Feasibility Study to Improve Atrial Fibrillation Outcomes Using a Digital Application for Cardiovascular Risk Reduction: Precursor to a Multicenter Randomized Trial

Study Protocol and Statistical Analysis Plan

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Purpose

An effective intervention to support cardiovascular risk factor (CVRF) reduction in individuals with AF that can be easily provided with existing resources does not exist, despite the evidence that even though CVRF reduction has been shown to decrease AF symptom severity and burden. The digital application, AF CARE, has been specifically designed to fill this critical need to support CVRF reduction in individuals with AF, and can be easily incorporated into the care delivered to individuals undergoing AF catheter ablation (CA), but its feasibility is unknown. Demonstrating that an available digital application can improve AF outcomes would be significantly impactful.

The specific aims of this study are to: 1). Test the feasibility of AF CARE in terms of acceptability, demand, usage, adherence, and integration (1), and 2). Determine the efficacy of AF CARE based on the pre-post assessment of CVRF (LS7 and/or blood tests), AF knowledge, AF Symptom Severity and Burden (AFSS), and QOL assessment at baseline, 3, and 6 months in the AF CARE group compared to the usual care (UC) group to provide estimates of effect size.

Background and Significance

Atrial fibrillation (AF) is the most common cardiac arrhythmia disorder in the United States, contributing to a five-time greater risk of stroke and is independently associated with increased mortality (2,3). Predictions of doubling the AF population is based on aging and increased prevalence of cardiovascular risk factors (4). A predicted lifetime risk of AF rises from 20% to 33% with the addition of a single elevated CVRF (4,5,6). Innovative interventions that promote the reduction of CVRF are needed to decrease AF symptom severity and burden.

Current AF treatment guidelines include CVRF reduction, and when reduced in a randomized group, particularly weight loss, there was a significant reduction in AF burden and AF symptoms compared to those who received usual care (7,8). A maintained weight loss of at least 10% contributed to the greatest reduction in AF symptoms and AF burden (9). While AF CA procedures significantly reduce AF symptom burden (10) and decrease AF associated mortality and morbidity (11), recurrences resulting in increased morbidity and mortality persist (12). Altering the disease substrate with CVRF reduction and modifying the electrical substrate with CA procedures has shown an improvement in post-AF ablation outcomes, with less AF symptom severity/burden (13,14).

Lifestyle modifications to reduce CVRFs are difficult. There is no consensus on which intervention for CVRF reduction is most effective (15), nor what delivery mode is most acceptable. The American Heart Association (AHA) Center for Health Technology and Innovation collaborated with the Stanford Center for Digital Health and PatientBond, a digital technology software company, to design a personalized digital application (app) that can be accessed via a smartphone, iPad, or personal computer (16). This digital app, AF CARE, delivers patient-specific messages to promote behaviors that will reduce

CVRF and improve AF knowledge, based on each individual's responses to 12 psychographic questions, 12 AHA Life's Simple 7 (LS7) questions, and specific biometrics. To date, the utility and effectiveness of AF CARE to reduce CVRF has not been tested.

Research Design

Phase I will be completed prior to randomization on 10 individuals with AF who will be asked to participate in interface testing of the digital platform for 1-3 months to identify potential programming modifications to enhance usage and adherence.
Then, the primary aim of Phase II of this study will be to determine feasibility of utilizing AF CARE to provide lifestyle modification support to patients with AF. The secondary outcome will be to compare the CVRF, AF knowledge, AF Symptom Severity and Burden, and QOL between and within the UC group and the CARE AF group. This feasibility study will use a prospective, RCT wait list design to allow for the determination of effect sizes to inform the power calculation for a multi-center trial, if found to be effective. (Phase I).

a. Sample: Sixty patients undergoing treatment for AF at Stanford Health Care.
Inclusion: ≥18 years old, BMI ≥ 28 kg/m^2 AND one additional CVRF, access and willingness to engage in digital technology, has a valid email address and a cell phone number, and able to ambulate and speak/read English
Exclusion: Class III/IV heart failure, MI or cardiac surgery in prior 3 months, severe renal/hepatic disease, active malignancy, current/recent (within 6 months) enrollment in weight loss program.

b. Participants will be recruited when they are being followed for the management of their atrial fibrillation in the Stanford clinic..

c. Procedure: Individuals meeting inclusion criteria, but not excluded, will be invited to participate. Once consented, demographics, biometrics and baseline measures will be collected. Both groups will be asked to enter initial responses into AF CARE and then will be randomized to either the digital platform AF CARE group and UC or Wait List Group. The UC wait list group will receive usual care for the first 3 months and then they will receive the digital platform (AF CARE) after 3 months of enrollment. Both groups will be appropriately referred for smoking cessation, behavioral medicine, endocrinology, and/or sleep clinic during initial and Month 3 visit, based on screening completed at that visit. Initial measures will be collected, and repeated at Month 3, Month 6, and Month 12.

Both AF CARE/UC and Wait List Groups	Initial	Month 3 (CA)	Month 6	Month 12
Medical History and Physical	X	X	X	X
Demographics	X			
Psychographic score	X			
AHA Life's Simple 7	X	X	X	X
Biometrics- pt reported (BP, HR, RR, waist, BMI)	X	X	X	X
Blood testing, if available: Lipid panel, Blood Sugar	X		X	X
6 Minute Walk Test	X	X	X	X
Jessa AF Knowledge Questionnaire	X	X	X	X
AF Symptom Severity Scale (AFSS)	X	X	X	X

Ambulatory Monitor (Zio patch)- if available	X	X	X	X
AF Effect on Quality of Life (AFEQT)	X	X	X	X
AF CARE Group -Access to AF CARE	X----------→			
Wait List Access to AF CARE		X----------→		

AF CARE GROUP: Patients will receive personalized messages twice weekly that will include behavior recommendations for CVRF reduction and AF education from the AHA library. Messages will be patient-specific based on the initially entered psychographic profile and data entered. Ongoing messages will include participant response requests and future messages elicited by AF CARE will be based on entered responses. During the protocol, 3 participant non-responses to communications will result in a message being sent to the research team to prompt a call to the participant to enforce the importance of the messaging. In addition, a participant posting a negative response (e.g."I do not know how to get my medicine refilled") will also result in a message being sent to the research team to determine if clinical follow-up is required.

Wait List **UC Group/AF CARE Group**: Participants will be given a weight loss goal of 10% and other recommendations for CVRF reduction based on their initial LS7 assessment. They will be provided written educational materials to review independently on AF and AF CA treatment. Participants in this group will receive personalized messages twice weekly that will include behavior recommendations for CVRF reduction and AF education from the AHA library starting at 3 months following randomization. Measurable Outcomes: (See Table above).

a.CVRF will be evaluated using the pre-post measures of the AHA Life's Simple 7, along with patient reported blood pressure, BMI, blood tests (lipids and glucose), and 6-minute walk test.

b.AF knowledge will be evaluated with the Jessa AF Knowledge Questionnaire

c.AF Symptom Severity and Burden will be measured with the AF Symptom Severity Scale

d. QOL will be measured with the AF Effect on Quality of Life Questionnaire, and the Patient Health Questionnaire-9

Data Analysis: Demographic data will be analyzed using descriptive statistics for continuous data and frequencies and percentages for categorical data.

The feasibility of AF CARE will be determined by calculating acceptability, demand, AF CARE usage, adherence, and qualitative interview data analysis.

Efficacy will be evaluated on CVRF, AF Knowledge, AF symptom severity and burden, and QOL using matched pair t-tests at baseline, 3 and 6, and 15 months to determine the differences between and within groups. This data will be used to calculate the sample size required in a future multicenter trial designed to achieve 80% power to detect a change of 10% from baseline.

d. Potential Pitfalls: Data integrity is an issue for self-reported measures in the usual care group. The level of usage with the AF CARE plan may be suboptimal or AF CARE may be ineffective in meeting study aims.

e. Sustainability: Sustainability will be determined by participant engagement and efficacy.

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