Clinical benefits of eplerenone in patients with systolic heart failure and mild symptoms when initiated shortly after hospital discharge: analysis from the EMPHASIS-HF trial

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Aims
Cardiovascular hospitalization (CVH) in patients with heart failure (HF) is associated with a high post-discharge rate of early re-admission and CV death. Eplerenone might be effective in reducing the incidence of these adverse clinical outcomes during this period.

Methods and results
The EMPHASIS-HF trial compared eplerenone with placebo added to standard therapy in 2737 patients with New York Heart Association class II HF and left ventricular ejection fraction $\leq 35\%$. We conducted a post hoc analysis in the 2338 patients randomized within 180 days of a CVH. The interaction between the time from the qualifying CVH to randomization and the primary outcome of CV death or hospitalization for HF (HHF), as well as other secondary outcomes, was assessed in Cox survival models. Most of the qualifying CVHs were HHF ($N = 1496, 64.0\%$), acute coronary syndromes ($N = 390, 16.7\%$), and arrhythmias ($N = 197, 7.2\%$). The median time of study drug initiation from qualifying CVH was 42 days. The relative rate reductions in CV death/HHF, HHF, and all-cause mortality were similar ($P$ for interaction $= 0.65, 0.44, \text{and } 0.40$, respectively) whether the treatment was initiated, $42$ or $42 + \text{days after qualifying CVH}$. Absolute rate reductions were $2.56\%\ [-2.87, -2.25]$ events per 100 patient $\times$ years in the $42$ days group and $-3.58\%\ [-6.37, -0.79]$ in the $42 + \text{days group}$. The adverse effects of eplerenone were also unaffected by the time from the qualifying CVH.

Conclusion
Eplerenone is safe, improves survival, and may prevent re-admission when initiated soon after a hospitalization for HF or acute coronary syndromes in patients with systolic HF and mild symptoms.

Keywords
Eplerenone • Systolic heart failure • Hospitalization • Timing • Treatment effect • EMPHASIS-HF

Introduction
Patients with heart failure (HF) have a high rate of hospitalization. Cardiovascular hospitalizations (CVHs) of patients with HF account for more than $80\%$ of the total amount spent on the care of these patients.1,2 The hospitalization rate and death rate of patients with HF are especially high after discharge for CVH. This high event rate is observed after hospitalization not only due to worsening HF but also due to other causes. The concept of ‘hospitalized HF’ has been promoted to better characterize this fact.3,4
Strong data exist to support the use of angiotensin-converting enzyme inhibitor (ACE-I), angiotensin receptor blocker (ARB), beta-blockers (BBs), and mineralocorticoid receptor antagonists (MRAs) in patients with chronic HF.1,2 MRAs added to standard therapy reduce mortality as well as hospitalization for chronic HF in patients with a reduced left ventricular ejection fraction (LVEF), irrespective of the severity of symptoms.6,7 Disappointingly, MRAs are prescribed at discharge in less than one-third of the eligible patients, representing even worse underutilization than for ACE-I/ARB and BBs.8 This may be because there are few data specifically about the effectiveness of any of these treatments, including MRAs, in relation to timing of initiation either during or after hospitalization.

We therefore examined the effect of eplerenone according to the timing of its use after hospital discharge in EMPHASIS-HF. The EMPHASIS-HF trial6 compared eplerenone with placebo added to standard therapy in patients with New York Heart Association (NYHA) class II HF and LVEF ≤ 35%.

Methods

The design and results of EMPHASIS-HF8 have been published. Importantly, in most patients, and per-protocol, therapy was initiated within 180 days after a CVH.

Patient selection

Patients included in EMPHASIS-HF were at least 55 years of age; in NYHA functional class II; had an LVEF ≤ 35% (or if between 31 and 35%, the QRS duration had to be > 130 ms); and were treated with the recommended or maximally tolerated dose of an ACE-I/ARB and a BB (unless contraindicated). In addition, included patients had been hospitalized for a cardiovascular reason within the past 6 months or had a B-type natriuretic peptide (BNP) level ≥ 250 pg/mL or N-terminal pro-BNP level ≥ 500 pg/mL for males and ≥ 750 pg/mL for females. Patients with an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m² need a potassium sparing diuretic, or any other significant comorbid condition was excluded.

In this post hoc analysis of the EMPHASIS-HF trial, the 399 patients who were recruited on the basis of an elevated BNP rather than a qualifying CVH have been excluded. We studied the remaining 2338 patients who had been hospitalized for a CV reason within 6 months from randomization.

Each center’s Ethics Committee approved the trial, and all patients provided written informed consent.

Timing of initiation of eplerenone

As only the time of admission, and not time of discharge date of the qualifying CVH, was recorded in the case record form, we considered timing since the qualifying CVH date of admission as a proxy variable. The population was divided into two groups according to the median time from the qualifying CVH (42 days).

Endpoint assessment

The primary efficacy endpoint for the EMPHASIS-HF trial was the composite of cardiovascular mortality or hospitalization for HF. Hospitalization for HF and all-cause mortality were secondary endpoints. All endpoints were independently adjudicated by an independent Critical Event Committee and were used for this post hoc analysis.

Statistical analysis

Baseline characteristics were expressed as mean (standard deviation) or proportions as appropriate.

Univariable time-to-event comparisons were made using log-rank test and univariable Cox proportional hazards models. Proportional hazards assumptions were verified. Interactions between the timing of the initiation of eplerenone since CV event and the effect of eplerenone on clinical outcomes were assessed by introducing an interaction term (time since qualifying CV event × eplerenone) within the models. Regardless of the P-value associated with this interaction term, we reported the associations between eplerenone and survival in each of the groups of time since CV events (i.e. < 42 or 42+ days). Survival probabilities were estimated using the Kaplan–Meier method.

As reported previously,11 analyses of all HF hospitalizations, including repeats, were carried out using negative binomial regression models. We compared the incidence rates of HF hospitalizations in patients initiated on eplerenone and placebo, respectively, within 42 and after 42 days since qualifying CV event. The negative binomial method allows for the different individual patient tendencies (frailties) for repeat hospitalizations, i.e. it takes into account the skewness in the distribution of number of HF hospitalizations.

All analysis was run in SAS version 9.2 and Stata/MP version 12.

Results

Comparison of baseline characteristics of patients in the <42 and 42+ days groups

Half of the patients in the <42 days group had a time since qualifying CVH less than 12 days (Table 1). Most of the qualifying hospitalizations were due to HF (71.9% in the <42 days group and 56.1% in the 42+ days group). Previous acute myocardial infarction or unstable angina was also frequent (10.9% in the <42 days group and 22.5% in the 42+ days group) as well as previous CVH due to arrhythmias (7.9% in the <42 days group and 9.0 in the 42+ days group).

Overall, patients in the <42 days group had similar baseline characteristics when compared with those in the 42+ days group, including similar age (68.5 vs. 68.8 years) and LVEF (26.4 vs. 26.1%). Patients in the <42 days group had a modestly higher probability of having an eGFR < 60 mL/min/1.73 m² (34.6 vs. 30.6%) or of being previously hospitalized for HF (56.3 vs. 50.8%).

In addition, we did not identify clinically significant differences according to treatment allocation in the <42 and 42+ days groups.

Comparison of event rate of patients in the <42 and 42+ days groups

Overall, during follow-up, 354 patients (15.1%) had CV death, 56 patients (2.4%) had non-CV death, and 415 patients (17.6%) had a first HF hospitalization. When repeat HF hospitalizations were considered, 722 HF hospitalizations were identified.

Regardless of the event considered, the event rates were lower in the 42+ days group (Figure 1). The primary outcome (i.e. composite of CV death and hospitalization for HF) was met in 277 patients (23.6%) in the 42+ days group and in 332 patients (28.6%) in the <42 days group, resulting, respectively, in rates of 14.1 and 11.8 events per 100 person-years of follow-up (hazard ratio (HR) = 0.82, 95% confidence interval (CI) = 0.70–0.97). Similarly, patients in the 42+ days group had a lower risk for a first HF hospitalization.
Effect of eplerenone on outcomes in the <42 and 42+ days groups

Regardless of the event considered, cumulative incidences of events in patients treated with eplerenone were lower than the rates observed in patients allocated to placebo in both the <42 and the 42+ days groups (Figure 2).

In the <42 days group, 139 patients (24.4%) in the eplerenone arm and 193 patients (32.5%) in the placebo arm met the primary outcome, resulting, respectively, in rates of 17.0 and 11.4 events per 100 person-years (HR = 0.68, 95% CI = 0.55–0.85, Figure 3). In the 42+ days group, 121 patients (20.5%) in the eplerenone arm and 156 patients (26.6%) in the placebo arm met the primary outcome, resulting, respectively, in rates of 13.6 and 10.0 events per 100 person-years (HR = 0.74, 95% CI = 0.58–
There was no significant interaction between the groups of time since the qualifying CVH and eplerenone treatment with regard to the primary outcome ($P = 0.65$).

The relative effect of eplerenone on all other outcomes was similar in the $<42$ and $42+$ days groups: HF hospitalization (HR = 0.64 in the $<42$ days group vs. 0.68 in the $42+$ days group, $P$ for interaction = 0.44, Figure 3), repeat HF hospitalization (RR = 0.63 in the $<42$ days group vs. HR = 0.49 in the $42+$ days group, $P$ for interaction = 0.13), and all-cause mortality (HR = 0.80 in the $<42$ days group vs. 0.85 in the $42+$ days group, $P$ for interaction = 0.40).

The absolute rate reduction with eplerenone was $-5.61 [-8.67, -2.55]$ events per 100 patient $\times$ years in the $<42$ days group and $-3.58 [-6.37, -0.79]$ events per 100 patient $\times$ years in the $42+$ days group for the primary endpoint. We observed an absolute rate reduction for HF hospitalization of $-4.43 [-6.96, -1.91]$ events per 100 patient $\times$ years in the $42+$ days group. Regarding all-cause deaths, we observed an absolute rate reduction of $-1.95 [-4.22, 0.32]$ events per 100 patient $\times$ years in the $<42$ days group and $-1.17 [-3.25, 0.90]$ events per 100 patient $\times$ years in the $42+$ days group.

### Sensitivity analysis: effect of eplerenone on outcomes in the $<30$ and $30+$ days groups

As a sensitivity analysis, we used a 30-day cut-off rather than the 42-day cut-off. In this analysis, the relative effect of eplerenone on all outcomes was not significantly different in the $<30$ and $30+$ days groups (all $P > 0.05$). Yet, the relative effect of eplerenone on the primary outcome tended to be greater in the $<30$ days group (HR = 0.60, 95% CI = 0.47–0.76) than in the $30+$ days group (HR = 0.81, 95% CI = 0.65–1.00, $P$ for interaction = 0.07).

### Safety of eplerenone in the $<42$ and $42+$ days groups

The incidence of adverse events was low in both groups and was similar in the $<42$ and $42+$ days groups (Table 2). Higher rates of hyperkalaemia were reported in the eplerenone group. However, the association between eplerenone and the rate of adverse events was unaffected by the timing since qualifying hospitalization (all $P$-values for interaction $>0.20$, Table 2).

### Discussion

The main result of this post hoc analysis of the EMPHASIS-HF study is that eplerenone improves survival and prevents re-admission when initiated soon after a CVH in patients with systolic HF and mild symptoms. The magnitude of the benefit from eplerenone was similar, on a relative scale, whether initiated $<42$ or $42+$ days after the qualifying CVH.

Strong data exist to support the use of ACE-I, ARBs, BBs, and MRAs in patients with chronic systolic HF. Clinical trials that demonstrated the clinical benefits of these medications in chronic HF were conducted in HF outpatients. The design of these trials made
physicians reluctant to introduce ACE-I\textsuperscript{12} or BBs,\textsuperscript{13} early after HF worsening. Regarding BBs, a trial was specifically designed to compare the effect of an in-hospital initiation of carvedilol with a later initiation of carvedilol performed in an outpatient setting.\textsuperscript{14} This trial was not powered to assess an impact of the timing of BBs initiation on outcome. However, it demonstrated that a much higher proportion of patients were treated at 60 days after discharge if BBs were initiated during the hospital stay. These results favouring an early introduction of HF treatments are also supported by observational data powered to report clinical outcomes. After a careful propensity score-based analysis that decreases treatment attribution bias, BBs initiated before or at discharge are associated with lower mortality and re-hospitalization following acute HF hospitalization.\textsuperscript{9,15} Similar observational results support the use of ACE-I at discharge from HF hospitalization.\textsuperscript{16} Consequently, the 2012 ESC guidelines\textsuperscript{7} no longer address safety issues of in-hospital initiation of HF treatment other than a cautionary reminder regarding BBs initiation (BBs ‘should usually be initiated in stable patients and used only with caution in recently decompensated patients’). Yet, even in the absence of evidence from randomized trials, clinical practice shifted to an introduction or up-titration of ACE-I/ARBs and BBs during hospital stay for a cardiovascular reason or soon after discharge.\textsuperscript{17,18} This concept was strongly supported by Fonarow\textsuperscript{17,19} and is now a key feature of the American Heart Association’s Get with the Guidelines program.\textsuperscript{19}

However, evidence-based therapies of chronic HF are not systematically initiated or up-titrated during in-patient treatment.\textsuperscript{21} Patients hospitalized for worsening HF are often discharged on the same pre-admission medications.\textsuperscript{22,23} The occurrence of worsening renal function caused by high-dose loop diuretics or renin–angiotensin system blockers may partly explain the lack of treatment intensification. In addition, during the weeks or months following discharge, little initiation or up-titration of HF treatments occurs.\textsuperscript{24,25}

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure2.png}
\caption{Survival curves for cardiovascular death or hospitalization for heart failure, hospitalization for heart failure, and all-cause mortality in patients in the eplerenone and placebo groups according to the timing since CVH.}
\end{figure}
Concerns about initiating MRAs shortly after admission or discharge for worsening HF appear to be even stronger than held for ACE-I/ARB and BBs, at least as judged by the even lower rate of prescription of MRAs.\(^8,21,25–27\) Most studies report MRA prescription in less than one-third of eligible patients,\(^8,21,25,27\) whereas prescription rates of ACE-I/ARBs and BBs are usually more than 70\%.\(^21,25–27\) Changes in prescription pattern take time. The EMPHASIS-HF trial\(^6\) was published in 2011, i.e. much later than the trials focusing on ACE-I, ARBs, and BBs. However, despite the publication of RALES in severe systolic HF in 1999, and the publication of the EPHESUS trial in 2003, low prescription rates of MRAs persisted in eligible patients in reports based on data acquired at the end of the 2000s.\(^27,28\)

One of the main explanations for the disconnection between guideline recommendations and clinical implementation is likely to be safety concerns regarding renal function and hyperkalaemia. A higher incidence of hospitalization for hyperkalaemia has been observed after the publication of the RALES trial.\(^29\) In addition, patients at high risk of hyperkalaemia and/or worsening renal function are often thought to be under-represented in the MRA clinical trials.\(^6,7\) However, we recently published a pre-specified subset analysis of EMPHASIS-HF, which showed that (i) a quarter of the patients randomized to eplerenone were older than 75 or had mild renal dysfunction and (ii) the benefit from eplerenone was significant in these patients at high risk for hyperkalaemia and/or worsening renal function.\(^30\) Consequently, in patients with chronic HF with reduced LVEF and mild symptoms, meeting specific inclusion and exclusion criteria of EMPHASIS-HF, eplerenone is both efficacious and safe when carefully monitored. In addition, in this study, we further demonstrated that the adverse event rate was unaffected by the timing of initiation of eplerenone. Specifically, the increase in the risk of hyperkalaemia with eplerenone was similar in the \(<42 \text{ and } 42+\) days groups. As a result, our analysis provides strong evidence of safety of an early initiation of eplerenone in patients at high risk for hyperkalaemia and/or worsening renal function.

![Figure 3](https://academic.oup.com/eurheartj/article-abstract/36/34/2310/2398253)
function as reported previously, strongly advocate for the initiation of eplerenone, within the spectrum of patients included in the EMPHASIS-HF trial, regardless of the timing since the previous CVH. Early initiation may be sensible enough, because of the potential for decreasing the high event rate observed within this post-discharge vulnerable period.

Clinical perspective

Patients with HF hospitalized for CV reasons continue to suffer from an exceedingly high rate of adverse outcomes. The effectiveness of the currently available disease-modifying HF drugs has not been tested in adequately powered trials during or early after a CVH. MRAs have been hypothesized to be good candidates for the treatment of acute HF syndromes. However, MRAs continue to be prescribed infrequently in eligible patients, probably because of concerns regarding their safety in patients at high risk for hyperkalemia and/or worsening renal function. We provide evidence that eplerenone reduces the high post-discharge event rate after a CVH in patients with systolic HF. We also provide evidence of the safety of eplerenone initiated early after discharge. Our results support the wider use of eplerenone early after a CVH in patients with systolic HF and mild symptoms and no contraindication to an MRA and with careful monitoring as conducted in the EMPHASIS-HF trial. Furthermore, our results suggest that randomized studies investigating in-hospital initiation and up-titration of MRAs are worth undertaking.

Limitations

This is a post hoc analysis of a clinical trial that was not powered to identify treatment effect modification according to the timing of treatment initiation. In addition, for power purposes, timing since prior hospitalization and randomization was dichotomized at its median. We did not find effect modification (i.e. interaction) in this analysis, but non-linear interaction modelling or large sample size might have resulted in different results.

Given the clinical trial nature of this study, and the inherent differences between clinical trials and registries, different effect modifications might be observed in the setting of usual care.

Conclusion

Eplerenone is safe and improves survival and prevents re-admission when initiated soon after a CVH in patients with systolic HF and mild symptoms. Initiation of eplerenone early after discharge from a CVH, including discharge from a HF hospitalization, should be encouraged, in patients meeting the inclusion criteria of EMPHASIS-HF.

Conflict of interest: The sponsor (Pfizer) was responsible for data management and final data analysis. J.J.M. has received grant support from the Eugene Braunwald Endowment for the Advancement of Cardiovascular Discovery and Care. H.K. has received travel reimbursements from Pfizer. D.J.V.V. has received Board Membership Fees from Amgen, Vifor, Sorbent, Johnson & Johnson, Biocontrol, and St Jude. S.P. has received consulting fees from Servier, Amgen, AstraZeneca, and Novartis; and has received a research grant from Pfizer. J.V. is an employee of Pfizer and received stock options and travel reimbursements from Pfizer. F.Z. has received fees for serving on the board of Boston Scientific; consulting fees from Novartis, Takeda, AstraZeneca, Boehringer Ingelheim, GE Healthcare, Relypsy, Servier, Boston Scientific, Bayer, Johnson & Johnson, and Resmed; and speaker's fees from Pfizer and AstraZeneca. B.P. has received fees for serving on the board of Novartis; consulting fees from Pfizer, Takeda, AstraZeneca, Boehringer Ingelheim, GE Healthcare, Relypsy, BG Medicine, Nile Therapeutics, and

Table 2  Adverse event rates by time since the qualifying CVH and treatment group

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<th>Interaction</th>
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<td>Adjudicated hospitalization for worsening renal function</td>
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aRate per 100 person-years of follow-up.
Clinical benefits of eplerenone in patients with systolic HF


References