Mineralocorticoid Receptor Antagonists and Cardiovascular Mortality in Patients With Atrial Fibrillation and Left Ventricular Dysfunction

Insights From the Atrial Fibrillation and Congestive Heart Failure Trial

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Background—Patients with heart failure (HF) and atrial fibrillation (AF) may differ from the larger HF population with respect to comorbidities, including renal impairment and overall prognosis. Associated cardiorenal interactions may mitigate the effects of pharmacological agents. Our primary objective was to assess the impact of mineralocorticoid receptor antagonists on cardiovascular mortality in patients with AF and HF enrolled in the Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial.

Methods and Results—All 1376 patients randomized in the AF-CHF trial were included. The median baseline creatinine was 105.2 (Q1 88.4, Q3 125.0) μmol/L, and the median estimated glomerular filtration rate was 62.3 (Q1 49.0, Q3 77.2) mL/min per 1.73 m². The renal function was moderately or severely impaired (ie, estimated glomerular filtration rate <60 mL/min per 1.73 m²) in 46.5% of patients. In multivariable analyses, increased creatinine was associated with worsening HF but not mortality. Mineralocorticoid receptor antagonists were prescribed in 44.8% and were independently associated with a 1.4-fold increase in total mortality (hazard ratio, 1.4; 95% CI [1.1–1.8]; *P*=0.005) and a 1.4-fold increase in cardiovascular mortality (hazard ratio, 1.4; 95% CI [1.1–1.9]; *P*=0.009). This was driven by an increased incidence of sudden cardiac death (hazard ratio, 2.0; 95% CI [1.3, 3.0]; *P*=0.001).

Conclusions—Renal dysfunction was highly prevalent in patients with AF and HF. Mineralocorticoid receptor antagonists were independently associated with an increased incidence of cardiovascular deaths, predominantly of presumed arrhythmic cause. Although these provocative findings merit prospective validation, they underscore the importance of careful monitoring of renal function and electrolytes in patients with AF and HF receiving mineralocorticoid receptor antagonists.

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Key Words: atrial fibrillation ■ heart failure ■ mineralocorticoid receptor antagonists ■ renal function ■ sudden death

Atrial fibrillation (AF) is common in patients with heart failure (HF), with a prevalence reaching 40% in advanced stages.[1,2] Although sound clinical trials support benefits associated with β-blockers, renin-angiotensin antagonists, and mineralocorticoid receptor antagonists (MRAs) in patients with HF in general, the subpopulation with concomitant AF has not been extensively studied. Patients with HF and AF may differ from the larger HF population with respect to comorbidities, concomitant medications, and overall prognosis.[1–8] The degree of renal dysfunction, structural, neurohormonal, and inflammatory changes associated with AF, and increased use of digitalis and antiarrhythmic agents may mitigate responses to HF therapy. For example, the prevalence of chronic kidney disease (CKD) is higher in patients with AF, because the 2 conditions share common risk factors and pathophysiological mechanisms.[9] Cardiorenal interactions may, therefore, compromise the efficacy of therapeutic agents for HF to a greater extent in patients with AF.

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Subsequent to the Randomized Aldactone Evaluation Study (RALES) trial, which demonstrated a survival advantage of spironolactone in patients with severe HF,[10] population-based data have cautioned that MRA may increase mortality in

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real-world practice[11,12] due, in part, to potential cardiorenal interactions.[12–14] Over a decade after the RALES trial, the degree of clinical benefit derived from MRA, particularly spironolactone, remains uncertain in patients with AF and HF on contemporary optimal HF therapy. Although the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial, which assessed the impact of eplerenone in New York Heart Association (NYHA) class II patients with HF, included 30% of patients with AF,[15] no prospective randomized trial has focused on MRA in patients with AF and HF. We, therefore, sought to assess the impact of MRA on cardiovascular mortality in the Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial, a study that exclusively enrolled patients with AF and systolic ventricular dysfunction.

Methods

Study Population

The AF-CHF trial randomized 1376 patients with HF, systolic dysfunction, and a recent history of AF to rhythm versus rate control strategies. The study protocol has been previously described.[16,17] In short, inclusion criteria consisted of a history of electrocardiographically documented AF, left ventricular ejection fraction (LVEF) ≤35%, and NYHA class II to IV symptoms within 6 months of randomization, or class I symptoms if the LVEF was ≤25% or if the patient was hospitalized for HF in the previous 6 months. Patients were excluded if they were expected to live <1 year, had persistent AF for >12 months, were candidates for heart transplantation within 6 months, had decompensated HF in the 48 hours before randomization, or had renal failure requiring dialysis. The study protocol was approved by each center's institutional review board, and all patients provided written informed consent.

Renal Function

Baseline serum creatinine levels were available in 1365 patients (99.2%). Renal function was also evaluated according to the estimated glomerular filtration rate (eGFR), using categories of CKD as follows[18]: normal, >90 mL/min per 1.73 m²; mildly impaired, 60–90 mL/min per 1.73 m²; moderately impaired, 30–60 mL/min per 1.73 m²; severely impaired, <30 mL/min per 1.73 m². The eGFR was calculated using the modification of diet in renal disease abbreviated equation,[18] where eGFR (mL/min per 1.73 m²)=$186 \times [Pcr]^{-1.154} \times [age]^{-0.203} \times [0.742$ if women]$\times [1.212$ if race is black].

Pharmacological Therapy

Recommended pharmacological therapy included anticoagulants, the maximum tolerated dose of β-blockers, and angiotensin-converting-enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) for all patients. As per current guidelines, spironolactone (12.5–50 mg/day) was recommended during the randomization period in patients receiving a loop diuretic with NYHA functional class III or IV symptoms, a serum creatinine ≤2.5 mg/dL, and a serum potassium ≤5.0 mEq/L. The assigned treatment strategy for AF (ie, rate versus rhythm control) was initiated immediately after randomization. Patients assigned to rhythm control systematically received amiodarone as the initial antiarrhythmic drug. Targets for rate control were heart rates <80 beats per minute at rest and <110 beats per minute during 6-minute walk tests. Recommended β-blockers were carvedilol, bisoprolol, and metoprolol. Clinicians were instructed to provide optimal medical therapy.

Outcomes

Patients were seen at 3 weeks and 4 months, followed by visits every 4 months through 4 years and then every 6 months until 6 years. As in the main intention-to-treat analysis,[17] the primary outcome for the current study was cardiovascular death. Secondary outcomes included presumed arrhythmic death, all-cause mortality, and worsening heart failure. A presumed arrhythmic death was defined as a sudden cardiovascular death occurring <1 hour after the onset of symptoms and deemed not be because of another cardiovascular cause, such as an ischemic event. Sudden deaths during sleep, unwitnessed deaths, and unmonitored deaths in previously stable patients were presumed to be arrhythmic in origin. All events were classified by an independent adjudicating committee blinded to the treatment assignment.

Statistical Analysis

Continuous variables were presented as mean±SD or median and interquartile range (Q1–Q3) according to their distribution and categorical variables as frequencies and percentages. Baseline variables were assessed overall and according to whether or not patients received MRA. Two-group comparisons were made using independent Student t, Mann-Whitney, or χ^2 tests, where appropriate. After verifying proportionality assumptions, univariable and multivariable Cox regression models were created for each of the 4 outcomes, ie, cardiovascular mortality, presumed arrhythmic death, all-cause mortality, and worsening heart failure. On the basis of substantive knowledge, the following exposure variables were included in all multivariable models, regardless of their statistical associations: AF-CHF treatment assignment (rate versus rhythm control), MRA therapy as a time-dependent variable, NYHA functional class, LVEF, creatinine, potassium, and use of a diuretic at baseline. Remaining baseline variables were assessed in univariable Cox regression models, and those significant at the 0.2 level were included in backward multivariable models and retained if the P value was <0.20. Variables considered for such models included patient demographics (eg, age at randomization, sex, body mass index), AF and HF history (eg, paroxysmal versus persistent AF, time since initial diagnosis of AF, hospitalization for HF within 6 months of randomization), comorbidities (eg, coronary artery disease, prior myocardial infarction, hypertension, diabetes mellitus requiring pharmacological therapy, prior stroke), medications (eg, ACE inhibitors or ARBs, lipid-lowering drug, oral anticoagulant, digoxin, β-blockers, antiarrhythmic agents), physical examination (eg, diastolic blood pressure, heart rate, peripheral edema), additional cardiac parameters (eg, QRS width, left atrial diastolic dimension, degree of mitral regurgitation, cardiomegaly, pulmonary congestion by chest x-ray), and blood tests (eg, serum sodium level). Digoxin, β-blockers, and antiarrhythmic agents were, along with MRA, modeled as time-dependent variables to account for changes over the course of the study. For each time-to-event outcome, Kaplan-Meier product limit curves were plotted according to whether patients received an aldosterone antagonist at baseline or not, with comparisons by log-rank tests.

In a second approach to multivariable modeling to assess the impact of MRA therapy on the 4 time-to-event outcomes, a propensity score was generated to adjust for baseline imbalances. This was derived from a nonparsimonious logistic regression model, with aldosterone antagonist therapy as the outcome variable. The following variables were included in the propensity score: treatment, age, sex, race, NYHA class, history of cerebrovascular event, LVEF, primary classification of AF, time since first diagnosis of AF, QRS width, left atrial diameter, hospitalization for HF within 6 months, digoxin, ACE inhibitors or ARBs, lipid-lowering drug, β-blocker, potassium level, and proportion of time spent in sinus rhythm. The propensity score was modeled as a continuous variable in multivariable Cox regression analyses that included MRA as a time-dependent variable. In a subgroup analysis of 183 patients in whom serial serum creatinine and potassium levels were available, similar models were created but with creatinine and potassium as time-dependent variables.

Because multivariable regression approaches without and with propensity scores yielded similar results for all outcomes, the former analyses are presented. All statistical analyses were performed using SAS software version 9.2 (SAS Institute Inc, Cary, NC). For all analyses, $P<0.05$ was considered statistically significant. The authors had full access to the data and take responsibility for its integrity.

Results

Baseline Characteristics

All 1376 patients randomized in the AF-CHF trial were included. Table 1 summarizes baseline characteristics in all patients and according to whether or not MRAs were prescribed. Data for eGFR calculations were available in 1354 (98.4%) patients. The median baseline creatinine level was 105.2 (Q1 88.4, Q3 125.0) μmol/L, and the mean baseline eGFR was 63.6±20.6 mL/min per 1.73 m². Renal function was impaired severely in 3.2% of patients, moderately in 43.3%, mildly in 44.1%, and was normal in 9.4%. Thus, nearly half the patients (46.5%) had at least moderate CKD (ie, eGFR <60 mL/min per 1.73 m²).

MRAs were received by 616 (44.8%) patients at baseline, who predominantly had eGFRs >30 mL/min per 1.73 m². As expected, patients receiving MRA had lower LVEFs, larger left atrial dimensions, more cardiomegaly and peripheral edema, a higher NYHA functional class, and were more frequently hospitalized for HF within 6 months before randomization. They also more frequently had persistent AF, had longer durations of AF, wider QRS complexes, more moderate renal dysfunction, and lower blood pressure. Patients on MRAs at baseline more often received ACE inhibitors or ARBs, diuretics, and digoxin but were less frequently prescribed lipid-lowering drugs.

Cardiovascular Outcomes and MRAs

Over the course of the study, 445 patients died, 357 of which were from cardiovascular causes, with 159 deaths of presumed arrhythmic cause. In addition, a total of 402 episodes qualified as worsening HF. In multivariable analyses, MRAs had no appreciable impact on episodes of worsening HF (hazard ratio [HR], 0.9; 95% CI [0.7–1.2]; *P*=0.40).

Figures 1 to 3 portray the unadjusted associations between MRA (predominantly spironolactone) therapy and total mortality (Figure 1), cardiovascular mortality (Figure 2), and arrhythmic deaths (Figure 3). In multivariable regression analyses, MRA therapy was associated with a 1.4-fold increase in total mortality (HR, 1.4; 95% CI [1.1–1.8]; *P*=0.005) and a 1.4-fold increase in cardiovascular mortality (HR, 1.4; 95% CI [1.1–1.9]; *P*=0.009), driven by an increase in presumed arrhythmic deaths (HR, 2.0; 95% CI [1.3–3.0]; *P*=0.001), with no effect on nonarrhythmic deaths. Table 2 summarizes the multivariable model for presumed arrhythmic deaths.

Cardiovascular Outcomes and Renal Function

In multivariable analyses, a higher baseline creatinine level was not associated with an increase in all-cause mortality or cardiovascular mortality. However, the risk of worsening HF increased with the serum creatinine level (HR, 1.09 per 27 μmol/L [0.3 mg/dL]; 95% CI [1.03–1.16]; *P*=0.0026). Model fits were comparable with creatinine and eGFR, such that the former was retained in multivariable analyses. Baseline potassium levels were not independently associated with mortality (total or cardiovascular), worsening HF, or arrhythmic deaths. However, in the small subset of patients in whom follow-up potassium levels were available (N=183; all from Montreal, Canada, or Denmark), lower serum potassium levels on follow-up were associated with an increase in cardiovascular mortality (*P*=0.003).

Concomitant HF Therapy

In multivariable analyses, digoxin was not associated with all-cause mortality or with worsening HF but was associated with a nonstatistically significant increased likelihood of presumed arrhythmic death (HR, 1.5; 95% CI [1.0–2.4]; *P*=0.07). In contrast, β-blockers were associated with a 40% reduction in total mortality (HR, 0.6; 95% CI [0.5–0.8]; *P*=0.0002) and cardiovascular mortality (HR, 0.6; 95% CI [0.4–0.8]; *P*=0.0002), as well as with a 50% reduction in arrhythmic death (HR, 0.5; 95% CI [0.3–0.7]; *P*=0.0004). Diuretic use was not predictive of mortality outcomes. The impact of ACE inhibitors or ARBs could not be assessed, because 95% of patients received such therapy.

Discussion

The AF-CHF trial provided a unique opportunity to assess the impact of MRAs on outcomes in patients with AF and HF, with nearly 45% of the study population receiving such therapy. MRAs were associated with a 1.4-fold increase in total and cardiovascular mortality in multivariable analyses. This was driven by a 2-fold increased risk of death of presumed arrhythmic cause, with no effect on nonarrhythmic death or hospitalizations for worsening heart failure. Importantly, the prescribed MRA was almost exclusively spironolactone, because eplerenone was introduced in the market after a vast majority of patients had been randomized. Although MRAs were recommended in patients with NYHA class III or IV symptoms, management decisions remained at the discretion of the treating physician. Notably, the functional status may have improved between the initial prescription of an MRA and enrolment in AF-CHF, explaining the discrepancy between the NYHA functional class distribution 6 months before randomization and at randomization.

Although multivariable regression models were not specifically designed to address the impact of other forms of heart failure therapy, β-blockers were associated with the expected reduction in total, cardiovascular, and arrhythmic mortality. The nonsignificant trend between digoxin and presumed arrhythmic deaths may be consistent with the results of a substudy of the DIG [Digitalis Intervention Group] trial, in which serum potassium levels <4 mEq/L predicted increased mortality in patients with CKD.[19] The interplay among digoxin, renal failure, and serum potassium levels merits further study.

Underlying reasons for the observed increased mortality, particularly sudden arrhythmic deaths, in patients with AF and HF receiving spironolactone remain speculative and may involve an interplay among the higher prevalence of renal dysfunction, greater use of digoxin and antiarrhythmic agents, potassium imbalances, cardiac structural or functional anomalies, and particularities related to the type of MRA prescribed.

In this AF-CHF substudy, renal dysfunction was found to be highly prevalent. CKD is associated with multiple comorbid conditions and markers of cardiovascular risk. In comparison with patients included in the EMPHASIS-HF trial,[15] patients in AF-CHF had more advanced CKD (eGFR 71.2±21.9 mL/min per 1.73 m² in the eplerenone group of EMPHASIS versus 63.6±20.6 mL/min per 1.73 m² in AF-CHF). The level of renal

Table 1.   Baseline Characteristics in All Patients and According to Whether or Not They Received an MRA

Variable	All Patients (N=1376)	No MRA (N=760)	MRA (N=616)	P Value*
Age at randomization, y	66.8±11.1	67.3±10.9	66.1±11.2	0.0410
Male sex, N (%)	1124 (81.7)	628 (82.6)	496 (80.5)	0.3138
Race, N (%)				<0.0001
White	1176 (85.5)	696 (91.6)	480 (77.9)	
Black	25 (1.8)	14 (1.8)	11 (1.8)	
Other	175 (12.7)	50 (6.6)	125 (20.3)	
Body mass index, kg/m²	27.9±5.2	27.8±5.1	28.0±5.4	0.4892
Coronary artery disease, N (%)	656 (47.8)	377 (49.6)	279 (45.5)	0.1313
Hypertension, N (%)	656 (47.7)	375 (49.3)	281 (45.6)	0.1689
Diabetes mellitus requiring medications, N (%)	283 (20.6)	164 (21.6)	119 (19.3)	0.3022
Prior TIA, stroke, or intracranial bleed, N (%)	124 (9.0)	81 (10.7)	43 (7.0)	0.0178
Left ventricular ejection fraction, %	26.9±6.0	27.5±5.9	26.2±6.1	<0.0001
Left atrial diastolic dimension, mm	49.1±7.3	48.3±7.2	50.1±7.4	<0.0001
At least moderate mitral regurgitation, N (%)	438 (33.7)	225 (31.5)	213 (36.4)	0.0632
Cardiomegaly on chest x-ray, N (%)	938 (78.2)	465 (72.5)	473 (84.8)	<0.0001
NYHA class at randomization, N (%)				0.0001
1–2	945 (68.7)	555 (73.0)	390 (63.3)	
3–4	431 (31.3)	205 (27.0)	226 (36.7)	
Worst NYHA class within 6 mo before randomization, N (%)				<0.0001
1–2	331 (24.1)	226 (29.8)	105 (17.0)	
3–4	1044 (75.9)	533 (70.2)	511 (83.0)	
Primary classification of AF, N (%)				0.0458
Persistent	944 (68.7)	504 (66.4)	440 (71.4)	
Paroxysmal	431 (31.3)	255 (33.6)	176 (28.6)	
Time since first diagnosis of AF, N (%)				<0.0001
0–6 mo	781 (56.8)	465 (61.2)	316 (51.3)	
6–12 mo	303 (22.0)	128 (16.8)	175 (28.4)	
≥12 mo	292 (21.2)	167 (22.0)	125 (20.3)	
QRS duration, ms	113.7±29.8	111.1±27.6	117±32.1	0.0006
Creatinine, μmol/L †	105.2 (88.4, 125.0)	103.0 (88.2, 124.8)	106.1 (88.4, 126.0)	0.0185
Estimated GFR, mL/min per 1.73 m²	63.6±20.6	64.9±21.5	62.1±19.4	0.0124
Estimated GFR category, %				0.0046
<30 mL/min per 1.72 m²	43 (3.2)	27 (3.6)	16 (2.6)	
30–60 mL/min per 1.72 m²	586 (43.3)	301 (40.2)	285 (47.0)	
60–90 mL/min per 1.72 m²	597 (44.1)	333 (44.5)	264 (43.6)	
>90 mL/min per 1.72 m²	128 (9.4)	87 (11.6)	41 (6.8)	
Serum potassium, mEq/L	4.3±0.5	4.3±0.5	4.3±0.6	0.6536
Heart failure therapy, N (%)				
ACE inhibitor or ARB	1315 (95.6)	712 (93.7)	603 (97.9)	0.0002
Aldosterone antagonist	616 (44.8)	0	616 (100)	N/A
β-blocker	1085 (78.9)	591 (77.8)	494 (80.2)	0.2720
Diuretic	1124 (81.7)	582 (76.6)	542 (88.0)	<0.0001
Digoxin	886 (64.4)	429 (56.5)	457 (74.2)	<0.0001
Lipid-lowering drug, N (%)	585 (42.5)	343 (45.1)	242 (39.3)	0.0292
Antiplatelet drug, N (%)	548 (39.8)	304 (40.0)	244 (39.6)	0.8833
Oral anticoagulant, N (%)	1215 (88.3)	661 (87.0)	554 (89.9)	0.0892
Implanted cardioverter-defibrillator, N (%)	97 (7.1)	52 (6.8)	45 (7.3)	0.7386
Hospitalization for HF within 6 mo before randomization, N (%)	754 (54.8)	358 (47.1)	396 (64.3)	<0.0001

(*Continued*)

Table 1.   Continued

Variable	All Patients (N=1376)	No MRA (N=760)	MRA (N=616)	P Value*
Heart rate, bpm	77.9±19.2	77.6±19.1	78.3±19.2	0.5428
Systolic blood pressure, mm Hg	118.9±19.4	122.3±19.5	114.7±18.3	<0.0001
Diastolic blood pressure, mm Hg	71.1±12.1	72.6±12.5	69.2±11.3	<0.0001
Peripheral edema, N (%)				0.0033
Mild (1+)	358 (26.1)	173 (22.8)	185 (30.1)	
Marked (≥2+)	67 (4.9)	33 (4.4)	34 (5.5)	
Pulmonary rales, N (%)	178 (13.0)	89 (11.7)	89 (14.5)	0.1294

MRA indicates mineralocorticoid receptor antagonist; TIA, transient ischemic attack; NYHA, New York Heart Association; AF, atrial fibrillation; GFR, glomerular filtration rate; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; N/A, not applicable; HF, heart failure; bpm, beats per minute.

*Comparing patients receiving MRA and those not receiving this therapy.

†Non-normally distributed continuous variables are summarized as median (Q1, Q3).

function was also lower than in other HF trials at large (eg, eGFR 70–73 mL/min per 1.73 m²).[20–22] Lower renal function combined with different comorbidities could increase the likelihood of cardiorenal interactions in the context of multiple inhibitors of the renin-angiotensin-aldosterone system. Atrial fibrillation begets CKD, and vice versa.[9] Common pathophysiological mechanisms are thought to include inflammation, oxidative stress, and activation of the renin-angiotensin-aldosterone system.[23–29] In addition, undesirable effects of AF may be further compounded by coexisting HF. For example, left atrial remodeling associated with AF leads to mitral annular dilatation and mitral regurgitation. Consequently, cardiac output and renal perfusion may be further reduced, lessening the benefits of MRAs.

Consistent with our findings, a large population-based study[11] demonstrated higher mortality after increases in prescriptions of spironolactone after publication of the RALES trial.[10] The increased mortality was thought to be mediated by associated hyperkalemia.[11–14] β-blocker prescriptions were also increasing during the same period, which may be of relevance for certain cardiorenal interactions.[13,14] Potassium levels

are influenced by complex interactions involving comorbidities (namely diabetes mellitus and renal disease) and concomitant therapies.[12,13] Interestingly, in the subgroup of 183 patients in whom follow-up potassium data were obtained, lower rather than higher potassium levels were associated with increased cardiovascular mortality. This relationship has been recently observed by others as well.[19] It may be speculated that hypokalemia is more likely to be undertreated in patients with CKD (as in the AF-CHF population), particularly when MRAs are prescribed, resulting in a higher incidence of sudden death. It may be reasonable, therefore, to target potassium levels of 4.0, as per recent recommendations.[19] Importantly, serum potassium and renal function were closely monitored in all MRA trials, underscoring important differences with real-world care.

Limitations of this post hoc analysis include the nonrandomized allocation of MRAs. Attendant biases were thoroughly addressed using 2 complementary statistical approaches: multivariable analyses that adjusted for baseline imbalances and potential confounders, and propensity-adjusted
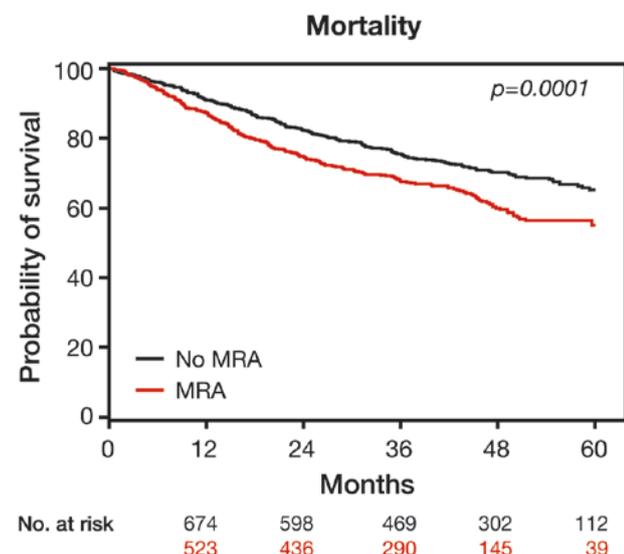

Figure 1. The Kaplan-Meier curves depict overall survival in patients with and without mineralocorticoid receptor antagonist (MRA) (predominantly spironolactone) therapy.
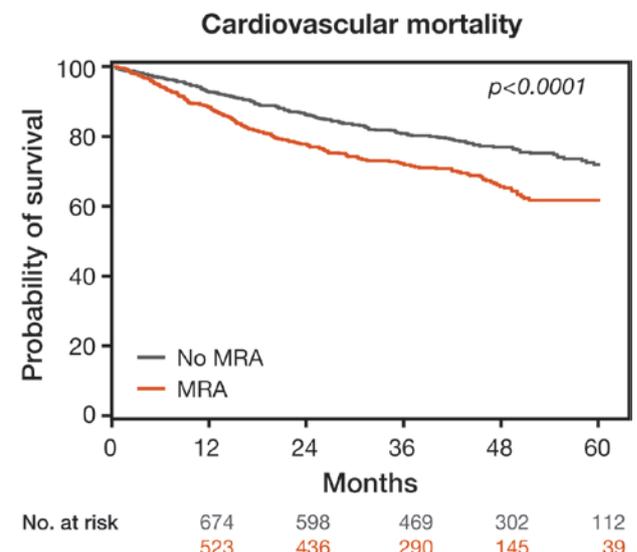

Figure 2. Freedom from cardiovascular mortality in patients with and without mineralocorticoid receptor antagonist (MRA) (predominantly spironolactone) therapy is plotted using the Kaplan-Meier product limit method.
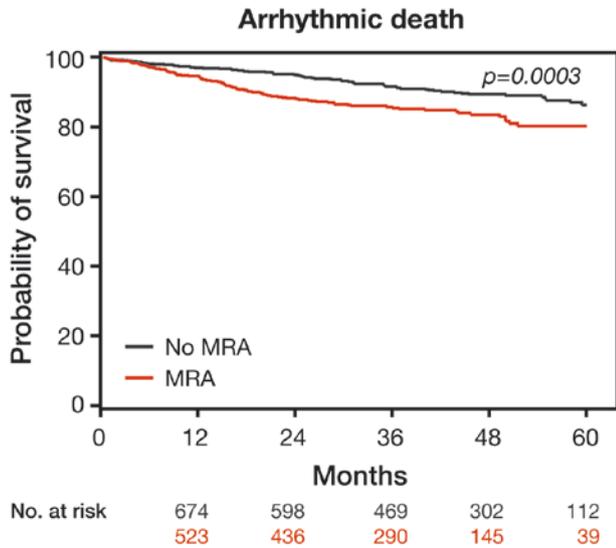
Arrhythmic death

Figure 3. Shown are Kaplan-Meier event-free survival curves for arrhythmic death in patients with and without mineralocorticoid receptor antagonist (MRA) (predominantly spironolactone) therapy.

Table 2. The Multivariable Model* for Presumed Arrhythmic Deaths in the AF-CHF Population

Parameter	Hazard Ratio	95% CI	P Value
Treatment group (rhythm vs rate control)	0.80	0.54–1.19	0.27
MRA (time dependent)	1.97	1.31–2.96	0.001
NYHA class 3–4 vs 1–2	0.80	0.52–1.21	0.28
Left ventricular ejection fraction, %	1.01	0.98–1.04	0.53
Mitral regurgitation (moderate or more vs none or mild)	1.37	0.94–2.02	0.11
Cardiomegaly on chest x-ray	1.73	0.97–3.08	0.06
Diastolic blood pressure (per 10 mm Hg)	0.86	0.73–1.02	0.09
Previous myocardial infarction	1.48	1.00–2.18	0.05
Baseline creatinine (per 27 μmol/L or 0.3 mg/dL)	1.06	0.95–1.18	0.32
Diuretics (baseline)	1.58	0.83–2.99	0.16
Potassium (baseline)	1.06	0.75–1.49	0.76
QRS width (per 10 ms)	1.07	1.01–1.13	0.02
ACE or ARB (baseline)	0.52	0.22–1.25	0.15
Digoxin (time dependent)	1.52	0.97–2.39	0.07
β-blockers (time dependent)	0.47	0.31–0.71	0.0004

AF-CHF indicates Atrial Fibrillation and Congestive Heart Failure; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; ACE, angiotensin-converting-enzyme; ARB, angiotensin-receptor blocker; HF, heart failure.

The following additional variables were associated with P values ≤0.20 in univariable analyses and were, therefore, considered in the multivariable model: age at randomization, body mass index, coronary artery disease, diabetes mellitus requiring medication, transient ischemic attack, stroke, or intracranial bleed, oral anticoagulant, antiplatelet agent, left atrial dimension (mm), serum sodium, hospitalization for HF in the 6 mo before randomization, peripheral edema, rales, radiological signs of pulmonary congestion.

*After backward selection of variables.

regression analyses. The 2 approaches yielded congruent results. Although multivariable analyses do not control for unmeasured variables, our findings cannot be explained by baseline differences in observed HF-related variables. Importantly, MRA-treated patients did not experience higher rates of worsening HF or nonarrhythmic deaths in adjusted analyses, suggesting that multivariable models adequately controlled for imbalances in unmeasured HF-related patient characteristics.

Increases in creatinine or potassium levels over time may have influenced the choice of medical therapy. Whereas baseline levels were systematically collected in all participants and included in multivariable analyses, data on follow-up creatinine and potassium levels were available only in a subgroup of 183 patients. Importantly, MRA use was modeled as a time-dependent variable, such that patient time was attributed to the exposure category under observation.

Our findings may not be generalizable to MRAs other than spironolactone. Substantial differences in the pharmacological properties of spironolactone and eplerenone[30] may be of clinical relevance. Spironolactone has 3 active metabolites and a much longer half-life than eplerenone, which has no active metabolites. Eplerenone has a much lower affinity for androgen, progesterone, and glucocorticoïd receptors than spironolactone, which enhances tolerability and may improve glucose control.[31] Spironolactone seems to increase cortisol levels in comparison with eplerenone,[31] and higher cortisol levels could predict cardiac events in HF.[32] Finally, it also seems that eplerenone produces more consistent inhibition of some nongenomic effects of aldosterone, such as coronary vasoconstriction and increased systemic vascular resistance.[33]

In the RALES trial (N=1663), which compared spironolactone with placebo, only 11% received β-blockers.[10] This is in stark contrast to 80% of patients in AF-CHF. This may be relevant to our findings, because some of the benefits of β-blockers and MRAs are produced by similar mechanisms.[34]

The proportion of patients enrolled in the RALES trial (spironolactone versus placebo) with AF cannot be deduced from the published data. In contrast, AF was present in ≈30% of the study population in EMPHASIS-HF.[15] In this trial, there was no detectible interaction between AF and the impact of eplerenone on the primary outcome of cardiovascular death or heart failure–related hospitalization. These disparate findings may reflect the fact that different MRAs were used in AF-CHF (ie, spironolactone) and EMPHASIS-HF (ie, eplerenone). Furthermore, the rate of sudden death was lower in EMPHASIS-HF (ie, 5%) compared with AF-CHF (ie, >10%). In addition, potassium and creatinine levels were closely monitored in EMPHASIS-HF, and a higher proportion of patients received implantable cardioverter-defibrillators.

Conclusions

In our analyses of patients with HF and AF, MRAs (predominantly spironolactone) were associated with increased cardiovascular and total mortality, driven by an increased incidence of sudden death. Our results should be considered hypothesis generating and require confirmation by prospective randomized clinical trials. Importantly, these findings may not be generalized to eplerenone and newer, more

selective, MRAs. Pathophysiological mechanisms remain to be elucidated and may include cardiorenal interactions and potassium imbalances. Close monitoring of serum potassium and renal function seems warranted in patients with AF and HF who receive MRAs. Prospective studies reassessing combinations of currently recommended HF therapy are required to optimize the pharmacological management of patients with AF and HF.

Sources of Funding

Disclosures

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CLINICAL PERSPECTIVE

Atrial fibrillation (AF) is common in patients with heart failure (HF), with a reported prevalence as high as 40%. Although sound clinical trials support benefits associated with β-blockers, renin-angiotensin antagonists, and mineralocorticoid receptor antagonists (MRAs) in patients with HF in general, the subpopulation with concomitant AF has not been extensively studied. This population is particularly prone to chronic kidney disease, such that cardiorenal interactions may compromise the efficacy of therapeutic agents for HF to a greater extent in patients with AF. We, therefore, sought to assess the impact of MRAs on cardiovascular mortality in the Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial, a study that exclusively enrolled patients with AF and systolic ventricular dysfunction. The AF-CHF trial provided a unique opportunity to assess the impact of MRAs on outcomes in patients with AF and HF, with nearly 45% of the study population receiving such therapy. The prescribed MRA was almost exclusively spironolactone, because eplerenone was introduced in the market after a vast majority of patients had been randomized. In multivariable analyses, MRAs were associated with a 1.4-fold increase in total and cardiovascular mortality. This was driven by a 2-fold increased risk of sudden death of presumed arrhythmic cause, with no effect on nonarrhythmic death or hospitalizations for worsening heart failure. Although these provocative findings merit prospective validation, they underscore the importance of careful monitoring of renal function and electrolytes in patients with AF and HF receiving MRAs.

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Mineralocorticoid Receptor Antagonists and Cardiovascular Mortality in Patients With Atrial Fibrillation and Left Ventricular Dysfunction: Insights From the Atrial Fibrillation and Congestive Heart Failure Trial

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