Morning Q&A Session

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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.

- Sean Pokorney Disclosure:

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- Samantha Johnson Disclosure:

  Employed by AHA/CHANGE AFib

- Devin Keating Disclosure:

  Employed by AHA/CHANGE AFib

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FAQ on Dronedarone: First line therapy for AF ?

- Is dronedarone efficacious?
- Is dronedarone safe?
- Where does dronedarone fit in?
- How can we improve our therapeutic decisions?

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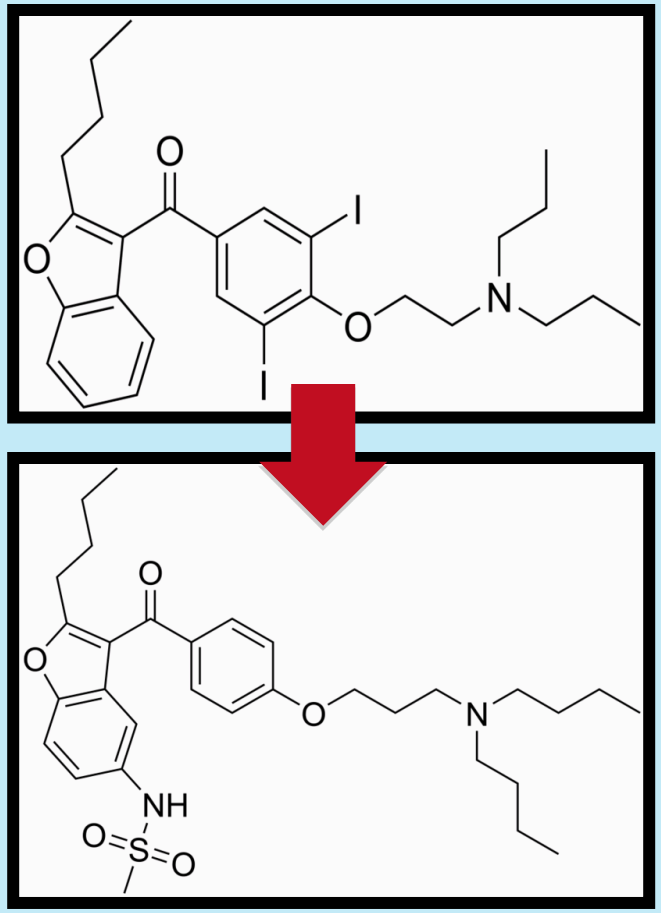

Dronedarone is a multi-channel blocker

- Class I-IV Vaughan-Williams properties
- Analog of amiodarone
  - Iodine moiety removed
  - Methylsulfonamide added to reduce lipophilicity

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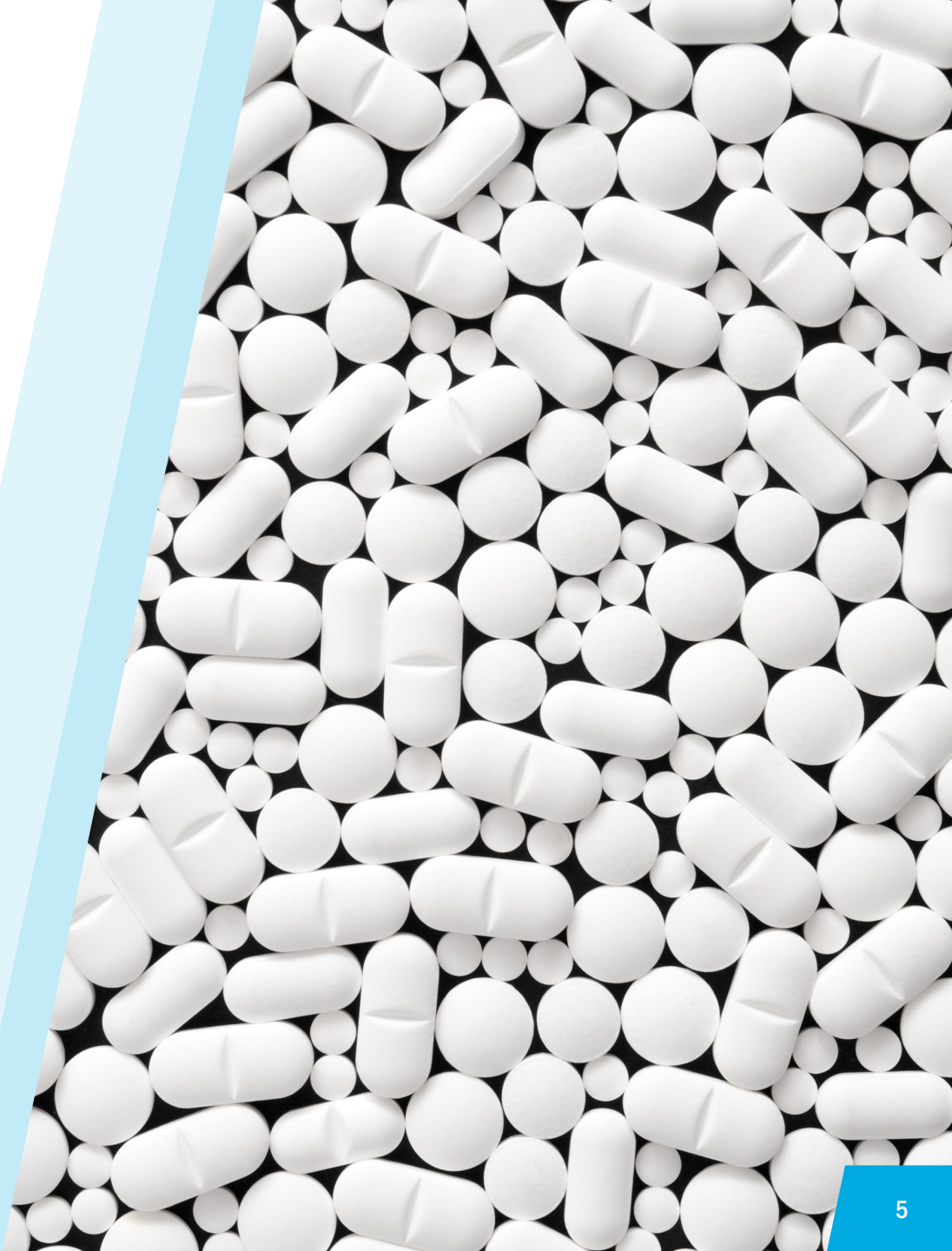
Dosing of Dronedarone

- 400 mg bid dose was lowest dose associated with electrocardiographic effects in phase I studies
- DAFNE – phase II dose selection trial
  - 400 mg reduced risk of recurrent AF
  - 600 & 800 mg poorly tolerated due to GI side-effects



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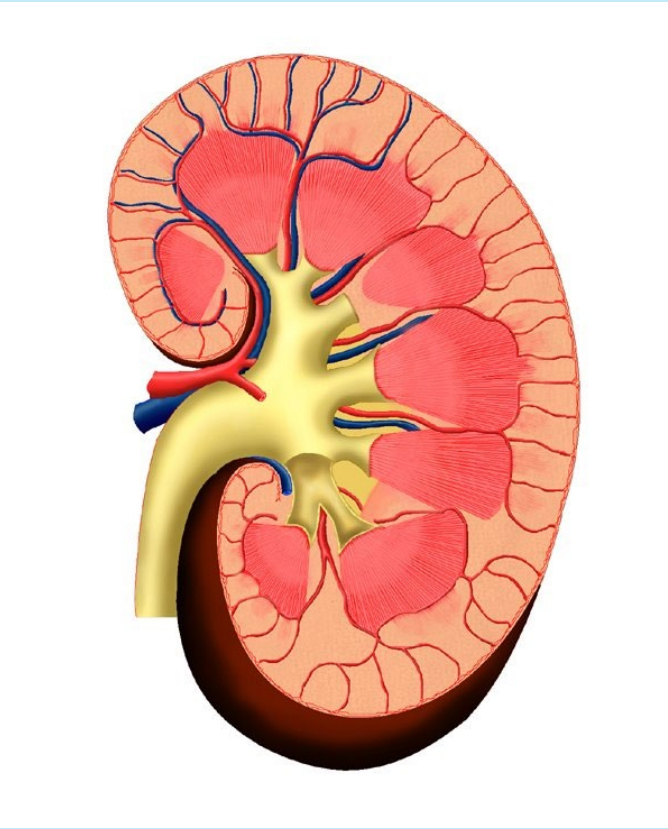
Pharmacokinetics of Dronedarone

- 15% bioavailable after first-pass metabolism
- Significant increase in AUC with food (2-3 fold)
  - Administer with meals
- Predominantly metabolized through CYP3A4
- Minimal renal clearance
- T1/2 = 30 hours

Effects on Serum Creatinine

- Inhibits the organic cation transporter -2 (OCT2)
  - Similar effect with cimetidine and trimethoprim
- Mean ⇧ Cr 0.1 mg/dL
- No effect on GFR



Exclusion Criteria

- Prior or planned treatment with rhythm control*
- Planned cardiothoracic surgery

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

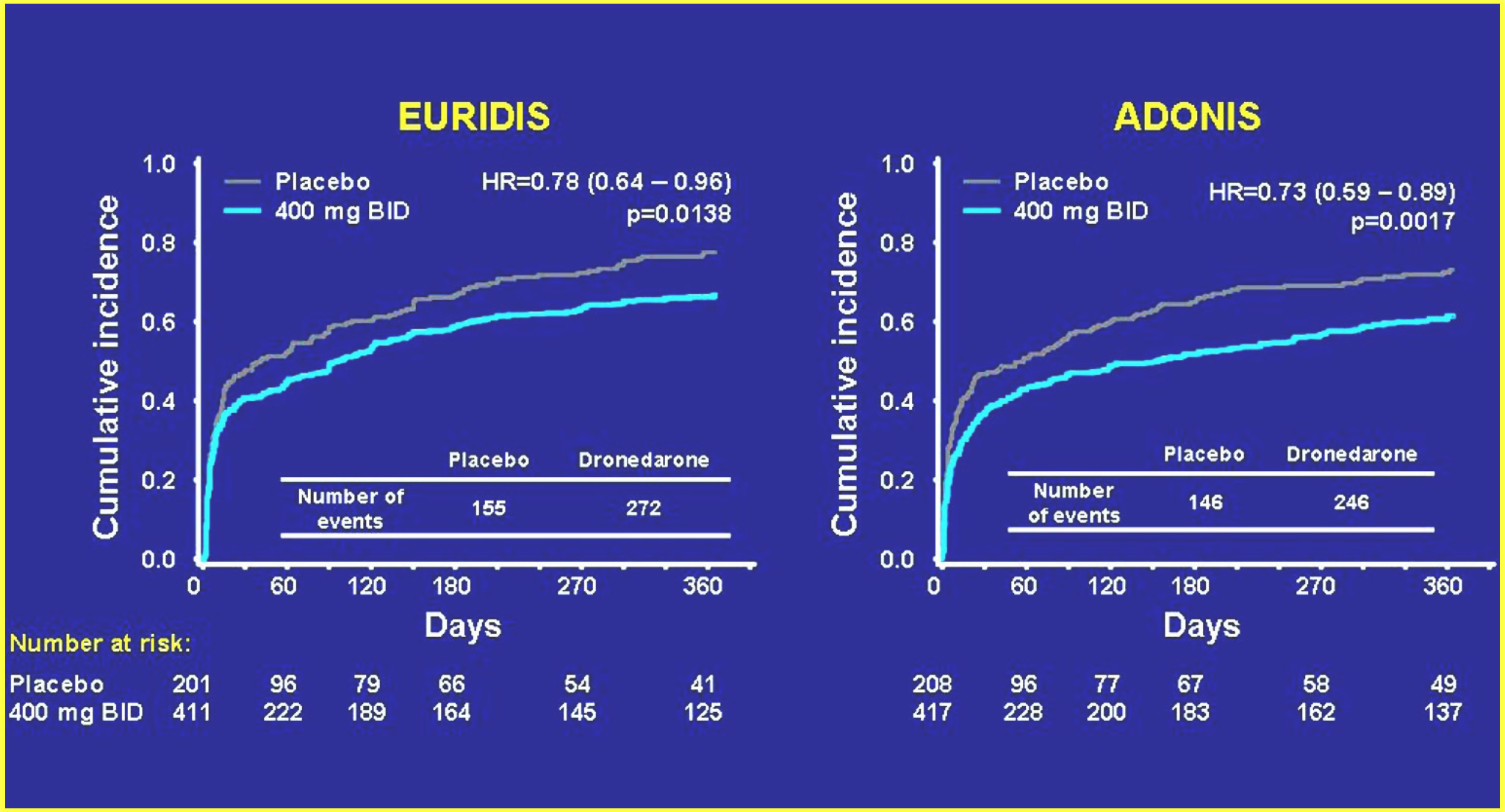
- PR interval >280 msec, or 2nd / 3rd degree AV block without a permanent pacemaker/cardiac implanted electronic device
- Corrected QT interval ≥500 msec

- 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.

Is Dronedarone Efficacious?

AF Recurrence in EURIDIS & ADONIS



Singh BN. N Engl J Med. 2007;357:987-99.

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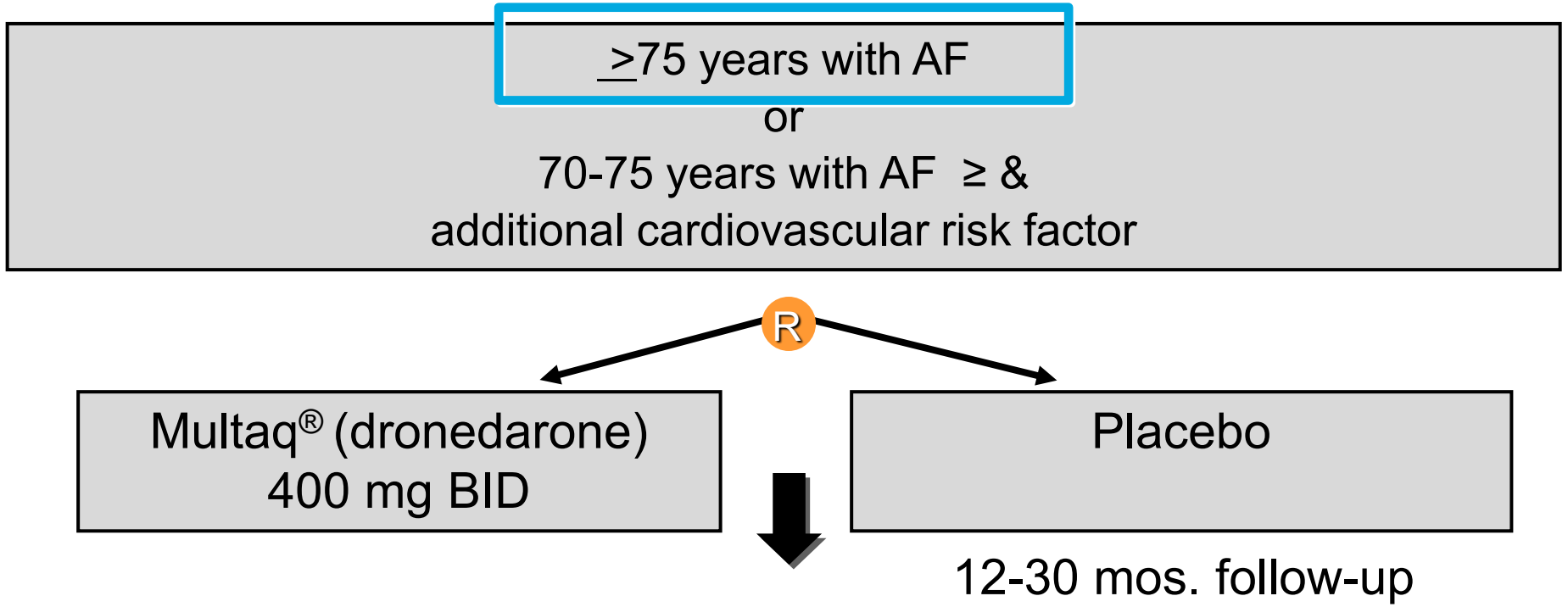
ATHENA Trial: Study Design



- Primary Endpoint: composite of all-cause mortality combined with cardiovascular hospitalization
- Secondary Endpoint: death from any cause, cardiovascular death, hospitalization for cardiovascular reasons

JCE 2008; 19.1/Heart Rhythm 2008

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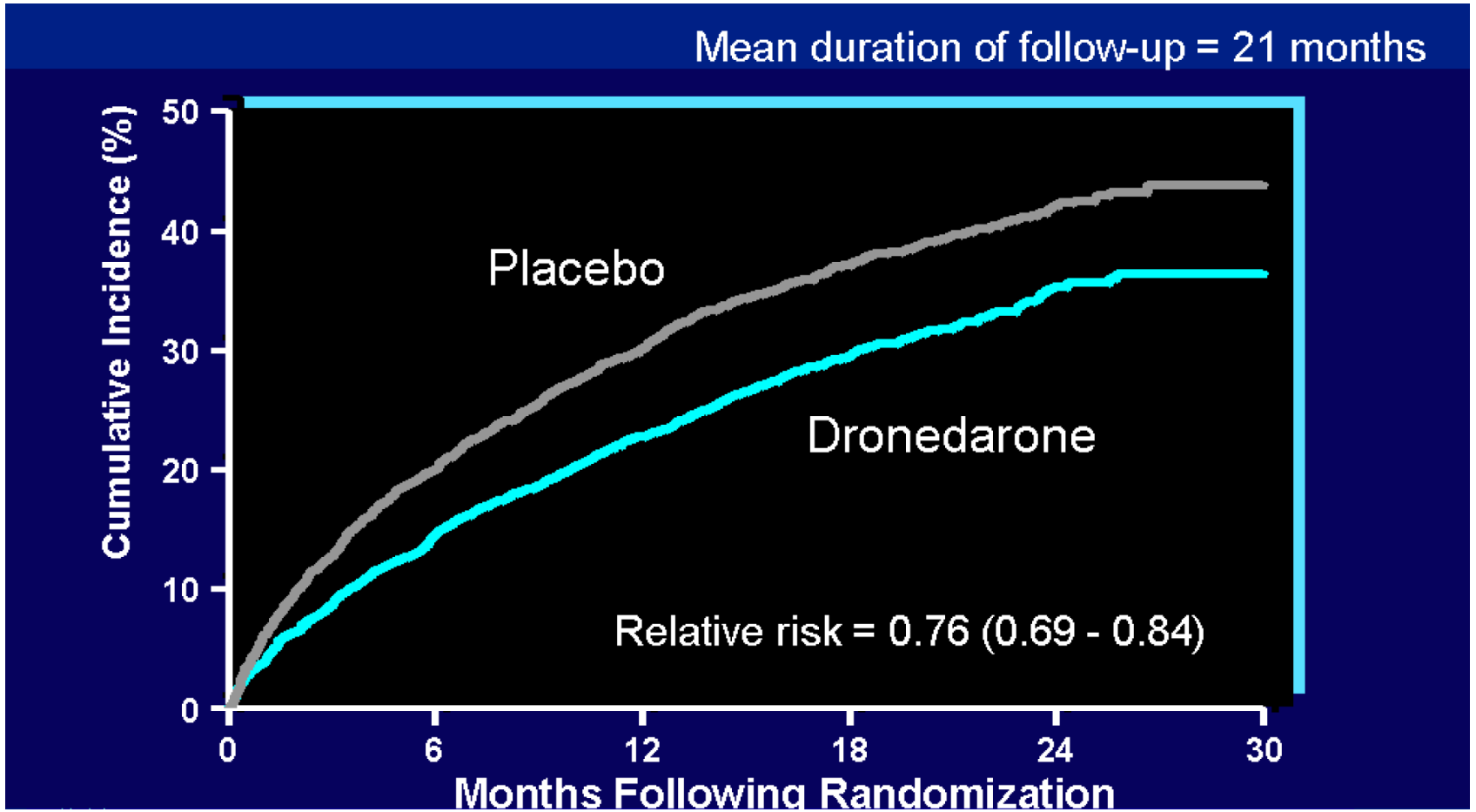
ATHENA: Primary Endpoint, All-cause Mortality and Cardiovascular Hospitalization



Hohnloser SH. N Engl J Med 2009;360:668-78.

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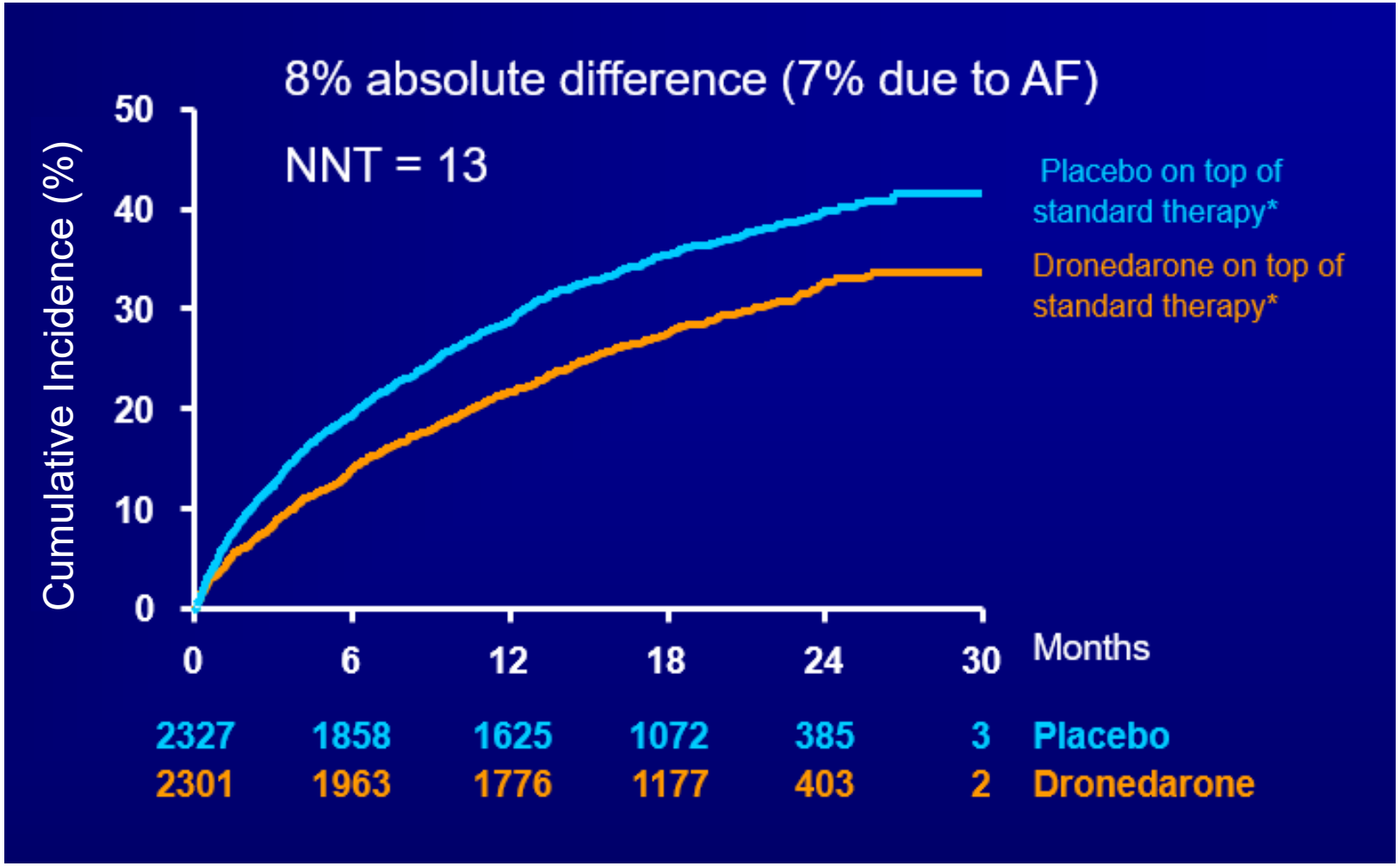
ATHENA: Cardiovascular Hospitalization



Hohnloser SH. N Engl J Med 2009;360:668-78.

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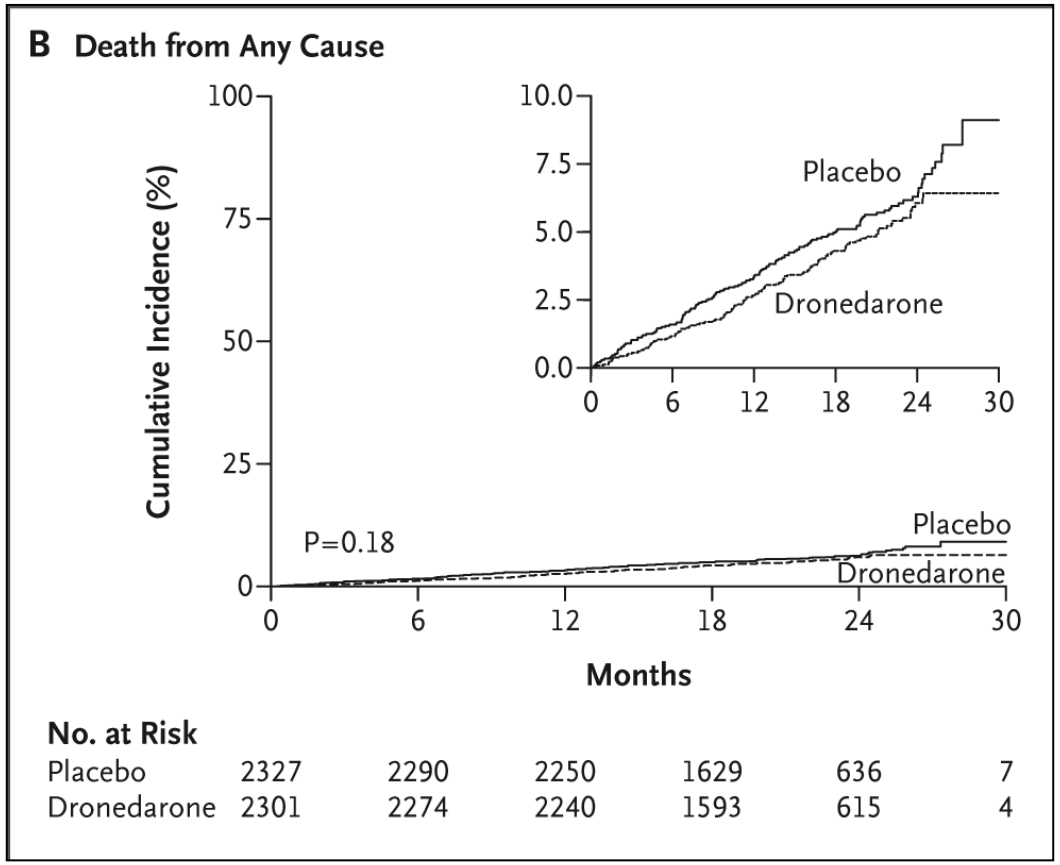
Death from Any Cause in ATHENA



Drug	Deaths/At Risk	HR (95% CI)	P-value
Placebo	139/2327	0.84 (0.66-1.08)	0.18
Dronedarone	116/2301		

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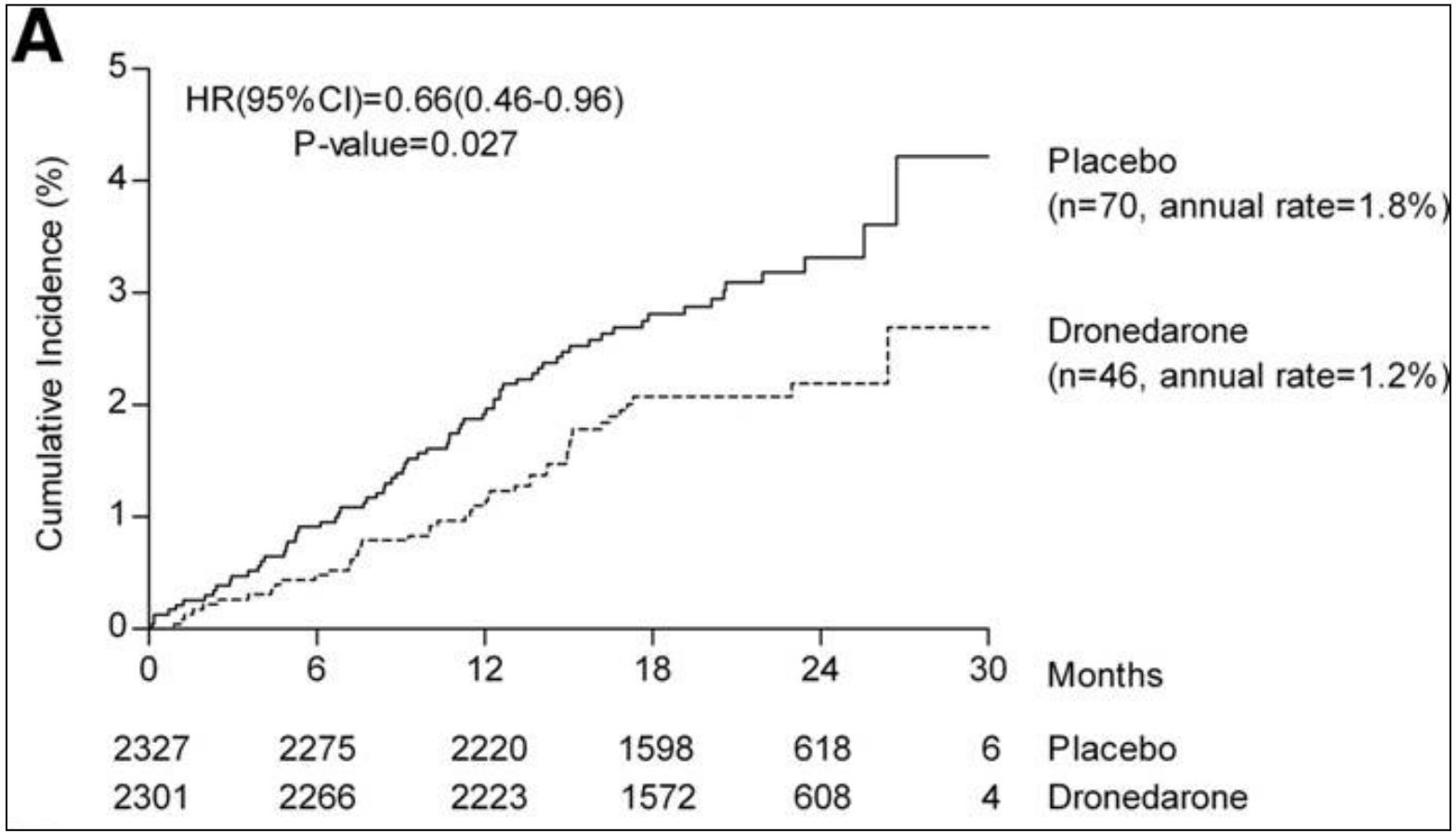
Hohnloser SH. N Engl J Med 2009;360:668-78.

ATHENA: Cumulative Risk of Stroke



Connolly SJ, et al. Circulation. 2009;1174-1180.

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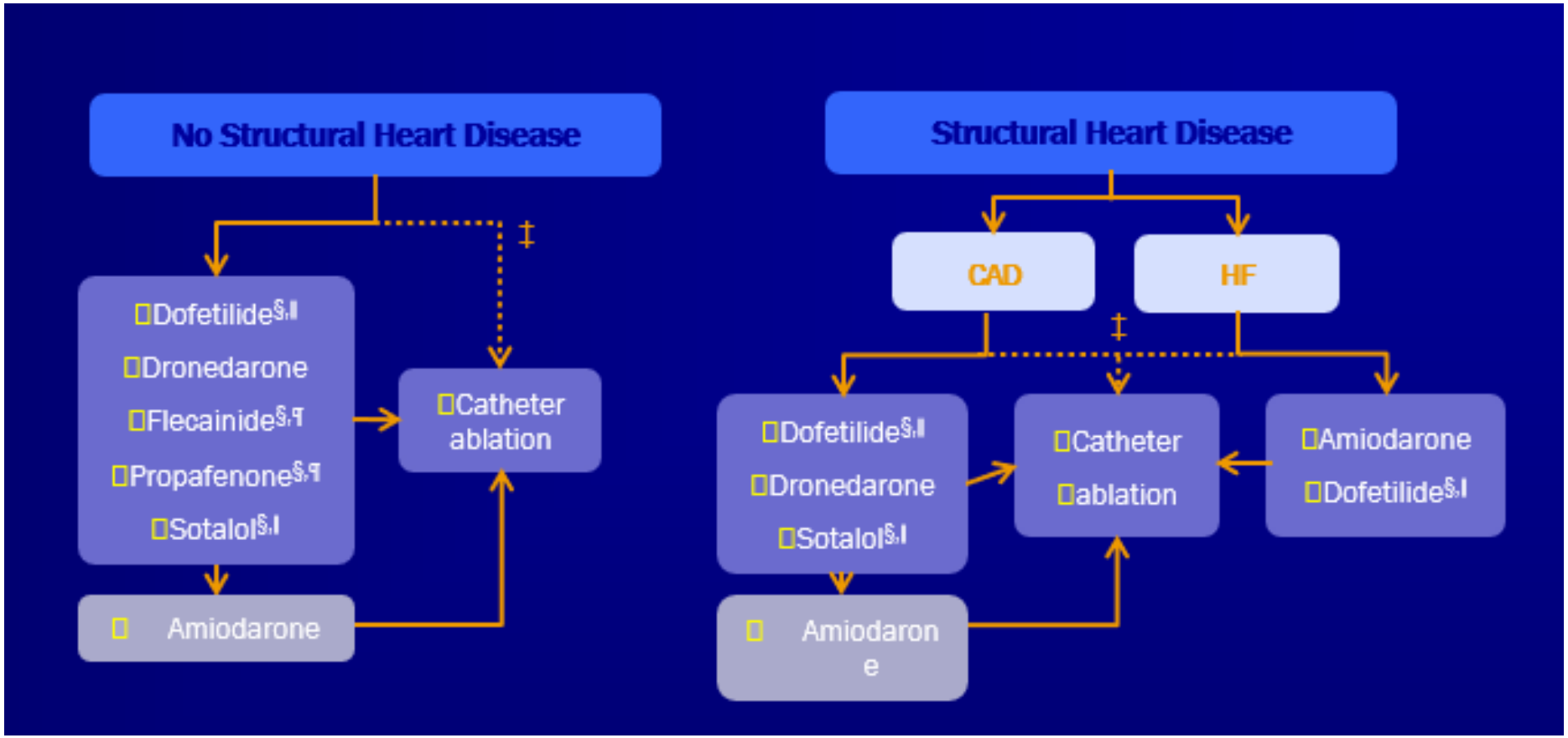
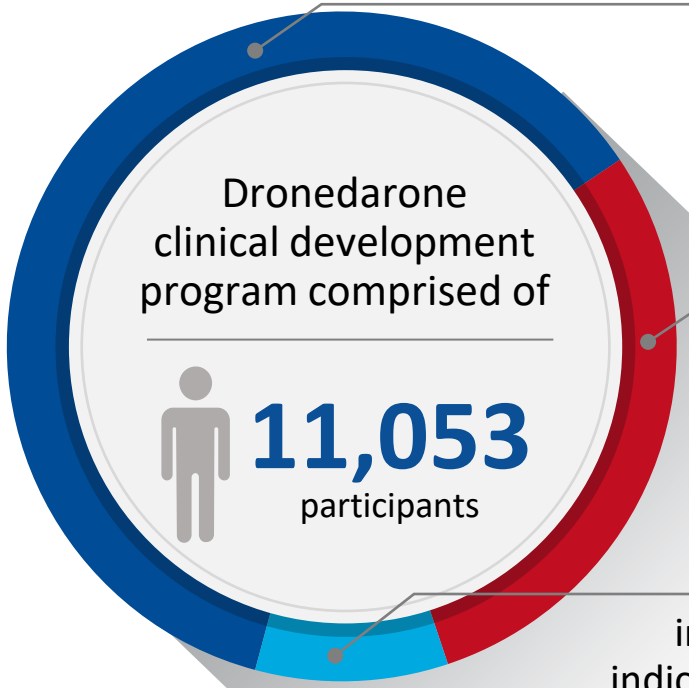
2014 AHA/ACC/HRS: Guidelines for Rhythm Control



AHA: American Heart Association; ACC: American College of Cardiology; HRS: Heart Rhythm Society; AF: atrial fibrillation; CAD: coronary artery disease; HF: heart failure.

January CT, et al. J Am Coll Cardiol. 2014;64:e1-e76.

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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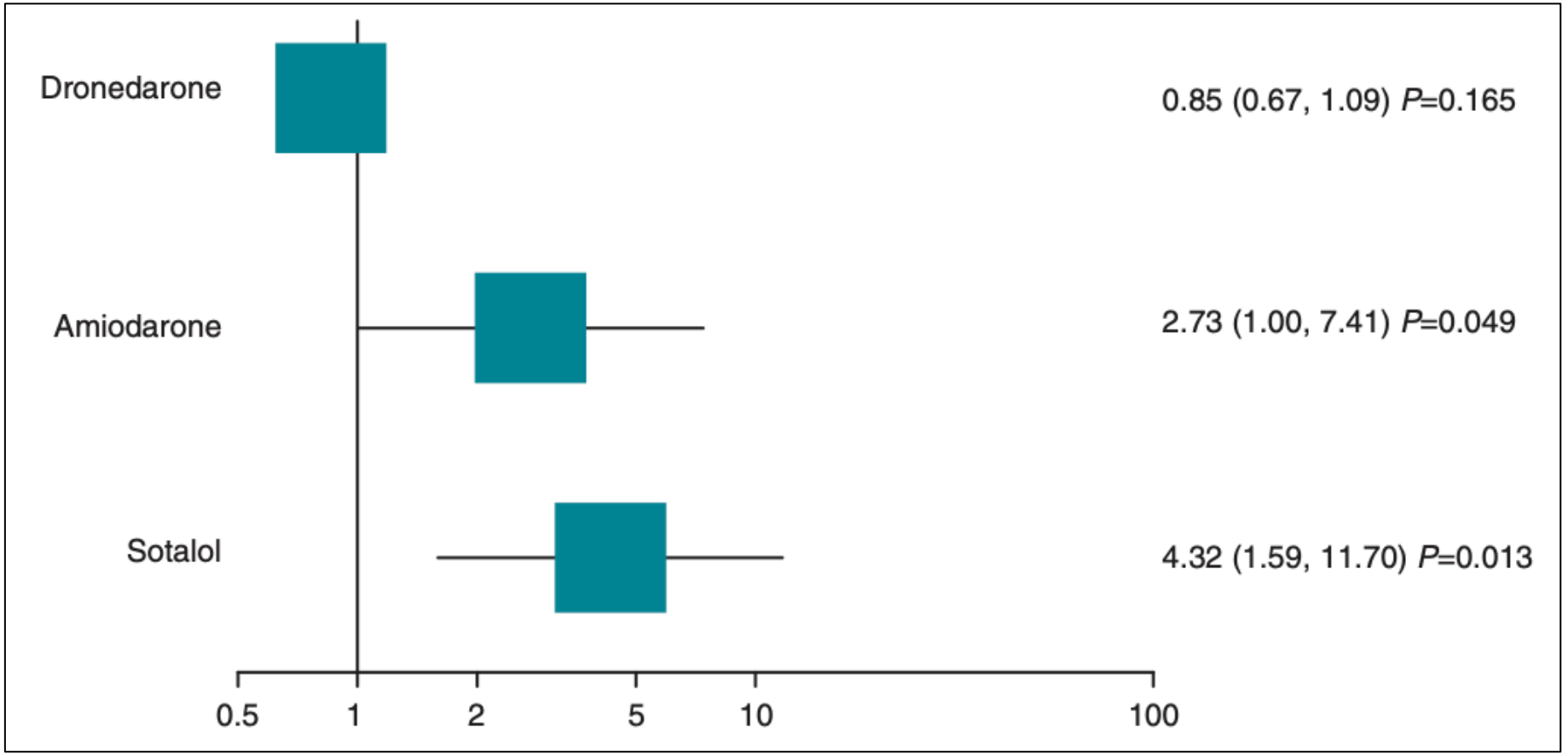
Effect on All-cause Mortality in Studies Involving >100 Patients



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

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

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Summarizing the Data

- Dronedarone reduces recurrent AF
- Dronedarone reduces CV hospitalization
- Association with decreased stroke
- No evidence of increased mortality

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Consent Conversation: A Patient's Perspective

"Why should I join CHANGE AFib?"

Sample Responses	Rationale
• ***'This study may help us develop a treatment strategy for patients like you with first detected AF'***	• There are no randomized clinical trials that address treatment strategy for patients with first-detected AF.
• ***'This is a safe and approved medication already used in other AFIB patient populations.'***	• Trial medication, Dronedarone, is a well-tolerated FDA-approved antiarrhythmic medication.
• ***'The earlier we can get your AF in control, the less likely you are to return to the hospital for emergent cardiac treatment.'***	• Prior studies have shown early introduction of rhythm control (within 1 year) is superior to usual care in improving cardiovascular outcomes.
• ***'There is evidence to suggest early initiation of dronedarone in patients like you may reduce hospitalizations and other heart problems, as well as improve quality of life.'***	• The trial hypothesis is that earlier administration of a well-tolerated antiarrhythmic drug proven to reduce hospitalization may result in improved cardiovascular outcomes and quality of life in patients first-detected AF.

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Consent Conversation: A Patient's Perspective

"What's in it for me?"

Sample Responses	Rationale
'Both groups will be receiving "usual care", meaning the current standard of care for patients with AF.'	Usual care will consist of AV nodal blocking agents for rate control and oral anticoagulation for stroke prevention.
'You have a 50/50 chance (like flipping a coin) of being in the dronedarone arm, which again, we think may improve your cardiovascular health.'	The trial uses a 1:1 randomization.
'Visits for the trial can be combined with your usual care visits and can take place either in-person or virtually.'	Follow-up visit windows are generous. The 6-month visit window is anywhere from 3-9 months and the 12-month visit window is ± 30 days. Trial visits can be conducted in-person OR virtually.
'Trial subjects will have a "second pair of eyes" from the research team engaged in their care.'	Considering trial subjects will receive more frequent oversight due to research requirements, trial subjects benefit from multiple care teams involved and committed to the management of a patient's care.

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Top FAQs

Does A Patient Have To Be Admitted To The Hospital to Be Eligible?

- No. Currently, a patient must have had an acute care encounter at the hospital for first-detected Atrial Fibrillation.
  "Acute Care Encounter" is defined as presenting to the hospital as:
  - An Inpatient Admission,
  - Evaluation/Treatment/Discharge from the Emergency Room or Observation Unit.

- **Stay tuned for Protocol V4.0 where we remove this Inclusion Criterion!**

Does A Subject's Acute Care Encounter Have To Be at MY Trial Site to Be Eligible?

- **NO.** Patients who have been seen for their acute care encounter at a facility other than your trial site are ELIGIBLE for enrollment.

- Previously, a patient's acute care encounter location needed to be at YOUR trial site. **This is NO longer required.**

- Under Protocol V4.0, while an acute care encounter will NOT be required, subjects may use this encounter as their baseline study visit.

- For example, if a CHANGE AFib eligible patient presents to your trial site but was seen at a different health care facility for their acute care encounter, that patient IS ELIGIBLE to be enrolled at your site for CHANGE AFib.

Can We Enroll Patients in the Outpatient Setting?

- **YES!** If you encounter a patient who meets eligibility criteria and has been diagnosed with first-detected AFib in the past 120 days, they can be enrolled & randomized from the outpatient setting.

- Keep in mind the following when enrolling outpatients:
  - As defined in the protocol, patients must have a new diagnosis within 120 days of randomization.
  - If a patient is randomized to the intervention (dronedarone) arm they must be contacted within 10 days of the randomization to confirm start of dronedarone prescription.
  - Their baseline case report form needs to be filled out completely with information from their index encounter.

Do Patients Need to have Paroxysmal AFIB?

Are patients with persistent AFib excluded?

- Patients with both paroxysmal and persistent AFib are eligible for participation.

- Based on the inclusion criteria, it is expected that most of the cohort will be patients with paroxysmal AFib.

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Do Patients Need to be Symptomatic to be Enrolled?

- There is no requirement as it relates to symptoms.

- Eligible patients are those with first-detected AFib
  - Diagnosis made within previous 120 days
  - No prior hospitalization for AFib

What is Considered ‘Usual Care’?

- 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.
- More specifically, oral anticoagulation in those with a CHA2DS-2VASc ≥ 2 in men or ≥3 in women, rate control, and treatment of concomitant cardiovascular conditions (e.g., CAD or HF).

How Should Patients with a Contingency Plan for Ablation be Handled?

- Patients with **planned ablation at the time of enrollment, or those patients where ablation is highly anticipated are NOT candidates** for CHANGE AFib.

- Recurrent AFib requiring escalation of rhythm control (including ablation) is
  - expected
  - not counted as an unplanned cardiovascular hospitalization event

- Patients may continue dronedarone after AFib ablation

At What Point is a Cardioversion Allowed After Randomization?

- A cardioversion is allowed at any time during the conduct of the trial (in either arm).

What is the Timeframe for the Bradycardia, PR Interval, & Corrected QT Interval Exclusions?

What if a patient has a single instance of bradycardia?

- Providers should evaluate the patient's most recent ECG(s), likely from the acute care encounter visit.

- For a single episode of bradycardia, the PI's judgment can be used.
  - If there is a transient bradycardia that was reversible, then that would not necessarily exclude participation.

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ECG: electrocardiogram; PI: Principal Investigator

What is Considered ‘Prior Antiarrhythmic Drug Therapy’?

How Does This Relate to Exclusion Criteria #1?

- Antiarrhythmic drug therapy means chronic outpatient therapy (>7 days)

- One time dosing of an antiarrhythmic drug or pharmacologic cardioversion are not considered “prior AAD therapy”

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Questions from the Group?

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/ Contact

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Thank You