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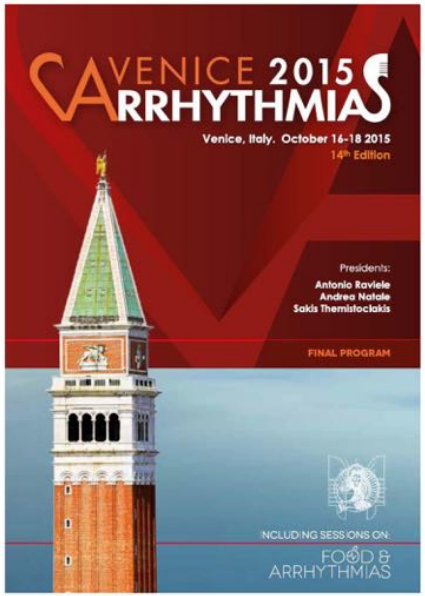
CARIM

AF in patients with CAD

Is dronedarone a good choice?



DRUG PROPHYLAXIS OF AF:
FOCUS ON DRONEDARONE

Friday 16-10-2015

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EUROPEAN Heart Rhythm ASSOCIATION

EUROPEAN SOCIETY OF CARDIOLOGY®

Disclosures Harry Crijns

- research grants, consulting fees
  - Boehringer-Ingelheim, Bayer, BMS, Pfizer, Atricure
- lecture fees
  - Biosense Webster, Boehringer-Ingelheim, Merck, Bayer, Atricure

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doi:10.1093/europace/eut293

Effect of dronedarone on clinical end points in patients with atrial fibrillation and coronary heart disease: insights from the ATHENA trial

Ron Pisters[1], Stefan H. Hohnloser[2], Stuart J. Connolly[3], Christian Torp-Pedersen[4], Lisa Naditch-Brûlé[5], Richard L. Page[6], and Harry J.G.M. Crijns[1*] for the ATHENA Investigators

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Aims This study aimed to assess safety and cardiovascular outcomes of dronedarone in patients with paroxysmal or persistent atrial fibrillation (AF) with coronary heart disease (CHD). Coronary heart disease is prevalent among AF patients and limits antiarrhythmic drug use because of their potentially life-threatening ventricular proarrhythmic effects.

Methods and results This *post hoc* analysis evaluated 1405 patients with paroxysmal or persistent AF and CHD from the ATHENA trial. Follow-up lasted 2.5 years, during which patients received either dronedarone (400 mg twice daily) or a double-blind matching placebo. Primary outcome was time to first cardiovascular hospitalization or death due to any cause. Secondary end points included first hospitalization due to cardiovascular events. The primary outcome occurred in 350 of 737 (47%) placebo patients vs. 252 of 668 (38%) dronedarone patients [hazard ratio (HR) = 0.73; 95% confidence interval

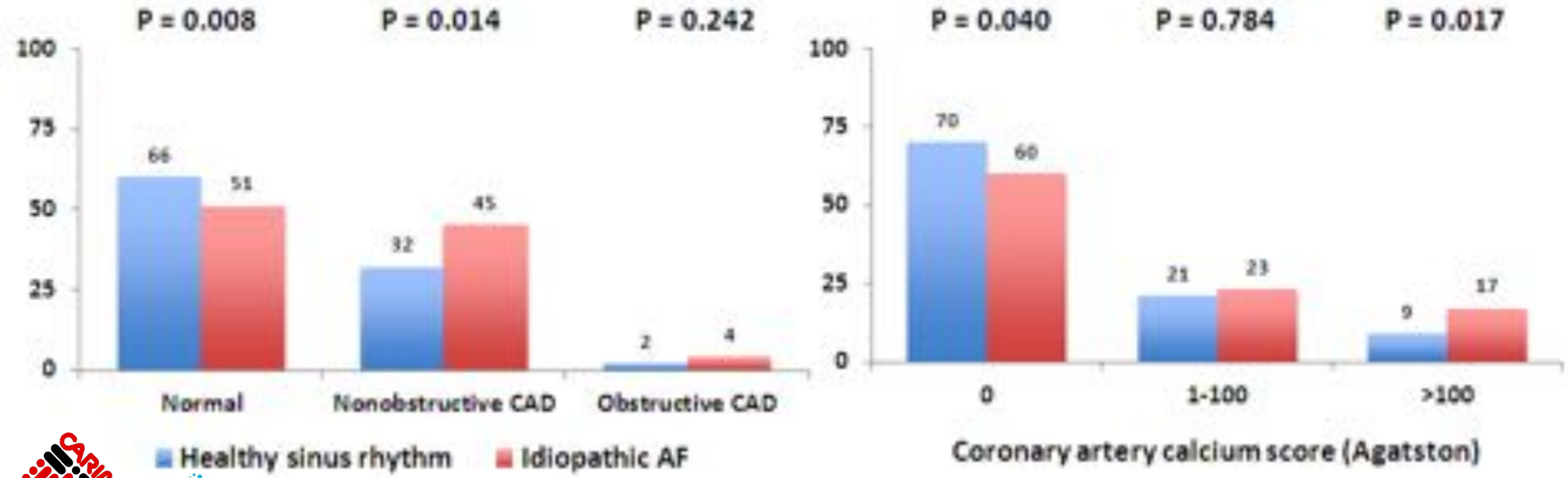
Why dronedarone in CHD patients with AF

- Coronary heart disease (CHD) is frequently associated with AF (30% in ATHENA / EHS-AF) [1,2)]
- Idiopathic AF is associated with concealed CAD (50% of patients) [3)]
- AF is strong predictor for cardiovascular morbidity and mortality in patients with CHD
- Current anti-arrhythmic drugs* are limited by moderate efficacy and safety/tolerability issues

1 Hohnloser S, *et al.* NEJM 2009
2 Nieuwlaat R, *et al.* Eur Heart J 2005
3 Weijs B *et al.* Heart Rhythm 2014
* Vaughan and Williams Class I and III

Half of patients originally diagnosed with idiopathic AF show concealed underlying CAD

Study on the prevalence of CT angiographic CAD in patients with lone AF compared to healthy SR control patients



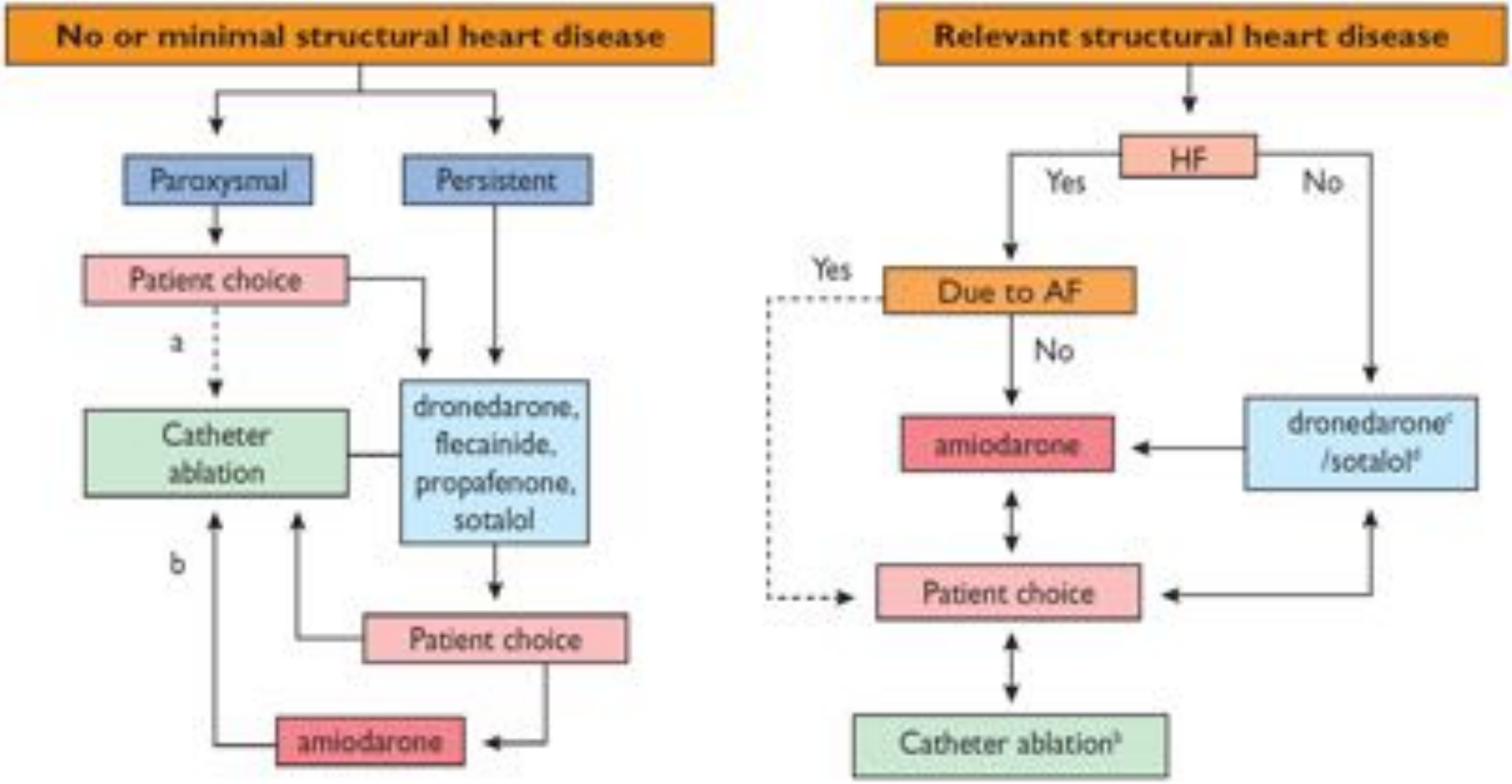
Weijs, *Heart Rhythm* 2012

- Evt nog dia torp pedesen betreffende mortality in AF and CHD

AAD for AF

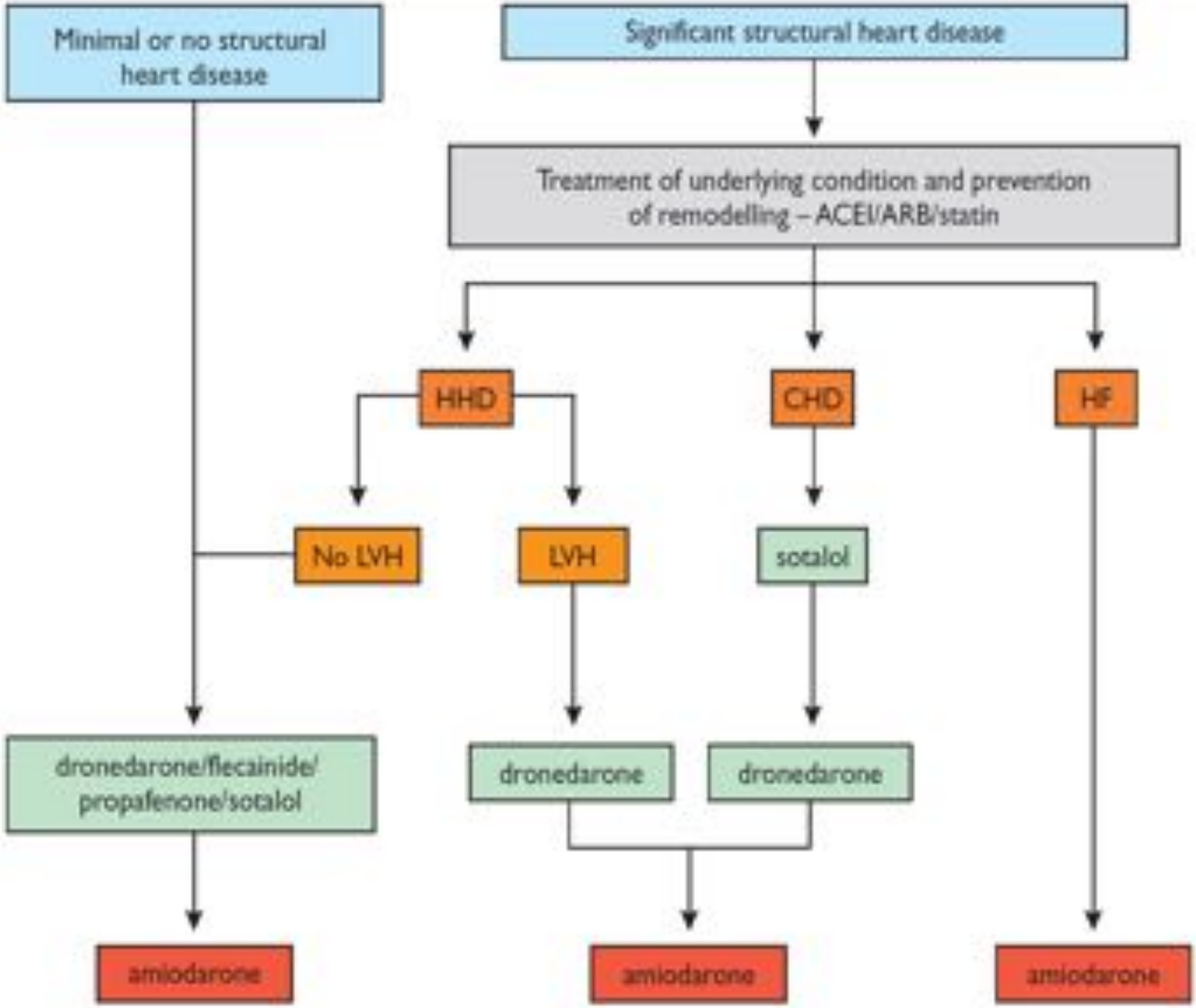
Choice depends on associated conditions

On top of relevant vascular preventive drugs including beta-blocker, ACE-I, ARB, statin, etc.



AF = atrial fibrillation; HF = heart failure. [a]Usually pulmonary vein isolation is appropriate. [b]More extensive left atrial ablation may be needed. [c]Caution with coronary heart disease. [d]Not recommended with left ventricular hypertrophy. Heart failure due to AF = tachycardiomyopathy.

Camm AJ et al. AF Guidelines. Eur Heart J 2012



ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; HHD = hypertensive heart disease; CHD = coronary heart disease; HF = heart failure; LVH = left ventricular hypertrophy; NYHA = New York Heart Association. Antiarrhythmic agents are listed in alphabetical order within each treatment box.

Camm AJ et al. AF Guidelines. Eur Heart J 2012

Preferred 1st line AAD

Scientific Initiatives Committee EHRA

Without structural heart disease	Hypertension and LV hypertrophy	CAD and normal LVEF	Heart failure in stable NYHA I/II class	Advanced heart failure (NYHA III/IV)
Class Ic 73%	β-blockers 43%	β-blockers 51%	β-blockers 51%	Amiodarone 73%
β-blockers 19%	Sotalol 24%	Sotalol 35%	Amiodarone 35%	β-blockers 38%
	Amiodarone 24%	Amiodarone 19%	Sotalol 19%	
		Dronedarone 11%	Dronedarone 11%	

Dagres N et al., Europace 2013

Scientific Initiatives Committee

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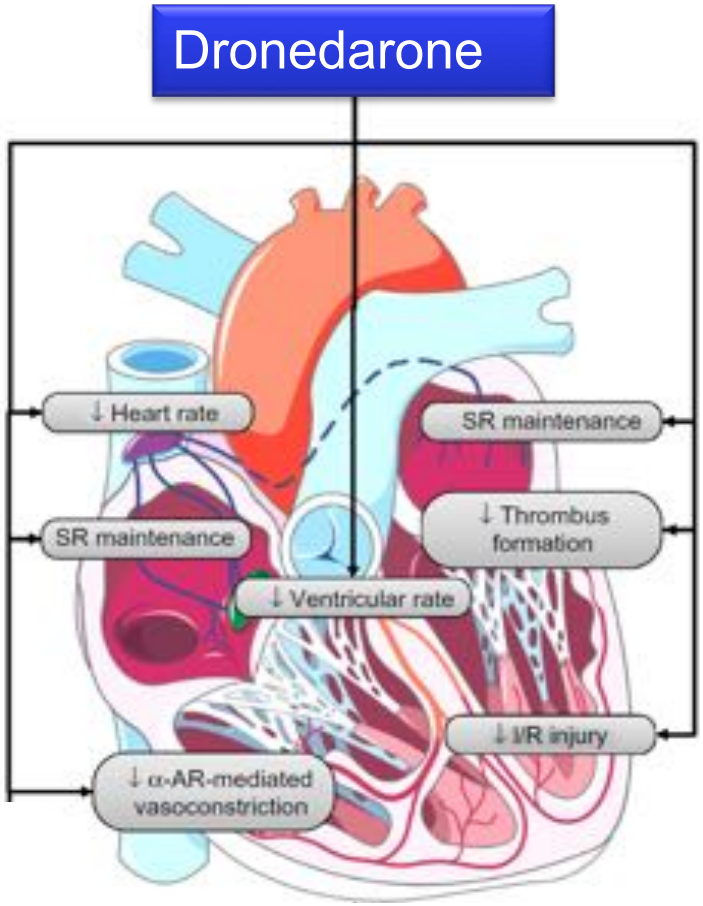
Why dronedarone in CHD patients with AF

- Effective in reducing MACCE [1)]
- SAFE, also in CHD patients with non-permanent AF [2)]
- Reduces both AF [3,4)] and heart rate during AF [4,5)]
- AAD with multiple non-ion channel properties
  - pleiotropic vascular effects
  - (atypical vascular AAD)

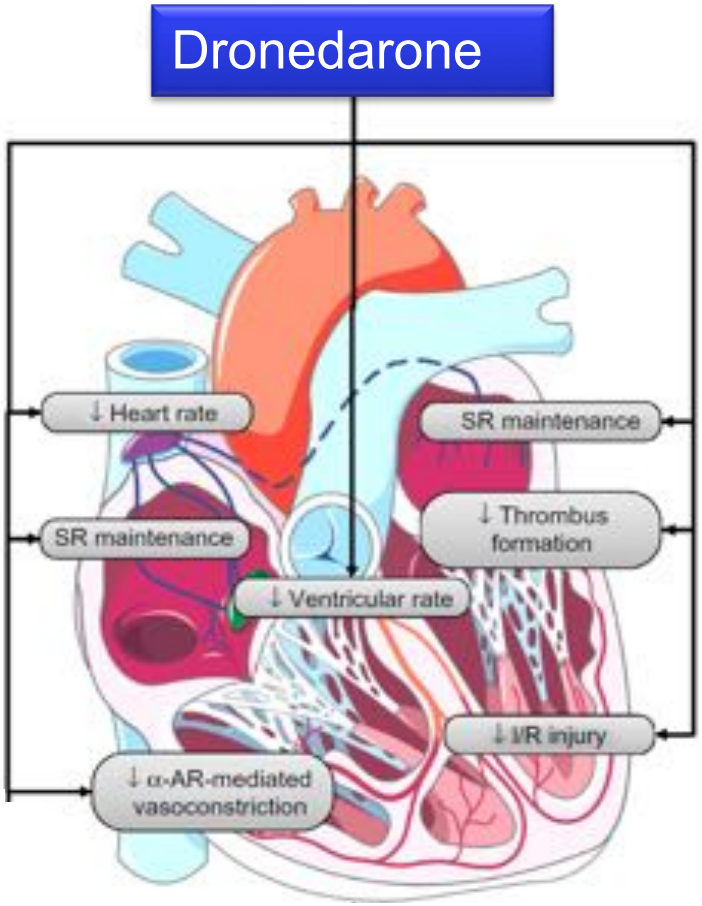


FROM: Heijman J, et al. Clinical Medicine Insights: Cardiology 2013

1 Hohnloser S et al, ATHENA trial, NEJM 2009
2 Pisters R et al. Europace 2014
3 Singh B, et al. EURIDIS & ADONIS, NEJM 2007
4 Page R, et al. Am J Cardiol 2011
5 Davy JM, et al. Am Heart J 2008

Dronedarone has multiple non-ion channel properties *(atypical vascular AAD)*

- Antiarrhythmic efficacy at atrial and ventricular level[1, 2]
- May prevent ventricular proarrhythmia via multichannel block
- Rate controlling effects[1)]
- Vasodilatory effects[2)]
- Anti-adrenergic effects[3)]
- RPP (Blood pressure) lowering properties[4,5)]
- Reduces AF induced oxidative stress (NOX-1/2, HIF-1a, F2-isoprostane, maintains microcirculation[6)]



FROM: Heijman J, et al. Clinical Medicine Insights: Cardiology 2013

1 Gautier P, *et al. J Cardiovasc Pharmacol.* 2003
2 Hodeige D, *et al. European Journal of Pharmacology* 1995
3 Guiraudou P, *et al. European Journal of Pharmacology* 2004
4 Pisters R, et al. Europace 2014
5 ATHENA data on file.
6 Bukowska A, *et al,* Br J Pharm 2013

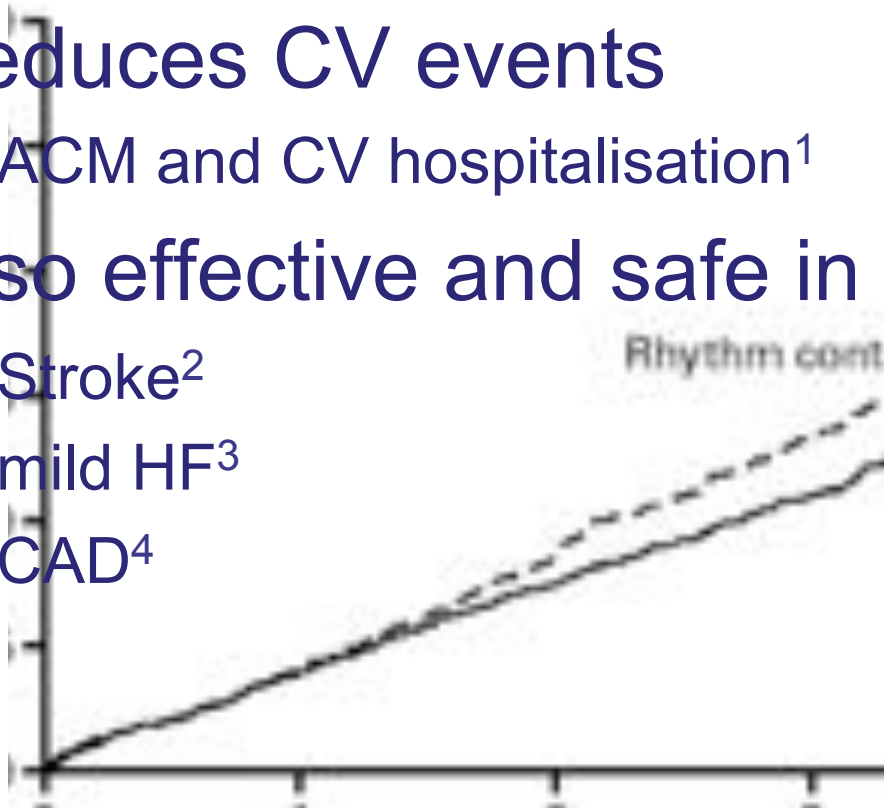
ATHENA was the only rate / rhythm control study that was positive for CV endpoints

No advantage of rhythm over rate control

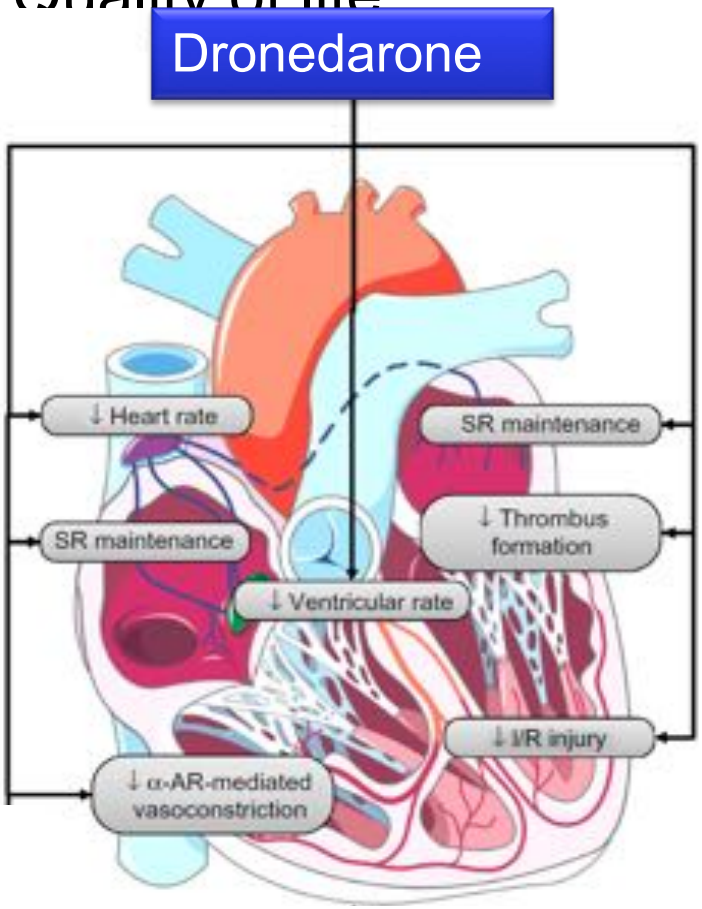
also used mean heart rate

rate / rhythm trials

- Reduces CV events
  - ACM and CV hospitalisation[1]
- Also effective and safe in
  - Stroke[2]
  - mild HF[3]
  - CAD[4]



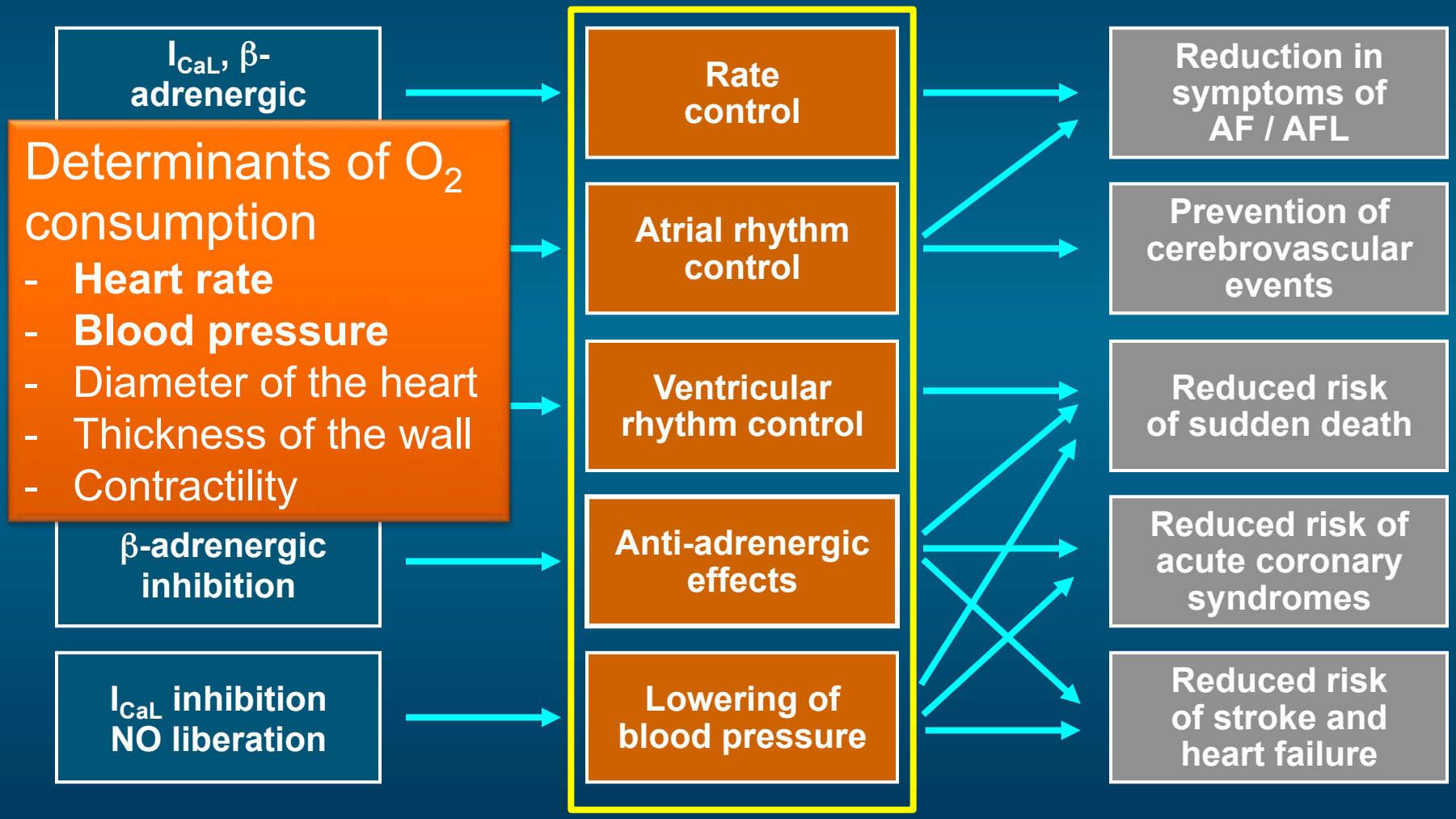
Quality of life



FROM: Heijman J, et al. Clinical Medicine Insights: Cardiology 2013

1 Hohnloser, S, *et al.* NEJM 2009
2 Connolly S, *et al.*, Circulation 2009
3 Hohnloser S, *et al.* Eur Heart J 2010
4 Pisters R, *et al.*, Europace 2014

Potential Ways in which Dronedarone Could Influence Morbidity and Mortality (especially in CHD)



BJP British Journal of Pharmacology

DOI 10.1111/j.1476-5381.2011.01784.x
www.bjphamacol.org

RESEARCH PAPER

Dronedarone prevents microcirculatory abnormalities in the left ventricle during atrial tachypacing in pigs

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Keywords
dronedarone; atrial fibrillation; microcirculation; acute coronary syndrome

Received
15 December 2010
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2 November 2011
Accepted
9 November 2011

BACKGROUND AND PURPOSE

ATHENA Trial Design

- Prospective double-blind trial to assess the efficacy of dronedarone in preventing CV hospitalization or death from any cause in AF/AFL patients with additional risk factors*

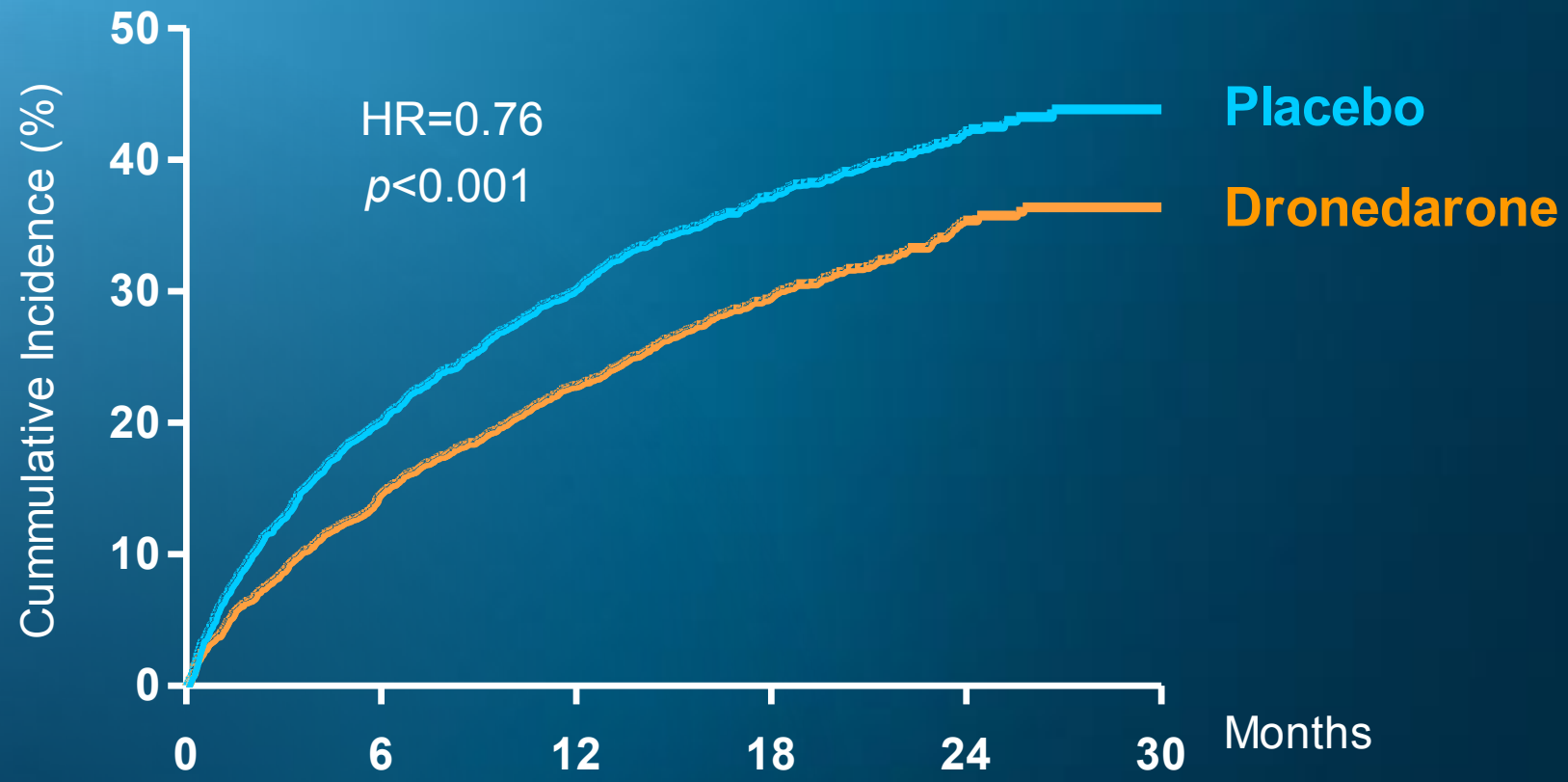
* Age ≥75 y or ≤75 y with hypertension, diabetes, prior stroke/TIA, LAD >50 mm or LVEF ≤0.40
# CHF NYHA Class IV or Class II-III with recent decompensation

Baseline Characteristics

	Placebo n=2327	Dronedarone n=2301	All patients n=4628
Age (mean; SD, years)	72 ± 9.0	72 ± 8.9	72 ± 9.0
Female gender	1038 (45%)	1131 (49%)	2169 (47%)
AF/AFL at baseline	586 (25%)	569 (25%)	1155 (25%)
Structural heart disease	1402 (61%)	1330 (58%)	2732 (60%)
Coronary heart disease	737 (32%)	668 (29%)	1405 (30%)
Valvular heart disease	380 (16%)	379 (17%)	759 (16%)
Non-ischemic cardiomyopathy	131 (6%)	123 (5%)	254 (6%)
History of CHF NYHA II/III	515 (22%)	464 (20%)	979 (21%)
LVEF < 0.45	285/2281 (13%)	255/2263 (11%)	540/4544 (12%)
LVEF < 0.35	87/2281 (4%)	92/2263 (4%)	179/4544 (4%)
Lone atrial fibrillation	139 (6%)	140 (6%)	279 (6%)

Hohnloser SH, *et al. NEJM* 2009;360:668-78.

Cardiovascular Hospitalization or Death (Primary Outcome)

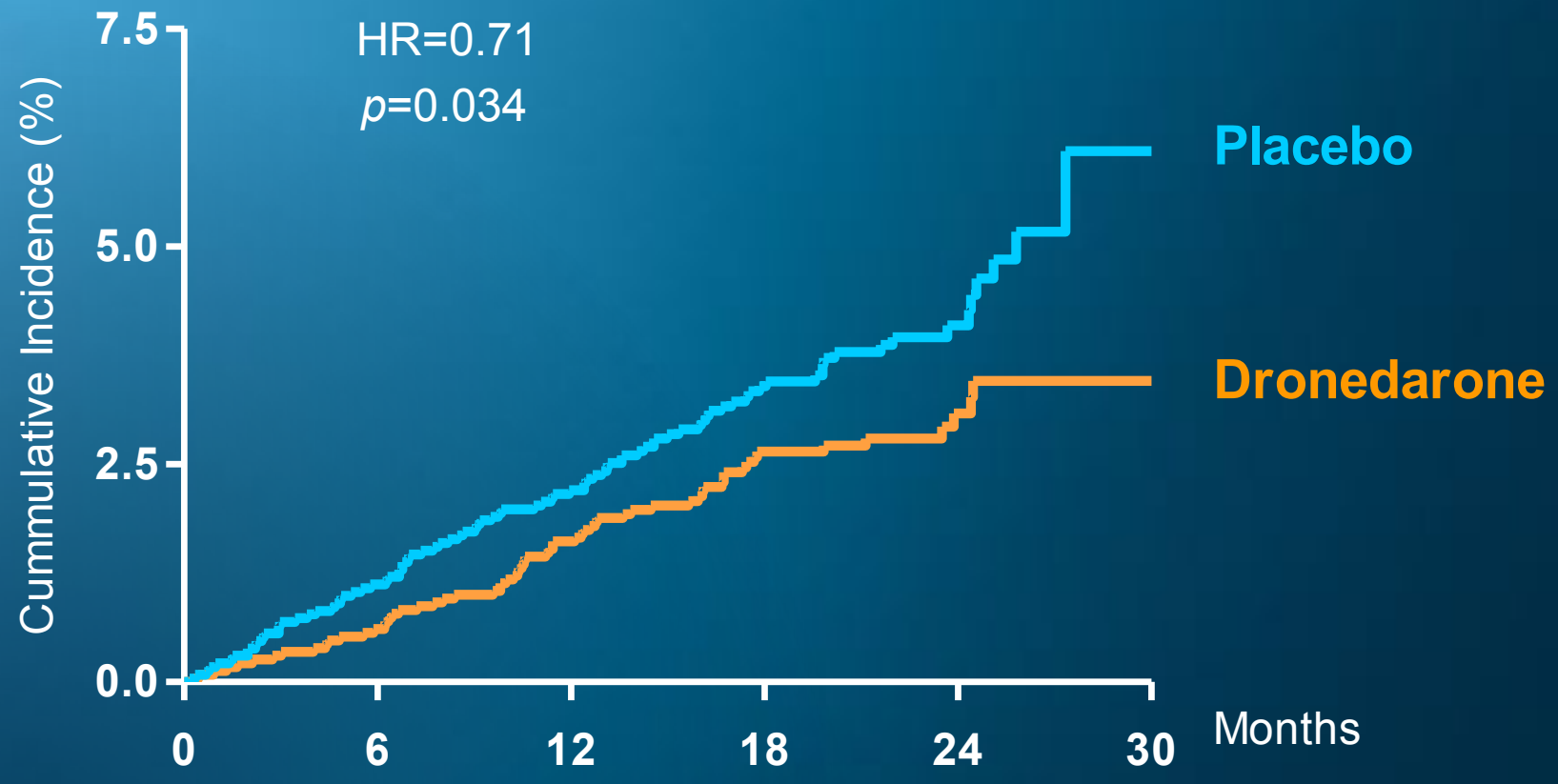


2327	1858	1625	1072	385	3	Placebo
2301	1963	1776	1177	403	2	Dronedarone

Mean follow-up 21 ± 5 months

Hohnloser SH, *et al. NEJM* 2009;360:668-78

Cardiovascular Death



2327	2290	2250	1629	636	7	Placebo
2301	2274	2240	1593	615	4	Dronedarone

Death from any Cause: HR=0.84, p=0.176

Hohnloser SH, et al. NEJM 2009;360:668-78.

Mean follow-up 21 ± 5 months

Characteristics – CHD vs no CHD

	CHD n=1405	No CHD n=3223	p-value
Age Mean (SD)	73.3 (7.9)	70.9 (9.3)	<0.001
Gender (male)	64%	48%	<0.001
Hypercholesterolemia	61%	37%	<0.001
Hypertension	88%	86%	ns(0.077)
Previous stroke or TIA	15%	13%	0.021
Diabetes	26%	18%	<0.001
CHF	39%	25%	<0.001
CHF NYHA Class III	23%	9%	<0.001
LVEF < 35%	8%	2%	<0.001
Chronic renal failure	6%	3%	<0.001
AF at baseline	26%	28%	ns (0.470)

post-hoc analysis

Pisters R, ... Crijns HJ. Europace 2014

Baseline Characteristics - CHD

	Placebo n=737	Dronedarone n=668
Age Mean (SD)	73.5 (8.2)	73.1 (7.7)
Gender (male)	66%	63%
Hypercholesterolemia	59%	62%
Hypertension	87%	89%
Previous stroke or TIA	14%	16%
Diabetes	27%	25%
CHF	39%	39%
CHF NYHA Class III	9%	9%
LVEF <35%	9%	8%
Chronic renal failure	5%	6%
AF at baseline	25%	27%

post-hoc analysis

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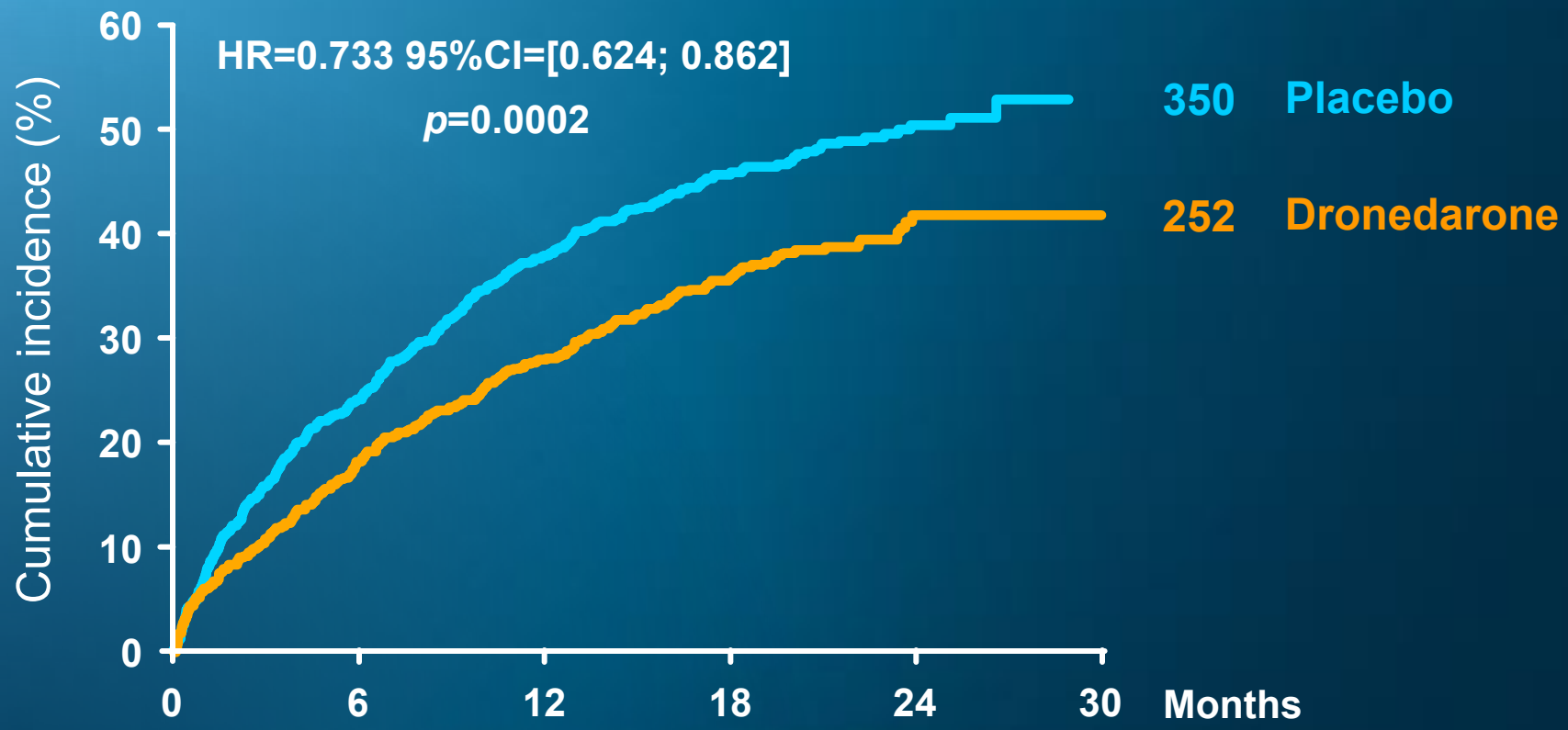
CV Hospitalization or Death from any Cause - CHD



737	560	458	285	109	0	Placebo
668	545	480	298	88	1	Dronedarone

post-hoc analysis

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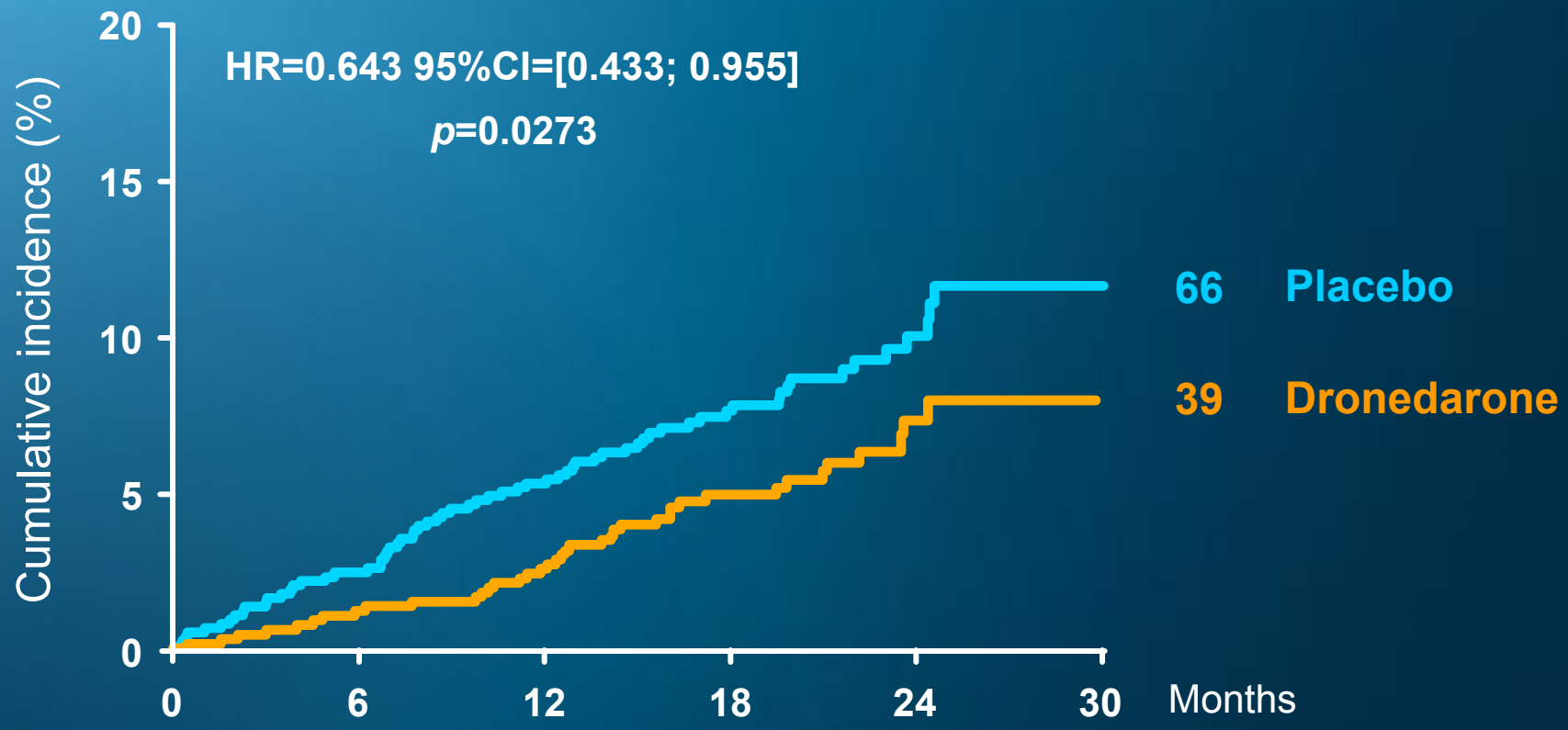
Death from any Cause - CHD



737	719	698	491	199	1	Placebo
668	660	651	445	166	1	Dronedarone

post-hoc analysis

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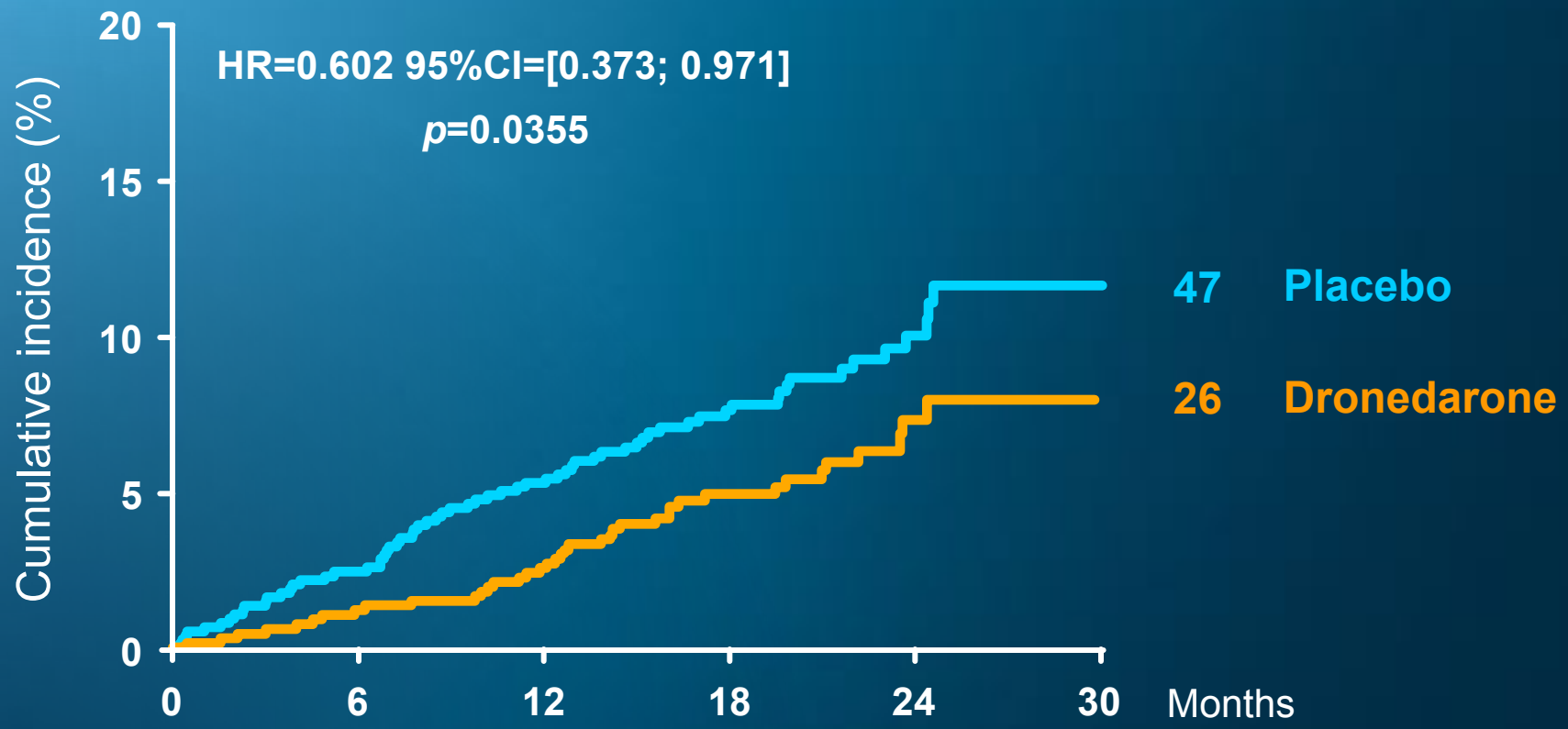
CV Death - CHD



737	719	698	491	199	1	Placebo
668	660	651	445	166	1	Dronedarone

post-hoc analysis

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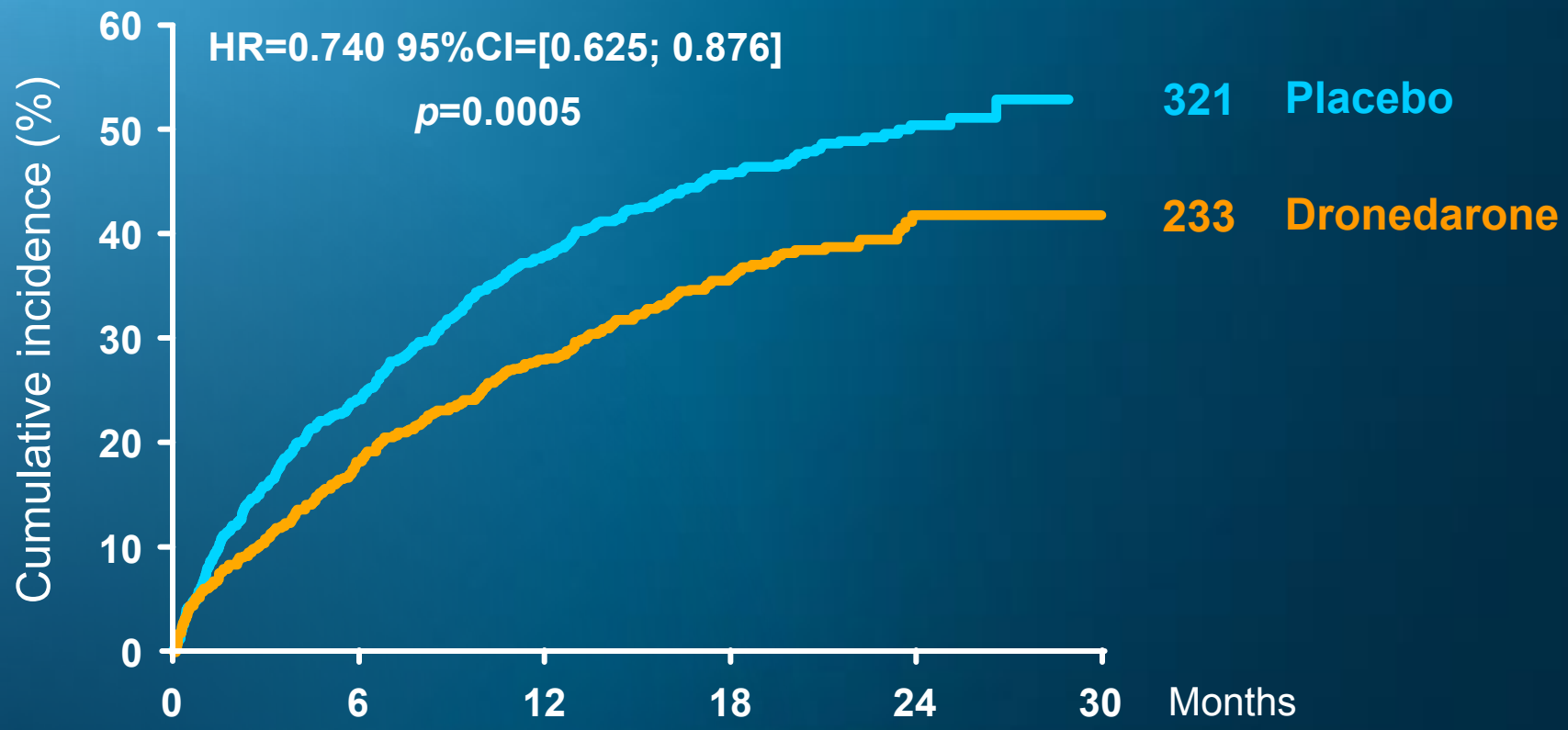
CV Hospitalization - CHD



737	560	458	285	109	0	Placebo
668	545	480	298	88	1	Dronedarone

post-hoc analysis

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Reasons for CV Hospitalization - CHD

	Placebo n=737	Dronedarone n=668
Any first CV hospitalization	**321 (43.6%)**	**233 (34.9%)**
AF related	129 (17.5%)	85 (12.7%)
Acute Coronary Syndrome	41 (5.6%)	32 (4.8%)
Stable angina pectoris	25 (3.4%)	14 (2.1%)
Transcutaneous intervention	17 (2.3%)	15 (2.2%)
Cardiovascular surgery	11 (1.5%)	6 (0.9%)
TIA or stroke (except ICH)	10 (1.4%)	6 (0.9%)
Worsening CHF	41 (5.6%)	38 (5.7%)
Ventricular Arrhythmia	4 (0.5%)	4 (0.6%)
Syncope	12 (1.6%)	5 (0.7%)
Implantation of a cardiac device	12 (1.6%)	9 (1.3%)
Blood pressure related	8 (1.1%)	7 (1.0%)
Major bleeding	8 (1.1%)	7 (1.0%)
Other	3 (0.4%)	5 (0.7%)

post-hoc analysis

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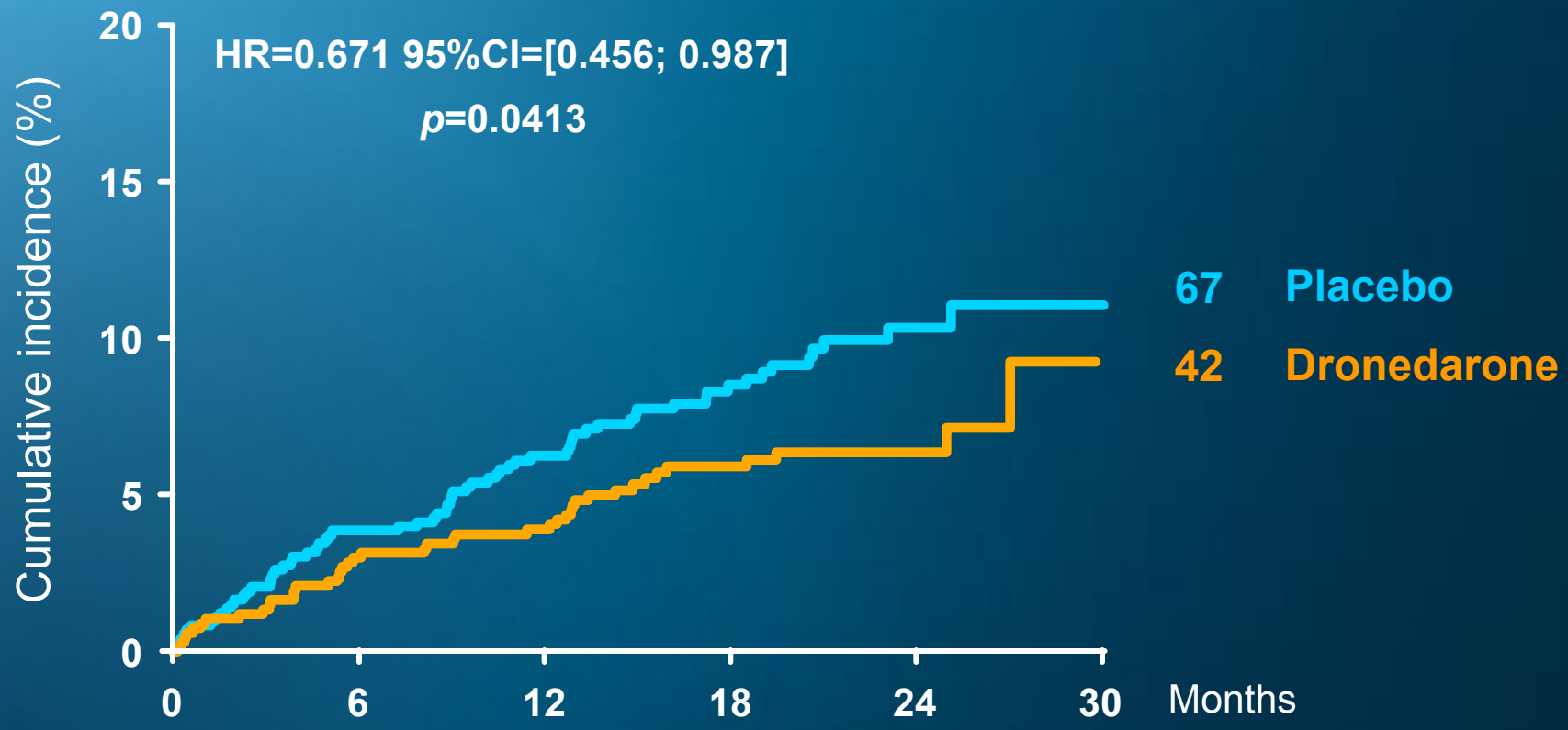
Time to First ACS - CHD



737	695	661	457	186	1	Placebo
668	642	630	424	154	1	Dronedarone

post-hoc analysis

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Effects of dronedarone independent of subgroups

Characteristic	N	Relative risk [95% CI]*	P-value†
Age (years)			
<65	183	0.52 [0.18;1.49]	
≥65 to <75	548	0.95 [0.52;1.73]	
≥75	674	0.52 [0.29;0.95]	0.317
Gender			
Male	904	0.60 [0.36;1.00]	
Female	501	0.77 [0.43;1.37]	0.543
Diabetes			
Yes	365	0.62 [0.29;1.32]	
No	1040	0.69 [0.44;1.09]	0.766
Stroke/TIA			
Yes	212	0.64 [0.27;1.49]	
No	1193	0.67 [0.44;1.03]	0.905
CHF			
Yes	548	0.73 [0.43;1.24]	
No	857	0.62 [0.35;1.09]	0.681
LVEF (%)			
<35	110	0.13 [0.03;0.57]	
≥35	1271	0.82 [0.54;1.24]	0.008
NYHA			
Class I or II	423	0.56 [0.27;1.16]	
Class III or IV	125	1.00 [0.45;2.21]	0.260
$CHADS_2$ score			
≤1	337	0.51 [0.22;1.17]	
≥2	1068	0.73 [0.47;1.13]	0.452
Hypertension			
Yes	1232	0.75 [0.50;1.12]	
No	173	0.22 [0.05;1.01]	0.093

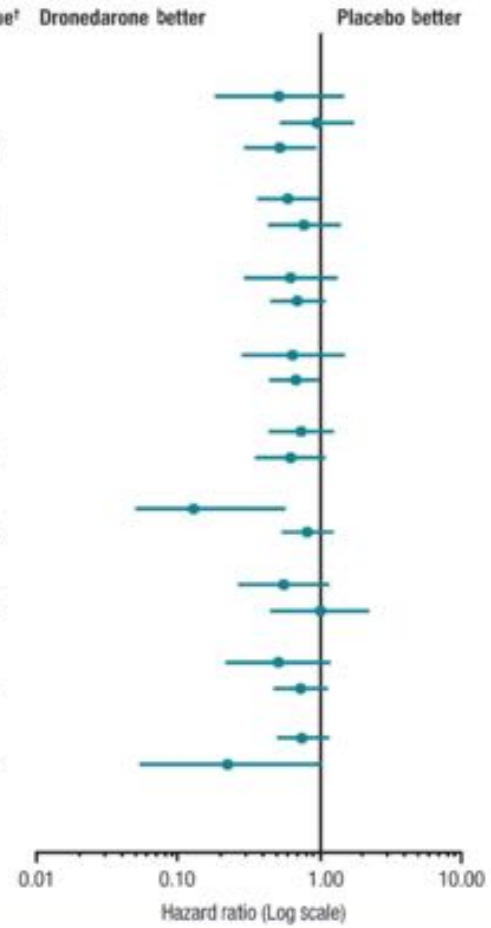

Figure 4 Specific subgroup analysis for acute coronary syndrome (ACS) in patients with coronary heart disease. The $CHADS_2$ score is a measure of the risk of stroke in patients with atrial fibrillation, with scores ranging from 0 to 6 and higher scores indicating a greater risk.[21] Congestive heart failure (CHF), hypertension, an age of 75 years or older, and diabetes are each assigned 1 point, and previous stroke or transient ischemic attack is assigned 2 points; the score is calculated by summing all the points for a given patient. CI, confidence interval; LVEF, left ventricular ejection fraction; TIA, transient ischemic attack; RR, relative risk. (*) Determined from Cox regression model. (†) P-value of interaction between baseline characteristic and treatment based on cox regression model.

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Rate pressure product is decreased by dronedarone

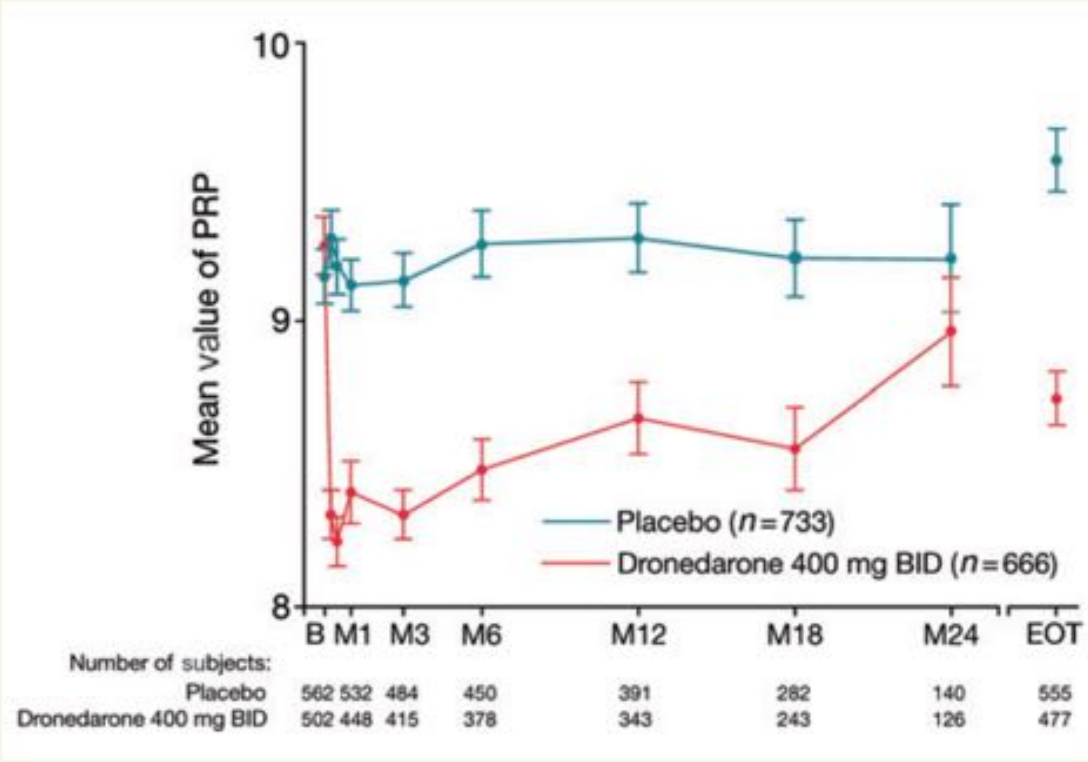

Figure 3 Pressure rate product over time in patients with coronary heart disease. B, baseline; EOT, end of treatment; M1, month 1; PRP, pressure rate product = (heart rate × systolic blood pressure)/1000.

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Adverse Events - CHD

Type of AE	Placebo n=733	Dronedarone n=666	p-value
Gastrointestinal disorders	**183 (25.0%)**	**203 (30.5%)**	**0.023**
Diarrhoea	**52 (7.1%)**	**78 (11.7%)**	**0.003**
Prolonged QT interval	**5 (0.7%)**	**21 (3.2%)**	**<0.001**
Cardiac disorders*	**92 (12.6%)**	**83 (12.5%)**	**ns**
Bradycardia	**13 (1.8%)**	**29 (4.4%)**	**0.007**
Sinus bradycardia	**1 (0.1%)**	**12 (1.8%)**	**0.001**
Asthenia	**13 (1.8%)**	**24 (3.6%)**	**0.044**
Blood creatinine increased	**10 (1.4%)**	**34 (5.1%)**	**<0.001**

post-hoc analysis

* AF related events were waived from reporting as AEs

Conclusions Dronedarone in CHD and AF

- In this post-hoc analysis of the CHD population in ATHENA dronedarone compared to placebo significantly reduced:
  - First CV hospitalization or death by 27%
  - Overall mortality by 36%
  - CV mortality by 40%
  - CV hospitalizations by 26%
- Fewer patients hospitalised for ACS
- Dronedarone is safe in AF and CHD
- Dronedarone safe and effective in AF patients with a more severe disease profile than overall ATHENA population

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Conclusions
Dronedarone in AF patients with CHD

- Dronedarone is a good choice to treat AF in CHD
- AADs for AF patients with CAD
  - Beta-blocker, Verapamil, Digitalis, Procoralan
  - Dronedarone, Sotalol, Amiodarone
- Dronedarone is
  - Safe (sotalol safe? Amiodarone safe?)
  - Effective in reducing AF recurrences
  - Prevents ACS (directly, indirectly)
  - Well tolerated

What I tell my patients who start an AAD for prevention of AF recurrence

- A recurrence is likely, but is not an indicator of drug failure
- If side effects or unacceptable recurrences: switch to …
  - Other AAD, combination of AADs, ablation, ablation plus AAD
- If recurrence
  - Stay put, do not exercise
  - Come to hospital as needed or use add-on rate control or PIP
- If alarm symptoms, … call
  - Unexplained (new) chest pain/dyspnea
  - Sudden change
  - Unexplained (pre)syncope
- In case of initiation of drugs (especially Ic drugs) I suggest to perform a coronary CT angiography
  - If CAD: (additional) prophylactic vascular therapy
  - CAG if deemed indicated
  - Call if alarm symptoms

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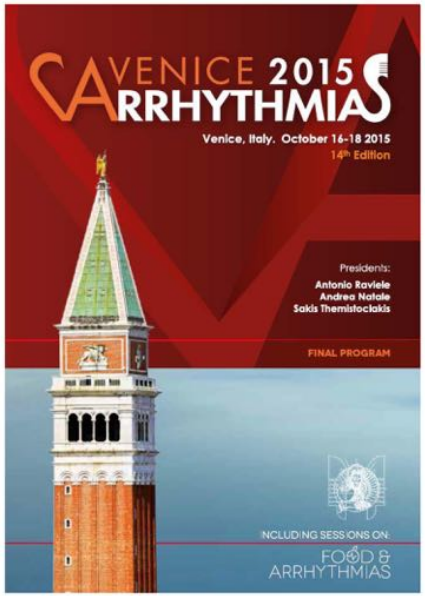
Thank you for your attention



DRUG PROPHYLAXIS OF AF: FOCUS ON DRONEDARONE

Friday 16-10-2015

EUROPEAN Heart Rhythm ASSOCIATION

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