Catheter Ablation versus Medical Rate Control of Atrial Fibrillation in Patients with Systolic Heart Failure and Myocardial Fibrosis – An MRI Guided Multi-Centre Randomised Controlled Clinical Trial.

AIMS

1. Primary aim:

o Investigate the impact of MRI-detected ventricular myocardial fibrosis on left ventricular function and clinical outcomes (mortality and heart failure related hospitalisation) in patients with atrial fibrillation and systolic heart failure after restoring sinus rhythm with catheter ablation.

2. Secondary aims:

o Determine the influence of myocardial fibrosis on other outcomes after catheter ablation, including ventricular and atrial structural and electrical remodelling, clinical symptoms and functional capacity.

o Determine whether the volume of myocardial fibrosis may influence the outcome after catheter ablation.

Atrial fibrillation and heart failure: Atrial fibrillation (AF) and heart failure (HF) are both emerging epidemics in developing countries with a significant influence upon morbidity and mortality. AF is estimated to affect 5.4% of the population over 55[1]. Additionally, HF affects 1.5-2% of the Australian population as extrapolated by worldwide data, almost half of whom have ischaemic cardiomyopathy. AF and HF share pathophysiological mechanisms with each condition driving the other. The restoration of sinus rhythm has the potential to improve LV function and clinical outcomes in patients with HF and concurrent AF. In recent times, catheter ablation (CA) has established itself as a superior to medical therapy[2], particularly in patients with HF[3], with an acceptable risk profile, albeit with a lower procedural efficacy compared to patients without HF[2,4]. Although, early clinical trials have demonstrated LVEF improved irrespective of HF aetiology[5-8], Other studies, including a meta-analysis suggested that pre-existing structural heart disease, such as prior myocardial infarction predicted reduced procedural efficacy[2] and poor recovery of systolic function[9]. A recently published randomised clinical trial which was led by this research group, specifically focused on patients with AF and idiopathic or otherwise unexplained cardiomyopathy (the CAMERA-MRI study), which showed that MRI detected myocardial fibrosis could predict the extent of ventricular recovery following catheter ablation[10]. The recent CASTLE-AF study published in the New England Journal of Medicine[11], reported improved mortality and unplanned HF hospitalisation following CA in all aetiologies of HF with concurrent AF, including ischaemic cardiomyopathy, however the impact of myocardial fibrosis or heart failure aetiology was not specifically evaluated. This randomised clinical trial will definitively examine the role of cardiac MRI (CMR) in all patients with AF and heart failure, including those with ischaemic cardiomyopathy or known contributing myocardial fibrosis.

CMR detected myocardial fibrosis: Myocardial fibrosis is a hallmark of cardiomyopathy and is generally considered irreversible. Discrete scar is seen in ischemic, and idiopathic dilated cardiomyopathy with characteristic topography[12]. Contrast-enhanced CMR is a well-established technique that identifies regional ventricular fibrosis by the presence of LGE. In

addition, T1 mapping, a histologically validated[13] MRI technique to detect diffuse fibrosis, has been described in heart failure including in the non-infarcted myocardium in patents with ischaemic cardiomyopathy[14]. The detection of myocardial scar by cardiac MRI, had been retrospectively correlated with procedural outcomes and mortality in patients with AF and heart failure undergoing catheter ablation[15].

Role of myocardial fibrosis in CA for AF and HF: There have been only a few studies to explore the role of myocardial fibrosis in AF and HF and its implications for outcome following CA, and none in the setting of ischaemic cardiomyopathy. Liang et al reported the outcomes of 15 patients with persistent AF, idiopathic cardiomyopathy (LVEF<50%) and the absence of late gadolinium enhancement (LGE) on MRI imaging undergoing catheter ablation. Patients showed an average improvement of 20% in absolute LVEF, with 94% normalising LV function[16]. Addison et al[15] retrospectively evaluated the outcomes of 172 patients with LVEF <50% undergoing catheter ablation all of whom has baseline cardiac imaging performed, with 25% having LGE present. After an average of 42 months follow-up, the presence of LGE was associated with a lack of recovery of LV function, increased AF recurrence in addition to worsened mortality and heart failure hospitalisations[15]. Furthermore, in an analysis of patients with HF and AF who underwent catheter ablation, the presence of known heart disease with fibrosis (such as ischaemic cardiomyopathy), predicted worsened procedural outcomes and mortality, compared to those with no known structural cause of heart failure.[9]

The CAMERA-MRI trial was the first randomised trial to selectively enrol and randomise patients with idiopathic or otherwise unexplained heart failure, excluding those with structural heart disease or known causes of heart failure such as ischaemic cardiomyopathy. In addition to showing a significant 18% absolute improvement in ejection fraction, the absence of late gadolinium enhancement on cardiac MRI predicted an even greater recovery (73% normalising LV function). A dose dependant relationship between MRI detected myocardial fibrosis (based on the percentage of myocardial LGE) and the extent of LV recovery (R=0.67, p=0.0094)[10] was also seen (Figure 2). Our group was also the first to publish that diffuse fibrosis in the setting of AF and HF is at least partially reversible following recovery of systolic function post catheter ablation, as evidenced by a reduction in native T1 mapping times consistent with a reduction in diffuse fibrosis.[17]

Rationale for the study: Although recent studies have revealed some promising results and notwithstanding the significant findings of the CASTLE-AF study, the ideal population to benefit from CA remains unclear. The CAMERA-MRI study highlighted the real utility of cardiac MRI in identifying those patients to achieve the best outcome following CA. This study aims to extend the utility of CMR as a risk stratification tool to other forms of HF with known contributing myocardial fibrosis, particularly ischaemic cardiomyopathy, which accounts for up to half of patients with AF and HF. It also aims to extend the utility of cardiac MRI beyond prediction of improvement in ventricular function, but also its impact upon clinical outcomes such as mortality and hospitalisation. Furthermore, whilst, CA is now a mainstream treatment for AF and its use in patients with HF, does carry increased risk compared to patients without HF[4]. Efforts to further optimise patient selection will ensure this resource is allocated to those patients likely to achieve the best outcomes.
Cardiac MRI is a widely available, non-invasive and safe investigatory tool which can allow catheter ablation to be appropriately targeted, and additionally avoid patients unlikely to benefit from an unnecessary or potentially harmful procedure. There is currently no clinical

guidance in this area, with all most large clinical trials in this area grouping heterogenous cohorts of HF patients together, making distinguishing the impact of myocardial fibrosis and structural heart disease upon clinical outcomes impossible to differentiate. This study will definitively address this crucial clinical question and provide clinicians with an easy and pragmatic tool to appropriately identify HF patients most likely to benefit from catheter ablation.

RESEARCH PLAN

Clinical trial infrastructure: This clinical trial will draw upon the clinical trial infrastructure utilised in the CAMERA-MRI trial, including the collaborative relationships between the participating institutions. After ethical approval, the following clinical trial bodies oversee the performance of the clinical trial. These will be formulated in accordance with NHMRC Australian Clinical Trials Guidelines.

- *The Trial Steering Committee* (TSC). This body will consist of a body of independent expert members and at least one chief investigator which will monitor the progress of the study and ensure that the study is meeting its required milestones and objectives in order to reach completion. The body will consist of:
    - An independent Chairperson (not involved directly with the study other than as a member of the Steering Committee)
    - Two or more other independent expert members (clinical and/or methodological)
    - The chief investigator (CIA)
    - o A lay representative
- *Data Safety and Monitoring Board* (DSMB). This will consist of a body of members independent to the investigators to ensure the study adheres to pre-specified objectives and ethical requirements. The DSMB will have access to unblinded data and advise on safety aspects of the study and whether there is an indication to halt or cease the study based on the findings.
- *Clinical Endpoint Adjudication Committee* (CEC). This will consist of members independent to the study investigators who will adjudicate clinical endpoints to ensure the unbiased assessment of occurrences of outcomes, in particular hospitalisations. The CEC will be blinded to treatment allocation of the study participants. The CEC will determine the need for interim analyses at a pre-specified number of primary endpoint events, and if required, advise the TSC upon progress and trial continuation.

Study design: This will be a multicentre open labelled randomised clinical trial assessing the impact of MRI detected myocardial fibrosis on clinical outcomes and ventricular function in patients with AF and HF. The broad study design is illustrated in Figure 1. The study population will be drawn from the heart failure services at major teaching hospitals in Australia and the United Kingdom including the Alfred Hospital, Royal Melbourne Hospital, Monash Medical Centre and St Bartholomew's Hospital in London, UK. Further Australian centres and international centres may be invited to participate over the course the study provided they have the appropriate resource infrastructure to performed catheter ablation and cardiac MRI and approved by the Trial Steering Committee.

Inclusion criteria: Patients will be enrolled if they meet the following inclusion criteria:

1. Age > 18 years

2. Left ventricular ejection fraction ≤45% (as determined by MRI)
    a. Initial screening transthoracic echocardiogram to assess eligibility
3. Failed at least one anti-arrhythmic medication and recurrence after at least one DCR
4. On established anti-heart failure medical therapy including ACE inhibition or ARB (or equivalent therapy) and/or betablocker therapy.
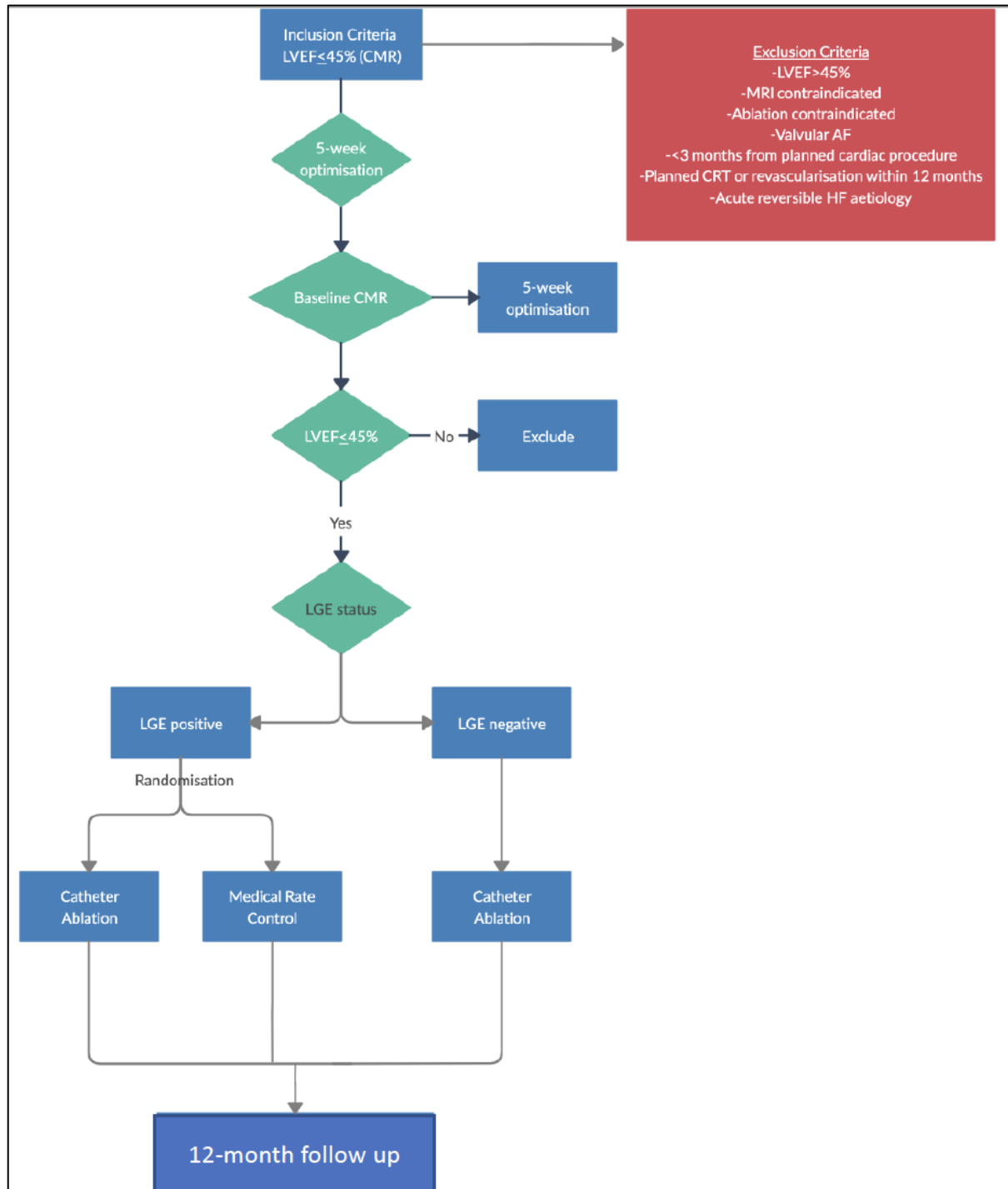
Figure 1: Proposed study design for the CAMERA-MRI II study. CMR-Cardiac MRI; LGE-late gadolinium enhancement; CRT-cardiac resynchronisation therapy.
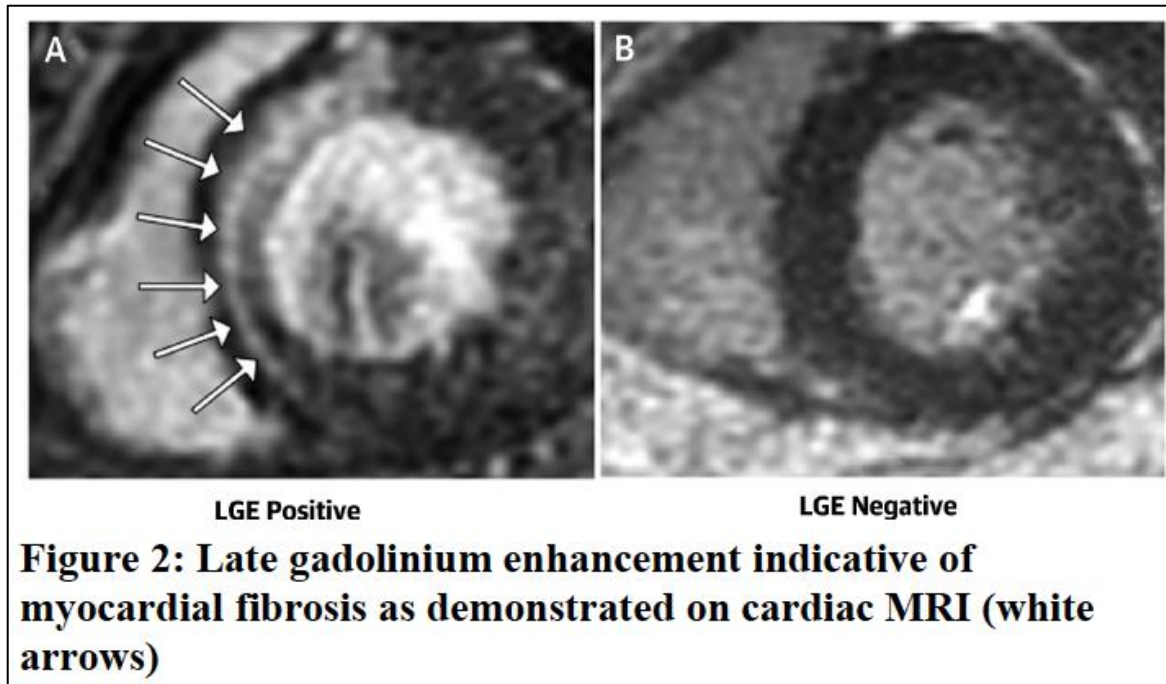
Exclusion criteria: Patients will be excluded in the event of any of the following criteria:

1. Any contraindications to CMR (i.e. eGFR <35mL/min, MRI-incompatible device)
2. Any contraindications to AF ablation (ASD closure, LAA thrombus, anticoagulation contraindication, continuous AF for >5 years deemed unlikely to restore or maintain sinus rhythm)
3. LVEF >45% (determined by CMR)
4. Valvular AF
5. Other acute reversible cause of heart failure (uncontrolled thyroid disease, excessive alcohol, active myocarditis)
6. Less than 3 months from CRT device implantation or other cardiac intervention (PCI/CABG)
7. Planned cardiac intervention within 12 months of enrolment.

Baseline assessment: Prior to baseline CMR assessment, all enrolled patients will undergo a 5-week period of medical optimisation (medical rate control (MRC), including 24-hour Holter monitor and heart failure pharmacological therapy prior to baseline CMR, aiming for average ventricular rate <90bpm).

In addition to CMR, baseline tests will include: clinical review (CR), trans-thoracic echocardiography (TTE), cardio-pulmonary exercise (CPX) testing (VO_2max), serum brain natriuretic peptide (BNP), 6-minute walk test (6MWT), short-form 36 health survey (SF-36) and Minnesota Living with Heart Failure Questionnaire (MLHFQ).

Cardiac MRI (CMR): CMR scans will be performed on a 3.0T scanner with cardiac gating and calibration capacity. Delayed enhancement using gadolinium will determine the presence of ventricular fibrosis (Figure 3). Delayed enhancement imaging will be performed 10 minutes after Magnevist injected directly into a vein via a cannula at a single dose of 0.4ml/kg up to a maximum dose of 40ml. The percentage of ventricular LGE in patients will be quantified and correlated with outcomes using methodology as previously described[10]. Pre and post contrast T1 times, to assess for diffuse fibrosis will also be obtained and correlated with outcomes using previously validated methodology[18], utilising the validated SmartT1 assessment protocol. Pulmonary venograms taken at the time of the procedure may be utilised for image integration for the purposes performing CA. Raw DICOM MRI data will be collated and assessed centrally to standardise reporting. MRI images will be analysed by investigators blinded to treatment allocation. MRI's performed at each centre will be reviewed by investigators to minimise inter-site variability in reporting.

Figure 2: Late gadolinium enhancement indicative of myocardial fibrosis as demonstrated on cardiac MRI (white arrows)

Randomisation: Following baseline CMR, provided patients still meet enrolment criteria, patients will be stratified according to the presence or absence of LGE. Patients with LGE present will be computer randomised 1:1 to either CA or ongoing MRC. Randomisation will occur in a box fashion on a centre basis to ensure even treatment allocation across study centres. Patients without LGE will be followed in a parallel treatment arms and all undergo CA as the CAMERA-MRI study clearly demonstrated the superiority of CA to MRC in this patient population. This will facilitate a comparison of procedural and clinical outcomes between LGE positive and LGE negative patients undergoing CA.

AF ablation procedure: Antiarrhythmic drugs (AAD) and oral anticoagulants will be continued in the peri-procedure period. Arrhythmia recurrence is defined as any atrial tachycardia or fibrillation episode lasting greater than 30 seconds that persists after a 12-week blanking period from the day of the procedure. Under general anaesthesia trans-oesophageal echocardiography will be performed immediately prior to of the procedure to exclude left atrial thrombus and to assist in double transseptal puncture. CA will be guided using a 3D mapping system with integration of the left atriogram obtained at the time of CMR. Ablation will be performed with an irrigated tip catheter to encircle the left and right sided PVs as confirmed by multi-polar catheter[19]. PV isolation will be mandatory with additional ablation at the discretion of the operator. Anti-arrhythmic medications will be continued for 6 months then at the discretion of the operator. Repeat ablation will be recommended >12 weeks from index procedure in the setting of AF recurrence unless contra-indicated clinically. An AliveCor monitor will be provided to all participants following CA for frequent remote monitoring for AF recurrence and overall AF burden in the months following the procedure.

Medical rate control: The adequacy of MRC will be assessed via serial 24-hour Holter monitoring at 3, 6 and 12 months. The definition of adequate rate control is between 60 and 80bpm at rest, average ventricular rate <100bpm on 24-holter monitoring and up to 110bpm

during moderate exercise, which will be assessed during a 6-minute walk test (6MWT)[20]. Patients with poorly controlled ventricular rates will be eligible to cross over the catheter ablation arm during the study period if there is an appropriate clinical indication as determined by the treating physician in conjunction with the Trial Steering Committee where possible.

Study follow-up: Patients will be followed for 12 months. Patients will be reviewed up at 6 weeks, 3 months, 6 months and 12 months following CA or from randomisation (for the MRC arm) according to the schedule detailed below. Cardiac MRI will be repeated at 12 months (see table 1, below).

Table 1: Study follow up protocol

	Baseline and follow up assessments					
	Clinic	CMR	TTE	24HM/AC	6MTW/CPEX/BNP	QOL
Baseline	✔	✔	✔	✔	✔	✔
6 weeks	✔					
3 months	✔			✔	✔	✔
6 months	✔		✔	✔	✔	✔
12 months	✔	✔	✔	✔	✔	✔

CMR-cardiac MRI; TTE-transthoracic echocardiography; 24HM-24 hour Holter monitoring; AC-AliveCor monitoring; 6MTW- 6-minute walk test; CPEX-cardiopulmonary exercise testing; BNP-brain natriuretic peptide pathology testing; QOL-quality of life assessments.

Key definitions:
- All-cause mortality is defined as:
  - All deaths including all heart transplants due to terminal heart failure (HF).
  - Heart transplanted patients will be dropped out and followed in respect of their vital status for the duration of the study
- Cardiovascular mortality
  - All deaths due to cardiovascular reasons including deaths due to worsening of HF, acute coronary syndrome, cerebrovascular accidents, or other cardiovascular events.
  - All heart transplants because of terminal HF.
- Worsening HF includes:
  - Patients requiring intravenous medication for HF (including diuretics, vasodilators or inotropic agents)

- A substantial increase in oral diuretic therapy for HF (i.e., an increase of furosemide ≥40mg or equivalent, or the addition of a thiazide to a loop diuretic) will be deemed to have worsening of HF or, rales and/or S3 sound, chest x-ray, worsening of dyspnoea, worsening of peripheral oedema and increase of New York Heart Association class will be assessed for determination of worsening of HF.
- Unplanned hospitalization includes:
  - Any in-hospital stay over one date change, and not planned by the Investigator. Same-day admissions are not included in the primary end point. Reasons for worsening of HF may include atrial fibrillation, acute coronary syndrome, and hypertension.
- Unplanned Hospitalization due to Cardiovascular Reason:
  - Any in-hospital stay over one date change due to cardiovascular reason, which includes worsening of HF, acute coronary syndrome, cerebrovascular accidents, or other cardiovascular events, and not planned by the Investigator

Primary endpoint (figure 3)
To determine if LGE-positive patients undergoing CA achieve a greater improvement in LV systolic function at 12 months compared to those allocated to medical rate control.

1. Baseline to 12-month change in LV ejection fraction (CMR) between:

   1. LGE positive and LGE negative patients undergoing CA
   2. LGE positive patients undergoing CA vs MRC group

Secondary endpoints

1.Impact of CA on clinical outcomes (all-cause mortality and HF hospitalisations)
     -LGE-positive and LGE-negative patients undergoing CA at 12 months
     -LGE-positive patients undergoing CA vs MRC at 12 months

2.Impact of myocardial fibrosis burden on LV recovery and clinical outcomes in CA vs MRC at 12 months.

3. Effect of CA on atrial and ventricular electrical remodelling.

4. Assess individual endpoints (all-cause mortality, unplanned HF hospitalisations, cardiovascular mortality).

5. Change from baseline to 12-month assessments between LGE-positive CA and MRC:
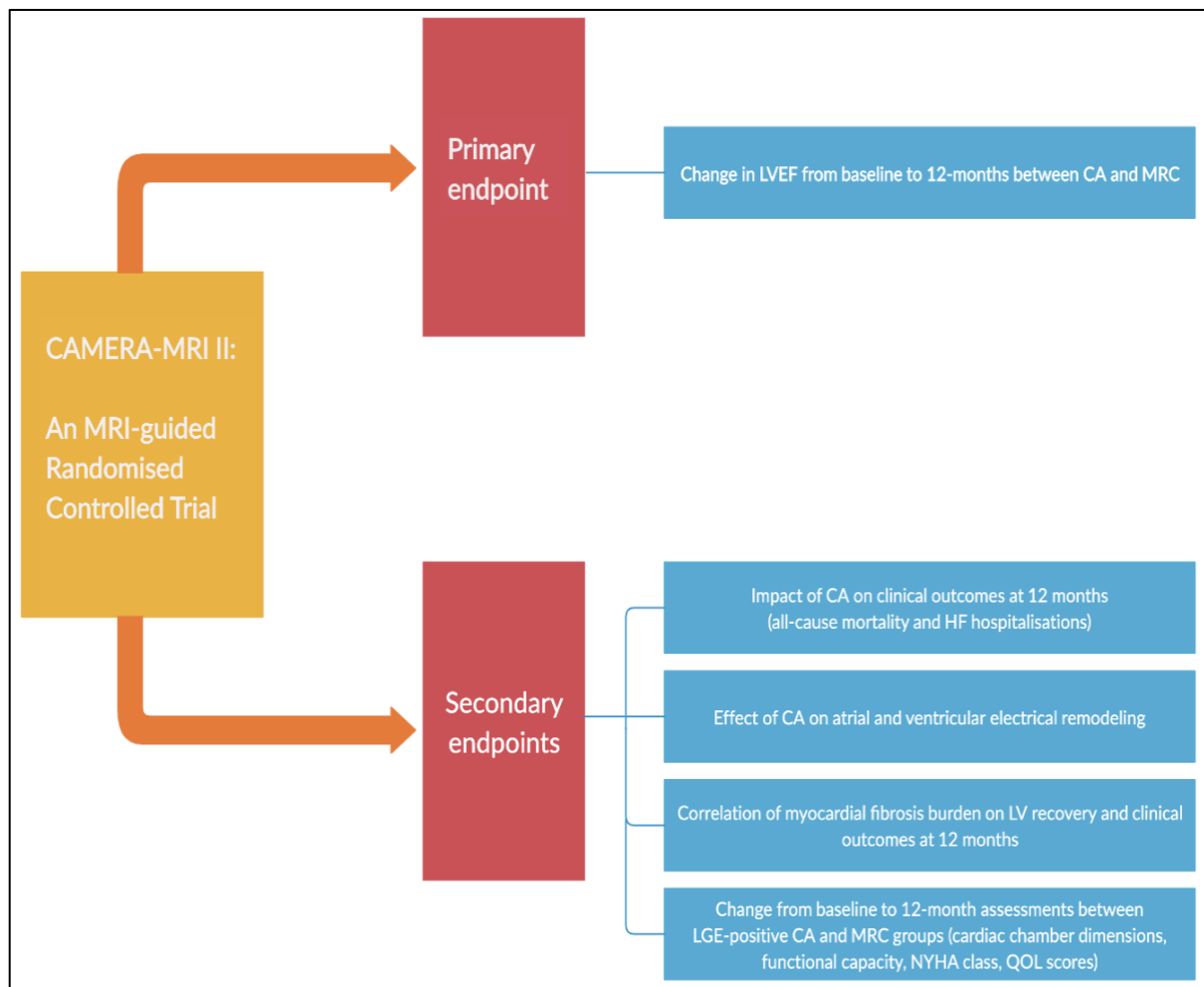- Cardiac dimensions (CMR and TTE)
- Serum BNP
- Functional capacity (6MWT, VO2 max-CPEX)
- Quality of life scores (SF-36 and MLHFQ)
- NYHA class

6. Impact of diffuse fibrosis (native and post contrast T1 mapping) on ventricular recovery and clinical outcomes.

7. Procedural complications.

8. AF recurrence and percentage burden (by AliveCor readings) in CA group.

Figure 3: Primary and secondary study endpoints.

Other analyses and sub-studies: The data generated by the main trial will also afford opportunity to explore several other aspects of CA in patients with HF including:

1. The effect of CA on ventricular remodelling. The MRI data will be used to definitively explore to what extent both focal and diffuse ventricular scarring in the setting of AF and HF is reversible by comparing baseline and follow-up CMR. This will provide insight into the impact of myocardial fibrosis on the long-term outcomes of these patients, and the extent to which the myocardium can reverse remodel. For the first time, CMR detected fibrosis can also be prospectively correlated with clinical endpoints such as mortality, and hospitalisation.

2. The effect of LV recovery upon atrial tissue. Patients undergoing CA will undergo detailed electroanatomical mapping performed at the same time as the procedure, to enable a detailed evaluation of atrial tissue in patients with and without ventricular fibrosis. Mapping will be performed by a contact force enabled ablation catheter to ensure that Measured parameters will include tissue voltage, conduction velocity, and the presence and distribution of atrial scarring. These findings will provide an insight into the mechanism of recurrence of AF.

Participants will be invited back for repeat EP study to evaluate for evidence of reversal of atrial remodelling (Figure 4).
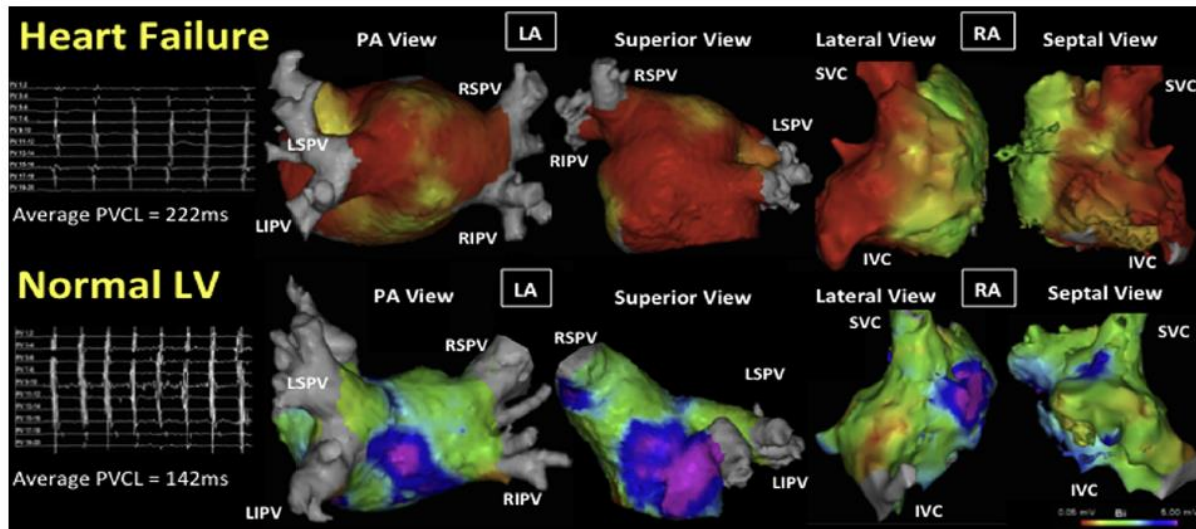
Figure 4: Electroanatomical mapping to understand the impact of heart failure and AF on atrial tissue will be performed and correlated for the first time with clinical outcomes.[10]

3. Data will be collated into long term registries to evaluate the long-term impact of catheter ablation beyond 5 years upon both clinical endpoints, LV function and long-term AF freedom burden assessment in these patients.

Statistical Analysis and Sample Size
Data will be analysed using SPSSv.26. All analyses will be conducted on an intention to treat basis using standard statistical methods for categorical and continuous data. The prior CAMERA-MRI study from our group demonstrated a mean improvement in LVEF of 11.6 ± 10.3 in the LGE-positive CA group, compared to 4.8 ± 8.5 in the MRC group at 6 months. We estimated a total sample size of 74 patients would be needed in order to reach a statistical power of 80% with the probability of type one error being 0.05. This was calculated using a standard deviation of 10.3 based on the CAMERA-MRI study[10]. The calculated sample size reflects the sample required to detect an improvement at 6 months based on the previous CAMERA-MRI trial. It is likely this benefit would be amplified at 12-months and therefore we feel the estimated sample size of 74 patients overall (37 per group) is sufficient to statistically power for the primary endpoint. We accounted for a 10% drop out rate, increasing the total sample size to 80 participants (40 per LGE-positive treatment group). Recruitment will continue until 80 LGE-positive patients have been randomised. Differences in proportions and categorical variables will be compared using chi-squared analysis or Fisher's exact test. Continuous variables will be analysed using Student's t-test. Confidence intervals for the difference of two independent proportions will be calculated using the Newcombe-Wilson score method (uncorrected). McNemar's test will compare proportions of paired samples.

Consent/Ethics
Informed consent will be obtained prior to study enrolment for all patients meeting eligibility, in keeping with the NHMRC guidelines for the conduct of research. Ethics will be sought

prior to undertaking patient screening and recruitment. This methodology has been successfully implemented by the investigators in a previous catheter ablation trial (CAMERA-MRI).

Preliminary data: There is limited preliminary data regarding the impact of myocardial fibrosis on outcomes post catheter ablation. The CAMERA-MRI study enrolled 68 patients with idiopathic cardiomyopathy and persistent AF. Of those patients undergoing catheter ablation, 14 patients had LGE present. Figure 5 illustrates the dose dependant relationship between the percentage of ventricular LGE and the percentage improvement from baseline of cardiac function. This study demonstrated a clear dose/response relationship between the percentage of LGE present and the extent of LV recovery (Figure 2). In a retrospective analysis of 172 patients with heart failure and atrial fibrillation, Addison et al demonstrated that in those patients failing to recover LV function following catheter ablation nearly half (48%) had LGE present on cardiac MRI, compared to only 4% of those patients who had LV recovery at follow up (p<0.001). Those patients also had worsened mortality and HF related admissions compared to those without LGE (Figure 6).
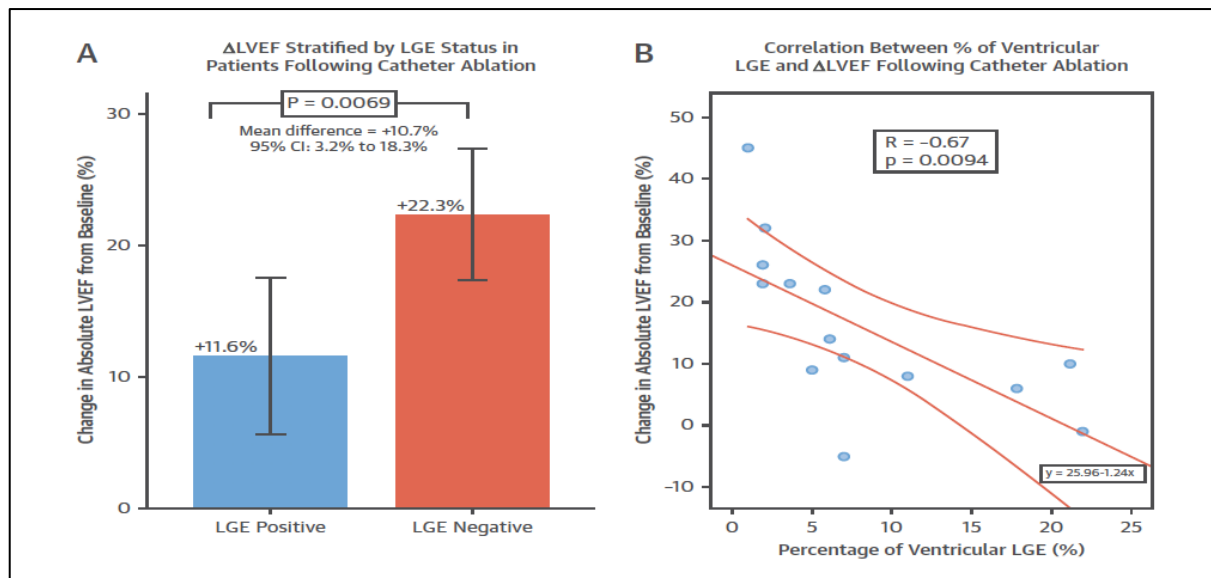
Figure 5: Relationship between LGE at baseline and percentage improvement in LVEF at 6 months post catheter ablation showing scar can influence LV recovery.[17]
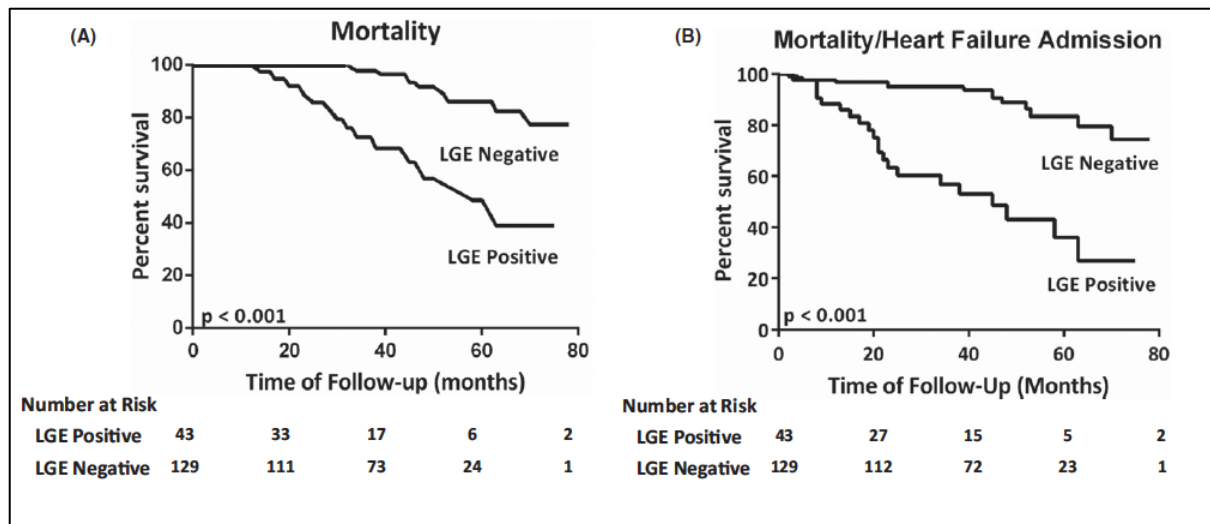
Figure 6: Impact of LGE on mortality and HF hospitalisation post catheter ablation.[15]

Table 2: Study timeline

Study Stage	Year 1	Year 2	Year 3	Year 4	Year 5
Administration, logistical set-up & ethics approval	X				
Recruitment	X	X	X		
Patient follow-up		X	X	X	X
Data compilation and analysis					X
Data collection and analysis for sub-studies			X	X	X
Manuscript preparation and publication				X	X

SIGNIFICANCE

The role of CA in AF and HF is an ongoing area of research and while the findings in CASTLE-AF provide some promise with regard to improvements in clinical outcomes, the challenges in performing CA in patients with HF (compared to those with normal LV function)[4] highlights the need to better identify the subset with HF most likely to benefit from CA. To date, no clinical trials have specifically evaluated the impact of CA in those with AF and HF based on the presence of myocardial fibrosis with regard to LV recovery and clinical outcomes.

Moreover, this study will provide comprehensive analysis of the impact of myocardial fibrosis on structural and electrical atrial and ventricular remodelling. It will also further define the role of CMR in stratifying HF subtypes and clarify the strengths and limitations of CA in the HF treatment armamentarium. The findings may support the use of CMR to pre-determine those most likely to benefit from CA and avoid those least likely to benefit from undergoing a potentially unnecessary and invasive intervention.

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