**PRINCIPAL INVESTIGATOR/PROJECT SUPERVISOR:**

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| **Title and Name** | Screening for cardiac amyloidosis in patients with newly identified conduction disease.  Dr Jithin Sajeev (Principal Investigator)  Dr Timothy Scully (Associate Investigator)  A/Prof Stephen Ting (Associate Investigator)  A/Prof Andrew Teh (Associate Investigator) Dr Jason Nogic (Associate Investigator)  Dr Brendan Wisniowski (Associate Investigator)  A/Prof James Hare (Associate Investigator) |

**PROJECT TITLE:**

***Screening for cardiac amyloidosis in patients with conduction disease***

1. **Background, aims, plans of investigation:**

Cardiac amyloidosis is a condition where misfolded, aggregated protein, known as amyloid, deposits into the cardiac myocardium and other cardiac structures, leading to fibrosis and a restrictive cardiomyopathy. There are two proteins that are known to cause cardiac amyloidosis. The first is light chains that are produced by plasma cells and is seen in patients with underlying haematological disorders. This form of cardiac amyloidosis is known as AL-amyloidosis. The second form of cardiac amyloidosis is caused by a protein produced by the liver known as transthyretin. This form of cardiac amyloidosis is known as transthyretin cardiac amyloidosis (ATTR-CM). Some patients are born with genetic mutations that lead to the misfolding of the transthyretin protein, this form of ATTR is known as variant transthyretin amyloidosis (ATTRv). In older patients, transthyretin can form amyloid fibrils without an underlying genetic pre-disposition. This form of ATTR is known as senile or wild-type transthyretin amyloidosis (ATTRwt). It is this form of cardiac amyloidosis that is becoming increasingly well recognised with recent breakthroughs in medical therapies now available for ATTR-CM wild type (2-4).

The incidence of ATTR-CM in Australia via histopathology is 12 in 1 000 000 persons per year while the incidence ATTR-CM reported in a Japanese cohort was reported at 1 per 10 000 persons per year. Post-mortem studies have found closer to 1 in 5 patients have some form of ATTR-CM after the age of 80(6). These figures suggest that there is a large proportion of ATTR-CM that is unrecognised. Currently, cardiac amyloidosis should be considered in patients with heart failure with preserved ejection fraction (HFpEF), particularly if they have additional features consistent with cardiac amyloid (7, 8).

These additional features include:

1. Increased left ventricular (LV) wall thickness (9).
2. Increased right ventricular thickness (9).
3. Refractory atrial fibrillation (9).
4. Complete heart block or syncope (9).
5. A history of bilateral carpal tunnel syndrome or spinal laminectomy (9).

However, the initial investigation that prompts the investigation of cardiac amyloidosis is a transthoracic echocardiogram with increased LV wall thickness. There are a number of issues with this as the sole approach to the identification of cardiac amyloidosis:

1. Not all patients with underlying cardiac amyloidosis have clinical signs of HFpEF that would warrant investigation with echocardiography (9, 10).
2. As many as 1/3 of patients with cardiac amyloid have normal LV wall thickness (8).
3. The development of overt heart failure with increased LV thickness is a relatively late sign of cardiac amyloid. Given the availability now of proven disease modifying therapies, earlier identification of patients with potential cardiac amyloidosis may lead to disease detection earlier in the disease progress and better clinical outcomes (9-11).

*Figure SEQ Figure \\* ARABIC 1Early Treatment of Cardiac ATTR*

This final point of early detection of cardiac amyloidosis is key. Patients with ATTR-CM can be staged based on the Gilmore staging system, which is a 3-stage system with stage 1 disease conferring the best prognosis while stage 3 disease confers the worst prognosis. Patients with stage 1A disease may have similar survival to age-matched individuals, particularly if they have access to disease modifying medications. In contrast, diagnosis of ATTR-CM with Gilmore stage II confers a median survival of 46.7 months and stage III patients have a life expectancy of 24.1 months (12).

# The gold standard for the detection of ATTR-CM is a 99-m technetium pyrophosphate (PYP) cardiac imaging scan, also known as bone scintigraphy, where the radiotracer is taken in by areas of myocardium that have amyloid fibrils present (13). It has been demonstrated that the bone scintigraphy may be positive for ATTR-CM before there any changes on echocardiogram or clinical signs of heart failure(14). The fact that the PYP scan may be positive before the echocardiogram provides an opportunity to screen for ATTR-CM prior to the development of cardiac symptoms. The issue is with selecting which patients should undergo ATTR-CM screening in the absence of classical echocardiographic findings. It is known that extra-cardiac manifestations of systemic ATTR amyloidosis, including carpal tunnel syndrome (usually bilateral), spinal canal stenosis and spontaneous ruptured tendons may precede the cardiac involvement of systemic ATTR by up to 10 years (figures 1 and 2). Identifying other conditions that may precede overt heart failure in ATTR-CM may also lead to earlier detection of the disease. To this end, conduction disease is a good potential candidate.

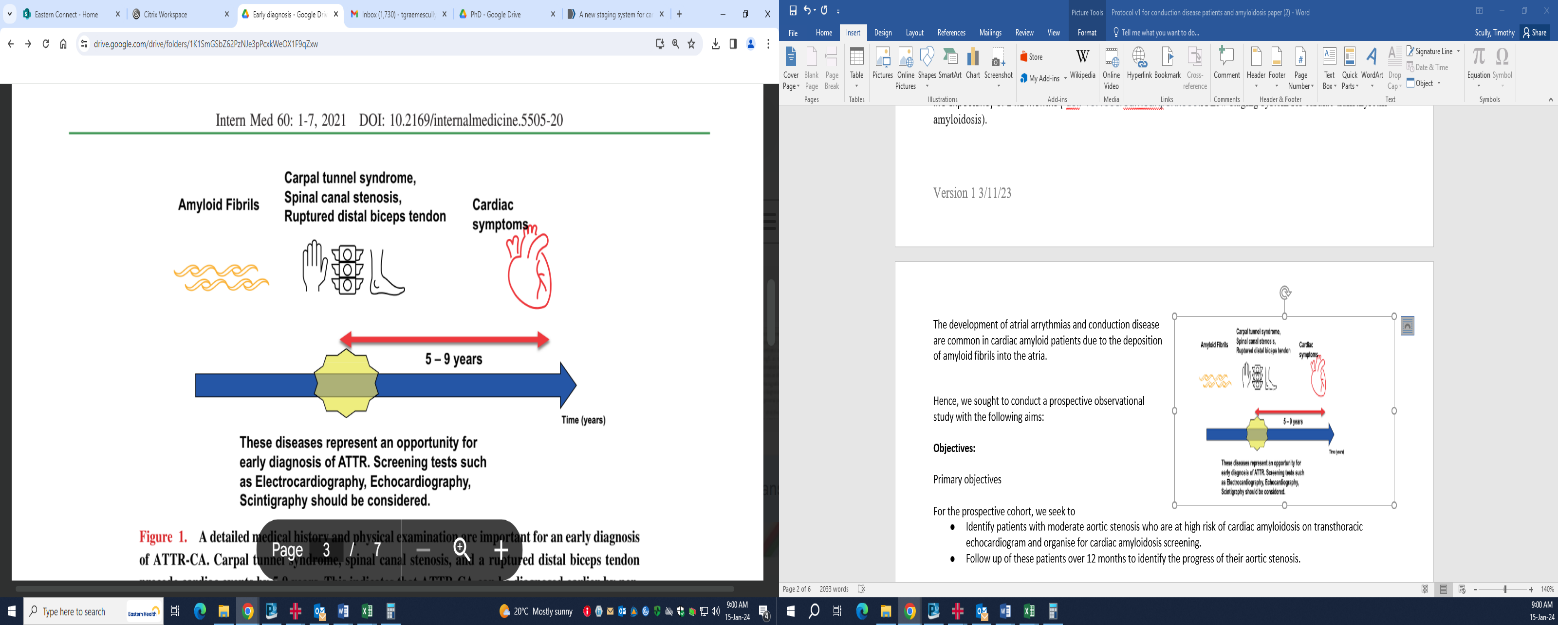
The development of atrial arrythmias and conduction disease are common in cardiac amyloid patients due to the deposition of amyloid fibrils into the atria. In a study of 782 patients with cardiac amyloidosis, conduction system disease requiring PPM is a common complication in CA that affects up to 20.6% of patients, with 50% of those patients requiring PPM prior to diagnosis of CA (15). At Eastern Health, 30% of patients with ATTR-CM have required the placement of a pacemaker, either prior to the diagnosis of ATTR-CM or during their treatment course. It has been suggested that amyloid deposits in the atria may precede amyloid infiltration into the ventricle, potentially providing an opportunity for earlier diagnosis of ATTR. To support this hypothesis, a retrospective cohort study studied patients with both cardiac amyloid and advanced conduction disease and found that in approximately 50% of cases, the implantation of a pacemaker preceded the diagnosis of ATTR-CM by 4 years (16). Additionally, in a retrospective study of patients with AL amyloidosis, 20% of patients diagnosed with AL amyloidosis had been diagnosed with arrhythmias 2 years preceding the diagnosis of AL amyloidosis(17).

Figure 1. Progression of cardiac amyloidosis from pre-cardiac stage to asymptomatic cardiac stage to clinical heart failure (1)

However, the feasibility of screening patients with conduction disease for cardiac amyloidosis is not known. We sought to conduct both a retrospective and prospective observational study to determine the prevalence of cardiac amyloidosis detected before and after the implantation of a targeted screening protocol.

*Figure SEQ Figure \\* ARABIC 2. How to Identify Transthyretin Cardiac Amyloidosis*

**Objectives:**

Primary objectives

Figure 2. Chronological relationship between known associated conditions of cardiac amyloidosis and overt cardiac failure (5)

For the prospective cohort, we seek to

Primary endpoint

* Prevalence of cardiac amyloidosis diagnosis inpatients 65 years or older undergoing permanent pacemaker implantation.

Secondary endpoints

1. Assessment of the average timing of conduction disease in the disease course of ATTR-CM. In patients with positive PYP scintigraphy scans, assessment of the degree of cardiac involvement with traditional echocardiographic parameters, ventricular and atrial strain. In addition, grading of heart failure symptoms on NYHA class and pro-BNP.
2. Comparison of prevalence of ATTR-CM in historic cohort of patients over 65 years old who received PPMs over the past 9 years who did not undergo routine screening.

1. **Descriptive study design**

Single-centre cohort study to assess the feasibility of screening older patients with new conduction disease requiring pacemaker insertion for cardiac amyloidosis. Retrospective review of similar population of patients who have received PPM implantation in past 5 years.

1. **Data sources and population**

Prospective cohort:

Adult patients aged 65 years or older who are prospectively identified either in the clinical setting or as inpatients to have new conduction disease that requires the implantation of a cardiac implantable electronic device.

Retrospective cohort:

All adult patients aged 65 years or older undergoing cardiac implantable electronic device from 2014 (start of electronic records) to 2023.

**E. Inclusion and exclusion criteria**

* Inclusion criteria
* Adult patients 65 or older who have new conduction disease requiring the implantation of a pacemaker.
* Exclusion criteria
  + Known cardiac amyloidosis.
  + Patients with a clear alternative cause of conduction disease including other infiltrative cardiomyopathies, ischaemia or medication induced conduction disease.
  + Patients with life expectancy < 12 months or severe comorbidities where screening would not be beneficial for the individual.

**F. Sample size**

The exact frequency of ATTR in patients with conduction disease as the presenting complaint is unknown. The prevalence of ATTR in other high-risk conditions are: HFpEF 5-17%, severe aortic stenosis (13-22%) and carpal tunnel syndrome (11.6%)(8, 18).It is reasonable to presume that the prevalence of ATTR in conduction disease is similar to these other conditions. Therefore, based on an expected frequency of 5%, a 5% two-tailed alpha-risk and a precision of ± 3%, we would estimate that 203 patients would be required. Given patient refusal and lost to follow up, we would aim to recruit 220 patients(19).

**G. Data analysis**

**WHAT STATISTICAL ANALYSES ARE REQUIRED FOR THIS PROPOSAL?**

* Demographic data, medical history, disease status, and clinical outcomes will be presented as proportions and summarised using descriptive statistics.
* Data will be tested for normality and parametric or non-parametric tests applied as appropriate, with mean ± standard deviation for parametric data and median with interquartile ranges for non-parametric data.

**H. Consent**

Prospective cohort:

Consent will be obtained during admission for cardiac electronic implantable device, either on the ward or in the pre-procedural waiting room of the Box Hill cardiac cath lab. If an elective device, consent will also be sought during the clinic appointment in the Box Hill Cardiology clinic rooms on level 2, building B. Patients will be identified by review of the Cardiology booking system (Health Track) on a daily basis to assess if any patient booked for a cardiac electronic implantable device is eligible for inclusion. Patients will be consented by a member of the research team or by one of the Cardiology registrars who will be their treating doctor at Box Hill Hospital. The PICF will be supplied to the patient by the individual who consents the patient. The patient will be given the PICF and be given a reasonable time to consider if they wish to participate. Follow up will be via phone contact or consultation in the Cardiology or Amyloidosis clinic. Those identified as positive will be offered genotyping and receive the current standard of care for cardiac amyloidosis as per the Amyloidosis clinic.

Retrospective cohort:

Given the retrospective nature of this part of the study, consent is not possible.

1. **Study procedures**

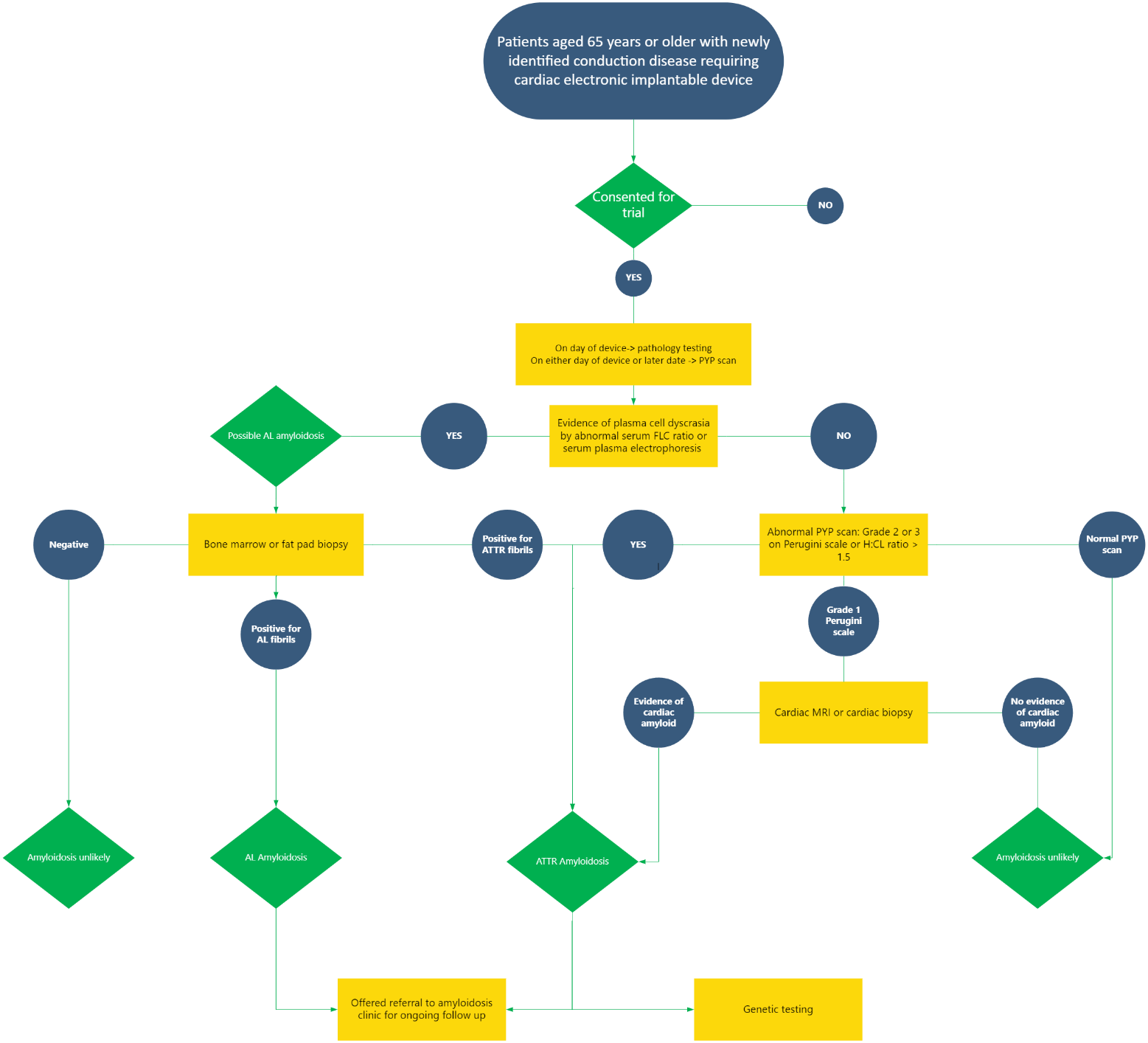
Prospective cohort:

* 65-year-old or older patients with conduction disease requiring the placement of a pacemaker will be invited to participate in the study. The participation in this screening study will have no impact on their regular treatment of their electrical conduction disease as there will be no delay in receiving a cardiac electronic implantable device and the screening process will not affect the devices’ function.
* Standard practice for patients receiving a cardiac electronic implantable device would include :1) Blood tests o nthe day of the procedure, 2) a echocardiogram prior to device insertion, if feasible, 3) an ECG on the day of device insertion and 4) a 2 week device clinic appointment for a wound check and device assessment.
* Patients that are included in the trial will undergo bone scintigraphy using a 99m Technitium-labelled pyrophosphate (PYP) scan and assessed using the Perugini scale to establish a diagnosis of ATTR-CM [[9](#_heading=h.4d34og8)]. PYP bone scans take 2 hours to complete and are done on-site at Box Hill hospital. They will not be required to do the PYP scan during their admission/presentation for cardiac electronic implantable device insertion.
* Patients will also undergo blood tests including a high -sensitive troponin, pro-BNP level, serum free light chain assay and serum immunofixation to assess for potential AL-amyloidosis. These tests can be done in addition to the standard blood tests that all patients get pre-procedurally on the day of their cardiac electronic device. These tests will not require the patient to have an additional blood test.
* The ECG on the day of implantation of the cardiac electronic implantable device will be recorded and interpreted for features of ATTR-CM. The ECGs will be read by the same person for each case to reduce inter-user variability. An ECG would be done on the day of a cardiac electronic device implantation regardless of whether a patient was involved in this study.
* Additionally, all patients will undergo a transthoracic echocardiogram to assess for signs of heart failure and other features of cardiac amyloidosis including both ventricular and atrial strain. Transthoracic echocardiograms should be performed as part of the work up for all patients with conduction disease so do not represent an additional test. Transthoracic echocardiograms are non-invasive tests that do not cause any harm to the patient and do not have any side effects. They do have a 1-hour time commitment and are conducted at Box Hill hospital.
* The results of the screening test will usually be available within 1 week of all tests being completed.
* A diagnosis of ATTR-CM is made when there is a Perugini scale of 2 or 3 or a heart to contra-lateral lung uptake ratio of > 1.5 and no evidence of plasma cell dyscrasia (13, 20).
* Patients with evidence of plasma cell dyscrasia identified during the screening process would be assessed by researcher BW (Amyloidosis expert/Haematologist) to guide need for either biopsy of bone marrow or other tissue to assess for the presence of potential AL amyloidosis.
* In patients with no evidence of plasma cell dyscrasia but a non-diagnostic PYP scan, there is a potential for early diagnosis of ATTR-CM with a Perugini score of 1, cardiac MRI and/or cardiac biopsy would be required on a case-by-case basis to investigate for other signs of ATTR-CM. If a cardiac MRI is required, patients will usually need to wait for 6 weeks until after their cardiac electronic implantable device is placed to be able to have a cardiac MRI. The cardiac MRI would be conducted at the Victorian Heart Hospital as Eastern Health does not have a cardiac MRI. There are no side effects from an MRI providing a patient does not have the usual contra-indications to a MRI, including metal wear in the body that is not compatible with a MRI scanner. Unlike PYP scans, there is no Medicare rebate for cardiac MRI for investigation of cardiac amyloidosis. When required, the cost of an MRI would be covered by the research team.
* Cardiac biopsy is very rarely required to clarify a diagnosis of cardiac amyloidosis. If any are required, the patient would be referred to the Alfred Hospital and reviewed by researcher JH (Amyloidosis expert/Cardiologist) to provide detailed consent regarding cardiac biopsy.
* Patients diagnosed with ATTR-CM will be offered genotyping to determine if they have either variant or wild-type ATTR amyloidosis. Different medication options are available for the patient depending of if they have the wild-type or genetic form of ATTR-CM. The research team would fund the cost of the genetic testing.
* Patients will have the option to opt-out at any point during the screening process.
* A letter explaining the tests conducted and the result of the tests will be provided to the patient’s GP to allow for continuity of care. Patients diagnosed with either ATTR-CM or AL amyloidosis will be offered referral to the Eastern Health amyloidosis clinic to facilitate further investigations and/or treatment as part of the standard of care for patients with known cardiac amyloidosis.
* Figure 3 provides a flow chart for the screening process.

Retrospective cohort:

* Patients who have had cardiac electronic implantable devices from January 2014 to December 2023 at Eastern Health will be identified using the Health Track database. All patients who are aged 65 years and older will be included.
* Information regarding the patient’s demographics and comorbidities (R-Table 1) will be collected from Eastern Health databases. Where available, patient’s medical records available through Eastern Health will be interrogated to determine the proportion of patients who were diagnosed with ATTR-CM at the time of cardiac electronic implantable device and which patients were later diagnosed with ATTR-CM following their device implantation (R-Table 2).

**Figure 3. Flow chart for study procedure**



**J. Ethical considerations.**

There is minimal risk with this project, as this project involves screening for a condition and does not involve any active treatment or changes to their routine management of conduction disease. All tests undergone by the patients included in this study are clinically indicated for the patient cohort. Therefore, residual risk to the patient is minimal. The consent process will have to take into account that the diagnosis of amyloidosis may be distressing to some patients and may not wish to take part in the screening process. In patients where a diagnosis is not reached in the initial screening steps (PYP scan and pathology tests), the invasive nature of tissue biopsy and/or the added burden of patient time in requiring additional investigations would be explained and patients would have the opportunity to opt-out at this stage of the trial. It is unknown what proportion of patients would require these additional investigations but based on prior screening of cardiac amyloidosis, around 10-20% of patients may require additional tests. Additionally, some patients may not wish to take part in the genotyping portion of the trial and would be afforded an opt-out opportunity at this stage of the trial.

If cardiac amyloid is detected, then patient will be referred to the state wide amyloid service that is based at Eastern Health.   
If unexpected alternative diagnosis are identified, then clinical referrals will be made with patient consent as appropriate to the relevant medical team.

Patient consents will be kept on site at Eastern Health in a secure location. At time of enrolment, each patient will be assigned a unique study code that will be linked to their Eastern Health UR. The master sheet that codes for each patient will be kept on site in a secure location. All data obtained for each patient will be entered into a password protected REDCaps database that only members of the research team can access, using the unique study code so the data is not identifiable.

The data obtained will be stored in accordance with the Victorian *Health Records Act 2001*.

The data will be destroyed according to Eastern Health policy.

**K. Presentation/ Publication**

It is intended that this research will be submitted for publication in a peer-reviewed journal and presentation at local/ national and international congresses.

**Prospective data collection**

**Table 1: Baseline Characteristics**

|  |  |  |
| --- | --- | --- |
|  | **Patients with ATTR-CM** | **Patients without ATTR-CM** |
| Age (years), mean ± SD |  |  |
| Males, n (%) |  |  |
| Body Mass Index (kg/m2), mean ± SD |  |  |
| **Comorbidities** |  |  |
| Coronary artery disease, n (%) |  |  |
| Hypertension, n (%) |  |  |
| Dyslipidaemia, n (%) |  |  |
| Diabetes, n (%)  -Diet controlled, n (%)  -Oral hypoglycaemics, n (%)  -Insulin treated diabetes, n (%) |  |  |
| Smoking history, n (%) |  |  |
| Current (smoking within 1 month prior to procedure), n (%) |  |  |
| Previously smoked, n (%) |  |  |
| Never smoked, n (%) |  |  |
| Chronic lung disease |  |  |
| Previous valvular surgery, n (%) |  |  |
| Family history of coronary artery disease, n (%) |  |  |
| Peripheral vascular disease, n (%) |  |  |
| Prior heart failure, n (%) |  |  |
| Cerebrovascular Disease, n (%) |  |  |
| Chronic oral anticoagulant use, n (%) |  |  |
| Carpal tunnel syndrome, n (%) |  |  |
| History of spinal stenosis or laminectomy, n (%) |  |  |
| **Baseline bloods at time of cardiac electronic implantable device** |  |  |
| Baseline creatinine (µmol/L), mean ± SD |  |  |
| eGFR (mL/min/1.73m2), n (%)  >60, n (%)  30-60, n (%)  <30, n (%) |  |  |
| Hb (g/L) |  |  |
| Hct (%) |  |  |
| WCC (109/L) |  |  |
| Platelet count (1012/L) |  |  |
| Troponin I ng/L |  |  |
| NT-proBNP, pg/mL |  |  |
| HbA1c (%) |  |  |
| **ECG** |  |  |
| Low voltage criteria, n (%) |  |  |
| Right bundle branch block n (%) |  |  |
| Left bundle branch block n (%) |  |  |
| QRS duration, ms |  |  |
| Atrial Fibrillation, n (%) |  |  |
| Sinus rhythm, n (%) |  |  |
| Sinus node dysfunction, n (%) |  |  |
| AV Block  Type 1, n (%)  Type 2a, n (%)  Type 2b, n (%)  Type 3, n (%) |  |  |
|  |  |  |

**Table 2: Screening for amyloidosis**

|  |  |  |
| --- | --- | --- |
|  | **Patients with ATTR-CM** | **Patients without ATTR-CM** |
| **Bone scintigraphy** |  |  |
| Completed bone scintigraphy |  |  |
| PYP- Perugini grade 0 |  |  |
| PYP- Perugini grade 1 |  |  |
| PYP- Perugini grade 2-3 |  |  |
| **AL amyloidosis screen** |  |  |
| Serum immunofixation |  |  |
| Presence of monoclonal protein |  |  |
| Serum Kappa and Lambda free light chains |  |  |
| Serum free light chain ratio |  |  |
| Was bone marrow biopsy or fat pad biopsy required |  |  |
| **Genotyping** |  |  |
| Underwent genotyping |  |  |
| Result |  |  |
| **CMR and cardiac biopsy** |  |  |
| Was CMR required for diagnosis |  |  |
| Was cardiac biopsy required for diagnosis |  |  |
| **Diagnosis** |  |  |
| No evidence of cardiac amyloidosis |  |  |
| AL amyloidosis |  |  |
| ATTR wild-type amyloidosis |  |  |
| Variant ATTR amyloidosis |  |  |

**Table 3. Patients diagnosed with ATTR-CM**

|  |  |  |
| --- | --- | --- |
| **Staging of ATTR-CM – At time of diagnosis** | **Patients with ATTR-CM** | **Patients without ATTR-CM** |
| Pro-BNP at time of diagnosis |  |  |
| Creatinine at time of diagnosis |  |  |
| eGFR at time of diagnosis |  |  |
| Troponin at time of diagnosis |  |  |
| Albumin at time of diagnosis |  |  |
| Gilmore stage at time of diagnosis |  |  |
| NYHA class at time of diagnosis |  |  |
| Prior hospitalizations for HF at time of diagnosis |  |  |
| Lasix dose at time of diagnosis |  |  |
| **Echocardiogram parameters** |  |  |
| LV function (subjective)   * Normal, n (%) * Mild >40, n (%) * Moderate 36-40, n (%) * Severe < 35, n (%) |  |  |
| LV EF (Objective), % |  |  |
| LVEDD (cm) |  |  |
| LV ESD (cm) |  |  |
| IV septum (cm) |  |  |
| Inferolateral wall (cm) |  |  |
| RV diameter (cm) |  |  |
| TAPSE (cm) |  |  |
| LV mass indexed, g/m2 |  |  |
| GLS, % |  |  |
| LA area, cm2 |  |  |
| LA volume, mL3 |  |  |
| RA area, cm2 |  |  |
| E velocity, m/s |  |  |
| A velocity, m/s |  |  |
| E:A ratio |  |  |
| Deceleration time, ms |  |  |
| Medial e’, m/s |  |  |
| Lateral e’, m/s |  |  |
| E:e’ medial |  |  |
| E:e’ lateral |  |  |
| E:e’ average |  |  |
| MR at least moderate, n (%) |  |  |
| LVOT diameter, cm |  |  |
| LVOT VTI, cm |  |  |
| Aortic peak velocity, m/s |  |  |
| Aortic peak gradient, mmHg |  |  |
| Aortic mean gradient, mmHg |  |  |
| LV stroke volume index, mL/m2 |  |  |
| Aortic valve area, cm2 |  |  |
| Aortic valve area index, cm2/m2 |  |  |
| Aortic stenosis high gradient, n (%) |  |  |
| Low flow low gradient with EF < 50%, n (%) |  |  |
| Low flow low gradient with EF ≥ 50%, n (%) |  |  |
| Peak TR velocity, m/s |  |  |
| TR at least moderate, n (%) |  |  |
| RVSP, mmHg |  |  |
| **Amyloid specific parameters** |  |  |
| Low flow low gradient AS, n (%) |  |  |
| LA volume indexed ≥ 60cm3,m2 , n (%) |  |  |
| IVS septum > 1.1 cm, n (%) |  |  |
| Increased LV mass indexed, n (%) |  |  |
| Myocardial contraction fraction, % |  |  |
| Myocardial contraction fraction < 30%, n (%) |  |  |
| Mitral S’ < 7cm/s, n (%) |  |  |
| Pericardial effusion, n (%) |  |  |
| Abnormal GLS ≥ -15%, n (%) |  |  |
| Relative apical sparing on GLS, n (%) |  |  |
| Apical LS, % |  |  |
| Mid LS, % |  |  |
| Basal LS, % |  |  |
| Atrial strain, % |  |  |

**Retrospective data collection**

**R- Table 1: Baseline Characteristics**

|  |  |  |
| --- | --- | --- |
|  | **Patients with ATTR-CM** | **Patients without ATTR-CM** |
| Age (years), mean ± SD |  |  |
| Males, n (%) |  |  |
| Body Mass Index (kg/m2), mean ± SD |  |  |
| **Comorbidities** |  |  |
| Coronary artery disease, n (%) |  |  |
| Hypertension, n (%) |  |  |
| Dyslipidaemia, n (%) |  |  |
| Diabetes, n (%)  -Diet controlled, n (%)  -Oral hypoglycaemics, n (%)  -Insulin treated diabetes, n (%) |  |  |
| Smoking history, n (%) |  |  |
| Current (smoking within 1 month prior to procedure), n (%) |  |  |
| Previously smoked, n (%) |  |  |
| Never smoked, n (%) |  |  |
| Chronic lung disease |  |  |
| Previous valvular surgery, n (%) |  |  |
| Family history of coronary artery disease, n (%) |  |  |
| Peripheral vascular disease, n (%) |  |  |
| Prior heart failure, n (%) |  |  |
| Cerebrovascular Disease, n (%) |  |  |
| Chronic oral anticoagulant use, n (%) |  |  |
| Carpal tunnel syndrome, n (%) |  |  |
| History of spinal stenosis or laminectomy, n (%) |  |  |
| **Baseline bloods at time of cardiac electronic implantable device** |  |  |
| Baseline creatinine (µmol/L), mean ± SD |  |  |
| eGFR (mL/min/1.73m2), n (%)  >60, n (%)  30-60, n (%)  <30, n (%) |  |  |
| Hb (g/L) |  |  |
| Hct (%) |  |  |
| WCC (109/L) |  |  |
| Platelet count (1012/L) |  |  |
| Troponin I ng/L |  |  |
| NT-proBNP, pg/mL |  |  |
| HbA1c (%) |  |  |
| **ECG** |  |  |
| Low voltage criteria, n (%) |  |  |
| Right bundle branch block n (%) |  |  |
| Left bundle branch block n (%) |  |  |
| QRS duration, ms |  |  |
| Atrial Fibrillation, n (%) |  |  |
| Sinus rhythm, n (%) |  |  |
| Sinus node dysfunction, n (%) |  |  |
| AV Block  Type 1, n (%)  Type 2a, n (%)  Type 2b, n (%)  Type 3, n (%) |  |  |

**R- Table 2: Presence of ATTR-CM**

|  |  |  |
| --- | --- | --- |
|  | **Patients with ATTR-CM** | **Patients without ATTR-CM** |
| **Bone scintigraphy** |  |  |
| Completed bone scintigraphy |  |  |
| PYP- Perugini grade 0 |  |  |
| PYP- Perugini grade 1 |  |  |
| PYP- Perugini grade 2-3 |  |  |
| **AL amyloidosis screen** |  |  |
| Serum immunofixation |  |  |
| Presence of monoclonal protein |  |  |
| Serum free light chain ratio |  |  |
| Abnormal serum free light chain ratio |  |  |
| **Genotyping** |  |  |
| Underwent genotyping |  |  |
| Result |  |  |
| **CMR and cardiac biopsy** |  |  |
| Was CMR required for diagnosis |  |  |
| Was cardiac biopsy required for diagnosis |  |  |
| **Diagnosis** |  |  |
| No evidence of cardiac amyloidosis |  |  |
| AL amyloidosis |  |  |
| ATTR wild-type amyloidosis |  |  |
| Variant ATTR amyloidosis |  |  |

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