Received: 4 September 2022 | Accepted: 21 October 2022

DOI: 10.1111/anec.13021

ORIGINAL ARTICLE

WILEY

Confirm Rx insertable cardiac monitor for primary atrial fibrillation detection in high-risk heart failure patients (Confirm-AF trial)

Mehmet K. Aktas MD, MBA[1] | Wojciech Zareba MD, PhD[2] | Javed Butler MD[3,4] | Arwa Younis MD[2,5] | Scott McNitt MS[2] | Mary W. Brown MS, RN[2] | Nikhila Rao BS[2] | Nilesh Rao BS[2] | Jonathan Steinberg MD[2,6] | Leway Chen MD, MPH[1] | Jeffrey D. Alexis MD[1] | Himabindu Vidula MD[1] | Ilan Goldenberg MD[2]

[1]Division of Cardiology, University of Rochester Medical Center, Rochester, New York, USA

[2]Clinical Cardiovascular Research Center, University of Rochester Medical Center, Rochester, New York, USA

[3]Baylor Scott and White Research Institute, Dallas, Texas, USA

[4]Department of Cardiology, University of Mississippi, Jackson, Mississippi, USA

[5]Clinical Electrophysiology, Department of Cardiology, Cleveland Clinic, Cleveland, Ohio, USA

[6]Summit Medical Group, Short Hills, New Jersey, USA

Correspondence
Mehmet K. Aktas, Division of Cardiology, Section of Electrophysiology, University of Rochester Medical Center, 601 Elmwood Avenue, Box 679C, Rochester, New York 14642, USA.
Email: mehmet_aktas@urmc.rochester.edu

Funding information
Abbott

Abstract

Background: Patients with heart failure (HF) represent a large population of patients who are at high risk for complications related to undiagnosed atrial fibrillation (AF). However, currently there are limited modalities available for early AF detection in this high-risk population. An implantable cardiac monitor (ICM) is inserted subcutaneously and can provide long-term arrhythmia information via remote monitoring.

Methods and Results: Confirm-AF is a prospective randomized, nonblinded, two arm, multicenter clinical trial to be performed in the United States, enrolling 477 patients with a history of HF hospitalization and left ventricular ejection fraction >35% from 30 medical sites. Patients will be randomized in a 2:1 fashion to undergo ICM implant with remote monitoring and symptom-triggered mobile app transmissions versus (vs.) Non-ICM management and follow-up. The primary objective of this trial is to compare the time to first detection of AF lasting > 5 min using an Abbott ICM compared to non-ICM monitoring in symptomatic HF patients. This article describes the design and analytic plan for the Confirm-AF trial.

Conclusions: The Confirm-AF trial seeks to accurately define the burden of AF in high-risk HF patients with LVEF > 35% using an Abbott ICM. A finding showing significantly higher incidence of AF along with improved clinical outcomes with ICM monitoring is expected to have substantial clinical implications and may change the method of monitoring high-risk HF patients.

KEYWORDS
atrial fibrillation, heart failure, implantable cardiac monitor, remote monitoring, stroke

[Correction added on 20 December 2022, after first online publication: The coauthors Nikhila Rao, BS, and Nilesh Rao, BS have been added to the author byline.]

1 | INTRODUCTION

Over 6 million people in the United States suffer from heart failure (HF) (Benjamin et al., 2018). By the year 2030 the prevalence of HF is expected to exceed 8 million people (Heidenreich et al., 2013). Heart failure accounts for 1 million hospital admissions each year, costing our economy in excess of $30 billion dollars per year (Heidenreich et al., 2013). Mortality in patients with HF remains high, and nearly half of all patients diagnosed with HF will die within 5 years (Loehr et al., 2008). More than half of all patients admitted with HF decompensation have preserved left ventricular systolic function (Andersson & Vasan, 2014; Savarese & Lund, 2017). Patients with HF and mildly reduced or preserved left ventricular systolic function are at high risk for developing atrial fibrillation (AF), the occurrence of which often contributes to HF decompensation and increases morbidity and all-cause mortality (Cikes et al., 2018; Goyal et al., 2018; Santhanakrishnan et al., 2016). Similarly, patients with AF are at high risk for developing HF due to loss of atrioventricular synchrony and rapid uncontrolled ventricular rates (Santhanakrishnan et al., 2016). Detection of AF can be challenging and may go undiagnosed in asymptomatic or minimally symptomatic patients through conventional monitoring methods. Patients with HF represent a large population who are at risk for complications related to undiagnosed AF. AF increases the risk of stroke five-fold and the risk of death nearly two-fold (Kannel et al., 1998). Moreover, strokes related to AF are twice as likely to be fatal or severely disabling compared to strokes due to other causes, such as ischemic small vessel disease or atheromatous large vessel disease (Lin et al., 1996). Cardiac implantable electronic devices (CIEDs), can be used for the early detection of AF in asymptomatic or mildly symptomatic patients with HF. However, current guidelines provide an indication for prophylactic implantable cardioverter defibrillator (ICD) only in HF patients with left ventricular ejection fraction (LVEF) ≤ 35% (Al-Khatib et al., 2018), whereas there are limited data for device-based detection of AF in HF patients with more preserved LVEF.

Implantable cardiac monitors (ICM) are devices that can be injected into the subcutaneous tissue and can provide automatic electrocardiographic recordings of asymptomatic arrhythmias as well as patient-triggered electrocardiographic recordings of symptomatic episodes during long-term follow-up. Implantable cardiac monitors are being paired with remote monitoring systems, capable of rapid remote review of electrograms. Accordingly, we hypothesize that a management strategy that incorporates ICM implantation in patients with HF and LVEF > 35% will result in a significantly higher rate of AF detection leading to arrhythmia related interventions compared to Non-ICM monitoring and follow-up in patients with HF.

2 | METHODS

2.1 | Objectives

The primary objective of this trial is to compare the time to first detection of AF lasting > 5 min using an Abbott ICM versus non-ICM monitoring in symptomatic HF patients.

The six secondary objectives of this trial, in prioritized order are:

1. Determine whether Abbott ICM versus non-ICM monitoring results in increased rate of initiation of guideline directed arrhythmic and HF interventions (AF ablation, initiation of anti-arrhythmic therapy, anticoagulation, beta-blocker and others) following detection of AF.
2. Compare the total number of cardiovascular hospitalization or death using Abbott ICM versus non-ICM monitoring.
3. Compare healthcare utilization (including emergency department visits, unplanned office visits, cardiovascular hospitalization or death) using Abbott ICM versus non-ICM monitoring.
4. Determine whether Abbott ICM versus non-ICM monitoring results in improved mean quality of life measured using the Kansas City Cardiomyopathy Questionnaire (KCCQ).
5. Determine the mean AF burden in the Abbott ICM arm. Rate of detection of arrhythmic events consisting of AF, sustained ventricular tachycardia, and high-risk bradyarrhythmias (high degree AV block or sinus pause > 5 s), whichever occurs first in the ICM versus non-ICM monitoring arms.

The tertiary objectives of this trial are specific to the myMerlin™ mobile app and include the following:

1. Compare the effect of patient-triggered transmissions on the time to Abbott ICM detection of arrhythmic events triggered by symptomatic recordings versus automatically detected arrhythmic event recordings.
2. Evaluate the rate of actionable interventions (including initiation of oral anticoagulation, guideline directed medical therapy, device and procedural interventions) following symptom-triggered event versus the rate of actionable interventions associated with automatic detected arrhythmic events.

2.2 | Design (Figure 1)

Confirm-AF is a prospective, randomized, nonblinded, two arm, multicenter clinical trial, which will be performed in the United States, enrolling patients from 30 sites. Subjects with a diagnosis of HF requiring initiation or augmentation of decongestive therapy (oral or intravenous), LVEF > 35% during the past 12 calendar months prior to consent date will be randomized in a 2:1 ratio to undergo insertion of an Abbott ICM versus non-ICM monitoring and management. Randomization will be stratified by the degree of LV dysfunction to ensure balanced enrollment of HF patients with mild LV dysfunction (LVEF 36%–49%) and those with preserved LVEF (≥50%), that is, heart failure with preserved ejection fraction (HFpEF).

2.3 | Patient eligibility

Patients with LVEF > 35% and symptomatic HF, as defined by a New York Heart Association (NYHA) functional class II, III, or ambulatory

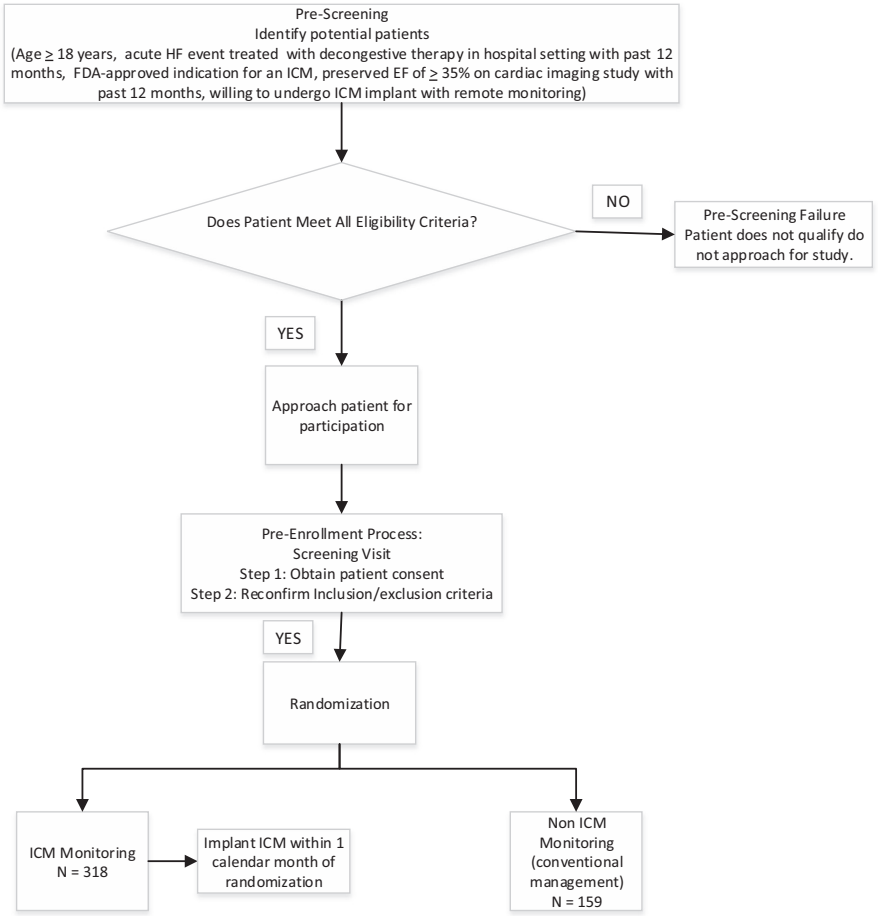

FIGURE 1 Confirm-AF enrollment flow diagram

class IV will be eligible for enrollment. A history of HF exacerbation requiring initiation or augmentation of decongestive therapy in a hospital setting (hospitalization or emergency department visit) during the past 12 calendar months will be required as an enrichment inclusion criterion. Patients who meet all inclusion and exclusion criteria listed in Table 1 will be given consideration for study enrollment.

2.4 | Recruitment

Screening for eligible patients will be performed in compliance with HIPAA requirements. Patients who meet all eligibility criteria and do not have any exclusions will be recruited by the research groups associated with each enrolling site. Logs will be kept at each center of all identified patients who meet the clinical eligibility criteria. For eligible patients who are not enrolled, the reason for nonenrolment (exclusion) will be recorded. A flow diagram of enrollment is presented in Figure 1.

2.5 | Consent

After a patient has been determined to meet eligibility criteria and not to have any exclusions from the Confirm-AF study, the research coordinator at each of the enrolling sites will offer enrollment into the study. All materials will be approved by the local IRB and Data Coordinating Center (DCC). After addressing all questions and

TABLE 1 Patient eligibility criteria

Inclusion Criteria

- Patients ≥18 of age (no upper age limit)
- HF exacerbation requiring initiation or augmentation of decongestive therapy in a hospital setting (hospitalization or emergency department visits) during the past 12 calendar months.
- LVEF > 35% on a cardiac imaging study (echocardiogram, nuclear imaging, cardiac magnetic resonance imaging) performed during the past 12 calendar months prior to consent date.
- One or more FDA-approved indications for an Abbott ICM (unexplained symptoms such as dizziness, palpitations, chest pain, syncope, and shortness of breath, as well as patients who are at risk for cardiac arrhythmias)
- Willing to undergo an Abbott ICM implant and agree to remote ICM monitoring.

Exclusion Criteria

- Existing cardiac implantable electronic device or planned implantation
- Known or documented history AF or atrial flutter any time in the past.
- Unable or unwilling to follow the study protocol.
- Unable or unwilling to sign the consent for participation.
- Participation in other clinical trials (observational registries are allowed with approval from the CDC).

concerns and an appropriate time period to consider the option of participating, the patient will be given the opportunity to sign the consent form. If available, electronic consenting will be utilized. The patient will receive a copy (paper or digital) of the signed consent form and the consent document will also be maintained in the center's records.

2.6 | Baseline evaluation

After the patient signs the consent and before randomization, all enrolled subjects will have a baseline reference examination, including a clinical history, physical exam, 12-lead ECG, and quality of life assessment using the Kansas City Cardiomyopathy Questionnaire.

2.7 | Randomization

The random assignment to one of the two study groups will be made by the DCC and transmitted to the enrolling clinical center by logging on to a Web-based automated program. Randomization will be made only after verification that the steps mentioned above have been completed. The date of randomization serves as the subject's date of entry, or enrollment date, into the clinical trial. Each randomized subject will remain counted as a member of the assigned treatment group to which the subject was assigned (intention-to-treat). For the purpose of analysis, subjects will not be censored at withdrawal, and every effort will be made to ascertain the occurrences or nonoccurrence of the primary endpoints.

2.8 | ICM group

Subjects randomized to the ICM intervention group arm of the trial will undergo implant of an Abbott ICM (Abbott Park, Illinois) implanted by a physician within 1 calendar month after randomization. All devices in the Confirm-AF trial will be market-released products and will be implanted according to standard sterile implant techniques per hospital protocols.

2.9 | ICM programming

The AF duration parameter in the Abbot ICM will be programmed to 30 s, which determines the shortest AF episode that will be stored by the device. The ICM triggers the storage of an electrogram (EGM) when a detected AF episode is longer than the programmed AF Duration. Along with the EGM, there is a scatter plot of the heart rate during the AF EGM. Figure 2 shows a screenshot of the available AF programming options in the Confirm Rx™ ICM.

The Abbot ICM also provides AF diagnostic data that contain the following information:

- AF Burden. Shows the percentage of time that the patient was in AF since the AF diagnostics data were last cleared. The data are presented as the daily percentage over a 1-year period that can be viewed and printed from Merlin.net. A 31-day burden trend is available on the programmer
- AF Summary. Histograms of the Mean Ventricular Heart Rate and the Duration of AF episodes since AF diagnostic data were last cleared.
- AF Statistics. Statistical data for AF episodes stored since AF diagnostic data were last cleared.
- Read Diagnostics button. Retrieves diagnostic data from the device and updates the data shown.
- Last Session. The date and time of the last programmer session.
- Last Remote Session. The date and time of the last remote session.
- Last Read. The date and time that the diagnostic data were last read.
- Last Cleared. The date and time that the diagnostic data were last cleared.

The settings for stored AF EGM will be programmed as follows: the AF Pre-Trigger Duration parameter, which determines the amount of time recorded before an AF episode is detected will be set to 30 s (nominal setting); the AF Post-Trigger Duration parameter determines the amount of time recorded after an AF episode is detected and will be set to 120 s (nominal setting).

2.10 | myMerlin™ mobile app

The myMerlin™ mobile app is an interface that is paired and used with an Abbott ICM. The app is available for download from the Apple App Store or from the Google Play Store. The myMerlin™ app uses Bluetooth wireless connectivity to securely and proactively communicate between the ICM and the smartphone. Following implant of the Abbott ICM, the device is paired with the patient's smartphone. In the event that a patient does not already own a smartphone, Abbott provides a smartphone with limited functionality (free of charge) to allow the patient to utilize remote monitoring. The app uses WiFi and/or cellular connections to transmit data from the Abbott ICM to the Merlin.net and can be reviewed by the clinician. The myMerlin™ mobile app performs a Daily Device Check. In the daily device check the app looks for new episodes and transmits the new data to Merlin.net. This capability can be modified by turning direct alerts for different arrhythmia types on or off. Subjects enrolled can also use the myMerlin™ the device is immediately paired with the patient's smartphone. In the event that a patient does not already own a smartphone, app to manually trigger an ICM recording and record symptoms (Fainting, Dizziness Fluttering, Shortness of breath, Fast heart rate or Other) from a dropdown menu with the app. The symptoms episodes are immediately transmitted to Merlin.net. The myMerlin™ mobile app also performs a scheduled follow based on the schedule set on Merlin.net. At the end of the scheduled follow-up, if programmed on Merlin.net, all device data and diagnostics can be cleared.

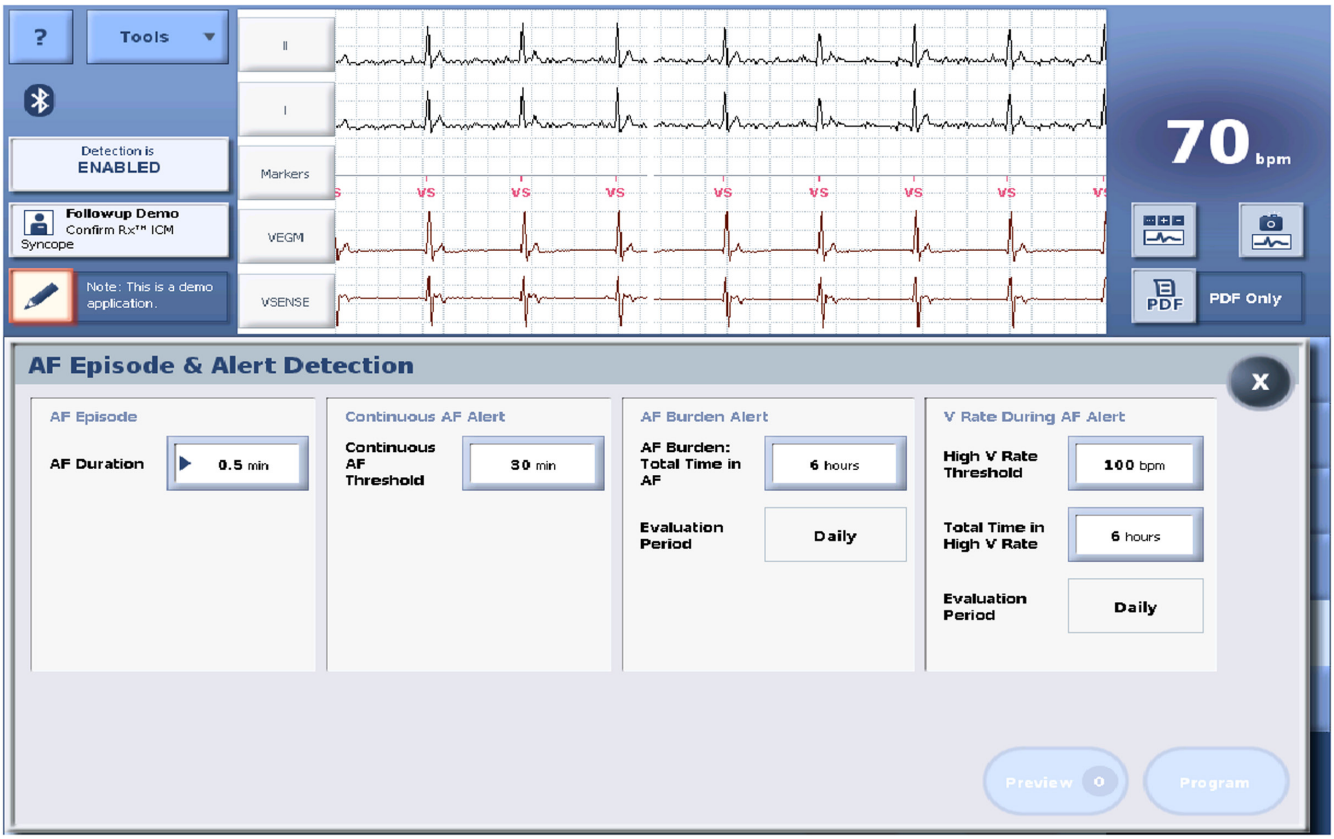

FIGURE 2 Screenshot showing Abbott programming options for AF episode and alert detection criteria in the confirm Rx™ implantable cardiac monitor

2.11 | Non-ICM group

Subjects randomized to the Non-ICM arm of the trial will undergo arrhythmia monitoring based on clinical indications and per standard available modalities including periodic electrocardiograms (ECG), Holter and/or event monitoring.

2.12 | Follow-up

Subjects randomized to the ICM arm will be enrolled in Abbott's Merlin.net Patient Care Network. Interrogations and remote downloads will be made available to both the patient's treating physician as well as the study DCC. Regular monthly downloads will be obtained from Merlin.net or when a patient triggers a recording for a symptomatic event. Merlin.net data will be transmitted on a monthly basis to the treating physician and the DCC, where it will be further reviewed independently by a blinded study arrhythmia adjudication committee. Patients will be followed for a time period of 2 years for clinical and subclinical arrhythmic events, medication and device interventions, clinical events, adverse events, and quality of life.

Follow-up information in both arms will be obtained through alternating remote and in-person cardiology clinics visits at 6-month intervals. At each follow-up visit a list of medications, an interim history focusing on occurrence of any arrhythmic events, adverse events, and physical exam will be recorded. Laboratory, electrocardiographic, Holter, event monitoring data that may have been acquired as standard of care will be recorded. Any assessment of LVEF (determined by echocardiography, nuclear imaging, cardiac magnetic resonance imaging) if acquired per standard of care, not mandated per protocol during follow-up will be recorded.

2.13 | End points

The primary endpoint of Confirm-AF is the time to first detection of AF lasting > 5 min in the ICM arm or captured by clinical symptoms and documented by ECG or Holter in the Non-ICM arm. All secondary endpoints are provided in Table 2. The Abbot ICM utilizes a unique mobile app (myMerlin™) that allows immediate arrhythmia transmission from the ICM and allows for annotation of symptoms (dizziness, palpitations, chest pain, syncope, and shortness of breath). Confirm-AF will include a tertiary app-specific endpoint to evaluate the impact of symptom-triggered arrhythmic events by use of the myMerlin™ mobile app (Table 2.)

TABLE 2 Endpoints of the confirm-AF trial

Primary Endpoint
• Time to first detection of AF lasting > 5 min[a]
Secondary Endpoints
• Rate of initiation of guideline directed arrhythmic and HF interventions (AF ablation, initiation of antiarrhythmic therapy, anticoagulation, beta-blocker and others) following detection of AF.
• Total number of cardiovascular hospitalizations or death.
• Healthcare utilization (including emergency department visits, unplanned office visits, cardiovascular hospitalization or death).
• Quality of life measured using the Kansas City Cardiomyopathy Questionnaire
• AF burden using the Abbott ICM
• Composite of identified arrhythmic events consisting of AF, sustained ventricular tachycardia, and high-risk bradyarrhythmia (high degree AV block or sinus pause > 5 s), whichever occurs first.
myMerlin™ app-specific Endpoints
• Time to ICM detection of arrhythmic events, triggered by symptoms versus automatically detected arrhythmic events.
• Rate of actionable interventions (including initiation of oral anticoagulation, guideline directed medical therapy, device and procedural interventions) following symptom triggered events versus the rate of actionable interventions associated with automatically detected arrhythmic events.

[a]Defined as ICM detected AF in the intervention arm or captured by clinical symptoms and documented by ECG or Holter in the Non-ICM arm.

2.14 | Core laboratories and committees

2.14.1 | Electrogram and device interrogation core laboratory

This lab consists of a director and co-director and their appointed staff. The core lab will review all ICM interrogations using electronic media downloaded from myMerlin™ or during device interrogations at the enrolling sites. The enrolling sites' interpretation and classification will be available to the core lab but they will form a final opinion of the nature of the detected arrhythmias. The core lab will review all interrogations to capture and adjudicate all events.

2.14.2 | Events Review Committee

A three-member Events Review Committee will review source documents obtained from each of the enrolling sites. The information will be used to determine the nature of any clinical and adverse events. Available medical records and source documents will be used to determine cause-specific mortality.

2.15 | Organizational structure

The organizational structure for Confirm-AF is presented in Figure 3. This is an investigator initiated clinical trial. Abbott will provide funding support for the trial through an unrestricted research grant to the University of Rochester School Medical Center.

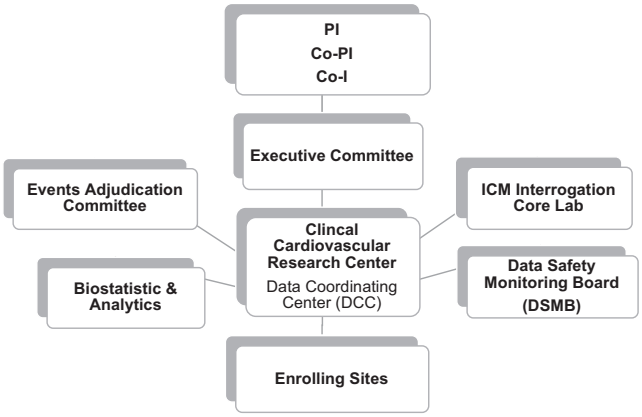

FIGURE 3 Confirm-AF trial organizational structure

2.16 | Statistical analysis

The Confirm-AF trial is designed to have 90% power to detect a 3-4-fold improvement in detecting AF over two-years among patients in the ICM versus Non-ICM group, with a two-sided significance level of 0.05. Among HF patients, prior published data show an annual rate of AF detection of 3%–4% per year using conventional management strategies (i.e., an event rate of 6%–8% at 2-years) (Ducharme et al., 2006; Pellicori et al., 2019). Prior published data in similar cohorts of HF patients with relatively preserved LVEF suggest an AF rate of 20%–30% at 2-years detected by ICM (Reiffel et al., 2017). Accordingly, for the sample size calculations, we estimated a clinical AF detection rate of 8% in the Non-ICM arm versus 23% AF detection rate in the ICM are at 2-years.

Ranges of sample size considerations are detailed in Table 3. Accordingly, the planned sample size will be 477 patients who will be randomized in a 2:1 ratio to Abbot ICM guided management ($n = 318$) versus non-ICM management ($n = 159$), assuming 20% loss of patients during trial follow-up. Randomization will be stratified by the degree of LV dysfunction to ensure balanced enrollment of HF patients with mild LV dysfunction (LVEF = 36%–49%) and those with preserved LVEF (≥50%).

Sample size calculations for the secondary endpoint of arrhythmia related interventions such as pharmacologic and device interventions in the Abbott ICM versus non-ICM arms, the following assumptions were made;

- Detection rate at 24 months of any arrhythmic episodes (AF, sustained ventricular tachycardia or ventricular fibrillation, atrioventricular block) in the ICM arm = 40% (Lin et al., 1996).
- Detection rate of clinical arrhythmic episodes (AF, sustained ventricular tachycardia or ventricular fibrillation, atrioventricular block) in the control arm = 10%.

TABLE 3 Ranges of sample size considerations for the confirm-AF trial

				Event rate estimates through 24 months	
Power	**Total *N***	**Control *N***	**ICM *N***	**Control**	**ICM**
90%	306	101	205	8%	28%
90%	393	130	263	8%	25%
90%	408	135	273	5%	20%
90%	432	143	289	8%	24%
90%	**477**	**159**	**318**	**8%**	**23%**
90%	603	199	404	6%	18%

Note: The primary event rate hypothesis is highlighted in bold.
Abbreviation: *N*, number of patients.

- Rate of arrhythmia related interventions based on ICM detected episodes in the intervention arm (initiation of oral anticoagulant therapy, rate versus rhythm control of AF, ablation, device therapy for brady/tachyarrhythmias) will occur in approximately 60% of patients with ICM detected arrhythmias (i.e., 24% of the patients in the ICM arm).
- Rate of arrhythmia related interventions based on clinical episodes in the control arm (initiation of oral anticoagulant therapy, rate versus rhythm control of AF, ablation, device therapy for brady/tachyarrhythmias) will occur in approximately 80% of patients with clinical arrhythmias (i.e., 8% of the patients in the control arm).

Power with 477 sample size and a 2:1 randomization will be >95%, assuming 20% dropout and deaths before 2 years and at two-year arrhythmia rates. The overall 2-sided significance level of 0.05 will be maintained by using smaller nominal alphas at these time points. The primary analysis will be based on the intention-to-treat (ITT) principle.

Event-free survival rates, as captured by the composite primary endpoint, will be displayed using the method of Kaplan–Meier. The planned data analysis will use a log-rank test to nonparametrically compare the ICM versus Non-ICM management groups. Additionally, the Cox proportional hazards regression model will be used to develop hazard ratios and their accompanying confidence intervals for the association of ICM management and the ability to detect the primary endpoint.

2.16.1 | Early termination

There will be significance tests for efficacy by the Database and Safety Monitoring Board (DSMB) at 12 months, 18 months and study end.

2.17 | Protection of human subjects

The study will be approved by a single Institutional Review Board (IRB) at the University of Rochester, NY, per recent NIH guidance. Enrolling sites will be provided with a written IRB approval to participate in the study. Devices used in this study have Food and Drug Administration (FDA) approval for the detection of AF.

An impartial DSMB will be appointed to independently monitor the conduct and the outcome of the trial. The DSMB will be responsible for monitoring the safety and well-being of the patients participating in this study and ensuring the ethical conduct of the trial. Since this study is a randomized clinical trial requiring an ICM implant in the intervention arm, data on clinical events including procedural complications, hospitalizations, stroke, and death will be collected during the study and provided to the DSMB for evaluation of risks associated with participation in the study. Efforts will be made to maintain confidentiality of study data. All study data will be coded with an unidentifiable study code. The study coordinator will maintain a key linking the patient's name with study data. The data center will also maintain a master key in a password protected data form separate from the main database.

Enrolling teams will adhere to all applicable FDA guidelines for clinical research, the Confirm-AF protocol, the "Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Patients," and the approved IRB regulations. At each encounter with a potential or enrolled study subject the Investigator will be responsible for protecting the subject and determining if further participation in the clinical trial is appropriate for that individual subject. The Investigators and Research Coordinators are charged with maintaining the integrity of the trial and utmost confidentiality of patient and clinical trial information.

3 | DISCUSSION

The Confirm-AF trial is a clinical investigation evaluating the benefit of an Abbott ICM for the detection of AF in patients with HF. We will enroll patients with LVEF > 35% and symptomatic HF (as defined by a NYHA Class ≥ II). All enrolled patients will also be required to have a history of HF hospitalization during the preceding 12 months, which is recognized to be a high-risk marker for arrhythmic and clinical adverse events in this population (Kelly et al., 2015).

There is significant overlap in the underlying pathophysiologic mechanisms that lead to the development of AF as well as HF, and it is well recognized that HF can trigger AF, and the reverse is also true (Anter et al., 2009). Atrial fibrillation with rapid ventricular rates can result in a tachycardia related cardiomyopathy, the prompt detection and treatment of which is often reversible (Gopinathannair et al., 2015). Furthermore, loss of organized atrial contraction during AF, which contributes to 25% of LV filling, can also trigger HF decompensation (Mountantonakis et al., 2012). Therefore, the timely detection and diagnosis of AF has significant clinical implications.

Currently there is no AF screening recommendation in high-risk HF patients. When AF is suspected clinicians rely primarily on ECG detection or Holter/event monitoring. However, a substantial proportion of patients with AF may have minimal symptoms and may even initially be asymptomatic. Furthermore, the use of intermittent

ECGs and Holter monitoring may be ineffective in detecting AF episodes in patients who have paroxysmal AF.

In the proposed trial, the detection of AF is expected to trigger a variety of interventions that may prevent HF decompensation and reduce the risk of long-term adverse outcomes. First and fore-most, timely detection of AF can facilitate the appropriate initiation of anticoagulation based on the subjects CHA_2DS_2-VASc score. Second, the detection of AF with rapid ventricular rates will expedite the titration of beta-blocker therapy so as to achieve adequate ventricular rate control. Third, the recognition of AF may prompt therapies tailored to maintain SR such as antiarrhythmics and/or catheter ablation especially given the recent evidence in support of maintaining SR in HF patients (Kirchhof et al., 2020; Marrouche et al., 2018).

The ICM has transformed our approach to screening and detection of arrhythmia in high-risk populations such as in patients following a cryptogenic stroke (Sanna et al., 2014). Insertion of an ICM is a low-risk procedure; however, the yield can be immensely valuable particularly in HF patients, who are known to be at high risk for development of atrial and ventricular tachyarrhythmias. In addition, the capability of the Abbott ICM to provide patient-triggered submissions using the myMerlin™ app offers the added benefit of prompting interventions that have the potential to avert a HF decompensation.

In conclusion, the Confirm-AF trial seeks to accurately define the burden of AF in high-risk HF patients with LVEF > 35% using an Abbott ICM. A finding of significant incidence of AF with ICM monitoring is expected to have substantial clinical implications and may change the method of monitoring high-risk HF patients.

AUTHOR CONTRIBUTIONS

Mehmet K. Aktas: Research grants from Boston Scientific, Medtronic, Biosense-Webster, Abbott, Astra Zeneca, Consulting fees from Abbott. Wojciech Zareba: Research grants from Boston Scientific, Biotronik, Zoll Inc. Javed Butler: Consultant, Abbott, Adrenomed, Amgen, Array, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, CVRx, G3 Pharmaceutical, Impulse Dynamics, Innolife, Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, Novo Nordisk, Roche, Vifor. Arwa Younis: None. Scott McNitt: None. Mary W. Brown: None. Jonathan S. Steinberg: Research grants from NIH, AliveCor; equity in AliveCor, National Cardiac, BraveHeart; consultant for Medtronic, National Cardiac, BraveHeart, Corfigo, Hillrom, Allergan, Atricure; other with ABIM. Leway Chen: Consulting Agreement with Abbott. Jeffrey Alexis: Research grant from Abbott. Himabindu Vidula: Research grant from Abbott. Ilan Goldenberg: Research grants from Boston Scientific, Zoll, Medtronic, Biosense-Webster, Biotronik, Abbott, Astra Zeneca.

FUNDING INFORMATION

Confirm-AF is sponsored by a research grant to the University of Rochester Medical Center from Abbott.

CONFLICT OF INTEREST

Dr. Wojciech Zareba is Editor-in-Chief of the journal and co-author of this article. They were excluded from the peer-review process and all editorial decisions related to the acceptance and publication of this article. Peer-review was handled independently by EiC/Co-editor, Dr. Mark Haigney to minimize bias.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICAL APROVAL

This study is conducted in accordance with Good Clinical Practice and ISO-14155 as guidance and in compliance with the Declaration of Helsinki.

ORCID

Mehmet K. Aktas https://orcid.org/0000-0002-9003-9384

REFERENCES

Al-Khatib, S. M., Stevenson, W. G., Ackerman, M. J., Bryant, W. J., Callans, D. J., Curtis, A. B., Deal, B. J., Dickfeld, T., Field, M. E., Fonarow, G. C., Gillis, A. M., Granger, C. B., Hammill, S. C., Hlatky, M. A., Joglar, J. A., Kay, G. N., Matlock, D. D., Myerburg, R. J., & Page, R. L. (2018). 2017 AHA/ACC/HRS guideline for Management of Patients with Ventricular Arrhythmias and the prevention of sudden cardiac death: Executive summary. *Circulation*, *138*, e210–e271.

Andersson, C., & Vasan, R. S. (2014). Epidemiology of heart failure with preserved ejection fraction. *Heart Failure Clinics*, *10*, 377–388.

Anter, E., Jessup, M., & Callans, D. J. (2009). Atrial fibrillation and heart failure. *Circulation*, *119*, 2516–2525.

Benjamin, E. J., Virani, S. S., Callaway, C. W., Chamberlain, A. M., Chang, A. R., Cheng, S., Chiuve, S. E., Cushman, M., Delling, F. N., Deo, R., De Ferranti, S. D., Ferguson, J. F., Fornage, M., Gillespie, C., Isasi, C. R., Jimenez, M. C., Jordan, L. C., Judd, S. E., Lackland, D., … On behalf of the American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke Statistics-2018 update: A report from the American Heart Association. *Circulation*. 2018;*137*:e67-e492.

Cikes, M., Claggett, B., Shah, A. M., Desai, A. S., Lewis, E. F., Shah, S. J., Anand, I. S., O'Meara, E., Rouleau, J. L., Sweitzer, N. K., Fang, J. C., Saksena, S., Pitt, B., Pfeffer, M. A., & Solomon, S. D. (2018). Atrial fibrillation in heart failure with preserved ejection fraction: The TOPCAT trial. *JACC Heart Failure.*, *6*, 689–697.

Ducharme, A., Swedberg, K., Pfeffer, M. A., Cohen-Solal, A., Granger, C. B., Maggioni, A. P., Michelson, E. L., McMurray, J. J., Olsson, L., Rouleau, J. L., Young, J. B., Olofsson, B., Puu, M., & Yusuf, S. (2006). Prevention of atrial fibrillation in patients with symptomatic chronic heart failure by candesartan in the candesartan in heart failure: Assessment of reduction in mortality and morbidity (CHARM) program. *American Heart Journal.*, *152*, 86–92.

Gopinathannair, R., Etheridge, S. P., Marchlinski, F. E., Spinale, F. G., Lakkireddy, D., & Olshansky, B. (2015). Arrhythmia-induced cardiomyopathies: Mechanisms, recognition, and management. *Journal of the American College of Cardiology.*, *66*, 1714–1728.

Goyal, P., Almarzooq, Z. I., Cheung, J., Kamel, H., Krishnan, U., Feldman, D. N., Horn, E. M., & Kim, L. K. (2018). Atrial fibrillation and heart failure with preserved ejection fraction: Insights on a unique clinical

phenotype from a nationally-representative United States cohort. *International Journal of Cardiology.*, *266*, 112–118.

Heidenreich, P. A., Albert, N. M., Allen, L. A., Bluemke, D. A., Butler, J., Fonarow, G. C., Ikonomidis, J. S., Khavjou, O., Konstam, M. A., Maddox, T. M., Nichol, G., Pham, M., Pina, I. L., & Trogdon, J. G. (2013). Forecasting the impact of heart failure in the United States: A policy statement from the American Heart Association. *Circulation Heart Failure*, *6*, 606–619.

Kannel, W. B., Wolf, P. A., Benjamin, E. J., & Levy, D. (1998). Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: Population-based estimates. *The American Journal of Cardiology.*, *82*, 2N–9N.

Kelly, J. P., Mentz, R. J., Mebazaa, A., Voors, A. A., Butler, J., Roessig, L., Fiuzat, M., Zannad, F., Pitt, B., O'Connor, C. M., & Lam, C. S. P. (2015). Patient selection in heart failure with preserved ejection fraction clinical trials. *Journal of the American College of Cardiology.*, *65*, 1668–1682.

Kirchhof, P., Camm, A. J., Goette, A., Brandes, A., Eckardt, L., Elvan, A., Fetsch, T., van Gelder, I. C., Haase, D., Haegeli, L. M., Hamann, F., Heidbüchel, H., Hindricks, G., Kautzner, J., Kuck, K.-H., Mont, L., Ng, G. A., Rekosz, J., Schoen, N., … Breithardt, G. (2020). Early rhythm-control therapy in patients with atrial fibrillation. *New England Journal of Medicine.*, *383*, 1305–1316.

Lin, H. J., Wolf, P. A., Kelly-Hayes, M., Beiser, A. S., Kase, C. S., Benjamin, E. J., & D'Agostino, R. B. (1996). Stroke severity in atrial fibrillation. The Framingham Study. *Stroke.*, *27*, 1760–1764.

Loehr, L. R., Rosamond, W. D., Chang, P. P., Folsom, A. R., & Chambless, L. E. (2008). Heart failure incidence and survival (from the atherosclerosis risk in communities study). *The American Journal of Cardiology.*, *101*, 1016–1022.

Marrouche, N. F., Brachmann, J., Andresen, D., Siebels, J., Boersma, L., Jordaens, L., Merkely, B., Pokushalov, E., Sanders, P., Proff, J., Schunkert, H., Christ, H., Vogt, J., & Bänsch, D. (2018). Catheter ablation for atrial fibrillation with heart failure. *New England Journal of Medicine.*, *378*, 417–427.

Mountantonakis, S. E., Grau-Sepulveda, M. V., Bhatt, D. L., Hernandez, A. F., Peterson, E. D., & Fonarow, G. C. (2012). Presence of atrial fibrillation is independently associated with adverse outcomes in patients hospitalized with heart failure. *Circulation: Heart Failure*, *5*, 191–201.

Pellicori, P., Urbinati, A., Kaur, K., Zhang, J., Shah, P., Kazmi, S., Capucci, A., Cleland, J. G. F., & Clark, A. L. (2019). Prevalence and incidence of atrial fibrillation in ambulatory patients with heart failure. *The American Journal of Cardiology.*, *124*, 1554–1560.

Reiffel, J. A., Verma, A., Kowey, P. R., Halperin, J. L., Gersh, B. J., Wachter, R., Pouliot, E., Ziegler, P. D., & REVEAL AF Investigators. (2017). Incidence of previously undiagnosed atrial fibrillation using Insertable cardiac monitors in a high-risk population: The REVEAL AF study. *JAMA Cardiology*, *2*, 1120–1127.

Sanna, T., Diener, H.-C., Passman, R. S., Di Lazzaro, V., Bernstein, R. A., Morillo, C. A., Rymer, M. M., Thijs, V., Rogers, T., Beckers, F., Lindborg, K., & Brachmann, J. (2014). Cryptogenic stroke and underlying atrial fibrillation. *New England Journal of Medicine.*, *370*, 2478–2486.

Santhanakrishnan, R., Wang, N., Larson, M. G., Magnani, J. W., McManus, D. D., Lubitz, S. A., Ellinor, P. T., Cheng, S., Vasan, R. S., Lee, D. S., Wang, T. J., Levy, D., Benjamin, E. J., & Ho, J. E. (2016). Atrial fibrillation begets heart failure and vice versa: Temporal associations and differences in preserved versus reduced ejection fraction. *Circulation*, *133*, 484–492.

Savarese, G., & Lund, L. H. (2017). Global public health burden of heart failure. *Cardiac Failure Review*, *3*, 7–11.

How to cite this article: Aktas, M. K., Zareba, W., Butler, J., Younis, A., McNitt, S., Brown, M. W., Rao, N., Rao, N., Steinberg, J., Chen, L., Alexis, J. D., Vidula, H., & Goldenberg, I. (2023). Confirm Rx insertable cardiac monitor for primary atrial fibrillation detection in high-risk heart failure patients (Confirm-AF trial). *Annals of Noninvasive Electrocardiology*, *28*, e13021. https://doi.org/10.1111/anec.13021