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Reduced Diuretic Dose in Patients Treated with Eplerenone – data from the EPHEBUS trial

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Abstract

Background: Loop-diuretics are used for congestion relief and dose-adaptations are usually a consequence of the clinicians' clinical judgement about the congestive status of the patient. In EPHEBUS (Eplerenone in Patients with Systolic Dysfunction after Myocardial Infarction) many of the patients had heart failure (HF) requiring diuretics for congestion relief. We thus hypothesized that blinded allocation to eplerenone would lead clinicians to reduce loop diuretics, as consequence of the improvement in patients' status.

Aims: To study the effect of eplerenone on the diuretic doses during the follow-up, and its prognostic implications.

Methods: Cox and mixed effect models were used over a median follow-up of 1.3 years in 6632 patients.

Results: A total of 6632 patients were included; at baseline 3352 (50.5%) did not have diuretics, 2195 (33.1%) had diuretic doses between 1 and 40 mg/day, and 1085 (16.4%) had diuretic doses above 40 mg/day. Patients with higher furosemide equivalent doses had a worse clinical status. Both baseline and follow-up incremental loop diuretic doses were associated with worse prognosis. Eplerenone treatment was associated with lower prescribed loop diuretic doses throughout the follow-up; lower doses were observed at 90 days, and decreased further at 180 days and beyond. Eplerenone treatment led to a mean furosemide equivalent dose reduction of -2.2 mg/day (-2.9 to -1.6) throughout the follow-up. Eplerenone was effective in reducing morbidity and mortality regardless of the baseline loop diuretic dose used: HR (95% CI) for the outcome of cardiovascular death or HF hospitalization =0.83 (0.75-0.92); p for interaction =0.54.

Conclusion: Eplerenone treatment led to a loop diuretic dose reduction during follow-up without evidence of treatment effect modification by loop diuretics. These findings suggest that eplerenone reduces congestive signs and symptoms, which enables clinicians to reduce loop diuretic doses.

Key-words: myocardial infarction; heart failure; systolic dysfunction; eplerenone; loop diuretics; congestion; treatment effect.

What is new?

The potential effect of eplerenone on the loop diuretic dose over time in patients who had a myocardial infarction with systolic dysfunction had not been described previously.

What are the clinical implications?

Patients taking eplerenone (versus those taking a placebo) had their loop diuretic dose decreased by their assistant physician; as the physicians could not be aware of the treatment assignment (double-blind randomized controlled trial), these findings likely mean that patients' improved their congestive signs and symptoms which led the clinicians to reduce loop diuretics. Eplerenone should be systematically considered in this setting because it may reduce morbidity and mortality, and also improve patients' congestive status.

Introduction

Loop diuretics are used for congestion relief and dose-adaptations are usually a consequence of the clinicians' clinical judgement about the congestive status of the patient¹⁻³: those with more severe signs and symptoms of congestion likely receive higher diuretic doses (in a tentative to relieve their congestion) and, as consequence of their worse clinical condition, have worse prognosis^{4, 5}.

In EPHESUS (Eplerenone, a Selective Aldosterone Blocker, in Patients with Left Ventricular Dysfunction after Myocardial Infarction) patients were randomized, to either eplerenone or placebo, if they had reduced ejection fraction and signs of heart failure (HF) or diabetes within two weeks after a myocardial infarction (MI)⁶. Consequently, many of these patients had HF (90%) and needed diuretics (60%) for congestion relief. In EPHESUS eplerenone had a beneficial effect which translated into reduced hospitalizations and death. One of the possible mechanisms associated with the treatment effect of eplerenone (and spironolactone) is a decrease of congestion by increasing diuresis and natriuresis, induced by a contraction in plasma volume, which we could assess with an indirect estimation based on hemoglobin and hematocrite^{7, 8}. Based on these effects, we hypothesized that clinicians would observe patients' clinical improvement which would lead them to reduce loop diuretics.

The aims of the present study are to: 1) characterize patients' according to the dose of loop diuretic they took at baseline; 2) assess the outcome associations of different doses of loop diuretics ; 3) study the effect of eplerenone on the diuretic doses during the follow-up; 4) explore whether the effect of eplerenone could have been modified by the diuretic doses at baseline.

Methods

Study design and population

The aims and methodology of the EPHESUS study have been previously described¹⁴. Patients enrolled in EPHESUS had an acute MI complicated by systolic dysfunction (i.e. LV ejection fraction $\leq 40\%$) and HF (documented by at least one of the following: presence of pulmonary rales, chest radiography showing pulmonary venous congestion, or the presence of a third heart sound) or diabetes. Indeed, patients with diabetes mellitus were not required to have evidence of HF. Patients entered the study at any point from 3-14 days after MI and were randomly assigned to treatment with eplerenone or placebo in addition to standard medical therapy, which could include angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs), β -blockers, diuretics, aspirin, statins as well as coronary reperfusion therapy. EPHESUS was an event-driven study with a mean follow-up duration of 16 months. The investigation conformed with the principles outlined in the Declaration of Helsinki¹⁵. Written informed consent was obtained for all subjects.

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Statistical analysis and end-points

Continuous variables are presented as mean \pm standard deviation and categorical variables as frequencies (percentages). Hazard ratios are presented with their 95% confidence intervals as HR (95% CI). Loop diuretic doses were converted to furosemide equivalents as follows: furosemide 40 mg = torsemide 10 mg = bumetanide 1 mg = piretanide 10 mg^{7,11}; patients not on loop diuretics at inclusion were coded 0 mg/day. Three groups were then created: patients without loop diuretics (0 mg/day), those with loop diuretics at doses \leq 40 mg/day, and those with doses $>$ 40 mg/day or intravenous (IV) diuretics. These subgroups were created based on the loop diuretic doses commonly used in clinical practice and also to keep sufficient patient numbers between the loop diuretic categories to perform the analyses, as patients with doses above 40 mg/day represented less than 20% of the population and those with doses above 80 mg/day less than 1%. We assessed the loop diuretic doses at baseline, the mean loop diuretic dose with all available data throughout the follow-up, and the dose at specific time-points (30, 90, 180, 270, 360 days); as EPHEBUS had a relatively short follow-up time (median = 1.3 years) observations beyond 1-year had few observations. We also performed a sensitivity analysis including only the patients who remained alive during the follow-up. Comparisons of furosemide equivalent groups at baseline were carried out using Pearson's Chi-2 test and one-way ANOVA test, as required. Cox regression models were performed to assess the associations between loop diuretic doses (continuous and categorical) and the study outcomes, which were: 1) a composite of cardiovascular death or hospitalization for HF; 2) an extended composite of cardiovascular death, HF hospitalization or IV diuretic use; 3) cardiovascular death; and 4) all-cause death. The use of IV diuretics was included in the exploratory extended composite outcome, because it is clinically meaningful by representing an objective intensification of HF therapy, associated with subsequent mortality, has the potential for increasing the number of events and therefore increasing the study power⁹. The loop diuretic-outcome associations were tested both in unadjusted/crude and adjusted fashion using the baseline diuretic dose, the mean diuretic dose throughout the follow-up, and the time-updated dose. Covariates for adjustment were: age, sex, Killip class, left ventricular ejection fraction, reperfusion therapy, hemoglobin, potassium, sodium, systolic blood pressure, heart rate, estimated glomerular filtration rate, body mass index, history of diabetes, history of hypertension, atrial fibrillation, chronic obstructive pulmonary disease, previous myocardial infarction, previous heart failure hospitalization, peripheral arterial disease. These covariates were selected based on their clinical relevance, prognostic association, and use on previous reports⁷. Prespecified interactions (based on the clinical hypothesis) between baseline loop diuretic dose and the study drug were performed. Cox proportional hazards assumptions were tested by plotting the Schoenfeld residuals vs. time without proportional hazards violation. We also performed a landmark analysis to assess the effect of the loop diuretic doses in the first 90 days of the trial and subsequent outcomes (cardiovascular death or heart failure hospitalization) excluding from the analysis the patients who died or were hospitalized in the first 90 days. Linear mixed effects models with repeated measures over time were performed to assess the loop-diuretic dose changes by treatment group

allocation (eplerenone vs. placebo). The diuretic doses and the interaction of the treatment by time were specified as fixed effects with random effects at the patient level. All analyses were performed using STATA version 15 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

Results

Characteristics of the study population by baseline loop diuretic dose

A total of 6632 patients were included; at baseline 3352 (50.5%) did not have diuretics, 2195 (33.1%) had diuretic doses between 1 and 40 mg/day, and 1085 (16.4%) had diuretic doses above 40 mg/day. Patients with higher furosemide equivalent doses had worse clinical status; they were older, more often female, had worse Killip class, lower ejection fraction, had coronary reperfusion performed less often, had more often HF symptoms, lower blood pressure, higher heart rate, poorer renal function, had more often diabetes, hypertension, a previous MI, angina, and previous HF hospitalization. **Table 1.**

Loop diuretic dose and outcome associations

Both higher baseline loop diuretic dose and increase in loop diuretics during the follow-up were associated with worse prognosis for all the studied outcomes. **Table 2.** However, after adjustment the associations were less marked, suggesting that an important component of confounding occurred i.e. patients with higher loop diuretics are sicker and is likely that their underlying illness is driving the outcome associations and not the diuretic doses themselves. For example, patients treated with furosemide equivalents higher than 40 mg/day had a crude HR (95%CI) of cardiovascular death or HF hospitalization of 4.96 (4.24-5.79), after adjustment for potential confounders the associations decreased to 2.33 (1.95-2.78). Similar findings were present for all the studied outcomes. **Table 2 & Figure 1.** The associations between the loop diuretic dose and outcomes were linear and are represented in the **Supplemental Figure 1**, by treatment group and for the outcome of cardiovascular death or heart failure hospitalization. In the **Supplemental Figure 2**, we also present the association of loop diuretic dose during follow-up in a continuous fashion with the distribution of the loop diuretic doses on the background for the outcome of cardiovascular death or heart failure hospitalization (similar associations were present for cardiovascular and all-cause death). The adjusted landmark analysis taking only the cumulative loop diuretic doses in the first 90 days and subsequent outcomes provided similar associations. **Supplemental Table 1.**

Eplerenone and loop diuretic dose

Eplerenone treatment was associated with reduced loop diuretic dose prescription throughout the follow-up. **Table 3, Figure 2 & Figure 3.** The loop diuretic dose reductions with eplerenone were already apparent at 90 days, and became more marked at 180 days and after. For example, at 180 days 14.2% of the patients had furosemide equivalent doses >40 mg/day in the placebo group vs. 11.6% in the eplerenone group, $p = 0.003$. **Table 3 & Figure 3.** Eplerenone treatment led to a mean furosemide

equivalent dose reduction of -2.2 mg/day (-2.9 to -1.6; $p < 0.001$) throughout the follow-up; a reduction that became statistically significant ($p < 0.05$) at day 90 and remained significant throughout the follow-up. **Figure 2.** These results were similar including only the patients that remained alive during the follow-up. **Supplemental Figure 3.**

Eplerenone treatment effect

Eplerenone was effective in reducing morbidity and mortality regardless of the baseline loop diuretic dose used: HR (95% CI) for the outcome of cardiovascular death or HF hospitalization = 0.83 (0.75-0.92); p for interaction = 0.54. Similar findings were observed for all the studied outcomes. **Table 4.**

Discussion

The present study shows that MI patients with HF or diabetes taking higher diuretic doses had worse clinical features (e.g. older age, worse Killip class, lower blood pressure, worse renal function, and previous hospitalization for HF). Higher diuretic doses were independently associated with worse prognosis with a substantial decrease in the strength of the associations after adjustment (suggesting a reverse causation effect). Patients taking eplerenone had their loop diuretic dose significantly reduced during follow-up without evidence of eplerenone's treatment effect modification by loop diuretics. These findings support the utility of eplerenone for reducing congestive signs and symptoms, leading clinicians to reduce the loop diuretic doses in their patients. These findings may help clinicians in better treating their patients and provide insight into the mechanisms of action of eplerenone in patients with the characteristics of those enrolled in EPHEUS.

In a previous report from the EPHEUS trial we have shown that eplerenone decreased body weight and plasma volume, whereas blood protein levels and potassium increased within a month, supporting a eplerenone-induced diuretic effect^{8,7}. The present report corroborates these findings from the perspective of the clinician i.e. even under blinded treatment clinicians probably noted the decongestion of the patients and reduced the diuretic doses accordingly. This dose reduction became statistically significant at day 90, suggesting that eplerenone may reduce the need for diuretics by improving cardiac function and patient clinical status, rather than having an early diuretic effect. Particularly, in the high-risk subset treated with furosemide equivalent dose higher than 40 mg/day, patients significantly decreased furosemide doses (below 40 mg/day) after 6 months of treatment with eplerenone, changes in therapy that were sustained over time. This finding is of particular relevance because patients taking higher diuretic doses have higher risk of subsequent events; this is likely not due to the diuretic dose itself but due to the patients' status, with sicker patients needed higher diuretic doses for congestion relief (as observed herein) i.e. reverse causation. In fact, more aggressive up-titration of loop diuretics or more potent loop diuretics (e.g. the ongoing TRANSFORM trial is testing the hypothesis that torasemide may improve outcomes compared to furosemide) might be indicated for achieving an efficient decongestion which is associated with better outcomes^{10, 11}. In the light of the recent DAPA-HF trial results¹², in which the SGLT-2 inhibitor dapagliflozin (vs. placebo) reduced

major cardiovascular events in patients with HF and reduced ejection fraction, 71% of the patients were treated with an MRA, raising the hypothesis that MRAs and SGLT-2 inhibitors may act synergistically towards congestion relief. Such hypothesis obviously warrants a dedicated testing aimed at better defining the fine tuning between proximal tubule (SGLT2i), loop of Henle (loop diuretic), collecting duct (MRA) sodium reabsorption inhibition, acknowledging that both SGLT-2 inhibitors and MRA may display pleiotropic beneficial effects in HF beyond their diuretic properties. Notwithstanding, loop diuretic dose is a marker of disease severity, a marker that was significantly reduced by randomized allocation to eplerenone, a finding that remained similar when including only the patients alive during the follow-up. The reduced need for diuretics in patients randomized to eplerenone may be secondary to the diuretic (supported by the weight loss and protein increase)⁸ and potential natriuretic effect of eplerenone¹³. As eplerenone also decreases natriuretic peptides, suggesting a reduction in cardiac filling pressures, it is possible that a hemodynamic effect also contributes for the reduction in the loop diuretic doses¹⁴. Since investigators were blinded to therapy, the diuretic dose reductions were performed after careful assessment of changes in patients' signs and symptoms, which improved in patients randomized to eplerenone. Unless contraindicated) all patients with a MI and a LVEF \leq 40% with HF or diabetes should receive a MRA (such as eplerenone); this treatment can favourably impact patients' outcomes and reduce the need of loop diuretics, which may translate patient's clinical improvement throughout the trial, even in those who did not have a major adverse cardiovascular event such as hospitalization or death. Loop diuretic dose changes could thus be used as a surrogate for patients' clinical status and possibly as an intermediate end-point in clinical trials of patients with MI and systolic dysfunction. An effect on blood pressure is not likely to play a major role in the clinicians' decision, as eplerenone in this context (MI with systolic dysfunction) did not cause blood pressure drop. At one year, the mean blood pressure had increased by 8/4 mmHg in the placebo group and by 5/3 mmHg in the eplerenone group⁶. An observed effect on worsening kidney function, along with alleviated congestive symptoms may also have triggered loop diuretic down-titration; in a previous report, we showed that several features were associated with an early worsening in kidney function (>20% after 1 month), including loop diuretic use at baseline¹⁵.

Limitations

Several limitations should be noted in the present analysis. This is a non-prespecified secondary analysis of a randomized controlled trial, therefore these findings should be regarded as hypothesis generating. The diuretic doses were recovered from the patients' case report form filled-in by the site clinicians, as consequence some dose-attribution errors might have occurred; despite the manual drug/dose-checking we performed. The reasons for diuretic dose changes were not captured in the study, which could provide additional granularity in our findings.

Conclusion

In patients with MI, systolic dysfunction and HF or diabetes, higher diuretic doses were independently

associated with worse prognosis, but eplerenone treatment led to a loop diuretic dose reduction during follow-up without evidence of treatment effect modification by loop diuretics. These findings suggest that eplerenone may reduce congestion, which enables clinicians to reduce the dose of loop diuretics.

Disclosures

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Bibliography

1. Ponikowski, P.; Voors, A. A.; Anker, S. D.; Bueno, H.; Cleland, J. G.; Coats, A. J.; Falk, V.; Gonzalez-Juanatey, J. R.; Harjola, V. P.; Jankowska, E. A.; Jessup, M.; Linde, C.; Nihoyannopoulos, P.; Parissis, J. T.; Pieske, B.; Riley, J. P.; Rosano, G. M.; Ruilope, L. M.; Ruschitzka, F.; Rutten, F. H.; van der Meer, P., 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* **2016**.
2. Yancy, C. W.; Jessup, M.; Bozkurt, B.; Butler, J.; Casey, D. E., Jr.; Colvin, M. M.; Drazner, M. H.; Filippatos, G.; Fonarow, G. C.; Givertz, M. M.; Hollenberg, S. M.; Lindenfeld, J.; Masoudi, F. A.; McBride, P. E.; Peterson, P. N.; Stevenson, L. W.; Westlake, C., 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol* **2016**.
3. Rossignol, P.; Hernandez, A. F.; Solomon, S. D.; Zannad, F., Heart failure drug treatment. *Lancet* **2019**, 393 (10175), 1034-1044.
4. Ellison, D. H.; Felker, G. M., Diuretic Treatment in Heart Failure. In *N Engl J Med*, United States, 2018; Vol. 378, pp 684-685.
5. Domanski, M.; Norman, J.; Pitt, B.; Haigney, M.; Hanlon, S.; Peyster, E., Diuretic use, progressive heart failure, and death in patients in the Studies Of Left Ventricular Dysfunction (SOLVD). *J Am Coll Cardiol* **2003**, 42 (4), 705-8.

6. Pitt, B.; Williams, G.; Remme, W.; Martinez, F.; Lopez-Sendon, J.; Zannad, F.; Neaton, J.; Roniker, B.; Hurley, S.; Burns, D.; Bittman, R.; Kleiman, J., The EPHEsus trial: eplerenone in patients with heart failure due to systolic dysfunction complicating acute myocardial infarction. Eplerenone Post-AMI Heart Failure Efficacy and Survival Study. *Cardiovasc Drugs Ther* **2001**, *15* (1), 79-87.
7. Duarte, K.; Monnez, J. M.; Albuissou, E.; Pitt, B.; Zannad, F.; Rossignol, P., Prognostic Value of Estimated Plasma Volume in Heart Failure. *JACC Heart Fail* **2015**, *3* (11), 886-93.
8. Rossignol, P.; Menard, J.; Fay, R.; Gustafsson, F.; Pitt, B.; Zannad, F., Eplerenone survival benefits in heart failure patients post-myocardial infarction are independent from its diuretic and potassium-sparing effects. Insights from an EPHEsus (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) substudy. *J Am Coll Cardiol* **2011**, *58* (19), 1958-66.
9. Okumura, N.; Jhund, P. S.; Gong, J.; Lefkowitz, M. P.; Rizkala, A. R.; Rouleau, J. L.; Shi, V. C.; Swedberg, K.; Zile, M. R.; Solomon, S. D.; Packer, M.; McMurray, J. J., Importance of Clinical Worsening of Heart Failure Treated in the Outpatient Setting: Evidence from the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF). *Circulation* **2016**.
10. Lala, A.; McNulty, S. E.; Mentz, R. J.; Dunlay, S. M.; Vader, J. M.; AbouEzzeddine, O. F.; DeVore, A. D.; Khazanie, P.; Redfield, M. M.; Goldsmith, S. R.; Bart, B. A.; Anstrom, K. J.; Felker, G. M.; Hernandez, A. F.; Stevenson, L. W., Relief and Recurrence of Congestion During and After Hospitalization for Acute Heart Failure: Insights From Diuretic Optimization Strategy Evaluation in Acute Decompensated Heart Failure (DOSE-AHF) and Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARESS-HF). *Circ Heart Fail* **2015**, *8* (4), 741-8.
11. Voors, A. A.; Ter Maaten, J. M., Tackling Early Heart Failure Deaths and Readmissions by Estimating Congestion. *JACC Heart Fail* **2015**, *3* (11), 894-5.
12. McMurray, J. J. V.; Solomon, S. D.; Inzucchi, S. E.; Kober, L.; Kosiborod, M. N.; Martinez, F. A.; Ponikowski, P.; Sabatine, M. S.; Anand, I. S.; Belohlavek, J.; Bohm, M.; Chiang, C. E.; Chopra, V. K.; de Boer, R. A.; Desai, A. S.; Diez, M.; Drozdz, J.; Dukat, A.; Ge, J.; Howlett, J. G.; Katova, T.; Kitakaze, M.; Ljungman, C. E. A.; Merkely, B.; Nicolau, J. C.; O'Meara, E.; Petrie, M. C.; Vinh, P. N.; Schou, M.; Tereshchenko, S.; Verma, S.; Held, C.; DeMets, D. L.; Docherty, K. F.; Jhund, P. S.; Bengtsson, O.; Sjostrand, M.; Langkilde, A. M., Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med* **2019**.
13. Zhang, Q.; Saito, Y.; Naya, N.; Imagawa, K.; Somekawa, S.; Kawata, H.; Takeda, Y.; Uemura, S.; Kishimoto, I.; Nakao, K., The specific mineralocorticoid receptor blocker eplerenone attenuates left ventricular remodeling in mice lacking the gene encoding guanylyl cyclase-A. *Hypertens Res* **2008**, *31* (6), 1251-6.
14. Montalescot, G.; Pitt, B.; Lopez de Sa, E.; Hamm, C. W.; Flather, M.; Verheugt, F.; Shi, H.; Turgonyi, E.; Orri, M.; Vincent, J.; Zannad, F., Early eplerenone treatment in patients with acute ST-elevation myocardial infarction without heart failure: the Randomized Double-Blind Reminder Study. In *Eur Heart J*, Published on behalf of the European Society of Cardiology The Author 2014. For permissions please email: journals.permissions@oup.com.: England, 2014; Vol. 35, pp 2295-302.
15. Rossignol, P.; Cleland, J. G.; Bhandari, S.; Tala, S.; Gustafsson, F.; Fay, R.; Lamiral, Z.; Dobre, D.; Pitt, B.; Zannad, F., Determinants and consequences of renal function variations with aldosterone blocker therapy in heart failure patients after

myocardial infarction: insights from the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study. *Circulation* **2012**, *125* (2), 271-9.

Table 1. Patients` characteristics by baseline loop diuretic dose (in mg/day)

Patients` characteristics	Loop Diur. =0	Loop Diur. ≤40	Loop Diur. >40	p-value
N.	3352	2195	1085	
Age (years)	61.3 ± 11.5	66.1 ± 10.9	67.7 ± 10.8	<0.001
Male	2507 (74.8%)	1493 (68.0%)	714 (65.8%)	<0.001
White race	3024 (90.2%)	1991 (90.7%)	969 (89.3%)	0.003
Killip I	631 (19.0%)	249 (11.4%)	132 (12.2%)	<0.001
II	2244 (67.4%)	1427 (65.4%)	606 (56.1%)	
III	380 (11.4%)	434 (19.9%)	281 (26.0%)	
IV	74 (2.2%)	71 (3.3%)	62 (5.7%)	
LVEF (%)	34.2 ± 5.4	32.5 ± 6.3	30.8 ± 6.7	<0.001
Reperfusion/revasc.	1723 (51.4%)	871 (39.7%)	412 (38.0%)	<0.001
HF symptoms	2962 (88.5%)	2015 (91.9%)	988 (91.1%)	<0.001
Hemoglobin (g/dL)	13.4 ± 1.7	13.3 ± 1.7	13.0 ± 1.8	<0.001
Potassium (mmol/L)	4.3 ± 0.4	4.3 ± 0.5	4.2 ± 0.5	<0.001
Sodium (mmol/L)	139.6 ± 4.4	139.6 ± 4.3	138.7 ± 4.2	<0.001
SBP (mmHg)	119.2 ± 16.2	119.4 ± 16.5	117.8 ± 17.4	0.024
DBP (mmHg)	72.8 ± 10.3	71.7 ± 10.7	70.5 ± 11.6	<0.001
Heart rate (beats/min)	73.3 ± 10.9	75.3 ± 11.9	77.7 ± 13.1	<0.001
eGFR (mL/min/1.73m ²)	72.8 ± 20.2	65.7 ± 20.3	60.2 ± 20.6	<0.001
Body mass index (kg/m ²)	27.3 ± 4.4	27.4 ± 4.5	27.7 ± 4.9	0.053
Diabetes	955 (28.5%)	715 (32.6%)	472 (43.5%)	<0.001
Hypertension	1915 (57.1%)	1407 (64.1%)	685 (63.1%)	<0.001
Atrial fibrillation	316 (9.4%)	332 (15.1%)	226 (20.8%)	<0.001
COPD	251 (7.5%)	229 (10.4%)	145 (13.4%)	<0.001
Previous MI	777 (23.2%)	642 (29.2%)	383 (35.3%)	<0.001
Angina	1290 (38.5%)	952 (43.4%)	493 (45.4%)	<0.001
PVD	336 (10.0%)	288 (13.1%)	199 (18.3%)	<0.001
Previous HFH	148 (4.4%)	190 (8.7%)	174 (16.0%)	<0.001
ACEi/ARB	2828 (84.4%)	1928 (87.8%)	995 (91.7%)	<0.001
Beta-blocker	2682 (80.0%)	1585 (72.2%)	694 (64.0%)	<0.001
Digoxin	271 (8.1%)	430 (19.6%)	303 (27.9%)	<0.001
Index Q-wave MI	2526 (76.1%)	1502 (69.8%)	675 (65.0%)	<0.001
Eplerenone allocation	1706 (50.9%)	1076 (49.0%)	537 (49.5%)	0.36

Legend: LVEF, left ventricular ejection fraction; HFH, heart failure hospitalization; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; PVD, peripheral vascular disease; IV, intravenous; Loop diur., loop diuretic in furosemide dose equivalents.

Table 2. Loop diuretic dose (in mg/day) and outcome associations

End-point	Diuretic	Dose	Events (%)	Crude HR (95%CI)	Adj. HR (95%CI)	p-value
CV death/HFH	Baseline	0	489 (14.6)	Ref.	Ref.	-
		≤40	536 (24.4)	1.78 (1.58-2.01)	1.21 (1.07-1.38)	0.004
		>40	426 (39.3)	3.22 (2.82-3.67)	1.64 (1.42-1.90)	<0.001
	Follow-up	0	237 (10.1)	Ref.	Ref.	-
		≤40	720 (23.3)	2.47 (2.13-2.86)	1.63 (1.39-1.90)	<0.001
		>40	494 (41.5)	4.96 (4.24-5.79)	2.33 (1.95-2.78)	<0.001
	Time-updated	0	358 (10.7)	Ref.	Ref.	-
		≤40	575 (26.2)	1.86 (1.58-2.19)	1.22 (1.03-1.45)	0.024
		>40	518 (47.7)	3.94 (3.30-4.69)	1.95 (1.59-2.38)	<0.001
CV death/HFH/IV diur.	Baseline	0	567 (16.9)	Ref.	Ref.	-
		≤40	612 (27.9)	1.76 (1.57-1.97)	1.24 (1.10-1.40)	<0.001
		>40	540 (49.8)	3.94 (3.50-4.43)	2.21 (1.94-2.52)	<0.001
	Follow-up	0	388 (15.7)	Ref.	Ref.	-
		≤40	813 (26.8)	1.77 (1.56-1.99)	1.15 (1.01-1.31)	0.029
		>40	518 (46.0)	3.45 (3.03-3.93)	1.58 (1.36-1.85)	<0.001
	Time-updated	0	446 (13.3)	Ref.	Ref.	-
		≤40	691 (31.5)	1.82 (1.55-2.15)	1.21 (1.01-1.44)	0.035
		>40	582 (53.6)	4.00 (3.34-4.79)	2.03 (1.65-2.49)	<0.001
CV death	Baseline	0	299 (8.9)	Ref.	Ref.	-
		≤40	320 (14.6)	1.69 (1.44-1.98)	1.11 (0.94-1.32)	0.21
		>40	271 (25.0)	3.11 (2.64-3.67)	1.53 (1.27-1.85)	<0.001
	Follow-up	0	166 (7.2)	Ref.	Ref.	-
		≤40	412 (13.5)	1.92 (1.60-2.29)	1.13 (0.94-1.38)	0.20
		>40	312 (24.2)	3.60 (2.98-4.35)	1.46 (1.18-1.82)	0.001
	Time-updated	0	281 (8.4)	Ref.	Ref.	-
		≤40	320 (14.6)	1.75 (1.49-2.06)	1.13 (0.95-1.34)	0.16
		>40	289 (26.6)	3.93 (3.34-4.63)	1.91 (1.58-2.31)	<0.001
All-cause death	Baseline	0	364 (10.9)	Ref.	Ref.	-
		≤40	363 (16.5)	1.58 (1.37-1.83)	1.03 (0.89-1.21)	0.66
		>40	305 (28.1)	2.89 (2.48-3.36)	1.43 (1.21-1.69)	<0.001
	Follow-up	0	193 (8.4)	Ref.	Ref.	-
		≤40	480 (15.7)	1.92 (1.63-2.27)	1.16 (0.97-1.38)	0.11
		>40	359 (27.9)	3.58 (3.00-4.26)	1.50 (1.22-1.83)	<0.001
	Time-updated	0	343 (10.2)	Ref.	Ref.	-
		≤40	359 (16.4)	1.61 (1.39-1.87)	1.04 (0.88-1.21)	0.66
		>40	330 (30.4)	3.70 (3.18-4.31)	1.80 (1.51-2.14)	<0.001

Median (pct₂₅₋₇₅) follow-up time = 1.3 (1.0-1.7) years.

Follow-up, mean diuretic dose per day during follow-up until the event of interest.

Legend: CV, cardiovascular; HFH, heart failure hospitalization; IV, intravenous.

Model adjusted on age, sex, Killip class, left ventricular ejection fraction, reperfusion therapy, hemoglobin, potassium, sodium, systolic blood pressure, heart rate, estimated glomerular filtration rate, body mass index, history of diabetes, history of hypertension, atrial fibrillation, chronic obstructive pulmonary disease, previous myocardial infarction, previous heart failure hospitalization, peripheral arterial disease.

Table 3. Eplerenone/Placebo treatment and loop diuretic doses (in mg/day) throughout the follow-up

Time	Diuretic dose	N (%) Placebo	N (%) Eplerenone	p-value
0 (randomization)	0	1646 (49.7)	1706 (51.4)	0.36
	≤40	1119 (33.8)	1076 (32.4)	
	>40	548 (16.5)	537 (16.2)	
30d	0	1616 (51.2)	1692 (52.7)	0.44
	≤40	1133 (35.9)	1106 (34.4)	
	>40	410 (13.0)	414 (12.9)	
90d	0	1566 (51.1)	1685 (53.9)	0.074
	≤40	1085 (35.4)	1052 (33.7)	
	>40	416 (13.6)	389 (12.4)	
180d	0	1544 (51.7)	1672 (54.8)	0.003
	≤40	1017 (34.1)	1023 (33.6)	
	>40	425 (14.2)	352 (11.6)	
270d	0	1441 (50.8)	1601 (55.0)	0.001
	≤40	984 (34.7)	966 (33.2)	
	>40	413 (14.6)	343 (11.8)	
360d	0	1244 (51.0)	1360 (54.6)	0.005
	≤40	841 (34.5)	837 (33.6)	
	>40	353 (14.5)	292 (11.7)	

Table 4. Treatment effect by baseline diuretic dose interaction

Outcome	N. (%) Placebo	N. (%) Eplerenone	HR (95%CI)	P-value	Interaction p
CV death/HFH	780 (23.5)	671 (20.2)	0.83 (0.75-0.92)	0.001	0.54
CV death/HFH/IV diur.	904 (27.3)	815 (24.6)	0.88 (0.80-0.97)	0.010	0.24
CV death	483 (14.6)	407 (12.3)	0.83 (0.72-0.94)	0.005	0.41
All-cause death	554 (16.7)	478 (14.4)	0.85 (0.75-0.96)	0.007	0.61

Median (pct₂₅₋₇₅) follow-up time =1.3 (1.0-1.7) years.

Legend: CV, cardiovascular; HFH, heart failure hospitalization; IV, intravenous.

Model with treatment (eplerenone or placebo) by baseline diuretic dose (0mg, ≤40mg, >40mg) interaction adjusted on age, sex, Killip class, left ventricular ejection fraction, reperfusion therapy, hemoglobin, potassium, sodium, systolic blood pressure, heart rate, estimated glomerular filtration rate, body mass index, history of diabetes, history of hypertension, atrial fibrillation, chronic obstructive pulmonary disease, previous myocardial infarction, previous heart failure hospitalization, peripheral arterial disease.

Figure 1. Kaplan-Meier curves for the outcome of CV death or HF hospitalisation by categories of mean loop diuretic dose (furosemide equivalents in mg/day)

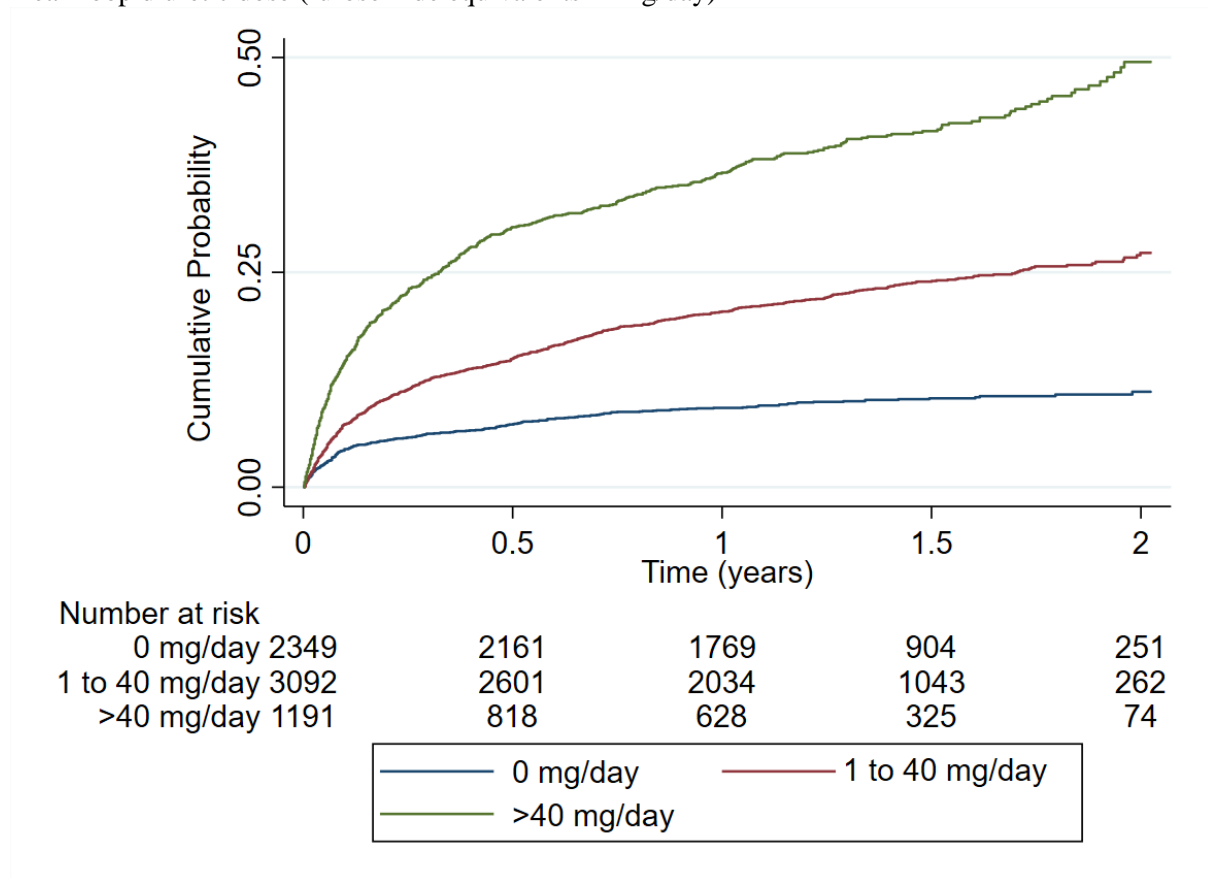
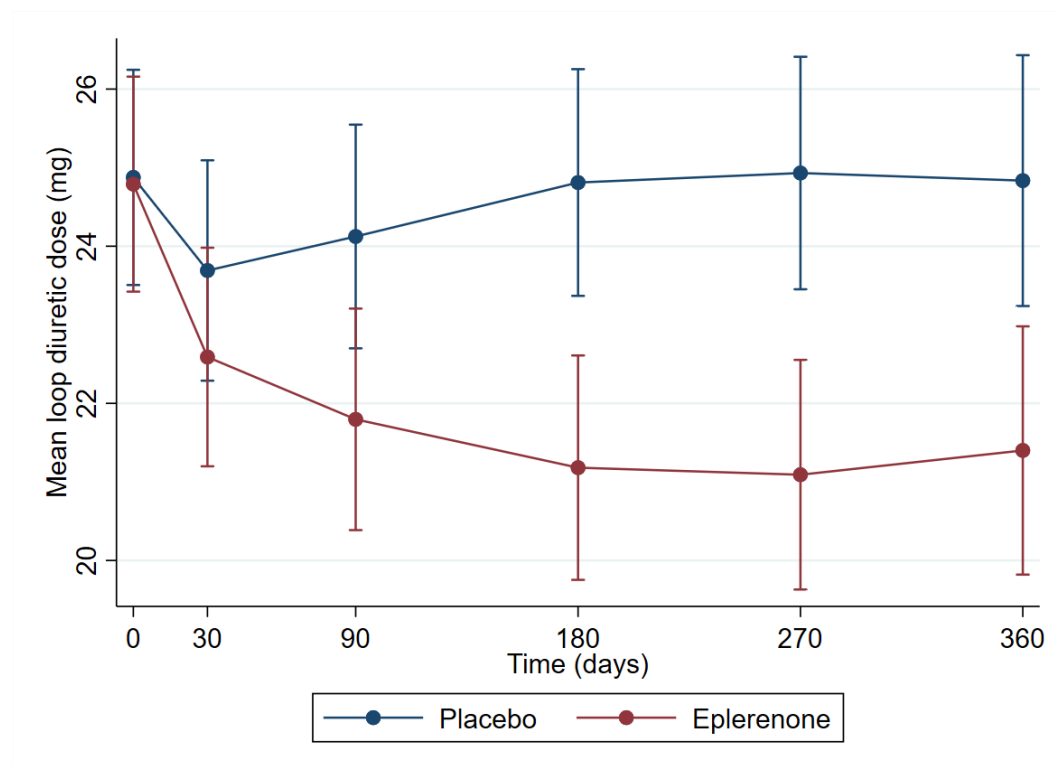


Figure 2. Effect of eplerenone/placebo on loop diuretic dose change over time

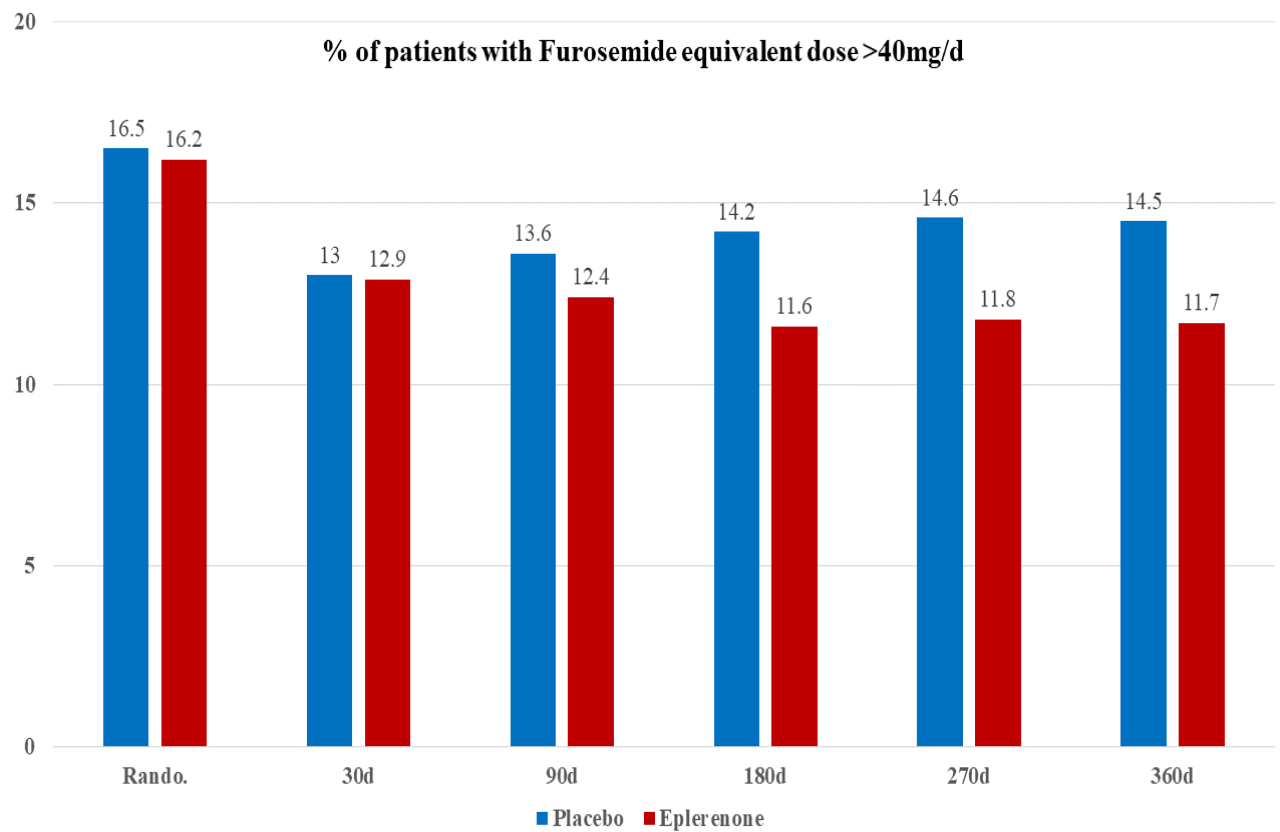


Mixed effect model with treatment by time interaction term.

Global mean loop diuretic reduction = -2.2mg (-2.9 to -1.6), $p < 0.001$.

The between-group difference became statistically significant ($p < 0.05$) at day 90 and remained significant throughout the follow-up.

Figure 3. Loop diuretic doses >40mg/day of furosemide equivalents by treatment allocation



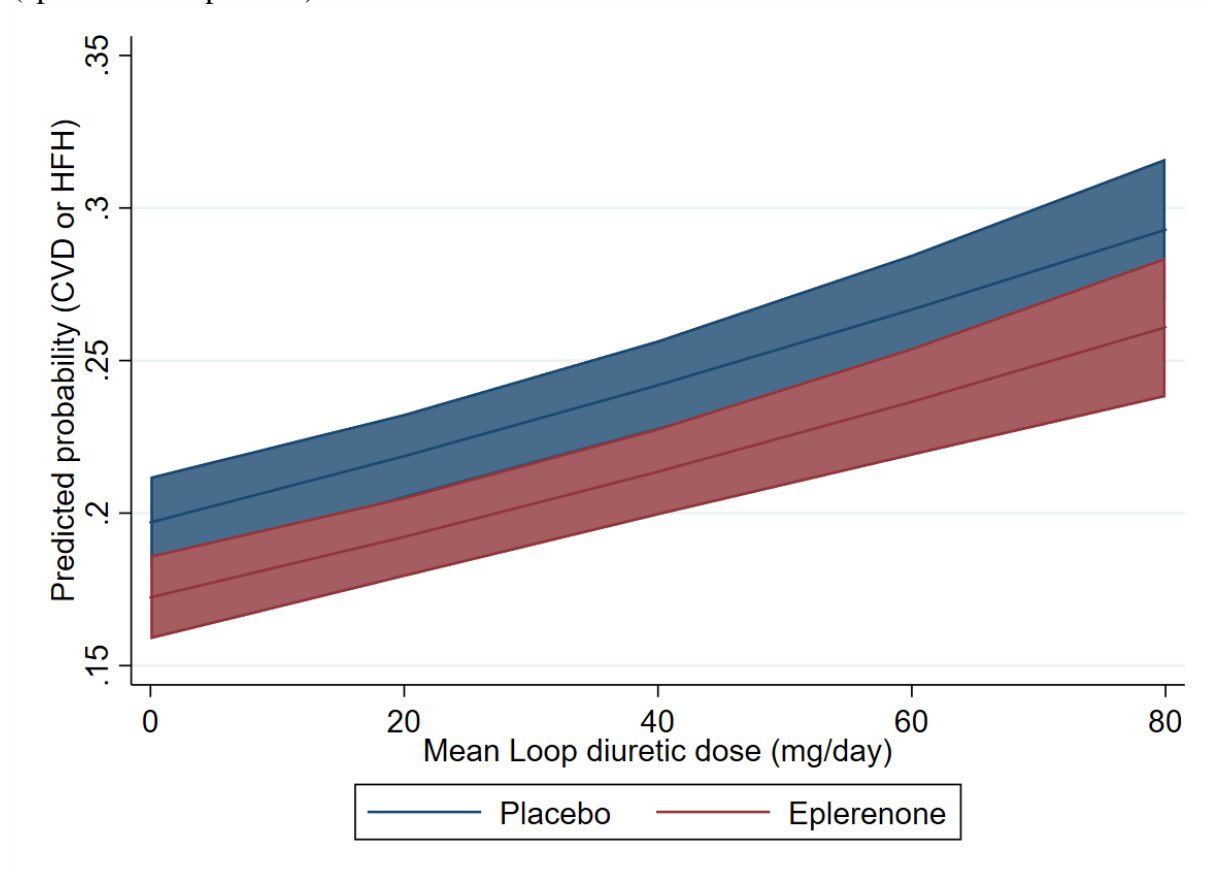
P-value <0.05 at 180, 270, and 360 days (see also the Table 3).

Supplemental Material

Supplemental Table 1. Landmark analysis considering only the diuretic doses in the first 90 days of the trial and subsequent events (cardiovascular death or heart failure hospitalization)

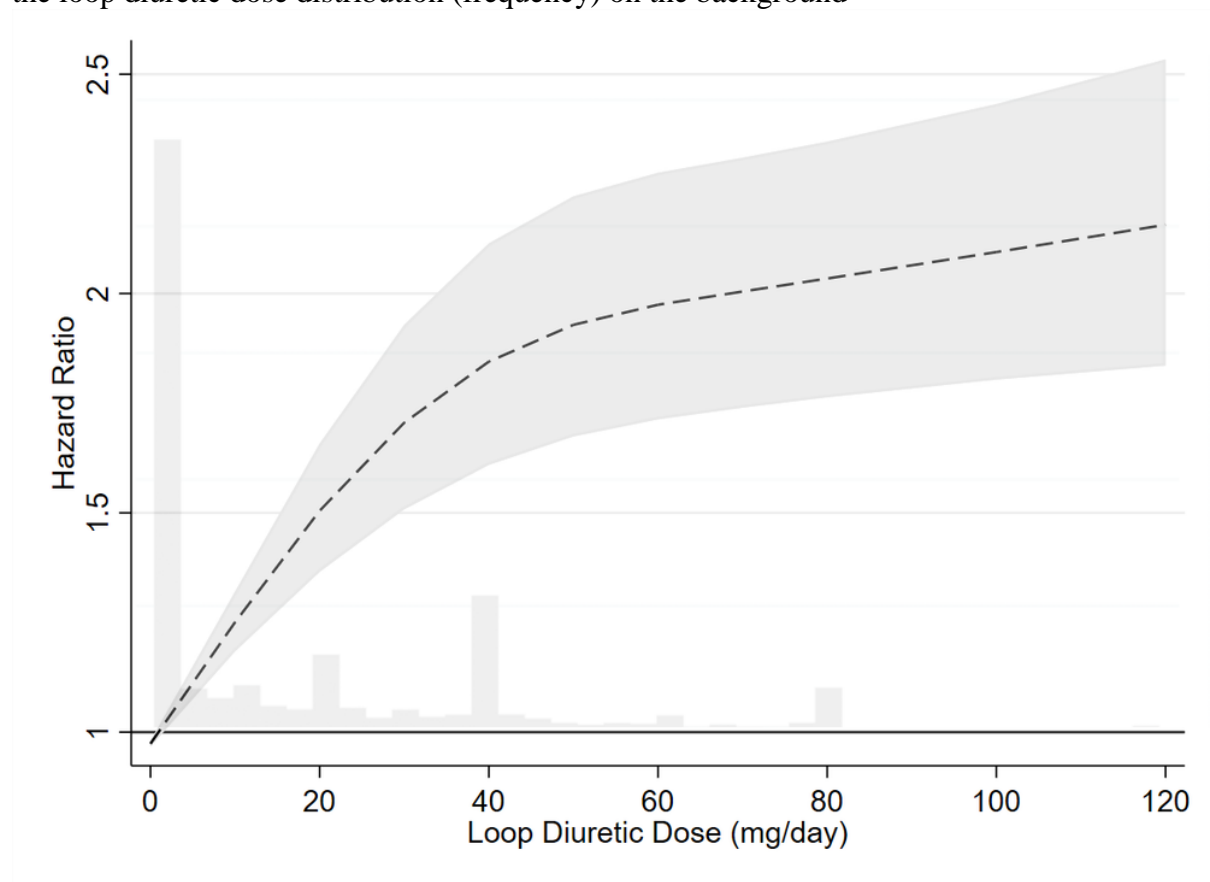
End-point	Diuretic	Dose	Events (%)	Adj. HR (95%CI)	p-value
CV death/HFH	90-day landmark	0mg	171 (6.4)	Ref.	-
		≤40mg	350 (13.5)	1.48 (1.22-1.80)	<0.001
		>40mg	179 (19.0)	1.76 (1.38-2.23)	<0.001

Supplemental Figure 1. Predicted probability of cardiovascular death or heart failure hospitalization by loop diuretic dose throughout the follow-up and by treatment allocation (eplerenone or placebo)

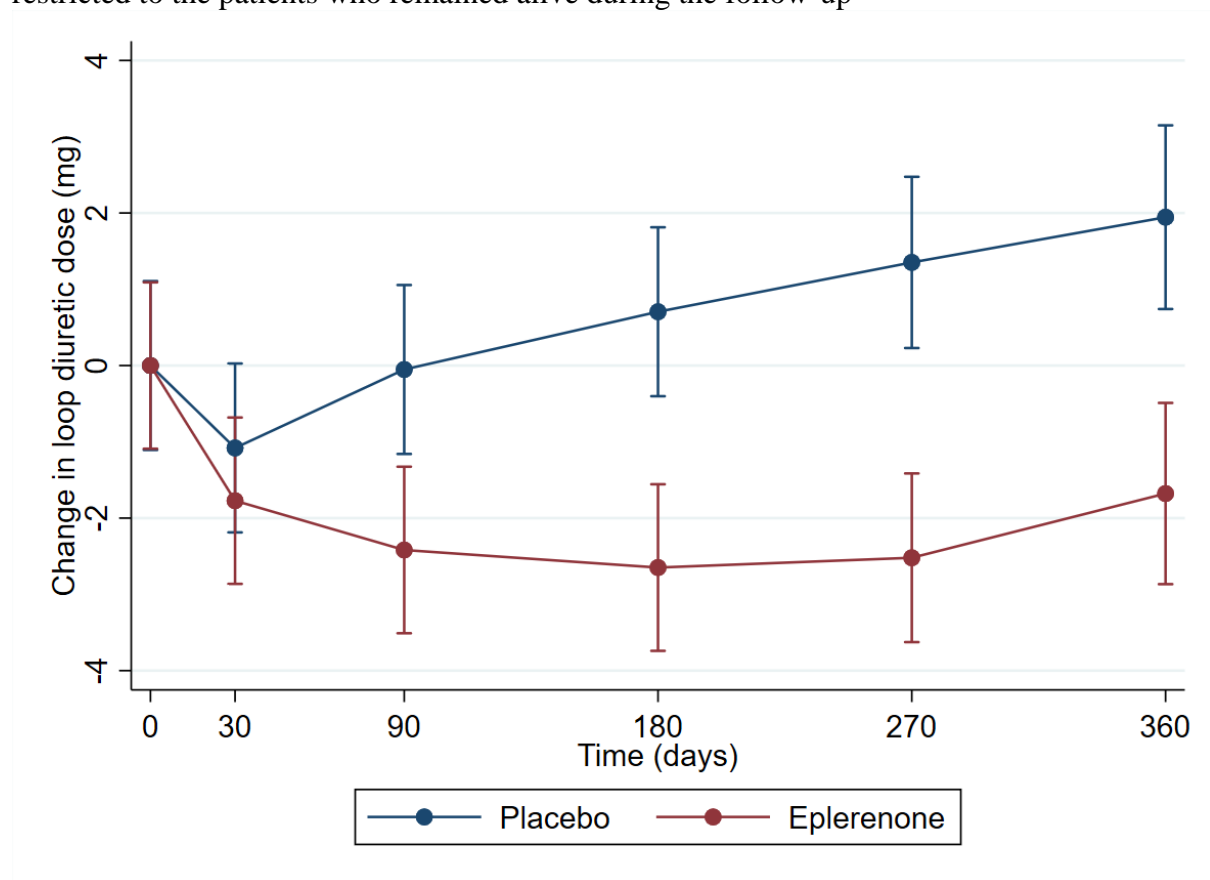


Legend: CVD or HFH, cardiovascular death or heart failure hospitalization.
Eplerenone treatment reduces the incidence of events regardless of the loop diuretic dose.

Supplemental Figure 2. Association of the mean loop diuretic dose with the outcome of cardiovascular death or heart failure hospitalization in a continuous (spline) fashion with a the loop diuretic dose distribution (frequency) on the background



Supplemental Figure 3. Effect of eplerenone vs. placebo on loop diuretic dose over time restricted to the patients who remained alive during the follow-up



Global mean loop diuretic reduction = -2.3mg (-2.9 to -1.6), $p < 0.001$.