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

CHANGE AFib is a collaboration between the American Heart Association and the Duke Clinical Research Institute, with support from Sanofi US Services Inc.
Featured Presenter

Jonathan P. Piccini, MD, MHS, FACC, FAHA, FHRS

• Principal Investigator of the CHANGE AFib trial
• Associate Professor of Medicine with Tenure at Duke University Medical Center and the Duke Clinical Research Institute.
• Director of the Cardiac Electrophysiology section at the Duke Heart Center
Agenda

Today we will cover

- CHANGE AFib trial objective and design
- Requirements of participating hospitals
- Trial visits and data collection
- How to participate
- Questions
Trial Objective and Design
About AFib

AFib is the most common sustained heart arrhythmia that can lead to blood clots, stroke, heart failure and other heart-related complications\(^1,2\)

AFib accounts for 1:3 arrhythmia-related hospitalizations

Afib contributes to ~158,000 deaths per year\(^1,3\)

More likely to have a stroke with AFib\(^4\)

84% of strokes in AFib patients could be prevented with effective treatment; ~50% of patients don’t receive proper therapy\(^5\)

12.1 million people in the US may be affected with AFib by 2030, more than 2x the number in 2010\(^6\)

AFib: atrial fibrillation.

Randomized Clinical Trials of Therapy for First-Detected AF
Atrial Fibrillation is a progressive disease

Rhythm control improves outcomes in patients with atrial fibrillation

ATHENA
CV hospitalization or death
HR 0.76 (0.69-0.84)

EAST-AFNET 4
CV death, stroke, HF or ACS hosp
HR 0.79 (0.64-0.94)


Impact of Duration of AF/AFL History

Drug Therapy

Catheter Ablation

<table>
<thead>
<tr>
<th>Relative Risk (95% CI)</th>
<th>Diagnosis to Ablation Time</th>
<th>Weight (%)</th>
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<tbody>
<tr>
<td></td>
<td>≤ 1 year Events N</td>
<td>&gt; 1 year Events N</td>
</tr>
<tr>
<td>Bisbal (2019)</td>
<td>0.64 (0.40, 1.02)</td>
<td>14    51    258  5.4</td>
</tr>
<tr>
<td>Bunch (2013)</td>
<td>0.87 (0.73, 1.03)</td>
<td>124   303   179  381  20.2</td>
</tr>
<tr>
<td>De Greef (2018)</td>
<td>0.77 (0.66, 0.90)</td>
<td>108   244   433  756  22.2</td>
</tr>
<tr>
<td>Hussein (2016)</td>
<td>0.61 (0.53, 0.71)</td>
<td>128   382   470  859  22.2</td>
</tr>
<tr>
<td>Kawaiji (2019)</td>
<td>0.75 (0.64, 0.88)</td>
<td>133   389   372  817  21.8</td>
</tr>
<tr>
<td>Lunati (2018)</td>
<td>0.68 (0.48, 0.98)</td>
<td>28    130   120  380  8.2</td>
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Random effects model (p for heterogeneity = 0.071; I^2 = 50.7%)

0.73 (0.65, 0.82) p for overall effect < 0.001
Why Dronedarone?

Well-tolerated

Effective at preventing recurrent AFib

Reduces CV hospitalization

Safe

Post-hoc analyses suggest it performs well in persons with early AFib

Dronedarone: A highly studied antiarrhythmic drug for the treatment of AF

6,813
in 6 trials* in AFib/atrial flutter\(^1\)\(^5\)

1,028
in 13 studies in non-AFib indications and 37 studies in healthy volunteers\(^7\)

3,236
in phase 3 trial in permanent AFib\(^6\)

11,053 participants

1.8 million patient-years
estimated cumulative dronedarone treatment time worldwide\(^+\)\(^7\)

*In the following clinical trials until 2011: ADONIS, ATHENA, DAFNE, DIONYSOS, ERATO, and EURIDIS. \(^+\)From July 1, 2009 through July 31, 2021. AFib: atrial fibrillation.

CHANGE AFib: Objective

First-Detected AFib:
- ECG evidence of atrial fibrillation
- Diagnosed in the previous 60 days

Objective
Determine if early treatment with the antiarrhythmic drug dronedarone improves cardiovascular and long-term outcomes in patients presenting to the hospital with first-detected Afib.

Patients enrolled and randomly assigned (1:1) to the study intervention.

- Intervention group receives dronedarone 400 mg orally twice daily in addition to usual care.
- Control group receives usual care alone (treatment at the discretion of the care team per routine clinical practice).
## Trial Design

<table>
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<th><strong>Design</strong>: Pragmatic Randomized Trial</th>
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<tr>
<td><strong>Sample Size</strong>: Approximately 3,000 patients</td>
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<td><strong>Targeted Number of Participating Sites</strong>: 200</td>
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### Patient Eligibility

- Age ≥ 60 years
- First-detected Atrial Fibrillation
- Estimated life expectancy of at least 1-year
- Capable of giving signed informed consent

### Duration of Follow Up: 12 months

Designed as an open-label pragmatic clinical trial nested within the GWTG®-Afib registry
**Patient Population: Inclusion & Exclusion Criteria**

*Patients presenting to the hospital*

### INCLUSION CRITERIA

- Adults aged ≥60 years
- First-detected AFib (AFib diagnosed in the previous 60 days)
- ECG documentation of AFib
- Estimated life expectancy of ≥1 year

### EXCLUSION CRITERIA

- PR interval >280 msec, or 2nd / 3rd degree AV block without a permanent pacemaker/cardiac implanted electronic device
- Corrected QT interval ≥500 msec
- NYHA class III/IV HF or hospitalization for HF in the last 4 weeks
- Reduced ejection fraction (LVEF ≤ 40%)
- Bradycardia (resting heart rate <50 bpm)
- Ineligible for OAC, unless CHA2DS2-VASc <3 (women) or <2 (men)

*Either catheter ablation or antiarrhythmic drug therapy.
AFib: atrial fibrillation; AV: atrioventricular; bpm: beats per minute; ECG: electrocardiogram; HF: heart failure; LVEF: left ventricular ejection fraction; OAC: oral anticoagulation; NYHA: New York Heart Association.*
Trial Design Specifics

- 3,000 patients enrolled and randomly assigned (1:1) to study intervention.
  - The study intervention will be treatment with oral dronedarone 400 mg twice daily in addition to usual care.
    - The comparator arm will be usual care alone*
- The treatment follow-up period will be 12 months.
- There will be two follow-up visits.
  - The first follow-up will occur approximately 6 months after patient enrollment (with a window of 3 to 9 months).
  - The second follow-up will occur 12 months after patient enrollment (with a window of 30 days).

*Usual care details outlined on next slide.
Usual Care and Concomitant Therapy

Comparator Arm: Usual Care Alone

• Usual care is defined as best-practice, guideline-directed therapy of AFib, including but not limited to:
  / stroke prevention therapy,
  / rate-control, and
  / treatment of risk factors.

• Participants (usual care alone) are initially treated without rhythm-control therapy
  / rhythm-control therapy (except dronedarone) may be initiated during follow-up to ameliorate AF–related symptoms despite adequate rate-control therapy.

Outcomes and Endpoints

N=3000
Eligible patients 60 years or older with ECG-documentation of first-detected AF

R 1:1
12-months follow up

Primary Endpoint:
CV hospitalization or death‡

Dronedarone 400 mg BID + Usual Care
Includes an AV nodal blocking agent † without an antiarrhythmic

Usual Care

†Beta-blocker, non-dihydropyridine calcium channel blocker, or digoxin.
‡Time from randomization to the first occurrence of CV hospitalization or death from any cause within 12 months of randomization
### Outcomes and Endpoints

#### Secondary Endpoints:
- **WIN Ratio**§ (according to the following hierarchy)
  1. All-cause mortality
  2. Ischemic stroke/Systemic embolism
  3. Hospitalization for new/worsening HF diagnosis
  4. Hospitalization for acute coronary syndrome
- CV hospitalization
- All-cause mortality

#### Tertiary Endpoints:
- Ischemic stroke/Systemic embolism
- Arrhythmia-related hospitalization
- HF hospitalization
- AFib progression
- Cardioversion
- Catheter ablation of AFib
- Days alive and out of hospital

#### Patient Reported Outcomes:
- AFEQT
- MAFSI

#### Safety Analysis:
- Key adverse/safety events of interest

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§Unmatched win ratio model compares every patient on the dronedarone arm with every patient in the usual care arm, noting “winner”, “loser” or “tied” for each comparison. For each pair the component outcomes will be compared in descending order of importance until one of the patients in the pair demonstrates a better outcome compared with the other.

AFEQT: Atrial Fibrillation Effect on QualiTy-of-life questionnaire; CV, cardiovascular; ECG: electrocardiogram; HF: heart failure; MAFSI: mayo AF-specific symptom inventory
Requirements of Participating Hospitals
Site Participation Requirements

CHANGE AFib will be conducted within 200 hospitals participating in the GWTG®-AFib Program

Hospitals interested in participating should be:

✓ Research ready
✓ Have established systems for obtaining IRB approval
✓ Willing to enroll in the GWTG-AFib program

IRB: institutional review board.
GWTG®-AFIB Overview

GWTG®-AFIB Quality Improvement Support

/ Dedicated AHA |ASA Quality Improvement Consultant

/ Vendor-provided technical support to assist with IT needs

/ Access to customized professional education conferences, workshops, webinars, and abstractor trainings

/ Access to GWTG®-AFIB Clinical Tools & Resources Library, including provider and patient education.

/ Opportunities to connect with fellow GWTG partners on best practices and engage in speaking opportunities.
Responsibilities of the Site Research Team

• Identify a site primary investigator & research coordinator
• Ensure that all trial staff meet training requirements
• Obtain and maintain IRB approval
• Enforce protocol adherence
• Dedicate time to screen, consent and recruit participants
• Schedule follow up visits to reach patients after discharge
• Enter your study data in the GWTG-AFib Registry
• Maintain and update the study regulatory binder
• Retain regulatory and patient records for 5 years
IRB Approval

Central or Local IRB Approval

• IRB approval is required.
  - Since we are inviting patients to participate this is not an exempt study.
• If an institution/hospital does not require use of their own or local IRB, AHA will facilitate the use of a central commercial IRB (Advarra).
• Institutional IRBs have the right to sign a waiver of oversight (rather than bring it up for review), which defers to the decision made by the central IRB.
• Either approach is acceptable, so long as one or the other is on record with each site.
• Each site will be responsible for maintaining a copy of their IRB, in case of audit. IRB copies must also be sent to the AHA.

Information for Advarra can be found at Change AFib
Trial Visits and Data Collection
## What Happens During Trial Visits?

<table>
<thead>
<tr>
<th>Assessments/ Procedures</th>
<th>Baseline</th>
<th>3-9 months</th>
<th>12 months/End of Study</th>
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<tbody>
<tr>
<td>Informed consent &amp; release of medical records</td>
<td>✗</td>
<td></td>
<td></td>
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<tr>
<td>Patient randomization</td>
<td>✗</td>
<td></td>
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<tr>
<td>Demographics</td>
<td>✗</td>
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<tr>
<td>Medical history</td>
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<tr>
<td>Echocardiographic data</td>
<td>✗</td>
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<tr>
<td>Atrial fibrillation history</td>
<td>✗</td>
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<tr>
<td>Vital signs</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
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<tr>
<td>Laboratory Data</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
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<tr>
<td>Pharmacotherapy (Drug Log)</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
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<tr>
<td>Adverse &amp; Safety Events</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
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<tr>
<td>Quality of Life Instruments (AFEQT &amp; MAFSI)</td>
<td>✗</td>
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<tr>
<td>Drug Discontinuation</td>
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<tr>
<td>Outcomes (Primary, Secondary, &amp; Tertiary)</td>
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<td></td>
<td>✗</td>
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<tr>
<td>Document cardiac procedures</td>
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REDCap

Patient E Consent
Patient Randomization
About REDCap

- REDCap is the database used for patient eConsent and randomization

- Each site is assigned their own unique REDCap project

- Each site user receives a unique to access the REDCap database

- Each site only has access to their own site records

For Questions about REDCap, eConsent, and Randomization, contact: ChangeAF@duke.edu
GWTG-AFib Data Collection

• **Data entry requirements (per patient) include**
  / 1 Baseline Data Form
  / 1 Follow-up Form at 3-9 Months
  / 1 Follow-up Form at 12 Months

• **Access the GWTG-AFib Registry at:**
  [https://aha.infosarioregistry.com/login](https://aha.infosarioregistry.com/login)

• **Email** [Changeafib@heart.org](mailto:Changeafib@heart.org) **with any questions or concerns**
GWTG-AFib Training

- Existing GWTG-AFib Module Abstractors
  - Training focused on Change AFib forms and elements

- Existing GWTG Abstractors, but new to the AFIB Module
  - AFIB Module Training Required

- New to GWTG Abstractors
  - Comprehensive Training Required

- Email Changeafib@heart.org with any questions or concerns
How to Participate
GWTG Contracting

What does my site need to do to join CHANGE AFib?

• If not already contracted, contract for GWTG-AFib
  / GWTG customers new to GWTG-AFib will sign an amendment
• Sign a separate CHANGE AFib site agreement
• Obtain IRB approval
Connect With Us!

How to reach the CHANGE AFib Team

/ Visit changeafib.org to learn more and complete the contact us form

/ Reach out to your local AHA contact

Save the Date

/ Webinar on Jan 24
QUESTIONS