

17th WORLD CONGRESS of ARRHYTHMIAS

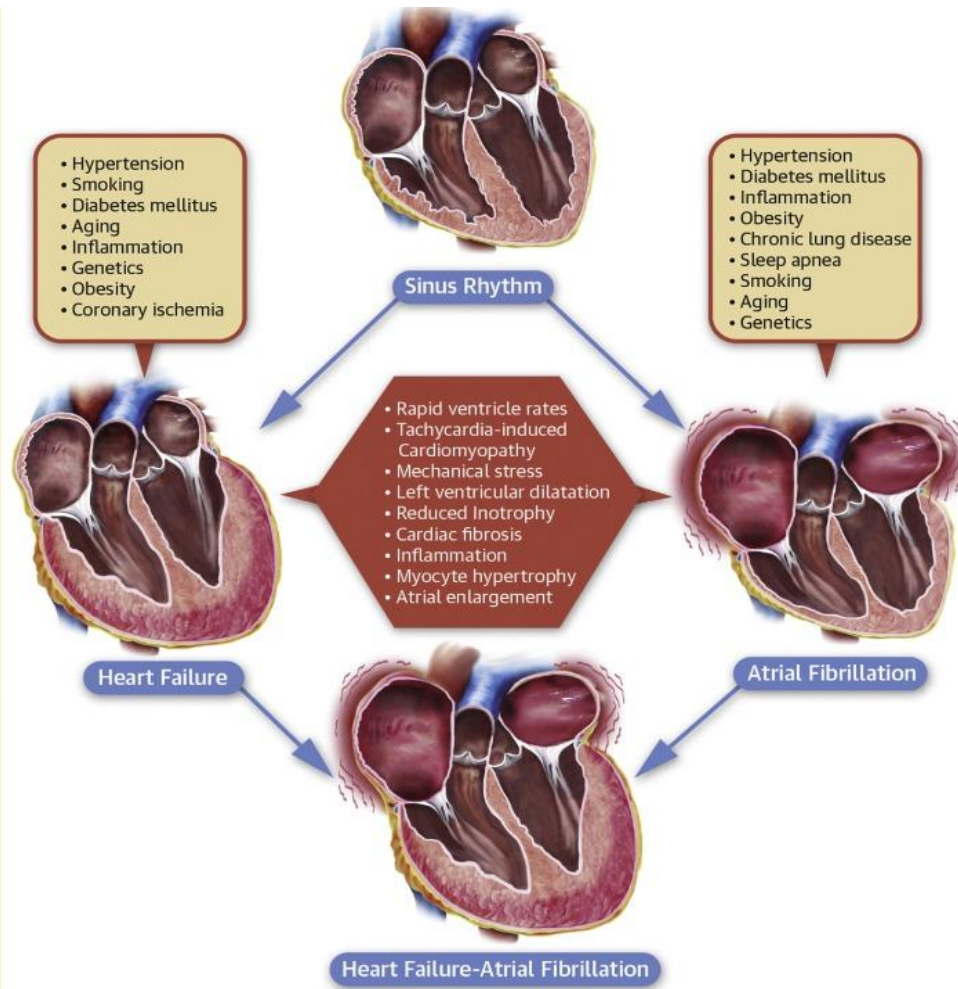
2-4 November, 2023 Istanbul/TURKEY
Elite World Convention Center



5 - 12:45 HALL 1 EHRA Joint Session

**Towards Optimal Therapy of the Twin Epidemic
Heart Failure and Atrial Fibrillation**

Optimal Medical Therapy of AF in HFpEF and HFrEF



John Camm

12 minutes

Declaration of Competing Interests

Editorial Role: Editor-in-Chief, Clinical Cardiology; Editor, European Textbook of Cardiology, ESC CardioMed.

Charities: Trustee of the Drug Safety Research Unit, the Atrial Fibrillation Association and the Arrhythmia Alliance

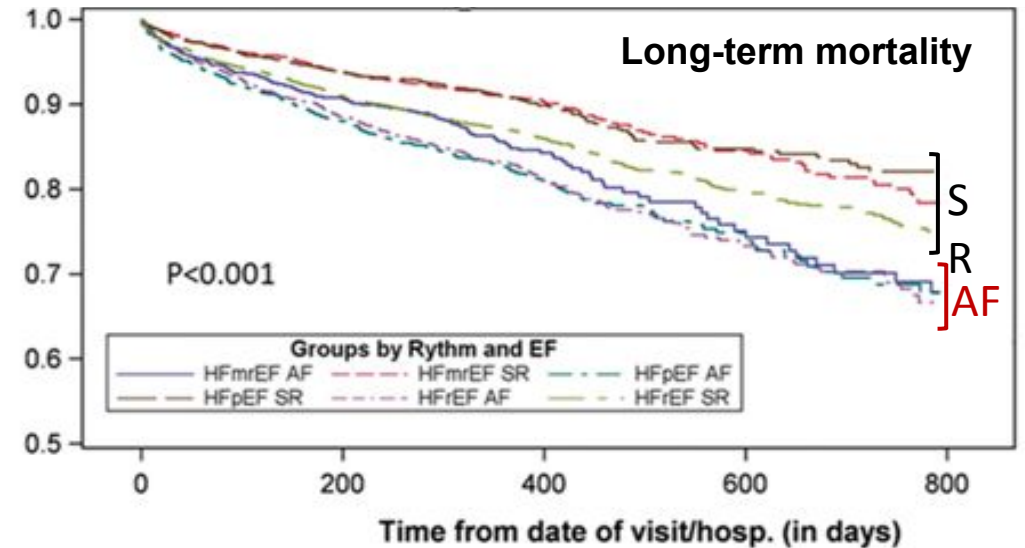
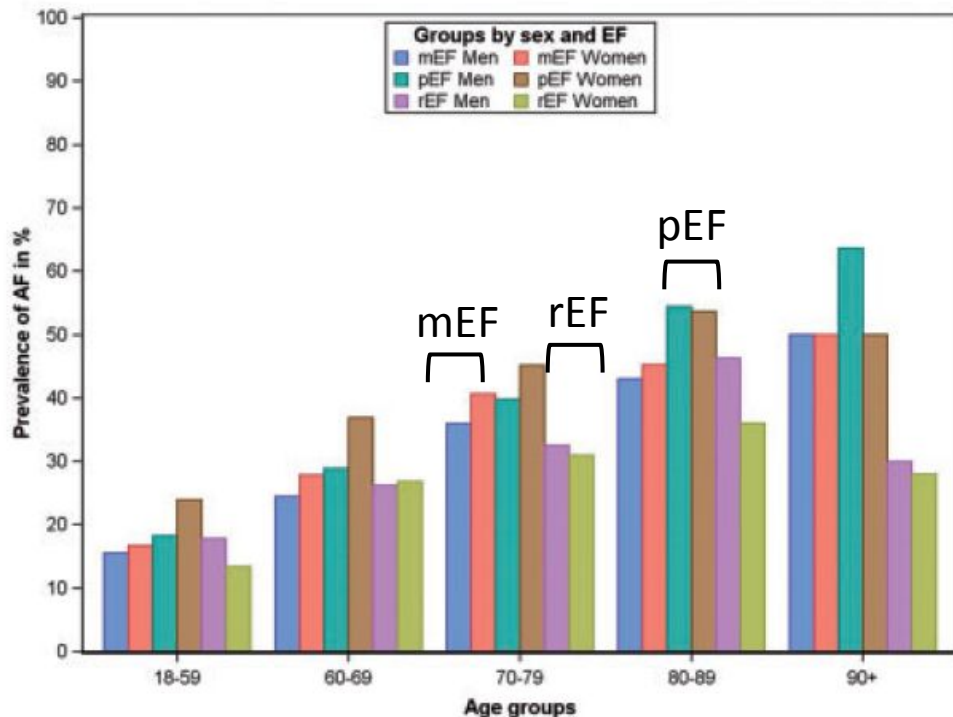
Directorship: Richmond Pharmacology Limited

Consultant/Advisor/Speaker: Acesion, Anthos, Incarda, Menarini, Milestone, Sanofi, Bayer, Daiichi Sankyo, Pfizer, Abbott, Biosense Webster, Biotronik, Boston Scientific, Medtronic, Johnson and Johnson

Prognostic Implications of AF in HF

European Society of Cardiology Heart Failure Long-Term Registry

14 964 HF patients (age 66 ± 13 years, 67% male;
53% HFrEF, 21% HFmrEF, 26% HFpEF)
Prevalence of AF was 27% in HFrEF, 29% in



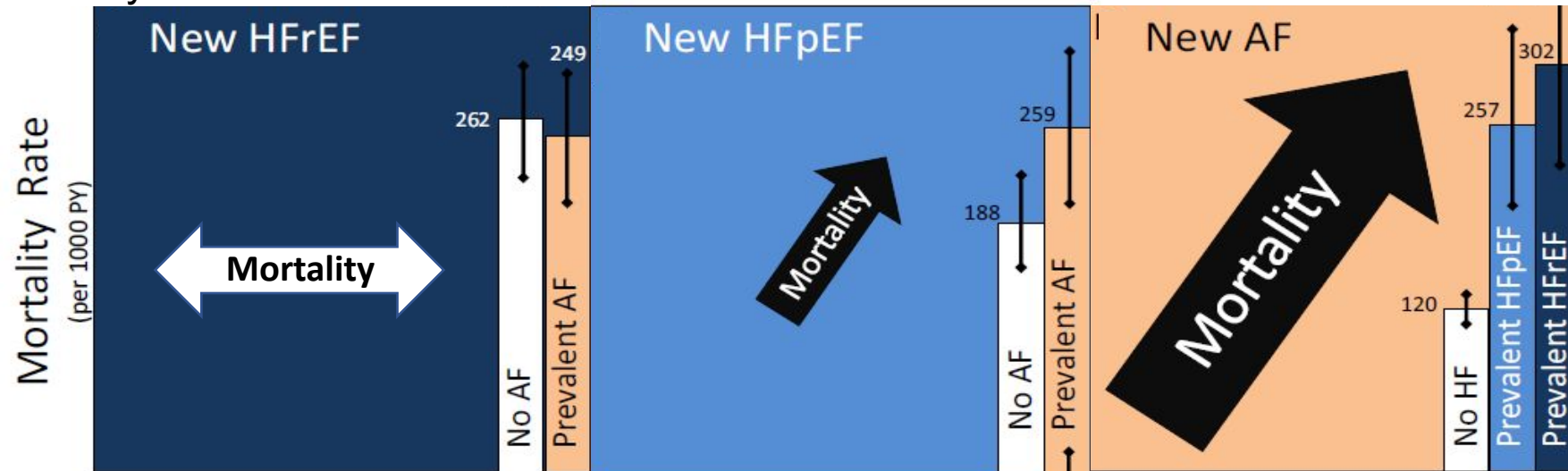
Heart Failure Population		Rhythm: AF vs SR	HR (95% CI)	p value
AHF	HFrEF		0.958 (0.828-1.108)	0.565
	HFmrEF		1.321 (1.026-1.702)	0.031
	HFpEF		1.444 (1.185-1.760)	<0.001
CHF	HFrEF		0.953 (0.778-1.168)	0.642
	HFmrEF		1.400 (0.988-1.985)	0.059
	HFpEF		1.523 (1.115-2.080)	0.008

Comparison of Death Rates in Individuals with AF and HF by Prevalence of the Other Condition

AF affects almost 50 million people around the world - prevalence 1-2% in Western World.

ARIC study observed that the lifetime risk of **AF** was approximately **1 in 3** in whites and **1 in 5** in African Americans

Rotterdam Study showed lifetime risk of **HF** in a European cohort **29%** for women and **33%** for men at age



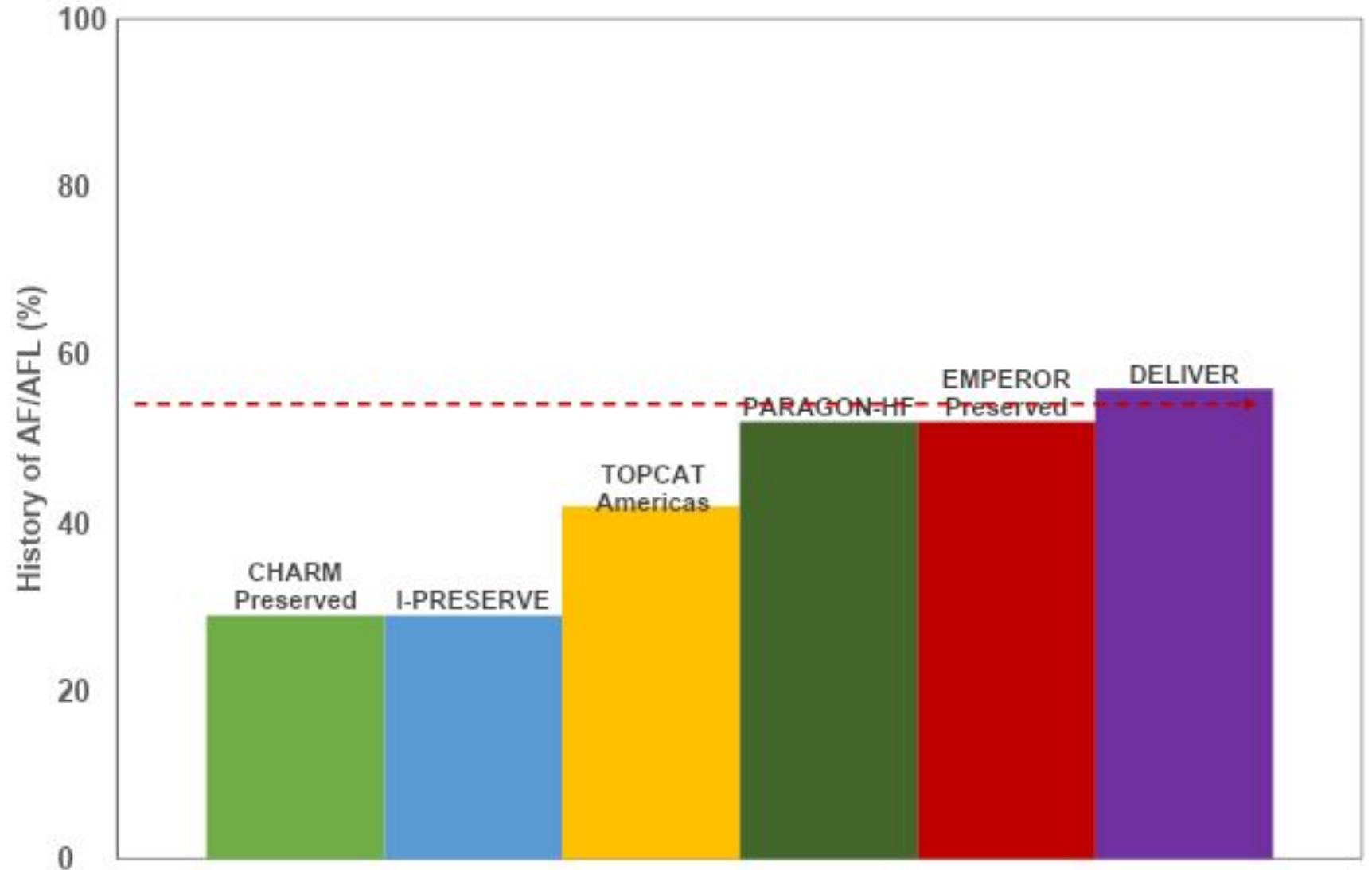
Heart failure occurs in more than 60 million people around the world. Prevalence in the Western world 30 per 1000 persons

AF prevalence in HFpEF ranging from 25% to 39%. AF prevalence in HFrEF: NYHA class I: 4.2% - class IV: 49.8%

HF confers a 2-fold to 4-fold risk of developing AF

AF Emerging as a Dominant Comorbidity in HFpEF

>50% of participants enrolled in contemporary HFpEF trials have a history of AF/AFL

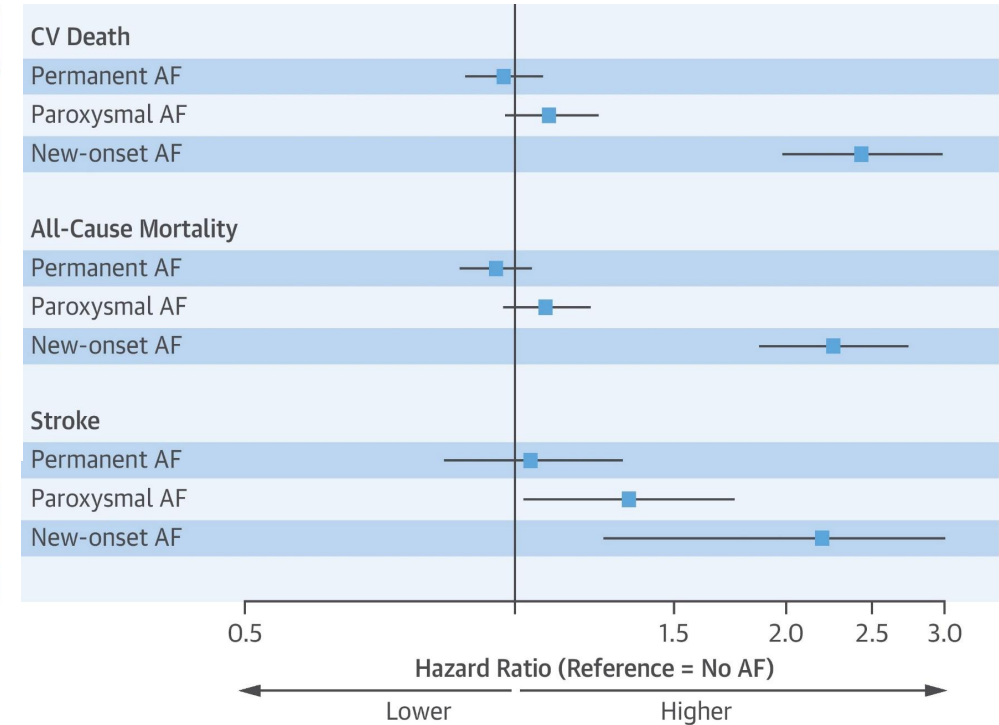
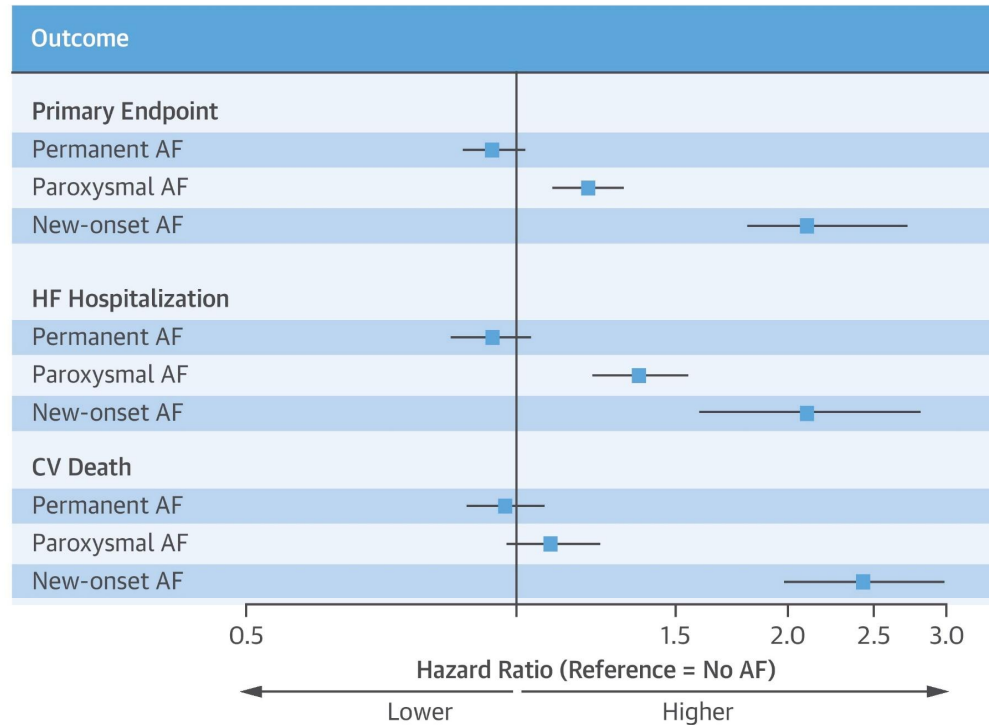


Type of AF at Randomization

Comparison between Those with AF and Those with no AF

PARADIGM-HF (Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure)
 ATMOSPHERE (Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure) trials.

- 15,415 patients
- 5,481 (35.6%) had a history of AF at randomization, and of these,
 - 1,645 (30.0%) had paroxysmal AF.
 - New onset AF occurred in 369 patients

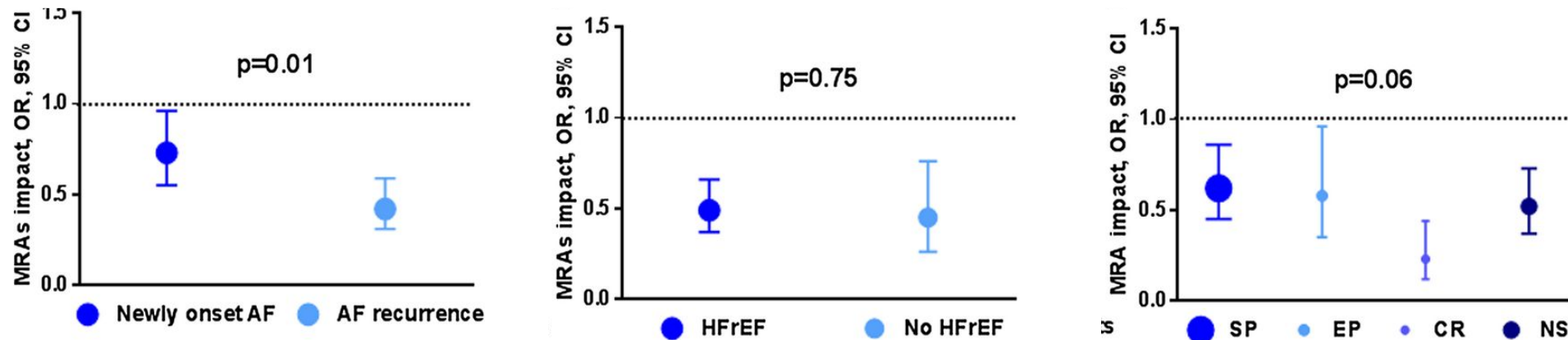


OAC used less in pts with paroxysmal (53%) and new onset (16%) AF than in patients with persistent or permanent AF (71%)

Effects of Mineralocorticoid Receptor Antagonists on Atrial Fibrillation Occurrence

24 studies with 7914 patients

Significant overall reduction in AF occurrence in the mineralocorticoid receptor antagonists–treated patients versus the control groups (**15.0% versus 32.2%, respectively; odds ratio, 0.55 [95% CI, 0.44–0.70]; $P<0.00001$**)
Greatest benefit was observed in cases of **recurrent AF episodes** (odds ratio, 0.42; 95% CI, 0.31–0.59 [$P<0.00001$]), especially in **populations with high AF occurrence rate**.

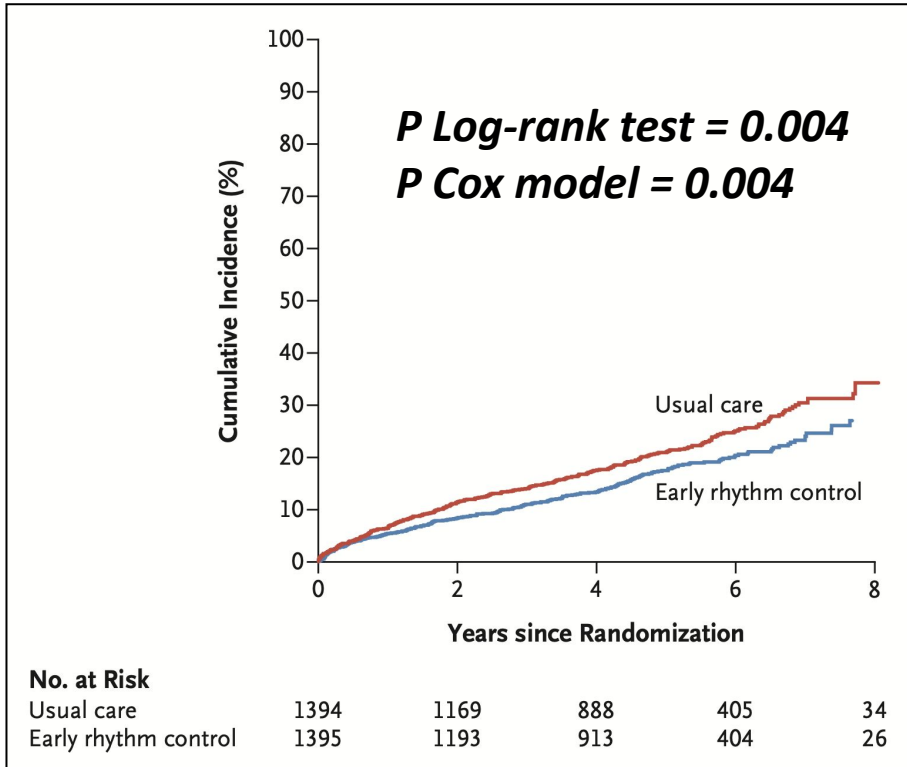


Meta-analysis suggest a substantial efficacy of MRAs in reducing the risk of AF in patients with or without HF, especially in the setting of AF recurrence prevention

CR indicates canrenone; EP, eplerenone; NS, nonspecified MRA; SP, spironolactone.

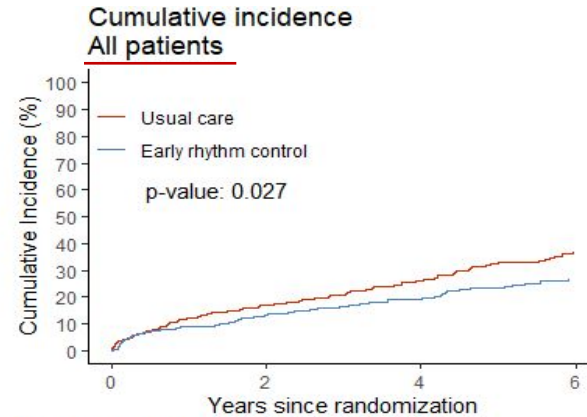
Alexandre J, et al. *J Am Heart Assoc.*2019;8:e013267. DOI: 10.1161/JAHA.119.013267.)

Primary Endpoint in Patients with HF

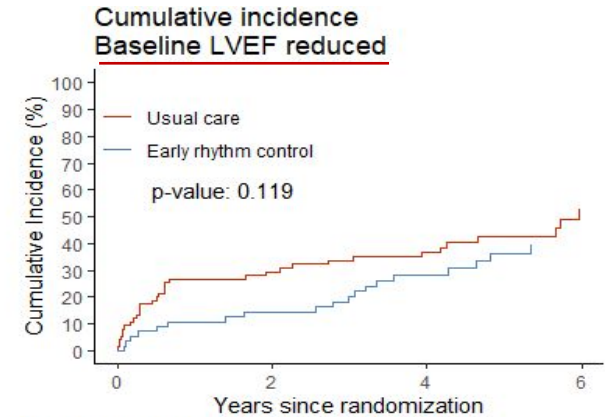


Primary Outcome

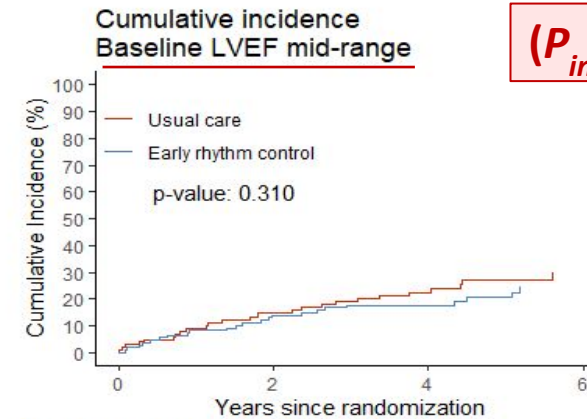
Composite of: Cardiovascular death, stroke, hospitalization with worsening of heart failure or acute coronary syndrome



	0	2	4	6
Usual care	402	315	223	91
Early rhythm control	396	316	226	92

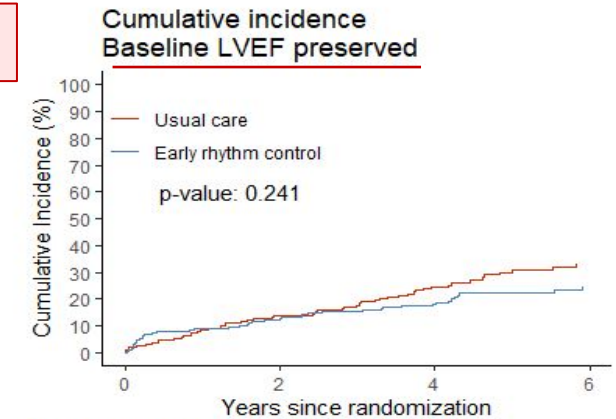


	0	2	4	6
Usual care	75	51	36	13
Early rhythm control	57	43	29	14



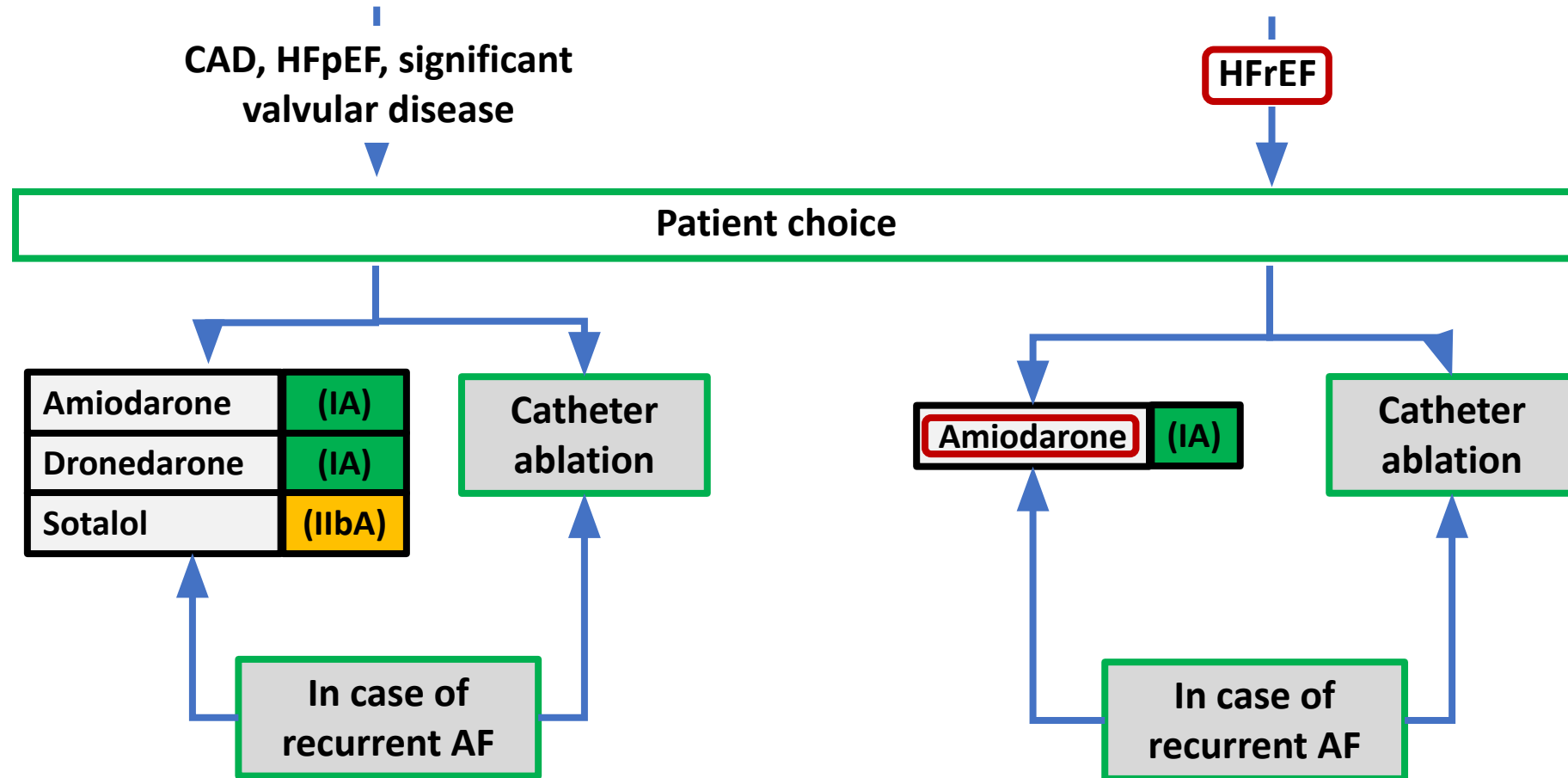
	0	2	4	6
Usual care	101	78	56	25
Early rhythm control	110	91	70	26

($P_{int} = 0.63$)



	0	2	4	6
Usual care	218	180	126	51
Early rhythm control	224	180	126	51

ESC Guidelines for Antiarrhythmic Medication for Heart Failure



Long-term AAD Treatment

Recommendations	Class	Level
Amiodarone is recommended for long-term rhythm control in all AF patients, including those with HFrEF. However, owing to its extracardiac toxicity, other AADs should be considered first whenever possible.	I	A
Dronedarone is recommended for long-term rhythm control in AF patients with: <ul style="list-style-type: none"> • Normal or mildly impaired (but stable) LV function, or • HFpEF, ischaemic, or VHD. 	I	A
Flecainide or propafenone is recommended for long-term rhythm control in AF patients with normal LV function and without structural heart disease, including significant LVH and myocardial ischaemia.	I	A
In AF patients treated with sotalol, close monitoring of QT interval, serum potassium levels, CrCl, and other proarrhythmia risk factors is recommended.	I	B
In AF patients treated with flecainide for long-term rhythm control, concomitant use of an atrioventricular nodal-blocking drug (if tolerated) should be considered.	IIa	C
Sotalol may be considered for long-term rhythm control in patients with normal LV function or with ischaemic heart disease if close monitoring of QT interval, serum potassium levels, CrCl, and other proarrhythmia risk factors is provided.	IIb	A
AAD therapy is not recommended in patients with permanent AF under rate control and in patients with advanced conduction disturbances unless anti-bradycardia pacing is provided.	III	C

Legacy of Excess Mortality with AAD in High-Risk Populations with LV Dysfunction

THE LANCET

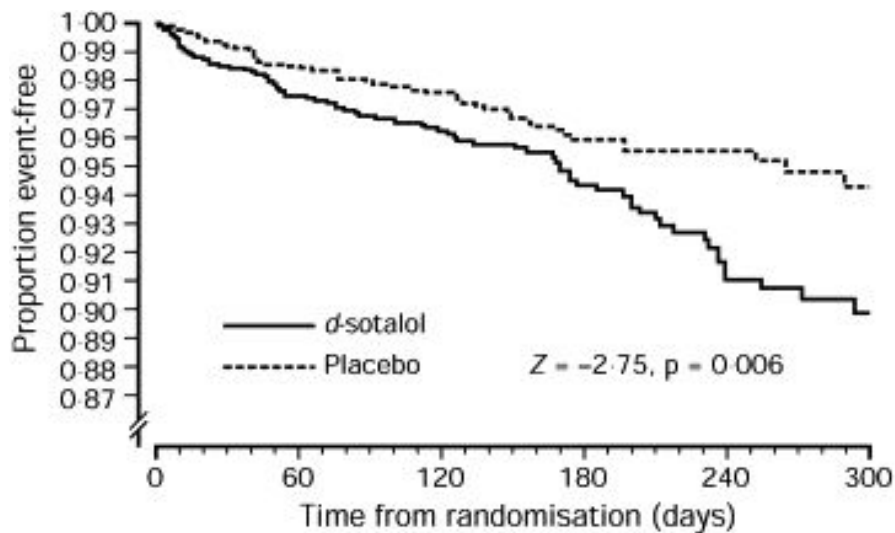
ARTICLES | VOLUME 348, ISSUE 9019, P7-12, JULY 06, 1996

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Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction

Prof Albert L Waldo, MD · Prof A John Camm, MD · Hans deRuiter, MD · Peter L Friedman, MD · Daniel J MacNeil, MD · John F Pauls · Prof Bertram Pitt, MD · Prof Craig M Pratt, MD · Prof Peter J Schwartz, MD · Enrico P Veltri, MD for the SWORD investigators · Show less

Published: July 06, 1996 · DOI: [https://doi.org/10.1016/S0140-6736\(96\)02149-6](https://doi.org/10.1016/S0140-6736(96)02149-6)



Patients at risk	0	60	120	180	240	300
Placebo	1572	1170	874	551	330	
d-sotalol	1549	1150	844	544	323	

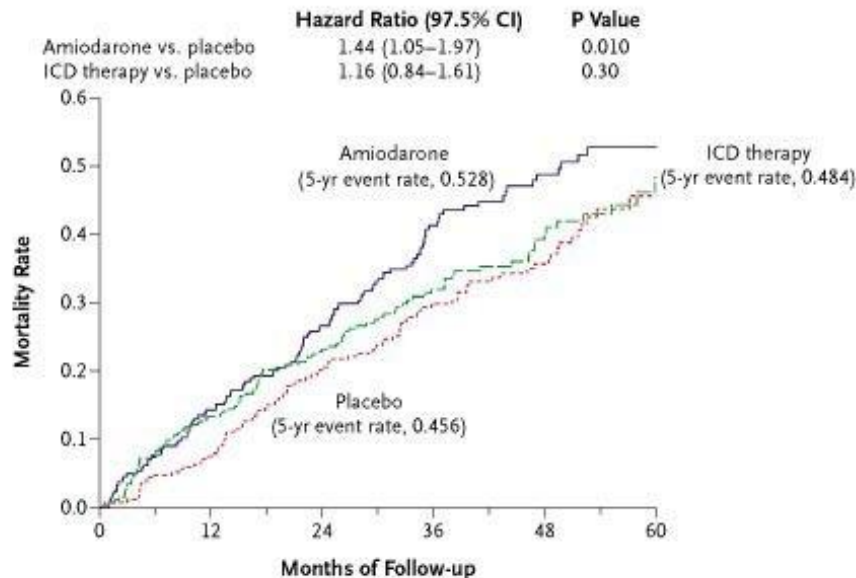
The NEW ENGLAND
JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 20, 2005 VOL. 352 NO. 3

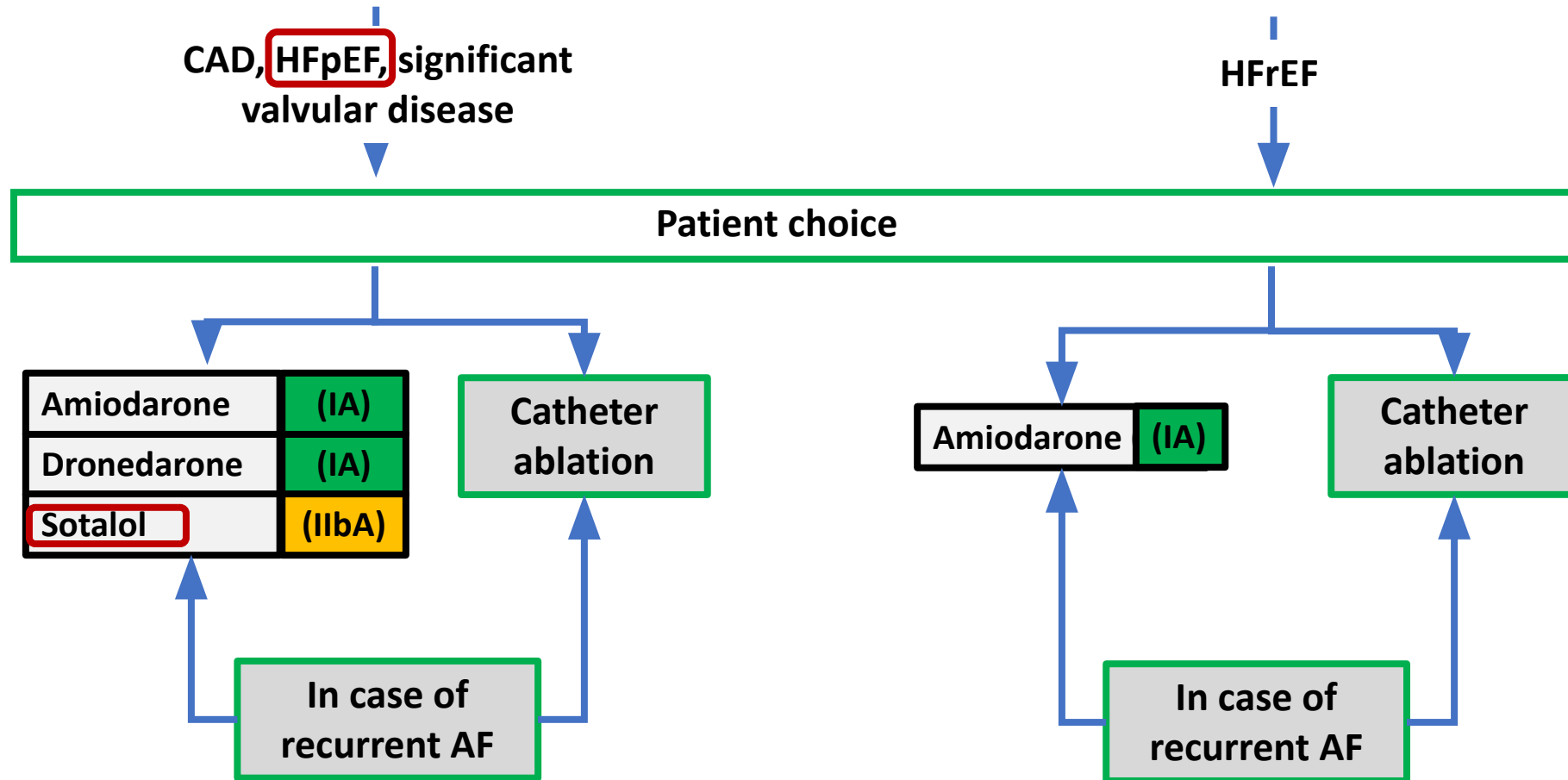
Amiodarone or an Implantable Cardioverter-Defibrillator for Congestive Heart Failure

Gust H Bardy, M.D., Kerry L Lee, Ph.D., Daniel B. Mark, M.D., Jeanne E. Poole, M.D., Douglas L. Packer, M.D.,

NYHA Class III



ESC Guidelines for Antiarrhythmic Medication for Heart Failure



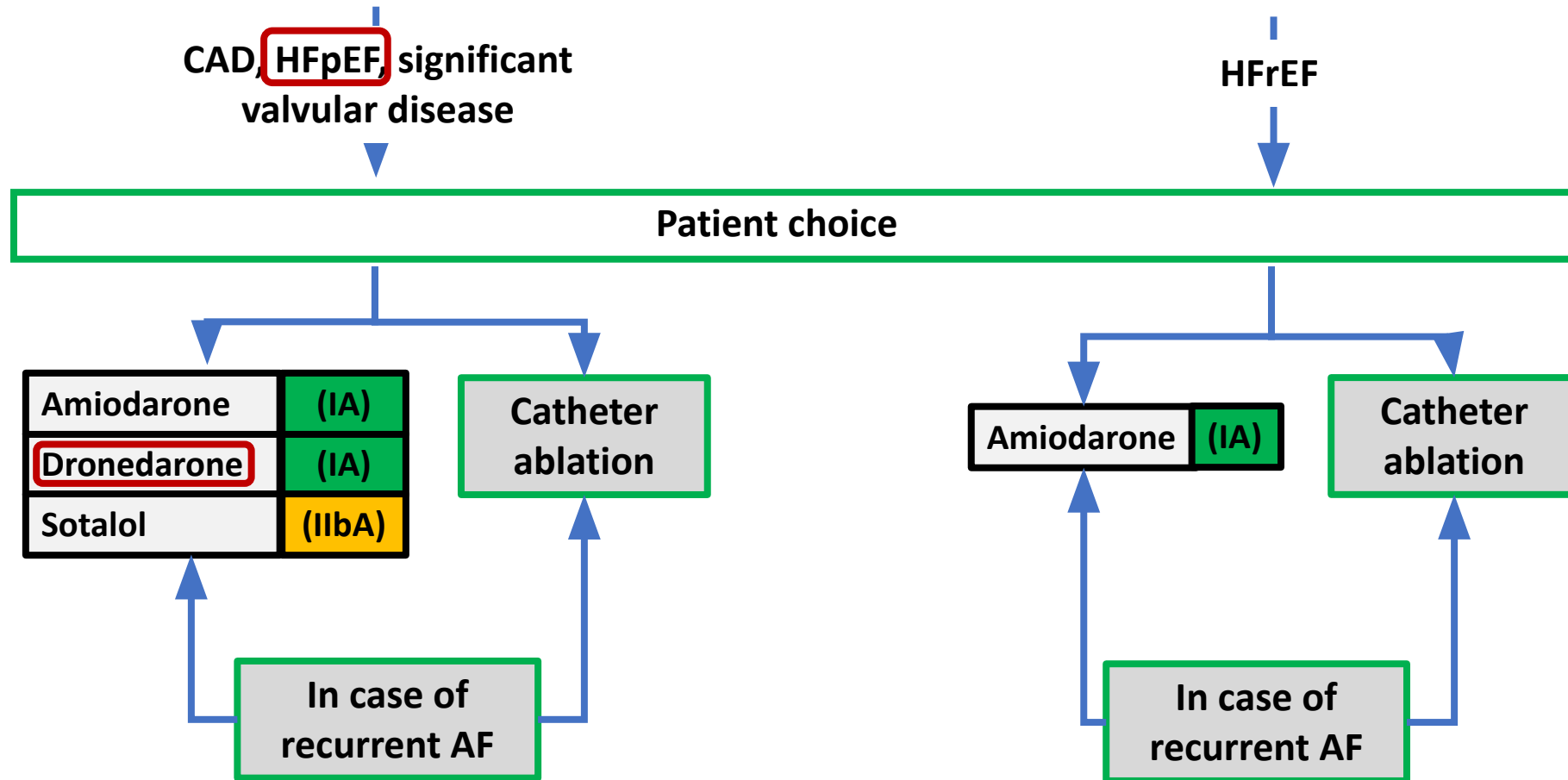
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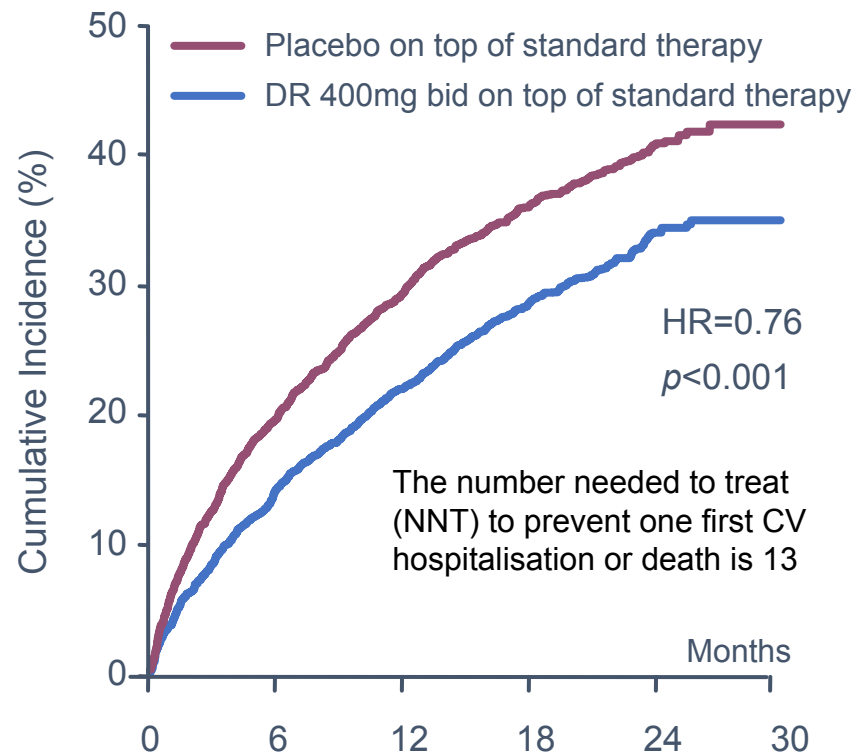


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ATHENA: 1^o Study Endpoint for All Patients and those with CHF and/or Impaired LVEF

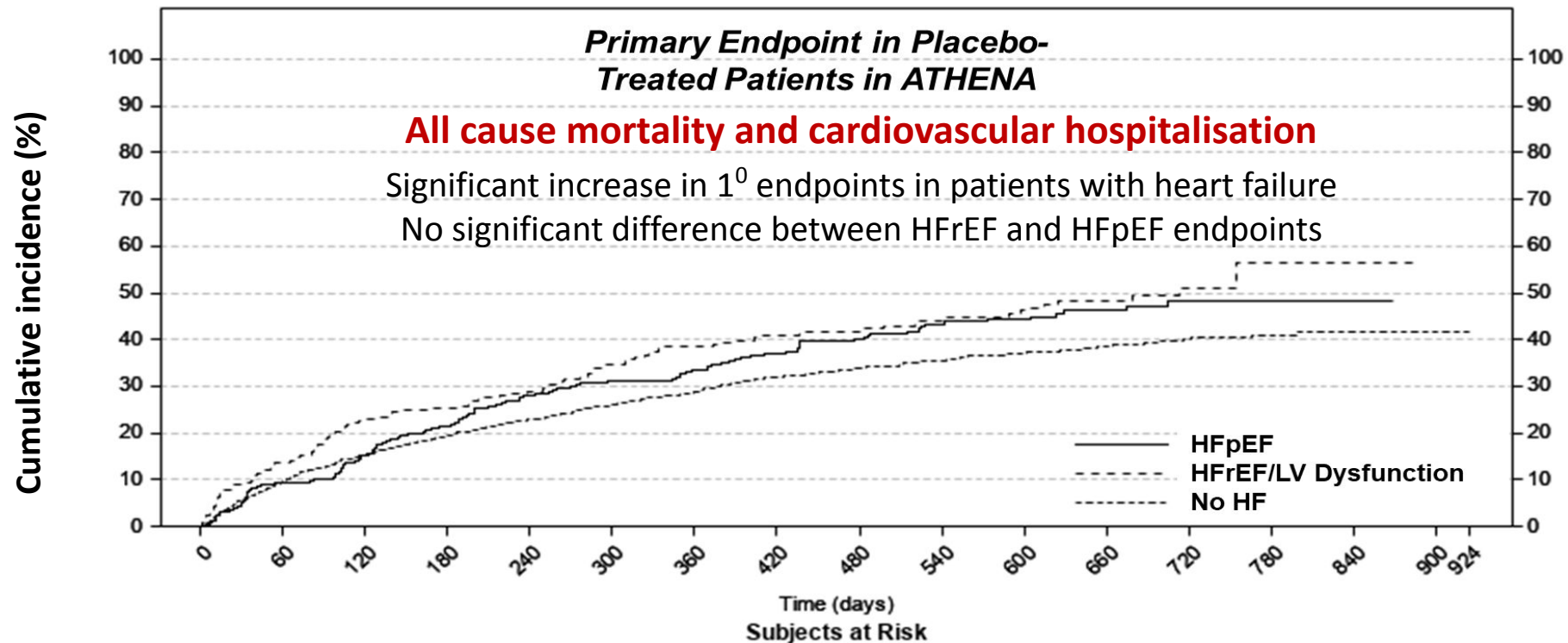
- ATHENA: global, multicenter trial of 4,628 pts with paroxysmal or persistent AF/AFL at high CV risk



Patient group	P (n)	D (n)	HR	95% CI	P-int
Patients without CHF	163	1629	0.76	0.68–0.86	0.22
Patients with CHF NYHA I/II	584	581	0.80	0.67–0.96	
Patients with CHF NYHA III	109	91	0.56	0.38–0.82	
Patients with LVEF ≤0.40	184	154	0.72	0.51–1.00	0.67
Patients					

Dronedarone for AF in Preserved and Reduced Ejection Fraction Heart Failure

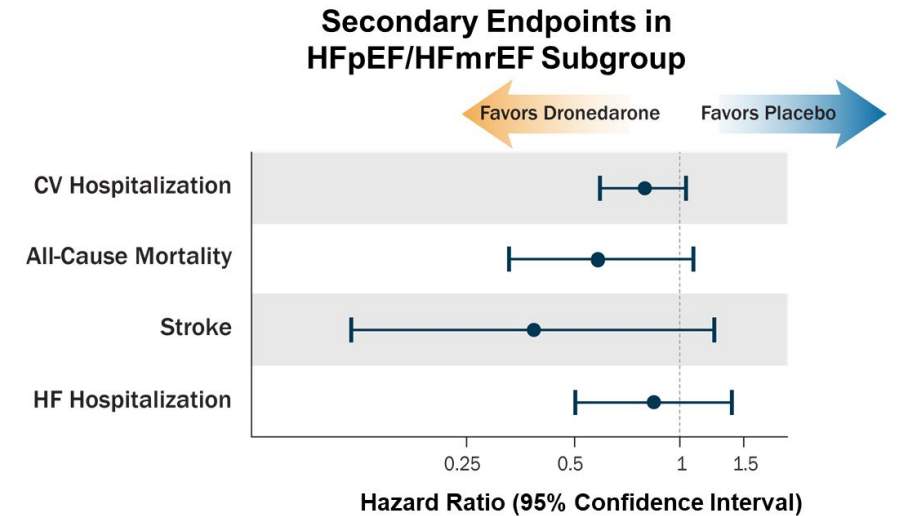
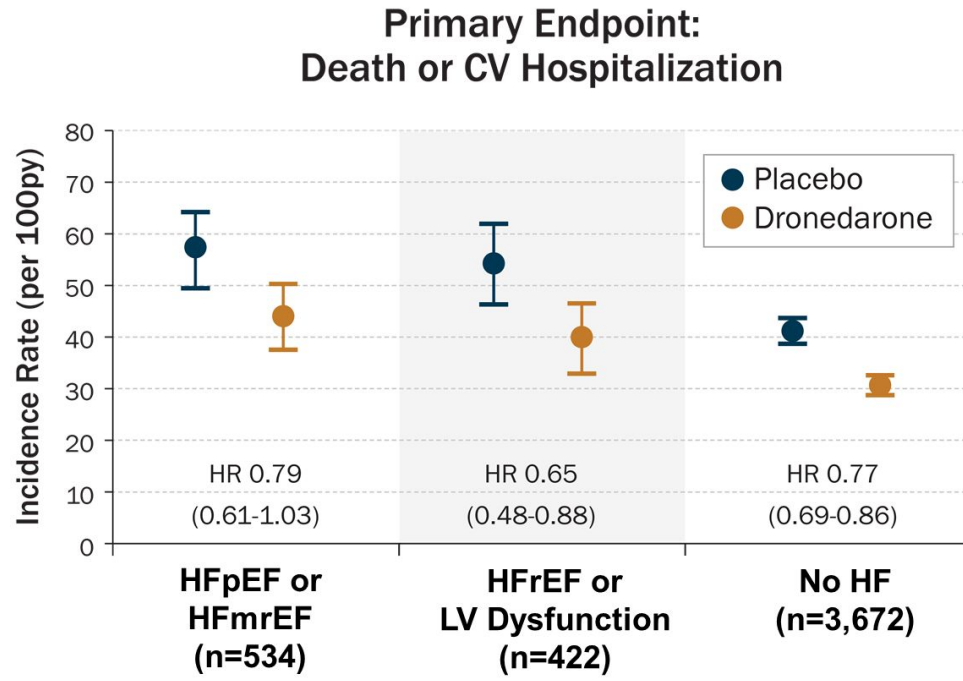
ATHENA: multicenter trial of 4,628 pts with paroxysmal or persistent AF/AFL at high CV risk
 534 (12%) had HFpEF, 422 (9%) had HFrEF or LV dysfunction, and 3,672 (79%) did not have HF



	0	60	120	180	240	300	360	420	480	540	600	660	720	780	840	900	924
HFpEF	268	243	227	211	193	185	178	154	132	113	92	72	35	11	3	0	0
HFrEF/LVD	221	191	170	165	157	144	136	121	107	92	74	54	28	11	2	0	0
No HF	1838	1662	1558	1482	1416	1361	1311	1147	1002	867	731	572	322	126	24	3	1

Dronedarone for AF in HFpEF

ATHENA trial: 534 (12%) had HFpEF or HFmrEF, 422 (9%) had HFrEF or LV dysfunction, and 3,672 (79%) did not have HF



“.....a trial of pharmacological **rhythm control** to assess symptomatic response with sinus rhythm is **reasonable**. **Dronedarone** may be used for pharmacological rhythm control, as it was associated with **reduced cardiovascular events** in patients with paroxysmal or persistent AF and HF **across the spectrum of EF** in a post hoc analysis of ATHENA.”

Safety Endpoints in HFpEF/HFmrEF Subgroup

	Dronedarone	Placebo
Treatment-Emergent AE	36%	36%
Serious AE	13%	13%
Permanent Drug Discontinuation	7%	4%

Dronedarone

- Less effective than amiodarone in rhythm control but has very few extracardiac side-effects
- Reduces CV hospitalizations and death in patients with paroxysmal or persistent AF or AFL and CV comorbidity
- Associated with **increased mortality in patients with recent decompensated HF** or permanent AF
- Dronedarone has the most solid safety data and may thus be a preferable first choice, however **not indicated in patients with HF and permanent AF**
- **Should not be used in NYHA class III or IV or unstable HF**, in combination with QT-prolonging drugs or with strong CYP3A4 inhibitors (e.g., verapamil, diltiazem) and in patients with CrCl <30 mL/min
- Concomitant use with dabigatran is contraindicated
- Combination with digoxin may significantly increase digoxin serum concentration
- When used with digitalis or beta-blockers their doses should be reduced
- Should be discontinued in case of excessive QT prolongation (>500 ms or >60 ms increase)
- A modest increase in serum creatinine ... reflects drug-induced reduction in CrCl and not a decline in renal function

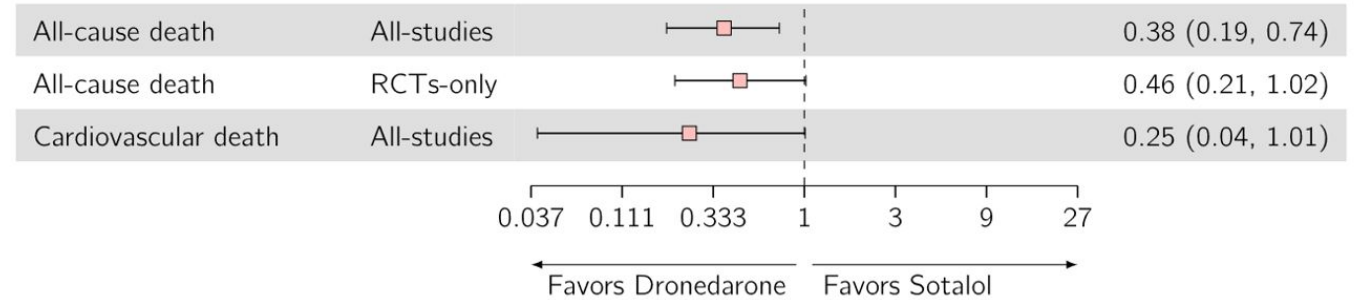
- Has atrioventricular nodal-slowing properties *Dronedarone for HFpEF not mentioned in table or text*

Dronedarone versus Sotalol in Patients with Atrial Fibrillation: A Systematic Literature Review and Network Meta-analysis

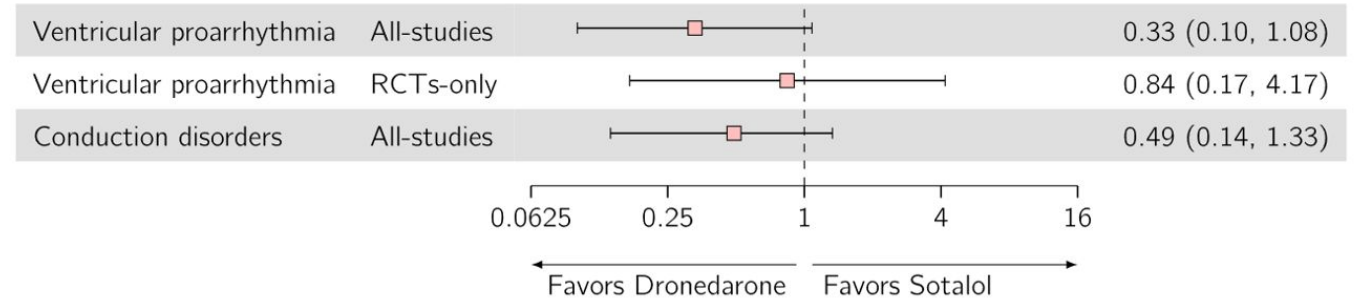
- 3,581 records identified and 40 unique studies included in NMA
- Dronedarone was associated with a statistically significantly lower risk of all-cause death compared with sotalol. This did not reach significance in the RCT analysis
- Risk of ventricular proarrhythmia numerically lower for dronedarone in all-studies
- Risk of AF recurrence and CV death not significantly different between dronedarone and sotalol in both all-studies and RCT-only analyses

Network Meta-Analysis of Safety Outcomes with Dronedarone and Sotalol

A. HRs



B. RRs



Abbreviations – HR: Hazard ratio; RCT: Randomized clinical trial; RR: Risk ratio.

Use of Antiarrhythmic Drugs in Heart Failure

The AIM-AF Study

		Amiodarone	Sotalolol	Class 1C	Dofetilide	Dronedarone
HFrEF	Total:	81%	18%	11%	19%	8%
	USA:	71%	25%	8%	38%	8%
	Europe:	91%	12%	4%	N/A	8%
HFpEF	Total:	60%	34%	36%	16%	23%
	USA:	56%	42%	18%	32%	18%
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Compliant with guidelines

Potential non-compliance with guidelines

Non-compliance with guidelines

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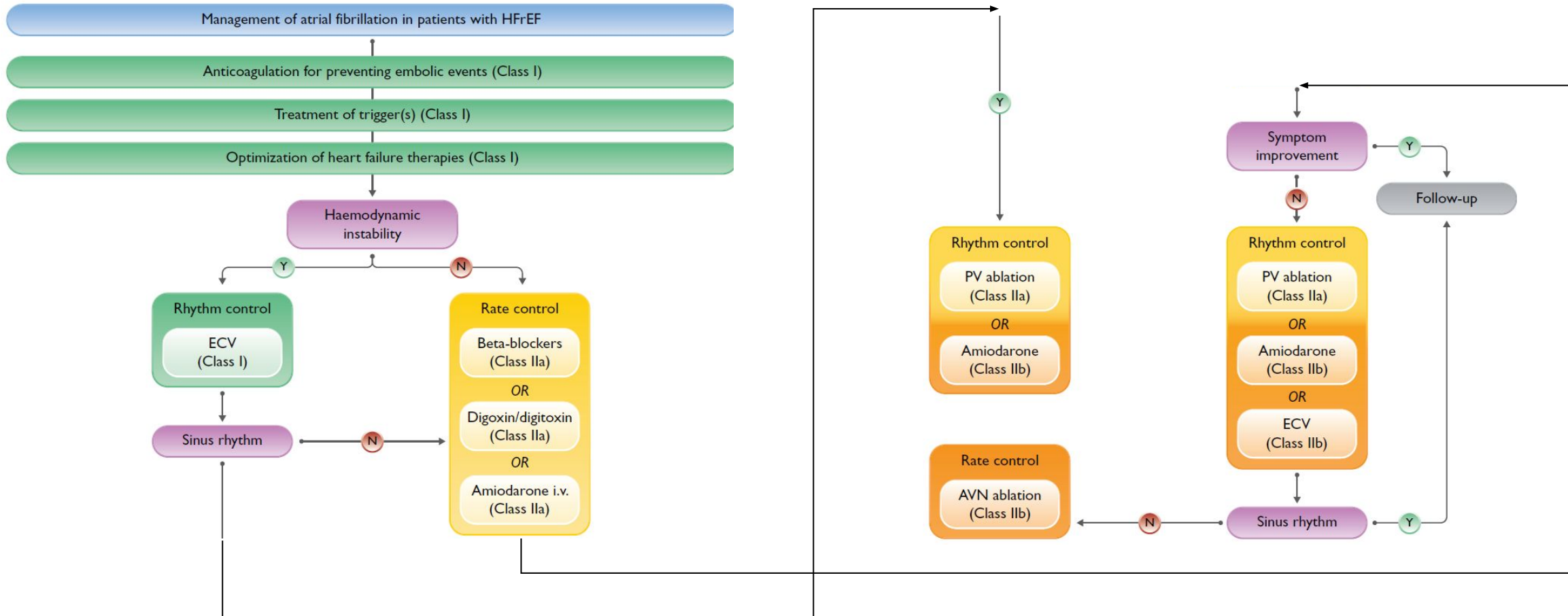
Compliant with guidelines

Potential non-compliance with guidelines

Non-compliance with guidelines

Management of Atrial Fibrillation

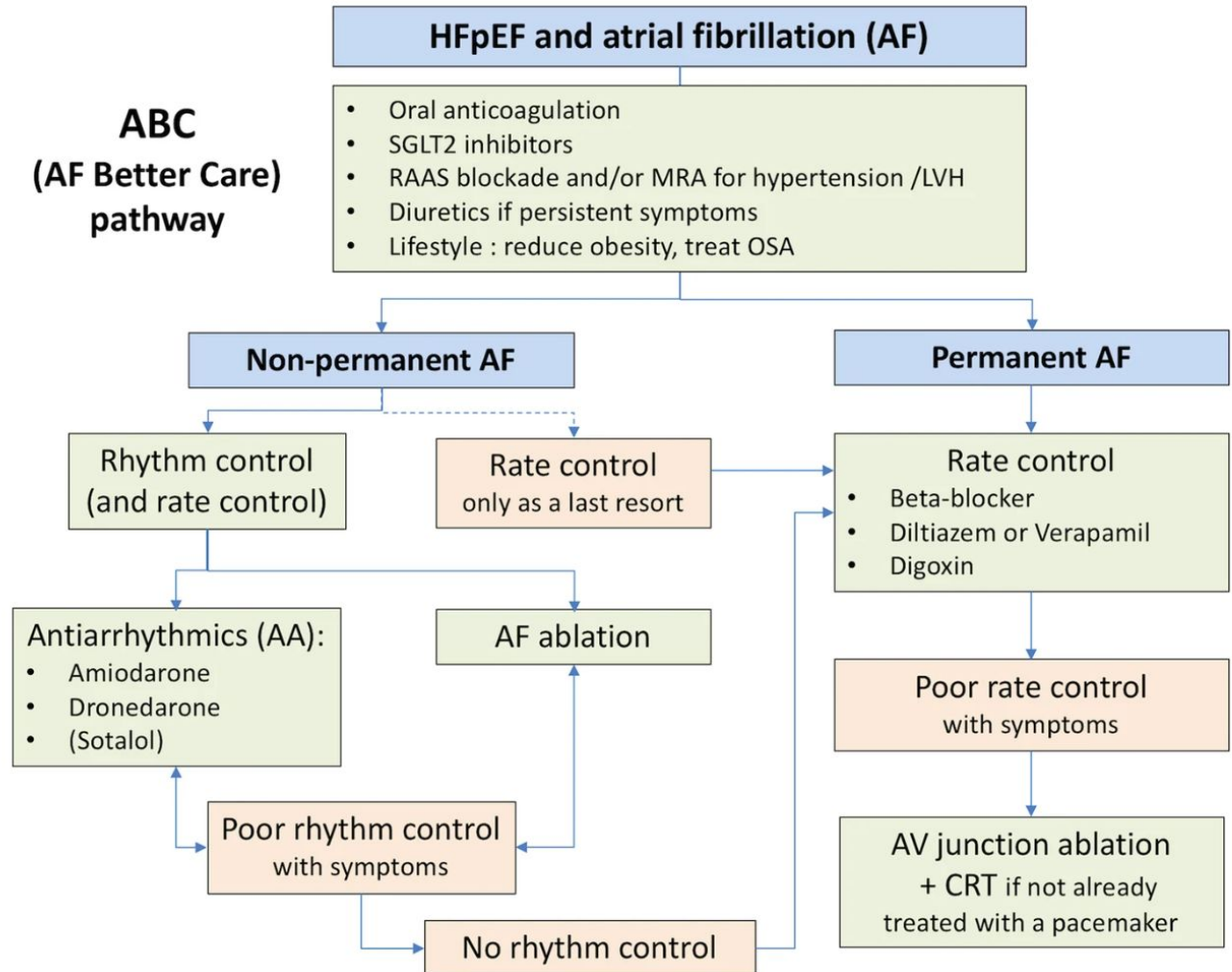
2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure



No mention of the treatment of AF in HFpEF or HFmrEF and atrial fibrillation; no recommendation for dronedarone

Conclusions

- It is important to differentiate between different types of HF (HFrEF versus HFpEF) when choosing AAD therapy
- Deviations from guidelines for the use of AADs are common, indicating a need for more education for healthcare providers
- The effect of SGLT2 inhibitors and MRAs on AF appear to be valuable in heart failure, but specific well-controlled observations in HF subtypes have not been performed
- Rate control therapy has not been well investigated in HFpEF
- Antiarrhythmic drug therapy has not been fully explored in either HFrEF or HFpEF



Thank you for your attention..

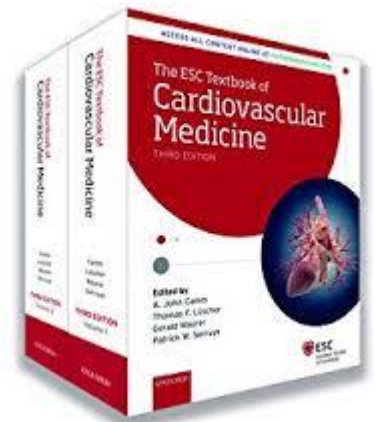


John Camm

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<https://www.stgeorges.nhs.uk/people/professor-john-camm>



2.11.2023, 11:45 - 12:45

HALL 1

EHRA Joint Session

Towards optimal therapy of the twin epidemic heart failure and atrial fibrillation

Chairperson : Jose Luis Merino (ES), Ali Oto (TR)

11:45 - 11:57	Optimal medical therapy of AF in HFpEF and HFrEF Speaker : A John Camm (UK)
11:57 - 12:09	Why and when ablation in HFpEF and HFrEF Speaker : Nassir Marouche (US)
12:09 - 12:21	Time to forget AV -node ablation in AF and HF or not ? Speaker : Boris Schmidt (DE)
12:21 - 12:33	How remote monitoring changed patient tailored HF and AF care ? Speaker : Kamal Sethi (IN)
12:33 - 12:45	Discussion