Eplerenone in Patients With Systolic Heart Failure and Mild Symptoms

Analysis of Repeat Hospitalizations

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Background—Eplerenone is known to reduce time to first hospitalization for heart failure or cardiovascular death in patients with heart failure and mild symptoms. In chronic diseases such as heart failure, characterized by repeat hospitalizations, analyzing all heart failure hospitalizations, not just the first, should give a more complete picture of treatment benefits.

Methods and Results—The Eplerenone in Mild Patients Hospitalization and SurvIval Study in Heart Failure (EMPHASIS-HF) trial compared eplerenone with placebo in 2737 patients with mild heart failure, followed for a median 2.08 years (interquartile range, 1.08–3.10 years). Data were collected on all hospitalizations, with a focus on those due to heart failure. Heart failure hospitalization rates in the eplerenone and placebo groups were 10.70 and 16.99 per 100 patient-years, respectively. Allowing for skewness in the frequency of hospitalizations by using the negative binomial generalized linear model, the rate ratio (eplerenone versus placebo) was 0.53 (95% confidence interval, 0.42–0.66; $P<0.0001$). A plot of cumulative hospitalization rates over time revealed that most of the reduced risk on eplerenone occurred in the first year of follow-up. Several baseline variables strongly predicted the risk of hospitalization. More complex statistical methods, adjusting for mortality (as informative censoring), made a negligible difference in these findings.

Conclusions—Eplerenone markedly reduces the risk of heart failure hospitalizations in patients with heart failure and mild symptoms to a greater extent than is captured by only studying the time to first hospitalization. Future clinical trials in heart failure would gain from incorporating repeat hospitalizations into their primary evaluation of treatment effects.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00232180.

(*Circulation*. 2012;126:2317-2323.)

Key Words: heart failure ■ hospitalization ■ recurrent events ■ clinical trial ■ eplerenone

The three major consequences of heart failure are symptoms, hospital admission due to worsening heart failure, and premature death.[1,2] Because symptoms are subjective and hard to quantify, and because drugs that improve symptoms have also been shown to increase mortality, death and hospital admission have become the most important end points used in clinical trials of new treatments for heart failure.[3–5] Typically, these are used together in a composite outcome, usually analyzed as time to first event. This approach, however, does not measure the true burden of hospital admissions due to worsening heart failure either for the individual or for healthcare systems, because patients may experience multiple, recurrent, admissions during the course of their illness.[6,7] Not only are these hospital admissions very distressing for patients and their caregivers, but they are also the major driver of the enormous cost of heart failure to healthcare systems.[8,9] Furthermore, it is not known whether treatments are as effective at reducing recurrent events as initial ones. Consequently, these recurrent, nonfatal events are important to quantify, although it is uncertain how this should be done statistically.[10–12] Earlier heart failure studies tried to address this issue with the "days alive and out of hospital" method.[13,14] Any analysis must also account for the competing risk of death, given that admission with worsening heart failure accentuates the risk of death (and that dead patients can no longer be admitted).[15]

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To address this problem further, we examined the frequency of first and recurrent admissions and their time course and predictors in the Eplerenone in Mild Patients Hospitalization and

Received April 17, 2012; accepted August 28, 2012.

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Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.112.110536**

Survival Study in Heart Failure trial (EMPHASIS-HF).[16,17] We also analyzed the effect of eplerenone on repeat admissions by using a statistical approach that accounts for death.[15]

Methods

Study Design and Patients

The design and primary results of the EMPHASIS-HF trial have been published previously.[16,17] In brief, EMPHASIS-HF tested the hypothesis that eplerenone would reduce the risk of death and the risk of hospitalization among patients with systolic heart failure and mild symptoms. A total of 2737 patients with New York Heart Association class II heart failure and an ejection fraction of no more than 35% were randomly assigned to receive eplerenone (up to 50 mg daily) or placebo, in addition to recommended therapy. The primary end point of the study was a composite of death from cardiovascular causes or hospitalization for heart failure. This article describes the analysis of the repeat hospitalizations, focusing on heart failure hospitalizations. All hospital admissions for suspected heart failure were adjudicated by a blinded end point committee. The previously published results were on all patient follow-up to May 25, 2010.[17] Because there was a subsequent median follow-up of 4.5 months on assigned double-blind treatment (pending a protocol amendment permitting all patients to receive eplerenone), this analysis uses these additional follow-up data.

Statistical Analyses

All analyses were conducted in accordance to the intention-to-treat principle. The 2 treatment groups were balanced with respect to baseline characteristics. Differences in these baseline characteristics, by the number of hospitalizations, were analyzed with analysis of variance for continuous variables and by the χ^2 test for categorical variables. The probability values reported are 2-sided.

Bar plots for the distributions of the number of hospitalizations per person were created, separately, for all-cause, cardiovascular and heart failure hospitalizations.

Cumulative Incidence of Heart Failure Hospitalizations

Cumulative incidence of heart failure hospitalizations were calculated for the 2 treatment groups. Analyses of heart failure hospitalization rates can be confounded by the competing risk of death, so to assess the impact of death on hospitalization rates, estimates of the cumulative number of heart failure hospitalizations were also calculated by using the Ghosh and Lin[15] nonparametric analysis of the hospitalization rates that allow for mortality as a competing risk.

Hospitalization Rates

The average number of hospital admissions per 100 patient-years of follow-up was calculated for heart failure hospitalizations. The rate per patient-year of follow-up was calculated by dividing the total number of heart failure hospital admissions in each treatment group by the total follow-up duration of all patients in that group. This simple analysis of heart failure hospitalizations (including repeats) is based on the Poisson distribution, which assumes that all patients have the same underlying risk of being hospitalized for heart failure. A more appropriate alternative approach that allows for the different individual tendencies (frailties) for repeat heart failure hospitalization recurrence uses the negative binomial distribution.

Modeling of Heart Failure Hospitalization Rates

The negative binomial regression model was used to obtain an estimate of the effect of eplerenone on the rate of heart failure hospitalizations.[11] The Poisson distribution is also commonly used to compare event rates in different groups, but does not account for the highly skewed distribution in the frequency of hospitalizations.[10] Alternatively, a survival-based technique is the Andersen-Gill extension of the Cox proportional hazards model.[12] The Poisson and Andersen-Gill regression models, however, both assume independence of events within individuals, an assumption that is clearly violated because recurrent hospitalizations within individuals will be dependent.[10] The negative binomial is considered an attractive distribution to use, because it naturally accommodates the different probabilities for events across members of the population. This distribution assumes that each patient has recurrent hospitalizations according to an individual-specific Poisson event rate, and that the Poisson rates vary according to a gamma distribution.[11] The gamma distribution is mathematically convenient and is a highly flexible distribution.[18] The negative binomial allows estimation of average rates of heart failure hospitalizations in the eplerenone and placebo groups, and estimation of the ratio of rates of hospitalizations for heart failure in the 2 groups, as well. In addition, the negative binomial regression model is simple and straightforward to use and, in contrast with the Andersen-Gill approach, does not require complicated data files (only 1 entry per patient). Simulation studies have also shown that the negative binomial produces results that are similar to the Andersen-Gill approach.[12]

Rate ratios, 95% confidence intervals, and probability values were calculated with the use of models adjusted for the following prespecified baseline covariates: sex, age, estimated glomerular filtration rate, ejection fraction, body mass index, hemoglobin value, heart rate, systolic blood pressure, diabetes mellitus, and a history of hypertension, myocardial infarction, atrial fibrillation, and a left bundle-branch block or QRS duration >130 ms. Sensitivity analyses were performed by means of unadjusted models.

Results

Incidence of Hospital Admissions

The crude frequencies for hospital admissions of different types, without accounting for differential length of follow-up, are presented in Table 1. Of the 2737 patients randomly assigned, 458 (17%) died and 1013 (37%) had at least 1 hospital admission for any cause during follow-up (median 25 months). The number of patients admitted for a cardiovascular cause was 753 (28%) of whom 463 (17%) were admitted for heart failure. There were 1985 hospital admissions in total (ie, taking account of first and repeat episodes), of which 1328 (67%) were cardiovascular; 793 (60%) of those were due to heart failure. This means that 40% of all hospital admissions were due to heart failure.

Including repeat episodes, there were 481 hospital admissions for worsening heart failure in the placebo group in comparison with 312 hospitalizations in the eplerenone group. This gives 35.0 hospitalizations per 100 patients in the placebo group in comparison with 22.9 hospitalizations per 100 patients in the eplerenone group, which is a difference of ≈12 hospitalizations per 100 patients.

There were 277 (20%) patients with at least 1 heart failure hospitalization in the placebo group in comparison with 186 (14%) patients in the eplerenone group. This represents a difference of 6 patients per 100, and a 32% relative risk reduction (95% confidence interval [CI], 20%–43% reduction; $P<0.0001$). Smaller reductions were observed in cardiovascular hospitalizations (21% relative risk reduction [95% CI, 11%–31%; $P=0.0001$]) and all-cause hospitalizations (16% relative risk reduction [95% CI, 7%–23%; $P=0.0007$]), indicating that the effect of eplerenone on admissions is predominantly confined to the admissions due to heart failure. This is illustrated in Figure 1, which shows bar plots for the distributions of the crude numbers of hospitalizations by treatment group. The treatment differences in cardiovascular hospitalizations that are not heart

Table 1. Number of Patients Hospitalized and Number of Hospital Admissions in EMPHASIS-HF

	Placebo	Eplerenone	% Reduction
No. of patients	1373	1364	. . .
Total follow-up years	2830.91	2916.07	. . .
No. of deaths	253	205	18.44
No. of CV deaths	215	178	16.66
All-cause hospitalization			
Patients with ≥1 admission	551	462	15.60
Patients with ≥2 admissions	256	195	23.33
Total admissions	1123	862	22.74
Cardiovascular hospitalization			
Patients with ≥1 admission	423	330	21.47
Patients with ≥2 admissions	174	112	35.21
Total admissions	773	555	27.73
Heart failure hospitalization			
Patients with no. of hospitalizations			
1	167	119	. . .
2	60	41	. . .
3	24	13	. . .
4	12	6	. . .
5	10	2	. . .
6	4	1	. . .
7	0	2	. . .
8	0	1	. . .
10	0	1	. . .
Patients with ≥1 admission	277	186	32.41
Patients with ≥2 admissions	110	67	38.69
Total admissions	481	312	34.71

CV indicates cardiovascular; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure.

failure, and hospitalizations that are not cardiovascular, are both much less than those due to heart failure and do not achieve statistical significance. So, although heart failure hospitalizations were only 40% of all hospitalizations observed, it was on these hospitalizations that the treatment effect was concentrated. All subsequent analyses are confined to heart failure hospitalization only.

Baseline Characteristics of Patients Hospitalized for Heart Failure

Several baseline characteristics were significantly associated with the risk of hospitalization (at least once) for heart failure (Table 2). Hospitalized patients tended to be older, have a higher heart rate, lower blood pressure, lower left ventricular ejection fraction, longer QRS duration/left bundle-branch block, lower body mass index, ischemic etiology, longer duration of heart failure, lower hemoglobin, higher serum creatinine levels, and lower estimated glomerular filtration rate. Additionally, those hospitalized were more likely to have a history of previous heart failure hospitalization, myocardial infarction, coronary artery bypass surgery, atrial fibrillation, and diabetes mellitus. There were no statistically significant differences in these characteristics in patients who were hospitalized for heart failure only once in comparison with those who were hospitalized twice or more.

Cumulative Rate of Heart Failure Hospitalizations

Figure 2 shows the cumulative crude number of admissions for heart failure per 100 patients in the 2 treatment groups, with early and continuing separation of the event curves for each treatment. By 1 year, the cumulative number of heart failure hospitalizations per 100 hundred patients was 20.26 on placebo in comparison with 9.20 on eplerenone, a treatment difference of 11.06 hospitalizations per 100 patients. Beyond 1 year, this difference continued to increase, but at a slower rate (14.84 at 2 years and 18.88 at 3 years). Figure 3 shows the ratio of the cumulative numbers of heart failure hospitalizations between the eplerenone and placebo groups. This ratio remained ≈0.4 for the first year, and attenuated slightly to 0.6 by 2 years, after which it then appeared to remain constant.

Estimates of the cumulative number of heart failure hospitalizations per 100 people by using the Gosh and Lin approach that did allow for death tended to be slightly lower than the estimate that ignored mortality, although it made a negligible difference in the treatment comparison.[15]

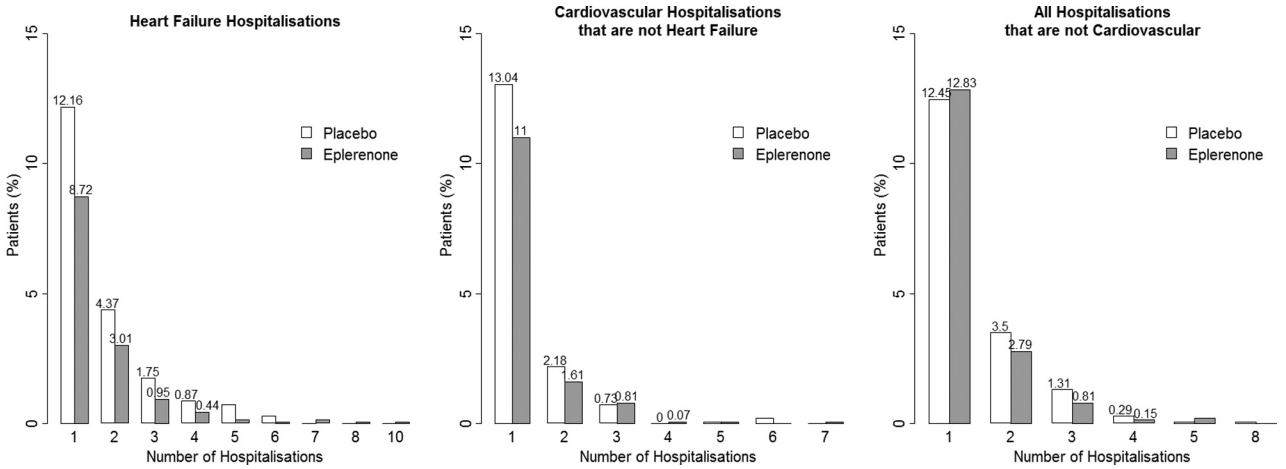

Figure 1. Distributions per person of (1) the number of heart failure hospitalizations, (2) cardiovascular hospitalizations that were not for heart failure, and (3) all hospitalizations that were not for cardiovascular disease.

Table 2. Baseline Characteristics According to Heart Failure Hospital Admission Status

Baseline Characteristics	No. of Heart Failure Hospitalizations 0 n=2274	1 n=286	≥2 n=177	P*
Age	68.3±7.6	69.9±7.8	70.6±7.6	<0.001
Female, n (%)	516 (22.7)	60 (21.0)	34 (19.2)	0.287
Heart rate, beats/min	72.9±15.2	76.2±17.0	76.0±15.7	<0.001
Systolic blood pressure, mm Hg	125±16.9	121±16.4	120±16.8	<0.001
Diastolic blood pressure, mm Hg	75.0±10.2	73.2±10.0	72.8±10.5	<0.001
Left ventricular ejection fraction, %	26.1±4.7	25.5±4.8	25.6±4.6	0.018
QRS duration, ms	120±46.0	124±35.3	130±44.7	0.003
Body mass index, kg/m^2	27.6±4.8	27.3±5.0	26.5±4.9	0.013
Ischemic heart disease, n (%)	1549 (68.1)	207 (72.4)	130 (73.4)	0.054
Duration of heart failure, y	4.48±5.62	5.74±6.06	5.72±6.40	<0.001
Hemoglobin, g/dL	13.9±1.5	13.4±1.7	13.5±1.5	<0.001
Serum creatinine, mg/dL	1.13±0.30	1.24±0.30	1.23±0.34	<0.001
Estimated GFR, mL/min per 1.73 m^2	72.2±21.8	62.9±17.6	65.0±23.4	<0.001
Estimated GFR <60 mL/min per 1.73 m^2, n (%)	694 (30.5)	135 (47.2)	83 (46.9)	<0.001
Serum potassium, mmol/L	4.32±0.43	4.29±0.43	4.30±0.42	0.183
Medical history, n (%)				
Hospitalization for heart failure	1127 (49.6)	190 (66.4)	123 (69.5)	<0.001
Hypertension	1516 (66.7)	189 (66.1)	114 (64.4)	0.650
Angina pectoris	1001 (44.0)	116 (40.6)	72 (40.7)	0.194
Myocardial infarction	1121 (49.3)	158 (55.2)	102 (57.6)	0.008
PCI	488 (21.5)	66 (23.1)	42 (23.7)	0.409
CABG	401 (17.6)	65 (22.7)	50 (28.2)	<0.001
Atrial fibrillation	678 (29.8)	107 (37.4)	59 (33.3)	0.012
Diabetes mellitus	665 (29.2)	122 (42.7)	72 (40.7)	<0.001
Stroke	208 (9.15)	35 (12.2)	19 (10.7)	0.112
LBBB or QRS duration >130 ms in nonpaced baseline ECG	873 (38.4)	137 (47.9)	101 (57.1)	<0.001

Plus-minus values are means SD. GFR indicates glomerular filtration rate; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; and LBBB, left bundle-branch block.

*P value comparison between those patients not hospitalized and those hospitalized at least once.

Heart Failure Hospitalization Rates

Rates of heart failure hospitalizations were defined in each treatment group as the total number of heart failure hospitalizations divided by the total number of years of follow-up. In the placebo group, there were 481 heart failure hospitalizations over 2830.91 years of follow-up in comparison with 312 heart failure hospitalizations over 2916.07 years of follow-up in the eplerenone group. Thus, heart failure hospitalizations rates, per 100 person-years, were 16.99 in the placebo group and 10.70 in the eplerenone group, a rate ratio of 0.63 (95% CI 0.55–0.73, $P<0.0001$). For those who died during follow-up (253 on placebo in comparison with 205 on eplerenone), the heart failure hospitalization rates per 100 person-years were 60.57 in the placebo group in comparison with 56.01 in the eplerenone group. So heart failure hospitalization rates were much higher before death and were rather similar between the 2 treatment groups.

Treatment with eplerenone greatly reduced the rate of heart failure hospitalization. The negative binomial regression model gave a rate ratio for the eplerenone group, in comparison with the placebo group, of 0.53 (95% CI, 0.42–0.66; $P<0.0001$).

Table 3 shows further results from a multivariable negative binomial regression model that relates treatment and prespecified baseline covariates to heart failure hospitalization rates. The rate ratio of heart failure hospitalizations, adjusted for prespecified covariates, for eplerenone versus placebo, was 0.53 (95% CI, 0.43–0.66; $P<0.0001$), practically identical to the unadjusted analysis.

Baseline covariates independently associated with a higher risk of ≥1 heart failure hospitalizations were estimated glomerular filtration rate <60 mL/min per 1.73 m^2, lower body mass index, lower hemoglobin level, higher heart rate, and lower systolic blood pressure. In addition, heart failure hospitalization rates were greater among patients with a history of diabetes mellitus or previous myocardial infarction. Left bundle-branch block or QRS duration >130 ms were also independently predictive.

Separate analyses were conducted for the first hospitalization only and for repeat hospitalizations (after the first). In the placebo and eplerenone groups there were 277 and 186 first heart failure hospitalizations, respectively, giving corre-

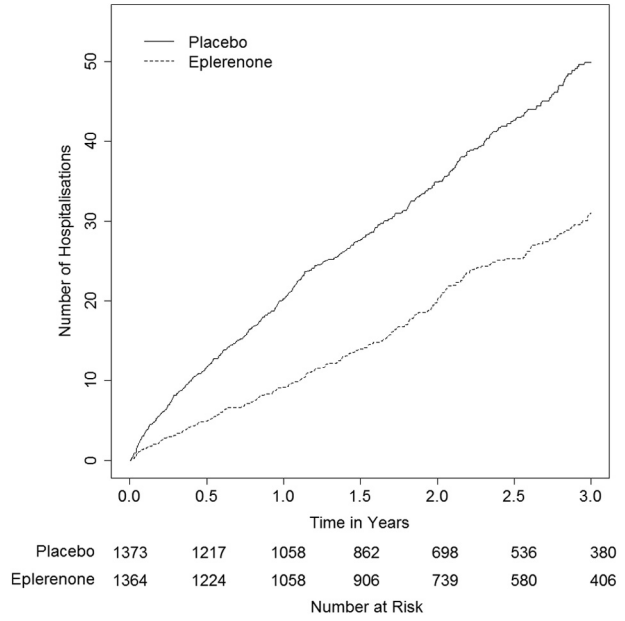

Figure 2. Estimated cumulative rate of heart failure hospitalizations per 100 patients, over time, by treatment group.

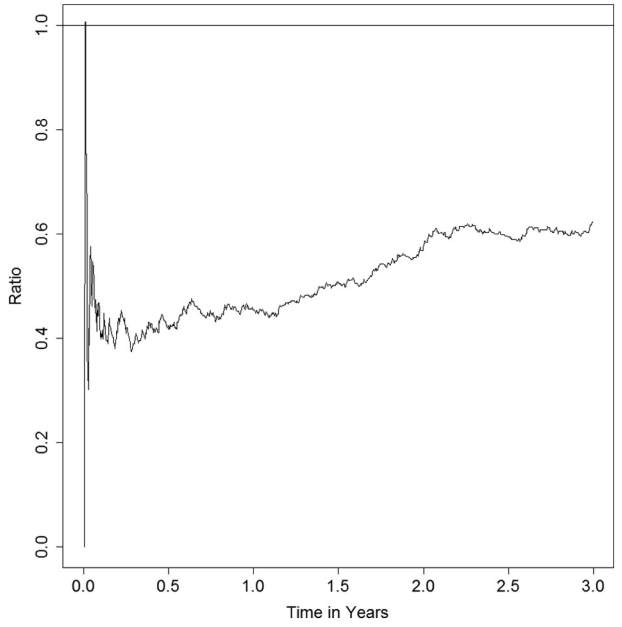

Figure 3. Risk ratio (eplerenone versus placebo) of the cumulative incidence of heart failure hospitalizations over time.

sponding rates of 9.7 and 6.4 per 100 patient-years and a Poisson rate ratio of 0.65 (95% CI, 0.54–0.73; $P<0.0001$). Note that this analysis was based on the Poisson distribution and did not need to allow for interdependence of hospitalizations within individuals, because the analysis took account of only first admissions. A negative binomial regression model was used to analyze repeat heart failure hospitalizations (excluding the first). This gave a rate ratio for the eplerenone, in comparison with placebo, of 0.52 (95% CI, 0.33–0.82; $P=0.004$).

Figure 4 shows the unadjusted and adjusted Cox proportional hazards ratios for conventional time-to-first-event analyses of the primary composite outcome of cardiovascular death or heart failure hospitalization and heart failure hospitalization, and rate ratios for the Poisson and negative binomial analyses of all, first, and repeat heart failure hospitalizations described above, as well.

Discussion

These analyses of EMPHASIS-HF show that in systolic heart failure with only mild symptoms, admission of patients to hospital because of worsening heart failure is common and repeat admission is frequent. Furthermore, eplerenone not only reduces the risk of first admissions but decreases the likelihood of second and subsequent admissions for heart failure (and, in so doing, the overall number of patients hospitalized and the total number of admissions for any reason).

In the placebo group, 110 patients had a second or subsequent hospital admission for heart failure in comparison with 167 patients who experienced a single heart failure hospitalization during follow-up. Crucially, the second and subsequent events experienced by these 110 patients would not count in a conventional time-to-first-event analysis. In other words, 204 (42%) of the total of 481 admissions for heart failure in the placebo group would have been unaccounted for in conventional analyses. These repeat events matter a great deal to patients (and their caregivers) and are an important contributor to the economic burden of heart failure, with most analyses showing that heart failure hospitalization accounts for 70% of the total cost of this condition to healthcare systems.[8,9] In this respect, it is also noteworthy that the patients studied had mild symptoms and were followed up for a relatively short period (median 25 months); it would be of interest to see similar analyses in more severely symptom-

Table 3. Variables Associated With Heart Failure Hospitalization Rates (Rate Ratio, 95% CI, and *P* Value) in a Multivariate Regression Model

	Rate Ratio	95% CI	*P*
Eplerenone vs placebo	0.53	(0.43–0.66)	<0.0001
Female	0.79	(0.60–1.04)	0.0979
Age per 10 y	1.14	(0.98–1.34)	0.0941
Estimated GFR <60 mL/min per 1.73 m^2	1.91	(1.50–2.43)	<0.0001
Left ventricular ejection fraction <30%	0.83	(0.65–1.06)	0.1441
Body mass index per 5 kg/m^2	0.83	(0.74–0.94)	0.0036
Hemoglobin per g/dL	0.90	(0.83–0.97)	0.0041
Heart rate per 10 beats/min	1.18	(1.10–1.26)	<0.0001
Systolic blood pressure per 10 mm Hg	0.83	(0.77–0.89)	<0.0001
Medical history			
Diabetes mellitus	1.99	(1.58–2.51)	<0.0001
Hypertension	0.92	(0.72–1.18)	0.5105
Myocardial infarction	1.30	(1.03–1.63)	0.0242
Atrial fibrillation	1.27	(1.00–1.62)	0.0522
LBBB or QRS duration >130 ms in nonpaced ECG	1.69	(1.35–2.11)	<0.0001

GFR indicates glomerular filtration rate; CI, confidence interval; and LBBB, left bundle-branch block.

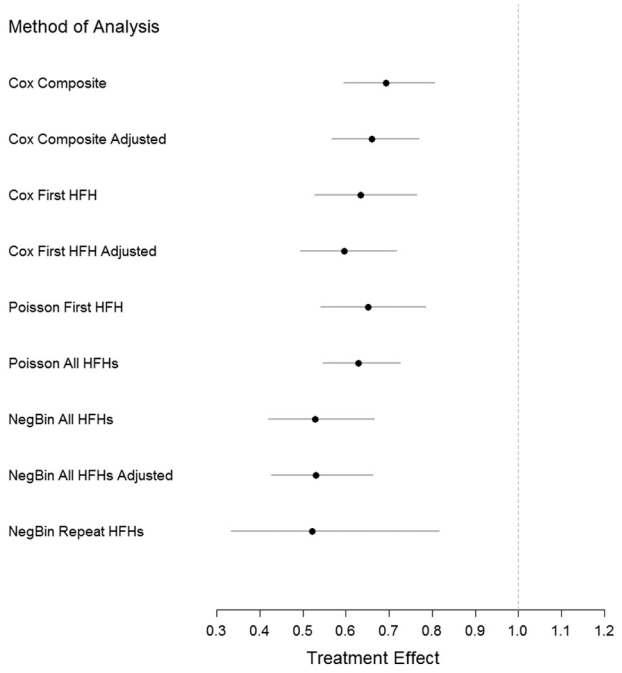

Figure 4. Unadjusted and adjusted Cox proportional hazards ratios (Cox) for conventional time-to-first-event analyses of the primary composite outcome of cardiovascular death or heart failure hospitalization (Composite) and heart failure hospitalization (HFH), and rate ratios for the Poisson and negative binomial (NegBin) analyses of all, first, and repeat heart failure hospitalizations, as well. The variables shown in Table 3 were used to adjust the Cox hazards ratios and negative binomial rate ratio for all heart failure hospitalizations.

atic patients and over longer periods of time. These recurrent episodes are important in at least 2 other ways. First, it is possible that a treatment might reduce the risk of a first recurrence but be less effective in reducing subsequent episodes, so that an overly optimistic assessment of the effect of treatment might be deduced from a time to first analysis (although the converse could also occur). Although this is a recognized concern with anti-infective and anticancer therapies, it is more hypothetical in cardiovascular disease, although reactivation of the renin-angiotensin-aldosterone system does occur during chronic angiotensin-converting enzyme inhibitor treatment. We did not find any diminution of effect of treatment with eplerenone. Second, we found that a relatively small fraction of patients contributed disproportionately to the overall burden of admissions, and this supports the findings of a similar analysis of the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy[7]. If these individuals could be identified, they would be an appropriate target for more intensive monitoring and treatment.

Although our data illustrate the importance of accounting for repeat admissions, there is controversy concerning which is the most appropriate approach to the statistical analysis of recurrent events.[10–12] A key issue is that recurrent events are not independent (as illustrated by the clustering of recurrent admissions in a small proportion of patients), rendering standard statistical techniques that treat events as independent observations invalid.[19,20] Death is a confounding factor in such analyses because, for example, in heart failure, patients who are hospitalized are more likely to die than those who are not (and the risk is increased more in those who experience more admissions).[13,19] A treatment difference in mortality also results in an unequal duration of follow-up between treatment groups. For example, in heart failure, it is known that occurrence of a hospitalization for worsening heart failure increases the risk of further admissions.[7,20] On the other hand, it is likely that admissions result in intensification of therapy, clearly relevant in the present trial where a nonstudy mineralocorticoid receptor antagonist may have been started. We used 2 approaches to take account of these concerns. One, the nonparametric method of Gosh and Lin was used to take account of the competing risk of death.[15] The other, a negative binomial generalized linear model, was used to account for the interdependence of events within an individual.[11]

The Gosh and Lin analysis did not substantially alter the estimate of the cumulative rate of heart failure admissions (Figure 2). Because our patients had mild symptoms, the risk of death was relatively low, so perhaps results of the 2 analyses might have been more different in a population with a higher mortality rate.

It is clear that taking account of only first admissions considerably underestimates the benefit of eplerenone on the burden of heart failure. Considering only first admissions for heart failure, in comparison with placebo, eplerenone treatment prevented 6 admissions per 100 patients treated being admitted at least once for worsening heart failure. However, considering all hospitalizations for heart failure, eplerenone prevented 12 hospital admissions per 100 patients treated. Our analyses have some limitations. They were not prespecified. The statistical power for some comparisons was limited as mentioned earlier. The differences between treatment groups may have been attenuated by open-label use of mineralocorticoid receptor antagonists in the placebo group during follow-up, in particular, after a first hospitalization (although this makes our analyses conservative).

In summary, our report illustrates the importance of recurrent events of patients with systolic heart failure, illustrates approaches to their analysis, and demonstrates the potential underestimation of the benefit of effective therapies if only initial events are accounted for in a conventional time-to-first-event end point. We suggest that analysis of recurrent events should be routine in clinical trials in patients with heart failure, as is the case in other disease states characterized by frequent recurrent episodes.[10]

Sources of Funding

This study was supported by Pfizer.

Disclosures

Dr Zannad reports receiving fees for serving on the board of Boston Scientific; consulting fees from Novartis, Takeda, AstraZeneca, Boehringer Ingelheim, GE Healthcare, Relypsa, Servier, Boston Scientific, Bayer, Johnson & Johnson, and Resmed; and speaker's fees from Pfizer and AstraZeneca and that his institution receives grant support from BG Medicine and Roche Diagnostics on his behalf. Dr McMurray's employer, Glasgow University, was paid by the trial sponsor, Pfizer, for his participation as an Executive

Committee member. He also received travel support and accommodations to attend committee meetings. Dr Krum reports receiving travel reimbursements from Pfizer. Harry Shi and Dr Vincent report being employees of Pfizer and receiving stock options and travel reimbursements from Pfizer. Dr Pocock reports receiving consulting fees from Servier, Amgen, AstraZeneca, and Novartis, and that his institution receives grants from Servier and AstraZeneca on his behalf. Dr Pitt reports receiving fees for serving on the board of Novartis; consulting fees from Takeda, AstraZeneca, Boehringer Ingelheim, GE Healthcare, Relypsa, BG Medicine, Nile Therapeutics, Merck, Forest Laboratories, and Novartis; grant support from Forest Laboratories and Novartis; and stock options from Relypsa, BG Medicine, Nile Therapeutics, and Aurasenc; and that his institution receives grant support from Forest Laboratories on his behalf and he and his institution receive grant support from Bayer.

References

1. Richard Hobbs FD. Clinical burden and health service challenges of chronic heart failure. *Br J Gen Pract*. 2010;60:611–615.
2. Ekman I, Cleland JG, Andersson B, Swedberg K. Exploring symptoms in chronic heart failure. *Eur J Heart Fail*. 2005;7:699–703.
3. Massie BM, Berk MR, Brozena SC, Elkayam U, Plehn JF, Kukin ML, Packer M, Murphy BE, Neuberg GW, Steingart RM. Can further benefit be achieved by adding flosequinan to patients with congestive heart failure who remain symptomatic on diuretic, digoxin, and an angiotensin converting enzyme inhibitor? Results of the flosequinan-ACE inhibitor trial (FACET). *Circulation*. 1993;88:492–501.
4. Neaton JD, Gray G, Zuckerman BD, Konstam MA. Key issues in end point selection for heart failure trials: composite end points. *J Card Fail*. 2005;11:567–575.
5. Skali H, Pfeffer MA, Lubsen J, Solomon SD. Variable impact of combining fatal and nonfatal end points in heart failure trials. *Circulation*. 2006;114:2298–2303.
6. Reduced costs with bisoprolol treatment for heart failure: an economic analysis of the second Cardiac Insufficiency Bisoprolol Study (CIBIS-II). *Eur Heart J*. 2001;22:1021–1031.
7. Goldenberg I, Hall WJ, Beck CA, Moss AJ, Barsheshet A, McNitt S, Polonsky S, Brown MW, Zareba W. Reduction of the risk of recurring heart failure events with cardiac resynchronization therapy: MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy). *J Am Coll Cardiol*. 2011;58:729–737.
8. Conard MW, Heidenreich P, Rumsfeld JS, Weintraub WS, Spertus J. Cardiovascular Outcomes Research Consortium. Patient-reported economic burden and the health status of heart failure patients. *J Card Fail*. 2006;12:369–374.
9. Stewart S, Jenkins A, Buchan S, McGuire A, Capewell S, McMurray JJ. The current cost of heart failure to the National Health Service in the UK. *Eur J Heart Fail*. 2002;4:361–371.
10. Glynn RJ, Buring JE. Ways of measuring rates of recurrent events. *BMJ*. 1996;312:364–367.
11. Greenwood M, Yule GU. An inquiry into the nature of frequency distributions representative of multiple happenings with particular reference to the occurrence of multiple attacks of disease or of repeated accidents. *J Roy Stat Soc*. 1920;83:255–279.
12. Jahn-Eimermacher A. Comparison of the Andersen-Gill model with poisson and negative binomial regression on recurrent event data. *Comput Stat Data An*. 2008;52:4989–4997.
13. Cleland JGF, Louis AA, Rigby AS, Janssens U, Balk AHMM. Noninvasive home telemonitoring for patients with heart failure at high risk of recurrent admission and death: The Trans-European Network-Home-Care Management System (TEN-HMS) study. *J Am Coll Cardiol*. 2005;45:1654–1664.
14. Jaarsma T, van der Wal MHL, Lesman-Leegte I, Luttik M, Hogenhuis J, Veeger NJ, Sanderman R, Hoes AW, van Gilst WH, Lok DJA, Dunselman PHJM, Tijssen JGP, Hillege HL, van Veldhuisen DJ. Effect of moderate or intensive disease management program on outcome in patients with heart failure: Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart failure (COACH). *Arch Intern Med*. 2008;168:316–324.
15. Ghosh D, Lin DY. Nonparametric analysis of recurrent events and death. *Biometrics*. 2000;56:554–562.
16. Zannad F, McMurray JJ, Drexler H, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pitt B. Rationale and design of the Eplerenone in Mild Patients Hospitalisation And SurvIval Study in Heart Failure (EMPHASIS-HF). *Eur J Heart Fail*. 2010;12:617–622.
17. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B; EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med*. 2011;364:11–21.
18. Hsu L, Gorfine M, Malone K. On robustness of marginal regression coefficient estimates and hazard functions in multivariate survival analysis of family data when the frailty distribution is mis-specified. *Stat Med*. 2007;26:4657–4678.
19. Solomon SD, Dobson J, Pocock S, Skali H, McMurray JJ, Granger CB, Yusuf S, Swedberg K, Young JB, Michelson EL, Pfeffer MA. Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) Investigators. Influence of nonfatal hospitalization for heart failure on subsequent mortality in patients with chronic heart failure. *Circulation*. 2007;116:1482–1487.
20. Anand IS, Carson P, Galle E, Song R, Boehmer J, Ghali JK, Jaski B, Lindenfeld J, O'Connor C, Steinberg JS, Leigh J, Yong P, Kosorok MR, Feldman AM, DeMets D, Bristow MR. Cardiac resynchronization therapy reduces the risk of hospitalizations in patients with advanced heart failure: results from the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial. *Circulation*. 2009;119:969–977.

CLINICAL PERSPECTIVE

The standard method of analysis of deaths and hospital admissions in clinical trials that only considers first events may no longer be the most appropriate approach as cardiovascular diseases become more chronic conditions, increasingly characterized by recurrent nonfatal episodes. We examined alternative approaches, taking account of repeat heart failure hospitalizations (HFHs) in the The Eplerenone in Mild Patients Hospitalization and SurvIval Study in Heart Failure trial (EMPHASIS-HF). During the median 25 months extended double-blind follow-up, 186 of 1364 (14%) of eplerenone-treated and 277 of 1373 (20%) of placebo-treated patients experienced at least 1 HFH, ie, a relative risk reduction of 32% (95% confidence interval, 20–43); $P<0.0001$, or 6 fewer HFHs per 100 patients treated. There were a total of 312 HFH (10.7 per 100 person-years) in the eplerenone group in comparison with 481 (17.0) in the placebo group, giving a rate ratio of 0.63 (95% confidence interval, 0.55–0.73); $P<0.0001$, or 12 fewer HFHs per 100 patients treated. Of the 481 total HFHs in the placebo group, 204 (42%) did not count in the time-to-first-event analysis. In the eplerenone and placebo groups, there were 186 (6.4 per 100 person-years) and 277 (9.7) first HFH, respectively, giving a Poisson rate ratio of 0.65 (95% confidence interval, 0.54–0.73); $P<0.0001$. A negative binomial regression model used to analyze repeat HFH (excluding the first), gave a rate ratio of 0.52 (95% confidence interval, 0.33–0.82); $P=0.004$. Analyses of repeat events may give a better assessment of the effect of treatment on the burden of chronic diseases such as heart failure.

Eplerenone in Patients With Systolic Heart Failure and Mild Symptoms: Analysis of Repeat Hospitalizations

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Circulation. 2012;126:2317-2323; originally published online October 5, 2012;
doi: 10.1161/CIRCULATIONAHA.112.110536
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539