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RESEARCH ARTICLE

Outpatient diuretic intensification as endpoint in heart failure with preserved ejection fraction trials: an analysis from TOPCAT

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Aims 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 HF and a preserved ejection fraction (HFpEF) may experience frequent episodes of outpatient worsening HF. The aim of this study was to evaluate the frequency, prognostic impact, and the effect of spironolactone on outpatient diuretic intensification (ODI), among 1767 patients enrolled in TOPCAT-Americas.

Methods and results 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. 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 hazard ratio (HR) for HF hospitalization or cardiovascular death 1.67, 95% confidence interval (CI) 1.36–2.04; HR for cardiovascular death 2.17, 95% CI 1.64–2.87); and HR for all-cause mortality 1.75, 95% CI 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 three-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 0.74, 95% CI 0.65–0.85; $p < 0.001$) compared with a 16% relative reduction of HF hospitalization or cardiovascular death (HR 0.84, 95% CI 0.70–0.99; $p = 0.044$). 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.

Keywords 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 and 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]

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While trials enrolling patients with HF and a reduced ejection fraction (HFrEF) have been relatively successful incorporating HF hospitalizations and cardiovascular death in their primary outcome, trials enrolling patients with HF 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 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 Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial (TOPCAT-Americas),[6,7] we aimed to assess (i) the impact of ODI on subsequent HF hospitalizations and cardiovascular death, (ii) the potential event rate increase by the inclusion of ODI, and (iii) 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 vs. 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 HFpEF (defined as HF with 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 filtration 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 enrolment 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 analysed in this study were HF hospitalizations (including an overnight stay in an acute care facility with intravenous diuretic therapy), cardiovascular and all-cause mortality, and ODI (as above defined).

Hospitalizations for HF 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 patient characteristics presented as mean ± standard deviation, median (percentile$_{25-75}$), 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, New York Heart Association (NYHA) functional class, systolic blood pressure, baseline potassium, diabetes, estimated glomerular filtration rate, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker 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 also studied the effect of spironolactone (vs. placebo) using a win ratio (WR) analysis that takes into account the timing and importance of outcomes.[12,13] The WR 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 WR. Additionally, we 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 WR or incidence rates with 95% confidence intervals (CIs). Two-tailed *p*-values of <0.05 were considered statistically significant. Statistical analyses were performed using STATA® Statistical Software version 16.1 (Stata Corp., College Station, TX, USA).

Results

Patient characteristics by outpatient loop diuretic intensification

A total of 1767 patients were included in this analysis; mean age 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 class III/IV 41% vs. 31%), had slightly lower hemoglobin (12.7 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 (HF hospitalization or cardiovascular death: HR 1.67, 95% CI 1.36–2.04; cardiovascular death alone: HR 2.17, 95% CI 1.64–2.87; and all-cause mortality: HR 1.75, 95% CI 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 5.97, 95% CI 4.47–7.96) and all-cause death (HR 4.38, 95% CI 3.51–5.46).

Table 1 Patient characteristics by outpatient loop diuretic intensification and primary outcome event (TOPCAT-Americas)

Characteristic	No ODI ($n = 1082$)	ODI ($n = 685$)	*p*-value
Age, years	71 ± 10	72 ± 10	0.18
Female sex, *n* (%)	541 (50.0)	341 (49.8)	0.93
White race, *n* (%)	823 (76.1)	561 (81.9)	0.004
BMI, kg/m^2	33.6 ± 8.7	34.4 ± 8.0	0.047
LVEF, %	58 ± 8	58 ± 8	0.29
NYHA class 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/1.73 m^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
Haemoglobin, g/dl	12.9 ± 1.7	12.7 ± 1.6	0.015
ACEi/ARB, *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)[a], *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

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; eGFR, estimated glomerular filtration rate based on the Chronic Kidney Disease Epidemiology Collaboration formula; HFH, heart failure hospitalization; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; ODI, outpatient diuretic intensification; SBP, systolic blood pressure.
[a]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

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

ACEi, angiotensin-converting enzyme inhibitor; ACM, all-cause mortality; ARB, angiotensin receptor blocker; BMI, body mass index; CVD, cardiovascular death; eGFR, estimated glomerular filtration rate; HFH, heart failure hospitalization; NYHA, New York Heart Association; ODI, outpatient diuretic intensification; py, person-years; SBP, systolic blood pressure.
*Adjusted for covariates age, sex, race, BMI, NYHA functional class, SBP, baseline potassium, diabetes, eGFR, ACEi/ARB treatment, and loop diuretic use at baseline.

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 0.66, 95% CI 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 three-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 two-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*). Moreover, 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 hospitalization or cardiovascular death).

Spironolactone treatment led to a 26% relative reduction of the extended composite of ODI or HF hospitalization or cardiovascular death (HR 0.74, 95% CI 0.65–0.85; $p < 0.001$) compared with a 16% relative reduction of HF hospitalization or cardiovascular death (HR 0.84, 95% CI 0.70–0.99; $p = 0.044$) (*Table 3* and *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; $p < 0.001$), and WR for cardiovascular death followed by HF hospitalization 1.23 (1.03–1.48; $p = 0.024$) (*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, $p < 0.001$) (online supplementary *Table S1*).

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 three-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

Table 3 **Spironolactone effect on the extended composite outcome including outpatient diuretic intensification and the composite of cardiovascular death or heart failure hospitalization**

Outcome	Placebo		Spironolactone		HR (95% CI)	z-score	*p*-value
	n (%) events	Event rate (100 py)	*n* (%) events	Event rate (100 py)			
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 = 73 759; Spiro. losses = 52 488 Outcome 2: Spiro. wins = 101 019; Spiro. losses =89 298 Outcome 3: Spiro. wins = 157 013; Spiro. losses = 104 533 Total: Spiro. wins = 331 791; Spiro. losses = 246 319; Ties = 202 456				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 = 73 759; Spiro. losses = 52 488 Outcome 2: Spiro. wins = 101 019; Spiro. losses = 89 298 Total: Spiro. wins = 174 778; Spiro. losses = 141 786; Ties = 464 002				WR = 1.23 (1.03–1.48) 1/WR = 0.81 (0.68–0.97)	−2.3	0.024

CI, confidence interval; CVD, cardiovascular death; HFH, heart failure hospitalization; HR, hazard ratio; ODI, outpatient diuretic intensification; py, person-years; Spiro, spironolactone; WR, win ratio.

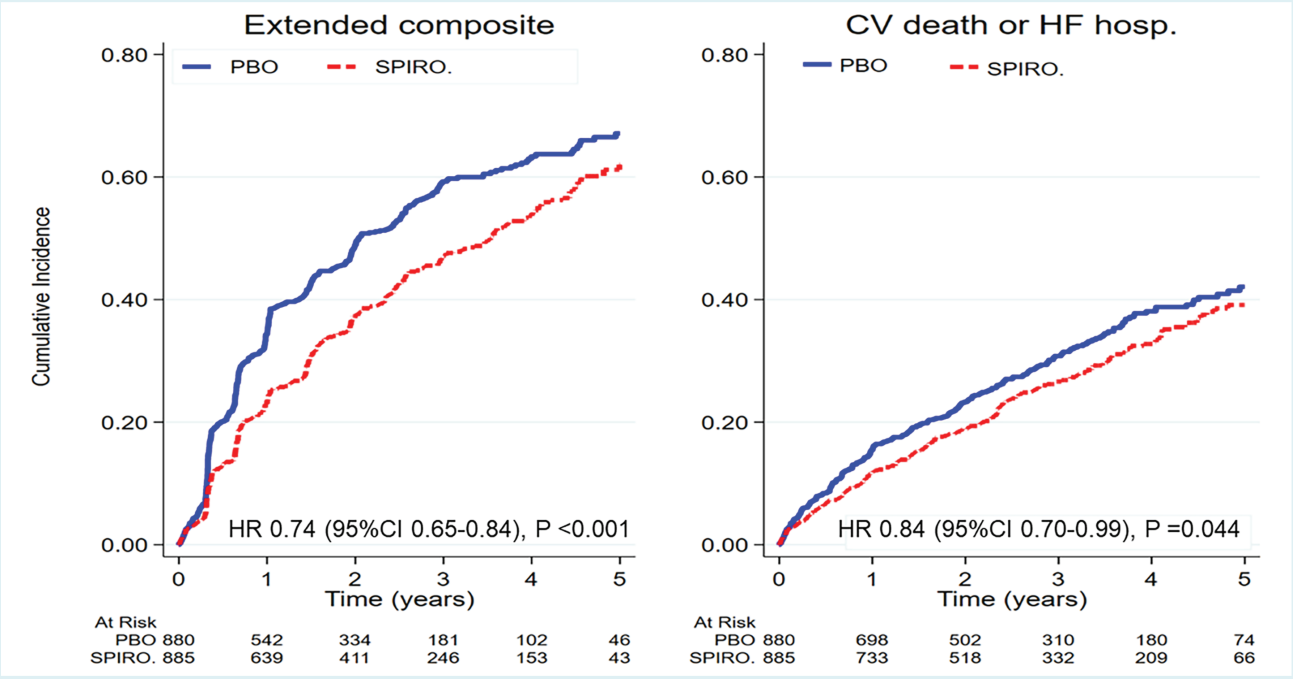

Figure 1 Spironolactone effect in the extended composite outcome including outpatient diuretic intensification (ODI) and the composite of cardiovascular death or heart failure hospitalization. CV, cardiovascular; HF, heart failure; PBO, placebo; SPIRO, spironolactone.

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 (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 shows 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 WR, 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 WR 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 intravenous diuretic therapy was adjudicated as a HF hospitalization; however, it is possible that some patients were treated with intravenous 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.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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