The Effect of DrOnedarone on Atrial Fibrosis and Atrial Fibrillation Recurrence Post-Ablation

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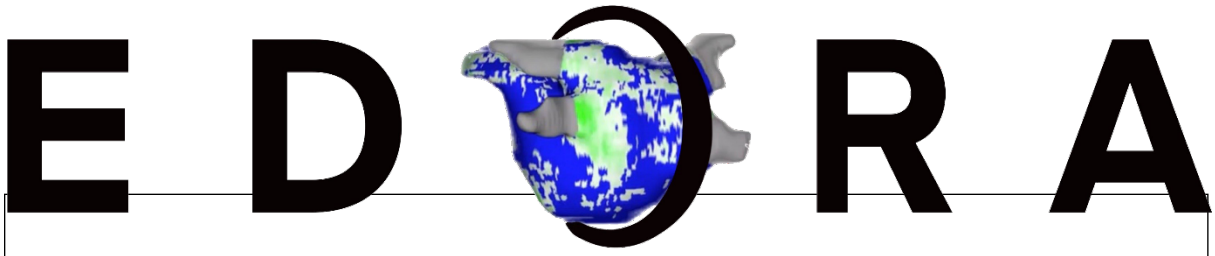
Version 4.0:
Revision Date: April 27th, 2022

TULANE UNIVERSITY
Academic Research Organization



fibrosis progression and T R I A L of DrOnedarone on atrial fibrillation Recurrence post-Ablation

PROTOCOL

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PROTOCOL TITLE:

The Effect of DrOnedarone on Atrial Fibrosis and Atrial Fibrillation Recurrence Post-Ablation
Short Title: EDORA

Lead Investigator and Author:
Nassir F. Marrouche, MD

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I confirm that I have read this protocol, I understand it, and I will conduct the clinical trial according to the protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and will adhere to the Ethical and Regulatory Considerations as stated. I confirm that if I or any of my staff are members of the Institutional Review Board, we will abstain from voting on this protocol, its future renewals, and its future amendments.

Investigator Name: _____

Investigator Signature: _____

Date: _____

Protocol Revision History

Revision Version:	Revision Date:	Revision Summary:

V1	December 8th, 2020	
V2	April 17th, 2021	Protocol modified for clarity
V3	July 6th, 2021	Section: Exclusion Criteria- updated and modified for clarity Section: Added participant replacement language Section: Equal Opportunity participation section added Section: ECG Check device- removed Section: Questionnaire- addition of AFSS Section: IMP and Matching Placebo section added Section: Concomitant section added Section: IP/Placebo kits: updated and modified dispensation of kits for clarity Section: Study schedule change, timeline of measure and participant visits Section: Data sharing, Data Safety, Data Integrity Monitoring section added Sections: FDA, Study Training and Monitoring, ClinicalTrials.gov and Study records access and retention added to protocol Appendices: Placebo composition, CMR protocol and Abbreviated Investigational Medicine Product Insert added
V4	April 27th, 2022	Section: Inclusion Criteria- updated and modified for clarity Section: Exclusion Criteria- updated and modified for clarity Section: Enrollment period criteria modified Section: Labs- updated and modified for clarity Section: IMP Safety Considerations- updated and modified Section: IMP and Matching Placebo: Administration- modified for clarity Section: IMP and Matching Placebo: Accountability- updated and modified for clarity Section: Tulane University trial information record retention updated Section: Preventice-updated and modified for clarity. Section: In between monitoring section added Section: Consent- electronic re-consent Section: Study Schedule- updated timeframes, removed X-ray Section: Study Design-clarified single blinded trial Section: AFSS&AFEQT Questionnaires: updated and modified for clarity Section: AE/SAE/UP- updated and modified for clarity Section: Definition of trial outcome using ECG device- modified Section: 3&12-month visit- updated Section: EoT visit- updated and modified for clarity Section: Steering Committee- updated Section: EDC- inserted name (Dacima) Section: DCC- amended name (Tulane University School of Medicine, Academic Research Organization (ARO) Section: Statistical Methods, Data Analysis, and Interpretation, Part E removed Section: Appendix B- updated and modified for clarity

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Statement of Compliance

International Conference on Harmonization Good Clinical Practice (ICH GCP)

The clinical trial will be carried out in accordance with the International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent forms must be obtained before any patient is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented into the trial.

In addition, all changes to the consent form will be IRB-approved. The IRB will determine whether a new informed consent form (ICF) needs to be obtained from study participants who provided consent using a previously approved consent form.

Health Insurance Portability and Accountability Act (HIPAA)

HIPAA is a federal law that required the creation of national standards to protect sensitive patient health information from being disclosed without the patient's consent or knowledge.[1] All study procedures, data sharing, and data disclosures will be conducted in accordance with HIPAA and, therefore, should be HIPAA compliant.

Background

[1] US Center for Disease Control (2018). Health Insurance Portability and Accountability Act of 1996. Retrieved on March 17, 2021, from www.cdc.gov/phlp/publications/topic/hipaa.html.

Atrial fibrillation (AF) is the most commonly diagnosed cardiac arrhythmia in the cardiology setting. In addition to its severe impact on quality of life (QoL), AF significantly increases the risk of stroke, heart failure, and mortality. Treating AF continues to be a challenge. While AF-related symptoms and stroke risk can be managed using; rate control strategies and anticoagulation, restoration and maintenance of the sinus rhythm are deemed essential to optimize exercise capacity, QoL[1] and stroke prevention. The CAPTAF trial demonstrated that a greater improvement in QoL was directly related to a greater reduction in AF burden in the ablation group compared to the antiarrhythmic drugs (AADs) group.[2] AF burden has been broadly used to describe the total time (%) a patient is in AF whilst being monitored. In the TRENDS[3] and ASSERT[4] clinical trials, cardioembolic stroke risk strongly correlated with the duration of AF burden. Therefore, AF recurrence and burden constitute an important therapeutic target in AF patients with atrial fibrillation. Over the last 20 years, catheter-based AF ablation procedures have been widely adopted as multiple clinical trials continue to highlight its efficacy in reducing AF recurrence and burden and in improving QoL.[2,5,6]

In trials reporting on an arrhythmia-free survival after catheter ablation, AADs were stopped after the initial 90-days of blanking period. The blanking period is a 3-month period post-ablation, where signs of early tachyarrhythmias due to the inflammatory nature of the procedure may be seen in some patients. This may provide predictive evidence that late tachyarrhythmias could develop and suggest failure in ablation. However, no significant evidence has been found and guidelines suggest against re-ablation during this window period.[32] A recently published randomized controlled trial (POWDER-AF) evaluated whether continued use of previously ineffective AADs beyond the blanking period reduces arrhythmia recurrence after catheter ablation. This trial showed that in patients who were free of AF during the blanking period and continued the use of their AAD ablation had significantly less tachyarrhythmia recurrences as compared to patients who stopped their drug therapy[7] altogether in a 12-month follow up after randomization. This observation might be explained by the possible influence of specific AADs on the atrial arrhythmogenic substrate, reducing the initiation and triggering of AF.

Left atrial (LA) fibrosis quantified through Delayed Enhanced Cardiac Magnetic Resonance Imaging (DE-MRI) represents a clinically effective tool for assessing the extent of atrial arrhythmogenic substrate.[8] It has been shown to be a significant predictor of AF ablation success[8] and major cardiovascular and cerebrovascular events in AF patients.[9] Marrouche et al. characterized the severity of AF patients' fibrosis using Utah Stage 1-4 classification. [stage I (<10%), stage II (10-20%), stage III (20-30%) and stage IV (>30%)]. They reported a 6% AF recurrence risk post-ablation for every 1% increase in LA fibrosis from baseline values.[8] Therefore, new fibrosis formation appears to be a novel marker of long-term ablation procedure outcomes. The generation of new fibrosis occurring post-ablation has also been associated with a significantly higher risk of atrial arrhythmia recurrence. Kheirkhahan's study also provides evidence that a 1% increase in fibrosis post-ablation increases the risk of AF recurrence by 3%.[10]

A greater volume of new fibrosis (≥ 21%) corresponded with a lower arrhythmia-free survival.[11] In addition to being a significant predictor of AF recurrence, a higher fibrotic burden strongly correlated with a higher risk of stroke (Figure 1), heart failure and mortality in AF patients across multiple studies[9,12,13].
King et al.[9] conducted a 5-year study based on follow-up data from 1,233 patients to quantify LA fibrosis via Late-Gadolinium Enhancement MRI (LGE-MRI).

The study showed atrial fibrosis to be a strong predictor of major cardiovascular and cerebrovascular events. Patients with LA fibrosis stage IV had a 67% increased risk compared to patients with stage I of

the disease. Akoum et al. demonstrated that atrial fibrosis is independently associated with appendage thrombus and spontaneous contrast[13]. Fibrosis is also shown to reduce LA appendage velocity, which is also associated with an increased risk of stroke. In conclusion, progression of fibrosis post-ablation was associated with worse outcomes. For this reason, regarding long-term management of AF, it would be appropriate to look for new therapeutic options that can target a reduction in the progression of fibrosis in order to promote positive outcomes and optimize disease management.

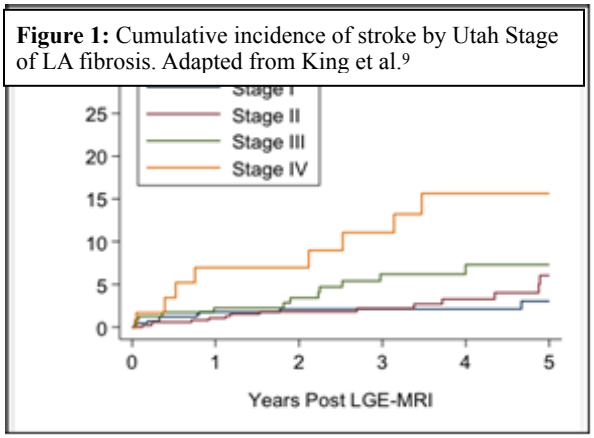

Figure 1: Cumulative incidence of stroke by Utah Stage of LA fibrosis. Adapted from King et al.[9]

Dronedarone is an anti-arrhythmic drug with properties belonging to Vaughan-Williams class I-IV. It has a similar structure to amiodarone (Class III AAD) and is effective in reducing AF recurrence, AF burden and cardiovascular hospitalization rates in both placebo-controlled trials[14,15] and in real-world studies[16]. Dronedarone exerts antiarrhythmic effects by inhibiting the outward K1 currents and increasing the refractory period[27]. Additionally, data from multiple prospective observational studies suggest dronedarone may improve QoL[17,18]. Dronedarone seems to have a reasonable safety profile [6], with fewer non-cardiovascular risks and a lower risk of ventricular pro-arrhythmia compared to other AADs.

Based on our preliminary data, dronedarone appears to have the potential to slow down the progression of cardiac fibrosis, with multiple mechanisms of action hypothesized. One of the main speculated mechanisms of action has been derived from pre-clinical publications and is based on dronedarone preventing vascular alterations that participate in structural remodeling and atrial maintenance substrate. Oxidative stress (ROS) generated in the myocardium promotes endothelial to mesenchymal transition (EndMT) by reducing endothelial nitric oxide (NO) production[19]. Numerous studies have shown that ROS and EndMT are major contributors towards cardiac fibrosis[20]. Circulating symmetric dimethylarginine (SDMA), a biomarker that reduces the synthesis of NO[21], is also associated with increase in atrial wall thickness in AF. Dronedarone stimulates nitric oxide synthase (NOS) which increases the bioavailability of NO[22], and reduces SDMA [23], playing a critical role in preserving the epithelial phenotype. In fact, there is an improvement in global antioxidant status after treatment with dronedarone[24].

Furthermore, a decrease in collagen deposition in the atria has been observed after treatment with dronedarone,[25] thereby improving atrial structure, decreasing wall thickness, and slowing down the development of cardiac fibrosis. Finally, during episodes of AF, factors known to induce atrial fibrosis growth such as, collagen-1 and fibronectin-1, are released into atrial tissues[26]. For this reason, rhythm control by means of AADs Class III may serve to limit the amount of time available for these biomarkers to disperse into atrial tissues as well as, proactively managing fibrosis progression.

Preliminary data from Dr Marrouche' s team at the University of Utah (Salt Lake City, UT) assessing fibrosis progression in AF patients (n = 17) that received standard of care (SOC) (n = 8) or dronedarone (Multaq®, n=9), are presented in Figure 2. Patients underwent two MRIs over

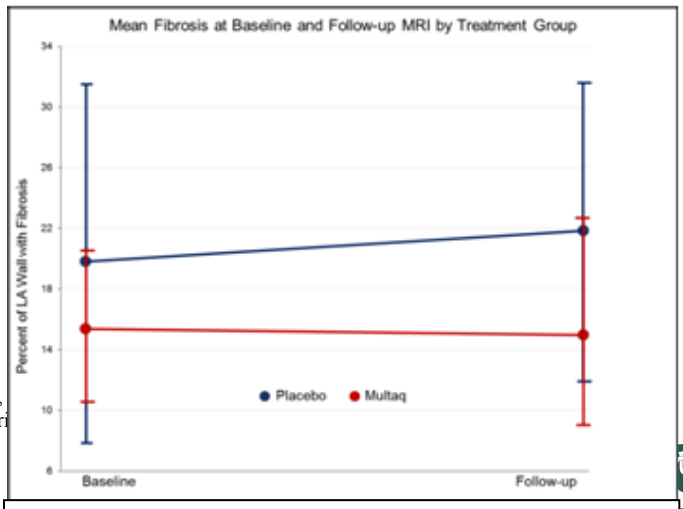

Figure 2: Mean fibrosis at baseline and follow-up by randomized treatment group. Preliminary data from the University of Utah.

the course of a median 365.5 days [IQR: 290-382] as part of their care. In the SOC group, they observed a 10% progression of fibrosis, whereas in the dronedarone group, there was only a 4.5% progression over this period. Dronedarone slowed atrial fibrosis progression by more than 50% relative to the SOC group. This reduction is clinically relevant, as each 1% increase in atrial fibrosis from baseline is associated with a 6% higher risk of AF recurrence after ablation. Although underpowered due to the small sample size, a trend is apparent between baseline and follow-up MRIs, and it appears as though vast differences exist. With an increased sample size, we may see more significant effects.

Purpose and Objectives

Purpose

Determine whether dronedarone is effective in slowing the progression of fibrosis and decreasing atrial arrhythmia (AA) recurrence (atrial fibrillation, atrial flutter, or atrial tachycardia) in patients who have undergone AF ablation therapy.

Aims

Aim 1: Determine if dronedarone reduces post-ablation incidences of atrial arrythmia recurrence compared to placebo.

Aim 2: Determine whether dronedarone is effective in slowing down the progression of fibrosis after ablation compared to SOC alone.

Study Design

EDORA is a multicenter, prospective, phase IV, randomized, and single-blinded clinical trial.

Patients with AF undergoing ablation will be stratified by age (>65 years and <65 years) and type of atrial fibrillation (paroxysmal and persistent). Upon stratification and ablation, they will be randomized to one of two trial groups. They will either receive dronedarone (i.e. Multaq®) 400mg BID (treatment group) or placebo (control group). The control group will be started on placebo and physicians will be advised to limit the initiation of AADs to essential cases only, avoiding amiodarone and dronedarone.

Each patient will receive a pre-ablation CMR scan to assess the extent of atrial fibrosis present, followed by scans at 3 and 12-month post-ablation. QoL changes will be evaluated from baseline and again at 3 months and 12-months via the AF Effect on QualiTy of life (AFEQT) questionnaire form. frequency, duration, and severity of an AF episode, if present will be evaluated from baseline and again at 3 months and 12-months via the Atrial Fibrillation Severity Scale (AFSS) questionnaire form.

Patients will be followed post-ablation for AA recurrence (atrial fibrillation, atrial flutter, or atrial tachycardia) and will receive continuous ECG monitoring via a 30-day ECG wearable monitoring device starting at discharge, then again at 3, 6, 9- and 12-months post-ablation. Patients will also be encouraged to use any personal devices that provide ECG readings (e.g. smartwatch, etc.) in between the study timepoints and to share this data with the corresponding research team.

Phone calls or study visits will be scheduled at the study participants' 6- and 9-month mark to assess for medication compliance, changes to their medical histories, medication history, and adverse event

reporting as well as to assess that all study devices are working accordingly. Evaluation as to whether a patient has reached any trial endpoints will also be analyzed at this time.

Physicians will be advised to avoid adjustments in drug therapy unless absolutely necessary (severely symptomatic patients, patients with newly diagnosed heart failure, New York Heart Association (NYHA) Class IV, etc.). Severely symptomatic patients will be defined as, study participants with non-tolerated palpitations or chest pain, dizziness, syncope, dyspnea, severe fatigue, or suddenly reduced ability to exercise.

Any initiation or change of an antiarrhythmic treatment in the treatment or control group will be considered as a secondary endpoint of the trial. Patients will continue to be monitored for fibrosis progression and AF burden via CMR scans and ECG monitoring device until the end of the follow-up period. In the case of AA recurrence after ablation, AAD initiation or change will be left to the discretion of the treating physician.

Post-trial Care

The long-term care of the patient will remain the responsibility of their primary treating physician and clinical care team.

Study Endpoints

Primary Endpoints

The primary endpoints of the study are defined as the first occurrence of AA (i.e. atrial fibrillation, atrial flutter, or atrial tachycardia) post-ablation and the progression of atrial fibrosis post-ablation.

1) **Post-ablation AA recurrence**
   Monitoring will start upon discharge, usually 24-48 hours after AF ablation.
   Defined as:
   a) Time to first AA episode lasting > 30 continuous seconds, after cardiac ablation (including tachyarrhythmias presented during the 90-day post ablation blanking period).

   This will be recorded by either the occurrence of a single positive AA ECG reading on the BodyGuardian® MINI Plus EL ECG monitoring study device, a 12-lead ECG, Holter monitor, or other ECG monitoring device. If there are technical difficulties or accessibility issues using the study device, patients can be monitored for AA throughout the trial via a 12-lead ECG or other heart monitoring device if necessary.

   b) New AAD initiation for AF recurrence after AF ablation, including initiation of the treatment during the blanking period, or with no available positive ECG reading.

2) **Progression of left atrial fibrosis**
   Monitoring will start at the baseline CMR scan prior to ablation and up to the end of the clinical trial.
   Defined as:

a) The percentage (%) of new fibrosis seen on the 12-month CMR scan compared to CMR scans taken at baseline and at 3-months post-ablation.

The primary endpoints will be compared between the treatment (dronedarone) and control arms (placebo) respectively.

Secondary Endpoints

1) **AAD initiation change or adjustment**
Any initiation or adjustment to AAD therapy after ablation in either the drug or control group. Any switches or titrations after PEP of AF recurrence is reached will be included. Treating physicians will be advised to limit initiation or adjustments to AADs to essential cases (e.g. severely symptomatic study participants).

2) **Incidence of symptomatic AA episodes**
AA episodes associated with palpitations, chest pain, dyspnea, dizziness, syncope, or unusual fatigue and weakness. AA incidence will be assessed via the AFSS questionnaire results.

3) Repeat ablation

4) Cardioversion

5) **AF burden**
Defined as the percentage of time in AF during the monitoring period, 24-48 hours and, at 3-month and 12-month post-ablation (via ECG readings). It will be calculated per follow-up period for each study participant as a time-weighted average (%).

6) **Quality of Life (QoL)**
Evaluated by the AFEQT and AFSS questionnaires at baseline, 3-month, and 12-month follow-up visits.

7) **Study Participant Safety**
Study participants will be evaluated at multiple timepoints across the study: their in-person 3-month and 12-month visits and their 6, 9 and 13-month phone calls. This evaluation includes any adverse events, especially adverse events (AEs) related to AAD treatment. AEs related to dronedarone are defined in the **Safety/Adverse Event Monitoring Plan** section of this protocol.

8) **Pre- and Post-Ablation Left Atrial Function Changes**
LA function will be measured as the LA emptying fraction and strain using cine-MRI sequences included in the CMR imaging (Please see **Appendix B: CMR Protocol**).

9) **Left Ventricle (LV) Structural and Functional Changes**
LV structure, or fibrosis (%), will be assessed using native T1 and ECV MRI sequences included in the CMR imaging. LV function will be measured as the ejection fraction (LVEF) and LV strain using cine-MRI sequences performed as part of the CMR protocol (see appendix)

Secondary endpoints will be analyzed at 3 (0-3) and 13-months (0-13) post-ablation and compared between the two trial arms.

Exploratory Endpoints:

1) **CV hospitalization**
2) **CV mortality**
3) **Stroke/Transient Ischemic Attacks**

Study Population

Multicenter US Clinical Trial
Total Patient Population: 330 study participants

Inclusion Criteria

Patients must meet the following criteria to be enrolled in the trial:

1. Male or female patients aged ≥ 18 years.
2. Patients diagnosed with paroxysmal or persistent AF[2] (evidenced by ECG rhythm strip evaluations or written documentation) and who are undergoing ablation of atrial fibrillation, regardless of whether they were receiving an AAD before enrollment or not.

Exclusion Criteria

Patients will be excluded from enrollment if any of the following criteria are present:

1. Any health-related gadolinium/MRI contraindications (e.g. allergy to gadolinium or similar agent, pacemakers, Implantable Cardioverter Defibrillators (ICD's), other devices/implants contraindicated for use of MRI, etc.)
2. Patients who are medically ineligible to be or are unwilling to be cardioverted electrically or by medications before ablation.

[2] "Paroxysmal" atrial fibrillation (AF) is defined here as an AF episode lasting within 7 days of onset and spontaneously resolving without the need for a pharmacological or electrical cardioversion. "Persistent" atrial fibrillation is defined here as any AF episode lasting beyond 7 days **or** any episode 7 days or less requiring a pharmacological or electrical cardioversion to terminate the abnormal rhythm.

3. Patients who have a known terminal illness with a prognosis less than 12 months at the time of the informed consent process.

4. Patients who are unable to or are unwilling to receive cardiac MRI (CMR) scans.

5. Patients who are incarcerated or become incarcerated during the trial period.

6. Patients who are unable or are unwilling to return to the study site/clinic for follow-up procedures such as, collecting IP/Placebo, collecting devices, blood draws

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7. Patients who have not successfully recovered from cardiac ablation[3].

8. Patients who do not meet quality standards for the baseline CMR scan[4]

9. 8. Patients weighing >300 lbs. as CMR quality may decrease with patients with increased BMI. Patients that have contraindications to dronedarone. (This includes patients with decompensated heart failure or New York Heart Association (NYHA) Class IV, second or third-degree atrioventricular (AV) block or sick-sinus syndrome [except when used in conjunction with a functioning pacemaker]), concomitant use of strong CYP-3A inhibitors or other Class I or III AADs, drugs or herbal products that prolongs the QT interval and may induce Torsade de Pointes.

10. Liver or lung toxicity related to previous use of amiodarone, severe hepatic impairment including any stage of cirrhosis, acute liver failure, and/or interstitial lung disease including pulmonary fibrosis and pneumonitis.

11. Symptomatic bradycardia <50bpm, QTc Bazett interval ≥500ms or PR interval >280ms,

12. Hypersensitivity to the active substance of Multaq® (dronedarone) or to any of its excipients.

13. Acute or chronic severe renal disease with a low glomerular filtration rate (GFR), <30 mL per minute per 1.73 m^2 will be excluded from the trial.

14. Patients with a history of prior left atrial ablation or valvular cardiac surgery (myocardial scarring/fibrosis from prior surgeries may confound data).

15. Patients with cognitive impairments who are unable to give informed consent.

16. Patients with physical ailments which may prohibit them from actively participating in the trial.

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[3] Patients may be excluded from the trial after the completion of their cardiac ablation. If it has been determined that the patient cannot tolerate the procedure well, then they should not be enrolled in the study. This determination will be made at the discretion of the patient's physician (i.e. site investigator).

[4] Patients who do not meet the standard baseline images should not be enrolled in the study (the decision will made at the discretion of the imaging specialist).

FOR FEMALE PATIENTS ONLY:

1. Pre-menopausal (last menstruation ≤1 year prior to screening visit) who:

a. Are pregnant or breast-feeding or plan to become pregnant during the study period or,

b. Are not surgically sterile or,

c. Are of childbearing potential and are unwilling to practice two acceptable methods of birth control or,

d. Do not plan to continue practicing two acceptable methods of birth control throughout the trial (highly effective methods of birth control are defined as those, used alone or in combination, that result in a low failure rate i.e. less than 1% per year when used consistently and correctly).

Study Participant Replacement

Study participants who discontinue participation prior to the end of clinical trial will not be replaced.

Equal Opportunity Participation

The EDORA trial does not and shall not discriminate on the basis of race, color, religion (creed), gender, gender expression, age, national origin (ancestry), disability, marital status, sexual orientation, or military status, in the operations of its clinical trial.

Treatment Groups

Each patient will be randomized after their AF ablation procedure visit to receive either dronedarone or placebo (sugar pill)[5] at discharge post-ablation. Patients partaking in this clinical trial may be newly diagnosed with AF or have undergone previous treatments for AF such as rate control, rhythm control, or direct current cardioversions.

Treatment Group (dronedarone [Multaq®])

Patients randomized to receive dronedarone will receive an initial dose after their cardiac ablation procedure. If a new AAD is initiated, i.e. not dronedarone, the trial drug will be discontinued. If drug discontinuation occurs, the patient will continue to be monitored for fibrosis progression and AA recurrence/AF burden post-ablation. The evaluation of co-primary endpoints as well as all secondary endpoints will continue to be recorded throughout the duration of the trial.

Control Group (Placebo)

Patients randomized to the control group will receive an initial placebo dose after cardiac ablation. In the case of AA recurrence, initiation of AADs will be left at the discretion of the treating physician, with recommendations to limit the use of AADs to essential cases only and to avoid prescribing amiodarone or dronedarone. In the case of a new AAD initiation, placebo treatment will be discontinued. The patient will continue to be monitored for fibrosis progression and AA recurrence/AF burden post-ablation. The

[5] Please see **Appendix A**: **Placebo Composition** for more information.

evaluation of co-primary endpoints as well as all secondary endpoints will continue to be recorded throughout the duration of the trial.

Randomization and Blinding

Randomization

Patients who meet the eligibility criteria will be randomly assigned in a 1:1 ratio (i.e. 50/50 chance of being assigned to either study arm). An Interactive Web Response System (IWRS) randomization software program will be used to assign each study participant to a study arm. Before randomization occurs, each study participant will be stratified by age (i.e. <65 years old and ≥65 years old) and AF type (i.e. persistent and paroxysmal). Once randomization occurs, each study participant will also be assigned a participant ID number.

Randomization will occur after cardiac ablation for two major reasons. First, we want to make sure that each enrolled participant has recovered well from the procedure prior to randomization. Secondly, site investigators may desire to perform more lesions during ablation if they are aware of how the study participant was assigned (e.g. unconscious bias). Therefore, to minimize bias and to maximize balance across groups, study participants will be randomized after cardiac ablation.

Blinding

This is a single blinded clinical trial. Therefore, study participants will be unaware as to whether they are receiving drug or placebo. Site investigators cannot be blinded to the treatment administered since these site investigators may also be medically treating the study participant at the same time. Site investigators will need to be fully aware of the medications and associated dosages administered to their study participants to maximize study participant safety. To mitigate bias, independent ECG rhythm readers and CMR scan readers will not have access to the patient's treatment arm. In addition, all investigators, study monitors, medical monitors, data analysts, and the study team may have access to information related to the treatment arms when required.

Investigational Medicinal Product (IMP) and Matching Placebo: Dronedarone (Multaq®)[6]

Dronedarone (Multaq®)

Dronedarone HCl ($C_{33}H_{44}N_2O_5S$) is a white powder and benzofuran derivative that is practically insoluble in water, yet freely soluble in methanol and methylene chloride. The mechanism of action is unclear. Dronedarone exhibits properties of all four Vaughn-Williams antiarrhythmic classes, but the contribution of each of these activities to the clinical effect is unknown. Bioavailability of dronedarone is about 4% without food. It increases to 15% when dronedarone is administered with a high fat meal. Please see **Appendix C: Abbreviated Investigational Medicine Product Insert**, for more information.

Dronedarone (Multaq®) or Matching Placebo Packaging and Labeling

A single panel, English only label will be applied to each bottle. Dronedarone, or Multaq®, 400 mg are provided as oblong shaped, white film-coated tablets for oral administration. Each tablet is engraved

[6] All pertinent investigational product (IP) information was obtained from the "**Highlights and Prescribing Information**" for dronedarone (Sanofi Pharmaceuticals) in Appendix B.

with a double wave marking on one side and the code "4142" on the other side. Dronedarone will be provided in bottles containing 60 tablets only. Packaging and labeling will be standardized across all study sites.

Dronedarone (Multaq®) or Matching Placebo Storage and Handling

All packages are stored at 25ºC (77ºF) with excursions permitted between 15ºC and 30ºC (or between 59ºF and 86ºF).

Dronedarone (Multaq®) or Matching Placebo Disposal

The destruction of all used and unused units delivered by McKesson will be the responsibility of study sites. Sites will be responsible for destroying the drug with oversight from their lead pharmacy. Recommendations for proper disposal may vary based on instituted laws. If a site does dispose of dronedarone, each site will dispose of dronedarone in accordance with the state and federal regulations. Site based documentation of IP destruction and/or disposal should be provided to Tulane University, Academic Research Organization (ARO). Tulane University ARO will provide Sanofi with documentation of destruction of all unused or partially used product.

Dronedarone (Multaq®) and Matching Placebo Dose and Dosing Regimen

Dronedarone or a matched dose of placebo will be administered orally twice a day for 12 months. The placebo used in this trial is a physical match to the drug product. The study participant will be required to document medication regimen adherence on paper or on an electronic drug diary.

The trial drug should be taken after a meal. It should also be taken with a large glass of water (~250 mL) and consumed over as short a time as possible. Study participants should be instructed to swallow the capsules whole and not chew them. Study participants who are randomly assigned to the treatment group will take two 400 mg dronedarone (Multaq®) tablets each day. Those assigned to the control group will take two placebo tablets each day. Please refer to the "**Dose Administration by Group Assignment**" table below for more information.

If the study participant forgets to take the scheduled dose, s/he should not take the dose more than 4 hours after the usual time and should continue treatment the next day. Any missed doses should be skipped altogether and should not be replaced or made up at the next scheduled dosing.

Dose Administration by Group Assignment		
Assigned Group:	***Number of Study Participants:***	***Dose:***
Treatment Group	n=165	400 mg dronedarone (Multaq®), taken orally twice a day for 1 year
Control Group	n=165	400 mg of placebo taken orally twice a day for 1 year

Dronedarone (Multaq®) and Matching Placebo Dose Administration

Based on their assigned study arm, study participants will receive either drug or placebo at two different timepoints during the study on-site. A 3-month supply of dronedarone or placebo will be dispensed after their cardiac ablation. (i.e. upon randomization). At their 3-month visit and/or at additional in-person visits, a 9-monthsupply (or remaining bottles of dronedarone or placebo) will be dispensed to all participants. During dispensation an additional bottle (1-month supply) of IP/Placebo may be provided to account for months with different number of days and/or to have extra in case of any unforeseen changes (e.g. extreme weather conditions causing delays in receiving drugs, IMP/Placebo loss or damage etc.) Please refer to the "**Investigational Product Administration Schedule**" below.

Investigational Medicinal Product and Placebo Administration Schedule		
Study Timepoints:	***Study Arm #1: Drug***	***Study Arm #2: Placebo***
Day of Cardiac Ablation (i.e. upon randomization)	3-months' supply of dronedarone (Multaq®) given to study participant on site	3-months' supply of placebo given to study participant on site
3- Month Visit and/or at additional visits	9-month supply or remaining supply of dronedarone (Multaq®) given to study participant on site	9-month supply or remaining supply of placebo given to study participant on site

IMP Safety Considerations

Accountability for Investigational Medicinal Product and Matching Placebo

The investigational medicinal product and matching placebo will be distributed to each trial site via McKesson (distribution center). Only participants enrolled in the study may receive study drug and only authorized site staff may supply or administer the study drug. The site investigator, institution or the head of the medical institution (where applicable) is responsible for ensuring adequate accountability of all used and unused drug and placebo. This includes acknowledgement of receipt of each shipment of the trial drug (quantity and condition).

Each trial site must keep an investigational medicinal product and matching placebo accountability record that capture:

- The date when the drug and placebo was received/dispensed
- Participant ID
- Lot Number
- Expiration Date
- Quantity of bottles received/dispensed
- Balance
- The date and quantity of used and unused IMP/Placebo returned to the site
- The destruction
- The initials of the person recording this information

Concomitant Medications

Concomitant use of the following is prohibited in all patients, regardless of treatment arm and needs to be discontinued at a minimum of 24 hours prior to receiving the first dose of trial treatment:

Use of strong CYP 3A inhibitors, such as ketoconazole, itraconazole, voriconazole, cyclosporine, telithromycin, clarithromycin, nefazodone, ritonavir, or drugs or herbal products that prolong the QT interval and might increase the risk of Torsade de Pointes, such as phenothiazine antipsychotics (e.g. prochlorperazine, chlorpromazine, fluphenazine, trifluoperazine, and thioridazine) tricyclic antidepressants (e.g. clomipramine, amitriptyline, nortriptyline, desipramine, imipramine, and doxepin) certain oral macrolide antibiotics (e.g. erythromycin, roxithromycin, azithromycin, and clarithromycin), and Class I (e.g. quinidine, procainamide, disopyramide, mexeletine, lidocaine, and tocainide) and III antiarrhythmics (e.g. sotalol, amiodarone, and dofelitide).

Medication history and current medication use will be assessed at all study related time points. Please refer to the "**Study Schedule**" and "**Schedule of Events**" sections for outlines of appropriate study procedures for each specific study timepoint.

Study Procedures and Data Elements

Clinical Site Selection

All EDORA recruiting sites will be pre-screened for eligibility. Prior to trial initiation, sites must have adequate recruitment potential and the proper infrastructure for fibrosis imaging (ability to perform CMRs). However, based on site recruitment and enrollment patterns (e.g. low enrollment, etc.), other suitable sites may be approached for study inclusion. Training materials providing detailed descriptions of MRI acquisition and image submissions will be developed and provided to each site accordingly.

Pre-Study Start Up

Six to eight months will be allotted for developing trial materials, IRB approvals, start-up activities, and patient enrollment. If a site needs to extend the enrollment period, they must first seek approval from Tulane University ARO.

Study Duration and Close Out

This study will span 13 months with the study participant receiving 12 months of study drug plus an additional one month of continuous ECG monitoring. In other words, approximately 13 months will be for follow-up after the last patient has been randomized into a treatment arm.

An additional 6 months is needed for data cleaning and validation, analysis, and other close out activities such as manuscript preparation.

Tulane University ARO may keep trial related information (e.g. biological sample results, ECG readings and reports, MRI scans and reports) for up to 7 years after the end of the clinical trial.

Pre-screening

Recruitment/Patient Identification Process

Patient recruitment will occur at all pre-screened participating centers. Participants may also be recruited from the community by direct advertising; emails, TV, flyers posted in public places, as well as online postings to study-site affiliated websites, social media platforms (Facebook, Twitter, and Instagram) and LinkedIn. The enrollment period is expected to last between 6 to 8 months Patients

will be introduced to the trial by their treating physician during clinic visits. Investigators will have medically pre-screened these individuals for suitability to enter the clinical trial at their clinic visit.
A one-page summary of the trial can be provided to patients at their visit informing them on how to participate should they wish to do so.

Screening Visit

Study Eligibility Assessment

The inclusion and exclusion criteria will be assessed by reviewing patient medical charts and during the verbal interview at the screening visit by a designated study site team member. All pre-screened medical eligibility must be documented as verified by the site investigator.

Informed Consent

The consent process begins from the time the patient has been identified and contacted for recruitment. Once the patient has met the eligibility criteria for the study, the site investigator or delegated study staff will provide a full description of the research purpose and personnel, procedures involved, risks and benefits, and reiterate that partaking in this clinical trial is completely voluntary. The patient will be informed of any change to risk throughout the course of the trial. It may be necessary to re-consent the patient to ensure that they are fully informed and still agree to participate. Any associated study costs and compensation, if applicable, will also be provided. Patients will be given sufficient time to read and sign the consent form and the study staff member obtaining the informed consent will answer any questions posed by the patient. If during the trial re-consenting is needed, the most current and approved informed consent form may be sent to participants for electronic review and signature.

Medical Assessment

Study participants will be asked about their medical history and current medication use. Anthropometric measures (e.g. height and weight) and vital signs such as blood pressure and heart rate will be assessed as part of the inclusion/exclusion criteria assessment. A complete physical examination will be performed during this time.
If an ECG for the patients has been taken within one month of enrolment, these patients do not require a repeat ECG reading at the Screening Visit and results will be recorded accordingly. Monitoring of vitals will also be performed at baseline and prior to each in person follow-up visit to provide close monitoring for patient safety.

Baseline Visit

Biological Samples

Blood samples may be drawn at baseline and at the 3-month and 12-month visits. The timeframe for blood draw results will be based on institutional requirements and left at the discretion of the treating physician. In addition, blood samples to assess for the presence of biomarkers of fibrosis, inflammation, and cardiovascular disease will be recorded at these visits. These include NT pro-BNP, soluble ST2, and C-reactive protein and Galectin-3.
All blood samples will be processed at the trials' local sites, and the results will be entered onto the electronic database capture platform, DACIMA (Software Inc), after each visit. Blood samples will not be shipped or stored after processing.

List of Study Labs	
Panel:	***Specific Tests:***
Liver Panel	ALT, AST, ALP, and GGT
Renal Panel	Creatinine, BUN/Cr, GFR
Cholesterol Panel	Total cholesterol, HDL, LDL, and Triglycerides
Basic Panel	HbA1c, CBC, BMP
Coagulation Panel	PT/INR, PTT
Inflammation/Fibrosis/CVD Biomarkers	NT-ProBNP, Soluble ST2, C-RP, and Galectin-3

Health Survey Administration

AFEQT Questionnaire

The AF Effect on QualiTy of life survey (AFEQT) is a questionnaire form that measures the patients' perceptions of their symptoms, functional impairments, treatment concerns, and overall satisfaction with their treatment. This questionnaire assesses 20 items categorized under 4 domains (symptoms, daily activities, treatment concern, treatment satisfaction). AFEQT has also been validated by comparison of mean scores too per clinicians' assessments. It has good convergent and divergent correlations with other well-established questionnaires (SF-36, EQ-5D SCL, AFSS, and GAD-7). Patients will be required to fill out this paper questionnaire at their baseline, 3-month and 12-month visits.

AFSS Questionnaire

The Atrial Fibrillation Severity Scale (AFSS) is a questionnaire form that measures burden of AF if present. The AF symptom burden score is derived from the AFSS summary score that averages the frequency, duration, and patient perceived severity of AF episodes. A higher score indicates greater AF burden. Patients will be required to fill out this 6-item paper questionnaire at their baseline, 3-month and 12-month visits.

Cardiac Magnetic Imaging (CMR)

CMR Protocol

All patients will undergo a CMR scan +/- 90 days (preferably within 30 days) prior to ablation using the CMR protocol (**MRI Sequence and Image Processing Software, Appendix B**). The purpose of the initial MRI is to quantify the degree of atrial structural remodeling or fibrosis prior to ablation. Patients are screened for metal fragments. If metal fragments are identified, the MRI team will scan the participant on a 1.5T scanner. If metal fragments are not identified, the MRI team will scan the participant on a 3T scanner. If a patient has a heart rate ≥ 90 beats per minute, they will be pre-medicated with a beta blocker prior to the MRI to obtain optimal images.

The patient will be injected with gadolinium (Gadovist, Class II macrocyclic gadolinium, low risk) or a similar agent, contrast enhancement. A brief period of time is taken to allow gadolinium to perfuse the tissues and wash-out to appropriate concentrations in the heart. The patient will then undergo CMR sequencing, which lasts approximately 20-25 minutes. Throughout the procedure, the patient is monitored for adverse reactions to the contrast. If the patient develops any contraindications listed in the

exclusion criteria prior to their follow-up scans, the patient will be excluded from receiving subsequent CMRs.

Atrial fibrosis progression will be compared and contrasted from the patient's baseline image to their follow-up CMR scans at 3 months and 1-year post-ablation. A pregnancy test will be performed at baseline and before every CMR scan during each study visit in pre-menopausal women. If a patient becomes pregnant during the trial (after baseline CMR scan), the patient will not be allowed to undergo any follow up CMR scans until 10 days post-partum.

All CMR images will be uploaded to Marrek, Inc., (Salt Lake City, UT) Merisight portal as they arrive from each clinical trial site. If the imaging specialist believes the baseline image does not meet quality standards, they will not be further processed. Therefore, the patient will be excluded from the EDORA trial. CMR scans will be uploaded onto the Merisight portal. Any reports in addition to the CMR scanned images will help to aid in Marrek's calculations and analysis.

Marrek, Inc., will analyze and process the images, verifying that the patient has a proportion of atrial fibrosis (not limited to advanced stage fibrosis). Utah Stages 1-4 will be used to classify patients based on the percentage of fibrosis. Access to Merisight will also be granted to additional analysts who will separately determine LA and LV function and strain and aid in MRI sequencing.

A final report from Marrek Inc. will be uploaded onto Merisight' s portal and uploaded onto DACIMA. All CMR scans will maintain identifying information to allow trial sites to verify that returned reports match the patients submitted identified information.

Baseline, 3 months, and 1-year CMR scans for 330 study participants will be pulled from Phillips IntelliSpace Picture Archiving and Communication System (PACS) and stored on DACIMA. All segmentations and images will also be stored on our encrypted server.

Day of Cardiac Ablation

After the baseline visit, patients will be scheduled for a cardiac ablation. Clinical investigators will schedule ablation procedures within 90days after CMR imaging has been completed.

Patients will be medically assessed by the site investigator. Patients who are deemed by the site investigator to have not tolerated the ablation well will not be enrolled in the study. Due to current hospital SOC, patients may be discharged up to 24 hours after ablation. Discharge may be expedited per physician discretion and other hospital-based policies (e.g. COVID-19, etc.).

Biometric Equipment

BodyGuardian® MINI Plus EL (ECG monitoring device)

Patients will receive an FDA-approved BodyGuardian® MINI Plus EL ECG monitoring device kit provided by Preventice Solutions. The patients will be educated on how the monitor works and will be instructed to wear it (attached to chest via a sticky patch) once every 3 months and to record their daily ECGs for thirty days, starting with immediate use after ablation (discharge,], 3, 6, 9 and 12 months).
The device also has the capability of recording rhythm strips in addition to continuous recordings by study participants if/when they experience any signs or symptoms of an arrhythmia.

BodyGuardian® MINI Plus devices for all patients will be sent directly from Preventice to the trial sites before patient enrollment. After cardiac ablation, a research member will instruct the patient on how to use the device. Once the 30-day monitoring period is over, the patient will be instructed to return that device to Preventice via a pre-paid shipping label.

At the 3-month and 12-month in-person visits, a research member will provide the participant with another device. Again, once the 30-day monitoring period is over, participants will send their devices back to Preventice via a pre-paid shipping label.

At the 6- and 9-month period, sites may ship participants devices to their preferred address (sites will be responsible for creating a shipping label). Once the 30-day monitoring period is over, participants will send their devices back to Preventice via a pre-paid label.
It is important to note that at these periods if devices are shipped to a participant address, the label must be removed (to remove any identifying information) before sending it back to Preventice.

The device must be worn for the entire period and can be worn during exercise and during showering/ bathing. Each patient will be assigned a unique identifier associated with the device at the participating site so that the patient's ECG transmissions will always be linked with their study participant ID. The readings from the strips will be uploaded directly onto the patient's smartphone application and sent automatically to DACIMA. Final reports will be uploaded onto DACIMA.
Trained experts blinded to treatment arm assignment at the ECG Core lab at the University of Washington, WA will be responsible for reviewing and analyzing all de-identified ECG recordings.

In the case where continuous heart monitoring may have been conducted as part of standard of care), clinical staff will upload the summary report onto DACIMA.

Patients will be informed that ECG rhythm strips and associated results are not read in real-time. If any readings are positive for AF or patients experience any AF related symptoms, they are advised to seek immediate medical attention.
Preventice has a stoplight notification protocol that allows them to identify critical and serious rhythm patterns. In this case, if such a rhythm is detected, Preventice may call sites to alert them that a participant should be immediately contacted.
Each site will create a master list that associates a participant with their device for emergency circumstances. It will be the sites responsibility to contact the participant and advise them to seek medical attention, if necessary.

In Between ECG Monitoring

Although not mandatory, participants will be encouraged to provide ECG data from any other personal device. For example, a smartwatch, Holter monitor, etc. This data collection will be from time points in between regularly scheduled ECG monitoring (i.e., in between 3,6,9- and 12-months). Patients may provide data sets to their site coordinator via email or at their in-person visits.

Definition of Trial Outcome using ECG Device

The trial outcome is defined by at least one ECG tracing indicating AA for >30 seconds. AA demonstrated by any ECG device can include AA occurrence during the 90-day blanking period.

If a repeat ablation is performed, but there is no AA recurrence demonstrated by ECG readings from SOC ECG device or any other ECG device, AA recurrence will be inferred for the purposes of the primary study analysis and assigned to the date of the repeat ablation.

Stratification, Randomization and Blinding

After cardiac ablation, trial staff will stratify each participant by age (< or ≥ 65 years old) and type of AF (persistent or paroxysmal). After stratification, study participants will be randomized using a web-based randomization service. Other confounding variables will be adjusted for primary outcome's analysis, including UTAH fibrosis staging. As this is a single-blind trial, only patients will be blinded to the assigned treatment arm.

Dosing and IMP Administration

Drug/placebo therapy starts the same day after the ablation procedure. A 3-month supply will be provided to all participants. Dronedarone 400mg or an oral placebo tablet will be administered twice daily (morning and evening) along with substantial meals. No dosing adjustment is needed in cases of mild renal impairment. Any adjustment to treatment would be considered a secondary endpoint and will not prompt an interruption in subsequent follow-up visits and assessments. Study participants will continue to be followed for primary and other secondary endpoints.

3-Month Visit

Sites will collect vital signs, weight, and blood samples for labs. During this on-site visit, study participants will complete the second set of AFEQT and AFSS questionnaires. Sites will review and document any changes within the medical history, current and concomitant medication use, and presence of any adverse events. Study participants will also receive another CMR. At this time, study participants may also receive some or the rest of the IMP or placebo (9-month supply) depending upon their enrollment date. This is to ensure that no patient receives drug that is about to expire and new drug (with increased expiration date) in the same visit. Also, while on site, study participants may work with the study team to troubleshoot research devices and ask any questions if needed. At this time, their six-month and nine-month visit/phone-calls will be scheduled. Any leftover drug will be provided to a research member at this time for suitable disposal.

6-Month and 9-Month Visits/Phone Calls

Similar to the 3-month visit, sites will review and document any changes within the medical history, current and concomitant medication use, and presence of any adverse events. Sites may also work with study participants to troubleshoot devices and address any questions or concerns. Sites will also check on medication adherence as well as discuss how study participants are managing with their medication supply. Sites may need to supply the rest of the IMP or placebo during these time points (scheduled/ unscheduled visits) depending on enrollment date. This is to ensure that no patient receives drugs that are about to expire. Any leftover drug will be provided to a research member at this time for suitable disposal.

12-Month Visit

The 12-month visit is the same as the 3-month visit. Sites will collect vital signs, weight, and blood samples for labs. During this on-site visit, study participants will complete their final AFEQT and AFSS questionnaires, discuss any changes in their medication and review any adverse events. Study participants will also receive their final CMR scan. If any questions or concerns arise related to the study devices, these can be addressed at this visit. Any leftover drug will be provided to a research member at this time for suitable disposal.

End of Trial (EoT) Visit Phone Call

A phone call will be scheduled towards the end of the clinical trial (around 13 months). Sites will review and document any changes within the medical history, current and concomitant medication use, and presence of any adverse events

Study Schedule

Screening Visit

- Obtain and document signed Informed Consent Form and HIPAA Authorization Form.
- Review medical history to determine eligibility based on the inclusion/exclusion criteria.
- Obtain patients demographic information.
- Complete Physical Examination
- Collect anthropometric data (height and weight), and vital signs
- Assessment of medication/concomitant therapy.
- ECG reading.
- Schedule baseline CMR prior to ablation procedure.

Baseline CMR Visit (Day -90 to 0)

- Verify inclusion/exclusion criteria.
- Document study eligibility has been verified by site investigator signature.
- Confirm medication/ concomitant therapy.
- Collect weight and vital signs.
- Obtain baseline CMR scan.
- Blood draw to obtain baseline creatinine levels, hepatic panel as well as biomarkers for fibrosis and inflammation.
- Obtain baseline AFEQT online questionnaire.
- Obtain baseline AFSS online questionnaire.
- Determine that the baseline scan meets standard requirements for enrollment.

Ablation Procedure (Day 0)

- Confirm medication/ concomitant therapy.
- Perform cardiac ablation (SOC).
- Collect weight and vital signs
- Determine that cardiac ablation was successful (i.e. well tolerated by patient)- requirement for enrollment
- Stratify and randomize into treatment arms (1:1 ratio).
- Dispense dronedarone or placebo (3-month supply) according to randomization assignment.
- Provide patient with ECG monitoring device

3-Month Visit (Day 90 ± 30)

- Collect weight and vital signs
- Confirm concomitant therapy or changes in medication.
- Obtain 3-month CMR scan.
- Blood draw to obtain creatinine levels, hepatic panel, as well as fibrosis/inflammatory biomarkers.
- Review medical history.
- Obtain 1st AFEQT online questionnaire.

- Obtain 1st AFSS online questionnaire.
- Assess for medication compliance.
- Assess for any adverse events.
- Dispense dronedarone or placebo (some/complete 9-month remaining supply) according to randomization assignment.
- Collect unused drug or placebo.
- Troubleshoot/ assess compliance of wearable device.

6-Month and 9-Month Visit/Phone Calls (Day 180 ± 30 and Day 270 ± 30)

- Review medical history and study outcomes.
- Assess for changes in study medication.
- Assess medication compliance.
- Dispense dronedarone or placebo (some/complete remaining supply)
- Provide/Ship patient's ECG monitoring devices.
- Assess compliance/troubleshoot study devices.
- Assess for any adverse events.

12-Month Visit (Day 365 ± 30)

- Collect weight and vital signs.
- Review medical history.
- Blood draw for biomarkers of fibrosis and inflammation.
- Confirm concomitant therapy or changes in medication.
- Obtain 1-year CMR scan.
- Obtain final AFEQT online questionnaire.
- Obtain final AFSS online questionnaire.
- Assess for medication compliance.
- Collect unused drug or placebo.
- Assess for any adverse events.
- Assess compliance/troubleshoot study devices.

End of Trial (EOT) Phone Call (Day 395 ± 30)

- Review medical history and study outcomes.
- Assess for changes in study medication.
- Assess medication compliance.
- Assess compliance/troubleshoot for study devices.
- Assess for any adverse events.

Data Sharing, Data Safety, and Data Integrity Monitoring

All recruited patients will be informed during the initial screening visit of the potential adverse events related to the trial when signing the informed consent form. Adverse event data collection and reporting are required as part of every clinical research trial.

Data Sharing Plan

Tulane University ARO views the sharing of resources with community partners and stakeholders as tantamount to our mission. This concept is at center of what it means to be an "engaged academic institution" – coordinating action and sharing resources to accomplish mutually beneficial objectives within the communities that are our university's neighbors. We approach our work with colleagues always with this commitment in mind. More precisely, data, models, and software that is not human-subjects sensitive and which is not subject to external copyright restrictions will be made available to the research community at large on a project web site. Human subjects' sensitive data will only be distributed when it can be done so in a manner that is compliant with all Federal, State, and local regulations, and respects the informed consent agreements with the subjects. Such data will be fully anonymized, and all potentially identifying features will be removed. Full documentation of the data set will be provided. Our findings will be communicated through publications at journals, conferences, and other scientific forums and will be made available on the project web site. As our data will come from multiple sources, and it brings novel combinations of data together, this heightens its potential future utility. We will permit and encourage the reuse of our products by the research community.

We commit to archive our data in accordance with any National Science Foundation (NSF), National Institutes of Health (NIH), and Tulane University ARO guidelines (e.g., de-identification according to IRB and HIPPA regulations) and resources, so future or secondary data collection uses can be steeped from this work. We will also respect the conditions of use of data collected from external sources such as Twitter postings or medical articles. If the University seeks to patent processes developed in the course of this work, it will act in accordance with the NSF Patent Policy.

Data Resource Sharing Plan

Our data sharing plan will comply with all NIH and Tulane University ARO policies for data sharing. Sharing of data and scientific findings with the research and clinical communities will be executed through publications in peer reviewed journals and presentations at scientific meetings. Data sharing will be implemented in a timely manner. We are very open to sharing EDORA project data with the general scientific community since we believe in the added value of other investigators working on these data.

Data Safety and Monitoring

Data Safety Monitoring Board (DSMB)

The study will be formally monitored by a Data and Safety Monitoring Board (DSMB). This is an independent board that will have a charter. They will monitor safety data on a regular basis to ensure the continuing safety of the patients involved in this clinical trial. Enrollment will not be paused during these safety reviews.

The DSMB can also recommend modifications to the data management and monitoring procedures in the trial or to the protocol. Every effort will be made to reach a consensus within the DSMB and with the Principal Investigator. In case of disagreement on recommended modifications, the Steering Committee will decide. The DSMB will meet at least two times a year at the discretion of the Chairperson. An emergency meeting may be called at any time throughout the trial should an unforeseen problem arise. The DSMB's full responsibilities, authorities, and procedures will be documented in the DSMB Charter.

Steering Committee (SC)

The Steering Committee (SC) will act to provide independent oversight of all aspects of the clinical trial. This includes the trials progress, adherence to the protocol and review of any new information regarding the trial's interventions/therapeutic area.

The Steering Committee may meet at any time after the start of the trial, on an ad hoc basis. The steering committee's full responsibilities, authorities, and procedures will be documented in the SC Charter.

Database Lock

Once the last patient has had their follow-up visit, the database cannot be locked until all data queries have been resolved. Quantitative data will be examined statistically, prior to locking the database. When all such verifications have been completed, the database will become locked, prior to any final data analyses for the EDORA trial.

Adverse Events (AEs) and Serious Adverse Events (SAEs)

An adverse event (AE) is any unforeseen medical occurrence experienced by a patient in the clinical trial. This event can constitute a disease, related signs or symptoms to the investigational drug or study device. All clinical investigators will evaluate and record these events on the appropriate form. Arrhythmias will not require reporting as an AE because the patient will be transmitting ECGs via their ECG device, and these will be reviewed and interpreted by the central monitoring team. A serious adverse event (SAE) is an adverse event that results in death, hospitalization, is life threatening or requires intervention.

For each AE+/SAE, the clinical investigator will record whether an intervention was also required:

- **Intervention-** Surgery or procedure
- **Other treatment**- medication initiation/change, discontinuation
- **None**- no action was taken

In addition, the clinical investigator will also record any clinical outcome of each AE+/SAE:

- Death
- AE resolved or the symptoms/signs that constitute the AE returned to baseline
- AE resolved with permanent sequalae
- Symptoms that constituted the AE are ongoing

Each participating clinical trial site and its investigator has a primary responsibility for the safety of the patients under his or her care. In person visits will occur at 3 and 12-months, and follow-up phone calls/ visits will be held at 6, 9-months and towards the end of the clinical trial (Month 13). Clinical investigators or the research team may schedule additional clinic visits according to their standard of

care or as needed to maintain patient safety during the trial. These visits as well as any new or worsening symptoms or events will also be recorded on DACIMA during this time.

All adverse events that occur after randomization will be evaluated throughout the follow-up periods and will be collected and stored on DACIMA.
Serious adverse events (SAE) must be reported in an expedited manner to the IRB and Tulane University ARO, to allow for optimal monitoring of patient safety and care.
Please refer to the Adverse Events & Reporting section for provided timelines on reporting AE, SAE and UP and completing the respective logs.

Adverse Events (AEs) and Serious Adverse Events (SAEs) Related to the EDORA Trial

a) Cardiac Ablation

Cardiac ablation is standard of care. Patients who have attempted to control their arrhythmia via AADs with no positive outcome and/or have suffered serious side effects from certain medications are advised to undergo this procedure. Most symptoms or side effects related to cardiac ablation are not from the procedure itself. Patients may complain of back ache from lying on the operation table for a longer time. Sore throat is a common side effect of the procedure due to the anesthetic use during intubation and some arrhythmia may be experienced afterwards (blanking period).

Direct effects of cardiac ablation include bleeding or infection at the site where the catheter was inserted, puncturing of the heart, damage to heart valves, damage to the heart's electrical system, which could worsen the arrhythmia and require a pacemaker to correct. In addition, venous thromboembolism, pulmonary vein stenosis, stroke or heart attack could occur. Renal damage from contrasting dye used during the procedure, and even death may occur in rare cases.

b) Dronedarone

Antiarrhythmic drugs such as, dronedarone can be prescribed as standard of care. They too carry adverse effects which include; pulmonary events (cough, dyspnea, pulmonary toxicity), thyroid toxicity (hypo- or hyperthyroidism), hepatic toxicity, bradycardia <50bpm, QT-interval prolongation, gastrointestinal events (loss of appetite, nausea, vomiting, abdominal pain and diarrhea), neurological events (dizziness, headache, asthenia, peripheral neuropathy), chest pain or discomfort, heart failure, decompensation in patients with heart failure, and an increase in serum creatinine.

Although a black box warning has been issued by the FDA, dronedarone's associated risk of death and stroke is based on patients with heart failure, decompensated heart failure, or permanent atrial fibrillation. These classes of patients fall into the exclusion criteria and thus, will not be enrolled in this trial. Dronedarone is also contraindicated in AF patients who cannot be cardioverted into normal sinus rhythm.

c) CMR Scan

There will be approximately 3 CMR scans throughout the trial period. The 1st CMR scan will be taken preferably within 90 days prior to ablation. Gadovist, Class II macrocyclic gadolinium, low risk, or a similar agent will be used as the contrasting agent to visualize the heart.
Discomfort in claustrophobic patients undergoing an MRI can happen in which case the image processing will be halted immediately.

Risks Associated with Gadolinium Contrast in CMR

Risks associated with gadolinium include:

- Discomfort, tingling, warmth of the lips, metallic taste in the mouth, nausea, or headaches. This risk is small (1 in 100 people) and in most instances these symptoms disappear very quickly.
- Type 1 hypersensitivity reaction. Clinical staff will stop its use immediately and will provide antihistamine medication or epinephrine, depending on the severity of the reaction. Severe reactions rarely occur, < 1 in 300,000 people.
- Approximately 4% of patients with severe kidney disease receiving gadolinium based contrasting agents are at a higher risk of developing Nephrogenic Systematic Fibrosis (NSF). Although rare, this disease can be serious, causing skin thickening (fibrosis) as well as thickening in other organs of the body such as, the brain, heart and bone and can even cause death. NSF has also been reported in those who have had recent major surgery, infection or have cancer.
  There have been no reports of NSF in patients receiving gadolinium who have normal kidney function. (Patients with acute or chronic severe kidney disease or with a low glomerular filtration rate (GFR), <30 mL per minute per 1.73 m^2 will be excluded from the EDORA trial).
- A pregnancy test will be conducted before each CMR scan as gadolinium may cause harm to the fetus. (Any pregnant patients at the time of enrollment will be excluded from the trial).

Unanticipated Problems

These can be incidents, experiences or outcomes that are unexpected but related to participating in the EDORA trial. These suggest that the trial places patients at a greater risk of harm than was previously known or recognized.

Categories that are considered UP:

- Adverse Device effects *(BodyGuardian® MINI Plus EL-ECG monitoring device)*
- Consent Deviation
- Data and Safety Monitoring Reports that indicate that frequency or magnitude of harms or benefits may be different than initially presented to the IRB
- Change in FDA labeling or withdrawal from marketing of a drug and or device used in the EDORA trial
- Breach of Privacy and Confidentiality *(e.g. unauthorized use of disclosure of protected health information.)*
- Incarceration of a participant
- Warning or determination letters issued by any funding agency or regulatory body including Office of Human Research Protections (OHRP), Department of Health and Human Services (DHHS), Food and Drug Administration (FDA)

Any unanticipated problems should be reported within 24 hours and a completed report will be required within 3 working days of the event. Once received, this report will be sent immediately (within 24 hours) to the DSMB. In accordance with IRB requirements, the investigator will be required to notify Tulane University ARO, their local IRB as well as the IRB of record (WCG).

In an unlikely event that the medical monitor believes that the unanticipated problem warrants immediate suspension in the trial, and the DSMB cannot be reached, the Principal Investigator will be informed, and all investigators will be told to cease enrollment in the trial. Again, only with the approval of the DSMB will the trial resume enrollment.
If the DSMB is notified of any SAEs that were unexpected, study related or unanticipated problems, decisions will be made as to whether the trial will continue without changes made to the protocol. If the

trial undergoes suspension, the Principal Investigator will be notified, and all clinical investigators will be instructed to report this to their local IRB or ethics board.

The DSMB will review all adverse events during their scheduled meetings. Tulane University ARO will prepare a summary report of all AEs for these meetings.

Adverse Events & Reporting

Adverse events do not necessarily require reporting to the IRB or Tulane University ARO (unless its frequency or intensity is greater than originally anticipated and are therefore deemed as serious). Local IRB requirements differ and therefore, the recommendation is for sites to follow their regulatory policies regarding this matter.
In accordance with IRB requirements, the investigator should notify Tulane University ARO, their local IRB as well as the IRB of record (WCG) of all SAEs within 24 hours.
A completed and comprehensive report will be required within 3 working days of the event. The medical monitor will assess all incoming SAE's that have been reported. The site investigator will need to sign all adverse event forms after full review.
All SAEs will be stored on DACIMA and will be readily available for review by DSMB members.

In an unlikely event that the medical monitor believes that an unexpected, but trial related SAE warrants an emergent cessation of enrollment in the trial, the DSMB Chair will be immediately consulted. If the board members concur with the medical monitors assessment, or the DSMB Chair cannot be reached, the Principal Investigator will be notified immediately, and all clinical investigators will be told to cease enrollment in the trial. Only with the approval of the DSMB will the trial resume.

Adverse Event (AE) Data Collection Procedures

All AEs, including serious adverse events (SAEs), whether anticipated or unanticipated, will be recorded according to the date of when they first occurred, the severity, and their duration, as well as any treatment that was prescribed.

Any medical condition that was present at the time of randomization, recorded in the patient's baseline medical history which remains unchanged or improves, will not be recorded as an AE at subsequent evaluations. However, worsening of a medical condition that was present at the time of randomization will be considered a new AE and must be reported.

Any abnormal laboratory results at the time of randomization, recorded in the patient's baseline history which remains unchanged will not be recorded as an AE. However, abnormal laboratory results drawn during the trial that are clinically significant will be recorded as an AE and the clinical investigator will assess the severity and relationship it may have to the clinical trial.

Follow-up of SAEs, Unexpected Events, and Related Events

Any SAEs that are unresolved at the time of the patient's termination from the trial will be followed by the clinical investigator until the events have been resolved, the patient is lost to follow-up, or the adverse event is otherwise explained or has stabilized.

For the safety and adverse events monitoring data, incidents of adverse events will be summarized by event type, grade, and body system. The proportion of patients with AEs will be calculated and presented with a 95% confidence interval.

Cardiac Resonance Imaging (CMR) Assessment of New Left Atrial (LA) Fibrosis

Baseline CMR to quantify baseline atrial fibrosis

Quantification of LA fibrosis will be obtained using methods previously described[8,28]. The LA wall will be segmented manually and regions of fibrosis in CMR images will be defined by an intensity threshold determined by expert inspection. Fibrotic tissue is detected when its enhancement is one-to-five standard deviations above the mean of normal tissue intensity. A 3D LA fibrosis map will be created using Corview Volume Rendering Software (Marrek Inc., Salt Lake City, UT). Inter-observer and intra-observer reproducibility for these techniques have been previously reported. Fibrosis will be represented as the volumetric percentage of left atrial wall enhancement.

Three-month CMR to visualize ablation-induced scars

Quantification of LA ablation induced scarring with CMR has been previously described[29]. 3-months post-ablation, endocardial and epicardial borders of the LA wall are contoured manually and blood pooling or other artifacts are omitted in scanned images. Pixel intensities are distributed as bimodal to distinguish normal from injured tissue. Pixels with lower intensities are chosen as normal tissue and ablation-induced lesions are defined at one to five standard deviations above the mean of normal tissue pixel intensity. The assessment of ablation induced scars is best before or at 3 months after the procedure. The lower threshold used in the later scans causes weak scar lesions to be detected and an inexperienced eye might mistake them for new fibrosis. Regions marked as the ablation lesion will be independently evaluated by two blinded experts to ensure correctness.

Twelve-month CMR to assess for new fibrosis formation

After segmentation and measurement of LA fibrosis on pre-ablation scans and on 3-month post-ablation scans, we will use the latter as baseline for our trial to see if any new enhancement has formed or regressed (Figure 3). Transient post-ablation lesions will be defined as enhancements detected on the first post-ablation scan but not in the second post-ablation scan. New fibrosis will be defined as enhancement detected on the second post-ablation scan and absent on the first post-ablation scan. Both of these parameters will be reported as the percentage of total LA area.

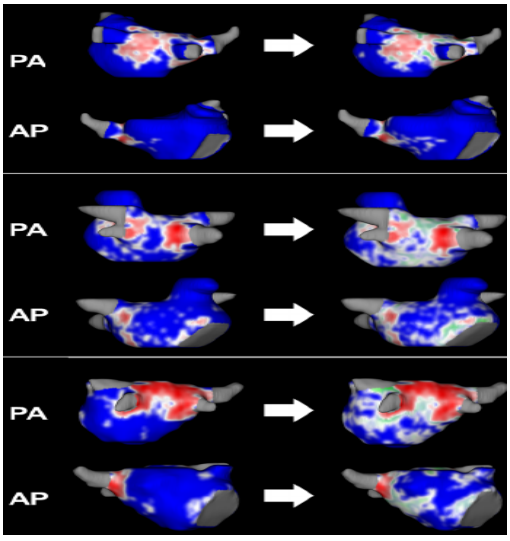


Figure 3: There is new enhancement detected on the post-ablation MRI of the left atrium. New fibrosis is displayed in green. The red area represents ablated regions. Adapted from Kheirkhahan et al.[10]

Statistical Methods, Data Analysis, and Interpretation

This is a prospective, randomized clinical trial to assess whether dronedarone is superior to placebo in decreasing AF recurrence and to SOC in reducing the progression of fibrosis after AF ablation.

A. Sample Size Estimation

Atrial Fibrosis Progression

Based on the assumption that the mean progression of fibrosis in the control group is 10%, the SD for the progression of fibrosis is 1.59. Predicting a 20% dropout rate, 86 randomized patients will provide >99% power with a 2-sided α= 0.05 to detect a reduction of 20% in fibrosis progression between dronedarone and the control arm. Given that an estimated 330 patients will be recruited, the study will have approximately 100% power to detect the group difference in atrial fibrosis progression.

Atrial Arrythmia (AA) Recurrence

The rate limiting factor in the required sample size is AA recurrence (atrial fibrillation, atrial flutter, atrial tachycardia). AA recurrence is defined as a one instance, continuous >30 second strip reading on either 12-lead ECG, Holter monitor or study devices (including during the blanking period)

AA recurrence will be based on the following assumptions:

- 50% of patients in the control group will have AA recurrence in 1-year, post-ablation (including during the blanking period) and,
- the relative reduction of AF recurrence will be by 33% in the dronedarone group compared to the control group and,
- 20% of subjects could be lost during the follow-up periods and,
- 2-sided α=0.05.

The EDORA trial will have a total of 330 patients participating, thus, 165 in each trial arm. Therefore, a calculated total of 138 AF recurrences will have 86% power to detect the group differences.

The study will be defined as successful if the hypotheses for both co-primary endpoints are positive, i.e., rejecting the null hypothesis. Therefore, in terms of overall type I error of the study, the sample size calculation does not need to adjust for the multiplicity. However, the type II error, i.e., the power for each individual test needs to be adjusted in this case to achieve the overall power of the study. For the endpoint of atrial fibrosis progression, given that 330 patients will be recruited, we have almost 100% power to detect the expected difference. For AF recurrence, the study will have at least 85% power. Therefore, for the two co-primary endpoints, the study will have at least 85% overall power for a positive outcome, i.e., the study is powered to detect the difference in both atrial fibrosis progression and AF recurrence between the two arms.

Most studies evaluating the effects of AAD after ablation started their monitoring after the 3-month blanking period. Our trial will start assessing for the primary endpoint of AF recurrence on the day of discharge, and so we expect a significantly higher event rate. A few recent studies reporting recurrence data during the first three months after ablation such as, the AMIO-CAT study showed a 53% AF recurrence rate after ablation in a placebo group and AF recurrence at 6 months was 48%. In the EAST-AF study, randomizing paroxysmal and persistent AF patients to short term AAD use vs control, the rate

of AF recurrence 3 months after ablation was 48% and 30% at 9 months follow-up. Recurrent 30-day monitoring using an ECG monitoring device in our study is expected to provide a higher event rate than observed in previous AAD vs control studies, in which monitoring was performed at a limited number of follow-up visits.

B. General Considerations for Data Analysis

Data analysis will be conducted to address the research questions. All statistical tests will be two-sided with a $p \leq 0.05$. Descriptive statistics such as, mean (SD) for continuous variables and frequency (%) for categorical variables will be provided for baseline information. The simple t-test/Wilcoxon rank sum test or chi-square tests will be applied to compare the demographic information and the baseline clinical measurements between the intervention and control groups to assess if randomization is successful at each site. Any imbalanced information will be included in the regression models to account for potential confounding variables in assessing treatment effects. All primary efficacy analysis will be performed in an intent-to-treat (ITT) manner.

C. Analysis of the co-primary endpoints

Analysis of AF Recurrence

Time-to-event-analysis will be conducted for AF recurrence. Patients with unobserved AF events during the study trial due to loss-of-follow-up/death or termination of the study will be treated as censored and the time to first AF recurrence will be treated as the outcome. Cumulative AF rates will be calculated by intervention conditions using the Kaplan-Meier (KM) method and compared using the log-rank test. Stratified KM curves will also be performed by Utah Stages at baseline (separate strata for Utah stages I - II, and III - IV) to investigate if the treatment effects vary across different stages. Cox proportional hazards models will be used to assess the intervention effects on the time to AF recurrence after discharge from the procedure. The proportional hazards assumption will be tested by means of graphical methods and statistical tests of lack of fit.

Due to the nature of the randomization in the study design, it is expected that the demographic characteristics and other important clinical factors will be balanced between the two groups. However, in addition to the primary predictor and the intervention condition, potential confounders will also be included in the model.

Due to the clustering effects at a physician level, we will include random effects of the physician in the model. We will also further investigate if the intervention effects are similar across the stages after controlling potential confounding effects by including the interaction of the intervention and the Utah stage in the models. In all the models, the estimated hazard ratio between the treatment and control groups with its 95% confidence interval will be provided.

Analysis of LA Fibrosis Progression

The primary outcome variable will be changes in the percentage of fibrosis from baseline, 3- and 12-months via CMR assessments in patients randomized to receive dronedarone vs. placebo.
We will apply models for longitudinal data to analyze the LA fibrosis progression over the follow-up period. The two most popular approaches for longitudinal data are the Linear Mixed-effects Model approach (LMM) and Generalized Estimating Equations (GEE). The LMM requires parametric assumption such as, normality on the random effects and model errors, and it is more powerful when the assumptions are met, but vulnerable to departures from the assumed distributions. GEE provides robust

estimates because it does not require any distribution assumption. Therefore, we will first investigate the distribution of the outcome, and if the distribution assumption is reasonable, we will use LMM model, otherwise, we will use GEE approach. Due to the clustering effect at a physician level, we will use random effects in LMM or working correlation in GEE model to account for the correlations. In all the models, the primary predictor is the intervention condition. We will also consider controlling other potential confounders if the data exhibits any. The intervention effect is assessed by the estimated coefficient of the primary predictor. The coefficient with right direction and a p value <0.05 indicates there is a significant intervention effect.

Per standard principles, the primary analyses will be done on an intention to treat basis (ITT), treating all randomized patients with available outcome data regardless of compliance. A Robustness Analysis will include a per protocol analysis, where only those patients who actually received their assigned treatment (e.g., those who received dronedarone per the dosing protocol) will be analyzed. In terms of missing data, the survival analysis approach to the AF recurrence outcome will censor any patients who drop out of the study without AF recurrence at the time of their last known contact. While we would propose such patients to have their first documented recurrence date counted as their failure date, alternative analysis approaches for the analysis of interval-censored data will also be considered for robustness.

For LA fibrosis regression, the missing data will be considered in the analysis. In the LMM model under 'missing at random', the factors associated with the missing values will be examined and then included to account for the missing values. As for the GEE approach, the likelihood of being observed for patients will be estimated and incorporated into the model to achieve unbiased estimates. Sensitivity analysis by multiple imputation will be conducted to assess how the missing data will impact the results. Patients will be considered lost to follow-up for the primary endpoint of fibrosis progression if they fail to attend any of the CMR visits.
The study is defined as positive if the analyses yield the coefficients of the intervention for both co-primary endpoints with a right direction and a p-value <0.05.

D. Analysis of the secondary endpoints

The secondary endpoints will be analyzed only as supporting evidence. There will be no intention to claim treatment benefits for the listed secondary endpoints. As such, data analysis for secondary endpoints are purely for descriptive purposes and not for drawing inferences.

Statistical Analysis Software
Statistical analysis will be performed using SAS version 9.4 and STATA version 14.

Food and Drug Administration (FDA) Approval

The EDORA trial will be using an FDA approved device as well as the FDA approved drug dronedarone. The ECG Preventice monitoring device will transmit ECG recordings every 30-days onto its respective application on a paired mobile device. As dronedarone is already a marketed drug, we have received an FDA IND exempt status to proceed with this clinical trial.
PIND Exempt No: 153638

Study Training & Monitoring

All enrolled sites will receive study protocol training via a site initiation visit (SIV). Prior to the SIV, all study staff should review and be familiar with the study protocol. In addition to study protocol training, the SIV will also cover use of the electronic data capture platform (DACIMA Software, Inc. Electronic Data Capture) and the Merisight Web Portal (for upload of CMR scans). Training for Montrium eTMF Connect and Preventice Cardiac Monitors web portal will be conducted via site self-review of vendor training material.

Following the SIV and site activation, all sites will be monitored via site monitoring visits (SMVs) per frequency specified in the clinical monitoring plan. As much as possible, all site monitoring will occur remotely via monitor access to the EDC, eTMF, and source document access as outlined in the clinical monitoring plan. To ensure contemporaneous data entry, all sites must enter data into the EDC within 3 business days. Sites are also responsible for responding to monitor queries in the EDC and/or eTMF within 5 business days. Prior to a SMV, the sites are to ensure that all study documentation is complete, up-to-date, and query-free. For additional information on site requirements, please refer to the clinical monitoring plan.

ClinicalTrials.gov Requirements

The EDORA trial is registered at ClinicalTrials.gov in accordance with Federal Regulations.
NCT: 04704050

Study Records Access and Retention

Electronic Data Capture Platform

Tulane University ARO will use DACIMA Clinical Suite by Dacima Software Inc. as the centralized clinical database. The DACIMA Clinical Suite is compliant with good clinical practices and FDA 21 CRF Part 11 requirements. Only enrolled participants will be entered into the EDC and will be assigned a consecutive number (that includes the site's number) by the site's Research Coordinator. All changes made to the clinical data will be captured in an electronic audit trail available for review. Sites are also responsible for maintaining source documents in a physical subject's binder .

Electronic Trial Master File (e-TMF)

Tulane University ARO will use eTMF Connect by Montrium as an electronic trial master file (eTMF). eTMF Connect uses a TMF reference model, which provides standardized taxonomy and reference for TMF content. Each trial site will be responsible for uploading regulatory documents on EDORA eTMF Connect.

Record Access

All medical records and study source documents will be made available to authorized representatives at Tulane University ARO, upon request, for verification of study documentation. All medical information and data generated from this clinical trial will be made available for inspection upon request by representatives of Tulane University ARO and the Institutional Review Board (IRB) for each clinical trial site.

Retention of Records

Records relating to the EDORA trial shall be retained for a period of 7 years after the completion of this clinical trial. Completion of this trial will be based on the planned analyses described in the protocol as well as completion of all publications relating to this clinical trial. All records shall be accessible for inspection and copying by authorized representatives of the regulatory authorities at reasonable times and in a reasonable manner [45 CFR §46.115(b)].

Schedule of Events[7]

PROCEDURES	SCREENING VISIT	BASELINE VISIT (DAY -90 TO 0)	DAY OF CARDIAC ABLATION (DAY 0)	3-MONTH VISIT (DAY 90±30)	6-MONTH VISIT/ PHONE CALL (DAY 180±30)	9-MONTH VISIT/ PHONE CALL (DAY 270±30)	12-MONTH VISIT (DAY 365±30)	13-MONTH PHONE CALL (END OF TRIAL) (DAY 395±30)
SIGNED ICF/ HIPAA FORM	X							
ASSESSMENT OF ELIGIBILITY CRITERIA								
REVIEW OF MEDICAL HISTORY	X							
HEIGHT, WEIGHT, VITAL SIGNS	X (Height measured here only)	X	X	X			X	
ECG	X							
INCLUSION/ EXCLUSION CRITERIA	X							
TRIAL MEDICATION								
RANDOMIZE			X					
ABLATION			X					
DISPENSE TRIAL MEDICATION			X 3-month supply	X Some/9-month supply	X (Remaining supply)	X (Remaining supply)		
DRUG COMPLIANCE				X	X	X	X	
CONCOMITANT THERAPY ASSESSMENT	X	X		X	X	X	X	

[7] All events listed under a study timepoint may be asynchronous. However, all events must occur within that timepoint. For more guidance, please review protocol sections "**Study Procedure and Data Elements**".

AE MONITORING			X	X	X	X	X	X
BLOOD DRAW		X		X			X	
RETURN OF TRIAL MEDICATION				X			X	
PHYSICAL AND MEDICAL EXAMINATION								
MEDICATION(S) REVIEW	X	X	X	X	X	X	X	X
REVIEW OF MEDICAL HISTORY		X	X	X	X	X	X	X
VITAL SIGNS		X	X	X			X	
PHYSICAL EXAM	X							
OTHER MEASURES								
CMR SCAN		X		X			X	
ECG MONITORING KIT (BodyGuardian® MINI Plus EL)			X	X	X	X	X	
AFEQT QUESTIONNAIRE FORM		X		X			X	
AFSS QUESTIONNAIRE FORM		X		X			X	

Appendix A: Placebo Composition

Placebo Composition (Provided by Sanofi Pharmaceuticals)

Ingredients	Compendial grade	Function	Unit quanity mg/tablet
Core tablet			
Microcrystalline cellulose	NF/Ph.Eur.	Diluent - binder	266.0
Starch (corn) - Maize starch	NF/Ph.Eur.	Diluent - disintegrant	38.0
Crospovidone (type A)	NF/Ph.Eur.	Disintegrant	15.2
Colloical silicon dioxide - Colloidal anhydrous silica	NF/Ph.Eur.	Flow agent aid	1.9
Lactose anhydrous[(a)]	NF/Ph.Eur.	Diluent - binder	435.1
Magnesium stearate[(b)]	NF/Ph.Eur.	Lubricant - antiadherent	3.8
Core mass :			*760*
Coating/Polishing			
Hydroxypropyl methylcellulose - Hypromellose	USP/Ph.Eur.	Film agent	7.25
Titanium dioxide (E171)	USP/Ph.Eur.	Opacifier	1.00
Polyethylene glycol 6000 - Macrogol 6000	NF/Ph.Eur.	Plasticizer	1.75
Purified water[(C)]	USP/Ph.Eur.	Coating solvent	(85.00)
Film-coating mass :			*10*
Carnauba wax	NF/Ph.Eur.	Polishing agent	(traces) 0.13
Film-coating mass :			*770*

[(a)]CEPs for BSE/TSE risk are provided in Appendix 3.1.A.2
[(b)]From vegetable origin
[(C)]Eliminated during the manufacturing process

Appendix B: CMR Protocol

The sequences and measurement performed will be the following:

1. Cine of LV – stack of SA slices covering whole LV, 2-, 3-, and 4-chamber
Assessment of LV function and strain
LV function: Ejection fraction (%)
LV strain: global longitudinal strain in % and strain rate in cm/s
2. Pre-Contrast T1 Mapping: 3 SA (base, middle, apex) slices
Assessment of LV fibrosis (in %)

3. MR Angiography - ECG-gated, respiratory navigated
Assessment of LA and LAA shape. Useful for LA wall segmentation

4. Cine of LA: stack of axial slices covering whole LA
Assessment of LA function and strain

For LA function and shape assessment, a stack of contiguous axial cine images covering the whole LA will be obtained. Tissue-tracking approach will be used to quantify LA strain and phasic volumes from the cine images, a method described previously. This method has been previously validated with excellent reproducibility (intra-class correlation coefficients between 0.90 to 0.97 for LA volumes and strain). Endocardial and epicardial LA borders will be defined at end-systole by a blinded operator. Using defined borders in each view, the software will track the LA myocardium in subsequent frames. The operator will validate the generated contours during the cardiac cycle for quality control. Images with poor tracking will be excluded. In each frame, the LA volume will be calculated. Maximum, minimum, and pre-atrial contraction LA volumes in cm (LAVmax, LAVmin, VPreA) will be extracted from volume curve. The point on the LA volume curve during diastole just before the fast descent following a period of stability in LA volume will be defined as pre-atrial contraction volume. At that point, the atrial strain rate is equal to zero. All measured volumes will be indexed to body surface area. LA sphericity index (LASI) will be calculated from LA endocardial shell segmented from CE-MRA and 3D LGE scans. The global longitudinal strain (in % (of shortening)) and strain rate (in cm/s) will be calculated by averaging all of the strain values obtained. Smax and SpreA will be identified from the strain curve.

LA function measurements (global emptying fraction, active and passive function) will be based on LA minimal, maximal, and pre-atrial kick volumes.

Total LA EF (in %) = [(LAVmax - LAVmin)/LAVmax]x100
Active LAEF (in %) = [(V_{PreA} - LAVmin)/ V_{PreA}]x100
Passive LAEF (in %) = [LAVmax - V_{PreA})/LAVmax]x100

5. Post Contrast T1 Mapping: 3 SA (base, middle, apex) slices
Assessment of LV fibrosis (in %)

6. TI-Scout

7. 3D LGE of LA
Assessment of LA fibrosis (in %)

Appendix C: Abbreviated Investigational Medicine Product Insert

1 INDICATIONS AND USAGE

MULTAQ® is indicated to reduce the risk of hospitalization for atrial fibrillation in patients in sinus rhythm with a history of paroxysmal or persistent atrial fibrillation (AF) *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

The recommended dosage of MULTAQ is 400 mg twice daily in adults. MULTAQ should be taken as one tablet with the morning meal and one tablet with the evening meal.

Treatment with Class I or III antiarrhythmics (e.g., amiodarone, flecainide, propafenone, quinidine, disopyramide, dofetilide, sotalol) or drugs that are strong inhibitors of CYP3A (e.g., ketoconazole) must be stopped before starting MULTAQ *[see Contraindications (4)]*.

3 DOSAGE FORMS AND STRENGTHS

MULTAQ 400 mg tablets are provided as white film-coated tablets for oral administration, oblong-shaped, engraved with a double wave marking on one side and "4142" code on the other side.

4 CONTRAINDICATIONS

MULTAQ is contraindicated in patients with:

- Permanent atrial fibrillation (patients in whom normal sinus rhythm will not or cannot be restored) *[see Boxed Warning, Warnings and Precautions (5.2)]*
- Symptomatic heart failure with recent decompensation requiring hospitalization or NYHA Class IV symptoms *[see Boxed Warning, Warnings and Precautions (5.1)]*
- Second or third-degree atrioventricular (AV) block, or sick sinus syndrome (except when used in conjunction with a functioning pacemaker)
- Bradycardia <50 bpm
- Concomitant use of strong CYP3A inhibitors, such as ketoconazole, itraconazole, voriconazole, cyclosporine, telithromycin, clarithromycin, nefazodone, and ritonavir *[see Drug Interactions (7.2)]*
- Concomitant use of drugs or herbal products that prolong the QT interval and might increase the risk of torsade de pointes, such as phenothiazine antipsychotics, tricyclic antidepressants, certain oral macrolide antibiotics, and Class I and III antiarrhythmics
- Liver or lung toxicity related to the previous use of amiodarone
- QTc Bazett interval ≥500 ms or PR interval >280 ms
- Severe hepatic impairment
- Pregnancy (Category X): MULTAQ may cause fetal harm when administered to a pregnant woman. MULTAQ is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations (8.1)]*.
- Nursing mothers *[see Use in Specific Populations (8.3)]*
- Hypersensitivity to the active substance or to any of the excipients

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Death in NYHA Class IV or Decompensated Heart Failure

MULTAQ is contraindicated in patients with NYHA Class IV heart failure or symptomatic heart failure with recent decompensation requiring hospitalization because it doubles the risk of death.

5.2 Cardiovascular Death and Heart Failure in Permanent AF

MULTAQ doubles the risk of cardiovascular death (largely arrhythmic) and heart failure events in patients with permanent AF. Patients treated with dronedarone should undergo monitoring of cardiac rhythm no less often than every 3 months. Cardiovert patients who are in atrial fibrillation (if clinically indicated) or discontinue MULTAQ. MULTAQ offers no benefit in subjects in permanent AF.

5.3 Increased Risk of Stroke in Permanent AF

In a placebo-controlled study in patients with permanent atrial fibrillation, dronedarone was associated with an increased risk of stroke, particularly in the first two weeks of therapy *[see Clinical Studies (14.4)]*. MULTAQ should only be initiated in patients in sinus rhythm who are receiving appropriate antithrombotic therapy *[see Drug Interactions (7.3)]*.

5.4 New Onset or Worsening Heart Failure

New onset or worsening of heart failure has been reported during treatment with MULTAQ in the post marketing setting. In a placebo-controlled study in patients with permanent AF increased rates of heart failure were observed in patients with normal left ventricular function and no history of symptomatic heart failure, as well as those with a history of heart failure or left ventricular dysfunction.

Advise patients to consult a physician if they develop signs or symptoms of heart failure, such as weight gain, dependent edema, or increasing shortness of breath. If heart failure develops or worsens and requires hospitalization, discontinue MULTAQ.

5.5 Liver Injury

Hepatocellular liver injury, including acute liver failure requiring transplant, has been reported in patients treated with MULTAQ in the post marketing setting. Advise patients treated with MULTAQ to report immediately symptoms suggesting hepatic injury (such as anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant pain, jaundice, dark urine, or itching). Consider obtaining periodic hepatic serum enzymes, especially during the first 6 months of treatment, but it is not known whether routine periodic monitoring of serum enzymes will prevent the development of severe liver injury. If hepatic injury is suspected, promptly discontinue MULTAQ and test serum enzymes, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase, as well as serum bilirubin, to establish whether there is liver injury. If liver injury is found, institute appropriate treatment and investigate the probable cause. Do not restart MULTAQ in patients without another explanation for the observed liver injury.

5.6 Pulmonary Toxicity

Cases of interstitial lung disease including pneumonitis and pulmonary fibrosis have been reported in patients treated with MULTAQ in the post marketing setting *[see Adverse Reactions (6.2)]*. Onset of dyspnea or non-productive cough may be related to pulmonary toxicity and patients should be carefully evaluated clinically. If pulmonary toxicity is confirmed, MULTAQ should be discontinued.

5.7 Hypokalemia and Hypomagnesemia with Potassium-Depleting Diuretics

Hypokalemia or hypomagnesemia may occur with concomitant administration of potassium-depleting diuretics. Potassium levels should be within the normal range prior to administration of MULTAQ and maintained in the normal range during administration of MULTAQ.

5.8 QT Interval Prolongation

Dronedarone induces a moderate (average of about 10 ms but much greater effects have been observed) QTc (Bazett) prolongation *[see Clinical Pharmacology (12.2), Clinical Studies (14.1)]*. If the QTc Bazett interval is ≥500 ms, discontinue MULTAQ *[see Contraindications (4)]*.

5.9 Renal Impairment and Failure

Marked increase in serum creatinine, pre-renal azotemia and acute renal failure, often in the setting of heart failure *[see Warnings and Precautions (5.4)]* or hypovolemia, have been reported in patients taking MULTAQ. In most cases, these effects appear to be reversible upon drug discontinuation and with appropriate medical treatment. Monitor renal function periodically.

Small increases in creatinine levels (about 0.1 mg/dL) following dronedarone treatment initiation have been shown to be a result of inhibition of creatinine's tubular secretion. The elevation has a rapid onset, reaches a plateau after 7 days and is reversible after discontinuation.

5.10 Women of Childbearing Potential

Premenopausal women who have not undergone a hysterectomy or oophorectomy must use effective contraception while using MULTAQ. Dronedarone caused fetal harm in animal studies at doses equivalent to recommended human doses. Counsel women of childbearing potential regarding appropriate contraceptive choices *[see Use in Specific Populations (8.1)]*.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of dronedarone is unknown. Dronedarone has antiarrhythmic properties belonging to all four Vaughan-Williams classes, but the contribution of each of these activities to the clinical effect is unknown.

12.2 Pharmacodynamics

- Electrophysiological Effects

Dronedarone exhibits properties of all four Vaughn-Williams antiarrhythmic classes, although it is unclear which of these are important in producing dronedarone's clinical effects. The effect of dronedarone on 12-lead ECG parameters (heart rate, PR, and QTc) was investigated in healthy subjects following repeated oral doses up to 1600 mg once daily or 800 mg twice daily for 14 days and 1600 mg twice daily for 10 days. In the dronedarone 400 mg twice-daily group, there was no apparent effect on heart rate; a moderate heart rate lowering effect (about 4 bpm) was noted at 800 mg twice daily. There was a clear dose-dependent effect on PR-interval with an increase of +5 ms at 400 mg twice daily and up to +50 ms at 1600 mg twice daily. There was a moderate dose related

effect on the QTc-interval with an increase of +10 ms at 400 mg twice daily and up to +25 ms with 1600 mg twice daily.

- DAFNE Study

DAFNE was a dose-response study in patients with recurrent AF, evaluating the effect of dronedarone in comparison with placebo in maintaining sinus rhythm. The doses of dronedarone in this study were 400, 600, and 800 mg twice a day. In this small study, doses above 400 mg were not more effective and were less well tolerated.

12.3 Pharmacokinetics

Dronedarone is extensively metabolized and has low systemic bioavailability; its bioavailability is increased by meals. Its elimination half-life is 13 to 19 hours.

Absorption

Because of presystemic first pass metabolism the absolute bioavailability of dronedarone without food is low, about 4%. It increases to approximately 15% when dronedarone is administered with a high fat meal. After oral administration in fed conditions, peak plasma concentrations of dronedarone and the main circulating active metabolite (N-debutyl metabolite) are reached within 3 to 6 hours. After repeated administration of 400 mg twice daily, steady state is reached within 4 to 8 days of treatment and the mean accumulation ratio for dronedarone ranges from 2.6 to 4.5. The steady-state C_{max} and exposure of the main N-debutyl metabolite is similar to that of the parent compound. The pharmacokinetics of dronedarone and its N-debutyl metabolite both deviate moderately from dose proportionality: a 2-fold increase in dose results in an approximate 2.5 to 3.0-fold increase with respect to C_{max} and AUC.

- **HOW SUPPLIED/STORAGE AND HANDLING**

MULTAQ 400-mg tablets are provided as white film-coated tablets for oral administration, oblong-shaped, engraved with a double wave marking on one side and “4142” code on the other side in:

- Bottles of 60 tablets, NDC 0024-4142-60
- Bottles of 500 tablets, NDC 0024-4142-50
- Box of 10 blisters (10 tablets per blister), NDC 0024-4142-10 Store at 25°C (77°F): excursions permitted to 15°C-30°C (59°F-86°F), [see USP controlled room temperature].

17 PATIENT COUNSELING INFORMATION

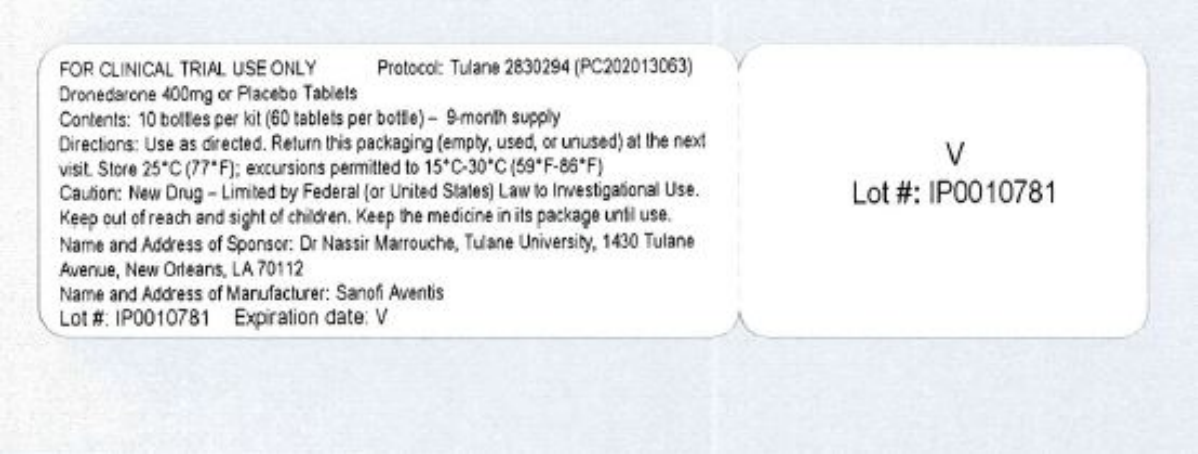
Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Administration Instructions

MULTAQ should be administered with a meal. Warn patients not to take MULTAQ with grapefruit juice.

- If a dose is missed, patients should take the next dose at the regularly scheduled time and should not double the dose.
- Advise patients to consult a physician before stopping treatment with MULTAQ.

Appendix D: Kit Labels



Variables

Expiration date: To be entered at the time of printing

V (Drug Name) To be entered at the time of printing

References

1. Hagens VE, Ranchor AV, Van Sonderen E, et al. Effect of rate or rhythm control on quality of life in persistent atrial fibrillation. Results from the Rate Control Versus Electrical Cardioversion (RACE) Study. *J Am Coll Cardiol*. 2004;43(2):241-247. doi:10.1016/j.jacc.2003.08.037

2. Blomström-Lundqvist C, Gizurarson S, Schwieler J, et al. Effect of Catheter Ablation vs Antiarrhythmic Medication on Quality of Life in Patients With Atrial Fibrillation: The CAPTAF Randomized Clinical Trial. *JAMA*. 2019;321(11):1059-1068. doi:10.1001/jama.2019.0335

3. Daoud EG, Glotzer TV, Wyse DG, et al. Temporal relationship of atrial tachyarrhythmias, cerebrovascular events, and systemic emboli based on stored device data: a subgroup analysis of TRENDS. *Heart Rhythm*. 2011;8(9):1416-1423. doi:10.1016/j.hrthm.2011.04.022

4. Van Gelder IC, Healey JS, Crijns HJGM, et al. Duration of device-detected subclinical atrial fibrillation and occurrence of stroke in ASSERT. *Eur Heart J*. 2017;38(17):1339-1344. doi:10.1093/eurheartj/ehx042

5. Marrouche NF, Brachmann J, Andresen D, et al. Catheter Ablation for Atrial Fibrillation with Heart Failure. *N Engl J Med*. 2018;378(5):417-427. doi:10.1056/NEJMoa1707855

6. Packer DL, Mark DB, Robb RA, et al. Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation: The CABANA Randomized Clinical Trial. *JAMA*. 2019;321(13):1261-1274. doi:10.1001/jama.2019.0693

7. Duytschaever M, Demolder A, Phlips T, et al. PulmOnary vein isolation With vs. without continued antiarrhythmic Drug trEatment in subjects with Recurrent Atrial Fibrillation (POWDER AF): results from a multicentre randomized trial. *Eur Heart J*. 2018;39(16):1429-1437. doi:10.1093/eurheartj/ehx666

8. Marrouche NF, Wilber D, Hindricks G, et al. Association of Atrial Tissue Fibrosis Identified by Delayed Enhancement MRI and Atrial Fibrillation Catheter Ablation: The DECAAF Study. *JAMA*. 2014;311(5):498-506. doi:10.1001/jama.2014.3

9. King JB, Azadani PN, Suksaranjit P, et al. Left Atrial Fibrosis and Risk of Cerebrovascular and Cardiovascular Events in Patients With Atrial Fibrillation. *J Am Coll Cardiol*. 2017;70(11):1311-1321. doi:10.1016/j.jacc.2017.07.758

10. Left atrial fibrosis progression detected by LGE-MRI after ablation of atrial fibrillation - Kheirkhahan - Pacing and Clinical Electrophysiology - Wiley Online Library. https://onlinelibrary.wiley.com/doi/abs/10.1111/pace.13866. Accessed February 29, 2020.

11. Kheirkhahan M, Baher A, Goldooz M, et al. Left atrial fibrosis progression detected by LGE-MRI after ablation of atrial fibrillation. *Pacing and Clinical Electrophysiology*. n/a(n/a). doi:10.1111/pace.13866

12. Daccarett M, Badger TJ, Akoum N, et al. Association of left atrial fibrosis detected by delayed-enhancement magnetic resonance imaging and the risk of stroke in patients with atrial fibrillation. *J Am Coll Cardiol*. 2011;57(7):831-838. doi:10.1016/j.jacc.2010.09.049

13. Akoum N, Fernandez G, Wilson B, Mcgann C, Kholmovski E, Marrouche N. Association of atrial fibrosis quantified using LGE-MRI with atrial appendage thrombus and spontaneous contrast on transesophageal echocardiography in patients with atrial fibrillation. *J Cardiovasc Electrophysiol*. 2013;24(10):1104-1109. doi:10.1111/jce.12199

14. Effect of Dronedarone on Cardiovascular Events in Atrial Fibrillation | NEJM. https://www.nejm.org/doi/pdf/10.1056/NEJMoa0803778?articleTools=true. Accessed February 29, 2020.

15. Dronedarone for Maintenance of Sinus Rhythm in Atrial Fibrillation or Flutter | NEJM. https://www.nejm.org/doi/10.1056/NEJMoa054686?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dwww.ncbi.nlm.nih.gov. Accessed February 29, 2020.

16. Safety and efficacy of dronedarone from clinical trials to real-world evidence: implications for its use in atrial fibrillation | EP Europace | Oxford Academic. https://academic.oup.com/europace/article/21/12/1764/5536329. Accessed February 29, 2020.

17. Goette A, Benninger G, Pittrow D, Paar WD, von Stritzky B, Bosch RF. One-year safety and quality of life outcomes in patients with atrial fibrillation on dronedarone: prospective, non-interventional study in German ambulatory care. *Herzschr Elektrophys*. 2015;26(2):148-154. doi:10.1007/s00399-015-0360-z

18. Lin J-L, Wu T-J, Chen C-P, et al. Observational study of dronedarone in Taiwanese patients with atrial fibrillation. *Journal of the Formosan Medical Association*. 2020;119(1, Part 1):59-68. doi:10.1016/j.jfma.2019.03.009

19. Roles of Vascular Oxidative Stress and Nitric Oxide in the Pathogenesis of Atherosclerosis. - PubMed - NCBI. https://www.ncbi.nlm.nih.gov/pubmed/28209797. Accessed February 29, 2020.

20. Endothelial to Mesenchymal Transition in Cardiovascular Disease | JACC: Journal of the American College of Cardiology. http://www.onlinejacc.org/content/73/2/190. Accessed February 29, 2020.

21. The role of asymmetric and symmetric dimethylarginines in renal disease | Nature Reviews Nephrology. https://www.nature.com/articles/nrneph.2011.31. Accessed February 29, 2020.

22. Involvement of nitric oxide in amiodarone- and dronedarone-induced coronary vasodilation in guinea pig heart. - PubMed - NCBI. https://www.ncbi.nlm.nih.gov/pubmed/15288583. Accessed February 29, 2020.

23. The protective effect of dronedarone on the structure and mechanical properties of the aorta in hypertensive rats by decreasing the concentration o... - PubMed - NCBI. https://www.ncbi.nlm.nih.gov/pubmed/31112581. Accessed February 29, 2020.

24. Dronedarone induces regression of coronary artery remodeling related to better global antioxidant status. - Abstract - Europe PMC. https://europepmc.org/article/med/30992541. Accessed February 29, 2020.

25. Dronedarone produces early regression of myocardial remodelling in structural heart disease. - PubMed - NCBI. https://www.ncbi.nlm.nih.gov/pubmed/29161309. Accessed February 29, 2020.

26. Atrial cardiomyocyte tachycardia alters cardiac fibroblast function: a novel consideration in atrial remodeling. - PubMed - NCBI. https://www.ncbi.nlm.nih.gov/pubmed/17720149. Accessed February 29, 2020.

27. Cellular and in vivo electrophysiological effects of dronedarone in normal and postmyocardial infarcted rats. - PubMed - NCBI. https://www.ncbi.nlm.nih.gov/pubmed/10604978. Accessed February 29, 2020.

28. Oakes RS, Badger TJ, Kholmovski EG, et al. Detection and Quantification of Left Atrial Structural Remodeling Using Delayed Enhancement MRI in Patients with Atrial Fibrillation. *Circulation*. 2009;119(13):1758-1767. doi:10.1161/CIRCULATIONAHA.108.811877

29. McGann CJ, Kholmovski EG, Oakes RS, et al. New magnetic resonance imaging-based method for defining the extent of left atrial wall injury after the ablation of atrial fibrillation. *J Am Coll Cardiol*. 2008;52(15):1263-1271. doi:10.1016/j.jacc.2008.05.062

30. Darkner S, Chen X, Hansen J, et al. Recurrence of arrhythmia following short-term oral AMIOdarone after CATheter ablation for atrial fibrillation: a double-blind, randomized, placebo-controlled study (AMIO-CAT trial). *Eur Heart J*. 2014;35(47):3356-3364. doi:10.1093/eurheartj/ehu354

31. Kaitani K, Inoue K, Kobori A, et al. Efficacy of Antiarrhythmic Drugs Short-Term Use After Catheter Ablation for Atrial Fibrillation (EAST-AF) trial. *Eur Heart J*. 2016;37(7):610-618. doi:10.1093/eurheartj/ehv501

32. Liang, J. J., & Dixit, S. (2018). Early Recurrences During the Blanking Period after Atrial Fibrillation Ablation. *Journal of atrial fibrillation*, *10*(5), 1726. https://doi.org/10.4022/jafib.172