Trial Updates & Protocol V3.0 Review

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Disclosures

- Jon Piccini Disclosure:

  R01AG074185 from the National Institutes of Aging. Grants for clinical research from Abbott, American Heart Association, Association for the Advancement of Medical Instrumentation, Bayer, Boston Scientific, iRhythm, and Philips. Consultant to Abbott, Abbvie, Ablacon, Altathera, Biotronik, Boston Scientific, Bristol Myers Squibb, LivaNova, Medtronic, ElectroPhysiology Frontiers, Pfizer, Sanofi, Philips, and Up-to-Date.

- Samantha Johnson Disclosure:

  Employed by AHA/CHANGE AFib

Key Objectives

1. Background & Trial Rationale
2. Protocol V3.0 Review
3. Trial Progress Update
4. Trial Next Steps

Background & Trial Rationale

About AFib

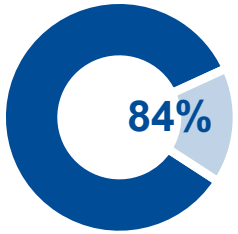
AFib is the most common sustained heart arrhythmia that can lead to blood clots, stroke, heart failure and other heart-related complications[1,2]

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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AF-Related Outcomes

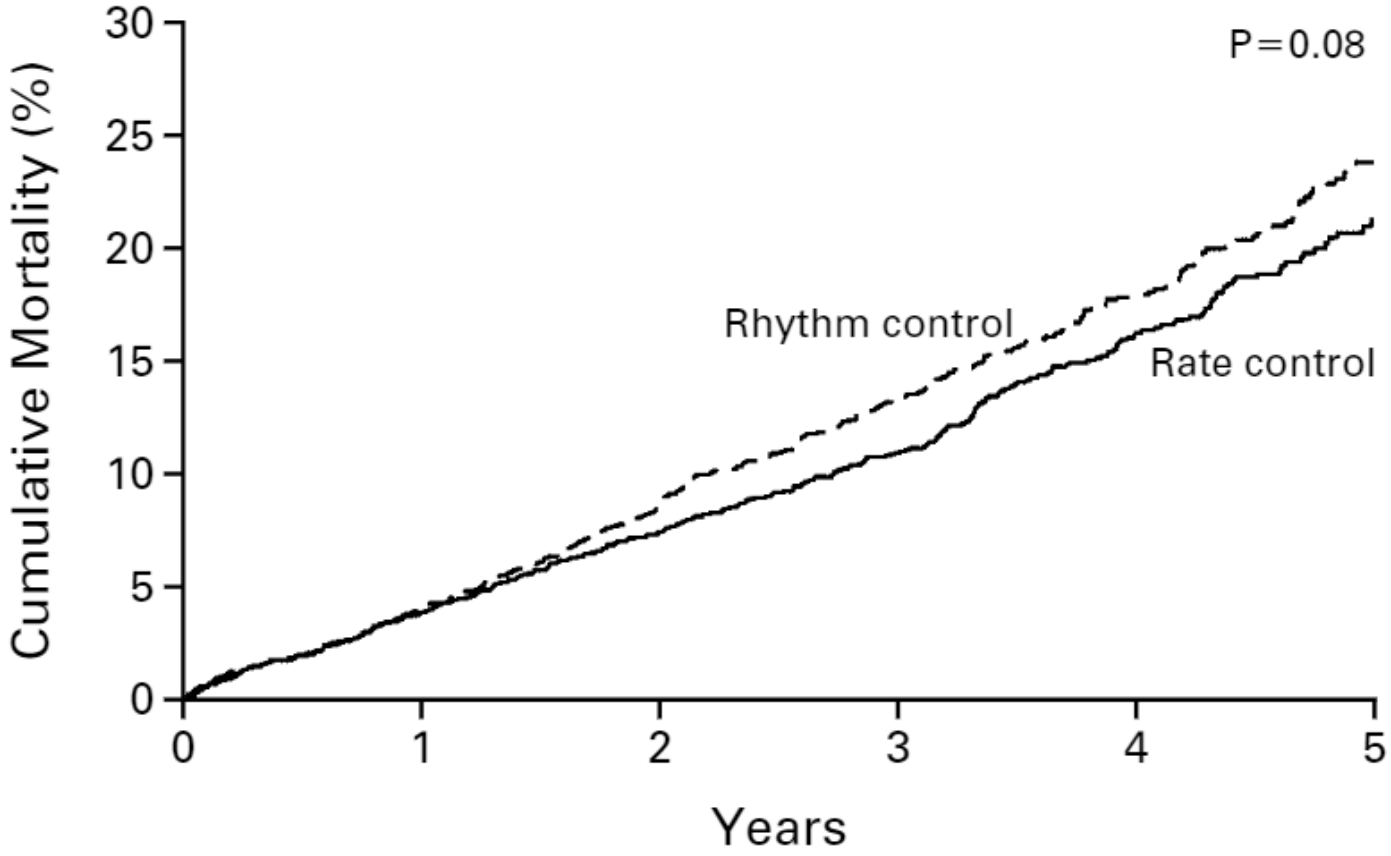
AF-related outcome	Death	Stroke	LV dysfunction/ heart failure	Cognitive decline/ vascular dementia	Depression	Impaired quality of life	Hospitalizations
Frequency in AF	1.5 to 3.5-fold increase	20% to 30% of all ischemic strokes, 10% of cryptogenic strokes	In 20% to 30% of AF patients	HR 1.4/1.6 (irrespective of stroke history)	Depression in 16% to 20% (even suicidal ideation)	> 60% of patients	10% to 40% annual hospitalization rate

Can rhythm control change these AF-related outcomes?

AF, atrial fibrillation; HR, heart rate; LV, left ventricle.

Hindricks G, et al. Eur Heart J. 2021;42:373-498.

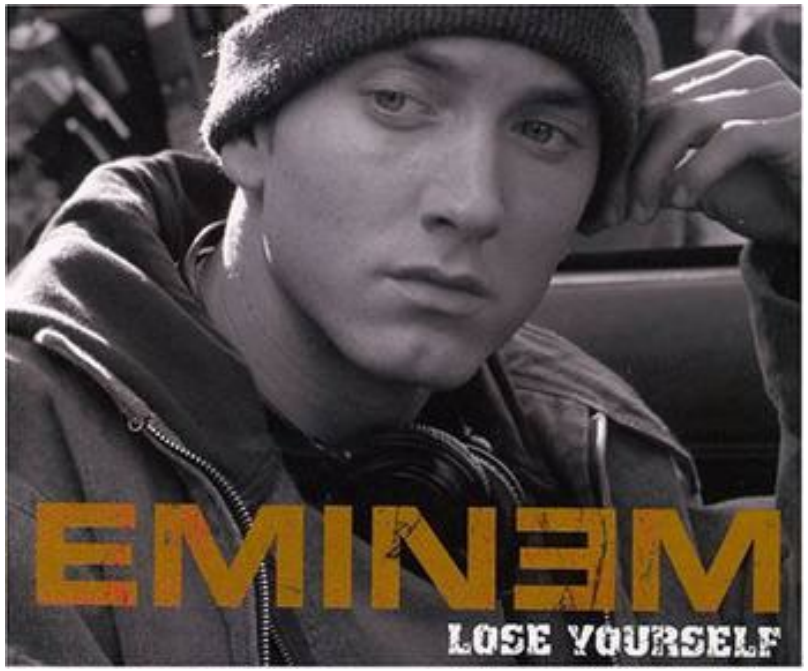
A Comparison of Rate Control and Rhythm Control in Patients With Atrial Fibrillation (AFFIRM)



No. of Deaths		number (percent)				
Rhythm control	0	80 (4)	175 (9)	257 (13)	314 (18)	352 (24)
Rate control	0	78 (4)	148 (7)	210 (11)	275 (16)	306 (21)

- *Wyse DG, et al. N Engl J Med 2002;347:1825-1833.*

AFFIRM – December 5th, 2002



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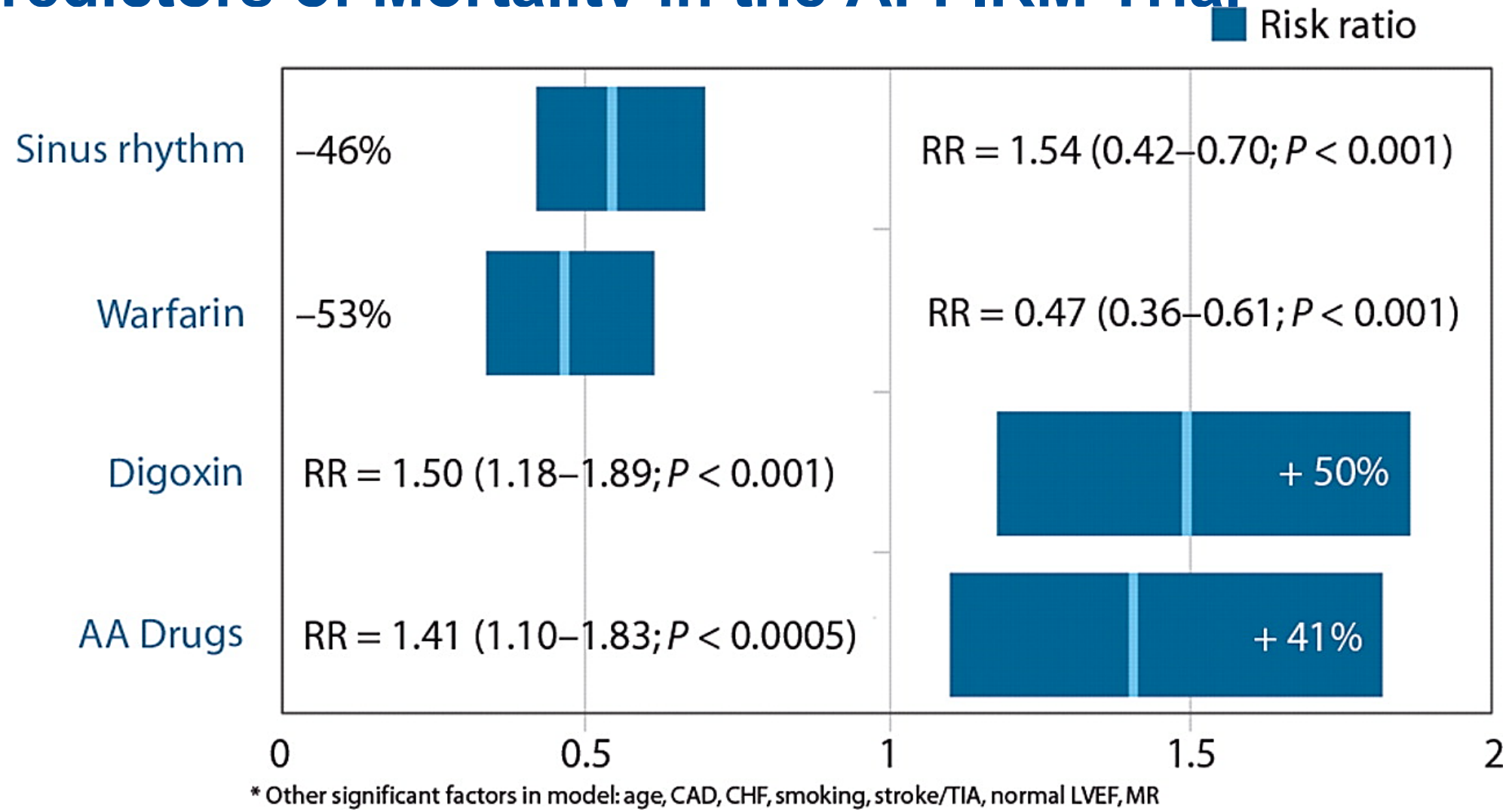
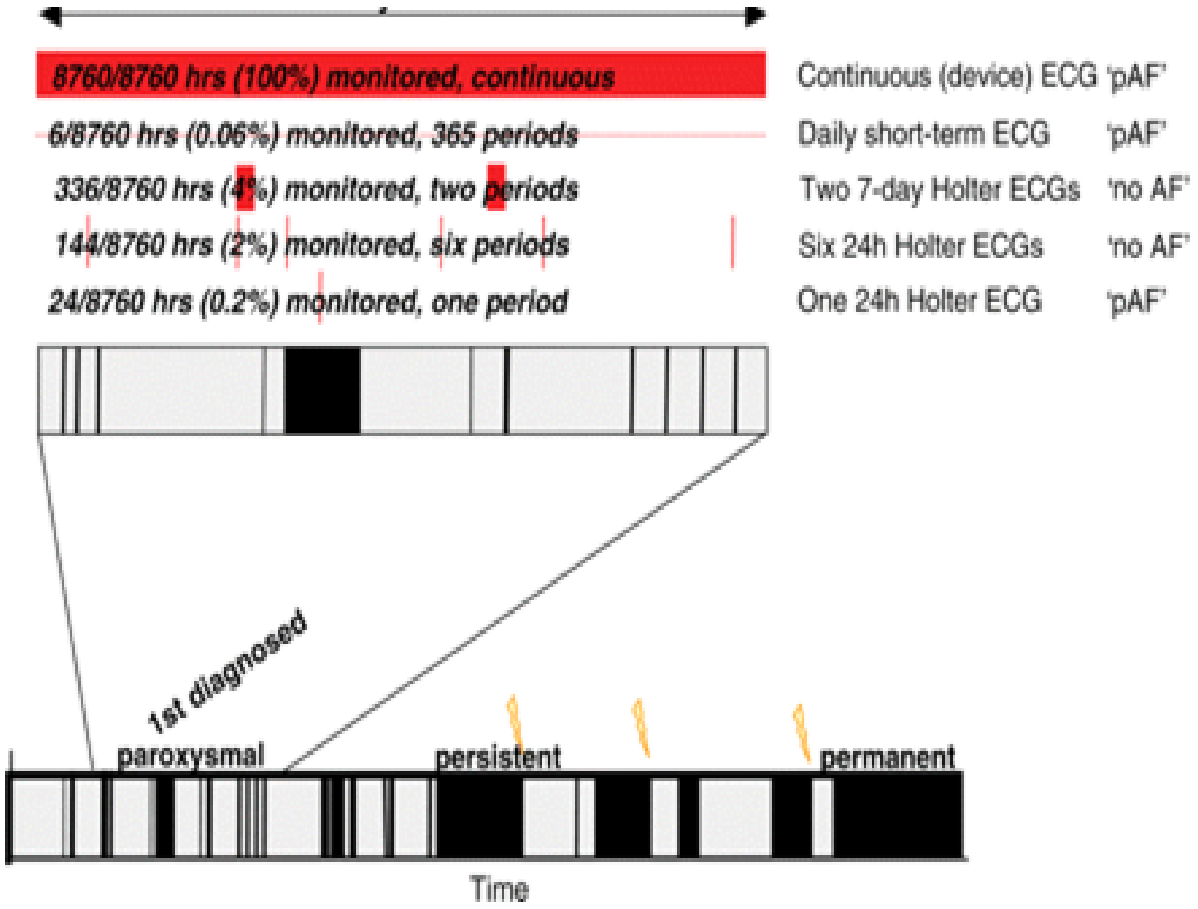
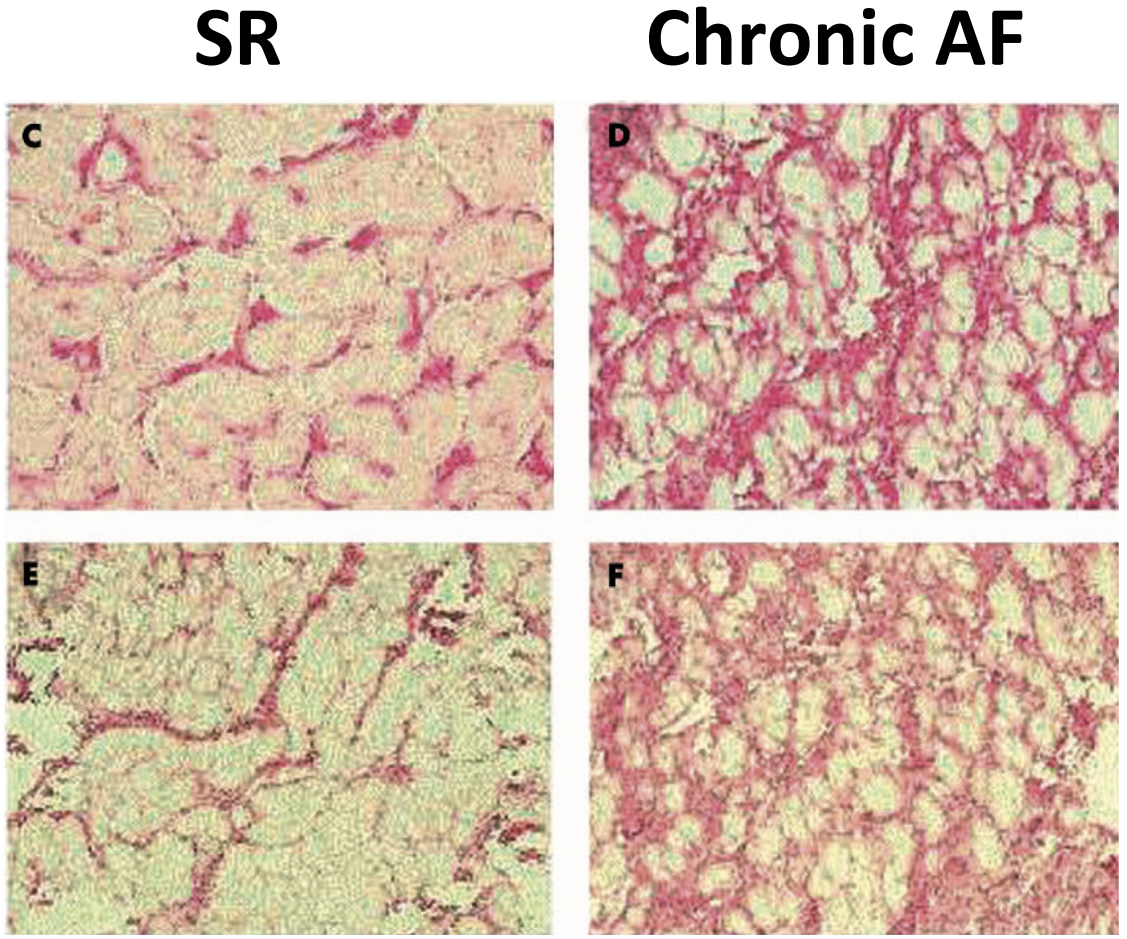
Predictors of Mortalitv in the AFFIRM Trial



- *RR, risk ratio.*
- *Aliot E, et al. Eur Heart J. 2008;(Suppl__H):10:H32-H54.*

Atrial Fibrillation is a Progressive Disease

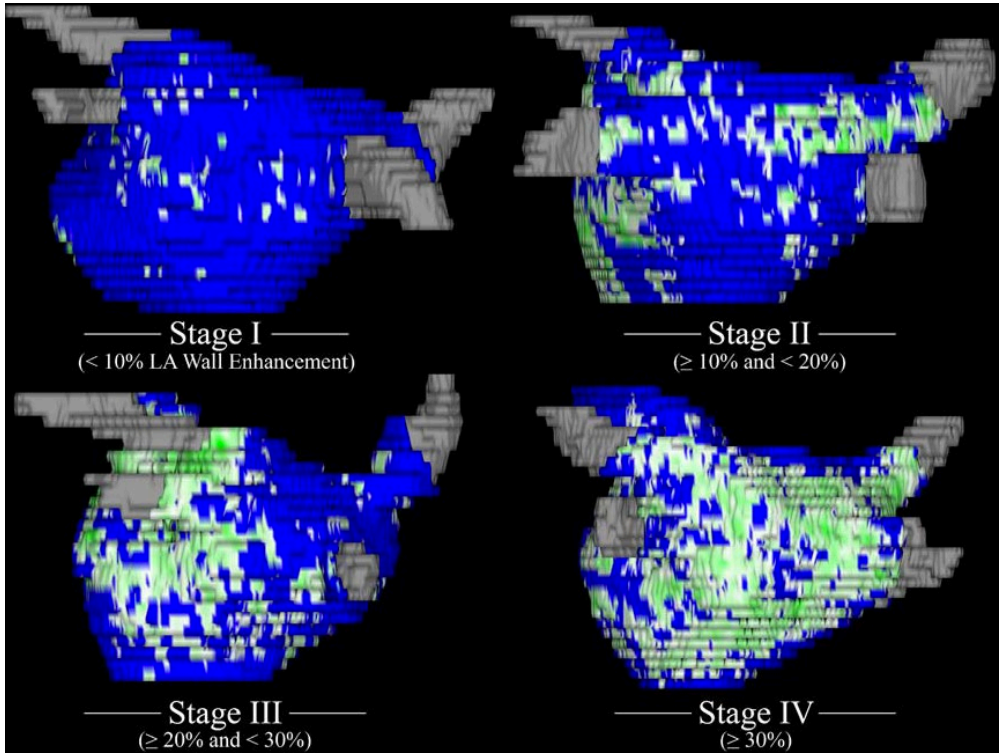


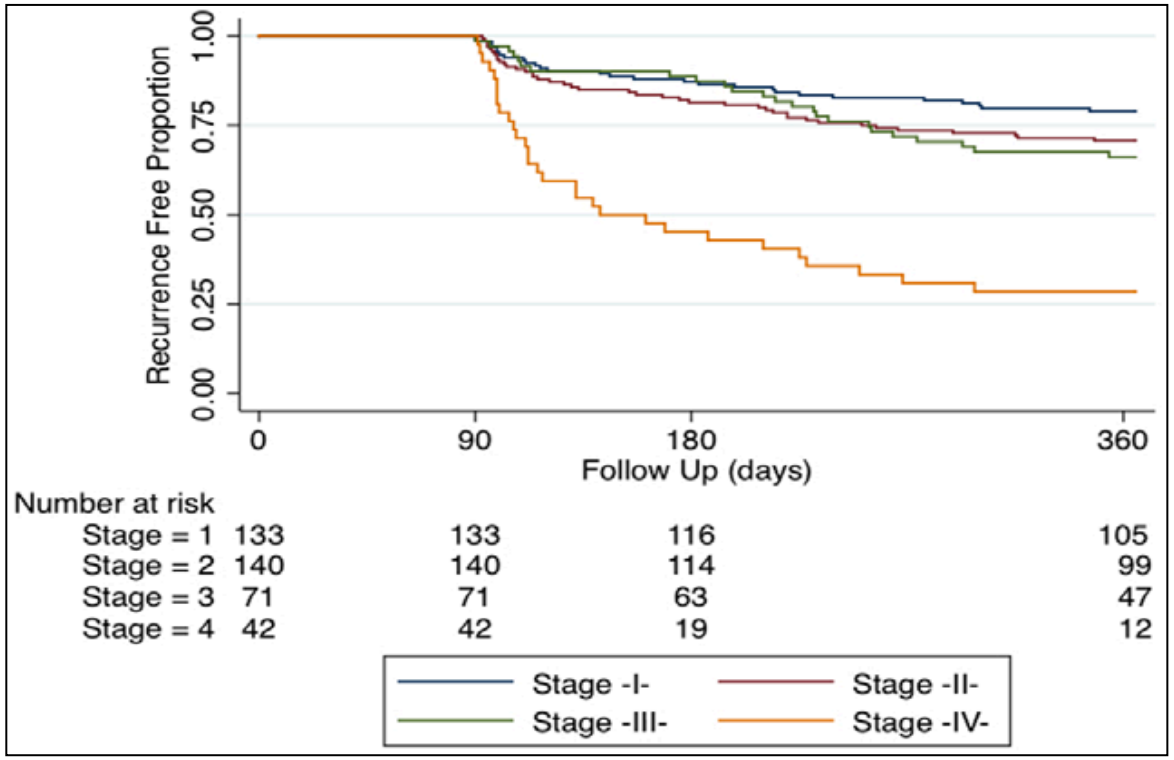


Kirchhof P. AFNET-EHRA. *Eur Heart J. 2009;*30:2969–2980.
Boltd A. *Heart* 2004;90:400–405.

Role of Late Gadolinium Enhancement MRI (LGE-MRI) in Identifying LA Wall Structural Remodeling

- 386 patients, 123 (31.9%) experienced recurrent atrial arrhythmias during 1-year FU[1]
- Extensive LGE (≥ 30% LA wall enhancement) predicts poor response to catheter ablation of AF[1]





Treat AFib EARLY to prevent additional remodeling[1]

Degree of fibrosis predicts success of AF ablation

Also holds true for 5-year follow-up[2]

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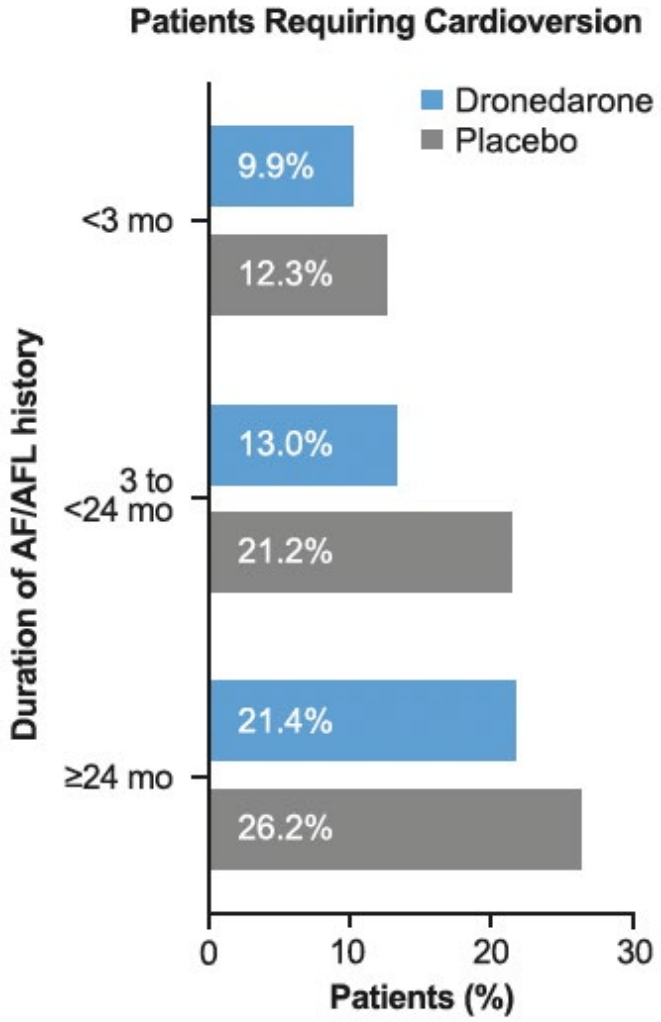
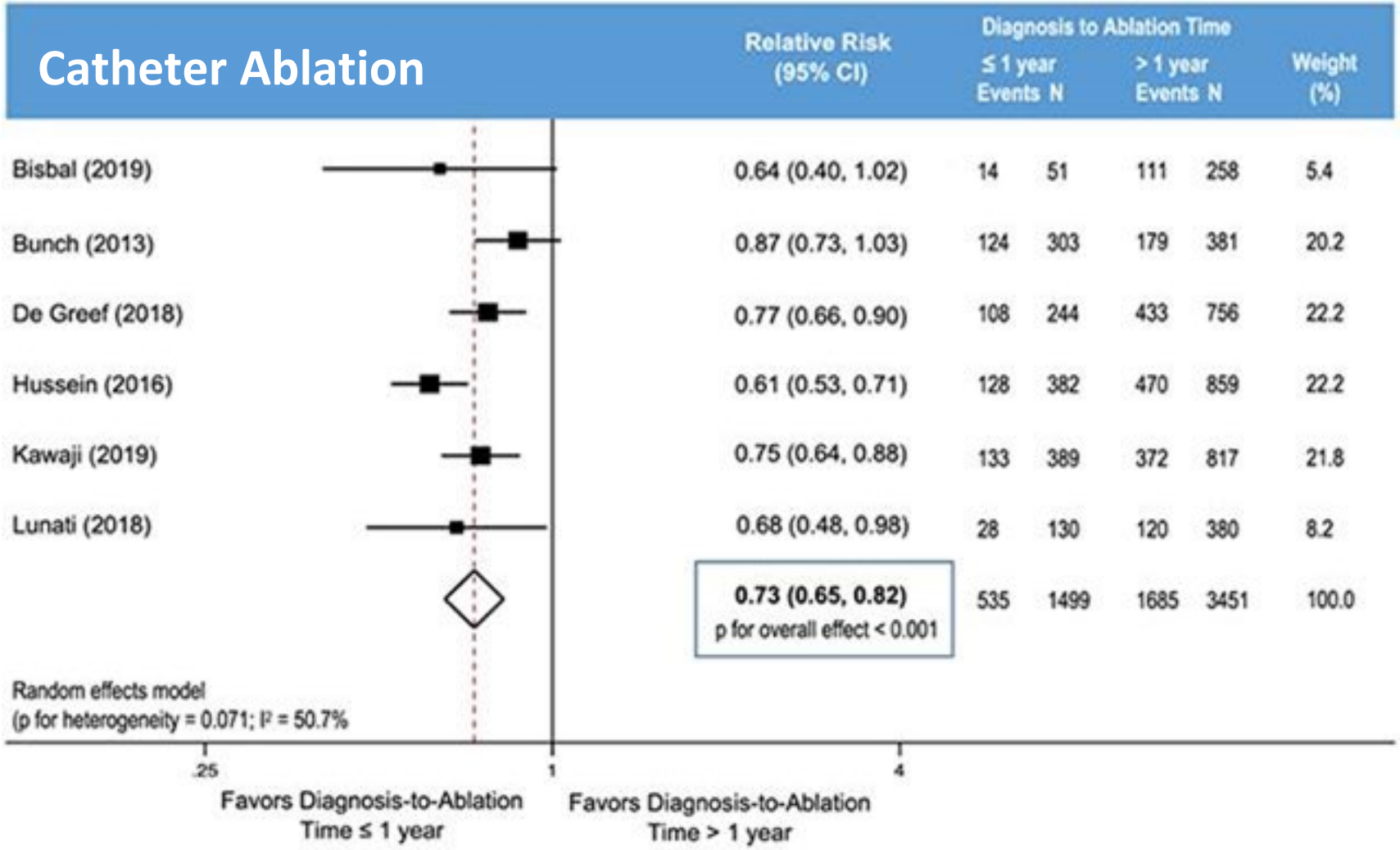
McGann C, et al. Circ Arrhythm Electrophysiol. 2014;7(1):23-30. Chelu MG, et al. J Am Heart Assoc. 2018;7(23):e006313.

Impact of Duration of AF/AFL History

Drug Therapy

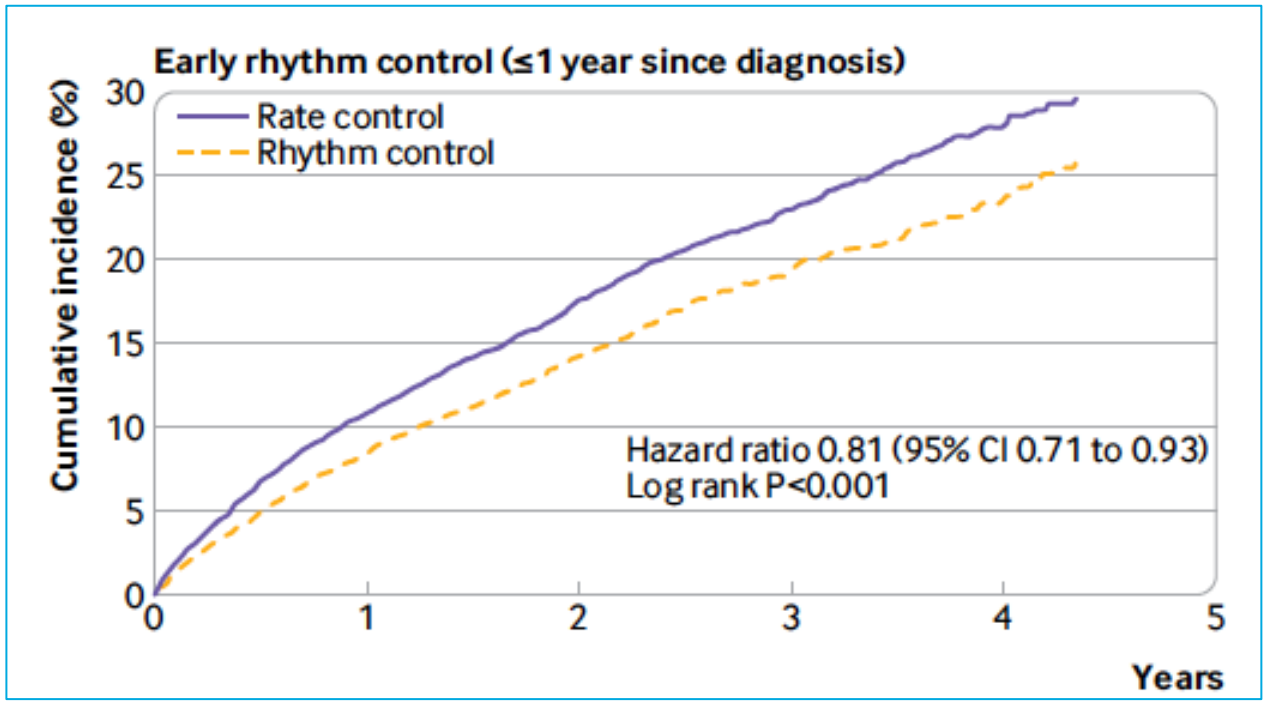


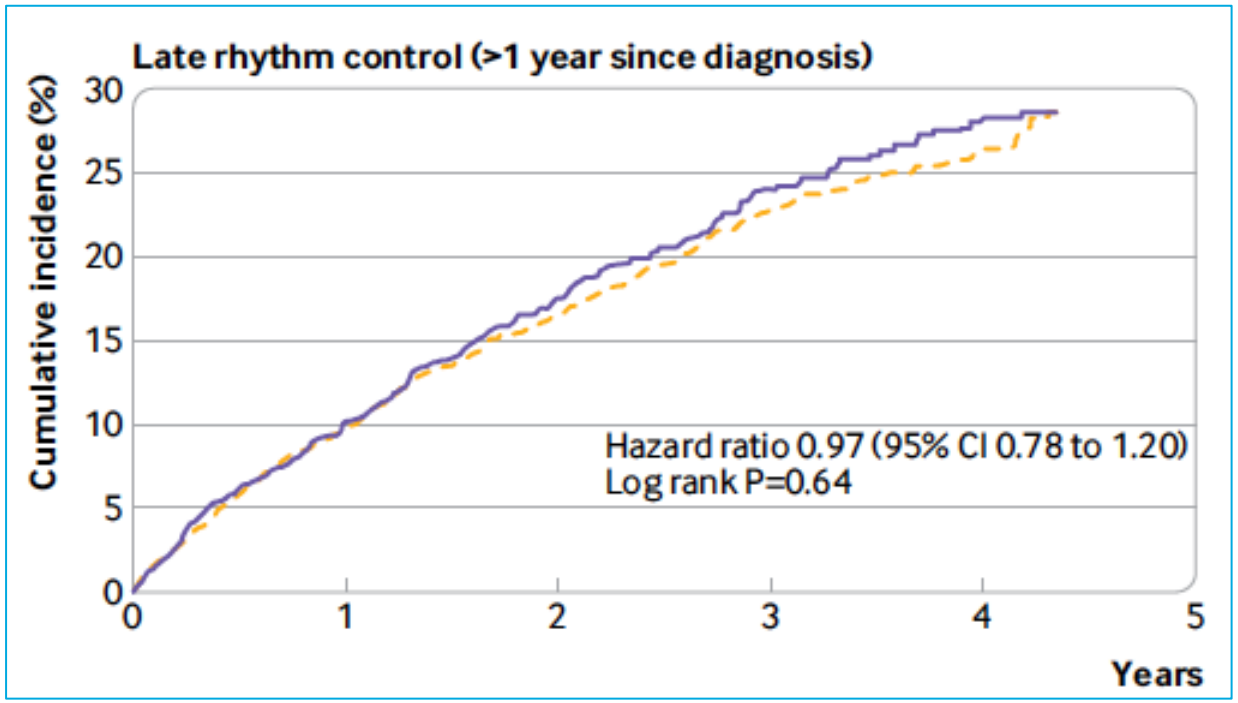


Chew DS. *Circ Arrhythm Electrophysiol*. 2020; 13: e008128.
Blomstrom-Lundqvist C. *Clin Cardiol*. 2020;43:1469–1477.

Treatment Timing & Outcomes with Rhythm Control in Patients with AF: National Cohort Study

- 22,635 adults with AFib & CV conditions, newly treated with rhythm control (AAD or ablation) or rate control
- Observational cohort, Korean National Health Insurance Service database, 2011-2015
- Early rhythm control = initiated within 1 year since diagnosis
- Composite outcome of death from CV causes, ischemic stroke, admission for HF or acute MI; medial FU 2.1 yrs





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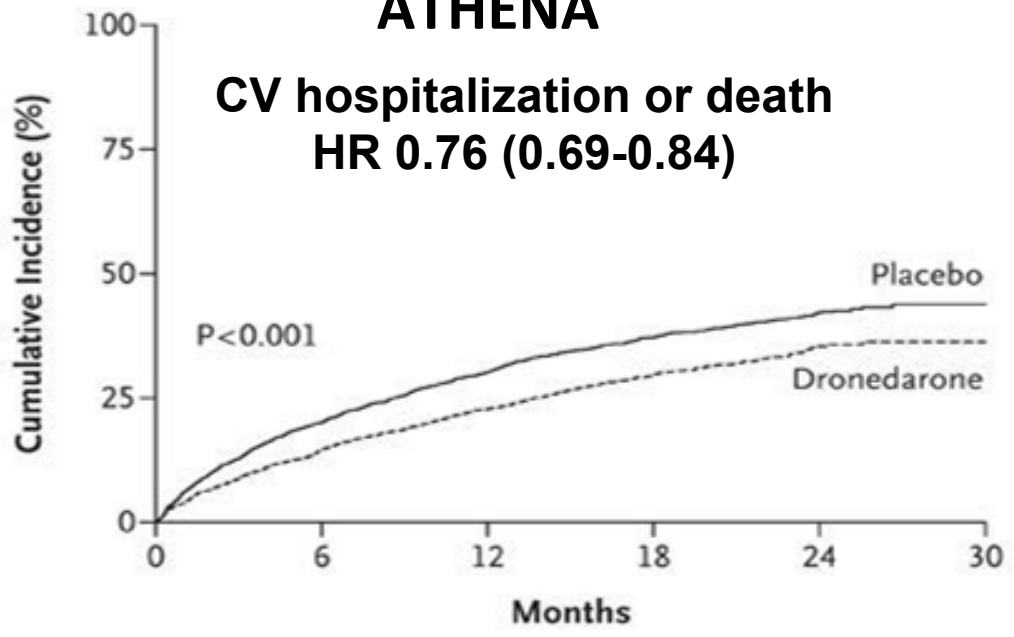
Kim D, et al. *BMJ*. 2021;373(11):n991.

Rhythm control improves outcomes in patients with AF

ATHENA

CV hospitalization or death
HR 0.76 (0.69-0.84)

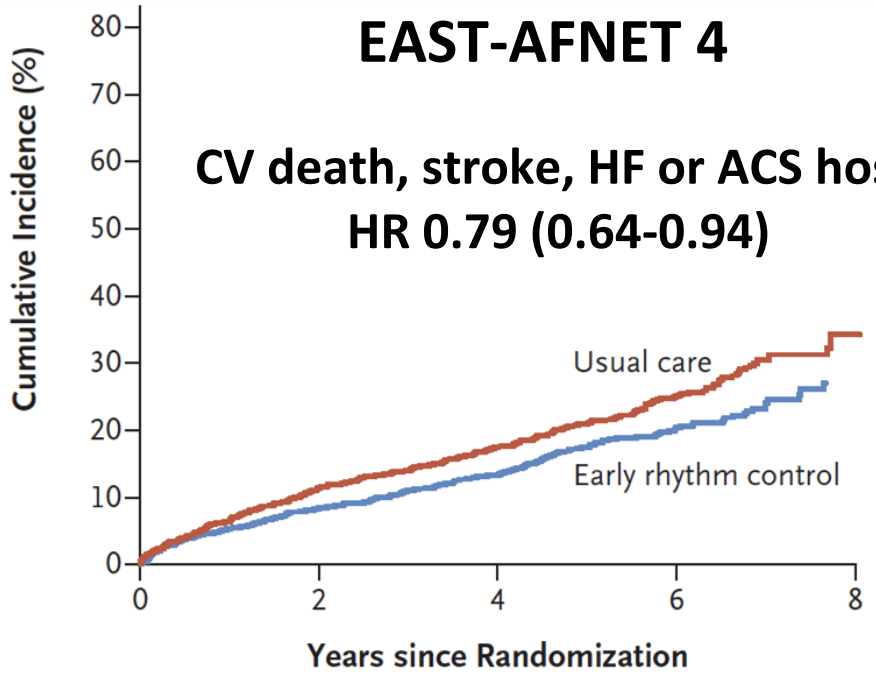


No. at Risk						
Placebo	2327	1858	1625	1072	385	3
Dronedarone	2301	1963	1776	1177	403	2

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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72-Year-Old Man With Hypertension and Dyspnea

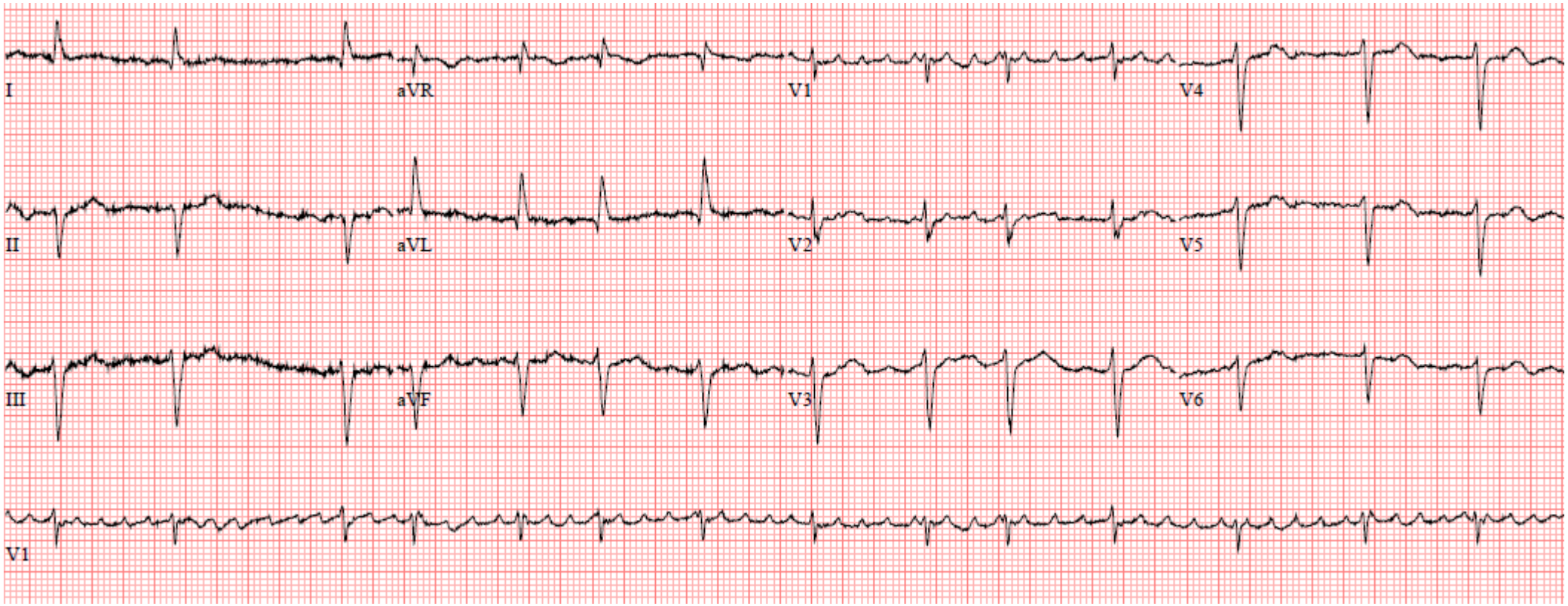

Image courtesy of Jonathan Piccini, MD.

72-Year-Old Man With Hypertension and Dyspnea

Mild fatigue with strenuous yard-work

Medications

- Apixaban 5 mg bid
- Metoprolol succinate XL 12.5 mg bid

Laboratory Evaluation

- TSH normal
- BNP 51 pg/mL
- eGFR 64 mL/min/1.73 m^2

Echo

- Normal LV function
- Mild RV dysfunction
- Left atrial diameter 4.0 cm

bid, twice daily; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; LV, left ventrical; RV, right ventrical; RVSP, right ventricular systolic pressure; TSH, thyroid stimulating hormone.

Patterns of care for first-detected atrial fibrillation: Insights from the Get With The Guidelines® – Atrial Fibrillation registry

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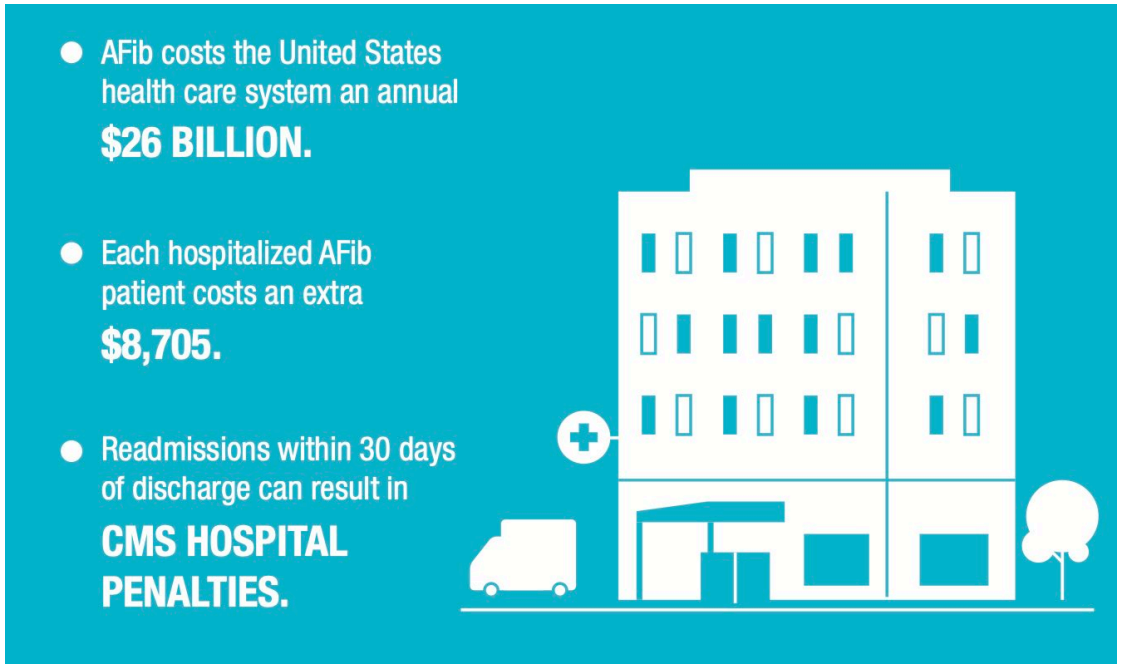
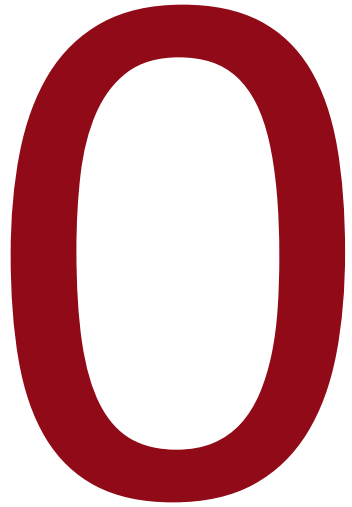


- 1 in 5 patients presenting for acute care of atrial fibrillation have first-detected AF
- Less than half of the patients with first-detected AF receive rhythm control at admission

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

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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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

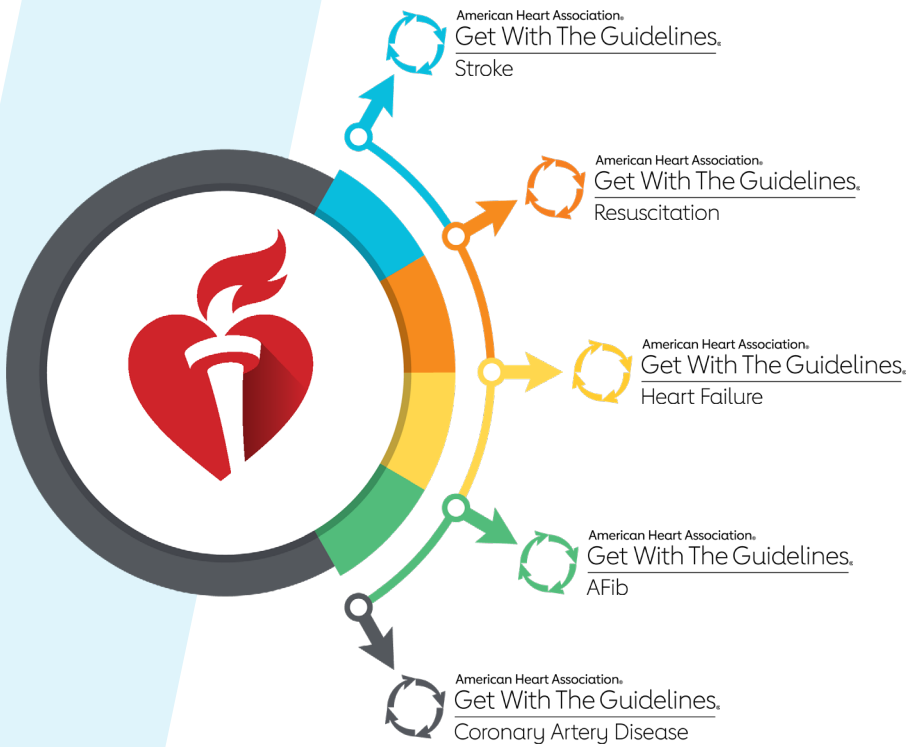
/ Nearly **50%** of all cardiovascular and **80%** of all stroke patients in the U.S. benefit from treatment at a GWTG hospital

/ **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



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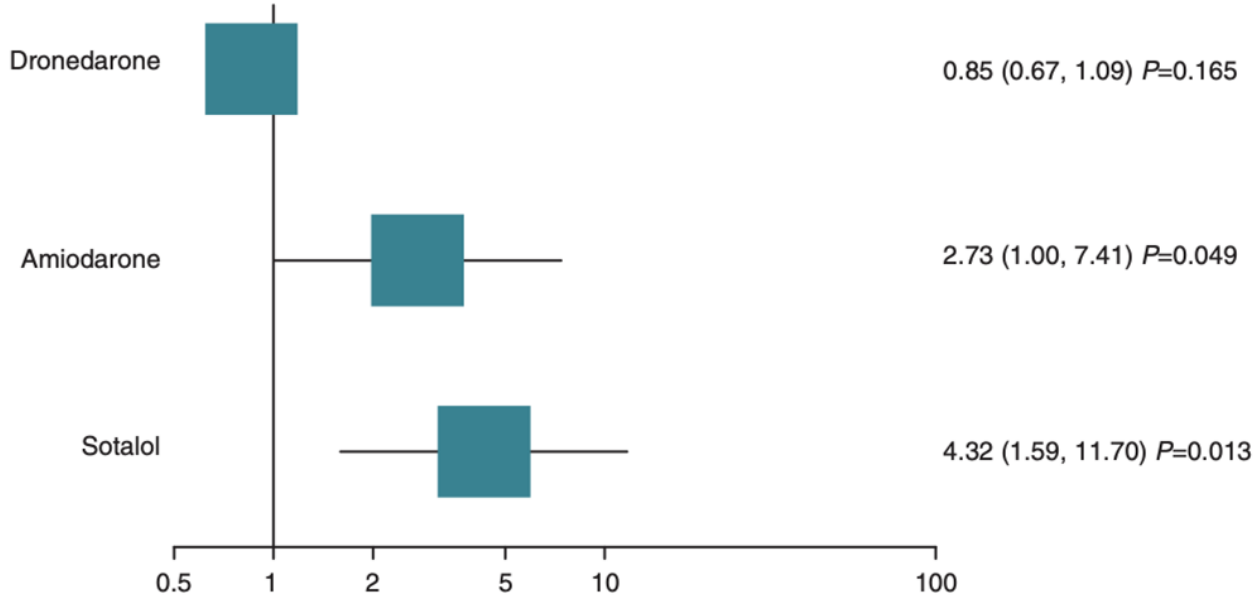
Why Dronedarone?

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



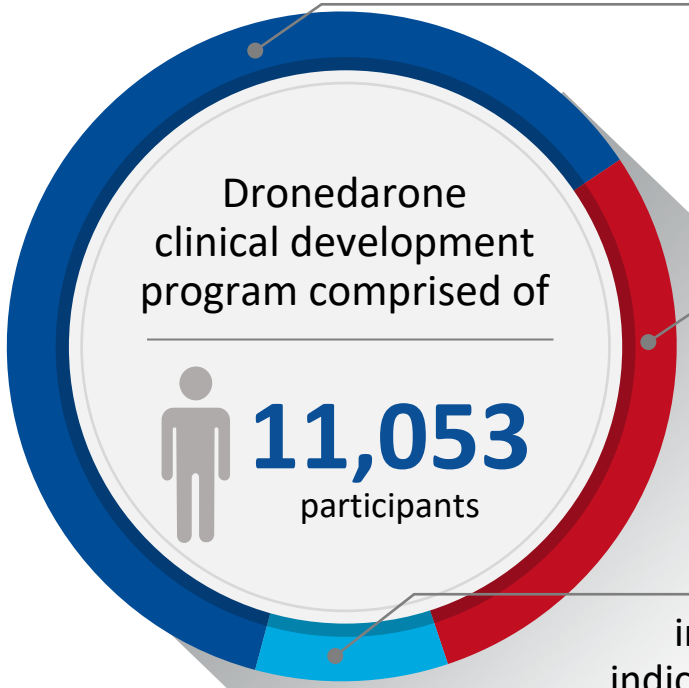
Effect on all-cause mortality in studies involving >100 patients in either arm. Odds ratios and 95% confidence intervals

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

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

CHANGE AFib

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.

CHANGE AFib

Protocol V3.0 Review

Trial Design

Design: Pragmatic Randomized Trial

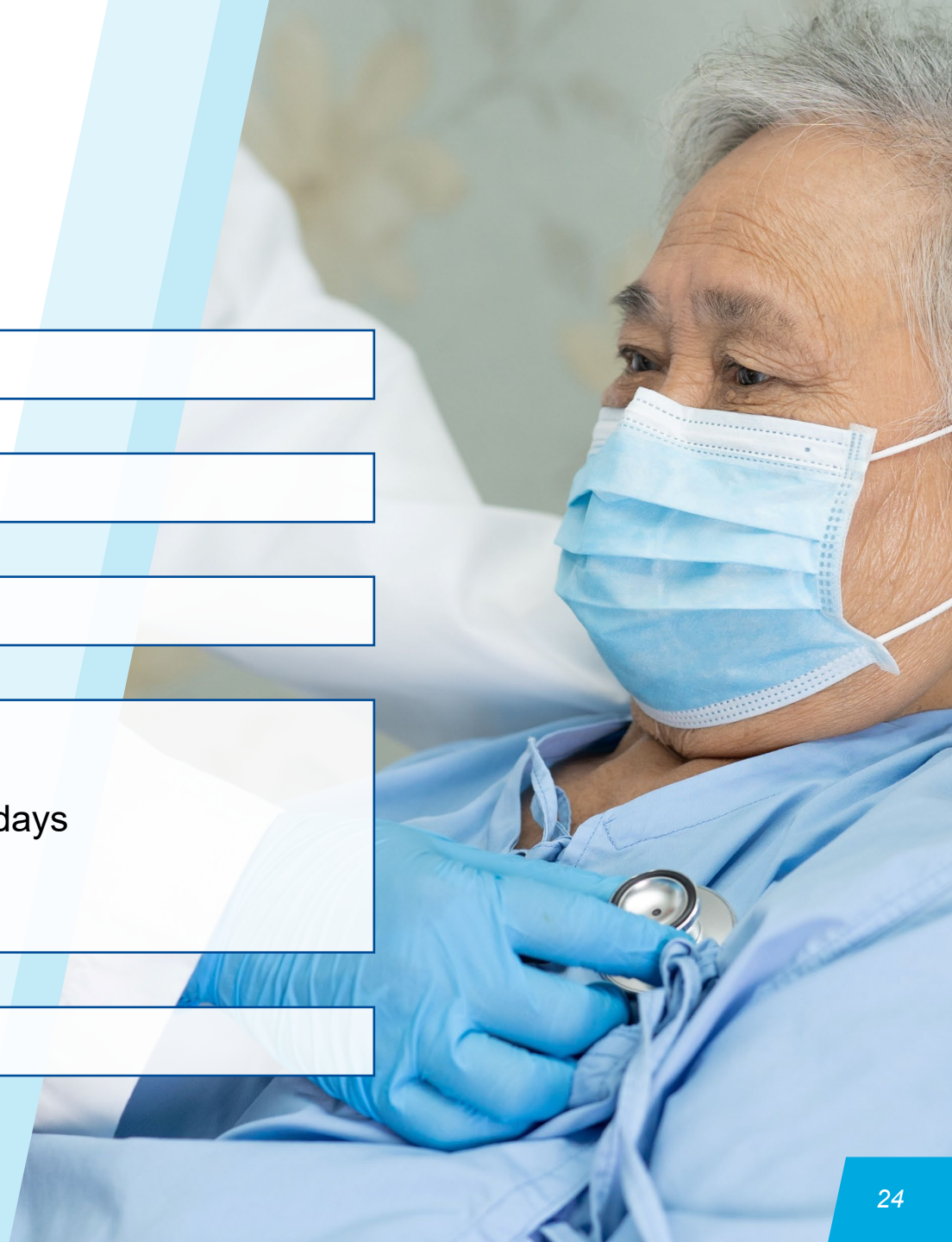
Sample Size: Approximately 3,000 patients

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

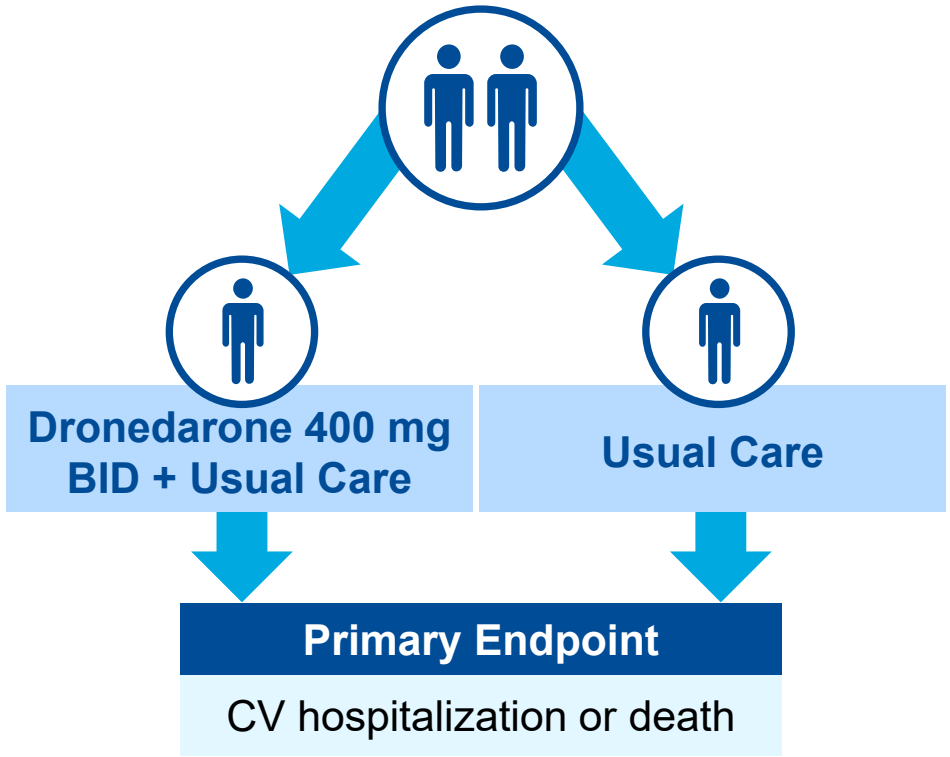


CHANGE AFib

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 presenting to the hospital with **first-detected AFib.**



First-Detected AFib:

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

Patients who present to the hospital (acute care encounter) for the initial diagnosis of AFib

OR

Patients who present to an outpatient clinic for follow-up from an AFib acute care encounter within 120 days of 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).

An acute care encounter is defined as an encounter and discharge from an ER, Observation Unit or Inpatient Admission.

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

- Prior hospitalization for AFib
- Permanent AFib
- Pregnancy
- Severe hepatic impairment

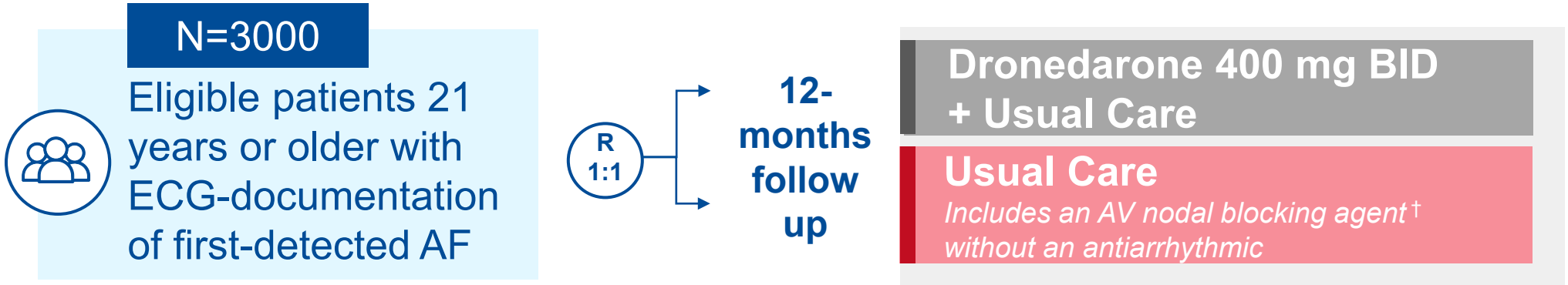
- **PR interval >280 msec**, or 2nd / 3rd degree AV block without a permanent pacemaker/cardiac implanted electronic device
- Corrected QT interval **≥500 msec**

- 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 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.

Outcomes and Endpoints



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

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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

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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.

CHANGE AFib

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,
  - Tate-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.

CHANGE AFib

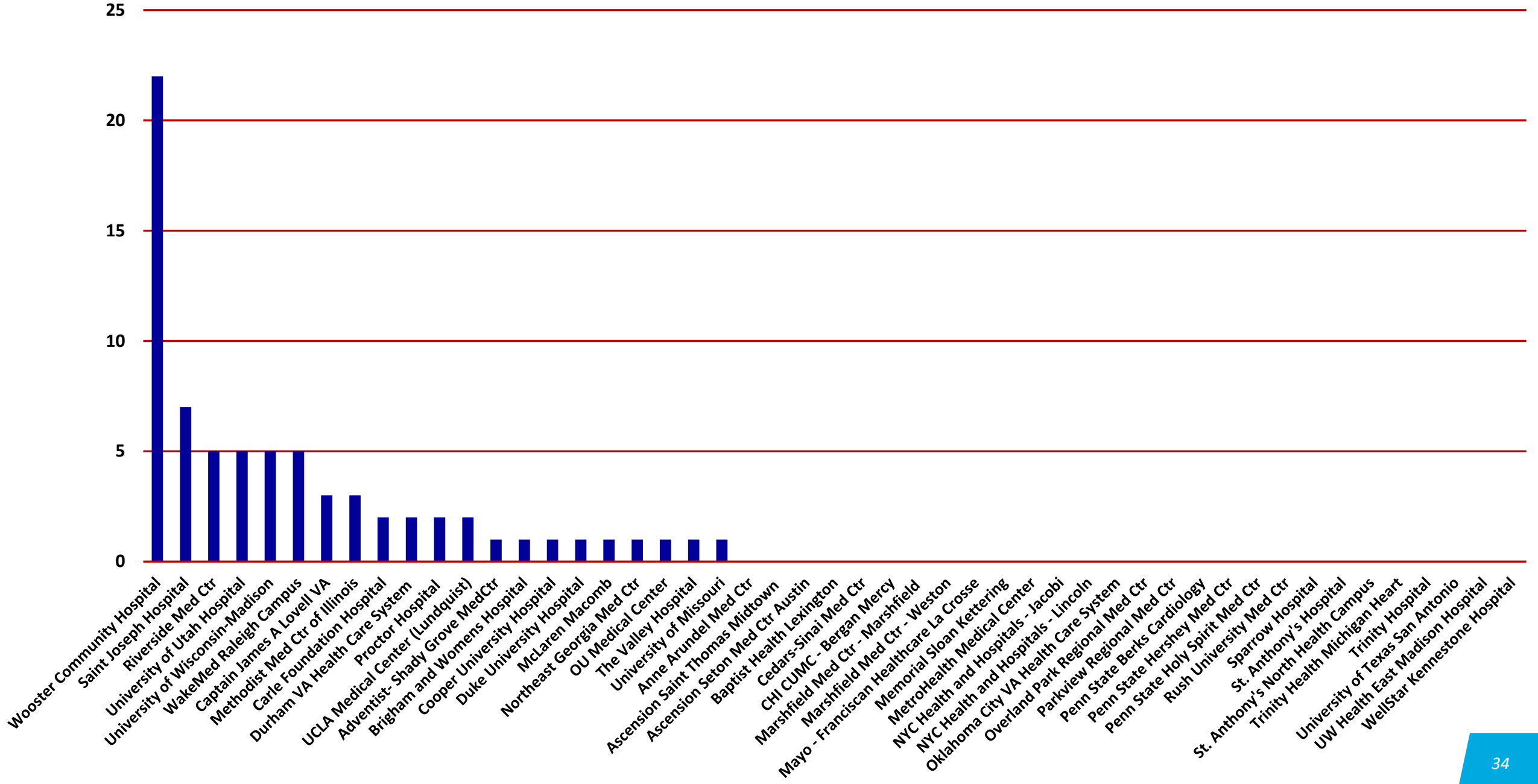
Trial Progress Update

Trial Progress – as of April 25, 2023

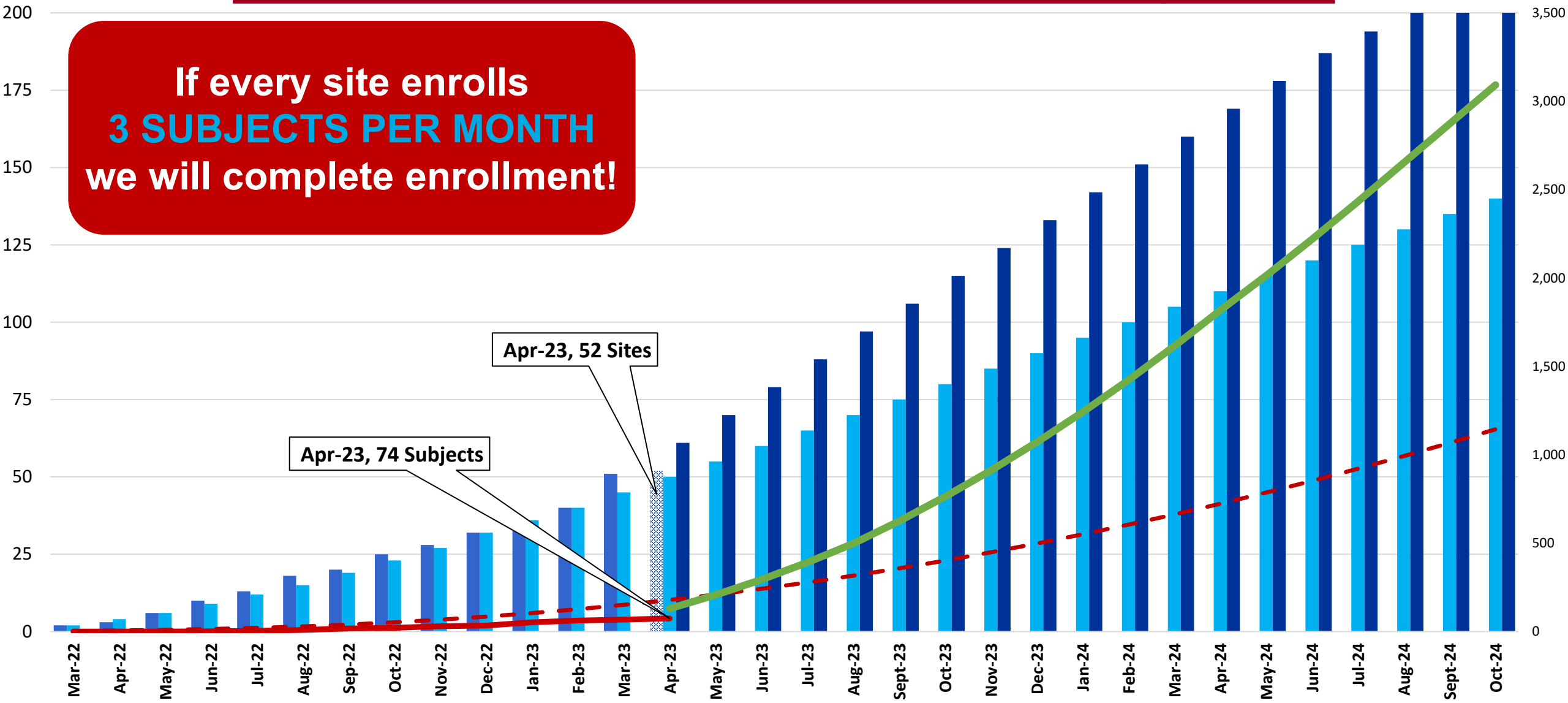
Site Status	Current Status	Trial GOAL!
Subject Enrollments	**74**	**3000**
Activated Sites	52	**200**
Sites in Onboarding	102	**-**
Sites Assessing Feasibility	123	**-**

CHANGE AFib

CHANGE AFib 74 Subject Enrollments from 21 Sites

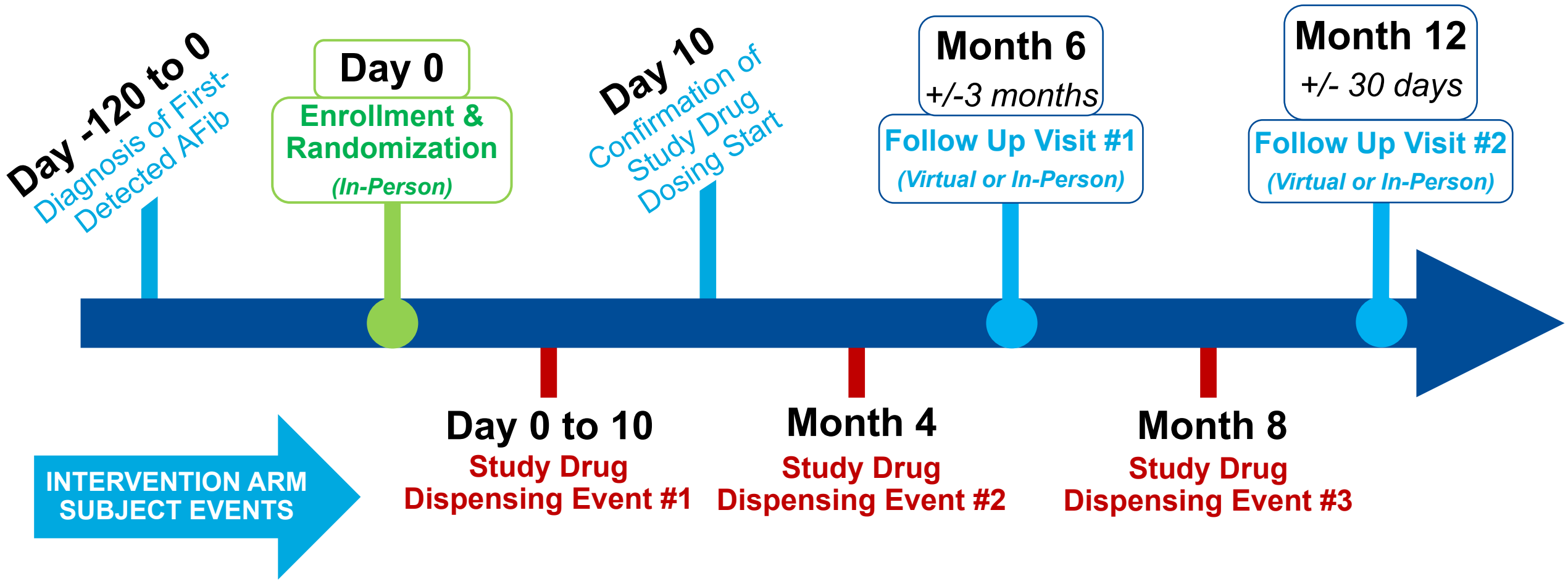


CHANGE AFib Activation & Enrollment Projections



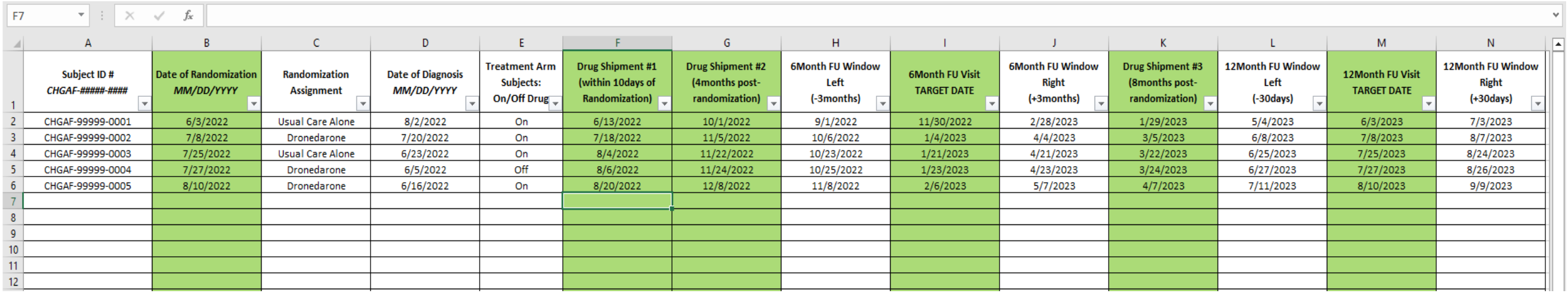
Trial
Next Steps

CHANGE AFib Schedule of Activities



Each study drug kit shipment will cover 4 months of drug supply, with 1 additional 1-month bottle as buffer

NEW CHANGE AFib *Subject Visit Tracker*

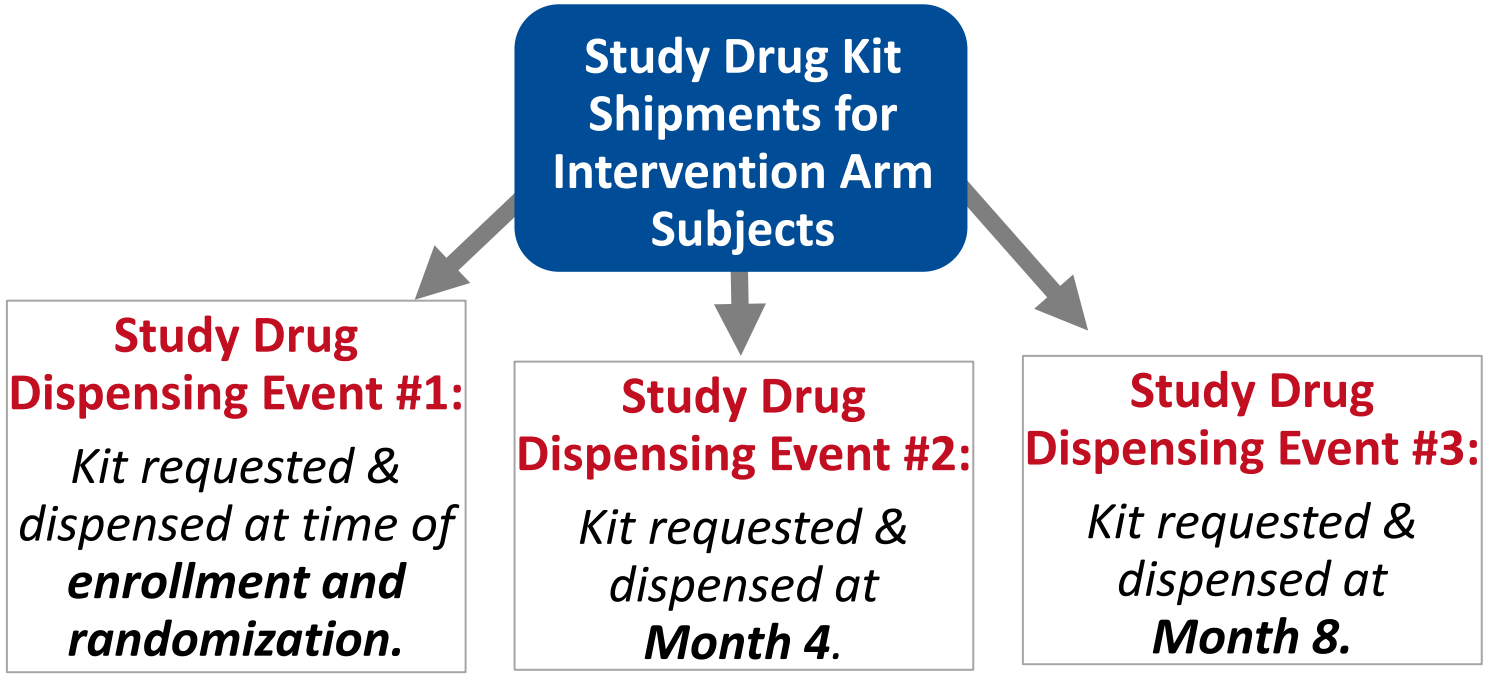


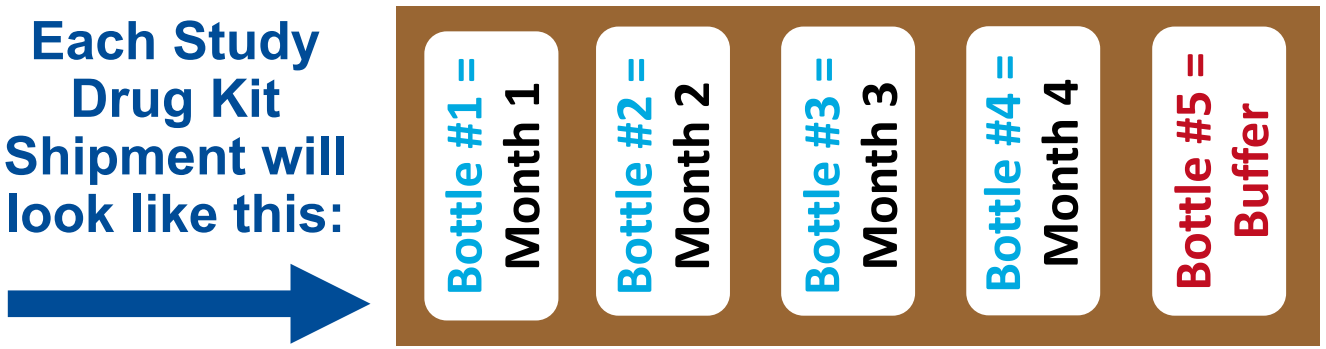
Subject ID # *CHGAF-#####-####*	Date of Randomization *MM/DD/YYYY*	Randomization Assignment	Date of Diagnosis *MM/DD/YYYY*	Treatment Arm Subjects: On/Off Drug	Drug Shipment #1 (within 10days of Randomization)	Drug Shipment #2 (4months post-randomization)	6Month FU Window Left (-3months)	6Month FU Visit TARGET DATE	6Month FU Window Right (+3months)	Drug Shipment #3 (8months post-randomization)	12Month FU Window Left (-30days)	12Month FU Visit TARGET DATE	12Month FU Window Right (+30days)
CHGAF-99999-0001	6/3/2022	Usual Care Alone	8/2/2022	On	6/13/2022	10/1/2022	9/1/2022	11/30/2022	2/28/2023	1/29/2023	5/4/2023	6/3/2023	7/3/2023
CHGAF-99999-0002	7/8/2022	Dronedarone	7/20/2022	On	7/18/2022	11/5/2022	10/6/2022	1/4/2023	4/4/2023	3/5/2023	6/8/2023	7/8/2023	8/7/2023
CHGAF-99999-0003	7/25/2022	Usual Care Alone	6/23/2022	On	8/4/2022	11/22/2022	10/23/2022	1/21/2023	4/21/2023	3/22/2023	6/25/2023	7/25/2023	8/24/2023
CHGAF-99999-0004	7/27/2022	Dronedarone	6/5/2022	Off	8/6/2022	11/24/2022	10/25/2022	1/23/2023	4/23/2023	3/24/2023	6/27/2023	7/27/2023	8/26/2023
CHGAF-99999-0005	8/10/2022	Dronedarone	6/16/2022	On	8/20/2022	12/8/2022	11/8/2022	2/6/2023	5/7/2023	4/7/2023	7/11/2023	8/10/2023	9/9/2023

- Aids in Protocol Visit Scheduling and Study Drug Dispensing Event planning.
- Template included on your USBs and posted on the trial website.

Study Drug Kit Configuration & Dispensation

- Patients randomized to the intervention (dronedarone) arm will receive 3 study drug kit shipments.
- Each study drug kit shipment will cover 4 months of drug supply, with 1 additional bottle as buffer.
- ***NOTE: 1 bottle = 1 month of dronedarone drug supply (60, 400mg tablets)***

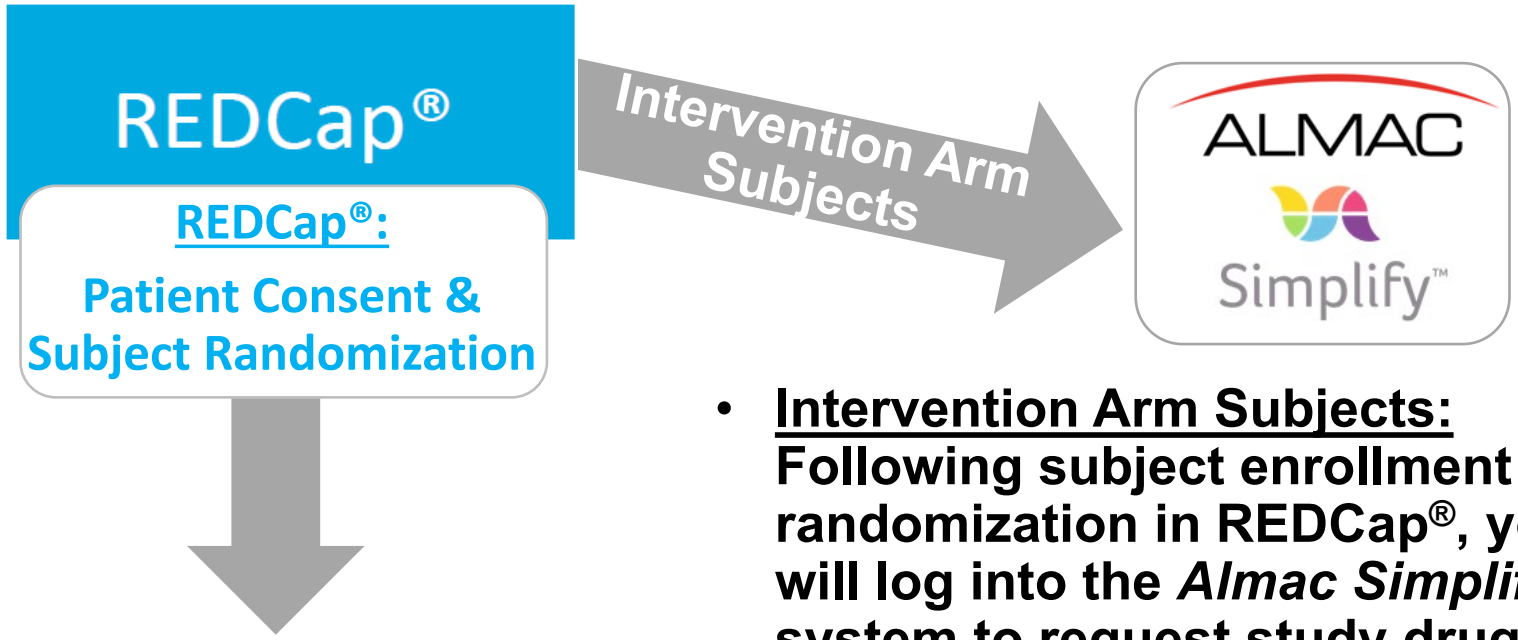




CHANGE AFib

Recap of Trial EDC & IRT Systems

- REDCap® remains to be the consent and randomization tool for all CHANGE AFib subjects.



- GWTG®-AFIB remains to be the EDC for all CHANGE AFib subject study visit data (baseline and both follow-up visits).

- **Intervention Arm Subjects:** **Following subject enrollment and randomization in REDCap®, your site will log into the *Almac Simplify™ IRT* system to request study drug kit dispensation.**
- **Register the subject, complete the DOF (Drug Order Form) and email the signed form to the central pharmacy depot for shipment initiation.**

CHANGE AFib

Acute Care Encounter Update

- Currently, eligible CHANGE AFib patients must have an acute care encounter for their first-detected atrial fibrillation diagnosis: **Inclusion Criteria #3.**

- While we recently removed the requirement for a patient's acute care encounter location to be at YOUR trial site, we're now revisiting this Inclusion Criteria to allow for increased subject enrollments.

- **COMING SOON: We will be rolling out Protocol V4.0 thus removing the acute care encounter requirement altogether!**

- **Continue to enroll under your current IRB-approved Protocol until further notice.**

- **As done previously, please begin to pre-identify patients that would fit this new I/E criteria and flag them for future Protocol V4.0 enrollment.**

CHANGE AFib

CHANGE AFib / **Contact**

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Thank You