**TAVI Thrombosis**

**Prothrombotic changes associated with aortic valve management**

Clinical Investigation Protocol

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**INTRODUCTION**

Aortic stenosis (AS) is the most common heart valve disease in the Western World. Transcatheter aortic valve implantation (TAVI) has expanded the therapeutic options available to patients suffering from severe AS. However, despite the rapidly expanding clinical use of TAVI, patients remain at high risk for both thrombotic (e.g., stroke and valve thrombosis) and bleeding complications. Optimal perioperative antithrombotic therapy is essential to minimise thrombosis without incurring excessive bleeding risk. Current antithrombotic recommendations for TAVI are extrapolated from percutaneous coronary intervention (PCI) data despite significant patient and procedural differences that result in different thrombotic risk profiles. Until this is addressed, clinicians are left to advise and treat their patients without essential information. This study has been explicitly designed to provide robust data to characterise the thrombotic risk associated with TAVI and compare these with PCI and aortic valve replacement (AVR). Such comparison forms a crucial platform for further investigation of TAVI-specific antithrombotic management regimes.

**BACKGROUND**

The use of TAVI for the management of severe aortic stenosis has exponentially increased over the last 10 years. Despite significant evolution in both the technology and our clinical experience there remains a high rate of thrombotic and bleeding complications associated with the procedure. Stroke is the most frequent and devastating adverse events attributable to thrombosis, with our data indicating an overt stroke rate of 4.1% with TAVI, compared to 1.5% for isolated AVR and 0.2% for elective PCI and subclinical strokes occurring on average in 75% of patients. Though thrombosis is minimized by anti-thrombotic prophylaxis, this requirement is moderated by the equally devastating consequences of bleeding, with major bleeding reported as high as 15-32% for TAVI.

Current international recommendations guiding perioperative antithrombotic prophylaxis are empirically derived from the PCI setting. However, there are clear differences between PCI and TAVI that suggest such extrapolation may not be appropriate.

Viscoelastic point-of-care coagulation testing (POCCT) using ROTEM® and TEG6s is available in the SAWMH theatres. Specific reagents allow for neutralisation of anti-thrombotic medication in the blood so as to characterise both the underlying thrombotic state and the temporal changes that occur during the procedures and thus allow for identification of optimal antithrombotic regimes.

***Area of need:***

Identifying antithrombotic regimes that can optimise the balance between thrombotic and bleeding complications, while minimising both, requires a thorough understanding of the pathophysiology, timing, and mechanisms of the pro-thrombotic changes that occur. POCCT will provide key insights as researchers seek to improve this understanding.

**AIMS AND HYPOTHESIS**

**Aim:** To provide a clearer mechanistic understanding of the pathobiology of thromboembolic events during and after TAVI that will provide a translatable foundation for optimal therapies.

**Hypothesis:** TAVI results in a more pronounced hypercoagulable state than PCI, similar to that of a bioprosthetic AVR. Consequently, the current extrapolation of PCI-derived antithrombotic regimes to the TAVI setting may provide inadequate protection against thrombus and thromboembolism. Optimal balance of adverse events demands TAVI-specific antithrombotic prophylaxis.

**RESEARCH PLAN**

**Design:** This is a prospective, observational study across three cohorts at St. Andrew’s War Memorial Hospital and The Princess Alexandra Hospital, Brisbane, Australia. Consecutive eligible patients will be considered for each of the following cohorts:

1. *Transfemoral (TF)-TAVI cohort:* Patients undergoing TAVI with the Edwards SAPIEN-XTTM prosthesis via the transfemoral access route.
2. *PCI cohort:* Patients undergoing ‘elective’ PCI for non-ST-segment myocardial infarction.
3. *AVR cohort:* Patients undergoing ‘elective’ isolated bioprosthetic AVR.

**Patient selection:** Potential candidates will be identified by the treating clinicians. To determine subject eligibility, the study investigators will conduct a standardised interview applying the eligibility criteria in Table 2.

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| **Inclusion Criteria** | **Exclusion Criteria** |
| Age > 18 years | Emergency or non-elective surgery / intervention |
| Informed consent for participation | Lacks capacity to consent for him or herself |
| Severe aortic stenosis (aortic valve area < 0.8cm2, mean aortic valve gradient > 40mmHg or peak jet velocity > 4m/s); AND,Planned management with either TF-/TAo-TAVI or isolated AVR; OR,Coronary artery disease (excluding life-threatening coronary artery occlusion, recent STEMI, or NSTEMI on heparin infusions, IV vasoactive agents such as GTN, dobutamine or dopamine);  | Medications known to: a) interact with coagulation assays; or b) have a known or suspected prothrombotic or coagulopathic action that cannot be corrected for by POCCT. |
| Stable haemoglobin > 100g/L | Known or suspected bleeding or clotting disorders |
| Preserved ejection fraction (>50%) | Severe liver, renal, respiratory or psychiatric disease (including substance abuse) |
|  | Enrolled in another study with a non-standard treatment intervention |

 ***Table 1:*** *Eligibility Criteria*

**Data collection:** A multidisciplinary approach has been adopted to ensure relevant experts address each of the assessment domains.

*Clinical history:* standardised data collection forms (attached) will be completed by researchers using medical records for all participants to identify pre-existing risk factors for thrombosis, bleeding or vascular disease, and to assign surgical-risk scores (STS and EuroSCORE II).

*Procedural record:* a standardised procedural record will be completed at the time of the procedure. This will consider all aspects of the procedure with implications for coagulation including, but not limited to: pre-procedural antithrombotic medication and timing, procedural duration, heparin dosing and timing, protamine administration and timing, duration of dysrhythmia (including rapid ventricular pacing and arrest) and patient temperature.

*Echocardiography:* will be performed pre-procedure to grade aortic stenosis and valve function, measure calcification, and identify intracardiac thrombi and spontaneous echo contrast. This is part of routine clinical care.

*Physiological Monitoring:* continuous haemodynamic monitoring and peri-operative telemetry will be employed to measure the duration of rapid ventricular pacing, and detect the burden of thrombogenic dysrhythmias.

***Blood samples:***

*Collection:* Sample collection will follow standard procedure using the arterial line (or similar) according to manufacturer recommendations. A two-syringe draw technique will be use with 10 mL aspirated from the access line prior to collection of the study bloods. Tubes will be filled completely by vacuum. Tubes will be inverted 3 to 7 times depending on tube type and manufacturer recommendation.

*Standard Laboratory testing:* 3 - 6 mL of blood will be collected prior to, during and post-procedure (Table 3) for standard laboratory full blood count, coagulation testing (prothrombin time/international normalized ratio, activated partial thromboplastin time and direct fibrinogen), and anti-Xa assay levels (the ‘gold standard’ for heparin measurement). A sample of citrated blood will be centrifuged to obtain platelet poor plasma and stored at -80°C until processing at the end of the study. Samples will be analysed and prepared by Queensland Medical Laboratories (QML) Pathology at St. Andrew’s Hospital and Queensland Pathology at the Princess Alexandra Hospital. Platelet poor plasma samples will be transferred to the Critical Care Research Group Labs based at the Prince Charles Hospital for specialised coagulation and platelet function markers.

*Point-of-care coagulation testing:* A further 3 - 6 mL of blood will be collected at pre-specified procedure-dependent times (Table 3) for POCCT with the TEG®6s, ROTEM®*Sigma* and activated clotting time as previously discussed. Similarly, Multiplate® analysis will measure platelet aggregation as determined by impedance aggregometry, with Hirudin anticoagulated whole blood added to cells variably containing platelet agonists.

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| **Time Point** | **TF-TAVI** | **PCI** | **AVR** |
| 1 | Post-anaesthetic/ pre-cannulation | Post-cannulation, pre-wire insertion | Post-anaesthetic induction/ pre-incision |
| 2 | 10 min post-heparin/ pre-BAV/TAVI | 10 min post-heparin | 10 min post-heparin |
| 3 | Post-TAVI deployment | Post-stent deployment | 20 min post-aortic cannulation |
| 4 | 10-20 min post-protamine | 10-20 min Post-protamine | 10-20 min post-protamine |
| 5 | 6 hr post-procedure | 6 hr post-procedure | 6 hr post-procedure |

***Table 3:*** *Procedure-specific time points for POCCT*

**Statistical Analyses:** It is expected that completion of this proposal will require the enrolment of 50 patients: 10 - 15 patients per group (TF-TAVI, PCI and AVR). The primary outcome measures for the study is maximum clot firmness provided by the ROTEM and maximum amplitude measured by TEG. Other ROTEM, TEG and Multiplate analyser parameters, and clinical incidence of bleeding/clotting complications form the secondary outcome measures. Parametric continuous variables will be reported as means ± standard deviations or, where non-normally distributed as median ± interquartile range. Differences between measures of central tendency will be assessed by analysis of variance (ANOVA) or Kruskal-Wallis test for parametric and nonparametric data, respectively. All other variables will be analyzed as categorical and reported as proportions with differences assessed by Pearson χ2 analysis or Fisher’s exact test, where appropriate. Pearson correlation coefficients will be calculated comparing continuous variables. Univariate cross-sectional time-based random effects models will be developed for each viscoelastic measure using the laboratory clotting indices in turn as the dependent variable. Both: i) paired comparisons between timepoints; and, ii) univariate time-series regression will also analysed for each variable. All statistical planning and analysis has/will be performed by Associate Professor Chris Anstey from the Sunshine Coast University Hospital, Department of Intensive Care.

**Outcomes**

This study will provide data to rationally determine the most suitable perioperative antithrombotic regime and form the platform for a large randomised clinical trial.