**Impact of Epicardial plaQUe composition and geometry on coronary hemodynamics and flow (iEquate).**

**PROTOCOL SYNOPSIS**

|  |  |
| --- | --- |
| Title | Impact of Epicardial plaQUe composition and geometry on coronary hemodynamics and flow (iEquate). |
| Objectives | Primary: To determine if calcified coronary plaque has a greater impact on coronary hemodynamics compared to fibro-fatty plaque.  Secondary:   1. To determine if there is a difference between iFR and FFR assessments of haemodynamics depending on plaque consistency. 2. To determine if necrotic core burden impacts coronary hemoydnamics. 3. To determine if lipid content impacts coronary hemodynamics. |
| Study Design | Prospective observational trial. |
| Planned Sample Size | 75-100 patients |
| Selection Criteria | 1. Age ≥ 18 years  2. Undergoing clinically indicated coronary angiogram.  3. Moderate coronary lesion (50-75%) in an epicardial vessel ≥ 2mm.  4. Willingness to give written informed consent |
| Study Procedures | After informed consent, patient’s undergoing coronary angiography who have moderate (50-75%) stenosis angiographically would undergo invasive hemodynamic assessments via a 0.014 inch coronary wire as part of routine clinical practice to determine need for percutaneous coronary intervention. Further to this, over the pressure wire, an optical coherence tomography (OCT) catheter would be passed to obtain intra-vascular imaging and plaque composition assessment. Data will be collected on the minimal luminal area (MLA), degree of calcification, fibroatheroma, necrotic core, lipid content and the geometry of the lesion. 3D rendering and computational fluid dynamic assessment will be performed. These variables will be examined in terms of relationship to the pressure wire value. If the lesion meets hemodynamic significance (i.e. iFR value ≤ 0.89 or FFR value ≤ 0.8) PCI may be performed if clinically suitable. |
| Statistical Procedures | Sample Size Calculation: This project is designed as a pilot to determine if there are trends correlating plaque consistency and hemodynamic impacts. If there are clear trends established, a larger study aimed at establishing statistical significance will be designed.  Analysis Plan: After data is collected, it will be de-identified but re-traceable. Data will be analysed on SPSS version 12. |
| Duration of the study | 60-90 weeks |

# Study Management

* 1. **Principal Investigator**

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* 1. **Statistician (if applicable)**

N/A

# INTRODUCTION AND BACKGROUND

* 1. **Background Information**

Epicardial coronary lesions composed of plaque can result in inadequate supply of blood to the myocardial tissue, resulting in a variety of clinical scenarios, including angina and acute coronary syndromes. Invasive coronary angiography identifies coronary lesions, however further assessments are often required to determine the need for percutaneous coronary intervention (PCI), to relieve the obstruction1,2. Specifically, haemodynamic assessments may be required to determine whether the lesion is of hemodynamic significance, and therefore whether there would be a benefit to intervening through coronary stenting of the lesion. This can be performed using pressure wire assessments, including fractional flow reserve (FFR), instantaneous wave free ration (iFR)3. There are other methods of intra-coronary physiological assessment including coronary flow reserve (CFR) and index of microvascular resistance (IMR). Currently, there is evidence that coronary interventions which are guided by haemodynamic assessment of lesion severity improves clinical outcomes2,3.

Plaque is composed of varying ratios of fibrous tissue, fibro-fatty tissue, necrotic/inflammatory tissue and dense calcium. Plaque composition can be analysed through intra-vascular imaging modalities, which include intra-vascular ultrasound (IVUS)4 and optical coherence tomography (OCT)5. The varying degrees of each component can be quantified manually, and also through inbuilt algorithms in the imaging device. Intra-vascular imaging is commonly used to assist in PCI, aiding in vessel sizing, and to determine the need for other interventional adjuncts (such as calcium modifying techniques).

* 1. **Research Question**

Do the various components of plaque have differing effects on coronary hemodynamics?

* 1. **Rationale for Current Study**

There is currently a paucity of evidence on the effects of plaque composition and geometry on the hemodynamic impact of the lesion. Identification of such trends may further improve the accuracy of determining which coronary lesions will require intervention, and may also serve to isolate therapeutic targets for plaque modification.

# STUDY OBJECTIVES

* 1. **Primary Objective**

To determine if calcified coronary plaque has a greater impact on coronary hemodynamics compared to fibro-fatty plaque.

* 1. **Secondary Objectives**

1. To determine if there is a difference between iFR and FFR assessments of haemodynamics depending on plaque consistency.
2. To determine if necrotic core burden impacts coronary hemoydnamics.
3. To determine if lipid content impacts coronary hemodynamics.

# STUDY DESIGN

* 1. **Type of Study**

Prospective observational trial.

* 1. **Study Design**

## *Inclusion Criteria*

1. Age ≥ 18 years

2. Undergoing clinically indicated coronary angiogram.

3. Moderate coronary lesion (50-75%) in an epicardial vessel ≥ 2mm.

4. Willingness to give written informed consent

## *Exclusion Criteria*

1. Clinical instability at time of procedure.

2. Difficulty in passing device passed the coronary lesion.

3. Plaque determined to be unstable angiographically by the operator.

*Procedure*

After informed consent, patient’s will undergo coronary angiography for a evidence based clinical indication. Consent for the research project will be obtained before undergoing the coronary angiogram. Patients who are subsequently identified to have moderate (50-75%) stenosis angiographically undergo invasive hemodynamic assessment using a 0.014 inch coronary wire. This is performed as part of routine best clinical practice to determine need for percutaneous coronary intervention. This involves FFR (Fractional Flow Reserve) and iFR (instantaneous wave-free ratio) which can be performed using the same wire, without the need for re-instrumentation of the coronary artery. If the pressure wire software available does not provide an iFR value, de-identified hemodynamic data may be sent to a core lab to derive the iFR value. The standard procedural protocol would be applied, with pharmacological stress or exercise-induced stress (using an Ergometer) used to stimulate hyperaemia within the artery in order to obtain pressure wire assessments. All hemodynamic values will be recorded. If a patient has consented to the research project before undergoing the coronary angiogram, and are found to have moderate stenosis, an OCT catheter will be passed over the coronary wire to obtain intra-vascular imaging and plaque composition assessment. Data will be collected on the minimal luminal area (MLA), plaque geometry (irregularity/angulation/length), degree of calcification, fibroatheroma, necrotic core, and lipid content. These variables will be examined in terms of relationship to the pressure wire value. 3D rendering of the vessels will be performed using software which incorporates the de-identified angiograms, OCT and hemodynamic data. This will facilitate computational fluid dynamic assessment of the 3D rendered artery, to understand associations between plaque geometries and flow patterns associated with higher degrees of energy loss. If the lesion meets hemodynamic significance (i.e. iFR value ≤ 0.89 or FFR value ≤ 0.8) PCI may be performed if clinically suitable.

*Post-procedural care*

Routine post-procedural care would involve 4 hours of nursing observation, and medical review pre-discharge (unchanged from the normal post-procedural monitoring protocol). The medical review will ensure whether there has been a procedural complication, including review of access site, review of ECG, and clinical history to ensure no chest pain or other concerning symptoms.

*Follow up*

The potential complications relating to this procedural are expected to be identified within the first 4 hours of the procedure, however, long term unexpected adverse outcomes will be determined through telephone follow up within the first 30 days post-procedure, which will be performed by the interventional cardiology fellow. Medical record follow up will be performed at one year to determine if there are any unforeseen cardiac events.

*Data collection and analysis*

100 cases will provide adequate data to correlate plaque composition and haemodynamic significance. After data is collected, it will be de-identified and untraceable. Data will be analysed on SPSS version 12.

* 1. **Number of Participants**

75-100 subjects

* 1. **Study sites**

This will be a two centre study, with all subjects being treated through the Royal North Shore Hospital Department of Cardiology and the North Shore Private Hospital Department of Cardiology.

* 1. **Expected Duration of Study**

Week 1-12: ethics submission and approval.

Week 13-52: Enrolment of patients and data collection

Week 53-72: Data analysis

Week 73-81: Composition and submission of manuscript for publication

* 1. **Primary and Secondary Outcome Measures**

Primary outcome measures: percentage of plaque calcium burden, percentage of plaque fibro-fatty burden, iFR measurement and FFR measurement.

Secondary outcome measures: percentage of necrotic core burden, lipid content, in addition to all primary outcome measures described.

1. **PARTICIPANT ENROLLMENT AND RANDOMISATION**
   1. **Recruitment**

All patients presenting for coronary angiography for all indications, including inpatient and outpatient procedures, will be considered for prospective recruitment. Patients may be identified and consented by any member of the research team, including Dr Avedis Ekmejian, Dr Usaid Allahwala, and Prof Ravinay Bhindi. At the time of consenting for the procedure, patients will be consented for the possibility of recruitment for the study depending on the outcome of the diagnostic angiogram. As discussed in the inclusion criteria, patients with moderate epicardial coronary lesions of vessels ≥ 2mm will be eligible for this study.

* 1. **Eligibility Criteria**
     1. **Inclusion Criteria**

1. Age ≥ 18 years

2. Undergoing clinically indicated coronary angiogram.

3. Moderate coronary lesion (50-75%) in an epicardial vessel ≥ 2mm.

4. Willingness to give written informed consent

* + 1. **Exclusion Criteria**

1. Clinical instability at time of procedure.

2. Difficulty in passing device passed the coronary lesion.

3. Plaque determined to be unstable angiographically by the operator.

# Informed Consent Process

An information sheet and consent form will be provided before the coronary angiogram. This will detail the procedural aspects, risks involved, collection of data, and how the data will be used, as well as the safe/confidential storage of data. Consent will be obtained by a medical practitioner within the cardiology service who is involved in the procedure, ensuring that all aspects in the consent form are understood, and an opportunity for further questions has been provided.

* 1. **Waiver of Consent**

This research protocol will not utilise a waiver of consent.

* 1. **Participant Withdrawal**
     1. **Reasons for withdrawal**

Patients will be able to withdraw consent at any time up to and including the time of the procedure. No data collected will be used on patients who have withdrawn consent, and only the clinically indicated component of the procedure will take place.

# STUDY VISITS AND PROCEDURES SCHEDULE

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Interventions | Elective Admission for coronary angiogram and/or percutaneous coronary intervention | Intra-coronary imaging and pressure/flow assessment | 4 hours post intra-coronary imaging and pressure/flow assessment | Discharge from hospital | 30 day follow up | One year follow-up |
| Informed Consent | ✓ | ✓ |  |  |  |  |
| Inclusion / Exclusion criteria | ✓ | ✓ |  |  |  |  |
| Demographics | ✓ |  |  |  |  |  |
| Medical History | ✓ |  |  |  | ✓ |  |
| Medications List | ✓ |  |  | ✓ |  |  |
| Height, Weight, Vital Signs | ✓ |  |  |  |  |  |
| Electrocardiogram |  | ✓ | ✓ |  |  |  |
| Insertion of 0.014 inch coronary wire for pressure/flow assessment as per standard protocol |  | ✓ |  |  |  |  |
| Insertion of intra-coronary imaging catheter for plaque consistency assessment |  | ✓ |  |  |  |  |
| Adverse Event & Serious Adverse Event Assessment |  | ✓ | ✓ | ✓ | ✓ | ✓ |

# ADVERSE EVENT REPORTING

*Definitions:*

Devices Events

An adverse event for devices is any undesirable clinical occurrence in a participant whether it is considered to be device related or not, that includes a clinical sign, symptom or condition and/or an observation of an unintended technical performance or performance outcome of the device.

For devices is any adverse medical occurrence that:

* led to a death;
* led to a serious deterioration in health of a patient user or other. This would
* include:
* a life threatening illness or injury;
* a permanent impairment of body function or permanent damage to a body
* structure;
* a condition requiring hospitalisation or increased length of existing
* hospitalisation;
* a condition requiring unnecessary medical or surgical intervention; or
* foetal distress, foetal death or a congenital abnormality/birth defect;
* might have led to death or a serious deterioration in health had suitable action or intervention not taken place.
* This includes: a malfunction of a device such that it has to be modified or temporarily/permanently taken out of service; or a factor (a deterioration in characteristics or performance) found on examination of the device.

Serious adverse event (SAE)

An unforeseen medical event that occurs in the course of clinical research that:

* results in participant death
* is life-threatening to the participant
* requires the inpatient hospitalisation or prolongation of existing hospitalisation for the participant leads to the participant having a persistent or significant disability/incapacity.

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in

Which the patient was at risk of death at the time of the event; it does not refer to an

event/reaction which hypothetically might have caused death if it were more severe.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

All adverse events that are suspected to be related to an investigational medicinal product and that are both unexpected and serious are considered to be SUSARs.

A serious adverse event for which there is some degree of probability that the event is an adverse reaction to the administered drug and the adverse reaction is unexpected.

Serious event NOT outlined in the study protocol or information sheet.

## *Assessment and Documentation of Adverse Events*

An adverse event form will be completed for all adverse events related to study procedures. Any member of the research team including Dr Avedis Ekmejian, Dr Usaid Allahwala and Prof Ravinay Bhindi, may determine if an adverse event has occurred and document as such.

## *Eliciting Adverse Event Information*

All procedural complications will be identified at the time of the procedure and before discharge of the patient. There are no expected long term adverse effects, however patients will be followed up via telephonic conversation by 30 days to determine if there have been any un-expected delayed complications.

## *Serious Adverse Event Reporting*

SAEs and SUSARs related to study procedures that are not part of the standard of care for coronary angiography patients will reported to the investigators and HREC within 7 days.

1. **STATISTICAL METHODS**
   1. **Sample Size Estimation**

The sample size generated is based on the volume of coronary angiography performed through Royal North Shore Hospital and North Shore Private Hospital. Currently, there are 1700-1800 diagnostic angiograms performed annually between these two institutions, of which 300 would proceed to a hemodynamic assessment of a coronary lesion. This study would serve as a pilot to observe trends relating plaque consistency and hemodynamic impact. If there are observable trends, detailed statistical analysis will be performed to determine sample size requirement. Outliers will be re-investigated before inclusion in the data analysis, with hemodynamic assessments and intra-coronary imaging re-evaluated.

* 1. **Statistical Analysis Plan**

Statistical analyses will be performed using SPSS software (version 22.0, SPSS Inc. Chicago).Baseline characteristics of study patients (demographics, past cardiac history, past medical history, home medications and premorbid ejection fraction) and admission characteristics (troponin, natriuretic peptide and ECG findings) will be summarized in terms of frequencies and percentages for categorical variables and mean standard deviation (SD) for continuous variables. These will also be reported according to need for ICU and death and compared using the t-test or Mann–Whitney U test for continuous and chi-square test for categorical variables. Bivariate analysis will be conducted to assess the association of different components of plaque composition with the hemodynamic impact of the plaque. Pearson correlation coefficient tests will be used for a linear correlation between continuous parameters and Spearman correlation coefficient test will be used for ordinal parameters. The odds ratios and associated 95 per cent confidence intervals for variables in the final model were reported. Significant level for this model was set at a p <0.05. Correlations among the predictors included will be checked to avoid collinearity.

* 1. **Interim Analyses (if applicable)**

# DATA MANAGEMENT

* 1. **Data Collection**

A dedicated member of the research team will be responsible for data collection and fill in the case report form on REDCap. Data for the case report form will be collected from multiple sources including procedural data, interviewing the patient, and review of electronic medical records.

* 1. **Data Storage**

Data will be stored on the Northern Sydney Local Health District REDCap server. Study investigators will have individual usernames and passwords in order to access the study database. Only select investigators can participate in data entry. Data storage and access will be password protected, and may be accessed by any member of the research team (Dr Avedis Ekmejian, Dr Usaid Allahwala and Prof Ravinay Bhindi). De-identified hemodynamic data used to derive iFR may be shared with a Core Lab using a secure portal. 3D rendered arteries will be stored on a dedicated laptop used only for the purposes of this research project.

* 1. **Data confidentiality**

Data will be confidential, with names coded (therefore untraceable) however patients can be re-identified. The coding will be safeguarded by a dedicated member of the research team.

* 1. **Study Record Retention**

Data will be retained for a minimum of 5 years post study completion or last publication.

# ADMINISTRATIVE ASPECTS

* 1. **Independent HREC approval**

This study has been approved by the Northern Sydney Local Health District HREC, reference number [TBC once approval received]

* 1. **Amendments to the protocol**

Any amendments will be submitted to the HREC for review prior to implementation as per HREC guidelines.

* 1. **Participant reimbursement**

Participants will not be reimbursed.

* 1. **Financial disclosure and conflicts of interest**

No financial disclosures or conflicts of interest.

# USE OF DATA AND PUBLICATIONS POLICY

The primary author will have sole authority over dissemination of results and publication. The primary author will take the lead in publication. All of the investigators will be acknowledged in publications. The database created during this study will only be used for this study, as outlined in this protocol. If the study investigators wish to use the data for another research purpose, or to share the data with other investigators, then explicit written approval (via a new HREC application) will be sought before doing so.

# REFERENCES

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