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.

TRIAL PI: Jonathan P. Piccini, MD, MHS, FHRS, FAHA
Associate Professor of Medicine
Director, Cardiac Electrophysiology
Duke University Medical Center

What is Get With The Guidelines® (GWTG)?

GWTG is the AHA's premier collaborative performance improvement program, demonstrated to improve adherence to evidence-based care of patients hospitalized with cardiovascular disease.

2,600+

/ Unique Contracted Hospitals

9,000,000+

/ Patient Records Entered

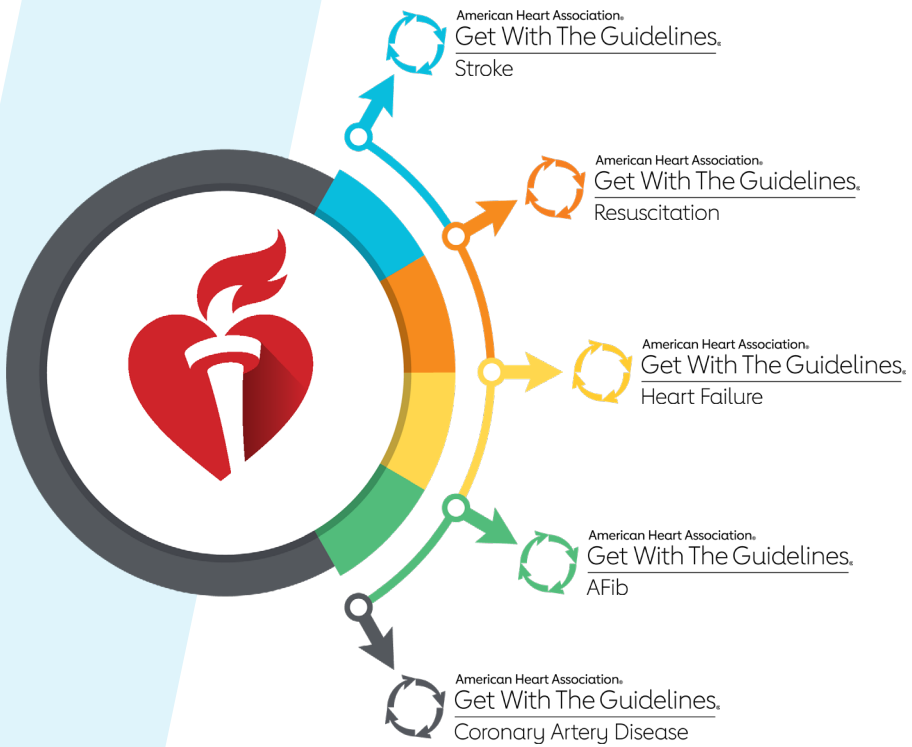
/ Nearly **50%** of all cardiovascular and **80%** of all stroke patients in the U.S. benefit from treatment at a GWTG hospital

/ **1/3** of the nation's **6,280** hospitals participate in at least one GWTG module. Many participate in two or more.

/ Nearly **80%** of the U.S. population has access to a GWTG participating hospital.

100

/ Dedicated Field Staff



CHANGE AFib /

About AFib

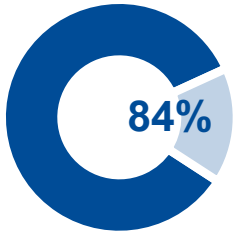
AFib is the most common sustained heart arrhythmia that can lead to blood clots, stroke, heart failure and other heart-related complications[1,2]

AFib accounts for **1:3** arrhythmia-related hospitalizations

Afib contributes to **~158,000** deaths per year[1,3]

5x

More likely to have a **stroke** with AFib[4]



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.

1. Centers for Disease Control. Patient Education Handout: Atrial fibrillation. Available at: www.cdc.gov/heartdisease/atrial_fibrillation.htm. Accessed October 4, 2021.
2. American Heart Association. Available at: https://www.heart.org/en/health-topics/atrial-fibrillation/what-is-atrial-fibrillation-afib-or-af. Accessed October 4, 2021.
3. American Heart Association. Available at: https://www.heart.org/en/professional/quality-improvement/get-with-the-guidelines/get-with-the-guidelines-afib/joining-forces-for-atrial-fibrillation-patients. Accessed October 4, 2021 **4.** Turakhia MP, et al. *Circ Arrhythm Electrophysiol.* 2015;81040–1047. **5.** Bufalino VJ, et al. *Circ Cardiovasc Qual Outcomes*. 202;13(7):e006780. **6.** Colilla S, et al. *Am J Cardiol*. 2013;112:1142–1147.

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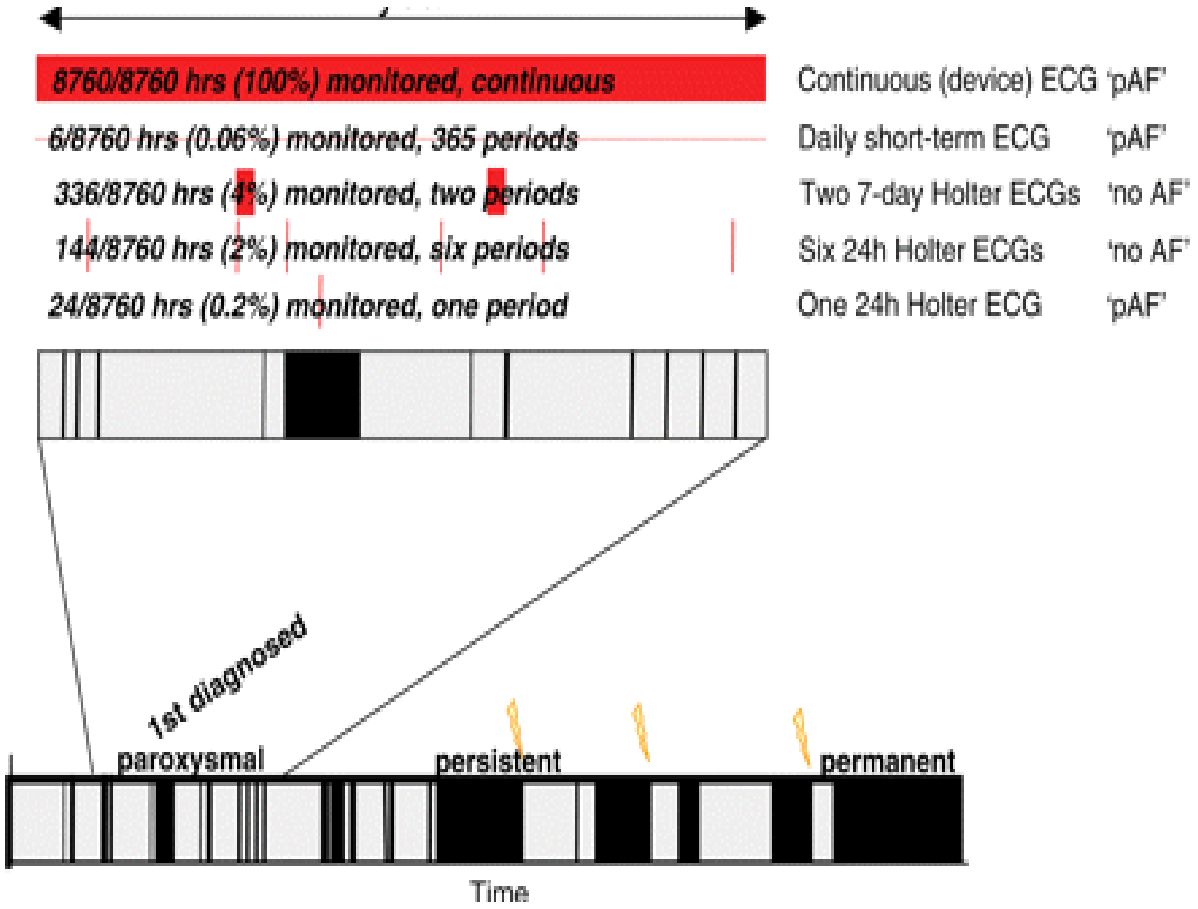
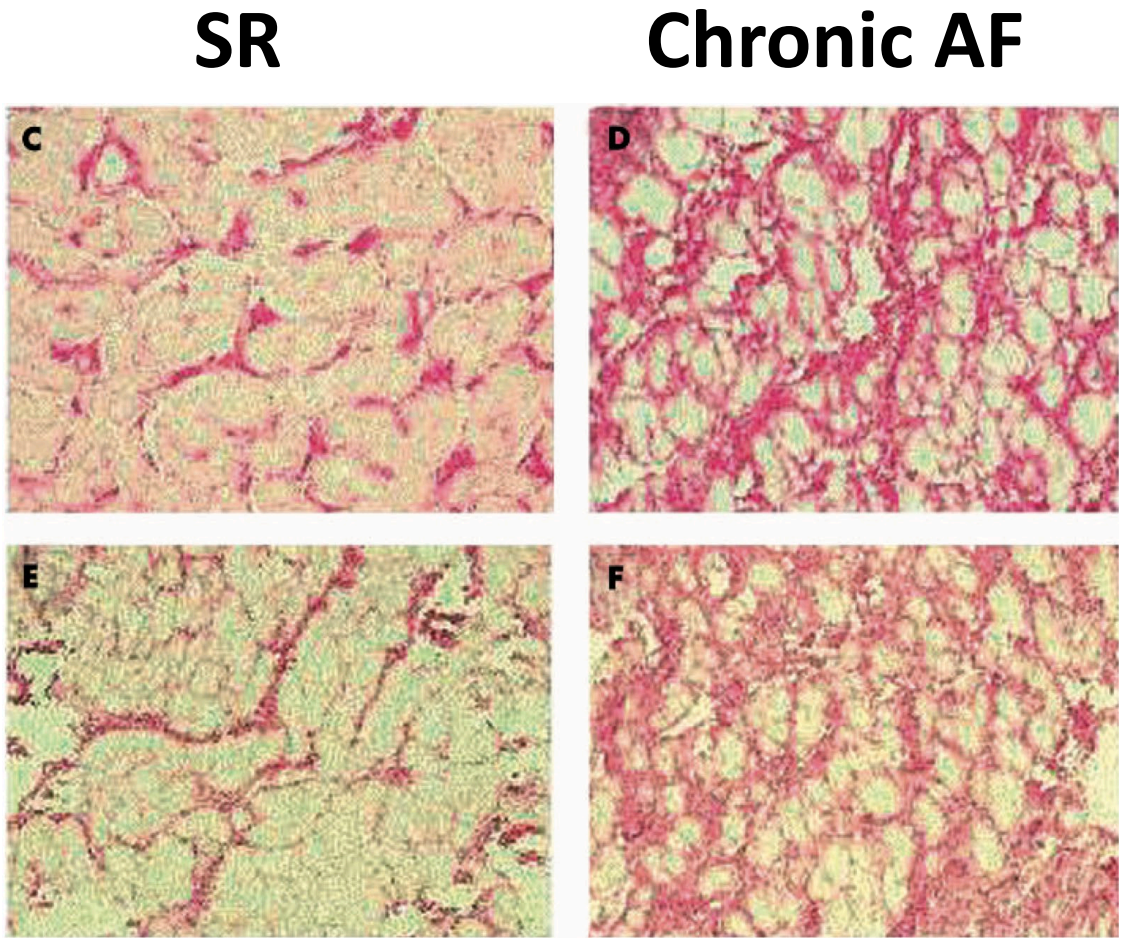
Atrial fibrillation is a progressive disease



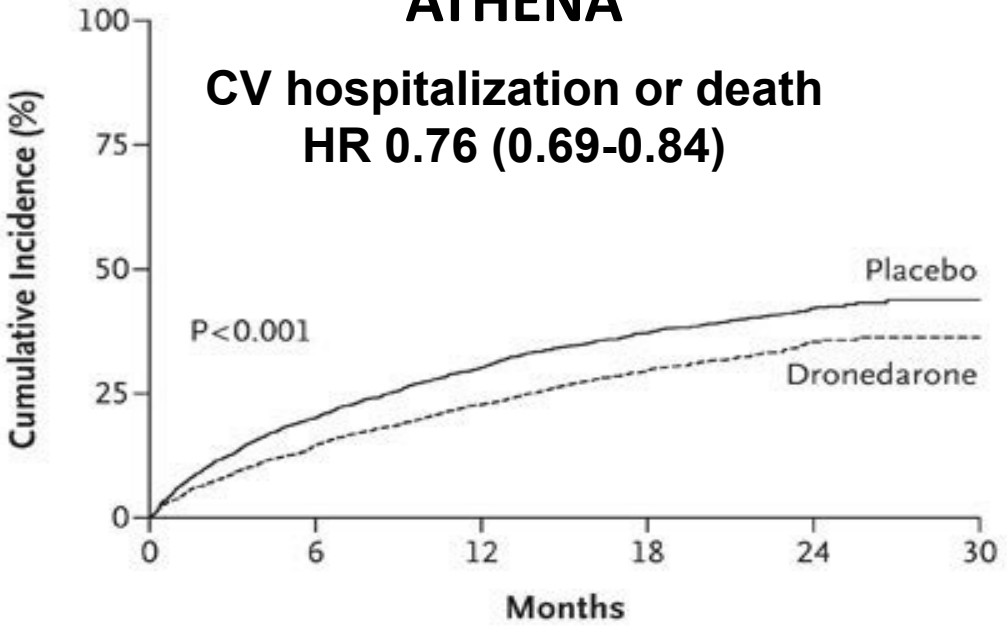


Kirchhof P. AFNET-EHRA. *Eur Heart J. 2009;*30:2969–2980.
Boltd A. *Heart* 2004;90:400–405.

Rhythm control improves outcomes in patients with AF

ATHENA

CV hospitalization or death
HR 0.76 (0.69-0.84)

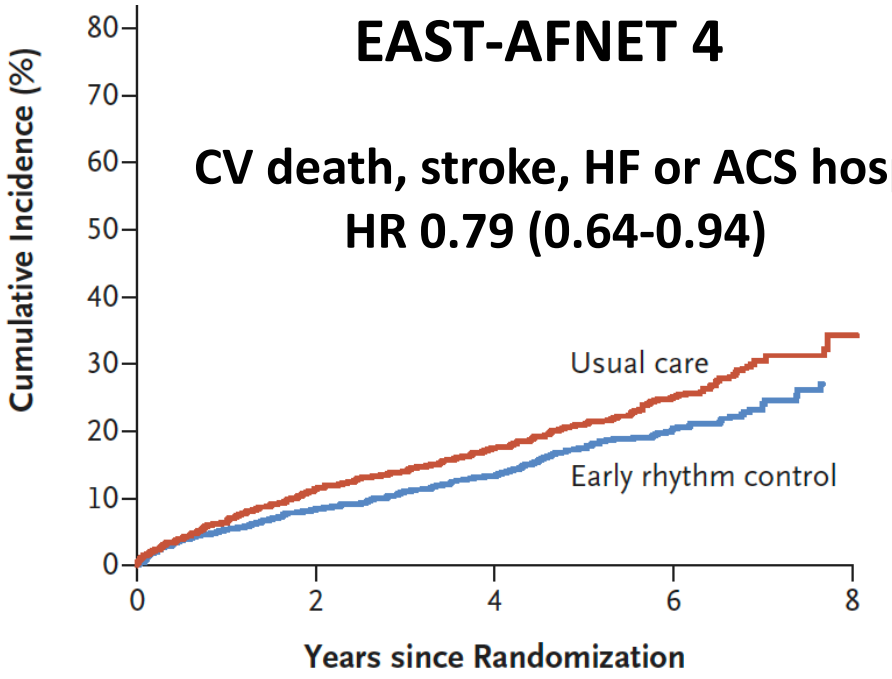


No. at Risk						
Placebo	2327	1858	1625	1072	385	3
Dronedarone	2301	1963	1776	1177	403	2

Hohnloser SH. *N Engl J Med* 2009;360:668-678.

EAST-AFNET 4

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



No. at Risk						
Usual care	1394	1169	888	405	34	
Early rhythm control	1395	1193	913	404	26	

Kirchhof P. *N Engl J Med*. DOI: 10.1056/NEJMoa2019422.

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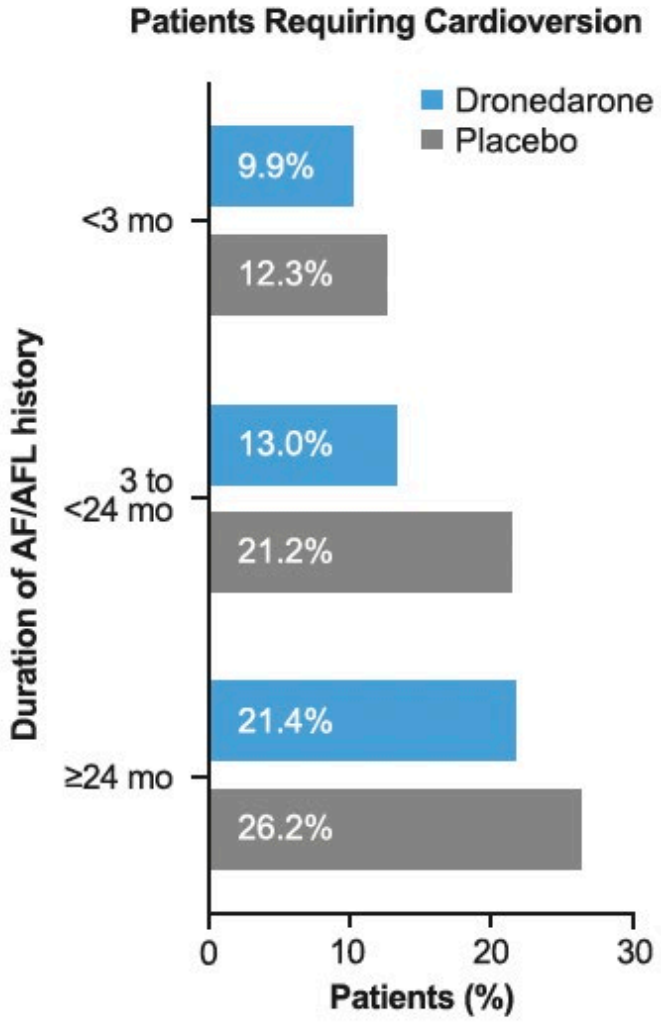
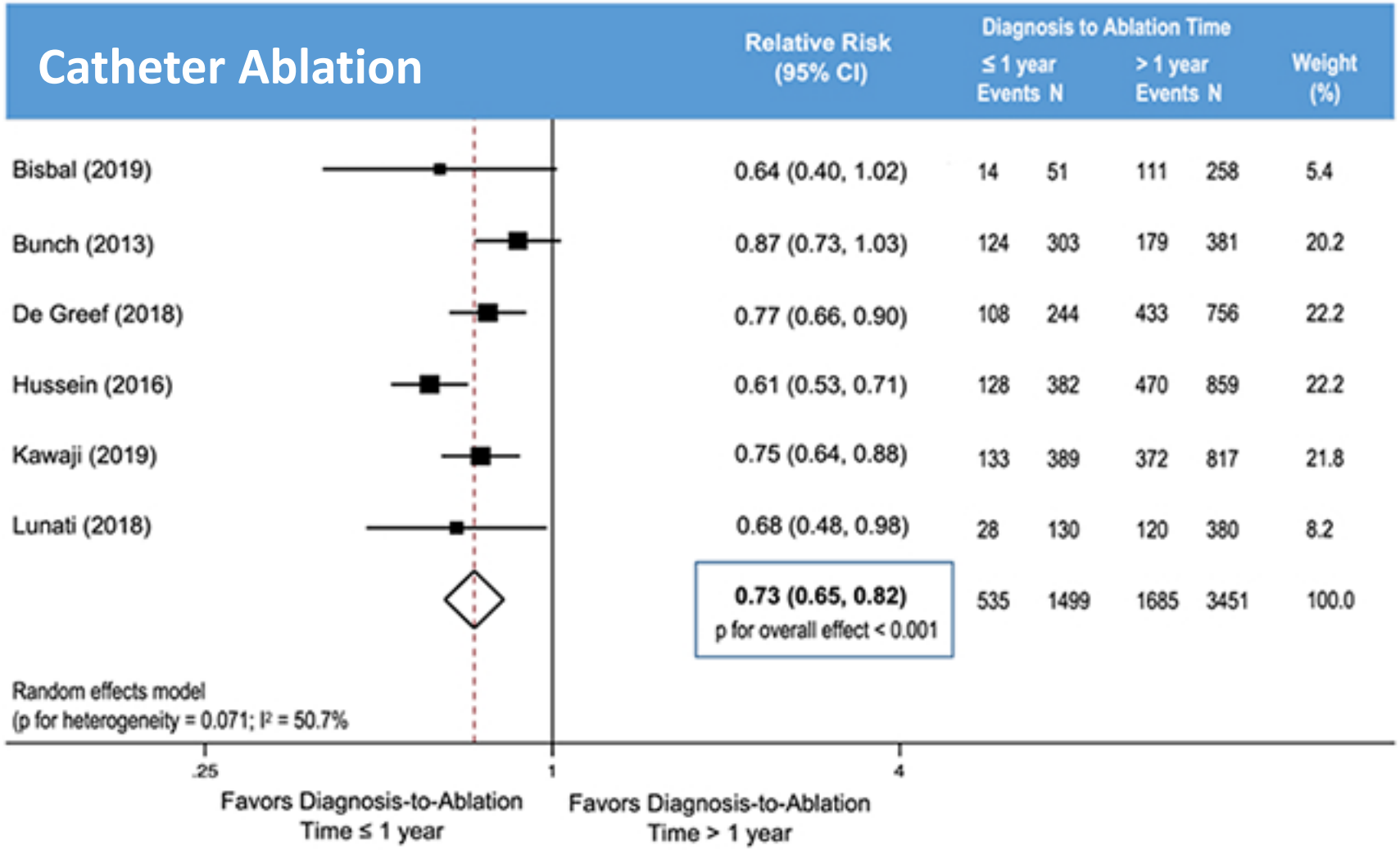
Impact of Duration of AF/AFL History

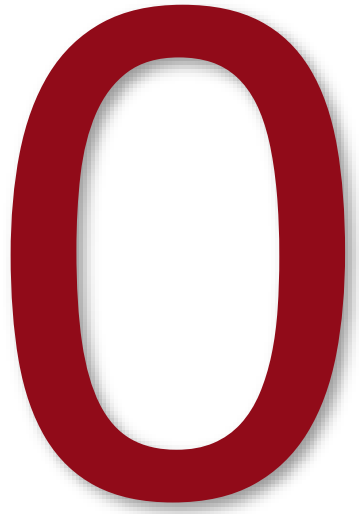
Drug Therapy





Chew DS. *Circ Arrhythm Electrophysiol*. 2020; 13: e008128.
Blomstrom-Lundqvist C. *Clin Cardiol*. 2020;43:1469–1477.

Randomized Clinical Trials of Therapy for First-Detected AF



Need for pragmatic trials that inform common & relevant clinical decisions

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Pragmatic Randomized Trials

- Inform clinical/treatment decision
- Enroll a diverse & relevant population
- Streamline procedures & data collection

Evaluate effectiveness in real-world practice conditions

Article

CLINICAL TRIALS

Clinical Trials
2015, Vol. 12(5) 436–441

DOI: 10.1177/1740774515598334
ctj.sagepub.com
SAGE

Exploring the ethical and regulatory issues in pragmatic clinical trials

Robert M Califf[1,2,*] and Jeremy Sugarman[3,4]

Abstract

The need for high-quality evidence to support decision making about health and health care by patients, physicians, care providers, and policy-makers is well documented. However, serious shortcomings in evidence persist. Pragmatic clinical trials that use novel techniques including emerging information and communication technologies to explore important research questions rapidly and at a fraction of the cost incurred by more "traditional" research methods promise to help close this gap. Nevertheless, while pragmatic clinical trials can bridge clinical practice and research, they may also raise difficult ethical and regulatory challenges. In this article, the authors briefly survey the current state of evidence that is available to inform clinical care and other health-related decisions and discuss the potential for pragmatic clinical trials to improve this state of affairs. They then propose a new working definition for pragmatic research that centers upon fitness for informing decisions about health and health care. Finally, they introduce a project, jointly undertaken by the National Institutes of Health Health Care Systems Research Collaboratory and the National Patient-Centered Clinical Research Network (PCORnet), which addresses 11 key aspects of current systems for regulatory and ethical oversight of clinical research that pose challenges to conducting pragmatic clinical trials. In the series of articles commissioned on this topic published in this issue of *Clinical Trials*, each of these aspects is addressed in a dedicated article, with a special focus on the interplay between ethical and regulatory considerations and pragmatic clinical research aimed at informing "real-world" choices about health and health care.

Keyword

Clinical trials, cluster-randomized trial, ethics, evidence-based medicine, learning health-care system, patient-centered outcomes research, pragmatic clinical trial

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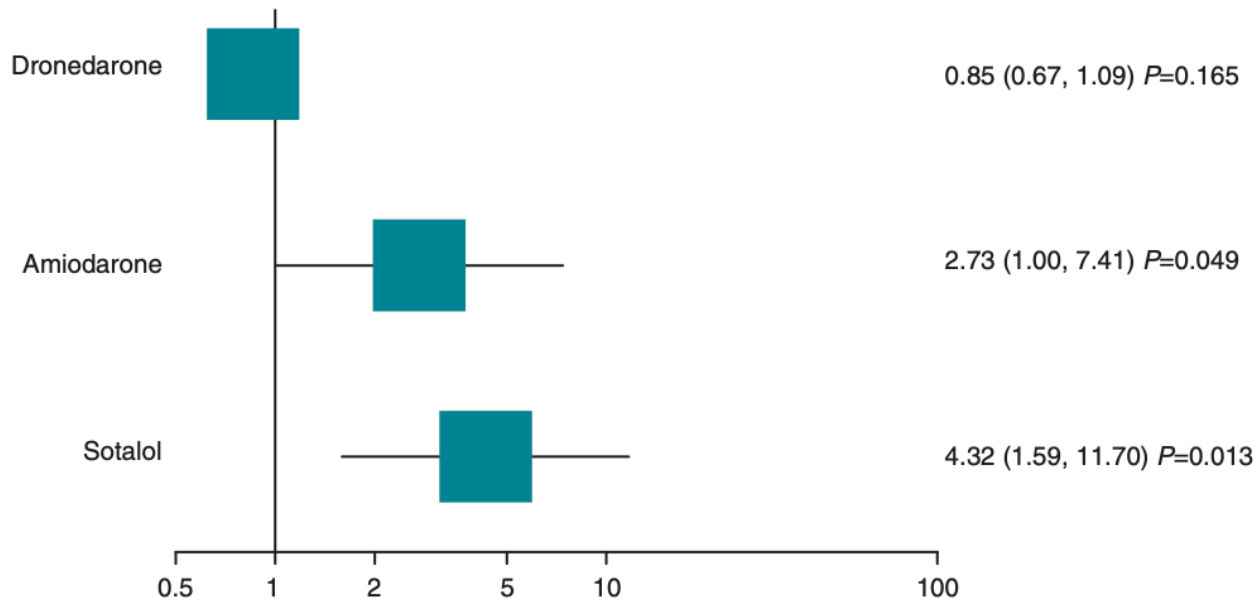
Califf & Sugarman. Clin Trials. 2015 Oct; 12(5): 436–441.

Why Dronedarone?

- Well-tolerated
- Effective at preventing recurrent AF
- Reduces CV hospitalization
- Safe
- Post-hoc analyses suggest it performs well in persons with early AF

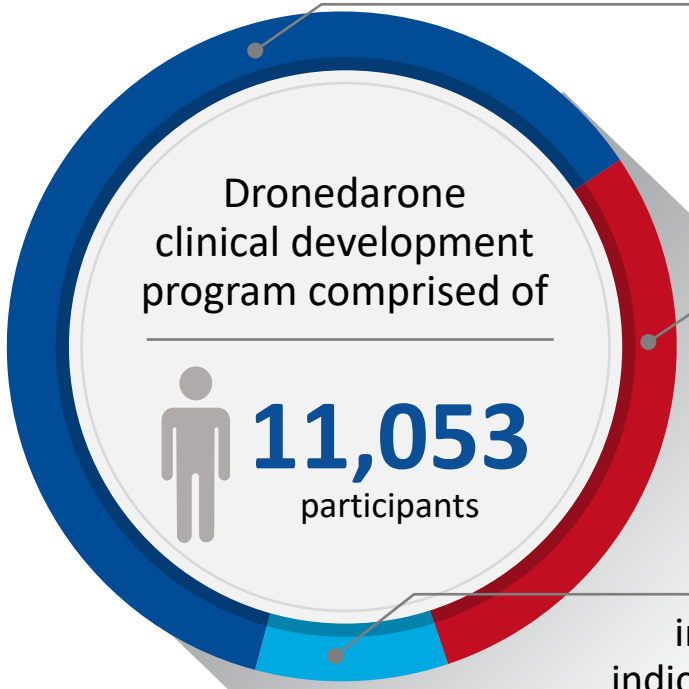


Effect on all-cause mortality in studies involving >100 patients in either arm. Odds ratios and 95% confidence intervals

Freemantle N. *Europace* (2011) 13, 329–345.

Blomstrom-Lundqvist C. *Clin Cardiol*. 2020;43:1469–1477.

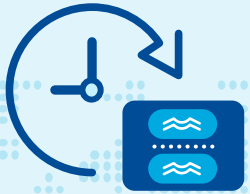
Dronedarone: A highly studied antiarrhythmic drug for the treatment of AF



6,813
in 6 trials* in AFib/atrial flutter[1-5]

3,236
in phase 3 trial in permanent AFib[6]

1,028
in 13 studies in non-AFib indications and 37 studies in healthy volunteers[7]



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.

1. Davy JM, et al. *Am Heart J*. 2008;156:527.e1-9. **2**. Hohnloser SH, et al. *N Engl J Med*. 2009;360:668-678. **3**. Le Heuzey JY, et al. *J Cardiovasc Electrophysiol*. 2010;21:597-605. **4**. Singh BN, et al. *N Engl J Med*. 2007;357:987-999. **5**. Touboul P, et al. *Eur Heart J*. 2003;24:1481-1487. **6**. Connolly SJ, et al. *New Engl J Med*. 2011;365:2268-2276. **7**. Sanofi. Data on file.

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Trial Design

Design: Pragmatic Randomized Trial

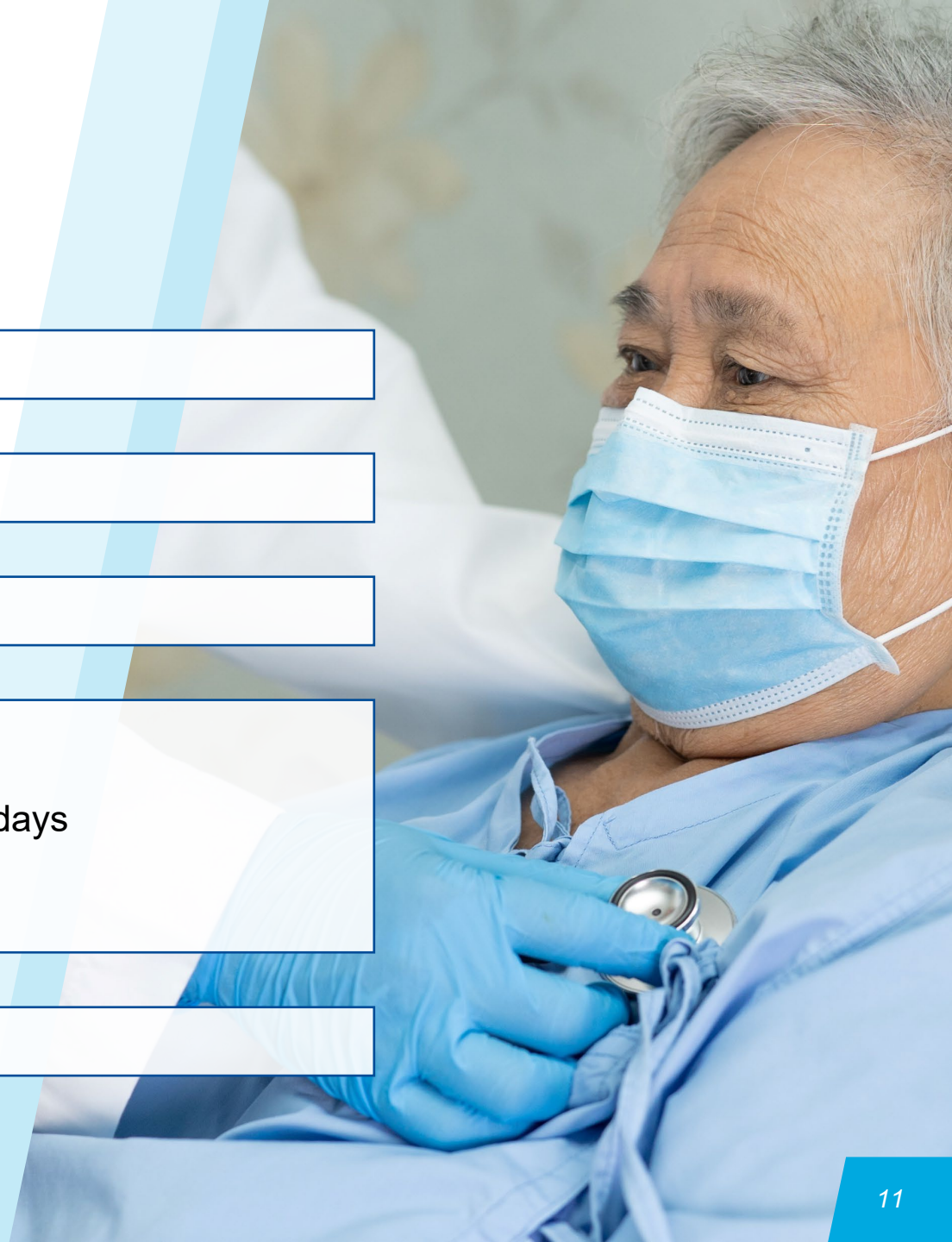
Sample Size: Approximately 3,000 patients

Targeted Number of Participating Sites: 200

Patient Eligibility

- Age ≥ 21 years
- First-detected Atrial Fibrillation diagnosed within previous 120 days
- Estimated life expectancy of at least 1-year
- Patient or LAR capable of giving signed informed consent

Duration of Follow Up: 12 months



CHANGE AFib

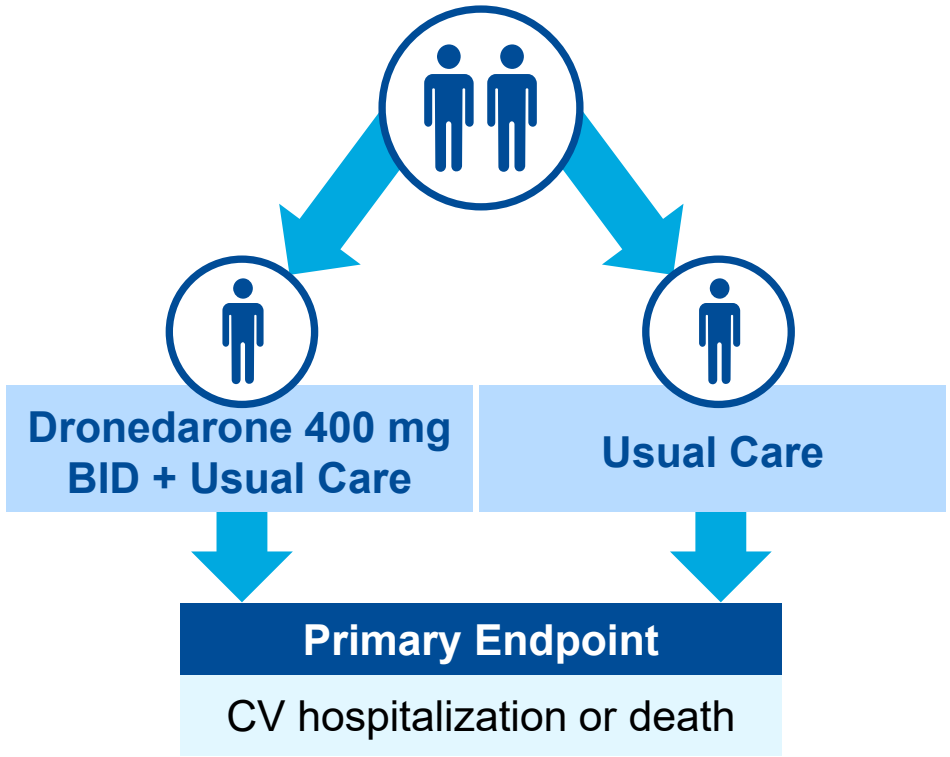
Designed as an open-label pragmatic clinical trial nested within the GWTG®-AFIB registry

CHANGE AFib: Objective

Determine if early treatment with the antiarrhythmic drug dronedarone improves **cardiovascular and long-term outcomes** in patients with **first-detected AFib.**

First-Detected AFib:

- ECG evidence of atrial fibrillation
- Diagnosed in the previous 120 days



Patients who present to a hospital or outpatient facility for their initial diagnosis of AFib

OR

Patients who present to a hospital or outpatient facility for follow-up within 120 days of their first-detected AFib initial diagnosis will be enrolled and randomized 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).

CHANGE AFib

Patient Population: Inclusion & Exclusion Criteria

INCLUSION CRITERIA

- Adults aged **≥21 years**
- First-detected AFib (AFib diagnosed in the previous 120 days)
- ECG documentation of AFib
- Estimated life expectancy of **≥1 year**

EXCLUSION CRITERIA

- Prior or planned treatment with **rhythm control***
- Planned cardiothoracic surgery
- Permanent AFib
- Pregnancy
- Severe hepatic impairment
- 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 CHA_2DS_2-VASc <3 (women) or <2 (men)

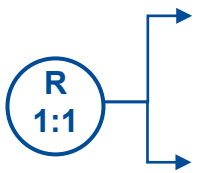
*Either catheter ablation or chronic antiarrhythmic drug therapy, which is defined as >7 days of outpatient therapy (one time dosing of an antiarrhythmic drug or pharmacologic cardioversion are not considered "prior AAD therapy.")

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.

Outcomes and Endpoints

N=3000

Eligible patients 21 years or older with ECG-documentation of first-detected AF



12-months follow up

Dronedarone 400 mg BID + Usual Care

Usual Care

Includes an AV nodal blocking agent† without an antiarrhythmic

Primary Endpoint:
CV hospitalization or death‡

†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

§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

CHANGE AFib

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).

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*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.

Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt L, Elvan A, Fetsch T, van Gelder IC, Haase D, Haegeli LM, Hamann F, Heidbuchel H, Hindricks G, Kautzner J, Kuck KH, Mont L, Ng GA, Rekosz J, Schoen N, Schotten U, Suling A, Taggeselle J, Themistoclakis S, Vettorazzi E, Vardas P, Wegscheider K, Willems S, Crijns H, Breithardt G and Investigators E-AT. Early Rhythm-Control Therapy in Patients with Atrial Fibrillation. *N Engl J Med*. 2020;383:1305-1316.

Conclusions

- No randomized trials that address treatment for first-detected AF.
- CHANGE AFIB is the first pragmatic randomized clinical trial in GWTG
- Test hypothesis that earlier administration of a well-tolerated antiarrhythmic drug improves cardiovascular outcomes & patient reported outcomes in patients first-detected AF.

Connect With Us!

How to reach the CHANGE AFib Team

AHA Site Managers:

Crystal.Glodek@heart.org

Jack.Goldberg@heart.org

Mariel.Dronson@heart.org

ChangeAFib@heart.org

Resources to Remember

For important trial information and today's meeting recording, go to the **Resources** page at **www.changeafib.org** or visit the QR Code to the left.

QUESTIONS