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ORIGINAL ARTICLE

Impact of Insulin Treatment on the Effect of Eplerenone: Insights From the EMPHASIS-HF Trial

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BACKGROUND: Patients with heart failure with reduced ejection fraction (HFrEF) and insulin-treated diabetes have a high risk of cardiovascular complications. Mineralocorticoid receptor antagonists may mitigate this risk. We aim to explore the effect of eplerenone on cardiovascular outcomes and all-cause mortality in HFrEF patients with diabetes, including those treated with insulin in the EMPHASIS-HF trial (Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms).

METHODS: The primary outcome was the composite of heart failure hospitalization or cardiovascular death. Cox models with treatment-by-diabetes subgroup interaction terms were used.

RESULTS: The median follow-up was 21 (10–33) months. Of the 2737 patients included, 623 (23%) had non-insulin-treated diabetes, 236 (9%) had insulin-treated diabetes and 1878 did not have diabetes. Patients with insulin-treated diabetes were younger, more often women, with higher body mass index, waist circumference, more frequent ischemic heart failure cause, impaired kidney function, and longer diabetes duration. Compared with patients without diabetes, those with insulin-treated diabetes had a 2-fold higher risk of having a primary outcome event. The hazard ratio (95% CI) for the effect of eplerenone, compared with placebo, on the primary outcome was 0.31 (0.19–0.50) in insulin-treated diabetes, 0.69 (0.50–0.93) in non-insulin-treated diabetes, and 0.72 (0.58–0.88) in patients without diabetes; interaction P=0.007. The annualized number needed-to-treat-to-benefit with regards to the primary outcome was 3 (95% CI, 3–4) in patients with insulin-treated diabetes, 16 (13–19) in patients with diabetes not receiving insulin, and 26 (24–28) in patients without diabetes.

CONCLUSIONS: Patients with insulin-treated diabetes experienced a greater benefit from eplerenone than those with diabetes not treated with insulin and people without diabetes.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT00232180.

Key Words: body mass index ■ eplerenone ■ heart failure ■ insulin ■ mineralocorticoid receptor antagonists

Patients with insulin-treated diabetes have a high risk of cardiovascular and other complications, often leading to hospitalization and death.[1] The risk of patients with diabetes treated with insulin is higher than the risk of patients with diabetes treated with oral antidiabetic drugs only (non-insulin-treated diabetes).[2–4] Insulin treatment is associated with long-standing diabetes, poor cardiometabolic profile (higher body mass index, abdominal obesity, heart rate, blood pressure, triglycerides, and lower HDL [high-density lipoprotein] cholesterol) and a higher prevalence of microvascular complications.[5–7] In patients with heart failure with

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WHAT IS NEW?

- Our work shows that in patients with heart failure with reduced ejection fraction enrolled in the EMPHASIS-HF trial (Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms), eplerenone had a greater benefit in patients with insulin-treated diabetes.

WHAT ARE THE CLINICAL IMPLICATIONS?

- These findings support the use of eplerenone in patients with heart failure with reduced ejection fraction and insulin-treated diabetes, and generate hypotheses for future trials, where the effect of mineralocorticoid receptor antagonists should be formally tested in patients with insulin-treated diabetes.

Nonstandard Abbreviations and Acronyms

ACE	angiotensin-converting enzyme
ARB	angiotensin receptor blocker
EMPHASIS-HF	Eplerenone in Patients With Systolic Heart Failure and Mild Symptoms
HDL	high-density lipoprotein
HFrEF	heart failure with reduced ejection fraction
HR	hazard ratio
RALES	Effect of Spironolactone on Morbidity and Mortality in Patients With Severe Heart Failure

reduced ejection fraction (HFrEF), those with insulin-treated diabetes had higher risk of heart failure rehospitalizations and mortality compared with patients with non-insulin-treated diabetes, and even more when compared with patients without diabetes.[7,8] Similar findings have been reported in patients with heart failure with preserved ejection fraction.[9,10]

Aldosterone-induced mineralocorticoid receptor activation impairs insulin sensitivity leading to insulin resistance and hyperinsulinemia, which may aggravate dysglycemia and diabetes progression.[11,12] By mitigating dysglycemia, mineralocorticoid receptor antagonists might provide additional benefits in patients with diabetes, including insulin-treated diabetes. Such hypothesis should be applied to eplerenone and not to spironolactone. Eplerenone is a selective antagonist of the mineralocorticoid receptor and spironolactone is not. Concordantly, spironolactone has been shown to increase the levels of glycated hemoglobin and cortisol, whereas eplerenone has not.[13] A beneficial effect of eplerenone in patients at high risk for hyperkalemia and worsening renal function, including patients with diabetes, has been previously reported in the EMPHASIS-HF trial (Eplerenone in Patients With Systolic Heart Failure and Mild Symptoms)[14] and in the subgroup analysis of the EMPHASIS-HF main report,[15] but the effect in patients taking insulin has not been studied yet.

In the present study, we sought to explore the effect of eplerenone in insulin-treated patients as well as diabetes patients not treated with insulin.

METHODS

The data used in these analyses can be made available upon reasonable request to the corresponding author.

The design, eligibility criteria, study procedures, and main results of the EMPHASIS-HF trial are published.[15] In brief, people aged ≥55 years were eligible if in New York Heart Association functional class II, with a left ventricular ejection fraction ≤35%, and treated with an ACE (angiotensin-converting enzyme) inhibitor or ARB (angiotensin receptor blocker) and a β-blocker (unless contraindicated). Patients were randomly assigned to receive eplerenone or matching placebo in addition to recommended therapy. The randomization procedure was stratified according to renal function, whereby patients with an estimated glomerular filtration rate between 30 and 50 mL/(min·1.73m^2) received 25 mg/d of eplerenone (or placebo) and patients with an estimated glomerular filtration rate above 50 mL/(min·1.73m^2) received 50 mg/d of eplerenone (or placebo).[16]

The study was approved by institutional ethics and institutional review board committees in all participating sites. All patients gave informed consent to participate in the trial.

Study Outcomes

The primary outcome in EMPHASIS-HF was a composite of time-to-first occurrence of heart failure hospitalization or death from a cardiovascular cause. We have also examined the individual components of the primary outcome, the composite of all-cause hospitalization or all-cause death and its individual components. The median follow-up time was 21 (10–33) months.

Statistical Analysis

Baseline characteristics are reported as means and SD or medians and interquartile range for continuous variables and frequencies with percentages for categorical variables. The outcome analyses were conducted on data from all patients who had undergone randomization, according to the intention-to-treat principle, with the use of Kaplan–Meier estimates and Cox proportional-hazards models. As specified,[15] overall hazard ratios (HRs), 95% CIs, and *P* values were calculated with the use of models adjusted for the following prespecified baseline prognostic factors: age, estimated glomerular filtration rate, left ventricular ejection fraction, body mass index, hemoglobin, heart rate, systolic blood pressure, diabetes, history of hypertension, previous myocardial infarction, atrial fibrillation, and left bundle-branch block or QRS duration >130 msec.

Diabetes was subcategorized in non-insulin-treated diabetes (for patients with diabetes taking only oral treatments or diet) and insulin-treated diabetes (for patients who had insulin prescribed at baseline), based on medication names available in the database. The analyses assessing the risk associated with diabetes treatment where adjusted in the same aforementioned variables except diabetes (which is the variable of interest here). The treatment effect in diabetes subgroups (no diabetes versus diabetes and no diabetes versus non-insulin-treated diabetes versus insulin-treated diabetes) was analyzed with the use of a Cox proportional-hazards model, without adjustment for covariates. The treatment-by-subgroup interaction was evaluated by means of a Cox proportional-hazards model with terms for treatment, subgroup, and their interaction. Annualized absolute risk reduction and number needed to treat to benefit were calculated from person-time estimates. Adverse events (hyperkalemia, hypokalemia, renal failure, and hypotension) were analyzed as described in the primary EMPHASIS-HF report.[15]

For purposes of external replication, we have also assessed the effect of spironolactone on the composite outcome of time-to-first occurrence of heart failure hospitalization or death from a cardiovascular causes by diabetes subgroups in patients with severe HFrEF enrolled in the RALES (the Effect of Spironolactone on Morbidity and Mortality in Patients With Severe Heart Failure) trial.[17] In RALES, only a small proportion (6%) of patients had insulin prescription (based on text available in the data set), hence these analyses were performed by diabetes subgroups (yes versus no).

A P value of <0.05 was considered significant. Statistical analyses were conducted using Stata version 16 (Stata Corp. College Station, TX).

RESULTS

Characteristics of the Patients

A total of 2737 patients were included in the analysis, 623 (23%) had non-insulin-treated diabetes, and 236 (9%) had insulin-treated diabetes and 1878 did not have diabetes. Compared with patients without diabetes and with those with non-insulin-treated diabetes, patients with insulin-treated diabetes were younger, more often women, Asian, with higher heart rate, body mass index, and waist circumference, more frequent ischemic cause HF, prior HF hospitalizations, hypertension, anemia, and impaired kidney function. The duration of diabetes was much longer in insulin-treated than in non-insulin-treated patients (11 versus 5 years) Table 1.

The characteristics of the patients subdivided into no diabetes versus non-insulin-treated diabetes managed with dietary and lifestyle measures only versus non-insulin-treated diabetes managed oral glucose-lowering treatment versus insulin-treated diabetes are presented in the Table I in the Data Supplement. The characteristics of the patients subdivided into no diabetes versus diabetes with duration below or equal to the median of 7 years versus diabetes with duration above the median of 7 years are presented in the Table II in the Data Supplement.

Risk Associated With Diabetes

Compared with patients without diabetes, those with diabetes had a 1.5-fold higher risk of having a primary outcome event, 1.4-fold higher risk of dying from cardiovascular causes, and a 1.4-fold higher risk of dying from any cause. The corresponding risk for patients with insulin-treated diabetes was higher: 2-fold for the primary outcome, 1.7-fold for cardiovascular death, and 1.8-fold for all-cause death Table 2. A similar pattern was observed for patients with longer diabetes duration (Table III in the Data Supplement).

Effect of Eplerenone Overall and by Diabetes Subgroup

Eplerenone had a large magnitude effect in patients with diabetes, particularly among patients with insulin-treated diabetes. The HR (95% CI) for the primary outcome was 0.54 (0.42–0.70) in patients with diabetes and 0.72 (0.58–0.88) in patients without diabetes; P for treatment-by-subgroup interaction, 0.093. In insulin and non-insulin-treated diabetes subgroups, the primary outcome HR (95% CI) was 0.31 (0.19–0.50) in insulin-treated diabetes, 0.69 (0.50–0.93) in non-insulin-treated diabetes; P for treatment-by-subgroup interaction, 0.007. The primary outcome event rate in patients with insulin-treated diabetes randomized to eplerenone was similar to the event rate observed in patients without diabetes randomized to placebo: 12.5 (8.4–18.6) events per 100 person-years among patients with insulin-treated diabetes versus 13.3 (11.7–15.2) events per 100 person-years among patients without diabetes. The annualized number needed to treat to benefit from eplerenone with regards to the primary outcome was 3 (95% CI, 3–4) in patients with insulin-treated diabetes, 16 (13–19) in patients with diabetes not receiving insulin, and 26 (24–28) in patients without diabetes. A similar pattern was observed for the other studied outcomes and when dividing patients by the duration of diabetes Table 3, Figures 1 and 2, and Table IV in the Data Supplement.

Diabetes Subgroups in RALES

In RALES, 822 patients were randomized to spironolactone and 841 to placebo (n=1663). Among the 1663 patients, 369 (22%) had diabetes and 102 (6%) had insulin prescription at baseline. For the outcome of first hospitalization for heart failure or cardiovascular death (primary outcome of EMPHASIS-HF), patients with diabetes had a higher event rate than

Table 1. Baseline Characteristics of the Patients by Diabetes Status and Treatment

Characteristics	No diabetes	Non-insulin-treated diabetes	Insulin-treated diabetes	*P* value*
N	1878	623	236	…
Age, y	68.8±7.7	68.6±7.5	67.5±7.1	0.040
Age ≥75 y	408 (21.7%)	117 (18.8%)	39 (16.5%)	0.078
Men	1461 (77.8%)	502 (80.6%)	164 (69.5%)	0.002
Race				<0.001
White	1619 (86.2%)	477 (76.6%)	172 (72.9%)	
Black	51 (2.7%)	10 (1.6%)	6 (2.5%)	
Asian	156 (8.3%)	111 (17.8%)	49 (20.8%)	
Other	52 (2.8%)	25 (4.0%)	9 (3.8%)	
Heart rate, bpm	71.0±12.7	73.0±12.0	74.3±11.2	<0.001
Heart rate ≥75 bpm	573 (30.5%)	242 (38.8%)	102 (43.2%)	<0.001
SBP, mm Hg	123.6±16.8	125.1±16.7	125.9±17.6	0.031
SBP <110 mm Hg	508 (27.1%)	144 (23.1%)	57 (24.2%)	0.12
DBP, mm Hg	74.7±10.2	74.9±10.2	73.9±10.6	0.47
DBP <70 mm Hg	784 (41.8%)	264 (42.4%)	100 (42.4%)	0.96
LVEF, %	27.0 (24.0–30.0)	27.0 (25.0–30.0)	27.0 (25.0–30.0)	0.14
LVEF <30%	1783 (94.9%)	597 (95.8%)	223 (94.5%)	0.61
QRS duration, ms	122.7±46.5	121.4±42.2	114.3±33.8	0.026
QRS ≥130 ms	612 (33.4%)	192 (31.1%)	67 (28.9%)	0.27
BMI, kg/m^2	27.2±4.7	28.0±4.9	29.1±5.7	<0.001
BMI <25, kg/m^2	594 (31.6%)	166 (26.6%)	58 (24.6%)	<0.001
BMI 25–30, kg/m^2	830 (44.2%)	275 (44.1%)	75 (31.8%)	
BMI >30, kg/m^2	454 (24.2%)	182 (29.2%)	103 (43.6%)	
Waist circumference, cm	98.1±13.2	101±13.1	103.6±15.3	<0.001
Waist circumference ≥102 men and ≥88 women	809 (46.7%)	316 (54.4%)	143 (65.6%)	<0.001
HF cause				<0.001
Nonischemic	643 (34.2%)	146 (23.4%)	57 (24.2%)	
Ischemic	1233 (65.7%)	475 (76.2%)	178 (75.4%)	
Unknown	2 (0.1%)	2 (0.3%)	1 (0.4%)	
Hospitalization for HF	975 (51.9%)	308 (49.4%)	157 (66.5%)	<0.001
Hypertension	1177 (62.7%)	463 (74.3%)	179 (75.8%)	<0.001
Diabetes duration, y	NA	5.0 (1.0–10.0)	11.0 (7.0–20.0)	<0.001
Diabetes duration >7 y	NA	235 (37.7%)	166 (70.3%)	<0.001
Diabetes treatment				
Metformin	NA	221 (35.5%)	53 (22.5%)	<0.001
Sulfonylurea	NA	282 (45.3%)	39 (16.5%)	<0.001
Dipeptidyl peptidase-4 inhibitor	NA	11 (1.8%)	4 (1.7%)	<0.001
Thiazolidinedione	NA	24 (3.9%)	2 (0.8%)	<0.001
Other glucose-lowering drugs	NA	29 (4.7%)	10 (4.2%)	<0.001
Angina pectoris	807 (43.0%)	286 (45.9%)	96 (40.7%)	0.29
Myocardial infarction	904 (48.1%)	341 (54.7%)	136 (57.6%)	0.001
PCI	377 (20.1%)	147 (23.6%)	72 (30.5%)	<0.001
CABG	325 (17.3%)	122 (19.6%)	69 (29.2%)	<0.001
Atrial fibrillation or flutter	612 (32.6%)	180 (28.9%)	52 (22.0%)	0.002
LBBB	470 (25.0%)	168 (27.0%)	50 (21.2%)	0.21
Stroke	177 (9.5%)	57 (9.2%)	28 (12.0%)	0.44
Hemoglobin, g/dL	13.9±1.5	13.7±1.7	13.3±1.6	<0.001

(*Continued*)

Table 1. Continued

Characteristics	No diabetes	Non-insulin-treated diabetes	Insulin-treated diabetes	*P* value*
Anemia	378 (20.1%)	152 (24.4%)	86 (36.4%)	<0.001
eGFR, mL/(min·1.73 m²)	71.6±21.8	70.8±21.8	64.8±21.4	<0.001
eGFR <60 mL/(min·1.73 m²)	613 (32.6%)	217 (34.8%)	109 (46.2%)	<0.001
Potassium, mmol/L	4.3±0.4	4.3±0.4	4.3±0.4	0.51
Potassium <4 mmol/L	478 (25.6%)	128 (20.7%)	62 (26.5%)	0.12
Potassium 4–5 mmol/L	1360 (72.9%)	481 (77.7%)	167 (71.4%)	
Potassium >5 mmol/L	28 (1.5%)	10 (1.6%)	5 (2.1%)	
ICD	250 (13.3%)	78 (12.5%)	34 (14.4%)	0.75
CRT	40 (2.2%)	15 (2.5%)	5 (2.2%)	0.92
ICD/CRT	123 (6.8%)	33 (5.4%)	17 (7.4%)	0.44
Any diuretic	1561 (83.6%)	540 (87.4%)	225 (95.7%)	<0.001
Loop diuretics	1384 (74.1%)	493 (79.8%)	213 (90.6%)	<0.001
ACE inhibitor/ARBs	1764 (93.9%)	577 (92.6%)	217 (91.9%)	0.32
β-blockers	1630 (87.3%)	536 (86.7%)	208 (88.5%)	0.78
Digoxin	491 (26.3%)	185 (29.9%)	64 (27.2%)	0.21
Antiarrhythmic	288 (15.4%)	78 (12.6%)	22 (9.4%)	0.018
Antiplatelet	1186 (63.5%)	447 (72.3%)	174 (74.0%)	<0.001
Anticoagulant	624 (33.4%)	173 (28.0%)	66 (28.1%)	0.020
Lipid-lowering therapy	1123 (60.1%)	413 (66.8%)	177 (75.3%)	<0.001
Eplerenone allocation	905 (48.2%)	339 (54.4%)	120 (50.8%)	0.025

ACE/ARBs indicates angiotensin-converting enzyme/angiotensin receptor blockers; BMI, body mass index; CABG, coronary artery bypass grafting; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, intracardiac defibrillator; LBBB, left bundle-branch block; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; and SBP, systolic blood pressure.

**P* value from trend across categories.

patients without diabetes: 33.7 (29.5–38.5) events per 100 person-years in patients with diabetes versus 27.2 (25.1–29.4) events per 100 person-years in patients without diabetes, *P*=0.007. The effect of spironolactone was similar in patients with and without diabetes: HR (95% CI) in patients with diabetes 0.71 (0.54–0.92) and in patients without diabetes 0.69 (0.59–0.81), *P* for treatment-by-subgroup interaction, 0.88. The subgroup of patients with possible insulin treatment (see methods section for details) was too small (only 63 patients with an event) to compute reliable estimates.

Adverse Events in EMPHASIS-HF

Compared with placebo, eplerenone treatment increased the proportion of patients who developed hyperkalemia (3.7% versus 8.0%) but reduced the proportion of patients who developed hypokalemia (2.3% versus 1.2%) and did not affect the onset of renal failure or hypotension. Patients with diabetes, including insulin-treated diabetes, did not experience excess risk for adverse events (interaction *P*>0.1 for all adverse events) Table 4.

DISCUSSION

In people with HFrEF and mild symptoms, participants with diabetes had worse outcomes than those without diabetes and among those with diabetes, patients treated with insulin had higher rates of hospitalization and death than individuals not treated with insulin. As a result, patients with diabetes, treated with insulin, had a 2-fold higher risk compared with patients without diabetes. Eplerenone reduced the risk of all outcomes substantially but the greatest relative and absolute risk reduction was observed in patients with diabetes treated with insulin (by 70% and 27%, respectively). The resulting NNT to avoid a primary outcome event in patients with diabetes receiving insulin was only 3, compared with 16 in those not receiving insulin and 26 in patients without diabetes.

The effect of eplerenone in insulin-treated patients was very large and one may argue that high-risk patients, such as those treated with insulin, may experience greater benefit from treatment simply because they have more events and thus larger margin for benefit.[18] However, high-risk patients in EMPHASIS-HF did experience a greater absolute benefit but a similar relative benefit compared with medium- and even low-risk patients (treatment-by-risk category

Table 2. Event Rates in Patients With and Without Diabetes

End point	IR per 100 person-years (95% CI)	Crude HR (95% CI)	*P* value	Adjusted HR (95% CI)*	*P* value
CV death or HF hospitalization					
No diabetes	11.4 (10.3–12.7)	Ref.	…	Ref.	…
Diabetes†	18.6 (16.4–21.1)	1.60 (1.36–1.88)	<0.001	1.48 (1.25–1.75)	<0.001
Non-insulin-treated	16.6 (14.2–19.4)	1.44 (1.19–1.73)	<0.001	1.33 (1.11–1.61)	0.003
Insulin-treated	24.5 (19.7–30.6)	2.09 (1.64–2.67)	<0.001	1.96 (1.52–2.52)	<0.001
HF hospitalization					
No diabetes	7.6 (6.7–8.6)	Ref.	…	Ref.	…
Diabetes†	13.5 (11.6–15.6)	1.74 (1.43–2.11)	<0.001	1.60 (1.31–1.95)	<0.001
Non-insulin-treated	11.7 (9.8–14.1)	1.52 (1.22–1.91)	<0.001	1.41 (1.13–1.77)	0.003
Insulin-treated	18.6 (14.5–24)	2.38 (1.79–3.15)	<0.001	2.21 (1.64–2.97)	<0.001
CV death					
No diabetes	5.9 (5.2–6.8)	Ref.	…	Ref.	…
Diabetes†	8.9 (7.5–10.5)	1.49 (1.20–1.86)	<0.001	1.38 (1.10–1.74)	0.005
Non-insulin-treated	8.3 (6.8–10.3)	1.4 (1.1–1.8)	0.007	1.3 (1.01–1.67)	0.042
Insulin-treated	10.3 (7.6–14.2)	1.74 (1.23–2.45)	0.002	1.66 (1.16–2.37)	0.005
All-cause death or all-cause hospitalization					
No diabetes	23.7 (21.9–25.5)	Ref.	…	Ref.	…
Diabetes†	33.7 (30.5–37.3)	1.39 (1.23–1.58)	<0.001	1.33 (1.16–1.51)	<0.001
Non-insulin-treated	29.9 (26.4–33.8)	1.24 (1.08–1.44)	0.003	1.18 (1.02–1.36)	0.03
Insulin-treated	45.9 (38.4–54.8)	1.85 (1.53–2.25)	<0.001	1.85 (1.51–2.25)	<0.001
All-cause hospitalization					
No diabetes	20.5 (18.9–22.2)	Ref.	…	Ref.	…
Diabetes†	29.8 (26.8–33.2)	1.42 (1.24–1.63)	<0.001	1.36 (1.18–1.56)	<0.001
Non-insulin-treated	26.2 (22.9–29.9)	1.26 (1.08–1.47)	0.004	1.19 (1.02–1.39)	0.03
Insulin-treated	41.3 (34.2–49.8)	1.92 (1.57–2.36)	<0.001	1.92 (1.56–2.38)	<0.001
All-cause death					
No diabetes	6.9 (6–7.8)	Ref.	…	Ref.	…
Diabetes†	10.3 (8.8–12.1)	1.50 (1.22–1.84)	<0.001	1.41 (1.14–1.74)	0.002
Non-insulin-treated	9.4 (7.7–11.4)	1.36 (1.08–1.72)	0.009	1.28 (1.01–1.62)	0.045
Insulin-treated	13 (9.8–17.2)	1.9 (1.39–2.58)	<0.001	1.83 (1.33–2.52)	<0.001

CV indicates cardiovascular; HF, heart failure; HR, hazard ratio; and IR, incidence rate.

*Model adjusted on age, estimated glomerular filtration rate, left ventricular ejection fraction, body mass index, hemoglobin, heart rate, systolic blood pressure, history of hypertension, previous myocardial infarction, atrial fibrillation, and left bundle-branch block or QRS duration >130 msec.

†Incorporates insulin and non-insulin-treated diabetes.

interaction, *P*=0.68).[18] This was not the case herein, where we did observe both and absolute and relative difference of treatment effect in insulin-treated patients where the relative risk reduction reached 69% compared with 31% in non-insulin-treated diabetes and 28% in patients without diabetes (interaction *P*=0.007). The large benefit of eplerenone in insulin-treated patients is not this obvious when comparing only patients with and without diabetes (irrespective of the diabetes treatment or duration). Despite a larger magnitude of eplerenone effect in patients with diabetes, no statistical heterogeneity (interaction) between treatment and diabetes status was found, HR (95% CI) in patients without diabetes 0.72 (0.58–0.88) and in patients with diabetes 0.54 (0.42–0.70); *P* for interaction, 0.093.

No effect heterogeneity between spironolactone and diabetes status was found in patients with HFrEF and severe symptoms enrolled in the RALES trial either (interaction *P*=0.88).[17] In should be noted, however, that RALES was a relatively small trial (n=1663 patients of whom 22% had a diagnosis of diabetes and only 6% had any insulin prescription) that included a very severe and high-risk population that does not reflect contemporary patients with HFrEF nor their treatments (RALES started almost 25 years ago). Perhaps more importantly, eplerenone and spironolactone differ in their selectivity for the mineralocorticoid receptor and may have different metabolic effects, with eplerenone presenting a more favorable metabolic profile than

Table 3. Treatment Effect of Eplerenone by Subgroups of Diabetes

Treatment effect	Events placebo	% Placebo	Event rate placebo	Events eplerenone*	% Eplerenone*	Event rate eplerenone*	ARR (95% CI)	NNT (95% CI)	HR (95% CI)	*P* value*	Interaction *P*†
CV death or HF hospitalization											
Overall effect	356	25.9	16.4 (14.8 to 18.2)	249	18.3	10.7 (9.5 to 12.2)	−5.7 (−6.0 to −5.3)	18 (17 to 19)	0.63 (0.54 to 0.75)	<0.001	…
No diabetes	215	22.1	13.3 (11.7 to 15.2)	150	16.6	9.5 (8.1 to 11.1)	−3.8 (−4.1 to −3.6)	26 (24 to 28)	0.72 (0.58 to 0.88)	…	0.093
Diabetes‡	141	35.3	25.4 (21.5 to 29.9)	99	21.6	13.4 (11.0 to 16.4)	−12.0 (−13.5 to −10.5)	8 (7 to 10)	0.54 (0.42 to 0.70)	…	
Non-insulin-treated	86	30.3	20.2 (16.3 to 24.9)	75	22.1	13.8 (11 to 17.3)	−6.4 (−7.6 to −5.3)	16 (13 to 19)	0.69 (0.5 to 0.93)	…	0.007
Insulin-treated	55	47.4	42.5 (32.6 to 55.4)	24	20.0	12.5 (8.4 to 18.6)	−30 (−36.8 to −24.2)	3 (3 to 4)	0.31 (0.19 to 0.50)	…	
HF hospitalization											
Overall effect	253	18.4	11.7 (10.3 to 13.2)	164	12.0	7.1 (6.1 to 8.2)	−4.6 (−5.0 to −4.2)	22 (20 to 24)	0.58 (0.48 to 0.71)	<0.001	…
No diabetes	149	15.3	9.2 (7.9 to 10.8)	94	10.4	5.9 (4.9 to 7.3)	−3.3 (−3.5 to −3.0)	30 (29 to 33)	0.65 (0.5 to 0.84)	…	0.27
Diabetes‡	104	26.0	18.7 (15.5 to 22.7)	70	15.3	9.5 (7.5 to 12.0)	−9.2 (−10.7 to −8.0)	11 (9 to 13)	0.52 (0.38 to 0.70)	…	
Non-insulin-treated	64	22.5	15 (11.8 to 19.2)	50	14.7	9.2 (7 to 12.1)	−5.8 (−7.1 to −4.8)	17 (14 to 21)	0.62 (0.43 to 0.89)	…	0.15
Insulin-treated	40	34.5	30.9 (22.7 to 42.1)	20	16.7	10.4 (6.7 to 16.1)	−20.5 (−26.0 to −16)	5 (4 to 6)	0.36 (0.21 to 0.61)	…	
CV death											
Overall effect	185	13.5	7.7 (6.7 to 8.9)	147	10.8	6 (5.1 to 7)	−1.7 (−1.9 to −1.6)	59 (53 to 63)	0.75 (0.6 to 0.93)	0.01	…
No diabetes	116	11.9	6.7 (5.6 to 8)	86	9.5	5.2 (4.2 to 6.4)	−1.5 (−1.6 to −1.4)	67 (63 to 71)	0.77 (0.58 to 1.02)	…	0.80
Diabetes‡	69	17.3	10.4 (8.2 to 13.2)	61	13.3	7.6 (5.9 to 9.8)	−2.8 (−3.4 to −2.3)	36 (29 to 43)	0.73 (0.52 to 1.03)	…	
Non-insulin-treated	44	15.5	8.8 (6.6 to 11.9)	47	13.9	7.9 (6 to 10.6)	−0.9 (−1.3 to −0.6)	111 (77 to 167)	0.89 (0.59 to 1.35)	…	0.20
Insulin-treated	25	21.6	15 (10.1 to 22.2)	14	11.7	6.7 (3.9 to 11.2)	−8.3 (−11.0 to −6.2)	12 (9 to 16)	0.44 (0.23 to 0.85)	…	
All-cause death or all-cause hospitalization											
Overall effect	569	41.4	30.4 (28 to 33)	462	33.9	22.9 (20.9 to 25.1)	−7.5 (−7.9 to −7.1)	13 (13 to 14)	0.76 (0.67 to 0.86)	<0.001	…
No diabetes	373	38.3	26.7 (24.2 to 29.6)	287	31.7	20.6 (18.3 to 23.1)	−6.1 (−6.5 to −5.9)	16 (15 to 17)	0.78 (0.67 to 0.91)	…	0.37
Diabetes‡	196	49.0	41.3 (35.9 to 47.5)	175	38.1	28.0 (24.1 to 32.4)	−13.3 (−15.1 to −11.8)	8 (7 to 8)	0.69 (0.57 to 0.85)	…	
Non-insulin-treated	122	43	33 (27.7 to 39.5)	128	37.8	27.4 (23 to 32.6)	−5.6 (−6.9 to −4.7)	18 (14 to 21)	0.84 (0.65 to 1.07)	…	0.017
Insulin-treated	74	63.8	70.4 (56 to 88.4)	47	39.2	29.6 (22.2 to 39.4)	−40.8 (−49.0 to −33.8)	2 (2 to 3)	0.46 (0.32 to 0.66)	…	
All-cause hospitalization											
Overall effect	491	35.8	26.3 (24 to 28.7)	408	29.9	20.2 (18.3 to 22.3)	−6.1 (−6.4 to −5.7)	16 (16 to 18)	0.77 (0.68 to 0.88)	<0.001	…
No diabetes	323	33.2	23.1 (20.8 to 25.8)	248	27.4	17.8 (15.7 to 20.2)	−5.3 (−5.6 to −5.1)	19 (18 to 20)	0.78 (0.66 to 0.92)	…	0.72
Diabetes‡	168	42.0	35.4 (30.4 to 41.2)	160	34.9	25.6 (21.9 to 29.8)	−9.8 (−11.4 to −8.5)	10 (9 to 12)	0.74 (0.60 to 0.92)	…	
Non-insulin-treated	104	36.6	28.2 (23.2 to 34.1)	115	33.9	24.6 (20.5 to 29.6)	−3.6 (−4.5 to −2.7)	28 (22 to 37)	0.88 (0.68 to 1.15)	…	0.062
Insulin-treated	64	55.2	60.9 (47.6 to 77.8)	45	37.5	28.4 (21.2 to 38)	−32.5 (−39.8 to −26.4)	3 (3 to 4)	0.51 (0.35 to 0.74)	…	

(*Continued*)

Table 3. Continued

Treatment effect	Events placebo	% placebo	Event rate placebo	Events eplerenone*	% eplerenone*	Event rate eplerenone*	ARR (95% CI)	NNT (95% CI)	HR (95% CI)	*P* value*	Interaction *P*†
All-cause death											
Overall effect	213	15.5	8.9 (7.8 to 10.2)	171	12.5	6.9 (6 to 8)	−2.0 (−2.2 to −1.8)	50 (45 to 56)	0.76 (0.62 to 0.92)	0.007	…
No diabetes	134	13.8	7.7 (6.5 to 9.2)	99	10.9	5.9 (4.9–7.2)	−1.8 (−2.0 to −1.6)	56 (50 to 63)	0.77 (0.59 to 0.99)	…	0.91
Diabetes‡	79	19.8	11.9 (9.5 to 14.8)	72	15.7	9.0 (7.1 to 11.3)	−2.9 (−3.5 to −2.4)	34 (29 to 42)	0.75 (0.54 to 1.03)	…	
Non-insulin-treated	48	16.9	9.7 (7.3 to 12.8)	54	15.9	9.1 (7 to 11.9)	−0.6 (−0.9 to −0.3)	167 (111 to 333)	0.94 (0.64 to 1.39)	…	0.13
Insulin-treated	31	26.7	18.6 (13.1 to 26.4)	18	15.0	8.6 (5.4 to 13.6)	−10.0 (−12.8 to −7.7)	10 (8 to 13)	0.46 (0.26 to 0.82)	…	

The event rates are reported per 100 person-years. ARR indicates absolute risk reduction; CV, cardiovascular; HF, heart failure; HR, hazard ratio; and NNT, number needed to treat to benefit.

*P value for the overall effect of eplerenone versus placebo in the whole study population.

†Interaction *P* value: upper *P* value corresponds to the 2-group interaction test between patients with and without diabetes, the lower *P* value corresponds to the 3-group global interaction test between insulin-treated diabetes, non-insulin-treated diabetes, and no diabetes.

‡Incorporates insulin and non-insulin-treated diabetes.

spironolactone.[13] Furthermore, spironolactone may worsen endothelial function and heart rate variability in patients with diabetes.[19] On top of these studies, our data suggest that eplerenone might be preferred over spironolactone in patients with HFrEF and insulin-treated diabetes.

In a previous secondary analysis of the EMPHASIS-HF trial, it was found that patients with increased abdominal obesity might have also experienced a greater benefit from eplerenone treatment.[20] Findings that complement the present analysis, as patients with insulin-treated diabetes have increased abdominal perimeter and abdominal obesity much more often than patients with non-insulin-treated diabetes patients and those without diabetes. Aldosterone is expressed in adipose tissue, and its gene expression has been found increased in the adipose tissue of both obese animals and humans, especially in abdominal adipose tissue.[21–23] Hence, this abdominal obesity hyperaldosteronism may enhance the beneficial effects of mineralocorticoid receptor antagonists, even more in the context of insulin-treated diabetes, a condition with a poor prognosis that increases both hyperaldosteronism and abdominal obesity in a vicious cycle that can be stopped with mineralocorticoid receptor antagonist administration in patients with HFrEF.

Recently, in the FIDELIO-DKD trial (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease; URL: https://www.clinicaltrials.

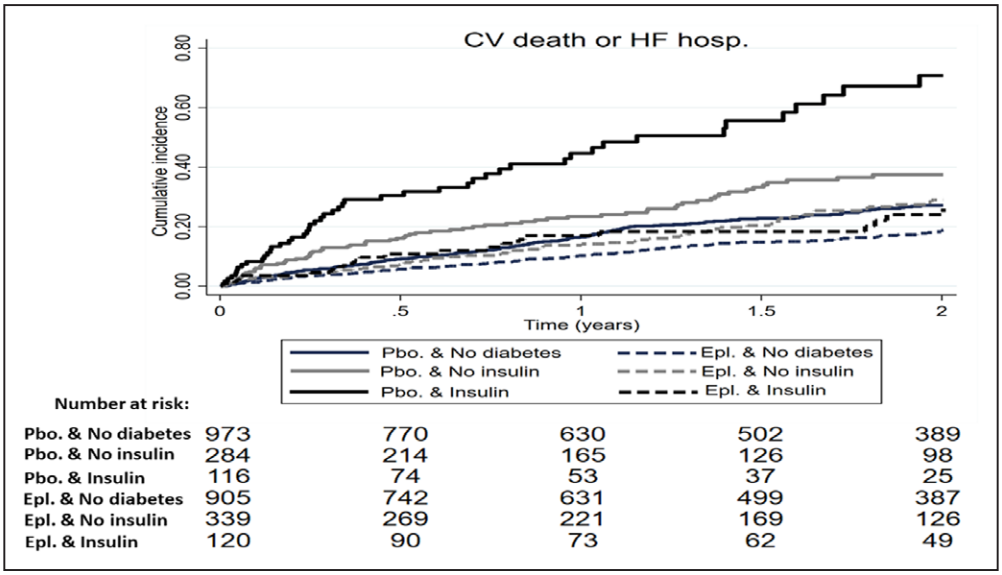

Figure 1. Cumulative incidence of primary outcome events by diabetes treatment and treatment group.
The event rates are highest among insulin-treated patients randomized to placebo (Pbo); however, insulin-treated patients randomized to eplerenone (Epl) have similar event rates to patients without diabetes randomized to placebo. CV indicates cardiovascular; and HF, heart failure.

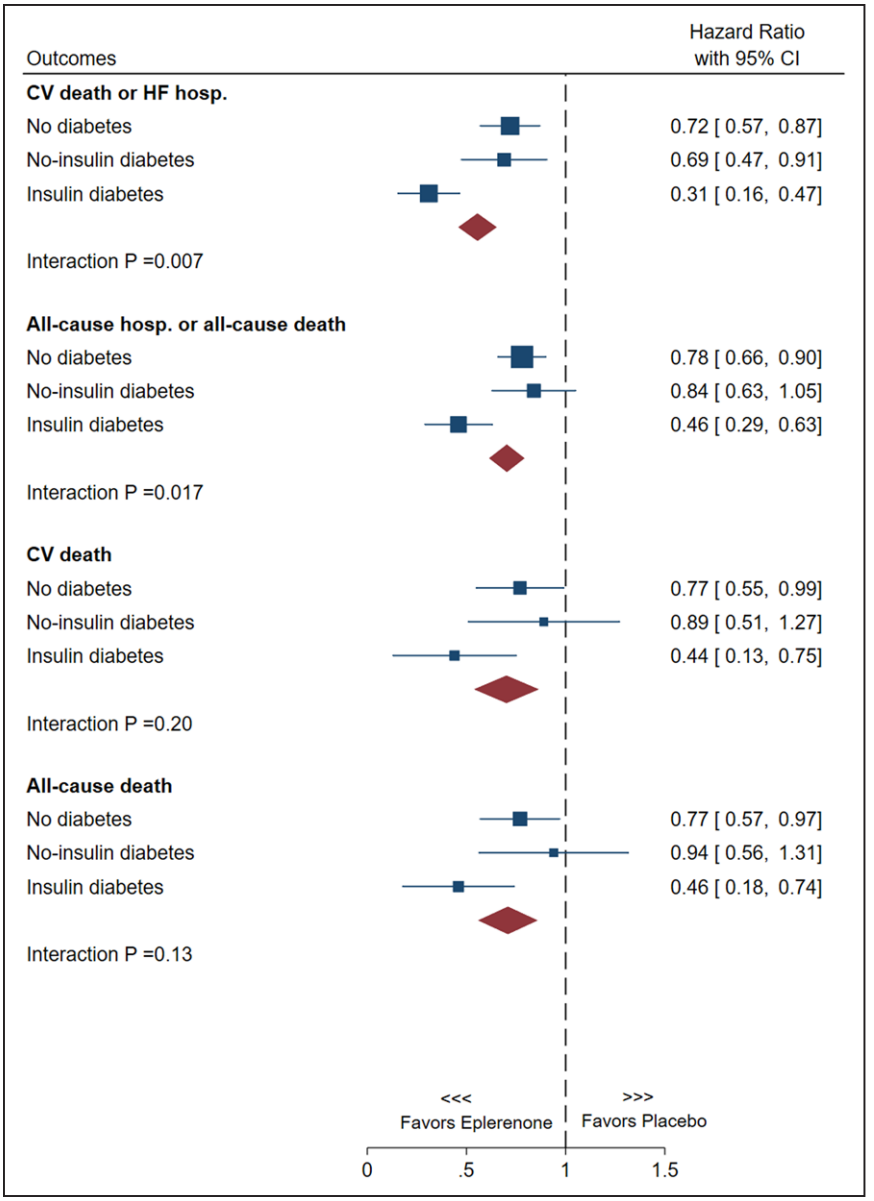

Figure 2. Treatment effects by diabetes subgroups.
CV indicates cardiovascular; and HF, heart failure.

gov; Unique identifier: NCT02540993), finerenone (compared with placebo) significantly reduced the combined risk of time to first occurrence of kidney failure, sustained decrease in estimated glomerular filtration rate ≥40%, or renal death in patients with type 2 diabetes and diabetic kidney disease.[24] These findings may be expanded in the ongoing FIGARO-DKD trial (Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease) URL: https://www.clinicaltrials.gov; Unique identifier: NCT02545049).

Together findings support the benefit of eplerenone and nonsteroidal mineralocorticoid receptor antagonists in patients with diabetes, whether the benefit may be larger in patients with insulin-treated diabetes is worth exploring. Our findings strongly suggest that that is the case, at least in patients with HFrEF and mild symptoms.

Limitations

Several limitations should be acknowledged in the present analysis. This is a post hoc analysis of a randomized controlled trial, where patients were randomized to eplerenone or placebo but not to insulin treatment. Therefore, the treatment effect in these subgroups may be enhanced (type I error) and these findings should be regarded as hypothesis-generating and require validation in future studies. Details about diabetes, such as diabetes type (type 1 or 2), glycated hemoglobin, or fasting plasma glucose were not recorded in the trial. Insulin dose was not recorded during the trial, therefore the impact of eplerenone on insulin dose could not be assessed. EMPHASIS-HF was conducted in at a time (2008–2011) where drugs that lower heart failure risk and cardiovascular mortality in patients with diabetes were not available (eg, sodium-glucose cotransporter

Table 4. Adverse Events by Subgroups of Diabetes

Adverse event	Events (%) placebo (n=1373)	Events (%) eplerenone (n=1364)	*P* value*	Interaction *P*†
Hyperkalemia				
Overall	50 (3.7)	109 (8.0)	<0.001	…
No diabetes (n=1878)	33/971 (3.4)	58/903 (6.4)	…	0.32
Diabetes‡	17/398 (4.3)	51/457 (11.2)	…	
Non-insulin-treated (n=623)	11/283 (3.9)	37/339 (10.9)	…	0.57
Insulin-treated (n=236)	6/115 (5.2)	14/118 (11.9)	…	
Hypokalemia				
Overall	31 (2.3)	16 (1.2)	0.032	…
No diabetes (n=1878)	21/971 (2.2)	11/903 (1.2)	…	0.69
Diabetes‡	10/398 (2.5)	5/457 (1.1)	…	
Non-insulin-treated (n=623)	5/283 (1.8)	4/339 (1.2)	…	0.60
Insulin-treated (n=236)	5/115 (4.3)	1/118 (0.8)	…	
Renal failure				
Overall	41 (3.0)	39 (2.9)	0.84	…
No diabetes (n=1878)	23/971 (2.4)	18/903 (2.0)	…	0.67
Diabetes‡	18/398 (4.5)	21/457 (4.6)	…	
Non-insulin-treated (=623)	11/283 (3.9)	18/339 (5.3)	…	0.28
Insulin-treated (n=236)	7/115 (6.1)	3/118 (2.5)	…	
Hypotension				
Overall	37 (2.7)	46 (3.4)	0.30	…
No diabetes (n=1878)	30/971 (3.1)	33/903 (3.7)	…	0.56
Diabetes‡	7/398 (1.8)	13/457 (2.8)	…	
Non-insulin-treated (n=623)	5/283 (1.8)	10/339 (2.9)	…	0.84
Insulin-treated (n=236)	2/115 (1.7)	3/118 (2.5)	…	

P values, including treatment-by-diabetes interaction *P*, were calculated from a logistic regression model.

**P* value for the overall effect of eplerenone vs. placebo in the whole study population.

†Interaction *P* value: upper *P* value corresponds to the 2-group interaction test between patients with and without diabetes, the lower *P* value corresponds to the 3-group global interaction test between insulin-treated diabetes, non-insulin-treated diabetes and no diabetes.

‡Incorporates insulin and non-insulin-treated diabetes.

2 inhibitors). Furthermore, treatments that now have an important disease-modifying effect in HFrEF were yet to be tested at the time EMPHASIS-HF was conducted (eg, angiotensin receptor neprilysin inhibitor and sodium-glucose cotransporter 2 inhibitors). As consequence, these findings may not be generalizable to patients with HFrEF taking contemporary life-saving therapies, regardless of the diabetes status.

CONCLUSIONS

In patients with HFrEF and mild symptoms enrolled in the EMPHASIS-HF trial, those with insulin-treated diabetes experienced a large magnitude benefit from eplerenone. This benefit reduced the event rate of these high-risk patients to rate that was similar of that found in patients without diabetes randomized to placebo.

ARTICLE INFORMATION

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Supplemental Material

Tables I–IV

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