

Eplerenone and Atrial Fibrillation in Patients with Systolic Heart Failure and Mild Symptoms – results from **EMPHASIS-HF***

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EMPHASIS-HF Study Group



Disclosure Information

- Karl Swedberg Grants/Contracts, consultant (moderate)
- Faiez Zannad Grants/contracts, consultant (moderate)
- John JV McMurray Grants/contracts, consultant (moderate)
- Henry Krum Grants/Contracts, consultant (moderate)
- Dirk J Van Veldhuisen Grants/Contracts, consultant (moderate)
- Harry Shi Pfizer employee
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- Stuart J Pocock Grants/Contracts, consultant, (moderate)
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Eplerenone is approved for treating heart failure after myocardial infarction in 72 countries,.

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Background

- ACE-inhibitors and ARBs may reduce the incidence of atrial fibrillation in patients with HF (as well as other types of cardiovascular disease) although not all studies have confirmed this finding.
- Aldosterone has a more pro-fibrotic action than angiotensin II but whether antagonists, which block activation of the mineralocorticoid receptor by aldosterone and other corticosteroids, reduce the incidence of AF is unclear, especially in patients with systolic heart failure already treated with an ACE inhibitor or ARB.

Aims

- We have examined the effect of the MRA eplerenone on the incidence of new onset atrial fibrillation/flutter (AFF) during follow-up in EMPHASIS-HF.
- We also report the relationship between baseline AFF and subsequent events and the effect of eplerenone in patients with and without AFF at baseline.

Inclusion Criteria

- Inclusion

- > 55 years of age
- NYHA functional class II
- Ejection fraction < 30% (or, if between 30% and 35%, QRS >130 msec)
- Treated with the recommended or maximally tolerated dose of ACE inhibitor (or an ARB or both) and a beta-blocker (unless contraindicated).
- within 6 months of hospitalization for a cardiovascular reason [or, if no such hospitalization, BNP > 250 pg/ml or Nt-pro-BNP >500 pg/ml (males) or 750 pg/ml (females).]

- Exclusion

- Serum potassium > 5.0 mmol/L
- eGFR < 30 ml/min/1.73 m²
- Need for a potassium-sparing diuretic
- Any other significant comorbid condition.

Atrial fibrillation/flutter

- Baseline AFF status was determined from three separate parts of the study case report form (CRF):
 - 1) the baseline ECG report
 - 2) the aetiology of HF report
 - 3) the medical history page.
- Patients without AFF at baseline had no report of AFF in any of these three CRF sections. Patients with AFF at baseline had a report of AFF in any one of these sections.

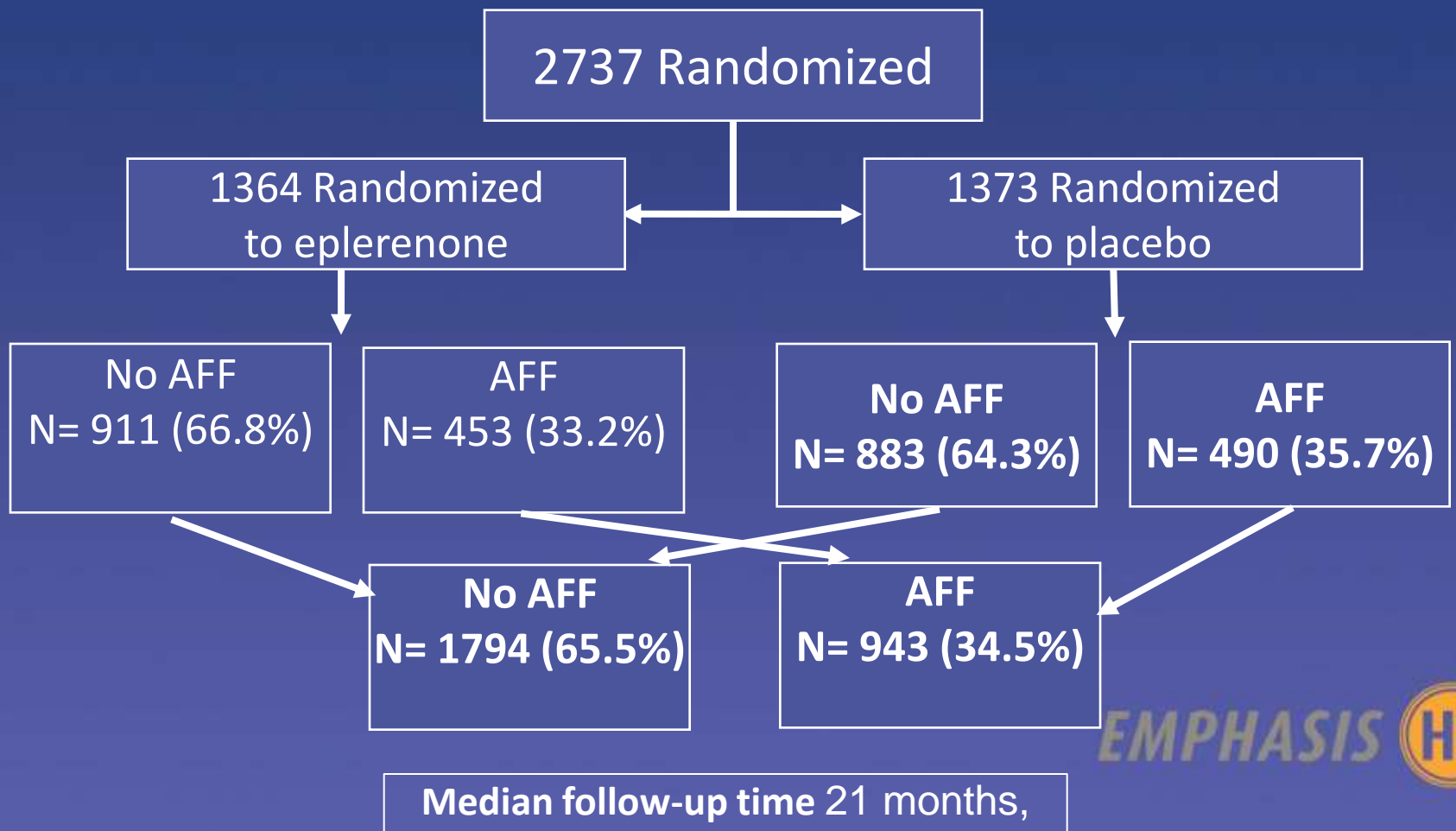
New Onset AFF

- Because new-onset AFF was a pre-specified endpoint, a specially designed CRF, focused on the occurrence of AFF during follow-up was collected at the end of the study for all patients.
- We also performed a sensitivity analysis by examining adverse events reports of AFF.
- Patients with new-onset AFF were defined as those without AFF at baseline who had an endpoint CRF report of AFF during follow-up (or, in the sensitivity analysis, an AE report of AFF).

Statistical Analyses

- Analyses on primary and secondary endpoints - using Cox PH model adjusted for the following prespecified baseline prognostic factors Age, eGFR, ejection fraction, body mass index, hemoglobin, heart rate, systolic blood pressure, diabetes mellitus, history of hypertension, prior myocardial infarction, and left bundle branch block or QRS duration >130 milliseconds.
- The treatment-by-baseline AFF subgroup interaction evaluation - using a Cox PH model with terms for treatment, baseline AFF, and interactions between treatment and baseline AFF subgroup.

Disposition of Patients



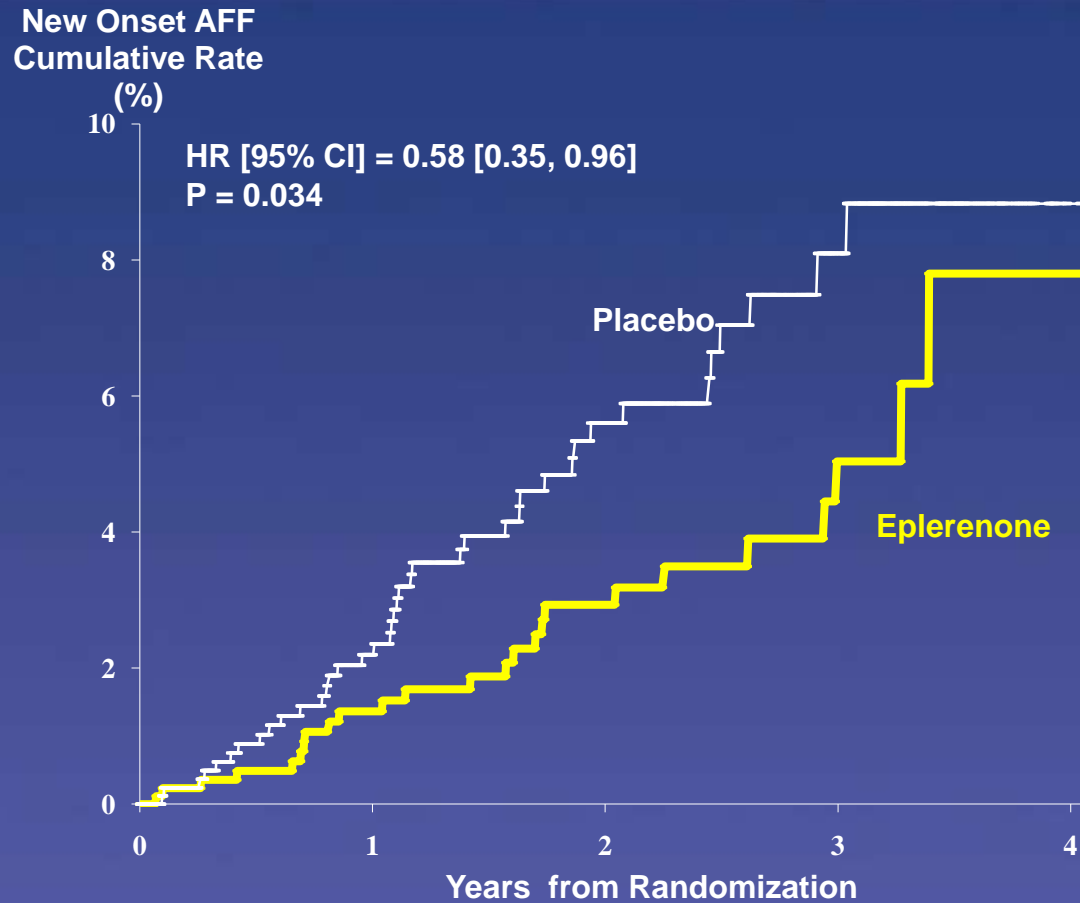
Baseline Characteristics

Characteristic	No AFF (N=1794)	AFF (N=943)
Mean age — yr	67.9	70.0
Female sex — no. (%)	25	17
Hypertension	64.5	70.2
Ischemic heart disease	71.2	64.5
Heart rate bpm	71.8	76.3
Diabetes mellitus %	33.7	26.9
Serum Creatinine – mg/dl	1.1	1.2
Ejection Fraction - %	26	26.3

Baseline Therapy

Medication	No AFF (N=1794)	AFF (N=943)
Diuretics %	87.2	92.2
ACE inhibitor or angiotensin-receptor blocker or both	95.7	95.3
Beta-blocker	90.4	91.2
Digitalis glycosides	23.2	49.6
Amiodarone	14.0	29.9
Lipid-lowering agent	71.6	59.5

New Onset Atrial Fibrillation/Flutter (AFF)



No. at Risk

Placebo	883	611	345	133
Eplerenone	911	627	397	162

New onset atrial fibrillation/flutter

	Eplerenone	Placebo N(%)	Hazard ratio*	95% CI	p
	N=911	N=883			
	N (%)	N (%)			
New onset atrial fibrillation/flutter	25 (2.7)	40 (4.5)	0.58	0.35-0.96	0.034

Effects of eplerenone by baseline AFF: without AFF

Total number of subjects	Eplerenone n = 911 (%)	Placebo n = 883 (%)	Hazard Ratio	P-value
Without AFF				
CV death/HF Hospitalization	160 (17.6%)	217 (24.6%)	0.70	<0.001
All-cause mortality or HF hospitalization	175 (19.2%)	228 (25.8%)	0.72	0.001
All-cause hospitalization	260 (28.5%)	294 (33.3%)	0.83	0.03
HF hospitalization	103 (11.3%)	150 (17.0%)	0.65	<0.001
All cause death or all cause hospitalization	292 (32.1%)	341 (38.6%)	0.81	<0.01
HF death or HF hospitalization	107 (11.7%)	156 (17.7%)	0.65	<0.001
CV hospitalization	201 (22.1%)	244 (27.6%)	0.77	<0.01

Effects of eplerenone by baseline AFF: with AFF

Total number of subjects	Eplerenone N = 453 N (%)	Placebo N = 490 N (%)	Hazard Ratio	P-value	P-value for interaction with/without AFF
With AFF					
CV death/HF Hospitalization	89 (19.6%)	139 (28.4%)	0.60	<0.001	0.41
All-cause mortality or HF hospitalization	95 (21.%)	148 (30.2%)	0.60	<0.001	0.28
All-cause hospitalization	148 (32.7%)	197 (40.2%)	0.70	<0.01	0.22
HF hospitalization	61 (13.5%)	103 (21.0%)	0.56	<0.001	0.49
All cause death or all cause hospitalization	170 (37.5%)	228 (46.5%)	0.70	<0.001	0.26
HF death or HF hospitalization	63 (13.9%)	106 (21.6%)	0.56	<0.001	0.49
CV hospitalization	103 (22.7%)	155 (31.6%)	0.63	<0.001	0.20

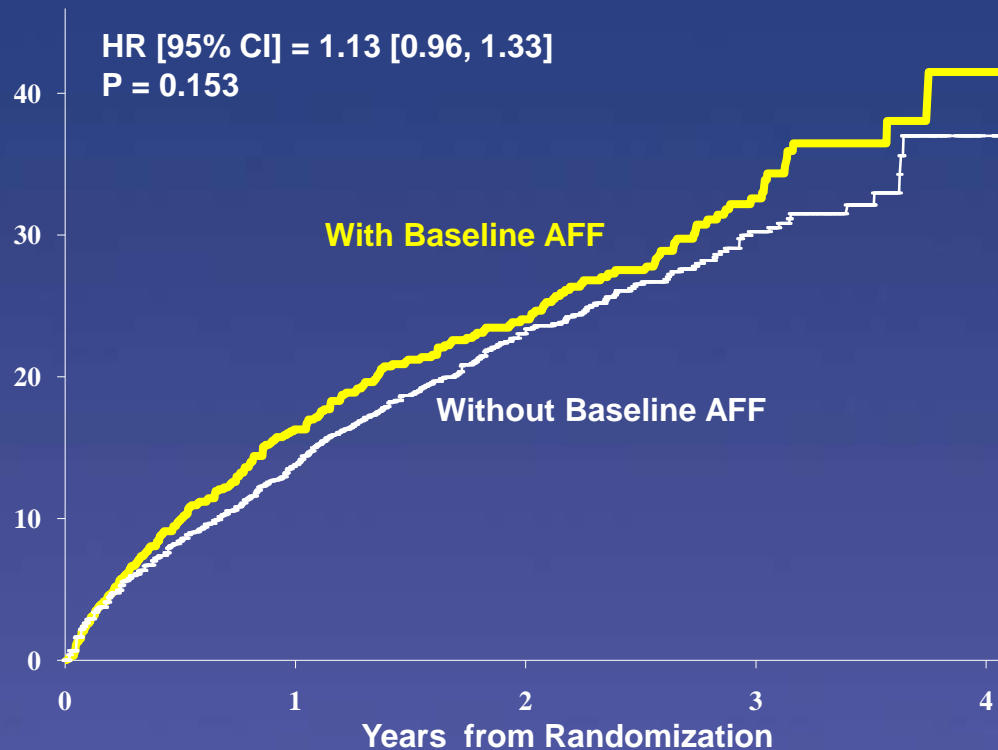
EMPHASIS 

Study outcomes by baseline AFF

	AFF (N=943) N (%)	No AFF (N=1 794) N (%)	P-value
HF Hospitalization/CV Death	228 (24.2%)	377 (21.0%)	0.153
HF Hospitalization	164 (17.4%)	253 (14.1%)	0.059
CV Death	122 (12.9%)	210 (11.7%)	0.643
All-cause mortality or heart failure (HF) hospitalization	243 (25.8%)	403 (22.5%)	0.153
All-cause mortality	139 (14.7%)	245 (13.7%)	0.789
All-cause hospitalization	345 (36.6%)	554 (30.9%)	0.019
All cause death or all cause hospitalization	398 (42.2%)	633 (35.3%)	0.008
HF death or HF hospitalization	169 (17.9%)	263 (14.7%)	0.067
CV hospitalization	258 (27.4%)	445 (24.8%)	0.355

CV death or HF hospitalization by baseline atrial fibrillation/flutter (AFF)

CV Death / HF
Hospitalization
Cumulative Rate (%)



No. at Risk

With AFF

943

602

385

161

2

Without AFF

1794

1171

689

270

4

Conclusions

- In patients with systolic heart failure and mild symptoms, addition of eplerenone to recommended therapy reduced the incidence of new onset atrial fibrillation or flutter.
- The effects of eplerenone on the risk of major cardiovascular events were similar in patients with and without atrial fibrillation or flutter at baseline.
- Atrial fibrillation or flutter at baseline did not increase the risk of most major study outcomes