The Intersection of Atrial Fibrillation and Heart Failure

Michael Bristow MD, PhD

Professor of Medicine (Cardiology),
CU AMC, Aurora, CO;

Director of Pharmacogenomics,
CU CVI, Boulder & Aurora, CO;

CEO, ARCA biopharma
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Disclosure

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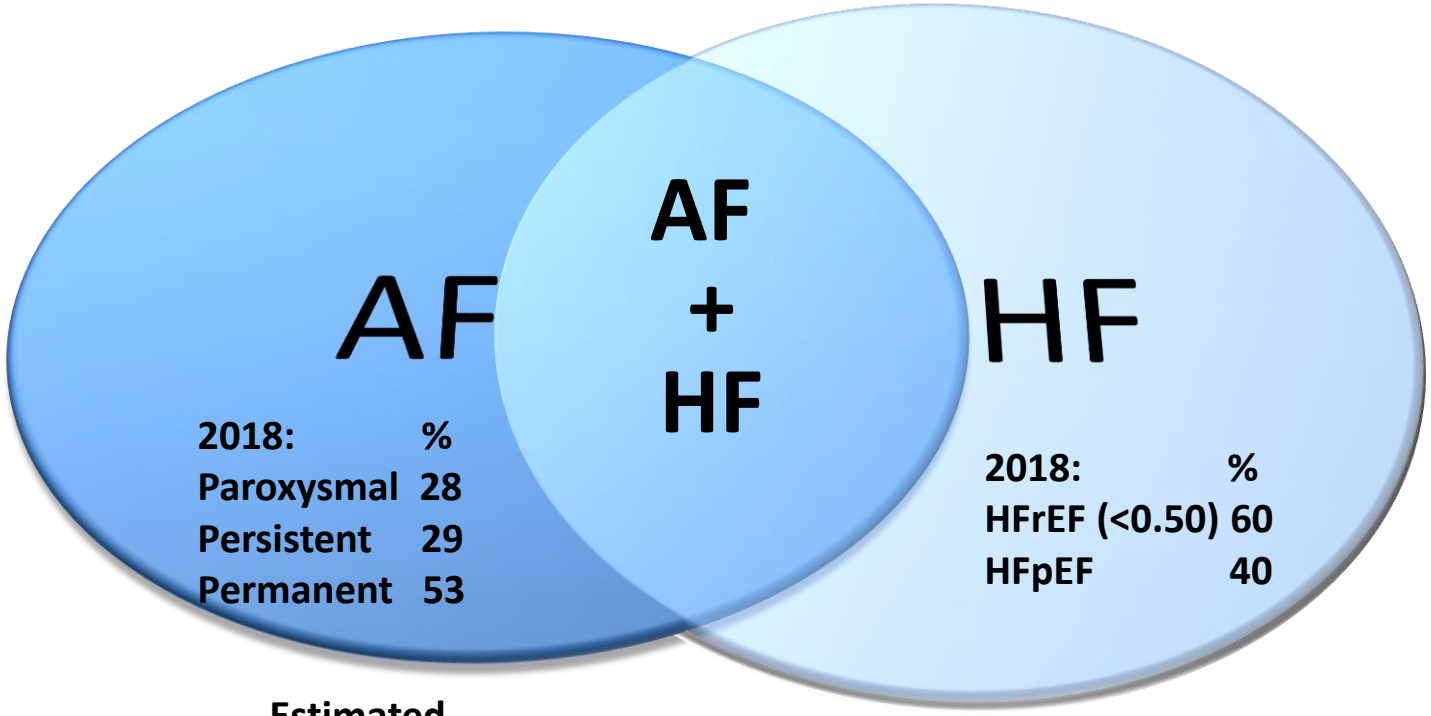
Intersection of AF and Heart Failure



Estimated Prevalence	AF	AF/HF	HF
2018	5.23M	2.84 (41%) ←	6.92M
2022	5.86M	3.09 (41%) ←	7.54M

1- "Atrial Fibrillation Therapeutics – Pipeline Assessment and Market Forecasts to 2017", Dec 2010
2- GlobalData – "Epicast Report: Chronic Heart Failure – Epidemiology Forecast to 2022", Jan 2013

The Intersection of atrial fibrillation and heart failure is a Dangerous Crossroads in a Bad Neighborhood

JACC: Heart Failure
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Published by Elsevier Inc.

EDITORIAL COMMENT

Treatment of the Heart Failure Patient With Atrial Fibrillation

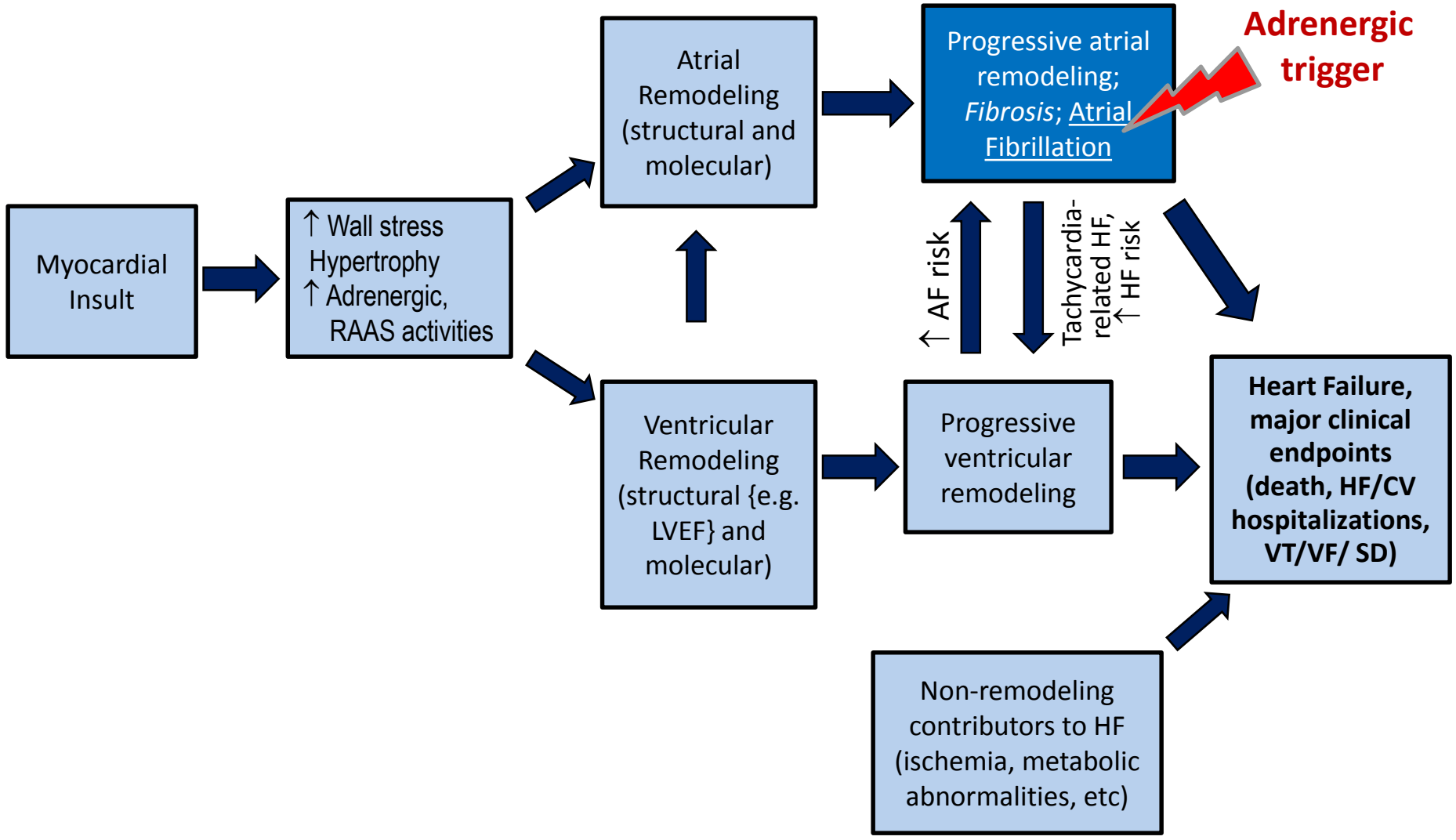
A Major Unmet Need*

Michael R. Bristow, MD, PhD,†‡
Ryan G. Aleong, MD†
Aurora, Colorado

JACC: Heart Failure 1:29-30, 2013

"However, all is not so sanguine at the **intersection of AF and HFrEF**, which occurs commonly (5) due to overlap in their underlying pathophysiologies (6). "

Pathophysiologies of AF and HFREF are similar



What does AF add to ACM risk in CV disorders?

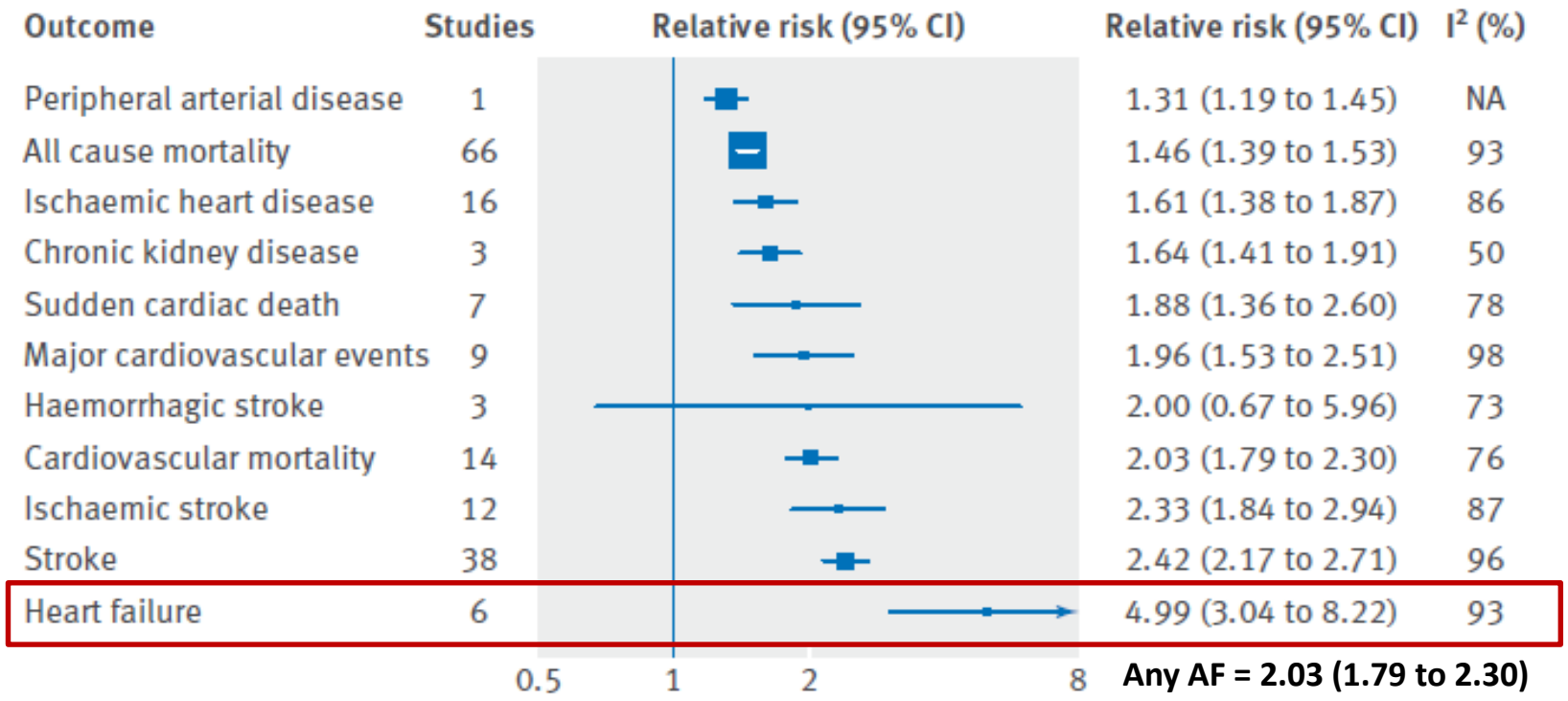


Fig 2 | Association between atrial fibrillation and all cause mortality and cardiovascular and renal disease, showing summary relative risks for each outcome examined. NA=not available

Odutayo et al, BMJ 354:i4482, 2016

What is the impact of AF in a HFrEF patient?

(Framingham, BEST trial data)

Permanent AF

- Modest increases (1.5-1.6 fold) in all-cause mortality and hospitalization burden (days in hospital/patient).[1] ***(However, this is a survivor analysis)***

New Onset AF

- Increase (by ~ 2 fold) in all-cause and cause specific mortality[1]
  - Similar to 1.6 fold increase in Framingham new onset AF study in CHF[2]
- Marked increase (by ~ 6 fold) in hospitalization burden, after the onset[1]

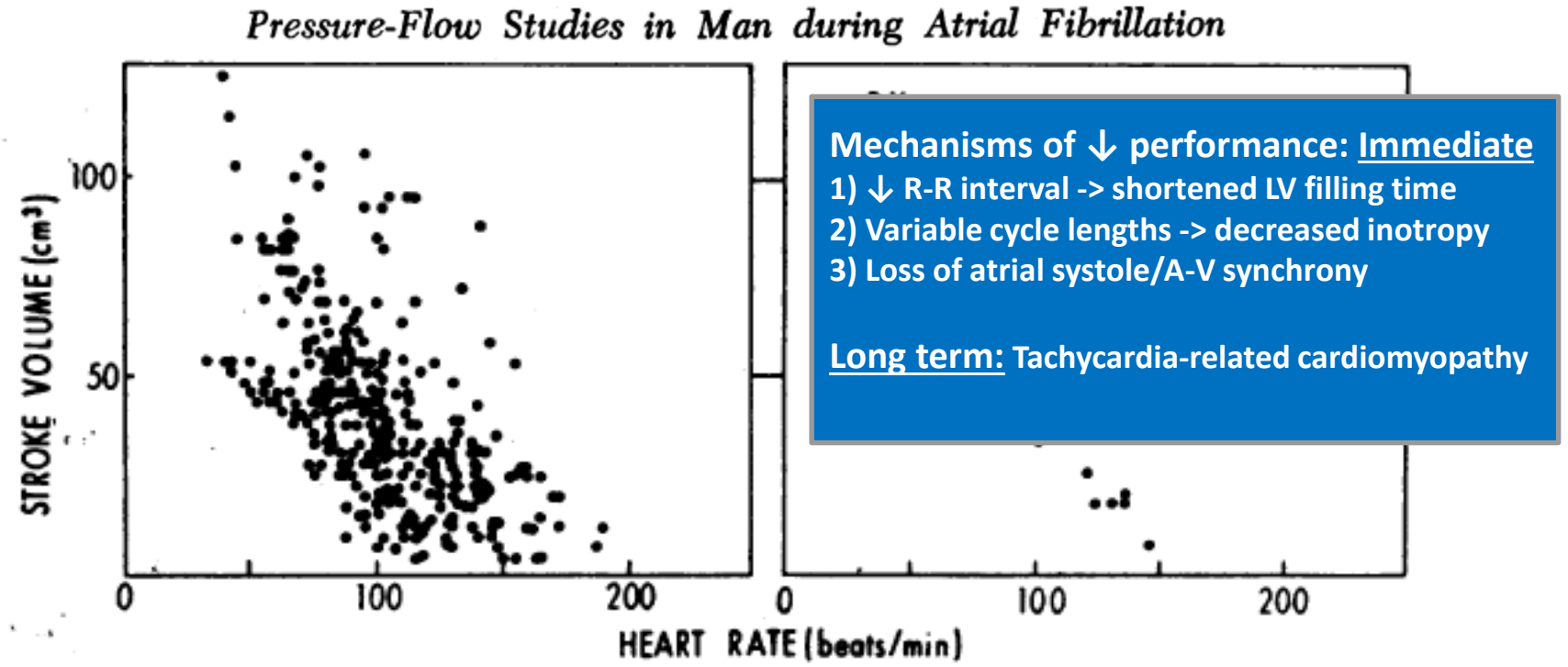
Conclusions

- New onset AF markedly increases HF morbidity and mortality
- For this and for stroke prevention reasons, in HFrEF patients AF should be aggressively prevented and treated → SR restored if it can be done *safely* with a reasonable chance of durability

[1]*Aleong et al. Am J Med 127:963-71, 2014*
[2]*Wang TJ et al. Circulation 107:2920, 2003*

C U V I

AF Leads to Reduced Cardiac Performance



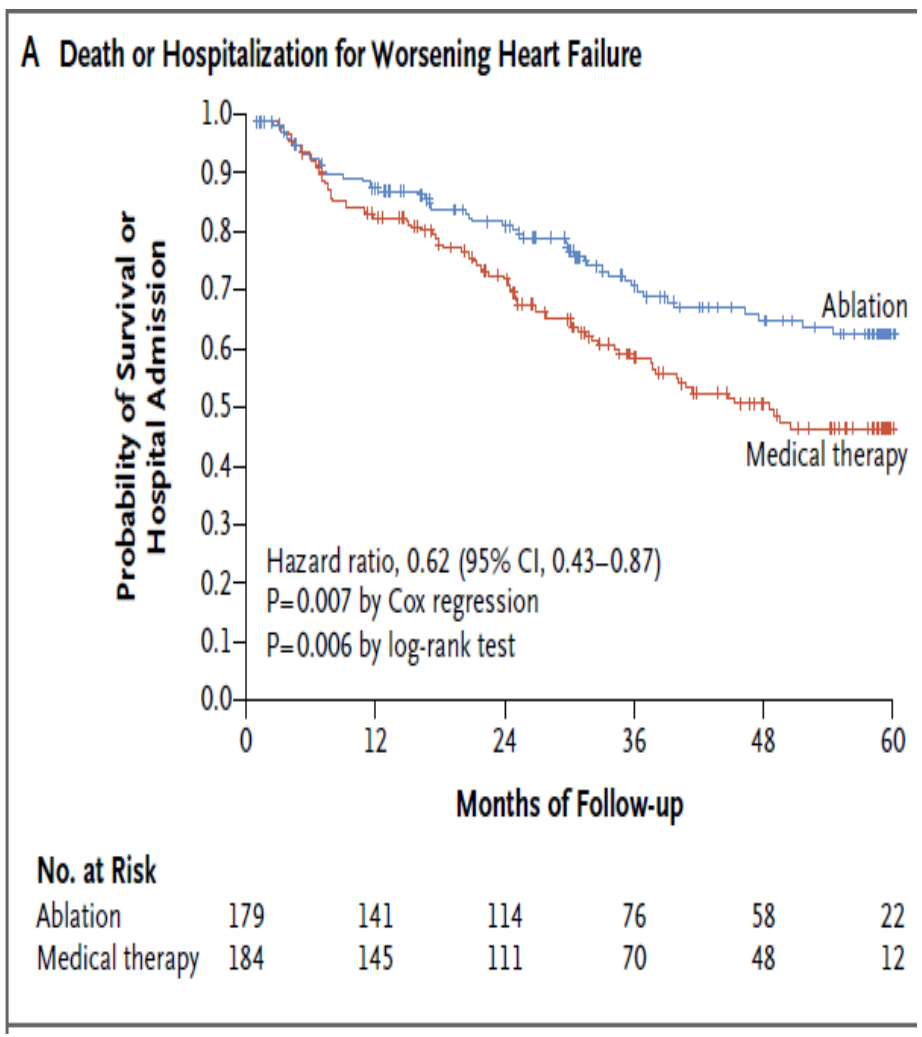
Mechanisms of ↓ performance: Immediate
1) ↓ R-R interval -> shortened LV filling time
2) Variable cycle lengths -> decreased inotropy
3) Loss of atrial systole/A-V synchrony

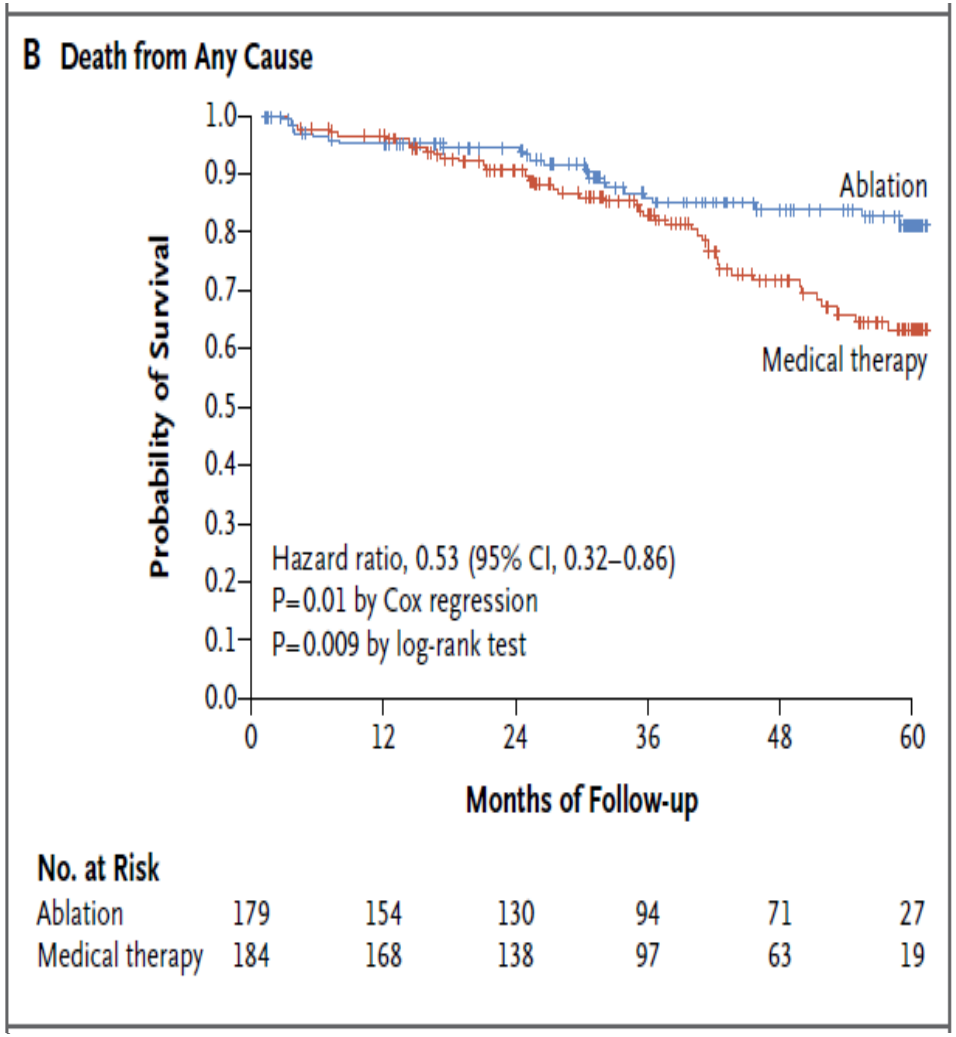
Long term: Tachycardia-related cardiomyopathy

Figure 5. The relationship of stroke volume and theoretical heart rate calculated from the previous R-R interval for individual beats in AF (13 patients in L panel, individual patient in R-panel).

Greenfield JC et al, JCI 47:2411-2421, 1968

CASTLE-AF 1EP (A) and 1st 2EP (B)



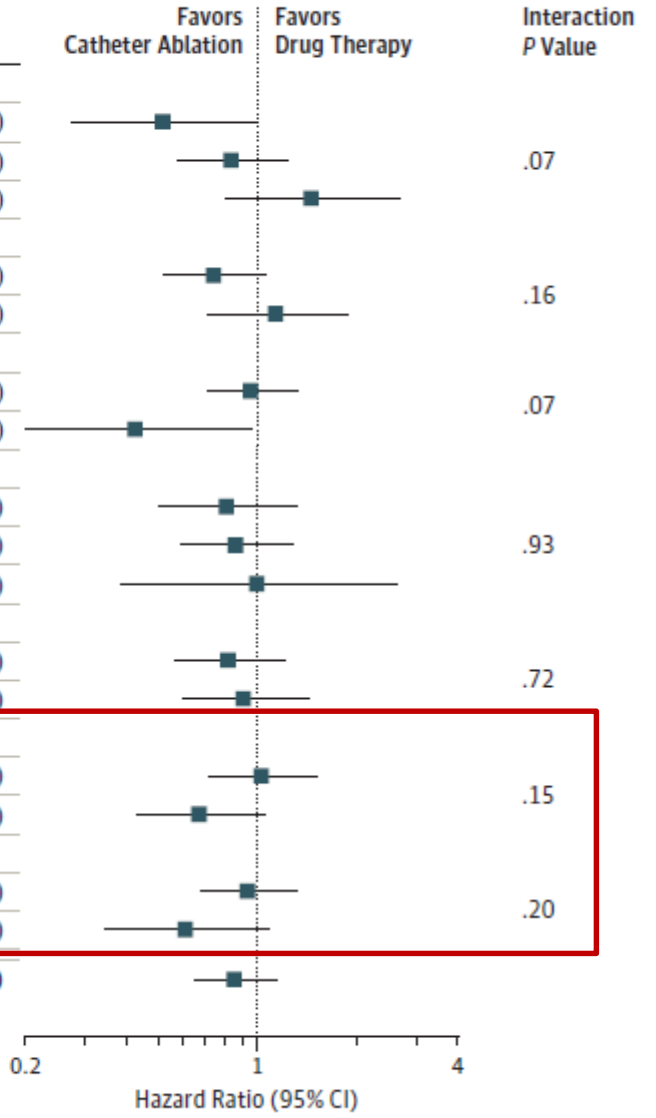


Marrouche NF et al, NEJM 378:417-428

CABANA, Subgroup Analyses

Figure 4. Primary End Point Subgroup Analysis (Intention to Treat)

Source	No. of Events/Patients (Person-Years)		Hazard Ratio (95% CI)	Interaction *P* Value
	Catheter Ablation	Drug Therapy		
Age, y				
<65	14/375 (1483)	27/391 (1498)	0.52 (0.27-1.00)	
≥65 and <75	50/577 (2159)	56/553 (2019)	0.84 (0.57-1.23)	.07
≥75	25/156 (514)	18/152 (529)	1.46 (0.80-2.67)	
Sex				
Male	54/695 (2670)	71/690 (2591)	0.74 (0.52-1.06)	.16
Female	35/413 (1485)	30/406 (1456)	1.14 (0.70-1.86)	
Minority status				
White	80/995 (3721)	82/984 (3654)	0.96 (0.71-1.31)	.07
Minority[a]	9/113 (434)	19/112 (393)	0.43 (0.20-0.95)	
Atrial fibrillation type[b]				
Paroxysmal	31/470 (1756)	38/476 (1761)	0.82 (0.51-1.31)	
Persistent	49/524 (1922)	55/518 (1860)	0.87 (0.59-1.28)	.93
Long-standing persistent	9/114 (477)	8/101 (426)	1.01 (0.39-2.61)	
Time since onset of atrial fibrillation, y				
≤1	50/540 (1922)	58/523 (1835)	0.83 (0.57-1.21)	.72
>1	39/560 (2207)	42/562 (2177)	0.92 (0.59-1.42)	
Baseline NYHA class[c]				
No heart failure or class I	55/719 (2735)	52/689 (2657)	1.04 (0.71-1.52)	.15
≥ Class II	34/378 (1396)	49/400 (1372)	0.68 (0.44-1.05)	
History of congestive heart failure				
No	68/934 (3506)	72/931 (3500)	0.95 (0.68-1.32)	.20
Yes	21/174 (650)	29/163 (547)	0.61 (0.35-1.08)	
All patients	89/1108 (4155)	101/1096 (4047)	0.86 (0.65-1.15)	



Packer DL et al. JAMA 321:1261-1274, 2019

Meta-analysis of atrial fibrillation prevention in β-blocker heart failure trials

Table 3 Incidence of onset of AF in each trial in HF

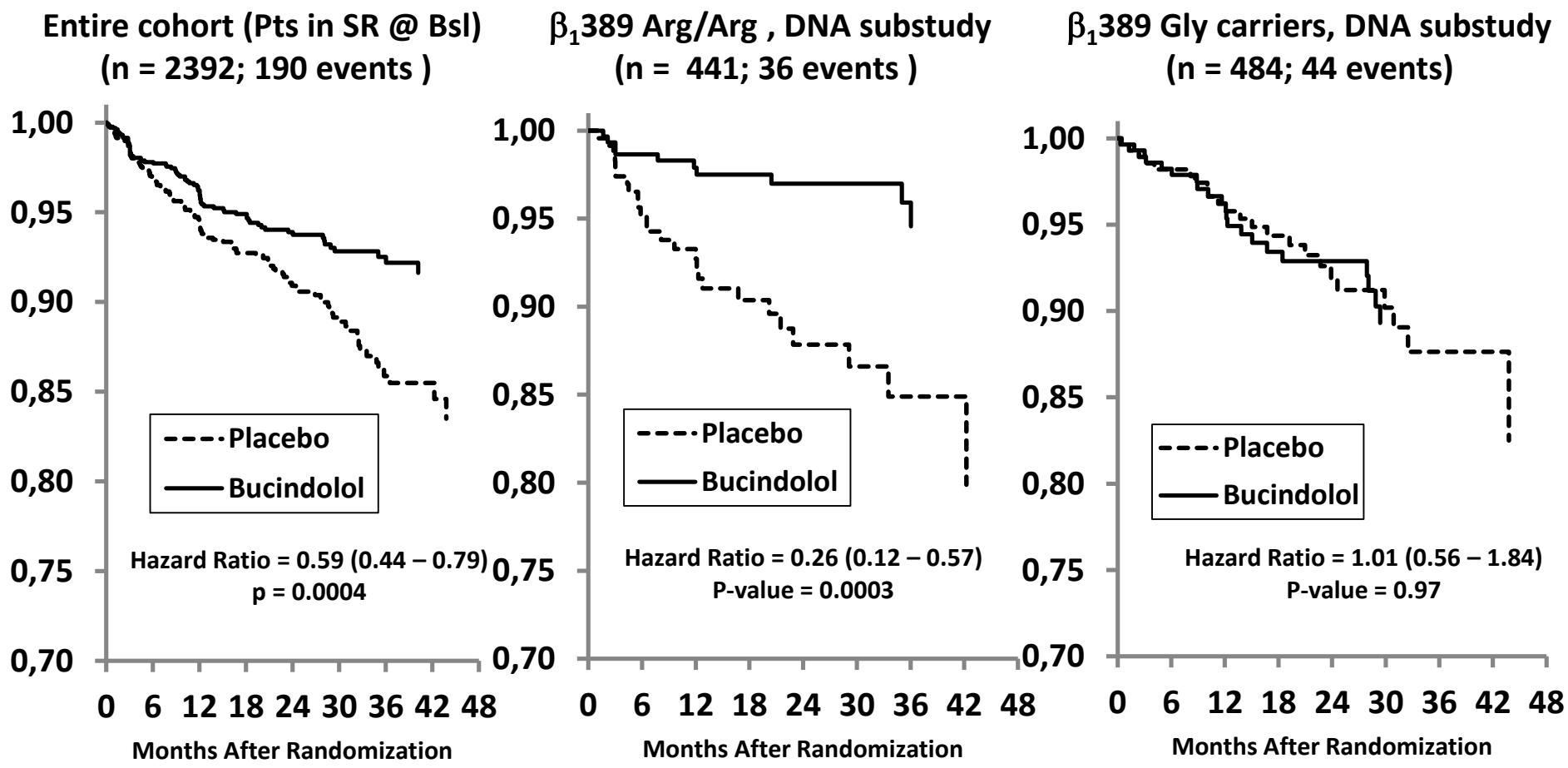
Data source	Beta-blockers (events/ number of patients)	Placebo (events/ number of patients)	Weight (%)	RR (95% CI)
CIBIS I[35](bisoprolol)[a]	9/280	13/276	4	0.68 (0.29–1.57)
MERIT HF (metoprolol)[48]	33/1677	54/1681	15	0.61 (0.39–0.94)
BEST (bucindolol)[31]	78/1208	111/1197	36	0.69 (0.52–0.92)
COPERNICUS (carvedilol)[47]	12/1156	22/1133	5.7	0.53 (0.26–1.07)
Waagstein (metoprolol)[26]	1/86	8/79	0.7	0.11 (0.01–0.89)
SENIORS (nebivolol)[34]	78/706	74/684	30.8	1.02 (0.75–1.37)
CAPRICORN (carvedilol)[12]	16/894	31/895	7.8	0.51 (0.28–0.93)
Total	227/6007 (3.8%)	313/5944 (5.3%)	100	0.73 (0.61–0.86)

[a]Complementary data from the investigators.

Abi Nasr I et al, EHJ 28: 457–462, 2007.

Kaplan-Meier curves for prevention of atrial fibrillation in BEST

Aleong et al, JACC Heart Fail; 1:338-44, 2013

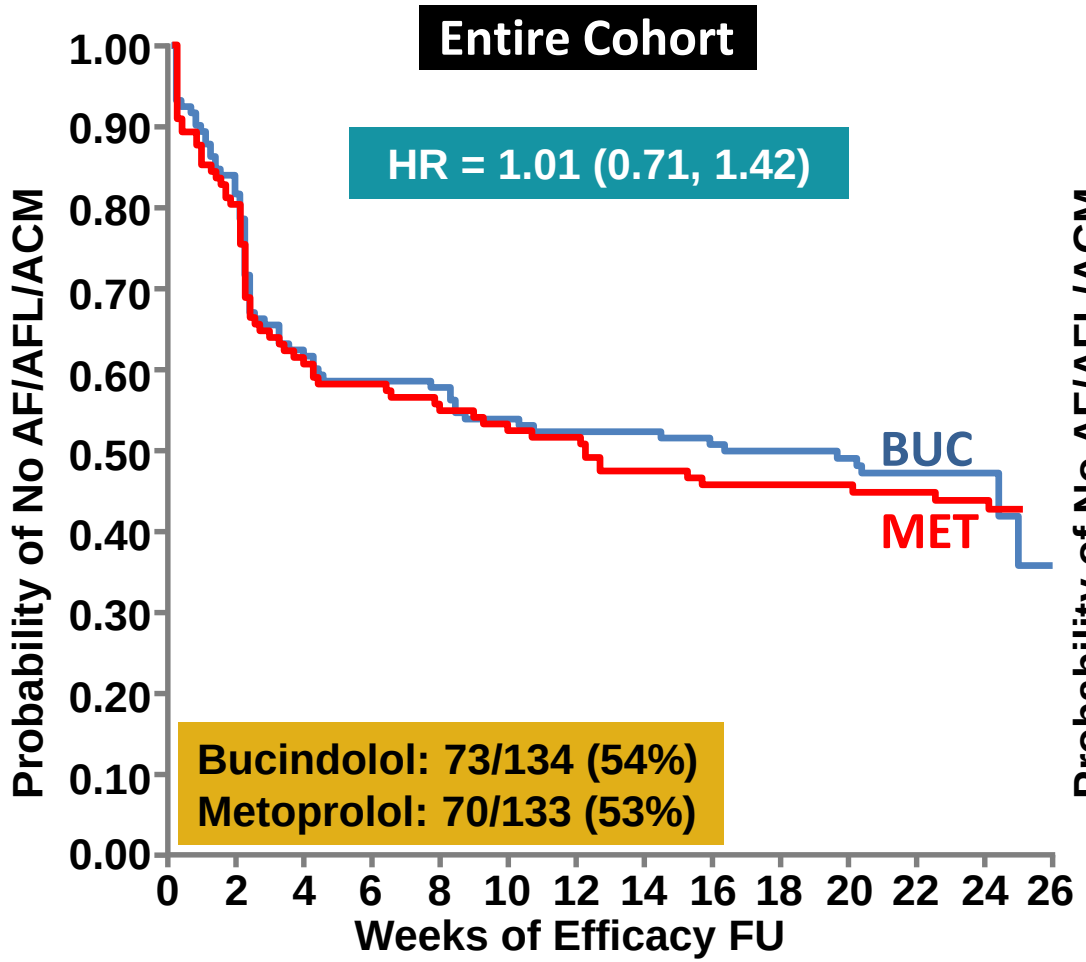


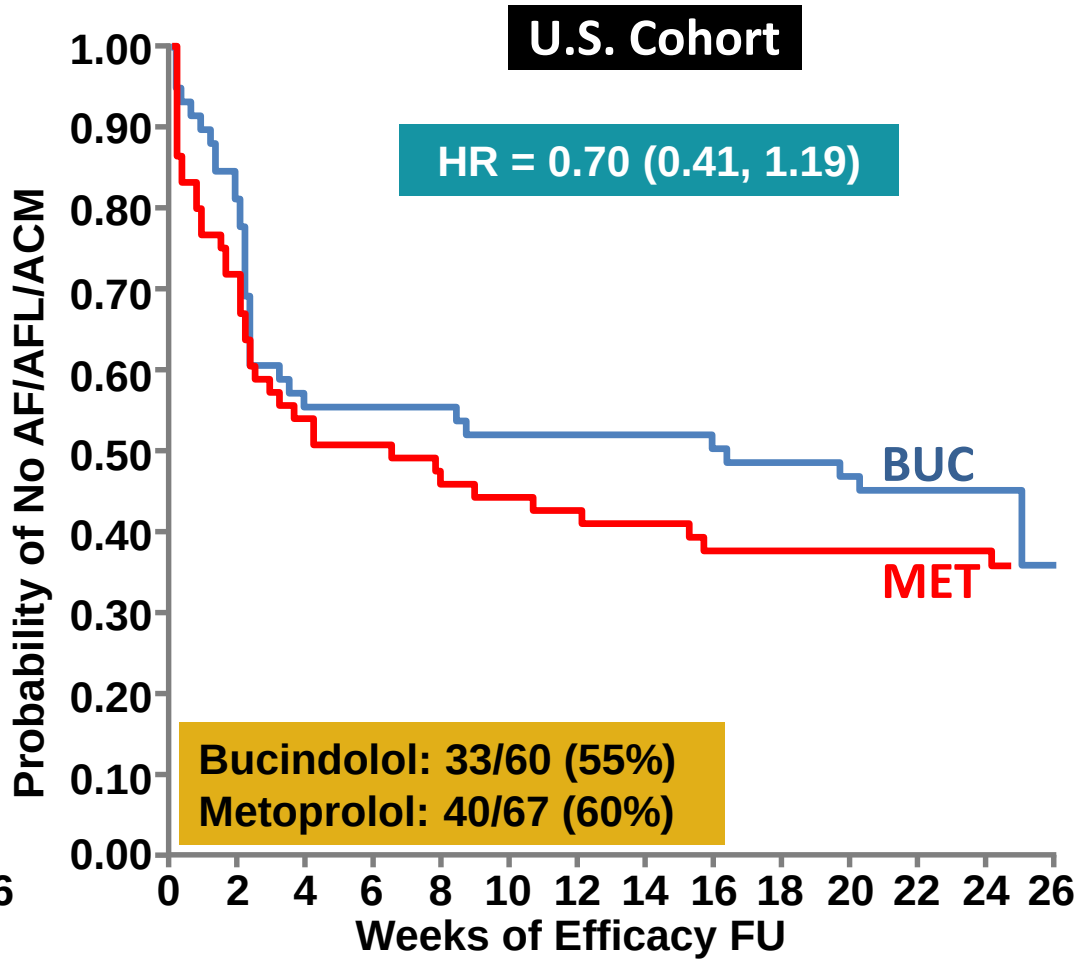
RES = = (Ln 0.26/Ln 0.59) = 2.55

Interaction p = 0.008

GENETIC-AF: Phase 2B Genetically-Targeted Trial

(Piccini et al, JACC-HF in press)



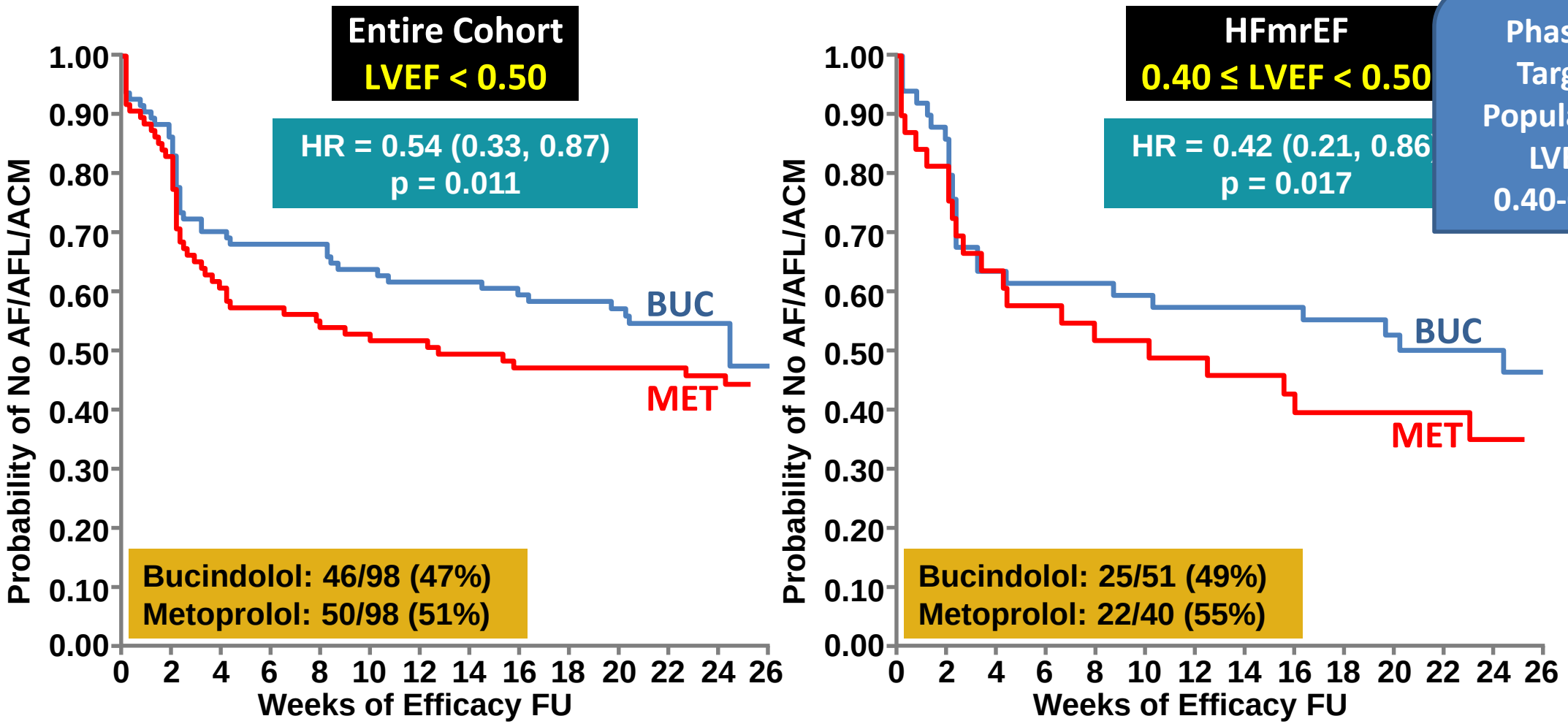


Time to AF/AFL/ACM – ECG based Detection

Cox proportional hazards model adjusted for the 4 randomization strata: 1) HF etiology, 2) LVEF, 3) rhythm at randomization 4) device type.

GENETIC-AF: Time to AF/AFL/ACM

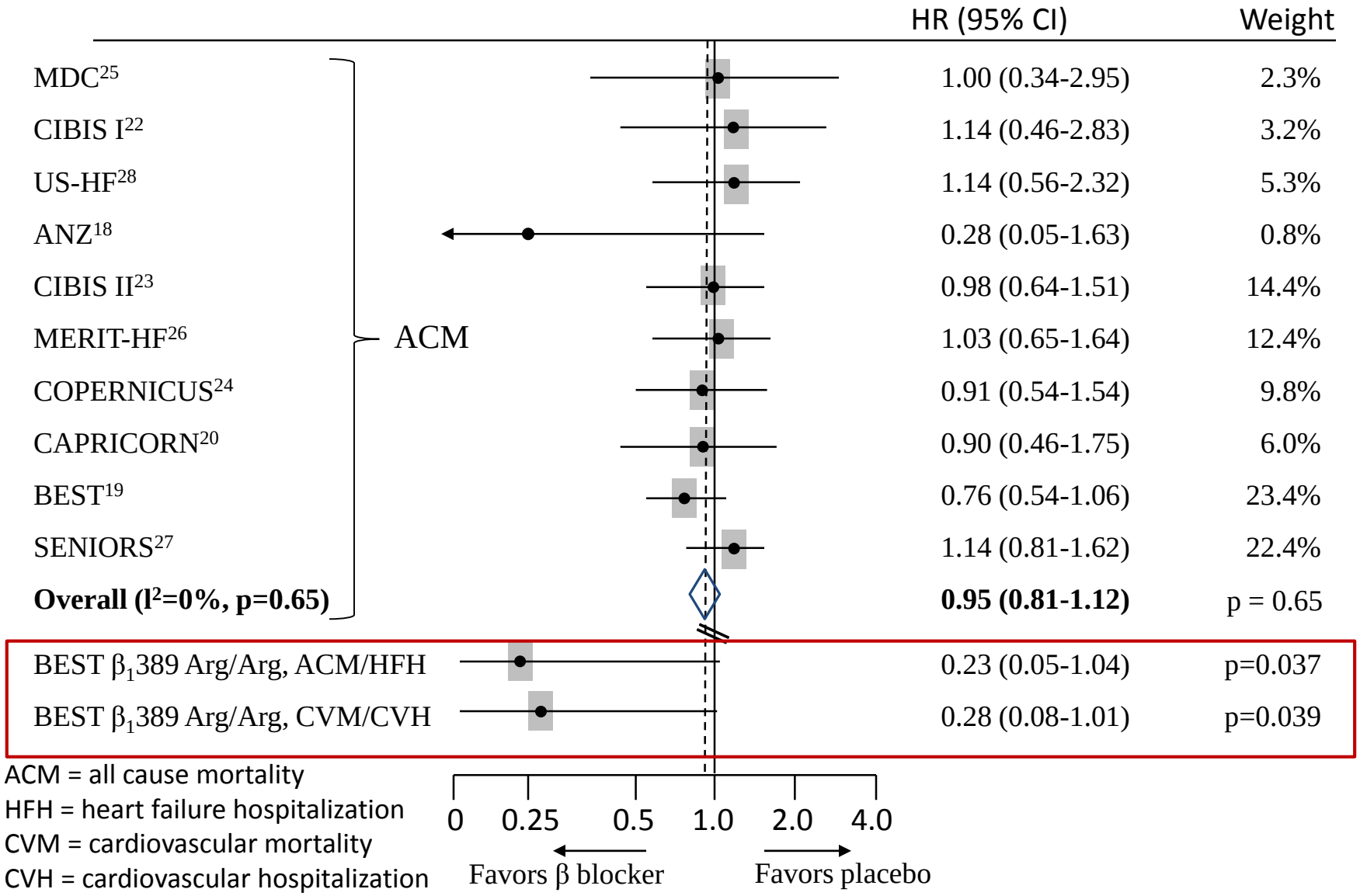
Excluding Pts with Long-standing (12/12+yrs) AF/HF Dx and AF Dx >2 years prior to HF Dx (*Piccini et al, JACC-HF in press*)



Cox proportional hazards model adjusted for: 1) HF etiology, 2) LVEF, 3) rhythm at randomization 4) device type, 5) Previous Class 3 AA use.

CU VI

β-blockers do not decrease HF endpoints in HFrEF patients in "permanent" AF (exception is bucindolol in $\beta_1$389 Arg/Arg genotype)



ACM = all cause mortality
HFH = heart failure hospitalization
CVM = cardiovascular mortality
CVH = cardiovascular hospitalization

Adapted from Kotecha D et al, Lancet 2014 and Kao D et al, EJHF 2013.

Why should we care about AF in heart failure patients?

- Same reasons as in non-HF pts (stroke risk, Sx, ↓ Ex tolerance)
- AF is a marker for HF progression
- AF itself may worsen HF
- AF ablation in HFrEF extremely promising
  - but relatively high recurrence rate, drug therapy still needed
- Drugs used to prevent AF may worsen HF, are proarrhythmic
  - New drugs that prevent AF in HF or LVD pts are needed
- In permanent AF
  - Some rate control drugs may worsen HF or are proarrhythmic
  - AF pts at risk for tachycardia-related worsening of HF
  - Evidence suggests β-blockers ineffective for ↓ing HF events; emerging data suggests excessive HR lowering (e.g. to < mid 70s) may be adverse

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