

# **ΚΟΛΠΙΚΗ ΜΑΡΜΑΡΥΓΗ ΣΤΗΝ ΚΑΡΔΙΑΚΗ ΑΝΕΠΑΡΚΕΙΑ. ΠΩΣ ΑΝΤΙΜΕΤΩΠΙΖΕΤΑΙ**

**Στράτος Θεοφιλογιαννάκος, MD, PhD**

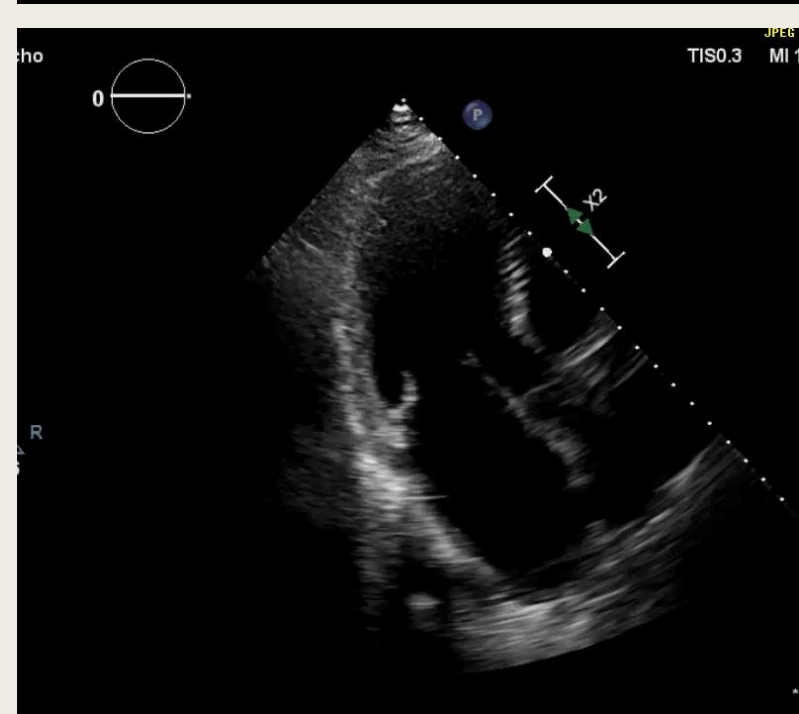
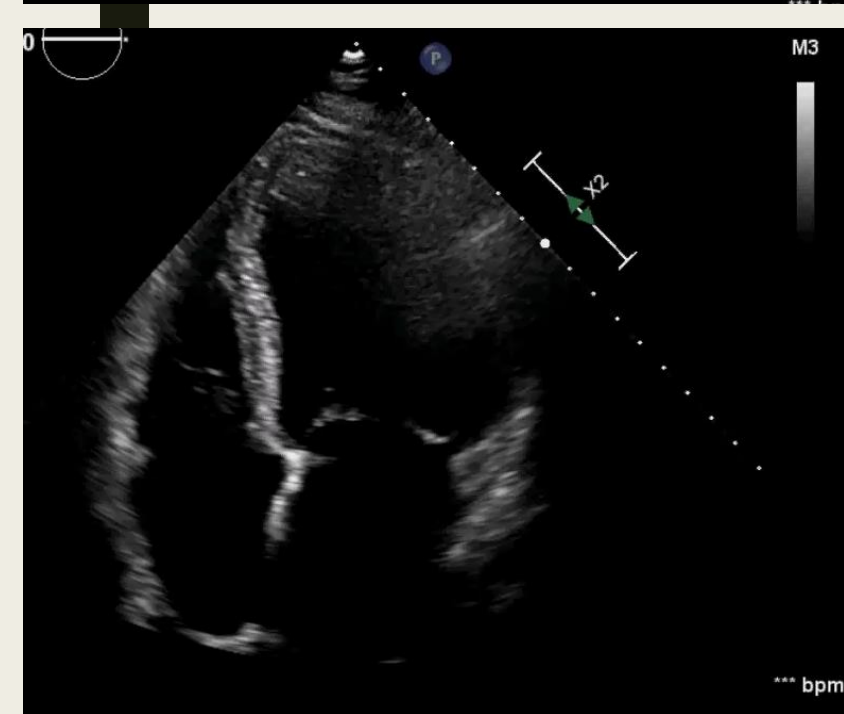
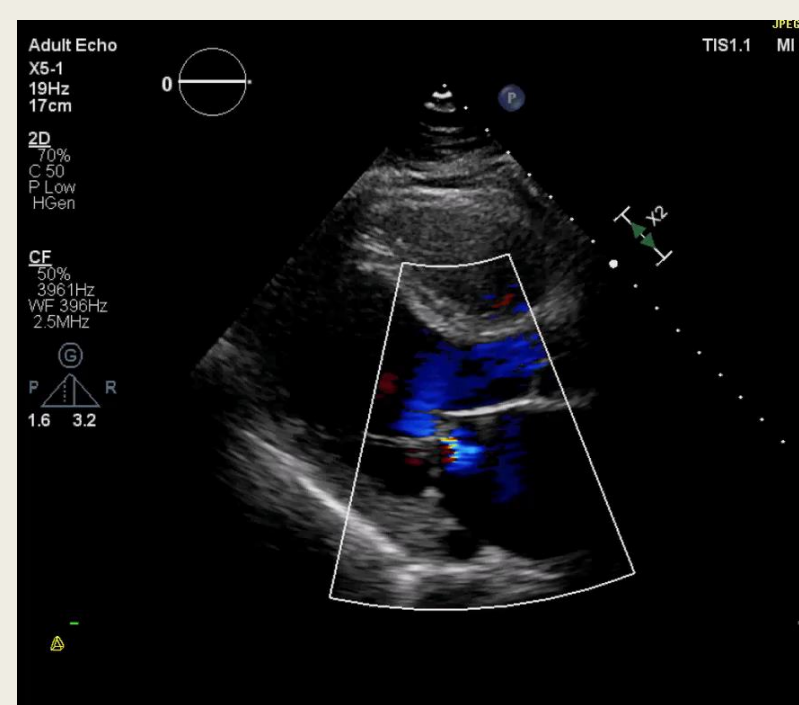
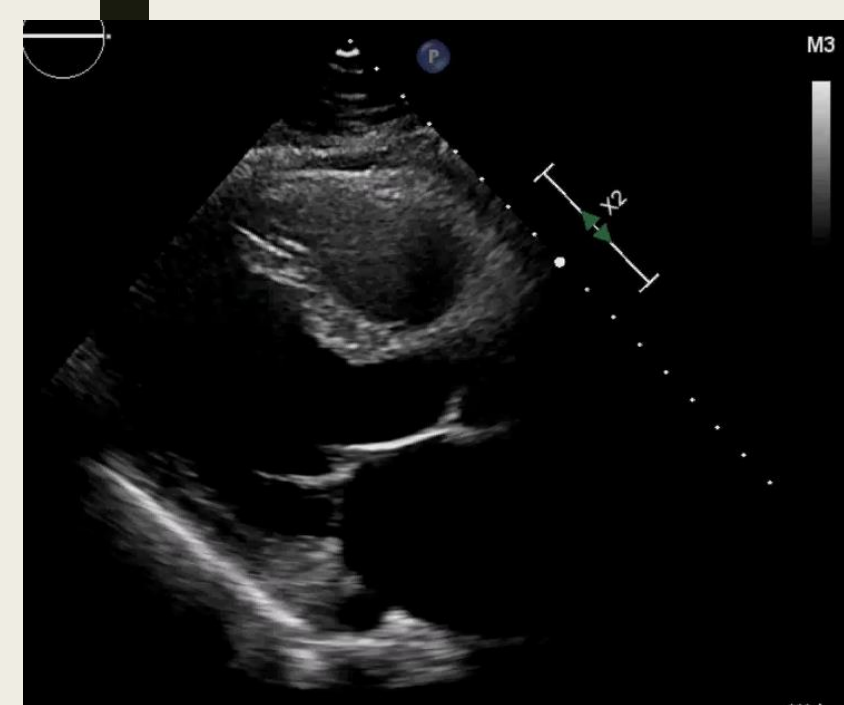
Ιατρείο Καρδιακής Ανεπάρκειας Γ Πανεπιστημιακή Καρδιολογική Κλινική ΑΠΘ  
Ιπποκράτειο Νοσοκομείο Θεσσαλονίκης  
&  
Κλινική Άγιος Λουκάς

# Περιστατικό

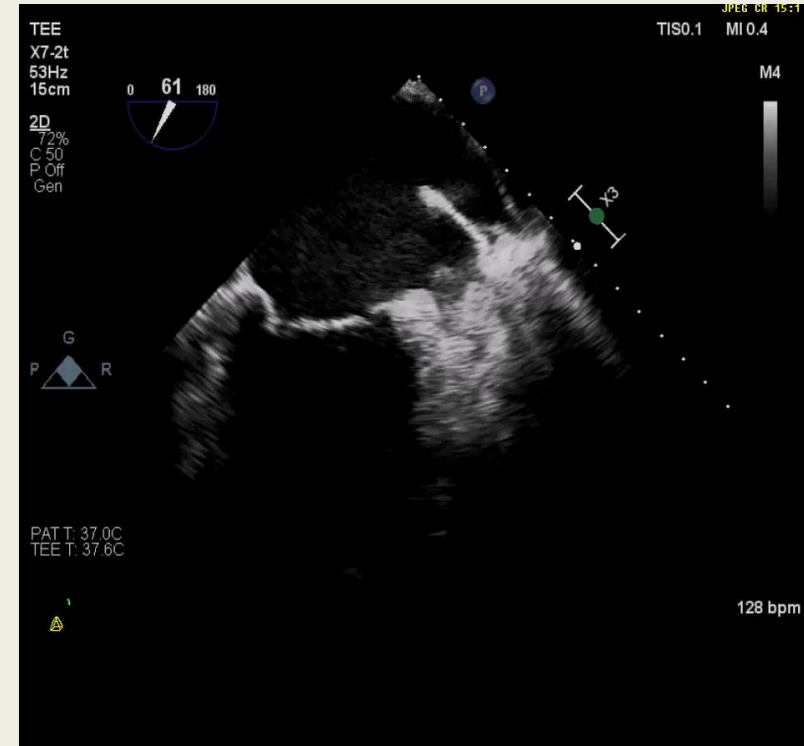
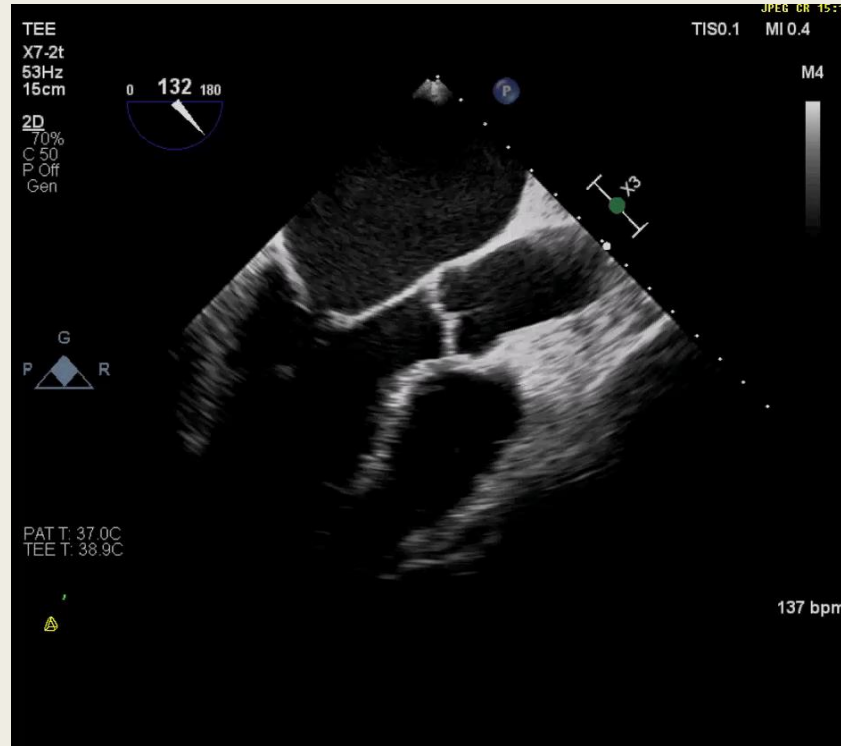
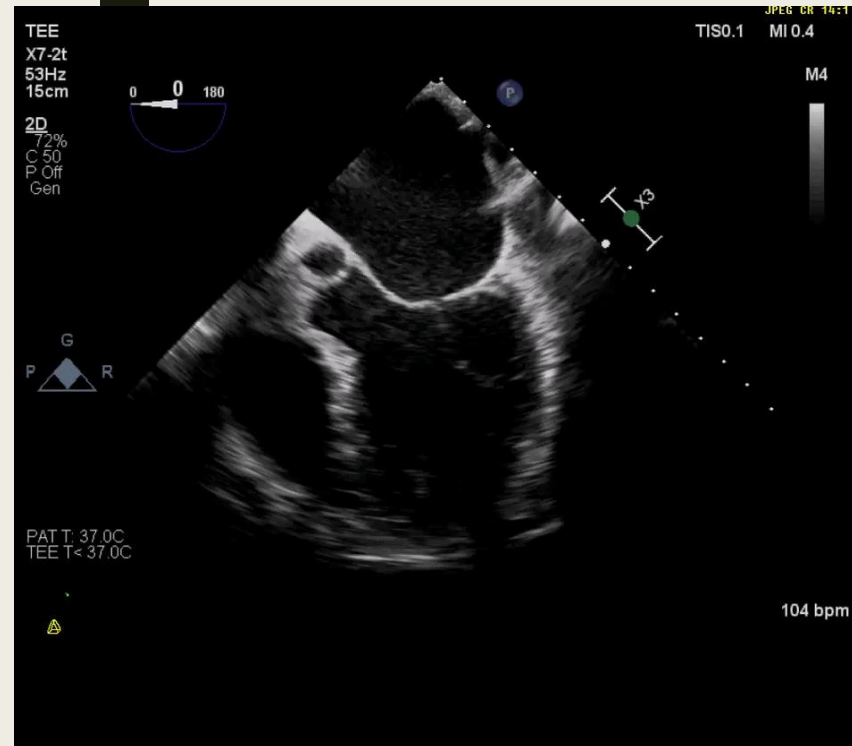
- Άνδρας 57 ετών
- Εισαγωγή για **δύσπνοια** και **αίσθημα παλμών**
- Χωρίς ιστορικό Δομικής Καρδιοπάθειας
- Φάρμακα: -
- Οικογενειακό Ιστορικό: -
- ΑΠ=140/90
- ΗΚΓ: **Ταχεία AF** (αγνώστου ενάρξεως)
- Εργαστηριακά:
  - Ht=48.2%, WBC=10000, PLT=234000
  - Ουρία= 33 mg/dl, Κρεατινίνη=1,12 mg/dl, Κάλιο=5,3 mmol/l, Νάτριο=143 mmol/l
  - **NT-proBNP= 3229 pg/ml**

# Α/Α ΘΩΡΑΚΑ

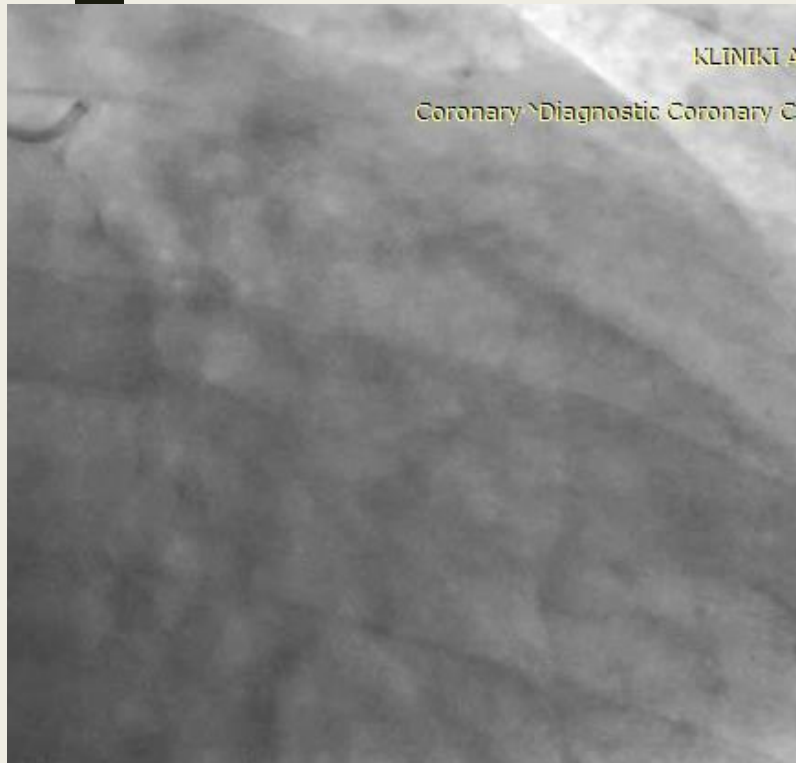




# 2η ημέρα νοσηλείας: **Παροδικό Ισχαιμικό ΑΕΕ**



# Στεφανιογραφικός έλεγχος



## Αγωγή Εισόδου

- Ενδοφλέβια διουρητικά (Φουροσεμίδη)
- Βισοπρολόλη (2.5 mg X 2)
- Διγοξίνη (0.125 mg X1)
- Επλερενόνη (25 mg X1)
- Ριβαροξαμπάνη (20 mg x 1)

## Αγωγή εξόδου:

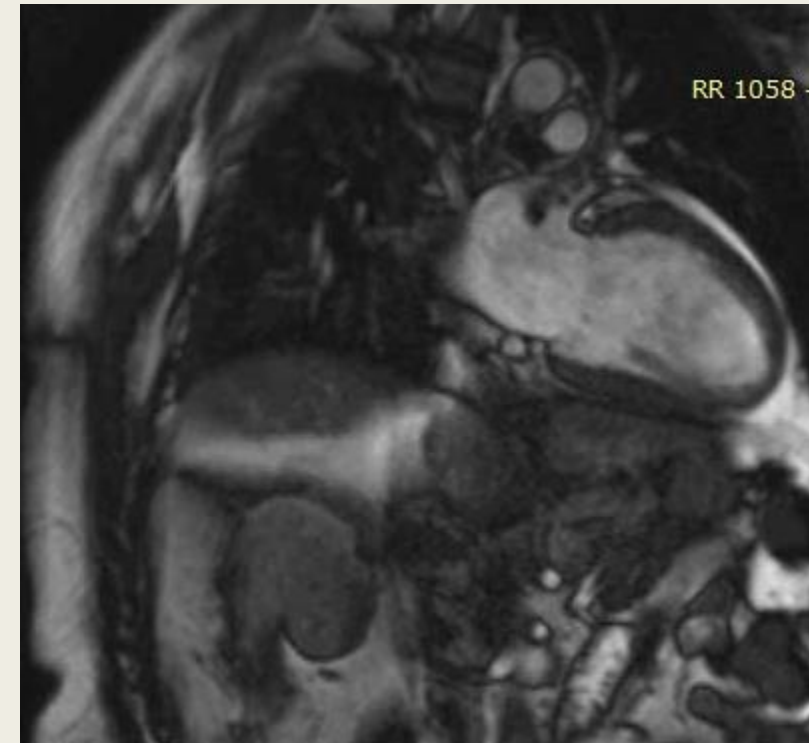
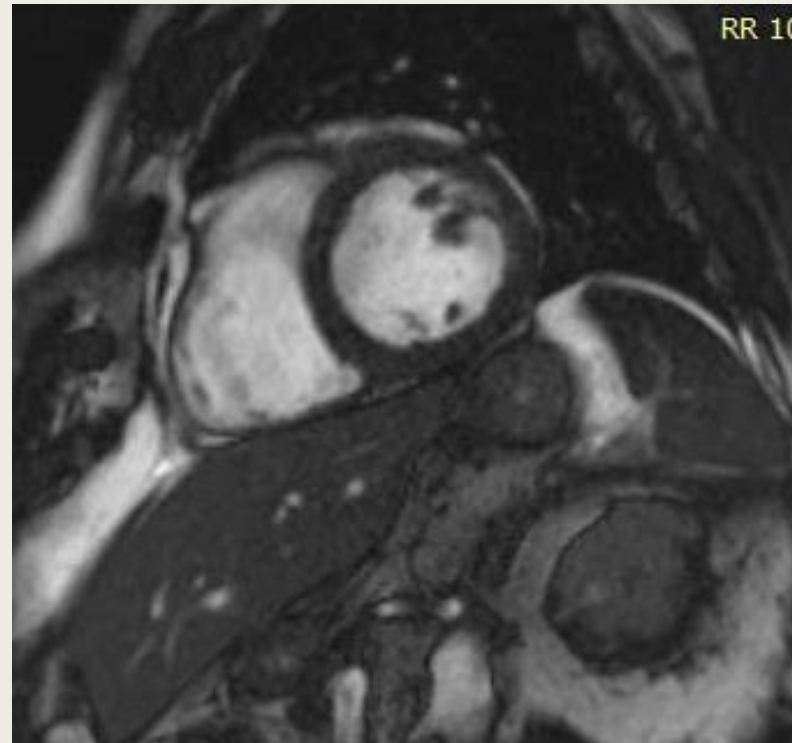
1. Βισοπρολόλη 2.5 mg X 2
2. Φουροσεμίδη 40 mg X1
3. Επλερενόνη 25 mg X1
4. Σακουμπιτρίλη/Βαλσαρτάνη 24/26 mg X2
5. Ριβαροξαμπάνη 20 mg x 1

## 6 εβδομάδες αργότερα:

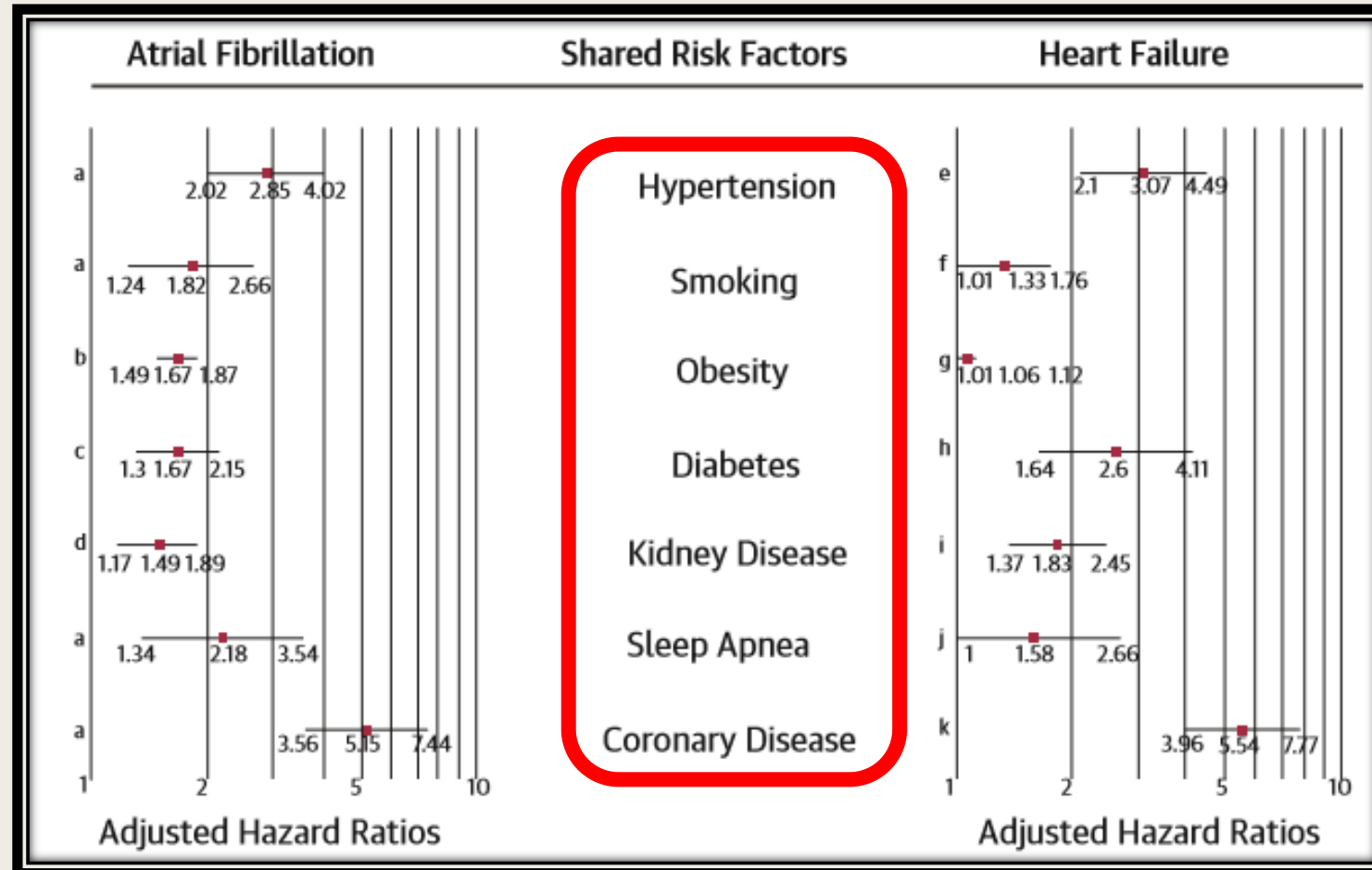
**Επιτυχής ηλεκτρική ανάταξη**

**6 μήνες αργότερα**

**Rhythm  
Control  
Strategy**

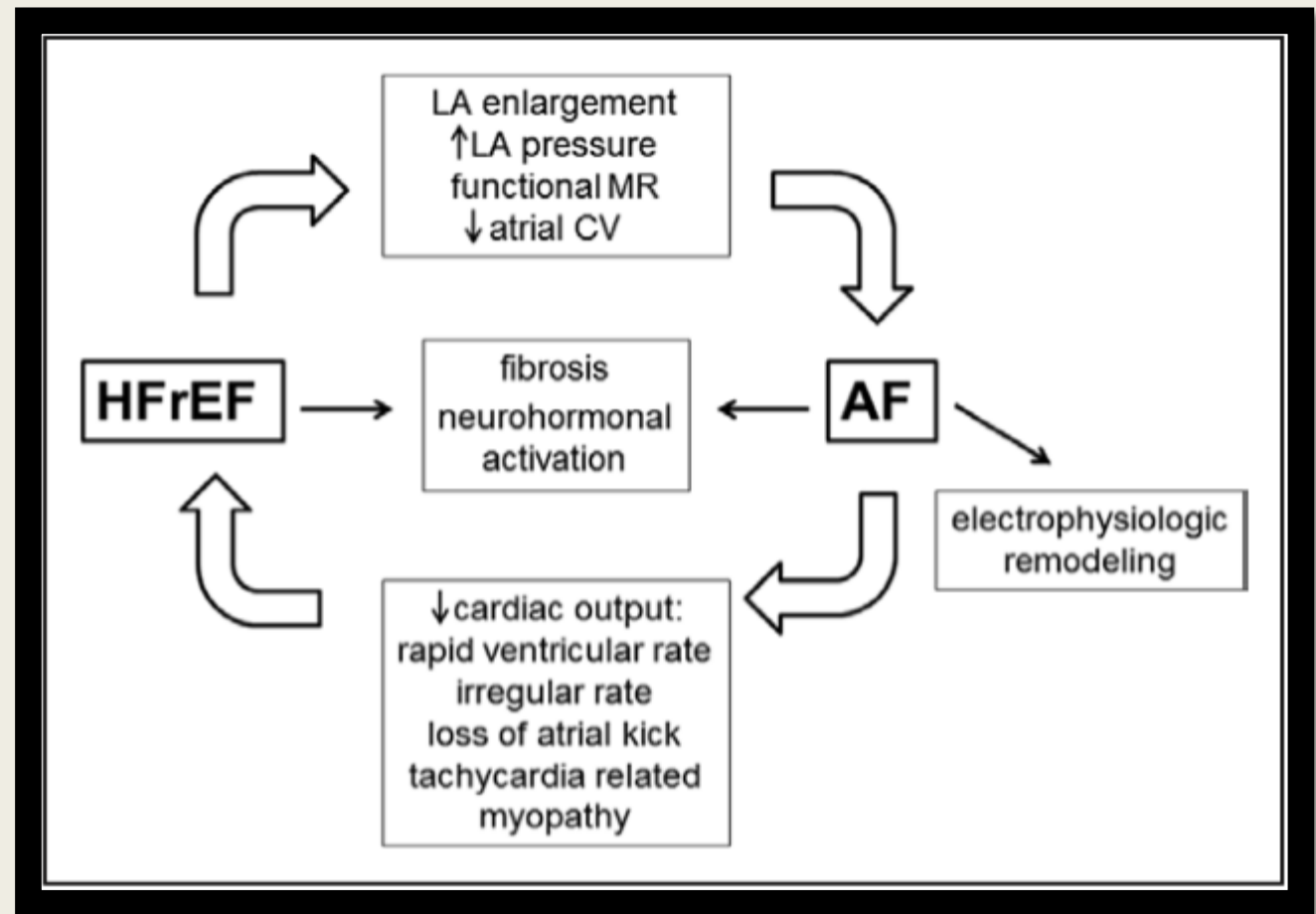


# Hazard Ratio of Incident AF and HF According to Shared Risk Factors

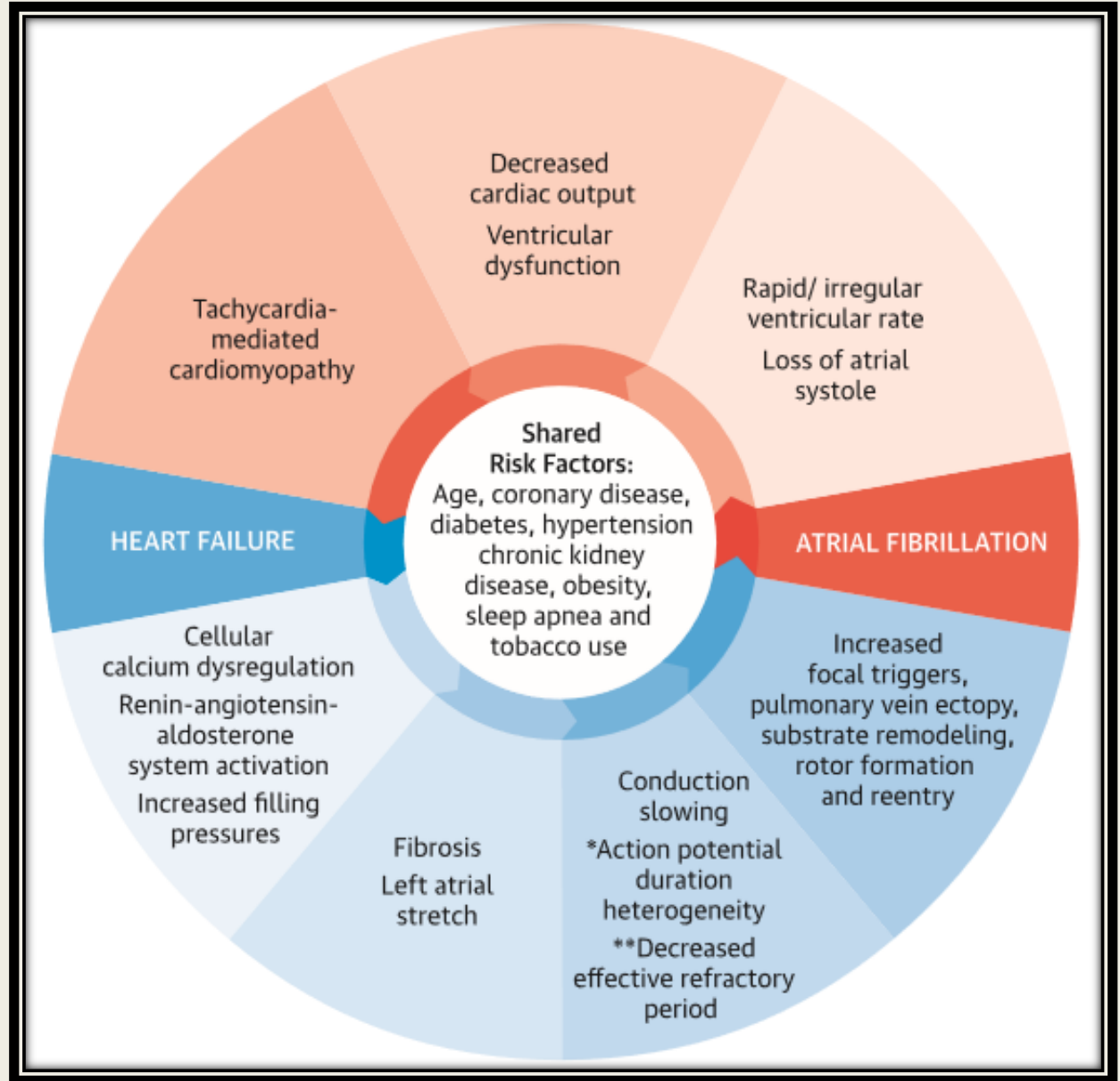


# AF and HFrEF: a vicious cycle

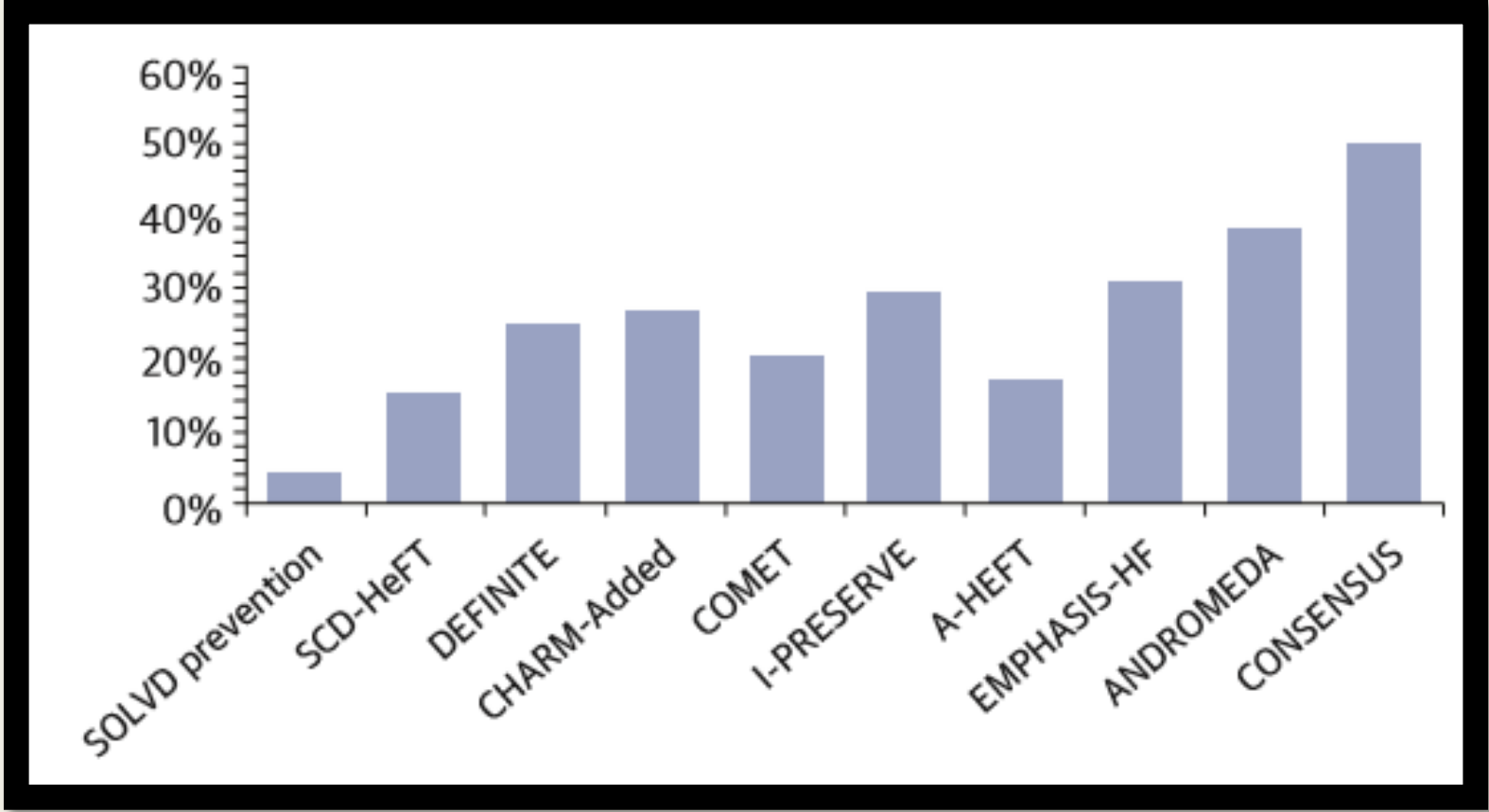
- ❖ AF and HFrEF share many fundamental predisposing risk factors, such as **hypertension, diabetes mellitus, ischemic and valvular heart disease**, and a predilection for increased incidence in the **elderly**, as well.



# The Physiological Relationship Between AF and HF



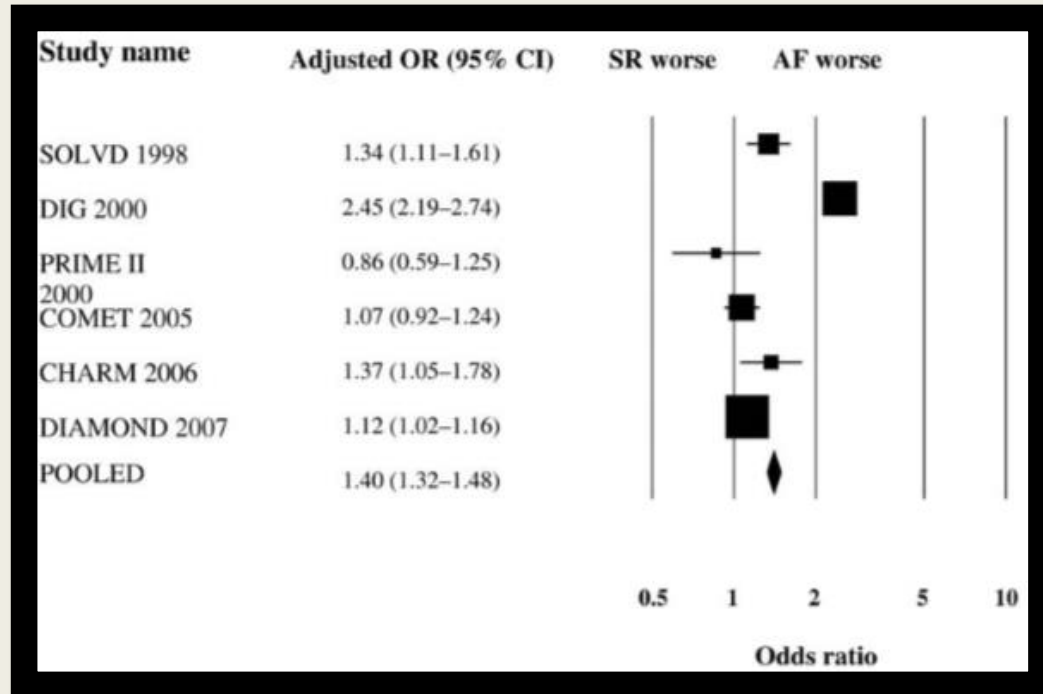
# Prevalence of AF in Patients Enrolled in HF Studies



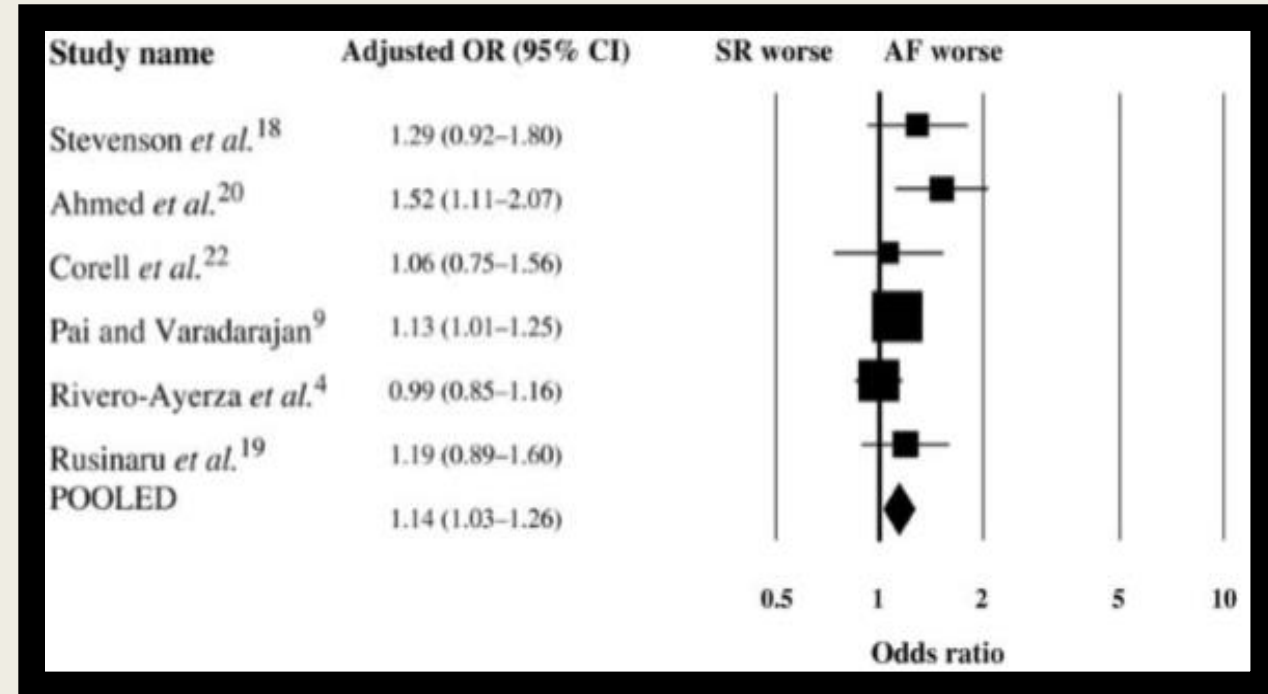
The bars represent percentages of patients with HF who had concomitant AF at enrollment in 10 clinical trials

# AF in HFrEF: a risk marker or a risk factor?

## Mortality outcomes in randomized trials



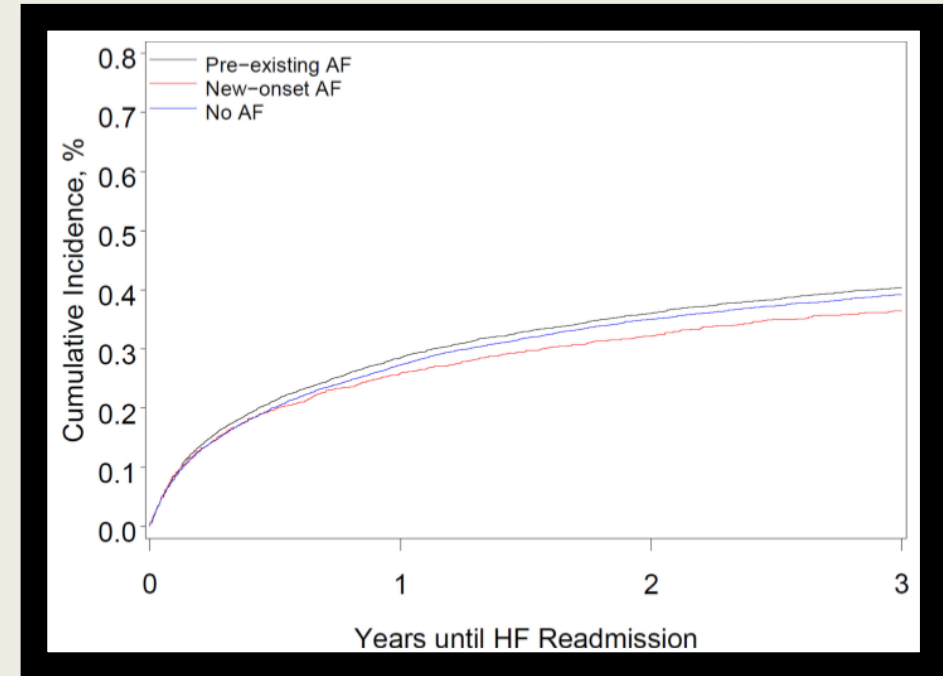
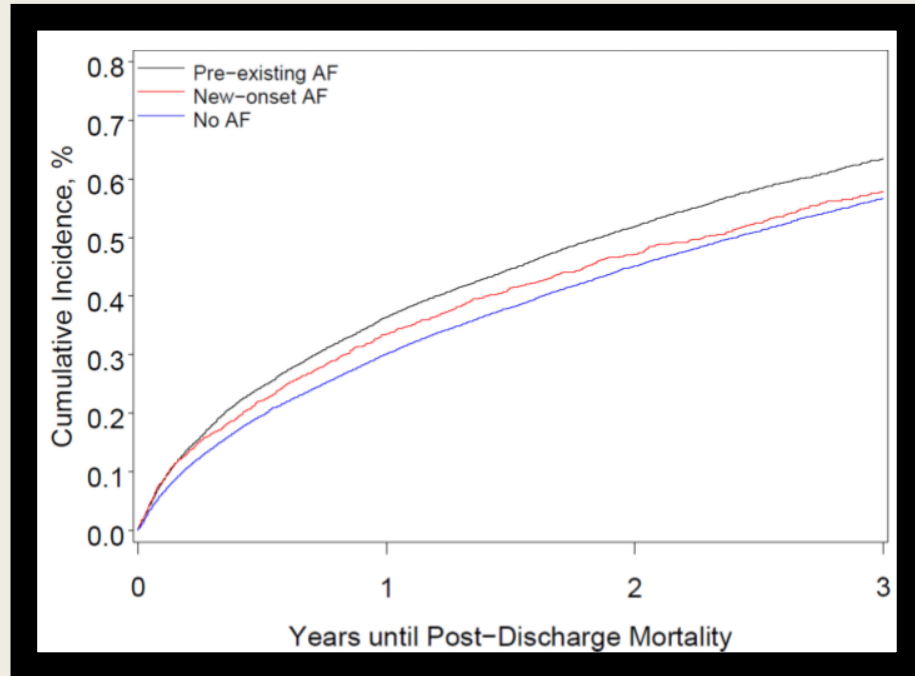
## Mortality outcomes observational trials



Meta-analysis of 16 studies involving 53 969 patients

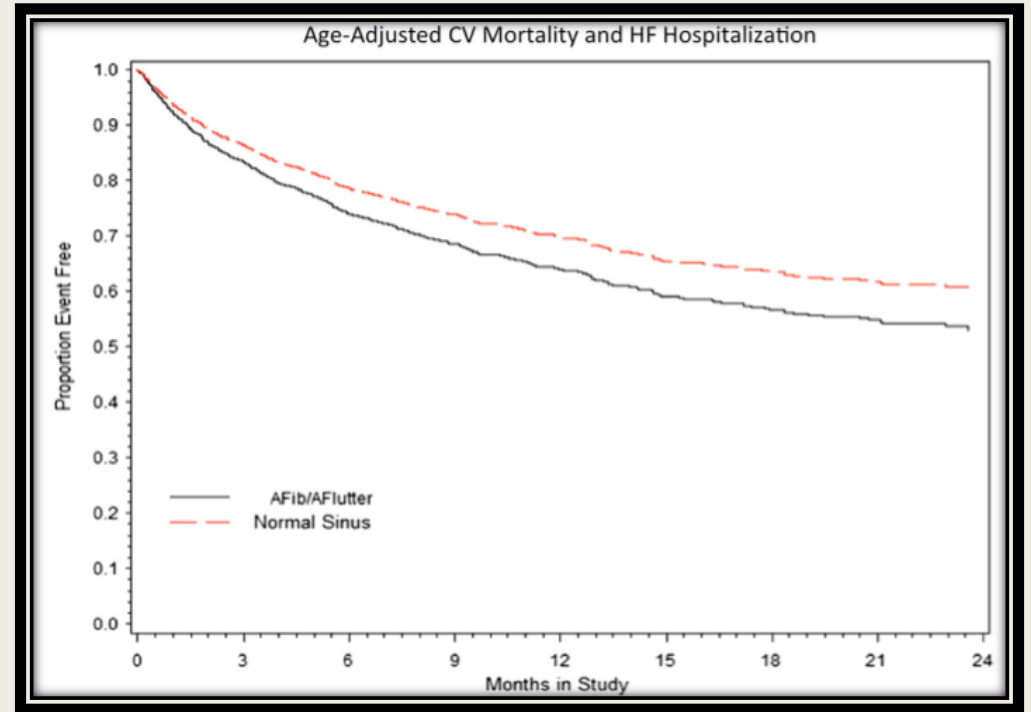
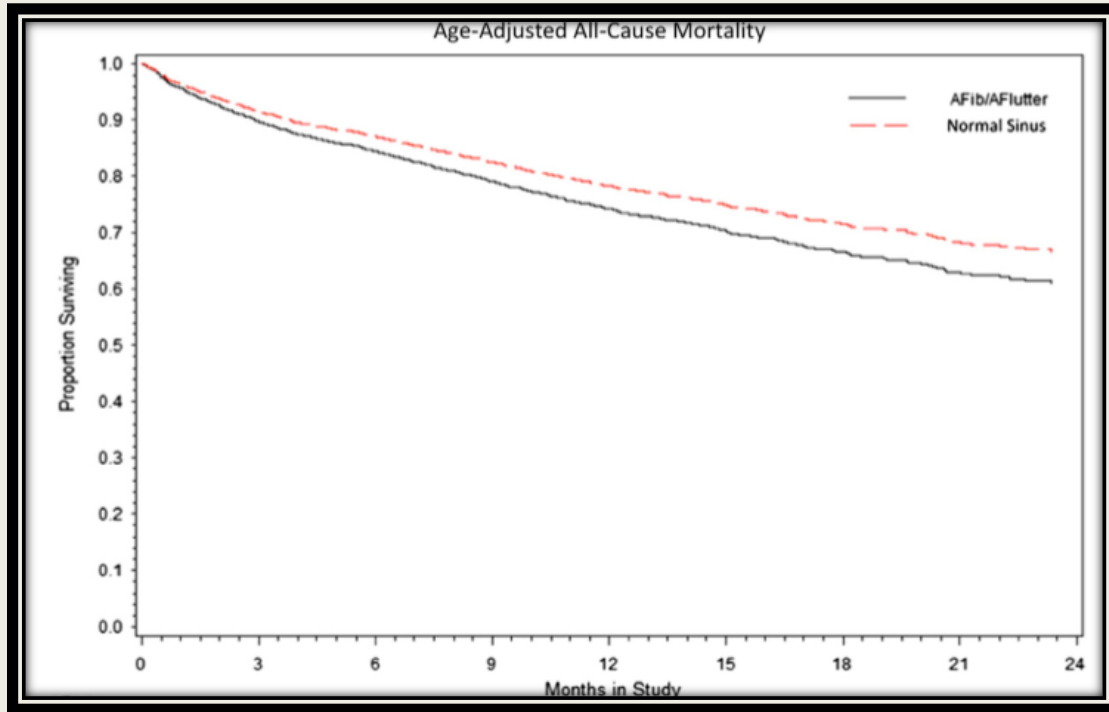
In conclusion, our current meta-analysis of 16 studies, and incorporating 53 969 CHF patients, demonstrates that **the presence of AF is associated with an adverse effect on mortality**, and that this effect is present **in both CHF patients with preserved and impaired LV systolic function**.

# Outcomes of Medicare Beneficiaries With HFrEF and AF



- **Both preexisting and new-onset atrial fibrillation were associated with greater long-term mortality among patients with heart failure.** Preexisting atrial fibrillation was associated with greater risk of readmission

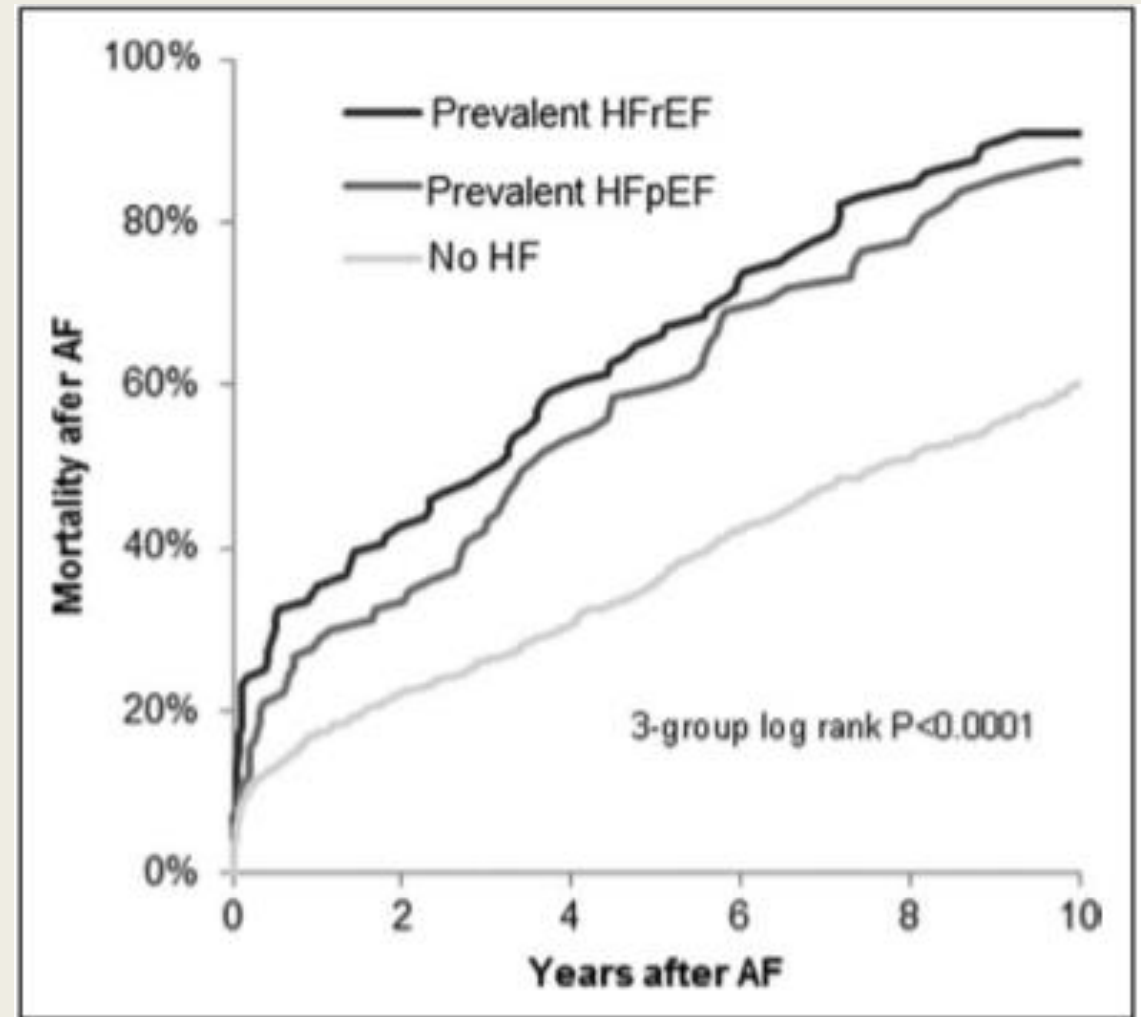
# Atrial Fibrillation on Initial ECG in Decompensated HFrEF



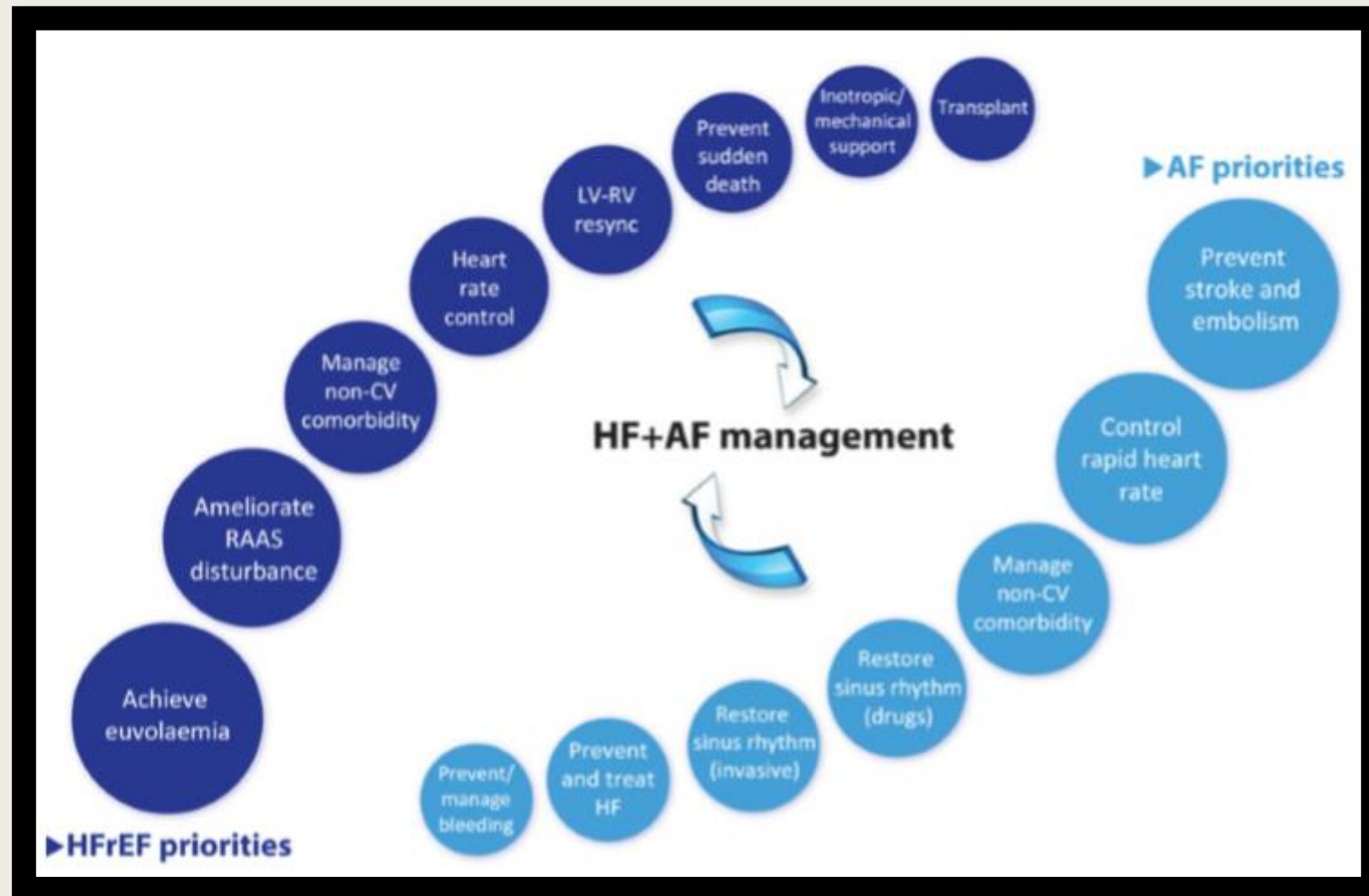
AF/AFL on initial ECG in patients hospitalized with HF with reduced ejection fraction is associated with lower use of evidence-based therapies and increased mortality and rehospitalization compared to patients in SR.

# Incidence of all-cause mortality of **new-onset** AF stratified by heart failure status

- ❖ Among 1737 individuals with **new AF**, 37% had HF. Patients with prevalent HFrEF and incident AF incurred a hazard ratio for all-cause mortality of 2.72, higher than those with HFpEF and those without HF

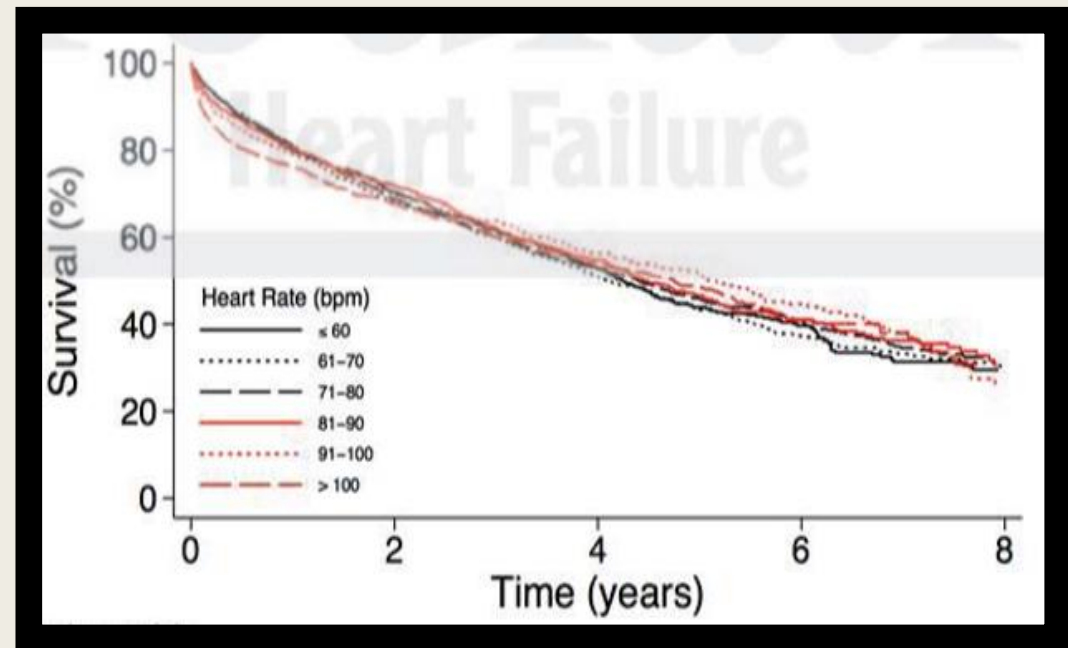
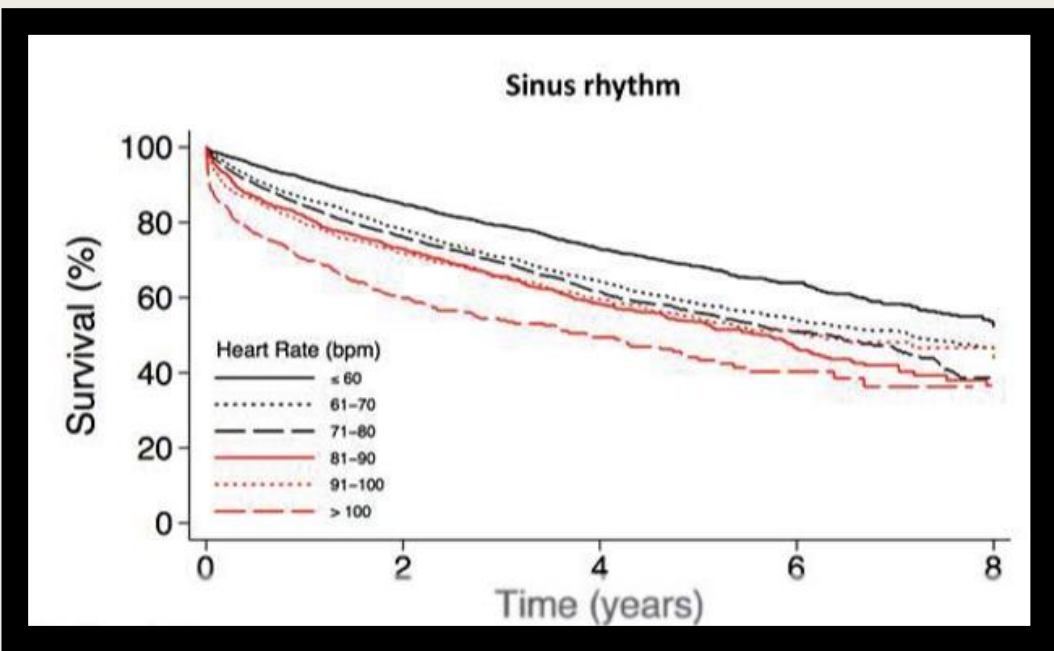


# Major priorities of management in patients with HFrEF and those with AF

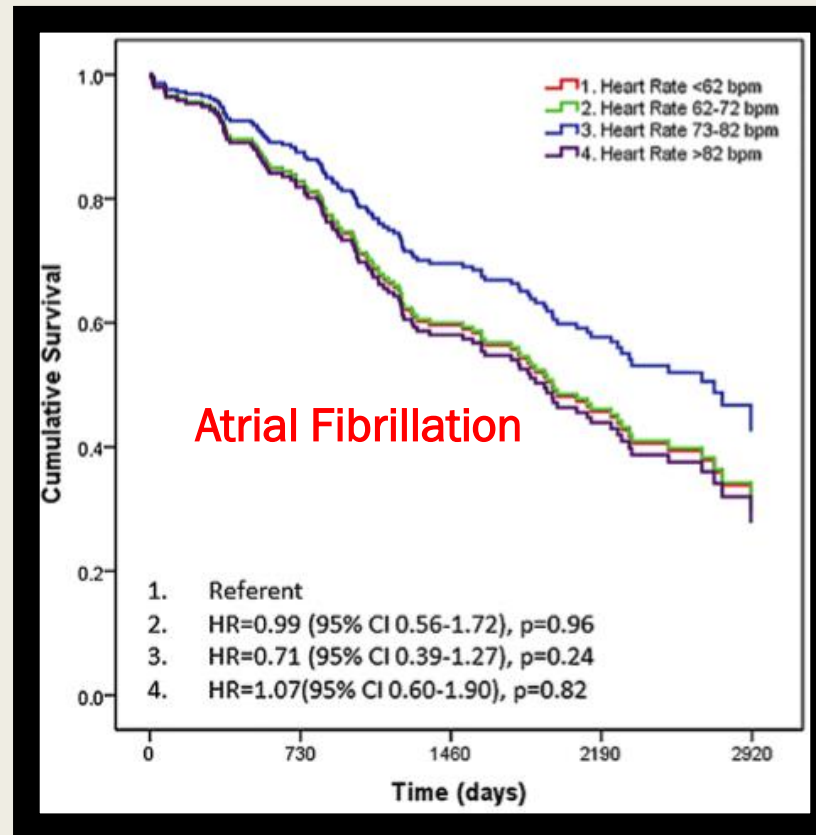


# Prognostic role of AF heart rate in HFrEF

- By access to Swedish Heart Failure registry patients with HFrEF (n=18 858) were divided into **sinus rhythm** (SR) (n=11 466) or **AF** (n=7392).
- The endpoint was all-cause mortality
- In patients with HFrEF, **a higher HR** was associated with increased mortality in SR, and in AF only if > 100 bpm.
- In beta-blocker use in SR, hazard ratio gradually increased with HR increment whereas in AF hazard ratio was significantly increased only in HR > 100 bpm (1.29, p = 0.003) compared to HR ≤ 60 bpm



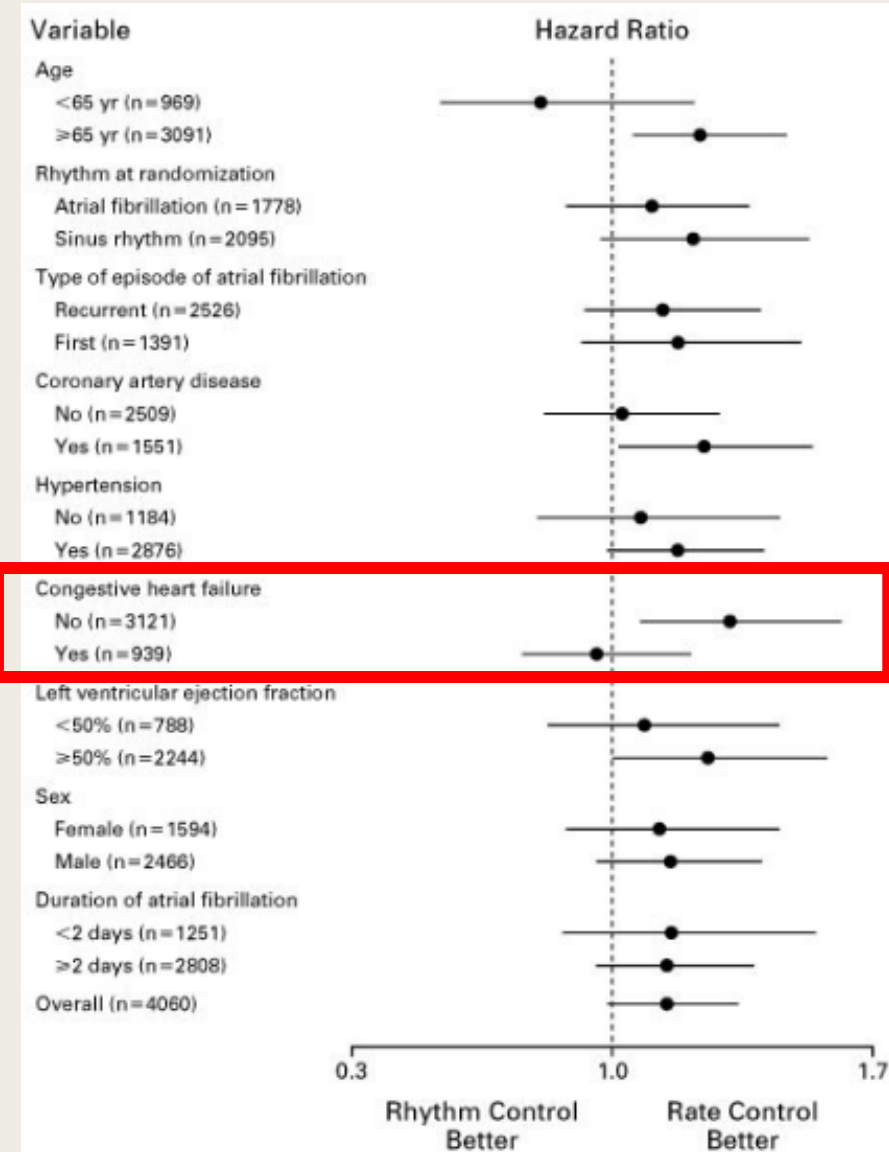
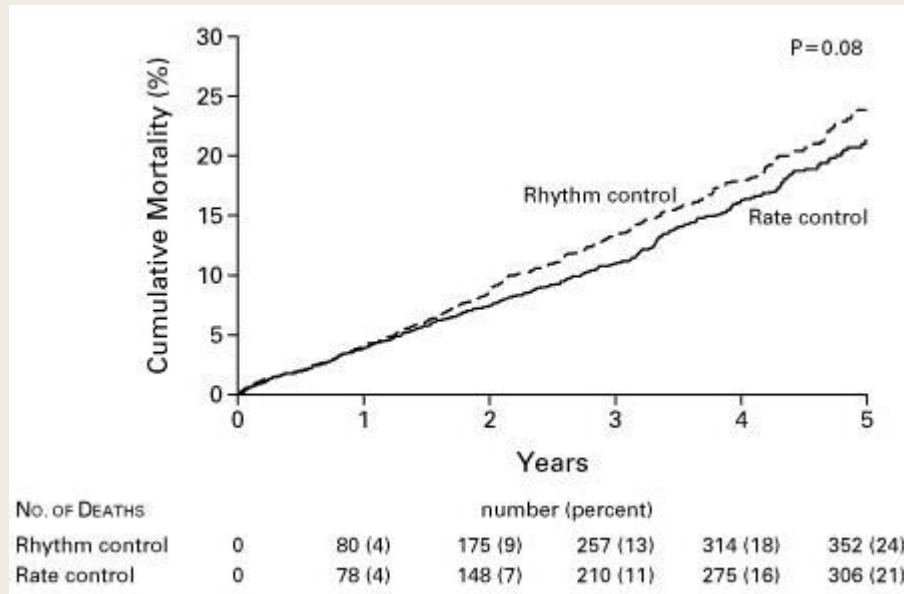
# What is the optimal heart rate in HFrEF patients with AF?



In patients with CHF and a reduced LVEF, slower resting ventricular rate is associated with better survival for patients in SR but not for those with AF.

# AF in HF: Rate or Rhythm Control?

Cumulative Mortality from Any Cause in the Rhythm-Control Group and the Rate-Control Group.

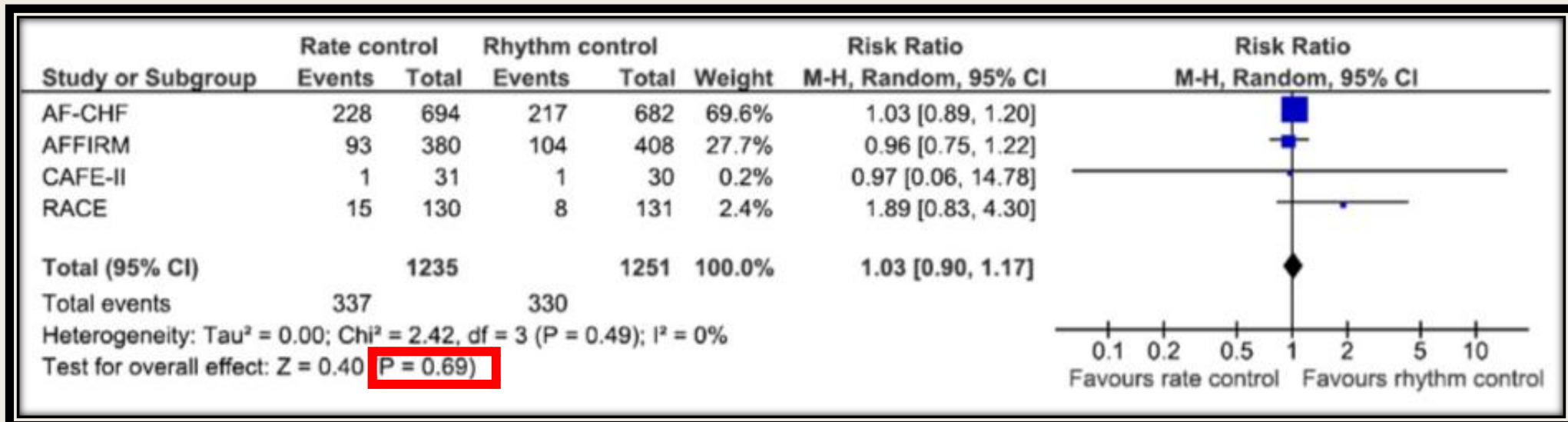


# Meta-analysis: Rate Control Vs Rhythm Control in patients with AF and Heart Failure

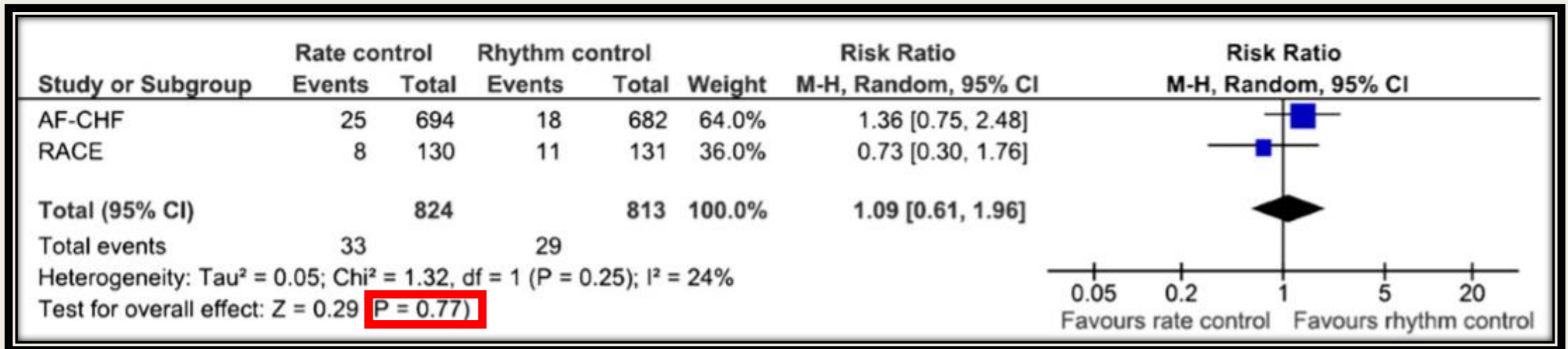
- ❖ Four RCTs with a total of 2486 patients with atrial fibrillation and heart failure were identified.

Trials	RACE [20,23]	AFFIRM [21,24]	AF-CHF [18]	CAFE-II [22]
AF population	Recurrent persistent AF or flutter for less than 1 year	Likely to be recurrent AF in pts older than 65 years old with risk factors for stroke or death	Paroxysmal or persistent AF less than 1 year	Persistent AF
Heart failure	NYHA II-III	LVEF less than 50%	LVEF equal or less than 35% and NYHA II-IV	NYHA II-III
No. pts	261	788	1376	61
Age	69 (mean)	71% >65 years	67 (mean)	72 ± 7
Male	65%	75%	82%	84%
Anticoagulation	Acenocoumarol or fenprocoumon 4 weeks before and after electrical cardioversion. Rate arm anticoagulated if more than 65 year-old or cardiac disease.	Both arms anticoagulated, if after 4-12 weeks with antiarrhythmic agents sinus rhythm is restored, anticoagulation could be stopped	Recommended for all pts: ACC/AHA/ESC 2006 AF guidelines	Recommended <sup>a</sup> for all pts: warfarin (INR 2-3)
Rate intervention	Digitalis, non-dihydropyridine calcium-channel blocker and beta-blocker	Beta-blocker, non-dihydropyridine calcium-channel blocker and digoxin.	Beta-blocker and digoxin. AV nodal ablation and pacemaker (if refractory)	Digoxin and beta-blocker
Rhythm intervention	Electrical cardioversion and sotalol, flecainide, propafenone or amiodarone	Many antiarrhythmic agents and/or electrical cardioversion	Electrical cardioversion and amiodarone (or sotalol or dofetilide)	Amiodarone and electrical cardioversion
Years follow-up	2.3 ± 0.6	3.5 (mean)	3.1 ± 1.6	1.2 (median)
Primary outcome	Composite of cardiovascular death, heart failure, embolism, bleeding, pacemaker implantation, severe adverse effects of drugs	All-cause mortality	Cardiovascular death	QoL SF-36vII at 1 year
Conclusions in HF subset	In patients with mild to moderate CHF, rate control is not inferior to rhythm control. However, if sinus rhythm can be maintained, outcome may be improved.	There was no significant improvement in mortality, hospitalisation, and NYHA class with the strategy of rhythm control in mild, moderate or severe ejection left ventricular dysfunction.	Primary outcome was not different in both interventions. Hospitalizations were more frequent in rhythm control.	Rhythm control improved the primary outcome, LV function and NT-proBNP. NYHA and 6MWT were similar in both interventions.
PEDro score	7	6	6	7

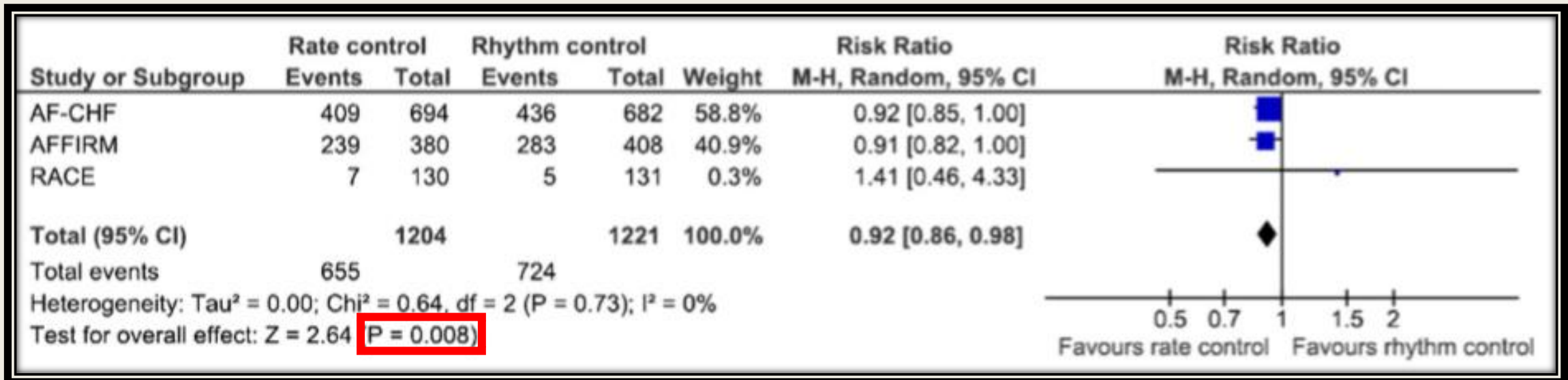
# Forest plot comparing **rate** and **rhythm** control for **total mortality** in patients with AF and HF



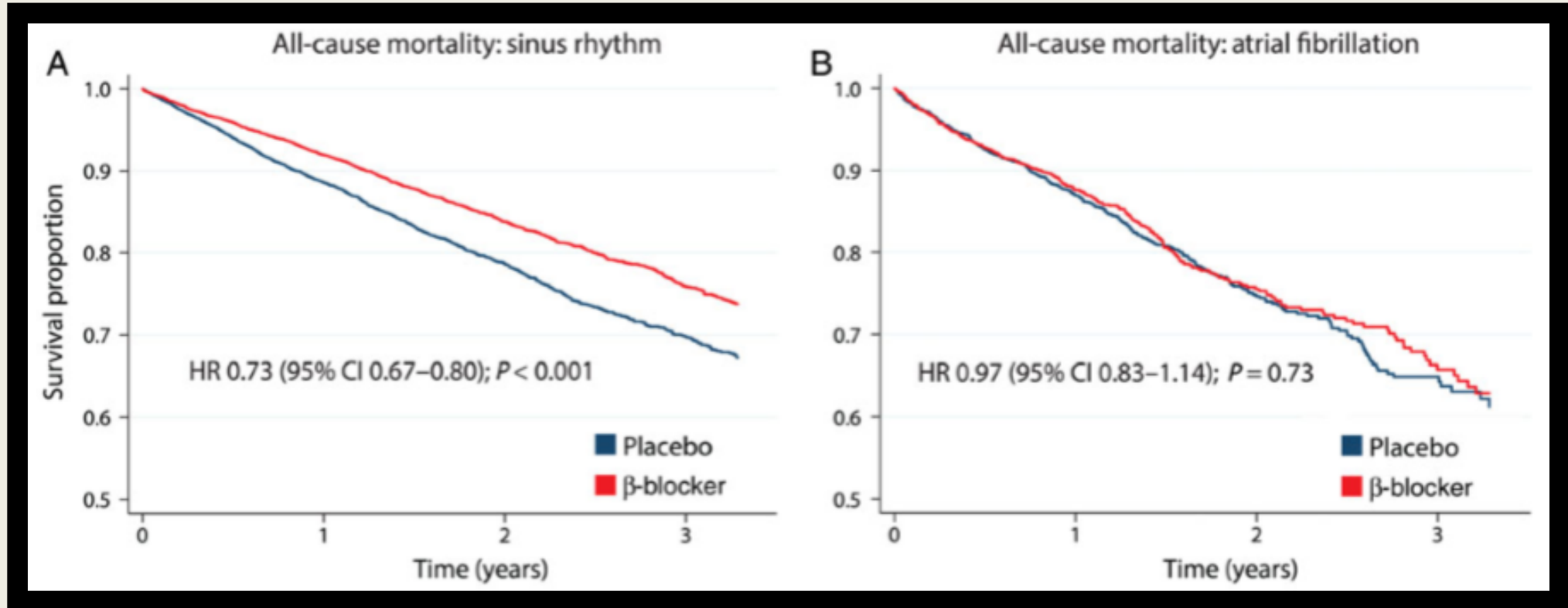
# Forest plot comparing **rate** and **rhythm** control for **stroke/thromboembolic events** in patients with AF and HF



# Forest plot comparing **rate** and **rhythm** control for **hospitalizations** in patients with AF and HF.



# **b-Blockers** in HFrEF with sinus rhythm and atrial fibrillation.



Hence clinicians should **not expect a prognostic benefit from b-blockers in HFrEF patients with concomitant AF**; however, there was no apparent harm and patients may have other indications, such as symptom or heart rate control.

# How to Use Beta-Blockers in HFrEF and Atrial Fibrillation?

**TABLE 1** Main Studies Assessing the Effect of BB Therapy on Mortality in HFrEF Patients

First Author, Year (Ref. #)	Study Type	No. of Patients	AF	Beta-Blocker Effect in SR	Beta-Blocker Effect in AF	Interaction p Value
Rienstra et al., 2013 (9)	Meta-analysis	8,680	1,677 (19)	<b>0.63 (0.54-0.73)</b>	0.86 (0.66-1.13)	0.048
Kotecha et al., 2014 (3)	Meta-analysis	18,254	3,066 (17)	<b>0.73 (0.67-0.80)</b>	0.97 (0.83-1.14)	0.002
Li et al., 2015 (10)	HF registry	18,858	7,392 (39)	<b>0.77 (0.63-0.94)</b>	<b>0.71 (0.61-0.84)</b>	0.637
Nielsen et al., 2016 (12)	AF registry, PS matching	39,741	39,741 (100)	–	<b>0.75 (0.71-0.79)</b>	–
Cadrin-Tourigny et al., 2017 (11)	RCT subanalysis, PS matching	1,376	1,376 (100)	–	<b>0.72 (0.55-0.95)</b>	–

Values are n, n (%), or hazard ratios (95% confidence intervals). **Bold** indicates statistically significant result.

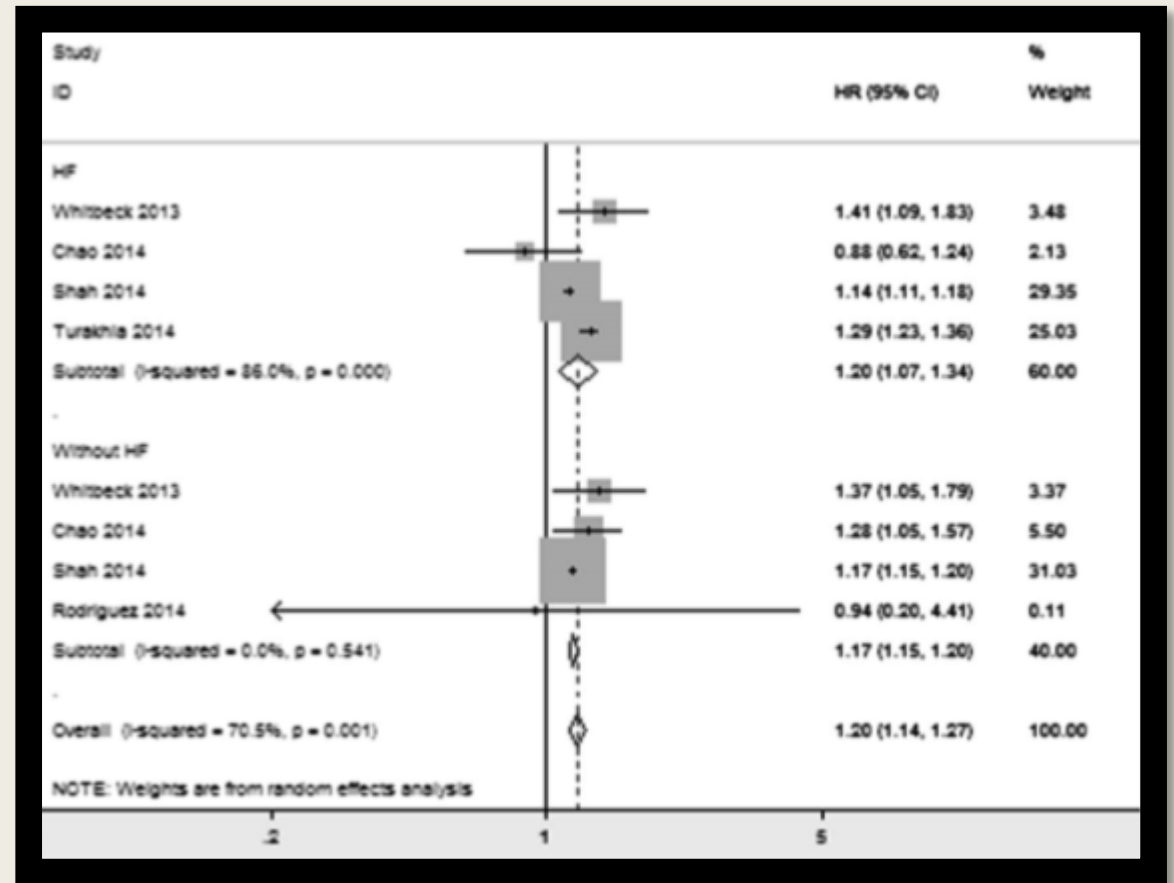
AF = atrial fibrillation; BB = beta-blockers; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; PS = propensity score; RCT = randomized controlled trial; SR = sinus rhythm.

The 2 meta-analyses of RCT showed no benefit of BB use, but both registries and the secondary RCT analysis showed a risk reduction for all-cause mortality, by BB in patients with HFrEF and AF, ranging between 25% and 29%.



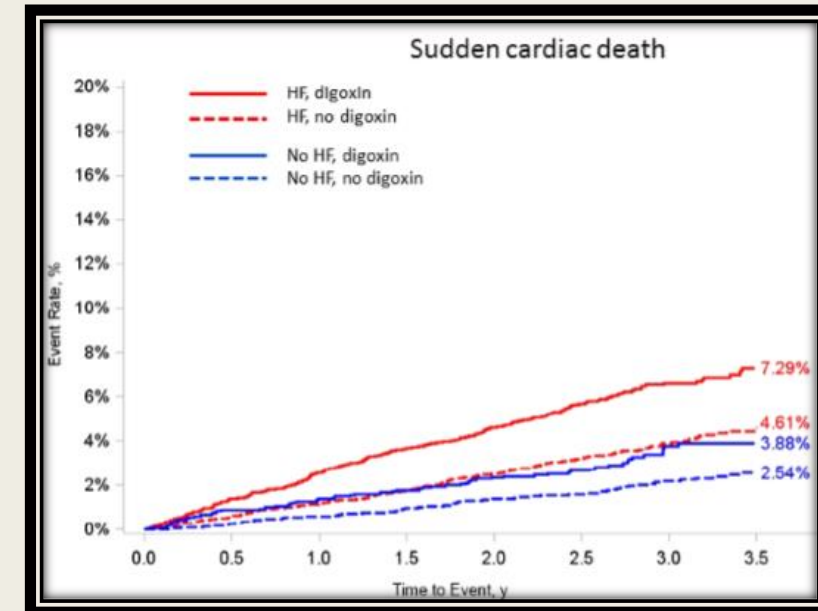
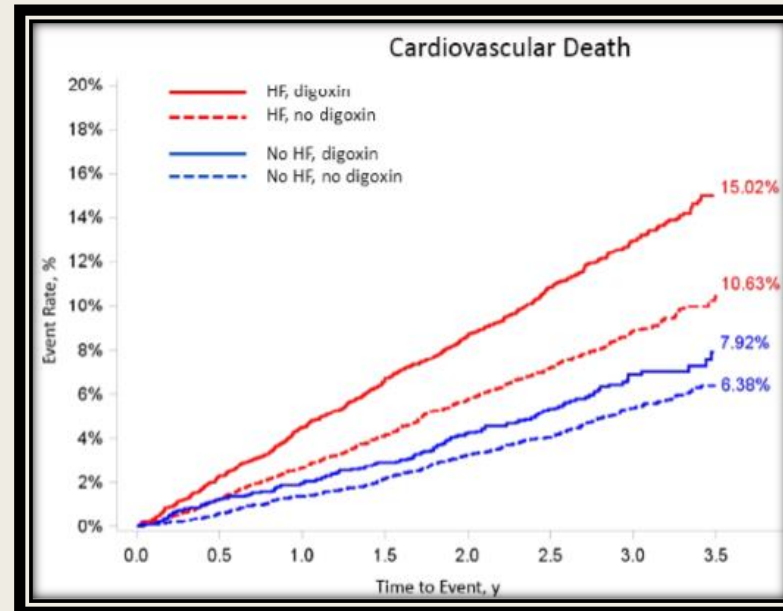
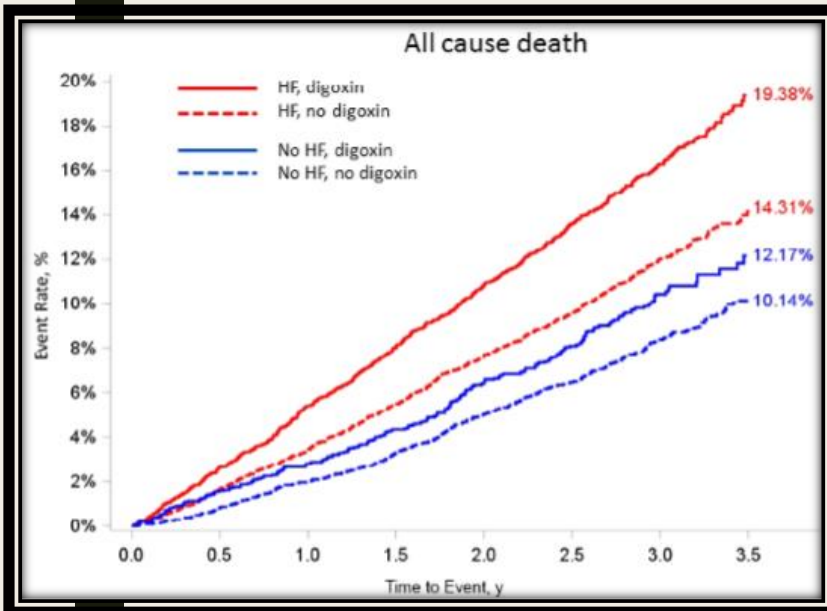
# Digoxin Is Associated With Increased All-cause Mortality in Patients With AF Regardless of Concomitant HF

- ❖ A meta-analysis of 8 carefully selected studies with 302,738 patients,
- ❖ Digoxin use was associated with increased risk of all-cause mortality in AF overall.



- ❖ Subgroup analysis further revealed that **digoxin was associated with increased all-cause mortality in patients with AF, which was complicated by HF, and in those subjects without HF.**

# Digoxin Use and Subsequent Clinical Outcomes in Patients With AF With or Without HFrEF ENGAGE AF-TIMI 48 Trial

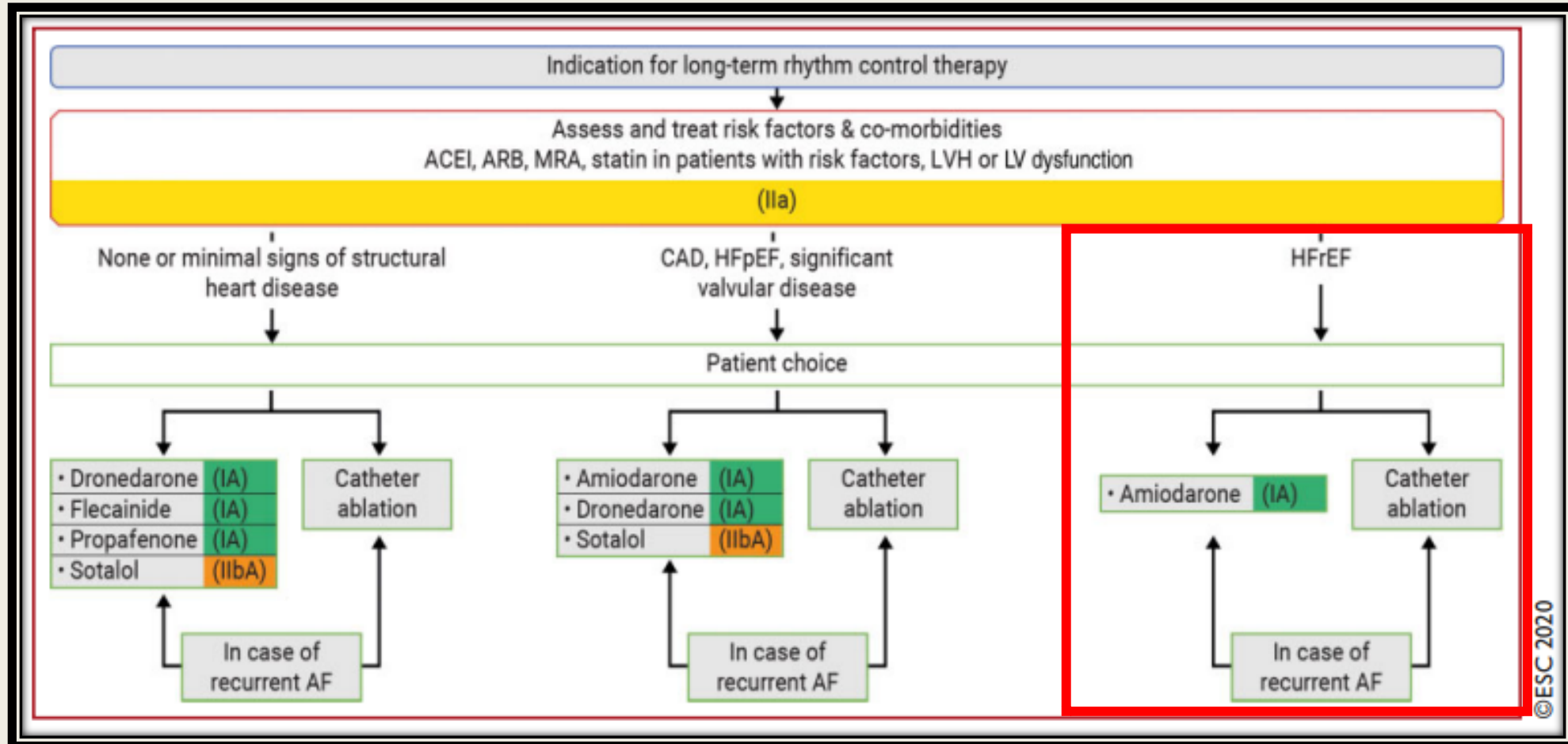


In this observational analysis of patients with atrial fibrillation with or without HF, **digoxin use was significantly associated with sudden cardiac death**. The association between digoxin use and worse clinical outcomes highlights the need to examine digoxin use, particularly when prescribed to control heart rate in patients with atrial fibrillation in a randomized trial.

# Recommendations for AF Rhythm Control in HF/ Antiarrhythmics in HF

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Ref <sup>c</sup>
Electrical cardioversion or pharmacological cardioversion with amiodarone may be considered in patients with persisting symptoms and/or signs of HF, despite OMT and adequate control of ventricular rate, to improve clinical/symptomatic status.	IIb	B	344
Amiodarone may be considered prior to (and following) successful electrical cardioversion to maintain sinus rhythm.	IIb	B	342, 360
Dronedarone is not recommended because of an increased risk of hospital admissions for cardiovascular causes and an increased risk of premature death in NYHA Class III–IV patients.	III	A	247, 347
Class I antiarrhythmic agents are not recommended because of an increased risk of premature death.	III	A	248, 364, 365

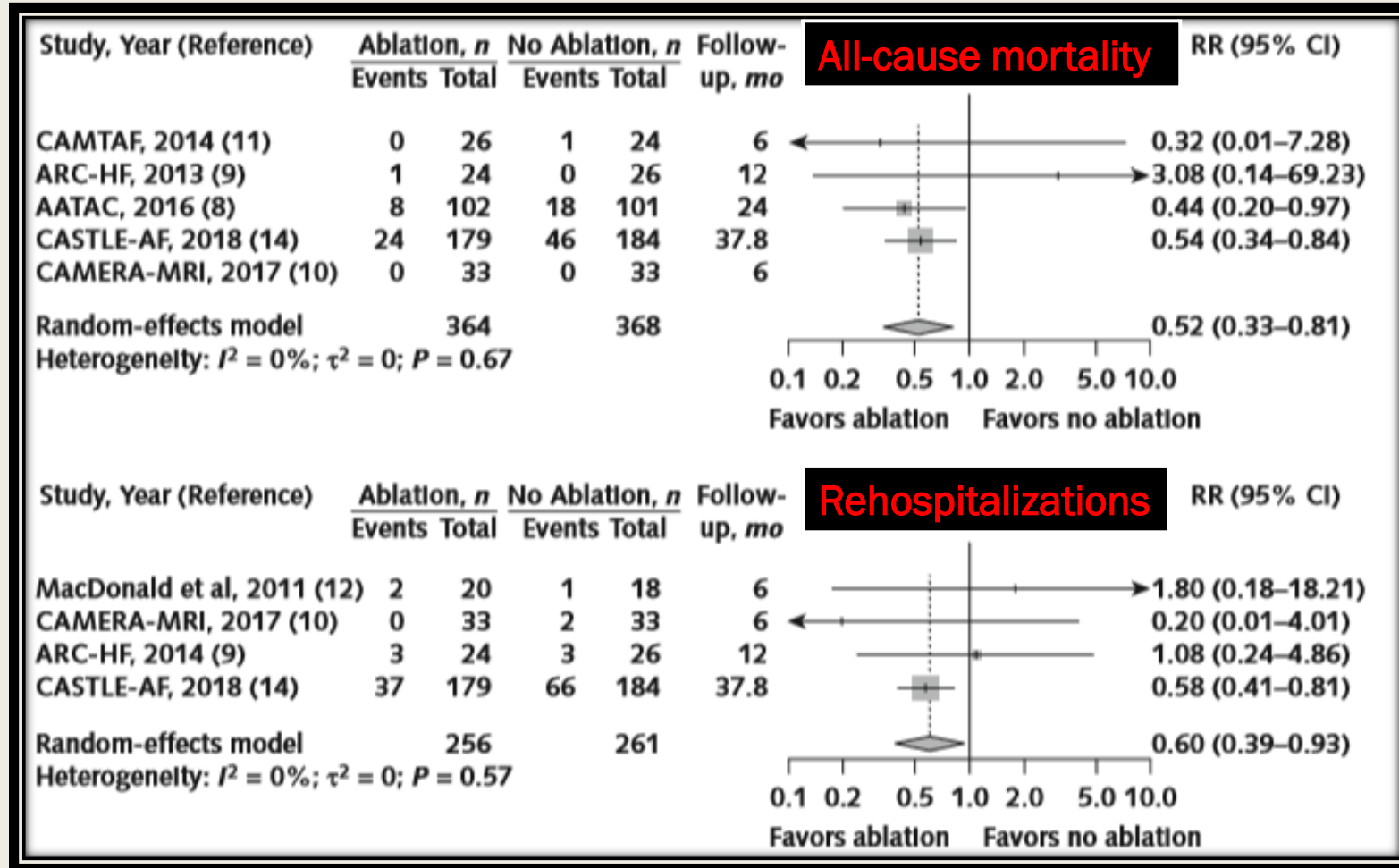
# Indication for long-term rhythm control therapy



# Randomized controlled trials of **catheter ablation for AF** in patients with **CHF**

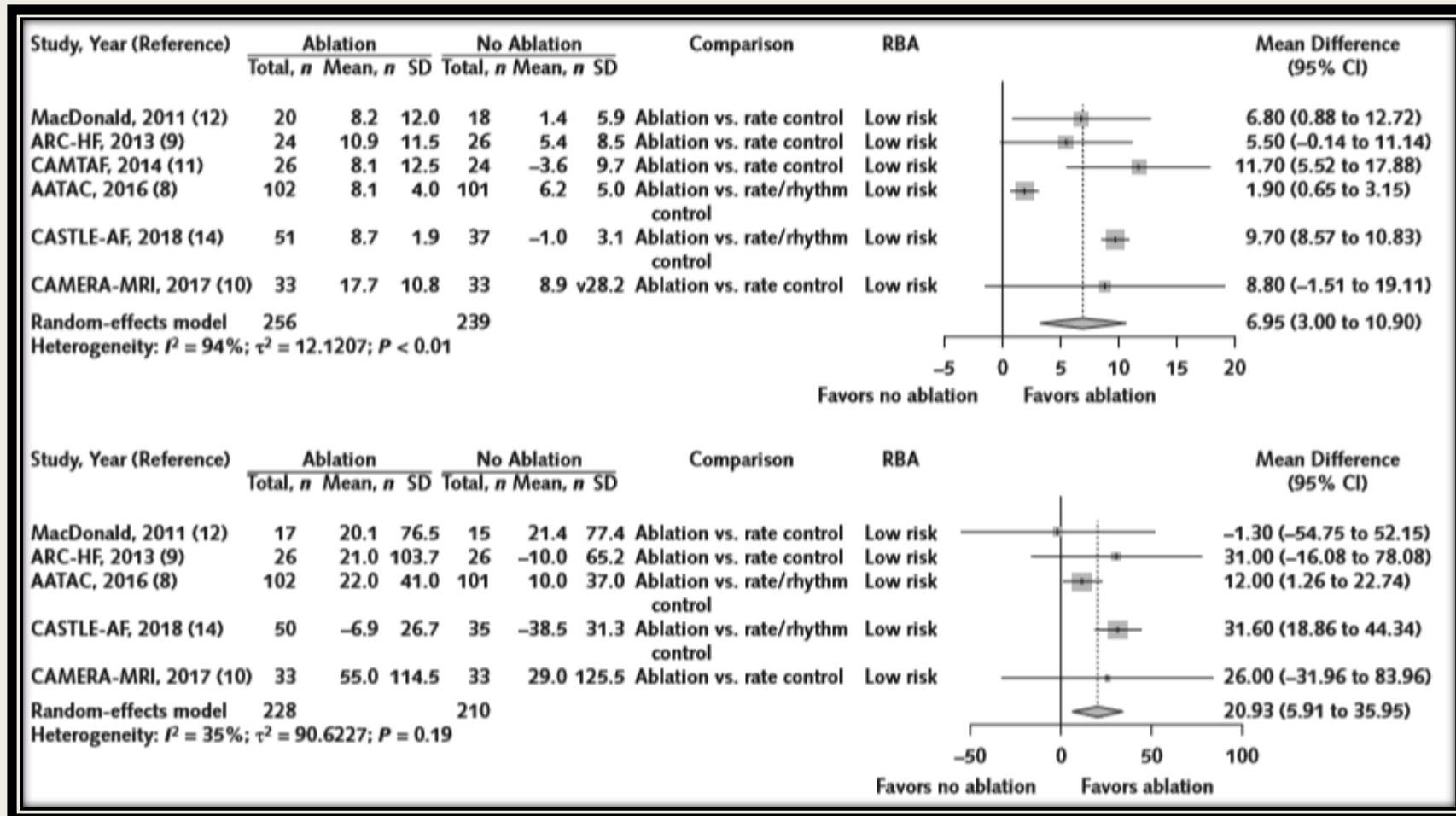
	Entry criteria	Study design
<b>Short-term trials with rate control as the comparator</b>		
MacDonald <sup>5</sup> (2011)	<i>n</i> = 41, NYHA class II–III, LVEF ≤ 35%, most had long-standing AF, N-terminal proBNP ≈ 2200 pg/mL	Unblinded ablation vs. rate control, follow-up 6 months
ARC-HF <sup>6</sup> (2013)	<i>n</i> = 52, NYHA class II–III, LVEF ≤ 35%, most had long-standing AF, mean BNP ≈ 350 pg/mL	Unblinded ablation vs. rate control, follow-up 12 months
CAMTAF <sup>7</sup> (2014)	<i>n</i> = 55, NYHA class II–III, LVEF ≤ 35%, most had long-standing AF, mean BNP ≈ 500 pg/mL	Unblinded ablation vs. rate control, follow-up 6 months
CAMERA-MRI <sup>8</sup> (2017)	<i>n</i> = 66, LVEF < 45%, preserved exercise tolerance, most had long-standing AF, mean BNP ≈ 260 pg/m	Unblinded ablation vs. rate control, follow-up 6 months
<b>Long-term trials with rhythm control (amiodarone) as the comparator</b>		
AATAC <sup>9</sup> (2016)	<i>n</i> = 203, NYHA class II–III, LVEF ≤ 40%, mean AF duration < 1 year	Unblinded ablation vs. amiodarone, follow-up 24 months
CASTLE-AF <sup>10</sup> (2018)	<i>n</i> = 397, NYHA class II–III, LVEF ≤ 35%, long-standing AF in 30%	Unblinded ablation vs. amiodarone or other membrane-active antiarrhythmic drugs follow-up 38 months

# Catheter Ablation of AF in Patients With Heart Failure A Meta-analysis of RCTs



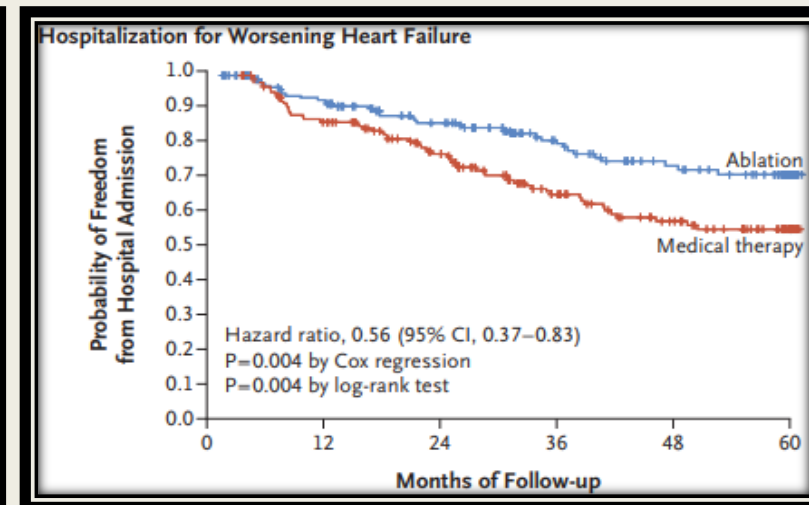
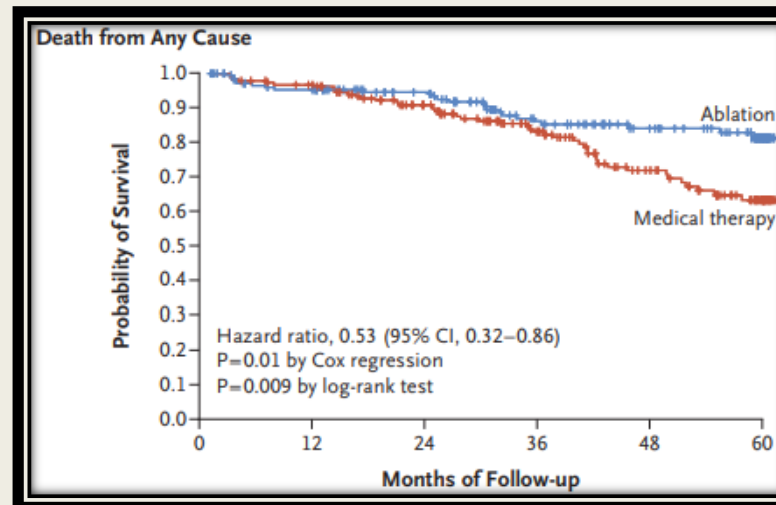
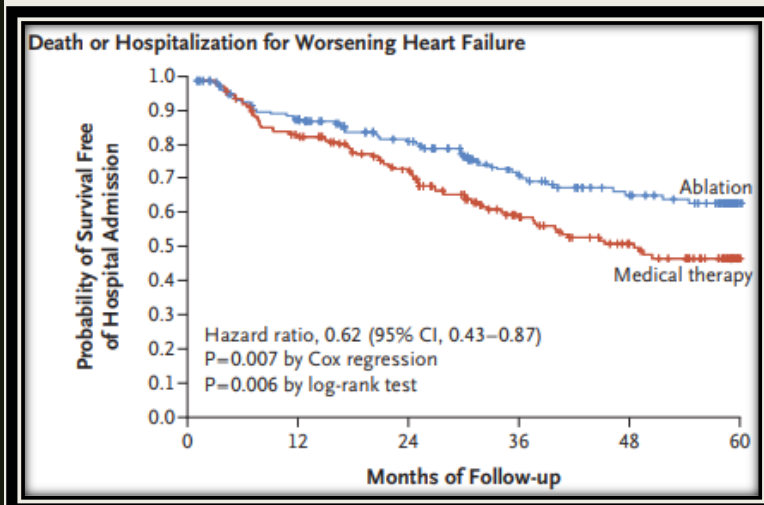
Forest plot of the decrease in all-cause mortality and HF hospitalization with catheter ablation compared with medical treatment for AF.

# Forest plot of the **improvement in LVEF** and **distance on the 6-minute walk test** with catheter ablation versus medical treatment.



# CASTLE-HF: Catheter Ablation for Atrial Fibrillation with Heart Failure

- Paroxysmal or persistent atrial fibrillation
- an absence of response to, side effects from, or unwillingness to take antiarrhythmic drugs
- NYHA class II, III, or IV
- LVEF < 35%
- All the patients had an ICD device or a CRT-D
- Recurrence was defined as any episode of atrial arrhythmia that lasted longer than 30 seconds



Furthermore, catheter ablation **reduced the burden of atrial fibrillation**, **increased the distance walked in 6 minutes**, and **improved the LVEF**.

# NOACs in Patients with AF and with or without Heart Failure

## Baseline Characteristics of 4 trials included in Meta-analysis

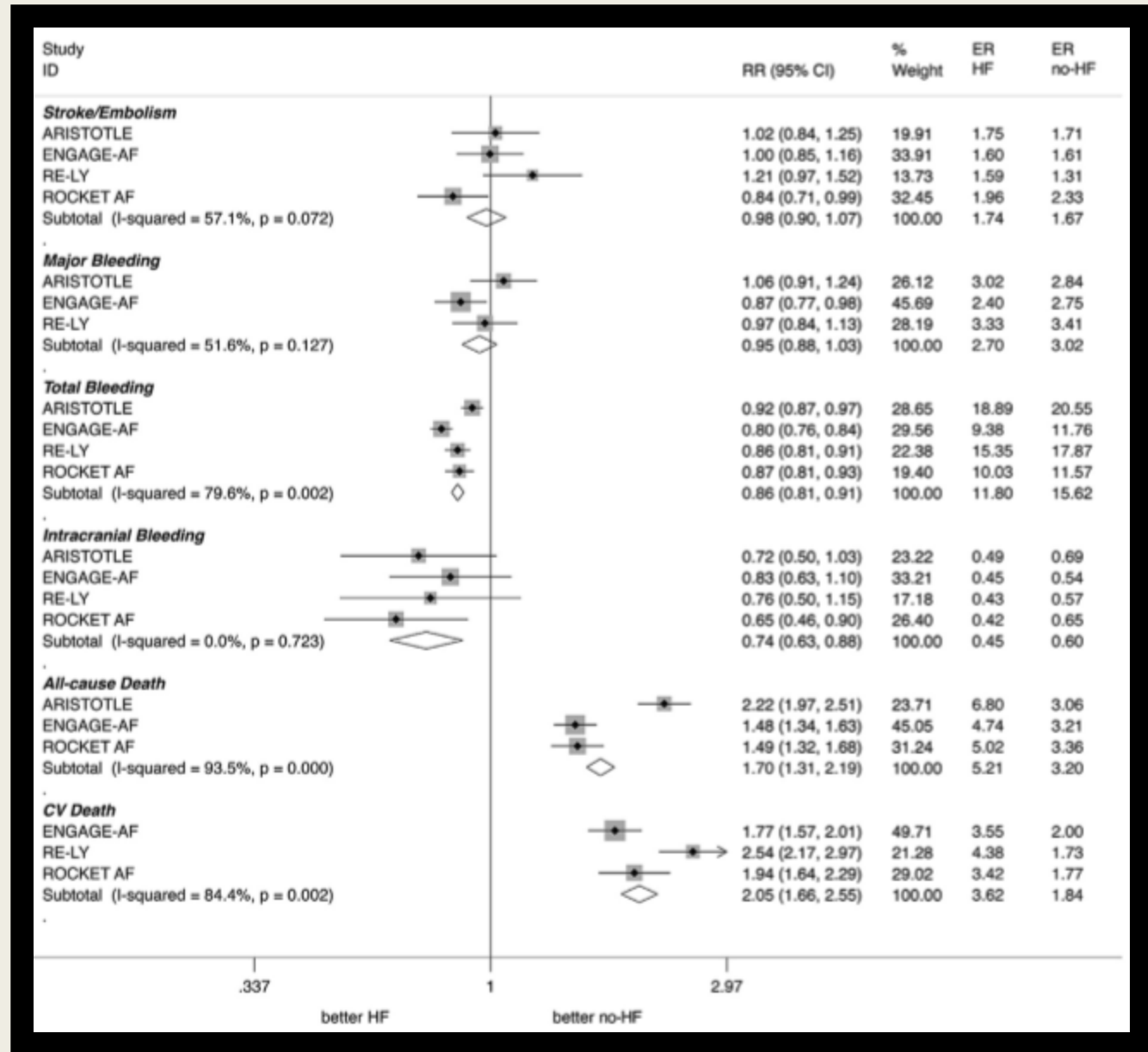
**TABLE 1** Baseline Characteristics of Trials Included in the Analysis

	ARISTOTLE		ENGAGE AF		RE-LY		ROCKET AF		TOTAL		HF vs. No HF
	HF	No HF	HF	No HF	HF	No HF	HF	No HF	HF	No HF	p Value
Year	2013		2015		2013		2013				
Treatment	Apixaban 5 mg twice daily		Edoxaban 60 mg once daily		Dabigatran 150 mg twice daily		Rivaroxaban 20 mg once daily				
FUP, yrs	1.5		2.8		2.0		1.94		NA		NA
Patients, %	5,943	8,728	8,145	5,926	3,263	8,835	9,033	5,138	26,384	28,627	NA
Females, %	33	35	38	38	34	39	39	40	36	38	<0.01
Age, yrs	69	71	70	75	68	73	72	74	70	73	0.03
CHADS <sub>2</sub>	2.46	1.88	3.00	2.60	2.65	2.00	3.70	3.15	2.95	2.41	0.22
Hypertension, %	83	90	94	93	75	80	93	86	86	87	<0.01
Diabetes, %	26	25	31	44	27	22	42	35	31	31	1.00
Prior MI/CAD, %	22	11	15	8	32	26	22	10	23	14	<0.01
NYHA functional classes I-II, %	57	NA	78	NA	NA	NA	69	NA	68	NA	NA
NYHA functional classes III-IV, %	23	NA	22	NA	NA	NA	31	NA	25	NA	NA
Aspirin, %	33	30	31	29	NA	NA	31	25	32	28	<0.01
Detsky quality score	100%		100%		95%		100%		100%		NA
Definition of HF	Symptomatic congestive HF within 3 months with reduced or preserved ejection fraction		Current presence or history of HF class C or D according to the AHA/ACC definition*		Presence of NYHA class II or higher HF symptoms within 6 months in patients with history of previous admission for HF		Left ventricular ejection <40%		NA	NA	NA

- A total of 55,011 patients were enrolled, 26,384 (48%) with HF, and 28,627 (52%) without HF.

# Outcome analysis in **HF** Vs **non-HF** subgroup

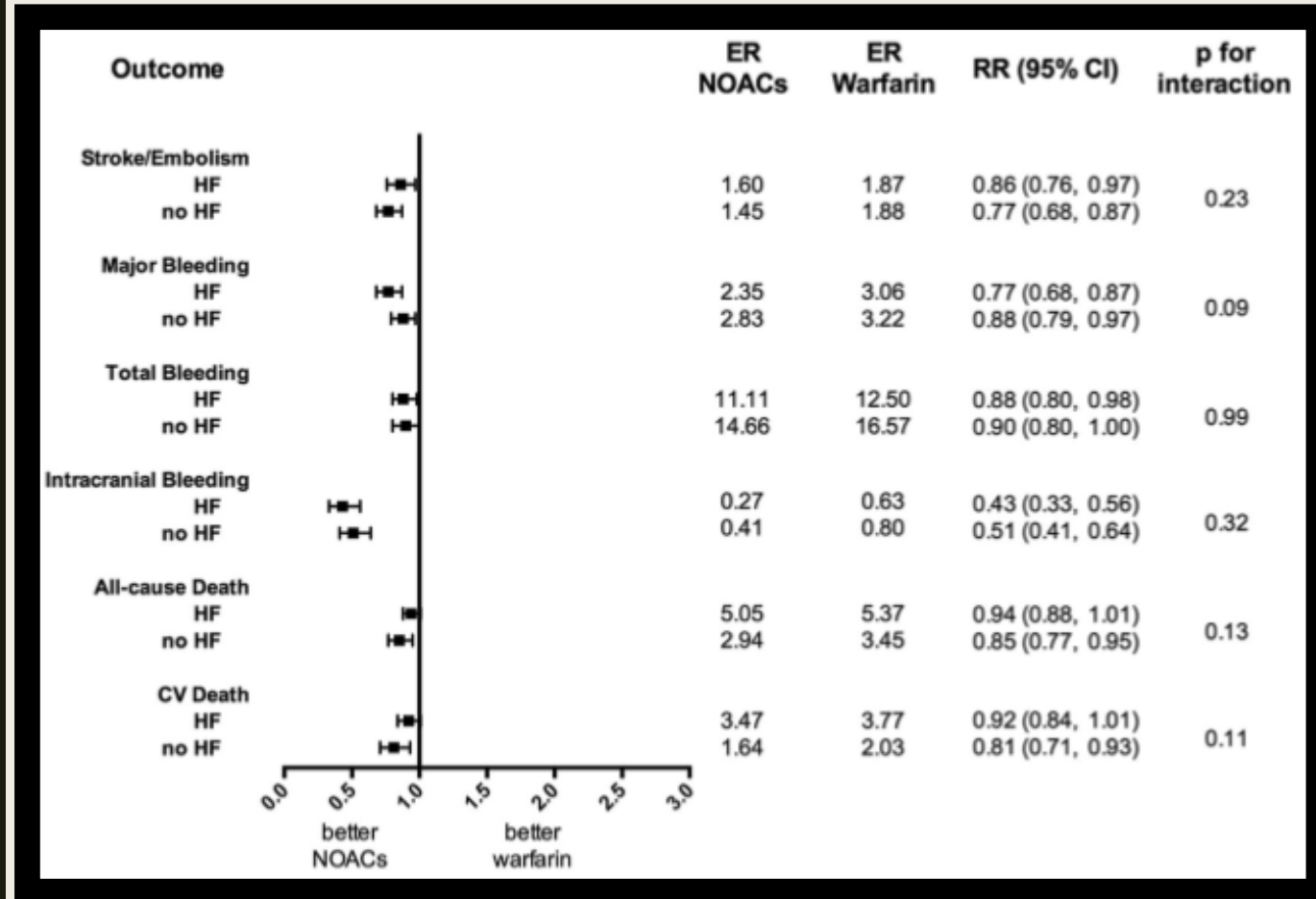
- ❑ Rates of Stroke/Systemic Embolism and major bleeding were comparable in patients with and without HF.
- ❑ HF patients had reduced rates of any and intracranial bleeding
- ❑ HF patients had increased rates of all-cause and CV death



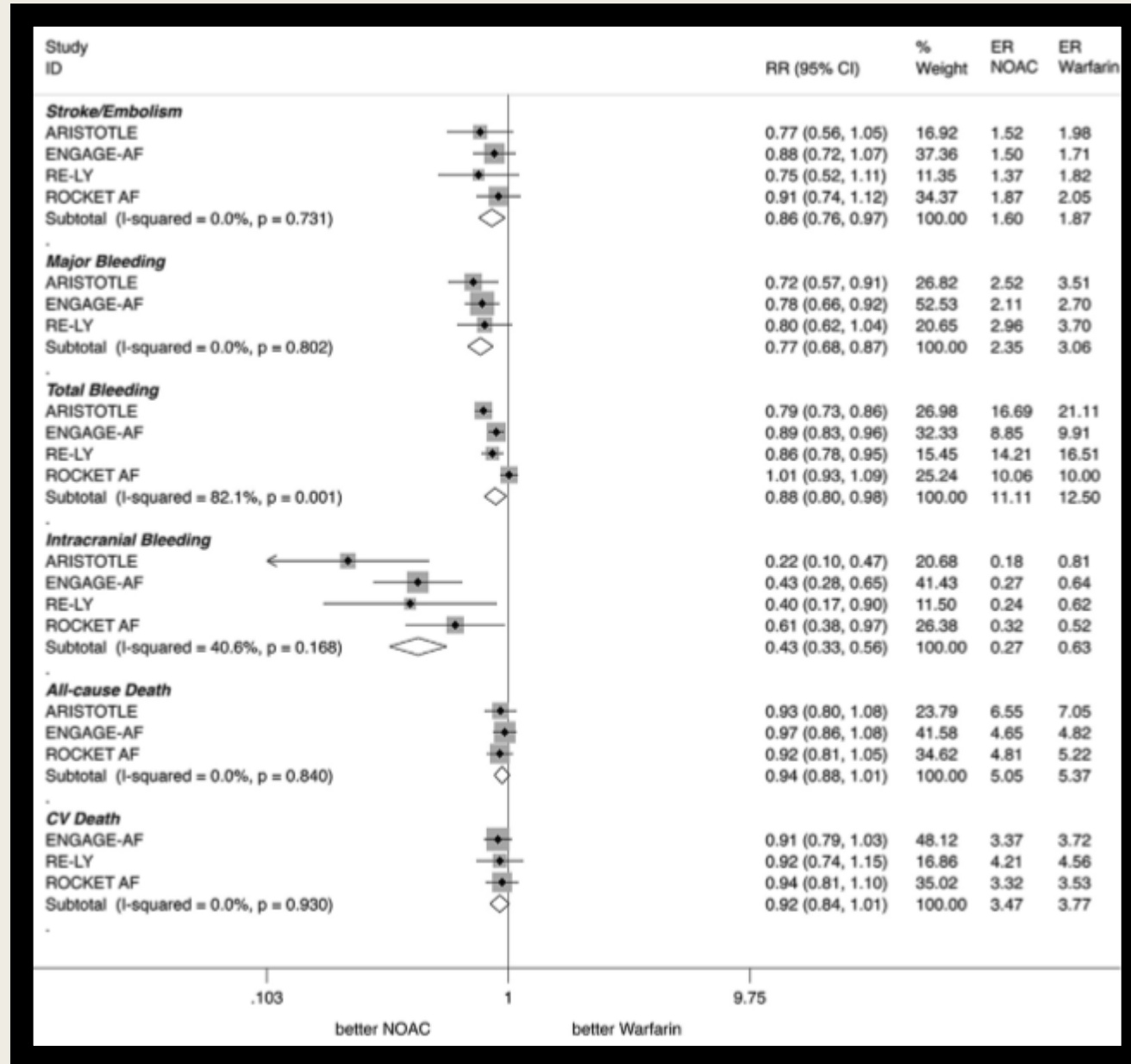
# Effects of NOACs in HF & no-HF subgroups

✓ NOACs, compared with warfarin significantly reduced SSE and major, intracranial, and any bleeding, regardless of the presence or absence of HF ( $p_{\text{interaction}} > 0.05$  for each).

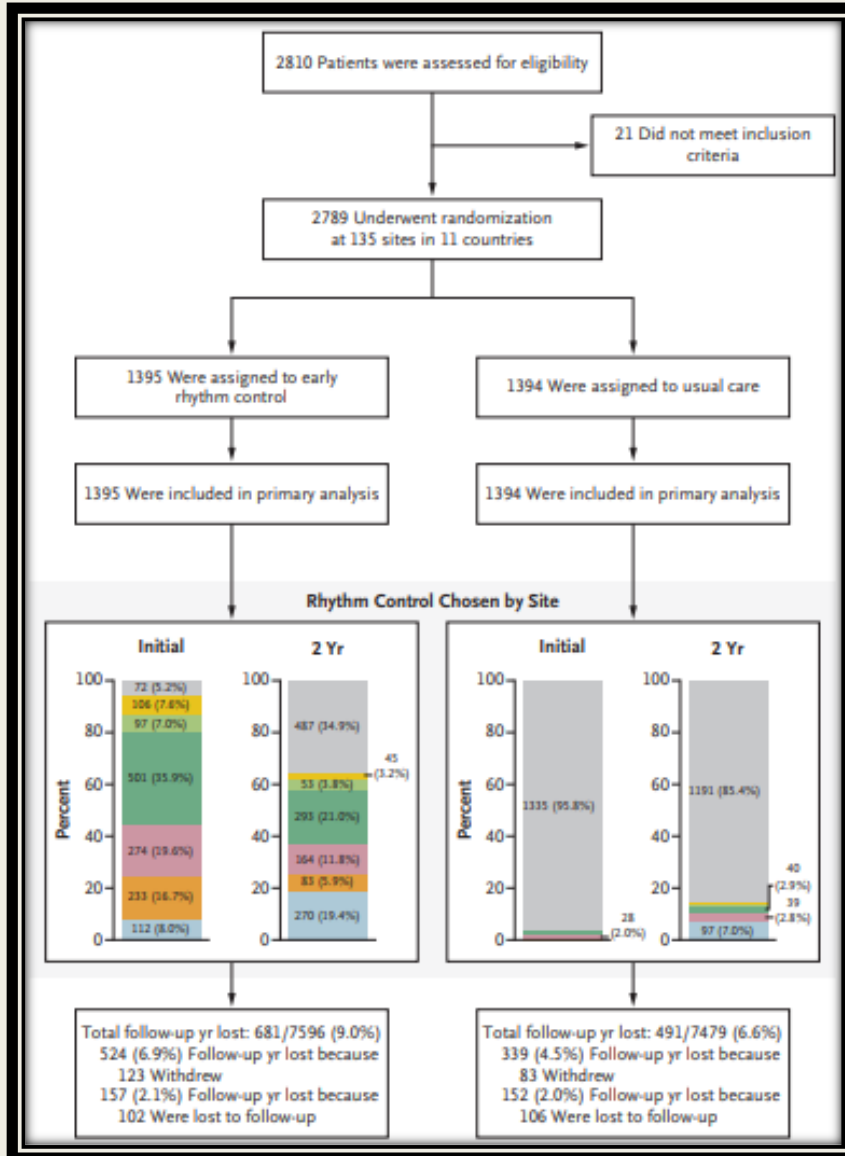
✓ No interactions in efficacy and safety of NOACs were observed between AF patients with and without HF



# Effects of NOACs in HF Group



# The Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST-AFNET 4)

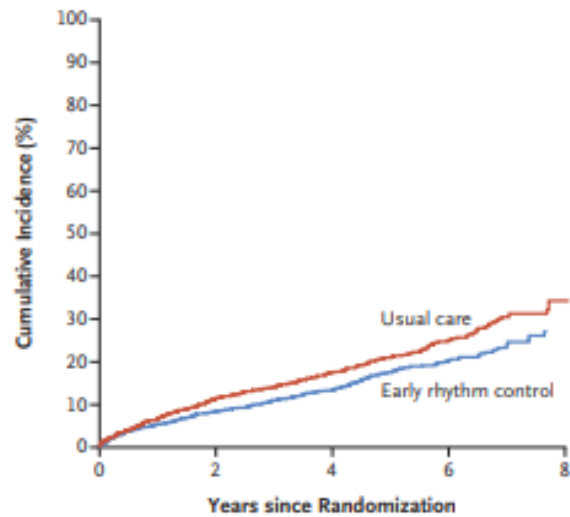


**Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.<sup>o</sup>**

Characteristic	Early Rhythm Control (N = 1395)	Usual Care (N = 1394)
Age — yr	70.2±8.4	70.4±8.2
Female sex — no. (%)	645 (46.2)	648 (46.5)
Body-mass index†	29.2±5.4	29.3±5.4
Type of atrial fibrillation — no./total no. (%)		
First episode	528/1391 (38.0)	520/1394 (37.3)
Paroxysmal	501/1391 (36.0)	493/1394 (35.4)
Persistent	362/1391 (26.0)	381/1394 (27.3)
Sinus rhythm at baseline — no./total no. (%)	762/1389 (54.9)	743/1393 (53.3)
Median days since atrial fibrillation diagnosis (IQR)‡	36.0 (6.0–114.0)	36.0 (6.0–112.0)
Absence of atrial fibrillation symptoms — no./total no. (%)§	395/1305 (30.3)	406/1328 (30.6)
Previous cardioversion — no./total no. (%)	546/1364 (40.0)	543/1389 (39.1)
<b>Concomitant cardiovascular conditions</b>		
Previous stroke or transient ischemic attack — no. (%)	175 (12.5)	153 (11.0)
At least mild cognitive impairment — no./total no. (%)¶	582/1326 (43.9)	584/1341 (43.5)
Arterial hypertension — no. (%)	1230 (88.2)	1220 (87.5)
Blood pressure — mm Hg		
Systolic	136.5±19.4	137.5±19.3
Diastolic	80.9±12.1	81.3±12.0
Stable heart failure — no. (%)**	396 (28.4)	402 (28.8)
CHA <sub>2</sub> DS <sub>2</sub> -VASC score††	3.4±1.3	3.3±1.3
Valvular heart disease — no./total no. (%)	609/1389 (43.8)	642/1391 (46.2)
Chronic kidney disease of MDRD stage 3 or 4 — no. (%)‡‡	172 (12.3)	179 (12.8)
Medication at discharge — no./total no. (%)§§		
Oral anticoagulation with NOAC or VKA	1267/1389 (91.2)	1250/1393 (89.7)
Digoxin or digitoxin	46/1389 (3.3)	85/1393 (6.1)
Beta-blocker	1058/1389 (76.2)	1191/1393 (85.5)
ACE inhibitors or angiotensin II receptor blocker	953/1389 (68.6)	979/1393 (70.3)
Mineralocorticoid-receptor antagonist	90/1389 (6.5)	92/1393 (6.6)
Diuretic	559/1389 (40.2)	561/1393 (40.3)
Statin	628/1389 (45.2)	568/1393 (40.8)
Platelet inhibitor	229/1389 (16.5)	226/1393 (16.2)

# EAST-AFNET 4 trial: Efficacy Outcome

❖ a median follow-up of 5.1 years per patient.



No. at Risk					
Usual care	1394	1169	888	405	34
Early rhythm control	1395	1193	913	404	26

**Figure 2.** Aalen-Johansen Cumulative-Incidence Curves for the First Primary Outcome.

The first primary outcome was a composite of death from cardiovascular causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome.

**Table 2.** Efficacy Outcomes.<sup>a</sup>

Outcome	Early Rhythm Control	Usual Care	Treatment Effect
First primary outcome — events/person-yr (incidence/100 person-yr)	249/6399 (3.9)	316/6332 (5.0)	0.79 (0.66 to 0.94)†
Components of first primary outcome — events/person-yr (incidence/100 person-yr)			
Death from cardiovascular causes	67/6915 (1.0)	94/6988 (1.3)	0.72 (0.52 to 0.98)‡
Stroke	40/6813 (0.6)	62/6856 (0.9)	0.65 (0.44 to 0.97)‡
Hospitalization with worsening of heart failure	139/6620 (2.1)	169/6558 (2.6)	0.81 (0.65 to 1.02)‡
Hospitalization with acute coronary syndrome	53/6762 (0.8)	65/6816 (1.0)	0.83 (0.58 to 1.19)‡
Second primary outcome — nights spent in hospital/yr	5.8±21.9	5.1±15.5	1.08 (0.92 to 1.28)§
Key secondary outcomes at 2 yr			
Change in left ventricular ejection fraction — %	1.5±9.8	0.8±9.8	0.23 (−0.46 to −0.91)¶
Change in EQ-5D score	−1.0±21.4	−2.7±22.3	1.07 (−0.68 to 2.82)¶
Change in SF-12 Mental Score**	0.7±10.6	1.6±10.1	−1.20 (−2.04 to −0.37)¶
Change in SF-12 Physical Score**	0.3±8.5	0.1±8.2	0.33 (−0.39 to 1.06)¶
Change in MoCA score	0.1±3.3	0.1±3.2	−0.14 (−0.39 to 0.12)¶
Sinus rhythm — no. of patients with feature/total no. (%)	921/1122 (82.1)	687/1135 (60.5)	3.13 (2.55 to 3.84)††
Asymptomatic — no. of patients with feature/total no. (%)‡‡	861/1159 (74.3)	850/1171 (72.6)	1.14 (0.93 to 1.40)††

# ΕΥΧΑΡΙΣΤΩ ΠΟΛΥ

- AF and HFrEF share many fundamental predisposing risk factors.
- the presence of AF is associated with an adverse effect on mortality in both HFrEF and HFpEF.
- In HFrEF, a higher HR was associated with increased mortality in SR, and in AF only if > 100 bpm.
- Beta-blockers may do not offer a prognostic benefit in HFrEF patients with concomitant AF.
- No mortality differences between Rhythm control and Rate control strategy in patients with HFrEF and AF.
- Catheter ablation for atrial fibrillation in patients with heart failure was associated with a significantly lower rate of a composite end point of death from any cause or hospitalization for worsening heart failure than was medical therapy.

