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ORIGINAL ARTICLE

Outpatient treatment of worsening heart failure with intravenous diuretics: first results from a multicentre 2-year experience

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Abstract

Aims The aim of this study is to examine the safety and efficacy of outpatient treatment of worsening heart failure (WHF) with intravenous diuretics.

Methods and results This is a multicentre retrospective observational research study. Patients with all types of heart failure (HF) were included: heart failure with reduced ejection fraction (HFrEF), heart failure with mildly reduced ejection fraction (HFmrEF), and heart failure with preserved ejection fraction (HFpEF). Patients included in this study were 18 years or older, had symptoms of WHF, had weight gain of more than 2 kg, and were not responding to uptitrating of oral diuretic therapy. Patients were treated for one or more days at the outpatient department with administration of intravenous loop diuretics with or without a bolus. In this study, 259 patients were included (mean age of 76 years, mean left ventricular ejection fraction of 41%). Rehospitalization rates for HF were 30.5% and 53.3%, respectively, at 30 days and 1 year. All-cause mortality was 5.8% and 26.3%, respectively, at 30 days and 1 year. Rehospitalization rates for HF and all-cause mortality were highest in patients with HFrEF. In a total of 322 individual outpatient treatments with intravenous diuretics, only one adverse event was registered.

Conclusions Outpatient treatment with intravenous diuretics of patients with WHF is a safe alternative strategy compared with the same treatment in hospitalized patients. However, only non-randomized data are available and rehospitalization rates for this group with WHF are high. No data are available on the best selection criteria and the cost-effectiveness of outpatient treatment with intravenous diuretics.

Keywords Outpatient treatment; Diuretics; Heart failure; Worsening heart failure

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Introduction

In the coming decade, heart failure (HF) represents a major global healthcare challenge due to its rising prevalence.[1] HF is a progressive condition and the outcome of HF is poor, despite advances in treatment options. Worldwide, the current prevalence of HF is estimated to be approximately 2–3%, corresponding to 65 million patients.[2] Annually, in the United States and Europe, more than 1 million patients are hospitalized with HF.[3,4] Approximately 50% of these patients are rehospitalized within 6 months of discharge and almost 30% die within 1 year.[5] Approximately 1–2% of the total national healthcare budget in Western countries is consumed by HF, mostly due to hospitalizations.[6]

For most patients with HF, the clinical course is characterized by clinical stability interrupted by episodes of worsening of symptoms.[5] Whereas some hospitalizations are due to acute HF, most patients with chronic HF have worsening signs and symptoms after a period of clinical stability that requires therapy [worsening HF (WHF)].[7] WHF is associated with

markedly worse prognosis and diminished quality of life.[8] Signs and symptoms of congestion are the main reason why patients with WHF seek urgent care.[9] Current HF guidelines therefore recommend intravenous loop diuretics as starting treatment to alleviate signs and symptoms of congestion.[10] The majority of patients with WHF are hospitalized and treated with intravenous diuretics.[11]

The extended period of clinical worsening before hospitalization offers a time window for intervention before hospitalization would be required.[12] Outpatient treatment of WHF with intravenous or subcutaneous diuretics might be an alternative strategy for hospitalization[13] (*Figure 1*). This has proven to be a safe method to relieve symptoms with a low risk of adverse events.[14] In this study, we present the first multicentre observational data of patients with WHF treated with outpatient intravenous diuretics.

Methods

This study is a multicentre retrospective observational cohort study. In the province of North Holland (the Netherlands), two outpatient HF care units in two large non-academic hospitals were developed for administration of intravenous diuretics for patients with WHF.

Study participation

Study participants were patients with heart failure with reduced ejection fraction (HFrEF), heart failure with mildly reduced ejection fraction (HFmrEF), and heart failure with preserved ejection fraction (HFpEF). Patients were included in the study at the outpatient department (by cardiologist resident or HF nurse), at the emergency department, at the coronary care unit, as a patient of a general practitioner, or after abnormal values of blood pressure and/or weight by home monitoring.

Patients were 18 years or older, had symptoms of WHF, had New York Heart Association (NYHA) class II, III, or IV symptoms, had weight gain of more than 2 kg, and were not responding to uptitrating of oral diuretic therapy. Patients with cardiac ischaemia, cardiac arrhythmias, systolic blood pressure lower than 90 mmHg or higher than 180 mmHg, peripheral oxygen saturation of <90%, serum sodium of <130 mmol/L, and serum potassium of <3.0 mmol/L or higher than 5.5 mmol/L were excluded.

Intervention with intravenous diuretics

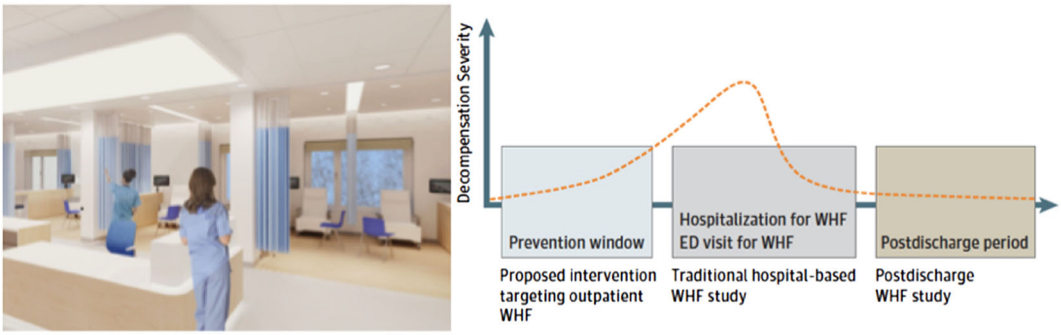
The dosage of the bolus and perfusor of loop diuretics at the outpatient HF care unit was based upon the home dosage of loop diuretics per protocol (*Table 1*). During treatment with intravenous diuretics (duration between 4 and 6 h), blood pressure, heart rate, and urine output were monitored. On the day of the treatment at the outpatient HF care unit, it was decided if patients should return for follow-up treatment the next day.

Table 1 Outpatient treatment protocol bolus and perfusor dosage of furosemide

Home dosage of loop diuretics	Bolus dosage of i.v. furosemide	Perfusor dosage of i.v. furosemide
40 mg furosemide or equivalent[a]	80 mg	—
80 mg furosemide or equivalent[a]	80 mg	120 mg in 4 h
120 mg furosemide or equivalent[a]	—	240 mg in 4 h
>240 mg furosemide or equivalent[a]	80 mg	240 mg in 4 h

i.v., intravenous.
[a]40 mg furosemide is equivalent to 1 mg bumetanide.

Figure 1 Example of an outpatient treatment centre for patients with WHF (left) and schematic representation of time course of disease trajectory (right; with permission from JAMA Cardiology[7]). ED, emergency department; WHF, worsening heart failure.



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When no return visit for the next day was necessary, patients were scheduled for a visit with the HF nurse within 1 week.

Study outcomes

Treated patients were included in an online study database (CASTOR EDC, GDPR compliant) by reviewing electronic patient records (EPIC and Chipsoft) from the start of the study (starting October 2018) with baseline patient characteristics, type of HF, severity of HF, vital parameters, medication use, and characteristics of the treatment at the outpatient HF care unit. Three outcome parameters (rehospitalization for HF, new visit to the outpatient HF care unit, and mortality) were collected at 30 days, 90 days, 6 months, and 1 year.

Statistical analysis

Data from CASTOR EDC were transferred to SPSS for data analysis. Baseline characteristics were presented in tabular form for the population as a whole. Outcome measurements were summarized using standard descriptive statistics. Dichotomous and categorical variables were described using percentages. To test for predictors for outcomes, multivariate analysis was performed with logistic regression [seven variables: age, sex, body mass index (BMI), HF hospitalization, dosage oral loop diuretics, type of HF, and kidney function].

Ethics

This study was reviewed by the local research committee of both participating hospitals (ACWO—Advice Committee Scientific Research). This study did not have to be reviewed and approved by an accredited Medical Ethics Review Committee (MERC). The Medical Research Involving Human Subjects Act does not apply to this study.

Results

Study outcomes

A total of 259 patients were treated from October 2018 to July 2020 and included in the study [mean age of 76 years, mean left ventricular ejection fraction (LVEF) of 41%]. Most patients were receiving recommended pharmacological therapy for chronic HF (87.6% with beta-blocker, 62.6% with angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers, or angiotensin receptor–neprilysin inhibitors (ARNIs), and 62.9% with mineralocorticoid receptor antagonist; *Table 2*). Eighty per cent of patients were previously admitted to the hospital for HF.

Almost all patients used loop diuretics as home medication. Of patients using furosemide, 37.9% had 40 mg as home dosage, 38.6% 41–80 mg, 6.8% 81–160 mg, and 16.7% more than 160 mg. At the outpatient department, most patients received a bolus of furosemide (82.2% and 79.3% 120 mg). Mean diuretic dosage of diuretic perfusor was 235.6 mg. A total of 42.9% of patients had more than one revisit to the outpatient department the same week (*Table 3*).

Readmission to the outpatient department was 30.5% at 30 days and 35.9% at 1 year. Rehospitalization rates for HF were 30.5% and 51.4%, respectively, at 30 days and 1 year. All-cause mortality was 5.8% and 26.3%, respectively, at 30 days and 1 year. Rehospitalization rates for HF and all-cause mortality were highest in the HFrEF group (*Table 4*, *Figure 2*).

Safety

In a total of 322 individual outpatient treatments with intravenous diuretics, only one adverse event was registered. This adverse event (hypotension) leads to interruption of treatment with intravenous diuretics.

Discussion

This is the first multicentre retrospective observational cohort study worldwide of 259 patients with WHF treated at an outpatient department with intravenous diuretics. Treatment with intravenous or subcutaneous diuretics of patients with WHF was proven effective earlier by relieving symptoms with a low risk of adverse events.[14] Our data suggest again that this treatment is a safe alternative to in-hospital treatment with intravenous diuretics for patients with WHF with a low risk of adverse events. Only one adverse event was registered (hypotension leading to interruption of treatment with intravenous diuretics) comparable with the low number of adverse events in earlier observational registries.

In the first 30 days after outpatient treatment, the majority of patients with outpatient readmission is already admitted for a new outpatient treatment with intravenous diuretics (30.5% in 30 days and 35.9% in 1 year). Possibly, patients should have been scheduled for more revisits within the first outpatient treatment or should have been hospitalized for HF. A large proportion of patients is also still hospitalized for HF after outpatient treatment: 30.5% in 30 days (28.6% in HFrEF and 38.0% HFpEF) and 53.3% in 1 year (59.9% in HFrEF and 49.3% in HFpEF). Multiple large randomized trials in patients with HF show high rates of rehospitalization for HF. For example, in the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial, rehospitalization rate for HF at 27 months was 12.8% in the sacubitril/valsartan group

Table 2 Baseline characteristics stratified by types of HF

Variable	Total (n = 259)	HFrEF (n = 147)	HFmrEF (n = 41)	HFpEF (n = 71)
Patients				
Age, years	76 ± 10	73 ± 11	79.4 ± 8	78 ± 9
Female, n (%)	97 (38)	40 (27)	15 (36)	42 (59)
BMI, kg/m^2	29.6 ± 7.0	28.3 ± 5.9	30.1 ± 8.1	31.8 ± 7.8
LVEF, %	41 ± 13	32 ± 8	47 ± 4	57 ± 6
MAGGIC risk score, 1 year mortality, %	23 ± 11	25 ± 12	22 ± 10	20 ± 9
MAGGIC risk score, 3 year mortality, %	47 ± 18	50 ± 18	46 ± 17	42 ± 16
Medical history, n (%)				
Myocardial infarction	110 (42.5)	75 (51.0)	18 (43.9)	17 (23.9)
Hypertension	169 (65.3)	85 (57.8)	27 (65.9)	57 (80.3)
Atrial fibrillation	171 (66.0)	92 (62.6)	26 (63.4)	53 (74.6)
Diabetes mellitus	110 (42.5)	67(45.6)	13 (31.7)	30 (42.3)
Previous stroke/TIA	46 (17.8)	26 (17.7)	6 (14.6)	14 (19.7)
COPD	55 (21.2)	28 (19.0)	12 (29.3)	15 (21.1)
Medication, n (%)				
ACEI	88 (34.0)	57 (38.8)	11 (26.8)	20 (28.2)
ARB	44 (17.0)	20 (13.6)	7 (17.1)	17 (23.9)
Beta-blocker	227 (87.6)	139 (88.4)	36 (87.8)	61 (85.9)
MRA	163 (62.9)	101 (68.7)	19 (46.3)	43 (60.6)
Loop diuretic	247 (95.4)	142 (96.6)	38 (92.7)	67 (94.4)
Thiazide diuretic	9 (3.5)	8 (5.4)	1 (2.4)	0 (0.0)
ARNI	30 (11.6)	25 (17.0)	2 (4.9)	3 (4.2)
SGLT2 inhibitor	2 (0.8)	1 (0.7)	0 (0.0)	1 (1.4)
CRT	42 (16.2)	34 (23.1)	7 (17.2)	1 (1.4)
ICD	26 (11.2)	24 (16.3)	1 (9.8)	1 (1.4)
Laboratory at baseline				
Haemoglobin, mmol/L	7.9 (3.2)	7.9 (2.8)	8.5 (5.9)	7.6 (1.0)
Sodium, mmol/L	139.0 (3.7)	138.6 (3.7)	139.6 (3.1)	139.5 (4.2)
Potassium, mmol/L	4.3 (0.6)	4.3 (0.6)	4.3 (0.6)	4.2 (0.6)
Serum creatinine, μmol/L	149.3 (61.9)	157.9 (69.0)	144.0 (54.4)	134.7 (45.8)
eGFR, mL/min/1.73 m^2	41.7 (18.1)	41.7 (18.8)	42.0 (16.7)	41.4 (17.4)
NT-proBNP, pg/mL	829.7 (971.1)	1048.3 (1115.6)	582.0 (585)	519.8 (671.6)

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide; SGLT2 inhibitor, sodium-glucose co-transporter 2 inhibitor; TIA, transient ischaemic attack.
Continuous variables are presented as means with standard deviation when normally distributed. Categorical variables are presented as n (%).

Table 3 Diuretic use at home and at outpatient department

Variable	Total (n = 259)	HFrEF (n = 147)	HFmrEF (n = 41)	HFpEF (n = 71)
Home dosage of loop diuretic, n (%)				
Low: 0–80 mg furosemide or equivalent[a]	141 (54.4)	75 (51.0)	24 (58.5)	42 (59.2)
Middle: 81–160 mg furosemide or equivalent[a]	39 (15.1)	19 (12.9)	7 (17.1)	13 (18.3)
High: >160 mg furosemide or equivalent[a]	79 (30.5)	53 (36.1)	10 (24.4)	16 (22.5)
Outpatient diuretic bolus, n (%)				
Bolus received	213 (82.2)	110 (74.8)	37 (90.2)	66 (93.0)
Bolus dosage of 40–80 mg	44 (20.7)	22 (20.0)	11 (29.7)	11 (16.7)
Bolus dosage of 120 mg	169 (79.3)	83 (80.0)	26 (70.3)	55 (83.3)
Diuretic dosage, mean (SD)	235.6 (123.1)	258.4 (136.1)	204.2 (93.9)	195.0 (84.1)
Readmission outpatient department, n (%)				
Total readmissions	111 (42.9)	69 (46.9)	15 (36.6)	27 (38.0)
1 readmission outpatient department	65 (58.6)	40 (58.0)	9 (60.0)	16 (59.3)
2 readmissions outpatient department	32 (28.8)	21 (30.4)	5 (33.3)	6 (22.2)
3 readmissions outpatient department	11 (9.9)	6 (8.7)	0 (0)	5 (18.5)
4 readmissions outpatient department	3 (2.7)	2 (2.9)	1 (6.7)	0 (0)

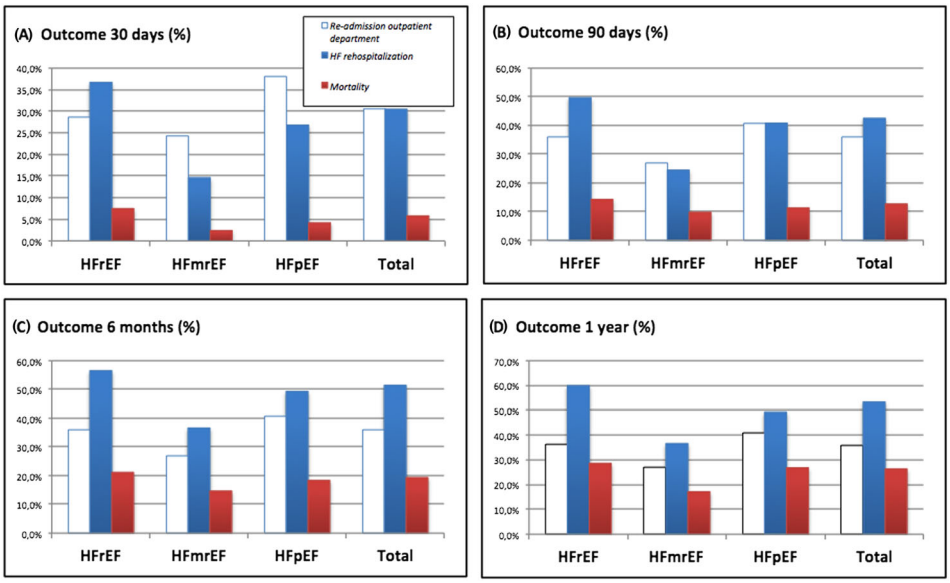
HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; SD, standard deviation.
[a]40 mg furosemide is equivalent to 1 mg bumetanide.

Table 4 Outcome data for outpatient treatment with intravenous diuretics (cumulative incidences in readmission outpatient department, HF rehospitalization, and all-cause mortality)

Variable	Total (n = 259)	HFrEF (n = 147)	HFmrEF (n = 41)	HFpEF (n = 71)
30 days, *n* (%)				
Readmission outpatient department	79 (30.5)	42 (28.6)	10 (24.4)	27 (38.0)
HF rehospitalization	79 (30.5)	54 (36.7)	6 (14.6)	19 (26.8)
All-cause mortality	15 (5.8)	11 (7.5)	1 (2.4)	3 (4.2)
90 days, *n* (%)				
Readmission outpatient department	93 (35.9)	53 (36.1)	11 (26.8)	29 (40.8)
HF rehospitalization	110 (42.5)	73 (49.7)	10 (24.4)	29 (40.8)
All-cause mortality	33 (12.7)	21 (14.3)	4 (9.8)	8 (11.3)
6 months, *n* (%)				
Readmission outpatient department	93 (35.9)	53 (36.1)	11 (26.8)	29 (40.8)
HF rehospitalization	133 (51.4)	83 (56.5)	15 (36.6)	35 (49.3)
All-cause mortality	50 (19.3)	31 (21.1)	6 (14.6)	13 (18.3)
1 year, *n* (%)				
Readmission outpatient department	93 (35.9)	53 (36.1)	11 (26.8)	29 (40.8)
HF rehospitalization	138 (53.3)	88 (59.9)	15 (36.6)	35 (49.3)
All-cause mortality	68 (26.3)	42 (28.6)	7 (17.1)	19 (26.8)

HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

Figure 2 Bar chart demonstrating outcome data for outpatient treatment with intravenous diuretics (cumulative percentage in readmission outpatient department, HF rehospitalization, and all-cause mortality): (A) 30 day outcome, (B) 90 day outcome, (C) 6 month outcome, and (D) 1 year outcome. HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.



(n = 4176) and 15.6% in the enalapril group (n = 4203).[15] Rehospitalization rate at 11 months in a large international database with 39 372 included patients was 27.4%.[16] This higher rate of HF rehospitalization could be explained by the high amount of co-morbidity in our patient group, as shown by the high Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score (estimation of mortality in HF and high mortality risk of 25.0% at 1 year, which was highest in the HFrEF group).[16] Possibly, it is a sign of selection bias, with patients with more severe stages of HF being selected for this new outpatient treatment in this introduction phase.

Comparable with other observational registries, the treated patient group is heterogenous and comprised different types of HF (HFrEF, HFmrEF, and HFpEF). Of the included 259 patients, 27% were patients with HFpEF, 59% of these patients were female. This specific category had higher rates

Table 5 Multivariate analysis with logistic regression: predictors of outcome (HF rehospitalization and mortality)

Predictor	Significance	95% CI	OR
30 day HF rehospitalization			
Dosage of home loop diuretics: middle	0.01***	0.23–0.79	0.42
Dosage of home loop diuretics: high	0.01**,***	0.16–0.80	0.36
1 year HF rehospitalization			
Dosage of home loop diuretics: middle	0.04**	0.24–0.95	0.48
Dosage of home loop diuretics: high	0.05**	0.20–0.99	0.44
Renal failure (eGFR $<$ 60 mL/min/1.73 m^2)	0.01***	0.16–0.70	0.34
1 year all-cause mortality			
BMI	0.01***	0.90–0.98	0.94

BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio.
Middle dosage of home loop diuretics: 81–160 mg furosemide or equivalent; high dosage of home loop diuretics: >160 mg furosemide or equivalent; 40 mg furosemide is equivalent to 1 mg bumetanide.
**$P < 0.05$.
***$P < 0.01$.

of outpatient readmissions and lower rates of rehospitalization, suggesting outpatient treatment as a valuable treatment strategy. Most patients were receiving recommended pharmacological therapy for chronic HF, but the use of beta-blockers and combined use of ACEIs, angiotensin receptor blockers, or ARNIs was lower than in other major HF trials.[15] We included more patients with atrial fibrillation than expected, which could not be explained only by the prevalence of atrial fibrillation in patients with HFpEF.

Patients were either treated with bolus (82%) followed by continuous infusion or continuous infusion alone at the discretion of the treating physician. The Diuretic Optimization Strategies Evaluation in Acute Heart Failure (DOSE-AHF) trial showed no significant difference between bolus and continuous infusion across a broad range of efficacy and safety endpoints.[17] Smaller studies did show that continuous infusion was associated with a lesser degree of renal dysfunction and greater diuresis.[18,19] Loop diuretics do need a threshold concentration to invoke natriuresis, necessitating a minimal drug dose prior to exceeding the baseline rate of sodium excretion.[20,21] The right dosage of diuretic therapy and the use of bolus therapy in outpatient treatment of WHF need to be decided.

Multivariable analysis with logistic regression for HF hospitalization showed that a higher dosage of home loop diuretics and renal failure are predictors for outcome. A higher home dosage of loop diuretics showed an odds ratio of <1 (protective effect) for 30 days and 1 year rehospitalization. A possible explanation is that patients with a low dosage of home loop diuretics had an insufficient outpatient dosage relative to their severity of HF. Patients with renal failure were also less likely to be rehospitalized for HF at 1 year. These patients might be treated with a higher dosage of intravenous diuretics at the outpatient department. A high BMI is a predictor for 1 year mortality, with a higher BMI leading to less mortality (*Table 5*). In literature, the correlation between a higher BMI and lower mortality is mentioned to be due to methodological limitations.[22]

A large advantage of outpatient treatment is the prevention of hospitalization. Patients can spend more time at home and experience a lower risk of hospital-related complications (like venous thrombosis or phlebitis). In times of reduced admission capacity and need for healthcare cost reduction, this new treatment strategy could lead to major cost savings. For each episode of WHF, it is estimated that an average of two treatments[14] is necessary (97.3% of patients needed three or less treatments). Based on the differences in reimbursement costs (€5970 for hospitalization and €1875 for <5 outpatient treatments[23]), the amount of HF hospitalizations in the Netherlands per year (32 500[24]), and the estimated prevention of 20% of HF hospitalizations when implementing outpatient treatment, healthcare cost savings could be as high as €25 million yearly.

The key limitation of observational studies is the lack of randomization; retrospective data are prone to multiple biases and are not a reliable basis for comparing treatments or strategies.[25] To assess the efficacy and safety of outpatient treatment with diuretics for patients with WHF compared with hospitalization, it is time to carry out the first multicentre randomized controlled trial with randomization between 'standard of care' (HF hospitalization and treatment with intravenous diuretics) and 'intervention' (outpatient treatment with intravenous diuretics).

Conflicts of interest

All authors declare they have no competing interests.

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