STUDY PROTOCOL

PROTOCOL TITLE:

Randomised clinical trial comparing drug-coated balloon to plain balloon for all peripheral AVF stenosis

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1. BACKGROUND AND RATIONALE

Recent trials comparing drug-coated balloon (DCB) to plain balloon for the treatment of arteriovenous fistula (AVF) stenosis have demonstrated improved target lesion patency with the use of DCB (Table 1) [1–4].

The common limitation of these studies is the selection of a single lesion in the AVF as the study lesion, leaving the other lesions (non-target) to be treated with plain balloon angioplasty. The earlier recurrence of non-target lesions not treated with DCB leads to repeat intervention and reduction in overall benefit of DCB.

Therefore, while the use of DCB appears promising in treating a single AVF stenotic lesion, the access circuit patency (lost when repeat intervention is performed to any segment of the AVF) is not improved significantly in the DCB group. For instance, our locally conducted study reported improved target lesion patency through to 12 months (12-month target lesion patency: 51% vs 34%, p=0.04), but not for access circuit patency (12-month access circuit patency: 45% vs 32%, p=0.16). Similarly, Trerotola reported improved target lesion patency at 9 months, but access circuit patency showed no significant difference at all time points [2].

The access circuit patency is the better and more meaningful outcome measure since it assesses the entire AVF circuit patency. The generalisability of these studies is therefore limited as it is common to have several lesions in the AVF circuit in the real-world. The true benefit of DCB in AVF interventions will be better assessed by treating all lesions with DCB and comparing the access circuit patency as the primary outcome measure.

There is no trial to date that has studied DCB in this manner and the cost-effectiveness of this strategy, both of which remain important gaps in evidence across the Asian as well as the global patient population.

2. Study Objective

To determine if the use of DCB for all AVF stenosis provides a higher access circuit primary patency compared with plain balloon angioplasty alone.

We hypothesise that use of DCB angioplasty for all peripheral AVF stenosis leads to improved access circuit primary patency at 6 months.

3. Study Design

We propose a prospective, single centre (Singapore General Hospital, Interventional Radiology Centre (IRC) and Interventional Nephrology Suite (INS)), multidisciplinary (Interventional Radiology, Vascular Surgery and Interventional Nephrology), randomised clinical trial comparing DCB to plain balloon for all

stenotic lesions, except central vein lesions, in failing mature AVF. Randomisation will be 1:1 and stratified by number of lesions (single versus multiple AVF stenoses).

Study population and procedure location:
Renal failure patients with malfunctioning AVFs referred to Singapore General Hospital for angioplasty will be assessed for eligibility and consent obtained by a team member. Both outpatient day surgery or inpatient referrals will be accepted for trial consideration.

The trial procedure will be performed as a day surgery or inpatient procedure depending on the source of referral and relative urgency of procedure. Patients referred from an inpatient source may be performed as a day surgery case after discharge from the ward if the need for angioplasty is not time-sensitive (i.e. not impending thrombosis from very low AVF flow).
The trial procedures will be performed in both Interventional Radiology Centre or Interventional Nephrology centre in Singapore General Hospital.

4. Principal investigator

Zhuang Kun Da, Consultant Interventional Radiologist, Singapore General Hospital.

5. Study Outcomes

Primary Outcomes

- Access circuit primary patency at 6 months*

Secondary Outcomes

- Access circuit primary patency at 12 months
- Access circuit assisted primary patency at 6 and 12 months
- Access circuit secondary patency at 6 and 12 months
- Number of repeat interventions at 12 months
- Procedural complication rates
- Mortality rates at 12 months and up to 5 years
- Complications during follow up^

The patency endpoints will be assessed clinically without routine fistulography or ultrasound. Clinically driven outcomes are favoured over routine imaging (fistulography / ultrasound) for the following reasons: scheduled imaging may lower patency due to the detection of asymptomatic AVF stenosis, prompting earlier treatments (that would have otherwise manifested only later); patients may decline to return for imaging follow up, resulting in missing data; and reduced study cost.

* Patency definitions are based on SIR reporting standards (Gray et al., 2003):

Primary patency is defined: interval following intervention until the next repeated access intervention.

Assisted primary patency is defined: interval following intervention until access thrombosis or a surgical intervention that excludes the treated lesion from the access circuit. Percutaneous treatments of either restenosis / occlusion of the previously treated lesion or a new arterial or venous outflow stenosis / occlusion (excluding access thrombosis) are compatible with assisted primary patency.

Secondary patency is defined: interval following intervention until the access is surgically declotted, revised or abandoned because of inability to treat the original lesion or choice of surgeon.

^Complications will be categorised according to SIR definitions of minor or major complications (Aruny et al., 2003)

Major complication:

1. require therapy, minor hospitalisation (< 48 hours),
2. require major therapy, unplanned increase in level of care, prolonged hospitalisation (>48 hours),
3. leads to permanent adverse sequelae, or
4. death

Minor complications:

1. requires no therapy with no consequence,
2. requires nominal therapy with no consequence; includes overnight admission for observation only.

6. Analysis plan

The 6-month access circuit primary patency (proportion) will be compared with the Fisher's Exact test. Other patency data will be presented as Kaplan Meier survival curves and compared with logrank test. Categorical data will be presented as numbers and percentages, continuous data as means +/- standard deviation.

7. Sample size calculation for the primary analysis

Hypothesis:

We hypothesise that DCB angioplasty for all peripheral AVF stenosis leads to improved access circuit patency compared to plain balloon angioplasty alone (80% vs 50%).

Final sample size

For the current study, assuming the 6 month access circuit patency of 50% in the control arm and expected patency of 80% in the active arm, power of 80% and two-sided α of 0.05, 86 patients are required in the study. Allowing for 10% dropout, a total of 94 patients will be recruited.

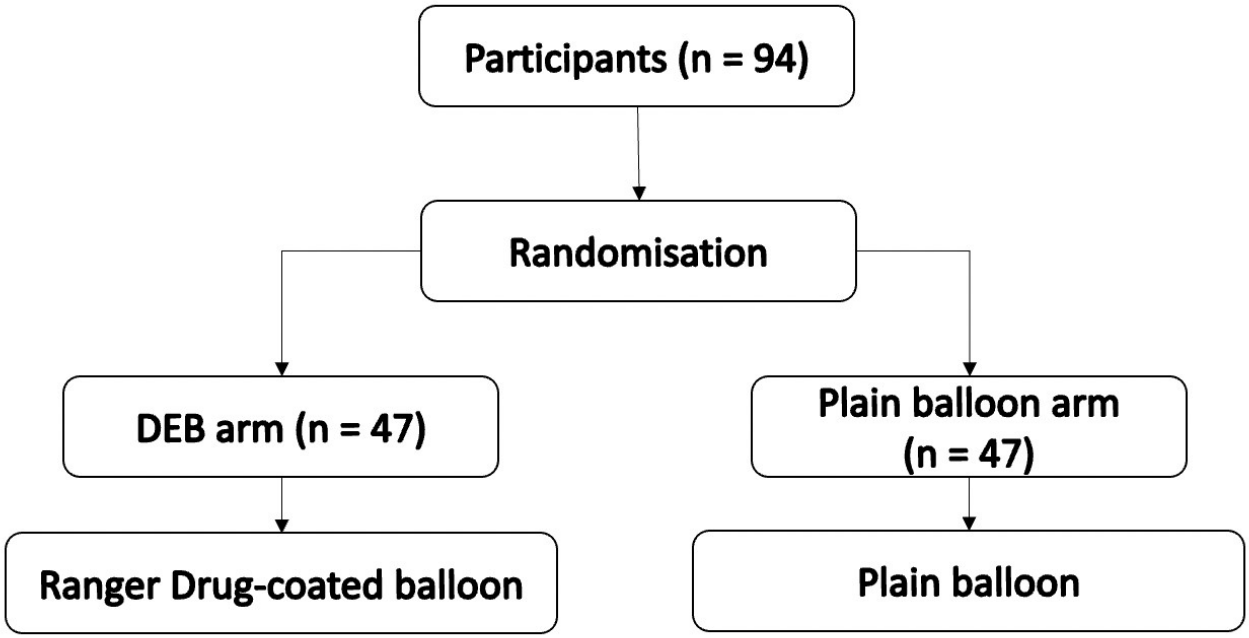
8. Methods

We will conduct an investigator initiated, partly industry sponsored (see budget), prospective, clinical trial at the Singapore General Hospital. The trial will be funded by a research grant from Boston Scientific.

Institutional Review Board approval will be obtained for the investigation protocol before start of the study. Informed consent will be obtained from all patients. In total, there will be 94 patients recruited. Patients with malfunctioning AVFs referred for percutaneous transluminal angioplasty (PTA) will be recruited and assessed for eligibility. Inclusion and exclusion criteria are detailed below (section 10).

Randomisation:
Randomisation will be performed via a web based system (RAND) in a 1:1 allocation ratio and stratified according to the number of AVF stenotic lesions (single versus multiple AVF stenotic lesions). AVF with multiple stenoses may have a worse outcome compared to AVF with single stenosis. Stratification will prevent an imbalance in the proportion of participants with multiple AVF stenosis in either study arm.

Blinding: The participants and study team members, except for the protocol administrator and procedurist, will be blind to study arm allocation. It is not possible to blind the protocol administrator and procedurist as they will have to perform randomisation and handle the angioplasty balloon respectively during the trial procedure. Fluoroscopy images of the trial balloons will not be labelled to maintain blinding after the trial procedure.



Study Procedure

Diagnostic fistulogram

All patients will undergo fistulogram of the AVF with a 22G cannula or sheath. The site, degree and length of the stenoses will be documented using digital measuring software available on the angiography machine.

Pre-dilatation

All eligible AVF stenoses will be treated with conventional balloon of an appropriate size (similar size to or 1 mm larger than reference vessel diameter) up to rated burst pressure, with each inflation lasting at least 1 minute. The choice of conventional balloon is at the procedurist's discretion. After angioplasty, fistulogram is performed to assess angiographic outcomes. In the presence of more than 30% residual stenosis after balloon angioplasty, repeat angioplasty with a larger plain balloon (in 1 mm increments) can be performed.

In the event of inability to efface the balloon waist with a conventional plain balloon, a high-pressure balloon or cutting balloon may be used at the operator's discretion.

The patient will be randomised into one of the two treatment arms after achieving less than 30% residual stenosis in the eligible AVF stenoses and exclusion of significant central vein stenosis.

(1) Control arm (plain balloon):

After allocation to the control arm, repeat angioplasty of the stenosis will be performed with the last used conventional (plain) balloon. Each inflation may be performed up to rated burst pressure and held for 3 minutes. Repeat fistulogram will be performed after angioplasty to assess for final angiographic outcome.

(2) Active arm (DCB):

After allocation to the active (DCB) arm, a Ranger DCB of an appropriate length (exceeding either side of the AVF stenosis by at least 1 cm to prevent geographic miss) and size (similar to or 1 mm larger than reference vessel diameter) is inflated up to rated burst pressure and held for 3 minutes to allow satisfactory elution of drug into the vessel wall. Repeat fistulogram will be performed after angioplasty to assess for final angiographic outcome.

Post-procedure monitoring and medication

Post procedure monitoring will be performed according to established clinical practice. Patients will be monitored for at least 4 hours after procedure if it is performed as a day surgery case. Inpatient cases will be monitored in the wards after the procedure.

All participants in both study arms, if not already on antiplatelet(s), will be started on 1 month of aspirin. Clopidogrel will be used in the event of aspirin allergy or intolerance. For participants already on antiplatelet agent prior to trial enrolment, no change will be made to the type or duration of existing antiplatelet treatment.

Follow up (imaging):

Clinically-driven angiography will be performed when there is dysfunction of the AVF such as poor flow or high recirculation.

Follow up:

All study subjects will receive a phone call consultation at 6 and 12 months after procedure. Electronic medical records review will be used to determine mortality status at 5 years.

9. Study Population

In this single centre trial, 94 participants will be enrolled. Renal failure patients with malfunctioning AVFs referred to Singapore General Hospital for angioplasty will be assessed for eligibility and consent obtained by a team member. Both outpatient day surgery or inpatient referrals will be accepted for trial consideration.

10. Inclusion and exclusion criteria

Inclusion criteria

1. Failing AVF with at least 1 AVF stenosis presenting with any clinical, physiological or haemodynamic abnormalities. Both de novo and recurrent stenosis are accepted.
2. AVF has been used successfully for at least 1 month (non-mature AVF are not allowed).
3. Less than 30% residual stenosis after angioplasty.
4. ≥ 21 years old
5. Informed and valid consent given.

Exclusion criteria

1. Thrombosed AVFs
2. Haemodynamically significant central vein stenosis
3. Target lesion not treatable with the available sizes of drug eluting balloon (up to 8mm)
4. Contraindication to antiplatelet therapy
5. Coagulopathy or thrombocytopenia that cannot be managed adequately with periprocedural transfusion.
6. Allergy / contraindication to paclitaxel.
7. Acute infection over proposed puncture site.
8. Women who are breastfeeding, pregnant * or planning on becoming pregnant during study.
9. Participant with medical conditions, which in the opinion of the investigator may cause noncompliance with protocol.
10. Currently participating in an investigational drug, biologic or device trial that may have an impact on the dialysis access or previous enrolment in this study.

*** Contraception and pregnancy testing:** All female participants of child-bearing age are to use birth control up to 12 month after trial enrolment. A urine pregnancy test should be taken to exclude pregnancy prior to trial enrolment.

11. Expected study period

Enrolment: Start Jan 2023 – Finishing Dec 2024.

Expected study duration: Start Jan 2023 – Finishing Dec 2029 (after 5 year follow up)

12. Information to be collected

1. Patient details:
    a. Age
    b. Gender
    c. Race
    d. Drug allergies
    e. Co-morbidities (diabetes mellitus, cerebrovascular disease, coronary artery disease, previous thromboembolic disease, hypertension, hyperlipidaemia, smoking, malignancy)
2. AVF details:
    a. Date of access creation
    b. Location of access (above or below elbow)
    c. Side of access (right, left)
    d. Type of access (radiocephalic, brachiocephalic, brachiobasilic, others)
    e. Number and dates of prior endovascular treatments
3. Procedure (both trial procedure and repeat procedure) details:
    a. Date of procedure
    b. Location of stenosis and presence of any new stenosis
    c. Pre-treatment AVF diameter and stenosis
    d. Length of stenosis (mm)
    e. Reference vessel diameter (mm)
    f. Date of prior angioplasty
    g. Balloon details (type, diameter, length, maximum inflation pressure, inflation duration)
    h. Post treatment residual stenosis, presence of rupture, stent deployment
4. Follow up / Endpoint
    a. Adverse event surveillance
    b. Anti-platelet medication
    c. Access circuit patency at 6 and 12 months
    d. Number of repeat interventions at 12 months
    e. Mortality at 12 months and up to 5 years

13. ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the Singapore Good Clinical Practice and the applicable regulatory requirements.

The Centralised Institutional Review Board (CIRB) must approve this final study protocol, including the final version of the Patient Information and Informed Consent Form, in writing, prior to enrolment of any patient into the study. The principle investigator is responsible for informing the CIRB of any amendments to the protocol or other study-related documents, as per local requirement.

Informed Consent
Participation is voluntary and eligible subjects should be competent to understand the implications of participation in the study. Before enrolment, all patients will have to give their written informed consent. The centre's local investigator ensures that the patient will be informed on the basis of the Informed Consent Form. If a patient is not capable of writing, informed consent can be given using a thumbprint or orally in the presence of at least one witness in accordance to the Medical Research Involving Human Subjects Act (article 6, subsection 2, altered WMO).

Confidentiality of Data and Patient Records
Information will be collected in hardcopy data collection forms which will form the source documents. The data will be entered into the electronic case report forms as soon as possible. Transcribed data in the electronic case report forms will be password-protected and access monitored. All investigators will ensure protections of subjects' personal data and subject names or identifiers will not be included on any reports or publications from the study. The list containing the links between enrolment numbers of each subject to their identity will be kept under lock and key in the PI's office, separate from the source documents. All hardcopy source documents will be archived for a duration of 7 years after the end of the study.

Investigator Responsibilities
The investigator is responsible for ensuring that the trial is conducted according to all signed agreements, the study protocol and good clinical practice (GCP) requirements.

Quality control and quality assurance
The investigators and their personnel filling the CRFs are responsible for filling the forms honestly and accurately. All forms must be filled prospectively. Quality control checking mechanisms are implemented in the online CRF system to prevent entry of inconsistent variables. The Principal Investigator will ensure accuracy of the data.

14. Safety

Patients enrolled in this trial will be exposed to the same risks shared by all patients undergoing in routine clinical practice. All devices used in this trial will be approved devices in the enrolling centres/countries.

Participants may encounter the "usual" risks associated with fistulogram and balloon angioplasty:

- Pain or discomfort during treatment
- Injury to the vessels (feeding artery, AVF and/or draining veins) leading to bleeding/hematoma generally can be controlled but may require surgery or stent(graft) and can lead to loss of AVF.
- Thrombosis of the AVF (which may require thrombolysis or surgery but can lead to loss of AVF)
- Infection
- Mild to moderate allergic reaction to contrast.
- Recurrence of the stenosis.

Uncommon or rare risk may be encountered:

- Severe allergic reaction to contrast
- Allergic reaction to heparin, including heparin induced thrombocytopenia
- Allergic reaction to other medicine and equipment used during procedure
- Allergic reaction to paclitaxel, aspirin and/or Plavix
- Significant bleeding secondary to dual anti platelet therapy.
- Loss of limb / amputation
- Pulmonary embolus
- Death

15 ADVERSE EVENT REPORTING

Standard definitions of adverse events will be used as follows:
Adverse event (AE):
Any untoward medical occurrence in a patient or clinical investigation subject which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a therapeutic product, whether or not related to the product.

Adverse device effect (ADE)
Adverse event related to the use of an investigational medical device, including any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device, and any event that is a result of a use error or intentional misuse.

Serious AE (SAE) is an adverse event that:
1. Led to death
2. Led to a serious deterioration in the health of the subject that:
a. resulted in a life-threatening illness or injury,
b. resulted in a permanent impairment of a body structure or body function
c. required in-patient hospitalization or prolongation of existing hospitalization
d. resulted in medical or surgical intervention to prevent permanent impairment to a body structure or body function
3. Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition

Unanticipated Adverse Device Effect (UADE)
Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the protocol or investigational plan, Investigator's Brochure, or any

other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Collecting, Recording and Reporting of Serious Adverse Events (SAEs) to CIRB
The reporting requirements will be in accordance to the reporting requirements published on CIRB website at the time when the event took place.

Only related SAEs (definitely/ probably/ possibly) will be reported to CIRB. Related means there is a reasonable possibility that the event may have been caused by participation in the clinical trial.

The investigator is responsible for informing CIRB after first knowledge that the case qualifies for reporting. Follow-up information will be actively sought and submitted as it becomes available.

Related AEs will not be reported to CIRB. However, the investigator is responsible to keep record of such AEs cases at the Study Site File.

Collecting, Recording and Reporting of Serious Adverse Events (SAEs) to the Health Sciences Authority (HSA)

The reporting requirements will be based on the reporting requirements published on HSA website at the time when the event took place.

Collecting, Recording and Reporting of Reportable Adverse Events relating to Medical Device to the Health Sciences Authority (HSA)
Adverse event (AE) in relation to human biomedical research means any untoward medical occurrence as a result of any human biomedical research which is NOT serious. Adverse event can be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease possibly/ probably/ definitely associated with the participant in the human biomedical research.

The reporting requirements will be will be based on the reporting requirements published on HSA website at the time when the event took place.

All adverse events relating to medical device which meets the three basic reporting criteria listed below, is considered as a reportable adverse event to HSA:

- An AE (or potential AE) has occurred.
- The medical device is associated with the AE.
- The AE leads to one of the following outcomes:
    - It becomes a serious threat to public health.
    - The death of a patient, user or other person.
    - Serious deterioration in state of health of patient, user or other person.
    - There is no death or serious injury in the initial AE but it might lead to death or serious injury of a patient, user or other person if the AE recurs.

16 Support requirement from BSC: (Study conduct budget / Device support

Device support

- 80 Ranger DEB balloons different lengths up to 8 cm, diameter 5- 8 mm on an 80cm shaft.
- 47 V18 0.018" 200cm wires

Other expenses

- 0.5 FTE research coordinator for 2 years
- Meetings / training /travelling for presentations.
- Printing / stationary

17 Costs not covered by trial

- Basic procedure costs
- High pressure balloons if necessary
- Larger or smaller balloons if necessary (also for non-target lesions)
- Stents/stent grafts if necessary
- Any other equipment needed during procedure

18. Literature/references

1. Irani, F. G. *et al.* Hemodialysis Arteriovenous Fistula and Graft Stenoses: Randomized Trial Comparing Drug-eluting Balloon Angioplasty with Conventional Angioplasty. *Radiology* **289**, 238–247 (2018).
2. Trerotola, S. O., Saad, T. F. & Roy-Chaudhury, P. The Lutonix AV Randomized Trial of Paclitaxel-Coated Balloons in Arteriovenous Fistula Stenosis: 2-Year Results and Subgroup Analysis. *Journal of Vascular and Interventional Radiology* **31**, 1-14.e5 (2020).
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4. Lookstein, R. A. *et al.* Drug-Coated Balloons for Dysfunctional Dialysis Arteriovenous Fistulas. *N Engl J Med* **383**, 733–742 (2020).