Ferreira Joao Pedro (Orcid ID: 0000-0002-2304-6138)

Outpatient diuretic intensification as endpoint in HFpEF trials: an analysis from TOPCAT

Short title: Outpatient diuretic intensification in HFpEF

João Pedro Ferreira, MD, PhD[1]; Jiankang Liu, PhD[2]; Brian L. Claggett, PhD[2]; Orly Vardeny, PharmD[3]; Bertram Pitt, MD[4]; Marc A. Pfeffer, MD, PhD[2]; Scott D. Solomon, MD[2]; Faiez Zannad, MD, PhD[1]

[1] Université de Lorraine, Inserm, Centre d'Investigations Cliniques Plurithématique 1433, and Inserm U1116, CHRU, F-CRIN INI-CRCT (Cardiovascular and Renal Clinical Trialists), Nancy, France.

[2] Cardiovascular Division, Brigham and Women's Hospital, Boston, Massachusetts, USA.

[3] Minneapolis VA Center for Care Delivery and Outcomes Research, University of Minnesota, Minneapolis, Minnesota, USA.

[4] Division of Cardiology, University of Michigan, Ann Arbor, Michigan, USA.

Contact to:

Dr João Pedro Ferreira

Centre d'Investigation Clinique 1433 module Plurithématique, CHRU Nancy - Hopitaux de Brabois, Institut Lorrain du Coeur et des Vaisseaux Louis Mathieu

4 rue du Morvan, 54500 Vandoeuvre les Nancy

Tel : +33 (0) 3 83 15 73 15

Fax : +33 (0) 3 83 15 73 24

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Mail: j.ferreira@chru-nancy.fr

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Abstract

Background: Outpatient treatment for the worsening of signs and symptoms of heart failure (HF) is usually not incorporated in the main outcomes of HF trials. Patients with heart failure with a preserved ejection fraction (HFpEF) may experience frequent episodes of outpatient worsening.

Objectives: To study the frequency, prognostic impact, and the effect of spironolactone on outpatient diuretic intensification (ODI), among 1767 patients enrolled in TOPCAT-Americas.

Methods: Time-updated Cox models and win ratio analysis. ODI was defined by a post-randomization loop diuretic dose increase or new initiation. The median follow-up was 2.9 years.

Results: At baseline, 1362 (77%) patients were taking loop diuretics. During the follow-up, 685 (38.8%) patients experienced ODI, which was associated with a higher risk of subsequent cardiovascular events and death: adjusted HR (95%CI) for HF hospitalization or cardiovascular death=1.67 (1.36-2.04), HR (95%CI) for cardiovascular death=2.17 (1.64-2.87), and HR (95%CI) for all-cause mortality=1.75 (1.41-2.16) ($p<0.001$ for all outcomes). Adding ODI to the composite of HF hospitalization or cardiovascular death increased the event-rate by 3-fold in the placebo group (from 10.4 to 29.9 events per 100 person-years). Spironolactone treatment led to a 26% relative reduction of the extended composite of ODI or HF hospitalization or cardiovascular death: HR (95%CI) 0.74 (0.65-0.85), p-value<0.001 compared with a 16% relative reduction of HF hospitalization or cardiovascular death: HR (95%CI) 0.84 (0.70-0.99), p-value=0.044. Using win ratio provided similar estimates.

Conclusion: In HFpEF, ODI was frequent and independently associated with subsequent cardiovascular events. Spironolactone significantly reduced an extended composite outcome incorporating ODI.

Key-words: outpatient diuretic intensification; heart failure with preserved ejection fraction; spironolactone; expanded outcomes; treatment effect.

Introduction

Heart failure (HF) patients experience frequent changes in their clinical status during the follow-up of a trial, however only a small proportion of these clinical changes are captured in the primary outcome of HF trials, which is usually a composite of first or recurrent HF hospitalizations plus cardiovascular death. Outpatient treatment for the worsening of signs and symptoms of HF is usually not incorporated in the main outcomes of HF trials.[1, 2] However, outpatient treatment intensification has major clinical importance, and in many settings and regions, outpatient HF clinics handle patients who would otherwise be hospitalized.[3]

While trials enrolling patients with a heart failure and a reduced ejection fraction (HFrEF) have been relatively successful incorporating HF hospitalizations and cardiovascular death in their primary outcome, trials enrolling patients with heart failure and a preserved ejection fraction (HFpEF) have been less successful despite adopting similar endpoints. The relative lack of success in meeting HFpEF trials' primary endpoint may be related to an important heterogeneity of this population with frequent hospitalizations not primarily due to HF.[4] A potential strategy to capture more events directly related to the worsening of HFpEF is to assess outpatient loop diuretic intensification (ODI) for congestion relief.[5] However, before adopting such strategy in future HFpEF trials, the impact of ODI on subsequent HF hospitalizations and cardiovascular mortality should be assessed.

Using data from the Aldosterone Antagonist Therapy for Adults with Heart Failure and Preserved Systolic Function trial (TOPCAT-Americas),[6, 7] we aim to assess the impact of ODI on subsequent HF hospitalizations and cardiovascular death, assess the potential event rate increase by the inclusion of ODI, and study the effect of spironolactone on an extended composite outcome that includes ODI.

Methods

Patient population

TOPCAT was a multinational, double-blind, randomized, placebo-controlled, parallel-group study that investigated the effects of spironolactone versus placebo on clinical outcomes in patients with HFpEF. The rationale and design of the study have been previously published.[8] In short, the trial included 3445 patients >50 years of age with symptomatic HF and preserved ejection fraction (defined as a left ventricular ejection fraction ≥45%), who were followed for a median of 2.9 years. Eligible patients had to have systolic blood pressure <140 mmHg, serum potassium <5.0 mmol/L, and either a prior HF hospitalization within 12 months or elevated natriuretic peptide levels (B-type natriuretic peptide ≥100 pg/mL or N-terminal pro–B-type natriuretic peptide ≥360 pg/mL). Key exclusion criteria were severe renal dysfunction (defined as estimated glomerular function rate <30 ml/ min/1.73 m^2 or serum creatinine ≥2.4 mg/dl), severe systemic illness with life expectancy of <3 years from randomization and use of an aldosterone antagonist or potassium sparing diuretic agent within 14 days before randomization.

Due to previously reported differences in patient demographics, event rates, adherence to study medication, responses to treatment, and outcomes among TOPCAT subjects enrolled in Russia and the Republic of Georgia, we restricted our analyses to the subset of TOPCAT subjects enrolled in the Americas (United States, Canada, Argentina, Brazil; N =1767).[6, 7, 9]

All patients provided informed consent. The protocol was approved by the Institutional Review Board at each of the participating centers prior to enrollment of the first patient. The study was overseen by the Institutional Review Board.

Outpatient loop diuretic intensification

At randomization and all subsequent visits (month 1, 2, 4, 8, 12, and every 6 months thereafter), we standardized the dose of oral loop diuretics to furosemide equivalents based on available data.[10] Even if the dose change had occurred outside the study visit, these had to be systematically recorded by the investigators at study visits (by updating the ongoing treatments for each patient). ODI was defined by any post-randomization increment in the dose of loop diuretic (furosemide equivalent) in relation to the randomization value or any new initiation of loop diuretics among patients who were not taking loop diuretics at baseline. The first ODI event was incorporated in our models. We did not include thiazide diuretics in the definition of ODI, as these are often used for the treatment of hypertension.

Study outcomes

The outcomes analyzed in this study were HF hospitalizations (including an overnight stay in an acute care facility with IV diuretic therapy), cardiovascular and all-cause mortality, and ODI (as above defined).

HF hospitalizations and fatal events were centrally adjudicated by an endpoint committee blinded to treatment group assignment.

Statistical analysis

For descriptive statistics of the baseline characteristics, the TOPCAT-Americas population was divided into patients with and without ODI during the follow-up, and the patients' characteristics presented as mean ± standard deviation, median

(percentile$_{25\text{-}75}$), or numbers and percentages, as appropriate. The groups were compared using parametric or non-parametric tests for continuous variables and chi-square tests for categorical variables. To study the association between ODI and outcomes, multivariable time-updated Cox models were performed adjusting for age, sex, race, body mass index, NYHA functional class, systolic blood pressure, baseline potassium, diabetes, estimated glomerular filtration rate, ACEi/ARB treatment, and loop diuretic use at baseline (consistent with previous TOPCAT-Americas reports).[11] To test whether the impact of ODI on outcomes would differ by treatment group (spironolactone or placebo), we performed time-updated Cox models with a treatment-by-ODI interaction term. Time-updated Cox models reset the follow-up time to restart at the ODI episode to assess the impact of ODI on subsequent outcomes (i.e., to study whether ODI impacts the subsequent risk of cardiovascular deaths or HF hospitalizations). The effect of spironolactone (vs. placebo) on the extended composite outcome of time-to-first of ODI, HF hospitalization or cardiovascular death, ODI alone, and the composite of HF hospitalization or cardiovascular death was assessed by the intention-to-treat principle by means of a Cox proportional hazards model and Kaplan-Meier curves. As cardiovascular mortality, HF hospitalizations, and ODI have different (decreasing) clinical importance, we have also studied the effect of spironolactone (vs. placebo) using a win ratio analysis that takes into account the timing and importance of outcomes.[12, 13] The win ratio compares all patient pairs (spironolactone vs. placebo) regarding the occurrence and timing of occurrence of events, starting on the event of greatest clinical importance (here cardiovascular death), followed by the second most important event (here HF hospitalization), and lastly the least important event (here ODI) to determine the number of “wins” and “losses”. For example, a patient

experiencing cardiovascular death in the placebo group and not in the spironolactone group, is considered a “win” for spironolactone (in patients dying in both treatment groups, the one to dying later in time is considered a “win”), then patients who do not die will be compared regarding HF hospitalizations using the same principles, and then among patients who neither died nor were hospitalized for HF, the occurrence of ODI is compared. The total number of “wins” is then divided by the total number of “losses” to provide the win ratio. Additionally, we have also explored the effect of spironolactone on outpatient diuretic decrease (ODD) i.e., follow-up loop diuretic doses lower than the baseline dose. Estimates were presented as hazard ratios (HRs) or win ratio (WR) or incidence rates (IRs) with 95% confidence intervals (CIs). Two-tailed p values <0.05 were considered statistically significant. Statistical analyses were performed using STATA® Statistical Software version 16.1 (STATA Corp, College Station, Texas).

Results

Patients’ characteristics by outpatient loop diuretic intensification

A total of 1767 patients were included in this analysis. The mean age of the patients was 72 years and 50% were women. At baseline, 1362 (77%) patients were taking loop diuretics, without significant differences between ODI and no ODI groups (p =0.49). Compared with patients without ODI (n =1082; 61.2%), patients in whom ODI was performed during the follow-up (n =685; 38.8%) were more frequently white (82% vs. 76%), more symptomatic (NYHA III/IV 41% vs. 31%), had slightly lower hemoglobin (12.7 g/dL vs. 12.9 g/dL), and received calcium channel blockers more frequently (43% vs. 36%). The proportion of patients with loop diuretic use did not significantly differ between groups at randomization (76% vs. 78%) and most

patients (70%) received furosemide as loop diuretic. ***Table 1***. The median (percentile$_{25-75}$) furosemide dose at randomization among those taking loop diuretics was similar between patients with and without ODI: 40 (40-80) mg in both groups.

Impact of loop diuretic dose intensification on subsequent outcomes

Patients in whom ODI was performed had higher risk of subsequent (time-updated) cardiovascular events (HF hospitalization and cardiovascular death) and all-cause mortality after adjustment for potential confounders: HR (95%CI) for HF hospitalization or cardiovascular death 1.67 (1.36-2.04), HR (95%CI) for cardiovascular death alone 2.17 (1.64-2.87), and HR (95%CI) for all-cause mortality 1.75 (1.41-2.16) ($p < 0.001$ for all outcomes). The increased risk of subsequent events associated with ODI was present both in the placebo and in the spironolactone groups (p for interaction >0.1 for all outcomes). ***Table 2***.

Of note, HF hospitalization was independently associated with subsequent cardiovascular death HR (95%CI) =5.97 (4.47-7.96) and all-cause death HR (95%CI) =4.38 (3.51-5.46).

Event-rates and spironolactone effect on the extended composite outcome including outpatient diuretic intensification

Spironolactone reduced the rate of ODI: 391 (44.4%) events with an incidence rate of 20.6 (18.6-22.7) events per 100 person-years in the placebo group vs. 294 (33.2%) events with an incidence rate of 13.2 (11.9-14.9) events per 100 person-years in the spironolactone group; HR (95%CI) =0.66 (0.57-0.77). In the placebo group, adding ODI to the composite of time-to-first of HF hospitalization or cardiovascular death increased the events from 276 (31.3%) cardiovascular deaths or HF hospitalizations to 493 (56.0%) ODI or HF hospitalization or cardiovascular

death, corresponding to nearly 3-fold event-rate (per 100 person-years) increase from 10.4 (9.1-11.7) cardiovascular death or HF hospitalization to 29.9 (27.4-32.6) ODI or HF hospitalization or cardiovascular death. In the spironolactone group, adding ODI to the composite of time-to-first of HF hospitalization or cardiovascular death increased the events from 242 (27.3%) cardiovascular deaths or HF hospitalizations to 420 (47.4%) ODI or HF hospitalization or cardiovascular death, corresponding to nearly 2-fold event-rate (per 100 person-years) increase from 12.4 (11.0-14.0) cardiovascular death or HF hospitalization to 21.5 (19.5-23.6) ODI or HF hospitalization or cardiovascular death. The addition of ODI to HF hospitalizations or cardiovascular death increased the overall (placebo and spironolactone groups) events by 22.4% (from 29.3% to 51.7%). ***Table 3***. Additionally, the addition of ODI to HF hospitalizations or cardiovascular death reduced the mean time-to-event from 904 days (for HF hospitalizations or cardiovascular death) to 837 days (for ODI, HF hospitalizations or cardiovascular death).

Spironolactone treatment led to a 26% relative reduction of the extended composite of ODI or HF hospitalization or cardiovascular death: HR (95%CI) 0.74 (0.65-0.85), p-value <0.001 compared with a 16% relative reduction of HF hospitalization or cardiovascular death: HR (95%CI) 0.84 (0.70-0.99), p-value =0.044. ***Table 3*** *&* ***Figure 1***. Using WR analysis provided very similar estimates: WR for cardiovascular death followed by HF hospitalization and lastly ODI (as the least “important” event) 1.35 (1.18-1.54), p-value <0.001, and WR for cardiovascular death followed by HF hospitalization 1.23 (1.03-1.48), p-value =0.024. ***Table 3***.

Consistent with the findings above described, patients randomized to spironolactone were more likely to have their loop diuretic doses reduced throughout the follow-up

than patients randomized to placebo: 37.9% on spironolactone vs. 28.7% on placebo, HR 1.42, 95%CI 1.18-1.71, P <0.001. ***Supplemental Table 1***.

Discussion

This study shows that ODI is strongly and independently associated with subsequent HF hospitalizations and cardiovascular death. Creating an extended composite outcome by adding ODI to the composite outcome of HF hospitalization or cardiovascular death led to a nearly 3-fold event-rate increase compared with HF hospitalization or cardiovascular death without ODI. Spironolactone significantly reduced the rate of the extended composite outcome by 26% compared with a 16% reduction of HF hospitalization or cardiovascular death, and the strength of the spironolactone effect was increased by the extended composite outcome (z-score =-4.6) compared with HF hospitalization or cardiovascular death (z-score =-2.0). These findings support the addition of ODI to the composite of HF hospitalization or cardiovascular death in HFpEF trials, as it allows to capture a higher proportion of clinically meaningful events, which may lead to an important increment in the event-rate and reduction of follow-up time, which may have impact in the design of future trials.

Most patients living with HF, experience worsening of HF signs and symptoms throughout the course of the disease. Often, worsening HF is handled in the outpatient setting with intensification of loop diuretic therapy. Thus, focusing only on HF hospitalizations underestimates the frequency and the clinical impact of outpatient worsening HF.[14] In TOPCAT-Americas, ODI was associated with a 2.2-fold higher risk of cardiovascular death and a 1.8-fold higher risk of death from any

cause, whereas a HF hospitalization was associated with a 6.0-fold higher risk of cardiovascular death and a 4.4-fold higher risk of death from any cause, supporting a greater risk of subsequent death after a HF hospitalization compared with ODI. The mortality risk associated with ODI observed in TOPCAT-Americas was similar to the risk independently observed in large cohort studies.[14] In TOPCAT-Americas both HF and non-HF hospitalizations were associated with a high risk of subsequent death; with a marked overlap in risk of cardiovascular and all-cause death between HF and non-HF hospitalizations.[15]

In patients with HFrEF enrolled in the Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF) trial, outpatient intensification of HF therapy was associated with a 4.8-fold higher risk of subsequent death, and a HF hospitalization was associated with a 5.9-fold higher risk of death.[16] Compared with enalapril, sacubitril/valsartan led to fewer loop diuretic dose increments during the follow-up.[17] Similar findings were observed in patients with HF post-myocardial infarction enrolled in the Eplerenone in Patients With Systolic Dysfunction After Myocardial Infarction (EPHESUS) trial, where eplerenone led to a reduction of loop diuretic dose during follow-up.[18] Also in HFrEF patients enrolled in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial, outpatient intensification of HF therapy was associated with a 2.7-fold higher risk of subsequent death, and a HF hospitalization was associated with a 3.0-fold higher risk of death, with dapagliflozin leading to a significant decrease of outpatient intensification of HF therapy.[19] These results show that, compared with outpatient intensification of HF therapy, HF hospitalizations are associated with a higher risk of subsequent mortality, but outpatient intensification of

HF therapy consistently show a strong prognostic impact and can be reduced by treatments that improve outcomes in HF, independently of any diuretic effect.

The mechanisms by which spironolactone led to a decrease in ODI are likely not (solely) related to a diuretic effect, because the mean spironolactone dose used in TOPCAT was as low as 15-20 mg/day, which is not a "diuretic" dose.[20] Moreover, spironolactone has proven to display anti-fibrotic, anti-adverse remodelling, and anti-inflammatory effects that lead to patients' improvement beyond any potential "diuretic" effect.[21-23]

Consistent with the reduction of ODI among patients randomized to spironolactone, these patients were also more likely to have loop diuretic dose reductions throughout the follow-up. Confirming the consistency of spironolactone effect to reduce the intensification of diuretic therapy.

Despite its clinical importance, ODI is a milder and less severe event compared with HF hospitalizations. One option that can be considered in order to incorporate events of different severity and with different prognostic importance is to create an event hierarchy using the win ratio, whereby cardiovascular death is considered the most important event, followed by HF hospitalization, and lastly ODI.[12, 24] In the example here shown for TOPCAT-Americas, the win ratio and the time-to-first Cox model provided very similar results (consistently with findings from other cardiovascular outcome trials).[12]

If the PARADIGM-HF and DAPA-HF data illustrate the importance of ODI in HFrEF, our findings from TOPCAT-Americas suggest that capturing ODI may also be important in HFpEF, a condition with predominance of elderly patients with multiple comorbidities where hospitalizations may be multifactorial (e.g., infections,

arrhythmias, worsening kidney function) and difficult to adjudicate as “true” HF hospitalizations. In fact, outpatient intensification of HF therapy may be more specific of worsening HF than hospitalizations which often occur at a very advanced stage of the disease along with multiple confounding factors.[25] Including ODI in the outcomes of HFpEF trials may allow to capture more HF-specific events and at earlier stages of disease progression. Furthermore, in TOPCAT-Americas, incorporating ODI along with HF hospitalization or cardiovascular death in an expanded outcome would have increased the relative proportion of events by 1.76-fold, compared with 1.14-fold in PARADIGM-HF, and 1.36-fold in DAPA-HF, suggesting that HFpEF patients are frequently treated in the outpatient setting. However, the potential increment in the study power achieved by the incorporation of ODI should be carefully weighted with the need of also capturing “harder” events as HF hospitalizations and mortality from cardiovascular causes.

Limitations

Some limitations should be acknowledged in this study. This is a secondary analysis of a randomized trial where ODI was not specified as endpoint and was not independently adjudicated, therefore these results should be regarded as hypothesis generating. Moreover, ODI was computed from the diuretic doses reported in the study visits and we cannot ascertain if these doses were correctly reported at all visits; nonetheless, we do not expect large variations in reporting between the spironolactone and the placebo groups. The reason for ODI was not reported, and a careful reporting of the signs and symptoms (and possible natriuretic peptides) leading to ODI should be required in a randomized trial incorporating ODI as part of the main outcomes of the trial. An overnight hospital stay for worsening HF or Emergency Department visits with IV diuretic therapy was adjudicated as a HF

hospitalization; however, it is possible that some patients were treated with IV diuretics in the outpatient setting, but the route of loop diuretic administration during the follow-up (outside hospital) was not available in the dataset.

Conclusions

In HFpEF patients enrolled in TOPCAT-Americas, ODI was frequent and was independently associated with subsequent HF hospitalizations and cardiovascular death. Spironolactone significantly reduced an extended composite outcome incorporating ODI along with HF hospitalizations and cardiovascular mortality.

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Disclosures

The authors have no relevant conflicts of interest to report regarding the content of this study.

References

1. Greene SJ, Mentz RJ, Felker GM. Outpatient Worsening Heart Failure as a Target for Therapy: A Review. *JAMA Cardiol*. Jan 31 2018;doi:10.1001/jamacardio.2017.5250
2. Packer M, Anker SD, Butler J, et al. Effect of Empagliflozin on the Clinical Stability of Patients with Heart Failure and a Reduced Ejection Fraction: The EMPEROR-Reduced Trial. *Circulation*. Oct 21 2020;doi:10.1161/circulationaha.120.051783
3. Ferreira JP, Rossignol P, Dewan P, et al. Income level and inequality as complement to geographical differences in cardiovascular trials. *Am Heart J*. Dec 2019;218:66-74. doi:10.1016/j.ahj.2019.08.019
4. Goyal P, Almarzooq ZI, Horn EM, et al. Characteristics of Hospitalizations for Heart Failure with Preserved Ejection Fraction. *Am J Med*. Jun 2016;129(6):635.e15-26. doi:10.1016/j.amjmed.2016.02.007
5. Ferreira JP, Metra M, Mordi I, et al. Heart failure in the outpatient versus inpatient setting: findings from the BIOSTAT-CHF study. *Eur J Heart Fail*. Oct 19 2018;doi:10.1002/ejhf.1323
6. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med*. Apr 10 2014;370(15):1383-92. doi:10.1056/NEJMoa1313731
7. Pfeffer MA, Claggett B, Assmann SF, et al. Regional Variation in Patients and Outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) Trial. *Circulation*. Jan 6 2015;131(1):34-42. doi:10.1161/circulationaha.114.013255
8. Desai AS, Lewis EF, Li R, et al. Rationale and design of the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial: a randomized, controlled study of spironolactone in patients with symptomatic heart failure and preserved ejection fraction. *Am Heart J*. Dec 2011;162(6):966-972.e10. doi:10.1016/j.ahj.2011.09.007
9. de Denus S, O'Meara E, Desai AS, et al. Spironolactone Metabolites in TOPCAT - New Insights into Regional Variation. *N Engl J Med*. Apr 27 2017;376(17):1690-1692. doi:10.1056/NEJMc1612601
10. Testani JM, Brisco MA, Turner JM, et al. Loop diuretic efficiency: a metric of diuretic responsiveness with prognostic importance in acute decompensated heart failure. *Circ Heart Fail*. Mar 1 2014;7(2):261-70. doi:10.1161/circheartfailure.113.000895
11. Beldhuis IE, Myhre PL, Bristow M, et al. Spironolactone in Patients With Heart Failure, Preserved Ejection Fraction, and Worsening Renal Function. *J Am Coll Cardiol*. Mar 9 2021;77(9):1211-1221. doi:10.1016/j.jacc.2020.12.057
12. Ferreira JP. The use of the win ratio in cardiovascular trials. JACC-HF2020.
13. Pocock SJ, Ariti CA, Collier TJ, Wang D. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. *Eur Heart J*. Jan 2012;33(2):176-82. doi:10.1093/eurheartj/ehr352
14. Madelaire C, Gustafsson F, Stevenson LW, et al. One-Year Mortality After Intensification of Outpatient Diuretic Therapy. *J Am Heart Assoc*. Jul 21 2020;9(14):e016010. doi:10.1161/jaha.119.016010

15. Pandey A, Patel KV, Ayers C, et al. Temporal association between hospitalization event and subsequent risk of mortality among patients with stable chronic heart failure with preserved ejection fraction: insights from the TOPCAT trial. *Eur J Heart Fail*. May 2019;21(5):693-695. doi:10.1002/ejhf.1460
16. Okumura N, Jhund PS, Gong J, et al. 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*. Apr 20 2016;doi:10.1161/circulationaha.115.020729
17. Vardeny O, Claggett B, Kachadourian J, et al. Reduced loop diuretic use in patients taking sacubitril/valsartan compared with enalapril: the PARADIGM-HF trial. *Eur J Heart Fail*. Mar 2019;21(3):337-341. doi:10.1002/ejhf.1402
18. Ferreira JP, Eschalier R, Duarte K, et al. Reduced Diuretic Dose in Patients Treated With Eplerenone: Data From the EPHESUS Trial. *Circ Heart Fail*. May 2020;13(5):e006597. doi:10.1161/circheartfailure.119.006597
19. Docherty KF, Jhund PS, Anand I, et al. Effect of Dapagliflozin on Outpatient Worsening of Patients With Heart Failure and Reduced Ejection Fraction: A Prespecified Analysis of DAPA-HF. *Circulation*. Oct 27 2020;142(17):1623-1632. doi:10.1161/circulationaha.120.047480
20. Ferreira JP, Rossello X, Pocock SJ, et al. Spironolactone dose in Heart Failure with Preserved Ejection Fraction: findings from TOPCAT. *Eur J Heart Fail*. May 25 2020;doi:10.1002/ejhf.1909
21. Cleland JGF, Ferreira JP, Mariottoni B, et al. The effect of spironolactone on cardiovascular function and markers of fibrosis in people at increased risk of developing heart failure: the heart 'OMics' in AGEing (HOMAGE) randomized clinical trial. *Eur Heart J*. Nov 20 2020;doi:10.1093/eurheartj/ehaa758
22. Ferreira JP, Verdonschot J, Wang P, et al. Proteomic and Mechanistic Analysis of Spironolactone in Patients at Risk for HF. *JACC Heart Fail*. Jan 28 2021;doi:10.1016/j.jchf.2020.11.010
23. Zannad F, Alla F, Dousset B, Perez A, Pitt B. Limitation of excessive extracellular matrix turnover may contribute to survival benefit of spironolactone therapy in patients with congestive heart failure: insights from the randomized aldactone evaluation study (RALES). Rales Investigators. *Circulation*. Nov 28 2000;102(22):2700-6.
24. Ferreira JP, Kraus BJ, Zwiener I, et al. Cardio/Kidney Composite End Points: A Post Hoc Analysis of the EMPA-REG OUTCOME Trial. *J Am Heart Assoc*. Mar 23 2021:e020053. doi:10.1161/jaha.120.020053
25. Rydén L, Thráinsdóttir I, Swedberg K. Adjudication of serious heart failure in patients from PROactive. *Lancet*. 2007:189-90. vol. 9557.

Table 1. Patients' characteristics by outpatient loop diuretic intensification (ODI) and primary outcome event (TOPCAT-Americas)

Characteristic Total N =1767	No ODI N =1082	ODI N =685	P-value
Age, years	71 ± 10	72 ± 10	0.18
Female, n (%)	541 (50.0%)	341 (49.8%)	0.93
White race, n (%)	823 (76.1%)	561 (81.9%)	0.004
BMI, Kg/m2	33.6 ± 8.7	34.4 ± 8.0	0.047
LVEF, %	58 ± 8	58 ± 8	0.29
NYHA III/IV, n (%)	337 (31.3%)	283 (41.4%)	<0.001
HFH in prior 6 months, n (%)	453 (41.9%)	300 (43.8%)	0.44
SBP, mmHg	128 ± 16	127 ± 16	0.66
Heart rate, bpm	69 ± 11	69 ± 11	0.34
eGFR, ml/min/1.73m^2	64.8 ± 22.4	63.9 ± 20.0	0.37
Serum potassium, mmol/L	4.2 ± 0.4	4.2 ± 0.4	0.43
Serum sodium, mmol/L	139.7 ± 3.2	139.7 ± 3.0	0.75
Hemoglobin, g/dL	12.9 ± 1.7	12.7 ± 1.6	0.015
ACEi/ARBs, n (%)	851 (78.7%)	544 (79.5%)	0.68
Beta-blocker, n (%)	845 (78.2%)	542 (79.2%)	0.59
Calcium Channel Blocker, n (%)	390 (36.1%)	292 (42.7%)	0.005
Loop diuretic (any), n (%)	840 (77.6%)	522 (76.2%)	0.49
Furosemide, n (%)	770 (71.2%)	473 (69.1%)	0.34
Torsemide, n (%)	36 (3.3 %)	28 (4.1 %)	0.40
Bumetanide, n (%)	36 (3.3 %)	21 (3.1 %)	0.76
Ethacrynic acid, n (%)	22 (2.0 %)	15 (2.2 %)	0.82

Legend: ODI, outpatient loop diuretic intensification; BMI, body mass index; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; HFH, heart failure hospitalisation; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate based on the CKD-EPI formula; ACEi/ARB, angiotensin converting enzyme inhibitors/angiotensin receptor blockers.
*Furosemide equivalents

Table 2. Impact of outpatient loop diuretic dose intensification or new initiation of loop diuretics (among patients not on loop diuretics at baseline) on subsequent (time-updated) outcomes

	Overall pop.		Placebo arm		Spiro. arm		
Outcome	**Event-rate (per 100py)**	**HR (95%CI) P-value***	**Event-rate (per 100py)**	**HR (95%CI) P-value***	**Event-rate (per 100py)**	**HR (95%CI) P-value***	**Interaction P**
HFH/CVD	No ODI 10.4 (9.3-11.5)	1.67 (1.36-2.04) P <0.001	No ODI 11.3 (9.8-13.0)	1.73 (1.31-2.27) P <0.001	No ODI 9.6 (8.3-11.1)	1.60 (1.18-2.16) P =0.002	0.97
	ODI 14.6 (12.5-17.0)		ODI 15.4 (12.5-18.8)		ODI 13.5 (10.6-17.3)		
CVD	No ODI 3.1 (2.6-3.7)	2.17 (1.64-2.87) P <0.001	No ODI 3.2 (2.5-4.2)	2.65 (1.81-3.89) P <0.001	No ODI 3.0 (2.4-3.9)	1.61 (1.04-2.49) P =0.034	0.21
	ODI 7.3 (6.0-8.8)		ODI 8.5 (6.7-10.8)		ODI 5.7 (4.1-7.9)		
ACM	No ODI 5.6 (4.9-6.4)	1.75 (1.41-2.16) P <0.001	No ODI 5.8 (4.8-7.0)	1.81 (1.34-2.43) P <0.001	No ODI 5.4 (4.5-6.5)	1.60 (1.16-2.20) P =0.005	0.61
	ODI 11.2 (9.6-13.0)		ODI 12.0 (9.9-14.6)		ODI 10.0 (7.9-12.8)		

*Adjusted for covariates age, sex, race, BMI, NYHA functional class, SBP, baseline potassium, diabetes, eGFR, ACEi/ARB treatment, and loop diuretic use at baseline.

Legend: ODI, outpatient loop diuretic intensification; HFH, heart failure hospitalization; CVD, cardiovascular death; ACM, all-cause mortality; BMI, body mass index; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate; ACE/ARB, angiotensin converting enzyme inhibitory/angiotensin receptor blocker.

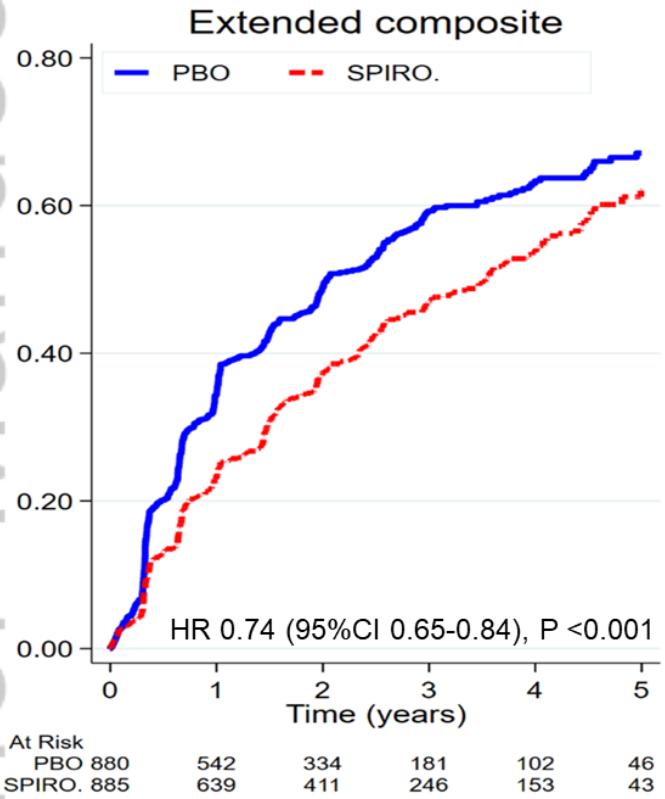
Table 3. Spironolactone effect on the extended composite outcome including outpatient diuretic intensification (ODI) and the composite of cardiovascular death or heart failure hospitalisation

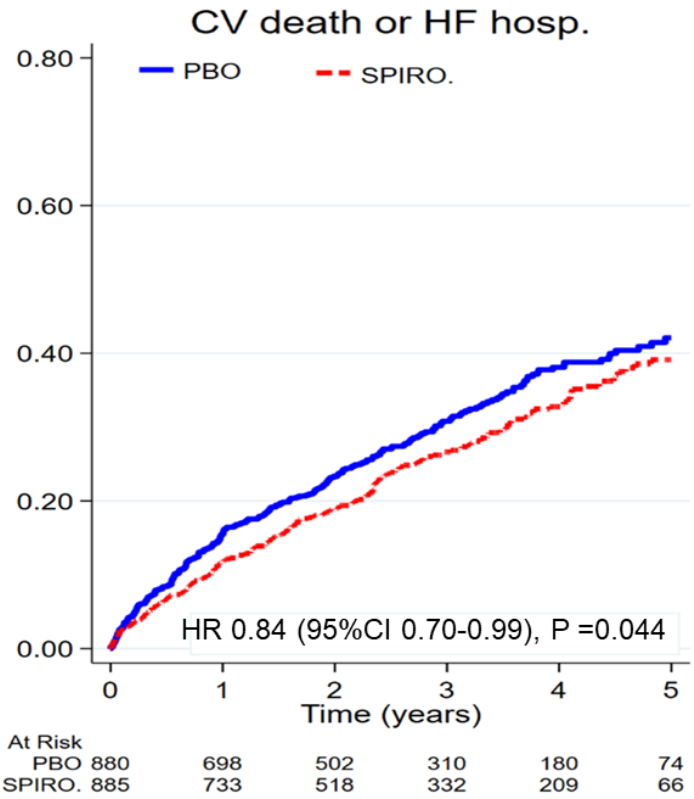
	Placebo		Spironolactone				
Outcome	**N (%) events**	**Event-rate (100py)**	**N (%) events**	**Event-rate (100py)**	**HR (95%CI)**	**Z-score**	**P-value**
Time-to-first Cox							
ODI/HFH/CVD	493 (56.0%)	29.9 (27.4-32.6)	420 (47.4%)	21.5 (19.5-23.6)	0.74 (0.65-0.84)	-4.6	<0.001
ODI	391 (44.4%)	20.6 (18.6-22.7)	294 (33.2%)	13.3 (11.9-14.9)	0.66 (0.57-0.77)	-5.4	<0.001
HFH/CVD	276 (31.3%)	10.4 (9.1-11.7)	242 (27.3%)	12.4 (11.0-14.0)	0.84 (0.70-0.99)	-2.0	0.044
Win-ratio							
1) CVD; 2) HFH; 3) ODI	Outcome 1: Spiro. wins =73759; Spiro. losses =52488 Outcome 2: Spiro. wins = 101019; Spiro. losses =89298 Outcome 3: Spiro. wins = 157013; Spiro. losses =104533 Total: Spiro. wins = 331791; Spiro. losses =246319; Ties =202456				WR =1.35 (1.18-1.54) 1/WR =0.74 (0.65-0.85)	-4.6	<0.001
1) CVD; 2) HFH	Outcome 1: Spiro. wins =73759; Spiro. losses =52488 Outcome 2: Spiro. wins = 101019; Spiro. losses =89298 Total: Spiro. wins = 174778; Spiro. losses =141786; Ties =464002				WR =1.23 (1.03-1.48) 1/WR =0.81 (0.68-0.97)	-2.3	0.024

Legend: ODI, outpatient loop diuretic intensification; HFH, heart failure hospitalization; CVD, cardiovascular death.

Figure 1. Spironolactone effect in the extended composite outcome including outpatient diuretic intensification (ODI) and the composite of cardiovascular death or heart failure hospitalisation

Legend: PBO, placebo; SPIRO., spironolactone; CV, cardiovascular; HF, heart failure.





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