Dynamic Data-Driven Management of Atrial Fibrillation Using Implantable Cardiac Monitors: The MONITOR-AF Study

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ABBREVIATIONS

AAD – antiarrhythmic drug
AE – adverse events
AF – atrial fibrillation
CA – catheter ablation
ECG – electrocardiogram
ICM – implantable cardiac monitor
IRB – Institutional Review Board
KCHRRF – Kansas City Heart Rhythm Research Foundation
MCOT – mobile cardiac outpatient telemetry
OAC – oral anticoagulation
SAE – serious adverse events

1 STUDY OBJECTIVES

1.1 Primary Objective

- Evaluate the differences in outcomes between implantable cardiac monitors (ICM) and routine management in patients with atrial fibrillation (AF).
- Freedom from AF and continued anti-arrhythmic drug (AAD) and oral anticoagulation (OAC) use following ICM implantation.

1.2 Secondary Objectives

- To evaluate differences in catheter ablation (CA) and AAD for rhythm control and AF-related complications in those with and without ICM.

2 BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

AF is the most frequent cardiac arrhythmia, with a global prevalence that is only expected to increase. A significant number of patients – up to 38% – may be asymptomatic, making management more difficult. [1] Regardless of symptoms, AF is associated with significant morbidities, including but not limited to heart failure, stroke, dementia, and death.

The management of AF is complex, with clinical decisions related to rate and rhythm control strategies with AADs and CA and stroke prevention. Like other chronic diseases, frequent routine assessments help select, assess, and change management strategies. Implantable cardiac monitors (ICMs) are another option that store electrocardiogram (ECG) tracings for years at a time, enabling continuous monitoring, assessment of AF burden, and therapy efficacy. Previous studies have demonstrated a threefold increase in AF detection, including asymptomatic AF in cryptogenic stroke, syncope, and after CA. using ICMs.[2-4] Their use in AF management has gained popularity for this reason.

2.2 Study Rationale

Even with its increasing popularity and use, the impact of ICMs on AF management is still being determined and can even be conflicting. Furthermore, the use of ICM is dependent on physician preference. We hypothesize that dynamic monitoring with ICMs is superior to conventional methods and should be used for all patients with AF. Thus, we aim to measure the outcomes of using ICM versus more traditional approaches in patients with AF.

3 STUDY DESIGN

We propose a multi-center, retrospective study to evaluate the use of ICM versus traditional, non-ICM methods such as ECGs, Holter, and mobile cardiac outpatient telemetry (MCOT) units, referred to as non-ICM from here on out, from 2018 to 2021. The primary outcome will be the evaluation of AF freedom at 12 months with continued AAD and OAC use. Secondary outcomes are described above. This study will be approved by the Institutional Review Board (IRB), and patient consent will not be required due to the nature of the study.

4 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Study Enrollment Procedures

4.1.1 Screening

Patients will be identified for screening via diagnosis codes for AF on chart review. This can be easily identified by querying current electronic medical record systems. If needed, patients with ICMs can be identified by lists maintained at each study center of those who undergo ICM insertion.

4.1.2 Consent and Enrollment

Patients who meet inclusion and exclusion criteria after screening will be directly enrolled in the study. No randomization will occur, but patients will be separated into an ICM and non-ICM arm. We will enroll approximately 2500 patients [n=1250 (ICM) and n=1250 (non-ICM)] from 2018-2021. No consent will be required due to the nature of the study.

4.2 Inclusion Criteria

- Patients > 18 years of age
- Present for management of AF
- ICM is inserted at the discretion of the treating physician

4.3 Exclusion Criteria

- Patients < 18 years of age
- Presence of a permanent pacemaker, implantable cardiac defibrillator, or cardiac resynchronization therapy
- Unable to tolerate ICM or traditional monitoring with ECG, Holter, or MCOT monitoring
- Unable to tolerate AAD, OAC, and CA as part of AF standard of care
- ICM inserted for cryptogenic stroke or syncope
- Was not followed > 12 months
- CA performed for AF before ICM implant

4.4 Adherence

The Investigator may make no changes or amendments to this protocol after the protocol has been agreed to and signed by all parties unless such change(s) or amendment(s) have been thoroughly discussed and agreed upon by the Investigator, the IRB, or the sponsor. Any change or amendment decided upon will be recorded in writing, the Investigator and the Sponsor will sign the written agreement, and the signed agreement will be appended to this protocol.

5 STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

No intervention or administration will be performed due to the observational nature of each phase. Charts of patients enrolled in the study will be reviewed for an initial monitoring method, any changes in

management, including AAD, OAC, CA, as per physicians' preference, arrhythmia recurrence, need for redo CA, and AF-related complication, for 12 months after enrollment. Lastly, the primary outcomes of AF freedom and continued AAD and OAC use will be noted at the end of the study duration.

5.2 Handling of Study Interventions

Screening, enrollment, and data collection will be performed by the Electrophysiology team and Kansas City Heart Rhythm Research Foundation (KCHRRF) members or respective institutions. Once data is collected, it will be analyzed by KCHRRF staff.

6 STUDY PROCEDURES

6.1 Description of Evaluation

Table 1. Variables for data collection will include but are not limited to the following.

Variables	*Description and Definition*
Age	## Years
Gender	0 = Male, 1 = Female
BMI	## kg/m2
Race	0 = Caucasian, 1 = African American, 2 = Hispanic, 3 = Asian, 4 = Other
Hypertension	0 = No, 1 = Yes
Hyperlipidemia	0 = No, 1 = Yes
Diabetes Mellitus	0 = No, 1 = Yes
Coronary Artery Disease	0 = No, 1 = Yes
CVA/TIA	0 = No, 1 = Yes
Peripheral Artery Disease	0 = No, 1 = Yes
Obstructive Sleep Apnea	0 = No, 1 = Yes
Compensated HF (EF > 35%)	0 = No, 1 = Yes
History of Smoking	0 = No, 1 = Yes
Thyroid Dysfunction	0 = None, 1 = Hypothyroidism, 2 = Hyperthyroidism
Chronic Obstructive Pulmonary Disease	0 = No, 1 = Yes
Gastrointestinal Disorders	0 = No, 1 = Yes
$CHADS_2VASC_2$ Score	##
Antiarrhythmic Drug	
History of Cardioversion	0 = No, 1 = Yes
Baseline AAD Use	0 = No, 1 = Yes
Duration of Arrhythmia	## Mos.
Left Atrial Size	## cm.
Left Ventricular Ejection Fraction	## %
Access to EP	0 = No, 1 = Yes
Compliance to OAC	0 = No, 1 = Yes
Attempted AAD	0 = No, 1 = Yes
Need for Catheter Ablation	0 = No, 1 = Yes
Time to Catheter Ablation	## Days
Number of Monitors used Post-CA	##

Type of Monitors Used	0 = MCOT, 1 = 48-Hr Holter
Need for Redo Ablation	0 = No, 1 = Yes
Time to Redo Ablation	## Days
CV-Related Hospital Duration	## Days
Length of Stay	## Days
AF-Related Hospitalization	0 = No, 1 = Yes
HF-Related Hospitalization	0 = No, 1 = Yes
Bleeding Complication	0 = No, 1 = Yes
Stroke and TIA	0 = No, 1 = Yes
Freedom of AF at 12 Mos.	0 = No, 1 = Yes
Continued OAC Use	0 = No, 1 = Yes
Continued AAD Use	0 = No, 1 = Yes

Abbreviations: BMI – body mass index, CVA = cerebrovascular accident, TIA – transient ischemic attack, AAD = antiarrhythmic drug, CV – cardiovascular, CA = catheter ablation, AF – atrial fibrillation, HF – heart failure, OAC – oral anticoagulation, MCOT – mobile cardiac outpatient telemetry

6.2 Randomization

No randomization will occur due to the nature of the study.

6.3 Follow-up Visits

Follow-up will occur up to 12 months after enrollment into the study. Follow-up visits and management changes will occur at the treating physician's discretion.

7 SAFETY ASSESSMENTS

There are no safety concerns for this study. Adverse AF, AAD, OAC, and ICM insertion events will be noted as outcomes.

8 INTERVENTION DISCONTINUATION

The study will only be discontinued if instructed by the IRB, primary investigator, or other oversight organization.

9 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

The null hypothesis is that there is no difference in outcomes between patients who underwent ICM insertion versus more traditional monitoring methods. Patients who start with traditional monitoring can cross into the ICM group at any time throughout the study. Primary and secondary endpoints are described below.

9.2 Sample Size and Randomization

We will aim for 2500 enrolled participants to result in a 99% power for statistical significance, assuming no difference in AAD, OAC, or CA use rates between those with ICM and non-ICM monitoring methods. We cannot control the exact number of subjects but will attempt a 1:1 allocation into the ICM and non-ICM arms to result in 1250 patients each.

9.3 Outcomes

Primary

- Access to care
- Time of AAD initiation
- Time of OAC initiation
- Time to CA
- Any changes or discontinuation of AAD post-ablation
- Any changes or discontinuation of OAC post-ablation
- Arrhythmia recurrence
- Redo Ablation

Secondary

- Systemic thromboembolic events
- All AF and cardiovascular related hospitalization
- Heart failure exacerbations
- Bleeding complications
- Cardiovascular mortality

9.4 Data Analyses

Statistical analysis will be performed on both continuous and categorical variables. As appropriate, continuous variables will be reported as mean ± standard deviation and compared with two-tailed T-tests and Mann-Whitney testing. Categorical variables will be reported as frequency and percentages and compared with Chi-square testing as appropriate. Cox proportional regression models will be used for hazard ratios and confidence intervals. A p-value < 0.05 will be used to determine statistical significance. Kaplan-Meier graphs will be calculated when appropriate. We will use SPSS [IBM, Armonk, New York] for all statistical analysis.

10 DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection

Data will be collected at each site(s) and recorded in paper or electronic forms.

10.2 Data Management

Physical and identifying data will be housed in a locked space at each site. De-identified data will be entered into a secure database at the KCHRRF system, from which they can be analyzed.

11 PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board Review

This protocol and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. Study activities should not begin until the document has been approved by the IRB of the investigator's institution or by a central IRB. Patient consent will not be required due to the nature of the study.

11.2 Participant Confidentiality

All reports and communications relating to patients in the study will identify each patient only by an investigative site number, the patient's initials, or the patient's study number. The investigator will maintain a patient identification log containing identifying information for each patient enrolled in the study. This document should contain sufficient information and detail to permit the identification of study patients in case follow-up is required. This information should be treated with strict adherence to professional standards of confidentiality and be kept by the investigator under adequate security and restricted access along with other study records.

11.3 Study Discontinuation

The IRB or principal investigator may discontinue the study at any time as part of their duties to ensure that research participants are protected.

12 ETHICAL CONSIDERATIONS

The study will undergo IRB approval and thus meet all institutional ethical guidelines. All other ethical considerations shall be per the Declaration of Helsinki.

13 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures developed.

14 REFERENCES

1. Israel, C.W., et al., *Long-term risk of recurrent atrial fibrillation as documented by an implantable monitoring device.* Journal of the American College of Cardiology, 2004. **43**(1): p. 47-52.
2. Reiffel, J.A., et al., *Rhythm monitoring strategies in patients at high risk for atrial fibrillation and stroke: A comparative analysis from the REVEAL AF study.* Am Heart J, 2020. **219**: p. 128-136.
3. Svendsen, J.H., et al., *Implantable loop recorder detection of atrial fibrillation to prevent stroke (The LOOP Study): a randomised controlled trial.* The Lancet, 2021. **398**(10310): p. 1507-1516.
4. Reiffel, J.A., et al., *Incidence of Previously Undiagnosed Atrial Fibrillation Using Insertable Cardiac Monitors in a High-Risk Population: The REVEAL AF Study.* JAMA Cardiology, 2017. **2**(10): p. 1120-1127.