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Eplerenone and Atrial Fibrillation in Mild Systolic Heart Failure

Results From the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure) Study

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Objectives The purpose of this study was to analyze the incidence of new atrial fibrillation or flutter (AFF) in the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure) database.

Background Aldosterone antagonism in heart failure might influence atrial fibrosis and remodeling and, therefore, risk of developing AFF. The development of new AFF was a pre-specified secondary endpoint in the EMPHASIS-HF study.

Methods Patients in New York Heart Association functional class II and with ejection fraction ≤35% were eligible for EMPHASIS-HF. History of AFF at baseline was reported by investigators using the study case report form. New onset AFF (in those with no history of AFF at baseline) was reported using a specific endpoint form; in a sensitivity analysis we also examined the effect of eplerenone on AFF reported as an adverse event.

Results New onset AFF was significantly reduced by eplerenone: 25 of 911 (2.7%) versus 40 of 883 (4.5%) in the placebo group (hazard ratio [HR]: 0.58, 95% confidence interval [CI]: 0.35 to 0.96; p = 0.034). The reduction in the primary endpoint with eplerenone was similar among patients with and without AFF at baseline (HR: 0.60, 95% CI: 0.46 to 0.79 vs. HR: 0.70, 95% CI: 0.57 to 0.85, respectively; p for interaction = 0.41). The risk of cardiovascular (CV) death or hospital admission for worsening heart failure, the primary endpoint, was not significantly different in subjects with and without AFF at baseline (both study groups combined: HR: 1.23, 95% CI: 0.81 to 1.86; p = 0.33).

Conclusions In patients with systolic heart failure and mild symptoms, eplerenone reduced the incidence of new onset AFF. The effects of eplerenone on the reduction of major CV events were similar in patients with and without AFF at baseline. (J Am Coll Cardiol 2012;59:1598–603) © 2012 by the American College of Cardiology Foundation

Atrial fibrillation is common in patients with chronic heart failure (HF), and its prevalence increases with the severity of the disease (1,2). The development of atrial fibrillation with an ensuing decline in cardiac function may also cause hemodynamic and symptomatic deterioration leading to a reduction in exercise capacity, as well as deterioration of functional class (3,4). This, in turn, may lead to hospital admission, other morbidity (e.g., stroke), and, possibly, to

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increased mortality. Development of atrial fibrillation is clearly undesirable in HF, and treatments that may prevent it are therefore conceptually attractive in HF.

The extent of activation of the renin-angiotensin-aldosterone system also increases with the severity of HF (5) and both angiotensin II and aldosterone may lead to atrial fibrosis and contribute to the development of atrial fibrillation or flutter (AFF) (6,7).

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have been shown to reduce the incidence of atrial fibrillation in patients with HF (as well as other types of cardiovascular disease) in meta-analyses including both primary and secondary prevention (8,9), although not all studies have confirmed this finding in primary prevention (10,11).

Activation of mineralocorticoid receptors by aldosterone and cortisol has deleterious effects in patients with cardiovascular disease (12). Treatment with mineralocorticoid receptor antagonists (MRA) has been demonstrated to reduce outcomes in patients with mild to severe systolic HF (13,14) as well as after myocardial infarction (15). Aldosterone has a more pro-fibrotic action than angiotensin II (12), but whether antagonists, which block activation of the mineralocorticoid receptor by aldosterone and other corticosteroids, reduce the incidence of AFF is unclear, especially in patients with systolic HF already treated with an ACE inhibitor or ARB. A small study has suggested that spironolactone may prevent the re-occurrence of AF in patients with normal left ventricular systolic function (16). We therefore prospectively examined this question in the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure) study. In EMPHASIS-HF, the MRA eplerenone, or placebo, was added to an ACE inhibitor or ARB, and a beta-blocker, in patients with systolic HF and mild symptoms (13). We also report the effect of eplerenone in patients with and without AFF at baseline and the relationship between baseline AFF and subsequent events.

Methods

The design of the trial has been published in detail (13,17). In brief, patients were eligible if they were at least 55 years of age, in New York Heart Association functional class II, had an ejection fraction of no more than 30% (or, if between 30% and 35%, QRS duration had to be >130 ms), and they were treated with the recommended or maximally tolerated dose of ACE inhibitor (or an ARB or both) and a beta-blocker (unless contraindicated). Randomization was to occur within 6 months of hospitalization for a cardiovascular reason or, if no such hospitalization, if plasma B-type natriuretic peptide was at least 250 pg/ml or N-terminal pro–B-type natriuretic peptide was at least 500 pg/ml in men (750 pg/ml in women). Key exclusion criteria were serum potassium >5.0 mmol/l, estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2, need for a potassium-sparing diuretic, and any other significant comorbid condition.

The trial was approved by each center's ethics committee. All patients provided written informed consent.

Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
AFF = atrial fibrillation or flutter
ARB = angiotensin receptor blocker
CI = confidence interval
CRF = case report form
eGFR = estimated glomerular filtration rate
HF = heart failure
HR = hazard ratio
MRA = mineralocorticoid receptor antagonist(s)

Study procedures. We used a computerized randomization system involving concealed study-group assignments to randomly assign patients to eplerenone or matching placebo with no stratification for subgroups. Eplerenone or matching placebo was started at a dose of 25 mg once daily (or 25 mg alternate days if eGFR was 30 to 49 ml/min/1.73 m^2) and increased after 4 weeks to 50 mg once daily (25 mg daily if eGFR was 30 to 49 ml/min/1.73 m^2), provided the serum potassium was no more than 5.0 mmol/l. Thereafter, investigators reviewed patients every 4 months and were instructed to decrease the dose of study drug if potassium was 5.5 mmol/l or more and to withhold it if potassium was 6.0 mmol/l or more. Potassium was to be rechecked within 72 h and study drug restarted only if potassium was <5.0 mmol/l. An electrocardiogram was recorded at baseline and at study closure.

Atrial fibrillation/flutter. BASELINE AFF. AFF status was determined from 3 separate parts of the study case report form (CRF): 1) the baseline electrocardiogram report; 2) the etiology of HF report and prior index hospitalization; and 3) the medical history page. Patients without AFF at baseline had no report of AFF in any of these 3 CRF sections. Patients with AFF at baseline had a report of AFF in any 1 of these sections.

NEW ONSET AFF. Because new onset AFF was a prespecified endpoint, a specially designed CRF focused on the occurrence of AFF during follow-up was collected during 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 adverse event report of AFF).

We also examined the impact of baseline AFF on primary and secondary outcomes and the effect of eplerenone by baseline AFF. The primary endpoint was the first occurrence of either death from cardiovascular causes or hospitalization for HF. The other key secondary endpoints were hospitalization for HF or death from any cause, death from any cause, death from cardiovascular causes, hospitalization for any cause, and hospitalization for HF.

Table 1 Baseline Characteristics in Patients With and Without AFF

	No AFF (n = 1,794)			AFF (n = 943)			
	Eplerenone (n = 911)	Placebo (n = 883)	Total (n = 1,794)	Eplerenone (n = 453)	Placebo (n = 490)	Total (n = 943)	p Value (No AFF vs. AFF)
Age, yrs	68 ± 7.6	67.9 ± 7.5	67.9 ± 7.5	70.1 ± 7.7	69.9 ± 7.7	70.0 ± 7.7	<0.0001*
Men, %	675 (74)	665 (75)	1,340 (75)	380 (84)	407 (83)	787 (83)	<0.0001*
Ischemic heart failure, %	659 (72.3)	619 (70.1)	1,278 (71.2)	292 (64.5)	316 (64.5)	608 (64.5)	0.0003*
Previous hospitalization for CHF, %	451 (49.5)	433 (49.0)	884 (49.3)	263 (58.1)	293 (59.8)	556 (59)	<0.0001*
Hypertension, %	588 (64.5)	569 (64.4)	1,157 (64.5)	322 (71.1)	340 (69.4)	662 (70.2)	0.0029*
Diabetes mellitus, %	330 (36.2)	275 (31.1)	605 (33.7)	129 (28.5)	125 (25.5)	254 (26.9)	0.0003*
Coronary artery bypass grafting, %	173 (19.0)	158 (17.9)	331 (18.5)	83 (18.3)	102 (20.8)	185 (19.6)	0.4717
EF, %	26 (4.6)	26 (4.7)	26 (4.7)	26.3 (4.7)	26.2 (4.7)	26.3 (4.7)	0.2034
Heart rate, beats/min	72.1 (14.4)	71.6 (14.6)	71.9 (14.5)	76.7 (17.3)	76 (16.6)	76.4 (16.9)	<0.0001*
Serum creatinine, mg/dl	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)	<0.0001*
Medications, %							
Diuretics	788 (86.5)	777 (88)	1,565 (87.2)	415 (91.6)	454 (92.7)	869 (92.2)	<0.0001*
ACE inhibitor/ARB	876 (96.2)	840 (95.1)	1,716 (95.7)	434 (95.8)	465 (94.9)	899 (95.3)	0.6976
Beta-blocker	820 (90.0)	801 (90.7)	1,621 (90.4)	413 (91.2)	447 (91.2)	860 (91.2)	0.4905
Digitalis glucosides	213 (23.4)	204 (23.1)	417 (23.2)	214 (47.2)	254 (51.8)	468 (49.6)	<0.0001*
Amiodarone	116 (12.7)	136 (15.4)	252 (14.0)	132 (29.1)	150 (30.6)	282 (29.9)	<0.0001*
Lipid-lowering agents	654 (71.8)	630 (71.4)	1,284 (71.6)	266 (58.7)	295 (60.2)	561 (59.5)	<0.0001*

Values are mean ± SD or n (%). *p Values were based on 2-sample *t* test for continuous variables and Fisher's exact test for categorical variables.
ACE = angiotensin-converting enzyme; AFF = atrial fibrillation or flutter; ARB = angiotensin receptor blocker; bpm = beats per minute; EF = ejection fraction; CHF = chronic heart failure.

Statistical analysis. The comparability of baseline characteristics between subjects without or with baseline AFF was assessed by 2-sample *t* test for continuous variables and Fisher's exact test for categorical variables.

The unadjusted and adjusted treatment effect on the risk of new onset AFF was assessed by Cox proportional hazards models without or with adjusting for the following prespecified baseline prognostic factors in the model: age, eGFR or serum creatinine, 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 ms.

Additionally, the subgroup analyses of the unadjusted treatment effect on the risk of primary and secondary outcomes were conducted on all randomized patients and according to the intention-to-treat principle stratified by subjects with or without baseline AFF using Kaplan-Meier estimates and Cox proportional hazards models including treatment as the only factor. The treatment-by-baseline AFF subgroup interaction was evaluated using a Cox proportional hazards model with terms for treatment, baseline AFF, and interactions between treatment and baseline AFF subgroup.

The association between baseline AFF and the risk of primary and secondary endpoints was assessed using Cox proportional hazards analyses including baseline AFF as the major factor in the model. Additionally, a multivariate Cox proportional hazards model was performed adjusting for the list of baseline characteristics that were found to be significantly imbalanced between patients without or with baseline AFF from Table 1.

Results

The study profile is presented in Figure 1 and the demographic characteristics of patients with and without AFF at baseline are presented in Table 1. Nine hundred and forty-three patients (34%) had AFF. Patients with AFF differed from non-AFF patients in almost all variables. Patients with AFF were significantly older and larger, had more prior hospitalizations, and had more hypertension but less diabetes. While ejection fraction was similar between those with and without AFF, patients with AFF had a higher heart rate and slightly higher serum creatinine. The balanced randomization between allocation groups was maintained despite absence of stratification for baseline AF.

New onset atrial fibrillation is presented in Figure 2, according to treatment group. Onset of new atrial fibrilla-

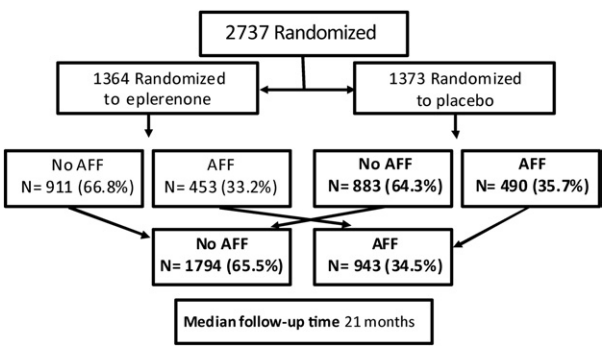

Figure 1 Study Profile

AFF = atrial fibrillation or flutter.

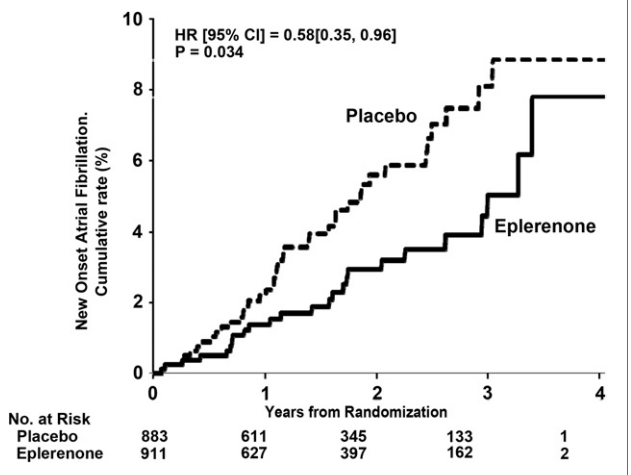

Figure 2 Incidence of Atrial Fibrillation or Flutter

New onset of atrial fibrillation or flutter in patients without atrial fibrillation or flutter at baseline. CI = confidence interval; HR = hazard ratio.

tion was significantly reduced by eplerenone and occurred in 25 of 911 eplerenone-treated patients (2.7%) versus 40 of 883 patients (4.5%) in the placebo group (hazard ratio [HR]: 0.58, 95% confidence interval [CI]: 0.35 to 0.96; p = 0.034). An adjusted analysis with covariables reduced the magnitude of the effect slightly (HR: 0.713, 95% CI: 0.485 to 1.050; p = 0.087).

Analysis of adverse event reports gave a similar finding with 55 and 76 cases reported for the eplerenone and placebo groups, respectively. Background use of ACE inhibitor or ARB did not influence the results (data not shown).

The effect of eplerenone on the primary endpoint (cardiovascular mortality or hospitalization for HF) was similar among patients with and without AFF at baseline (HR: 0.60, 95% CI: 0.46 to 0.79 vs. HR: 0.70, 95% CI: 0.57 to 0.85, respectively; p for interaction = 0.411) (Fig. 3). There were also similar effects of eplerenone on other major endpoints with no interaction according to the presence or absence of AFF at baseline. When adjusting for background use of an ACE inhibitor or an ARB at baseline, there was no significant interaction with the findings and treatment effect was maintained (data not shown).

The risk of the primary and secondary mortality and morbidity endpoints according to baseline AFF status (for both treatment groups combined) was not significantly higher in subjects with and without baseline AFF (HR: 1.13, 95% CI: 0.96 to 1.33; p = 0.152). For other major adjudicated cardiovascular endpoints, the findings were

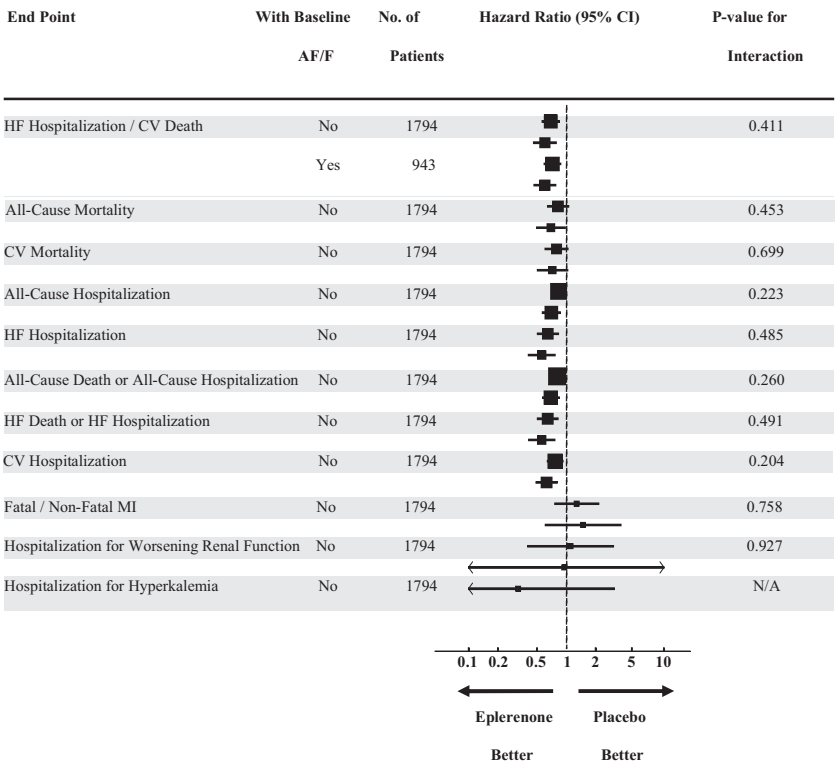

Figure 3 Effects of Eplerenone by Baseline Atrial Fibrillation or Flutter

Effects of eplerenone on major endpoints with interaction according to the presence or absence of atrial fibrillation or flutter at baseline. AF/F = atrial fibrillation/flutter; CI = confidence interval; CV = cardiovascular; HF = heart failure; MI = myocardial infarction.

similar between these groups except for all-cause hospitalization, which was associated with increased risk by AFF (HR: 1.17, 95% CI: 1.03 to 1.34) as well as all-cause death or all-cause hospitalization (HR: 1.18, 95% CI: 1.05 to 1.34). Adjusted analyses with covariables as in Table 2 showed similar results.

Discussion

In patients with systolic HF and mild symptoms, addition of eplerenone to recommended therapy reduced the incidence of new atrial fibrillation by 42%. Furthermore, the benefits of eplerenone in patients with a history of atrial fibrillation, or current atrial fibrillation, at baseline were similar to those in patients without atrial fibrillation. These benefits were obtained even though nearly all patients were also treated with other effective and recommended pharmacological agents (i.e., ACE inhibitors/ARBs and beta-blockers). Atrial fibrillation is a common arrhythmia in patients with HF and is related to the severity of HF. The annual incidence of atrial fibrillation in this trial was around 3%, which corresponds to an annual incidence of 4% to 5% in the COMET (Carvedilol Or Metoprolol European Trial) study (18) and the SHIFT (Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial) study (19) as more symptomatic patients in New York Heart Association functional class III were included in the latter 2 trials. The prognostic importance of atrial fibrillation per se is unclear, and in the present analysis we could not find an independent prognostic risk for cardiovascular events or death by AFF over and above other risk factors in HF. This observation is in agreement with the recent meta-analysis by Wasywich et al. (20).

Whether or not atrial fibrillation is an independent predictor of outcome in HF, its occurrence is commonly associated with symptom deterioration, and in addition atrial fibrillation increases the risk of stroke (21), necessitating treatment with anticoagulation with its associated inconvenience, cost, and bleeding hazard. Consequently, atrial fibrillation is best avoided, if possible. Unfortunately, there are few treatment options for preventing atrial fibrillation in HF. Although retrospective analyses and small prospective studies have suggested that ARBs (and ACE inhibitors) might prevent atrial fibrillation (8), this finding has not been confirmed in large prospective trials (10,11) and, in any case, atrial fibrillation still occurs frequently in patients taking these drugs, as shown in the present study. Beta-blockers may also reduce the incidence of AFF but should, in any case, be used routinely in systolic HF. (22). Beta-blockers were used extensively in EMPHASIS-HF and despite this (and the use of ACE inhibitors and ARBs), eplerenone still reduced the incidence of AFF. Additional prevention can be achieved by class III antiarrhythmic drugs, which have been shown to reduce the incidence of atrial fibrillation in HF (23), but these agents have unacceptable toxicity and uncertain safety in patients with acute and severe HF (23,24). By comparison, eplerenone is a well-tolerated and safe alternative that has substantial additional clinical benefits, provided it is initiated under monitoring of serum potassium and creatinine as in our study.

The mechanism, or mechanisms, through which eplerenone reduced the incidence of atrial fibrillation is uncertain. Renin-angiotensin-aldosterone system activation may contribute to atrial remodeling and fibrosis in HF, which are thought to be key triggers of atrial fibrillation. MRAs attenuate structural remodeling of the atria in animal models and improve electrical remodeling, at least in part by reducing fibrosis in animal models (7,25,26). MRAs may also reduce cardiac electrical instability by reducing the risk of hypokalemia.

Study limitations. Our results may not be applicable to all patients with mild symptoms, because in this study patients were required to have additional factors known to increase cardiovascular risk, including age ≥55 years, in most cases an ejection fraction <30%, and a recent cardiovascular hospitalization. Although the incidence of new atrial fibrillation was collected prospectively using a specific investigator-completed CRF, we did not carry out ambulatory monitoring. Consequently, we are likely to have underestimated the incidence of atrial fibrillation, particularly paroxysmal atrial fibrillation, unless such episodes resulted in deterioration in symptoms necessitating physician contact or admission to hospital. Our sensitivity analysis based on adverse event reporting suggests that our findings are robust, but the magnitude of underreporting remains uncertain.

Conclusions

In patients with systolic HF and mild symptoms, addition of eplerenone to recommended therapy reduced the incidence of new onset AFF. The effects of eplerenone on the risk of major cardiovascular events were similar in patients with and without AFF at baseline.

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Key Words: aldosterone antagonism ■ atrial fibrillation ■ heart failure.