A New Horizon in the Treatment of Atrial Fibrillation

Dronedarone Overview

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Atrial Fibrillation

- 심방세동은 지속성 부정맥 중에서 가장 흔하다.
  - 서양 인구의 1-2%; silent AF가 1/3
  - 고령화로 50년 후 유병률은 최소 2배로 예상
  - 현재 40세 정상인; 향후 25%는 일생 중 AF를 경험
- 심방세동과 뇌졸중
  - 평균 5배의 위험성 증가
  - 다른 원인에 의한 것보다 치명적이거나 후유증이 큼
  - 1.5배의 진료비

- Frustrations
  - Rate control vs. rhythm control
  - Strict vs. *laissez-faire* rate control
  - Early detection; silent or asymptomatic nature of AF
  - Ablation; Mortality?
- Hopes
  - Ablation; reduce symptomatic burden, cure in some patients?
  - New anticoagulants
  - New antiarrhythmic agent(s)

AFFIRM (the Atrial Fibrillation Follow-up Investigation of Rhythm Management) NEJM 2002;347:1825-33
RACE II (RAte Control Efficacy in permanent atrial fibrillation) NEJM 2010;362:1363-73

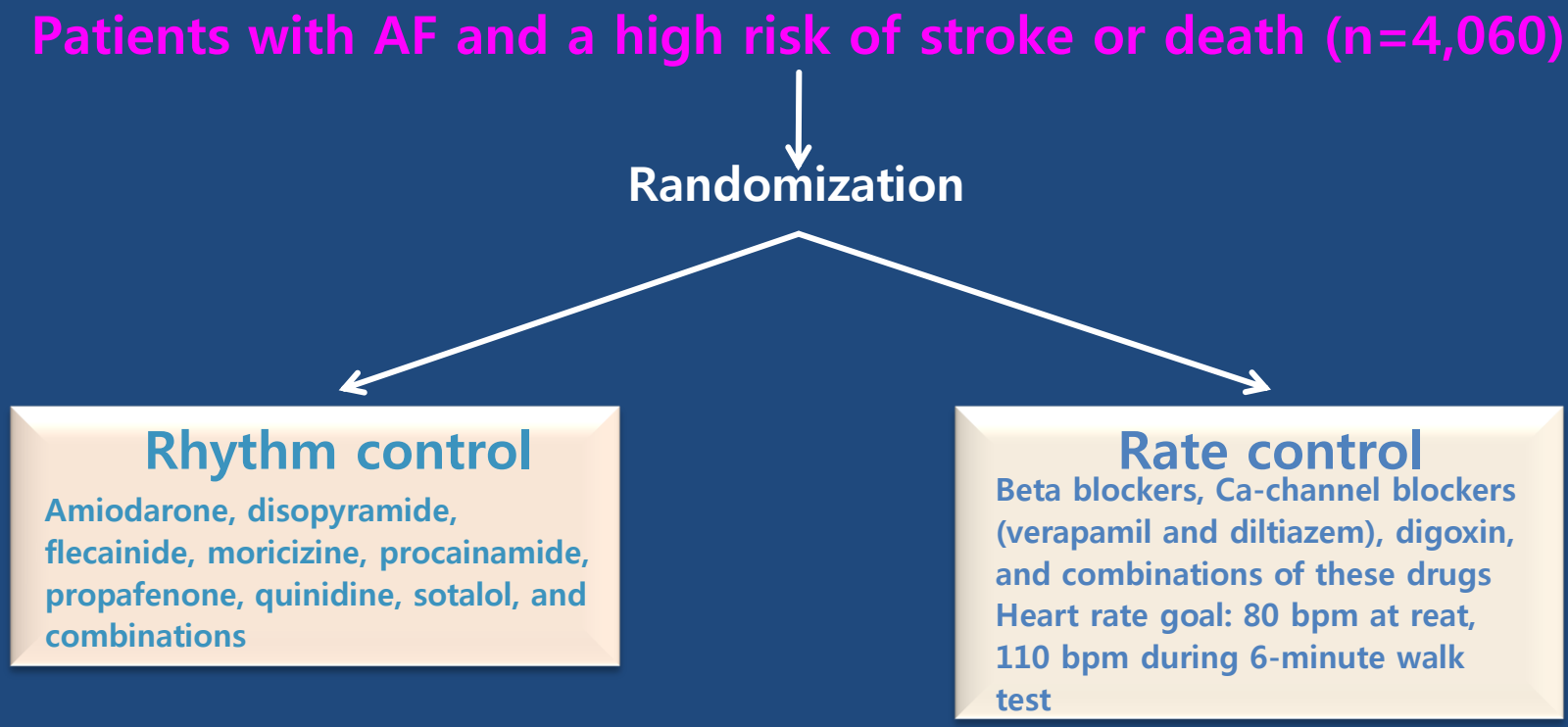
Rate vs. Rhythm Control

Trial	Ref	Patients (*n*)	Mean age (years)	Mean follow-up (years)	Inclusion criteria	Primary outcome parameter	Patients reaching primary outcome (*n*)		
							Rate control	Rhythm control	*P*
PIAF (2000)	92	252	61.0	1.0	Persistent AF (7–360 days)	Symptomatic improvement	76/125 (60.8%)	70/127 (55.1%)	0.32
AFFIRM (2002)	86	4060	69.7	3.5	Paroxysmal AF or persistent AF, age ≥65 years, or risk of stroke or death	All-cause mortality	310/2027 (25.9%)	356/2033 (26.7%)	0.08
RACE (2002)	87	522	68.0	2.3	Persistent AF or flutter for <1 years and 1–2 cardioversions over 2 years and oral anticoagulation	Composite: cardiovascular death, CHF, severe bleeding, pacemaker implantation, thrombo-embolic events, severe adverse effects of antiarrhythmic drugs	44/256 (17.2%)	60/266 (22.6%)	0.11
STAF (2003)	88	200	66.0	1.6	Persistent AF (>4 weeks and <2 years), LA size >45 mm, CHF NYHA II–IV, LVEF <45%	Composite: overall mortality, cerebrovascular complications, CPR, embolic events	10/100 (10.0%)	9/100 (9.0%)	0.99
HOT CAFÉ (2004)	89	205	60.8	1.7	First clinically overt persistent AF (≥7 days and <2 years), age 50–75 years	Composite: death, thrombo-embolic events; intracranial/major haemorrhage	1/101 (1.0%)	4/104 (3.9%)	>0.71
AF-CHF (2008)	90	1376	66	3.1	LVEF ≤35%, symptoms of CHF, history of AF (≥6 h or DCC <last 6 months)	Cardiovascular death	175/1376 (25%)	182/1376 (27%)	0.59
J-RHYTHM (2009)	91	823	64.7	1.6	Paroxysmal AF	Composite of total mortality, symptomatic cerebral infarction, systemic embolism, major bleeding, hospitalization for heart failure, or physical/ psychological disability	89/405 (22.0%)	64/418 (15.3%)	0.012

Rate vs. Rhythm Control

Trial	Ref	Deaths from all causes (in rate/rhythm)	Deaths from cardiovascular causes	Deaths from non-cardiovascular causes	Stroke	Thrombo-embolic events	Bleeding
PIAF (2000)	92	4	1/1	1[a]	ND	ND	ND
AFFIRM (2002)	86	666 (310/356)	167/164	113/165	77/80	ND	107/96
RACE (2002)	87	36	18/18	ND	ND	14/21	12/9
STAF (2003)	88	12 (8/4)	8/3	0/1	1/5	ND	8/11
HOT CAFÉ (2004)	89	4 (1/3)	0/2	1/1	0/3	ND	5/8
AF-CHF (2008)	90	228/217	175/182	53/35	11/9	ND	ND

AFFIRM: rate vs. rhythm control



- Primary endpoint: overall mortality
- Composite secondary endpoint: death, disabling stroke, disabling anoxic encephalopathy, major bleeding, and cardiac arrest
- Mean follow-up 3.5 years

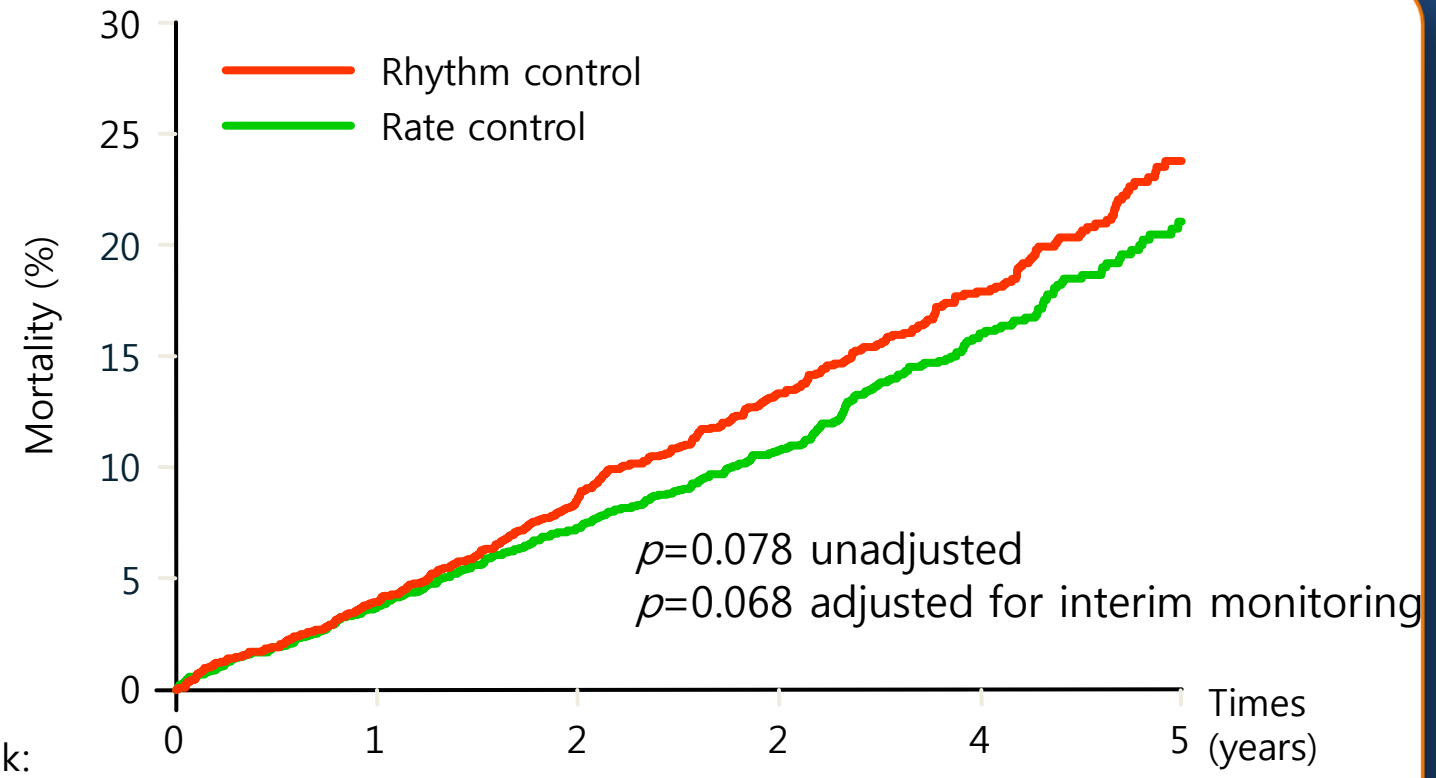
AFFIRM investigators. *N Engl J Med.* 2002;347:1825-33.

AFFIRM: Initial & subsequent therapy

no. of patients (%)	Rate-Control Group		Rhythm-Control Group	
	Used drug for initial therapy	Used drug at any time	Used drug for initial therapy	Used drug at any time
Rate control				
Data available	1957	2027	1266	2033
Digoxin	949 (48.5)	1432 (70.6)	417 (32.9)	1106 (54.4)
Beta-blocker	915 (46.8)	1380 (68.1)	276 (21.8)	1008 (49.6)
Diltiazem	583 (29.8)	935 (46.1)	198 (15.6)	610 (30.0)
Verapamil	187 (9.6)	340 (16.8)	56 (4.4)	204 (10.0)
Rhythm control				
Data available	1265	2027	1960	2033
Amiodarone	2 (0.2)	207 (10.2)	735 (37.5)	1277 (62.8)
Sotalol	1 (0.1)	84 (4.1)	612 (31.2)	841 (41.4)
Propafenone	2 (0.2)	45 (2.2)	183 (9.3)	294 (14.5)
Procainamide	0	30 (1.5)	103 (5.3)	173 (8.5)
Quinidine	2 (0.2)	14 (0.7)	92 (4.7)	151 (7.4)
Flecainide	0	29 (1.4)	88 (4.5)	169 (8.3)
Disopyramide	0	7 (0.3)	42 (2.1)	87 (4.3)
Moricizine	0	2 (0.1)	14 (0.7)	35 (1.7)
Dofetilide	0	5 (0.2)	0	13 (0.6)
Warfarin		(85.0)		(70.0)

The AFFIRM Investigators. N Engl J Med. 2002;347:1825-1833

AFFIRM- AADs did not reduce mortality in AF



Patients at risk:

Rhythm control	2033	1932	1807	1316	780	255
Rate control	2027	1925	1825	1328	774	236

AFFIRM investigators. *N Engl J Med.* 2002;347:1825-33.

Guidelines for the Management of Patients with Atrial Fibrillation

- 2006 ACC/AHA/ESC guidelines
  Circulation 2006;114:e257-e354

- 2010 ESC guideline update
  Europace 2010 Oct;12(10):1360-420

- 2010 Canadian guideline update
  Canadian J Cardiol 2011 Jan-Feb;27(1):74-90

- 2011 ACCF/AHA/HRS focused update guidelines
  Circulation 2011 Mar;123(10):e269-e367

- Detection of AF
- Management of AF
  - Antithrombotic management
  - Rate and rhythm management
  - Long-term management
  - Upstream therapy
- Specific populations

Antithrombotic Management

2010 ESC guideline

- Stroke risk stratification — CHA_2DS_2-VASc score
- Antithrombotic treatment — New agents
- Bleeding risk stratification — HAS-BLED score
- Optimal INR
- Special situations

Paroxysmal AF, Perioperative anticoagulation, stable vascular disease, ACS±PCI, Elective PCI, NSTEMI, Acute STEMI with primary PCI, Acute stroke, Atrial flutter, Cardioversion, TEE-guided cardioversion, Non-pharmacological methods to prevent stroke

Antithrombotic Management

Focused update, 2011 ACC/AHA/HRS

- No change!!!!!
  - New antithrombotic agents are not approved by FDA

Antithrombotic Management

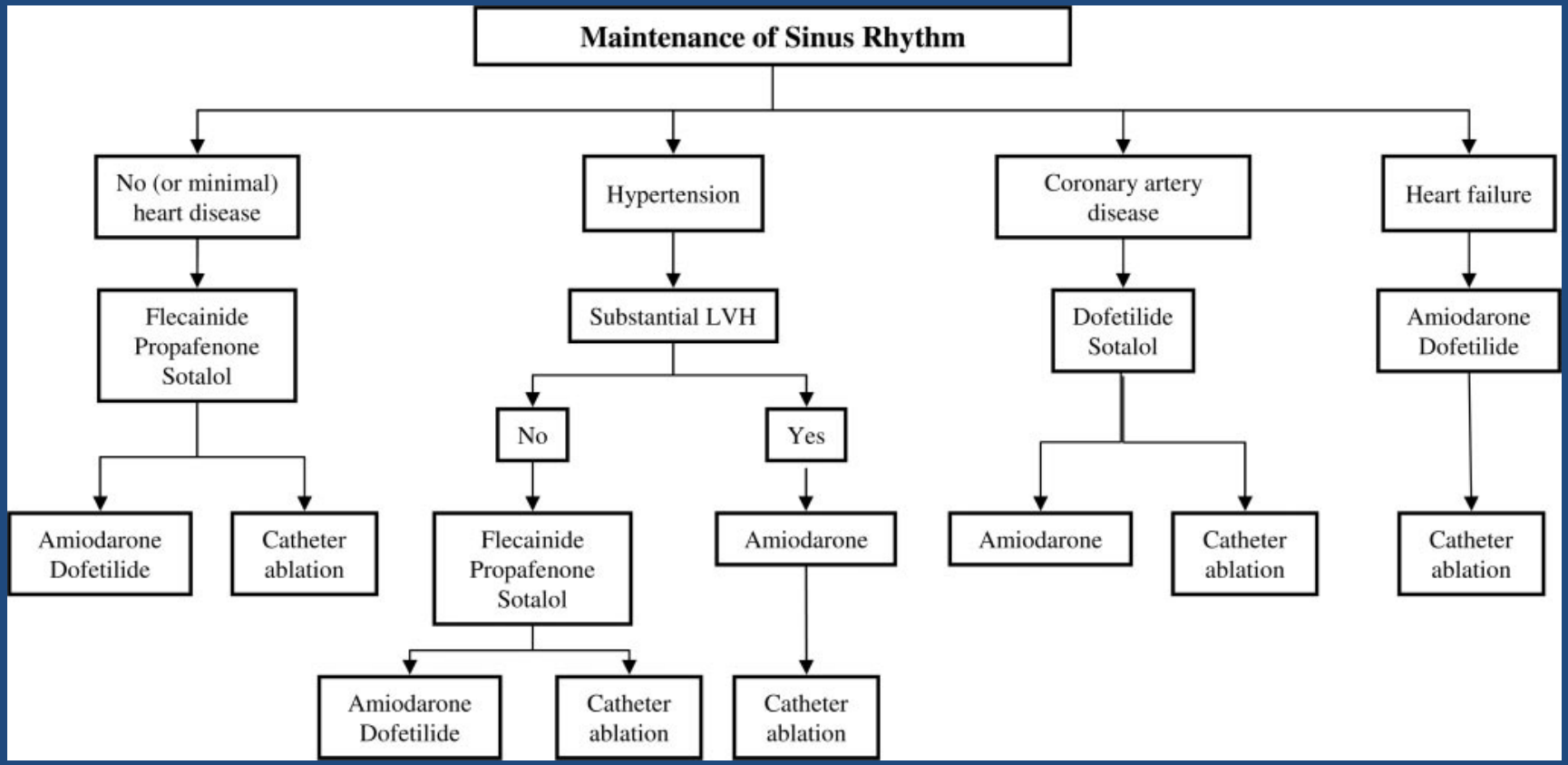
2011 Canadian Update

- A new antithrombotic agent, dabigatran is preferred
  - Antithrombotic potency: at least same as warfarin
  - Side effect: much less than warfarin

- Detection of AF
- Management of AF
  - Antithrombotic management
  - Rate and rhythm management
  - Long-term management
  - Upstream therapy
- Specific populations

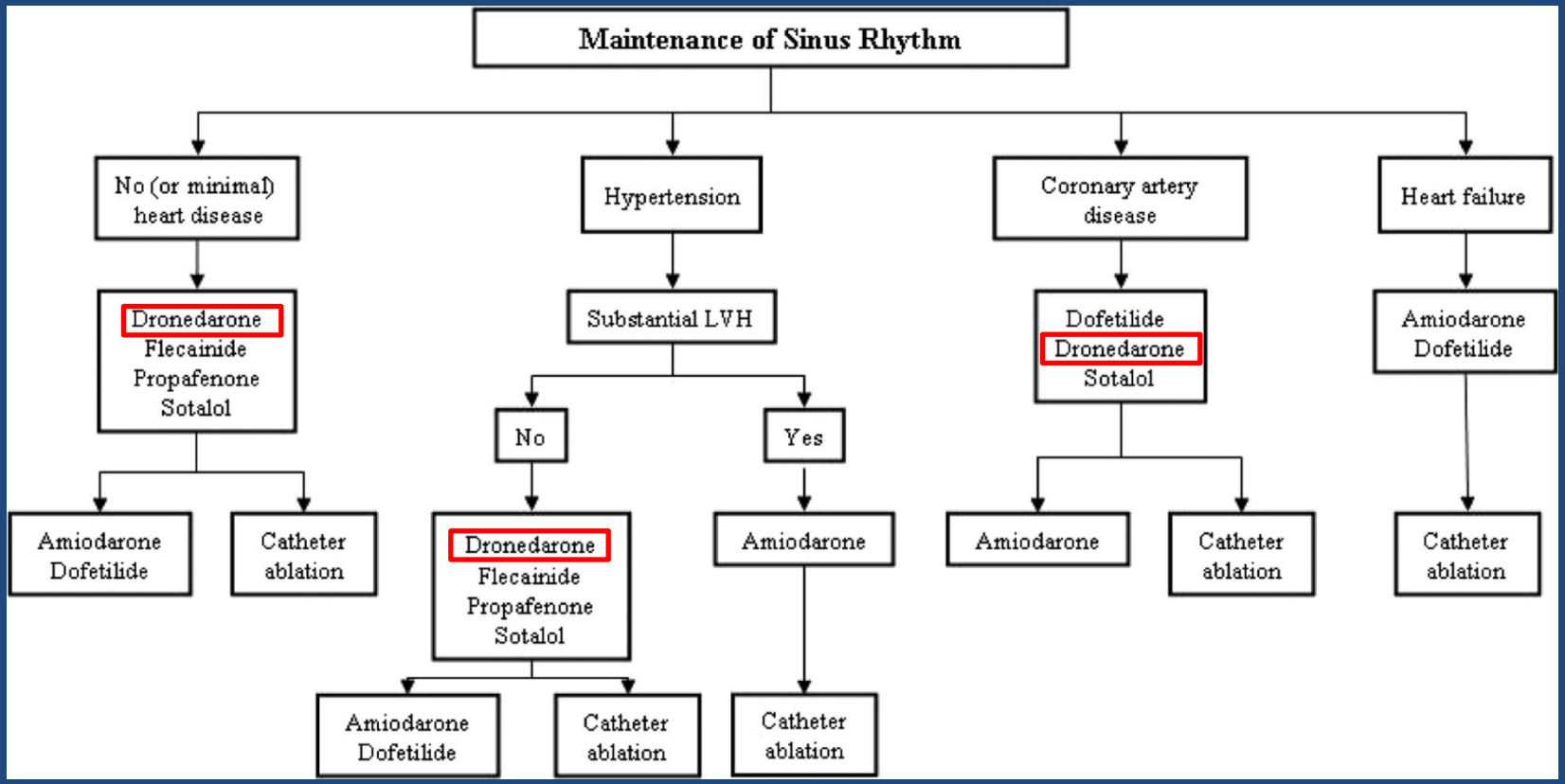
2006 ACC/AHA/ESC Guideline

Maintenance of Sinus Rhythm



Focused Updates, 2011 ACC/AHA/HRS

Maintenance of Sinus Rhythm



2011 Focused Updates, ACC/AHA/HRS Use of Dronedarone in AF

- Class IIa
  - Dronedarone is reasonable to decrease the need for hospitalization for cardiovascular events in patients with paroxysmal atrial fibrillation or after cardioversion of persistent AF. Dronedarone can be initiated during outpatient therapy (*Level of evidence: B*)

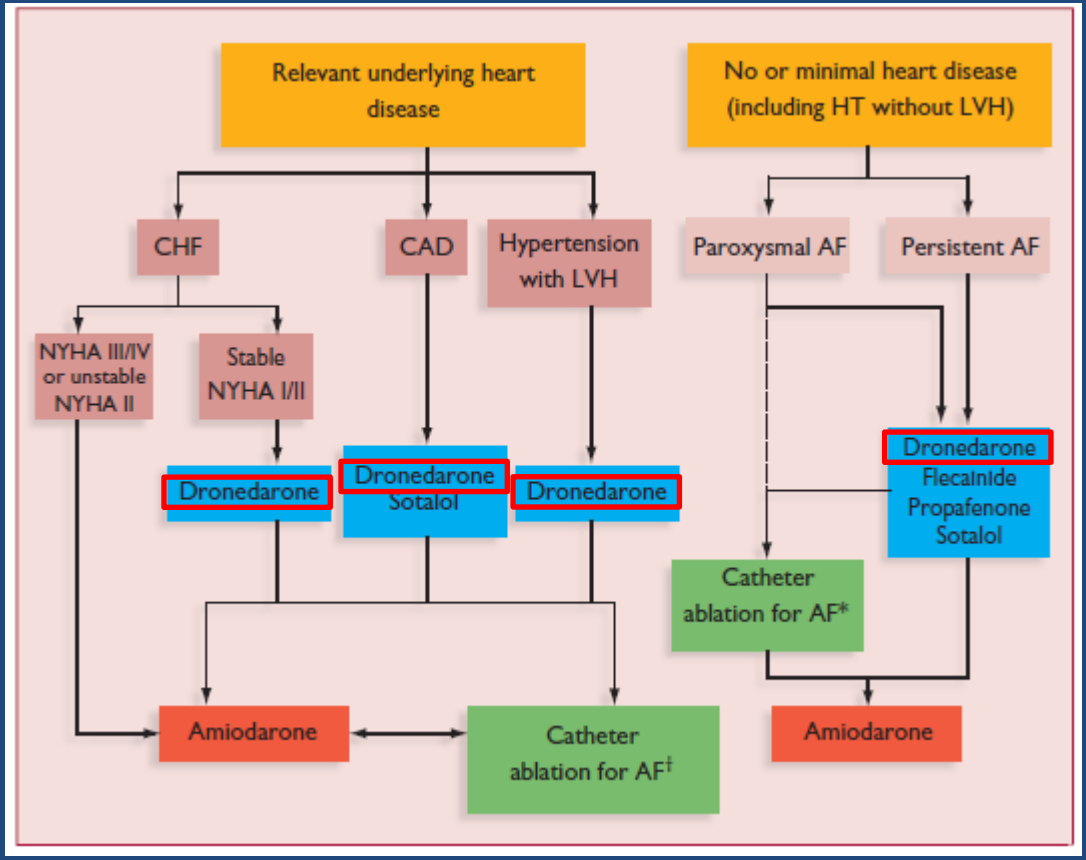
- Class III – harm
  - Dronedarone should not be administered to patients with class IV heart failure or patients who have had an episode decompensated heart failure in the past 4 weeks, especially if they have depressed left ventricular function (Left ventricular ejection fraction ≤ 35%). (*Level of evidence: B*)

Rate and Rhythm Management
2010 ESC guideline

- Acute rate and rhythm management
  - Acute rate control
  - Pharmacological cardioversion
  - 'Pill-in-the-pocket' approach
  - Direct current cardioversion

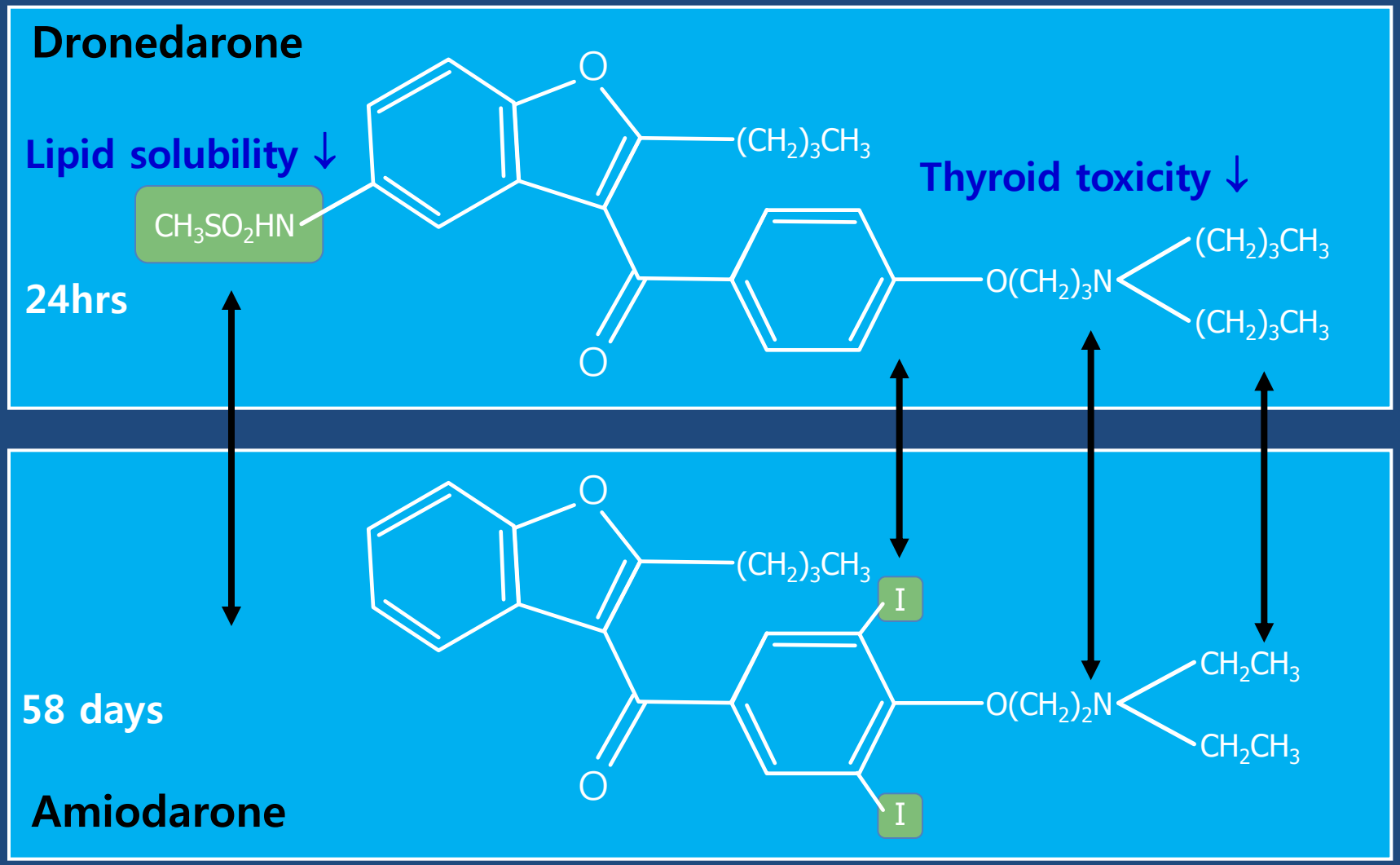
- Long-term management
  - General management
  - Long-term rate control
    - Pharmacological rate control
    - AV node ablation and modification
  - Long-term rhythm control

2010 ESC guideline
Long-term Rhythm control



What is Dronedarone?

Dronedarone and Amiodarone



Kathofer *et al. Cardiovasc Drug Rev.* 2005;23(3):217-30.

Dronedarone: A new AAD for AF/AFL

Absorption

- At least **70% absorption** in healthy subjects
- First-pass effect results in absolute **bioavailability of 15%**
- **Food** increases bioavailability by **2- to 4.5-fold**
- T_{max} = 3-6 hours
- C_{max} = 84-147 ng/ml
- Steady state is reached within 4 to 8 days

Metabolism

- Extensively metabolised, mainly by **CYP3A4**
- Metabolite SR35021 may contribute to the pharmacologic activity of dronedarone (3-10x less potent)

Distribution

- Highly bound (>99%) to human plasma protein (mostly albumin)
- Mean volume of distribution from 1,200 to 1,400 l (after IV administration)

Elimination

- Major route of excretion is in **feces (84%)**
- No unchanged dronedarone is excreted in urine
- Terminal half-life of dronedarone is **25-30 hours** after repeated administration of 400mg BID

Special populations

- Gender, age and weight have a limited influence on dronedarone PK

Dronedarone's clinical programme

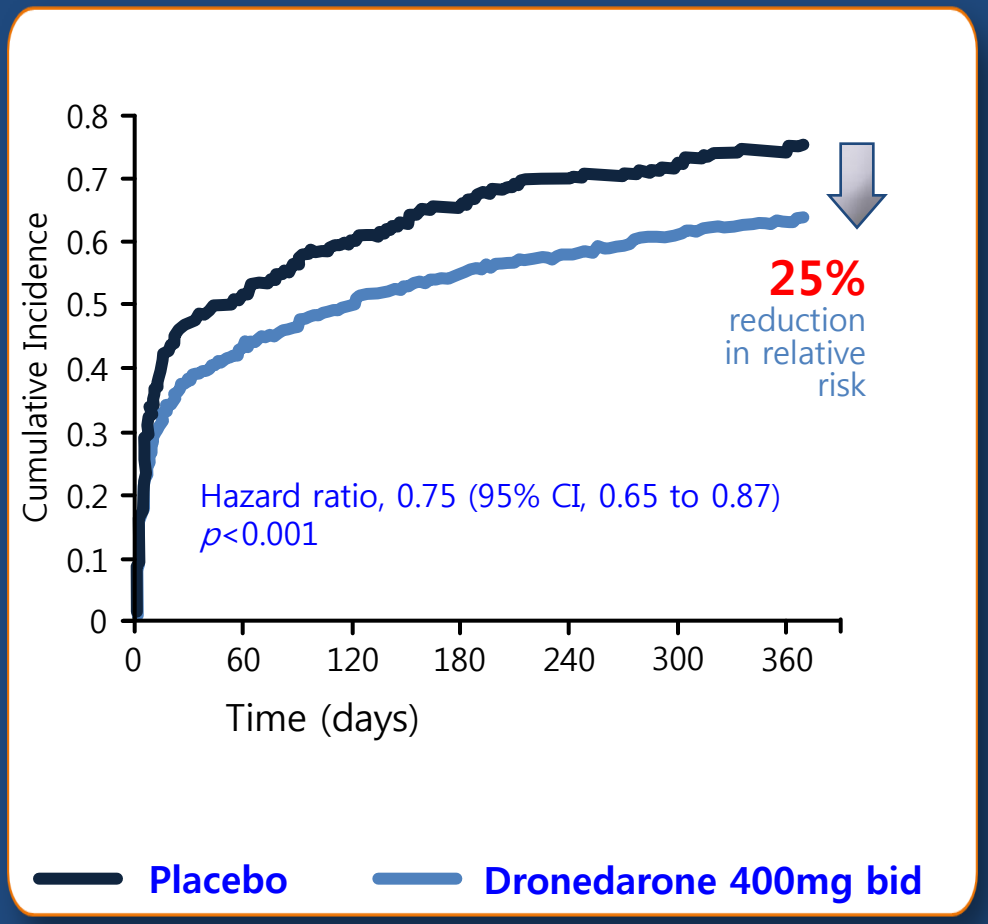
	DAFNE[1]	EURIDIS/ ADONIS[2]	ERATO[3]	ATHENA[4]	DIONYSOS[5]	ANDROMEDA[6]
Trial objective	Dose finding study	Effect of dronedarone on maintenance of sinus rhythm	Effect of dronedarone in the control of mean 24-hour ventricular rate	Evaluate the efficacy and safety of dronedarone in the prevention of CV hospitalisation or all-cause death	Investigate efficacy and safety of dronedarone versus amiodarone for the maintenance of sinus rhythm	Evaluate the potential benefit of dronedarone on all cause death or hospitalisation for worsening heart failure
Patient population	Persistent AF	Paroxysmal/ persistent AF	Permanent AF	Paroxysmal/ Persistent AF	Persistent AF	Unstable recently decompensated CHF patients
Patient status at baseline	In AF but eligible for AAD treatment and cardioversion	In sinus rhythm	In permanent AF	In sinus rhythm or AF but eligible for cardioversion	In AF but eligible for AAD treatment and cardioversion	N/A
Number of patients	102	1237	174	4628	504	627
Dronedarone Versus	Placebo	Placebo Both arms received standard therapy*	Placebo Both arms received standard therapy*	Placebo Both arms received standard therapy*	Amiodarone	Placebo
Primary endpoint	Time to first AF recurrence	Time to first AF/AFL recurrence	Change in mean ventricular rate measured by 24-hour Holter on Day 14 compared to baseline	CV hospitalisation or all-cause mortality	Treatment failure defined as recurrence of AF OR premature study drug discontinuation for intolerance or lack of efficacy	Death from any cause or hospitalisation for worsening heart failure

*Standard therapy may have included rate control agents (beta-blockers, and/or Ca-antagonist and/or digoxin) and/or anti-thrombotic therapy (Vit. K antagonists and/or aspirin and other antiplatelet therapy) and/or other CV agents such as ACEIs/ARBs and statins

1. Touboul P, *et al. Eur Heart J.* 2003;24:1481-7.
2. Singh BN, *et al. N Engl J Med.* 2007;357:987-99.
3. Davy *et al. Am Heart J.* 2008;156:527.e1-527.e9.
4. Hohnloser SH, *et al. N Engl J Med* 2009;360:668-78.
5. Le Heuzey JY et al. *J Cardiovasc Electrophysiol.* 2010 21(6):597-605
6. Køber L, *et al. N Engl J Med.* 2008;358:2678-87.

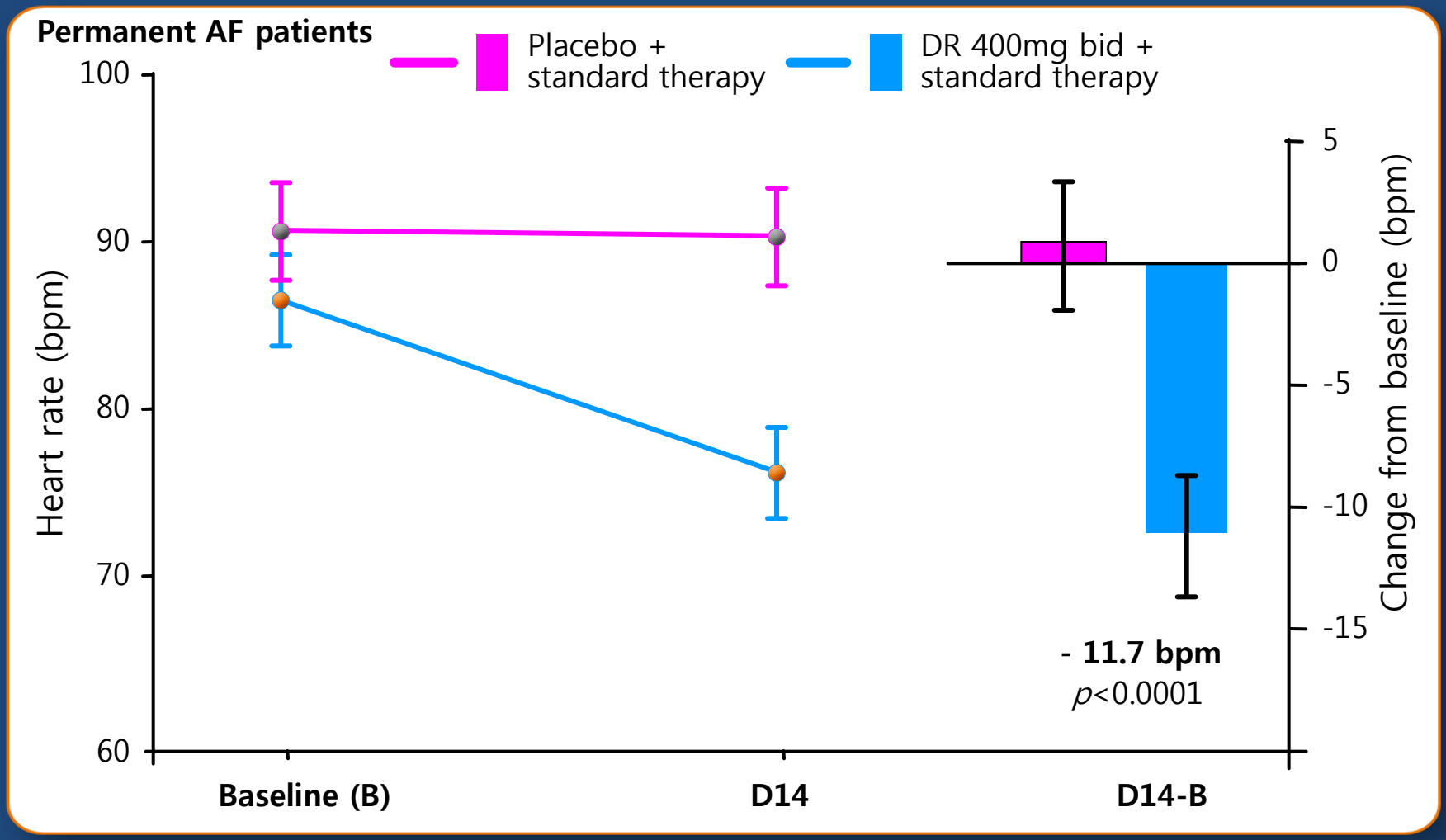
Dronedarone Showed a Significant Reduction in First AF Recurrence in Combined Trials

N = 1244



Singh BN et al. N Engl J Med 2007;357:987–99

Dronedarone significantly decreased ventricular rate by 11.7 bpm



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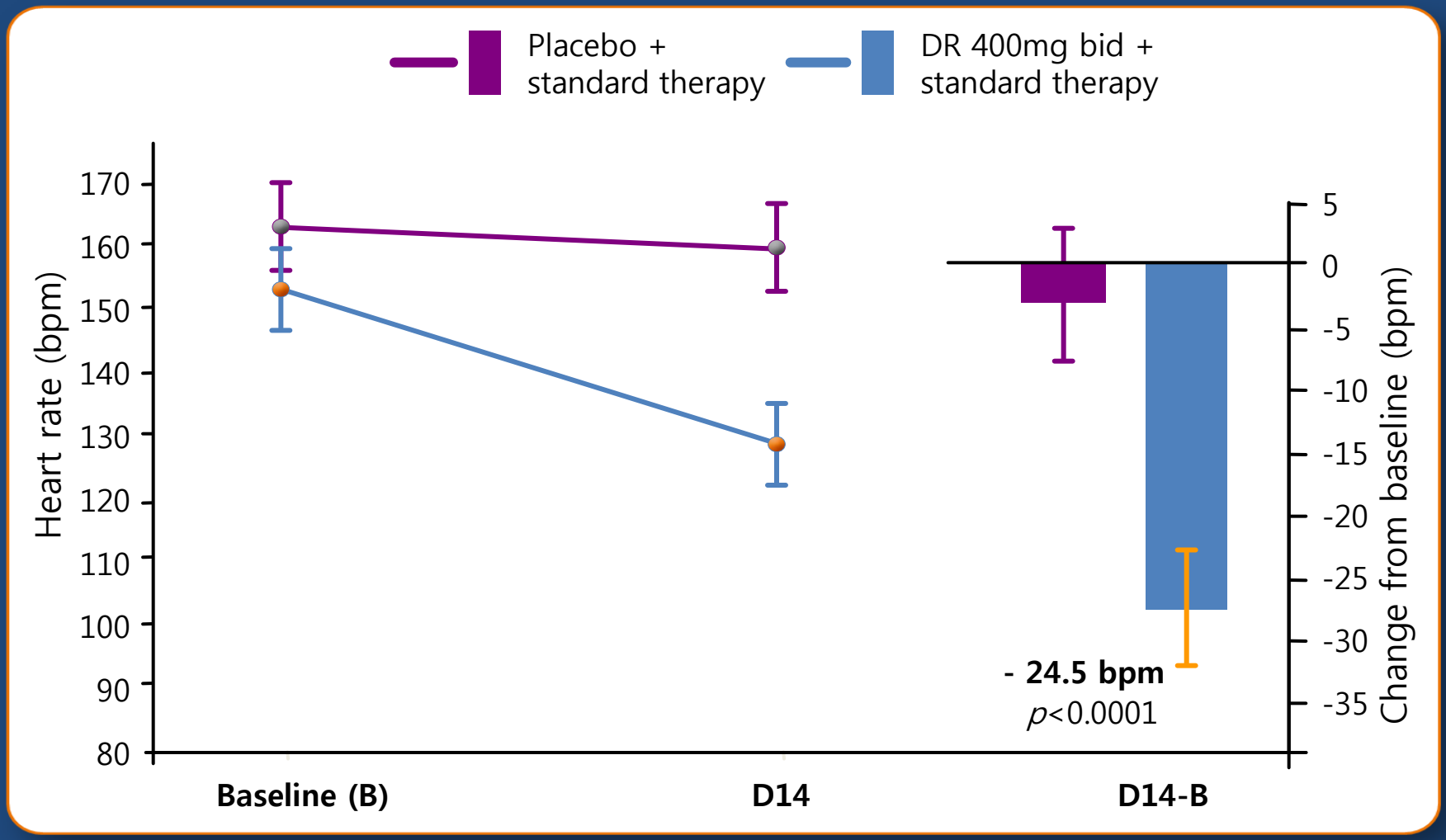
Davy *et al. Am Heart J.* 2008;156:527.e1-527.e9.

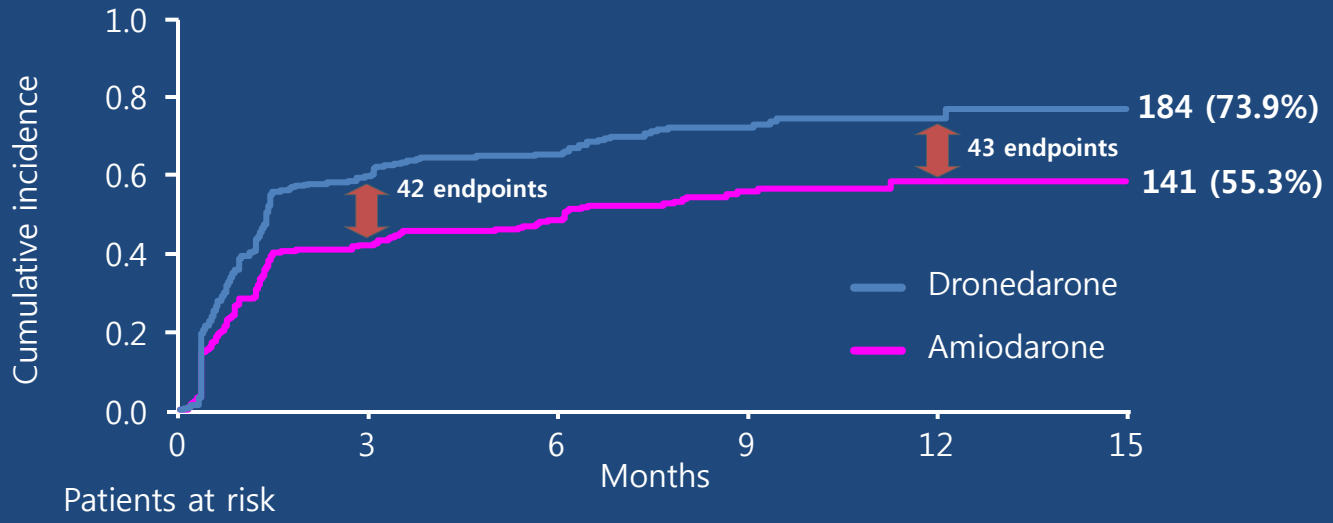
Dronedarone ; maximal exercise ventricular rate

Permanent AF patients



Davy *et al. Am Heart J.* 2008;156:527.e1-527.e9.

DIONYSOS; Primary Endpoint



RRR (95%CI) = 1.59 (1.28;1.98)
***p*-value <0.001**

Patients at risk

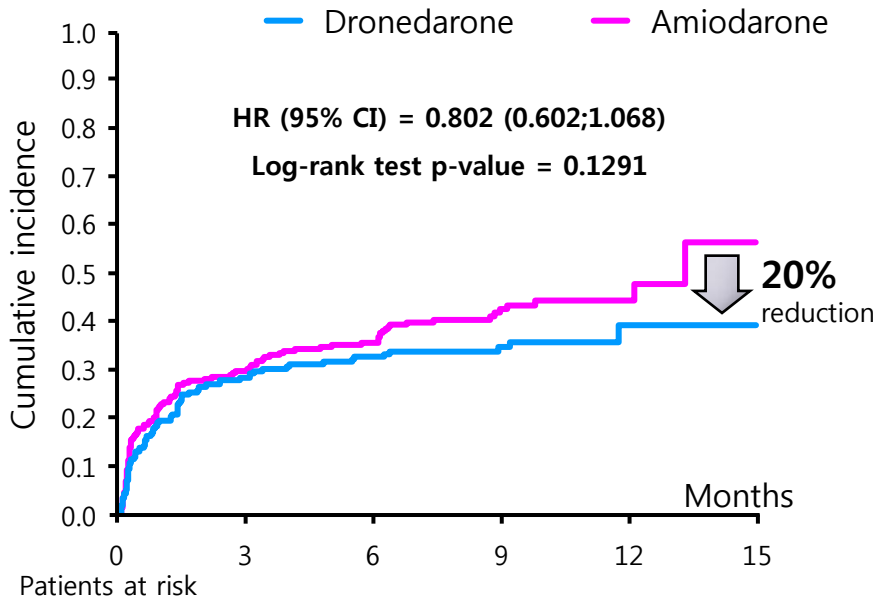
249	99	84	40	12	0
255	146	126	61	13	0

Number of patients with endpoint	Dronedarone (n=249)	Amiodarone (n=255)
ECG documented AF endpoint	**158 (63.5%)**	**107 (42.0%)**
Documented AF after conversion	91 (36.5%)	62 (24.3%)
Unsuccessful electrical cardioversion	29 (11.6%)	16 (6.3%)
No spontaneous conversion and no electrical cardioversion on day 10 to day 28	38 (15.3%)	29 (11.4%)
Premature study drug discontinuation	**26 (10.4%)**	**34 (13.3%)**
Lack of efficacy	1 (0.4%)	0
Intolerance	25 (10.0%)	34 (13.3%)

Le Heuzey JY et al. *J Cardiovasc Electrophysiol*. 2010 21(6):597-605.

DIONYSOS; safety profile

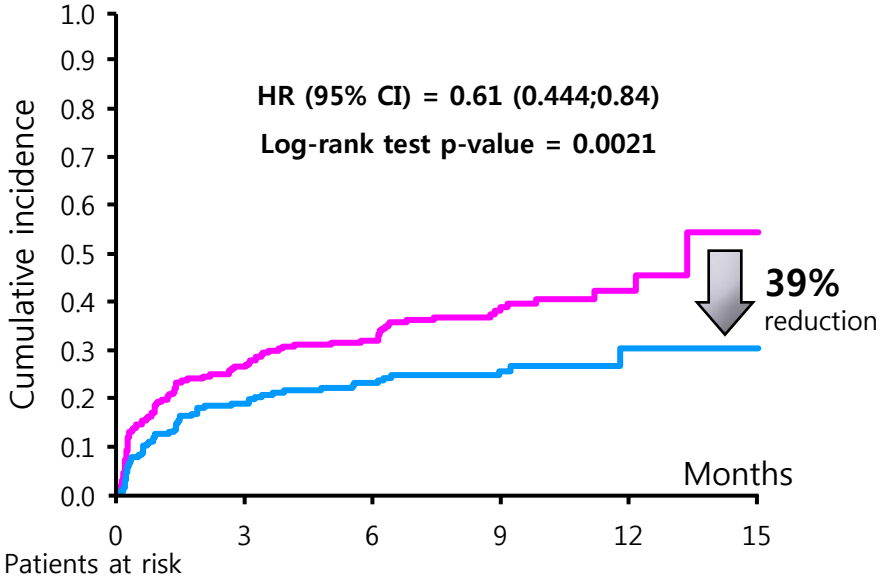
Main Safety Endpoint



Patients at risk

Dronedarone	249	157	127	63	12	0
Amiodarone	255	168	152	76	17	0

Main Safety Endpoint focusing on Organ Toxicity



Patients at risk

Dronedarone	249	179	148	73	14	0
Amiodarone	255	175	160	82	19	0

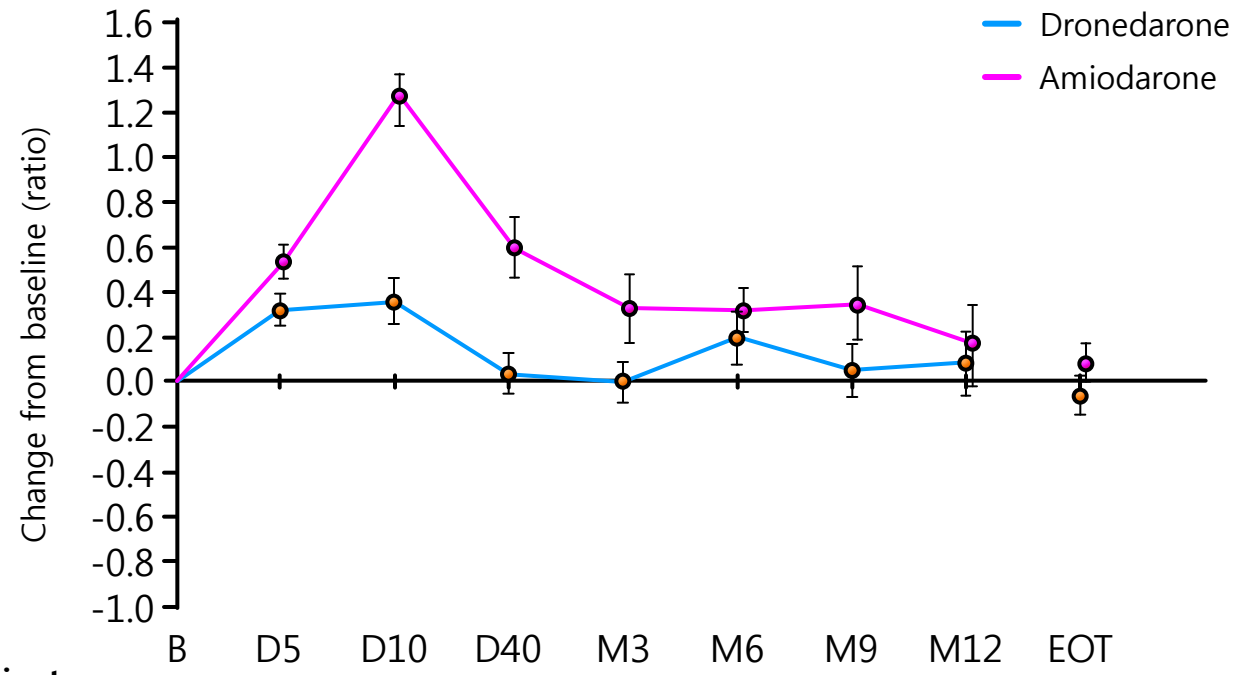
- The incidence of the MSE was non-significantly **reduced by 20%** in the dronedarone group compared with the amiodarone group (p=0.1291)
- The pre-specified safety endpoint that excluded GI side effects showed a **statistically significant 39% decrease in favor of dronedarone** (p=0.0021)

Dronedarone is not associated with the organ toxicity seen with amiodarone

First main safety endpoint	Dronedarone 400 mg BID (n=249)	Amiodarone 600 mg for 28 D then 200 mg OD (n=255)
Number of patients with endpoint	**83 (33.3%)**	**107 (42.0%)**
Thyroid events	**2 (0.8%)**	**15 (5.9%)**
Hypothyroidism	**2 (0.8%)**	**7 (2.7%)**
Hyperthyroidism	**0**	**3 (1.2%)**
Thyroid function test abnormal (requiring medical intervention)	**0**	**5 (2.0%)**
Neurological events	**3 (1.2%)**	**17 (6.7%)**
Tremor	**0**	**5 (2.0%)**
Sleep disorder	**3 (1.2%)**	**12 (4.7%)**
Skin events	**2 (0.8%)**	**4 (1.6%)**
Photosensitivity reaction (skin)	**2 (0.8%)**	**4 (1.6%)**
Eye events	**1 (0.4%)**	**3 (1.2%)**
Photophobia	**0**	**2 (0.8%)**
Vision blurred	**1 (0.4%)**	**1 (0.4%)**
Gastrointestinal events	**32 (12.9%)**	**13 (5.1%)**
Diarrhea	**20 (8.0%)**	**5 (2.0%)**
Nausea	**10 (4.0%)**	**6 (2.4%)**
Vomiting	**2 (0.8%)**	**2 (0.8%)**
Premature study drug discontinuation due to any AE	**13 (5.2%)**	**28 (11.0%)**
Hepatic events Liver enzymes (AST/ALT)	**30 (12.0%)**	**27 (10.6%)**

- Dronedarone is associated with less bradycardia when compared to amiodarone, 2.0% vs 6.3% respectively

Dronedarone is not associated with the INR increase observed with amiodarone



Number of patients

Dronedarone	**237**	**227**	**208**	**211**	**182**	**150**	**89**	**40**	**233**
Amiodarone	**240**	**232**	**215**	**211**	**190**	**175**	**118**	**54**	**239**

- There was a **decreased risk in the incidence of haemorrhagic events** of 49.6% (number of events: dronedarone 14/249; amiodarone 29/255; *p*=0.03)

ATHENA

A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular Hospitalisation or death from any cause in patiENts with Atrial fibrillation/atrial flutter (AF/AFL)

Hohnloser SH, et al. J Cardiovasc Electrophysiol. 2008;19:69-73; Hohnloser SH, et al. N Engl J Med. 2009;360:668-78.

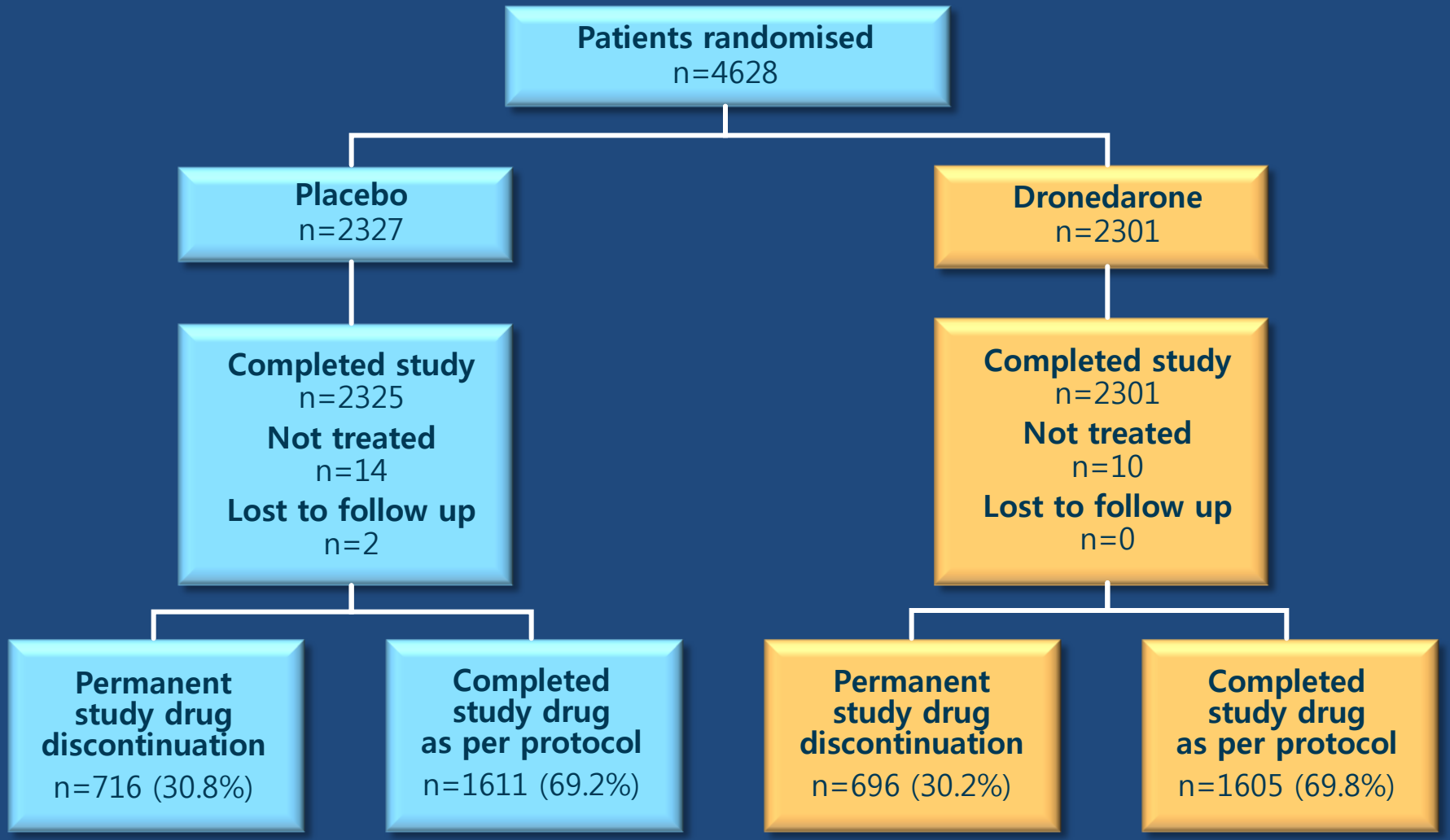
Study Endpoints

- Primary endpoint
  - Combined endpoint of cardiovascular hospitalisation and death from any cause
- Secondary endpoints
  - Death from any cause
  - Cardiovascular death
  - Hospitalisation for cardiovascular reasons

Hohnloser SH, *et al. N Engl J Med* 2009;360:668-78.

Kirchhof P, et al. Europace 2007;9:1006-1023; Hohnloser SH, et al. J Cardiovasc Electrophysiol. 2008;19:69-73.

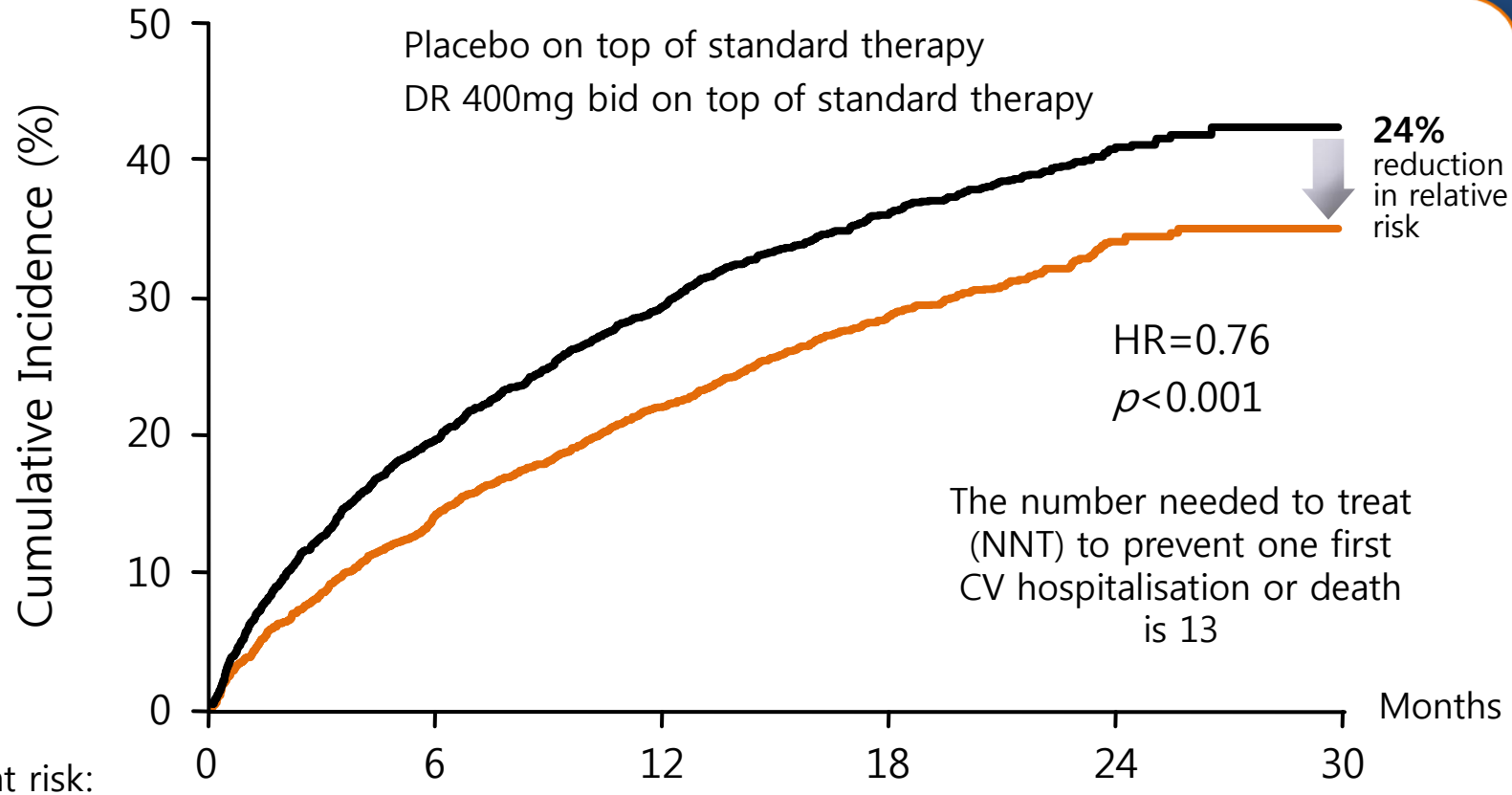
Study Flow



Hohnloser SH, *et al. N Engl J Med* 2009;360:668-78.

Kirchhof P, et al. Europace 2007;9:1006-1023; Hohnloser SH, et al. J Cardiovasc Electrophysiol. 2008;19:69-73.

Dronedarone significantly decreased risk of unplanned CV hospitalisation or death from any cause by 24%



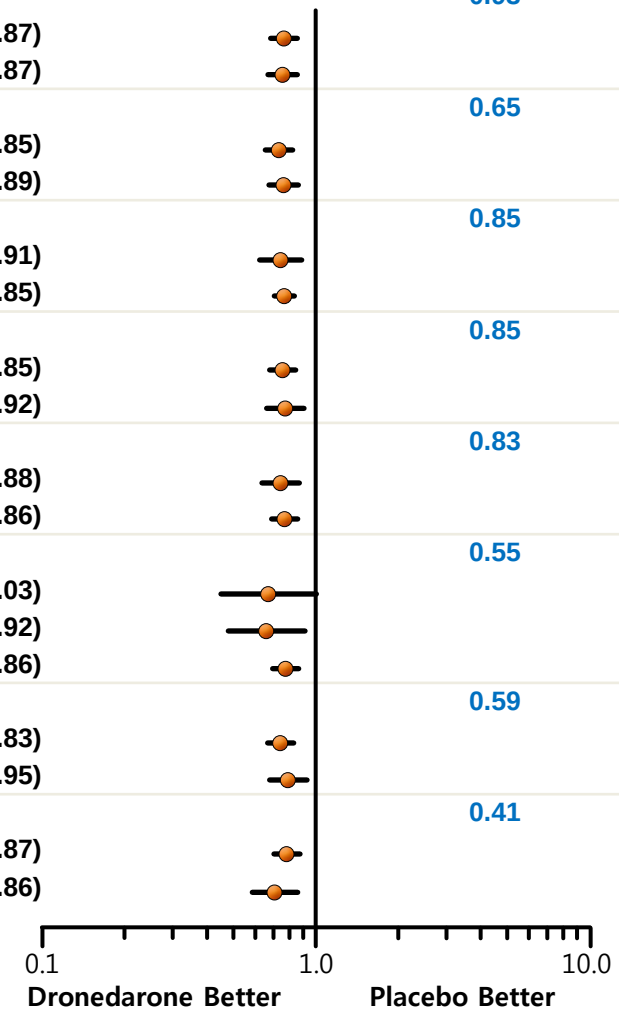
Patients at risk:

Placebo	2327	1858	1625	1072	385	3
DR 400mg bid	2301	1963	1776	1177	403	2

Any unplanned hospitalisation (i.e., admission with an overnight stay in the hospital) was classified by the investigator as a hospitalisation due to either CV or non-CV causes

Dronedarone reduced unplanned CV hospitalisation or all-cause death across important subgroups

Characteristic	n	HR (95% CI)	*p* value for interaction
Age (years)			0.93
<75	2703	0.76 (0.67–0.87)	
≥75	1925	0.75 (0.65–0.87)	
Gender			0.65
Male	2459	0.74 (0.64–0.85)	
Female	2169	0.77 (0.67–0.89)	
Presence of AF/AFL			0.85
Yes	1155	0.74 (0.61–0.91)	
No	3473	0.76 (0.68–0.85)	
Structural Heart Disease			0.85
Yes	2732	0.76 (0.67–0.85)	
No	1853	0.77 (0.65–0.92)	
Congestive Heart Failure			0.83
Yes	1365	0.75 (0.64–0.88)	
No	3263	0.76 (0.68–0.86)	
LVEF (%)			0.55
<35	179	0.68 (0.44–1.03)	
[35-45[	361	0.66 (0.47–0.92)	
≥45	4004	0.78 (0.70–0.86)	
ACE/ARB			0.59
Yes	3216	0.74 (0.66–0.83)	
No	1412	0.79 (0.66–0.95)	
Beta Blocking Agents			0.41
Yes	3269	0.78 (0.69–0.87)	
No	1359	0.71 (0.58–0.86)	



Any unplanned hospitalisation (i.e., admission with an overnight stay in the hospital) was classified by the investigator as a hospitalisation due to either CV or non-CV causes

Hohnloser SH, *et al. N Engl J Med* 2009;360:668-78.

Dronedarone significantly decreased risk of CV death by 29% and arrhythmic death by 45%

	Placebo n=2327	Dronedarone n=2301	HR	95% CI	*p value*
All death	139	116	0.84	0.66; 1.08	0.18
Non-CV death	49	53	1.10	0.74; 1.62	0.65
CV death	90	63	0.71	0.51; 0.98	0.03
Cardiac non-arrhythmic death	18	17	0.95	0.49; 1.85	0.89
Cardiac arrhythmic death	48	26	0.55	0.34; 0.88	0.01
Vascular non-cardiac	24	20	0.84	0.47; 1.52	0.57

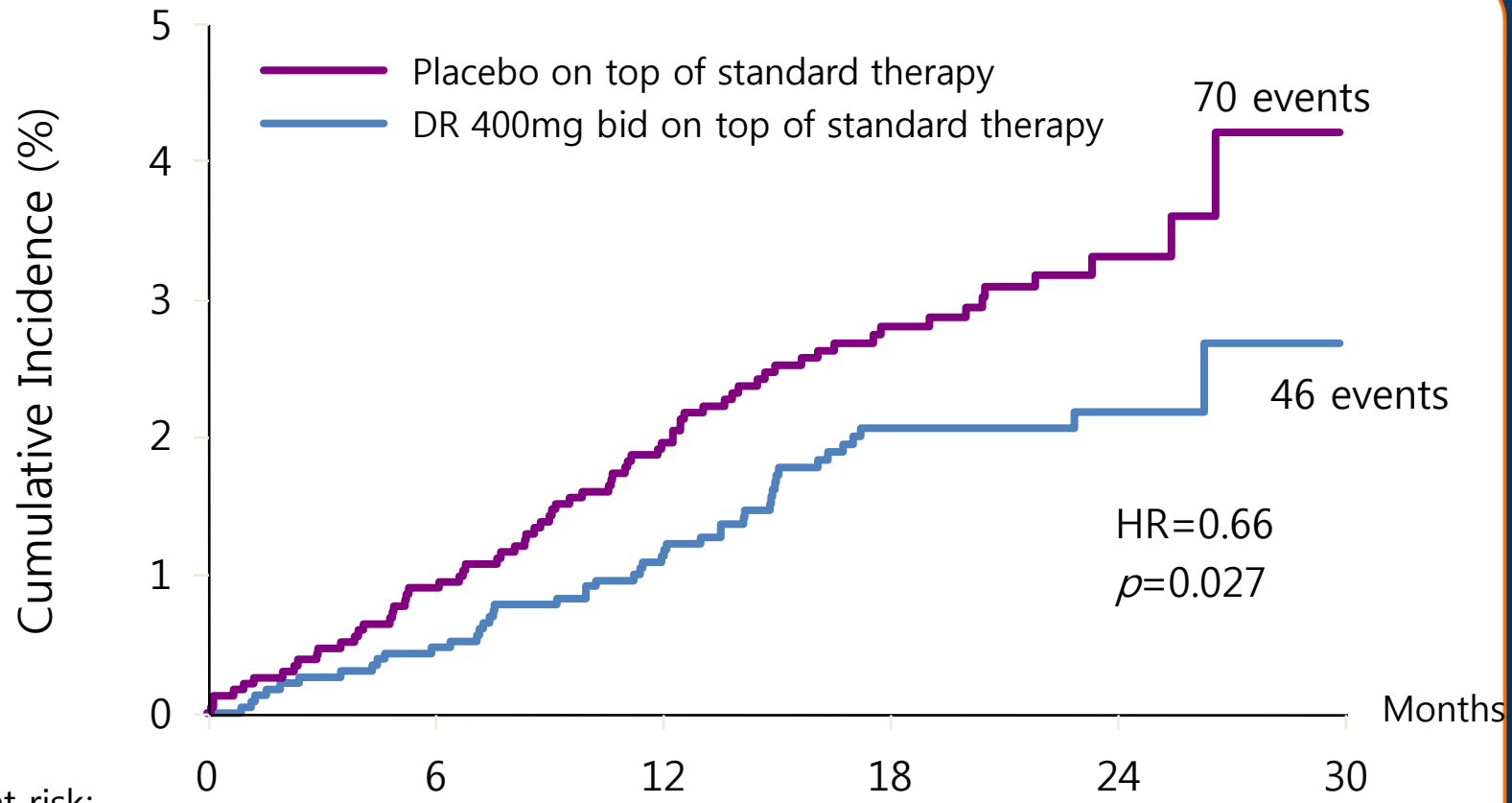
Hohnloser SH, *et al. N Engl J Med* 2009;360:668-78.

Stroke Prevention in Rate vs. Rhythm Control Trials

	n	Rate Control	Rhythm Control	RR (95% CI)	p
AFFIRM	4,917	5.7%	7.3%	1.28 (0.95-1.72)	0.12
RACE	522	5.5%	7.9%	1.44 (0.75-2.78)	0.44
STAF	266	1.0%	3.0%	3.01 (0.35-25.3)	0.52
PIAF	252	0.8%	0.8%	1.02 (0.73-2.16)	0.49
Total	**5,957**	**5.0%**	**6.5%**	**1.28 (0.98-1.66)**	**0.08**

J Am Coll Cardiol 2003; 41 (suppl):130A

Dronedarone reduced the risk of stroke by 34%



Patients at risk:

Placebo	**2327**	**2275**	**2220**	**1598**	**618**	**6**
DR 400mg bid	**2301**	**2266**	**2223**	**1572**	**608**	**4**

Mean follow-up 21 ± 5 months

Mean follow-up 21 ±5 months. Connolly *et al; Circulation.* 2009;120:1174-1180.

Connolly SJ, et al. Circulation. 2009;120:1174-80.

ATHENA: Study Summary

- The ATHENA trial is the **largest** morbidity-mortality study with an antiarrhythmic drug (AAD) ever conducted in AF patients
- Dronedarone is **the only AAD with proven reduction in CV hospitalisation or death**
- The reduction in CV hospitalisation or death was consistent across a number of subgroups in a population representative of AF
- Dronedarone also significantly **reduced cardiovascular mortality**, specifically **arrhythmic death**
- Dronedarone significantly reduced the incidence of CV hospitalisations
  - For AF-related as well as non-AF-related reasons
- The reduction in CV outcomes observed in ATHENA with dronedarone were achieved without serious safety concerns with a low risk for pro-arrhythmia and no organ toxicity after a mean follow-up of **21 months**

In a clinical programme of over 7,200 AF patients, dronedarone demonstrated a favourable safety profile[1-7]

Low risk of extra-cardiac toxicities[7]
Thyroid, pulmonary, dermatologic

Low risk of pro-arrhythmias[7]
< 0.1% patients

No clinically relevant interaction with OACs[7]

No liver, thyroid or lung monitoring[7]

Can be Initiated and administrated in an outpatient setting[7]

Can be used in patients taking warfarin

OAC=Oral anticoagulant

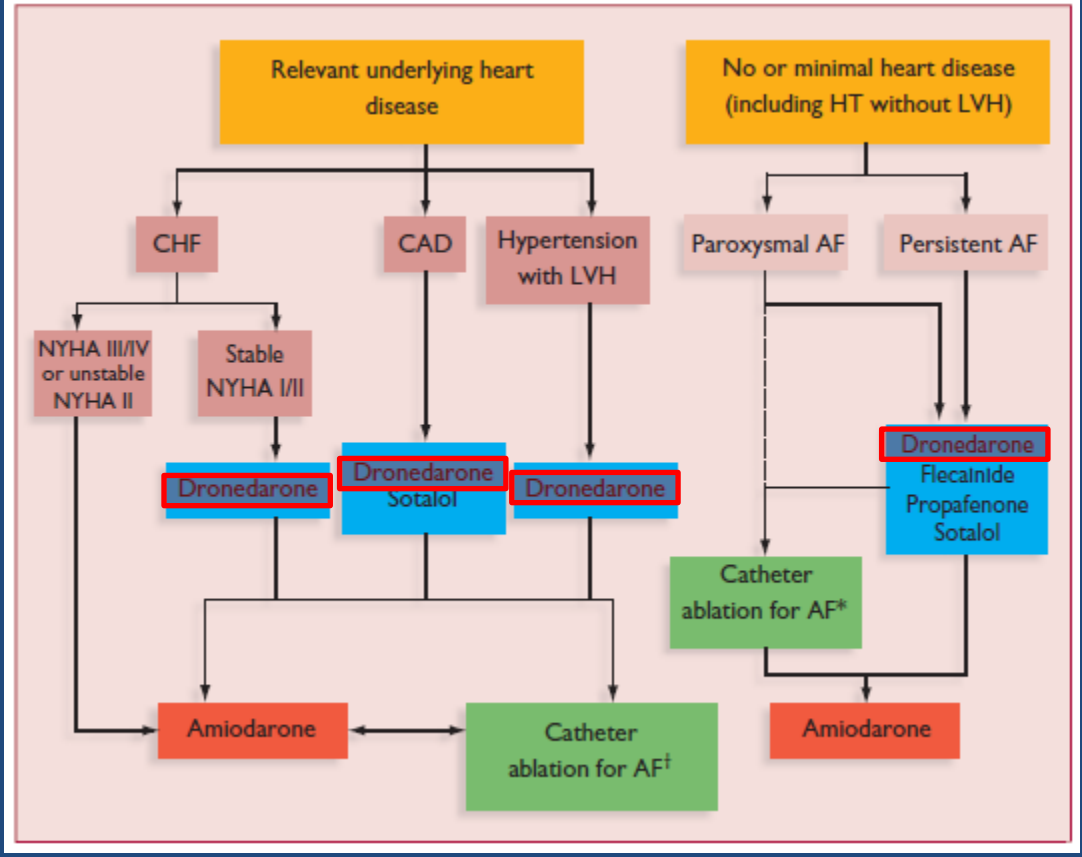
1. Touboul P, et al. *Eur Heart J.* 2003;24:1481-7.
2. Singh BN, et al. *N Engl J Med.* 2007;357:987-99
3. Davy et al. *Am Heart J.* 2008;156:527.e1-527.e9
4. Hohnloser SH et al. *N Engl J Med* 2009;360:668-78
5. Le Heuzey JY et al. *J Cardiovasc Electrophysiol.* 2010 Apr 6 Epub
6. Køber L, et al. *N Engl J Med.* 2008;358:2678-87
7. MULTAQ SmPC

Dronedarone demonstrated a favourable tolerability profile in over 7,200 patients[1-7]

Adverse drug reactions that occurred in at least 1% of patients and were more frequent than placebo[2]	**Placebo** (n=2875)	**Dronedarone 400 mg twice daily** (n=3282)
Gastrointestinal		
Diarrhea	**6%**	**9%**
Nausea	**3%**	**5%**
Abdominal pain	**3%**	**4%**
Vomiting	**1%**	**2%**
Dyspeptic signs and symptoms	**1%**	**2%**
General		
Asthenic conditions	**5%**	**7%**
Cardiac		
Bradycardia	**1%**	**3%**
Skin and subcutaneous tissue Including rashes (generalised, macular, maculo-papular, erythematous), pruritus, eczema, dermatitis, dermatitis allergic	**3%**	**5%**

1. Touboul P, et al. *Eur Heart J.* 2003;24:1481-7.
2. Singh BN, et al. *N Engl J Med.* 2007;357:987-99
3. Davy et al. *Am Heart J.* 2008;156:527.e1-527.e9
4. Hohnloser SH et al. *N Engl J Med* 2009;360:668-78
5. Le Heuzey JY et al. *J Cardiovasc Electrophysiol.* 2010 21(6):597-605.
6. Køber L, et al. *N Engl J Med.* 2008;358:2678-87
7. MULTAQ Prescribing Information

2010 ESC guideline
Long-term Rhythm control



Permanent AF is associated with a high risk of events

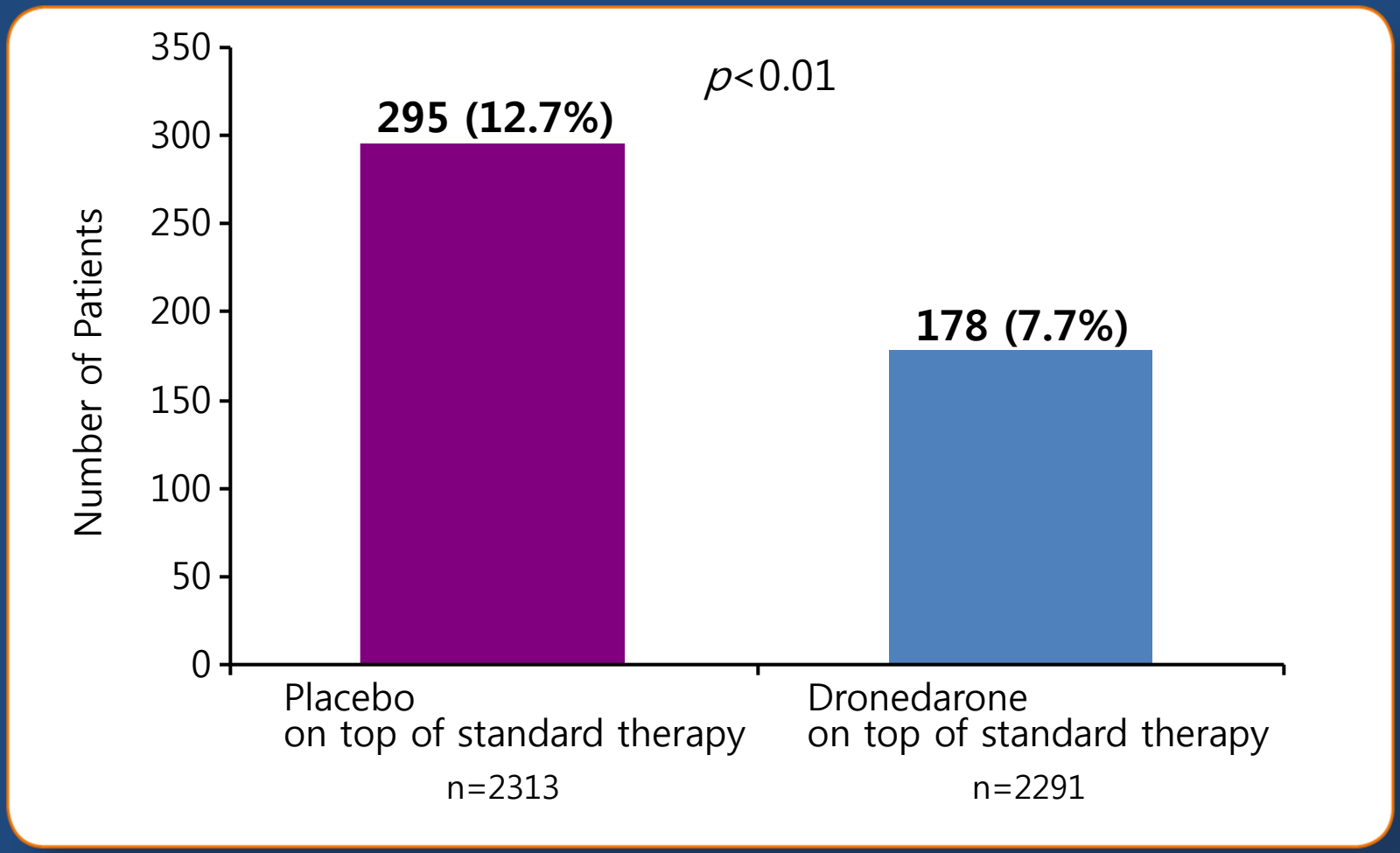
- Findings from Euro Heart survey*

Major adverse events during 1 year	First Detected (n=708) [n, proportion]	Paroxysmal (n=1170) [n, proportion]	Persistent (n=886) [n, proportion]	Permanent (n=112 6) [n, proportion]	*p*-value
All cause death	43 (5.7)	43 (3.5)	27 (3.0)	100 (8.2)	<0.001
CV death	14 (1.9)	15 (1.3)	19 (2.1)	43 (3.6)	0.001
Ischemic stroke	9 (1.3)	22 (1.9)	11 (1.2)	19 (1.6)	0.582
TIA	5 (0.7)	9 (0.8)	12 (1.4)	30 (2.5)	0.001
Coronary artery disease	46 (6.6)	63 (5.6)	38 (4.3)	71 (6.1)	0.005
Heart failure	66 (9.5)	109 (9.6)	75 (8.5)	195 (16.6)	<0.001

Eur. Heart J. 2008; 29, 1181-1189

The incidence of "permanent" AF was significantly lower with dronedarone

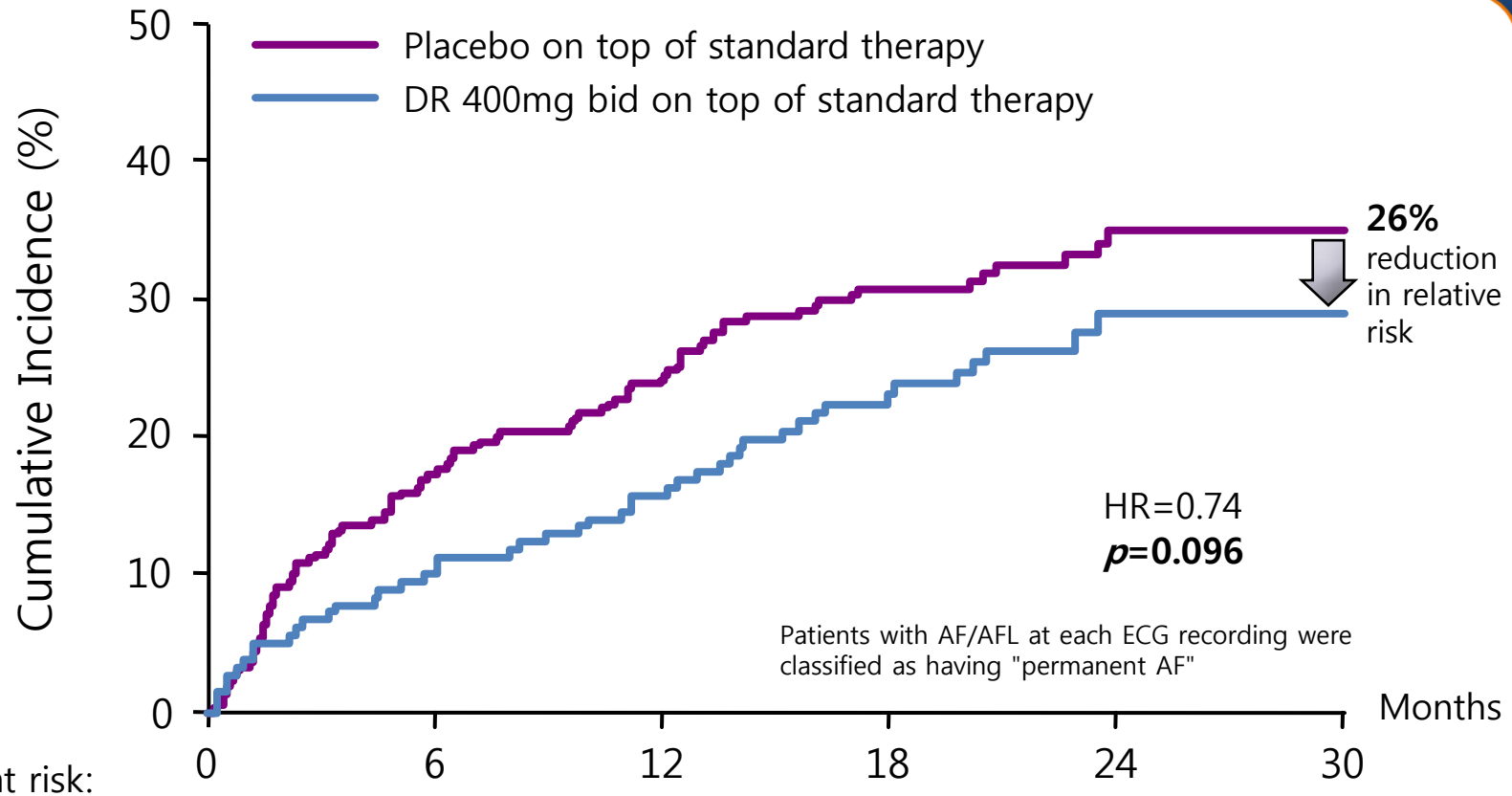
"Permanent" AF Patients



Mean follow-up 21 ±5 months.
Page R, *et al. AHA Scientific Sessions* 2008
Page R, *et al. Circulation.* 2008;118:S_827

Patients with AF/AFL at each ECG recording were classified as having "permanent AF"

Dronedarone the risk of unplanned CV hospitalisation or death in "permanent" AF patients



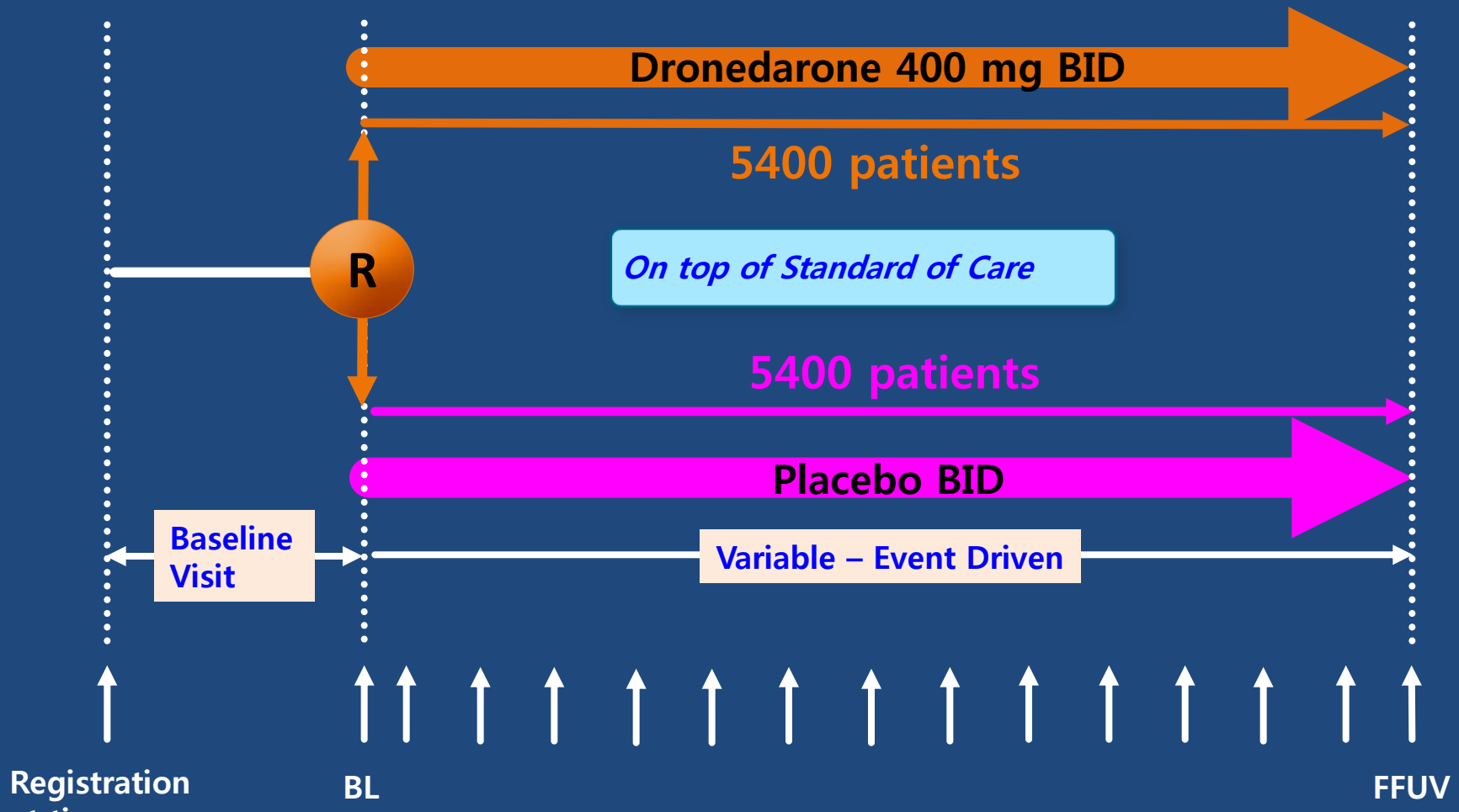
Patients at risk:

Placebo	295	244	224	151	60	0
DR 400mg bid	178	160	150	110	47	1

Mean follow-up 21 ±5 months.
Page R, et al. *AHA Scientific Sessions* 2008.
Page R, et al. *Circulation.* 2008;118:S_827.

Any unplanned hospitalisation (i.e., admission with an overnight stay in the hospital) was classified by the investigator as a hospitalisation due to either CV or non-CV causes

PALLAS: Study design



Scheduled visits on D7, M1, M4, M8, M12, M16, M22, M28, M34
Phone contacts on M19, M25, M31
Additional liver function lab assessments at M 2, M 3, M 5, M6, M 10

PALLAS Is an Indication Seeking Trial in Permanent AF

- Primary and Co-primary Endpoint
  - To demonstrate the efficacy of dronedarone in patients with permanent AF and additional risk factors in preventing:

    1. Major cardiovascular events (stroke, systemic arterial embolism, myocardial infarction or cardiovascular death)
    2. First unplanned cardiovascular hospitalization or death from any cause

- Secondary Endpoint
  - To demonstrate the efficacy of dronedarone in preventing cardiovascular death
  - To assess that dronedarone is well tolerated in this population

ATHENA Patients are Different from PALLAS Patients

ATHENA Patients (4,628)

Paroxysmal / Persistent AF

- age ≥ 75 years with/ without additional risk factors
- age ≥ 70 years and ≥ 1 risk factor
  - hypertension
  - diabetes
  - prior stroke/ TIA
  - LA ≥ 50 mm
  - LVEF≤ 0.40
- Age < 70 years were no longer eligible according to protocol amendments on Mar 8th 2006
- Age < 65 years: 18.9%

PALLAS Patients (10,800)

Permanent AF (at least 6 months)

- Age ≥ 65 years with at least one of the following risk factors or combination of risk factors:
  - Coronary artery disease
  - MI, Re-vascularization
  - Prior stroke or TIA
  - Symptomatic heart failure
  - LVEF≤ 0.40
  - Peripheral arterial occlusive disease
- Age ≥ 75 years with both hypertension and diabetes mellitus

PALLAS Patients are At Higher CV Risk than ATHENA Patients

Patient characteristics: ATHENA, ATHENA population matching the Multaq® indication and PALLAS*

	Multaq®	
	ATHENA N=2301	PALLAS N=1572
AF at baseline	**24.7%**	**100%**
Age, 65-75 yr	40.1%	48.4%
Age, ≥75 yr	41.2%	51.5%
Cardiovascular medical history		
Coronary artery disease	28.7%	41.2%
Hypertension	86.9%	81.6%
Patients with CHF	**29.2%**	**69.1%**
LVEF ≤35%	**4.1%**	**8.3%**
Cardiovascular baseline medications		
Beta-blockers	70.8%	72.9%
Calcium antagonists	14.4%	9.6%
Digoxin	14.0%	32.9%
Vitamin K antagonists	61.0%	82.2%

*Characteristics for patients randomised to dronedarone in the ATHENA and PALLAS studies

CHF = congestive heart failure; LVEF = left ventricular ejection fraction; TIA = transient ischemic attack; yr = year

Hohnloser SH, et al. N Engl J Med 2009;360:668-78. Data on file, Sanofi

PALLAS: Baseline Characteristics

Characteristic	Dronedarone (N=1619)	Placebo (N=1617)
Age		
Mean — yr	75.0±5.9	75.0±5.9
65 to <75 yr — no. (%)	783 (48.4)	779 (48.2)
≥75 yr — no. (%)	836 (51.6)	838 (51.8)
Male sex — no. (%)	1051 (64.9)	1040 (64.3)
Heart rate — bpm	77±16	78±16
Systolic blood pressure — mm Hg	133±17	133±17
Inclusion risk criteria — no. (%)		
Coronary artery disease	661 (40.8)	666 (41.2)
Symptomatic heart failure†	233 (14.4)	240 (14.8)
Left ventricular ejection fraction ≤40%	345 (21.3)	335 (20.7)
Previous stroke or transient ischemic attack	436 (26.9)	458 (28.3)
Peripheral arterial disease	187 (11.6)	213 (13.2)
Age ≥75 yr plus hypertension and diabetes	294 (18.2)	276 (17.1)
$CHADS_2$ score‡		
Mean	2.8±1.2	2.9±1.2
≥2 — no. (%)	1427 (88.1)	1444 (89.3)
Duration of permanent atrial fibrillation >2 yr — no. (%)	1119 (69.1)	1124 (69.5)
Heart failure — no. (%)		
No history	512 (31.6)	535 (33.1)
New York Heart Association class I	234 (14.5)	209 (12.9)
New York Heart Association class II	732 (45.2)	749 (46.3)
New York Heart Association class III	141 (8.7)	124 (7.7)
Other risk factors		
Previous myocardial infarction	392 (24.2)	420 (26.0)
Prior coronary-artery bypass grafting	236 (14.6)	206 (12.7)
Permanent pacemaker	229 (14.1)	218 (13.5)
Hypertension	1352 (83.5)	1385 (85.7)
Diabetes mellitus	573 (35.4)	598 (37.0)

Connolly SJ et al. N Engl J Med 2011 Nov

PALLAS: Study Outcomes

Table 2. Study Outcomes.*

Outcome	Dronedarone		Placebo		Hazard Ratio (95% CI)†	P Value
	No. of Events	Rate/100 Patient-Yr	No. of Events	Rate/100 Patient-Yr		
First coprimary outcome	43	8.2	19	3.6	2.29 (1.34–3.94)	0.002
Second coprimary outcome	127	25.3	67	12.9	1.95 (1.45–2.62)	<0.001
Death						
From any cause	25	4.7	13	2.4	1.94 (0.99–3.79)	0.049
From cardiovascular causes	21	4.0	10	1.9	2.11 (1.00–4.49)	0.046
From arrhythmia	13	2.5	4	0.8	3.26 (1.06–10.0)	0.03
Stroke						
Any‡	23	4.4	10	1.9	2.32 (1.11–4.88)	0.02
Ischemic	18	3.4	9	1.7	2.01 (0.90–4.48)	0.08
Systemic embolism	1	0.2	0	0.0	NA	NA
Myocardial infarction or unstable angina	15	2.9	8	1.5	1.89 (0.80–4.45)	0.14
Myocardial infarction	3	0.6	2	0.4	1.54 (0.26–9.21)	0.63
Unplanned hospitalization for cardiovascular causes	113	22.5	59	11.4	1.97 (1.44–2.70)	<0.001
Hospitalization for heart failure	43	8.3	24	4.6	1.81 (1.10–2.99)	0.02
Heart-failure episode or hospitalization§	115	23.2	55	10.7	2.16 (1.57–2.98)	<0.001

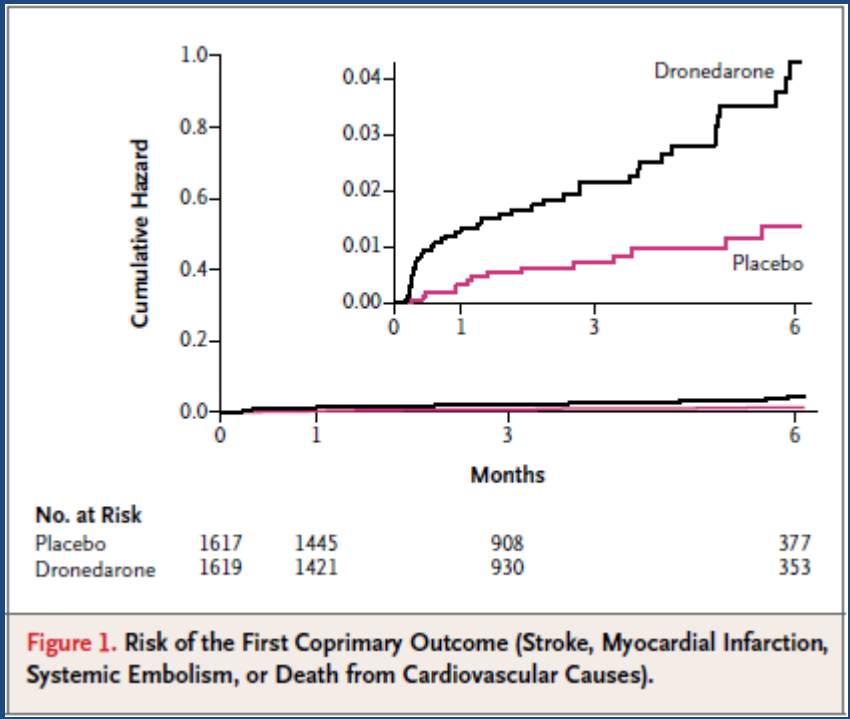


Figure 1. Risk of the First Coprimary Outcome (Stroke, Myocardial Infarction, Systemic Embolism, or Death from Cardiovascular Causes).

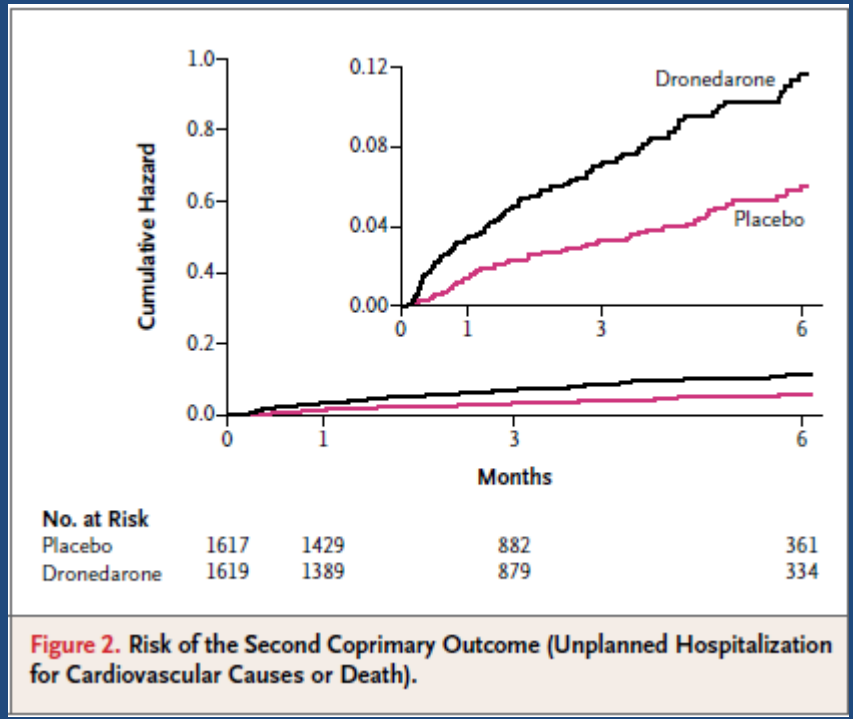


Figure 2. Risk of the Second Coprimary Outcome (Unplanned Hospitalization for Cardiovascular Causes or Death).

HR 2.29 (1.34 - 3.94), p=0.002

HR 1.95 (1.45 – 2.62), p<0.001

Table 3. Adverse Events and Abnormalities on Laboratory Testing.*

Event	Dronedarone (N=1614)	Placebo (N=1609)	P Value
	number (percent)		
Any adverse event	797 (49.4)	600 (37.3)	<0.001
Any serious adverse event	113 (7.0)	77 (4.8)	0.008
Any adverse event leading to treatment discontinuation	212 (13.1)	80 (5.0)	<0.001
Any reported liver-function abnormality	61 (3.8)	28 (1.7)	<0.001
Asthenic conditions (asthenia, fatigue)	89 (5.5)	46 (2.9)	<0.001
Breathing abnormalities (dyspnea)	75 (4.6)	36 (2.2)	<0.001
Diarrhea	101 (6.3)	38 (2.4)	<0.001
Electrocardiographic investigations (QT prolonged)	33 (2.0)	16 (1.0)	0.02
Edema (peripheral edema)	60 (3.7)	29 (1.8)	<0.001
Gastrointestinal or abdominal pain	33 (2.0)	15 (0.9)	0.009
Increased creatinine level	49 (3.0)	11 (0.7)	<0.001
Lower respiratory tract or lung infection	40 (2.5)	42 (2.6)	0.81
Nausea or vomiting	76 (4.7)	28 (1.7)	<0.001
Neurologic signs or symptoms (dizziness)	76 (4.7)	39 (2.4)	<0.001
Rate and rhythm disorders (bradycardia)	67 (4.2)	19 (1.2)	<0.001
Renal failure or impairment	35 (2.2)	12 (0.7)	<0.001
Upper respiratory tract infection	34 (2.1)	35 (2.2)	0.89
Alanine aminotransferase and bilirubin†			
Alanine aminotransferase >3 times ULN	22 (1.5)	7 (0.5)	0.05
Alanine aminotransferase >3 times ULN and bilirubin >2 times ULN	1 (<0.1)‡	0	NA

Key Messages on MULTAQ® Updated Labeling (EMA, Sep 22nd 2011)

The CHMP has confirmed a positive Benefit/Risk (B/R) balance for MULTAQ® in Europe and agreed upon an updated labeling.

MULTAQ® should be now prescribed for the maintenance of sinus rhythm **after successful cardioversion** in adult clinically stable patients with paroxysmal or persistent atrial fibrillation (AF). Due to its safety profile MULTAQ® should only be prescribed after alternative treatment options have been considered.

In addition to current **contraindications** mentioned in the previous labeling, MULTAQ® should not be prescribed in patients with:

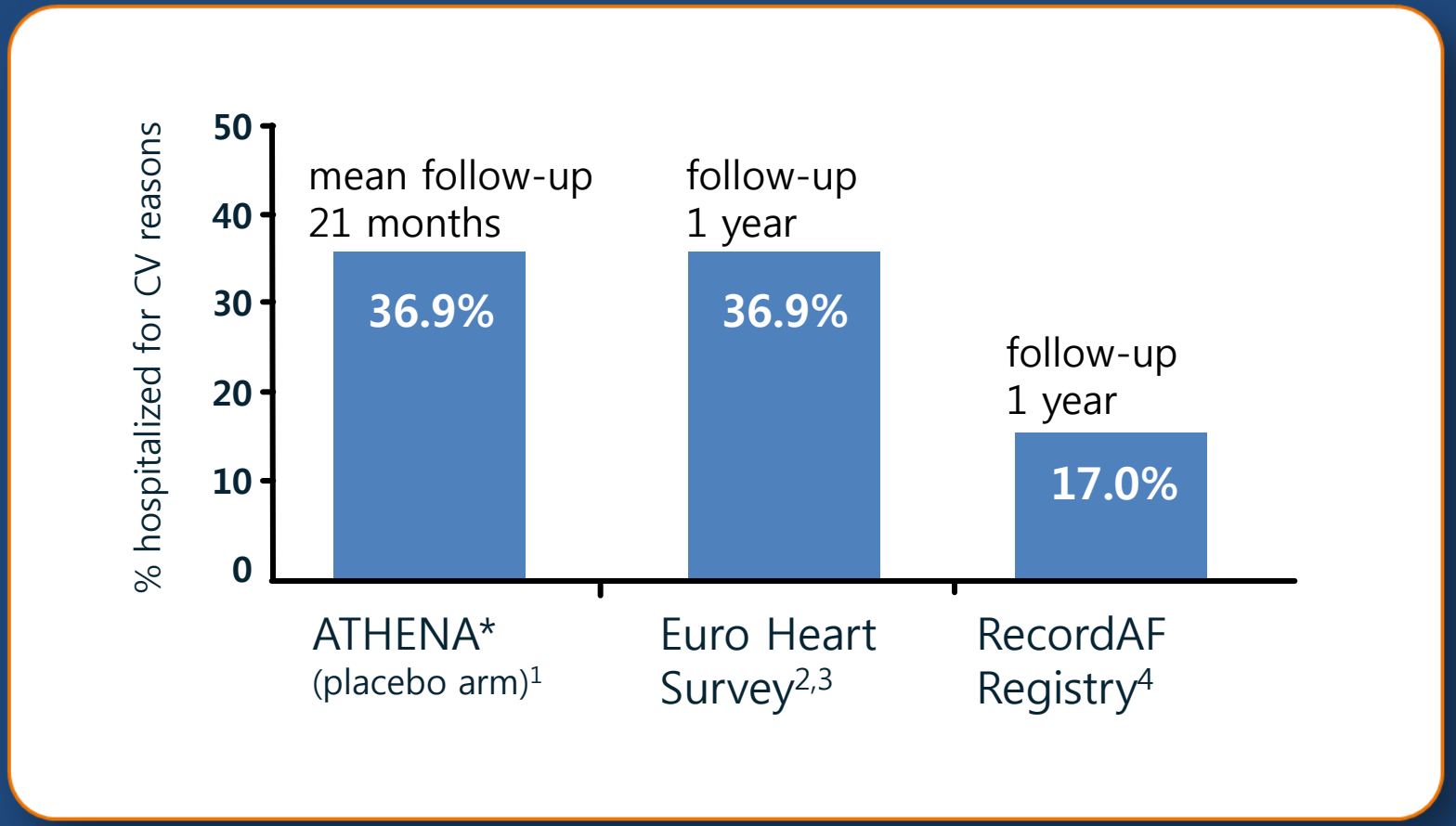
- **Permanent AF** (AF duration > 6 months or duration unknown, and attempts to restore sinus rhythm no longer considered by the physician),
- **History of, or current heart failure or left ventricular systolic dysfunction,**
- **Liver and lung toxicity related to previous use of amiodarone.**

The updated MULTAQ® labeling also includes new recommendations for clinical assessment and **monitoring of cardiac, hepatic and pulmonary function, as well as measurement of plasma creatinine**, to ensure appropriate patient management.

If AF reoccurs discontinuation of dronedarone should be considered.

감사합니다

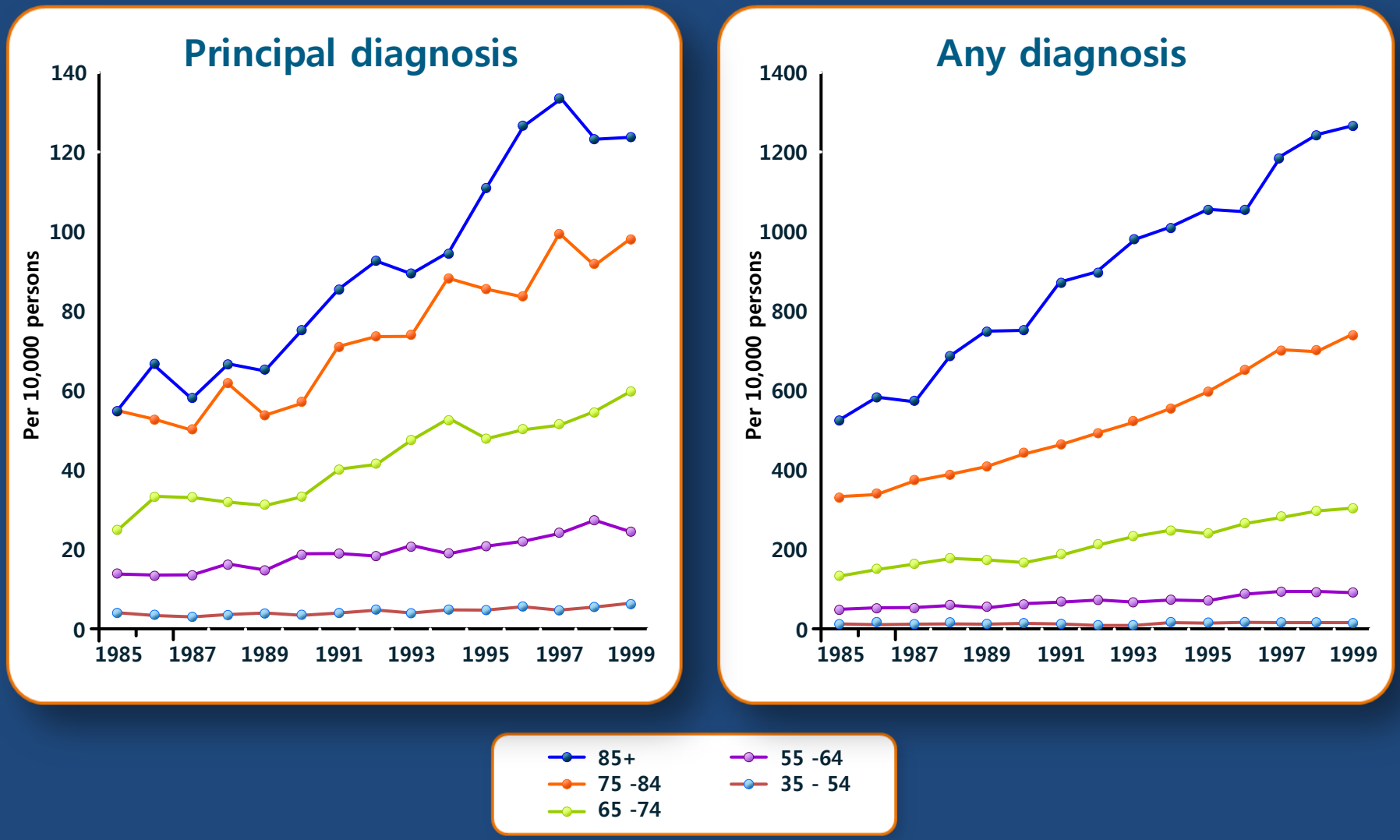
High hospitalization rates among AF patients



1. Hohnloser SH et al. N Engl J Med 2009;360:668-78
2. Nieuwlaat R et al. European Heart Journal 2008:29;1181–1189
3. Multaq European Public Assessment Report
4. Camm J. RecordAF Registry. Scientific sessions AHA 2009

*First hospitalization due to cardiovascular event

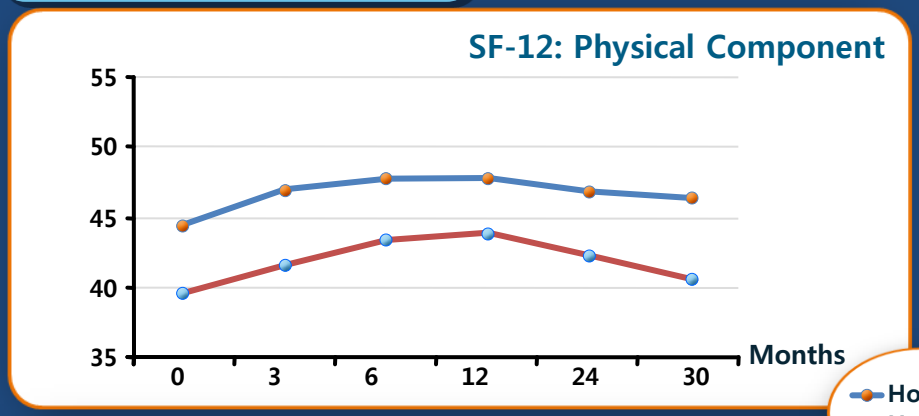
Increasing trends in hospitalization for AF: USA 1985-1999

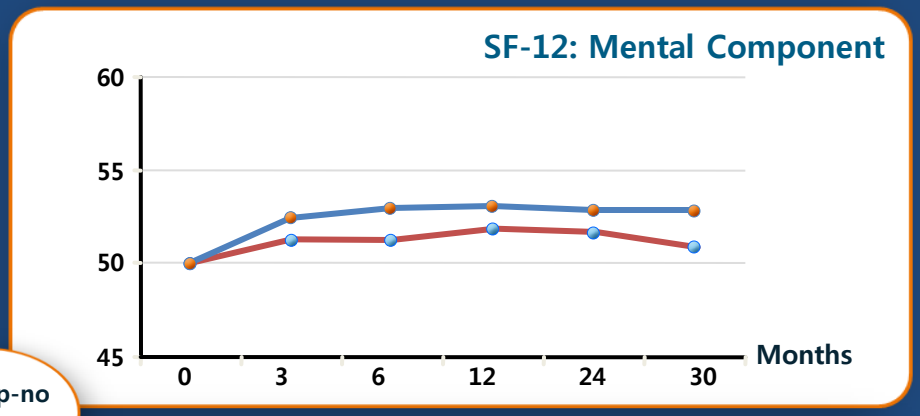


Wattigney W., *Circulation* 2003; 108:711- 6.

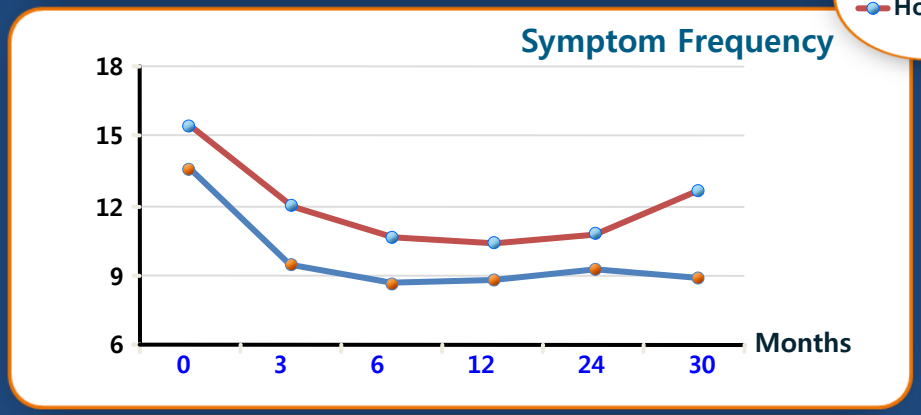
Hospitalization impacts health-related QoL

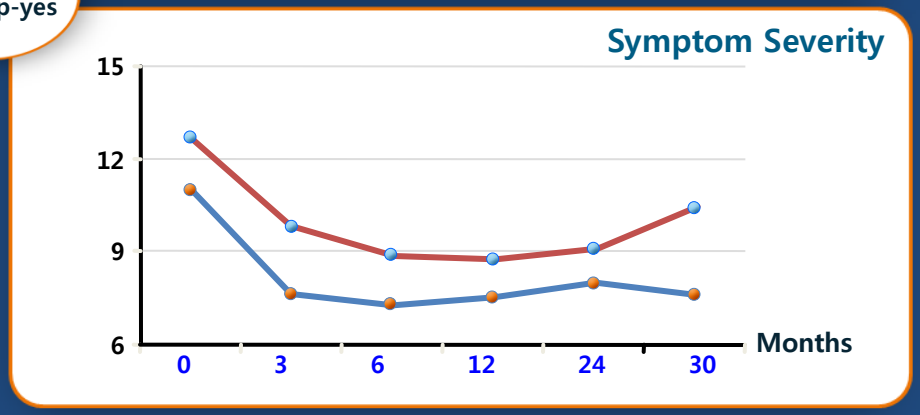
FRACTAL registry





Hosp-no
Hosp-yes





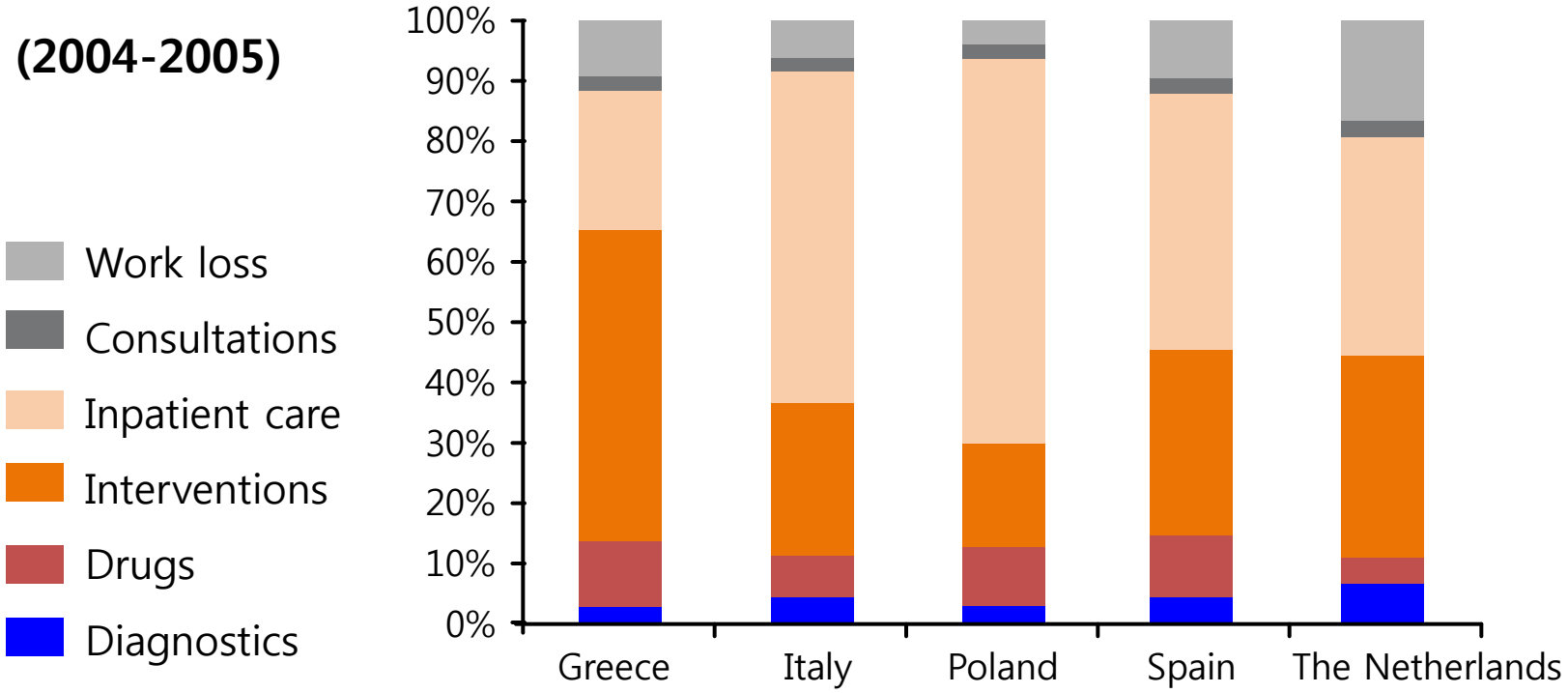
- In a large registry of first-onset AF patients (JCE 2007; 18 : 628-33), hospitalizations during 2 years of follow-up were associated with reduced HRQOL and higher patient-reported symptoms
- Interventions that prevent hospitalizations in AF patients would therefore be expected to improve or preserve HRQOL

Reynolds M *et al. J. Cardiovasc. Electrophysiol. 2007; 18 : 628 – 33 and Poster Presentation ISPOR* 2009 Citation: Value in Health 2009;12:A340.

In Europe 70% of the cost of AF management is driven by inpatient care and interventional procedures

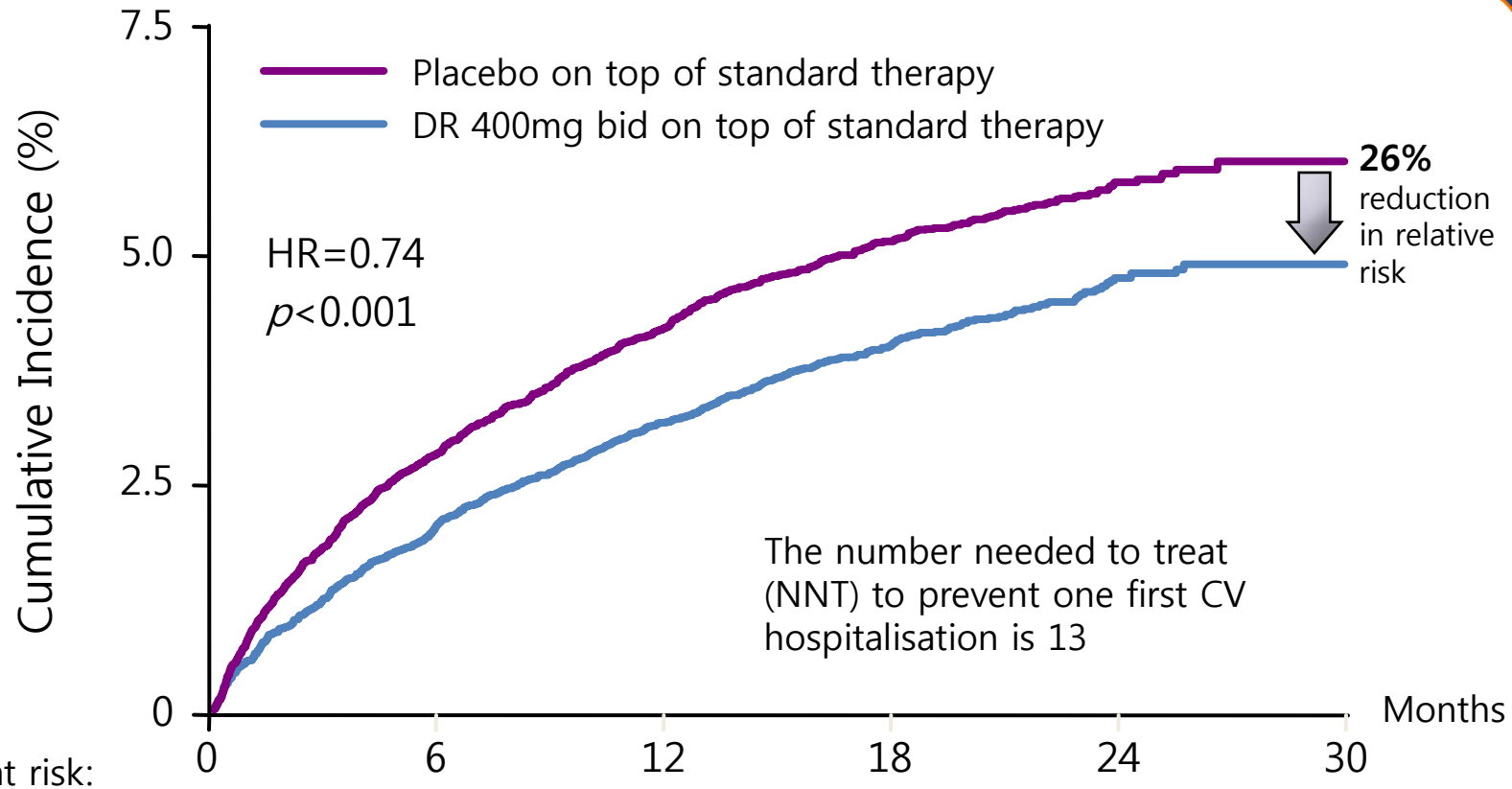
EuroHeart Survey

(2004-2005)



Ringborg *et al. Europace* 2008; 10:403–11.

Dronedarone significantly decreased unplanned CV hospitalisation by 26%



Patients at risk:

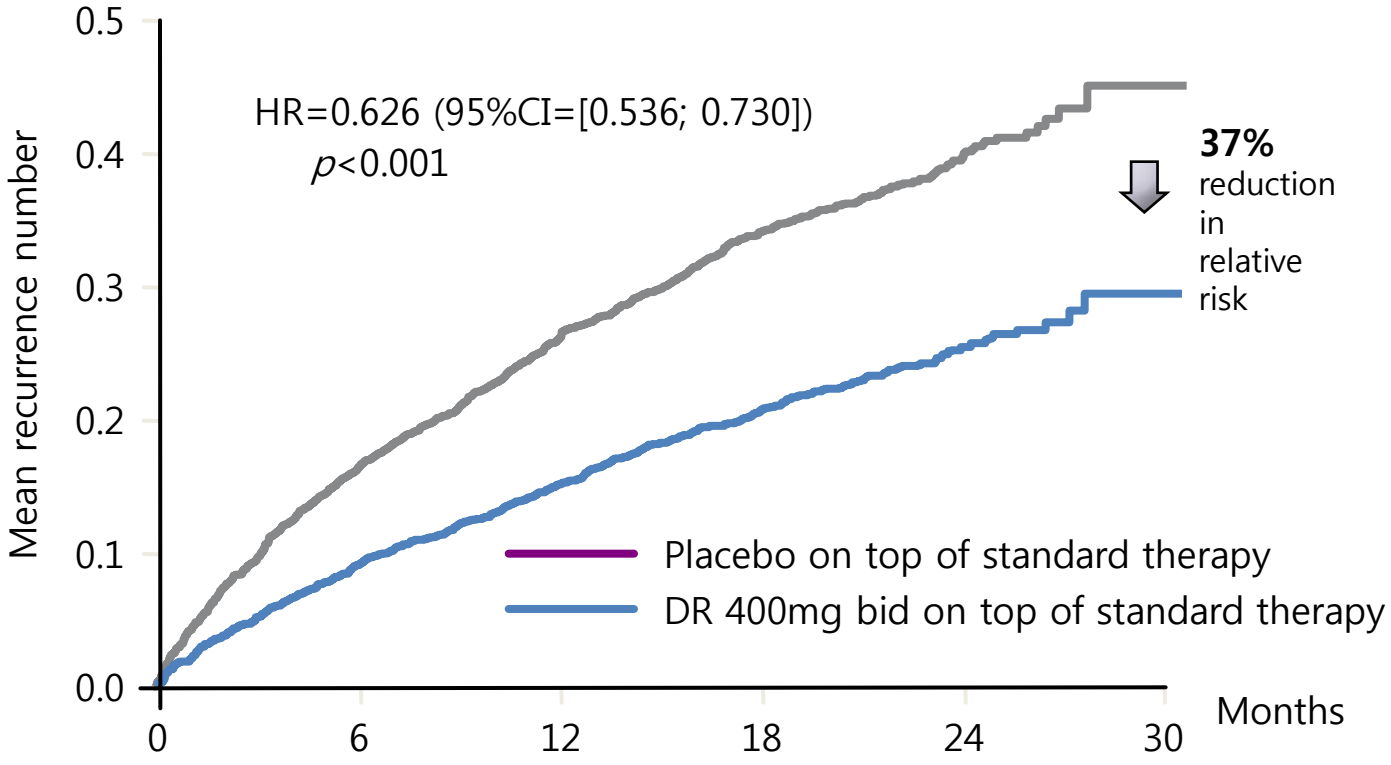
Placebo	2327	1858	1625	1072	385	3
DR 400mg bid	2301	1963	1776	1177	403	2

Any unplanned hospitalisation (i.e., admission with an overnight stay in the hospital) was classified by the investigator as a hospitalisation due to either CV or non-CV causes. Mean follow-up 21 ±5 months.

Hohnloser SH, *et al. N Engl J Med* 2009;360:668-78.

Dronedarone significantly reduced all unplanned AF related CV hospitalisations by 37%

Dronedarone demonstrates a sustained therapeutic impact on AF-related events

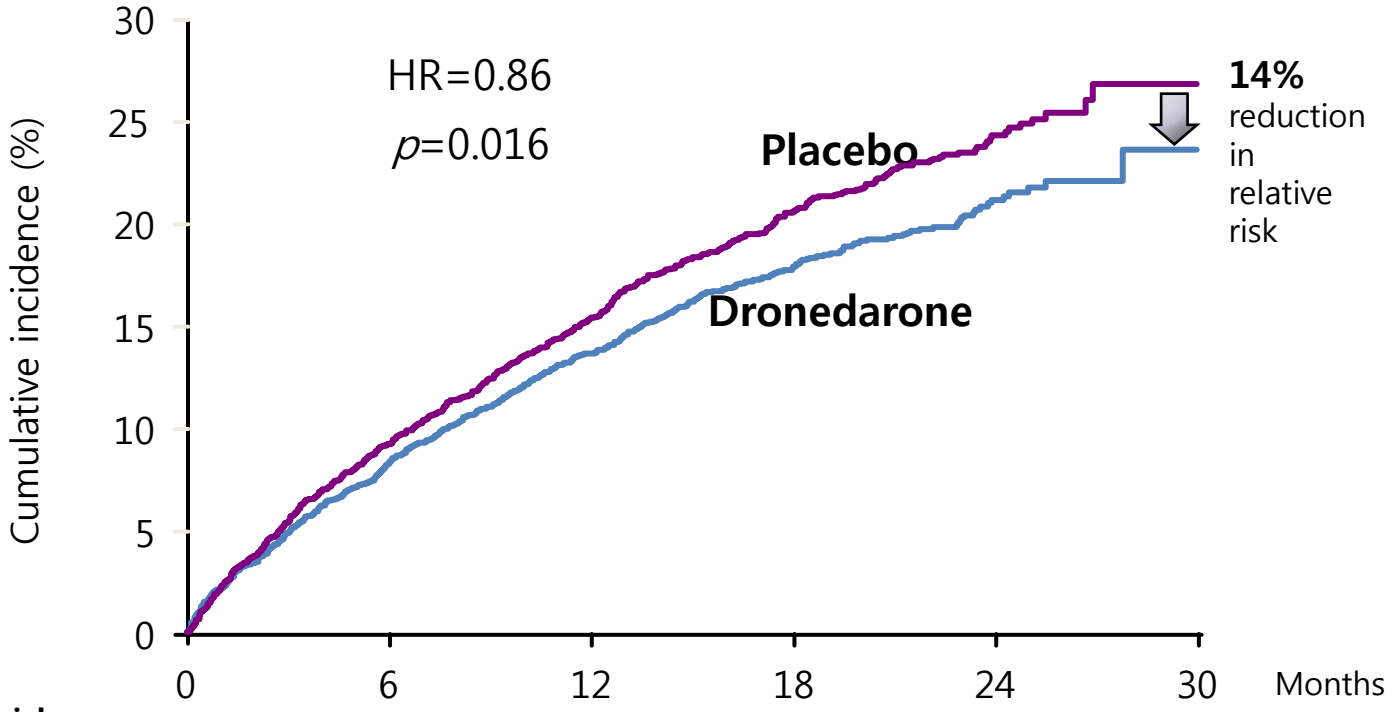


Placebo	**2327**	**2290**	**2250**	**1629**	**636**	**7**
DR 400mg bid	**2301**	**2274**	**2240**	**1593**	**615**	**4**

Page R, *et al. Eur Heart J* 2009;30(Abstract Suppl):450.
Hohnloser SH et al. *N Engl J Med* 2009;360:668-78
Europace. 2011 Aug;13(8):1118-26.

Any unplanned hospitalisation (i.e. admission with an overnight stay in the hospital) was classified by the investigator as a hospitalisation due to either CV or non-CV causes

Significant decrease in the rate of non-AF related CV hospitalizations by 14%



Patients at risk:

Placebo	**2327**	**2093**	**1929**	**1326**	**497**	**3**
DR 400mg bid	**2301**	**2096**	**1957**	**1338**	**479**	**2**

Mean follow-up 21 ± 5 months - on Study

Europace. 2011 Aug;13(8):1118-26.

Significant reduction in total unplanned CV hospital days

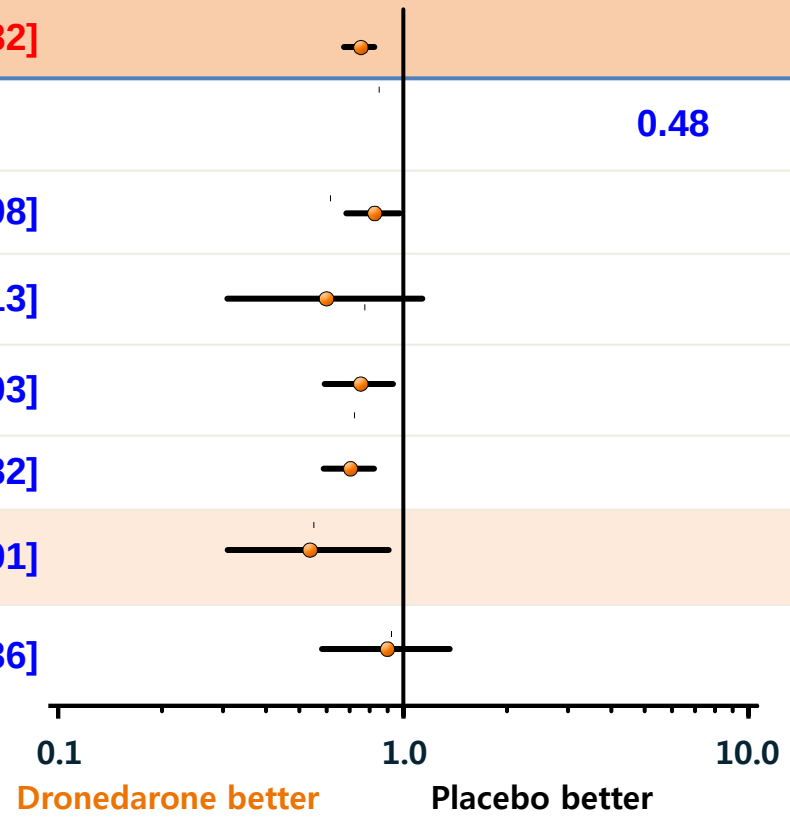
	Placebo n=2313	Dronedarone n=2291	RRR	*p*
Patients with at least one hospitalization	**745 (32.2%)**	**530 (23.1%)**		**<0.001**
Total hospital days	**9,073**	**5,875**	**35%**	**<0.001**
CCU/ICU	**1,138**	**599**	**47%**	**0.015**
Medium care	**1,525**	**833**	**45%**	**<0.001**
Ward	**6,410**	**4,443**	**30%**	**<0.001**

Dronedarone led to a decrease of 1.02 CV hospitalization days/patient/year
For a 1,000 patients treated with dronedarone for one year, the healthcare system would save 1,020 CV hospitalization days

Europace. 2011 Aug;13(8):1118-26.

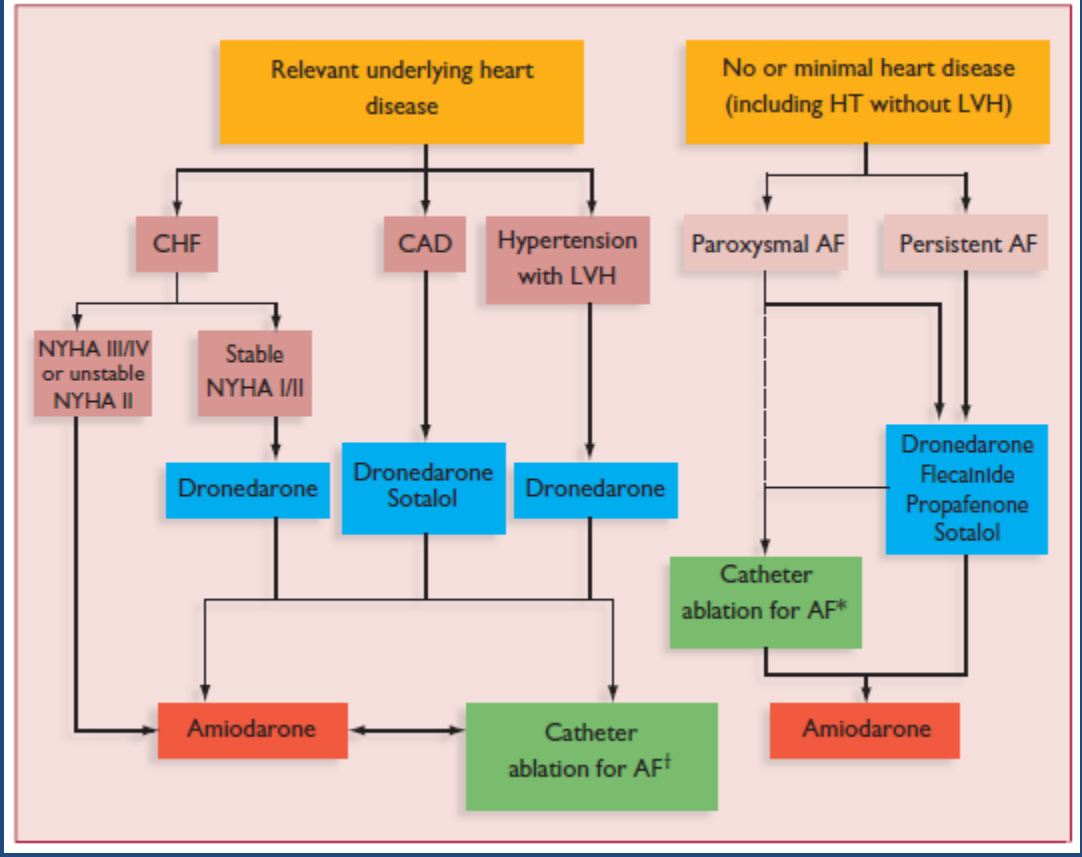
Reduction in CV hospitalizations consistent across regions

Population	N	HR	[95% CI]	Interaction *p*-value
All ATHENA	4,628	0.74	[0.67;0.82]	
				0.48
North America	1,403	0.82	[0.68;0.98]	
South America	206	0.59	[0.31;1.13]	
Western Europe	1,042	0.74	[0.59;0.93]	
Eastern Europe	1,439	0.70	[0.59;0.82]	
Asia	268	0.53	[0.31;0.91]	
Other*	270	0.89	[0.58;1.36]	



Europace. 2011 Aug;13(8):1118-26.

2011 ESC guideline
Long-term Rhythm control



PALLAS

N Engl J Med 2011 Nov

PALLAS: Inclusion Criteria

Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy

- Permanent AF/AFL with an age ≥ 65, and
- At least 1 risk factor
  - Coronary artery disease
  - Previous stroke or TIA
  - Symptomatic CHF
    - NYHA FC II – III, or
    - Admission for CHF management within 1 year
  - LV EF ≤ 40%
  - Peripheral arterial disease
  - Combination of an age ≥ 75, HT, and DM

PALLAS: Exclusion Criteria

- Paroxysmal or persistent AF/AFL
- ICD
- Sustained daytime bradycardia < 50/min
- QTc > 500 msec

PALLAS: Outcomes

- Primary outcomes
  - Composite of stroke, myocardial infarction, systemic embolism, or cardiovascular death
- Secondary outcomes

•Cardiovascular death
•Arrhythmic death
•Cardiovascular hospitalization
•Total night in hospital
•Acute coronary syndrome

•Stroke or systemic embolization
•CHF hospitalization
•CHF episodes
•Deth from any cause

Dronedarone inhibits the secretion of creatinine in the kidneys, but is not indicative of renal toxicity[1,2]

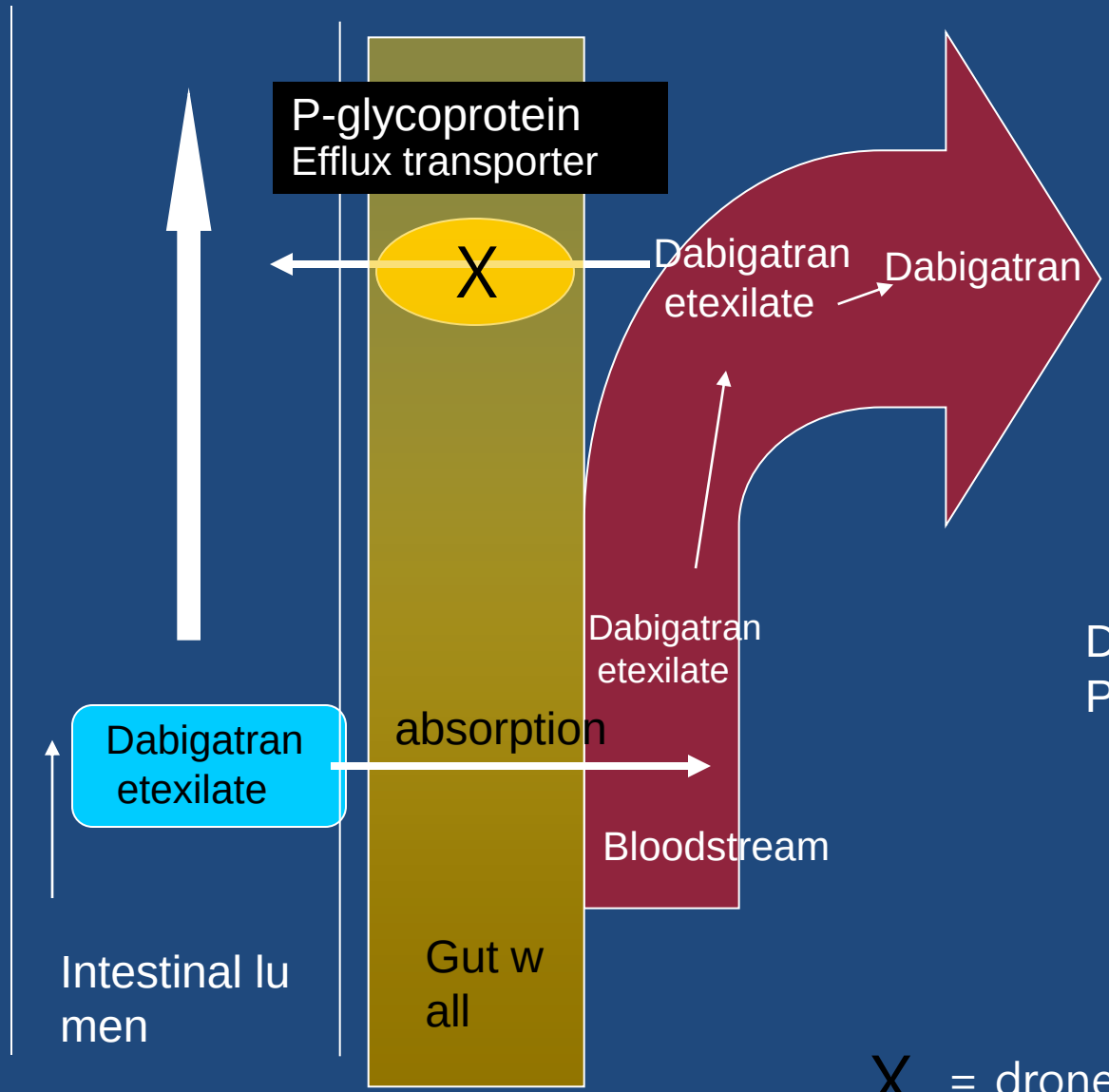
- Plasma creatinine values should be measured **7 days after** initiation of dronedarone
- An increase in plasma creatinine has been observed with dronedarone 400 mg twice daily in healthy subjects and in patients, which occurs early after treatment initiation and reaches a plateau after 7 days
- If an increase in creatininemia is observed, this value should be used as the new reference baseline taking into account that this may be expected with dronedarone
- An increase in creatininemia should not necessarily lead to the discontinuation of treatment with ACE-inhibitors or Angiotensin II Receptors Antagonists

1. MULTAQ SmPC
2. Tschuppert *et al. Br J Clin Pharmacol* 2007;64(4):785-91.

Conclusions

- Rhythm control efficacy (EURIDIS/ADONIS study)
  - In paroxysmal or persistent atrial fibrillaiton
  - After successful cardioversion
- Rate control efficacy
  - Even in permanent atrial fibrillaiton (ERATOR study)
  - But should not be used in permanent atrial fibrillation (PALLAS study)
- Cardiovascular hospitalization and death (ATHENA study)
  - In paroxysmal or persistent atrial fibrillation
  - Exclude unstable heart failure
- Dronedarone is less effective than amiodarone, but less toxic (DIONYSOS study)
  - No need for loading, fixed dose regimen
  - No interaction with warfarin

Mechanism of Dronedarone - Dabigatran Interaction

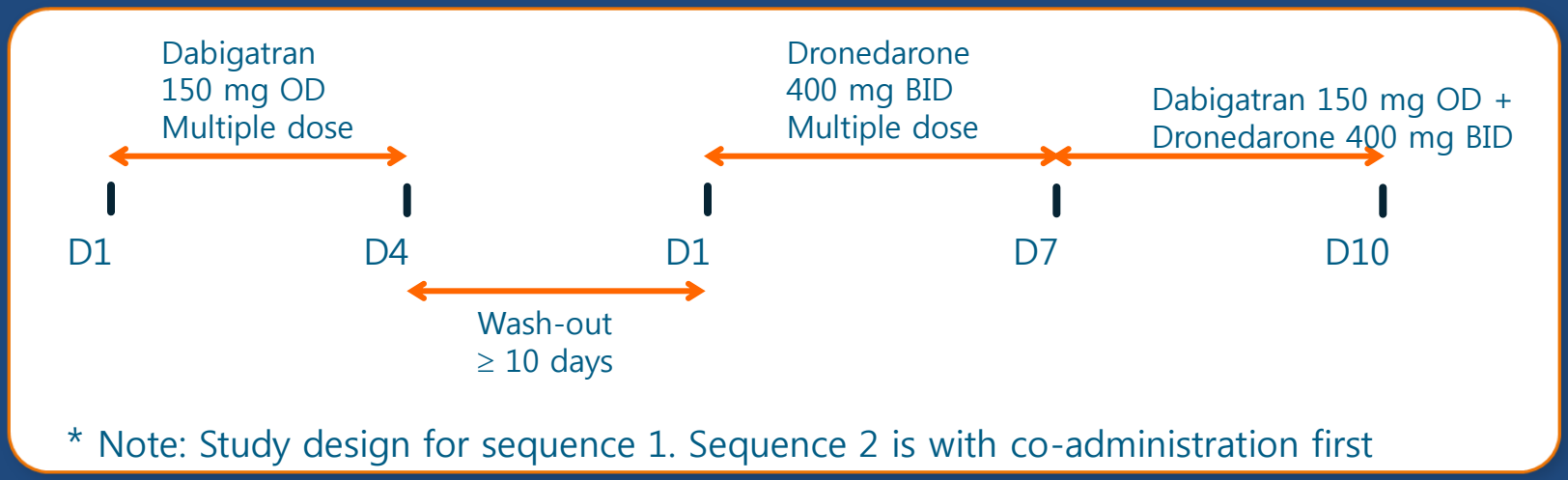


Dabigatran etexilate is a P-glycoprotein substrate

X = dronedarone blockade of P-gp

Dabigatran Interaction Study

- Phase I, single-center, open-label, randomized, two-sequence, two-period, two-treatment crossover study with a minimum 10-day washout period
- Subjects received repeated doses of dabigatran etexilate 150 mg OD for 4 days, and then repeated doses of dronedarone 400 mg BID for 10 days coadministered with dabigatran etexilate 150 mg OD for 4 days; or the opposite



* Note: Study design for sequence 1. Sequence 2 is with co-administration first

- Study population: 16 healthy male and female subjects (81.3% males) aged 18-45 years were randomized

Brunet A. *et al. Poster Presentation* ESC 2011.

Dabigatran Interaction Study: PK results

Dronedarone dosage Population	Dabigatran dosage	Dabigatran ratio with/without dronedarone
400 mg bid, 10 days Healthy subjects	150 mg od, 4 days	C_{max} : **1.73** [1.54 – 1.93] AUC_{0-24} : **1.99** [1.79 – 2.21] CL_{R0-24} : **1.10** [0.92 – 1.30]

- Interaction at plasma level (1.73 – 1.99-fold) consistent with that observed with dabigatran and other P-gp inhibitors such as amiodarone and verapamil in Phase 1 studies in healthy subjects[1]
- No significant interaction observed on renal clearance
- Dronedarone exposures at steady-state are in the range of historical data at 400 mg BID

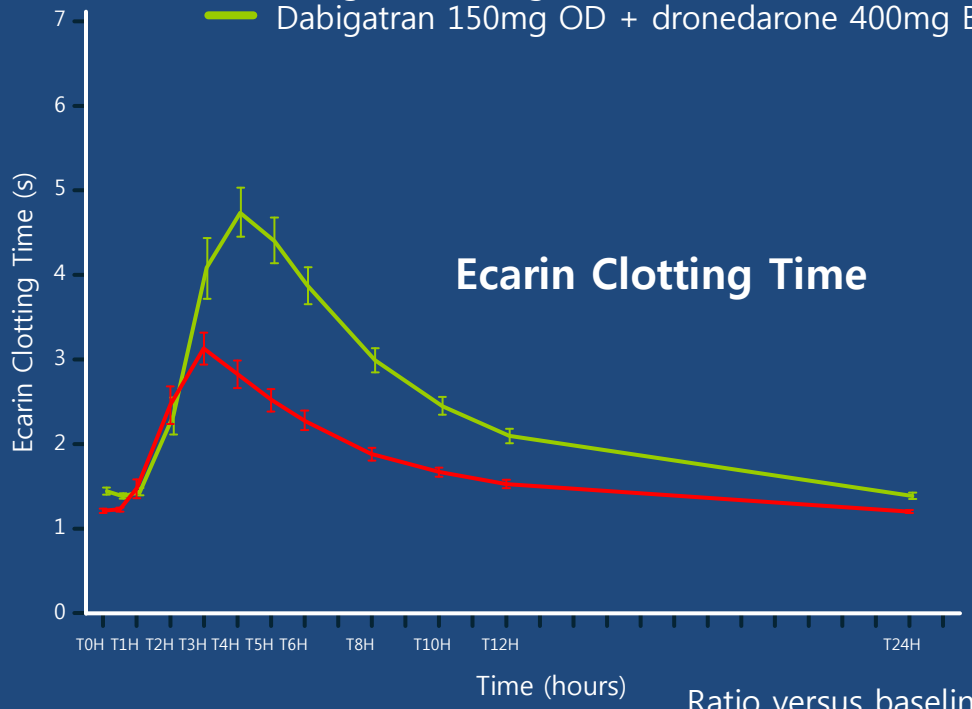
1. Dabigatran FDA Briefing document, August 2010, page 47.

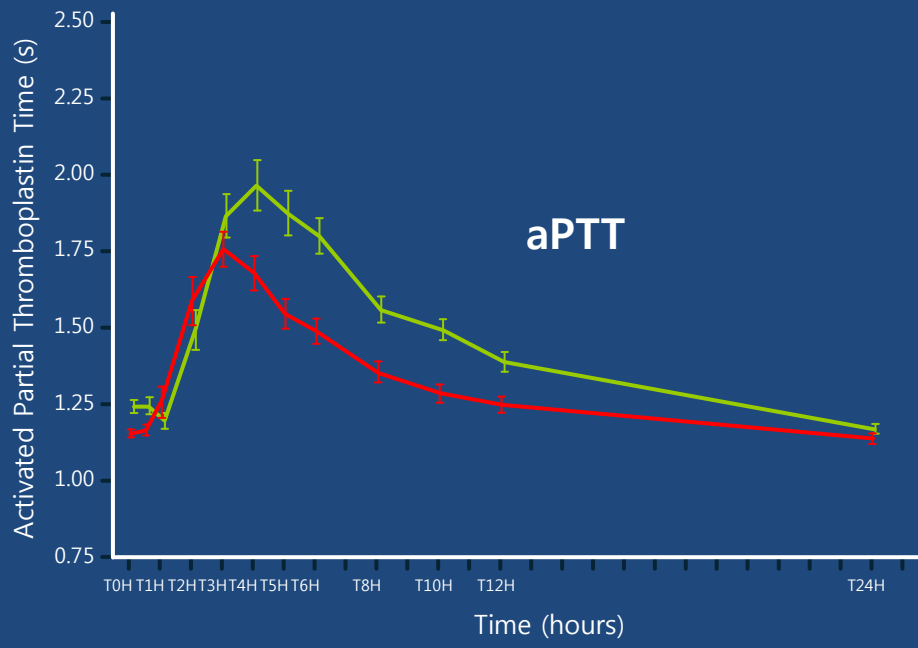
Brunet A. *et al. Poster Presentation* ESC 2011.

Dabigatran Interaction Study: PD results

Dabigatran 150mg OD alone (*)
Dabigatran 150mg OD + dronedarone 400mg BID (**)

* assessments done on Day 4
** assessments done on Day 10





Ratio versus baseline (mean +/- SEM)

	Max % increase versus baseline		Treatment ratios of max % increase vs baseline
	Dabigatran alone	Dabigatran + dronedarone	Dabigatran + dronedarone vs dabigatran alone
ECT	221%	381%	1.72
aPTT	73%	96%	1.32

- The effect of dronedarone on the ECT profile of dabigatran is similar with the observed PK interaction (consistent with the linear PK/ECT relationship)
- The effect of dronedarone on the aPTT profile of dabigatran was lower than the observed PK interaction.

Brunet A. *et al. Poster Presentation* ESC 2011.

Dronedarone AF/AFL Pool: DAFNE, EURIDIS, ADONIS, ERATO and ATHENA Overview of Hepatic Adverse Events

	Placebo (N=2875)		Dronedarone 400 mg BID (N=3282)		Dronedarone 600 mg BID (N=66)		Dronedarone 800 mg BID (N=62)	
AE	**73**	**(2.5%)**	**95**	**(2.9%)**	**4**	**(6.1%)**	**2**	**(3.2%)**
SAE	**29**	**(1.0%)**	**28**	**(0.9%)**	**0**	**(0%)**	**0**	**(0%)**
AE leading to discontinuation	**7**	**(0.2%)**	**10**	**(0.3%)**	**0**	**(0%)**	**0**	**(0%)**
SAE leading to hospitalization	**26**	**(0.9%)**	**28**	**(0.9%)**	**0**	**(0%)**	**0**	**(0%)**
SAE leading to death	**2**	**(<0.1)**	**1**	**(<0.1)**	**0**	**(0%)**	**0**	**(0%)**

Note: Selected events using : SOC "HEPATOBILIARY DISORDERS" or SMQ "LIVER RELATED INVESTIGATIONS SIGNS and SYMPTOMS" broad + narrow selection

Data on file, sanofi-aventis

Post-marketing Spontaneous Hepatobiliary Reports with Multaq®.

- 155 post-marketing spontaneous cases of hepatobiliary adverse events in the company pharmacovigilance database Jul 2009 – 21 Nov 2010
- Of these, 87 are serious cases:
  - 71 cases were reported by a health care professional (HCP) directly to the company
  - 10 cases were HCP reports forwarded to the company by health authorities,
  - 1 serious literature report and 5 consumer reports.

	PSUR 1 1-Aug-2009 to 31-Jan-2010	PSUR 2 1-Feb-2010 to 31-Jul-2010	Post-PSUR 2 1-Aug-2010 to 21-Nov-2010	Total
Exposure - patients	58,554	81,300	40,820*	182,244
HCP serious	13 (1)**	39	30 (4)**	82 (5)**
HCP non-serious	5	37	19	61
Consumer serious	1	2	2	5
Consumer non-serious	0	1	6	7
Total	19	79	48	155

* Exposure for Aug-Sep, 2010

** Number of serious cases with non-serious hepatic events

PSUR: Product Safety Update Report

Data on file, sanofi-aventis

Pool of AF/AFL placebo-controlled studies (DAFNE, EURIDIS, ADONIS, ERATO, ATHENA) Overview of "Pulmonary" Adverse Events

	Placebo		Dronedarone 400 mg BID		Dronedarone 600 mg BID		Dronedarone 800 mg BID	
	(N=2875)		(N=3282)		(N=66)		(N=62)	
AE	**22**	**(0.8%)**	**21**	**(0.6%)**	**0**	**(0%)**	**1**	**(1.6%)**
SAE	**6**	**(0.2%)**	**8**	**(0.2%)**	**0**	**(0%)**	**0**	**(0%)**
AE leading to discontinuation	**7**	**(0.2%)**	**10**	**(0.3%)**	**0**	**(0%)**	**0**	**(0%)**
SAE leading to death	**0**	**(0%)**	**1**	**(<0.1%)**	**0**	**(0%)**	**0**	**(0%)**

Note: Selected events using : SOC "RESPIRATORY DISORDERS" or SMQ "PULMONARY INVESTIGATIONS SIGNS and SYMPTOMS" broad + narrow selection

Data on file, Sanofi

Post-marketing Spontaneous Pulmonary Reports with Multaq® of June 1, 2011

		PSUR 1	PSUR 2	PSUR 3	Update
	Reference period	01-Jul-2009 to 31-Jan-2010	01-Feb-2010 to 31-Jul-2010	01-Aug-2010 to 31-Jan-2011	01-Feb-2011 to 01-Jun-2011
	Duration of reference period	**7 months**	**6 months**	**6 months**	**4 months**
Pulmonary events	**Counts**	**3 cases**	**13 cases**	**18 cases**	**19 cases**
	Reporting rate per 1,000 patient years	0.14	0.26	0.26	0.31
	Reporting risk per 1,000 patients treated	0.05	0.16	0.12	0.17
	Proportional reporting percent	1.30	3.23	3.91	5.40
Interstitial lung disease	**Counts**	**1 case**	**4 cases**	**1 case**	**6 cases**
	Reporting rate per 1,000 patient years	0.05	0.08	0.01	0.10
	Reporting risk per 1,000 patients treated	0.02	0.05	0.01	0.05
	Proportional reporting percent	0.43	0.99	0.22	1.70

Note: Sales data presented do not correspond precisely to the PSUR reference period, but the closest 6-month reporting interval.

- **Based on IMS data, around 400,000 patients have been prescribed with Multaq® since launch.**
- **No definite causal relationship has been established between these pulmonary events and dron edarone.**

Data on file, Sanofi

PSUR: Product Safety Update Report

Adverse Effects of Amiodarone

Adverse effect	Frequency (%)
Serious effects	
Pulmonary toxicity	2 to 17
Hyperthyroidism	2
Hypothyroidism	6
Liver toxicity	1
Optic neuropathy	Unknown
Proarrhythmia	<1
Bradycardia	2 to 4
Minor effects	
Nausea, anorexia	30
Corneal microdeposits	>90
Photosensitivity	4 to 9
Blue discoloration of skin	<9

Am Fam Physician. 2003 Dec 1;68(11):2189-96.

Dronedarone is not associated with organ toxicity compared to amiodarone

First main safety endpoint	Dronedarone 400 mg BID (n=249)	Amiodarone 600 mg for 28 D then 200 mg OD (n=255)
Number of patients with endpoint	**83 (33.3%)**	**107 (42.0%)**
Thyroid events	**2 (0.8%)**	**15 (5.9%)**
Hypothyroidism	**2 (0.8%)**	**7 (2.7%)**
Hyperthyroidism	**0**	**3 (1.2%)**
Thyroid function test abnormal (requiring medical intervention)	**0**	**5 (2.0%)**
Neurological events	**3 (1.2%)**	**17 (6.7%)**
Tremor	**0**	**5 (2.0%)**
Sleep disorder	**3 (1.2%)**	**12 (4.7%)**
Skin events	**2 (0.8%)**	**4 (1.6%)**
Photosensitivity reaction (skin)	**2 (0.8%)**	**4 (1.6%)**
Eye events	**1 (0.4%)**	**3 (1.2%)**
Photophobia	**0**	**2 (0.8%)**
Vision blurred	**1 (0.4%)**	**1 (0.4%)**
Gastrointestinal events	**32 (12.9%)**	**13 (5.1%)**
Diarrhea	**20 (8.0%)**	**5 (2.0%)**
Nausea	**10 (4.0%)**	**6 (2.4%)**
Vomiting	**2 (0.8%)**	**2 (0.8%)**
Premature study drug discontinuation due to any AE	**13 (5.2%)**	**28 (11.0%)**
Hepatic events Liver enzymes (AST/ALT)	**30 (12.0%)**	**27 (10.6%)**

- **Dronedarone is associated with less bradycardia when compared to amiodarone, 2.0% vs 6.3% respectively**

J Cardiovasc Electrophysiol. 2010 Jun 1;21(6):597-605.