DESIGN PAPER

# Use of continuous cardiac monitoring to assess the influence of atrial fibrillation burden and patterns on patient symptoms and healthcare utilization: The DEFINE AFib study

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**BACKGROUND** Atrial fibrillation (AF) has a significant impact on health and quality of life. The relationship of AF burden and temporal patterns of AF on patient symptoms, outcomes, and healthcare utilization is unknown. Insertable cardiac monitors (ICMs) are a strategic and as yet untapped, tool to investigate these relationships.

**OBJECTIVE** The DEFINE Atrial Fibrillation (DEFINE AFib) study will evaluate how AF burden and patterns are associated with changes in AF-related healthcare utilization (AFHCU) and patient-reported quality of life.

**METHODS** This is a prospective, observational, multicenter study with a unique design that supports a complete method of assessing AF as a multifactorial disease. Patients with AF implanted with an ICM will be enrolled in the study and managed through an app-based research platform on their smartphone. Patients will be remotely monitored and patient-reported outcomes will be collected via the app. AFHCU will be confirmed via the participant's medical record.

**RESULTS** The primary analysis will evaluate whether summary and episodic measurements collected by ICMs are associated with changes in AFHCU. Secondary analyses will determine the relationship between AF characteristics and quality of life, timing and severity of AF-related complications, patient engagement, reliability of patient-reported outcomes, data from other digital rhythm detectors, and heterogeneity in care quality and AFHCU.

**CONCLUSION** The DEFINE AFib study will provide valuable insights into the association between dynamic measures of AF and AFHCU in a patient population with known AF. The results may demonstrate the impact of ICM-detected AF on patient outcomes and help isolate novel AF patterns predictive of clinical risk.

**KEYWORDS** Atrial fibrillation; AF burden; Risk prediction; Insertable cardiac monitor; Healthcare utilization; Digital data collection; Survey

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## Introduction

Atrial fibrillation (AF) is the most frequent clinically significant cardiac arrhythmia.[1] When diagnosed clinically, AF is associated with increased risk for stroke, heart failure (HF), cognitive decline, cardiovascular (CV) morbidity, and mortality.[2] It is also a major contributor to the costs of healthcare.[3]

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**KEY FINDINGS**

- Atrial fibrillation (AF) has a significant impact on health and quality of life.
- The relationship of AF burden and temporal patterns of AF on patient symptoms, outcomes, and healthcare utilization is unknown.
- The DEFINE AFib study will evaluate how AF burden and patterns are associated with changes in AF-related healthcare utilization and patient-reported quality of life.

The prevalence of AF is predicted to rise significantly in the coming years due to the aging of the population and growing frequency of other AF risk factors.[4] While AF increases the risk of adverse healthcare events, predicting these events is difficult. Continuous rhythm monitoring and predictive analytics may help predict and prevent AF-related adverse events and AF-related healthcare utilization (AFHCU). Considering the rising burden and clinical sequalae of AF, strategies that enable appropriate risk stratification for healthcare utilization and clinical management are needed.

Prior studies have demonstrated that device-detected AF is associated with the same types of clinical outcomes as AF diagnosed through standard clinical practice, including stroke, mortality, and HF.[5–7] However, AF detected via implantable cardiac devices, including insertable cardiac monitors (ICMs), can be transient and short in duration, and the related morbidity may be less than clinically detected AF. Both the amount and changes in patterns of device-detected AF required to increase the risk of CV morbidity and mortality are unclear. While previous studies have shown that increasing AF burden is both a primary and a modifying risk factor for stroke, healthcare utilization, and all-cause mortality,[8,9] the relation between AF burden and patient risk is not linear. Therefore, specific AF burden thresholds for determination of individualized patient risk for a variety of meaningful outcomes have not been established. Accordingly, physicians are not clear when or how to intervene when AF is detected by ICM monitoring.[10,11] However, a shift from acute, reactive care to routine outpatient management in known AF patients with long-term electrocardiographic monitoring via ICMs is associated with reductions in AF- and HF-related hospitalizations, total CV-related events, and associated healthcare utilization compared with patients without long-term monitoring.[12] Therefore, a key requirement to advance the management of AF patients is the development of tools that can assess important variables such as AF burden or patterns of AF that, alone or in combination with other clinically important variables, improve the risk prediction for AF-associated clinical outcomes with better sensitivity than current risk stratification modalities.

The DEFINE Atrial Fibrillation (DEFINE AFib) study was designed to characterize the association between summary and episodic measurements collected by ICMs and AFHCU in patients with device-detected AF. These data will inform how data collected by ICMs can be used to guide the appropriate care of patients with device-detected AF. The study has a novel and unique design that supports a more complete method of assessing AF as a multifactorial disease. A digital research app–based platform will be used to both increase accessibility across demographic groups while reducing the burden of data collection on participants and research staff. This approach allows for more frequent, but more thoughtful, data collection. The ability to integrate with existing digital consumer platforms when available enables passive data collection to better characterize each participant's disease state. Importantly, the ability for the research protocol to adapt to each participant through unique task scheduling and data sharing should reduce attrition and provide more benefits for participation.

## Methods

### Study design

The DEFINE AFib study (NCT04926857) is a prospective, observational, single-arm, multicenter study. Though it is not designed to be powered for specific hypotheses, a sample size of 5000 patients was determined with the goal of having an adequate number of endpoint events to develop risk-prediction models using statistical methods or artificial intelligence (AI). These algorithms will identify periods of increased risk of endpoint events, representing reactive healthcare utilization that could be shifted to preventive medicine, thus obtaining incremental clinical benefit beyond what is available as standard of care.

A retrospective analysis of the Optum de-identified electronic health record dataset (2007–2019), linked to the Medtronic CareLink database of ICM devices, estimated that in a cohort of 5000 patients, selected from a population of ICM patients indicated for AF management, suspected AF, or cryptogenic stroke, 600 (12%) would have at least 1 ischemic stroke event and 2350 (47%) would have at least 1 healthcare utilization in a 5-year follow-up period. Of the healthcare utilization events, 1050 (21%) were estimated to be AF related. This retrospective analysis also suggested that 50% of patients may not provide complete transmission data needed for longitudinal risk modeling. Thus, the risk modeling approach would be likely to differ by endpoint (Table 1).

A planned interim analysis will be performed within 2 years of first enrollment. The objective will be to reassess the assumptions and determine if the sample size or follow-up duration of the study needs to be adjusted. Based on the interim analysis, details of how the study objectives will be analyzed (eg, types of statistical models used) are subject to revision.

### Study population

The study will be performed in the United States. The full eligibility criteria are shown in Table 2. As detailed in Table 2, individuals who received an implantable loop recorder as

**Table 1** Endpoint event estimates

| Endpoint | Statistical: regression (320 endpoints) | AI: random forest (320–800 endpoints) | AI: deep learning (>800 endpoints) |
|---|---|---|---|
| Healthcare utilization (all) | | | 1175 |
| Healthcare utilization (AF related) | | 525 | |
| Ischemic stroke | 300 | | |

AF = atrial fibrillation; AI = artificial intelligence.

standard of care for the following were eligible for the study: monitoring following cryptogenic stroke, AF management, monitoring after AF ablation, or monitoring for suspected AF or palpitations. The study cohort will include all enrolled participants, but nonconfirmed events will not contribute to the study's endpoints.

## Ethical conduct

This study is conducted in compliance with international ethical and scientific quality standards, known as good clinical practice. Good clinical practice includes review and approval by an independent Institutional Review Board before initiating a study, continuing review of an ongoing study by Institutional Review Board, and obtaining and documenting the freely given informed consent of a participants before initiating the study.

## Study objectives

The primary objective is to evaluate whether summary and episodic measurements collected by ICMs are associated with increased AFHCU. Other secondary objectives are listed in Table 3.

## Data collection

The study utilizes the Reveal LINQ and LINQ II ICMs (Medtronic) along with a research application for the Apple iPhone developed by Medtronic. The research application (or study app) allows for the remote enrollment and follow-up of patients by first administering electronic consent, passively collecting patient health data, and deploying scheduled and triggered surveys to collect patient-reported outcome measures. The ICM will collect and transmit cardiac measurements through the CareLink network.

Interested patients will download the study app and complete a brief in-app screening questionnaire to determine eligibility. Eligible patients will be invited to proceed through the app to review and sign a digital consent document. Should the patient have any questions regarding the study, the patient will have access to a phone number that connects them with a study help desk. Following consent, patients will create a profile; opt into sharing location, electronic health record data, and other optional components of the study; and complete a baseline medical history survey and medication log.

**Table 2** Eligibility

**Inclusion criteria**

- Age 22 y or older
- Self-reported history of AF and has received a Reveal LINQ or LINQ II ICM for the following device-logged indications:
  - Cryptogenic stroke
  - AF management and postablation management
  - Suspected AF and palpitations
- $CHA_2DS_2$-VASc $\geq$**2 in men and ≥3 in women***
- Access and ability to use an Apple iPhone compatible with Medtronic's research app (iOS v. 13.X or higher)
- Willingness to comply with CareLink transmissions, remotely administered instructions, and remote survey participation
- ICM managed by a physician who is part of a participating clinical trial site

**Exclusion criteria**

- Patients with more than 24 mo since LINQ ICM implantation
- More than 48 mo elapsed since LINQ II implantation

AF = atrial fibrillation; $CHA_2DS_2$-VASc = congestive heart failure, hypertension, age $\geq$75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65-74 years, sex category; ICM = insertable cardiac monitor.

*The protocol was amended to remove this criterion 21 months after first enrollment to be more inclusive of the patient population with AF management.

Following consent, data will be collected directly from the patient's iPhone on an ongoing basis as shown in Table 4. Health, medication, and quality-of-life surveys will be administered at baseline and at regularly scheduled intervals. AFHCU and symptom surveys will be deployed at various time points based on ICM summary and episodic measurements, and when participants cross predetermined healthcare locations by using geofencing with anonymized location services (if enabled). Participants who chose to enable geofencing upon enrollment would trigger surveys by crossing a predetermined healthcare location geofence (~12,000 healthcare facilities). Surveys distributed due to geofencing included a healthcare utilization survey to check whether the participant was visiting a healthcare facility for an AF-related event and a modified Mayo AF-Specific Symptom Inventory symptom survey to characterize the presence and severity of AF-related symptoms. The study team was blinded to any and all patient locations; only the data collected from the survey were used in the analyses.

Last, patients will be provided AF burden data from their ICM device, with subsequent patient impact surveys to understand how patients respond to and interact with their ICM device data and how access to their data influences their management of AF and their relationship with their healthcare providers. To limit oversampling of survey data among patients with frequent healthcare utilization or qualifying AF episodes, no triggered surveys will be deployed within 7 days of a previously deployed survey of the same kind. To limit the opportunity for duplicate surveys, each survey will have an expiration that is dependent upon how frequently that survey type is issued. Patients will have the ability to terminate their participation in the study at any time.

All study data were de-identified, and patients were issued a study ID at enrollment that was used as part of data

**Table 3** Study objectives

| |
|---|
| **Primary objective** |
| To evaluate whether summary and episodic measurements collected by ICMs are associated with increased AFHCU. |
| **Secondary objectives** |
| 1. To evaluate whether summary and episodic measurements collected by LINQ ICMs including AF episode duration, number of AF episodes, and overall AF burden are associated with quality of life (in patients with device-detected AF). |
| 2. To evaluate whether summary and episodic measurements collected by LINQ ICMs are able to predict when patients are at increased risk for specific clinical outcomes (individual analyses will be conducted for each of the following endpoints when the number of validated events allows): confirmed nonhemorrhagic stroke, systemic embolism, and/or TIA; confirmed cardiovascular-related hospitalization; AF-related or HF-related hospitalization. |
| 3. To evaluate whether summary and episodic measurements collected by LINQ ICMs are able to predict when patients with device-detected AF are at increased risk for specific clinical outcomes, specifically in patients with a history of cardiovascular disease or HF, prior catheter ablation for AF, prior ischemic stroke, or cryptogenic ischemic stroke. |
| 4. To characterize patient preferences for viewing and interacting with device data. |
| 5. To evaluate whether ancillary lifestyle data collected from the Apple iPhone (when available and not limited to activity, exercise, sleep, weight, diet, glucose, blood pressure) in combination with device summary and episodic measurements, as well as patient-reported symptoms accessible through LINQ ICMs, improve prediction of nonhemorrhagic stroke–related healthcare utilization, systemic embolism–related healthcare utilization, TIA-related healthcare utilization, HF-related healthcare utilization, cardiovascular healthcare utilization, and/or AFHCU in patients with device-detected AF. |
| 6. To evaluate how clinical actions for AF impact the association between summary and episodic measurements from market-released LINQ ICMs and all-cause healthcare utilization or AFHCU. |
| 7. To determine the reliability of patient-reported healthcare utilization. |

AF = atrial fibrillation; AFHCU = atrial fibrillation–related healthcare utilization; $CHA_2DS_2$-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65–74 years, sex category; HF = heart failure; ICM = insertable cardiac monitor; TIA = transient ischemic attack.

collection across data capture systems, including CareLink data, which in turn was de-identified prior to storage in a 21 CFR Part 11 compliant study database.

## Data adjudication

In addition to study surveys deployed to patients via the study app, healthcare utilization will also be reported by clinical study site personnel via case report forms with access to patient medical records. Events will be reviewed and queried for clarification if needed. Reported healthcare utilizations will be reviewed and categorized by study staff prior to independent physician review for appropriateness.

All LINQ-detected AF episodes will first be evaluated by the Medtronic AccuRhythm AI 2.0 algorithm. All episodes with a high probability of false positivity (approximately 50%) will be filtered and the remaining potentially true positive episodes will be adjudicated by 2 cardiac technicians. Any disagreement among the cardiac technicians will trigger review by a third, independent reviewer. As a final quality control measure, a random sampling of 5% of all episodes adjudicated by a cardiac technician will be reviewed by 3 independent physicians.

## Discussion

The DEFINE AFib study is one of the largest studies focused on the complex and dynamic nature of AF to provide greater insights into the impact of onset, timing, duration, and the overall AF burden on AFHCU in a patient population with a self-reported history of AF. Many analyses have demonstrated that among patients with noncontinuous/paroxysmal AF, various levels of AF are potentially important,[5–8] but definitive thresholds required for treatment decisions have not been established. One of the obstacles to finding an answer to this question is that AF can result in multiple adverse events, each with its own potential threshold effect. Although AF-related strokes occur and have catastrophic consequences, the majority of events for which patients present to the hospital for AF treatment are HF exacerbations (along with associated morbidity and mortality) and management of AF symptoms. Moreover, the amount of AF to induce changes in AF-related risk could differ depending on an individual's risk factors. Kaplan and colleagues[9] demonstrated that there is an interaction between AF duration and $CHA_2DS_2$-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65–74 years, sex category) score that can further risk-stratify patients with AF for stroke and systemic embolism and may be useful in guiding therapy. The DEFINE AFib study is designed not only to evaluate AF-related risk of AFHCU at the population level, but also to individualize risk at the per-patient level using ICM data.

The DEFINE AFib study is novel in both its design and execution. The study is administered via a digital, app-based research platform that removes the need for any in-person study visits. Patients can provide consent for participation, choose data sharing preferences, and complete study tasks through their smartphone. This method of conducting clinical research, ideally, provides greater opportunity for participation among patient groups that typically are excluded from research due to the visit burden associated with clinical trial enrollment. The digital foundation of this study also allows for study tasks to be administered to participants at opportune times to capture the most pertinent information close to the

**Table 4** Data collection and survey cadence

| Data collection tool | Survey (through app) | Description | Survey cadence |
|---|---|---|---|
| Informed consent | Patient eligibility and informed consent | Self-report screening tool for patient eligibility in the study | At enrollment |
| Medical history | Patient history | Medical history assessment survey | At enrollment |
| | Medication history | Assesses patient's medication list at enrollment; then is updated over time through prompts | At enrollment |
| Quality of life | EQ-5D-5L | Generalized quality-of-life questionnaire | At enrollment and every subsequent 3 mo |
| | AFEQT | AF-specific quality-of-life questionnaire | At enrollment and every subsequent month |
| Symptom and symptom severity | MAFSI and modified EHRA symptom severity | Survey to assess impact of AF-related symptoms on the patient | Monthly/healthcare facility geofence trigger/daily AF burden triggers |
| Medication | SMAQ | Medication adherence survey assessing medication usage and compliance | At enrollment and every subsequent 3 mo |
| Patient app | Patient impact | Survey to understand how the patient uses AF-related data provided in their app | Every 6 mo, starting 6 mo postenrollment |
| Medication list | Current medications | Medication tracking tool routinely updated by the patient | At enrollment and every subsequent 6 mo |

AFEQT = Atrial Fibrillation Effect on Quality-of-Life; EHRA = European Heart Rhythm Association; MAFSI = Mayo AF-Specific Symptom Inventory; SMAQ = Simplified Medication Adherence Questionnaire.

time of detected, specific events. One such example is the deployment of a symptom tracking tool that is triggered when a patient has specific AF burden patterns detected on their ICM. More broadly, the DEFINE AFib study will also provide important data on how the known AF patient population interacts with their health data in a digital setting.

While previous large-scale studies have been conducted on digital platforms, they have been limited to consumer devices that are only capable of point-in-time assessments for the presence or absence of AF. The most recent AF clinical practice guidelines emphasize symptom management with a focus on AF burden.[2] ICMs offer the opportunity to capture true AF burden over time and its association with AFHCU. Additionally, previous smartphone-based studies have been conducted with no clinical site data contributions to act as a "source of truth" for clinical event reporting.[13] The DEFINE AFib study aims to strike a balance between accessibility for patient participation and novel data collection tools for more expansive insight into AF as well as medical grade implantable device data paired with clinical trial site electronic medical records as trusted and reliable methods to collect AF burden data and clinical outcomes. Together, these data will provide a robust dataset that is both broad and deep with regard to the impact and clinical consequences of AF on this patient population.

## Limitations

Remotely administered studies provide numerous benefits for participant inclusivity, study execution, and data collection. However, there are still potential limitations with this type of study design. The study is single arm and strictly observational, only enrolling known AF participants who are already indicated for, and have received, an ICM. Although the study will be able to evaluate the impact of clinical actions on AF burden and patient-reported outcomes, the study is not designed to evaluate the efficacy of each therapy. Additionally, the study requires each participant to enroll with their own smartphone, as one will not be provided for participation in the study. The impact of these requirements may limit the total population able to participate and could be biased toward a younger or more affluent cohort compared with the larger known AF population. Digital access and literacy were intentionally addressed int the study design and operations. Even before the study launch, the DEFINE AFib study operations team made great effort to ensure that appropriate participant support structures were available both at study sites as well as through a trained "help desk" call center. These efforts were put forth to mitigate any potential technology centered impedance on participation and improve generalizability.

The unique format of this study is also heavily reliant on patient participation in a remote setting. This poses 3 possible challenges. First, study enrollment via a smartphone app may be challenging for some potential study participants and could inadvertently cause some otherwise qualified to not participate. Second, the study is reliant on strong participant compliance with regard to completing study questionnaires and assigned tasks. This dependence on patient-initiated

engagement could cause some participants to be prematurely lost to follow-up or cause some responses to be more heavily weighted toward participants with certain characteristics. Last, patient-reported outcomes are collected outside of a supervised setting and could have unintended entry errors due to varying levels of health or digital literacy among the cohort.

## Conclusion

This study will provide valuable insights into the association between dynamic measures of AF and AFHCU in a known AF patient population. Coupling remote monitoring and a smartphone app provides unique advantages for AF patient management. The results may demonstrate the impact of ICM-detected AF on patient outcomes and help isolate novel AF patterns predictive of clinical risk. Foundational data from the study will lead to the creation of an AI algorithm that will continue to evolve in enhancing AF care and minimizing AFHCU while decreasing AF-related morbidity and mortality.

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**Patient Consent:** Informed consent was obtained from participants before initiating the study.

**Ethics Statement:** This study was approved by an independent IRB and conducted in compliance with international ethical and scientific quality standards known as good clinical practice.

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