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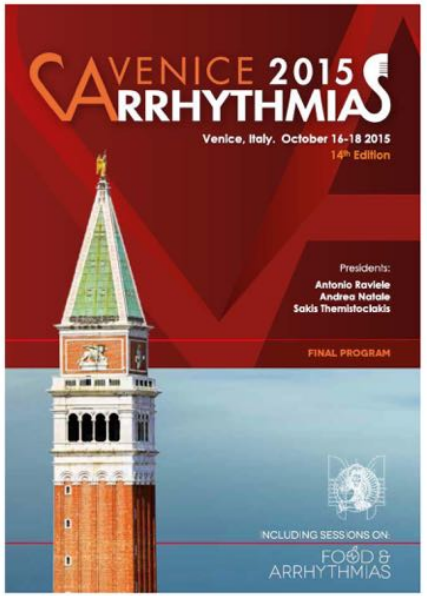
Dronedarone

What is the future?



DRUG PROPHYLAXIS OF AF:
FOCUS ON DRONEDARONE

Friday 16-10-2015

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Maastricht, The Netherlands

Disclosures Harry Crijns

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

The past of Dronedarone

The most extensively studied AAD in AF

Studies	N	Population	Objectives
Rhythm and Rate Control			
DAFNE[1]	270	Persistent AF	Dose ranging - cardioversion and maintenance of sinus rhythm
EURIDIS[2]	612	Paroxysmal/Persistent AF/ AFL	Maintenance of sinus rhythm
ADONIS[2]	625	Paroxysmal/Persistent AF/ AFL	Maintenance of sinus rhythm
ERATO[3]	174	Permanent AF	Ventricular rate control
DIONYSOS[4]	504	Persistent AF	Comparative trial vs amiodarone
Recently Decompensated CHF			
ANDROMEDA[5]	627 / 1000	Unstable CHF and LV dysfunction (25% AF)	Morbidity-mortality study
Clinical Outcomes			
ATHENA[6]	4628	Paroxysmal/Persistent AF/ AFL	Prevention of cardiovascular hospitalisation or death from any cause
PALLAS[7]	3149 / 10800	Permanent AF	Prevention of major CV events and CV hospitalisation or death from any cause

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. *Le Heuzey JY et al. J Cardiovasc Electrophysiol. 2010 Apr 6 Epub*
5. *Køber L, et al. N Engl J Med. 2008;358:2678-87.*
6. *Hohnloser SH, et al. N Engl J Med 2009;360:668-78*
7. *Connolly SJ, et al. N Engl J Med 2011*

Future *medical management* of AF

- Suppression of symptoms
  - safe and effective drugs **D**
- Recognition of patient at risk
  - beyond the CHA_2DS_2–VASc score
- Stroke prevention
  - safe anticoagulants
  - Impact of non-anti-thrombotic drugs (on top of anticoagulation) **D**
- Reduce AF progression rate **D**
- Optimal rate control
  - Safe and effective rate control drugs **D**
  - Multi-modality drugs
- Early rhythm control **D**

Future: dronedarone

- Dronedarone is a class III antiarrhythmic agent
  - maintenance of SR in patients with AF
  - Like amiodarone antiadrenergic (ie, beta blocking) properties
  - Multiple transmembrane ion channel actions: potassium, sodium, calcium currents
- In contrast to amiodarone (half-life of 50 days), dronedarone has a half-life of 24 hours
- Dronedarone is highly bound to plasma proteins, no significant tissue accumulation
  - systemic long-term side effects (liver toxicity, pulmonary fibrosis, thyroid dysfunction) rare
- Hepatic metabolism >>> numerous potential drug interactions
  - Do not combine with ketoconazole, class I antiarrhythmic drugs
  - Dose adjust when combined with digoxin, warfarin, statins, dabigatran

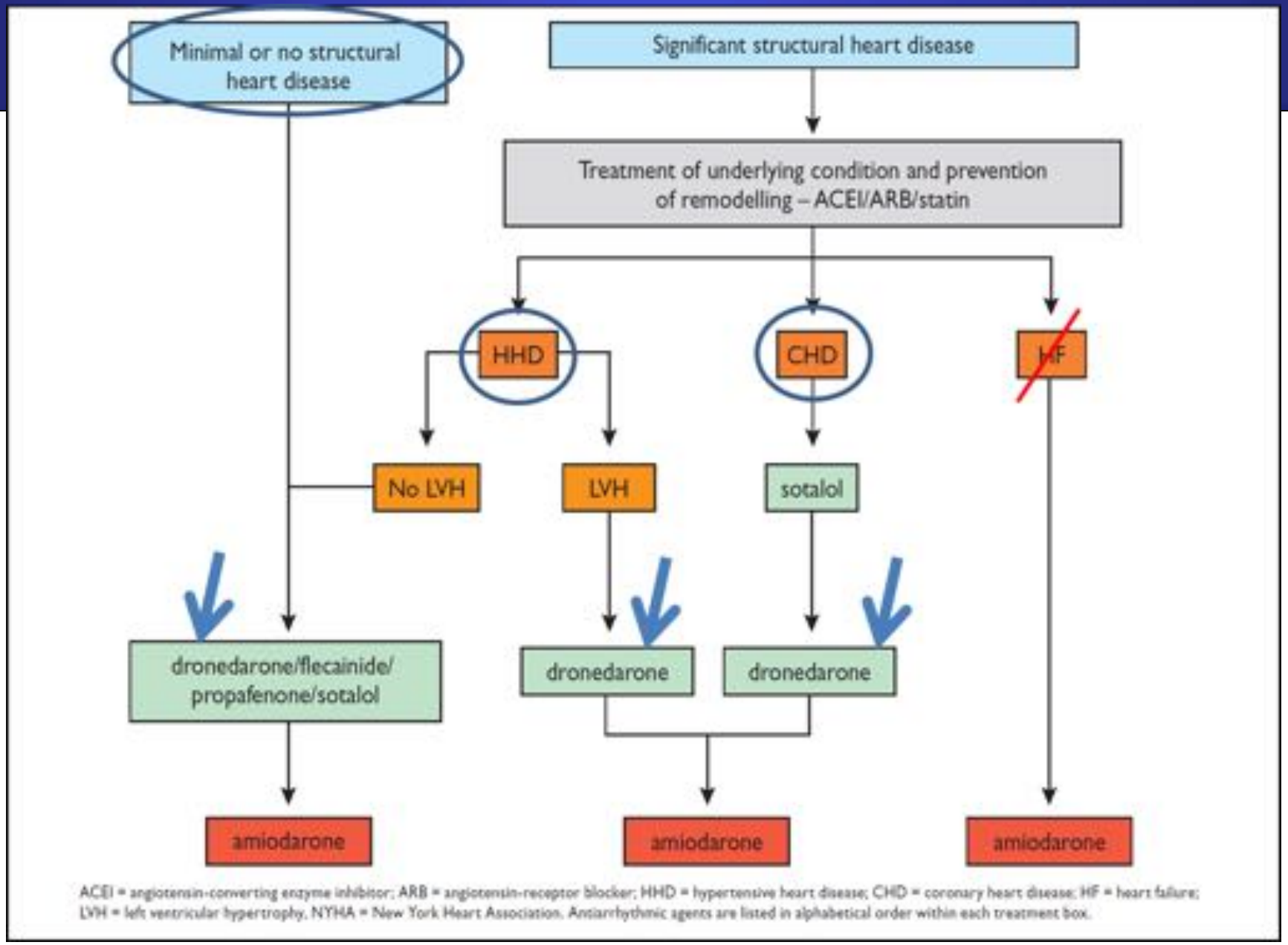
Future: dronedarone

- Maintenance of SR
  - Amiodarone >>> Dronedarone >>> Placebo
  - Dronedarone preferred in paroxysmal and recurrent persistent AF, in CAD, hypertensive heart disease (± LVH), minimal HD
  - Avoid completely in permanent AF or HF (Class III and IV)
- Do not use exclusively as rate control medication
- Dronedarone rarely effective for chemical CV to SR (less than 10 percent of patients)
- Loading before ECV: at least 4 days in advance
- Hepatic function testing at initiation and once or twice within the first six months and yearly thereafter
- ECG annually and at the time of any clinical change

Future: dronedarone

- Dronedarone is usually well tolerated
  - Crampy abdominal pain, diarrhea, nausea, and rash
  - Rarely: heart failure, QT prolongation, and liver toxicity
- Because of the potential for QT prolongation and torsades des pointes, concomitant use of dronedarone and class I or III antiarrhythmic drugs that prolong the QT interval is contraindicated
- Allow least 5 half-lives between changes in antiarrhythmic agents except for amiodarone.
- Dronedarone can usually be started immediately after amiodarone discontinuation unless there is clinically significant bradycardia or QT prolongation

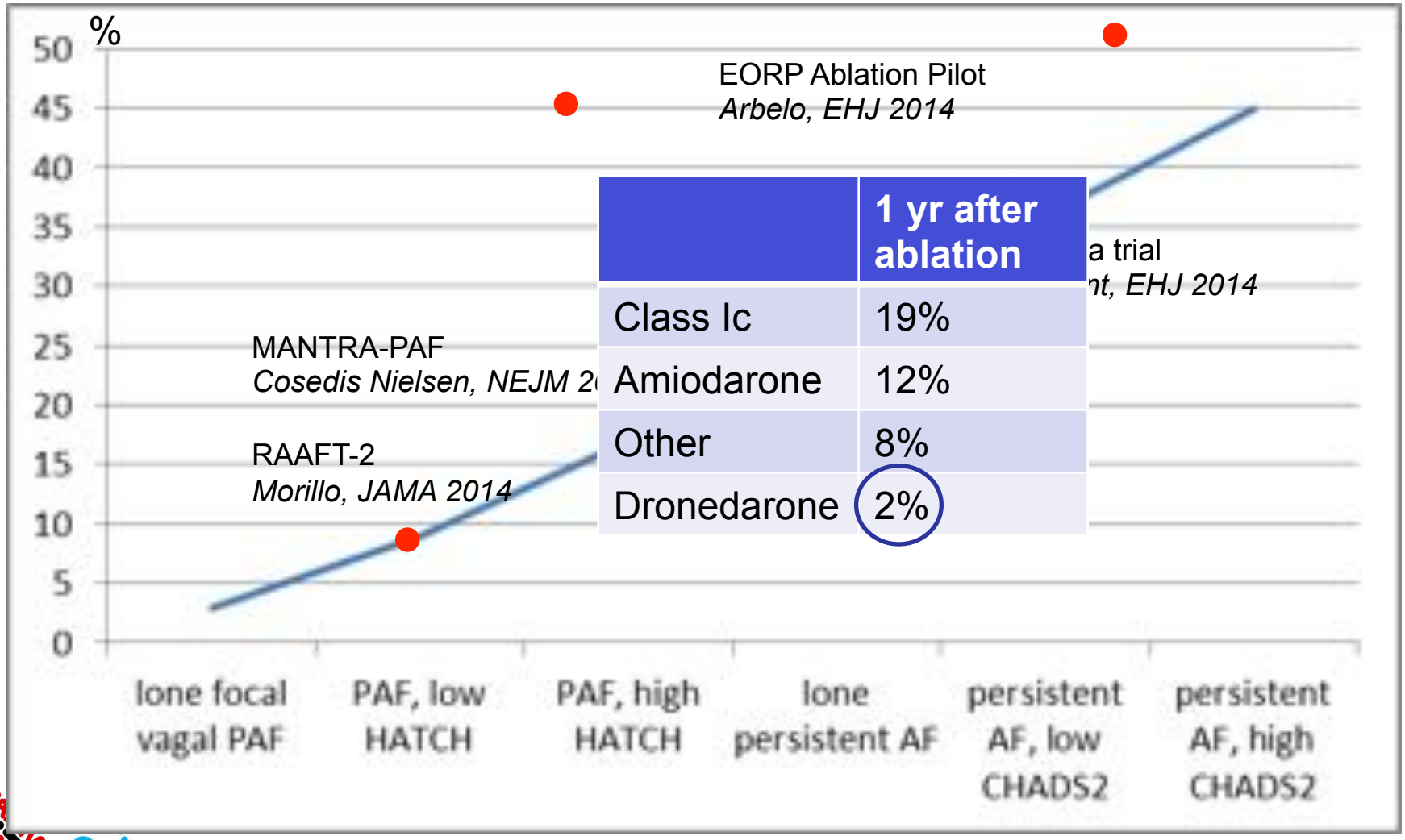
Paroxysmal and non-permanent AF



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

Future of Dronedarone

AAD use after ablation (12-24 months)



	1 yr after ablation
Class Ic	19%
Amiodarone	12%
Other	8%
Dronedarone	2%

The need for AAD to control Sx > ablation is underestimated in clinical studies

Effects of amiodarone & dronedarone on clinical outcomes in AF patients

	AFFIRM	AF-CHF	ATHENA
Amiodarone use	63% of pts	82% of pts	none
Total mortality	↑ P=0.08	↔	↔
CV mortality	n.a.	↔	↓ P=0.03
Hospitalization	↑ P<0.001	↑ P=0.001	↓ P<0.001
Stroke	↑ P=0.79	↔	↓ P=0.027

AFFIRM Investigators. NEJM 2002;347:1825-33
Roy et al. NEJM 2008;358:2667-77
Hohnloser et al. NEJM 2009;360:668-78

Kirchhof P et al. Yearly rate of **Stroke, Death and Myocardial Infarction** in 100.000 patients in randomised atrial fibrillation studies after 2000. EAST Design Paper Am Heart J 2013,

Trial	Number of patients	Stroke		Death		MI	
		active group	Compa-rator	active group	Compa-rator	active group	Compa-rator
ACTIVE W [40]	6700	2.4	1.4	4	4	0.88	0.55
AF-CHF [11]	1376	1.8	1.8	1.8	1.8	9.5	
AFFIRM [41]	4060	1.2	1.2	5	5	5	
AMADEUS [42]	4576	0.9	1.3	3.2	2.9	0.8	0.6
ANDROMEDA [43]**	627			50	24		
ARISTOTLE [7]	18201	1.3	1.6	3.5	3.9	0.5	0.5
ATHENA [27]	4628	1.2	1.8	2.8	3.4	1.5	2.1
AVERROES	5600	0.9	2.5	3.4	4.4	0.7	0.8
EURIDIS/ADONIS [30]	1237	0.5	0.7	1	0.7		
Flec-SL [10]	635			0	0		
PALLAS [29]	3236	4.4	1.9	4.7	2.4	0.6	0.4
RACE [20]	522	3.3	3.4				
RACE II [9]	614	1.6	3.9	5.6	6.6		
Re-LY [5]	18113	1	1.6	3.6	4.1	0.7	0.5
ROCKET AF [6]	14117	2.1	2.4	1.9	2.2	1	1.1
SAFE-T [45]	665	2	2	4.4	2.8		
SOPAT [46]	1012			1			
SPORTIF III [47]	3410	1.6	2.3			1.1 / 0.6	
SPORTIF IV [48]	3922	1.6	1.2	3.6	3.8	1	1.4
Sum	93766	1.5	1.7	3.5	3.5	1.0	0.7

PALLAS - EMA press release

- Dronedarone not in permanent AF
- Only prescribed for maintaining sinus rhythm
- After alternative treatment options have been considered
- Because increased risk on liver, lung or cardiovascular adverse events

PALLAS - EMA press release

- Contraindicated:
  - In unstable hemodynamic conditions
  - Current or prior HF or LV dysfunction (NYHA III+IV)
- Avoid in patients with less severe HF (NYHA I+II)
- Combination with **digoxin** and with **dabigatran** is discouraged (P-glycoprotein inhibitor)

Abstract Send to:

[illegible]

Dabigatran-dronedarone interaction in a spontaneous reporting system.

[illegible]
Author information

Abstract

OBJECTIVES: To investigate the risk of bleeding events associated with concurrent administration of dabigatran-dronedarone compared with dabigatran standalone therapy using the Food and Drug Administration Adverse Event Reporting System (FAERS) database and to identify the characteristics of patients with bleeding events associated with concurrent use of dabigatran and dronedarone.

DESIGN: Retrospective data mining analysis.

SETTING: United States, from the dabigatran approval date (October 19, 2010) through the fourth quarter of 2011.

PATIENTS: Cases from FAERS with bleeding events (combined in a single term based on adverse event reports such as hemorrhage and rectal hemorrhage) as the adverse event.

INTERVENTION: Cases listing concomitant use of the terms Pradaxa, dabigatran, or dabigatran etexilate with Multaq or dronedarone as the suspect drug from FAERS and cases listing dabigatran and dronedarone as standalone therapies were extracted for analysis.

MAIN OUTCOME MEASURE: Risk of bleeding among those using dabigatran-dronedarone concomitantly compared with those using dabigatran standalone therapy.

RESULTS: 100 dabigatran-dronedarone interaction reports and 14,313 reports concerning bleeding events were extracted from FAERS. Of 100 dabigatran-dronedarone interaction cases, 51 were associated with bleeding events. The odds ratio (OR) for risk of bleeding in patients using dabigatran and dronedarone concomitantly compared with those using neither of the suspect drugs was 13.00 (95% CI 9.45-20.14). The OR for risk of bleeding in patients using only dabigatran compared with those using neither of the suspect drugs was 16.36 (15.00-17.19).

CONCLUSION: The likelihood of reporting bleeding events to FAERS among patients using dabigatran only was similar to that among patients using dabigatran and dronedarone concomitantly.

PMID: [illegible] [PubMed - indexed for MEDLINE]

Digoxin and mortality in AF
Post-hoc ROCKET trial

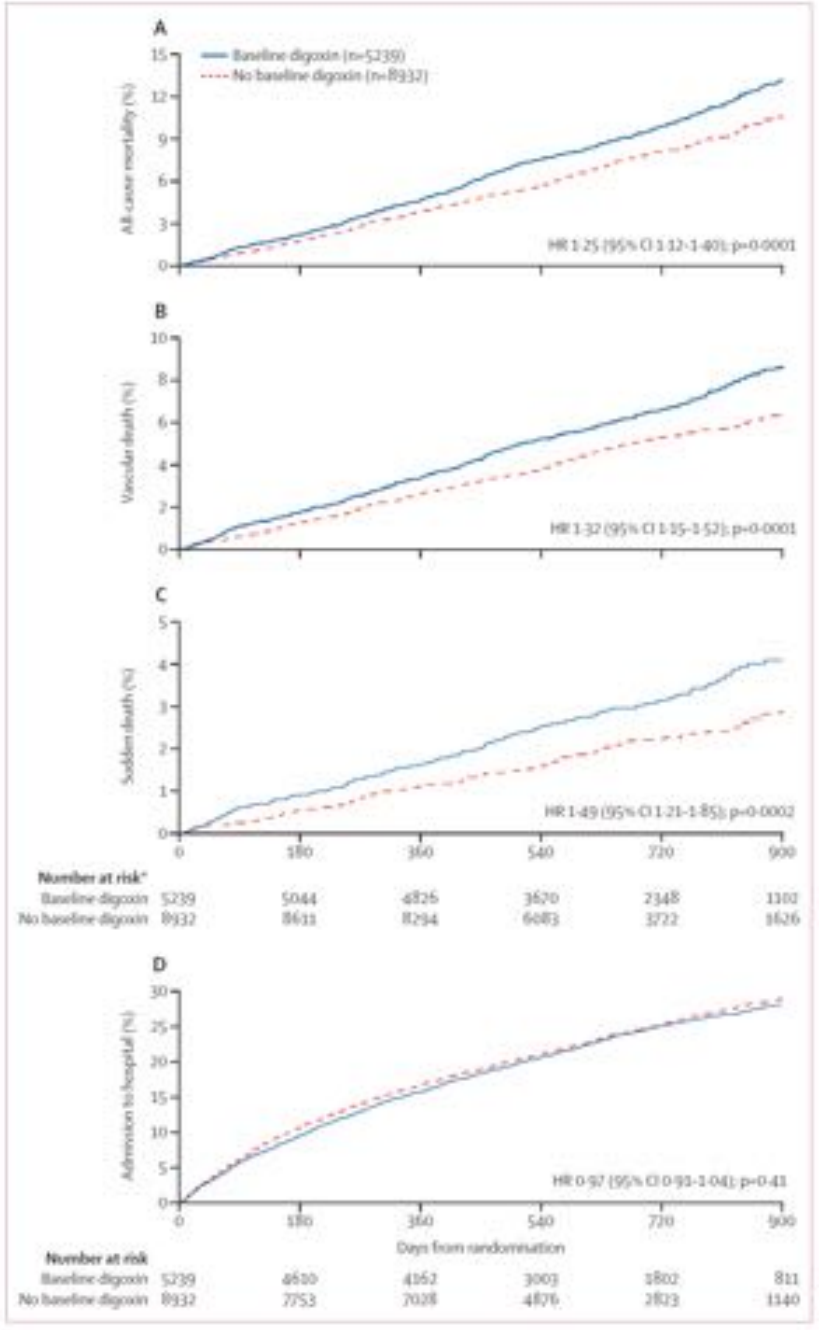


Figure: Kaplan-Meier curves for (A) all-cause mortality, (B) vascular death, (C) sudden death, and (D) admission to hospital at baseline versus none
*Applies to A–C.

Washam JB, ROCKET AF, *Lancet 2015*

- Washam JB, ROCKET AF, *Lancet 2015*
- Turakhia MP, TREAT-AF, *JACC 2014*
- Whitbeck MG, AFFIRM EHJ 2013
- **Mulder BA, RACE-II, *Heart Rhythm,* 2014**
- **Gheorghiade M, AFFIRM, EHJ 2013**
- **Fauchier, Loire Valley study, ESC-HFA congress June 3, 2015**

→ Do not withdraw digitalis

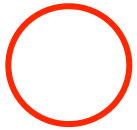
→ Dose adjusted to age, body weight, renal function (70-70-70 rule)

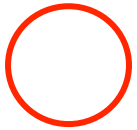
→ Aim for RACE-II heart rate (<110)

→ At serum level < 1.0 ng/ml decreased mortality in DIG trial (SR plus HF, Lancet 1997)

Dronedarone – interaction with digoxin

diovascular events. Eligible patients were randomized to receive dronedarone 400 mg twice daily or matching first co-primary outcome was a composite of stroke, myoc tion, systemic embolism, or cardiovascular death. The se mary outcome was unplanned cardiovascular hospitalizat Other outcomes were death from cardiovascular causes





Dronedarone increases digoxin levels

- Increased digoxin level might be the driver of increased mortality in patients receiving dronedarone (like in DIG trial)

Dronedarone interacts with digoxin leading to increased arrhythmic death (less likely)

Hohnloser S, et al. PALLAS post-hoc analysis. Circulation AE 2014

Dronedarone – clinical practice

*Editorials published in the *Journal of the American College of Cardiology* views of the authors and do not necessarily represent the views of *J* American College of Cardiology.

From the Department of Cardiology, Division of Clinical Electro J.W. Goethe University, Frankfurt, Germany. Dr. Hohnloser serves as a to and has received honoraria from Sanofi-Aventis, Boehringer Ingelhei Myers Squibb, Pfizer Inc., Bayer HealthCare, and St. Jude Medical, Inc.

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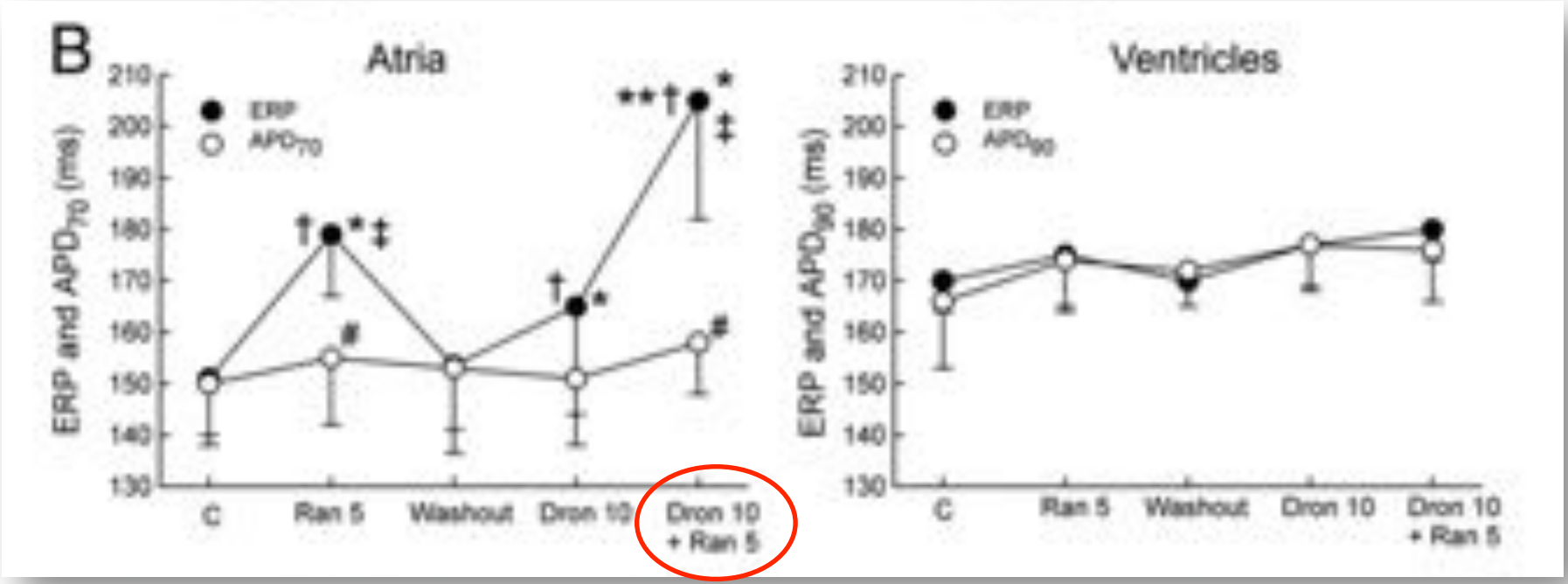
Hohnloser S Editorial with Friberg J Am Coll Cardiol 2014

Enhancing safety of AF drugs

- Atrial selective drugs
  - channels specific for the atria
    - Ik-ur, Ik-Ach, peak Ina, inactivated-state Na channels
  - use-dependent effects
    - Ina (more affected in **fast A** than **slower V**)
- ASD enhancing efficacy of low dose non-ASD
  - allowing for **low dosages for both drugs**
    - Ik-ur + Ikr
    - ranolazine + dronedarone
- Multiple-action-drugs
  - blocking own PA
    - amiodarone, dronedarone, vernakalant, ranolazine

Synergistic effects of Ranolazine and Dronedarone

Canine isolated coronary-perfused RA, LA, LV and PV preparations



Burashnikov A, et al. JACC 2010

Inclusion Criteria

- Paroxysmal AF

- Dual chamber pacemaker
  - Atrial arrhythmia algorithm detection
  - Implanted at least 3 months prior to the screening

- AF Burden (AFB)*

≥ 1% and ≤ 70% → ≥ 2% and ≤ 70%

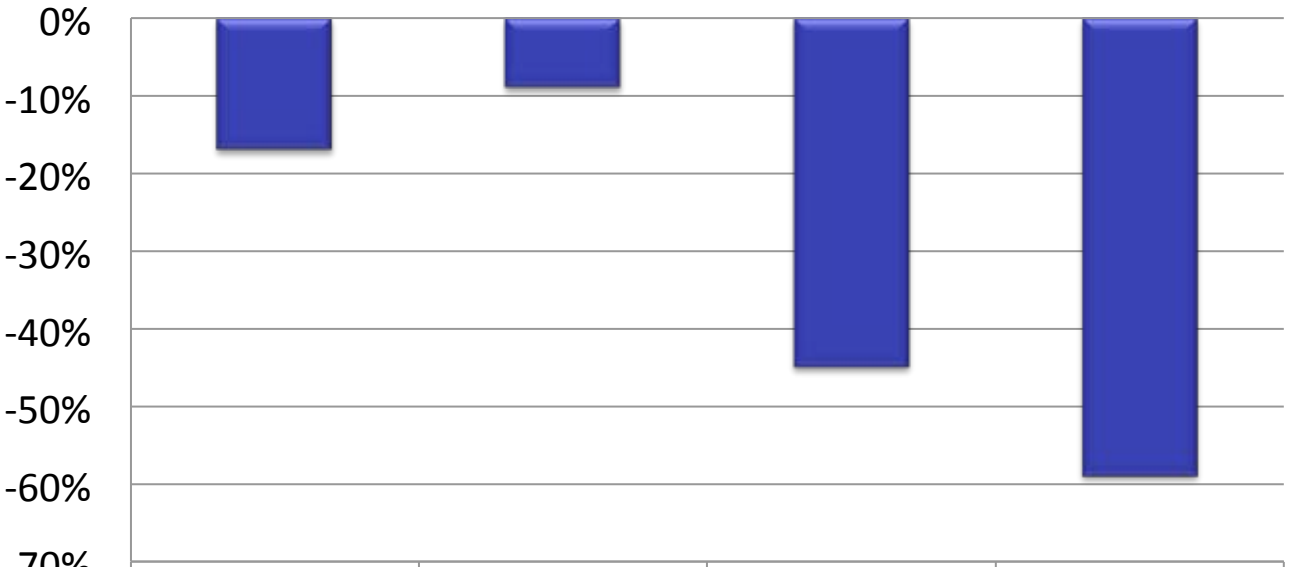
Screening → Randomization

***AF burden: total time a subject is in AF expressed as a percentage of total recording time**

A Study to Evaluate the Effect of Ranolazine and Dronedarone When Given Alone and in Combination in Patients With Paroxysmal Atrial Fibrillation (HARMONY)

HARMONY
A STUDY IN PAROXYSMAL ATRIAL FIBRILLATION

AF burden reduction compared to placebo



	Ranolazine 750 mg	Dronedarone 225 mg	Ranol 750 + Droned 150	Ranol 750 + Droned 225
AF burden reduction	-17%	-9%	-45%	-59%

Presented at HRS 2014, San Francisco

Conclusion
Future of Dronedarone

- Dronedarone is used appropriately
  - No major safety concerns (digoxin, dabigatran)
  - It is applied in less complex patients (Ic drugs)
- Safety and efficacy may be further enhanced
  - Low dose combined with an atrial selective AAD
- ‘There is more to learn about its use’

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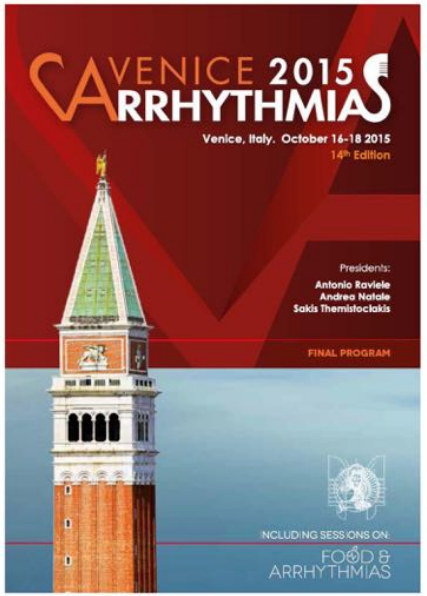
Thank you for your attention



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