Protocol Title:
Pragmatic Randomized Clinical Trial of Early Dronedarone versus Usual Care to Change and Improve Outcomes in Persons with First-Detected Atrial Fibrillation (CHANGE AFIB)

Protocol Number: 4.0 – 12MAY2023

Amendment Number: 3.0

Compound: Dronedarone

Brief Title: CHANGE AFIB

Study Phase: Post-market pragmatic clinical trial

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Regulatory Agency Identifier Number(s): NCT05130268

Authors:
This protocol was cowritten by the Duke Clinical Research Institute (DCRI) and the American Heart Association (sponsor). The outline of this template is consistent with the Guidelines for Good Pharmacoepidemiology Practices (GPP), The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist, and International Conference on Harmonisation (ICH) Guidance for Industry, E6 Good Clinical Practice (GCP): Consolidated Guidance.

1. Protocol Synopsis

PROTOCOL TITLE	Pragmatic Randomized Clinical Trial of Early Dronedarone versus Usual Care to Change and Improve Outcomes in Persons with First-Detected Atrial Fibrillation (CHANGE AFIB)
PROTOCOL TYPE	Randomized Pragmatic Clinical Trial
SPONSOR	American Heart Association
STUDY DESIGN	Multicenter, prospective, randomized, open-label clinical trial.
STUDY OBJECTIVE	Determine if early treatment with dronedarone is superior to usual care for the prevention of cardiovascular hospitalization or death from any cause in patients with first-detected atrial fibrillation.
STUDY HYPOTHESIS	We hypothesize that earlier administration of a well-tolerated antiarrhythmic drug proven to reduce hospitalization may result in improved cardiovascular outcomes and quality of life in patients with first-detected atrial fibrillation
TREATMENT REGIMEN(S) & RANDOMIZATION	Participants will be randomly allocated (1:1) to treatment with dronedarone on top of usual care versus usual care alone.
DURATION OF STUDY PARTICIPATION	Enrollment will occur over approximately 1.5 years, and subjects will be followed for 12 months.
NUMBER OF SUBJECTS	3000
NUMBER OF SITES	Total number: approximately 200

INCLUSION CRITERIA	1. Age >=21 years 2. First-detected atrial fibrillation (defined as atrial fibrillation diagnosed in the previous 120 days) 3. Electrocardiographic documentation of atrial fibrillation.* 4. Estimated life expectancy of at least 1 year 5. Patient or legal authorized representative capable of giving signed informed consent, which includes

* Electrocardiographic documentation includes a standard 12 lead electrocardiogram, mobile ECGs, ambulatory monitoring (e.g., Holter), telemetry, or electrograms from cardiac implanted electronic devices (i.e., pacemaker).

	compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
EXCLUSION CRITERIA	1. Patients with prior or planned treatment with rhythm control, either catheter ablation or chronic (>7 days) antiarrhythmic drug therapy.[†] 2. Planned cardiothoracic surgery. 3. New York Heart Association class III or IV heart failure or a hospitalization for heart failure in the last 4 weeks. 4. Patients with reduced ejection fraction (LVEF ≤40%). 5. Permanent atrial fibrillation. 6. Ineligible for oral anticoagulation, unless CHA_2DS_2-VASc is less than 3 in women or 2 in men. 7. Bradycardia with a resting heart rate < 50 bpm 8. PR interval >280 msec or 2nd degree or 3rd degree atrioventricular block without a permanent pacemaker/cardiac implanted electronic device. 9. Corrected QT interval ≥500 msec. 10. Pregnancy or breast feeding. 11. Severe hepatic impairment in the opinion of the investigator.
PRIMARY ENDPOINT	Time to first cardiovascular hospitalization or death from any cause through 12 months from randomization.
SECONDARY OUTCOMES	Evaluated through 12 months from randomization • WIN Ratio (according to the following hierarchy) 1. All-cause mortality 2. Ischemic stroke or systemic embolism 3. Hospitalization for new/worsening diagnosis of heart failure 4. Hospitalization for acute coronary syndrome • Cardiovascular hospitalization • All-cause mortality
TERTIARY OUTCOMES	Evaluated through 12 months from randomization • Ischemic stroke or systemic embolism • Arrhythmia-related hospitalization • Hospitalization for new/worsening diagnosis of heart failure • AF progression

[†] Acute use of an antiarrhythmic drug in the hospital is not exclusionary. For the purpose of this trial, prior antiarrhythmic drug therapy is defined as chronic antiarrhythmic drug therapy (>7 days).

	• Cardioversion • Catheter ablation of AF • Days alive and outside of the hospital
PATIENT REPORTED OUTCOMES	• Change in Atrial Fibrillation Effect on Quality of Life (AFEQT) from baseline to 12 months • Change in Mayo AF-Specific Symptom Inventory (MAFSI) from baseline to 12 months
INTERIM ANALYSES	Evaluation of safety and overall endpoint data will be performed every 6 months and evaluated by the data safety and monitoring board. There will be an aggregate analysis of the primary event rate every 6 months (after 500 participants have reached 6-month follow-up). A formal interim analysis for efficacy and futility will be performed after 50% of the anticipated events have occurred.

Protocol Title: Pragmatic Randomized Clinical Trial of Early Dronedarone versus Usual Care to Change and Improve Outcomes in Persons with First-Detected Atrial Fibrillation

Brief Title: CHANGE AFIB

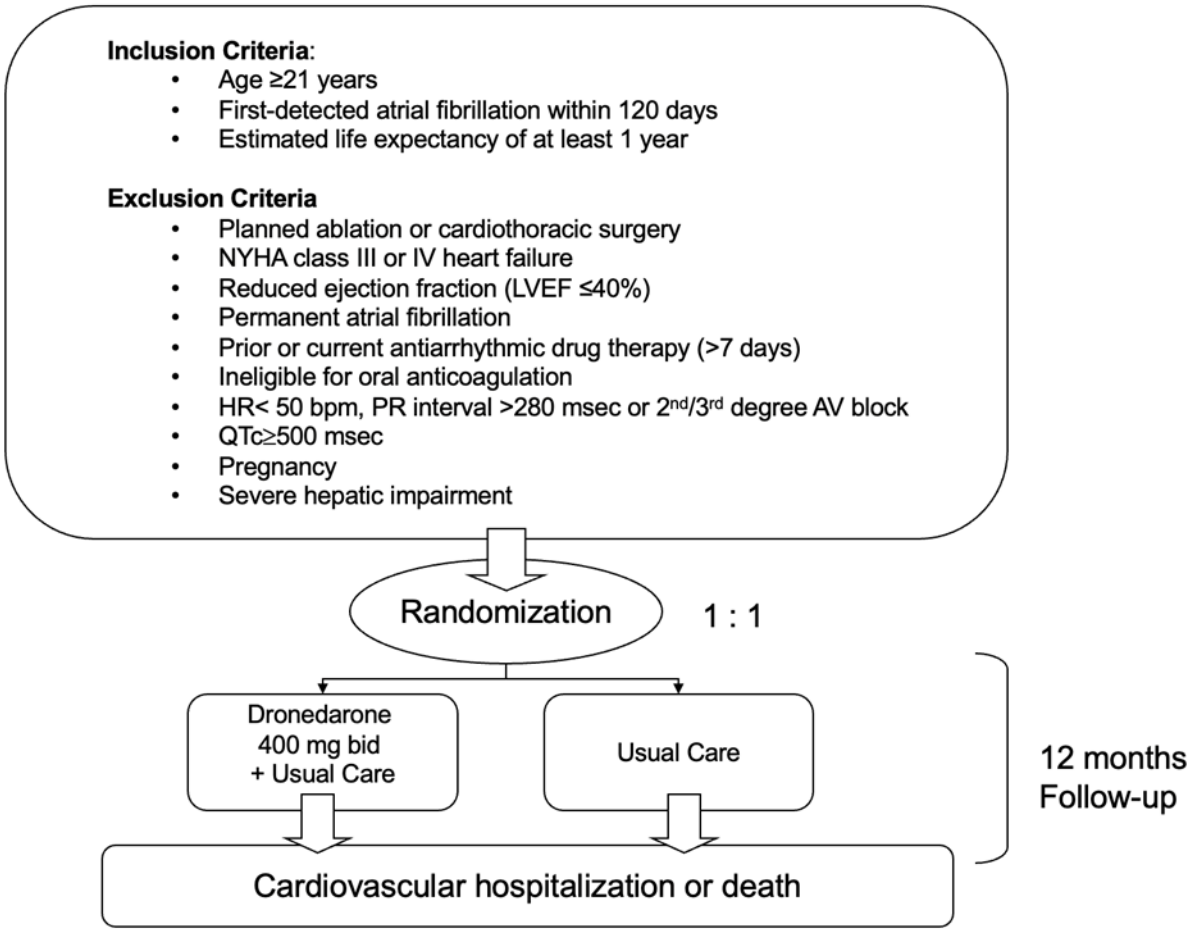
Rationale: While there are several completed clinical trials that address treatment strategy in patients with symptomatic and recurrent atrial fibrillation (AF), there are no randomized clinical trials that address first-line pharmacologic treatment for first-detected AF. Frequently, these patients are started on an atrioventricular nodal blocking agent (beta-blocker or non-dihydropyridine calcium channel blocker) in addition to oral anticoagulation if their stroke risk is elevated (according to **CHA_2DS_2-VASc)**. *We hypothesize that earlier administration of a well-tolerated antiarrhythmic drug proven to reduce hospitalization may result in improved quality of life and cardiovascular outcomes in patients presenting with first-detected AF.*

Objectives: Determine if treatment with dronedarone is superior to usual care alone for the prevention of cardiovascular hospitalization or death from any cause in patients with first-detected AF.

Brief Summary:
While there are several completed clinical trials that address treatment strategy in patients with symptomatic and recurrent AF, there are no randomized clinical trials that address treatment for first-detected AF. In usual care, these patients are often started on an atrioventricular nodal blocking agent (beta-blocker or non-dihydropyridine calcium channel blocker) along with stroke prevention therapy. *We hypothesize that earlier administration of a well-tolerated antiarrhythmic drug proven to reduce hospitalization may result in improved cardiovascular outcomes and quality of life in patients with first-detected AF.*

The purpose of this study is to determine if treatment with dronedarone on top of usual care is superior to usual care alone for the prevention of cardiovascular hospitalization or death from any cause in patients with first-detected AF. All patients will be treated with guideline-recommended stroke prevention therapy according to the CHA_2DS_2-VASc score. The treatment follow-up period will be 12 months. There will be two follow-up visits. Consistent with the pragmatic nature of the trial, the 1st follow-up will occur at 6 months (with a window of ±3 months) and the 2nd will occur at 12 months (with a window of ±30 days). Approximately 3000 patients will be enrolled and randomly assigned (1:1) to study intervention. The study intervention will be dronedarone 400 mg twice daily in addition to usual care versus usual care alone.

1.1. Study Schema



1.2. Schedule of Activities

TRIAL VISIT DATA CAPTURE REQUIREMENTS & SCHEDULE[1]

Trial Visit Data Capture Requirements	Baseline Visit (0-120 days post AFib DX)[2]	Follow Up Visit 1: 6 Month (± 3 months)	Follow Up Visit 2: 12 Month/End of Study (± 30 days)
Eligibility Confirmation (via Inclusion/Exclusion criteria)	X		
Informed Consent	X[3]		
Randomization	X[4]		
First-Detected Atrial Fibrillation Diagnosis Data	X[5]		
Quality of Life Instruments (AFEQT & MAFSI)	X		X
Medical History Data	X		
Demographic Data	X		
Ejection Fraction Data	X		
Vital Signs Data	X	X	X
Clinical Laboratory Data	X	X	X
Study Drug Shipment Request from Central Pharmacy	X[6]	X[6]	X[6]
Study Drug Accountability	X[7]	X[7]	X[7]
Documentation of Cardiac Procedures, if applicable		X	X
Outcomes (Primary, Secondary, & Tertiary)		X	X
Concomitant Medications	X	X	X
Adverse Events & Safety Events	X	X	X

[1]This schedule of activities table reflects the collection of data that is being conducted in the course of the patient's clinical care. This is a pragmatic trial and consistent with the design, there are no diagnostic procedures or laboratory studies required by the protocol. All of the data recorded are data captured in the course of the patient's clinical care.

[2]Baseline Visit may occur during an acute care encounter or during an outpatient visit occurring within 120 days of diagnosis.

[3]Consent must occur at the Baseline Visit (time of study enrollment) which may be an acute care encounter or outpatient visit occurring within 120 days of diagnosis.

[4]Randomization to occur at the Baseline Visit. Baseline Visit can be an acute care encounter or outpatient visit occurring within 120 days of diagnosis.

[5]*First-Detected Atrial Fibrillation Diagnosis* can be confirmed in either the acute care or outpatient setting via electrocardiographic documentation. Electrocardiographic documentation includes a standard 12 lead electrocardiogram, mobile ECGs, ambulatory monitoring (e.g., Holter), telemetry, or electrograms from cardiac implanted electronic devices (i.e., pacemaker). An acute care encounter is a visit to an emergency department, observation unit, or hospital admission.

[6]Study Drug shipments will be generated by the study team via the Central Pharmacy Vendor once every 4 months throughout the full duration of subject participation (12-months) for intervention arm subjects. These timepoints are referred to as 'Study Drug Dispensing Events'.

[7]Confirmation subject has received their study drug shipment and started taking the study drug within 10 days of Randomization. Study Drug Accountability should continue to be conducted by the study team at each study follow up visit and study drug dispensing event timepoint.

2. Introduction

2.1. Background & Rationale

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice, accounting for one-third of arrhythmia-related hospitalizations.[1] As many as 1 in 4 people develop AF over their lifetime after the age of 40 years.[2] The prevalence and burden of AF in the United States is substantial[3]; the age-adjusted incidence and prevalence has increased over the last 3 decades.[4, 5] Moreover, the number of Americans with AF is expected to increase 150% by 2050.[4, 6-10] The goals of care in the treatment of AF include (1) the management and reduction of risk factors, (2) prevention of tachycardia (rate control), (3) prevention of stroke, and (4) improvement of symptoms. Reduction or elimination of symptoms often requires rhythm control. Historically, randomized clinical trials have not demonstrated a mortality or stroke benefit with a rhythm control versus a rate control strategy.[11-13]

Despite the failure of prior randomized clinical trials to demonstrate the superiority of rhythm control, the recent EAST-AFNET 4 trial demonstrated that early introduction of a comprehensive rhythm-control strategy (within one year of diagnosis) is superior to guideline-based usual care in improving cardiovascular (CV) outcomes at a mean follow-up of 5 years.[14] The EAST-AFNET 4 trial found that early rhythm control reduced the primary outcome of CV death, stroke, hospitalization for HF, or acute coronary syndrome (HR 0.79, 96% confidence interval 0.66-0.94, p = 0.005). EAST-AFNET 4 also demonstrated a reduction in the risk of stroke with early introduction of rhythm control (HR 0.65, 95% CI 0.44-0.98), a finding that was also observed with dronedarone in the ATHENA trial. In addition, maintenance of sinus rhythm has been associated with improved quality of life and increased exercise capacity in some patients. Outside of clinical trials, a quality-of-life study from the Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation (RECORD-AF) found that rhythm control was associated with better quality of life.[15]

There are several antiarrhythmic drugs (AADs) available for rhythm control of AF.[16] Class I antiarrhythmic agents are predominantly limited to younger patients without coronary artery or structural heart disease. Patients with advanced chronic kidney disease, prolonged QT intervals, and/or severe left ventricular hypertrophy should not be treated with sotalol or dofetilide. Even when sotalol or dofetilide can be used, patients are often hesitant to start a medication that requires an inpatient hospitalization for drug loading and laboratory evaluation every 3 months. Amiodarone has been shown to be the most effective AAD for maintaining sinus rhythm in patients with AF;[17-19] however, based on its side effect profile, amiodarone is only recommended as a first-line agent under specific clinical circumstances.[16] Moreover, despite its efficacy, amiodarone has high rates of discontinuation due to frequent adverse events.[18, 20] In addition to its unfavorable side effects, several studies, including those of patients at risk for sudden cardiac death, have demonstrated an association between amiodarone use and higher mortality, as well as lower functional status.[21-24] In contrast to amiodarone, dronedarone is a much better tolerated antiarrhythmic medication.[25] In randomized controlled trials, dronedarone has been shown to prevent recurrent AF, improve rate control, and decrease cardiovascular hospitalization in patients with AF.[26, 27]

While there are several completed clinical trials that address treatment strategy in patients with symptomatic and recurrent AF, there are no randomized clinical trials that address treatment for first-detected or new-onset AF. After appropriate evaluation for oral anticoagulation, these patients are often started on an atrioventricular nodal blocking agent (beta-blocker or non-dihydropyridine calcium channel blocker). *We hypothesize that earlier administration of a well-tolerated antiarrhythmic drug proven to reduce hospitalization may result in improved quality of life and cardiovascular outcomes in patients with first-detected AF.*

2.2. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of dronedarone may be found in the investigator's brochure and package insert.

2.2.1. Risk Assessment

Dronedarone is approved by the Food and Drug Administration to reduce the risk of hospitalization for AF in patients with paroxysmal or persistent AF. The efficacy and safety of dronedarone 400 mg twice daily was evaluated in five controlled studies, ATHENA, ANDROMEDA, EURIDIS, ADONIS, and DAFNE, involving more than 6,000 patients with AF, including more than 3200 patients who received dronedarone.[26-31] As with any therapeutic agent, there are known risks with dronedarone therapy. These risks include hepatic injury, heart failure exacerbation, increased exposure to digoxin (2.5 fold increase), increased plasma concentration of tacrolimus, sirolimus, and other CYP 3A substrates, and very rare instances of pulmonary toxicity. The risks of dronedarone are felt to be outweighed by its benefits. The guideline recommendations provided by the European Society of Cardiology and AHA/ACC/HRS are commensurate with this risk benefit assessment.[32, 33]

2.2.2. Benefit Assessment

While there are no completed randomized clinical trials to guide selection or initiation of rhythm control therapies in patients with first-detected AF, there are recent trials that suggest benefit with both dronedarone antiarrhythmic therapy and early-initiation of rhythm control in persons with AF. The recent EAST-AFNET 4 trial demonstrated that early introduction of a comprehensive rhythm-control strategy (within one year of diagnosis) is superior to usual guideline-recommended care in improving cardiovascular (CV) outcomes at 5 years.[14] The median time from new-onset AF to randomization in the EAST-AFNET4 trial was 36 days. The trial found that early rhythm control reduced the primary outcome of CV death, stroke, hospitalization for HF, or acute coronary syndrome (HR 0.79, 95% confidence interval 0.66-0.94, p = 0.005). EAST-AFNET 4 also demonstrated a reduction in the risk of stroke with early introduction of rhythm control (HR 0.65, 95% CI 0.44-0.98), a finding that was also observed with dronedarone in the ATHENA trial. Thus, we hypothesize that early initiation of dronedarone in patients with new-onset AF will lead to a reduction in CV hospitalization or death.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
Determine if treatment with dronedarone on top of usual care is superior to usual care for the prevention of cardiovascular hospitalization or death from any cause in patients with first-detected AF.	• Time to cardiovascular hospitalization or death from any cause within 12 months of randomization.
Secondary	
To assess the efficacy of treatment with dronedarone on top of usual care compared to usual care for the following outcomes occurring within 12 months of randomization:	1. WIN Ratio (according to the following hierarchy) a. All-cause mortality b. Ischemic stroke or systemic embolism c. Hospitalization for new/worsening diagnosis of heart failure d. Hospitalization for acute coronary syndrome 2. Cardiovascular hospitalization 3. All-cause mortality
Tertiary	

To assess the efficacy of treatment with dronedarone on top of usual care compared to usual care for the following outcomes occurring within 12 months of randomization:	• Ischemic stroke or systemic embolism • Arrhythmia-related hospitalization • Hospitalization for new or worsening heart failure • AF progression • Cardioversion • Catheter ablation of AF • Days alive and out of the hospital
Patient Reported Outcomes	
	• Change in Atrial Fibrillation Effect on Quality of Life (AFEQT) from baseline to 12 months • Change in Mayo AF-Specific Symptom Inventory (MAFSI) from baseline to 12 months

Primary Outcome:

The primary study outcome is the first occurrence of unplanned CV hospitalization or death from any cause within 12 months of randomization. All unplanned hospitalizations (i.e. admission with an overnight stay in an acute care healthcare facility/hospital) for cardiovascular causes will

be considered a cardiovascular hospitalization. Similar to the ATHENA trial, the pre-specified causes of cardiovascular hospitalization will be defined as shown in Table 1.[34]

Table 1. Main Causes for Cardiovascular Hospitalization*

- Atherosclerosis related (cardiac, neurologic, or peripheral) hospitalization
- Myocardial infarction/acute coronary syndrome
- Stable angina pectoris or atypical chest pain
- Syncope/near-syncope
- Transient ischemic attack or stroke
- Atrial fibrillation, atrial flutter, atrial tachycardia, or any other supraventricular arrhythmia
- Ventricular arrhythmia
- Cardiovascular surgery, LVAD implantation, or cardiac transplantation
- Implantation of a permanent pacemaker, hemodynamic monitor, loop monitor, implantable cardioverter defibrillator, cardiac resynchronization device, or any other cardiac implanted electronic device
- Implantation of a left atrial appendage closure device
- Percutaneous coronary, cerebrovascular, valvular, or peripheral intervention
- Blood-pressure related hospitalization (hypotension, hypertension, or shock)
- Cardiovascular infection
- Major bleeding requiring hospitalization
- Pulmonary embolism or deep venous thrombosis
- New or worsening heart failure, including pulmonary edema or dyspnea of cardiac etiology

*This list represents the most frequent or main causes but is not exhaustive. Other documented causes of cardiovascular hospitalization will be included.

Secondary Outcomes:

1. **WIN Ratio:** The WIN ratio will be the key secondary endpoint.[35] Among the randomized patients, every patient in the dronedarone arm will be compared with every patient in the usual care arm. Within each pair of patients, the component outcomes will be compared in descending order of importance until one of the patients in the pair demonstrates a better outcome compared with the other. For the purpose of this trial the hierarchy of component outcomes are shown in **Table 2**. The components in the WIN ratio hierarchy are similar to the endpoints considered in the recent EAST-AFNET4 trial.

Table 2. Hierarchy of Outcomes for the WIN Ratio
1. All-cause mortality 2. Ischemic stroke or systemic embolism 3. Hospitalization for new/worsening diagnosis of heart failure 4. Hospitalization for acute coronary syndrome

2. **Cardiovascular Hospitalizations:** Given the importance of CV hospitalization as an outcome[36] from a clinical perspective, patient perspective, and economic perspective[37], there will be two analyses of CV hospitalization. The key secondary endpoint will be time to first unplanned CV hospitalization (similar to the component of the primary endpoint). However, a second exploratory analysis of unplanned cardiovascular hospitalization using a method to account for repeated events (Anderson-Gill extension) will also be performed.
3. **All-cause mortality.** The final secondary endpoint of interest is all-cause mortality. For descriptive purposes, deaths will be categorized by the site investigators according to the following categories: cardiovascular and non-cardiovascular. Cardiovascular deaths will be further classified into arrhythmic vs non-arrhythmic according the modified Hinkle-Thaler criteria, as used in several landmark cardiovascular trials. Patients who are well and (1) have a witnessed sudden collapse or (2) those found dead, but known to be alive and well in the previous 24 hours (e.g. no signs or symptoms of cardiorespiratory distress) will be defined as having arrhythmic death.[38]

Tertiary Outcomes:

- **Ischemic Stroke or Systemic Embolism:** The occurrence of ischemic stroke will be defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction. Symptoms or signs must persist ≥24 hours, unless the stroke is documented by CT, MRI or autopsy, in which case the duration of symptoms/signs may be less than 24 hours. Stroke may be classified as ischemic (including hemorrhagic transformation of ischemic stroke), hemorrhagic, or undetermined. Systemic embolism will be defined as acute arterial insufficiency or occlusion of the extremities or any non-CNS organ associated with clinical, imaging, surgical/autopsy evidence of arterial occlusion in the absence of other likely mechanism (e.g., trauma, atherosclerosis, or instrumentation).[39]
- **Arrhythmia-Related Hospitalization** will be defined as any unplanned hospitalization (i.e. admission with an overnight stay in an acute care healthcare facility/hospital) due to any tachy- or brady-arrhythmia.

- **Hospitalization for new or worsening heart failure** will be defined as any unplanned hospitalization (i.e. admission with an overnight stay in an acute care healthcare facility/hospital) due to a new diagnosis or worsening symptomatic heart failure.
- **AF Progression** will be defined as the transition from (a) paroxysmal to persistent or (b) persistent to permanent AF.[40]
- **Cardioversion** (either pharmacologic or electrical) with or without transesophageal echocardiographic guidance will be a tertiary endpoint.
- **Ablation of AF** including catheter ablation, surgical ablation, or hybrid (endocardial and epicardial ablation) ablation will be a tertiary endpoint.
- **Days Alive and Out of the Hospital.** Days alive and out of the hospital (DAOH, also referred to as "home time") is an emerging clinical trial endpoint that is both pragmatic and patient centered. [41] It is highly correlated with traditional time-to-event mortality and hospitalization outcomes.[42]

Patient reported outcomes. The inclusion of patient reported outcomes in clinical trials is widely recommended, including in the study of interventions for AF. [39, 43, 44] Patient reported quality of life will be defined according to the two prespecified AF-related quality of life instruments: (1) the Atrial Fibrillation Effect on Quality of Life (AFEQT) and (2) the Mayo AF-Specific Symptom Inventory (MAFSI).[45]

a. The AFEQT[46] is a 21-item, AF-specific health-related QOL questionnaire that assesses the impact of AF on patient-reported quality of life. The AFEQT includes a summary score (calculated from 18 of the questions) and subscale scores in three domains: symptoms, daily activities, and treatment concern. The summary and subscale scores range from 0 (corresponds to complete AF-related disability) to 100 (no AF-related disability). A change of 5 or more points in the AFEQT has been identified as a benchmark for a clinically meaningful difference in an individual patient.[47] Changes from baseline will be assessed overall as well as the proportion of patients in each treatment group who improved their AFEQT scores (12-month value minus baseline value) by ≥5, ≥10, ≥15, and ≥20 points. We will also conduct an analysis examining patterns of quality of life at baseline and 12 months by severity levels. AFEQT scores at baseline and 12 months will be divided into categories: severely impaired from AF (scores <70), mildly to moderately impaired (scores 70-89), and minimally impaired/asymptomatic (scores ≥90).[48]
b. The MAFSI was developed as a modification and update of the AF Symptom Checklist.[49] The trial will use a modified MAFSI[50] questionnaire comprised of a 10-item AF symptom checklist that asks about both the frequency and severity of each symptom. The frequency of symptoms is recorded as 0 (never), 1 (rarely), 2 (sometimes), 3 (often), or 4 (always). These responses are summed for a total Frequency Score that ranges from 0 (no AF symptoms) to 40 (worst score). Similarly, MAFSI Severity Scores are recorded as 1 (mild), 2 (moderate), or 3 (extreme). Severity scores are summed and range from 0 (no AF symptoms) to 30 (most severe AF symptoms). For an individual patient, a clinically meaningful change in the MAFSI has not previously been established and therefore will be considered to be about ¼ of the pooled baseline standard deviation (SD), or 1.6 points for the Frequency Score and 1.3 points for the Severity Score.[45] We will

also conduct a responder analysis for the MAFSI Frequency Score (>9, 4-9, and <4 to indicate severely symptomatic, mild to moderately symptomatic, and minimally symptomatic).[45]

The AFEQT and MAFSI will be collected on the trial case report form and will be administered by site coordinators at baseline and the 12-month follow-up visit.

4. Study Design

4.1. Overall Design

Dronedarone was approved in 2009 by the Food and Drug Administration to reduce the risk of CV hospitalization in patients with AF or atrial flutter. However, it is unknown if dronedarone (or any antiarrhythmic medication) can reduce CV hospitalization or death in patients with first-detected AF. This trial has been designed to address this important question. In order to facilitate the trial enrollment, data collection, and generalizability to clinical practice, the CHANGE AFIB study has been designed as an open-label pragmatic clinical trial nested within the Get With The Guidelines (GWTG) Atrial Fibrillation registry. At present the overall GWTG program is being implemented in over 2,300 hospitals across the U.S. and is comprised of over 9 million patient records, with an estimated 650,000 new patient records entered per year. The trial will utilize the existing GWTG registry network, data collection architecture, and experience to facilitate both enrollment and conduct of the trial.

The comparator arm will be "usual care." Thus, this study will compare usual care plus dronedarone versus usual care alone. While usual care often varies from center to center, usual care typically consists of an atrioventricular blocking agent (beta-blocker, non-dihydropyridine calcium channel blocker, or digoxin) without an antiarrhythmic drug.‡ As dronedarone has anti-adrenergic rate controlling properties, a low dose of beta-blocker or calcium-channel blocker is recommended in the USPI when starting dronedarone. In the dronedarone arm concomitant digoxin use will be contraindicated due to P-gp interaction based upon data from the PALLAS trial.[29, 51] All patients will receive oral anticoagulation for stroke prevention according to current guideline recommendations.[33]

CHANGE AFIB will leverage several critical advantages as a pragmatic clinical trial.[52] Data collection will be integrated into the Get With The Guidelines AFIB registry.[53, 54] The use of the GWTG-AFIB registry will also enhance subject recruitment and ensure the enrollment of a diverse group of patients. The randomized intervention will be compared with usual care thus further enhancing generalizability. Follow-up visits will be minimized to reduce patient burden. Moreover, follow-up visits will have "windows" to accommodate variation in follow-up intervals at different centers.

‡ Orally administered antiarrhythmic drugs for the treatment of atrial fibrillation include Vaughan-Williams class I and III medications, including flecainide, propafenone, sotalol, dofetilide, dronedarone, and amiodarone. Note, beta-blockers (class II) and non-dihydropyridine calcium channel blockers (class IV) are not membrane active antiarrhythmic medications.

4.2. Justification for Study Drug Intervention and Dose

Dronedarone is a non-iodinated benzofuran similar to amiodarone but is not associated with thyroid or pulmonary toxicity in randomized clinical trials or post-marketing observational studies.[55, 56] Dronedarone has electrophysiological characteristics spanning all 4 Vaughan-Williams anti-arrhythmic classes, with primarily class III effects. Initial trials suggested that dronedarone prolonged the time to recurrence of AF and reduced cardiovascular death and hospitalization.[26, 27]

The landmark ATHENA trial evaluated the efficacy and safety of dronedarone in patients with atrial arrhythmias (atrial fibrillation or atrial flutter). This trial did not include patients with a recent history of NYHA class IV heart failure or recent hospitalization for decompensated heart failure (<4 weeks). Approximately 30% of the ATHENA population had NYHA class I-III heart failure. ATHENA demonstrated that dronedarone 400 mg twice daily (in combination with background therapy) reduced the combined endpoint of CV hospitalization or death from any cause by 24% ($p<0.001$) compared with placebo. Of course, the ATHENA trial was not conducted in the special population of patients with a new diagnosis of AF. There are no randomized trials or guideline recommendations for antiarrhythmic therapy at the time of first-detected AF. A subgroup analysis from the ATHENA trial suggests that optimal outcomes may be achieved in those patients with shorter duration of AF (time from diagnosis).[57] Similar observations have also been made in patients undergoing other forms of rhythm control, including catheter ablation.[58] In this trial, patients with first-detected AF will be randomized to dronedarone on top of usual care versus usual care alone. Patients randomized to the intervention arm will be prescribed and treated with Dronedarone 400 mg bid. This dose has been chosen as it is the Food and Drug Administration approved dose as well as the dose recommended in current international guidelines.[26, 33] Dronedarone has also been shown to be an effective rate control agent as well. In the ERATO study, treatment with dronedarone 400 mg twice daily led to a mean reduction of 24.5 beat/min in patients with permanent AF when compared with placebo. In the EURIDIS/ADONIS studies the mean difference in patients with paroxysmal/persistent AF during AF recurrence was 14 beats/min.[27] Moreover, the dronedarone treated patients experienced improved rate control without any reduction in exercise tolerance as measured by maximal exercise.[59]

5. Study Population

- Eligible patients enrolled in GWTG-AFIB who provide informed consent will undergo randomization in a 1:1 fashion, to dronedarone on top of usual care or usual care alone.

5.1. Inclusion Criteria

Participants are eligible to be included in the study if the following apply:

1. Age 21 years or older.
2. First-detected atrial fibrillation (defined as atrial fibrillation diagnosed in the previous 120 days)
3. Electrocardiographic documentation of atrial fibrillation. [§]
4. Estimated life expectancy of at least 1 year
5. Patient or legal authorized representative capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Patients with prior or planned treatment with rhythm control, either catheter ablation or chronic (>7 days) antiarrhythmic drug therapy.[**]
2. Planned cardiothoracic surgery
3. New York Heart Association class III or IV heart failure or a hospitalization for heart failure in the last 4 weeks
4. Patients with reduced ejection fraction (LVEF ≤40%)
5. Permanent atrial fibrillation
6. Ineligible for oral anticoagulation, unless CHA_2DS_2-VASc is less than 3 in women or 2 in men.
7. Bradycardia with a resting heart rate < 50 bpm
8. PR interval >280 msec or 2nd degree or 3rd degree atrioventricular block without a permanent pacemaker/cardiac implanted electronic device.
9. Corrected QT interval ≥500 msec.
10. Pregnancy or breast feeding
11. Severe hepatic impairment in the opinion of the investigator

[§] Electrocardiographic documentation includes a standard 12 lead electrocardiogram, mobile ECGs, ambulatory monitoring (e.g., Holter), telemetry, or electrograms from cardiac implanted electronic devices (i.e., pacemaker).
[**] Acute use of an antiarrhythmic drug in the hospital is not exclusionary. For the purpose of this trial, prior antiarrhythmic drug therapy is defined as chronic antiarrhythmic drug therapy (>7 days).

6. Study Intervention, Usual Care, and Concomitant Therapy

The study intervention will be treatment with oral dronedarone 400 mg twice daily in addition to usual care. The comparator arm will be usual care alone. Usual care will be defined as best-practice, guideline-directed therapy of AF, including but not limited to (a) stroke prevention therapy, (b) rate-control, and (c) treatment of risk factors. More specifically, oral anticoagulation in those men with a CHA_2DS-$_2VASc$ score of 2 or greater or women with a CHA_2DS-$_2VASc$ score of 3 or greater, rate control, and treatment of concomitant cardiovascular conditions (e.g. coronary artery disease or heart failure) will be required in all trial participants. As defined in the protocol, those randomized to the dronedarone arm will be prescribed 400 mg oral dronedarone twice daily. Similar to the approach in the EAST trial, those randomized to usual care alone will initially be treated without rhythm-control therapy[14], however rhythm-control therapy (except dronedarone) may be initiated during follow-up in the usual care arm to ameliorate AF–related symptoms despite adequate rate-control therapy per current guideline recommendations. In the dronedarone arm concomitant digoxin use is contraindicated due to P-gp interaction based upon data from the PALLAS trial.[29]

6.1. Measures to Minimize Bias: Randomization

This is an open-label study; however, the specific intervention to be taken by an enrolled participant will be randomly assigned. Participants will be randomly assigned 1:1 to dronedarone on top of usual care or usual care alone. Randomization will be stratified by site and will be created with a random block size. All participants will be centrally assigned to randomized study intervention using an interactive web response system (IWRS). The site will contact the IWRS prior to the start of study intervention administration for each participant. The site will record the intervention assignment on the applicable case report form, if required. Potential bias will be reduced by the use of central randomization. Site staff and participants will not know the randomized sequence of treatment assignment prior to enrollment. Before the study is initiated, the log-in information and directions for the IWRS will be provided to each site.

6.2. Study Intervention Compliance

The intervention will be prescribed by the treating physician. Study drug will be supplied as part of the study. Participants in the intervention arm will have the study drug prescription generated on their behalf by the PI or treating physician. The study team will communicate with the Central Pharmacy vendor to initiate the study drug kit request and shipment direct to the subject's mailing address of choice. Subjects in the intervention arm will be contacted within 10 days of randomization to verify that they have received their study drug shipment and have started taking their prescription for dronedarone. Participants will self-administer the study intervention at home. Subjects in the intervention arm will receive 3 study drug kit shipments throughout their participation in the trial. Each study drug kit shipment will contain 4-months of study drug supply. Study drug compliance will be assessed at each visit. There is one guideline-recommended therapeutic dose of dronedarone. Any deviation(s) from the prescribed dosage regimen should be recorded. At the end of the study, the patient's physicians will determine whether to stop or continue dronedarone.

6.3. Concomitant Treatment

Concomitant drug therapy will be recorded in the case report form at baseline and all follow-up periods. In the dronedarone arm concomitant digoxin use is contraindicated due to P-gp interaction based upon data from the PALLAS trial.[29] Observational data have observed a small increased risk of bleeding in patients treated with dronedarone and direct acting oral anticoagulants, however, there is no apparent increased risk of intracranial bleeding.[60]

Cardioversion (pharmacologic or electrical) is not an exclusion and is permitted throughout the trial. Patients who are planned or scheduled to undergo catheter ablation during screening or at the baseline visit are not eligible. Following enrollment, if a patient experiences escalation of symptoms or refractory symptoms, escalation of rhythm control interventions, including catheter ablation, can be considered if deemed necessary by the patient's treating physician.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the schedule of activities for the last participant in the study. A participant is considered to have completed the study if he/she has completed all periods of the study including the last study visit at 12 months, or if deceased during the follow-up period.

Patients should not be discontinued when they experience a primary endpoint event. They should continue in the trial until the end of study visit at the end of follow-up. The study intervention therapy should be continued unless deemed otherwise by the treating physician or if the patient requires initiation of a different antiarrhythmic medication.

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study until they complete 12-month follow-up/final visit.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon. The participant will be permanently discontinued from the study intervention and the study at that time. If the participant withdraws consent for disclosure of future information, any data collection before withdrawal of consent can be used.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if he/she fails to complete the final 12 month visit and is unable to be contacted by the study site.
The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, [3] telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up.

8. Study Assessments and Procedures

Patient eligibility will be evaluated. Eligible patients who express interest in participating and express informed consent will undergo enrollment and randomization. Patients can be enrolled in the inpatient setting during an acute care encounter or in the outpatient setting so long as their new-onset atrial fibrillation was diagnosed in the prior 120 days. Atrial fibrillation can be documented by any electrocardiographic technology that provides an electrocardiographic tracing. Appropriate methods of diagnosis include a standard 12 lead electrocardiogram, mobile ECGs, ambulatory monitoring (e.g. Holter), telemetry, or electrograms from cardiac implanted electronic devices (i.e. pacemaker). At the baseline encounter (enrollment and randomization) data on the inclusion and exclusion criteria will be recorded in REDCap and the randomization module in REDCap will assign a treatment arm if participant meets all inclusion and exclusion criteria. The GWTG-AFIB registry data and additional data on the patient's medical and cardiovascular history will be recorded in the Get With The Guidelines CHANGE AFIB case report form. There are no special laboratory testing procedures or interventional procedures required by the protocol other than the randomized treatment. All data, including electrocardiographic, echocardiographic, laboratory, and other baseline data will be obtained as part of the participant's usual care. The two quality-of-life measures will be recorded at baseline and the 12 month follow-up visit as well as previously detailed.

There are two pre-specified follow-up encounters. The first will occur at 6 months with an eligibility window between 3 and 9 months. This encounter can be either in-person or a virtual assessment. At the 6-month visit, the 6-month follow-up form will be completed in the Get With The Guideline CHANGE AFIB case report form. The second pre-specified encounter will be the final follow-up encounter at 12 months (window of ± 30 days). Similar to the 6 month encounter, the final visit can be either in-person or a virtual assessment. At this final follow-up visit, the final visit module will be completed in the Get With The Guideline CHANGE AFIB case report form. Participants will also complete the final quality-of-life assessments at this same encounter. Patients who withdraw early or experience mortality will also have the final follow-up form completed.

8.1. Outcomes Assessments

Planned timepoints for all assessments are provided in the assessment table. Get With The Guidelines (GWTG) has several quality control assessments. Bi-annual data quality reports are provided by Duke Clinical Research Institute, which highlight the health of the GWTG data set, levels of element completion, and any areas of inconsistency. GWTG has an annual audit process, where a random sample of hospitals are selected for chart re-abstraction to independently assess data quality. GWTG sites are trained on the detailed data definitions provided to sites. Sites will be familiar and comfortable with the level of detail provided in the data definitions for various CHANGE AFIB endpoints. A nationwide audit was conducted among 147 hospitals and results were published in the *American Heart Journal* validating the health and reliability of the GWTG data set.[61]

8.1.1. Pregnancy

Women of reproductive age should use measures to prevent pregnancy during the study. Nevertheless, in case of pregnancy, the sponsor and coordinating center should be notified immediately. Follow-up of the pregnancy will be mandatory until the outcome has been determined. Pregnancy will be recorded as an adverse event in all cases and dronedarone should be immediately discontinued. Pregnancy will be considered a severe adverse event only if it fulfills the severe adverse event criteria.

8.2. Adverse Events (AEs) Serious Adverse Events (SAEs), and Other Safety Reporting

All participating centers will receive adequate training regarding pharmacovigilance (PV) specifications and reporting of adverse events among patients taking dronedarone as part of their onboarding process. Due to the pragmatic nature of the study, all Adverse Events should be reported by the individual facilities, as instructed by current regulations. Participating centers will be responsible to inform Sanofi of any Adverse Events or product technical complaints (i.e., changes in tablet odor, color, taste etc.) to Sanofi PV via email at CL-CPV-Receipt@Sanofi.com. In the event of email failure, adverse events can also be sent by e-Fax Number (+33 1 60 49 70 70) or fax machine at (011 33 1 60 49 70 70) immediately, but in any event within three business days after becoming aware of the adverse event. Any additional documentation of these cases will be conducted by Sanofi U.S. PV.

Prior clinical trials and observational data have demonstrated that individuals taking dronedarone have higher rates of diarrhea (9% vs 6% in ATHENA), bradycardia (3% versus 1% in ATHENA), QT-interval prolongation[††] (28% vs 19%) and cutaneous rash (5% versus 3%) than patients taking placebo. The case report form will query and document the occurrence of these and other adverse/safety events of interest as shown in **Table 3**.

Table 3. Pre-specified Safety Events of Interest
Symptomatic bradycardia
2nd or 3rd degree atrioventricular block
Pacemaker implantation
QT prolongation
Cutaneous rash

[††] QT prolongation was defined as QTc Bazett >450 msec in males or >470 msec in females.

Hepatic injury. *Hepatic injury will be defined as AST or ALT greater than 3x the upper limit of normal or clinical findings of hepatic insufficiency (jaundice, ascites, etc).*
New-onset heart failure (Note that this event is also an efficacy endpoint)
Heart failure hospitalization (Note that this event is also an efficacy endpoint)
Ventricular arrhythmia (including sustained ventricular tachycardia or nonsustained polymorphic VT/torsades)
Major bleeding. *Note Major bleeding will be defined according to International Society on Thrombosis and Haemostasis (ISTH) criteria: 1) Fatal bleeding, and/or 2) Symptomatic bleeding in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome), and/or 3) Bleeding causing a fall in hemoglobin level of 20 g L−1 (1.24 mmol L−1) or more, or leading to transfusion of two or more units of whole blood or red cells.*[62]

Initiation of dronedarone is contraindicated in patients with severe heart failure (NYHA class IV) or NYHA Class II - III heart failure with a recent decompensation requiring hospitalization or referral to a specialized heart failure clinic in the prior 4 weeks. Similar patients in the ANDROMEDA trial receiving dronedarone were observed to have a greater than 2-fold increase in mortality compared to placebo.[30] Accordingly, patients with NYHA class III and IV heart failure or any individual with a heart failure hospitalization in the last 4 weeks will be excluded from the trial. Additionally, any patients with an ejection fraction less than or equal to 40% will be excluded from the trial. The trial will document hospitalization for new or worsening heart failure during the follow-up period. It is important to note that dronedarone competes with creatinine for the renal tubular cation transport pathway, inhibiting tubular secretion of creatinine by approximately 18% and subsequently increasing serum creatinine without affecting renal function. This is of importance when considering down-titration/discontinuation of ACE/ARBs.

9. Statistical Considerations

The statistical analysis plan will be finalized before the first data and safety monitoring board (DSMB) meeting with blinded review of data, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary efficacy endpoints, patient reported outcomes, and key safety outcomes.

9.1. Statistical Hypotheses

The primary efficacy objective is to determine if treatment with dronedarone on top of usual care is superior to usual care for the prevention of unplanned cardiovascular hospitalization or death from any cause within 12 months of randomization in patients with first-detected atrial fibrillation.

- The null hypothesis is that the hazard rate of first unplanned cardiovascular hospitalization or death from any cause through 12 months of follow-up in the dronedarone + usual care arm is not different from the hazard rate in the usual care arm.

Key secondary efficacy objectives are to assess the efficacy of treatment with dronedarone on top of usual care versus usual care on

- WIN Ratio
- Time to first unplanned CV hospitalization
- All-cause mortality

There will also be a **patient reported outcomes** study. Patient reported change in quality of life at 12 months compared to baseline, assessed by the AFEQT and by the MAFSI AF-related quality of life questionnaires.

The key safety objective is to characterize the incidence of specific safety events of interest in patients taking dronedarone versus usual care (defined in **Table 3**).

9.1.1. Multiplicity Adjustment

Formal statistical hypothesis testing will be restricted to the primary objective and the WIN ratio (the first secondary objective). Type I error (one-sided α=0.025) will be controlled for these objectives using the gatekeeping testing strategy adapted from Maurer & Bretz (2013),[63] accounting for one unblinded interim analysis. The details of multiplicity adjustment are described in Section 9.4 below.

9.2. Analysis Sets

Population	Description
Intent-to-treat (ITT)	• All randomized participants will be included in the analyses according to the intervention arm they were assigned,

Population	Description
	regardless of treatment initiation, discontinuation or switching.
On treatment population and on-treatment period	• All randomized participants who took the assigned treatment will be included in the analyses according to the intervention arm they were assigned until they switch or discontinue the assigned treatment regimen. Follow-up will be censored 5 days after treatment switching or discontinuation, i.e. all events occurring until 5 days after discontinuation or switching to the other treatment group will be attributed to the randomized group and all events occurring later than 5 days after discontinuation or switching will be censored. Participants in the usual care arm who start dronedarone drug therapy will be considered to have switched treatment regimen. Participants in the dronedarone arm who temporarily suspend or are non-adherent with dronedarone for >14 consecutive days will be considered to have discontinued treatment.

9.3. Statistical Analyses

9.3.1. General Considerations

- A detailed Statistical Analysis Plan (SAP) will be developed and contained in a separate document. Study population details including the number randomized to each treatment arm, the number completing the study, and lost to follow-up will be described. Baseline participant characteristics will be summarized as means, standard deviations, medians, and/or 25th, 75th percentiles for continuous variables, and as counts and percentages for categorical variables. Unless otherwise stated, tests of hypotheses about the efficacy of dronedarone will be one-sided (α=0.025) and effect estimates will be presented with nominal 95% confidence intervals (CI).

9.3.2. Primary Efficacy Estimand Analysis

Question of Interest	Does the treatment with dronedarone on top of usual care reduce cardiovascular hospitalization or death from any cause in patients with first-detected atrial fibrillation without heart failure compared to usual care alone?
Objective Description / Study Population	Primary objective of the study / All randomized participants
Endpoint	Time from randomization to the first occurrence of unplanned cardiovascular hospitalization or death from any cause within 12 months of randomization

Intercurrent Events	Early study withdrawal or lost-to-follow-up: follow-up will be censored at the last date when patient event status was known. Analysis will assume that censoring is non-informative. All other intercurrent events will be ignored in these analyses.
Population Summary	Hazard ratio estimate based on a Cox proportional hazards model. Values below 1.0 suggest benefit from the treatment with dronedarone and usual care versus usual care alone.

The Cox proportional hazards model will be fit for time to first event with the treatment group as exposure variable. The treatment effect will be presented as a hazard ratio (dronedarone on top of usual care vs. usual care) and a 95% CI and P-value.

9.3.3. Key Secondary Efficacy Estimand Analysis

9.3.3.1. WIN Ratio

Question of Interest	To assess the efficacy of treatment with dronedarone on top of usual care versus usual care on **adverse outcomes** in patients with first-detected AF.
Objective Description / Study Population	Key secondary objective of the study / All randomized participants
Endpoint	Multivariate endpoint consisting of the measures listed in Table 2
Intercurrent Events	All other intercurrent events will be ignored in these analyses.
Population Summary	WIN ratio estimate. Values above 1.0 suggest benefit from the treatment with dronedarone and usual care versus usual care alone

Unmatched WIN ratio model according to Finkelstein and Schoenfeld method (1999) compares every patient on the dronedarone arm with every patient in the usual care arm, noting ‘winner’, ‘loser’, or ‘tied’ for each comparison. For each pair, the component outcomes will be compared in descending order of importance until one of the patients in the pair demonstrates a better outcome compared with the other. The hierarchy of component outcomes are shown in **Table 2**. For example, the dronedarone arm is a ‘winner’ or ‘loser’ according to who had an all-cause death first. If that is unknown, then whether they are labelled a ‘winner’ or ‘loser’ depends on who had an ischemic stroke or systemic embolism first, except all-cause mortality. In a similar way using the rest of hierarchy of outcomes, decide a ‘winner’ or ‘loser’. Otherwise, they are considered tied. The win ratio is the total number of dronedarone arm winners divided by the total number of dronedarone arm losers. A 95% CI and P-value will be obtained by Luo’s method (2015).[64] Statistical significance will be determined using the multiplicity adjustment methods described below in **Table 4**.

9.3.3.2. Cardiovascular Hospitalization

Question of Interest	To assess the efficacy of treatment with dronedarone on top of usual care versus usual care on the rate of first occurrence of unplanned **cardiovascular hospitalization** in patients with first-detected AF.
Objective Description / Study Population	Key secondary objective of the study / All randomized participants
Endpoint	Main analysis: Time from randomization to the first occurrence of unplanned cardiovascular hospitalization within 12 months of randomization. Exploratory analysis: Overall rate of all recurrent cardiovascular hospitalization events within 12 months of randomization.
Intercurrent Events	Death – follow-up will be censored at date of death. Hazard ratio for cardiovascular hospitalization will be estimated among participants still alive and in follow-up. Early study withdrawal or lost-to-follow-up – follow-up will be censored at the last date when patient event status was known. Analysis will assume that censoring is non-informative. All other intercurrent events will be ignored in these analyses.
Population Summary	Main analysis: Hazard ratio estimate based on a Cox proportional hazards model for time to first event. Exploratory analysis: Hazard ratio estimate based on a proportional intensity model developed by Anderson & Gill (1982) using all recurrent events. Hazard Ratio values below 1.0 suggest benefit from the treatment with dronedarone and usual care versus usual care alone

For the main analysis the Cox proportional hazards model will be fit for time to first event with the treatment group as exposure variable. Follow-up will be censored early if death occurs prior to cardiovascular hospitalization. The treatment effect will be presented as a cause-specific hazard ratio (dronedarone on top of usual care vs. usual care) and a nominal 95% CI.

For the exploratory analysis a generalization of the Cox model to handle recurrent events, developed by Anderson & Gill (1982), with robust standard errors to account for individual patients' heterogeneity. Even though the Anderson-Gill approach assumes independence between all observed event times irrespective whether these event times correspond to the same patient or to different patients, this approach will be the analysis method for the total number of events of cardiovascular hospitalization. The treatment effect will be presented as a hazard ratio (dronedarone on top of usual care vs. usual care) and a nominal 95% CI.

9.3.3.3. All-cause Mortality

Question of Interest	To assess the efficacy of treatment with dronedarone on top of usual care versus usual care on the rate of **all-cause mortality** in patients with first-detected atrial fibrillation
Objective Description / Study Population	Key secondary objective of the study / All randomized participants
Endpoint	Time from randomization to death within 12 months of randomization
Intercurrent Events	Early study withdrawal or lost-to-follow-up – follow-up will be censored at the last date when patient event status was known. Analysis will assume that censoring is non-informative. All other intercurrent events will be ignored in these analyses.
Population Summary	Hazard ratio estimate based on a Cox proportional hazards model. Values below 1.0 suggest benefit from the treatment with dronedarone and usual care versus usual care alone

The Cox proportional hazards model will be fit for time to death with the treatment group as exposure variable. The treatment effect will be presented as a hazard ratio (dronedarone and usual care vs. usual care) and a nominal 95% CI.

9.3.4. Tertiary Efficacy Endpoints Analysis

Analysis methods for the tertiary efficacy endpoints will be provided in the statistical analysis plan.

9.3.5. Patient reported outcomes (12-month change in quality of life)

Question of Interest	To estimate the effect of treatment with dronedarone versus usual care on 12-month **change in patient reported quality of life** in patients with first-detected AF.
Objective Description / Study Population	Patient reported outcomes study / All randomized participants who did not die during follow-up
Endpoints	12-month change in quality of life compared to baseline, assessed by AFEQT Overall Score and by MAFSI Total Severity score.

Intercurrent Events	Death – 12-month change in quality of life will be assessed in participants who were alive at the 12-month follow-up assessment. Early study withdrawal, lost-to-follow-up, or missing assessment – analysis will assume that missing data due to withdrawal, lost-to-follow-up or other reasons is not informative conditional on patient demographics, heart failure status, time since AF diagnosis, and baseline value of quality of life assessments. Analysis will adjust for missing data using inverse probability weighting.
Population Summary	Difference in mean change from baseline between dronedarone versus usual care, estimated using analysis of covariance. For the AFEQT, a mean difference greater than zero suggests benefit from treatment with dronedarone versus usual care alone. For the MAFSI, a mean difference less than zero suggests benefit from treatment with dronedarone versus usual care alone.

This objective will be assessed using Analysis of Covariance (ANCOVA) with the 12-month change in quality of life (12-month score – baseline score) as response variable, treatment group as exposure, and baseline score as covariates. Inverse probability weighting will be used to adjust for missing data. The treatment effect will be presented as the difference between mean 12-month change (dronedarone and usual care vs. usual care) and a nominal 95% CI.

9.3.6. Safety Analyses

All safety analysis will be performed in the on-treatment (OT) population during the on-treatment period. A linearized event rate for each safety endpoint (see Section 8.2) for each treatment group will be calculated as percentage per patient year, and the approximate 95% CI for the difference of linearized event rates will be calculated as

$$\left(\frac{r_D}{T_D} - \frac{r_U}{T_U}\right) \pm 1.96 \sqrt{\frac{r_D}{T_D^2} + \frac{r_U}{T_U^2}},$$

where subscript *D* and *U* denote the dronedarone and usual care arms, respectively, and *r* is the total number of occurrences of the safety outcome, and *T* is the total patient time (years).[65]

9.3.7. Other Analyses

<u>On treatment analysis of efficacy endpoints</u>
As sensitivity analyses, the primary and key secondary objectives will be tested using the OT population during the on-treatment period.

<u>Pre-Specified Subgroups of Interest</u>
Subgroup analyses for the primary outcome will be performed to assess whether the therapeutic effect is consistent across all patients, or whether it varies according to specific patient

characteristics. These analyses will focus on whether the relative therapeutic effect differs according to the following baseline variables:

- Age (<70 years vs. ≥70 years)
- Sex (male vs. female)
- Race (white vs. racial minorities)
- AF type (paroxysmal vs. persistent, or long-standing persistent)
- Left atrial dimension (<50 mm versus >=50 mm)
- AF duration (<30 days versus ≥30 days)
- Structural heart disease (present vs. absent)
- Hypertension (present vs. absent)
- Chronic kidney disease (estimated eGFR ≤60 vs. >60 ml/min)
- CHA_2DS_2-VASc score (0-1 vs. ≥2 excluding sex)
- Sleep Apnea (present vs. absent)
- BMI (<30 vs. ≥30)
- Heart failure vs no heart failure
- Left ventricular ejection fraction (LVEF) (41-55 vs. >55)
- Recent hospitalization for AF vs None

Cox proportional hazards regression modeling will be used to assess whether treatment effect is heterogeneous across pre-specified subgroups. For each subgroup analysis, the Cox proportional hazards model will be fit for time to first event including the subgroup as a stratification factor, and the treatment group and interaction between treatment and subgroup as covariates. The treatment effect within each subgroup level will be presented as a hazard ratio (dronedarone on top of usual care vs. usual care) and a 95% CI. Heterogeneity will be assessed by presenting the interaction P-value, using a two-sided test.

9.4. Data Safety & Monitoring Board & Interim Analysis

There will be a Data and Safety Monitoring Board (DSMB) in this pragmatic clinical trial. The DSMB will be an independent group of experts that advises the principal investigator, steering committee, and study investigators. The DSMB will consist of one statistician and two clinicians with expertise in clinical trials and in the management of AF. The members of the DSMB will serve in an individual capacity and provide their expertise and recommendations.

The DSMB will meet approximately every 6 months to monitor the recruitment and conduct of trial, data quality and timeliness, the distribution of therapies within the study groups, the occurrence of safety and other events selected to their discretion during the course of the trial. The DSMB chair will receive a quarterly report between two regular meetings.

Since the event rate of the primary outcome is closely associated with the statistical study power, a blinded sample size and power analysis based on the overall event rate will be included in the regular DSMB report. Recommendations for the sample size adjustment by DSMB will be made before the interim analysis based on trying to maintain ≥ 85% power for the primary outcome and allow to increase as much as 35% but no reduction.

If a clinically significant imbalance in efficacy or safety events between the groups is observed at any time, the DSMB Chair may request an unblinded analysis. Similarly, if the DSMB identifies any other concerns, the Chair can call a separate meeting. A DSMB charter providing operating procedures and responsibilities will be discussed, drafted, and implemented by the DSMB and an unblinded statistician.

In addition to these routine safety reviews, an interim analysis for efficacy and futility of the primary objective is planned at approximately 50% of total information, i.e. when 50% of the expected total number of events (approximately 733 events, see **Table 4** below) are collected. The Lan-DeMets spending function similar to the O'Brien-Fleming boundaries will be used to monitor the efficacy of the primary outcome as a guide for the DSMB. See **Table 4** for the details of these procedures. This spending function is conservative in that priority is given to preserving power for the final analysis with the use of stringent stopping rules early in the study. For futility, conditional power will be calculated under originally hypothesized hazard ratio, the null hypothesis and the observed trend at the interim analysis and will be compared with 10%. The futility stopping rules will be considered non-binding by the DSMB in their review of interim data.

If the primary endpoint is declared to be statistically significant in the favorable direction at a one-sided alpha level of 0.025, WIN ratio as the first key secondary endpoint will be tested according to an OBF-like boundary. See **Table 4** for the details of these procedures.

Table 4. Significance level for the primary endpoint and WIN ratio

	At the interim analysis at 50%	**At the final analysis**	**One-sided nominal significance level**
One-sided significance level for the primary hypothesis	0.0153	0.0245	0.025
One-sided significance level for WIN ratio if the primary endpoint is declared significant	0.0153	0.0245	0.025

The Steering Committee will approve the timing of all interim analyses proposed by the DSMB. If the DSMB determines there is absence of futility, acceptable safety, and pre-trial assumptions regarding the endpoint event rate and other factors are correct, the trial will continue as planned.

9.5. Sample Size Determination

- With a planned accrual time of 1.5 years, a fixed follow-up period of 1 year, an assumed lost to follow up of 20% before 12 months (assuming exponential distribution for time-to-censoring), a two-sample log-rank test with two-sided alpha of 0.05, a cumulative incidence function (CIF) of 30% at 12 months in the usual care arm, an assumed hazard ratio of 0.79, one interim analysis using the Lan-DeMets spending function similar to the O'Brien-Fleming boundaries, a planned sample size of 3000 patients (1500 patient per arm) provides approximately 89% study power as shown in the following table:

Table 5. Study power and number of events with 3000 patients
Estimated by Markov chain Monte Carlo simulations with 10,000 iterations

Hazard Ratio (Dronedarone vs. Usual care)	0.78	0.79	0.80
Nominal Power	0.92	0.89	0.86
Total number of events	730	733	737

- The study will be conducted at sites participating in the GWTG-AFIB Registry. Some sites will be centers that are established GWTG-AFIB sites and others will be recruited to participate in GWTG-AFIB for the purpose of this study. We will attempt to achieve a total of up to 200 sites. There have been more than 40,000 patients included in the GWTG-AFIB Registry. For the purpose of this pragmatic trial, patients will be approached at the time of their first-detected AF episode. Preliminary query of the GWTG-AFIB database suggests that greater than 1400 patients were enrolled each year in GWTG with new-onset AF and no heart failure. Using the Jan 2020 GWTG-AFIB data harvest, there were a total of 8,192 patients meeting the inclusion/exclusion criteria (see Table 6). As we plan to include sites beyond GWTG-AFIB sites, we plan to enrol 3000 patients in 18 months.

Table 6. Distribution of Admissions for GWTG-AFIB Registry Patients

Admission Year	Frequency (patients)	Percent	Cumulative Frequency (patients)	Cumulative Percent
2013	65	0.79%	65	0.79%
2014	390	4.76%	455	5.55%
2015	1229	15.00%	1684	20.56%
2016	1429	17.44%	3113	38.00%
2017	1750	21.36%	4863	59.36%
2018	1871	22.84%	6734	82.20%
2019	1458	17.80%	8192	100.00%

In the ATHENA trial a post-hoc analysis was conducted that analyzed events according to the duration of AF history.[26] Using event rates in the placebo and dronedarone arms among patients with a duration of AF history <3 months (45% of the ATHENA study cohort), the expected hazard ratio for dronedarone vs. placebo was ~0.79 for the primary endpoint of CV hospitalization or death evaluated through 12 months of follow-up. The event accumulation in placebo arm through 12 months in the ATHENA trial was CIF% of approximately 10%, 20%, 25%, and 30% at 3, 6, 9, and 12 months, respectively, as shown in **Figure 1**.[26] The estimated sample size by various statistical power and hazard ratio are shown in **Table 7**. To account for one interim analysis using the Lan-DeMets spending function similar to the O'Brien-Fleming boundaries, the estimated sample size should be inflated by 1.01.[66] Therefore, the study will enroll approximately 3000 patients.

Figure 1. Event accumulation in placebo arm through 12 months in the ATHENA trial

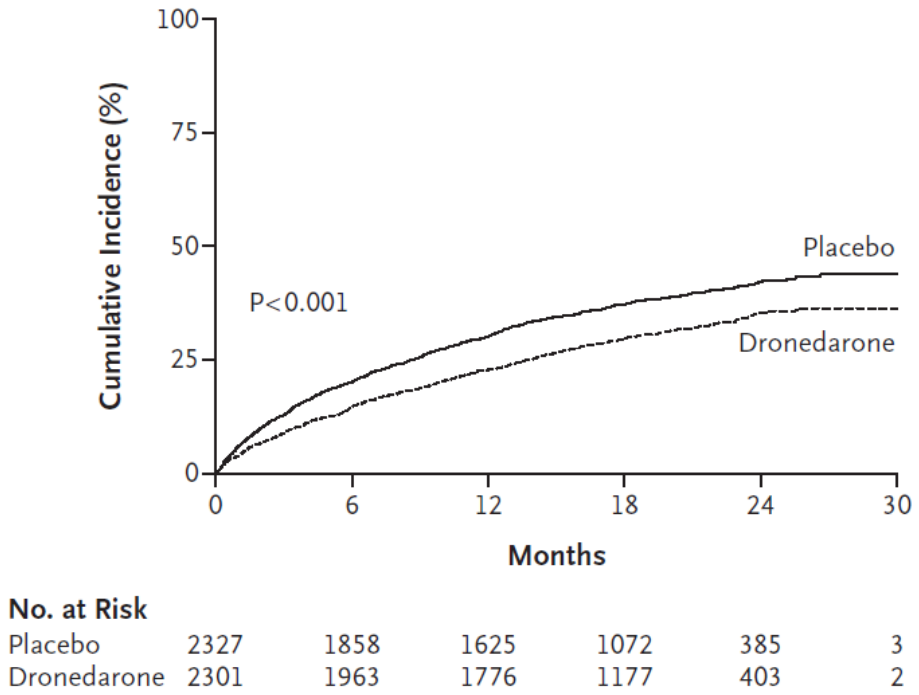


Table 7. Total sample size estimated with 20% attrition by 12 months, two-sided log-rank test, alpha=0.05, placebo CIF curve like ATHENA (30% with event by 12 months)

	Hazard Ratio (Dronedarone vs. Placebo)					
Nominal Power	**0.75**	**0.76**	**0.77**	**0.78**	**0.79**	**0.80**
0.85	1794	1960	2148	2364	2612	2898
0.86	1848	2018	2212	2434	2688	2984
0.87	1904	2080	2280	2508	2770	3074
0.88	1964	2146	2352	2588	2858	3172
0.89	2030	2216	2430	2674	**2954**	3278
0.90	2100	2294	2514	2766	3056	3392

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
  - Applicable ICH Good Clinical Practice (GCP) guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, and all other applicable local regulations.

10.1.2. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or their legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Electronic Informed Consent (eIC) may be used to either supplement or replace paper-based informed consent processes.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.

- A copy of the ICF(s) must be provided to the participant or their legally authorized representative.

10.1.3. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs. The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in Get With The Guidelines AFIB.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 5 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.4. Study and Site Start and Closure

First Act of Recruitment
The study start date is the date on which the clinical study will be open for recruitment of participants.

Study/Site Termination
- The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor.
- Study sites will be closed upon study completion.
- A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.
- The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators and the IECs/IRBs of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.5. Registry Organization and Leadership

Duke University and Duke Clinical Research Institute (DCRI) along with the sponsor (American Heart Association) will be responsible for the CHANGE AFIB trial and its design, implementation, and leadership. A Steering Committee that includes representatives from

cardiology, electrophysiology, biostatisticians and clinical trialists will govern the operations of the trial. The Scientific Advisory Committee consists of Executive Co-Chairmen, an Executive Committee, and a Steering Committee.

Steering Committee

The Steering Committee will include prominent US thought leaders in clinical trial conduct, experts in the evaluation and management of atrial fibrillation, and the study leadership. An appropriately qualified representative from Sanofi will have a voting seat on the Steering Committee. The Steering Committee will be responsible for the scientific leadership of the CHANGE AFIB Trial. The Steering Committee will be led by the study Chair.

10.1.6. Intended Use of Information and Publication

Data generated from the study will be published. The Steering Committee will also serve as the Publication Committee and shall oversee the publication of study data. The Publication Committee will function as an independent body of scientific and medical experts acting to fulfill the study sites' obligations to the study participants, and shall act to facilitate, encourage, and coordinate complete and accurate dissemination of the results of the study.

All manuscripts approved by the Publication Committee shall conform to the Uniform Requirements for Manuscript Submitted to Biomedical Journals, including, but not limited to the standards for authorship.

- The steering committee will submit all manuscripts or abstracts to the American Heart Association, Duke Clinical Research Institute, and Sanofi for approval before submission. This allows all organizations to provide comments and ensure accuracy of any included statements.

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

There are no required laboratory tests for the purpose of this trial, however, laboratory data that is conducted in the course of usual care will be collected in the case report forms. Regarding potential guidance in the event of hepatic injury: ALT [or AST] >3 × upper limit of normal (ULN) and total bilirubin >2 × ULN (> 35% direct bilirubin) OR ALT [or AST] >3 × ULN and international normalized ratio (INR) > 1.5 (if INR measured) may indicate severe liver injury (Hy's law), and must be reported in an expedited manner.

11. References

1. Wann LS, Curtis AB, January CT, Ellenbogen KA, Lowe JE, Estes NA, 3rd, Page RL, Ezekowitz MD, Slotwiner DJ, Jackman WM, Stevenson WG, Tracy CM, Fuster V, Ryden LE, Cannom DS, Le Heuzey JY, Crijns HJ, Lowe JE, Curtis AB, Olsson SB, Ellenbogen KA, Prystowsky EN, Halperin JL, Tamargo JL, Kay GN, Wann LS, Jacobs AK, Anderson JL, Albert N, Hochman JS, Buller CE, Kushner FG, Creager MA, Ohman EM, Ettinger SM, Stevenson WG, Guyton RA, Tarkington LG, Halperin JL and Yancy CW. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (Updating the 2006 Guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2011;57:223-42.
2. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, D'Agostino RB, Massaro JM, Beiser A, Wolf PA and Benjamin EJ. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation*. 2004;110:1042-6.
3. Feinberg WM, Blackshear JL, Laupacis A, Kronmal R and Hart RG. Prevalence, age distribution, and gender of patients with atrial fibrillation: analysis and implications. *Archives of internal medicine*. 1995;155:469.
4. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, Seward JB and Tsang TS. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation*. 2006;114:119-25.
5. Chamberlain AM, Gersh BJ, Alonso A, Chen LY, Berardi C, Manemann SM, Killian JM, Weston SA and Roger VL. Decade-long trends in atrial fibrillation incidence and survival: a community study. *Am J Med*. 2015;128:260-7 e1.
6. Novaro GM, Asher CR, Bhatt DL, Moliterno DJ, Harrington RA, Lincoff AM, Newby LK, Tcheng JE, Hsu AP and Pinski SL. Meta-analysis comparing reported frequency of atrial fibrillation after acute coronary syndromes in Asians versus whites. *The American journal of cardiology*. 2008;101:506-9.
7. Go AS, Hylek EM, Phillips KA, Chang YC, Henault LE, Selby JV and Singer DE. Prevalence of diagnosed atrial fibrillation in adults. *JAMA: the journal of the American Medical Association*. 2001;285:2370-2375.
8. Furberg CD, Psaty BM and Manolio TA. Prevalence of atrial fibrillation in elderly subjects (the Cardiovascular Health Study). *The American journal of cardiology*. 1994;74:236-241.
9. Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP, White R, Furberg CD and Rautaharju PM. Incidence of and risk factors for atrial fibrillation in older adults. *Circulation*. 1997;96:2455-2461.
10. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ and Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. *JAMA: the journal of the American Medical Association*. 1994;271:840-844.
11. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Kellen JC, Greene HL, Mickel MC, Dalquist JE and Corley SD. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med*. 2002;347:1825-33.
12. Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, Bourassa MG, Arnold JM, Buxton AE, Camm AJ, Connolly SJ, Dubuc M, Ducharme A, Guerra PG, Hohnloser SH, Lambert J, Le Heuzey JY, O'Hara G, Pedersen OD, Rouleau JL, Singh BN, Stevenson LW,

Stevenson WG, Thibault B, Waldo AL, Atrial F and Congestive Heart Failure I. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med*. 2008;358:2667-77.
13. Van Gelder IC, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T, Said SA, Darmanata JI, Timmermans AJ, Tijssen JG and Crijns HJ. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med*. 2002;347:1834-40.
14. Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt L, Elvan A, Fetsch T, van Gelder IC, Haase D, Haegeli LM, Hamann F, Heidbuchel H, Hindricks G, Kautzner J, Kuck KH, Mont L, Ng GA, Rekosz J, Schoen N, Schotten U, Suling A, Taggeselle J, Themistoclakis S, Vettorazzi E, Vardas P, Wegscheider K, Willems S, Crijns H, Breithardt G and Investigators E-AT. Early Rhythm-Control Therapy in Patients with Atrial Fibrillation. *N Engl J Med*. 2020;383:1305-1316.
15. Ha AC, Breithardt G, Camm AJ, Crijns HJ, Fitzmaurice GM, Kowey PR, Le Heuzey JY, Naditch-Brule L, Prystowsky EN, Schwartz PJ, Torp-Pedersen C, Weintraub WS and Dorian P. Health-related quality of life in patients with atrial fibrillation treated with rhythm control versus rate control: insights from a prospective international registry (Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation: RECORD-AF). *Circ Cardiovasc Qual Outcomes*. 2014;7:896-904.
16. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Jr., Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW and American College of Cardiology/American Heart Association Task Force on Practice G. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2014;64:e1-76.
17. Roy D, Talajic M, Dorian P, Connolly S, Eisenberg MJ, Green M, Kus T, Lambert J, Dubuc M, Gagne P, Nattel S and Thibault B. Amiodarone to prevent recurrence of atrial fibrillation. Canadian Trial of Atrial Fibrillation Investigators. *N Engl J Med*. 2000;342:913-20.
18. Singh BN, Singh SN, Reda DJ, Tang XC, Lopez B, Harris CL, Fletcher RD, Sharma SC, Atwood JE, Jacobson AK, Lewis HD, Jr., Raisch DW, Ezekowitz MD and Sotalol Amiodarone Atrial Fibrillation Efficacy Trial I. Amiodarone versus sotalol for atrial fibrillation. *N Engl J Med*. 2005;352:1861-72.
19. Investigators AFADS. Maintenance of sinus rhythm in patients with atrial fibrillation: an AFFIRM substudy of the first antiarrhythmic drug. *J Am Coll Cardiol*. 2003;42:20-9.
20. Goldschlager N, Epstein AE, Naccarelli G, Olshansky B and Singh B. Practical guidelines for clinicians who treat patients with amiodarone. Practice Guidelines Subcommittee, North American Society of Pacing and Electrophysiology. *Archives of internal medicine*. 2000;160:1741-8.
21. Packer DL, Prutkin JM, Hellkamp AS, Mitchell LB, Bernstein RC, Wood F, Boehmer JP, Carlson MD, Frantz RP, McNulty SE, Rogers JG, Anderson J, Johnson GW, Walsh MN, Poole JE, Mark DB, Lee KL and Bardy GH. Impact of implantable cardioverter-defibrillator, amiodarone, and placebo on the mode of death in stable patients with heart failure: analysis from the sudden cardiac death in heart failure trial. *Circulation*. 2009;120:2170-6.
22. Fishbein DP, Hellkamp AS, Mark DB, Walsh MN, Poole JE, Anderson J, Johnson G, Lee KL, Bardy GH and Investigators SC-H. Use of the 6-min walk distance to identify variations in treatment benefits from implantable cardioverter-defibrillator and amiodarone: results from the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial). *J Am Coll Cardiol*. 2014;63:2560-8.

23. Thomas KL, Al-Khatib SM, Lokhnygina Y, Solomon SD, Kober L, McMurray JJ, Califf RM and Velazquez EJ. Amiodarone use after acute myocardial infarction complicated by heart failure and/or left ventricular dysfunction may be associated with excess mortality. *Am Heart J*. 2008;155:87-93.
24. Saksena S, Slee A, Waldo AL, Freemantle N, Reynolds M, Rosenberg Y, Rathod S, Grant S, Thomas E and Wyse DG. Cardiovascular outcomes in the AFFIRM Trial (Atrial Fibrillation Follow-Up Investigation of Rhythm Management). An assessment of individual antiarrhythmic drug therapies compared with rate control with propensity score-matched analyses. *J Am Coll Cardiol*. 2011;58:1975-85.
25. Piccini JP, Hasselblad V, Peterson ED, Washam JB, Califf RM and Kong DF. Comparative efficacy of dronedarone and amiodarone for the maintenance of sinus rhythm in patients with atrial fibrillation. *J Am Coll Cardiol*. 2009;54:1089-95.
26. Hohnloser SH, Crijns HJ, van Eickels M, Gaudin C, Page RL, Torp-Pedersen C, Connolly SJ and Investigators A. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med*. 2009;360:668-78.
27. Singh BN, Connolly SJ, Crijns HJ, Roy D, Kowey PR, Capucci A, Radzik D, Aliot EM, Hohnloser SH, Euridis and Investigators A. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. *N Engl J Med*. 2007;357:987-99.
28. Boriani G, Blomstrom-Lundqvist C, Hohnloser SH, Bergfeldt L, Botto GL, Capucci A, Lozano IF, Goette A, Israel CW, Merino JL and Camm AJ. Safety and efficacy of dronedarone from clinical trials to real-world evidence: implications for its use in atrial fibrillation. *Europace*. 2019;21:1764-1775.
29. Connolly SJ, Camm AJ, Halperin JL, Joyner C, Alings M, Amerena J, Atar D, Avezum A, Blomstrom P, Borggrefe M, Budaj A, Chen SA, Ching CK, Commerford P, Dans A, Davy JM, Delacretaz E, Di Pasquale G, Diaz R, Dorian P, Flaker G, Golitsyn S, Gonzalez-Hermosillo A, Granger CB, Heidbuchel H, Kautzner J, Kim JS, Lanas F, Lewis BS, Merino JL, Morillo C, Murin J, Narasimhan C, Paolasso E, Parkhomenko A, Peters NS, Sim KH, Stiles MK, Tanomsup S, Toivonen L, Tomcsanyi J, Torp-Pedersen C, Tse HF, Vardas P, Vinereanu D, Xavier D, Zhu J, Zhu JR, Baret-Cormel L, Weinling E, Staiger C, Yusuf S, Chrolavicius S, Afzal R, Hohnloser SH and Investigators P. Dronedarone in high-risk permanent atrial fibrillation. *N Engl J Med*. 2011;365:2268-76.
30. Kober L, Torp-Pedersen C, McMurray JJ, Gotzsche O, Levy S, Crijns H, Amlie J, Carlsen J and Dronedarone Study G. Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med*. 2008;358:2678-87.
31. Dagres N, Varounis C, Iliodromitis EK, Lekakis JP, Rallidis LS and Anastasiou-Nana M. Dronedarone and the incidence of stroke in patients with paroxysmal or persistent atrial fibrillation: a systematic review and meta-analysis of randomized trials. *Am J Cardiovasc Drugs*. 2011;11:395-400.
32. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau JP, Lettino M, Lip GYH, Pinto FJ, Thomas GN, Valgimigli M, Van Gelder IC, Van Putte BP, Watkins CL and Group ESCSD. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2021;42:373-498.

33. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, Jr., Ellinor PT, Ezekowitz MD, Field ME, Furie KL, Heidenreich PA, Murray KT, Shea JB, Tracy CM and Yancy CW. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. *Circulation*. 2019;140:e125-e151.
34. Hohnloser SH, Connolly SJ, Crijns HJ, Page RL, Seiz W and Torp-Petersen C. Rationale and design of ATHENA: A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular Hospitalization or death from any cause in patiENts with Atrial fibrillation/atrial flutter. *J Cardiovasc Electrophysiol*. 2008;19:69-73.
35. Ferreira JP, Jhund PS, Duarte K, Claggett BL, Solomon SD, Pocock S, Petrie MC, Zannad F and McMurray JJV. Use of the Win Ratio in Cardiovascular Trials. *JACC Heart Fail*. 2020;8:441-450.
36. Nieuwlaat R. The value of cardiovascular hospitalization as an endpoint for clinical atrial fibrillation research. *Europace*. 2011;13:601-2.
37. Amin AN, Jhaveri M and Lin J. Hospital readmissions in US atrial fibrillation patients: occurrence and costs. *Am J Ther*. 2013;20:143-50.
38. Hinkle LE, Jr. and Thaler HT. Clinical classification of cardiac deaths. *Circulation*. 1982;65:457-64.
39. Calkins H, Gliklich RE, Leavy MB, Piccini JP, Hsu JC, Mohanty S, Lewis W, Nazarian S and Turakhia MP. Harmonized outcome measures for use in atrial fibrillation patient registries and clinical practice: Endorsed by the Heart Rhythm Society Board of Trustees. *Heart Rhythm*. 2019;16:e3-e16.
40. Holmqvist F, Kim S, Steinberg BA, Reiffel JA, Mahaffey KW, Gersh BJ, Fonarow GC, Naccarelli GV, Chang P, Freeman JV, Kowey PR, Thomas L, Peterson ED, Piccini JP and Investigators O-A. Heart rate is associated with progression of atrial fibrillation, independent of rhythm. *Heart*. 2015;101:894-9.
41. Fanaroff AC, Cyr D, Neely ML, Bakal J, White HD, Fox KAA, Armstrong PW, Lopes RD, Ohman EM and Roe MT. Days Alive and Out of Hospital: Exploring a Patient-Centered, Pragmatic Outcome in a Clinical Trial of Patients With Acute Coronary Syndromes. *Circ Cardiovasc Qual Outcomes*. 2018;11:e004755.
42. Greene SJ, O'Brien EC, Mentz RJ, Luo N, Hardy NC, Laskey WK, Heidenreich PA, Chang CL, Turner SJ, Yancy CW, Hernandez AF, Curtis LH, Peterson PN, Fonarow GC and Hammill BG. Home-Time After Discharge Among Patients Hospitalized With Heart Failure. *J Am Coll Cardiol*. 2018;71:2643-2652.
43. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, Akar JG, Badhwar V, Brugada J, Camm J, Chen PS, Chen SA, Chung MK, Nielsen JC, Curtis AB, Davies DW, Day JD, d'Avila A, de Groot N, Di Biase L, Duytschaever M, Edgerton JR, Ellenbogen KA, Ellinor PT, Ernst S, Fenelon G, Gerstenfeld EP, Haines DE, Haissaguerre M, Helm RH, Hylek E, Jackman WM, Jalife J, Kalman JM, Kautzner J, Kottkamp H, Kuck KH, Kumagai K, Lee R, Lewalter T, Lindsay BD, Macle L, Mansour M, Marchlinski FE, Michaud GF, Nakagawa H, Natale A, Nattel S, Okumura K, Packer D, Pokushalov E, Reynolds MR, Sanders P, Scanavacca M, Schilling R, Tondo C, Tsao HM, Verma A, Wilber DJ and Yamane T. 2017

HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm*. 2017;14:e275-e444.
44. Calvert M, Kyte D, Mercieca-Bebber R, Slade A, Chan AW, King MT, Hunn A, Bottomley A, Regnault A, Chan AW, Ells C, O'Connor D, Revicki D, Patrick D, Altman D, Basch E, Velikova G, Price G, Draper H, Blazeby J, Scott J, Coast J, Norquist J, Brown J, Haywood K, Johnson LL, Campbell L, Frank L, von Hildebrand M, Brundage M, Palmer M, Kluetz P, Stephens R, Golub RM, Mitchell S and Groves T. Guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols: The SPIRIT-PRO Extension. *Jama*. 2018;319:483-494.
45. Mark DB, Anstrom KJ, Sheng S, Piccini JP, Baloch KN, Monahan KH, Daniels MR, Bahnson TD, Poole JE, Rosenberg Y, Lee KL, Packer DL and Investigators C. Effect of Catheter Ablation vs Medical Therapy on Quality of Life Among Patients With Atrial Fibrillation: The CABANA Randomized Clinical Trial. *JAMA*. 2019;321:1275-1285.
46. Spertus J, Dorian P, Bubien R, Lewis S, Godejohn D, Reynolds MR, Lakkireddy DR, Wimmer AP, Bhandari A and Burk C. Development and validation of the Atrial Fibrillation Effect on QualiTy-of-Life (AFEQT) Questionnaire in patients with atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2011;4:15-25.
47. Simon DN, Thomas LE, O'Brien EC, Fonarow GC, Gersh BJ, Kowey PR, Reiffel JA, Naccarelli GV, Spertus JA, Peterson ED and Piccini JP. Clinically important difference in the Atrial Fibrillation Effect on QualiTy-of-Life (AFEQT) score: Results from the ORBIT-AF registry. *Circ Cardiovasc Qual Outcomes*. 2018;9:A130.
48. Packer DL, Piccini JP, Monahan KH, Al-Khalidi HR, Silverstein AP, Noseworthy PA, Poole JE, Bahnson TD, Lee KL, Mark DB and Investigators C. Ablation Versus Drug Therapy for Atrial Fibrillation in Heart Failure: Results From the CABANA Trial. *Circulation*. 2021;143:1377-1390.
49. Bubien RS, Knotts-Dolson SM, Plumb VJ and Kay GN. Effect of radiofrequency catheter ablation on health-related quality of life and activities of daily living in patients with recurrent arrhythmias. *Circulation*. 1996;94:1585-91.
50. Wokhlu A, Monahan KH, Hodge DO, Asirvatham SJ, Friedman PA, Munger TM, Bradley DJ, Bluhm CM, Haroldson JM and Packer DL. Long-term quality of life after ablation of atrial fibrillation the impact of recurrence, symptom relief, and placebo effect. *J Am Coll Cardiol*. 2010;55:2308-16.
51. Hohnloser SH, Halperin JL, Camm AJ, Gao P, Radzik D, Connolly SJ and investigators P. Interaction between digoxin and dronedarone in the PALLAS trial. *Circ Arrhythm Electrophysiol*. 2014;7:1019-25.
52. Ford I and Norrie J. Pragmatic Trials. *N Engl J Med*. 2016;375:454-63.
53. Desai NR, Sciria CT, Zhao X, Piccini JP, Turakhia MP, Matsouaka R, Fonarow GC and Lewis WR. Patterns of Care for Atrial Fibrillation Before, During, and at Discharge From Hospitalization: From the Get With The Guidelines-Atrial Fibrillation Registry. *Circ Arrhythm Electrophysiol*. 2021;14:e009003.
54. Lewis WR, Piccini JP, Turakhia MP, Curtis AB, Fang M, Suter RE, Page RL, 2nd and Fonarow GC. Get With The Guidelines AFIB: novel quality improvement registry for hospitalized patients with atrial fibrillation. *Circ Cardiovasc Qual Outcomes*. 2014;7:770-7.
55. Le Heuzey JY, De Ferrari GM, Radzik D, Santini M, Zhu J and Davy JM. A short-term, randomized, double-blind, parallel-group study to evaluate the efficacy and safety of

dronedarone versus amiodarone in patients with persistent atrial fibrillation: the DIONYSOS study. *J Cardiovasc Electrophysiol*. 2010;21:597-605.
56. Tave A, Goehring E, Desai V, Wu C, Bohn RL, Tamayo SG, Sicignano N, Juhaeri J, Jones JK and Weiss SR. Risk of interstitial lung disease in patients treated for atrial fibrillation with dronedarone versus other antiarrhythmics. *Pharmacoepidemiol Drug Saf*. 2021;30:1353-1359.
57. Blomstrom-Lundqvist C, Marrouche N, Connolly S, Corp Dit Genti V, Wieloch M, Koren A and Hohnloser SH. Efficacy and safety of dronedarone by atrial fibrillation history duration: Insights from the ATHENA study. *Clin Cardiol*. 2020;43:1469-1477.
58. Chew DS, Black-Maier E, Loring Z, Noseworthy PA, Packer DL, Exner DV, Mark DB and Piccini JP. Diagnosis-to-Ablation Time and Recurrence of Atrial Fibrillation Following Catheter Ablation: A Systematic Review and Meta-Analysis of Observational Studies. *Circ Arrhythm Electrophysiol*. 2020;13:e008128.
59. Davy JM, Herold M, Hoglund C, Timmermans A, Alings A, Radzik D, Van Kempen L and Investigators ES. Dronedarone for the control of ventricular rate in permanent atrial fibrillation: the Efficacy and safety of dRonedArone for the cOntrol of ventricular rate during atrial fibrillation (ERATO) study. *Am Heart J*. 2008;156:527 e1-9.
60. Gandhia SK, Reiffel JA, Boironc R and Wieloch M. Risk of Major Bleeding in Patients With Atrial Fibrillation Taking Dronedarone in Combination With a Direct Acting Oral Anticoagulant. *Am J Cardiol*. 2021;159:79-86.
61. Xian Y, Fonarow GC, Reeves MJ, Webb LE, Blevins J, Demyanenko VS, Zhao X, Olson DM, Hernandez AF, Peterson ED, Schwamm LH and Smith EE. Data quality in the American Heart Association Get With The Guidelines-Stroke (GWTG-Stroke): results from a national data validation audit. *Am Heart J*. 2012;163:392-8, 398 e1.
62. Schulman S and Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3:692-4.
63. Maurer W and Bretz F. Multiple testing in group sequential trials using graphical approaches. *Statistics in Biopharmaceutical Research*. 2013;5:311-320.
64. Luo X, Tian H, Mohanty S and Tsai WY. An alternative approach to confidence interval estimation for the win ratio statistic. *Biometrics*. 2015;71:139-145.
65. Liu GF, Wang J, Liu K and Snavely DB. Confidence intervals for an exposure adjusted incidence rate difference with applications to clinical trials. *Stat Med*. 2006;25:1275-86.
66. Jennison C and Turnbull BW. *Group Sequential Methods with Applications to Clinical Trials*. New York, NY: Chapman & Hall/CRC; 2000.