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Atrial Fibrillation Lifestyle Project

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Proposal**: ATRIAL FIBRILLATION LIFESTYLE PROJECT (ALP)**

Rationale

Atrial fibrillation (AF) is a chronic progressive disease characterized by exacerbations and remissions. It remains the most common sustained arrhythmia seen in clinical practice, and represents a major burden to healthcare systems (1,2). Current evidence indicates that the overall prevalence of AF is in the range of 1-2% of the general population, with a prevalence that increases significantly with age (from 1-4% at 60 years to 6-15% at 80 years) (1,2). In addition to reductions in quality of life, functional status, and cardiac performance, patients with AF have a five-fold increased risk of stroke and doubling of risk of overall mortality (3–5). As a result, AF imposes a significant economic burden on health care systems, with the direct costs of AF management accounting for approximately 1% of total healthcare expenditures (4,6).

The contemporary management of AF is centered on a reduction in the morbidity and mortality associated with AF (*i.e.,* the prevention of tachycardia-induced cardiomyopathy, and stroke or systemic thromboembolism), as well as on symptomatic improvement with consequent reduction in AF-related emergency room visits or hospitalizations (7). The majority of patients have AF that is not associated with severe heart valve disease, termed non-valvular atrial fibrillation. Sixty percent of cases of non-valvular AF are associated with other modifiable risk factors, including: obesity, diabetes, hypertension, or sleep apnea (8). Treating modifiable risk factors has been shown to improve morbidity and mortality in patients with AF. For example, treatment of hypertension improves survival in patients with AF by 7.8% over a five-year period (9).

Hypertension, obesity, and diabetes are associated with left ventricular diastolic dysfunction, increased left atrial pressure and increased left atrial volume (10). Left atrial volume is a marker of risk of AF. The longer one is in AF, the larger their left atrial volume becomes and the higher their mortality (11,12).

Current state of knowledge

Treatment of AF with antiarrhythmic drugs or catheter ablation has not been shown to improve survival (13–15). The AFFIRM study enrolled 4,000 participants where half received a 'rhythm control strategy' using antiarrhythmic medications in attempts to maintain sinus rhythm, compared to participants who used medication to control heart rate, but accept AF. In this study, the maintenance of normal sinus rhythm was approximately 50% over five years for antiarrhythmic drugs and no survival benefit was shown. Catheter ablation is initially 70% effective at maintaining sinus rhythm, but over a five-year period approximately 50% of participants have reverted back into AF (14,15). These trials, however, did not focus on treating underlying modifiable cardiovascular risk factors.

Recently, small cohort studies combining exercise, diet, and antiarrhythmic medications and/or ablation have shown improvements in cardiovascular risk factors *and* reduction in AF symptoms and frequency (16–18). In the Arrest-AFIB study (19), 69 patients participated in risk-factor modification following AF catheter ablation. They were compared to 88 controls that declined the risk-factor management program. Cardiovascular risk factors in the intervention group were modified according to American Heart Association guidelines. Targets included 10% body weight loss, disordered sleep management, along with blood pressure and glycemic control. Once targets were achieved, participants were prescribed 200 minutes of moderate intensity exercise per week. In the intervention group, 10% were lost to follow-up with mean intervention time of 3.5 years. After multiple ablations, 87% of the participants in the risk factor modification group, compared to 48% of the control arm participants, maintained normal sinus rhythm (19).

Higher levels of physical activity (PA) and cardiorespiratory fitness is associated with an improved cardiovascular risk factor profile, a reduction in all-cause mortality and cardiovascular events, as well as a decrease in the incidence of AF (21-25). Moreover, there is strong support for the efficacy of exercise-based rehabilitation in reducing cardiovascular and total mortality, and number of cardiovascular procedures in patients with coronary artery disease (22). Malmo and colleagues (26) enrolled 51 participants in a three-month program of high-intensity aerobic and interval training and showed a reduction in AF and improvement in cardiovascular risk factors.

The Legacy trial investigated the effects of diet intervention (20). The study followed 355 participants with Body Mass Index (BMI) 27 kg/m^2 or greater that participated in a weight loss program; 38% of the participants sustained a weight lost 10% of total body weight or greater. Greater than 10% weight loss resulted in a six-fold reduction in the recurrence of AF and improved cardiovascular risk factors compared to those who lost less weight and whose weight loss fluctuated (20).

Obstructive sleep apnea (OSA) is known to be highly prevalent in AF (27). A meta-analysis looking at both cohort and randomized trials of continuous positive air pressure (CPAP) for OSA in patients with AF resulted in a 42% low risk of AF recurrence (28). Thus, CPAP treatment for moderate or greater sleep apnea combined with exercise and diet may improve AF outcomes.

A major limitation of previous AF trials is lack of randomization and short duration of follow-up. In addition, no studies have investigated an intervention program that combines supervised exercise sessions, regular, structured diet and lifestyle education sessions, and risk factor management. There have been no meta-analyses on the effects of exercise and diet on AF symptoms given that there exist only a handful of studies to date. A Cochrane review (29) of randomized controlled exercise interventions in AF patients reported no differences in mortality and quality of life, and reported only small differences in exercise capacity, but the review did not evaluate symptom severity of AF nor did they measure reductions in risk factors commonly associated with AF. The review suggested a need for more randomized clinical trials (given that only six were included in this initial review) (29). Not only are there very few lifestyle intervention studies on AF, no studies have compared a structured in-hospital diet and exercise program *versus* a home-based exercise and diet program. We do not know whether positive effects are sustained once supervised interventions are terminated; nor do we know the necessary intensity to achieve and sustain target reduction in cardiovascular risk, left atrial remodeling, and AF burden.

Richmond Hospital has successfully run a Cardiac Rehabilitation program for over 20 years. The 8-week program includes supervised exercise sessions (two per week), in conjunction with diet and stress management classes (one each per week). The program has reported low voluntary dropout rates (*e.g.*, two dropouts of 100 patients in the last six months of the program). At present, cardiologists do not typically refer patients with AF to cardiac rehabilitation. For the current project, during the first six months (Phase 1) we plan to extend the duration of the existing Cardiac Rehabilitation exercise program to three months and we plan to use moderate to high intensity interval training combined with resistance exercises as per current literature in exercise and patients with AF. In addition, study participants will receive a heart rate and step tracker to guide intensity and duration for a home-based walking program and will maintain a minimum of 10 to 20 minutes of total body resistance training at home.

Richmond also has a successful bariatric surgery program where 200 patients per year are treated first with diet therapy, followed by mainly laparoscopic sleeve gastrectomy. Similar to the Legacy study described above, we will enroll participants with BMI greater than or equal to 27 kg/m^2 in a diet intervention run by dietitians from the Richmond Bariatric program. The goal of the nutrition component will be to reduce total body weight by at least 10%. The diet intervention will be an individualized, healthy diet program promoting reduced carbohydrate content, smaller portions, and mindful eating (30). During months six to twelve of the intervention (Phase 2), participants will continue with a home-based aerobic exercise program combined with resistance training that was learned in the hospital cardiac rehabilitation program. Participants will monitor their sessions using the heart rate and step tracker along with self-reported exercise logs. Motivated participants are free to join a community gym. The individual exit diet counseling will encourage participants to follow the final diet prescribed.

AF is a symptom of underlying cardiovascular risk factors and a marker of increased mortality and morbidity. We need to shift our focus to the treatment of these underlying risk factors in patients with AF. Diet, exercise, and risk factor management can be used to modify these risk factors both in the short term, and potentially with sustained effect. This study employs a randomized design to test a six-month supervised intensive exercise, diet, and risk factor management program, followed by a six-month home-based exercise and diet program. Based on previous studies, we hypothesize that this should lead to an improvement in cardiovascular risk factors, a reduction in AF burden, and possible improvements in left atrial remodeling.

3. Hypotheses:

i) Patients with paroxysmal non-valvular AF that complete a supervised six-month program of exercise, diet, and life style modification will exhibit reduced recurrent AF and reduced cardiovascular risk factors when compared to a similar group of patients who receive usual care.

ii) The intervention group will show improvements in physical fitness, cardiovascular risk factors, and AF symptoms and severity at both the six-month and one-year follow-up assessments compared to the usual care group.

iii) A reduction in medication costs and emergency room visits will help offset the cost of the intervention.

4. Objectives: The objectives of this study are to demonstrate changes in symptoms and severity of AF following an exercise, diet, and risk factor modification intervention in patients with AF. Demonstrating that a comprehensive cardiac rehabilitation program is feasible and cost-effective will help us design a future larger-scale, multi-centre study.

i) **Primary outcomes include:**

a. Burden of AF, including both frequency and symptoms.

i. The frequency of AF will be measured with 48-hour Holter monitor recording, looking at percent of time in AF at baseline, six months and one year follow up.

ii. Symptoms of AF will be assessed using the Canadian Cardiovascular Society Severity in Atrial Fibrillation Scale (CCS-SAF) (31), and the Atrial Fibrillation Symptom Severity Scale (AFSS) (32); both are validated tools to assess burden of AF symptoms.
iii. The 36-item Short Form Survey Instrument (33) and the EQ-5D-3L (34) will be used to measure quality of life.

ii) Secondary outcomes include:

a. Left atrial remodeling will be measured by LA volume index, diastolic function grade, and estimate of LA pressure via echocardiography at baseline and one year follow-up.
b. Cardiovascular risk factors will be compared at baseline, six months and one year. These include: Systolic Blood Pressure, Hemoglobin A1C (marker of average blood sugar over 3 months), body mass index, waist circumference, and low density lipoprotein (LDL cholesterol), apnea hypopnea index (AHI), and fitness classification (metabolic equivalents (METS) achieved on exercise stress test).
c. Using pharmanet data, total cost of all medications and specific cost for antiarrhythmic agents, antihypertensive agents, diabetes and cholesterol lowering medications will be recorded and compared at baseline and one year. Hospital Emergency visits will also be compared.

5. Methodology

5.1 Proposed Study Design: This is a parallel-group randomized controlled trial. Consecutive patients meeting eligibility criteria that are seen for routine cardiology follow-up, or those referred by family physicians, will be invited to participate in this study. Patients who accept the possibility of a year-long diet counseling and exercise program will be randomized and stratified to 'control arm' *versus* 'intervention arm.' Forty patients will be randomized to control arm and 40 patients randomized to the intervention arm. Intervention will include Phase 1, a six month program including three months of diet counseling combined with home exercise, followed by three months (starting at week 13) of an in-hospital, Cardiac rehabilitation exercise program. Phase 1 also includes risk factor management by an internist who specializes in cardiovascular risk factors. Phase 2 of the intervention will include six months of home-based maintenance exercise and diet (starting at week 25). Assuming approximately 40% of eligible patients agree to participate (based on our experience that there is a high willingness to participate in both research studies and the cardiac rehabilitation program), and given that we were able to recruit 200 research participants in one year for a previous study (35), we estimate that it is feasible to recruit a total of 80 participants over a three to six month period.

5.2 Participants: Patients will provide written, informed consent. All study procedures will be reviewed and approved by the UBC Clinical Ethics board and the VCH operational approval process.

Inclusion Criteria: Patients with paroxysmal, non-permanent, non-valvular AF who have a BMI ≥ 27 kg/m^2, or central obesity using abdominal circumference with ethnicity-specific values recommended by Canadian diabetes association (36); plus one of hypertension, diabetes, moderate or severe sleep apnea, or consumption equal to or greater than three glasses of alcohol per day. Participants must be over 18 years of age and under 75 years.

Exclusion Criteria: Patients with permanent AF, estimated survival less than 2 years, left ventricular ejection fraction < 40%, and/or prior cardiac valve surgery. Other exclusions include: inability to walk on a treadmill, defibrillator, entry exercise test positive for ischemia (37), and/or absolute and relative contraindications to exercise testing (37).

5.3 Study Procedure: All participants will undergo baseline, maximal effort exercise testing described in data collection section 5.4. Peak heart rate (HR_{peak}), total METS, and Borg rating of perceived exertion scale will be recorded (37). Maximal exercise tests will be repeated at six months and one year in all participants. All participants in the intervention and control arms will be screened for obstructive sleep apnea with a home sleep apnea test (level three study). Dr. Ahmed (Respirologist at Richmond hospital) will assess any patients with at least moderate sleep apnea, an apnea hypopnea index over 20. Dr. Ahmed has expertise in sleep apnea and is a co-investigator of this study. CPAP will be recommended and for one year for patients with apnea hypopnea index of > 30, or > 20 with excessive day time sleepiness. CPAP machines will be loaned by the sleep clinic to patients who do not have insurance coverage for one year. LA volume index, pressure and grade of diastolic dysfunction will be measured by echocardiography at baseline and one year. The same technician will perform all echocardiograms using the same echocardiogram machine, and one cardiologist blinded to participant's study arm will review the results.

5.3.1 Control Arm: Participants will receive usual medical therapy for AF as per Canadian Cardiovascular Society Guidelines.(7). Participants will continue usual follow up by family physician and cardiologists. Participants will receive a step tracker and a handout from the American Heart Association regarding Guidelines for Physical Activity (*Note:* AHA have easy to understand physical activity guidelines, along with infographics on their webpage; the

Canadian Society does not have material that is accessible to a lay audience). Details are provided in the exercise prescription document, briefly; the AHA recommends 30 minutes of moderate intensity activity five days a week, totaling to 50 minutes per week).

5.3.2 Intervention Arm: Participants randomized to the intervention arm will receive a combination of supervised diet and exercise sessions over a six-month period in addition to usual medical therapy for AF as per Canadian Cardiovascular Society Guidelines (7) and risk factor management by an internist who specializes in cardiovascular risk factors.

For 6 months participants will visit Richmond hospital for all sessions of Cardiac Rehabilitation, diet, and stress management classes, along with any recommended consults with the internist.

Intervention Arm Phase 1a: Three-month dietary counseling program will include:

1. Week 1: Initial 60-minute individual consult with dietitian.
1. Weeks 2 -13: 1-hour nutrition group class (groups of 10-20). See section 9 of application for description of topics and evidence to support curriculum. Some of the classes will be devoted to cognitive behavioral therapy, and four classes will be devoted to stress management (lead by a psychologist). Given the association between stress and hypertension, (39) stress management may also be beneficial in reducing modifiable risk factors.
2. Week 24: Final 60-minute individual consult with a dietitian.

Intervention arm Phase 1b: Six-month exercise program (weeks 1-24) will include:

2. Week 1: 60 minutes individualized intake session with cardiac rehabilitation exercise specialists.
3. Weeks 2 to 52: Home exercise walking program: This will be recorded using a step tracker. Individual participant exercise prescription will be based on baseline exercise stress test (a modified Bruce protocol (38), supervised by cardiologist; these are a standard part of patient care and done regularly at the PI's cardiology clinic and at Richmond Hospital). Exercise stress test results provide information regarding target peak HR, METs and individual limitations. A positive stress test would be a result that would exclude a participant from the trial. The HR_{peak} will be used to prescribe target intensities during the supervised exercise component (described below). A minimum of 30 minutes five days a week of moderate aerobic activity will be the goal during the first three months of the home exercise program (participants will build towards this goal by following a structure home-based exercise plan, detailed in section 9 of ethics application "exercise prescription"). Participants will maintain a log of their daily exercise routines (included section 9, "exercise prescription").
4. Week 13 to 24: Three-month Cardiac Rehabilitation Program at Richmond hospital: Participants will exercise for one hour twice weekly at Richmond Hospital Cardiac Rehabilitation Centre. Participants can choose a cohort that participates in am or evening and or weekend classes to accommodate work schedules. Participants will exercise using a combination of aerobic – interval training following methods informed by Malmo's (26) study, combined with whole body resistance training using an elastic band (Theraband ®). Details regarding exercise prescription are shown in section 9 of the ethics application. There will be a maximum of 10 participants per exercise session with two instructors. For the first two weeks, three additional research assistants will be present to ensure a 2:1 ratio of participants to study team member. Having additional facilitators will help participants become familiar with the equipment and will make the interval transitions easier to manage during those first four classes. After this orientation phase, participants should be able to manage their intervals with less assistance and two trained cardiac rehabilitation experts should be sufficient. The aerobic machines are state of the art and exercise prescription (target heart rates and workload) will be based on initial cardiologist-supervised baseline exercise test, personal limitations, and progress during home program. A nurse and physiotherapist trained in cardiac rehabilitation will supervise patients. Staff will monitor blood pressure, heart rate, and rating of perceived exertion (using Borg's 10-point scale) at each session in addition to weekly body weights in order to ensure participants are meeting target exercise intensities (data sheet in section 9 of ethics application).
5. Week 13-24: Home-based exercise program supplement. In addition to the in-hospital, supervised exercise program, participants will be prescribed individualized home exercise regimes. These will increase incrementally as the participants proceed through the program. Participants will maintain a log of their daily exercise routines and track steps and heart rate with a step tracker.

Phase 2: Intervention Arm: Six month home-based diet and exercise program (weeks 25-52) will include:

1. Home based with step/activity tracker to track steps and HR (along with participant exercise log).

2. Check ins from research assistant by phone if participant's exhibit a significant reduction in physical activity detected by the step tracker. Participants will be informed that data from their step trackers will be downloaded regularly to monitor daily steps and intensity of activity (based on HR). No other data can be monitored through the step tracker. If a participant's activity drops 50% below the previous month's average over a two-week period, the research assistant will telephone the participant to ensure equipment is working properly, to discuss barriers, and to encourage them to maintain the fitness regime.
3. An optional weekly walking group will be available for participants (leaving Minoru park) to encourage adherence.

Treatment of Obstructive Sleep Apnea (OSA): This will involve the same treatment offered to the control arm (see section 5.3, above).

A six-month exercise program that begins with low-intensity exercise, followed by a three-month supervised interval training should be sufficient to effect changes in modifiable risk factors including BMI, blood pressure, and glycemic control. It should also be sufficient to lead to increased exercise capacity. A meta-analysis on cardiofit exercise programs in older adults reported an average of 23 weeks in length resulted in significant improvements in cardiorespiratory fitness (40). Months six to twelve will test the efficacy of a home-based program and investigate whether the results at six months are sustained at one year.

5.4 Data Collection

All measurements (save demographics and medical history) will be collected at baseline, six months, and one year in both groups.

1. Patient demographics: age, sex, ethnicity, education, income, and living situation.
2. Medical history: medications and cost; hospital emergency visit and admission < 1yr, known coronary artery disease defined by prior myocardial infarction or presence of 50% stenosis on CT or invasive angiogram; admission for heart failure, prior stroke; average daily glasses of alcohol, smoking status (including frequency and amount); the Canadian Cardiovascular Society Severity in Atrial Fibrillation (CCS-SAF) Scale, (31) the Atrial Fibrillation Symptom Severity Scale (AFSS) (32), the 36-item Short Form Survey Instrument (33) and the EQ-5D-3L (34).
3. Anthropometrics: Body mass index (BMI), waist circumference, neck circumference, modified mallampati score (41) and blood pressure.
4. Blood work: Hemoglobin AIC, total cholesterol, creatinine, low-density lipoprotein, high-density lipoprotein, triglycerides, ALT, c-reactive protein, electrolytes, and brain natriuretic peptide.
5. Level 3 home sleep study: Apnea-hypopnea index, minimum saturation, and time spent with saturation < 90%, Epworth Sleepiness Scale (42).
6. Godin's leisure time physical activity measure will be used measure baseline physical activity levels (43).
7. Exercise Stress Test at maximal effort: Maximum METs achieved, peak heart rate, and rating of perceived exertion.
8. 48-hour Holter monitor: 48-hour heart rhythm monitor to determine frequency and duration of AF measured as the percent of time in AF.
9. Echocardiography at base line and one year: measurements: LA volume, LA pressure, diastolic function, grade, calculated biplane LVEF, and left ventricular hypertrophy.

All data sheets are attached in section 9 of the application. There is a data sheet for each: sleep study, echo, blood work, stress test, physical exam, and Holter monitor.

5.4 Data Analysis (and sample size)

This is a parallel, randomized control study. The researcher analyzing results will be blinded to the patient's group. A statistician will be hired to analyze data and a statistician from C2E2 (UBC) has reviewed the study design. Normally distributed data will be analyzed using repeated measures analysis of variance (ANOVA) to calculate changes over time (baseline, six-months, one-year) within each group. Between groups analyses on differences from baseline will be analyzed using independent *t*-tests. Statistical significance will be set *a priori* as $p<.05$. Continuous variables will be described by group using mean (SD) (or median (P25, P75) if the data are skewed); and categorical variables will be described by frequency (percent).

To calculate effect size for the intervention group, we considered the moderate effect sizes reported in exercise studies measuring cardiorespiratory changes (e.g., Huang et al. (2016) (40) reported a moderately high effect size of 0.64 for aerobic changes following an exercise program in older adults). Using G-power software (*alpha* = .05), the

sample size required to achieve 80% power to detect an effect is 22 per group (two-tailed, or repeated measures design) (44). Based on the data from Malmo and colleagues (26) reporting a large effect size (1.0) for the difference in time spent in AF pre- and post-exercise, a sample size of less than 10 participants would achieve a power of 80%. The AF studies to-date report low attrition rates. For example, Pathak et al. (19) reported 10% attrition in the risk factor intervention group, and Malmo et al.(26) reported a 0% attrition in the three-month interval-training program. Given that the Richmond Cardiac Rehabilitation program similarly reports low drop-out rates (of approximately 2%), we have allowed for greater than 10% attrition. Including 40 participants in the intervention arm, and 40 participants in the control arm will allow for more than 10% drop out while still maintaining adequate power to detect an effect.

6. Summary and Impacts on Practice

Richmond has experience in recruiting patients with AF, cardiac rehabilitation, and bariatric diet therapy program. Our Richmond team of specialists, combined with strong partnerships with our colleagues at VGH that have experience with research trials will help guide us in implementing a successful research project.

This study uses a reproducible intensive supervised cardiac rehabilitation program that includes exercise, diet, and risk factor modification for patients with paroxysmal, non-valvular AF. We expect that a six-month intervention will show significant improvement in fitness and weight loss and improvements in AF symptoms and frequency, and cardiovascular risk factors when compared to a control group with paroxysmal AF and similar baseline characteristics who do not receive a supervised diet and exercise program. The supervised program is followed by a six-month home-based exercise and diet program, which gives us the opportunity to look further at adherence, and whether the benefits of the six-month intensive hospital-based program can be sustained at home. A follow-up study could retest the baseline results at two years and up to five years if effects are sustained. If both the phase 1 cardiac rehabilitation and diet six-month program and phase 2 home-based program are successful, then this study could be repeated with only a home-based or community-based intervention as a lower cost alternative.

The missing piece in studies of antiarrhythmic therapy and catheter ablation for patients with paroxysmal AF is the inclusion of risk factor modification. With attention to diet, exercise, and cardiovascular risk factor modification it should be possible to obtain high rates of maintenance of normal sinus rhythm. This exercise, diet and risk factor modification model can be added to usual care or catheter ablation aiming for optimal five-year reduction in AF. Alternatively patients could be randomized to diet and exercise, versus usual care post-catheter ablation. In future trials, a loop recorder could possibly be implanted to give more accurate information of AF recurrence rates.

Future studies with longer follow up can also focus on a more robust cost benefit analysis. Demonstrating that an exercise and diet intervention is cost-effective and efficacious in reducing the burden of AF can potentially be used to encourage government funding and physicians to prescribe exercise and diet to all patients with paroxysmal AF. Ultimately a large, multi-centre trial that combines exercise, diet, and risk factor modification in patients with paroxysmal AF compared to usual care can be designed to determine whether this intervention reduces mortalisty, cardiac events, and stroke.

Dissemination plans:

We plan to submit an abstract summarizing the mid-point study results in hope of an oral presentation at the Canadian Cardiovascular Congress October 2019. We then plan to write a research paper and publish our results (regardless of the direction of our findings) in the Canadian Cardiovascular Society Journal (the Canadian Journal of Cardiology).

Dr. Orenstein presented the background and research plan at Internal Medicine rounds Richmond Hospital in November, 2017 and will present the background research and study proposal and methods at Grand Rounds Richmond Hospital in June 2018. Once the results are completed Dr. Orenstein will present again at Internal Medicine Rounds Richmond Hospital. Dr. Andrade and or Dr. Isserow will have the opportunity to present the results at VGH Cardiology rounds.

If we observe significant improvements in AF risk factors, we plan to apply for funding through the Heart and Stroke Foundation's "Grants-in-aid" program to support operating costs of a larger scale (longer duration) study on exercise, diet, and lifestyle intervention in patients with AF

The final study results will be reported after completion of one-year follow up.

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