Randomised Evaluation of the iMpact of cathEter ablation on psychological DIstress and neurocognitive function in Atrial fibriLlation (The REMEDIAL study)

STUDY PROTOCOL

Background:

Atrial fibrillation (AF) is the commonest sustained arrhythmia encountered in clinical practice (1) with increasing prevalence in the ageing population. Its incidence doubles from 4% in individuals older than 60 years to 8% of persons older than 80 years and approximately 25% of individuals aged 40 years and older will develop AF during their lifetime (2).

Although there is no survival advantage with rhythm control over rate control (3), literature supports that rhythm control improves AF symptoms and overall quality of life particularly in patients with substantial symptoms associated with AF (4, 5). Most clinical studies have focussed on the physical manifestations of AF when examining quality of life. However, recent data has demonstrated that patients with high burden of AF suffer from significant psychological distress. Indeed there was a surprisingly high and previously unreported incidence of suicidal ideation in this population. In an observational study we demonstrated an improvement in psychological distress and suicidal ideation in patients undergoing curative ablation compared with observational controls undergoing medical therapy. Outcomes were linked to AF burden.

While current AF guidelines recommend a symptoms-based approach in deciding the choice of management strategy, it is important to recognize severity of AF-related symptoms may be governed by markers of psychological distress such as anxiety and depression. Sears et al (6) showed that higher levels of reported negative emotions were more strongly associated with a greater number of reported AF symptoms. Depression and anxiety was thought to be more

important than number of AF episodes in predicting AF symptom severity. In a specific population with paroxysmal AF and an implantable cardioverter defibrillator (ICD) with atrial tachyarrhythmia therapies in situ, Camm et al (7) reported the number of device-counted and treated AF episodes to be one factor associated with symptom severity, and also found psychological distress to be a more powerful predictor of AF symptoms than any device-recorded objective measure of AF burden.

Several other aspects of personality style have also been associated with the subjective experience of AF. Ong et al (8) showed had more symptom preoccupation and severity of symptoms in patients with lower levels of optimism. Additionally, anxiety sensitivity was related to poorer health-related quality of life (HRQoL) and psychological distress. In a study by Lane et al (9) to determine how HRQoL, depression, and anxiety change over the first 12 months following diagnosis of AF, patients who perceived more stress at the time of diagnosis were noted to have a sharper decrease or a slower increase in state anxiety over the 12 months. Perceived stress was also related significantly and positively to the slope of the mental health component, indicating that patients who perceived more stress in their lives at the time of diagnosis had a mental health QoL score that improved at a greater rate over the 12-month follow-up period. Illness identity were significantly inversely correlated with the physical health slope over 12 months, suggesting that the more symptoms' patients attributed to their AF at time of diagnosis, the sharper the deterioration or the slower the improvement in physical health over the 12 months. Gehi et al (10) found that psychological comorbidities including depression, anxiety, and somatization are associated with worsened general health status and AF attributed symptom severity and that greater severity of depression and anxiety symptoms was associated with more frequent visits to seek medical attention for AF.

The effect of catheter ablation on quality of life and psychological distress has been evaluated in non-randomized studies. Sang et al (11), at 12- month follow up, of their cohort of paroxysmal AF showed significant reduction in depression and anxiety in 26.5% and 21.4% patients in the ablation group. They postulated that the improvement may have been from attainment of sinus rhythm which enabled them to be more physically active and subsequently regain a positive affective disposition and freedom from anti-arrhythmic drugs and anticoagulation and their consequent side effects. As discussed above we have also previously shown a significant improvement in psychological distress in patients undergoing AF ablation compared with a cohort having ongoing medical management. However, to date, there are no randomized studies comparing quality of life and impact on psychological distress between medical management and catheter ablation.

Neurocognitive function and atrial fibrillation:

The types and rates of complications that occur in patients undergoing radiofrequency catheter ablation (RFA) to prevent recurrent AF vary from series to series. The overall rate of major complications has been reported to be as high as 4 percent with vascular access complications being the most frequent (12) . The risk of stroke or TIA has been reported to occur in between 0.5 to 1.0% of patients (13). These events frequently arise from endocardial damage caused by ablation which may trigger thrombus formation despite use of anticoagulation.

Besides symptomatic embolic events, AF ablation also carries a risk of silent cerebral embolic lesions (SCE). Lickfett et al (14) first reported this in a small group of patients in their study by performing MRI before and after ablation. In a larger cohort Gaita et al (15) showed an incidence of 14% SCE on MRI scans post ablation compared to baseline imaging pre procedure. In this study the ACT value maintained during the procedure strongly related

to the incidence of SCE: 9% of patients with an ACT > 250 reported SCE following the procedure compared to 17% within those maintaining lower ACT values. Since these initial studies, numerous further studies have been undertaken. The reported incidence of SCI in these studies was variable and dependent both on the degree of intra-procedural anticoagulation and the type of ablation technology being used. Irrigated catheters and the Cryoballoon have a lower incidence than solid electrode catheters (15). When the procedural ACT is maintained consistently above 300, the incidence of SCI with irrigated catheters or cryoablation is approximately 5-10%. However, with the solid tip catheter event rates were between 30-40%. These latter catheters are no longer in use.

While these lesions have been described as "silent", pathology studies have demonstrated that they correspond to areas of endothelial and glial cell proliferation (16) and therefore may be associated with cognitive dysfunction. Thus, although the lesions disappear over time with repeated MRI imaging, they nevertheless are associated with pathological change. We have previously evaluated the prevalence of cognitive impairment after RFA in a study of 150 patients (17). 60 patients were undergoing ablation for paroxysmal AF, 30 for persistent AF, 30 for supraventricular tachycardia, and 30 matched AF patients awaiting RFA (the control group) all underwent eight neuropsychological tests at baseline and at 2 and 90 days after RFA. The prevalence of neurocognitive dysfunction at day 90 was 13, 20, 3, and 0 percent, respectively, indicating that AF ablation is associated with subtle neuro-cognitive decline.

On the other hand, it is also well recognised that AF itself is associated with various forms of dementia including both classical Alzheimer's disease and also multi-infarct dementia. In a registry that included 90 patients with paroxysmal and 90 patients with persistent AF, as well as 90 matched controls (18), cognitive impairment was significantly greater in persistent and

paroxysmal AF patients compared to controls. Observational studies have suggested that catheter ablation may reduce the risk of cognitive decline in AF patients.

Thus, it is unclear where the balance of cognitive risk lies.

To date there are no randomised studies of neurocognitive function comparing changes over time in AF ablation versus medically managed patients.

Hypotheses:

We hypothesise that:

1 There will be a high prevalence of psychological distress and suicidal ideation in a consecutive cohort of AF patients referred for management and consideration of catheter ablation.

2. That psychological distress relates to personality type.

3. That successful management of AF with catheter ablation will result in a significantly greater improvement in markers of psychological distress and neurocognitive function compared to ongoing medical management.

Methodology:

A total of 100 patients with AF referred to the arrhythmia centre at Royal Melbourne Hospital and Alfred Hospital for further management will be enrolled. Participants will undergo sequential randomisation on a 1:1 basis between medical management and catheter ablation. Concealment of allocation will be achieved by using sequentially numbered, opaque

sealed envelopes (SNOSE) scheme. The investigators will be blinded to the treatment allocation. The randomisation envelopes will be prepared by an independent statistician.

Inclusion criteria:

- Paroxysmal and persistent AF cohort who have failed 1 antiarrhythmic drug and are eligible for at least 2 antiarrhythmic drugs.
- Age 18-80y
- Able to give valid consent

Exclusion criteria:

- Severe valvular heart disease
- Patients treated for suicidal ideation
- Patients being treated for severe depression, anxiety or mood disorders
- Pre-existing neurological or clinically evident neurovascular condition
- Anticipated difficulty with neurocognitive assessment (deafness, language difficulties)
- Contraindication for systemic anticoagulation
- Patients who sustain a new cerebrovascular accident during study period
- Patients needing repeat ablations
- Rheumatic mitral valve disease
- Pregnancy

Baseline assessment:

A. Evaluation for potential exclusions and to allow accurate cohort assignment

a. All patients enrolled will undergo thorough history and physical examination at baseline to ensure they do not have any exclusion criteria. INR (International Normalized Ratio) results will be recorded for patients who are on warfarin to confirm therapeutic anticoagulation

b. Transthoracic echocardiogram: All patients a detailed echocardiogram will be performed to assess LV systolic function and rule out significant valvulopathy and strain variables of LA reservoir function. This study is clinically indicated in all patients with cardiac arrhythmias.

c. Transesophageal echocardiogram: All patients will undergo a trans-oesophageal echocardiogram pre-procedure to rule out left atrial clots which is clinically indicated prior to AF ablation.

B. Study specific assessments

a. Validated tools for the assessment and quantification of both overall quality of life and AF-specific quality of life will be administered in all patients:

i. SF-36 generic quality of life instrument:

SF-36 V2 consists of 36 items that assess eight health domains: physical functioning, role limitations because of physical problems, bodily pain, general health perception, vitality, social functioning, role limitations because of emotional problems and mental health. In addition to these eight subscales, physical component summary (PCS) and mental component summary (MCS) scores are also generated, which are normalised to an overall population mean of 50±10 (19). For all subscales, higher scores represent better functioning and QoL

ii. University of Toronto AF Severity Scale (AFSS):

The University of Toronto Atrial Fibrillation Severity Scale (AFSS) is a self-administered questionnaire that includes an instrument to measure the presence and severity of individual symptoms attributable to AF over a 4 week recall period, with 7 individual symptoms quantified on a 5-point Likert scale and higher values reflecting more severe AF symptoms (AFSS Symptom Score)

b. Validated tools for the assessment and quantification of personality type and a chronic anxiety state will be administered:

i. Global Measure of Perceived Stress Scale (PSS)

The PSS measures the degree to which life situations are appraised as stressful. Each item is scored on a 5-point Likert scale from 0 to 4, with higher total scores indicating greater perceived stress. The Cronbach α co-efficient of internal consistency is 0.85 and test-retest stability 0.85.

ii. Type D scale (DS-14)

The Type D personality denotes a high degree of negative affectivity and social inhibition in the underlying personality, and has been identified as a risk factor for adverse cardiovascular outcomes. It is a 14-item questionnaire, with each item scored between 0 and 4. Cronbach's α co-efficient of internal consistency is between 0.86 and 0.88.

c. Validated tools for the assessment and quantification of symptoms of anxiety and depression will be administered:

i. Beck Depression Inventory Short Form (BDI-SF-13):

This score is performed in order to specifically identify participants reporting thoughts of self-harm. Based on participant responses to these questions, all those reporting suicidal ideation will be assessed and referred as appropriate for further management.

ii. Hospital Anxiety and Depression Scale (HADS)

This features 14 items specifically designed to evaluate symptoms of anxiety and depression in medical populations, with minimal influence from somatic symptoms that may falsely elevate the scores. Cronbach's α for the full scale in cardiac patients is 0.89. Items are scored on a 4-point scale from 0 to 3, and an overall score provides a reflection of overall psychological distress, with a cutoff of ≥15 used to identify significant distress

d. All subjects will undergo neurological assessment at each study visit with the Mini-Mental State Exam (MMSE) and the National Institutes of Health (NIH) Stroke Scale.

e. Neuropsychological testing will comprise of 8 tests, based on the Canadian Study of Health and Aging, administered to all patients by a trained

interviewer (20). The results will be given as the number of correct answers or the time taken to complete the test. Testing will be administered at baseline, immediate post-procedure (within 24-48 hours) and at 3, 6, 9 and 12 months These tests include the following:

i. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Auditory Verbal Learning Test (Immediate and Delayed) requires patients to listen to a list of 10 words read to them by the examiner and then to immediately recall as many of those words as possible. This procedure is repeated three times with the same word list, with the order of word presentation changed on each occasion. After a 10-min delay filled with other cognitive tasks, patients must recall as many words from the word list as possible. The number of words recalled at this point is measured.

ii. Trail Making Task Part A requires patients to connect numbered circles in sequence as quickly as possible. The number of seconds required to complete the task is measured

iii. Trail Making Task Part B requires patients to connect a series of circles that contain a sequence of numbers and letters in the correct but alternating order (i.e., numeric and alphabetical). The number of seconds required to complete the task is measured

iv. Digit Symbol Substitution Test from the Wechsler Adult Intelligence Scale–Revised requires patients to reproduce on paper, within 90 s, as many coded symbols as possible in blank boxes beneath randomly generated digits, according to a coding scheme for pairing digits with

symbols. The number of boxes completed in 90 s is counted, and errors are deducted from this

v. Controlled Oral Word Association Test consists of presenting the patient with a letter and asking the patient to spontaneously generate as many words as possible for the given letter within 60 s. This task is repeated for three separate letters (F-A-S)

vi. CERAD Semantic Fluency Test requires patients to name as many words as possible from a predefined category (e.g., animals, clothing, first names) within 60 s. The number of words correctly named from the relevant category is measured

vii. Grooved Pegboard Test (Dominant Hand) requires patients to place 25 keyed pegs in an array of holes with randomly oriented slots using only their dominant hand. The number of seconds required to complete the task is measured.

viii. Grooved Pegboard Test (Nondominant Hand) requires patients to place 25 keyed pegs in an array of holes with randomly oriented slots using only their nondominant hand. The number of seconds required to complete the task is measured.

Follow- up

All patients will be followed up at 3, 6, 9 and 12 months with all neuropsychological testing repeated during each visit. Trans-thoracic echocardiograms to quantify LA reservoir function will be performed at 6 and 12 months. Changes in anticoagulation and medication regimens will be recorded.

Rhythm and AF burden assessment: This will be performed either via continuous intracardiac monitoring (ICM) using an implantable loop recorder (Reveal LINQ™, Medtronic) or a pre-existing dual chamber device; or via twice daily monitoring with the KardiaMobile™ (AliveCor, USA) ECG monitoring device. If none of these options was feasible, 24-hour holter monitoring was performed at 3, 6 and 12 months during follow up, and if symptoms occurred.

Outcomes measures:

Primary outcomes will include between group comparative analysis of:

1. Hospital Anxiety and Depression Scale (HADS) during follow up.
2. Cognitive ability as assessed by results of Trial Making tests A and B.
3. SF-36 score during follow up.

Secondary outcomes will include between group comparative analysis of:

1. Beck Depression Inventory score.
2. University of Toronto AF symptom severity Score.
3. Perceived Stress Scale Scores
4. Consortium to Establish Registry for Alzheimer's Disease (CERAD) Auditory Verbal Learning test.
5. CERAD Semantic Fluency Test
6. Grooved Peg Board Testing in Dominant Hand
7. Grooved Peg Board Testing on Non-Dominant Hand.
8. Symbol Digit Modalities Testing
9. Mini-mental State examination.

10. Left atrium reservoir function assessments on strain imaging and parameters on echocardiogram.

Statistical analysis:

Categorical variables will be reported as count and percentages, while continuous variables as mean and standard deviations (SD). Continuous outcomes at each endpoint can be analysed using a 2-sample t-test. However, a more comprehensive analysis of continuous outcomes, including additional explanatory variables will be based on a mixed linear model with the participant as the random factor and treatment, site and time as fixed factors. 95% confidence intervals (CI) will be reported. A p-value <0.05 will be considered significant. All analyses will be based on an intention-to-treat model.

Mean treatment differences between groups at baseline and at each follow-up period can be estimated from this model.

Based on our previous results from a non-randomised study looking psychological distress in patients with atrial fibrillation, the average HADS score (score range 0-21) was noted to be around 11 (in the abnormal range) in this cohort. A useful clinical effect of catheter ablation would be to reduce the mean HADS score to the normal range – the upper limit of which is 7. This corresponds to a mean difference of 4 points. Using this mean difference, and assuming a standard deviation of 5.5, in order for the study to reach a power of 80% with type 1 error of 5%, a minimum of 31 patients will have to be enrolled in each arm.

Sample size calculations were also considered for several other measures, using power of 80% and type I error rate of 5%. These are shown below, with the assumptions about the means and standard deviation in each arm. In cases where the standard deviations differ between arms, the higher value was used for the sample size calculation.

302 Background data considered in sample size calculations are shown in the table below:

Outcome measure	Untreated		Treated		Scale range	SD (either)
	Mean	SD	Mean	SD		
AFSS (pilot study at Melbourne Health)	9.7	1.0	2.2	1.8	0-35	
BDI [21]	17	9.7	5.4	3	0-63	
SF-36 v2 (PCS) [22]	43.8	10.7	47.0	11.0		
SF-36 v2 (MCS) [22]	44.3	12.1	49.8	9.1		
Trail Making test A [23]	50.9	9.9	47.4	9.8		
Trail Making test B [23]	318.9	66.9	279.4	63.8		

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304 The table below shows the sample size calculated for each of the additional outcomes
305 considered.

Outcome measure	Untreated (means)	Treated (means)	SD assumed in each arm	Sample size in each arm
AFSS	10	3	8.75	26
BDI II	20	10	7.5	10
SF-36 v2 (PCS)	48	54	11	54
SF-36 v2 (MCS)	44	50	10	44
Trail Making Test A	51	45	9	37
Trail Making Test B	320	280	65	43

A sample size of 50 participants in each arm would be sufficient for all scores except for the subscale of SF-36 v2 where-in this sample size would be suitable for detecting an effect of the order of 7 points.

Significance of proposal:

The association between psychological distress and AF burden is strong. This study will provide insights into the clinical spectrum and predictors of psychological distress in patients with atrial fibrillation. This study will also be the first of its kind to assess in a randomised fashion the impact of catheter ablation in neurocognitive function of patients with atrial fibrillation follow up till one year. More importantly, we will able to assess the response and improvement of this distress with appropriate and timely management. Comparing improvement of quality of life between medical management and catheter ablation may be a genuine way of evaluating clinical outcomes. Traditional parameters, such as survival, healing or regression of disease, are not always sufficient ways to evaluate different treatments. The correlation between physical health and wellbeing can be rather weak. Considering this, there is an increasing demand to find new criteria to evaluate risks and advantages with new treatments focusing on the patient's subjective view. Should a significant improvement in HRQOL be with catheter ablation, it will help define priorities and arrange new care programs with limited waiting periods for these elective procedures. Because of the limited resources in health care, there is also a need for instruments that assess the effectiveness of various treatments.

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