MULTAQ® (dronedarone)

FDA Cardiovascular and Renal Drugs Division Advisory Committee Meeting

March 18, 2009

sanofi-aventis

Introduction

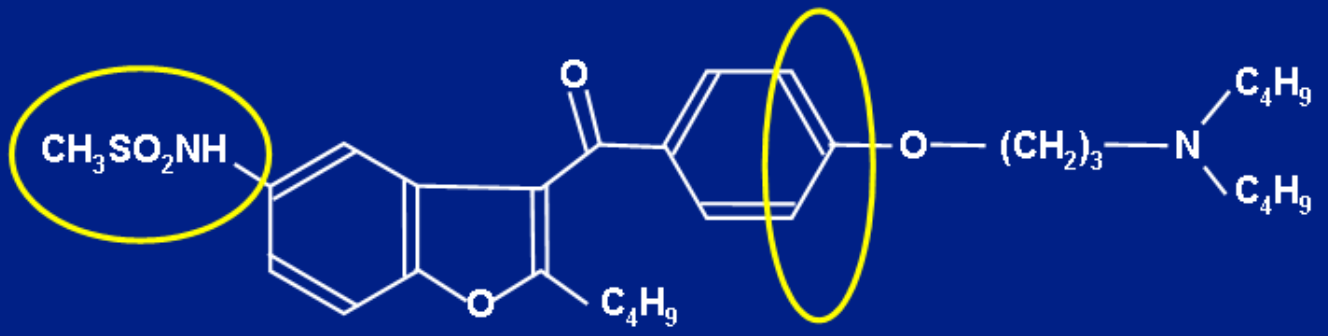
Richard Gural, PhD
sanofi-aventis

Medical Need

- Atrial fibrillation is a complex and common form of cardiac arrhythmia in the United States population
- Current treatment options treat symptoms but do not address the risk of morbidity/mortality and cardiovascular hospitalization
- There is an unmet medical need for drugs that improve morbidity-mortality beyond reducing recurrences of atrial fibrillation

Characteristics of Dronedarone

- Multi-channel blocker
- Class I-IV Vaughan-Williams properties
- Dronedarone is an amiodarone analog
- Iodine removed in order to improve thyroid safety
- Methylsulfonamide group added to reduce lipophilicity



Dronedarone (MW=593)

Pharmacokinetics of Dronedarone

- Absorption
  - Well absorbed
  - ~ 15% bioavailability following extensive first pass metabolism
  - Significant food effect: 2-3x AUC drug to be administered with meal
- Elimination
  - Extensively metabolized predominantly through CYP3A4
  - Minimal renal excretion
  - Half-life ~ 30 h
- Intrinsic factors affecting exposure
  - Age
  - Body Weight
  - Gender
- Extrinsic factors affecting exposure
  - Inhibitors and inducers of CYP3A4

Phase 2/3 Clinical Development Program

Rhythm and Rate Control	N	Population	Objectives
DAFNE	270	AF	Efficacy and safety in AF cardioversion and maintenance of sinus rhythm
EURIDIS	612	AF/AFL	Maintenance of sinus rhythm in AF/AFL
ADONIS	625	AF/AFL	Maintenance of sinus rhythm in AF/AFL
ERATO	174	Permanent AF	Ventricular rate control
DIONYSOS	504	AF	Reduction of recurrence of AF or premature study drug discontinuation for intolerance or lack of efficacy
Special Populations			
ANDROMEDA	627	Recent severe episode CHF and LV dysfunction	Reduction of hospitalization for worsening heart failure or death in patients with unstable severe CHF with LVD
Clinical Outcomes			
ATHENA	4628	AF/AFL	Reduction of cardiovascular hospitalization or death from any cause in patients with AF/AFL

DAFNE: Dose Selection for Future Studies

- Dronedarone 400 mg BID was lowest dose associated with significant changes on ECG in normal volunteers
- Doses of 400, 600 or 800 mg BID were studied in patients with AF/AFL
- Dronedarone 400 mg BID was associated with significant reduction in risk of recurrent atrial fibrillation
- Doses of dronedarone 600 mg BID and 800 mg BID were poorly tolerated

Regulatory History

- NDA filed June 10, 2005 included
  - Benefit based on studies of maintenance of sinus rhythm & ventricular rate control
  - DAFNE, EURIDIS, ADONIS, ERATO, and ANDROMEDA
- NDA not approvable, August 29, 2006
  - 400 mg dose BID "delayed the time to the first recurrence of arrhythmia and also decreased symptomatic recurrence"
  - Unfavorable benefit/risk "largely because of adverse outcomes in ANDROMEDA"
- New NDA filed July 31, 2008
  - Included previous data and ATHENA results
  - Priority review granted
- DIONYSOS filed February 2009
  - Not reviewed by FDA

Indication Under Discussion

Multaq® is indicated in patients with either a recent history of or current non-permanent atrial fibrillation or flutter with associated risk factors. Multaq® has been shown to decrease the combined risk of cardiovascular hospitalization or death.

Appropriate and Inappropriate Patient

- **Appropriate patients**
  - Patients with recent history of or current non-permanent atrial fibrillation or flutter with associated risk factors
- **Inappropriate patients**
  - Patients with symptoms of heart failure at rest or with minimal exertion within the last month or
  - Patients hospitalized for heart failure within the last month

Presentation Outline

Introduction	**Richard Gural, PhD** **sanofi-aventis**
Unmet Medical Need in AF/AFL Dronedarone Rate and Rhythm Studies	**Gerald Naccarelli, MD** **Hershey Medical Center**
Effect of Dronedarone on Major Cardiovascular Events: The ANDROMEDA and ATHENA Trials	**Milton Packer, MD** **UT Southwestern Medical Center at Dallas**
Safety of Dronedarone in Atrial Fibrillation/Flutter Trials	**Paul Chew, MD** **sanofi-aventis**
Benefit Risk of Dronedarone for Treatment of Atrial Fibrillation	**John Camm, BSc, MD, FRCP** **St. George's, University of London**

External Experts

Tomas Berl, MD	University of Colorado Denver Division of Renal Diseases and Hypertension
Irwin Klein, MD	Long Island Jewish Medical Associates
James H. Lewis, MD	Georgetown University Medical Center
Samuel Cohen, MD, PhD	University of Nebraska Department of Pathology and Microbiology

Internal Experts

Christophe Gaudin, MD	Cardiovascular Clinical Development
John Newton, PhD	Metabolism and Pharmacokinetics
Steve O'Connor, PhD	Cardiovascular Research
David Radzik, MD	Cardiovascular Clinical Development
Martin Roessner, MS	Biostatistics
Nigel Roome, PhD	Drug Safety Evaluation
Linda Scarazzini, MD	Drug Safety and Risk Management

Unmet Medical Need in AF/AFL Dronedarone Rate and Rhythm Studies

Gerald V. Naccarelli, MD
Penn State University College of Medicine
The Milton S. Hershey Medical Center

Atrial Fibrillation / Flutter Is Associated with Increased Morbidity and Mortality

- **Death: 2-fold ↑ in risk**
- **Cardiovascular hospitalization: 2 to 3-fold ↑ in risk**
- **Thromboembolism / stroke: 4.5-fold ↑ in risk**
- **Tachycardia-induced worsening of associated myocardial ischemia or heart failure**
- **Adverse atrial and ventricular remodeling due to tachycardia-induced cardiomyopathy**

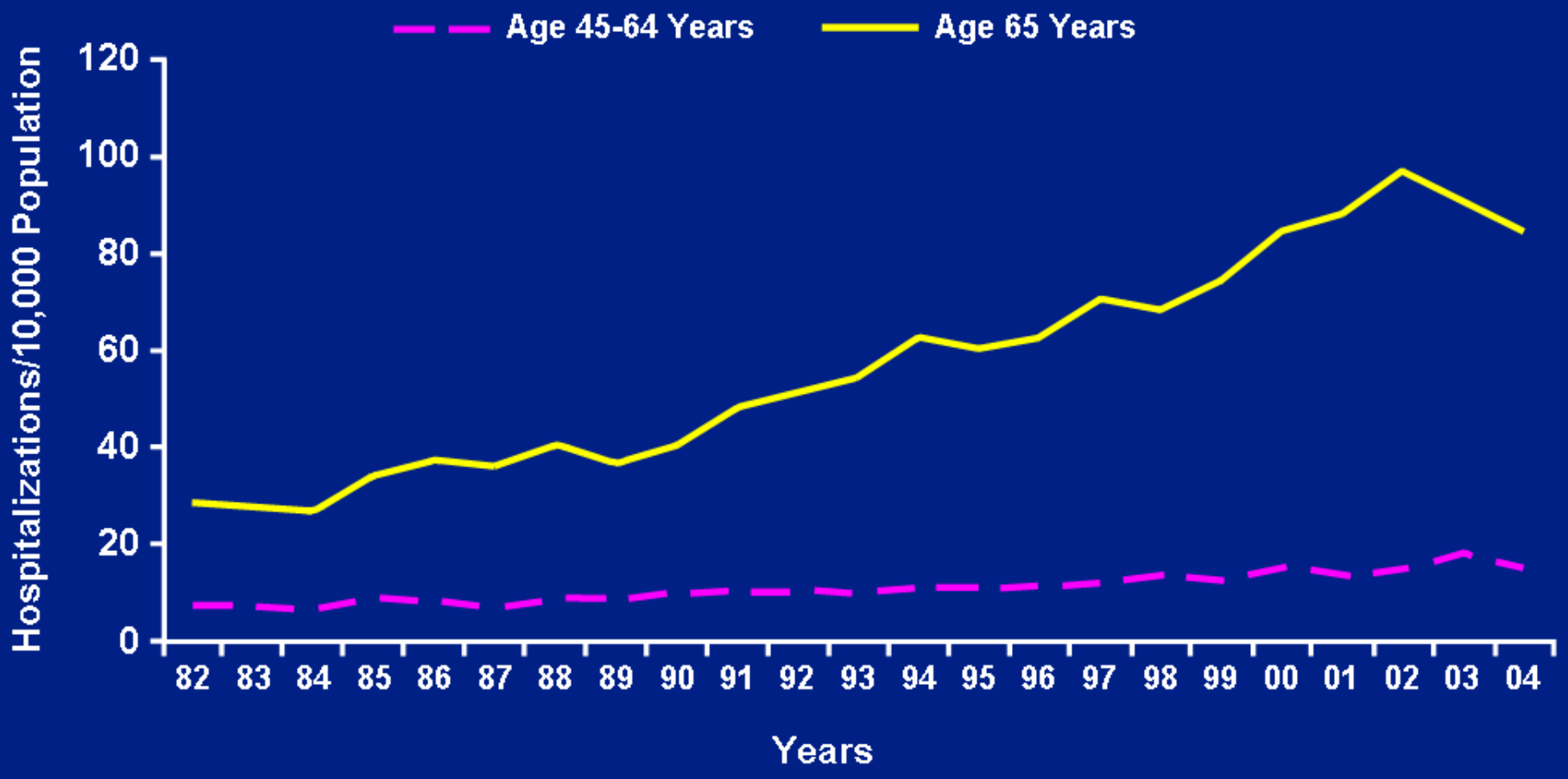
Krahn AD, et al al. *Am J Med.* 1995;98:476-484
Benjamin EJ, et al. *Circulation.* 1998;98:946-952.

Clinical Consequences of Atrial Fibrillation/Flutter

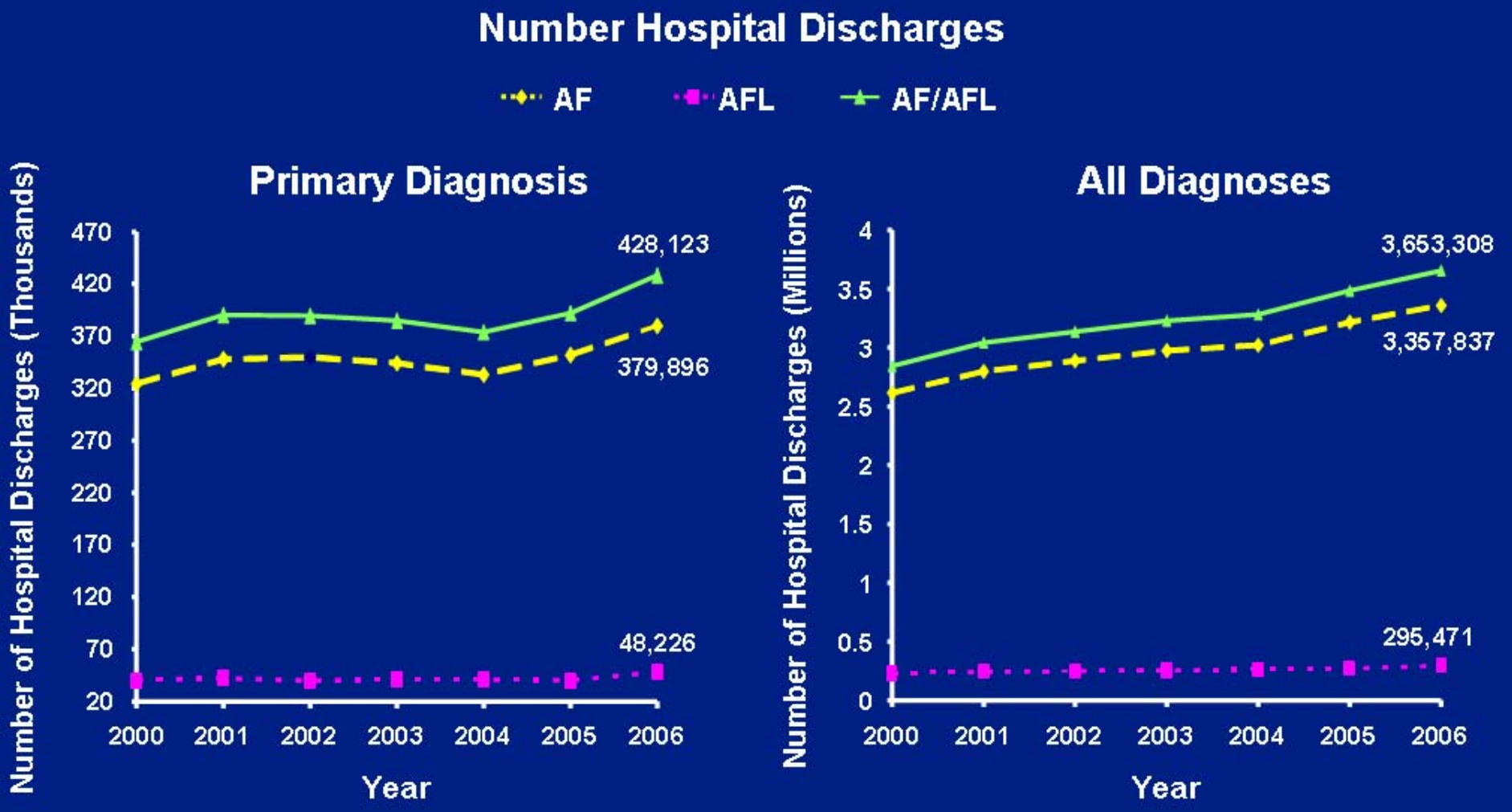
- **Recurrence and/or persistence of arrhythmia in patients with AF/AFL is associated with:**
  - Impaired quality of life secondary to recurrent symptoms and reduced exercise tolerance
  - Increased risk of cardiovascular death and cardiovascular hospitalization
    - Due to AF/AFL and its effect on cardiocirculatory function
    - Due to cardiovascular conditions commonly associated with AF/AFL

Krahn AD, et al al. *Am J Med.* 1995;98:476-484
Benjamin EJ, et al. *Circulation.* 1998;98:946-952.

Hospitalization Rates for Atrial Fibrillation: 1982 to 2004



USA Hospital Discharge, 2000-2006: AF, AFL, & AF/AFL Combined

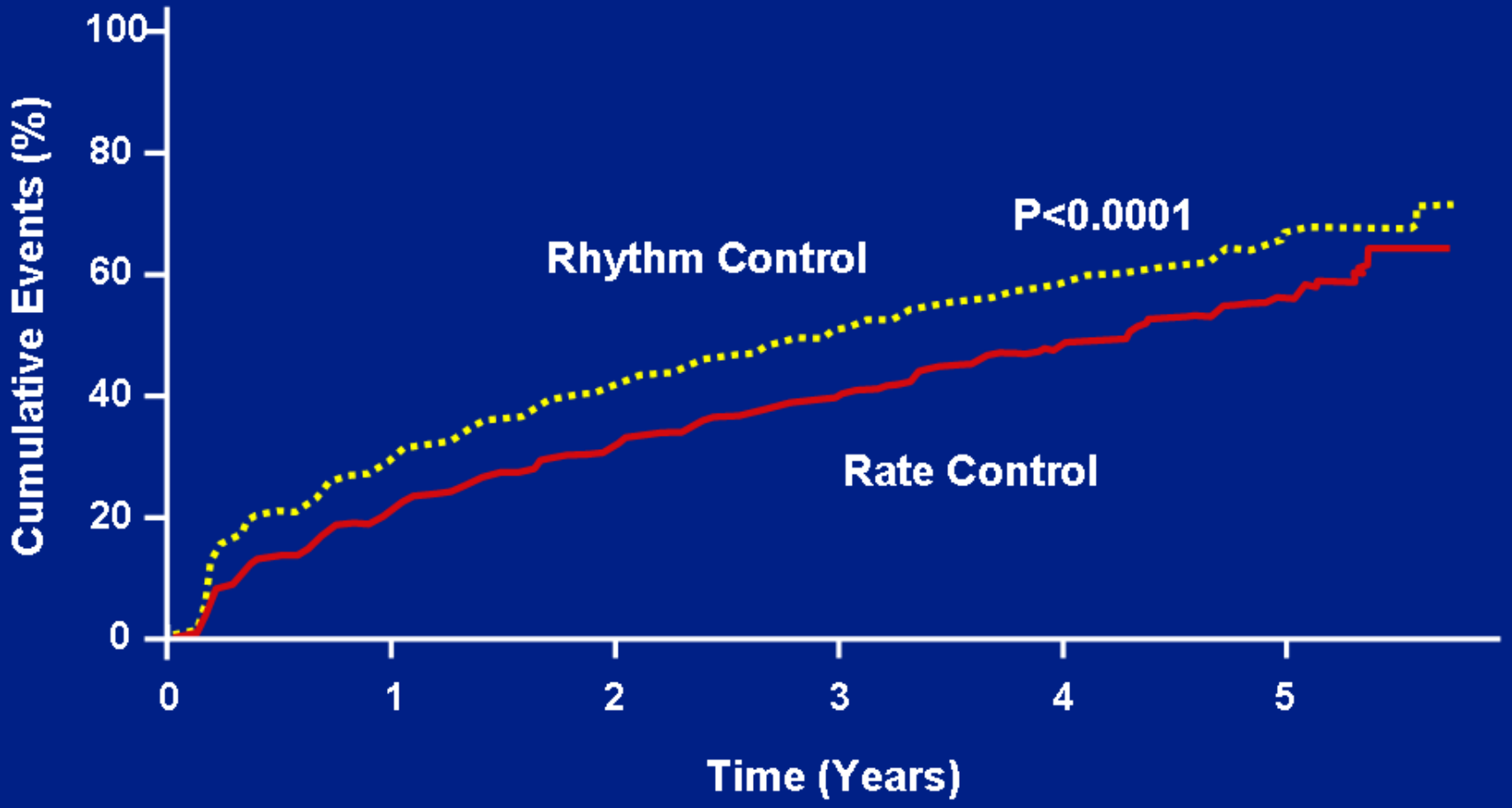


Source: AHRQ, Health Care Cost Utilization (HCUP) Survey & US Census, 2000-2006

Long-Term Effects of AF Drugs in Patients with Non-permanent AF Have Not Been Defined

- **Development of drugs for the treatment of patients with atrial fibrillation or flutter have focused their attention on recurrence of the arrhythmia**
- **Drug development programs have focused on mortality in high-risk non-AF patients to exclude possibility of proarrhythmic effect**
- **Endpoints such as time to first recurrence of atrial fibrillation ignored the possible effects of treatment on morbidity and mortality**

AFFIRM: Control of Atrial Fibrillation May Not Reduce Risk of Death or CV Hospitalization



Modified: Wyse DG, et al. Heart Rhythm2004;1:531-537

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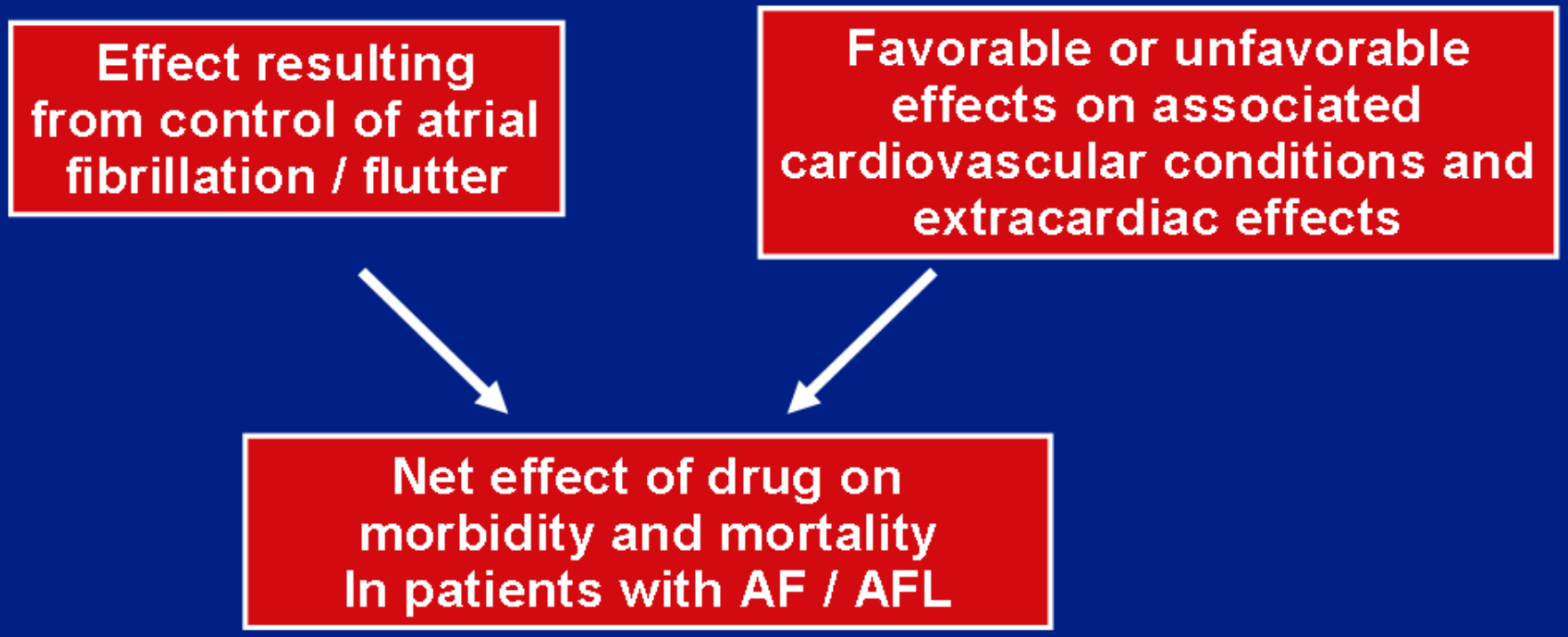
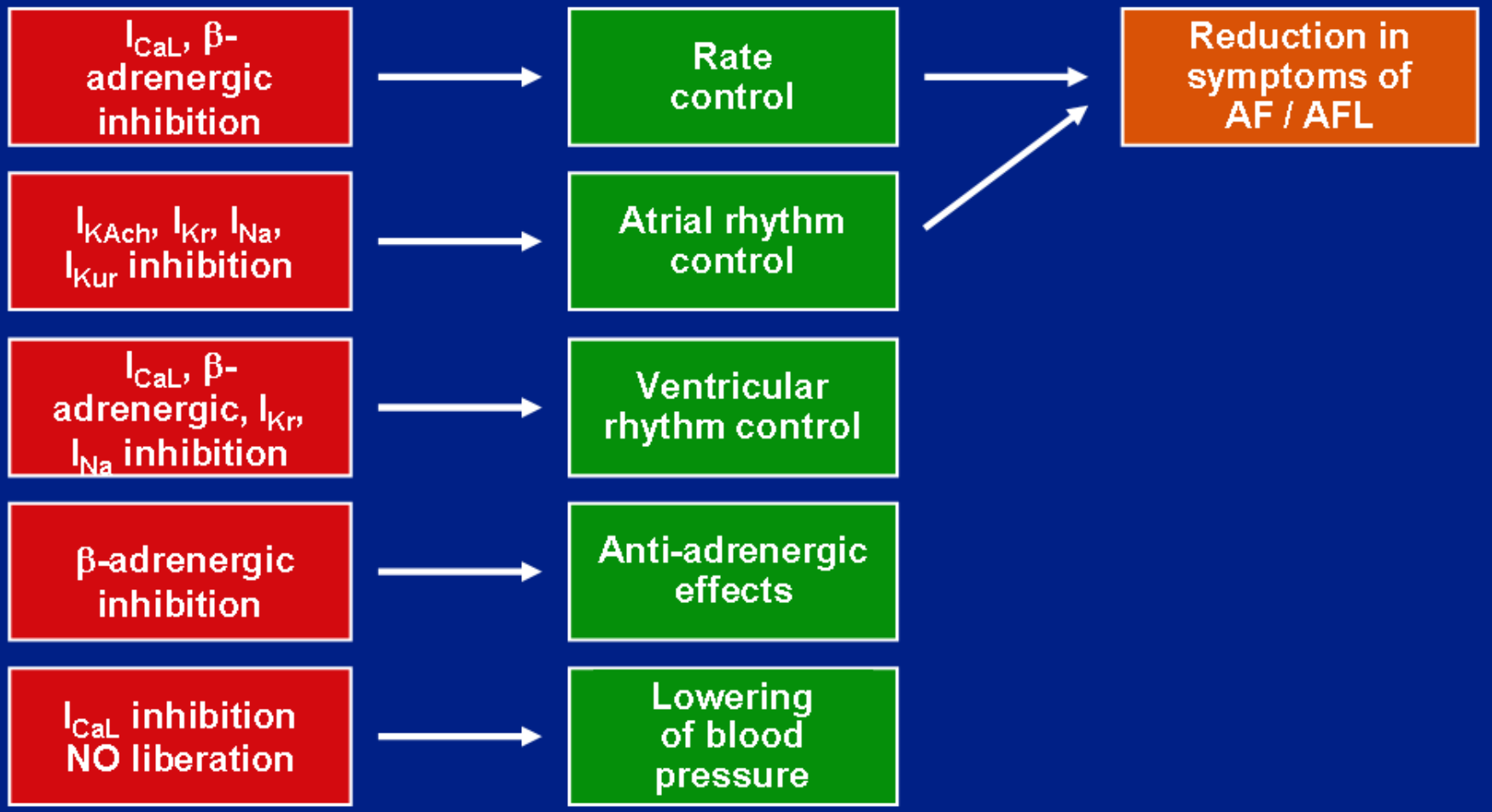
Current Treatments for AF/AFL Patients Have Not Been Shown to Reduce Risk of Death or Hospitalization

Rate Control	Rhythm Control	Prevention of Stroke	Reduced Death or Cardiovascular Hospitalization
Pharmacologic • Ca^{2+} blockers • β-blockers • Digitalis Non-pharmacologic • Ablate & pace	Pharmacologic ▪ Class IA ▪ Class IC ▪ Class III Non-Pharmacologic ▪ Cath ablation ▪ Pacing ▪ Surgery (MAZE, PV Isolation) ▪ Implantable atrial defibrillator	Pharmacologic • Warfarin • Thrombin Inhibitor • Aspirin Nonpharmacologic • Removal/isolation LA appendage	????

How Treatments Given to Patients with AF/AFL Can Affect Morbidity and Mortality



Potential Ways in which Dronedarone Could Influence Morbidity and Mortality



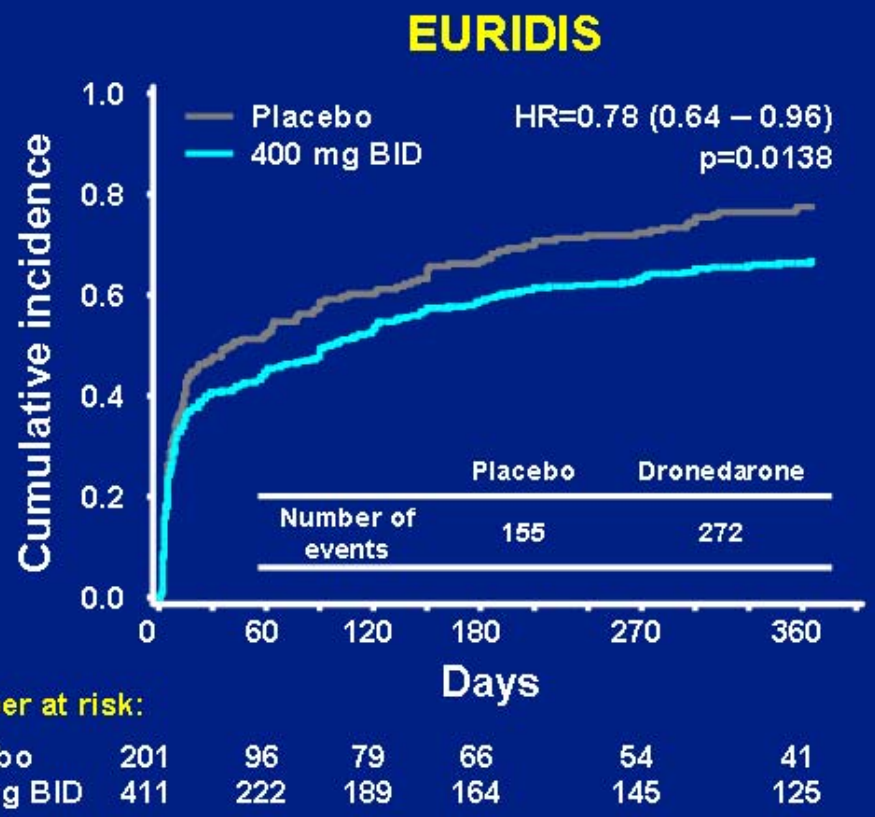
Trials to Evaluate Efficacy of Dronedarone in Prevention of Recurrence of AF/AFL

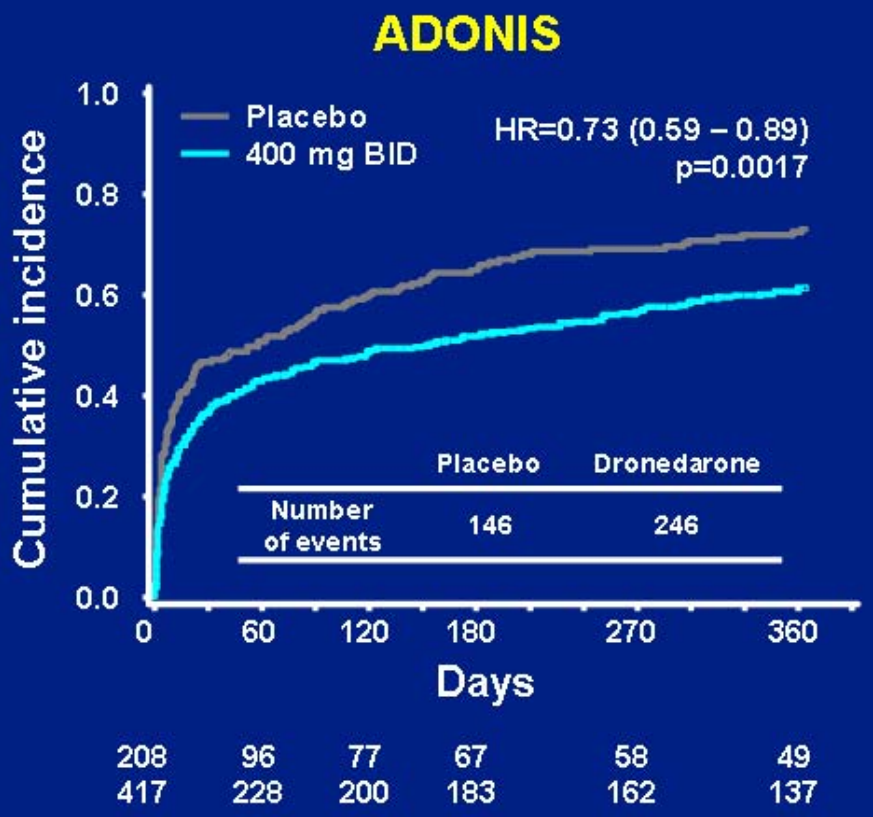
Four trials assessed the efficacy of dronedarone to maintain sinus rhythm in patients with non-permanent atrial fibrillation or flutter

	Control	Dronedarone	Target Patients
DAFNE	Placebo (n=66)	400mg BID (n=76) 600mg BID (n=66) 800mg BID (n=61)	AF/AFL to be cardioverted
EURIDIS	Placebo (n=201)	400mg BID (n=411)	AF/AFL within 3 mo; SR at randomization
ADONIS	Placebo (n=208)	400mg BID (n=417)	
DIONYSOS	Amiodarone (n=255)	400mg BID (n=249)	AF/AFL to be cardioverted

Touboul P, et al. Eur Heart J 2003;24:1481-1487
Singh BN, et al. N Engl J Med 2008;358:2678-2687

EURIDIS and ADONIS Primary Endpoint: First Recurrence of AF/AFL

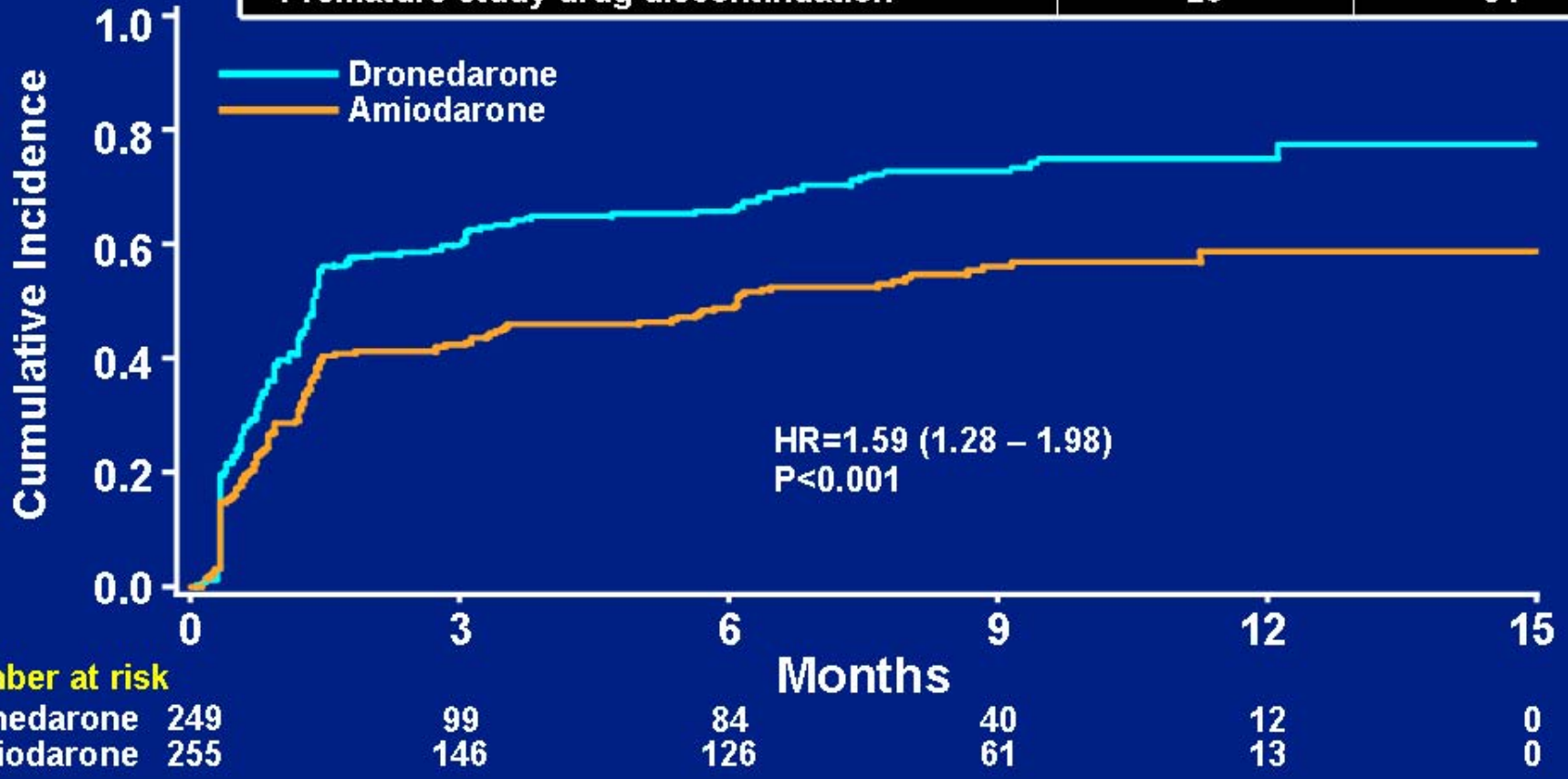




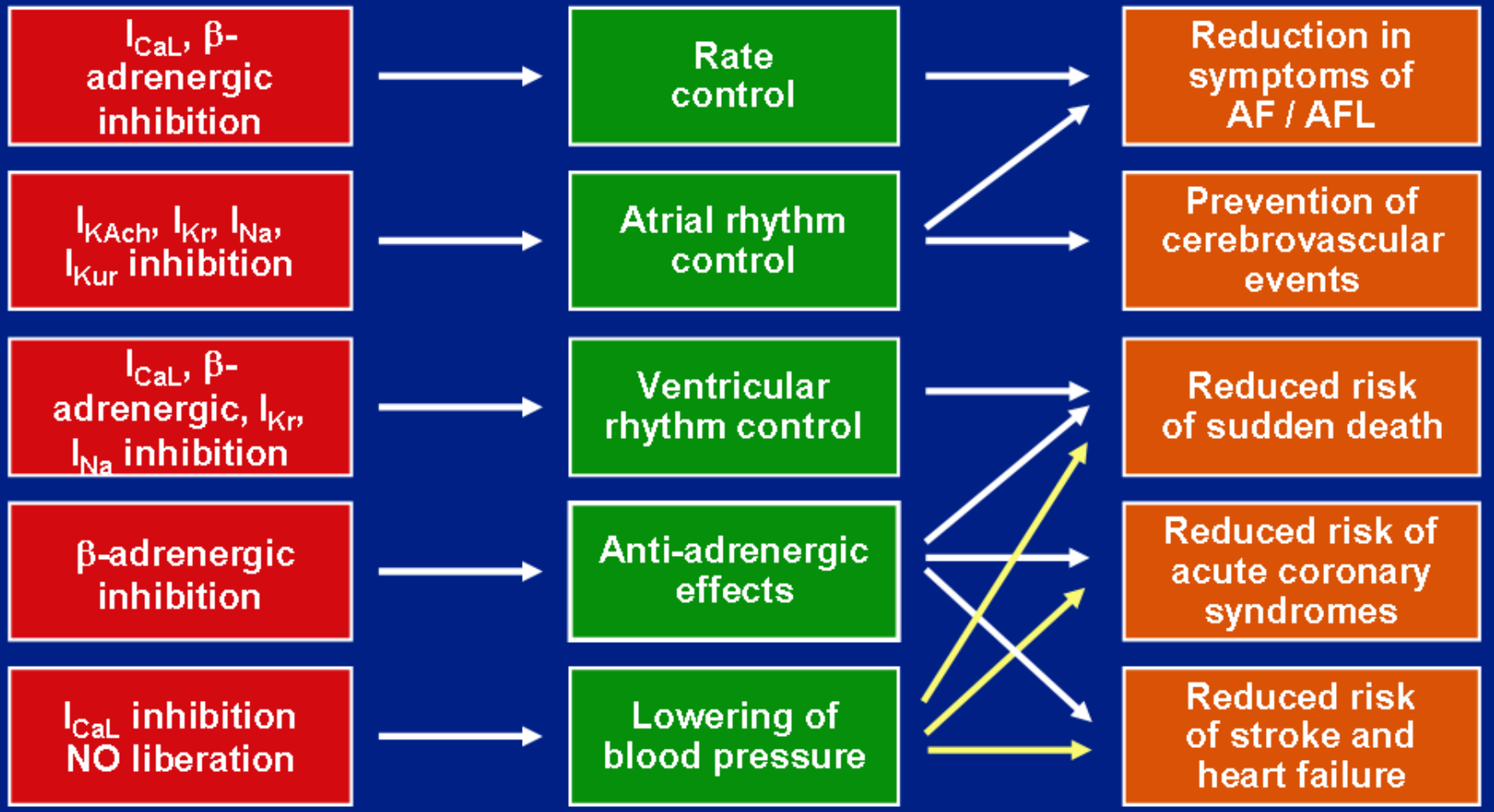
Singh BN, et al. N Engl J Med 2008;358:2678-2687

DIONYSOS Primary Endpoint: AF Recurrence or Premature Study Drug Discontinuation

	Dronedarone	Amiodarone
AF recurrence or premature discontinuation	184	141
Recurrence of AF	158	107
Premature study drug discontinuation	26	34

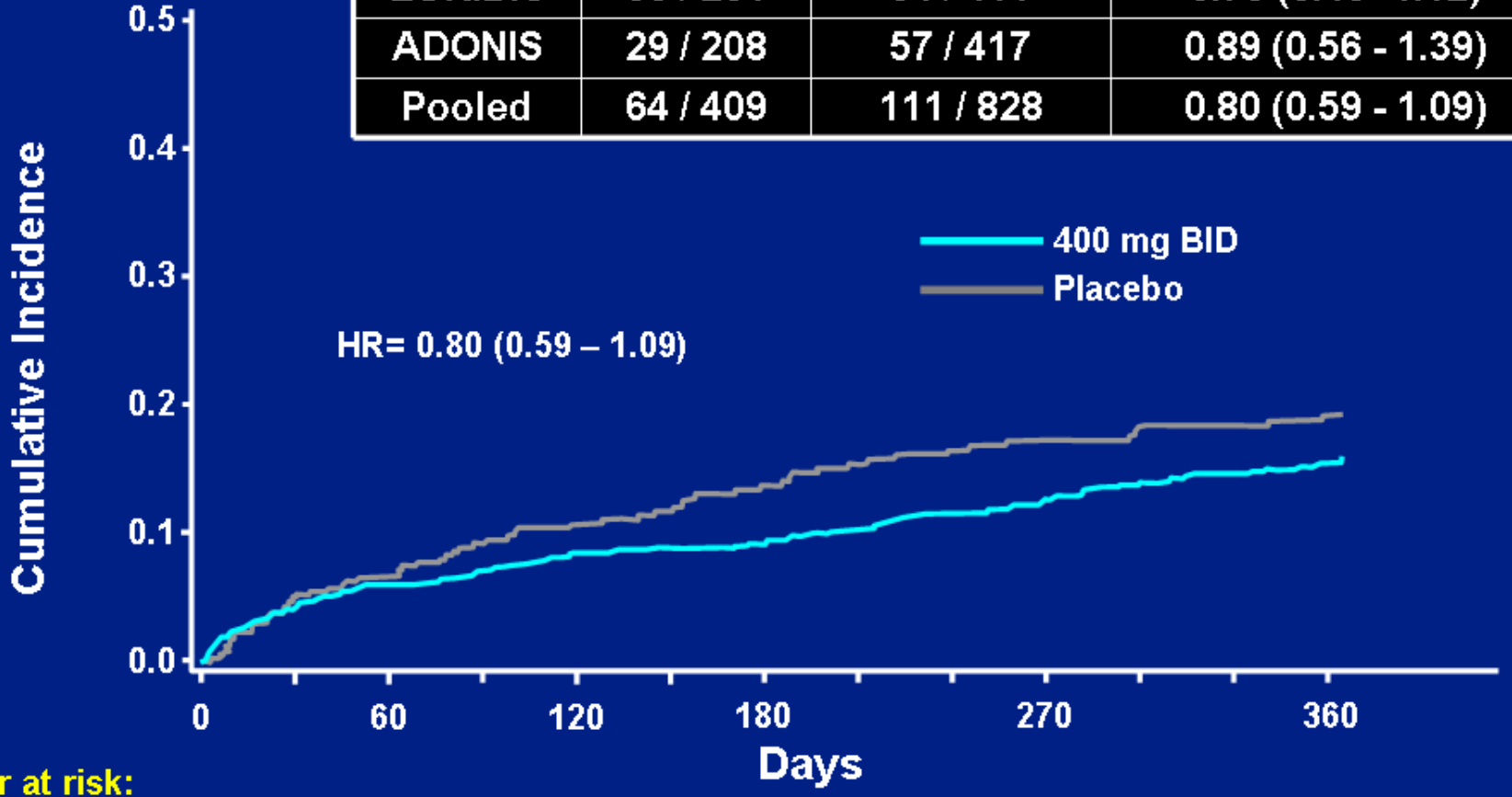


Potential Ways in which Dronedarone Could Influence Morbidity and Mortality



EURIDIS / ADONIS: Effect on Death or CV Hospitalization (Post-Hoc Analysis)

Trial	Placebo	Dronedarone	Relative risk (95% CI)
EURIDIS	35 / 201	54 / 411	0.73 (0.48 -1.12)
ADONIS	29 / 208	57 / 417	0.89 (0.56 - 1.39)
Pooled	64 / 409	111 / 828	0.80 (0.59 - 1.09)



Number at risk:

Placebo	409	328	285	58	224	200
400 mg BID	828	687	619	83	522	470

Singh BN, et al. N Engl J Med 2008;358:2678-2687

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Summary and Conclusions

- Patients with AF/AFL have an increased risk of death and CV hospitalization
- Current antiarrhythmic drugs for suppression of AF/AFL have not demonstrated reduction in the risk of death and CV hospitalization
- Randomized placebo-controlled clinical trials have shown that dronedarone prevents the recurrence of AF/AFL
- Dronedarone has properties that can be expected to reduce the risk of death and CV hospitalization; a reduction in such risk was observed in post-hoc analyses of EURIDIS and ADONIS

Effect of Dronedarone on Major Cardiovascular Events: The ANDROMEDA and ATHENA Trials

Milton Packer, MD
University of Texas Southwestern Medical Center at Dallas

History of Dronedarone Development

Prevention of Recurrence of Atrial Fibrillation or Flutter

EURIDIS

ADONIS

DIONYSOS

What is the long-term effect of treatment on the risk of major cardiovascular events?

Key FDA Questions About Dronedarone to be Addressed in This Presentation

- What effect on morbidity / mortality could have been anticipated before ANDROMEDA and ATHENA?
- What were the findings of the ANDROMEDA trial and how can these findings be explained?
- What were the findings of the ATHENA trial and were they consist with earlier studies?

- Did implementation or modification of the protocol have a meaningful effect on the results of the ATHENA trial?
- Was the effect on CV hospitalization in ATHENA due entirely to a reduction in hospitalizations for atrial fibrillation?
- Did dronedarone reduce the risk of CV death in the ATHENA?

- How do we reconcile results of ATHENA and ANDROMEDA with respect to use in LVEF < 0.35 or class III patients?

Effect of Amiodarone on Morbidity and Mortality in Large-Scale Trials

Trial	Patients Enrolled	Effect on CV events
CAMIAT (Lancet 1997)	Post-myocardial infarction; ↑ VPCs	No effect on total mortality; ↓ sudden death (if CHF)
EMIAT (Lancet 1997)	Post-myocardial infarction, EF< 0.40	No effect on total mortality ↓ risk of sudden death;
SCD-HeFT (NEJM 2005)	Heart failure, EF< 0.35 (30% class III)	No effect on total mortality or on hospitalizations
CHF-STAT (NEJM 1995)	Heart failure, EF< 0.40 (43% class III-IV)	No effect on total mortality; ↓ risk of CHF death; ↑ LVEF
AF-CHF (NEJM 2008)	Heart failure, EF≤ 0.35 (32% class III-IV)	No effect on total mortality or cardiovascular mortality
GESICA (Lancet 1994)	Heart failure (80% class III-IV)	↓ Risk of total mortality; ↓ risk of CHF hospitalization

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GESICA (Lancet 1994)	Heart failure (80% class III-IV)	↓ Risk of total mortality; ↓ risk of CHF hospitalization

Because it is *not* associated with an increased risk of death, amiodarone is currently regarded as the first choice antiarrhythmic drug in the management of nonpermanent atrial fibrillation in patients with heart failure, especially in those with class III-IV symptoms — even though it is not FDA-approved for this indication.

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GESICA (Lancet 1994)	Heart failure (80% class III-IV)	↓ Risk of total mortality;

Required to be clinically stable

Enrolled outpatients

Excluded recent decompensation

Required to be clinically stable

Could Dronedarone Exert Favorable Effects on CV Events Not Seen With Amiodarone?

Effect on Diastolic Blood Pressure (mm Hg)

	Placebo	Dronedarone
EURIDIS	+ 1.5 ± 10.8	– 2.1 ± 11.1
ADONIS	+ 1.5 ± 14.9	– 1.0 ± 17.5
ATHENA	– 1.1 ± 10.9	– 3.4 ± 10.5

	Amiodarone	Dronedarone
DIONYSOS	+ 1.1 ± 13.5	– 2.1 ± 12.0

Amiodarone has not altered blood pressure in trials vs placebo

Shown are changes (mean ± SD) from baseline (mm Hg) after 2-4 weeks of treatment; these changes are representative of those seen throughout these trials.

EURIDIS / ADONIS: Effect of Dronedarone on Death or Cardiovascular Hospitalization

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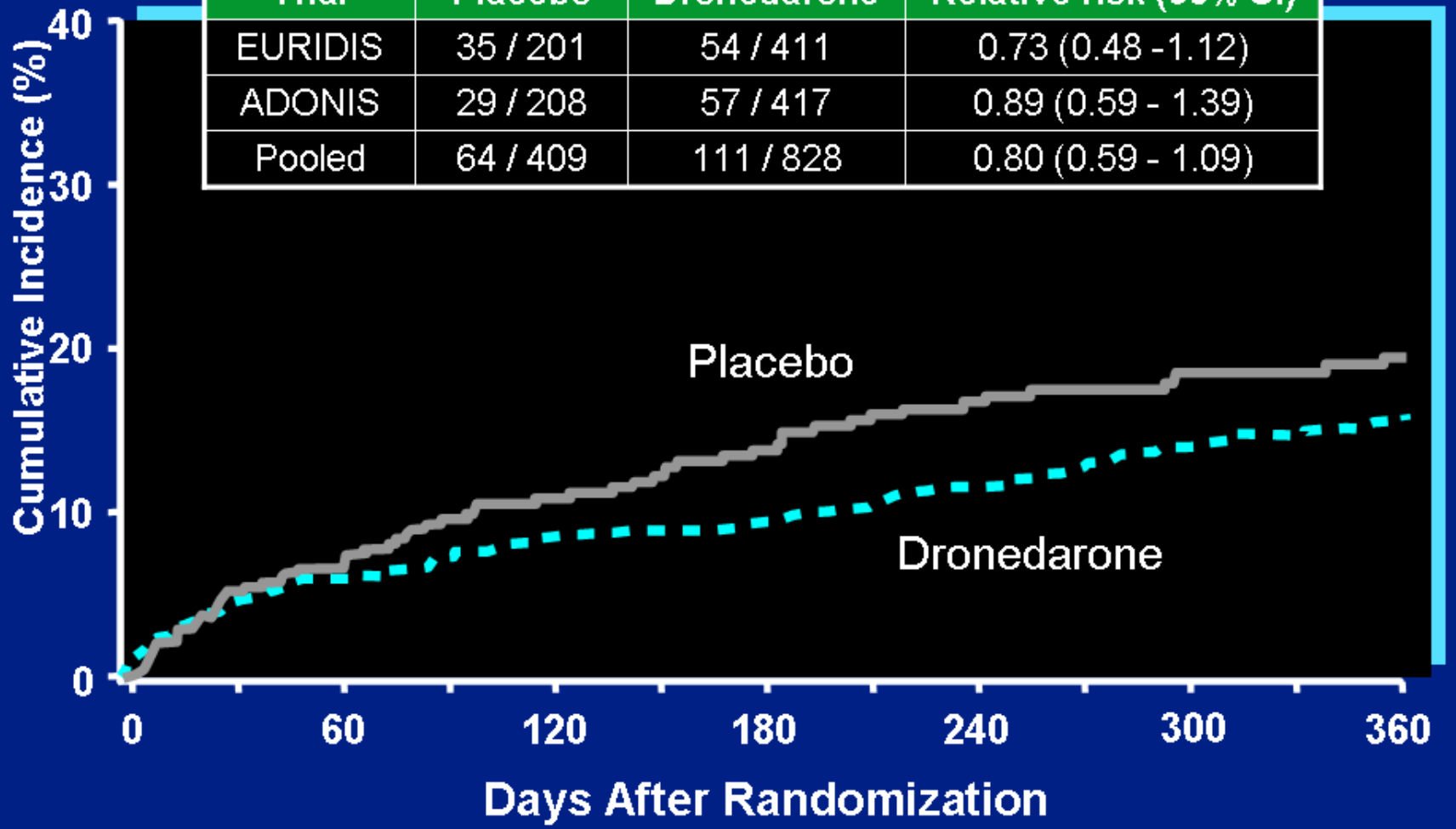


Analysis does not include cerebrovascular events.
If such events are included, RR is 0.74 (0.55-0.99)

ANDROMEDA: Background

Prevention of Recurrence of Atrial Fibrillation or Flutter

EURIDIS

ADONIS

DIONYSOS

Effect on Major Events in High Risk Patients

ANDROMEDA

Patients hospitalized for decompensated heart failure

ANDROMEDA: Target Patient Population

- ANDROMEDA focused on patients who had highest possible risk of major cardiovascular event.
- Patients hospitalized for decompensated heart failure have not generally been enrolled in survival trials designed to evaluate the safety of antiarrhythmic drugs. Previous trials have largely focused on stable post-infarction patients or patients with stable heart failure.
- Patients were to be enrolled whether or not they had a history of atrial fibrillation or flutter; AF (if present) may have been long-standing or recent onset.

ANDROMEDA: Entry Criteria

Key Inclusion Criteria

- Hospitalized for worsening heart failure at randomization
- Dyspnea or fatigue at rest or on slight exertion within month
- NYHA class II-IV symptoms requiring diuretic
- Echocardiographic wall motion index ≤ 1.2 ($\approx$ LVEF ≤ 0.35)

Key Exclusion Criteria

- Pulmonary edema within 12 hr; cardiogenic shock requiring IV pressors or mechanical ventilation; recent acute MI
- QTc > 500 ms; serum $K^+ < 3.5$ mmol/L; history of TdP
- Heart rate < 50 bpm; PR > 0.280 sec; sinus pause $\geq$ 3 sec; 2º or 3º AV block unless paced
- Use of class I or III anti-arrhythmic drugs; drugs known to cause TdP; or potent CYP3A4 inhibitors

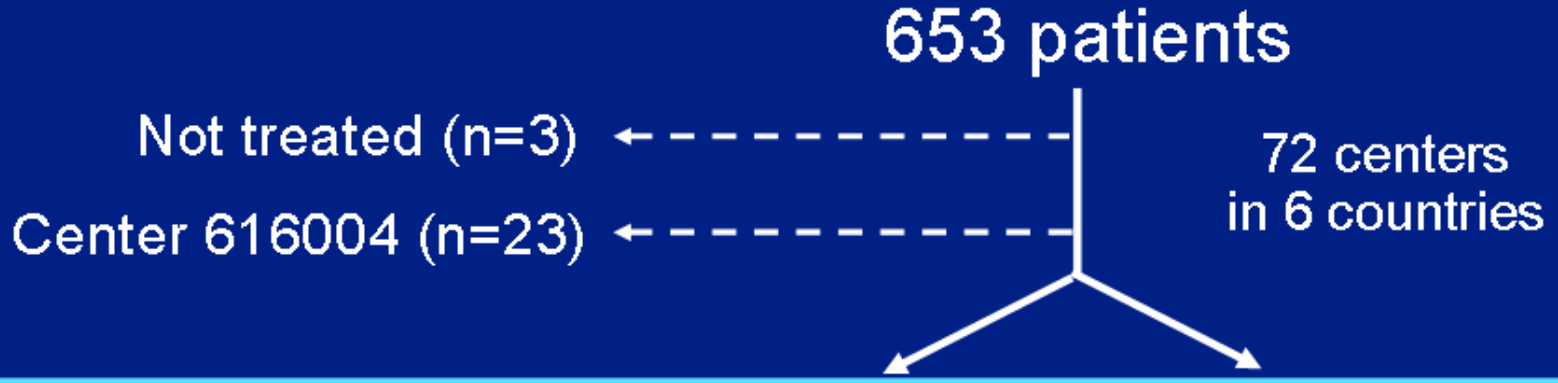
ANDROMEDA: Baseline Characteristics

	Placebo	Dronedarone
Age (years)	72	71
Men	76%	74%
Coronary artery disease	63%	67%
Wall motion index	0.9	0.9
History of AF/AFl	40%	37%
Recent onset, cardioverted	6%	8%
Recent onset, not cardioverted	13%	10%
Long-standing AF	21%	19%
NYHA Class III-IV	62%	58%
Peripheral edema	47%	44%
ACE inhibitor	84%	88%
Beta-blocker	61%	62%
Spironolactone	39%	42%

ANDROMEDA: Study Design

- Eligible patients were randomly assigned (1:1 ratio) to double-blind treatment with dronedarone 400 mg BID or placebo for a planned duration of ≥ 12 months.
- The primary endpoint was the combined risk of all-cause mortality or hospitalization for heart failure.
- Sample size of 1000 patients was based on an event rate of 50% in the placebo group, a relative risk reduction of 20% in the dronedarone group, 12-month recruitment, average follow-up of 1.5 years, 2-sided $\alpha = 0.05$, and power of 90%.

ANDROMEDA: Patient Disposition



	Placebo	Dronedarone
Randomized and treated	317	310
Followed for vital status	317	310

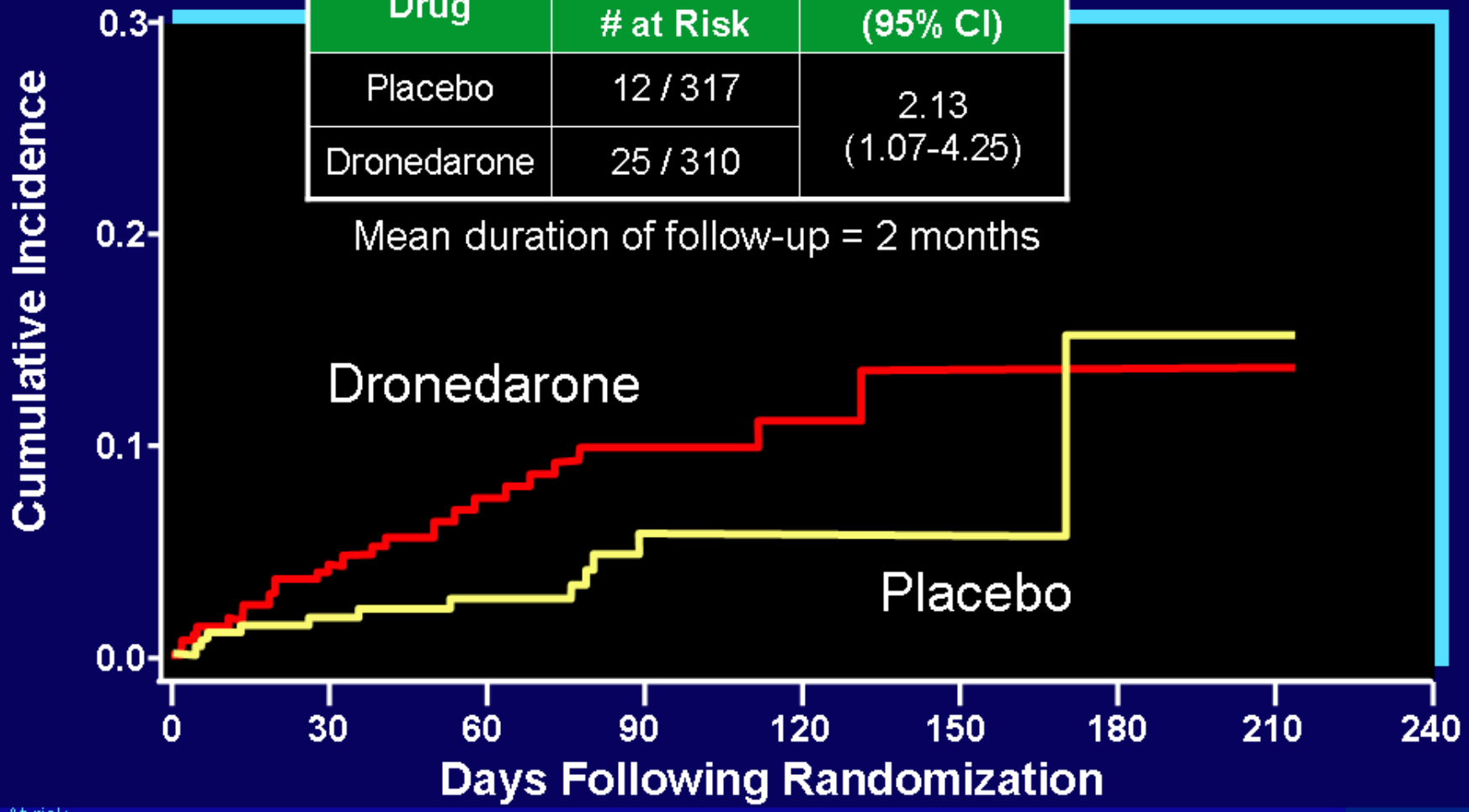
ANDROMEDA: Early Termination

- An independent Data and Safety Monitoring Board was constituted to periodically review the results of the trial.
- The Board identified all-cause mortality was the primary safety measure and prespecified early termination if $P < 0.05$ for between-group difference in risk of death.
- The Board did not specify intervals for interim monitoring, but instead compared differences in mortality rates in the two treatment groups after every 1-2 deaths.
- Seven months into the study, the Board recommended early termination of enrollment and study treatment because of increased risk of death in dronedarone group.
- After discontinuation of study treatment, all patients were to be followed (double-blind) for an additional 6 months.

ANDROMEDA: Mortality Results at Time of DSMB Recommendation

Drug	# Events / # at Risk	Relative Risk (95% CI)
Placebo	12 / 317	2.13 (1.07-4.25)
Dronedarone	25 / 310	

Mean duration of follow-up = 2 months



At risk								
PBO	317	256	181	103	50	18	6	1
DRO	310	257	174	104	59	22	5	1

ANDROMEDA: Adjudicated Mode of Cardiovascular Death

	Placebo	Dronedarone
Cardiovascular death	9	24
Sudden death	6	10
Nonsudden death	3	14
Myocardial infarction	2	0
Worsening heart failure	2	10
Documented arrhythmia	2	6
Procedure related	0	1
Other cardiovascular	0	2
Presumed cardiovascular	3	5

No arrhythmia or sudden death was related to torsade de pointes

ANDROMEDA: Components of Effect on First Cardiovascular Hospitalization

Reason for CV hospitalization	Placebo	Dronedarone
Any CV hospitalization	**50**	**71**
Atrial fibrillation and other supraventricular rhythm disorders	1	4
Worsening heart failure	30	35
Myocardial ischemia	8	13
Stroke	3	4

Effect of dronedarone on CV hospitalization, P = 0.024

ANDROMEDA: Possible Explanations

The results of the ANDROMEDA trial represent:

- A chance finding related to the uncertainty associated with the frequent interim monitoring of small numbers of events in a trial that was terminated early.
- A true finding related to differences in the use of certain background medications following randomization.
- A true finding that can be explained by a deleterious effect of dronedarone in recently unstable patients who were hospitalized for decompensated heart failure and who did not have nonpermanent atrial fibrillation.

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Can CHF Trials With Small Number of Events Lead to Nonreplicable Results?

	Initial Study		Definitive Study	
Trial	**#**	**Results**	**#**	**Results**
Feldman (vesnarinone)	46	62% ↓ risk of death (P=0.002)	802	Increased risk of death
ELITE (losartan)	49	46% ↓ risk of death (P=0.035)	530	No reduction in risk of death
RESOLVD (metoprolol)	20	3x ↑ CHF hospital-izations (P<0.05)	342	↓ CHF hospitalizations
IMPRESS (omapatrilat)	39	47% ↓ in risk of death or CHF admissions (P=0.05)	986	No reduction in death or CHF hospitalizations
Torre-Amione (IMT)	8	80-90% ↓ risk of death (P=0.022)	245	No reduction in risk of death

Could the Mortality Difference in ANDROMEDA Have Been a False Positive Result?

- Statistical simulations (n=10,000) of the conditions that characterized the conduct of the ANDROMEDA trial (i.e., number of patients enrolled, number of deaths, frequency of interim analyses) indicate that the false positive error rate for concluding the existence of difference in mortality between the placebo and dronedarone groups was 18%, not 5%.

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Increases in Serum Creatinine May Have Led to Differential Use of RAAS Agents

	Placebo	Dronedarone
Patients taking ACE inhibitor or ARB at baseline	84.2%	88.4%
Patients who discontinued ACE inhibitor or ARB during study	5.7%	13.2%
Patients who were started and maintained on ACE inhibitor or ARB during study	8.5%	3.9%

Adjustment for Use of RAAS Agents Did Not Alter Effect of Dronedarone

Risk factors	Risk subgroups	Relative risk (95% CI)
ACE inhibitor or ARB	Yes / No	0.21 (0.10 - 0.43)
Creatinine clearance	≥ 50 / < 50 ml/min	0.65 (0.27 - 1.60)
Beta-blocker	Yes / No	0.79 (0.39 - 1.62)
Weight	Continuous	0.99 (0.97 - 1.02)
Spironolactone	Yes / No	1.05 (0.51 - 2.17)
Digitalis	Yes / No	1.10 (0.54 - 2.27)
Baseline NYHA class	III / II	1.18 (0.56 - 2.50)
Wall motion index	Continuous	1.18 (0.25 - 5.67)
Dronedarone	Yes / No	1.83 (0.89 - 3.78)

ANDROMEDA: Possible Explanations

The results of the ANDROMEDA trial represent:

- A chance finding related to the uncertainty associated with the frequent interim monitoring of small numbers of events in a trial that was terminated early.
- A true finding related to differences in the use of certain background medications following randomization.
- A true finding that can be explained by a deleterious effect of dronedarone in recently unstable patients who were hospitalized for decompensated heart failure and who did not have nonpermanent atrial fibrillation.

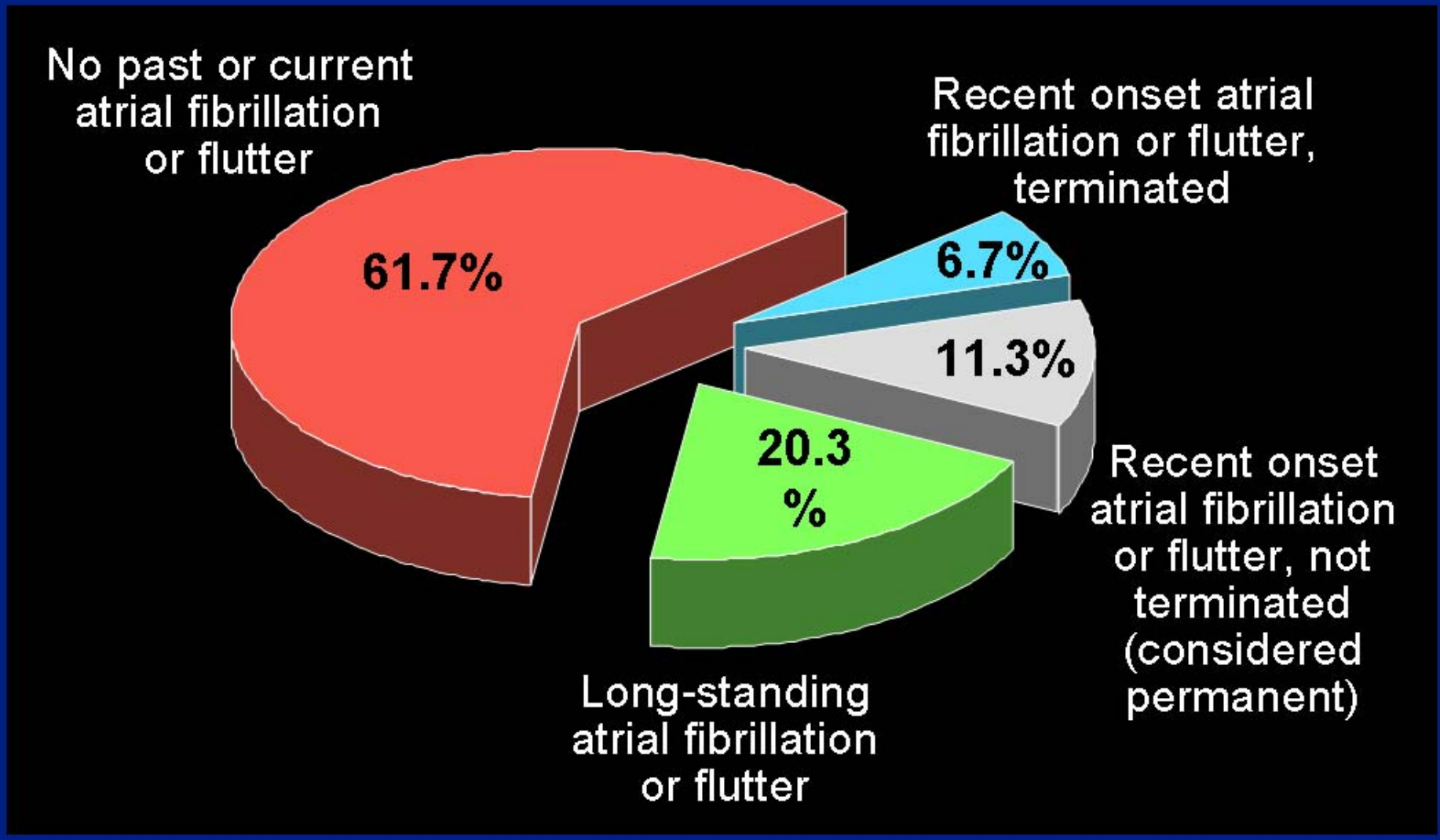
ANDROMEDA Enrolled Only Patients With Recent Clinical Instability

Key Inclusion Criteria

- Hospitalized for worsening heart failure at randomization
- Dyspnea or fatigue at rest or on slight exertion within month
- NYHA class II-IV symptoms requiring diuretic
- Echocardiographic wall motion index ≤ 1.2 (≈ LVEF ≤0.35)

	Placebo n/N	Dronedarone n/N	Hazard ratio (95% CI)
Class II	5/121	7/131	1.28 (0.41-4.03)
Class III	7/183	17/173	2.50 (1.04-6.04)

Patients in ANDROMEDA Did Not Generally Have Nonpermanent Atrial Fibrillation



Dronedarone Did Not Increase Risk in Patients With Nonpermanent Atrial Fibrillation

Type of Atrial Fibrillation or Flutter	Placebo Group (# Deaths / # Patients at Risk)	Dronedarone Group (# Deaths / # Patients at Risk)
No past or current atrial fibrillation or flutter	6 / 191 (3.1%)	11 / 196 (5.6%)
Long-standing atrial fibrillation or flutter	5 / 66 (7.6%)	11 / 61 (18.0%)
Recent (< 6 months) onset or recurrence of atrial fibrillation or flutter – arrhythmia not terminated	0 / 42 (0.0%)	2 / 29 (6.9%)
Recent (< 6 months) onset or recurrence of atrial fibrillation or flutter – arrhythmia terminated	1 / 18 (5.6%)	1 / 24 (4.2%)

ATHENA: Background

Prevention of Recurrence of Atrial Fibrillation or Flutter

EURIDIS
ADONIS
DIONYSOS

Effect on Major Events in High Risk Patients

ANDROMEDA

ATHENA

Effect on Major Events in Patients at Risk of AF Recurrence

ATHENA Focused on Patients Likely to Receive the Drug in Clinical Practice

	ANDROMEDA	ATHENA
Primary intent of the trial	Focus on patients with heart failure, who may or may not have had atrial fibrillation	Focus on patients at risk of AF recurrence, who may or may not have had heart failure

ATHENA: Inclusion Criteria

Patients at risk of AF / AFl recurrence:

- In sinus rhythm but with AF/AFL within 6 months; or
- In AF/AFL with likelihood of conversion to sinus rhythm

Patients believed to be in permanent AF were not enrolled.

To achieve target # of events, patients were at ↑ CV risk:

- ≥ 70 yr with no additional risk factors; or
- < 70 yr with one or more of the following: (1) hypertension (≥ 2 classes of anti-BP drugs; (2) diabetes; (3) prior stroke, TIA or systemic embolism; (4) LA diameter ≥ 50 mm; (5) LV ejection fraction < 0.40.
- After protocol amendment, all patients had to be ≥ 75 yr if no risk factors or ≥ 70 yr if one or more risk factors.

ATHENA: Exclusion Criteria

Exclusion Criteria Identical to ANDROMEDA

- Pulmonary edema within 12 hr; cardiogenic shock requiring IV pressors or mechanical ventilation; recent acute myocardial infarction
- QTc > 500 ms; serum K^+ < 3.5 mmol/L; history of TdP
- Heart rate < 50 bpm; PR > 0.280 sec; sinus pause ≥ 3 sec; 2º or 3º AV block unless paced
- Use of class I or III anti-arrhythmic drugs; drugs known to cause TdP; or potent CYP3A4 inhibitors

Exclusion Criteria New to ATHENA

- Class IV heart failure within 4 weeks
- Estimated glomerular filtration rate <10 mL/min

ATHENA: Baseline Characteristics

	Placebo	Dronedarone
Age (years)	72	72
Men	55%	51%
AF/AFl at baseline	25%	25%
LV ejection fraction	0.57	0.57
% with LVEF < 0.45	13%	11%
% with LVEF < 0.35	4%	4%
Heart failure	30%	29%
Class II	17%	16%
Class III	5%	4%
ACE inhibitor	69%	70%
Beta-blocker	71%	71%
Oral anticoagulants	60%	61%

ATHENA: Identification of Primary and Secondary Endpoint Events

- Eligible patients were randomized (1:1 ratio) to double-blind treatment with dronedarone 400 mg BID or placebo.
- The primary endpoint was the combined risk of all-cause mortality or cardiovascular hospitalization.
- Secondary endpoints were (1) all-cause mortality; (2) cardiovascular hospitalization; and (3) cardiovascular death.
- Investigator determinations were used to analyze prespecified primary or secondary endpoints.

ATHENA: Assumptions Underlying Estimates of Sample Size

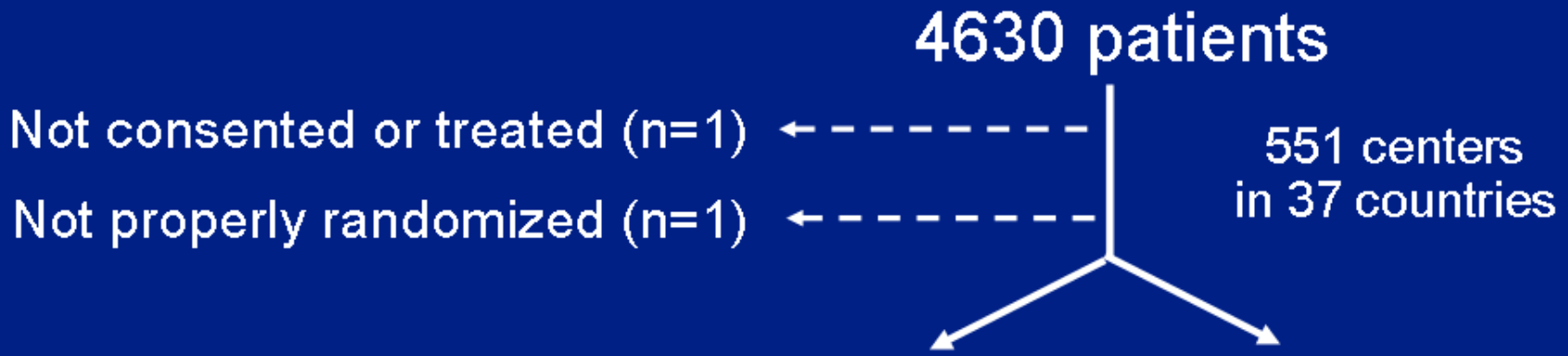
Estimates in Original Protocol

- Initial estimate of sample size was 3700 (1850 in each arm) based on 20% rate of a primary event on placebo and a 15% reduction in risk. A total of 970 primary events would provide 80% power (2-sided α=0.05).

Revisions Specified in Protocol Amendment

- Less than expected rate of death during the trial led to increase in sample size to 4300 (2150 in each arm). A total of 260 deaths was targeted to allow the study to have 90% power to exclude a 50% increase in risk of death if the point estimate were 1.0.

ATHENA: Patient Disposition



	Placebo	Dronedarone
Randomized	2327	2301
Completed follow-up for all-cause mortality	2325	2301
Completed follow-up for CV hospitalization	2320	2298

ATHENA Was Designed With a Key Efficacy and a Key Safety Objective

Efficacy	Safety
All-cause mortality or cardiovascular hospitalization	All-cause mortality
Primary determinant of sample size in original protocol	Primary determinant of sample size in protocol amendment

ATHENA: All-Cause Mortality or Cardiovascular Hospitalization

Drug	Number of events / number at risk	Relative risk (95% CI)
Placebo	917 / 2327	0.76 (0.69-0.84)
Dronedarone	734 / 2301	

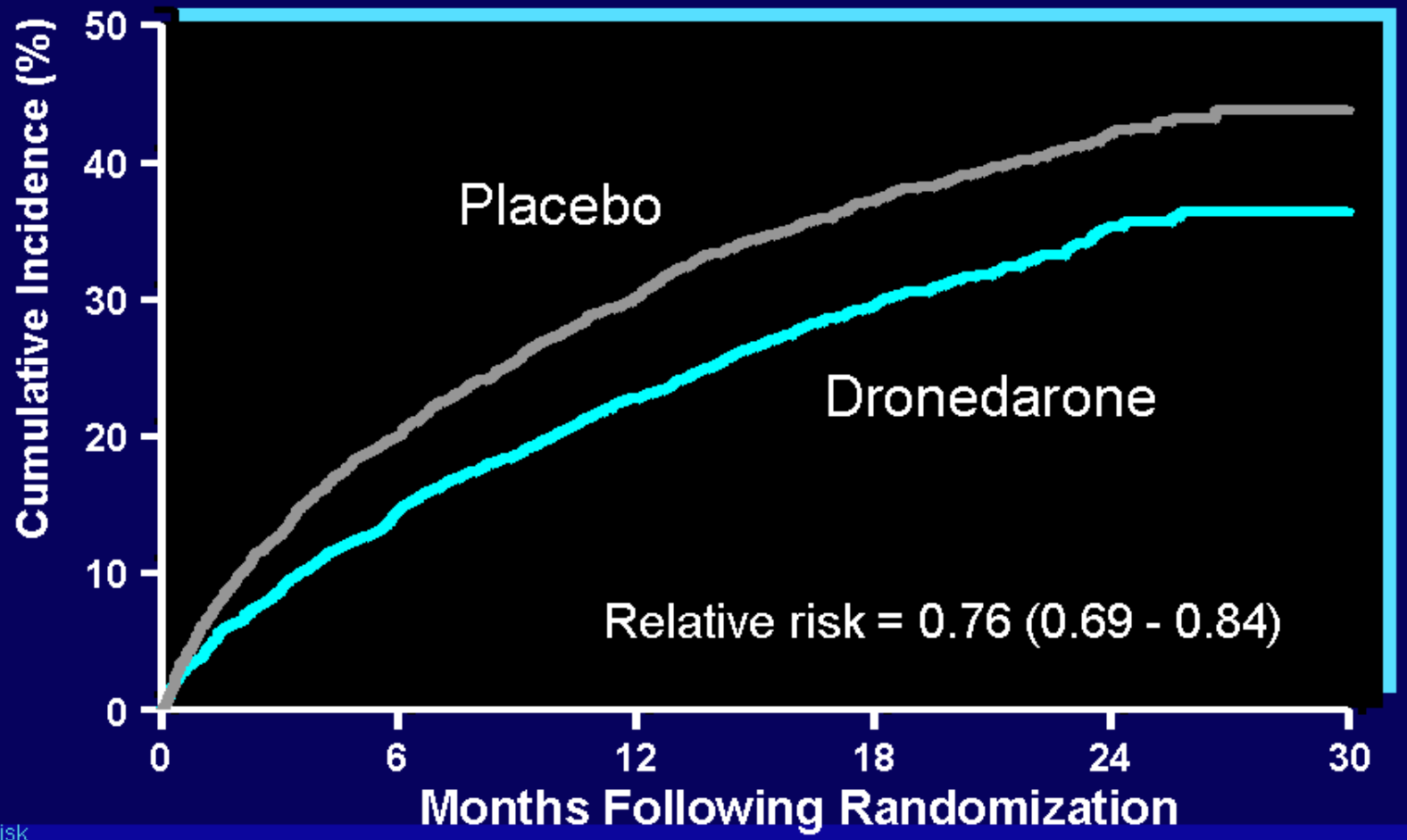
1651 events

$P = 2 \times 10^{-8}$

Treatment with dronedarone resulted in one fewer death or cardiovascular hospitalization for every 12 patients with atrial fibrillation / flutter treated for 21 months

ATHENA: All-Cause Mortality or Cardiovascular Hospitalization

Mean duration of follow-up = 21 months



At risk						
PBO	2327	1858	1625	1072	385	3
DRO	2301	1963	1776	1177	403	2

ATHENA Was Designed With a Key Efficacy and a Key Safety Objective

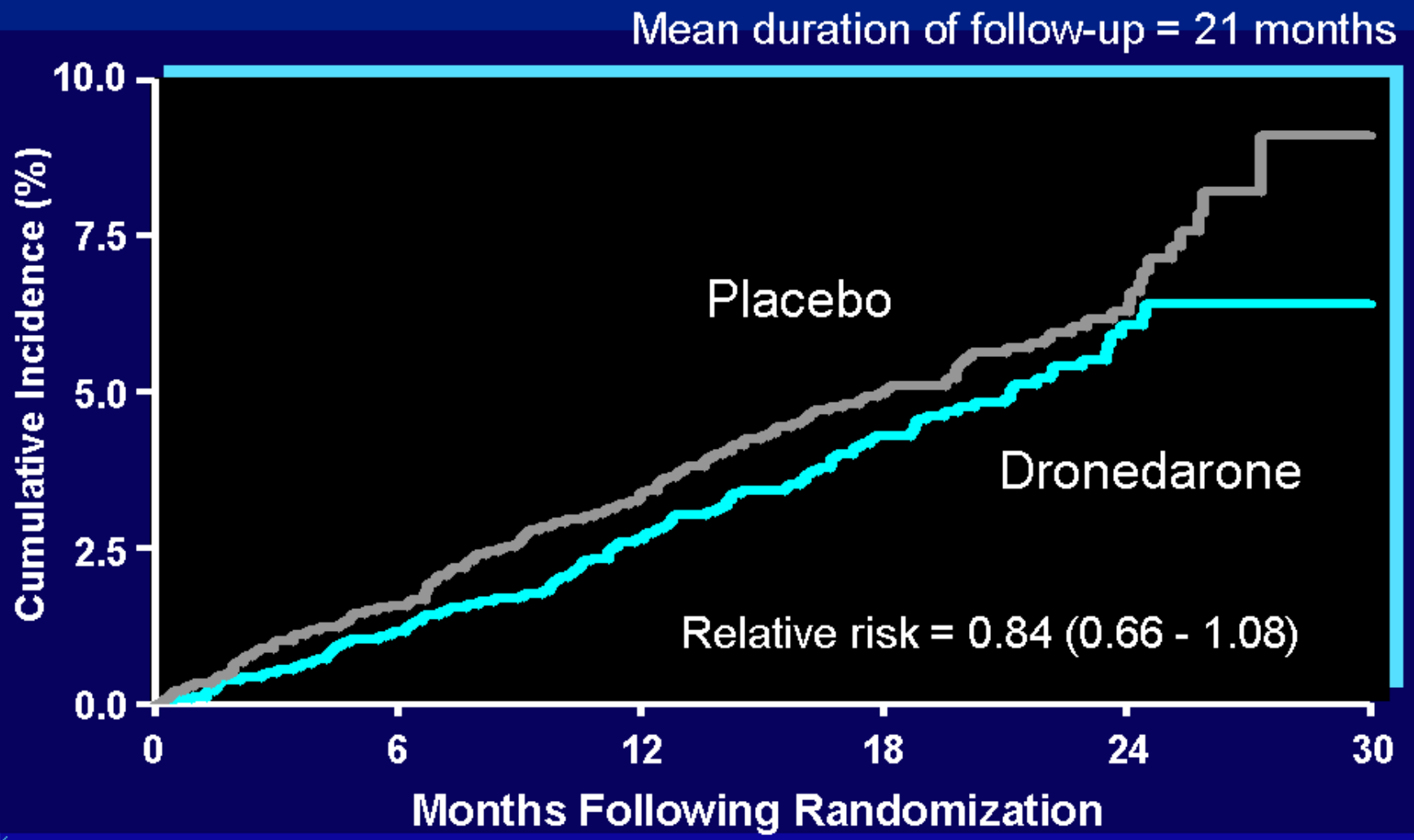
Efficacy	Safety
All-cause mortality or cardiovascular hospitalization	All-cause mortality
Primary determinant of sample size in original protocol	Primary determinant of sample size in protocol amendment

ATHENA: All-Cause Mortality

Drug	Number of Events / Number at Risk	Relative Risk (95% CI)
Placebo	139 / 2327	0.84 (0.66-1.08)
Dronedarone	116 / 2301	

Counts based on all events until closure of trial

ATHENA: All-Cause Mortality



At risk						
PBO	2327	2290	2250	1629	636	7
DRO	2301	2274	2240	1593	615	4

ATHENA Was Designed With a Key Efficacy and a Key Safety Objective

Efficacy	Safety
All-cause mortality or cardiovascular hospitalization	All-cause mortality
Primary determinant of sample size in original protocol	Primary determinant of sample size in protocol amendment
Did the results confirm EURIDIS and ADONIS?	Did the results confirm ANDROMEDA?

ATHENA: All-Cause Mortality or Cardiovascular Hospitalization

Drug	Number of Events / Number at Risk	Relative Risk (95% CI)
ATHENA Trial (Patients in Sinus Rhythm with History of Atrial Fibrillation or Flutter)		
Placebo	917 / 2327	0.76 (0.69-0.84)
Dronedarone	734 / 2301	
EURIDIS + ADONIS Trials (Patients in Sinus Rhythm with History of Atrial Fibrillation or Flutter)		
Placebo	64 / 409	0.80 (0.59 - 1.09)
Dronedarone	111 / 828	

Analysis of EURIDIS and ADONIS does not include cerebrovascular events.
If such events are included, RR is 0.74 (0.55-0.99)

Mortality Results of ATHENA Are Discordant With Those of ANDROMEDA

ANDROMEDA

Drug	# Events / # at Risk	Relative Risk (95% CI)
Placebo	12 / 317	2.13 (1.07-4.25)
Dronedarone	25 / 310	

ATHENA

Drug	# Events / # at Risk	Relative Risk (95% CI)
Placebo	139 / 2327	0.84 (0.66-1.08)
Dronedarone	116 / 2301	

Key FDA Questions About Dronedarone to be Addressed in This Presentation

- What effect on morbidity / mortality could have been anticipated before ANDROMEDA and ATHENA?
- What were the findings of the ANDROMEDA trial and how can these findings be explained?
- What were the findings of the ATHENA trial and were they consist with earlier studies?

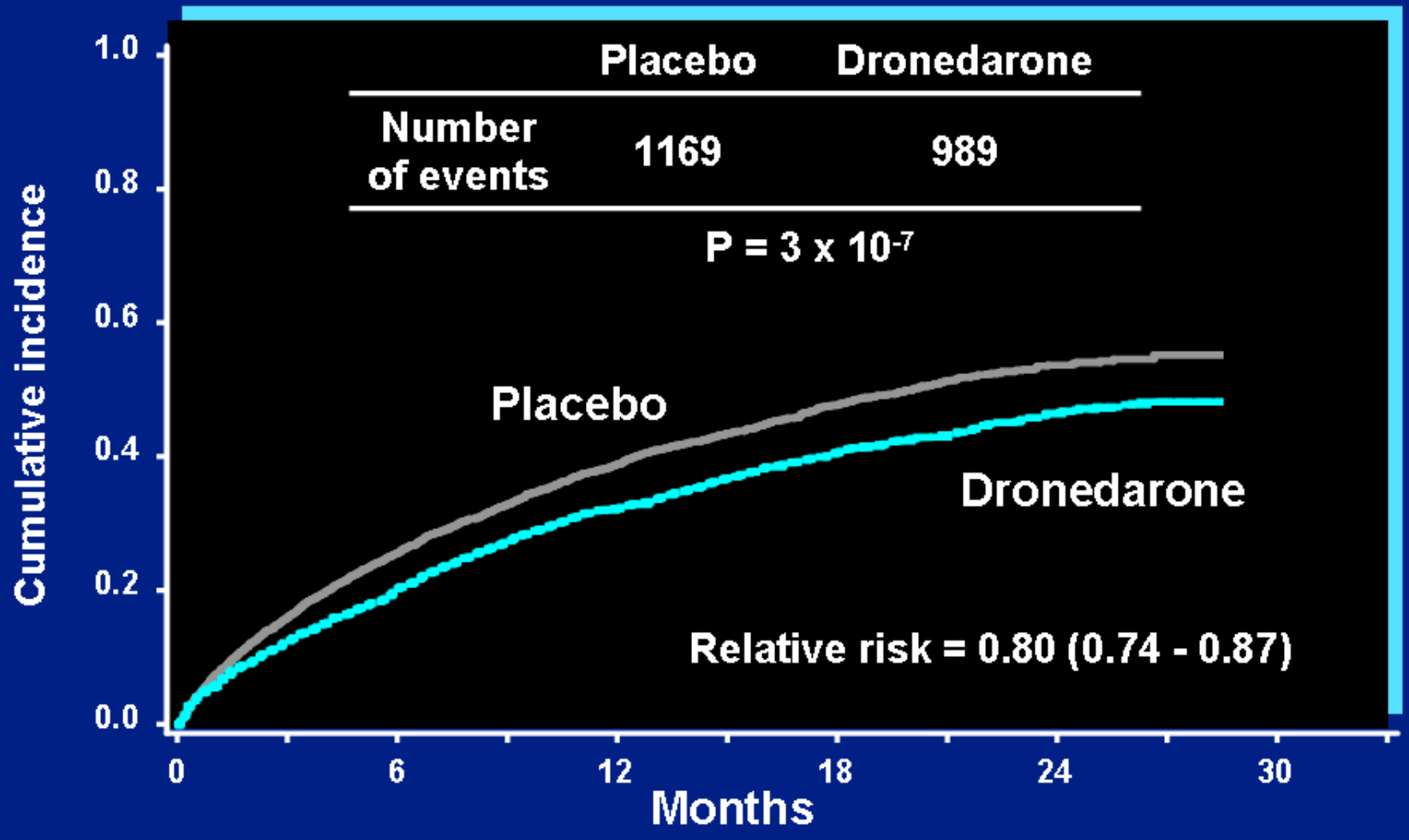
- Did implementation or modification of the protocol have a meaningful effect on the results of the ATHENA trial?
- Was the effect on CV hospitalization in ATHENA due entirely to a reduction in hospitalizations for atrial fibrillation?
- Did dronedarone reduce the risk of CV death in the ATHENA?

- How do we reconcile results of ATHENA and ANDROMEDA with respect to use in LVEF < 0.35 or class III patients?

Questions Raised by FDA Reviewer About Study Implementation

- Questions about the identification of cardiovascular deaths and cardiovascular hospitalizations by investigators based on a predefined list of events.
- Questions about the results of the classification of cardiovascular deaths by Steering Committee.
- Questions about operational modifications in the cut-off dates used to terminate follow-up in individual patients at the end of the trial.

ATHENA: Combined Risk of All-Cause Mortality or All-Cause Hospitalizations



ATHENA: Study Objectives

Efficacy	Safety
All-cause mortality or cardiovascular hospitalization	All-cause mortality

Cardiovascular hospitalization

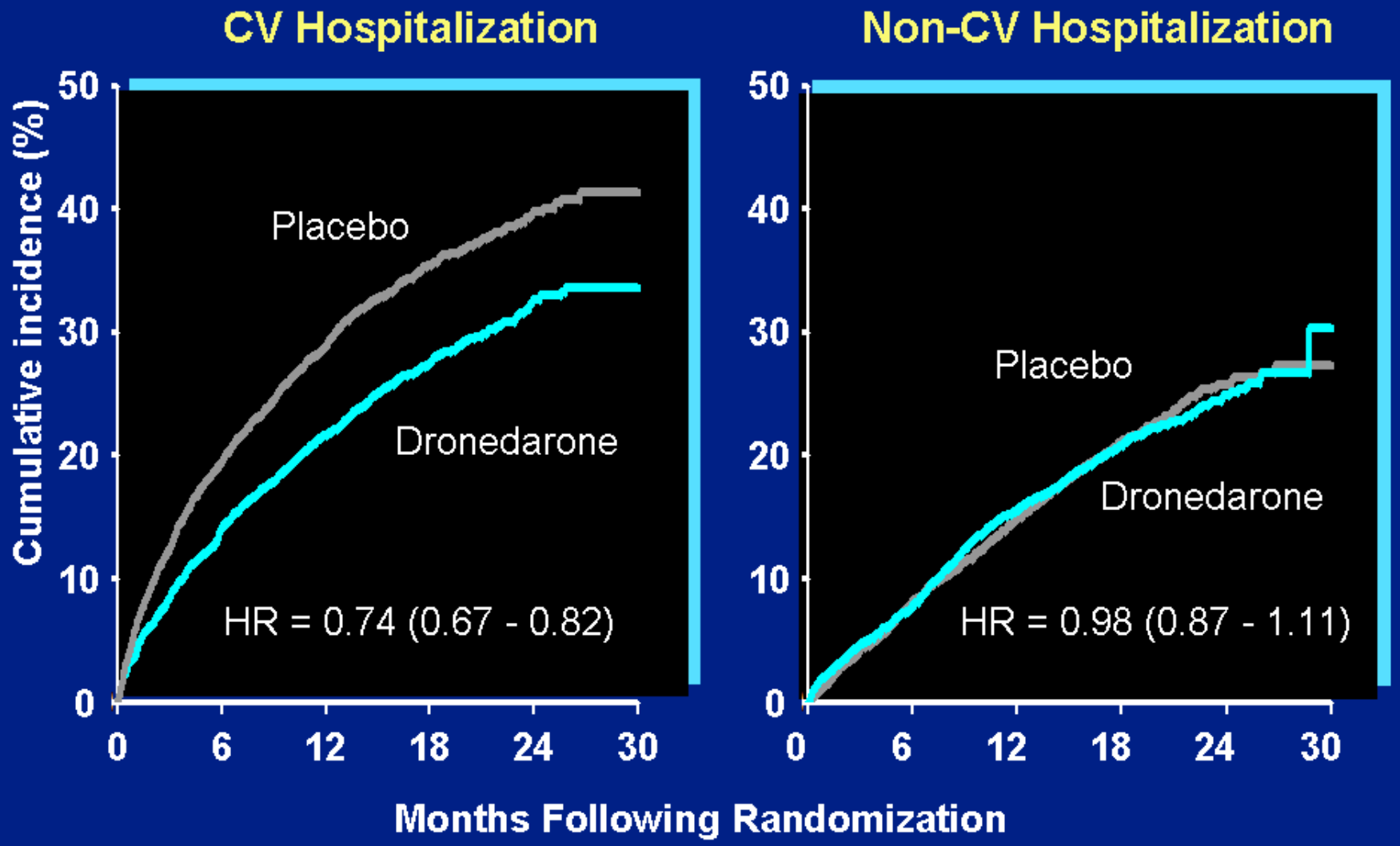
Cardiovascular death

Secondary endpoints were examined to look for internal consistency of components of the composite primary endpoint

ATHENA: Time to First Hospitalization for Cardiovascular Reason

Drug	Number of Events / Number at Risk	Relative Risk (95% CI)
Hospitalization for Cardiovascular Reason		
Placebo	859 / 2327	0.74 (0.67-0.82)
Dronedarone	675 /2301	
Hospitalization for Non-Cardiovascular Reason		
Placebo	533 / 2327	0.98 (0.87-1.11)
Dronedarone	516 / 2301	

ATHENA: Time to First CV and Non-CV Hospitalization



ATHENA: Major Components of Effect on First Cardiovascular Hospitalization

Reason for CV hospitalization	Placebo	Dronedarone	Hazard ratio (95% CI)
Any cardiovascular hospitalization	859	675	0.74 (0.67 – 0.82)
AF and other supraventricular rhythm disorders	457	296	0.62 (0.53 – 0.71)

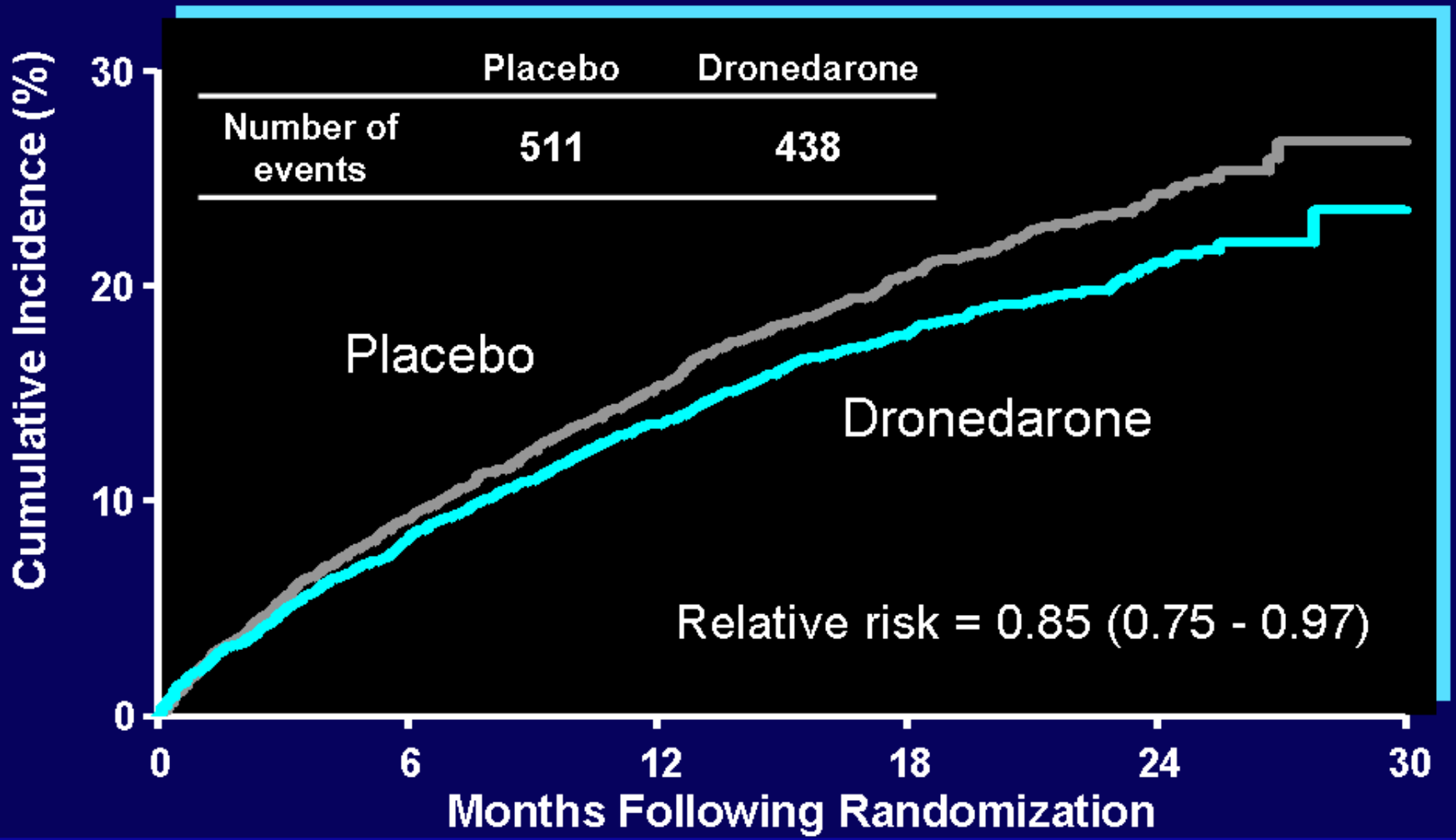
ATHENA: Major Components of Effect on First Cardiovascular Hospitalization

Reason for CV hospitalization	Placebo	Dronedarone	Hazard ratio (95% CI)
Any cardiovascular hospitalization	859	675	0.74 (0.67 – 0.82)
AF and other supraventricular rhythm disorders	457	296	0.62 (0.53 – 0.71)
Worsening heart failure	92	78	0.81 (0.60 – 1.09)
Myocardial infarction or unstable angina	61	48	0.74 (0.51 – 1.08)
TIA or stroke (except ICH)	35	28	0.75 (0.46 – 1.24)

Effect of Dronedarone on Non-AF Cardiovascular Hospitalizations

Reason for CV hospitalization	Hazard ratio (95% CI)	
	ATHENA	EURIDIS + ADONIS
Myocardial Infarction or unstable angina	0.74 (0.51 – 1.08)	0.72 (0.24 – 2.21)
TIA or stroke (except ICH)	0.75 (0.46 – 1.24)	0.15 (0.02 – 1.45)

ATHENA: Time to First CV Hospitalization Not Due to AF / AFL (Post-Hoc)



At risk						
PBO	2327	2093	1929	1326	497	3
DRO	2301	2096	1957	1338	479	2

ATHENA: Study Objectives

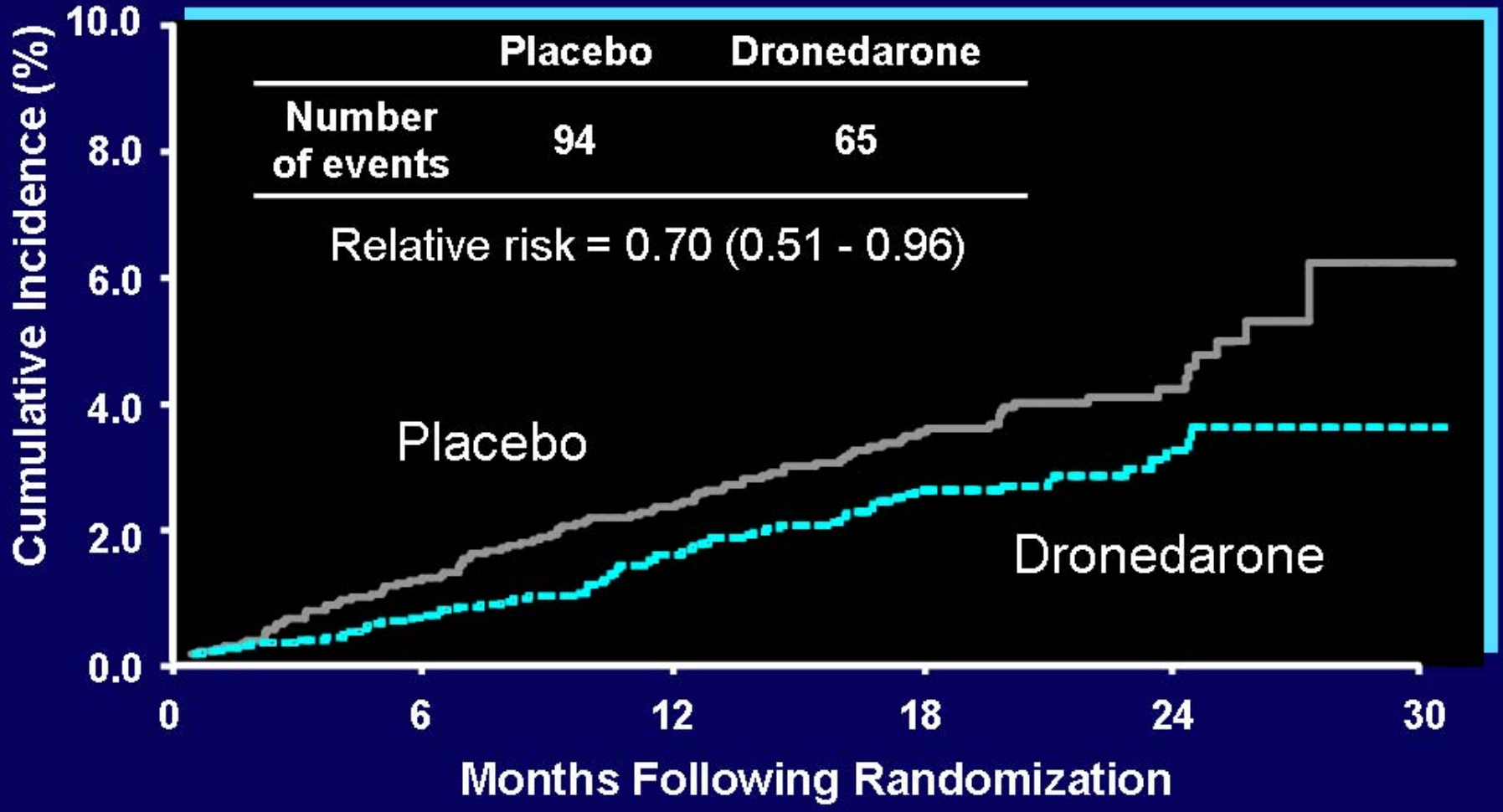
Efficacy	Safety
All-cause mortality or cardiovascular hospitalization	All-cause mortality

Cardiovascular hospitalization

Cardiovascular death

Secondary endpoints were examined to look for internal consistency of components of the composite primary endpoint

ATHENA: Cardiovascular Death



At risk						
PBO	2327	2290	2250	1629	636	7
DRO	2301	2274	2240	1593	615	4

ATHENA: Most Common Reasons for Cardiovascular Death

Reason for Cardiovascular Death	Placebo	Dronedarone
Any cardiovascular death	94	65
Sudden cardiac death	35	14
Ventricular tachycardia or fibrillation	3	2
Stroke	18	11
Myocardial infarction or unstable angina	7	5
Pulmonary or peripheral embolism	6	2
Congestive heart failure	10	13
Cardiogenic shock	2	5

ATHENA: Study Objectives

Efficacy	Safety
All-cause mortality or cardiovascular hospitalization	All-cause mortality

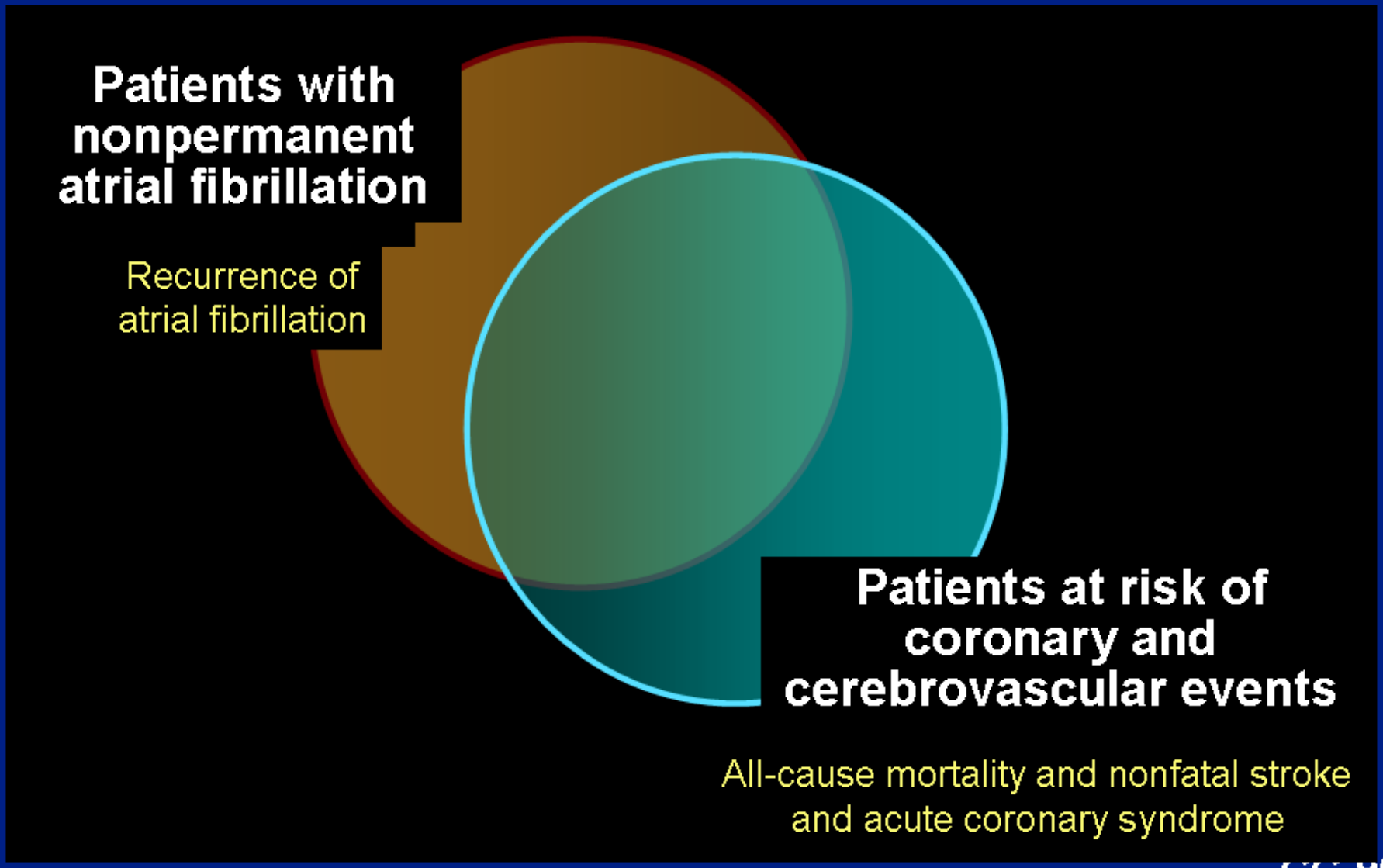
Cardiovascular hospitalization

Relative risk
0.74
(0.67 - 0.82)

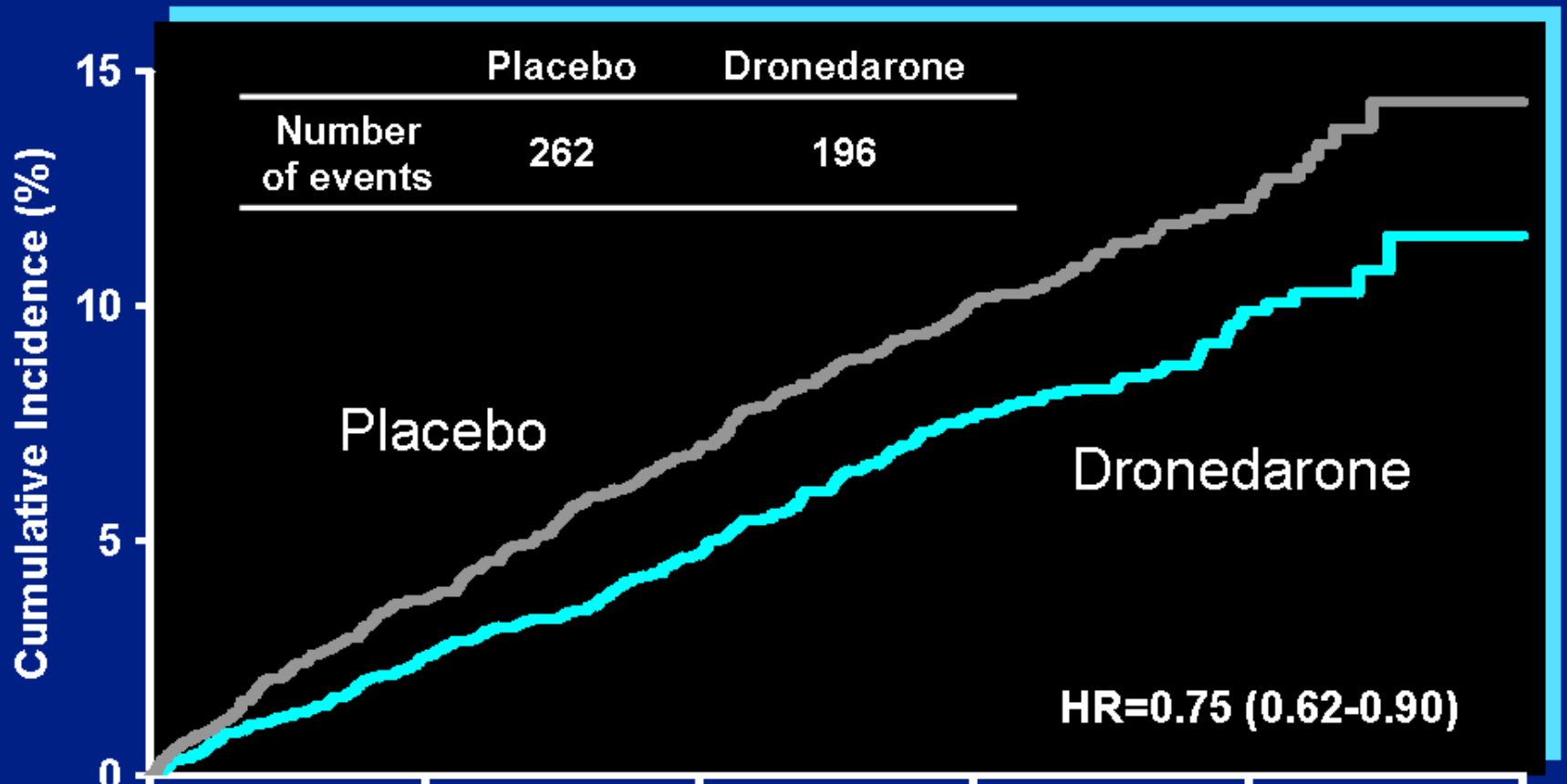
Cardiovascular death

Relative risk
0.70
(0.51 - 0.96)

Patients in ATHENA Overlap Those in Other Major CV Event Trials



ATHENA: All-Cause Mortality, Stroke and Acute Coronary Syndrome (Post-Hoc)



At risk						
PBO	2327	2240	2166	1547	599	6
DRO	2301	2243	2193	1541	586	4

Effect was observed even though more patients in the dronedarone group stopped beta-blockers post randomization

ATHENA: Effect on Cerebrovascular and Coronary Arterial Thromboembolic Events

	Placebo	Dronedarone	Relative risk (95% CI)
Stroke			
Stroke or TIA	90	63	0.70 (0.51-0.97)
Stroke	70	46	0.66 (0.46-0.96)
Hospitalization for CVA	55	38	0.69 (0.46-1.05)
Fatal ischemic stroke	18	11	0.62 (0.29-1.31)
Acute Coronary Syndrome			
MI or unstable angina	96	68	0.71 (0.52-0.97)
Hospitalization for ACS	89	62	0.70 (0.51-0.97)
Fatal ACS	7	5	0.72 (0.23-2.27)

Reduction in risk of stroke still apparent in patients receiving anticoagulants

Key FDA Questions About Dronedarone to be Addressed in This Presentation

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- What were the findings of the ANDROMEDA trial and how can these findings be explained?
- What were the findings of the ATHENA trial and were they consist with earlier studies?

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- Did dronedarone reduce the risk of CV death in the ATHENA?

- How do we reconcile results of ATHENA and ANDROMEDA with respect to use in LVEF < 0.35 or class III patients?

Approach to Reconcilitation of the Results of ATHENA and ANDROMEDA

If we assume that the mortality results of the ANDROMEDA trial are not due to the play of chance, how do we identify patients who will benefit (ATHENA-like) and not be harmed?

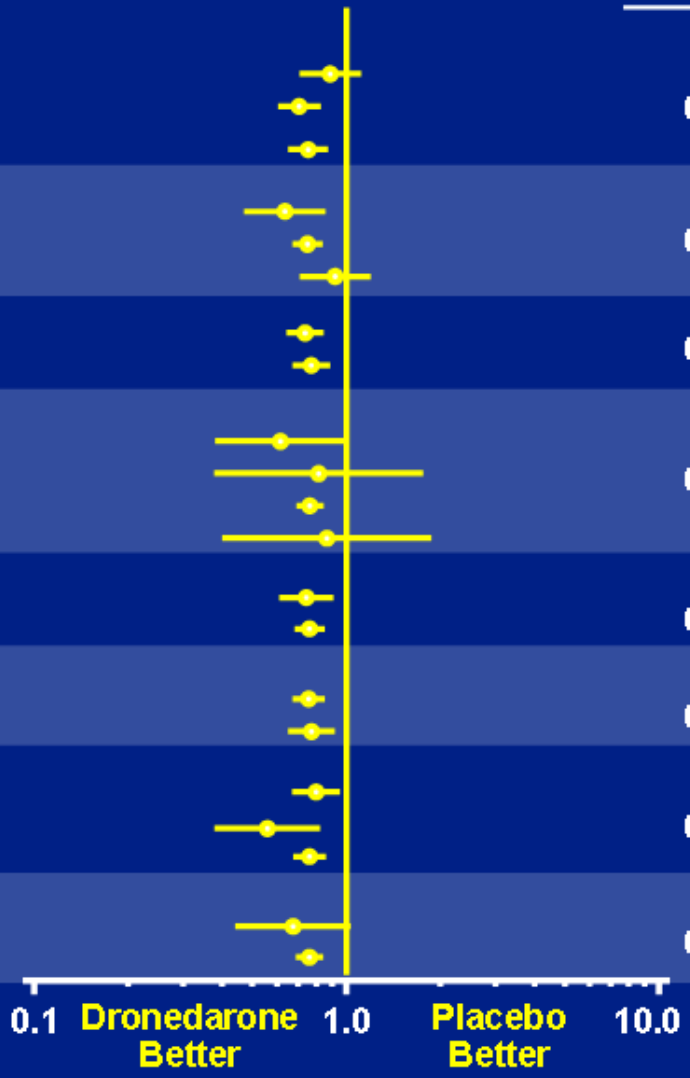
Nonpermanent AF	Dronedarone can be appropriately used in these patients	
No symptoms of CHF		
EF > 0.35		
Class II heart failure		
EF ≤ 0.35	Should dronedarone be prohibited in all of these patients?	Can dronedarone be used in a specific subset of these patients?
Class III CHF		
Class IV CHF	Dronedarone should not be used in these patients	
No past or current AF		
Long-standing AF		

Reconciliation Needs to Focus on Patients With LVEF < 0.35 and Class III Heart Failure

- It is not *feasible* to ask physicians to distinguish
  - — patients with class II from those with class III symptoms of heart failure
  - — patients with a LVEF of 0.34 from those with a LVEF of 0.36
- It is not *appropriate* to exclude patients with LV ejection fraction < 0.35 or with class III heart failure if there is an identifiable subset of these patients who have a favorable benefit-to-risk relation when dronedarone is used as indicated.

Assessment of Benefit: Subgroup Analyses of Primary Endpoint in ATHENA

	N	RR [95% CI]	P-value
Age (years)			
< 65	873	0.89 [0.71;1.11]	
65-75	1830	0.71 [0.60;0.83]	0.27
≥ 75	1925	0.75 [0.65;0.87]	
Weight (Kg)			
≤ 60	505	0.64 [0.47;0.86]	
60-100	3571	0.75 [0.67;0.84]	0.18
≥ 100	552	0.92 [0.71;1.20]	
Gender			
Male	2459	0.74 [0.64;0.85]	0.65
Female	2169	0.77 [0.67;0.89]	
Race			
Asian/oriental	304	0.62 [0.38;1.00]	
Black	50	0.81 [0.38;1.76]	0.82
Caucasian	4137	0.76 [0.69;0.85]	
Other	137	0.87 [0.40;1.87]	
Presence of AF/AFL			
Yes	1155	0.74 [0.61;0.91]	0.85
No	3473	0.76 [0.68;0.85]	
Structural Heart Disease			
Yes	2732	0.76 [0.67;0.85]	0.85
No	1853	0.77 [0.65;0.92]	
NYHA Class			
Class I or II	1165	0.80 [0.67;0.96]	
Class III	200	0.56 [0.38;0.82]	0.22
No CHF	3263	0.76 [0.68;0.86]	
LV Ejection Fraction			
< 0.35	179	0.68 [0.44;1.03]	0.58
≥ 0.35	4365	0.76 [0.69;0.84]	



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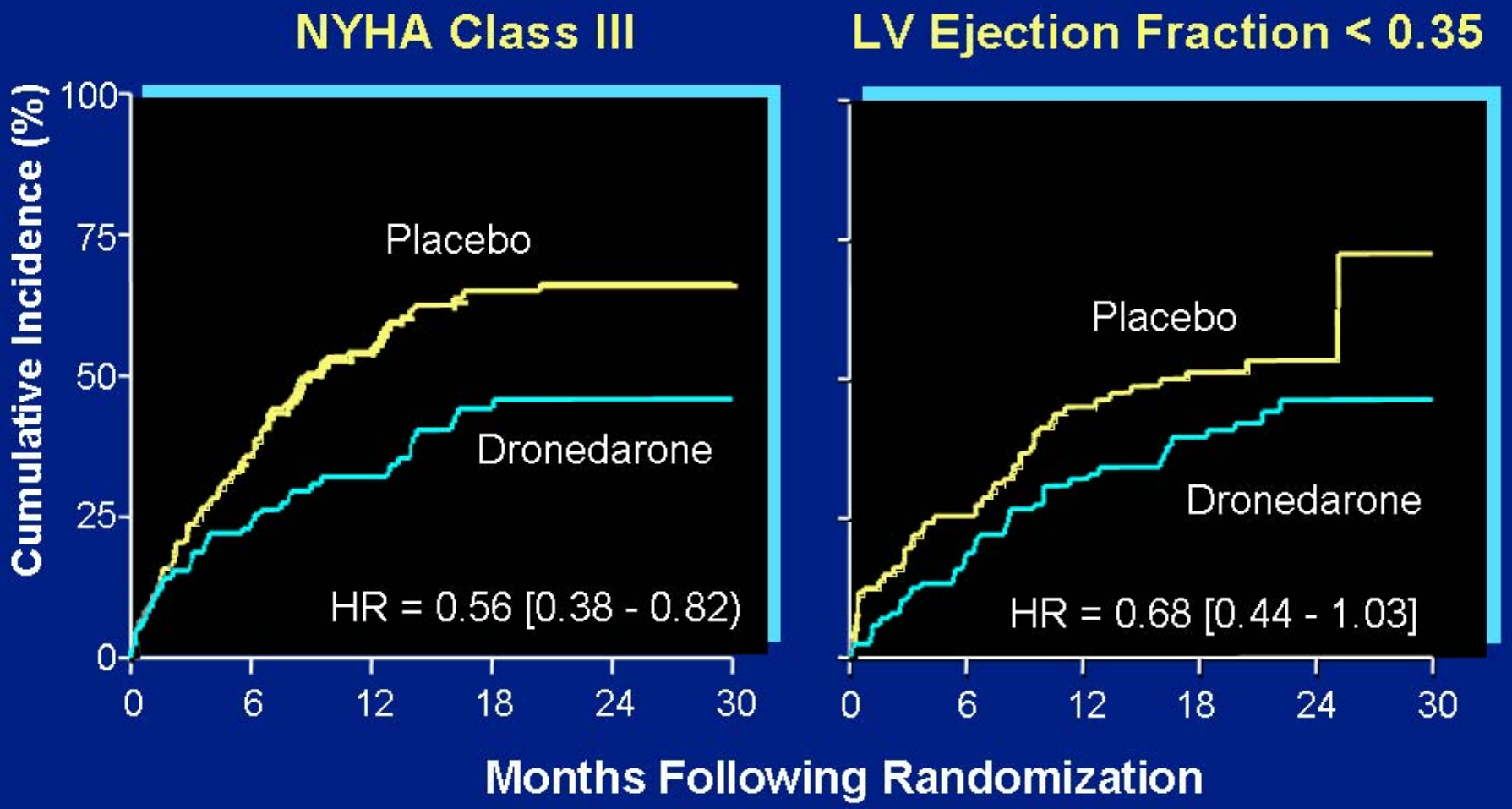
ATHENA: Benefits in Patients With NYHA Class III or LV Dysfunction

Effect on Death or Cardiovascular Hospitalization



Assessment of Risk: Subgroup Analysis of All-Cause Mortality in ATHENA

Subgroup		# Patients	Relative risk (95% CI) Dronedarone: placebo
LV ejection fraction	< 0.35	179	0.55 (0.25-1.21)
	≥ 0.35	4365	0.89 (0.69-1.15)
NYHA Class	III	200	0.66 (0.32-1.34)
	I-II	1165	0.93 (0.59-1.47)
Diuretics	Yes	2492	0.58 (0.41-0.81)
	No	2136	1.36 (0.93-1.98)
Beta-blockers	Yes	3269	0.74 (0.55-1.01)
	No	1359	1.08 (0.71-1.64)
ACE inhibitors	Yes	3216	0.80 (0.59-1.08)
	No	1412	0.95 (0.62-1.45)

ATHENA: Mortality Effects in LV Ejection Fraction and NYHA Class Subgroups

Subgroup		Placebo n/N	Dronedarone n/N	Hazard ratio (95% CI)
LV ejection fraction	< 0.35	16/87	10/92	0.55 (0.25-1.21)
	≥ 0.35	121/2194	106/2171	0.89 (0.69-1.15)
NYHA Class	III	21/109	12/91	0.66 (0.32-1.34)
	I-II	38/584	35/581	0.93 (0.59-1.47)

- Benefit (assessed by primary endpoint) was similar in patients with LVEF < 0.35 and with class III heart failure than in other subgroups.
- Risk (assessed by all-cause mortality) was not greater and was numerically lower in these patients than in other subgroups.
- Ratio of benefit-to-risk was not less favorable in patients with LVEF < 0.35 and with class III heart failure than in other subgroups.

Approach to Reconcilitation of the Results of ATHENA and ANDROMEDA

If we assume that the mortality results of the ANDROMEDA trial are not due to the play of chance, how do we identify patients who will benefit (ATHENA-like) and not be harmed?

Nonpermanent AF	Dronedarone can be appropriately used in these patients	
No symptoms of CHF		
EF > 0.35		
Class II heart failure		
EF ≤ 0.35	Should dronedarone be prohibited in all of these patients?	Can dronedarone be used in a specific subset of these patients?
Class III CHF		
Class IV CHF	Dronedarone can be used effectively and safely in a **specific subset** of these patients (i.e., ATHENA-like)	
No past or current AF		
Long-standing AF		

ANDROMEDA and ATHENA: Summary of Findings

1. The ATHENA trial demonstrated that dronedarone reduces the combined risk of all-cause mortality or cardiovascular hospitalization in patients with recent history or recent onset of atrial fibrillation.

   Both a reduction in cardiovascular mortality and cardiovascular morbidity contributed significantly to the effect of the drug on the primary endpoint.

   All examined subgroups, including patients with class III heart failure and with a LV ejection fraction < 0.35, showed benefit.

ANDROMEDA and ATHENA: Summary of Findings

2. The effects of dronedarone in ATHENA differed dramatically from those in ANDROMEDA.

	ANDROMEDA		ATHENA	
Drug	**Placebo**	**Dronedarone**	**Placebo**	**Dronedarone**
All-cause mortality	12	25	139	116
Cardiovascular Hospitalizations				
Supraventricular arrhythmia	1	4	457	296
Heart failure	30	35	92	78
Myocardial ischemia	8	13	61	48
Cerebrovascular accident	3	4	35	28

ANDROMEDA and ATHENA: Summary of Findings

3. Differences between ANDROMEDA and ATHENA may have been due to imprecision of the estimates of risk due to frequent interim monitoring of a small number of events in ANDROMEDA.

	ANDROMEDA	ATHENA
Number of deaths	37	255
Median duration of follow-up	2 months	22 months
Interim monitoring	After every 1-2 deaths	At prespecified intervals
Monitoring boundaries	Nominal P<0.05	Accounted for multiplicity of analyses
Terminated early	Yes	No

ANDROMEDA and ATHENA: Summary of Findings

4. Differences between ANDROMEDA and ATHENA may have been due to lack of overlap in types of patients enrolled in the ANDROMEDA and ATHENA trials.

Types of Patients	ATHENA	ANDROMEDA
No symptoms of CHF	Yes	No
EF > 0.35		
EF ≤ 0.35	Stable with nonpermanent atrial fibrillation	Recently unstable without indication for dronedarone
Class II CHF		
Class III CHF		
Class IV CHF	No	Yes
No history of atrial fibrillation		
Permanent atrial fibrillation		

Selection of Patients With AF for Treatment With Dronedarone

Types of Patients	ATHENA-Type Patients	ANDROMEDA-Type Patients
No symptoms of CHF	If clinically stable during the past month	
EF > 0.35		
EF ≤ 0.35	If clinically stable during the past month	If hospitalized for heart failure or class IV symptoms within the last month
Class II CHF		
Class III CHF		
Class IV CHF		If hospitalized for heart failure or class IV symptoms within the last month
No past or current AF		
Permanent AF		

APPROPRIATE USE

INAPPROPRIATE USE

Safety of Dronedarone in Atrial Fibrillation/Flutter Trials

Paul Chew, MD

Dronedarone
Placebo-Controlled Atrial Fibrillation/Flutter Trials

	Placebo (N=2875)	Dronedarone 400 mg BID (N=3282)
Patient-years	3383.4	3684.5
Median extent of exposure (month)	14.5	12.7
Number of patients		
Up to 12 months	1812	1998
Up to 18 months	1156	1145
Up to 24 months	430	425

Five trials in AF/AFL patients DAFNE, EURIDIS, ADONIS, ERATO and ATHENA

Note: protocols: DRI3550/DAFNE, EFC3153/EURIDIS, EFC4788/ADONIS, EFC4508/ERATO, EFC5555/ATHENA

DIONYSOS

	Dronedarone 400 mg BID (N=249)	Amiodarone 600 mg/200 mg (N=255)
N	249	255
Mean (SD)	201.6 (111.2)	222.2 (109.9)
Median extent of exposure (month)	7.0	7.6

Note: protocols: EFC94968/DIONYSOS

AF/AFL Pool: Safety by System Organ Class (1of 2)

System Organ Class	Placebo (N=2875) %	Dronedarone 400 mg BID (N=3282) %
Any Class	67.5	70.4
Gastrointestinal disorders	20.8	24.1
Infections and infestations	23.4	22.5
General disorders and administration site conditions	14.5	16.2
Nervous system disorders	16.0	15.8
Musculoskeletal and connective tissue disorders	15.9	15.7
Respiratory, thoracic and mediastinal disorders	13.8	13.7
Investigations	8.8	13.4
Cardiac disorders	9.8	11.7
Skin and subcutaneous tissue disorders	7.4	10.2
Injury, poisoning and procedural complications	8.9	8.3
Vascular disorders	7.9	7.3

AF/AFL Pool: Safety by System Organ Class (2 of 2)

System Organ Class	Placebo (N=2875) %	Dronedarone 400 mg BID (N=3282) %
Metabolism and nutrition disorders	8.1	6.5
Psychiatric disorders	5.0	5.0
Eye disorders	4.2	4.4
Renal and urinary disorders	4.6	4.3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4.5	3.8
Reproductive system and breast disorders	2.3	2.6
Ear and labyrinth disorders	2.6	2.3
Blood and lymphatic system disorders	2.2	1.9
Hepatobiliary disorders	1.5	1.6
Endocrine disorders	1.2	1.2
Surgical and medical procedures	0.8	0.8
Immune system disorders	0.6	0.5
Congenital, familial and genetic disorders	<0.1	<0.1
Social circumstances	0%	<0.1

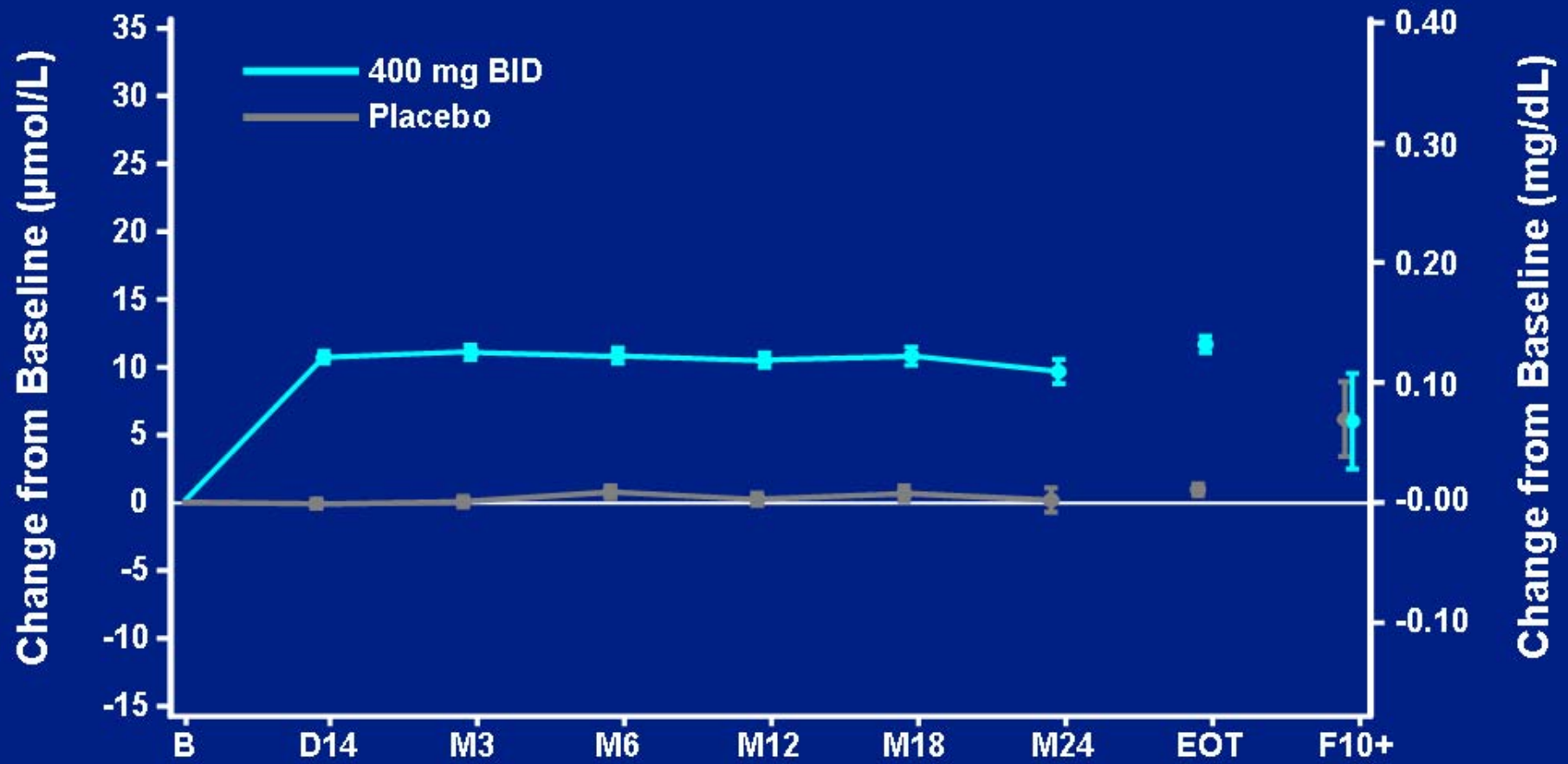
GI Adverse Events

5 Pooled Trials	Placebo (%) (N=2875)	Dronedarone (%) (N=3282)
Diarrhea	5.8	9.0
Nausea	3.1	4.9
Vomiting	1.1	2.0
Any GI TEAEs leading to discontinuation	1.8	3.2

Renal Adverse Events

5 Pooled Trials	Placebo (%) (N=2875)	Dronedarone (%) (N=3282)
Blood creatinine increased	1.1	4.0
Blood urea increased	0.6	1.0
Renal failure	0.5	0.6
Renal failure acute	0.2	0.6

ATHENA
Mean Change in Serum Creatinine

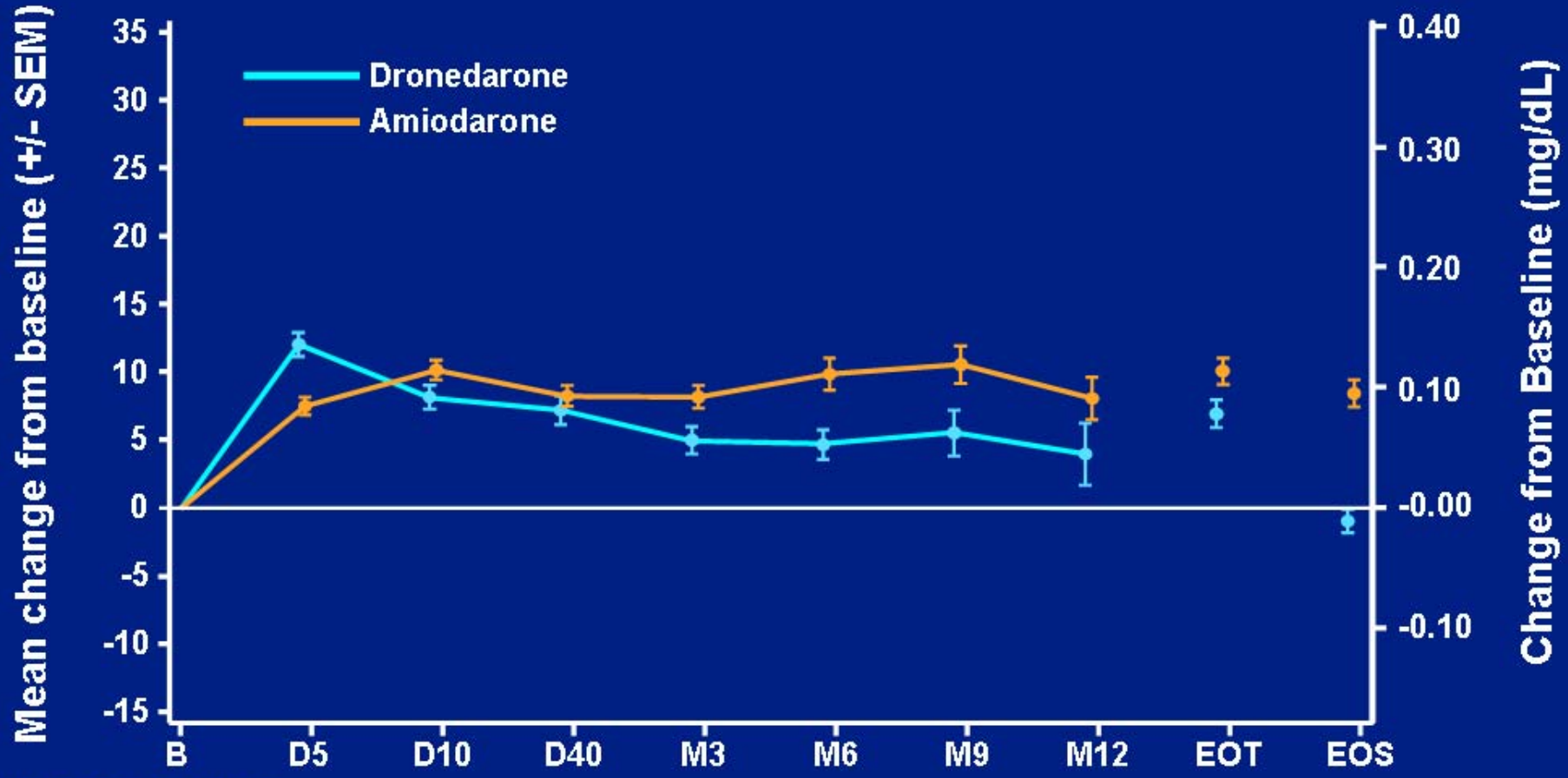


Number of patients									
400 mg BID	2284	2085	1954	1828	1657	1209	604	2205	172
Placebo	2304	2151	1997	1859	1658	1206	613	2265	131

B: Baseline, EOT: Last post baseline assessment before treatment discontinuation F10+: Period]EOT+1day ; EOT+10days]
Only scheduled time points are considered

CC-113

DIONYSOS
Mean Change in Serum Creatinine



Number of patients:										
Dronedarone	241	234	209	215	196	166	105	46	238	240
Amiodarone	250	245	220	217	206	191	128	52	249	249

CC-114

Investigator-reported Cardiac Rhythm Adverse Events

5 Pooled Trials	Placebo (%) (N=2875)	Dronedarone (%) (N=3282)
Bradycardia	1.3	3.3
Electrocardiogram QT prolonged	0.5	1.3
Sinus bradycardia	0.5	1

HR and QTcB Changes
EURIDIS, ADONIS, ATHENA

EURIDIS, ADONIS, ATHENA	Placebo (%)	Dronedarone (%)
≤50 bpm and decrease ≥15 bpm versus baseline	4.5	10.6
QTcB ≥500ms	3.9	6.4
QTcB increase from baseline ≥60 ms	8.8	15.6

Ventricular Tachyarrhythmia Adverse Events

5 Pooled Trials	Placebo (%) (N=2875)	Dronedarone (%) (N=3282)
Ventricular tachycardia	0.4	0.4
Ventricular extrasystoles	0.2	0.3
Ventricular fibrillation	0.1	0.1
Torsade de Pointes	0	<0.1

Thyroid Adverse Events

5 Pooled Trials	Placebo (%) (N=2875)	Dronedarone (%) (N=3282)
Hypothyroidism	0.2	0.6
Hyperthyroidism	0.4	0.3
Abnormal thyroid function test	<0.1	0.0

Neurological Adverse Events

5 Pooled Trials	Placebo (%) (N=2875)	Dronedarone (%) (N=3282)
Insomnia	1.5	1.5
Tremor	0.6	0.6
Sleep disorder	0.1	0.3

Pulmonary Adverse Events

5 Pooled Trials	Placebo (%) (N=2875)	Dronedarone (%) (N=3282)
Interstitial lung disease	<0.1	<0.1
Pulmonary fibrosis	<0.1	<0.1
Pneumonitis	<0.1	<0.1

Hepatic Adverse Events

5 Pooled Trials	Placebo (%) (N=2875)	Dronedarone (%) (N=3282)
Any hepatic TEAEs	2.5	2.9
Liver function analyses	0.9	1.4
Any serious hepatic TEAEs	1.0	0.9
Any hepatic TEAEs leading to discontinuation	0.2	0.3

Patients with ALT > 3 ULN and Total Bilirubin > 2 ULN

ALT > 3 ULN and Total bilirubin > 2 ULN	Placebo 3383 pt-yrs	Dronedarone 400 mg BID 3822 pt-yrs	Amiodarone 600mg/200mg 155 pt-yrs
N (%)	2 (0.06%)	4 (0.10%)*	1 (0.65%)
95%, CI	0.01 – 0.21	0.01 – 0.19	0.02 – 3.54

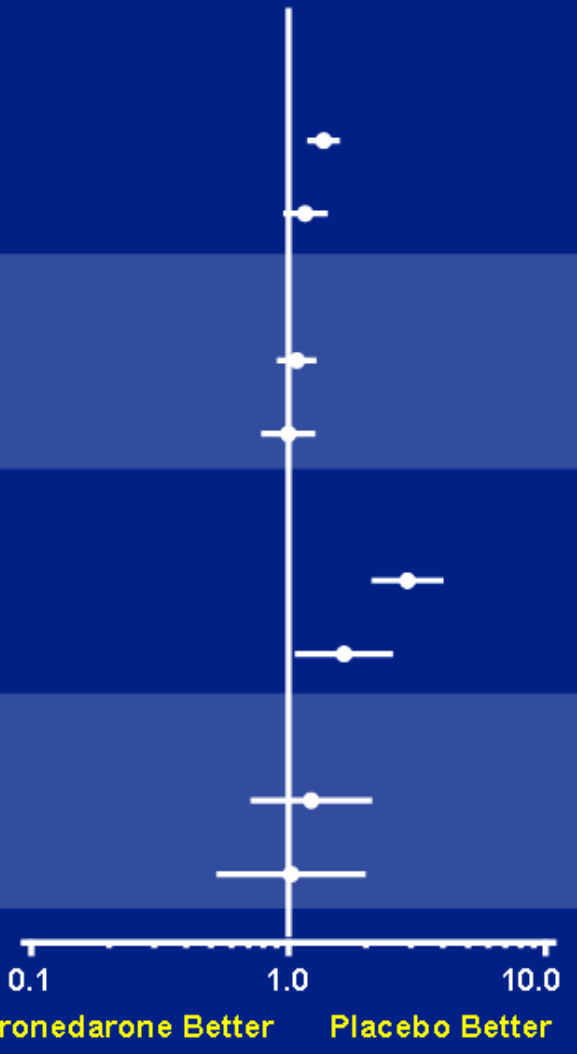
*2 patients in ATHENA and 2 in DIONYSOS
Patients number:DIONYSOS 504002003/ 528010001/40001004-ATHENA 36002003/ 616013004-EURIDIS 56004012/ANDROMEDA 208129007

DIONYSOS
Safety Events of Interest

	Dronedarone 400 mg BID (N=249)	Amiodarone 600 mg/200 mg OD (N=255)
Number of patients with any event of interest	76 (30.5%)	107 (42.0%)
Thyroid events	3 (1.2%)	20 (7.8%)
Hypothyroidism	3 (1.2%)	10 (3.9%)
Hyperthyroidism	0	4 (1.6%)
Thyroid function test abnormal	0	6 (2.3%)
Hepatic events (AST/ALT ≥2 ULN and > 0.5 ULN vs. baseline value)	32 (12.8%)	35 (13.7%)
Neurological events	3 (1.2%)	24 (9.4%)
Tremor	0	7 (2.7%)
Sleep disorder	3 (1.2%)	17 (6.7%)
Skin events (Photosensitivity reaction)	3 (1.2%)	5 (2.0%)
Eye events	1 (0.4%)	5 (2.0%)
Photophobia	0	2 (0.8%)
Vision blurred	1 (0.4%)	3 (1.2%)
Gastrointestinal events	32 (13.3%)	18 (7.1%)
Diarrhea	22 (8.8%)	7 (2.7%)
Nausea	10 (4.0%)	9 (3.5%)
Vomiting	2 (0.8%)	2 (0.8%)
Pulmonary events	0	0

Baseline Beta-Blocker Use in 5 Pooled Trials AE Profile

Characteristic	N	RR [95% CI][a]	P-value[b]
Any class Any event			
With beta-blockers	3978	1.37 [1.18;1.59]	
Without beta-blockers	2179	1.16 [0.95;1.42]	0.160
Heart Failure			
With beta-blockers	3978	1.08 [0.90;1.29]	
Without beta-blockers	2179	1.00 [0.78;1.27]	0.622
Bradyarrhythmia / Bradycardia			
With beta-blockers	3978	2.91 [2.10;4.02]	
Without beta-blockers	2179	1.65 [1.06;2.55]	0.062
Hypotension			
With beta-blockers	3978	1.23 [0.71;2.11]	
Without beta-blockers	2179	1.02 [0.52;2.00]	0.777

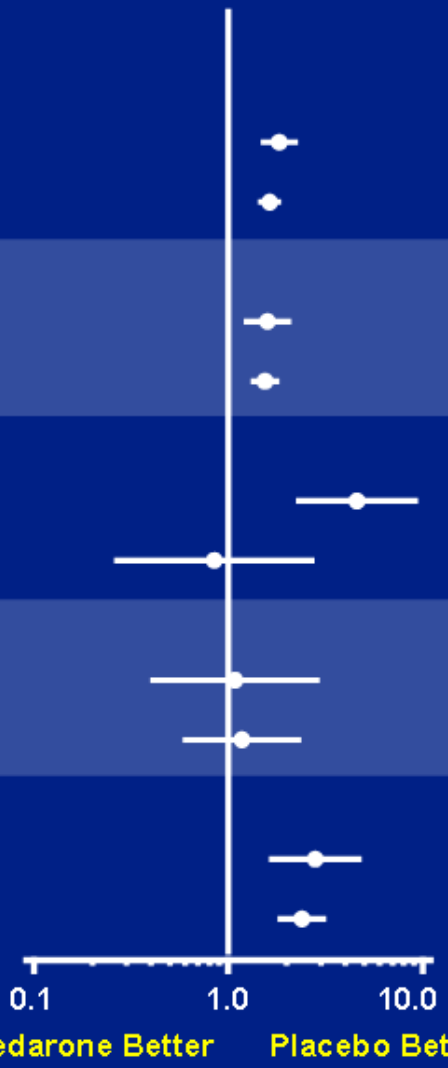


[a] Relative Risk dronedarone vs placebo
[b] Pvalue of interaction between specific event and treatment based on logistic regression

CC-124

Baseline Digitalis Use in 5 Pooled Trials AE Profile

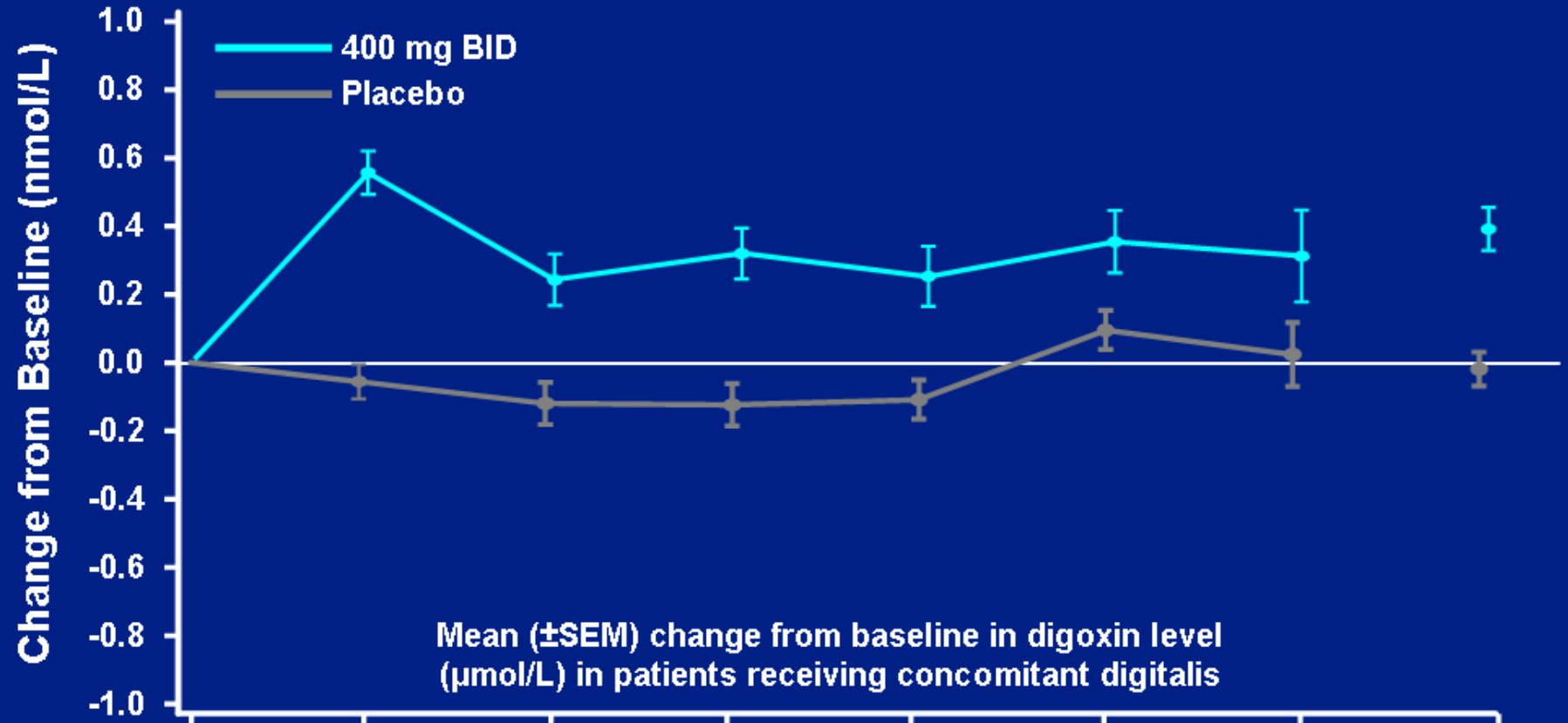
Characteristic	N	RR [95% CI][a]	P-value[b]
Any class Any event			
With digitalis	968	1.83 [1.46;2.28]	
Without digitalis	5189	1.63 [1.42;1.88]	0.158
Diarrhea or Nausea and vomiting symptom			
With digitalis	968	1.59 [1.20;2.10]	
Without digitalis	5189	1.55 [1.31;1.83]	0.628
Digitalis or Digoxin Intoxication			
With digitalis	968	4.59 [2.23;9.44]	
Without digitalis	5189	0.85 [0.26;2.77]	0.009
Ventricular Arrhythmia			
With digitalis	968	1.08 [0.40;2.95]	
Without digitalis	5189	1.18 [0.58;2.37]	0.908
Bradyarrhythmia or Bradycardia			
With digitalis	968	2.80 [1.62;4.85]	
Without digitalis	5189	2.39 [1.79;3.20]	0.479



[a] Relative Risk dronedarone vs. placebo
[b] Pvalue of interaction between specific event and treatment based on logistic regression

CC-125

ATHENA
Mean Change in Digoxin Level from Baseline

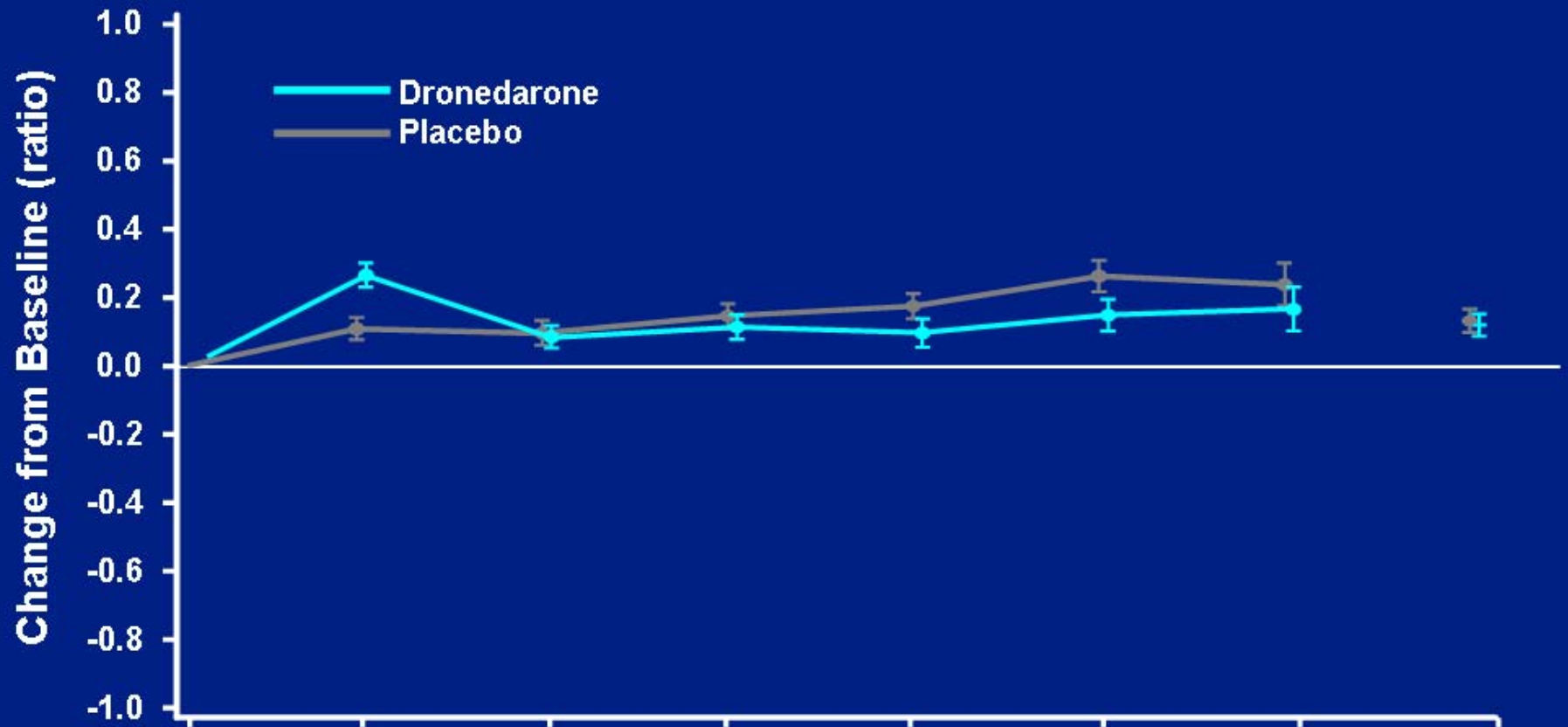


Number of patients	B	D14	M3	M6	M12	M18	M24	EOT
400 mg BID	255	184	132	118	99	65	32	230
Placebo	256	207	168	142	135	102	49	237

B: Baseline, EOT: Last post baseline assessment before treatment discontinuation
Only scheduled time points are considered.

CC-126

Mean Change in INR
Patients Taking Oral Anticoagulants in ATHENA



Number of patients	B	D14	M3	M6	M12	M18	M24	EOT
400 mg BID	1355	1205	1114	1008	887	640	316	1315
Placebo	1346	1222	1113	1004	888	636	327	1320

B: Baseline, EOT: Last post baseline assessment before treatment discontinuation
Only scheduled time points are considered.

CC-127

Risk Management: Identified and Potential Risks

- **Identified Risks**
  - Use in AF/AFL patients with symptomatic heart failure at rest or with minimal exertion within the last month or hospitalized for heart failure within the last month
  - Concurrent use of medications that could result in serious drug-drug interactions (potent CYP3A4 inhibitors; Class I and III antiarrhythmic drugs; TdP inducing drugs)
  - Management of serum creatinine increase
- **Potential risks**
  - Use of concurrent medications requiring caution (digoxin; statin)
  - Amiodarone-like events (hepatic; pulmonary; skin; neurologic)

Mitigation Through Proposed Labeling

- **Identified Risks**
  - **Symptoms of heart failure at rest or with minimal exertion within the last month or hospitalized for heart failure within the last month**
    - Contraindication for treatment initiation
  - **Drug-drug interactions**
    - Contraindicated: Potent CYP3A4 inhibitors; Class I and III antiarrhythmic drugs; TdP inducing drugs
  - **Management of serum creatinine increase**
    - Warning: Measure at Day 7-14, use value as reference
- **Potential risks**
  - **Other Drug-Drug interactions**
    - Digoxin: Give 50% of the dose, monitor plasma levels, titrate
    - Statins: Dosing recommendation as per statin PI, monitor clinical signs of muscular toxicity
  - **Potential amiodarone-like events**

Risk Management Beyond Labeling

	Medication Guide	Targeted Education/ Outreach	KAB surveys Utilization studies	Database Case-control studies	Enhanced pharmaco-vigilance
Identified Risks					
Use in symptomatic/ hospitalized HF	✓	Communi-cation Plan and Tools targeted at Patients, Physicians, Pharmacists	✓		
DDI with potent CYP3A4 inhibitors	✓		✓		
Creatinine increase	✓		✓		
Potential Risks					
DDI Digoxin, statins	✓			✓	
Amiodarone-like effects ILD, hepatic reaction				✓	Standardized collection forms
Neuropathy, Severe skin disorders				✓	

Dronedarone Safety Conclusions

- **Safety well characterized in 3282 AF/AFL patients with mean follow-up of 12.7 months**
  - GI (mild to moderate diarrhea)
  - Renal (creatinine increase – plateau early and reversible)
  - Cardiac (bradycardia mild to moderate)
  - Skin rash (mostly non-serious)
- **Predictable drug interactions are manageable**
  - Beta-blockers
  - Digoxin
  - Statins
- **No significant interaction with oral anticoagulants**

Benefit Risk of Dronedarone for Treatment of Atrial Fibrillation

A. John Camm, MD
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Atrial Fibrillation/Flutter

- **Rapidly growing prevalence:**
  - Currently 2.5 million Americans, but may rise to 15 million by 2050
- **Associated with:**
  - Increased mortality (2 fold)
  - Increased hospitalisations (10% per year)
  - Increased stroke (4.5 fold)
  - Increased heart failure (2-3 fold)
  - Substantial costs (approx. 1-2% health care budget)

Unmet Medical Need

- **Thrombo-embolism**
  - Partially addressed with conventional anticoagulation
- **Rhythm control**
  - Moderately effective antiarrhythmic agents are available which may "suppress AF recurrence" but at a cost of cardiac or extra-cardiac adverse effects
- **Rate control**
  - Adequate rate control difficult to achieve with conventional rate control agents (heart rate at target in only 67% in AFFIRM study)
- **Morbidity-mortality**
  - Anticoagulant agents have some effect; antiarrhythmic agents have not been shown to have any positive effect. This is the major unmet medical need

Identified Benefits of Dronedarone

- **Prolongation of time to first CV hospitalization or death:**
  - **ATHENA primary endpoint: RRR-24%; consistent across major subgroups**
- **Numerical reduction of all cause mortality:**
  - **Not statistically significant, but**
  - **Unlikely that dronedarone is associated with an increased mortality (upper 95% CI = 1.08)**
  - **Exploratory analyses show marked reductions of all and CV hospitalizations, CV and sudden cardiac deaths**

Antiarrhythmic Benefits of Dronedarone

- **Rhythm control**
  - Delays recurrences of AF (DAFNE, EURIDIS, ADONIS, ATHENA)
  - Decreases AF symptomatic episodes (DAFNE, EURIDIS, ADONIS)
  - Reduces the number of AF episodes over time (ATHENA)
- **Rate control**
  - Decreases ventricular rate during AF recurrences (DAFNE, EURIDIS, ADONIS)
  - Provides incremental rate control, on top of standard agents in permanent AF (ERATO)

Dronedarone and Other AADs

AAD	Potential adverse effects	Dronedarone
Flecainide Propafenone	Ventricular tachycardia Conversion to atrial flutter with rapid conduction Aggravation/provocation of heart failure	Low risk of ventricular tachycardia No report of atrial flutter with rapid conduction No increased heart failure in stable patients
Dofetilide	Torsades de Pointes	Low risk of Torsade de Pointes (1 case reported)
Sotalol	Torsades de Pointes Bradycardia Aggravation/provocation of heart failure Exacerbation of asthma/COPD	Low risk of Torsade de Pointes (1 case) Low incidence of significant bradycardia No increased heart failure in stable patients Little observed effect on pulmonary disease
Amiodarone	Photosensitivity, pulmonary toxicity, GI upset, bradycardia, hepatic toxicity, thyroid dysfunction, eye complications	Lower incidence of amiodarone-like side effects

Dronedarone Safety Profile

- *GI side effects* (nausea and diarrhea) are not dangerous, occur early, and are manageable
- Increased serum creatinine is well characterised, is not due to renal toxicity, and is managed easily
- Drug/drug interactions extensively studied and can be managed e.g., the dose of digoxin and some statins require reduction because dronedarone increases their concentration
- Multi-organ toxicities (thyroid, neurologic, pulmonary, hepatic) noticeably less than with amiodarone, but will be further studied during the risk evaluation and mitigation strategy
- Recently "unstable" heart failure patients must be avoided

Benefits in the Management of Patients with AF/AFL and Associated CV Risk Factors

Addresses major unmet medical needs

- **To treat atrial arrhythmia safely**
  - **Effective rhythm and rate control without liabilities**
- **More importantly to improve CV outcomes**
  - **Beyond merely reducing AF recurrences, positively impacts other components of CV risk, such as coronary events and strokes (ATHENA)**
  - **First antiarrhythmic drug to reduce the combined risk of CV hospitalization or death**

What Does this Mean for the Patient?

- Little proarrhythmic risk associated with treatment
- Outpatient initiation – single dose regimen
- No deleterious impact on OAC management
- Potential for better compliance and adherence
- Decreased AF and CV hospitalizations

Which Patient?

- **Appropriate Patient**
  - Recent history of AF or current non-permanent AF in patients with associated cardiovascular risk as recruited in the ATHENA trial

Excellent Benefit Risk

- **Inappropriate Patient**
  - Symptoms of heart failure at rest or with minimal exertion, or hospitalisation for heart failure within the last month, as recruited in the ANDROMEDA trial

Poor Benefit Risk

Benefit Risk Assessment Conclusion

The benefit risk for dronedarone in the treatment of appropriate patients is uniquely positive

<u>It supports the indication under discussion</u>:

"Multaq is indicated in patients with either recent history of, or current non-permanent atrial fibrillation or flutter and with associated risk factors.

Multaq has been shown to decrease the combined risk of cardiovascular hospitalization or death"

MULTAQ® (dronedarone)

FDA Cardiovascular and Renal Drugs Division Advisory Committee Meeting

March 18, 2009

sanofi-aventis

CC-143