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Title: Eplerenone in patients with systolic heart failure and mild symptoms: Analysis of repeat hospitalizations.

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ABSTRACT

Background: Eplerenone is known to reduce time to first hospitalization for heart failure or cardiovascular death in patients with mild heart failure. In chronic diseases such as heart failure, characterised by repeat hospitalizations, analysing 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 trial (EMPHASIS-HF), compared eplerenone with placebo in 2737 patients with mild heart failure, followed for a median 2.08 years (IQR: 1.08 to 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 to 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 negligible difference to these findings.

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

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

INTRODUCTION

The three major consequences of heart failure are symptoms, hospital admission due to worsening and premature death.[1,2] Because symptoms are subjective and hard to quantify, and because drugs which improve symptoms have also been shown to increase mortality, death and hospital admission have become the most important endpoints used in clinical trials of new treatments for heart failure.[3-5] Typically, these are used together in a composite outcome, usually analysed as time to first event. This approach does not, however, measure the true burden of hospital admissions due to worsening heart failure either for the individual or for health care systems as patients may experience multiple, recurrent, admissions during the course of their illness.[6,7] Not only are these very distressing for patients and their care-givers but hospital admissions are also the major driver of the enormous cost of heart failure to health care systems.[8,9] Furthermore, it is not known whether treatments are as effective at reducing recurrent events as initial ones. Consequently, these recurrent, non-fatal, 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]

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 SurvIval Study in Heart Failure trial (EMPHASIS-HF).[16,17] We also analysed the effect of eplerenone on repeat admissions 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 randomized to receive eplerenone (up to 50mg daily) or placebo, in addition to recommended therapy. The primary endpoint of the study was a composite of death from cardiovascular causes or hospitalization for heart failure. This paper describes the analysis of the repeat hospitalizations, focussing on heart failure hospitalizations. All hospital admissions for suspected heart failure were adjudicated by a blinded endpoint committee. The previously published results were on all patient follow-up to 25 May 2010.[17] Since 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 utilizes these additional follow-up data.

Statistical Analyses

All analyses were carried out in accordance to the intention to treat principle. The two treatment groups were balanced with respect to baseline characteristics. Differences in these baseline characteristics, by the number of hospitalizations, were analysed with ANOVA for continuous variables and the chi-square test for categorical variables. P-values reported are two-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 two 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 using the Ghosh and Lin[15] non-parametric analysis of the hospitalizations 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.

Modelling 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 as recurrent hospitalizations within individuals will be dependent.[10] The Negative Binomial is considered an attractive distribution to use, as 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, as well as estimation of the ratio of rates of hospitalizations for heart failure in the two groups. Additionally, 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 one 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 P-values were calculated with the use of models adjusted for the following pre-specified baseline covariates: gender, age, estimated GFR, 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 greater than 130msec. 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 randomized, 458 (17%) died and 1013 (37%) had at least one 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%) included heart failure. There were 1985 hospital admissions in total (i.e. taking account of first and repeat episodes), of which 1328 (67%) were cardiovascular, with 793 (60%) of those 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, compared with 312 hospitalizations in the eplerenone group. This gives 35.0 hospitalizations per 100 patients in the placebo group, compared with 22.9 hospitalizations per 100 patients in the eplerenone group, which is a difference of approximately 12 hospitalizations per 100 patients.

There were 277 (20%) patients with at least one heart failure hospitalization in the placebo group, compared 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% to 43% reduction, $P<0.0001$). Smaller reductions were observed in cardiovascular hospitalizations (21% relative risk reduction [95% CI 11% to 31%, $P=0.0001$]) and all-cause hospitalizations (16% relative risk reduction [95% CI 7% to 23%, $P=0.0007$]), indicating that the effect of eplerenone on admissions is predominantly confined to those 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 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 GFR. 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 compared 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 two treatment groups, with early and continuing separation of the event curves for each treatment. By one year, the cumulative number of heart failure hospitalizations per 100 hundred patients was 20.26 on placebo, compared to 9.20 on eplerenone, a treatment difference of 11.06 hospitalizations per 100 patients. Beyond one year, this difference continued to increase, but at a slower rate (14.84 at two years and 18.88 at three years). Figure 3 shows the ratio of the cumulative numbers of heart failure hospitalizations between the eplerenone and placebo groups. This ratio remained around 0.4 for the first year, and attenuated slightly to 0.6 by two years, after which it appeared to then remain constant.

Estimates of the cumulative number of heart failure hospitalizations per 100 people 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 negligible difference to the treatment comparison.[15]

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 compared to 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 to 0.73, P<0.0001). For those who died during follow-up (253 on placebo compared with 205 on eplerenone), the heart failure hospitalization rates per 100 person years were 60.57 in the placebo group compared with 56.01 in the eplerenone group. So heart failure hospitalization rates were much higher prior to death and were rather similar between the two 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, as compared with the placebo group, of 0.53 (95% CI 0.42 to 0.66, P<0.0001).

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

Baseline covariates independently associated with a higher risk of one or more heart failure hospitalizations were: estimated GFR less than 60ml/min/1.73m^2, lower body-mass index, lower hemoglobin level, higher heart rate and lower systolic blood pressure. Additionally, heart failure hospitalization rates were greater amongst patients with a history of diabetes or previous myocardial infarction. Left bundle-branch block or QRS duration greater than 130 msec were also independently predictive.

Separate analyses were carried out 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 corresponding rates of 9.7 and 6.4 per 100 patient years and a Poisson rate ratio of 0.65 (95% CI 0.54 to 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, as the analysis took account of only first admissions. A Negative Binomial regression model was used to analyse repeat heart failure hospitalizations (excluding the first). This gave a rate ratio for the eplerenone, compared with placebo, of 0.52 (95% CI 0.33 to 0.82, P=0.004).

Figure 4 shows the unadjusted and adjusted Cox proportional hazard ratios for conventional time to first event analyses of the primary composite outcome of cardiovascular death or heart failure hospitalization and heart failure

hospitalization, as well as rate ratios for the Poisson and Negative Binomial analyses of all, first and repeat heart failure hospitalizations, described above.

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 compared 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 care-givers) 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 health care systems.[8,9] In this respect it is also noteworthy that the patients studied had mild symptoms and were followed for a relatively short period (median 25 months); it would be of interest to see similar analyses in more severely symptomatic patients and over longer periods of time. These recurrent episodes are important in at least two other ways. Firstly, it is possible that a treatment might reduce the risk of a first recurrence but be less effective in reducing subsequent episodes and 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). While this is a recognized concern with anti-infective and anti-cancer therapies, it is more hypothetical in cardiovascular disease, although re-activation 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. Secondly, 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. If these individuals could be identified they would be an appropriate target for more intensive monitoring and treatment.

While 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 which 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 results in intensification of therapy, clearly relevant in the present trial where a non-study mineralocorticoid receptor antagonist may have been started. We used two approaches to take account of these concerns. One, the non-parametric method of Gosh and Lin was employed to take account of the competing risk of death.[15] The other, a Negative Binomial Generalised 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 two analyses might have been more different in a population with a higher mortality rate.

What is clear is 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, compared 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, particularly 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" endpoint. 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 characterised by frequent recurrent episodes.[10]

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FIGURE LEGENDS

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

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.**

Figure 4 **Unadjusted and adjusted Cox proportional hazard 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), as well as rate ratios for the Poisson and Negative Binomial (NegBin) analyses of all, first and repeat heart failure hospitalizations. The variables shown in table 3 were used to adjust the Cox hazard ratios and Negative Binomial rate ratio for all heart failure hospitalizations.**

Table 1 Number of patients hospitalised and number of hospital admissions in EMPHASIS-HF.

	Placebo	Eplerenone	% Reduction
Number of patients	1373	1364	-
Total follow-up years	2830.91	2916.07	-
Number of deaths	253	205	18.44
Number 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

Table 2 Baseline characteristics according to heart failure hospital admission status.

Baseline characteristics	Number of heart failure hospitalizations			P-Value‡
	0	1	≥2	
	N=2274	N=286	N=177	
Age*	68.3±7.6	69.9±7.8	70.6±7.6	<0.001
Female – no. (%)	516 (22.7)	60 (21.0)	34 (19.2)	0.287
Heart rate – beats/minute	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	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 - msec	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 – no. (%)	1549 (68.1)	207 (72.4)	130 (73.4)	0.054
Duration of heart failure - yr	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	72.2±21.8	62.9±17.6	65.0±23.4	<0.001
Estimated GFR < 60 ml/min/$173m^2$ – no. (%)	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 – no. (%)				
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>130msec in non-paced baseline ECG	873 (38.4)	137 (47.9)	101 (57.1)	<0.001

*Plus-minus values are means SD. GFR denotes glomerular filtration rate, PCI percutaneous coronary intervention, CABG coronary artery bypass graft, LBBB left bundle-branch block and ECG electrocardiography. ǂP-value comparison between those patients not hospitalized and those hospitalized at least once.

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-value
Eplerenone vs placebo	0.53	(0.43,0.66)	<0.0001
Female	0.79	(0.60,1.04)	0.0979
Age per 10 years	1.14	(0.98,1.34)	0.0941
Estimated GFR < 60 ml/min/173m^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/minute	1.18	(1.10,1.26)	<0.0001
Systolic blood pressure per 10 mmHg	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>130msec in non-paced ECG	1.69	(1.35,2.11)	<0.0001

Figure 1

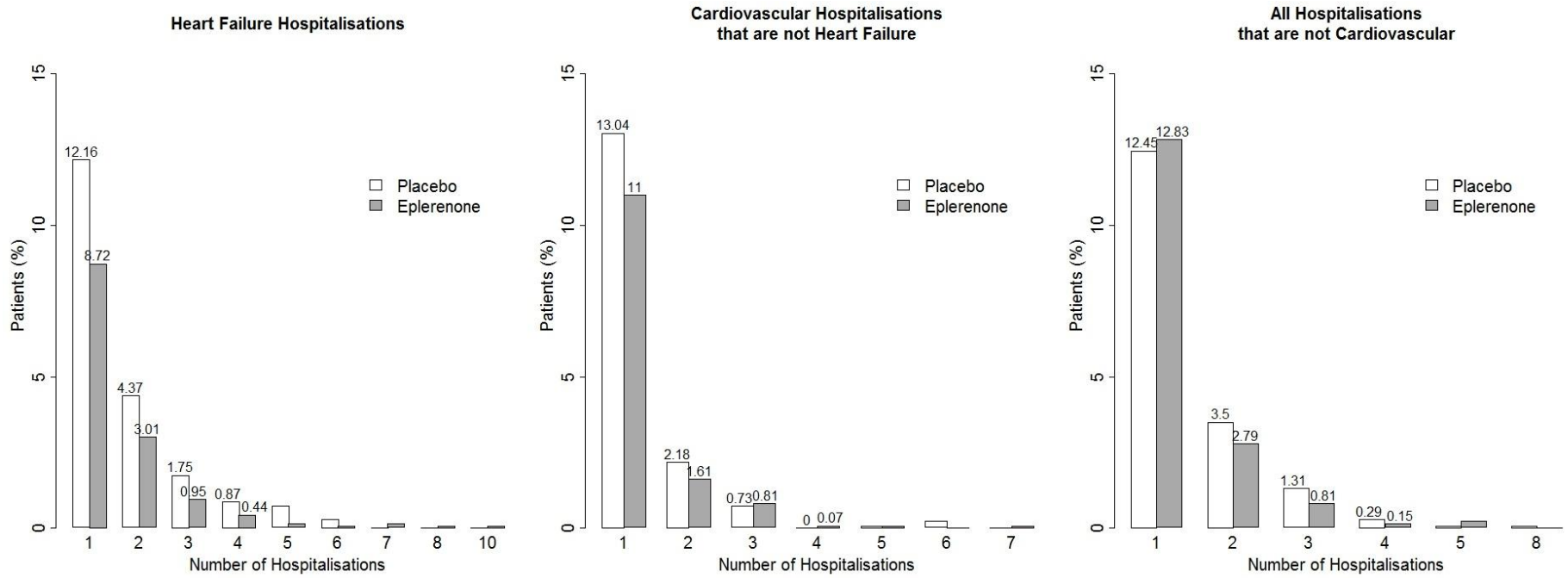

Heart Failure Hospitalisations
Patients (%)
Number of Hospitalisations
Placebo
Eplerenone
12.16
8.72
4.37
3.01
1.75
0.95
0.87
0.44
Cardiovascular Hospitalisations
that are not Heart Failure
13.04
11
2.18
1.61
0.73
0.81
0
0.07
All Hospitalisations
that are not Cardiovascular
12.45
12.83
3.5
2.79
1.31
0.81
0.29
0.15

Figure 2

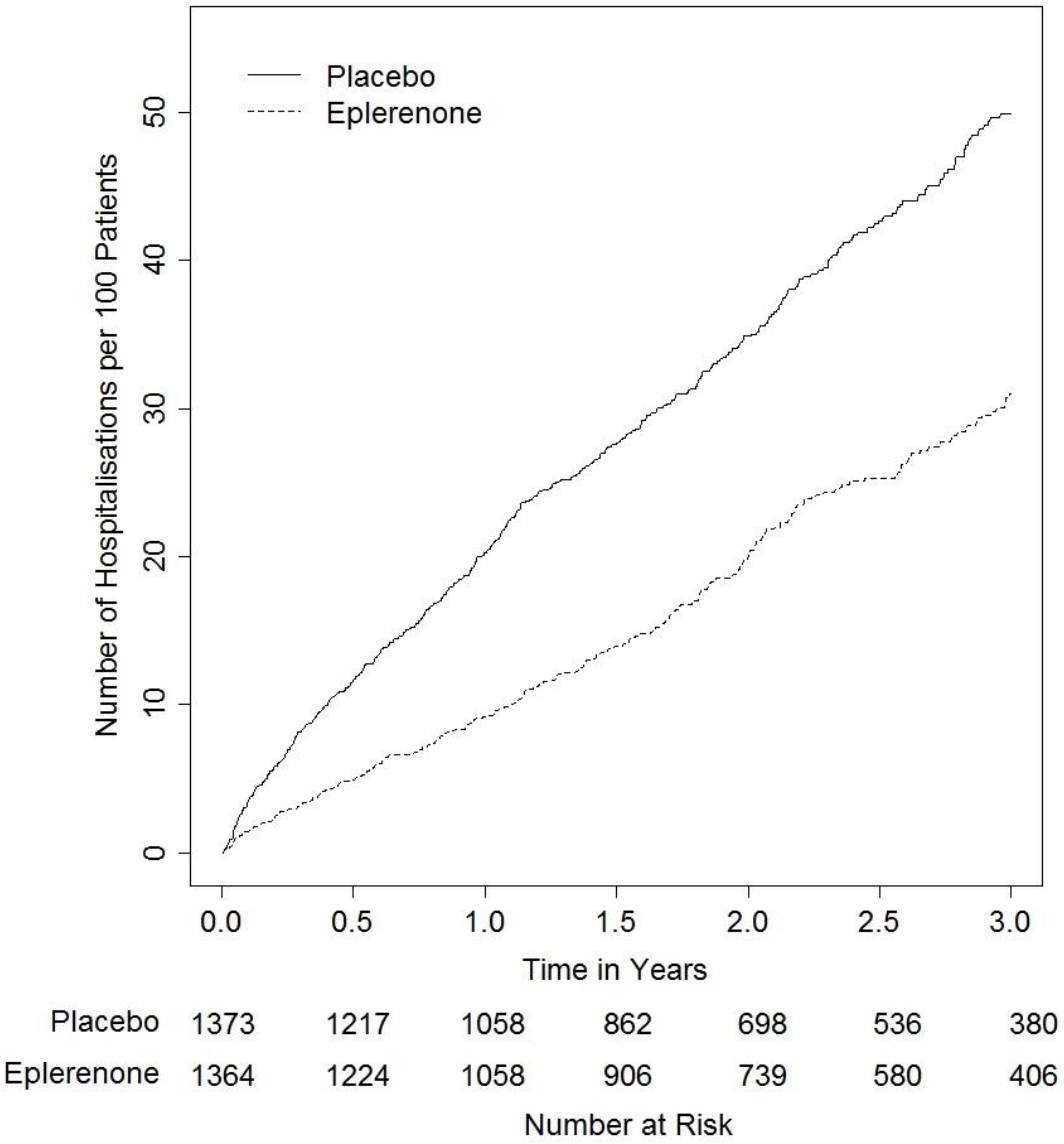

Placebo
Eplerenone
Number of Hospitalisations per 100 Patients
0
10
20
30
40
50
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Time in Years
Placebo 1373 1217 1058 862 698 536 380
Eplerenone 1364 1224 1058 906 739 580 406
Number at Risk

Figure 3

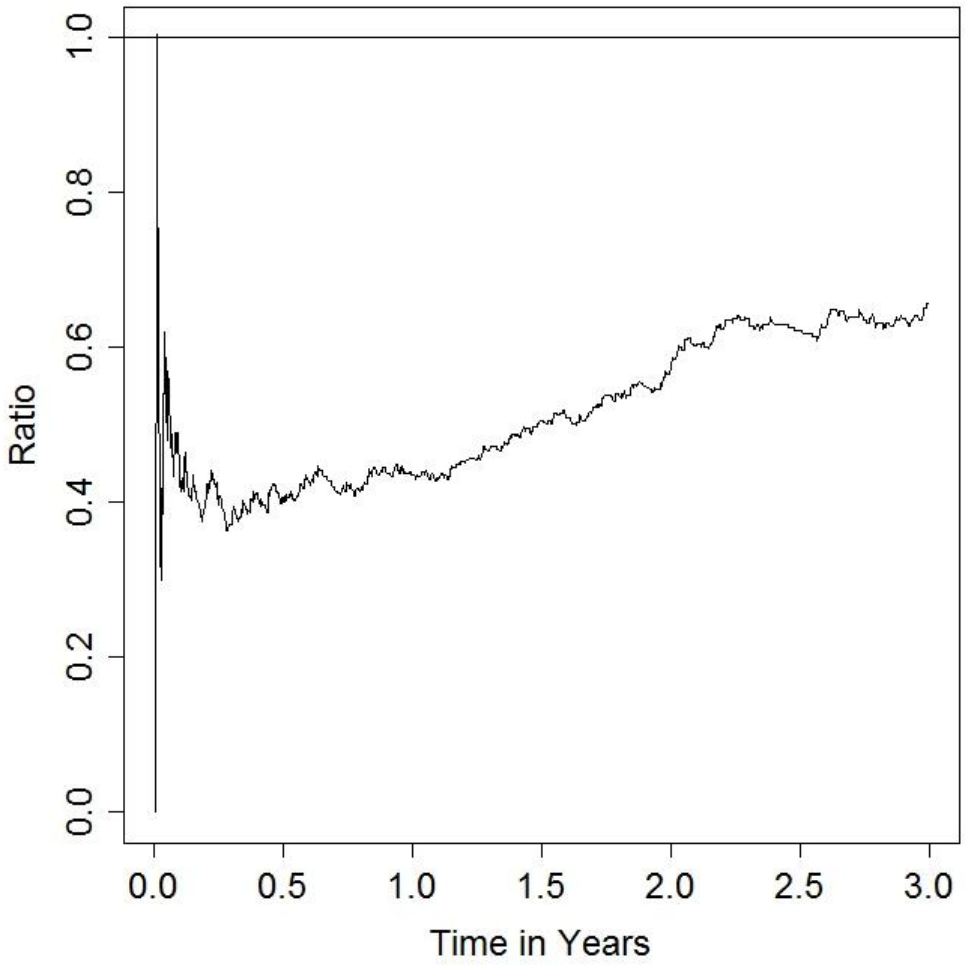
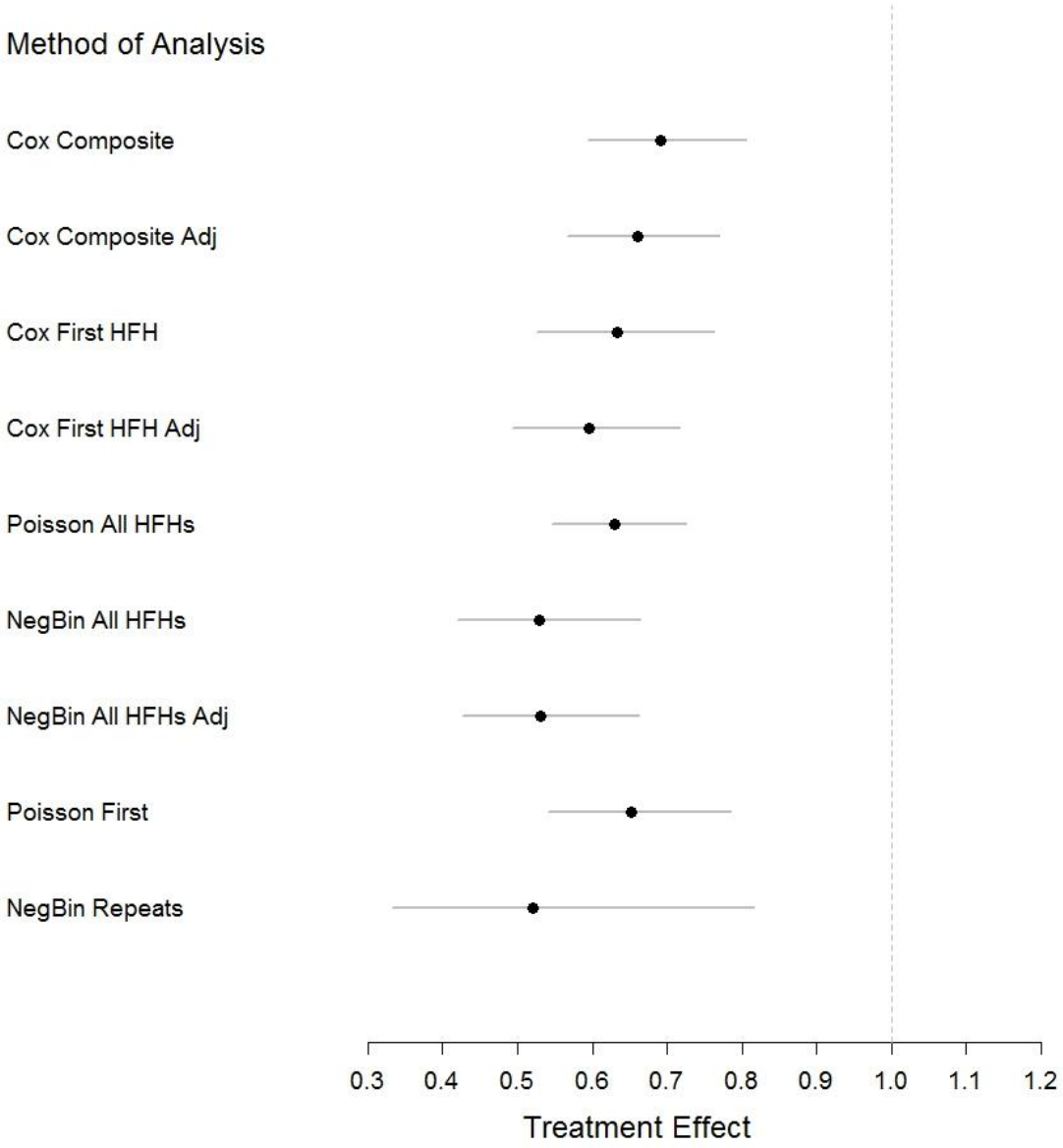


Figure 4


Method of Analysis
Cox Composite
Cox Composite Adj
Cox First HFH
Cox First HFH Adj
Poisson All HFHs
NegBin All HFHs
NegBin All HFHs Adj
Poisson First
NegBin Repeats
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
Treatment Effect