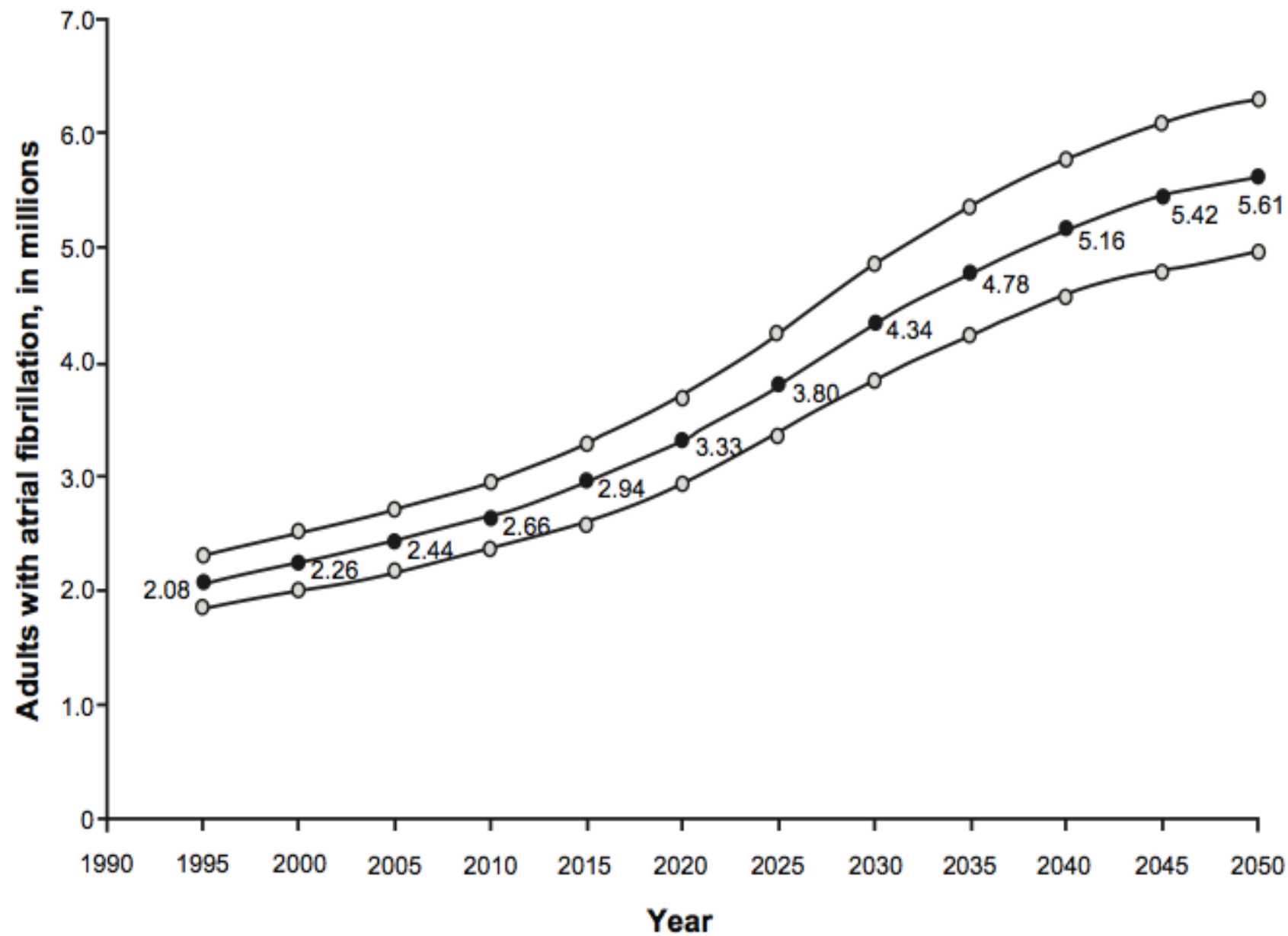


Fibrillazione atriale e tachicardiomiopatia: prima l'uovo o la gallina?

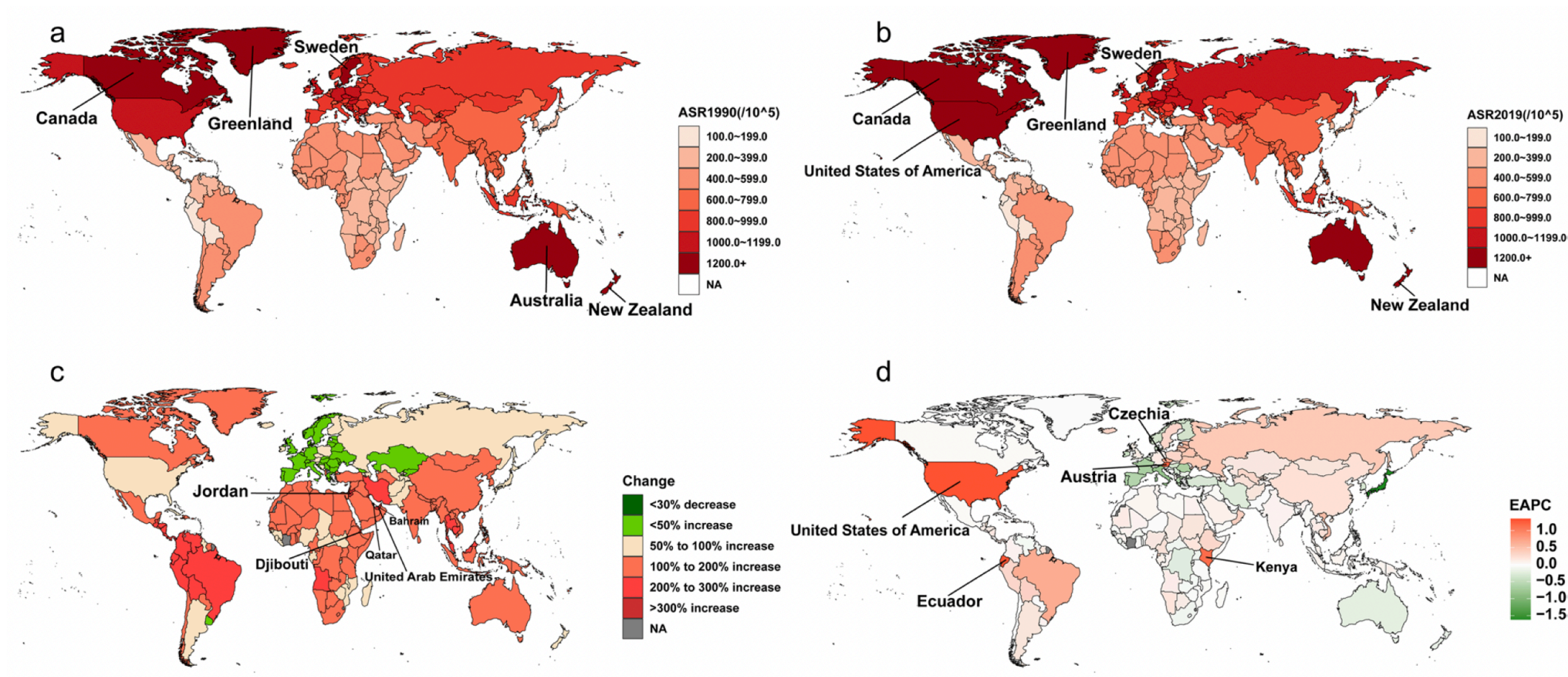
Alessandro Politano

Policlinico Casilino

Roma

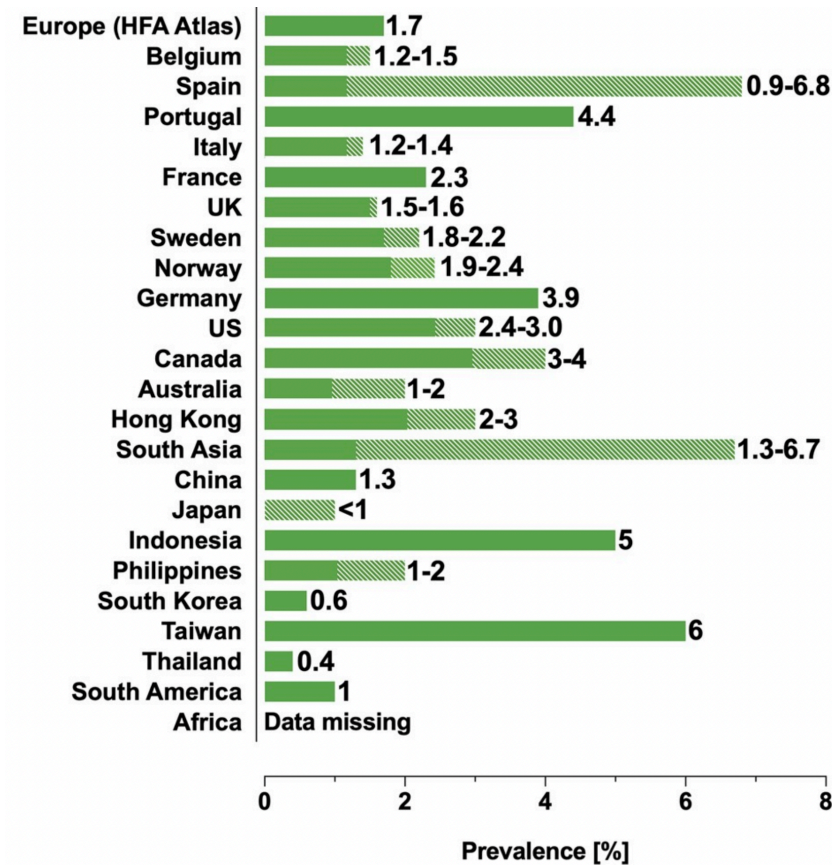


AF affects more than 59 million people world-wide



HF prevalence/incidence/costs/mortality

64 million affected worldwide



Prevalence

Prevalence 1-3% in general adult population

Overall prevalence ↑

Prevalence in HFrEF ↔

Prevalence in HFpEF ↑

Incidence

Incidence 1-20 cases per 1,000 person-years or per 1,000 population

Incidence stable/declining ↔

Incidence in HFrEF ↓

Incidence in HFpEF ↘

Mortality

Mortality remains high

30-day Mortality ~2-3%

1-year Mortality ~15-30%

3-year Mortality ~30-50%

5-year Mortality ~50-75%

CVD
HFrEF ↓

Non-CVD
HFpEF ↑

Costs

Annual health care costs up to €25,500 per year

Increasing due to major demographic changes (>65 years)

Main cost drivers:

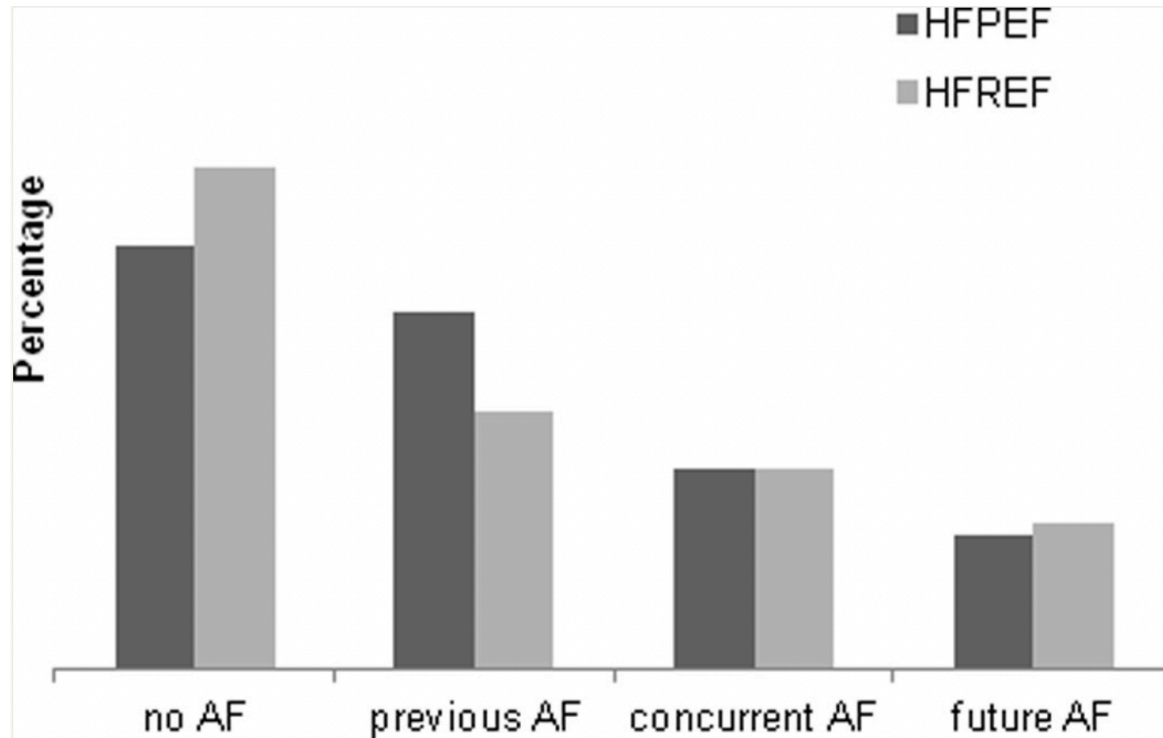
- Directs costs (~70%)
- Non-CVD comorbidities
- Invasive procedures
- Medications/Diagnostics
- Outpatient visits

Atrial Fibrillation Begets Heart Failure and Vice Versa

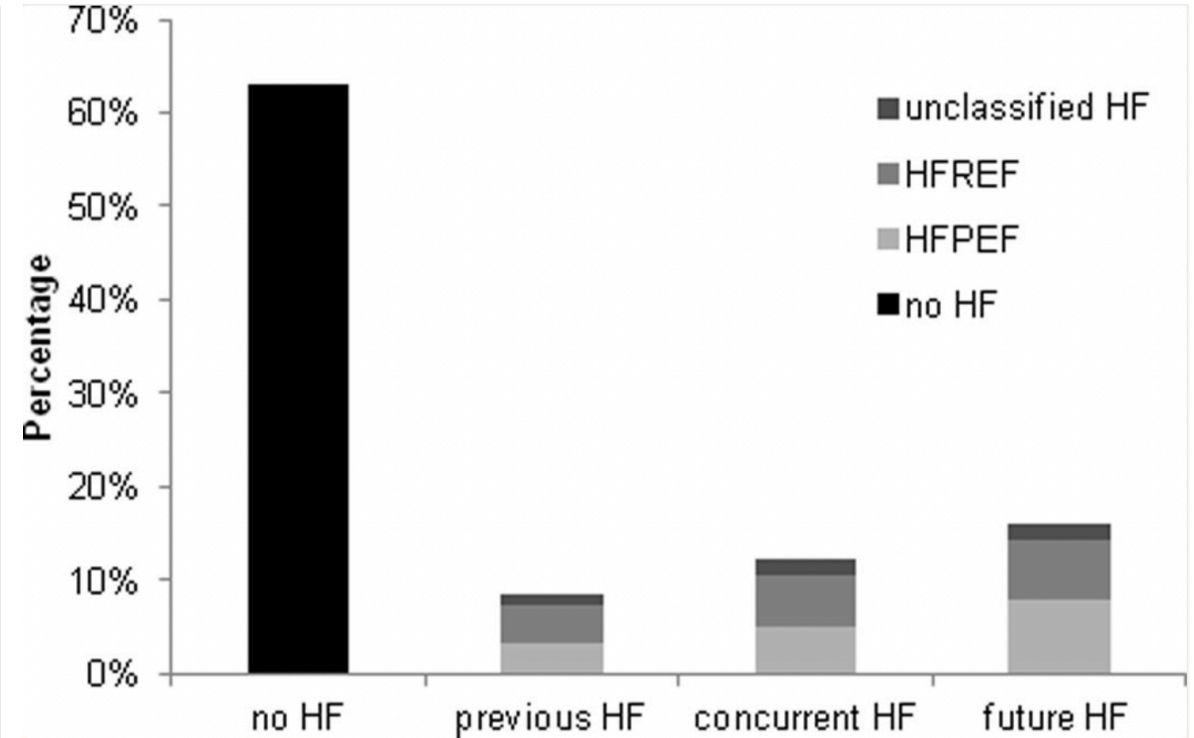
- By the year 2030, there will be 12 million Americans with AF, and over 8 million with HF.
- Beyond sharing common predisposing risk factors such as hypertension, diabetes, ischemic heart disease, and valvular heart disease, it is clear that AF and HF are closely interrelated, with each disease predisposing to the other.
- When present in combination, AF and HF portend a worse prognosis than either condition alone.
- AF coexists with both HF with preserved and reduced ejection fraction (HFpEF, HFrEF).

Temporal association of AF and HF subtypes

995 pt with New onset HF (57% had AF): 41% HFpEF ; 44% HFrEF



1737 pt with New AF (37% had HF): HFpEF 32% vs 23% rEF

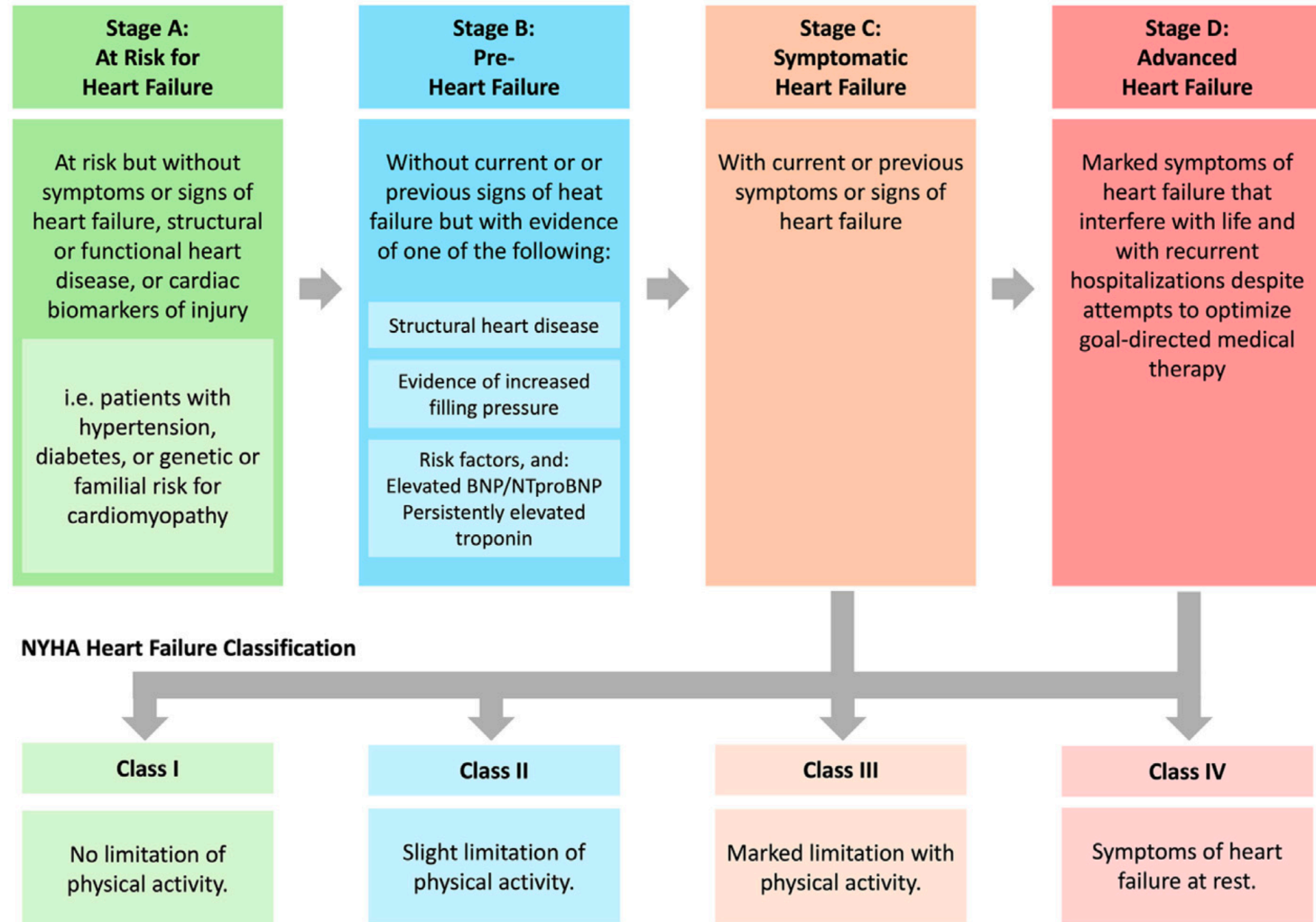


Prevalent HF: newly diagnosed AF 15% at 5 years;
AF alone predisposes to increased risk of HF, most common HFpEF (HR:4.8)

Heart failure classification using left ventricular ejection fraction

HF Classification According to LVEF	Criteria
HFrEF (HF with reduced LVEF)	• LVEF $\leq$ 40%
HFimpEF (HF with improved LVEF)	• Previous LVEF $\leq$ 40% and a follow up LVEF $>$ 40%
HFmrEF (HF with mildly reduced LVEF)	• LVEF 41%–49% • Evidence of spontaneous or provokable increased LV filling pressure
HFpEF (HF with preserved LVEF)	• LVEF $\geq$ 50% • Evidence of spontaneous or provokable increased LV filling pressure

AHA/ACC/HFSA Heart failure stages



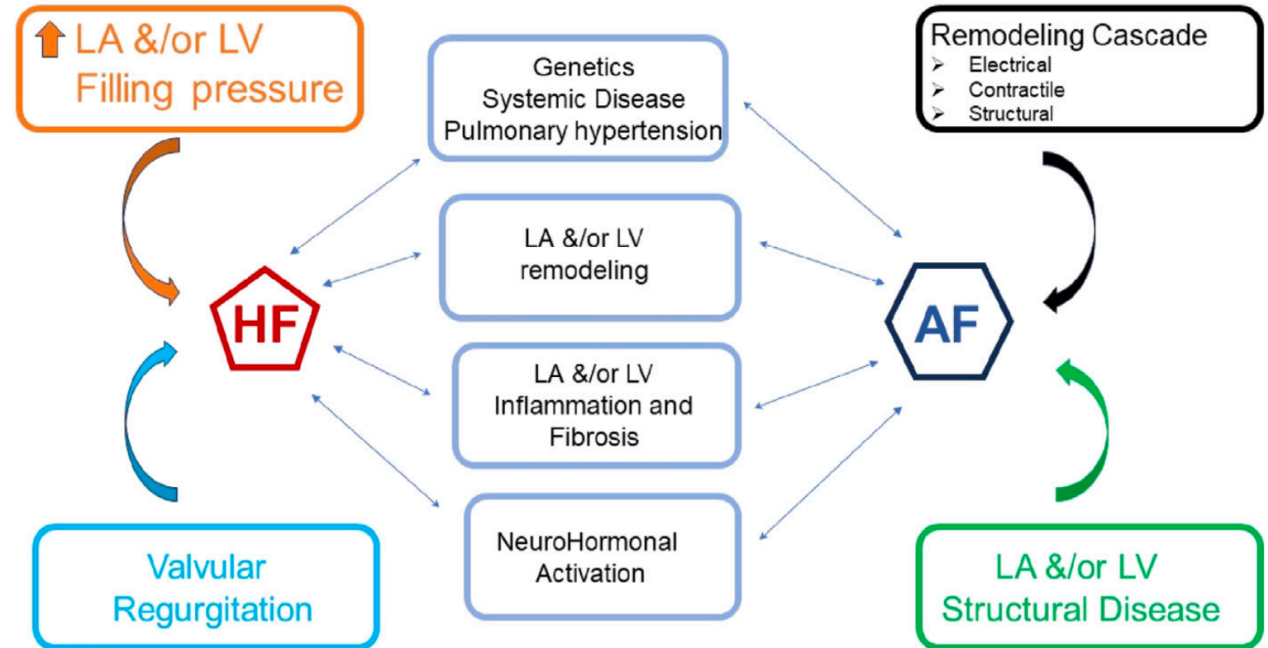
The ACC/AHA/ACCP/HRS guidelines stages of atrial fibrillation

Stage 1	Stage 2	Stage 3				Stage 4
At Risk For Atrial Fibrillation	Pre-Atrial Fibrillation	Atrial Fibrillation				Permanent Atrial Fibrillation
Presence of modifiable and non-modifiable risk factors associated with atrial fibrillation. Modifiable • Obesity • Lack of fitness • Hypertension • Obstructive sleep apnea • Alcohol • Diabetes Non-Modifiable • Genetics • Male sex • Age	Evidence of structural or electrical findings further predisposing patients: • Atrial enlargement • Frequent atrial ectopy • Short bursts of atrial tachycardia • Atrial flutter • Other high-risk scenarios	Patients may transition among different substages				No further attempts at rhythm control after discussion between patient and clinician
		Paroxysmal (3A)	Persistent (3B)	Longstanding Persistent (3C)	Successful Ablation (3D)	
		Intermittent and terminates within ≤ 7 days of onset	Continuous and sustains ≥ 7 days and requires intervention.	Continuous for ≥ 12 months in duration	Freedom from atrial fibrillation after percutaneous or surgical intervention to eliminate atrial fibrillation	

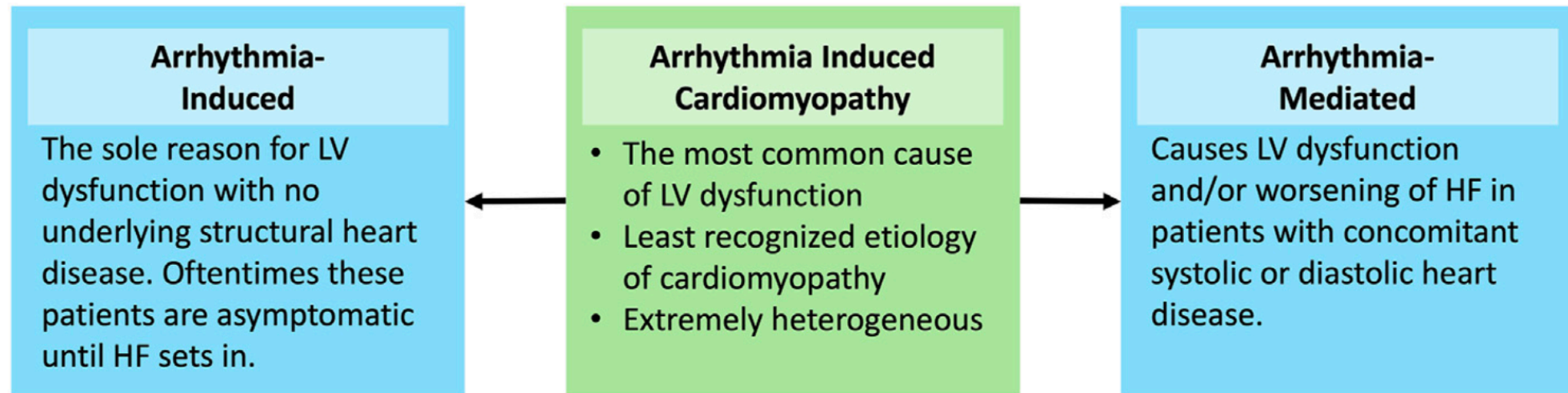
Interrelationship between heart failure (HF) and atrial fibrillation (AF)

Atrial cardiomyopathy

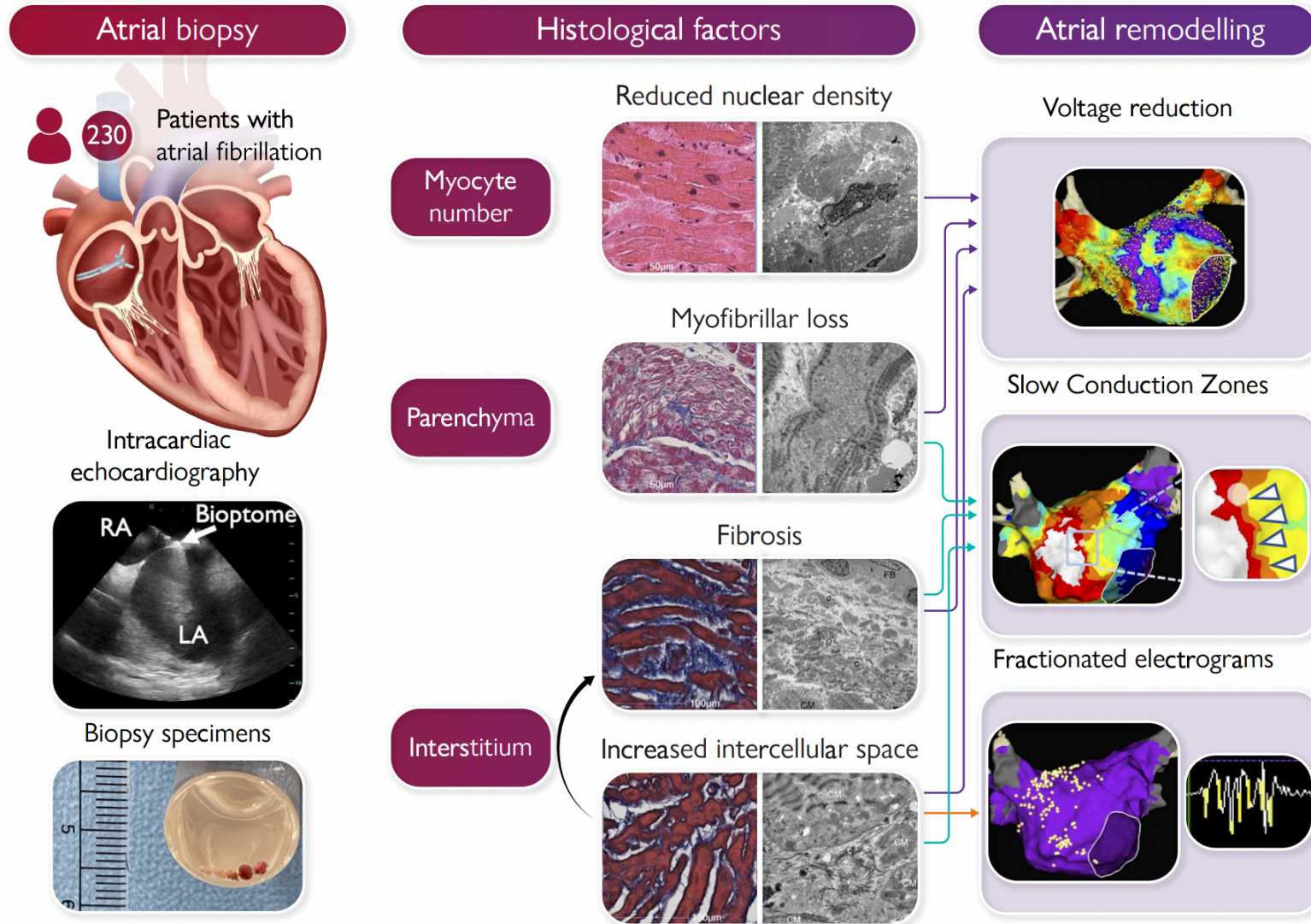
“any complex of structural, architectural, contractile, or electrophysiological changes affecting the atria with the potential to produce clinically relevant manifestations.”



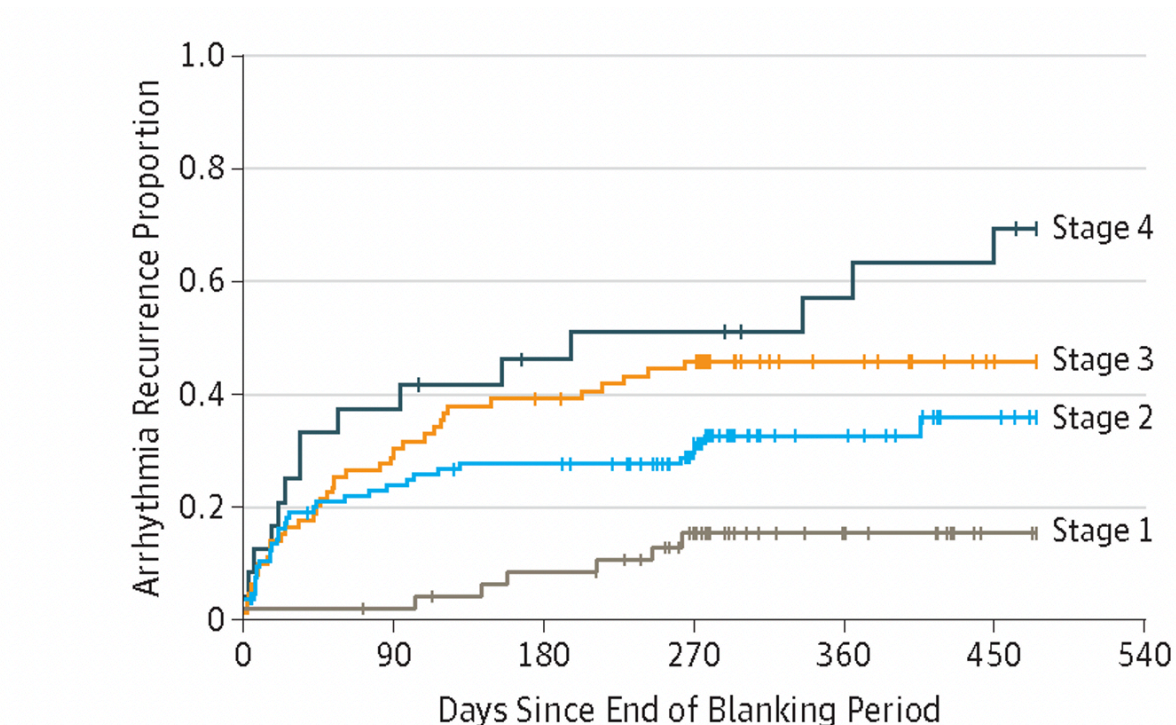
Arrhythmia-induced versus arrhythmia-mediated cardiomyopathy



Histological validation of atrial structural remodelling in patients with atrial fibrillation



Association of Atrial Tissue Fibrosis Identified by Delayed Enhancement MRI and Atrial Fibrillation Catheter Ablation: The DECAAF Study

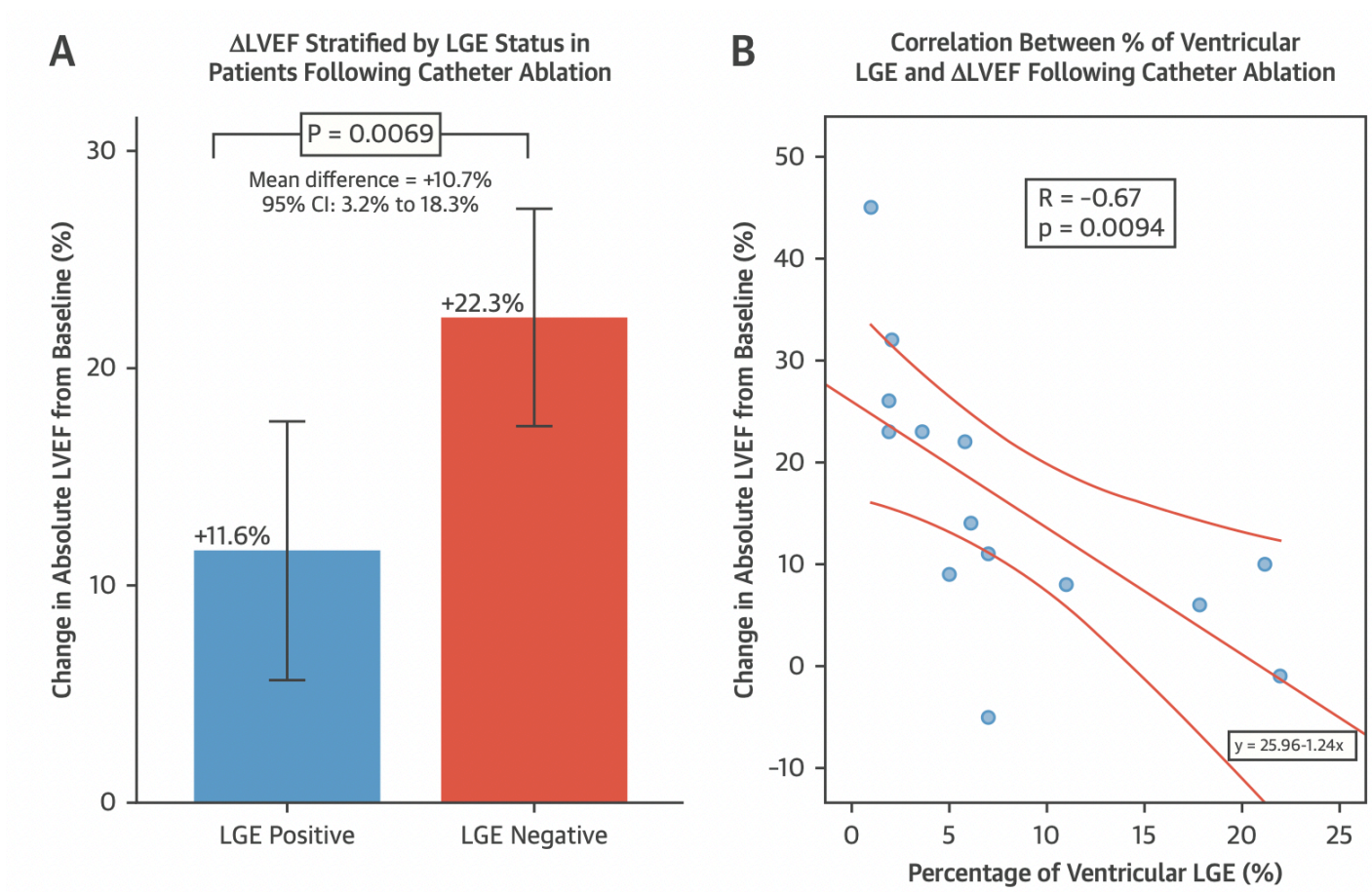


No. at risk

Stage 4	24	15	11	10	7	6
Stage 3	80	56	47	41	19	12
Stage 2	107	79	74	58	26	15
Stage 1	49	47	43	33	13	4

Stage	Absolute Risk (95% CI) by No. of Days After 90-d Blanking Period	
	325 d	475 d
Without covariate adjustment ^a		
1	0.15 (0.08-0.30)	0.15 (0.08-0.30)
2	0.33 (0.24-0.43)	0.36 (0.26-0.48)
3	0.46 (0.36-0.58)	0.46 (0.36-0.58)
4	0.51 (0.33-0.72)	0.69 (0.49-0.88)
With covariate adjustment ^b		
1	0.12 (0.03-0.21)	0.14 (0.03-0.23)
2	0.31 (0.21-0.39)	0.36 (0.25-0.48)
3	0.45 (0.33-0.55)	0.49 (0.35-0.60)
4	0.55 (0.28-0.71)	0.65 (0.39-0.80)

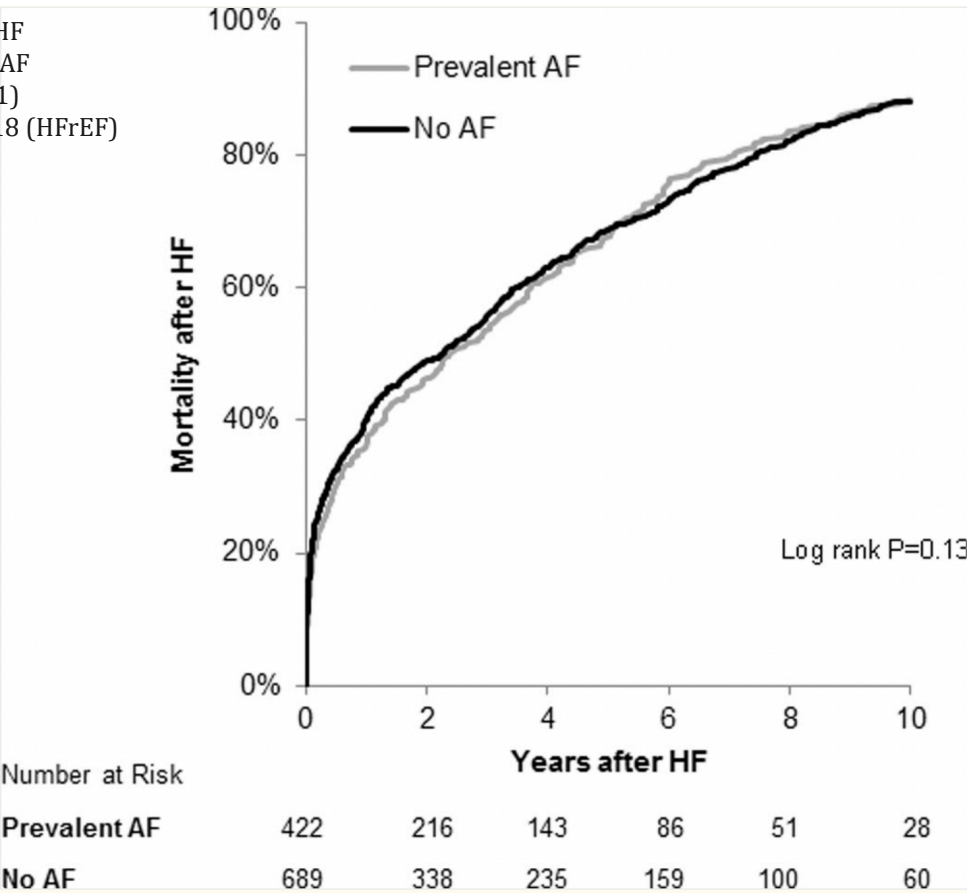
Catheter Ablation Versus Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction: The CAMERA-MRI Study



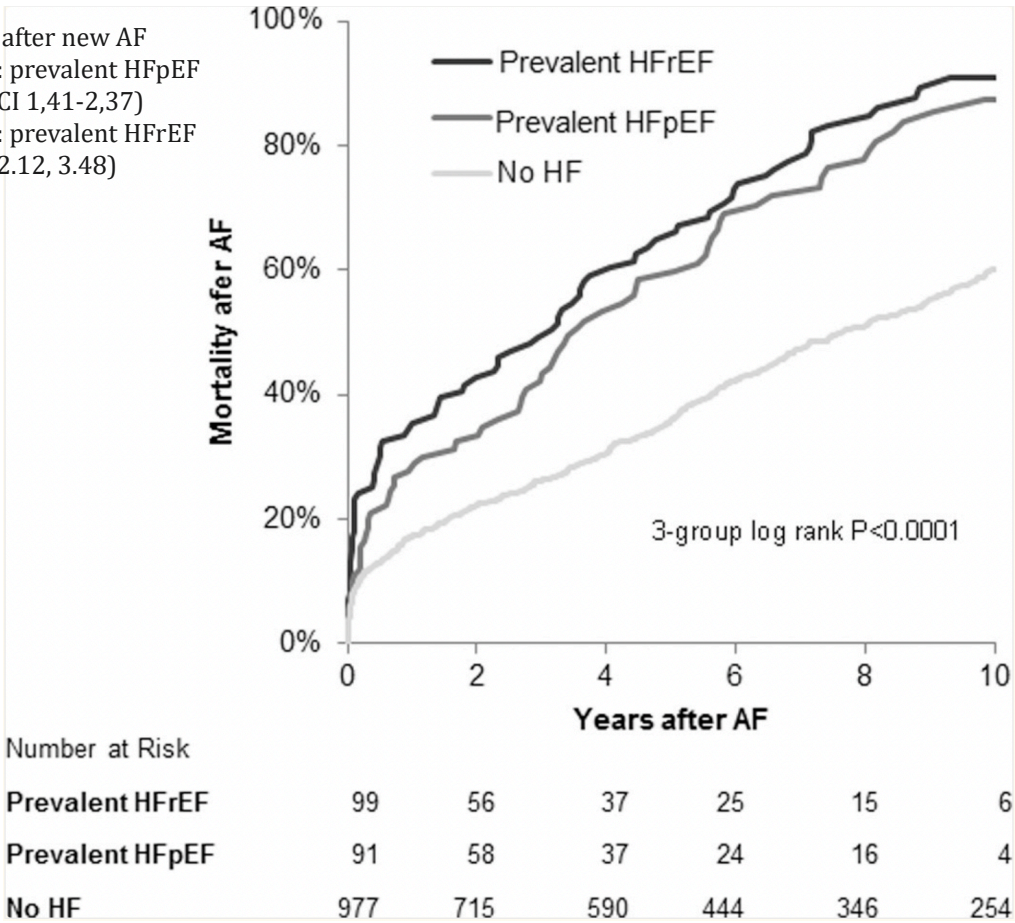
Prognosis of atrial fibrillation with heart failure

Mortality rate in HF and AF (Framingham)

Mortality after new HF
 Predictor: prevalent AF
 HR 1,25 (CI 1,04-1,51)
 HR 1,33 (HFpEF), 1,18 (HFrEF)

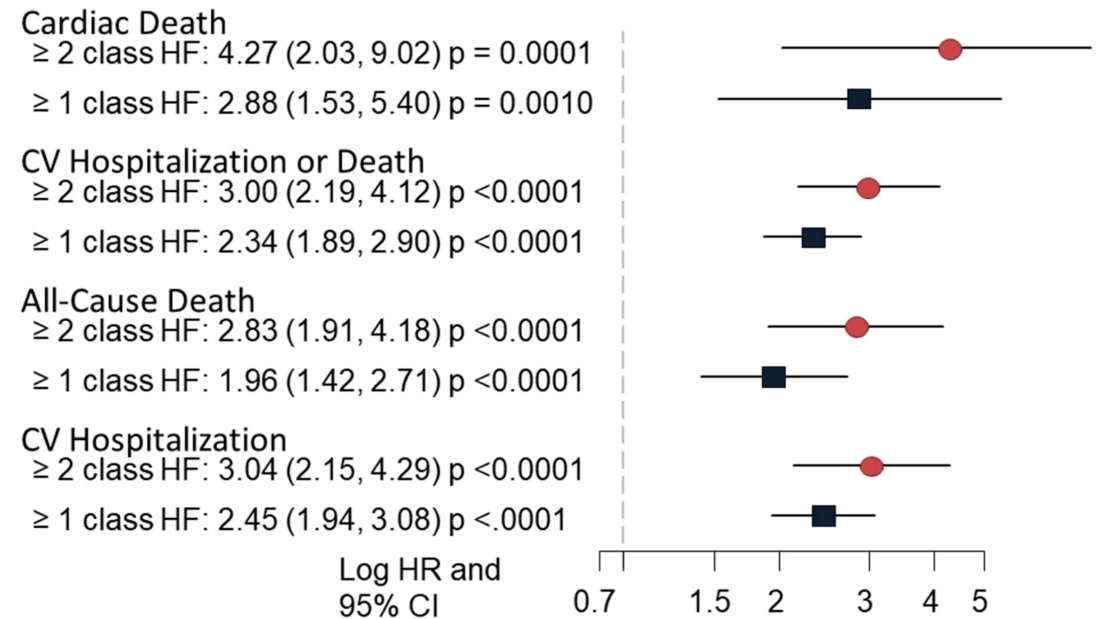


Mortality after new AF
 Predictor: prevalent HFpEF
 HR 1,83 (CI 1,41-2,37)
 Predictor: prevalent HFrEF
 HR 2,72 (2.12, 3.48)



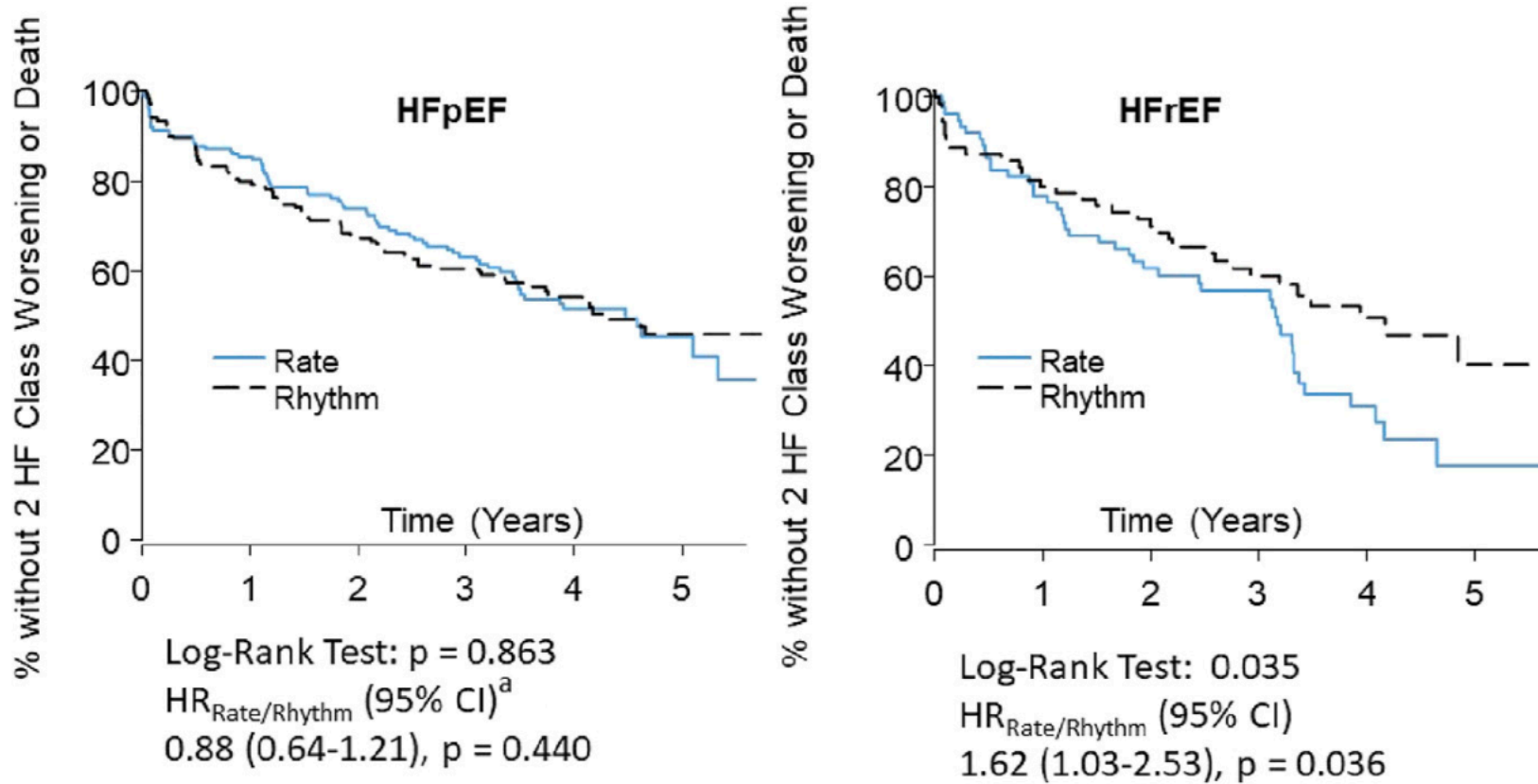
Impact Of Initial Heart Failure Emergence On Clinical Outcomes Of Atrial Fibrillation Patients In the AFFIRM Trial

- Subjects with no history of HF, without clinical HF and normal LVEF, randomized rate vs rhythm control
- Principal outcome: time to development of a composite of NYHA $\geq$ II HF and/or CV death.



AF and HF Clinical Outcomes in rate vs rhythm control strategies

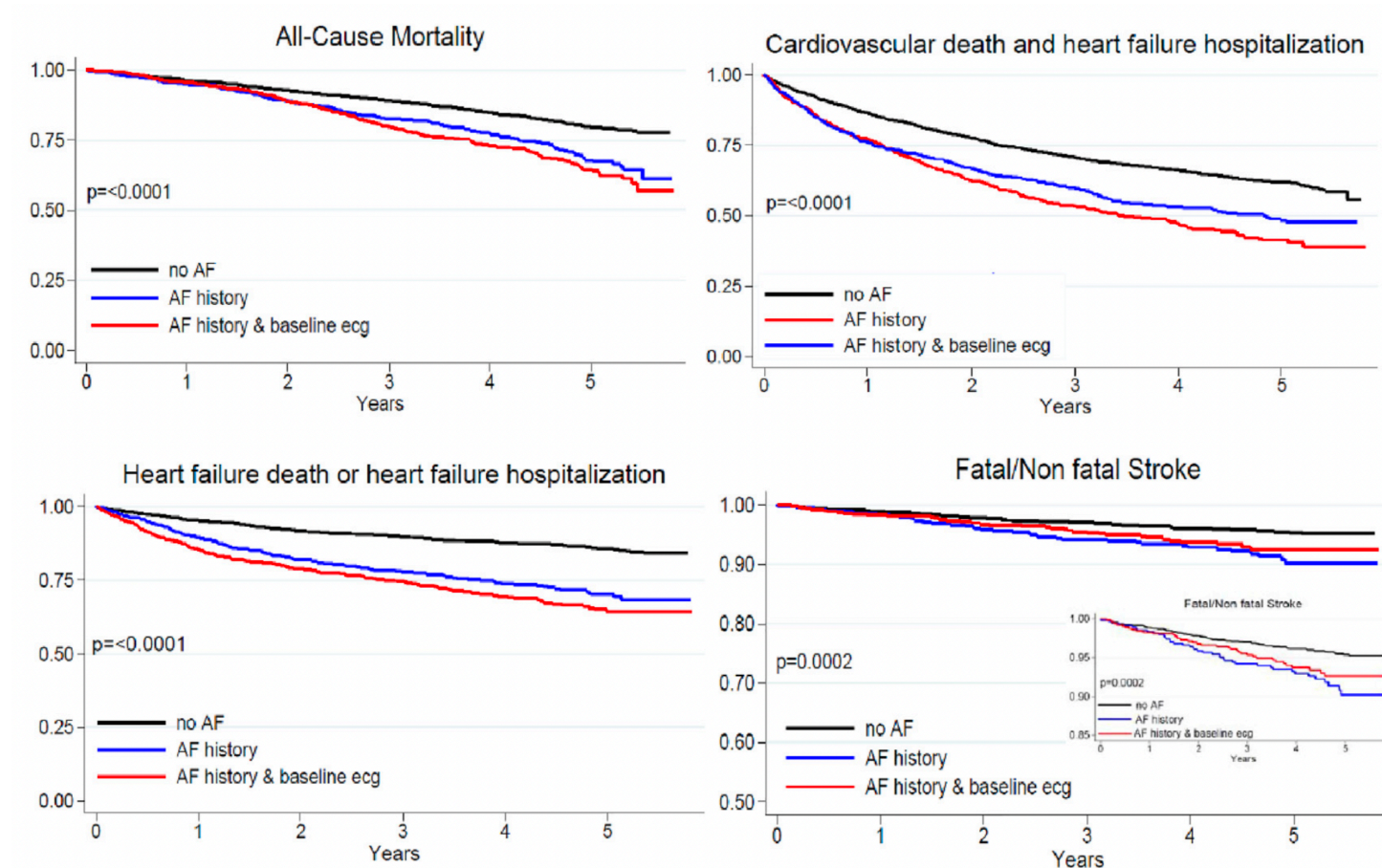
Impact Of Initial Heart Failure Emergence On Clinical Outcomes
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Impact Of Initial Heart Failure Emergence On Clinical Outcomes Of Atrial Fibrillation Patients In the AFFIRM Trial

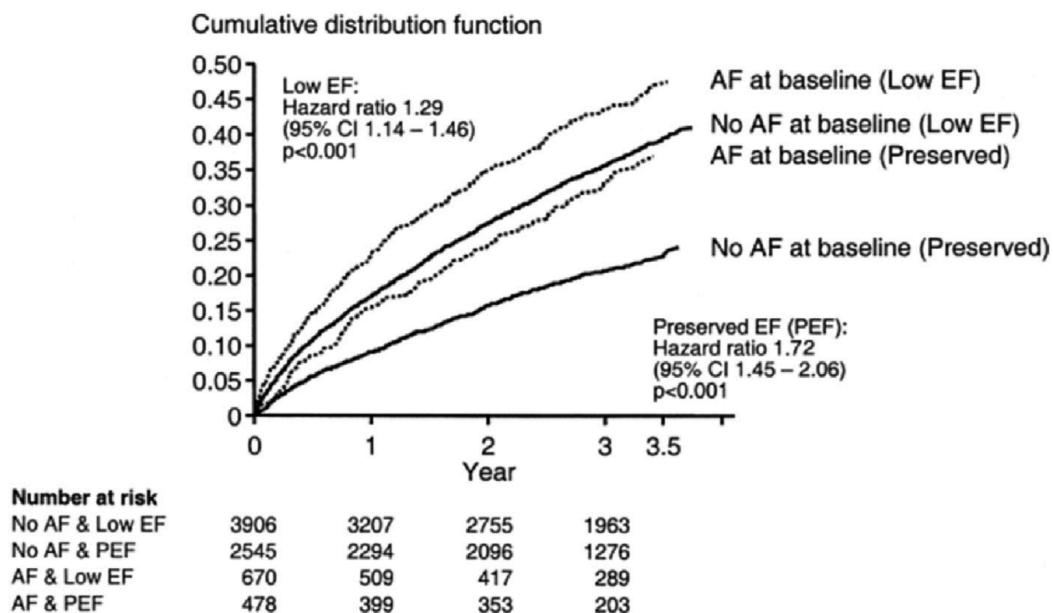
- ✓ Delaying HF emergence is associated with effective Rhythm control with documented sinus rhythm
- ✓ This observation suggests that the beneficial effects of rhythm control can be demonstrated after a significant period of AF suppression and burden reduction (2 or more years follow up)

Mortality and morbidity during long-term follow-up of subjects with HF in the Candesartan in Heart Failure Assessment of Reduction in Mortality (CHARM study)

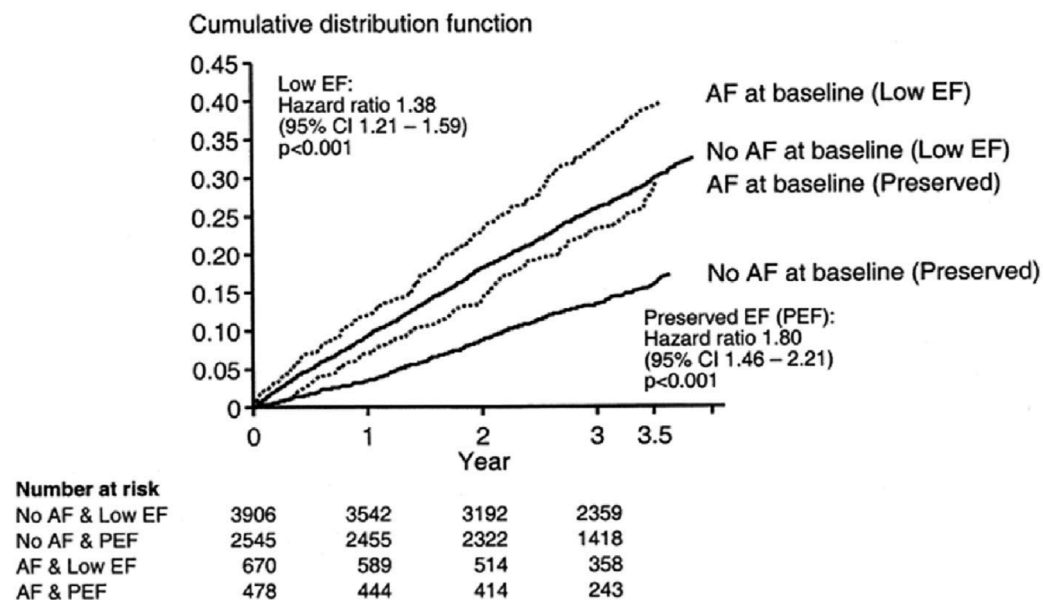


Impact of AF on HF hospitalizations and total mortality in the CHARM study

HF hospitalizations

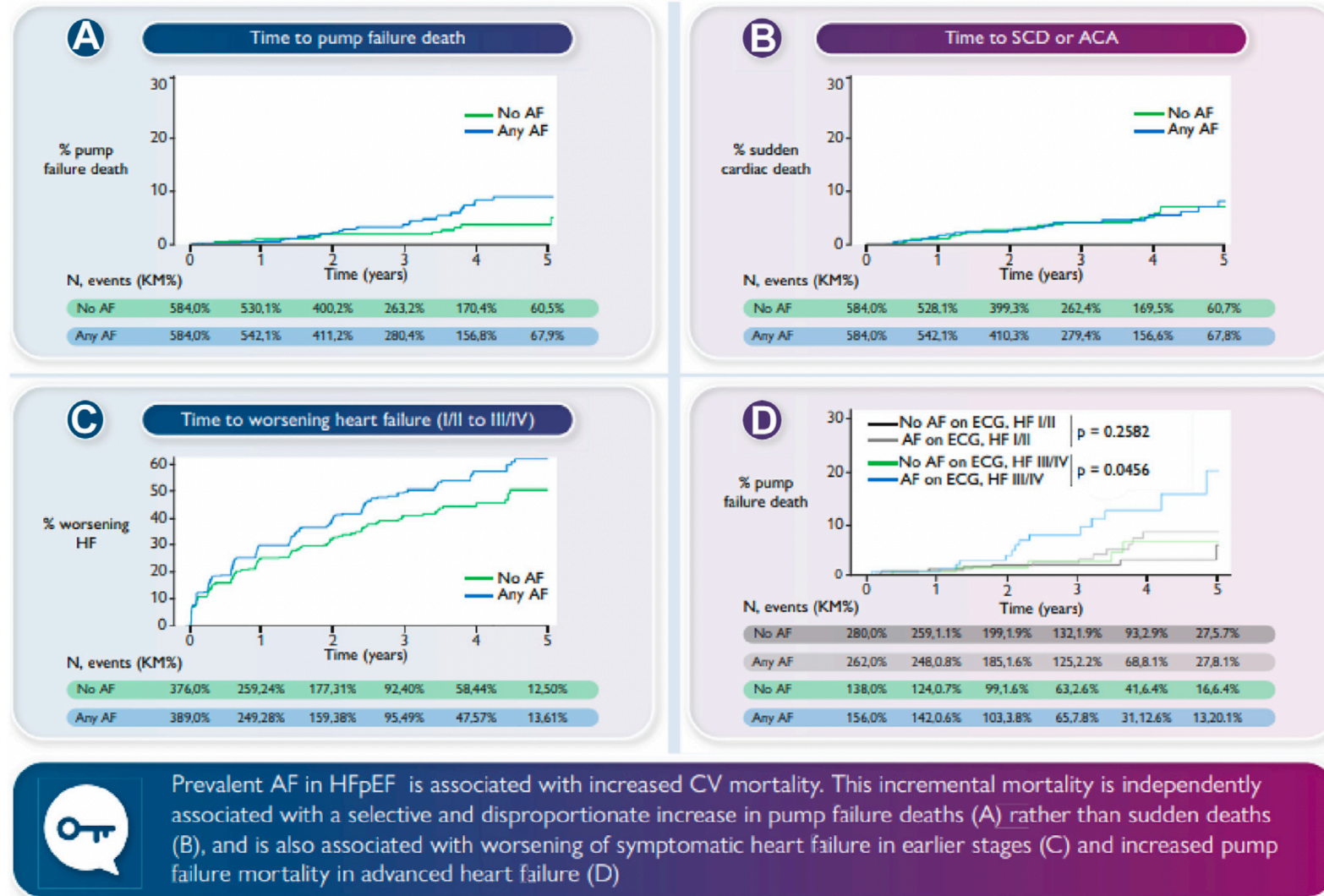


Total mortality

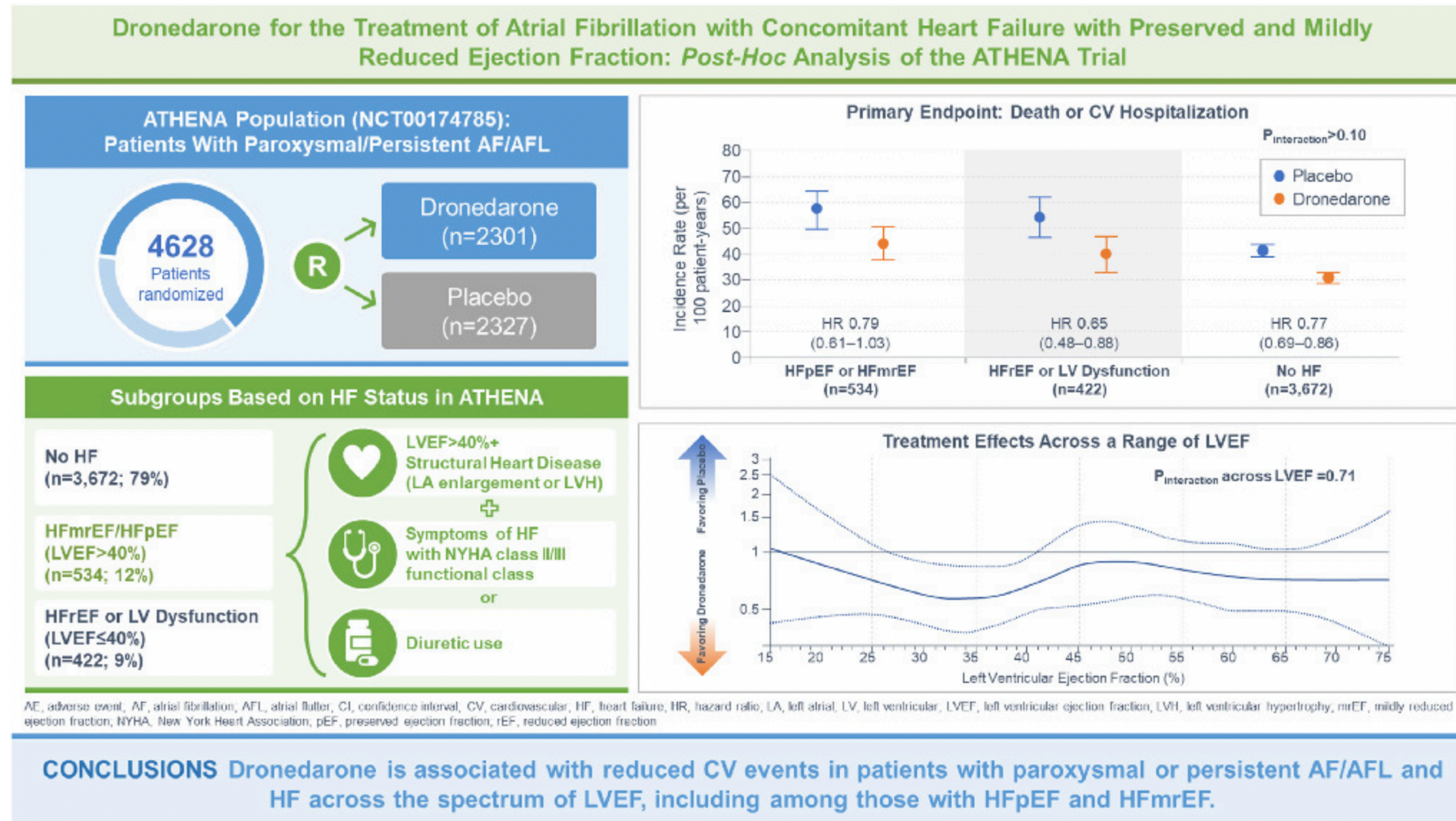


Treatment of Preserved Cardiac Function HF with an Aldosterone Antagonist (TOPCAT) study

Post-hoc propensity score matched analysis



AF and HF Clinical Outcomes in Antiarrhythmic Drug Rhythm control strategies vs Rate



Populations in AF with HFpEF

Summary of populations in atrial fibrillation with heart failure with preserved ejection fraction in randomized clinical trials with mortality and morbidity end points

Trial	Comparison	HF Type or Subgroups	AF Type
AFFIRM Trial	Rhythm: 47 Rate: 60	LVEF $\geq$ 50%, NYHA II/III	In SR at randomization, AF likely to be recurrent
ATHENA Trial	Dronedaron: 266 Placebo: 268	LVEF >40%, NYHA II/III Structural HD	Paroxysmal or persistent
ATHENA Trial ^a Less Stringent HF	Total: 2353	LVEF >40%, NYHA II/III, No Required Structural HD	Paroxysmal or persistent
CABANA Trial	CA: 51 Drug Therapy: 50	LVEF $\geq$ 40% and <50%, NYHA II/III/IV	Paroxysmal or persistent
CABANA Trial	CA: 295 Drug Therapy: 315	LVEF $\geq$ 50%, NYHA II/III/ IV	Paroxysmal or persistent
CABANA HF Substudy	CA: 378 Drug therapy: 400	91.3% LVEF $\geq$ 40%, NYHA II/III/IV	Paroxysmal or persistent
EAST-AFNET 4 Trial HFmrEF substudy	Rhythm: 110 Usual care: 101	LVEF 40%–49%	First, paroxysmal or persistent
EAST-AFNET 4 Trial HFpEF substudy	Rhythm: 224 Usual care: 218	LVEF $\geq$ 50%	First, paroxysmal or persistent
RAFT AF	CA: 81 Rate: 90	LVEF >45%	High-burden paroxysmal/persistent AF

Outcomes in AF with HFpEF

Summary of outcomes in atrial fibrillation with heart failure with preserved ejection fraction randomized clinical trials with mortality and morbidity end points

Trial	All-Cause Death (ACD) (Rhythm/Rate)	CV Death, Stroke, HHF, $\pm$ ACS (Rhythm/Rate)	Death or CVH/Death or HF Event
AFFIRM Trial	HR (95% CI): 0.92 (0.45–1.89), $P = .815$	CVD—HR (95% CI): 0.62 (0.21–1.80), $P = .377$	CVH/D: HR (95% CI): 0.80 (0.51–1.26), $P = .338$
ATHENA Trial	HR (95% CI): 0.59 (0.33–1.09) ACD: Favored Dronedaron vs placebo in HFpEF/HFmrEF but not significant	Favored Dronedaron but not significant	CVH/D HR (95% CI): 0.78 (0.68–0.89)
ATHENA Trial ^a Less Stringent HF	HR (95% CI): 0.65 (0.45–0.95)	HHF HF (95% CI): 1.01 (0.74–1.39)	HR (95% CI) 0.78 (0.68–0.89)
CABANA Trial	HR (95% CI): 0.43 (0.09–2.13)		
CABANA Trial	HR (95% CI): 0.40 (0.18–0.88)		
CABANA Trial HF Substudy	HR (95% CI): 0.57 (0.33–0.96)	CVD—HR (95% CI): 0.70 (0.31–1.57) Dth/Stk/Bld/CA—HR (95% CI): 0.64 (0.41–0.99)	CVH/D—HR (95% CI): 0.84 (0.70–1.02) HHF—HR (95% CI): 0.89 (0.56–1.44)
EAST-AFNET 4 Trial HFmrEF Substudy		Incidence/100 PYAR treatment effect (95% CI): 0.77 (0.44–1.34); $P = .35$, KM logrank $P = .31$	
EAST-AFNET 4 Trial HFpEF substudy		Incidence/100 PYAR treatment effect (95% CI): 0.81 (0.56–1.18); $P = .28$, KM logrank $P = .24$	
RAFT AF	CA: 22 of 90 (24.4%) vs Rate: 21 of 81 $P = .6$		D/HF Event—HR (95% CI) 0.88 (0.48–1.61); $P = .672$

Populations in AF with HFrEF

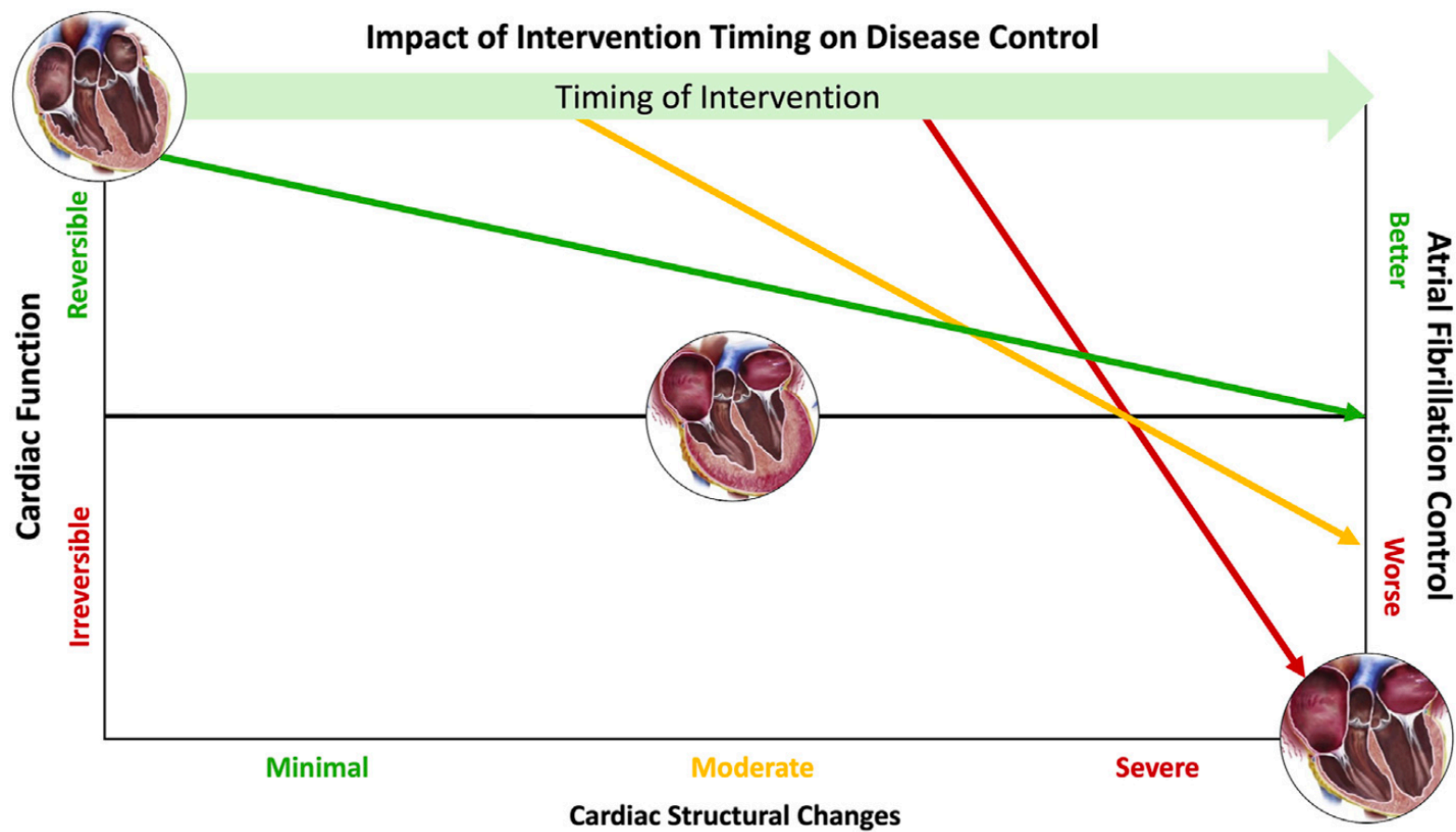
Summary of large atrial fibrillation and heart failure with reduced ejection fraction populations in randomized clinical trials with mortality and/or morbidity end points

Trial	Comparison and N	HF Type or Subgroups	AF Type
AATAC Trial	CA for AF: 102 AMIO: 101	LVEF < 40%, NYHA II/III, ICD/CRT-D	Persistent
AF-CHF Trial	Rhythm: 682 Rate: 694	LVEF < 35%, NYHA II/III/IV	Paroxysmal or persistent
AFFIRM Trial	Rhythm: 95 Rate: 81	LVEF < 50%, NYHA II/III	In SR at randomization, AF likely to be recurrent
AMICA Trial	CA: 68 BMT: 72	LVEF ≤ 35%, NYHA II/III, ICD/CRT-D or indication	Persistent/long-standing persistent
ATHENA Trial	Dronedarone: 201 Placebo: 221	LVEF ≤ 40%, NYHA II/III	Paroxysmal or persistent
CABANA Trial	CA: 32 Drug Therapy: 35	LVEF < 40%, NYHA II/III/IV	Paroxysmal or persistent
CASTLE-AF Trial	CA: 179 Med. Therapy: 184	LVEF ≤ 35%, NYHA II/III/IV, ICD/CRT-D	Paroxysmal or persistent
EAST-AFNET 4 Trial HF Substudy	Rhythm: 57 Usual care: 75	LVEF < 40%	First episode/paroxysmal/ persistent
RAFT AF	CA: 124 Rate: 116	LVEF ≤ 45%, NYHA II/III	High-burden paroxysmal/ persistent AF
DIAMOND-CHF	Dofetilide: 190 Placebo: 201	LVEF ≤ 35%, NYHA III/IV	

Outcomes in AF with HFrEF

Summary of outcomes in large atrial fibrillation and heart failure with reduced ejection fraction populations in randomized clinical trials with mortality and/or morbidity end points

Trial	All-Cause Death (ACD)/CV Death (CVD) (Rhythm/Rate)	CV Hospitalizations(H) or HHF (Rhythm/ Rate)	LVEF Improvement	Minnesota QOL HF Questionnaire Reduction
AATAC Trial	CA: 8 (8%), Amio 18 (18%) log-rank $P = .037$, RR (95% CI): 0.44 (0.20–0.96)	Unplanned H CA: 32 (31%), Amio: 58 (57%), log-rank $P < .001$ RR (95% CI): 0.55 (0.39–0.76)	Mean ± SD CA: 8.1±4, Amio: 6.2±5.0 $P = .02$	Mean ± SD CA: 11±19, Amio: 6±17 $P = .04$
AF-CHF Trial	HR (95% CI): 0.97 (0.80–1.17), $P = .73$	Worse HF—HR (95% CI): 0.87 (0.72– 1.06), $P = .17$ CVH - Rhythm: 658 (70%), Rate: 601 (67%)	Mean ± SD Rhythm: 8.0±10.0% for, Rate: 4.5±10.6%, $P = .19$	
AFFIRM Trial	HR (95% CI): 1.06 (0.66–1.71), $P = .819$	CVH—HR (95% CI): 1.33 (0.90–1.96), $P = .158$		
AMICA Trial	ACD: 8 patients in each group (NS)	SAE Worsening of heart failure CA: 15 (15.3), BMT: 21 (21.0), $P = .36$	Mean (95% CI) CA: 8.8% (5.8% to 11.9%), BMT: 7.3% (4.3% to 10.3%), $P = .36$	Mean CA: 11.2, BMT 8.9, $P = .42$
ATHENA Trial		CVH/D—HR (95% CI): 0.65 (0.48–0.88)		
CABANA Trial	HR (95% CI): 1.43 (0.17–12.05)			
CASTLE-AF Trial	HR (95% CI): 0.53 (0.32–0.86), $P = .01$	HHF—HR (95% CI): 0.56 (0.37– 0.83), $P = .004$ CVH—HR (95% CI): 0.72 (0.52– 0.99), $P = .04$	Median [IQR] CA: 8.0% [2.2–19.1], BMT 0.2% [–3.0–16.1], $P = .005$	
EAST-AFNET 4 Trial HF substudy			Mean ± SD Rhythm: 17.28±13.45, Usual Care: 18.10±10.73, $P = .66$	
RAFT AF	CA: 28 of 124(22.6%) vs Rate: 43 of 116(37.1%) $P = .06$		6.3 (2.7–9.9), $P = .019$	–5.8 (–12.4–0.7), $P = .012$
DIAMOND-CHF	HR (95% CI): 1.01 (0.75–1.36)	HHF—HR (95% CI): 0.64 (0.46–0.91)		



Key points

- ✓ Regardless of which begins first, AF and HF frequently coexist and exacerbate each other.
- ✓ Their increasing prevalence creates considerable morbidity and mortality, which creates significant challenges for management and strain on the healthcare system.
- ✓ Although the incidence of AF is higher in HFrEF, the prognosis of AF in HFpEF is worse.
- ✓ Although no screening guidelines exist, early detection of AF in HF is crucial as it increases mortality by 1.5 and 2.7-fold in men and women, respectively.
- ✓ Recognizing this is important for appropriately treating these diseases and mitigate the development of irreversible remodeling.