative biomarkers (S-100β and NSE) will be compared. The adjusted mean difference and 95% CI will be reported for each biomarker. Intraoperative characteristics will be compare with t-tests and mean differences with 95% CIs will be reported.

DISCUSSION

Axillary artery cannulation for achieving ACP with moderate levels of hypothermia is the currently preferred approach for establishing cerebral perfusion during aortic surgery. We describe the first prospective, randomised controlled trial evaluating the safety and efficacy profile of ACP via cannulation of the innominate artery in comparison to axillary artery cannulation.

We selected new severe ischaemic brain lesions as defined by DW-MRI as our primary safety end-point. DW-MRI has a sensitivity and specificity of 92% and 97% respectively in detecting new ischaemic lesions. Identification of restriction in diffusion of water molecules suggests cerebral ischaemia. Normal tissue appears gray on DW-MRI due to the Brownian motion and diffusion of water molecules. Ischaemic tissue however, due to the prevention of normal loss of MRI signal by restricted diffusion, appears bright white. These differences are apparent within 5 days of injury.[25]

DW-MRI as a modality to assess neurologic injury has been validated in the transcatheter aortic valve implantation (TAVI) population, and more recently in aortic surgery studies and trials. These studies have demonstrated that the number of new ischaemic lesions, in addition to the size of these lesions together is the most prognostically significant measure.[23-25] Recent literature shows that the rate of new ischaemic brain lesions on DW-MRI after aortic surgery ranges from 40 to 60%.[5 30 31] A recent clinical trial in neonatal aortic arch surgery also employed DW-MRI as a surrogate of neuronal injury comparing ACP to DHCA. This non-inferiority trial used location, number of lesions and size of lesions to characterise severity of injury.[5] We used these data to inform our primary end point.

By comparing DW-MRI pre-operatively and post-operatively, we will be able to effectively quantify new, significant ischaemic brain lesions. Furthermore, given that DW-MRI is highly sensitive for ischaemic brain lesions, it also has an ability to detect “silent” brain injury. Silent brain injury has been shown to be a risk factor for delayed neurological decline. [25 32 33] Retrospective studies evaluating innominate or axillary artery cannulation have primarily assessed clinical end-points such as stroke or temporary neurological deficits. As such events are relatively rare, it is difficult to assess for true differences in outcomes between treatment modalities with the sample sizes available for aortic surgery. Thus, new, severe ischaemic brain lesions found on DW-MRI serves as a useful surrogate marker for risk of neurological injury. The high incidence of new ischaemic brain lesions post-aortic surgery allows us to efficiently assess our outcome with a relatively small sample size of 110 subjects.

In addition to imaging, this trial aims to assess neurological injury by comparing pre-operative and post-operative levels of circulating biomarkers of neuronal injury, specifically, NSE and S-100β. There is extensive literature that shows that proteins that are synthesised by astroglial cells or neurons, and that cross the blood brain barrier can be correlated in peripheral blood with brain injury.[34-37] S-100β is a small dimeric cytosolic protein that exists in multiple forms, with the beta form noted to be highly specific for the central nervous system.[34] NSE is a

dimer found in neurons, and belongs to a group of hydrolytic enzymes. It is also present in erythrocytes, platelets, plasmatic cells, and lymphocytes, which is why it is present in peripheral blood at very low physiologic concentrations.[34]

Given that these biomarkers are present at levels from nil to very low physiologic concentrations at baseline, and S-100β especially is very sensitive for detection of intracranial pathology, elevations in these markers post-operatively will suggest neuronal injury secondary to the procedure. Collecting pre-operative and post-operative samples will allow us to correlate serum levels with neuronal injury secondary to the aortic surgery specifically.

Furthermore, we will use two neurocognitive tests to detect neurocognitive decline post-operatively, and will assess for differences between both cannulation strategies. Studies evaluating neuronal injury post aortic surgery or TAVI have shown that neuronal injury does not always manifest overtly as stroke, but rather can present more subtly as neurocognitive decline. These features are often most prominent in those that have pre-existing neurologic disease or vascular dementia.[38] As a part of our neurocognitive testing, we have chosen to use both the MMSE and MOCA. These are commonly used cognitive screening tools in clinical practice. The MMSE is designed to assess language and memory while the MOCA is designed to detect mild to moderate cognitive impairment. It has been found to have high sensitivity and specificity for detecting mild cognitive impairment. Although more sophisticated neurocognitive testing does exist, due to time constraints of performing such testing, and the lack of generalisability with such tests, the MOCA and MMSE were chosen for ease of administration, and reproducibility of results. Furthermore, MOCA and MMSE have been employed in a number of cardiac surgery studies evaluating neurocognitive decline.[27-29 38]

It is important to recognise that there are important limitations of this trial. We have limited this randomised controlled trial to elective procedures on the ascending aorta and proximal arch. Patients planned for total arch replacement are excluded. Secondarily, we are not studying patients undergoing aortic dissection or urgent/emergent operations. Emergency

operations such as for aortic dissection would introduce many confounding variables and significantly impact the ability to accurately assess the safety and efficacy of innominate artery cannulation in comparison to axillary artery cannulation. In addition, our follow-up period ends at 1 to 3 months post-operatively; therefore the long-term outcomes of the different antegrade cerebral perfusion strategies will not be assessed. However, the catastrophic consequences of inadequate cerebral perfusion are usually apparent soon after surgery. Furthermore, our trial assumes competency of the operating aortic surgeon for establishing both cerebral protection strategies. Poor outcomes that may be linked to techniques by surgeons less familiar with either the innominate or axillary artery cannulation technique will not be known since only surgeons who routinely practice aortic surgery are participating in this study.

ETHICS AND DISSEMINATION

The protocol and consent form was initially approved at the lead site (St. Michael's Hospital Research Ethics Board; protocol 15-071) and subsequently by all other participating local research ethics boards. This study is being carried out in accordance with the current International Conference on Harmonization Guideline for Good Clinical Practice, Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans and applicable local laws and regulations. Protocol modifications will be communicated to each participating site and their respective Research Ethics Committees. In addition, protocol amendments will be uploaded to clinicaltrials.gov. As much data as possible will be contained in the published manuscript (and accompanying supplementary material) which is anticipated to occur in 2018/2019. There are no plans to provide public access to the participant-level database.

Patient Safety

All subject related information including case report forms, evaluation forms, reports, etc. will be kept strictly confidential. All records will be kept in a secure, locked location and only research staff will have access to the records. Subjects will be identified only by means of a coded number specific to each subject. All computerised databases will identify subjects by numeric codes only, and will be password protected.

An independent Data Safety and Monitoring Board (DSMB) composed of experts in cardiac surgery and peri-operative care will be assembled to ensure patient safety, receive safety reports, provide feedback to the trial steering committee, and ensure the study follows the highest ethical standards. The DSMB will be provided data on safety after enrollment of 1/3 and 2/3 of patients. The safety data will include all adverse events listed as primary and secondary outcomes. The DSMB will consider clinical and statistical significance, consistency of data over time, consistency of the direction of risk and benefit-risk ratios if there is consideration for recommendation for early trial discontinuation. In addition to receiving regular safety data reports, the DSMB will have the ability to request additional safety analyses or additional interim analyses and make any further recommendations to the steering committee about the safe conduct of the trial after considering all the available data and any new external data from relevant studies.

CONCLUSION

This randomised controlled trial is essential to definitively determine adequate brain protection strategies for patients undergoing aortic surgery on the ascending aorta and proximal arch with the use of moderate hypothermia and unilateral antegrade cerebral perfusion. Innominate artery cannulation is rapidly gaining interest as an alternative to axillary artery cannulation, however,

there are no high quality prospective data to inform whether or not the two strategies are similar with respect to cerebral protection. Innominate artery cannulation has the potential to decrease surgical times, and reduce complications associated with an axillary approach such as brachial plexus injury, seroma formation, and limb ischaemia. Decreased surgical times could lead to significant cost savings. The ACE CardioLink-3 trial will be the first randomised controlled trial designed to prospectively assess and compare the safety and efficacy of the innominate artery cannulation technique with the current standard of practice, axillary artery cannulation, for establishing ACP for patients having proximal aortic surgery. These data should aid surgeons in informed surgical decision making when considering cannulation techniques for aortic surgery.

Data Sharing Participant consent and REB approval has not been sought for external data sharing so no additional data will be available beyond what is contained in manuscripts (and accompanying supplemental material) which are anticipated to be published in 2018/2019.

Contributors VG, MDP, CDM and SV conceived the study and designed the study protocol. VG, MDP, CDM and SV significantly contributed to the planning of analyses of the data. VG, MDP, AG, CDM and SV drafted the manuscript. VG, MDP, MWAC, MO, RGGM, JB, IH, FVC, AG, JH, KET, ND, HT, TRM, DAL, AQ, MM, PJ, CDM, SV critically revised the manuscript for important intellectual content; reviewed and approved the final manuscript and agree to be accountable for all aspects of the work.

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Figure Legends

Figure 1 Surgical technique used in innominate artery cannulation (with permission from Garg et al.).[16]

A: The innominate vein is isolated, retracted and the base of the innominate artery mobilised. Two purse string sutures are placed on the anterior wall of the proximal innominate artery before dilators and the cannula are inserted over a guidewire. **B:** Antegrade cerebral protection is initiated by clamping the base of the innominate artery and connecting the afferent limb of the cardiopulmonary bypass circuit to the 14 or 16 Fr cannula. **C:** After the distal anastamosis is completed, antegrade cerebral protection is discontinued, and the aortic line is connected to the 8 mm side limb. The graft is clamped distally and full cardiopulmonary bypass is resumed. Proximal reconstruction is performed.

Figure 2 Study schematic of the ACE CardioLink-3 randomised trial.

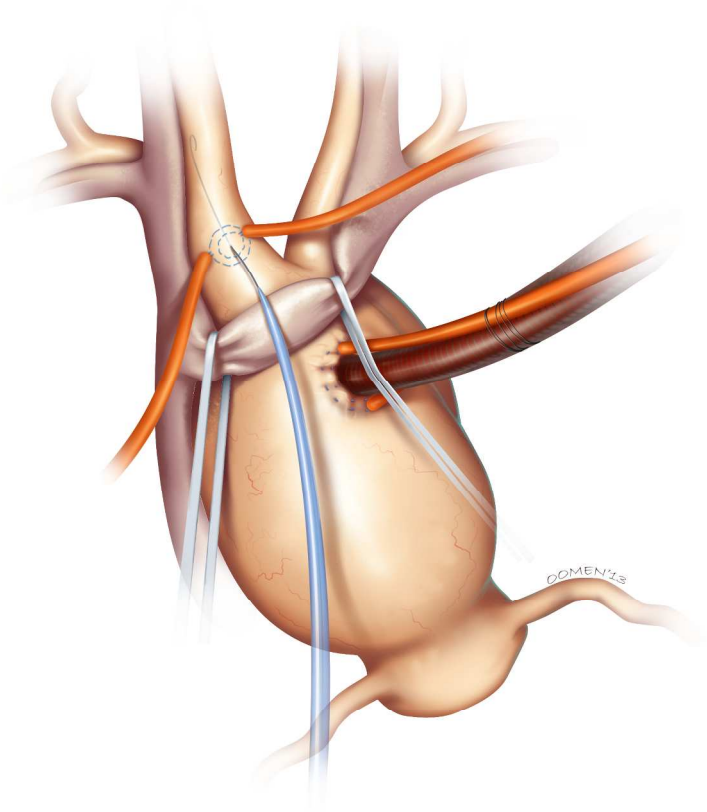

Figure 1 Surgical technique used in innominate artery cannulation (with permission from Garg et al.).16 A: The innominate vein is isolated, retracted and the base of the innominate artery mobilised. Two purse string sutures are placed on the anterior wall of the proximal innominate artery before dilators and the cannula are inserted over a guidewire.

216x270mm (300 x 300 DPI)

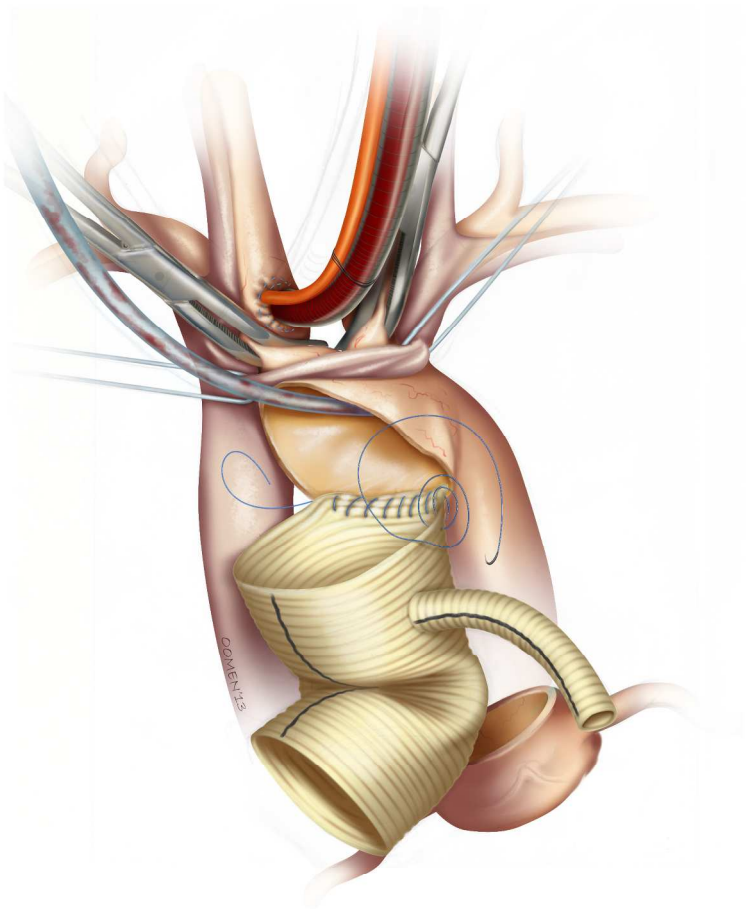

Figure 1 Surgical technique used in innominate artery cannulation (with permission from Garg et al.).16
B: Antegrade cerebral protection is initiated by clamping the base of the innominate artery and connecting the afferent limb of the cardiopulmonary bypass circuit to the 14 or 16 Fr cannula.

203x254mm (300 x 300 DPI)

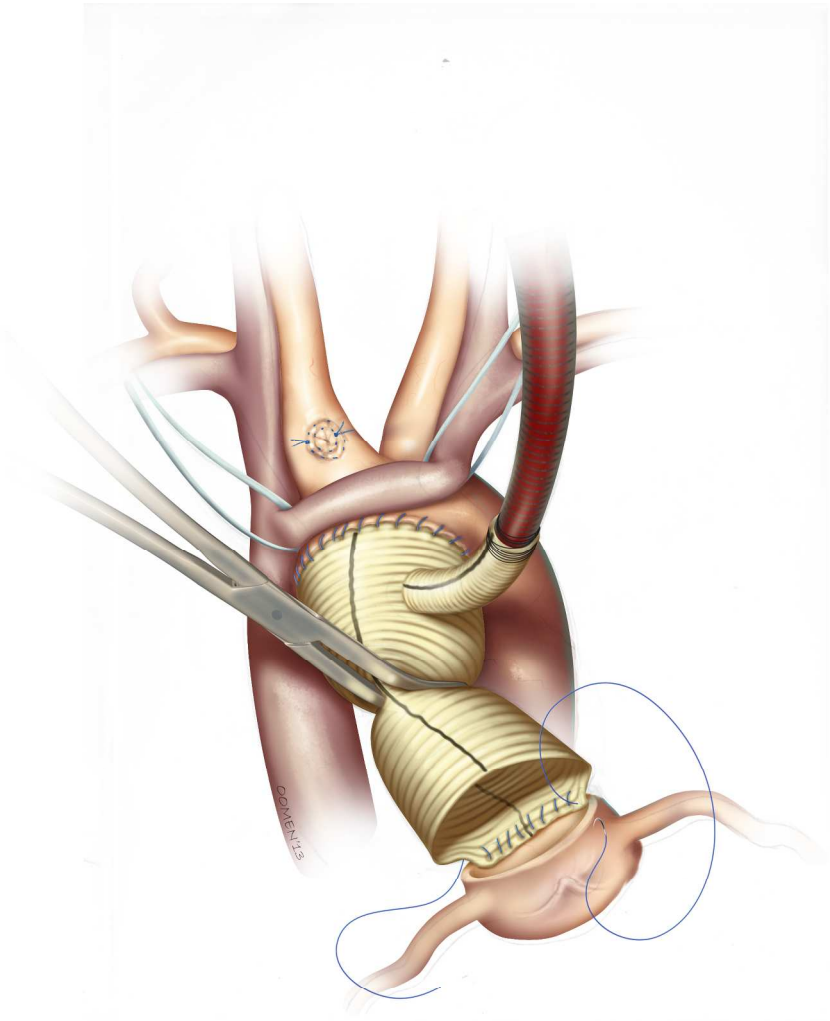

Figure 1 Surgical technique used in innominate artery cannulation (with permission from Garg et al.).16
C: After the distal anastamosis is completed, antegrade cerebral protection is discontinued, and the aortic line is connected to the 8 mm side limb. The graft is clamped distally and full cardiopulmonary bypass is resumed. Proximal reconstruction is performed.

203x254mm (300 x 300 DPI)

Figure 2

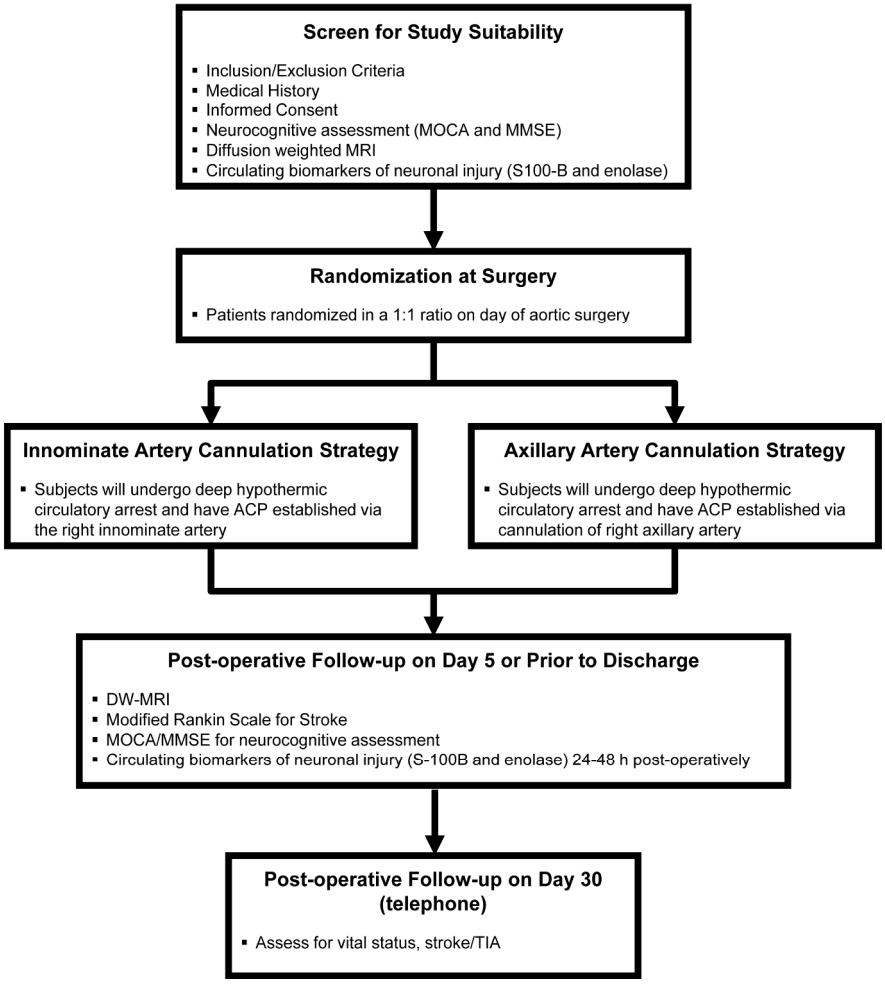

Figure 2 Study schematic of the ACE CardioLink-3 randomised trial.

199x254mm (300 x 300 DPI)

Appendix 1

List of study sites

1. St. Michael's Hospital, University of Toronto, Toronto, ON, Canada
2. Toronto General Hospital, University of Toronto, Toronto, ON, Canada
3. London Health Sciences Center, Western University, London, ON, Canada
4. Royal Jubilee Hospital, University of British Columbia, Victoria, BC, Canada
5. University of Alberta Hospital, University of Alberta, Edmonton, AB, Canada
6. Institut Universitaire de Cardiologie et de Pneumologie de Québec, Université Laval, Laval, QC, Canada

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1,5
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2,6
	2b	All items from the World Health Organization Trial Registration Data Set	1, 6 to 9, 12,13,18
Protocol version	3	Date and version identifier	Protocol v.1.3; 26-Aug-2016
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	18
	5b	Name and contact information for the trial sponsor	18
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16,17

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4,5
	6b	Explanation for choice of comparators	4,5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7,8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Not applicable
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Not applicable
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Not applicable
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8,9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10 to 12, Figure 2

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not applicable
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10,11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Not applicable

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10 to 13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12,13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12,13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12,13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16,17
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Not applicable
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8 to 12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Not applicable
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	16

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not applicable
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Not applicable
	31b	Authorship eligibility guidelines and any intended use of professional writers	18
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Not applicable
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Axillary versus Innominate Artery Cannulation for Antegrade Cerebral Perfusion in Aortic Surgery: Design of the Aortic Surgery Cerebral Protection Evaluation (ACE) CardioLink-3 Randomised Trial

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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Evidence based practice, Patient-centred medicine, Surgery
Keywords:	Stroke < NEUROLOGY, Cardiothoracic surgery < SURGERY, Hypertension < CARDIOLOGY

Axillary versus Innominate Artery Cannulation for Antegrade Cerebral Perfusion in Aortic Surgery: Design of the Aortic Surgery Cerebral Protection Evaluation (ACE) CardioLink-3 Randomised Trial

Vinay Garg,[1] Mark D Peterson,[2,3] Michael W A Chu,[4] Maral Ouzounian,[3,5] Roderick G G MacArthur,[6] John Bozinovski,[7] Ismail El-Hamamsy,[8] F Victor Chu,[9] Ankit Garg,[1] Judith Hall,[10] Kevin E Thorpe,[10,11] Natasha Dhingra,[2] Hwee Teoh,[12,13] Thomas R Marotta,[14,15] David A Latter,[2,3] Adrian Quan,[12] Muhammad Mamdani,[15-19] Peter Juni,[10,16] C David Mazer,[20,21] Subodh Verma[3,12,22]

[1]Department of Internal Medicine, University of Toronto, Toronto, ON, Canada
[2]Division of Cardiac Surgery, Li Ka Shing Knowledge Institute of St Michael's Hospital, Toronto, ON, Canada
[3]Department of Surgery, University of Toronto, Toronto, ON, Canada
[4]Division of Cardiac Surgery, London Health Sciences Center, University of Western Ontario, London, ON, Canada
[5]Division of Cardiovascular Surgery, Peter Munk Cardiac Centre, University Health Network, Toronto, ON, Canada
[6]Division of Cardiac Surgery, University of Alberta Hospital, University of Alberta, Edmonton, AB, Canada
[7]Division of Cardiac Surgery, Royal Jubilee Hospital, University of British Columbia, Victoria, BC, Canada
[8]Division of Cardiac Surgery, Montreal Heart Institute, Université de Montréal, Montreal, QC, Canada
[9]Division of Cardiac Surgery, Department of Surgery, Hamilton General Hospital, McMaster University, Hamilton, ON, Canada
[10]Applied Health Research Centre, Li Ka Shing Knowledge Institute of St Michael's Hospital, Toronto, ON, Canada
[11]Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada
[12]Division of Cardiac Surgery, Keenan Research Centre for Biomedical Science and Li Ka Shing Knowledge Institute of St Michael's Hospital, Toronto, ON, Canada
[13]Division of Endocrinology & Metabolism, Li Ka Shing Knowledge Institute of St Michael's Hospital, Toronto, ON, Canada
[14]Department of Diagnostic and Therapeutic Neuroradiology, Keenan Research Centre for Biomedical Science of St Michael's Hospital, University of Toronto, Toronto, ON, Canada
[15]Department of Medicine, University of Toronto, Toronto, ON, Canada
[16]Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada
[17]Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada
[18]Institute for Clinical Evaluative Sciences UofT, Toronto, ON, Canada
[19]Li Ka Shing Centre for Healthcare Analytics Research and Training (LKS-CHART), St. Michael's Hospital, Toronto, ON, Canada
[20]Department of Anesthesia, Li Ka Shing Knowledge Institute of St Michael's Hospital, Toronto, ON, Canada
[21]Department of Anesthesia, University of Toronto, Toronto, ON, Canada
[22]Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada

Correspondence to:
Dr C David Mazer, Department of Anesthesia, St Michael's Hospital, Suite 1-028e, Shuter Wing, 30 Bond Street, Toronto, Ontario, Canada, M5B 1W8. Phone: 416-864-5825; Fax: 416-864-6014. Email: mazerd@smh.ca *OR* Dr Subodh Verma, Division of Cardiac Surgery, St Michael's Hospital, 8th Floor, Bond Wing, 30 Bond Street, Toronto, Ontario, Canada, M5B 1W8. Phone: 416-864-5997; Fax: 416-864-5881. Email: vermasu@smh.ca

Word count: 3,998

Keywords: innominate artery, axillary artery, antegrade cerebral perfusion, randomised trial, moderate hypothermia

ABSTRACT

Introduction: Neurological injury remains the major cause of morbidity and mortality following open aortic arch repair. Systemic hypothermia along with antegrade cerebral perfusion (ACP) is the accepted cerebral protection approach, with axillary artery cannulation being the most common technique used to establish ACP. More recently, innominate artery cannulation has been shown to be a safe and efficacious method for establishing ACP. Inasmuch as there is a lack of high quality data comparing axillary and innominate artery ACP, we have designed a randomised, multicentre clinical trial to compare both cerebral perfusion strategies with regards to brain morphologic injury using diffusion weighted MRI (DW-MRI).

Methods and analysis: 110 patients undergoing elective aortic surgery with repair of the proximal arch requiring an open distal anastamosis will be randomised to either the innominate artery or the axillary artery cannulation strategy for establishing unilateral ACP during systemic circulatory arrest with moderate levels of hypothermia. The primary safety endpoint of this trial is the proportion of patients with new radiologically significant ischaemic lesions found on post-operative DW-MRI compared with pre-operative DW-MRI. The primary efficacy endpoint of this trial is the difference in total operative time between the innominate artery and the axillary artery cannulation group.

Ethics and dissemination: The study protocol and consent forms have been approved by the participating local research ethics boards. Publication of the study results is anticipated in 2018 or 2019. If this study shows that the innominate artery cannulation technique is non-inferior to the axillary artery cannulation technique with regards to brain morphologic injury, it will establish the innominate artery cannulation technique as a safe and potentially more efficient method of antegrade cerebral perfusion in aortic surgery.

Trial registration number: The trial is registered at clinicaltrials.gov Identifier: NCT02554032.

Strengths

- Multicentre randomised controlled trial
- Rigorous design to address an important unanswered question with clinically relevant primary and secondary outcomes
- Strong research team with experts in thoracic aortic surgery and cerebral perfusion techniques

Limitations

- Study population limited to elective procedures of the ascending aorta and proximal arch, excluding aortic dissections and emergency operations
- Patient outcomes only followed to 3 months
- Study requires surgeons skilled in both cannulation techniques

INTRODUCTION

Thoracic aortic aneurysms are associated with substantial morbidity and mortality, Accordingly, aortic surgery is common, with approximately 200,000 surgical cases annually worldwide.[1-3] The natural history of unrepaired aortic aneurysms is poor, with a high incidence of aortic dissection, rupture and death.[1 2 4]

Surgery involving the ascending aorta and aortic arch is complex and several techniques have been developed to safely interrupt or modify the circulation to the brain. Despite advances in cannulation, cerebral perfusion, and temperature management, neurological injury remains the most dreaded complication of aortic arch surgery.[3 5] Manifestations of such injury may range from fatal, or severe/irreversible injury to milder transient ischaemic attack (TIA), or neurocognitive injury.[2 3 5 6]

Current practice for proximal aortic arch surgery with regards to neuro-protection strategies include deep hypothermic circulatory arrest (DHCA) alone, retrograde cerebral perfusion (RCP) with DHCA, antegrade cerebral perfusion (ACP) with DHCA, and moderate hypothermic circulatory arrest with ACP.[6 7] In addition to moderate hypothermia, ACP via right axillary artery cannulation has become a preferred approach for cerebral protection during aortic surgery.[7] Although ACP via the axillary artery has been shown to improve survival and neurologic outcomes after aortic aneurysm repair compared to retrograde cerebral perfusion, there are several associated risks.[6-14] The axillary approach increases the risk of brachial plexus injury, seromas, arm hyper-perfusion and limb ischaemia and it requires additional surgical dissection, increasing the total operative time required, particularly in patients with obesity or challenging anatomy.[10 15] A novel approach for delivering ACP via cannulation of the innominate artery has recently emerged (Figure 1).[16] First devised by Banbury and colleagues in 2000, several retrospective studies and case series have shown innominate artery cannulation to be relatively safe with a low rate of surgical mortality and neurological injury.[10 16-22] A retrospective

analysis comparing innominate artery cannulation with axillary artery cannulation showed no significant differences in neurological complications.[15] However, data evaluating innominate artery cannulation is confounded by potential selection bias with respect to the complexity of patients chosen for each strategy. Although worldwide many surgeons have adopted the innominate artery cannulation strategy in favor of the axillary artery strategy, there are no randomised trial data to help objectively evaluate safety and efficacy of this technique. Given the grave consequences of inappropriate and/or inadequate cerebral protection, a randomised trial to compare each surgical strategy is needed. We describe herein the protocol for the prospective Aortic Surgery Cerebral Protection Evaluation (ACE) CardioLink-3 Randomised Trial that has been designed to establish the efficacy and safety of innominate artery cannulation versus axillary artery cannulation for ACP in patients undergoing proximal aortic arch surgery with hypothermic circulatory arrest.

Study Purpose

The purpose of this trial is to compare innominate artery cannulation to axillary artery cannulation as a means of cerebral protection during moderate hypothermic circulatory arrest in subjects undergoing surgery for aneurysms of the ascending aorta and proximal arch. The primary safety objective of this study is to determine whether the innominate artery cannulation technique is non-inferior to the axillary artery cannulation technique for establishing ACP with regards to brain morphologic injury on diffusion weighted magnetic resonance imaging (DW-MRI). The primary efficacy objective is to determine if the innominate artery technique is superior to the axillary artery technique with respect to surgical operative time.

The secondary objectives are to determine whether innominate artery cannulation for ACP is non-inferior to axillary artery cannulation with regards to post-operative 30-day mortality, and clinical and biomarker evidence of neurological injury and cognitive dysfunction.

METHODS

Study Design Summary

This is a multi-centre, two-arm randomised controlled, non-inferiority trial comparing a novel strategy for establishing ACP via innominate artery cannulation versus traditional axillary artery cannulation, in patients 18 years and older, undergoing elective repair of the ascending aorta and proximal arch requiring moderate hypothermic circulatory arrest and an open distal anastomosis. Patients undergoing surgery for aortic dissection, emergent or urgent operations, and total arch repair will be excluded. Furthermore, patients who cannot undergo MRI, or are using an investigational drug/device at the time of enrolment, or are a part of another clinical trial will also be excluded. Patients will be eligible for randomisation regardless of the proximal extent of the aortic repair (i.e. root replacement vs. valve repair/replacement vs. supracoronary aortic repair). The patient will only remain in the study if the surgeon confirms the technical acceptability of either technique, as to allow for safe randomisation. Patients will then be randomly allocated 1:1 to undergo either the innominate or axillary cannulation strategy (Figure 2). All participating centres are academic hospitals within Canada who have expertise in cardiac and aortic surgery (Appendix 1). The trial has been registered at clinicaltrials.gov (Identifier: NCT02554032).

Randomisation

Patients will be randomised in a 1:1 ratio, stratified by surgical centre, on the day of the scheduled ascending aorta operation to either the innominate artery cannulation strategy or the axillary artery cannulation strategy for establishing ACP during hypothermic circulatory arrest. The randomised assignments will be generated on a computer by a study statistician and will employ random permuted blocks of varying sizes. Randomisation will be centralised, web-

based, and generated by the Applied Health Research Center at the Li Ka Shing Knowledge Institute of St Michael's Hospital.

Surgical Strategy

The surgical strategy will be standardised amongst the enrolling aortic surgeons/centres.

Innominate artery cannulation

After median sternotomy and systemic heparinisation, the distal aneurysmal ascending aorta will be cannulated using a standard 7 or 8 mm arterial cannula. Standard central venous cannulation is employed and cardioplegia management is left at the discretion of the individual surgeons; cardio-pulmonary bypass (CPB) and systemic cooling will be initiated. During the cooling phase, the ascending aorta and proximal arch will be mobilised, the innominate vein will be isolated and gently dissected, and the base of the innominate artery will be exposed. Two purse string sutures of 4-0 polypropylene will be placed on the anterior wall of the proximal innominate artery. Once the nasopharyngeal temperature is approximately 26°C the innominate artery will be cannulated with a 0.035-in. J wire, and sequentially dilated using 8/10F and 12/14F dilators. A 14F or 16F cannula with side perforations for gentle dispersion of the perfusate will then be inserted over a guidewire. The period of circulatory arrest with ACP will be initiated by clamping the base of the innominate artery and connecting the afferent limb of the cardiopulmonary bypass (CPB) circuit to the cannula using a 3/8 to 1/4 connector. Moderately cold blood (24-26°C) will be delivered at a flow rate of 10-12 mL/kg/min to achieve a right brachial pressure of 50-70 mmHg. The distal anastamosis will be performed as either a beveled hemiarch or an end-to-end anastamosis using a woven polyester graft with an 8 mm side limb. Once the distal anastamosis is complete the aortic line will be connected to the side limb of the graft, air will be flushed from the graft, the graft clamped and full CPB will be resumed. At that time, ACP will be discontinued. Following five minutes at 26^{o}C, re-warming will resume and the proximal reconstruction will be completed.[16]

Axillary artery cannulation

Patients randomised to the control group will undergo axillary artery cannulation as routinely performed. The details of this operation have been previously described.[15]

Outcomes

Primary outcome

The primary safety endpoint of this trial is the proportion of patients with new radiologically significant ischaemic lesions. Two independent neuroradiologists who are blinded to treatment assignment will adjudicate this primary endpoint. New radiologically significant ischaemic lesions will be defined as severe white matter injury or an infarction involving the basal ganglia, thalamus or internal capsule or a large hemispheric infarction present on the post-operative DW-MRI. Each patient will have a preoperative DW-MRI to serve as the baseline study for comparison, to ensure the highest quality data. Severe white matter injury will be defined as 6 or more punctate lesions, or 2 or more lesions of 4 mm or larger size.[5] We have included the size of the ischaemic lesions as a defining criterion for severity as the volume of ischaemic lesions is a known independent predictor of stroke outcome.[23 24] Furthermore, it has been shown that the number of DW-MRI lesions is only likely to be clinically relevant if the individual lesion is large. [5 25 26]

The primary efficacy endpoint of this trial is the difference in total operative time between the innominate artery cannulation group and the axillary artery cannulation group.

Secondary Outcomes

Differences in the following secondary outcomes between both surgical strategies will be assessed:

1. 30-day all-cause post-operative mortality.

2. Post-operative stroke or TIA in hospital and at 30 days.
3. Neurocognitive dysfunction at post-operative day 4 and at 3 month follow up as assessed by the MMSE and MOCA tests. Both the MOCA and MMSE have been validated for cognitive screening in patients with cerebrovascular disease.[27-29]
4. DW-MRI parameters including number of total ischaemic lesions, total ischaemic volume of lesions, single lesion volume, watershed injury, intraparenchymal haemorrhage, cerebral haemorrhage, intraventricular haemorrhage, subdural haemorrhage, subarachnoid haemorrhage, partial cerebral sinovenous thrombosis.
5. Pre-operative and post-operative serum levels of circulating biomarkers of neuronal injury (S-100β and neuron specific enolase)
6. Post-operative sepsis, delirium, seizure, encephalopathy, atrial fibrillation, post-operative MI, re-operations.
7. Total length of ICU stay, and number of hours of required intubation and ventilation
8. Seroma, brachial plexus injury, reduced arm mobility and pain, arm ischaemia
9. Total CPB time, total cross-clamp time, total systemic circulatory arrest time, total ACP time, total cooling time (minutes), re-warming time, nadir nasopharyngeal temperature (degrees C), post-operative haemoglobin, peri-operative RBC transfusion, peri-operative inotrope or vasopressor use.
10. Cerebral oximetry will be monitored intraoperatively using bilateral non-invasive near-infrared spectroscopy. The following data will be evaluated: baseline O_2 saturation while awake, total number of desaturations i.e. < 20% of baseline, the total area under the curve of % saturation over time below 20% of baseline, minimal value reached and the maximum change from baseline values.

Data Collection

Preoperative

The screening visit will occur at the time of the initial appointment where the patient will be seen by the cardiac surgeon for evaluation and consideration of aortic surgery. Patients who are booked for elective ascending aortic surgery with a planned open distal anastamosis and moderate hypothermic circulatory arrest will be assessed for eligibility in the clinical trial. Study co-ordinators will review the study with potential participants and upon agreement to participate, obtain informed written consent.

The following baseline information will then be collected at either this initial visit, or at the time of the pre-operative anaesthesia clinic visit:

Clinical information

Demographics (age, sex), medical history including hypertension, diabetes mellitus, dyslipidemia, heart failure or LV dysfunction (latest ECHO or cardiac catheterisation), NYHA class, previous history of stroke, TIA, or systemic embolism, renal disease, peripheral vascular disease, coronary artery disease, previous coronary angioplasty with or without stent, COPD, smoking history, pulmonary hypertension (from latest ECHO or cardiac catheterisation), congenital aortic disease, previous cardiac surgery, history of atrial fibrillation, EuroSCORE II.

Physical examination information

Height (cm), weight (kg), body surface area.

Laboratory/tests

We will obtain baseline haemoglobin (g/L), creatinine (μmol/L), baseline biomarkers of neuronal injury (S-100β and neuron specific enolase), and a 12-lead ECG.

Imaging

DW-MRI will be completed prior to the surgical date.

Neurocognitive tests

MMSE and MOCA will be carried out pre-operatively.

Intraoperative

Intra-operative data collection will include total operative time (from skin incision, to closure of the skin), total CPB time, total cross-clamp time, total circulatory arrest time, total ACP time, total cooling time, re-warming duration, nadir nasopharyngeal temperature, mean arterial systolic and diastolic blood pressure, nadir haemoglobin concentration (g/L), intra-operative RBC transfusion (units) and intra-operative inotrope or vasopressor use.

Post-operative

Post-operative data will include total ICU stay, total ventilation time, post-operative hospital stay, in-hospital mortality, delirium, re-operations, post-operative MI, inotropic support, seizure, development of renal failure, atrial fibrillation, post-operative stroke, transfusion, sepsis, and pulmonary complications. Serum S-100β and NSE levels will be drawn post-operatively at 24-48 hours. At post-op day 4 (±3 days), the patient will undergo post-operative DW-MRI. On the day of discharge, the patient will undergo testing for stroke/TIA using the Modified Rankin Scale in addition to repeat neurological physical examination. Neurocognitive testing will also be carried out on the day of discharge, and at the surgical follow up visit conducted at 1 to 3 months post-operatively, using MOCA and MMSE tests.

Study Follow-up

Subjects will be followed daily during their post-operative course in hospital. A phone call at

post-operative day 30 will be conducted to assess for vital status, stroke and TIA, In addition, there will be a follow up visit in 1 to 3 months post-operatively to reassess neurocognitive status.

Study Sample Size and Power

In this trial, the primary endpoint is the number of patients with new radiologically signifcant ischaemic brain lesions on DW-MRI, comparing pre-operative and post-operative imaging. In accordance with previous literature, we anticipate that about 50% of patients will develop new, radiologically significant ischaemic lesions in the axillary cannulation group (control group).[5] Based on a consensus of investigators from surgery, anaesthesia, neuroradiology and critical care, we have determined that an absolute difference of 25% is an acceptable non-inferiority margin. Finally, we have set the power of this trial at 80% (for the 25% margin) and a one-sided Type I error of 5% (non-inferiority comparisons are one sided by definition). Under these assumptions and conditions, a sample size of 100 subjects (50 per group) is required. Finally, we factor in a 10% attrition rate to arrive at a final sample size of 110. This sample size also gives us greater than 80% power to detect a difference of 45 minutes in total operative time between the axillary artery and innominate artery cannulation strategies.

Data Analysis

The primary safety analysis is a non-inferiority comparison of the proportion of patients acquiring new severe brain lesions. The observed difference will be compared against the non-inferiority margin of 25% using a one-sided z-test. Since the intention-to-treat approach employed in superiority trials biases towards no difference, it is inappropriate in the non-inferiority trial where lack of difference is the goal. Therefore, the primary analysis will be a per-protocol analysis. The difference in proportions and 90% confidence intervals (corresponds more closely to the one sided test being used) will be reported. Given the non-inferiority design for the primary safety variable, non-inferiority comparisons of this outcome will use a one-sided alpha of 0.025.

Our primary efficacy endpoint, total operative time, will be tested for superiority. Thus the total operative time will be compared with a two-sided t-test (alpha 0.05), and the mean difference and 95% confidence interval will be reported.

Binary outcomes (30-day mortality, stroke/TIA, neurocognitive dysfunction, delirium, seizures, encephalopathy, adverse events, local complications) will be compared using a chi-square test or Fisher's Exact test if expected counts are less than 5. For each outcome the absolute risk difference and 95% CI will be reported. The quantitative DW-MRI parameters will be compared by t-tests and mean differences with 95% CIs will be reported. Whether or not patients experienced none, a single or multiple new lesions will be compared by a chi-square test. The mean levels of post-operative biomarkers (S-100β and NSE) will be compared. The adjusted mean difference and 95% CI will be reported for each biomarker. Intraoperative characteristics will be compared with t-tests and mean differences with 95% CIs will be reported. The p values to be reported will not be corrected for multiple comparisons. We will finalise the statistical analysis plan prior to locking of the database.

DISCUSSION

Axillary artery cannulation for achieving ACP with moderate levels of hypothermia is the currently preferred approach for establishing cerebral perfusion during aortic surgery. We describe the first prospective, randomised controlled trial evaluating the safety and efficacy profile of ACP via cannulation of the innominate artery in comparison to axillary artery cannulation.

We selected new radiologically significant ischaemic brain lesions as defined by DW-MRI as our primary safety end-point. DW-MRI has a sensitivity and specificity of 92% and 97% respectively in detecting new ischaemic lesions. Identification of restriction in diffusion of water molecules suggests cerebral ischaemia. Normal tissue appears gray on DW-MRI due to the

Brownian motion and diffusion of water molecules. Ischaemic tissue however, due to the prevention of normal loss of MRI signal by restricted diffusion, appears bright white. These differences are apparent within 5 days of injury.[25]

DW-MRI as a modality to assess neurologic injury has been validated in the transcatheter aortic valve implantation (TAVI) population, and more recently in aortic surgery studies and trials. These studies have demonstrated that the number of new ischaemic lesions, in addition to the size of these lesions together is the most prognostically significant measure.[23-25] Recent literature shows that the rate of new ischaemic brain lesions on DW-MRI after aortic surgery ranges from 40 to 60%.[5 30 31] A recent clinical trial in neonatal aortic arch surgery also employed DW-MRI as a surrogate of neuronal injury comparing ACP to DHCA. This non-inferiority trial used location, number of lesions and size of lesions to characterise severity of injury.[5] We used these data to inform our primary end point.

By comparing DW-MRI pre-operatively and post-operatively, we will be able to effectively quantify new, significant ischaemic brain lesions. Furthermore, given that DW-MRI is highly sensitive for ischaemic brain lesions, it also has an ability to detect “silent” brain injury. Silent brain injury has been shown to be a risk factor for delayed neurological decline. [25 32 33] Retrospective studies evaluating innominate or axillary artery cannulation have primarily assessed clinical end-points such as stroke or temporary neurological deficits. As such events are relatively rare, it is difficult to assess for true differences in outcomes between treatment modalities with the sample sizes available for aortic surgery. Thus, new, radiologically significant ischaemic brain lesions found on DW-MRI serves as a useful surrogate marker for risk of neurological injury. The high incidence of new ischaemic brain lesions post-aortic surgery allows us to efficiently assess our outcome with a relatively small sample size of 110 subjects.

In addition to imaging, this trial aims to assess neurological injury by comparing pre-operative and post-operative levels of circulating biomarkers of neuronal injury, specifically, NSE and S-100β. There is extensive literature that shows that proteins that are synthesised by

astroglial cells or neurons, and that cross the blood brain barrier can be correlated in peripheral blood with brain injury.[34-37] S-100β is a small dimeric cytosolic protein that exists in multiple forms, with the beta form noted to be highly specific for the central nervous system.[34] NSE is a dimer found in neurons, and belongs to a group of hydrolytic enzymes. It is also present in erythrocytes, platelets, plasmatic cells, and lymphocytes, which is why it is present in peripheral blood at very low physiologic concentrations.[34]

Given that these biomarkers are present at levels from nil to very low physiologic concentrations at baseline, and S-100β especially is very sensitive for detection of intracranial pathology, elevations in these markers post-operatively will suggest neuronal injury secondary to the procedure. Collecting pre-operative and post-operative samples will allow us to correlate serum levels with neuronal injury secondary to the aortic surgery specifically.

Furthermore, we will use two neurocognitive tests to detect neurocognitive decline post-operatively, and will assess for differences between both cannulation strategies. Studies evaluating neuronal injury post aortic surgery or TAVI have shown that neuronal injury does not always manifest overtly as stroke, but rather can present more subtly as neurocognitive decline. These features are often most prominent in those that have pre-existing neurologic disease or vascular dementia.[38] As a part of our neurocognitive testing, we have chosen to use both the MMSE and MOCA. These are commonly used cognitive screening tools in clinical practice. The MMSE is designed to assess language and memory while the MOCA is designed to detect mild to moderate cognitive impairment. It has been found to have high sensitivity and specificity for detecting mild cognitive impairment. Although more sophisticated neurocognitive testing does exist, due to time constraints of performing such testing, and the lack of generalisability with such tests, the MOCA and MMSE were chosen for ease of administration, and reproducibility of results. Furthermore, MOCA and MMSE have been employed in a number of cardiac surgery studies evaluating neurocognitive decline.[27-29 38]

It is important to recognise that there are important limitations of this trial. We have limited this randomised controlled trial to elective procedures on the ascending aorta and proximal arch. Patients planned for total arch replacement are excluded. Secondarily, we are not studying patients undergoing aortic dissection or urgent/emergent operations. Emergency operations such as for aortic dissection would introduce many confounding variables and significantly impact the ability to accurately assess the safety and efficacy of innominate artery cannulation in comparison to axillary artery cannulation. In addition, our follow-up period ends at 1 to 3 months post-operatively; therefore the long-term outcomes of the different antegrade cerebral perfusion strategies will not be assessed. However, the catastrophic consequences of inadequate cerebral perfusion are usually apparent soon after surgery. Furthermore, our trial assumes competency of the operating aortic surgeon for establishing both cerebral protection strategies. Poor outcomes that may be linked to techniques by surgeons less familiar with either the innominate or axillary artery cannulation technique will not be known since only surgeons who routinely practice aortic surgery are participating in this study.

ETHICS AND DISSEMINATION

The protocol and consent form was initially approved at the lead site (St. Michael's Hospital Research Ethics Board; protocol 15-071) and subsequently by all other participating local research ethics boards (Appendix 2). This study is being carried out in accordance with the current International Conference on Harmonization Guideline for Good Clinical Practice, Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans and applicable local laws and regulations. Protocol modifications will be communicated to each participating site and their respective Research Ethics Committees. In addition, protocol amendments will be uploaded to clinicaltrials.gov. As much data as possible will be contained in the published manuscript (and accompanying supplementary material) which is anticipated to occur in 2018 or 2019. There are

no plans to provide public access to the participant-level database. All principal investigators will have access to the final cleaned data set. Site Principal Investigators will have access to their own site's data. All data sets will be password protected and any data to be disseminated will be de-identified.

Patient Safety

All subject related information including case report forms, evaluation forms, reports, etc. will be kept strictly confidential. All records will be kept in a secure, locked location and only research staff will have access to the records. Subjects will be identified only by means of a coded number specific to each subject. All computerised databases will identify subjects by numeric codes only, and will be password protected.

An independent Data Safety and Monitoring Board (DSMB) composed of experts in cardiac surgery and peri-operative care will be assembled to ensure patient safety, receive safety reports, provide feedback to the trial steering committee, and ensure the study follows the highest ethical standards. The DSMB will be provided data on safety after enrollment of 1/3 and 2/3 of patients. The safety data will include all adverse events listed as primary and secondary outcomes. The DSMB will consider clinical and statistical significance, consistency of data over time, consistency of the direction of risk and benefit-risk ratios if there is consideration for recommendation for early trial discontinuation. In addition to receiving regular safety data reports, the DSMB will have the ability to request additional safety analyses or additional interim analyses and make any further recommendations to the steering committee about the safe conduct of the trial after considering all the available data and any new external data from relevant studies.

CONCLUSION

This randomised controlled trial is essential to definitively determine adequate brain protection strategies for patients undergoing aortic surgery on the ascending aorta and proximal arch with the use of moderate hypothermia and unilateral antegrade cerebral perfusion. Innominate artery cannulation is rapidly gaining interest as an alternative to axillary artery cannulation, however, there are no high quality prospective data to inform whether or not the two strategies are similar with respect to cerebral protection. Innominate artery cannulation has the potential to decrease surgical times, and reduce complications associated with an axillary approach such as brachial plexus injury, seroma formation, and limb ischaemia. Decreased surgical times could lead to significant cost savings. The ACE CardioLink-3 trial will be the first randomised controlled trial designed to prospectively assess and compare the safety and efficacy of the innominate artery cannulation technique with the current standard of practice, axillary artery cannulation, for establishing ACP for patients having proximal aortic surgery. These data should aid surgeons in informed surgical decision making when considering cannulation techniques for aortic surgery.

Contributors VG, MDP, CDM and SV conceived the study and designed the study protocol. VG, MDP, CDM and SV significantly contributed to the planning of analyses of the data. VG, MDP, AG, CDM and SV drafted the manuscript. VG, MDP, MWAC, MO, RGGM, JB, IH, FVC, AG, JH, KET, ND, HT, TRM, DAL, AQ, MM, PJ, CDM, SV critically revised the manuscript for important intellectual content; reviewed and approved the final manuscript and agree to be accountable for all aspects of the work.

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Competing Interests MDP has received research grant support and speaker/consulting honoraria from Edwards Lifesciences. MWAC has received speaker/consulting honoraria from Medtronic, Canada, Edwards Lifesciences, Livanova, Symetis. There are no other conflicts to declare.

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Figure Legends

Figure 1 Surgical technique used in innominate artery cannulation (with permission from Garg et al.).[16]

A: The innominate vein is isolated, retracted and the base of the innominate artery mobilised. Two purse string sutures are placed on the anterior wall of the proximal innominate artery before dilators and the cannula are inserted over a guidewire. **B:** Antegrade cerebral protection is initiated by clamping the base of the innominate artery and connecting the afferent limb of the cardiopulmonary bypass circuit to the 14 or 16 Fr cannula. **C:** After the distal anastamosis is completed, antegrade cerebral protection is discontinued, and the aortic line is connected to the 8 mm side limb. The graft is clamped distally and full cardiopulmonary bypass is resumed. Proximal reconstruction is performed.

Figure 2 Study schematic of the ACE CardioLink-3 randomised trial.

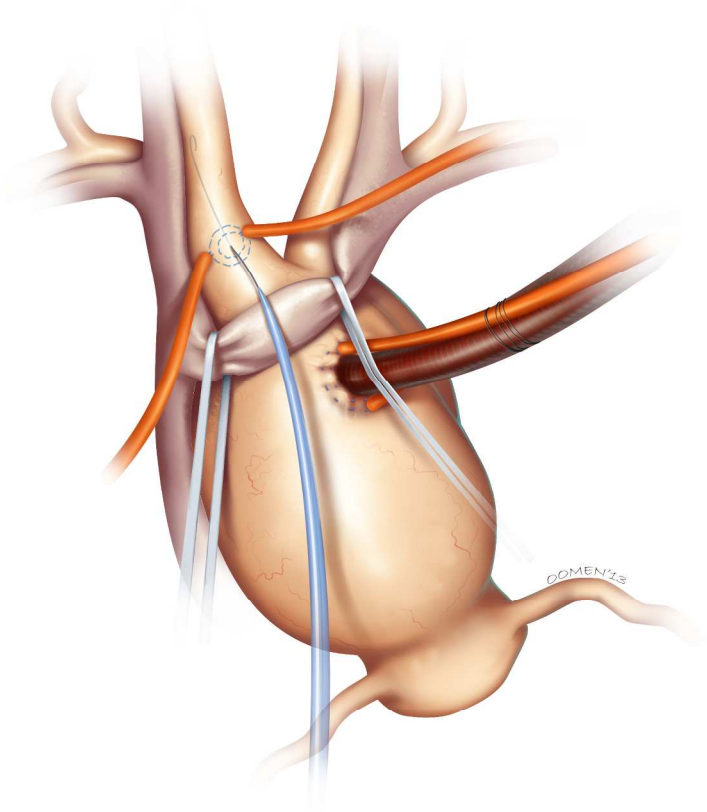

Figure 1 Surgical technique used in innominate artery cannulation (with permission from Garg et al.).16 A: The innominate vein is isolated, retracted and the base of the innominate artery mobilised. Two purse string sutures are placed on the anterior wall of the proximal innominate artery before dilators and the cannula are inserted over a guidewire.

216x270mm (300 x 300 DPI)

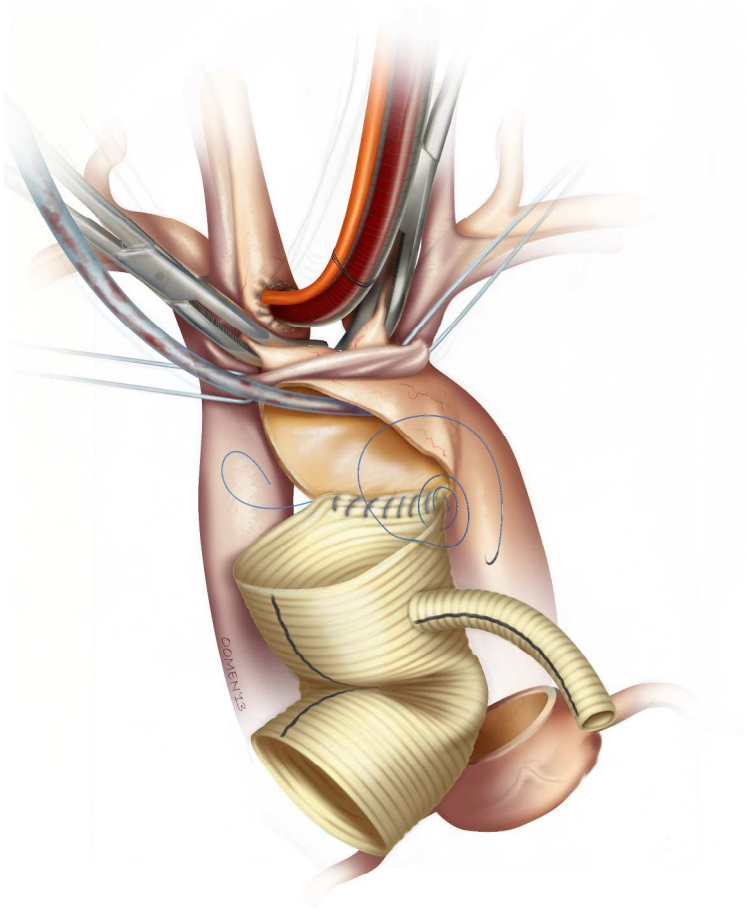

Figure 1 Surgical technique used in innominate artery cannulation (with permission from Garg et al.).16
B: Antegrade cerebral protection is initiated by clamping the base of the innominate artery and connecting the afferent limb of the cardiopulmonary bypass circuit to the 14 or 16 Fr cannula.

203x254mm (300 x 300 DPI)

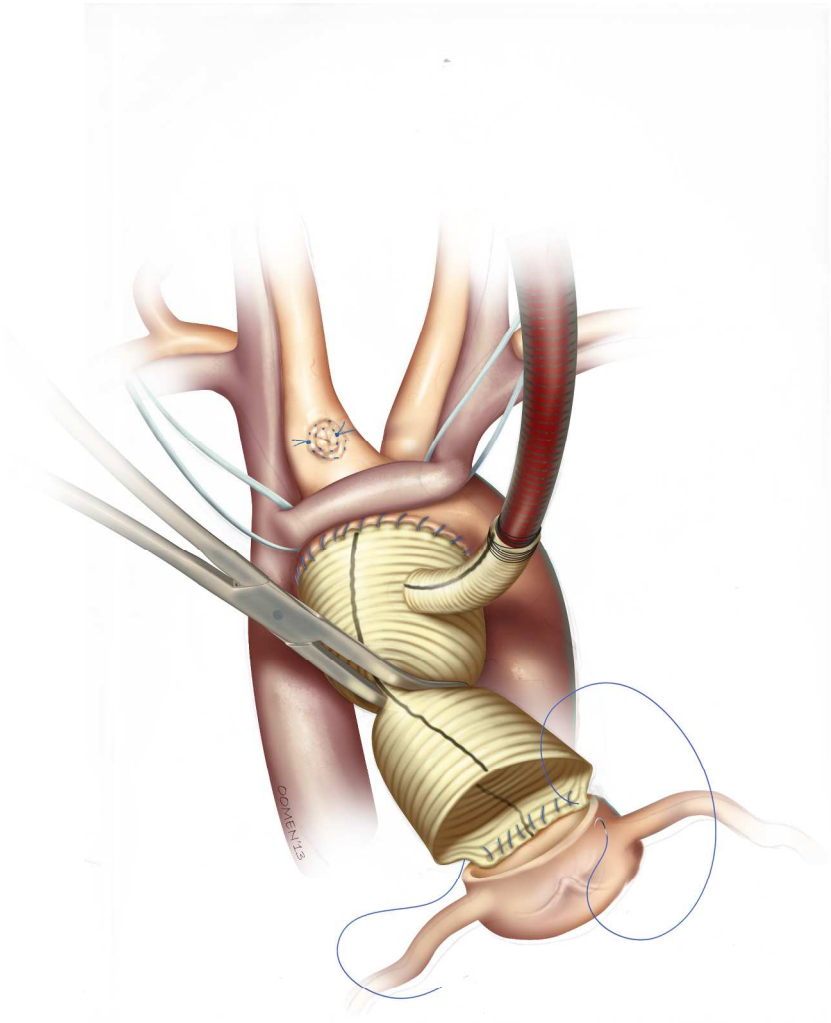

Figure 1 Surgical technique used in innominate artery cannulation (with permission from Garg et al.).16 C: After the distal anastamosis is completed, antegrade cerebral protection is discontinued, and the aortic line is connected to the 8 mm side limb. The graft is clamped distally and full cardiopulmonary bypass is resumed. Proximal reconstruction is performed.

203x254mm (300 x 300 DPI)

Figure 2

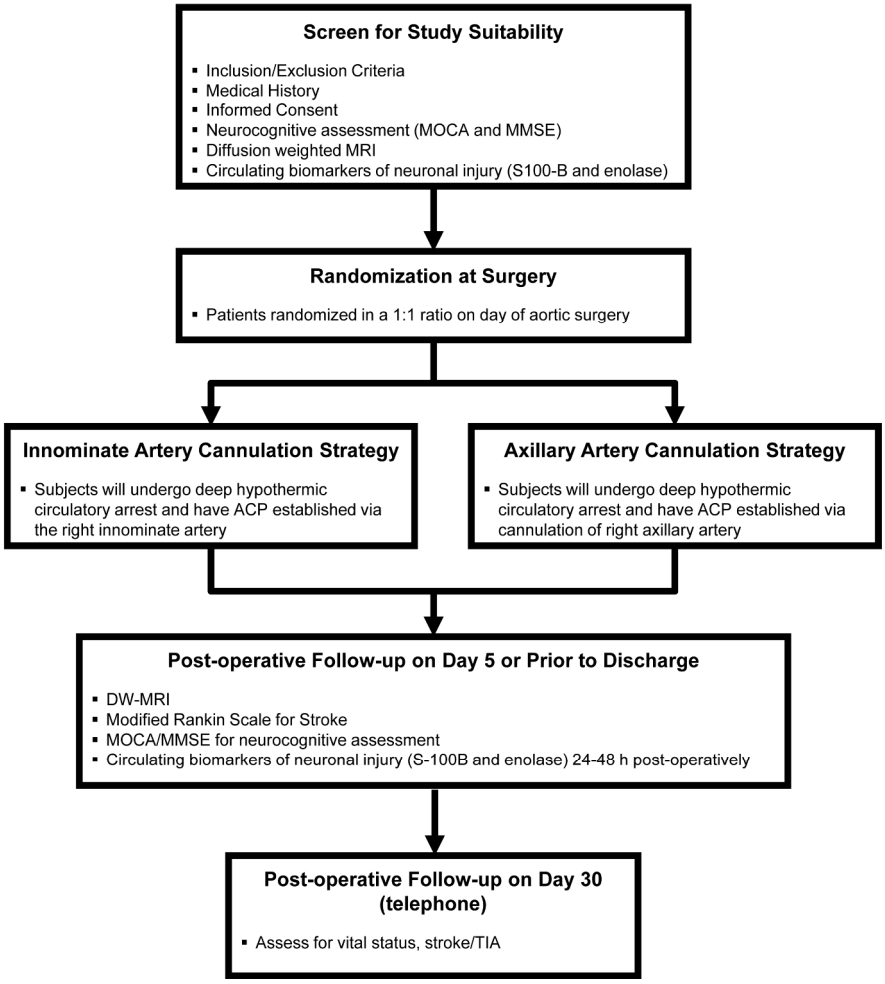

Figure 2 Study schematic of the ACE CardioLink-3 randomised trial.

199x254mm (300 x 300 DPI)

Appendix 1

List of study sites

1. St. Michael's Hospital, University of Toronto, Toronto, ON, Canada
2. Toronto General Hospital, University of Toronto, Toronto, ON, Canada
3. London Health Sciences Center, Western University, London, ON, Canada
4. Royal Jubilee Hospital, University of British Columbia, Victoria, BC, Canada
5. University of Alberta Hospital, University of Alberta, Edmonton, AB, Canada
6. Institut Universitaire de Cardiologie et de Pneumologie de Québec, Université Laval, Laval, QC, Canada

Appendix 2

Institutions whose ethics committees have reviewed and approved the conduct of the Aortic Surgery Cerebral Protection Evaluation (ACE) CardioLink-3 Randomised Trial:

1. St. Michael's Hospital, University of Toronto, Toronto, ON, Canada
2. University Health Network, University of Toronto, Toronto, ON, Canada
3. London Health Sciences Center, Western University, London, ON, Canada
4. Royal Jubilee Hospital, Vancouver Island Health Authority, Victoria, BC, Canada
5. University of Alberta Hospital, University of Alberta, Edmonton, AB, Canada
6. Institut Universitaire de Cardiologie et de Pneumologie de Québec, Université Laval, Laval, QC, Canada

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1,5
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2,6
	2b	All items from the World Health Organization Trial Registration Data Set	1, 6 to 9, 12,13,18
Protocol version	3	Date and version identifier	Protocol v.1.3; 26-Aug-2016
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	18
	5b	Name and contact information for the trial sponsor	18
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16,17

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4,5
	6b	Explanation for choice of comparators	4,5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6, Appendix 1
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7,8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Not applicable
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Not applicable
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Not applicable
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8,9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10 to 12, Figure 2

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not applicable
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10,11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Not applicable

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10 to 13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12,13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12,13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12,13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16,17
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Not applicable
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8 to 12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Not applicable
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	16

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not applicable
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
	31b	Authorship eligibility guidelines and any intended use of professional writers	18
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Not applicable
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.