Queensland Government
Metro North
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Project Protocol

Targeted Pre and Post-operative Blood Pressure Control Reduces Incidence of Type II Endoleak after EVAR: A Randomised, Controlled Trial

BOLD Study

Version 1.4

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RESEARCH SUMMARY

Title	Targeted Pre- and Post-operative Blood Pressure Control Reduces the Incidence of Type II Endoleak after EVAR
Acronym	**BOLD** Study **B**lood pressure c**O**ntro**L** for en**D**oleak
Investigators	Dr K Pattabathula MBBS Dr J Jenkins MBBS FRACS Dr M Ogg MBChB M McGrath CN
Design	Prospective, randomised controlled trial
Hypothesis	The pre-operative and post-operative targeting and maintenance of a patient's systolic blood pressure <120mmHg will reduce the likelihood of a type II endoleak at 6-weeks.
Participants	Patients undergoing elective endovascular aneurysm repair (EVAR) at the Royal Brisbane and Women's Hospital and The Prince Charles Hospital
Methodology & Procedures	Patients will be randomized to either INTERVENTIONAL or CONTROL groups. Both groups will have their blood-pressure checked twice-daily for 3-weeks pre- and 6-weeks post-operatively. In the INTERVENTIONAL arm, we will intend to treat the patient's systolic blood-pressure to <120mmHg during this period.
Primary Endpoint	1. Incidence of Type II Endoleak at 6-weeks post-EVAR
Secondary Endpoints	1. Sac size at 6-weeks, 6-months and 12-months post-EVAR 2. Vascular morbidity (return to OT) 3. Number of aortic re-interventions at 12-months post-EVAR 4. Adverse effects from anti-hypertensive medications 5. Cardiac morbidity (first occurrence of MI, CVA, arrhythmia) 6. Mortality (all-cause)
Req. Funding	AUD $40,000
Ethics	NHMRC Human Research Ethics Application submitted and *pending* RBWH Human Research Ethics Committee Site Specific Application submitted and *pending* ANZCTR Trial Registration Application submitted and *pending*

INTRODUCTION & RATIONALE

Context

Abdominal aortic aneurysm (AAA) is an important, potentially life-threatening pathology that represents a significant burden of care for Vascular surgical centres worldwide. AAA is present in 2-8% of the general population, and its incidence rises sharply in those over 60 years of age[1]. In an aging population then, the prevalence of AAA will foreseeably increase. Ruptured AAA without immediate surgical intervention is almost uniformly fatal. Elective repair of asymptomatic aneurysms of a threshold size, wherein the risks of the surgery are outweighed by the risk of rupture, is the standard of care for suitable patients.

There are two surgical techniques, endovascular aneurysm repair (EVAR) or open repair, which have proven safety in the appropriate patient[2]. The superiority of the less-invasive EVAR, in short-term morbidity and mortality, to open repair has been well-established[3,4]. Regardless, there are important limitations to its success. The Achilles heel of EVAR is an endoleak, which is defined as a persistence of blood flow into the aneurysm sac after stent deployment. Consequently, the aneurysm sac remains pressurised and may sporadically rupture, thereby warranting closer surveillance and potential re-intervention. Large registries have approximated the re-intervention rate for EVAR at 5% and a continued rupture rate of 1% per year[5,6].

Endoleaks are categorised by the origin of blood flow. Type II endoleak is the most common, occurring in 20-50% of patients, and refers to backbleeding into the sac from collateral arteries[7]. If noted at the time of surgery, this type of endoleak is usually managed conservatively as most spontaneously resolve. However, type II endoleak associated with an increasing sac size is an indication for surgery. It is the leading cause for EVAR re-intervention, with some earlier high-volume studies reporting up to 20% of patients requiring secondary intervention in a mean follow-up of 3-years[8]. Further, persistent type II endoleak after EVAR has been associated with adverse late outcomes including rupture or repeat intervention with a high rate of conversion to an open surgical approach[9,10].

Rationale

Naturally therefore, Vascular surgeons have been invested in non-operative management options for patients with persistent type II endoleaks. Two seminal publications have assessed the relationship of controlling blood pressure and the incidence of type II endoleak. Miura et al. demonstrated a significant reduction in the incidence of type II endoleak after an intensive 2-day post-operative targeted blood pressure control, using intravenous anti-hypertensive in

an intensive-care setting[11]. Lo Sapia et al. demonstrated that pre-surgical targeted blood pressure control, by Cardiologists, to a systolic blood pressure (SBP) <130mmHg, significantly reduces type II endoleak, sac expansion and re-intervention rates[12]. We believe this is proof of concept.

Current Practice

Presently, Vascular surgeons do not treat hypertension in the peri-procedural setting unless it is precipitating unless it is an acute clinical threat, such as in hypertensive crisis, and instead we aim for 'normotension' which has a broad upper limit. Vascular surgeons do not currently set pre- and post-operative blood-pressure targets, and do not regularly initiate or refer to physicians to initiate anti-hypertensive medications. To our knowledge, no study has evaluated the effect of treating systemic hypertension on the incidence of type II endoleak using a prospective, randomised and controlled trial.

OBJECTIVES

The aim of this study is to establish, in a randomised and controlled fashion, that a significant reduction in the incidence of type II endoleak can be achieved by pre- and post-operative blood pressure control.

METHODOLOGY

1. Study Type/Design/Location
   1.1. Design
   - The study is designed as a multi-centre prospective randomised, controlled clinical trial.

   1.2. Location
   - The study is intended to occur at the Royal Brisbane and Women's Hospital (RBWH) and the Prince Charles Hospital (TPCH). The RBWH and TPCH are a tertiary surgical referral centres in a major Australian city. The Vascular Surgery departments at the RBWH is a comparatively high-volume centre, staffed by 7 specialists, which routinely performs 20-40 elective EVARs per year.
   - Pending RBWH HREC approval and further funding, we intend to deploy the study at several other high-volume Vascular surgical centres including the Princess Alexandra Hospital, Gold Coast University Hospital, Sunshine Coast University Hospital and Townsville Hospital.
     - We will submit proposals to these hospitals after HREC assessment, as this is an understood barrier to wider interest.

2. Subjects/Patients

2.1. Inclusion Criteria

- Infrarenal abdominal aortic aneurysm >50mm, including asymptomatic and inflammatory aneurysms
- Booked and consented for elective Endovascular Aneurysm repair at the study locations.

2.2. Initial Exclusion criteria

- EVAR for ruptured or symptomatic aneurysms
- <50-years of age
- Known secondary cause of hypertension that causes concern regarding safety of the protocol; including end-stage renal disease (ESRF), any organ transplant in the 3-months before enrolment
- Orthostatic hypotension
    - Defined as: one-minute standing SBP <110mmHg at the enrolment appointment
- End-stage medical condition with a prognosis <12-months
- Recent cardiovascular event (e.g myocardial infarction) and/or recent emergency cardiovascular procedure (incl. percutaneous coronary intervention, CABG)
- Current diagnosis of congestive cardiac failure (CCF)
    - Defined as; New York Heart Association (NYHA) Class 3-4 symptoms OR echocardiogram-estimate of Left Ventricular Ejection Fraction <30% OR Cardiologist-determined diagnosis of CCF
- Arm circumference that prohibits consistent and accurate blood pressure measurement
- Participation in another interventional clinical study
- Documented cognitive impairment, including a diagnosis of dementia AND/OR active or recent excessive alcohol/substance use <3-months prior to enrolment

2.3. Secondary Exclusion criteria (to be applied after EVAR)

- Following EVAR procedure, the patient's operative notes/images will be reviewed, and further exclusions will be made. These exclusions are made because they are significant compounding influences on the incidence of Type II endoleak:
    - EVAR stent-grafted not used to the manufacturer's Instructions For Use (IFU)
    - Ongoing presence of a Type Ia/Ib, III or IV endoleak noted at the time of completion angiography; thereby not excluding treated leaks

3. Identification and Recruitment

3.1. Identification of Patients

- Patients are booked for EVAR procedure during an outpatient appointment, once the patient and the surgeon have agreed that EVAR is the most suitable treatment option. To avoid influence on patient or surgeon decision making, the patient's details are only given to the Investigators after the patient has been booked and consented for EVAR.
- The investigators will then review the patient's medical chart, against the Inclusion Criteria (2.1) and Initial Exclusion Criteria (2.2).

3.2. Recruitment

- The identified group of patients will be contacted by the Investigators, either in-person or via phone-call.
- The study is explained by one of the Investigators, with specific reference to the indications and aims of the study, the model including titration of anti-hypertensives, frequency of visits and monitoring.
- A copy of the Patient Information and Consent Form (PICF, Appendix 2) will be given to the patient, either in a hard-copy form, fax or e-mail as per their preference.
    - A second copy of the Consent Form will be given to patients for their personal records.
- Patients will be given a minimum of 1-week to peruse the information and sign the Consent Form. The time to decide about participation in the study will not delay surgery.

3.3. Sample Size

- A Queensland Institute of Medical Research (QIMR Berghofer) biostatistician was employed to calculate the appropriate power of the study. An estimated 30% reduction in the incidence of type II endoleak at 12-months was deemed to be clinically significant. Given this, the estimated sample size was 186 patients to capture a reduction in incidence from 40% to 28% with a significance level of a=0.05 and a desired power of 0.80, with equal group sizes. An incidence of 0.11 to 0.24, with a confidence level of 95% and desired power of 0.8.
    - Sample size calculations were performed in PASS 2019 (version 19.0.4). The two-sided Z-test (pooled variance) with a significance level of 0.05 was used to determine the sample size required to achieve 80% power to detect a 30% difference in the incidence of type II endoleaks after 6-weeks between the control group (presumed type II incidence of 40%) and the intervention group, assuming equal sample sizes in each

group. Although it is expected that the intervention group will result in a lower incidence of endoleak after 6-weeks, this cannot be known for certain and as such, a two-sided test was used. Percent reductions 5% lower or higher than 30% were also provided as a sensitivity analysis as well as the number of participants required if 20% of participants were to drop out of the study prior to the 6-week follow-up timepoint.

4. Measurements

4.1. Checklist

- A repeat checklist will be done with the patient during the initial consultation, to ensure that they meet the Inclusion (2.2)/Exclusion Criteria (2.2)

4.2. Initial Recording

- Age, Gender, BMI
- Medical history including hypertension, dyslipidaemia, diabetes, smoking status, arrhythmia
- Medication list including baseline antihypertensives, antiplatelet/anticoagulants (Aspirin, Clopidogrel, Warfarin or Novel oral anticoagulants)
- Pre-operative blood tests including Haemoglobin (Hb), Renal indices (Creatinine Cr, estimated glomerular filtration rate eGFR)
- Initial resting and seated blood-pressure are recorded.

4.3. *Pre*-EVAR evaluation (to allow for randomisation of factors thought to predict for endoleak incidence) of the radiological appearance of the aneurysm will be completed by the Investigators

- Patency of internal iliac arteries (IIA)
- Patency and size of inferior mesenteric artery (IMA)
- Patency and size of median sacral artery
- Number of lumbar vessels
    - Visualised on pre-operative CT scan
- Pre-operative IMA or IIA embolization/coiling
- Morphology of the aneurysm
    - Sac size
    - Diameter
    - Volume
    - Pre-Stent Neck Size
    - Presence of thrombus in aneurysm sac

4.4. *Post*-EVAR evaluation will occur by the Investigators

- Type of stent-graft used
- Presence of extension pieces

- Instructions For Use (followed/not followed)
- Balloon angioplasty of main body/limbs
- Use of endoanchors
- Presence and type of endoleaks at completion angiography
- Heparin and Protamine dose administered intra-operatively

5. Procedures/Interventions

5.1. Elective endovascular aneurysm repair, as deemed indicated by a Consultant Vascular Surgeon and per standard clinical practice.

5.2. Standard practice with bifurcated endovascular grafts used for patients who had anatomy compliant with the manufacturer's instructions for the use of the Zenith Flex (Cook Medical), Endurant (Medtronic), Excluder (W.L. Gore & Associates), and Powerlink (Endologix Inc.) endografts will be used.

6. Endpoints

6.1. Primary endpoints

1. Incidence of type 2 endoleak (continuous variable, in millimetres)

6.2. Secondary endpoints

1. Sac size at 6-week post-operative scan (continuous variable, in millimetres)
2. Number of aortic re-intervention at 6-weeks (continuous variable)
3. Number of ruptured aneurysm at 6-weeks (continuous variable)

6.3. Other endpoints

1. Adverse effects of anti-hypertensive treatment
2. Vascular morbidity including return to theatre
3. Cardiac morbidity
    a. First occurrence of a major cardiovascular event incl. myocardial infarction (MI), cerebrovascular accident (CVA), new-onset arrhythmia
4. All-cause mortality

7. Study Plan

7.1. See Appendix 1 for graphical format of Study Protocol

7.2. Randomization

- As they are enrolled, patients will be randomized to 2 pre-assigned groups using the "Research Randomizer" (Version 4.0) software. Randomization will involve 186 participants, divided into 2 blocks of 93 patients. Patients will be given a Study Identification Number (SIN) ranging from 001 to 186. These SINs will be matched to the patient's medical record URN on a secure, password-encrypted Queensland Health computer. The SIN allows the investigators to re-identify the patients.

- Groups will be randomised per the aforementioned demographic (Measurements 3.0), clinical (Measurements 3.1) and pre-EVAR evaluation (Measurements 3.2) prior to the intervention
- The participants will be randomised to 1 of 2 groups;
    - (1) Intervention group (Intention to treat to a goal SBP <120mmHg)
    - (2) Control group
- These will then follow the surveillance timeline and intervention timeline detailed below and in Appendix 1.
- Following the EVAR surgery, the secondary exclusion criteria (Subjects/Patients 2.3) will be applied
- These will then again, follow the surveillance timeline and intervention timeline detailed below and in Appendix 1.
- We intend to follow each study group at 6-months and 12-months, as would be standard surveillance post-EVAR for the same endpoints.

7.3. Treatment Algorithm

- An online form has been created via Google Forms. Patients will self-enter their SIN, and be allowed to then enter their AM and PM blood-pressures into the system daily, which autopopulates an Excel spreadsheet that is reviewed daily by the investigators.
- Patients will also keep paper records, to be reviewed weekly in formal appointments via telehealth, phone or in-person (as per patient preference).
- All decisions regarding anti-hypertensive medications will be in accordance with the established Australian therapeutic guidelines, to ensure consistency in approach. This will likely involve either the uptitration of the dose of an existing antihypertensive, or an addition of a second or third medication. Medications expected to be used include:
    - Angiotensin-modulating drugs incl. ACE inhibitor or ARB
    - Beta-blocker
    - Calcium channel blocker
    - Diuretics: Loop diuretics, thiazide diuretics, potassium sparing diuretics
    - Alpha-1 receptor blockers and sympatholytics may be used.
- The regimen of types of anti-hypertensives will be recorded and may be presented as a point of discussion
- The decisions regarding blood pressure management will be made by the investigators, and any amendment to an existing anti-hypertensive regimen will be assessed by a qualified senior pharmacist, to ensure minimal harm to patients.

- Prescriptions will be provided to patients via mail or in-person, and we have an intention to cover the costs of new medications during the proposed trial period.
- A physician endocrinologist will be consulted for advice regarding advanced or complex anti-hypertensive regime changes, as necessary.
- Intervention Group (Goal SBP <120mmHg)
    - If the patient's median blood pressure is >120mmHg after 1-week of treatment, participants will be initiated on an uptitrated anti-hypertensive regime. At each subsequent review, again, if the median blood pressure is >120mmHg, the anti-hypertensive regime will be again amended. This will continue until either the participant meets the target blood pressure.
    - This is an *intention* to treat approach, and will not necessarily mandate the aggressive treatment of hypertension that would be outside accepted and safe clinical practice.
    - Specifically, this will likely involve either the uptitration of the dose of an existing anti-hypertensive (either an ACE inhibitor or an ARB) and the addition of a second or third mechanism of action anti-hypertensive such as a beta-blocker, calcium channel blocker or diuretic. Other anti-hypertensive medications including thiazide-type diuretics, loop diuretics, potassium-sparing diuretics, alpha1-receptor blockers and sympatholytics may be used.
- As is standard practice, the patient may require a blood-test (full blood count and renal indices) after manipulation of their medications. The investigators will organise blood tests at the appropriate interval and act on the results.
- The study is focused on primarily pharmaceutical management of blood pressure. Enrolment in the study does not preclude the patient from the standard lifestyle recommendations and background therapy for hypertension; that is, general advice regarding weight loss, smoking cessation, dietary amendments and exercise, which is expected to be standard amongst both groups.
- Patients will be counselled regarding the symptoms of hypotension, particularly the indications for urgent presentation to medical attention. As is detailed in Risk and Safety (9.4), patients will have access to a phone hotline service to express any issues or concerns regarding new medications, symptomatic hypotension. Further, patients will be given phone numbers for Emergency services.
- All patients will undergo contrast-enhanced computed tomography (CT) scanning with non-contrast, early and delayed arterial phasing at 6-weeks to confirm presence or absence of type 2 endoleak. This is in keeping with standard practice.

8. Analysis

8.1. All data will be collected prospectively. Data will be stored using Microsoft Excel, Jamovi and IBM SPSS.

8.2. The data will be analysed according to an intention-to-treat basis. Comparisons between control and intensive groups of the primary outcome of the incidence of type II Endoleaks at 6-weeks will be performed using the Pearson X2 two-sided test. Secondary outcomes will be analysed with Chi-square/Fisher's exact tests for binary outcomes and t-tests/Mann-Whitney U tests for continuous outcomes. Baseline characteristics between the groups will be compared and all data summarised by means with standard deviations (or medians with interquartile ranges) for continuous variables as appropriate and frequencies with percentages for categorical variables. Statistical significance will be defined as a <0.05 (two-sided).

ETHICAL CONSIDERATIONS

9. Patient care

9.1. Benefits

- This study evaluates a fundamentally preventative and non-invasive method to reduce the incidence of type II endoleak. We believe this has clinical benefits, in that patients are less likely to require frequent surveillance, re-intervention and are less susceptible to aneurysm growth and rupture.
- Secondarily, involvement in this study allows more frequent assessment of patient's blood pressure, which therefore fosters a higher quality of general medical care attended to the patient given the proven cardiovascular benefits of blood-pressure control.
- From a financial standpoint, EVAR is a fundamentally expensive procedure with the majority of the cost attributed to the price of the individual components of a stent-graft. A key financial advantage to EVAR is the shorter intensive care admission, shorter in-hospital recovery and lower likelihood of short-term morbidity requiring re-admission. However, with the need for patient surveillance imaging and outpatient appointments and the cost of potential re-intervention, EVAR's long term costs may not compensate its initial cost. A fundamentally cheap alternative therefore, such as reducing a patient's blood pressure with anti-hypertensive medications, has clinic-economic benefit.

9.2. Consent and Patient Information

- All patients will have an in-person or phone consultation regarding the study during which an investigator will specifically explain the indications for this research, the details of involvement and the follow-up required.
- A participant information and consent form (PICF) is attached in Appendix 2.
- All patient will sign an information and consent form, detailing the above, and allowing for written consent for dissemination of de-identified patient information for publication.
- Patient information is not intended for use in future publications or project. It is intended that the groups outcomes may be monitored for long-term outcomes, which is standard practice in surgical centres. If this data is retrospectively reviewed for a different research project with an intent to be disseminated, patients will be re-consented or a separate low/negligible risk application will be submitted.

9.3. Data Storage and Confidentiality

- Any information obtained in connection with this research project will remain confidential. Data collected and information obtained will be kept secure on two platforms; (1) a password-encrypted Queensland Health computer drive, accessibly only by the principal or associate investigators on a Queensland health campus and (2) an encrypted USB memory stick.
- At present, patient information is stored to the same degree of security as intended in the study. Patient information will not be made more vulnerable for access by third-party or agencies because of this study.
- Data collected in this study will only be accessible to the investigators and will firmly not be accessible by a third-party or agency. If a patient requests their information, such as a list of their blood-pressure measurements, this will be freely given to them.
- Information obtained in this study will be kept for a minimum of 5-years and maximum of 15-years, on the aforementioned database, and will be discarded in the appropriate manner thereafter.

9.4. Risk and Safety

- It can be argued that targeting specific blood-pressure is the standard of care of patients with hypertension. This is usually managed in an outpatient capacity within the format of preventative care by a patient's primary care practitioner. Therefore, the investigators do not intend to more aggressively treat blood-pressure than would otherwise be standard practice. The difference between the

INTERVENTION group and the CONTROL group is that the investigators will *attempt* to treat a patient's blood-pressure to a target in the interventional arm.

- The inherent risks of titration of a patient's blood pressure include symptomatic hypotension and renal damage. These exist as standard risks even in the outpatient preventative management of systemic hypertension. We will continue with standard practice of blood tests after certain anti-hypertensives are introduced.
- The investigators will contact each patient's primary care practitioner with a phone-call and a paper document regarding the patient's enrolment in the trial. We will not interfere with a primary care practitioner's assessment and treatment of blood-pressure but will request that changes in blood-pressure are recorded and the information provided to the investigators.
- We will provide a day-time hours hotline for the patients. This will allow them to phone our principle or associate investigators for advice regarding the execution of the study, and particularly, if the patient's have concerns about taking the medication OR if the patient wishes to note that they are experiencing symptoms.
    - We will then make the appropriate clinical judgement, and advise the patient to present to medical attention if required.
    - Patients will also be given out-of-business-hours contact details, including GP line and Emergency services, to contact should they have any immediate concerns about their blood-pressure agents, side-effects or symptomatic or orthostatic hypotension. We expect this is unlikely.
- We acknowledge the harm to patients of twice-daily blood-pressure monitoring as a temporary physical squeeze via a mechanical compression to the arm. Again, we believe this is standard care in patients with hypertension in the community and may be considered within the realm of normal practice for those without hypertension who are pre-intervention for abdominal aortic aneurysms.
- We acknowledge the harm of a blood test, which is likely to be prescribed after any changes in anti-hypertensive regimes that may impact renal or hepatic function. This test is likely to occur at an external testing facility, such a private pathology practice e.g QML/Sullivan & Nicolaides/Queensland Pathology
- It will be made clear to the patient that their participation or lack of participation will not affect the care they receive. Patients will be approached once they have been booked for surgery, therefore not influencing patients' or surgeons' choice to proceed to a planned operative treatment.
- No additional stressors will be placed on the patient who will follow their normal pre and post-operative course otherwise.

RESOURCES & FUNDING

The study will be organised by an already-employed full-time Vascular Surgery Principal House Officer and Vascular Surgery Research Clinical Nurse Consultant. Further resources that will be required are access to a senior Pharmacist and a consultant Physician/Endocrinologist. The latter two parties have been approached and have agreed to participate.

We intend to apply for further Research Grants to facilitate funding of a full-time Research Nurse to facilitate recruitment and organisation of the study. If further grants are achieved, we intend to extend the study across multiple centres. Further, we may employ a clinician, such as a Cardiologist, to more closely supervise the blood-pressure titration.

10. Costs and Funding

- At present, the study organisation and execution funding will be provided by the Vascular Surgical Department.
- See attached Site-Specific Application (SSA) for detailed breakdown of expenses.
- The additional cost to patients regarding their attendance at appointments and prescriptions for the antihypertensive regime will be supported by established Pharmaceutical benefits schemes and if required, will be supported by funding provided by the Vascular Surgical department.

DISSEMINATION OF FINDINGS

The intended route for dissemination of findings is a publication in a high-impact Vascular Surgical journal or presentation at national or international Vascular Surgical meetings. If a clinically significant finding is proven, we would expect that the study fostered future research into the relationship between blood-pressure and endoleak.

If the Ethics committees prefer that a PILOT study be performed in the first instance, we would initiate this prior to undertaking the intended larger multi-centre RCT.

LIST OF ATTACHMENTS

Appendix 1: Study Protocol (Flowchart Format)

Appendix 2: Participant Information and Consent For (PICF)

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