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Loop diuretic discontinuation in chronic heart failure patients: A retrospective study

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Abstract

Introduction and Objectives: The use of loop diuretics is central in managing congestion in heart failure (HF), but their impact on prognosis remains unclear. In euvolemic patients, dose reduction is recommended, but there is no recommendation on their discontinuation. This study aims to assess the impact of loop diuretic discontinuation on the prognosis of outpatients with HF with reduced ejection fraction.

Methods: This retrospective cohort study collected data from medical records of patients followed in an outpatient HF clinic at a university hospital center. Patients were included if they had been on loop diuretics and these were discontinued. Demographic, clinical and laboratory data were collected, and number and type of congestive events during the one-year period after discontinuation were recorded.

Results: Among 265 patients on loop diuretics, almost half (129) discontinued them at some point. Patients had optimized medical therapy, low median age, low New York Heart Association class, low B-type natriuretic peptide values, normal blood pressure, controlled heart rate and kidney function within normal limits. Among 122 patients with one year of follow-up, 18 (14.8%) had a congestive event. Fifteen events (83.3%) were low-dose diuretic reinitiation at a scheduled visit. There were only three worsening heart failure events (2.5%) during the one-year period. A significant improvement in kidney

function from discontinuation to the one-year follow-up appointment was also observed.

Conclusions: In our cohort, loop diuretic discontinuation was possible and safe in a large proportion of patients. The results should be interpreted with caution and cannot be extrapolated to a broader population of HF patients.

Suspensão de diuréticos de ansa em doentes de Insuficiência Cardíaca Crónica: Um estudo retrospetivo

Resumo

Introdução e objetivos: O uso de diuréticos de ansa é fundamental na gestão da congestão na insuficiência cardíaca (IC), mas o seu impacto no prognóstico permanece incerto. Em doentes euvolémicos, a redução da dose é recomendada, mas não existe até ao momento qualquer recomendação quanto à sua suspensão. Este estudo tem por objetivo avaliar o impacto da suspensão de diuréticos de ansa no prognóstico de doentes de ambulatório de IC com fração de ejeção reduzida.

Métodos: Este estudo de coorte retrospetivo recolheu dados de processos clínicos eletrónicos de doentes acompanhados numa consulta externa de IC de ambulatório de um Centro Hospitalar Universitário. Os doentes foram incluídos caso estivessem medicados com diuréticos de ansa e estes tivessem sido suspensos em algum momento. Foram recolhidos dados demográficos, clínicos e laboratoriais, e registado o número e tipo de eventos congestivos durante um ano após a suspensão.

Resultados: Entre 265 doentes medicados com diuréticos de ansa, quase metade (129) suspendeu o seu uso em algum momento. Os pacientes tinham terapêutica médica otimizada, idade mediana baixa, classe da New York Heart Association e valores de péptidos natriuréticos tipo B baixos, pressão arterial normal, frequência cardíaca controlada e função renal dentro dos limites normais. Dos 122 doentes com um ano de seguimento, 18 (14,8%) tiveram um evento. Quinze eventos (83,3%) foram reintroduções de diurético em baixa dose numa consulta programada. Existiram apenas três eventos de agravamento de insuficiência cardíaca (2,5%) durante um ano. Também foi observada uma melhora significativa na função renal desde a suspensão até a consulta de seguimento de um ano.

Conclusões: Na nossa coorte, a suspensão de diuréticos de ansa foi possível e segura numa grande proporção de doentes. Os resultados devem ser interpretados com cautela e não podem ser extrapolados para uma população mais alargada de doentes com IC.

KEYWORDS

Chronic heart failure, Loop diuretics, Worsening heart failure

PALAVRAS-CHAVE

Insuficiência cardíaca crónica, Diuréticos de ansa, Evento de insuficiência cardíaca

Introduction

Treatment of chronic heart failure (HF) with reduced ejection fraction (HFREF) is based on four main drug classes that have a prognostic impact, namely angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor/neprilysin inhibitors (ARNIs), beta-blockers (BBs), mineralocorticoid receptor antagonists (MRAs), and sodium-glucose co-transporter 2 inhibitors (SGLT2is).[1]

The use of loop diuretics in HF management is central when congestion is detected.[1] Despite the evidence regarding loop diuretics in HF,[2,3] their use remains largely empirical. A previous meta-analysis including studies with a small number of patients has shown an association between loop diuretic use and reductions in HF disease progression, as well as improvements in patients' functional capacity.[4.] There is still, however, a clear lack of evidence concerning the impact of loop diuretics on HF prognosis. In HF management, loop diuretic dose is frequently increased for a period in order to reduce congestion. In euvolemic patients, diuretic dose reduction is recommended in various guidelines and position papers. Nevertheless, there are currently no recommendations concerning their discontinuation. Although this is a frequent decision in clinical practice, the underlying evidence is scarce and conflicting.[5-8] Additionally, the recent indication for use of SGLT2is in HFREF may also have an impact on the need for diuretic maintenance, as does the use of ARNIs, which have been associated with the ability to maintain lower doses of loop diuretics.[3,8-10] This link is particularly important, as loop diuretic use can lead to electrolytic changes, neurohumoral activation, worsening of kidney function and symptomatic hypotension, which may limit drug uptitration as part of guideline-directed medical therapy (GDMT).[1,11]

Objectives

The aim of this study was to retrospectively assess the impact of loop diuretic discontinuation on the prognosis of euvolemic outpatients with HFREF. The primary endpoint was analysis of congestive events within one year of diuretic discontinuation.

Methods

Study design and setting

This is a retrospective cohort study of HFREF patients followed in an outpatient HF clinic at a university hospital center. This article follows the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) reporting checklist for cohort studies.

Participants

We assessed all consecutive patients who attended the HF clinic in 2020. Patients included were aged >18 years, had a HFREF diagnosis, were on loop diuretics (such as furosemide or torasemide) and discontinued their use at some point.

Patients in New York Heart Association (NYHA) functional class IV or hospitalized in the three months prior to baseline were excluded, to assure patient stability. Other reasons for exclusion were clinical evidence of congestion at the time of diuretic discontinuation, loop diuretics taken for other conditions, or discontinuation due to any reason other than euvolemia (such as starting hemodialysis).

All electronic medical records (EMRs) of included patients were reviewed from first registration at the HF clinic to November 30th, 2022.

Ethics

Data used in this study follow the principles of the Declaration of Helsinki. The study was approved by the hospital's ethics committee in September 2022 (reference 239-22). Written informed consent was not required, as the study was based on secondary data collection.

Variables

Demographic, clinical, echocardiographic and blood and urine laboratory data were collected for included patients. During follow-up, we screened for any recorded diuretic discontinuation. All worsening HF (WHF) events caused by congestion were recorded. For the purposes of this paper, we used a definition of WHF events that is broader than usual, but consistent with the most recent publications on the subject,[12-16] including all inpatients and outpatients requiring unscheduled reassessments resulting in an increase in diuretics, namely anticipated outpatient visits resulting in an increase in diuretic dose, unscheduled day-hospital visits, emergency room visits, and hospitalizations. Although they are not part of the WHF definition, we also recorded diuretic resumptions in scheduled visits due to objective signs of congestion, and included them as congestive events, to further clarify any relapse of congestion after diuretic discontinuation. The impact of other variables – including GDMT and cardiac resynchronization

therapy (CRT) – on the occurrence of these events was also analyzed.

Data sources

Data was collected at a baseline appointment, i.e. the first available appointment in the EMR at which the patient was prescribed loop diuretics. Data on events occurring within one year of discontinuation were recorded. We then examined the available appointments at one year of follow-up, to assess patients' clinical course during this period. Echocardiographic and laboratory data were obtained in a three-month window prior to each visit. Estimated glomerular filtration rate (eGFR) was calculated using the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, based on serum creatinine, gender, and age. Events within one year from discontinuation were recorded. Follow-up visits were recorded as the nearest to one year of follow-up, whenever available. Data were marked as missing whenever they were nonexistent or impossible to obtain.

Statistical analysis

Continuous variables were expressed as medians and interquartile range (IQR). Categorical variables were presented as absolute (n) and relative (%) frequencies. Missing data were excluded from calculations. Chi-square tests were used to compare categorical variables between groups, while the Mann-Whitney U test was used to compare continuous variables between groups. The Wilcoxon signed-rank test was used to compare continuous variables in the same patients at different time points, and McNemar's test was used to compare categorical variables at two different time points in the same patients. Significance was set at a two-tailed p-value <0.05 for all statistical tests. The statistical analysis was performed using IBM SPSS statistical software, version 27.0 (IBM SPSS Inc., Chicago, IL, USA).

Results

Baseline

A total of 381 patients were identified for inclusion in the study. Of these, 252 individuals were excluded (mostly due to absence of diuretic prescription or discontinuation in the available medical records) (Figure 1). Hence, a total of 129 patients were included. At baseline, patients' median age was 57 years (IQR 48-63), and 83 patients (64%) were male (Table 1). The majority of these patients had HF with non-ischemic etiology (78.3%), in most cases idiopathic cardiomyopathy (42.6%). The median left ventricular ejection fraction (LVEF) was 30% (IQR 22.8-35.0). A total of 34 patients (28.6%) were in NYHA class I, 80 (67.2%) were in class II and five (4.2%) were in class III. Signs of congestion were present in 25 patients (19.5%).

Table 1 Patient characteristics.

	Baseline (n=129)	Discontinued (n=129)	p[a]	1 year (n=118)	p[b]
Male gender, n (%)	83 (64.3)	83 (64.3)		75 (63.6)	
Age (years), median (IQR)	57.0 (48.0-63.0)	59.00 (50.5-65.0)		60.0 (51.0-66.0)	
Time since discontinuation, weeks, median (IQR)	-	-		55.0 (52.0-67.0)	
Cause of HF, n (%)					
Ischemic	28 (21.7)				
Idiopathic	55 (42.6)				
Familial	11 (8.5)				
Alcoholic	12 (9.3)				
Other	23 (17.8)				
Diuretic, n (%)					
Furosemide	126 (97.7)	126 (97.7)			
Torasemide	3 (2.3)	3 (2.30)			
Diuretic resumption, n (%)				16 (13.6)	
Diuretic dose, mg					
Furosemide, median (IQR) (n=126)	40 (20-40)	20 (20-40)	<0.001[c]	40 (20,40) (n=15)	0.317[1]
Torasemide (n=3)	5 mg (n=3)	2.5 mg (n=1) 5 mg (n=2)		10 mg (n=1)	
LVEF, %, median (IQR)	30.0 (22.8-35.0) (n=110)	38.0 (29.3-49.0) (n=88)	<0.001[c]	37.50 (28.8- 46.5) (n=38)	0.429[1]
NYHA class, n (%)					
I	34/119 (28.6)	79/125 (63.2)		64/117 (54.7)	
II	80/119 (67.2)	46/125 (36.8)		49/117 (33.7)	
III	5/119 (4.2)	0/125		4/117 (3.4)	
Congestion, n (%)	25/128 (19.5)	0		7/118 (5.9)	
Pulmonary congestion, n (%)	16/128 (12.5)	0		4/118 (3.4)	
Systemic congestion, n (%)	12/128 (9.4)	0		5/118 (4.2)	
Pulmonary and systemic congestion, n (%)	3/128 (2.3)	0		2/118 (1.69)	
SBP (mmHg), median (IQR)	120.0 (110.0-130.0) (n=121)	118.0 (110.0-130.0) (n=125)	0.742[c]	118.0 (110.0-130.0) (n=111)	0.688[c]
DBP, mmHg, median (IQR)	70.0 (60.3-80.0) (n=120)	70.0 (61.0-77.0) (n=119)	0.300[c]	70.0 (63.0-75.0) (n=107)	0.460[c]
HR, bpm, median (IQR)	70.0 (60.0-80.0) (n=118)	65.0 (60.0-72.0) (n=119)	0.016[c]	65.0 (60.0-72.0) (n=105)	0.194[c]
K+, mEq/l, median (IQR)	4.6 (4.3-4.9) (n=71)	4.7 (4.5-5.0) (n=92)	0.019[c]	4.8 (4.5-5.1) (n=78)	0.717[c]
Creatinine, mg/dl, median (IQR)	0.90 (0.73-1.12) (n=74)	0.90 (0.77-1.11) (n=90)	0.888[c]	0.89 (0.76-1.03) (n=77)	<0.001[c]
eGFR, ml/min/1.73 m^2, median (IQR)	95.0 (70.0-105.3) (n=74)	91.7 (70.6-101.5) (n=90)	0.521[c]	92.8 (75.5-104.6) (n=77)	0.003[c]
BNP, pg/ml, median (IQR)	81.7 (38.3-180.8) (n=50)	50.0 (20.3-86.5) (n=61)	0.122[c]	40.3 (20.9- 121.9) (n=51)	0.134[c]
ARNI, n (%)	9/129 (7.0)	28 (21.7)	<0.001[d]	27 (22.9)	0.125[d]

ACEI/ARB, n (%)	119/129 (92.2)	99 (76.7)	<0.001[d]	86 (72.9)	0.021[d]
BB, n (%)	121/129 (93.8)	121 (93.8)	>0.999[d]	111 (94.1)	>0.999[d]
MRA, n (%)	90/128 (70.3)	102 (79.1)	0.036[d]	98 (83.1)	0.092[d]
SGLT2i, n (%)	5/128 (3.9)	29 (22.5)	<0.001[d]	36 (30.5)	0.001[d]
CRT, n (%)	6 (4.7)	19 (14.7)	<0.001[d]	21 (17.8)	0.500[d]

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; BB: beta-blocker; BNP: B-type natriuretic peptide; CRT: cardiac resynchronization therapy; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; HF: heart failure; HR: heart rate; IQR: interquartile range; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor antagonist; NYHA: New York Heart Association; SBP: systolic blood pressure; SGLT2i: sodium-glucose cotransporter 2 inhibitor.

[a] Differences between baseline and discontinuation appointments.

[b] Differences between discontinuation and 1-year follow-up appointments.

[c] Related-samples Wilcoxon signed-rank test.

[d] McNemar's test; significance set at p<0.05, two-tailed.

Regarding GDMT, 7% of patients were on ARNIs, 92.2% on ACEIs or angiotensin receptor blockers (ARBs), 93.8% on BBs, 70.3% on MRAs and 3.9% on SGLT2is. Six patients (4.7%) had a CRT device implanted. All patients were on loop diuretics. The median furosemide dose was 40 mg (IQR 20-40), and three patients were taking 5 mg of torasemide.

Diuretic discontinuation

The median time between baseline and loop diuretic discontinuation was 20 months (IQR 9.5-46.0). At discontinuation, all patients were euvolemic, with 63.2% in NYHA class I and the rest in NYHA class II. (Table 1).

From baseline to discontinuation, these patients showed a significant increase in LVEF, to a median of 38% (p<0.001). There was a significant decrease in heart rate, from a median of 70 bpm to a median of 65 bpm (p=0.016). A significant increase in potassium was seen, from median 4.6 mEq/l to 4.7 mEq/l (p=0.019).

During this period GDMT was optimized, with significant increases in ARNIs (p<0.001), MRAs (p=0.036) and SGLT2is (p<0.001). CRT device implantation also increased (p<0.001). There was a decrease in median furosemide dose from baseline (median 20 mg, IQR 20.0-40.0; p<0.001), up to the appointment at which discontinuation was decided.

Follow-up

A total of 122 patients were followed for events for one year after discontinuation, and 118 had a one-year follow-up appointment at the HF clinic (median 60 weeks; IQR 51-66).

Information was available for all 129 included patients on events for the first six months, during which eight events were recorded. No events occurred in the first six months in the seven patients for whom

events could not be recorded for a full year (Table 2).

Table 2 Events.

Follow-up period	6 months	1 year
Number of events, n (%)	8 (6.2)	18 (14.8)
Weeks to event, median (IQR)	13.5 (7.5-17.3)	27.0 (13.8-37.5)
Diuretic resumption, n (%)	8 (6.2)	18 (14.8)
Type of event, n (%)		
Diuretic resumption at appointment	6 (75.0)	15 (83.3)
Unscheduled appointments	1 (12.5)	1 (5.6)
Emergency department due to HF	0 (0)	1 (5.6)
Hospitalizations due to HF	1 (12.5)	1 (5.6)

HF: heart failure; IQR: interquartile range.

Of the 122 patients followed for one year, 18 (14.8%) had a single congestive event. Fifteen patients restarted diuretics at a scheduled visit (83.3%), one patient had an unscheduled visit (5.6%), one had an emergency department visit due to HF (5.6%), and one was hospitalized due to HF (5.6%), yielding only three WHF events (2.5%). The median time to event occurrence was 27 (IQR 13.8-37.5) weeks.

Of the 118 patients with a follow-up appointment, 13.6% had resumed diuretics at the time of the visit. At this appointment, 54.7% of patients were in NYHA class I, 33.7% in class II and 3.4% patients in class III (Table 1).

From discontinuation to one-year follow-up, a statistically significant decrease was seen in creatinine ($p<0.001$), with a corresponding increase in eGFR ($p=0.003$). The number of patients taking an ACEI/ARB decreased significantly ($p=0.021$), and a significant increase was observed in patients taking SLGT2is ($p<0.001$).

Impact of variables on events at one year

Table 3 presents a comparison of patients with and without events at one-year follow-up. Patients with events were significantly more congestive at one year ($p<0.001$). More events were recorded among patients with an implanted CRT device at discontinuation (33.3% vs. 12.5%; $p=0.024$). These patients had a lower median LVEF at discontinuation than those without CRT (34.5% vs. 39.5%), although this was not significant ($p=0.387$) (Appendix 1, Supplementary Table S2). No other parameters were significantly different between the groups ($p>0.05$).

Table 3 Impact of variables on events.

	Events at 1 year		p[a]
	With events (n=18)	Without events (n=104)	
Male gender, n (%)	12/18 (66.7)	66/104 (63.5)	0.794[b]

Age at diuretic discontinuation, median (IQR)	63.00 (48.8-67.5)	59.00 (51.0-64.0)	0.296[c]
Diuretic discontinued, n (%)			
Furosemide	18/18 (100)	101/104 (97.1)	0.466[b]
Torasemide	0/18 (0)	3/104 (2.9)	
Furosemide dose at discontinuation, mg, median (IQR)	30 (20-40)	20 (20-40) (n=101)	0.105[c]
NYHA class at discontinuation, n (%)			
I	11/17 (64.7)	64/101 (63.4)	0.915[b]
II	6/17 (35.3)	37/101 (36.6)	
III	0/18	0/101	
NYHA class at 1-year follow-up, n (%)			
I	9/18 (50.0)	55/99 (55.6)	0.563[b]
II	9/18 (50.0)	40/99 (40.4)	
III	0/18 (0)	4/99 (4.0)	
LVEF at discontinuation, %, median (IQR)	34.5 (26.8-50.0) (n=12)	39.0 (31.0-48.0) (n=71)	0.501[c]
LVEF at 1-year follow-up, %, median (IQR)	40.5 (26.3-49.3) (n=10)	37 (29.3-46.0) (n=28)	0.708[c]
Congestion at 1-year follow-up, n (%)	4/18 (22.2)	3/100 (3.0)	0.001[b]
Pulmonary congestion at 1-year follow-up, n (%)	3/18 (16.7)	1/100 (1.0)	<0.001[b]
Systemic congestion at 1-year follow-up, n (%)	2/18 (11.1)	3/100 (3.0)	0.116[b]
SBP at discontinuation, mmHg, median (IQR)	119.5 (110.0-130.0)	118.0 (109.5-130.0) (n=101)	0.647[c]
SBP at 1-year follow-up, mmHg, median (IQR)	121.0 (110.0-128.5)	118.0 (108.5-130.0) (n=93)	0.709[c]
DBP at discontinuation, mmHg, median (IQR)	71.5 (68.3-79.5) (n=16)	70.0 (60.0-77.5) (n=97)	0.486[c]
DBP at 1-year follow-up, mmHg, median (IQR)	70.0 (62.5-80.0)	70.0 (62.5-75.0) (n=89)	0.679[c]
HR at discontinuation, bpm, median (IQR)	64.0 (57.8-70.0) (n=16)	66.0 (60.5-73.0) (n=97)	0.438[c]
HR at 1-year follow-up, bpm, median (IQR)	64.0 (60.0-77.8) (n=16)	65.0 (60.0-71.5) (n=89)	0.979[c]
K+ at discontinuation, mEq/l, median (IQR)	4.8 (4.6-5.2) (n=16)	4.70 (4.5-5.0) (n=69)	0.398[c]
K+ at 1-year follow-up, mEq/l, median (IQR)	4.8 (4.5-5.0) (n=14)	4.8 (4.5-5.1) (n=64)	0.481[c]
Creatinine at discontinuation, mg/dl, median (IQR)	1.0 (0.7-1.1)-(n=16)	0.9 (0.8-1.1) (n=68)	0.628[c]
Creatinine at 1-year follow-up, mg/dl, median (IQR)	0.9 (0.8-1.1) (n=14)	0.86 (0.75-1.02) (n=63)	0.658[c]
eGFR at discontinuation, ml/min/1.73 m^2, median (IQR)	79.94 (59.1-110.5) (n=16)	93.5 (72.7-99.7) (n=68)	0.661[c]
eGFR at 1-year follow-up, ml/min/1.73 m^2, median (IQR)	89.0 (67.3-111.3) (n=14)	92.9 (79.4-102.6) (n=63)	0.792[c]
BNP at discontinuation, pg/ml, median (IQR)	40.2 (15.3-72.8) (n=15)	53.6 (20.6-92.8) (n=43)	0.263[c]
BNP at 1-year follow-up, pg/ml, median (IQR)	75.3 (28.1-116.9) (n=14)	36.7 (20.3-123.0) (n=37)	0.447[c]
ARNI at discontinuation, n (%) (n=122)	3/18 (16.7)	21/104 (20.2)	0.728[b]
ARNI at 1-year follow-up, n (%) (n=118)	4/18 (22.2)	23/100 (23.0)	0.942[b]
ACEI/ARB at discontinuation, n (%) (n=122)	15/18 (83.3)	81/104 (77.9)	0.602[b]
ACEI/ARB at 1-year follow-up, n (%) (n=118)	13/18 (72.2)	73/100 (73.0)	0.946[b]
BB at discontinuation, n (%) (n=122)	18/18 (100)	97/104 (93.3)	0.257[b]

BB at 1-year follow-up, n (%) (n=118)	18/18 (100)	93/100 (93)	0.247[b]
MRA at discontinuation, n (%) (n=122)	15/18 (83.3)	80/104 (76.9)	0.545[b]
MRA at 1-year follow-up, n (%) (n=118)	16/18 (88.9)	82/100 (82.0)	0.473[b]
SGLT2i at discontinuation, n (%) (n=122)	5/18 (27.8)	22/104 (21.2)	0.532[b]
SGLT2i at 1-year follow-up, n (%) (n=118)	6/18 (33.3)	30/100 (30.0)	0.777[b]
CRT at discontinuation, n (%) (n=118)	6/18 (33.3)	13/104 (12.5)	0.024[b]
CRT at 1-year follow-up, n (%) (n=122)	6/18 (33.3)	15/100 (15.0)	0.061[b]

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; BB: beta-blocker; BNP: B-type natriuretic peptide; CRT: cardiac resynchronization therapy; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; HR: heart rate; IQR: interquartile range; K+: potassium; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor antagonist; NYHA: New York Heart Association; SBP: systolic blood pressure; SGLT2i: sodium-glucose cotransporter 2 inhibitor.

[a] Differences between groups with and without events.

[b] Related-samples Wilcoxon signed-rank test.

[c] McNemar's test; significance set at $p<0.05$, two-tailed.

Nineteen patients whose LVEF recovered to ≥50% at discontinuation were analyzed for events at one year, to check for possible differences. Four events were found (21.1%). The number of events in this group was similar to the other patients, with no statistically significant differences (Appendix 1, Supplementary Table S1).

Discussion

The present study aimed to assess the impact of the discontinuation of loop diuretics on the prognosis of patients with HFREF. The traditionally hospital-based concept of WHF has shifted in recent years toward the inclusion of HF outpatients who require an increase in diuretics,[12-14] but a consensus on its definition has yet to be reached.[15] In our work, we considered all events that required an unscheduled reassessment and an increase in loop diuretics, even in an outpatient setting, in line with the latest definition of WHF in accordance with a position paper from the Heart Failure Association of the European Society of Cardiology.[16]

In our cohort of patients with HFREF, 265 were on loop diuretics, which it was possible to discontinue at some point in almost half (129 patients, 48.7%). Only 18 patients (14.8%) had a congestive event among the 122 patients with one year of follow-up, and 15 of these events (83.3%) were simply loop diuretic resumption at a scheduled visit, with a low diuretic dose. Therefore, only three (2.5%) WHF events occurred during the one-year follow-up. This clearly shows that in selected patients with HFREF, diuretics can be safely discontinued.

Patients in our trial were well treated in terms of GDMT: at discontinuation, 98.45% were on ACEIs/ARBs/ARNIs, 93.8% on BBs and 79.1% on MRAs. The number of patients on SGLT2is was low,

as most data were collected prior to the publication of DAPA-HF,[17] the first trial showing the benefit of SGLT2is in HFREF. It is also worth noting that our patients had a low median age, with low B-type natriuretic peptide (BNP) values and NYHA class, normal blood pressure and controlled heart rate, with creatinine, eGFR and potassium values within normal ranges. These patient characteristics may have enabled diuretic discontinuation.

Furthermore, GDMT was optimized from baseline to discontinuation, with significant increases in ARNIs (and thus decreases in ACEIs/ARBs), MRAs and SGLT2is. This, as expected, led to clinical and laboratory improvement, with a significant improvement in LVEF, along with significant reductions in heart rate, which are associated with improvement in clinical outcomes.[18,19] It also enabled a significant reduction in furosemide doses, supporting the physician's decision to discontinue the drug. There was also a significant rise in potassium levels, possibly attributable to the significant increases in MRA use.[20,21]

Discontinuation of diuretics was dictated solely by assessing congestion with physical examination for most patients (natriuretic peptide [NP] data were available in only 61 patients). Although there are numerous tools available to assess congestion, as well as many different alternatives under investigation,[3,22,23] it was interesting to note how safe discontinuation was possible in these patients using only semiology.

Significant improvements in kidney function were observed from discontinuation to one-year follow-up. This is an unexpected finding, as patients with HF experience significant deterioration in kidney function along their journey.[24] A possible explanation is diuretic discontinuation, as SGLT2is and ARNIs are known to protect kidney function from deterioration, but do not improve it.[25-27]

There were no significant differences in LVEF between patients with and without events. Furthermore, patients who completely recovered LVEF (≥50% at discontinuation) did not have significantly fewer events than other patients; from our results, it is not possible to establish a link between LVEF and relapse of congestion. Other echocardiographic parameters (left ventricular global longitudinal strain, left atrial ejection fraction or left atrial volume index)[28-30] could have a role in discriminating between patients with and without events, but this was not addressed in our study. Interestingly, patients with CRT devices at discontinuation had more events than those without, with significant differences. Despite CRT, these patients showed a trend for lower median LVEF, which could help explain this result.

A small number of previous studies have explored loop diuretic discontinuation in stable HF outpatients, with conflicting results. ReBIC-1, a double-blind, multicenter, randomized controlled trial (RCT), randomized 188 stable HF outpatients to either furosemide discontinuation or maintenance, with a follow-up of three months.[9] The study reported that HF events were infrequent and did not differ between the furosemide discontinuation and maintenance groups. Furosemide resumption was also similar between groups, as was patient-reported perception of dyspnea, favoring furosemide discontinuation in stable outpatients with no signs of congestion. The findings of the present study are in line with those of the ReBIC-1 trial, as events were infrequent and few patients had to restart loop diuretics – but with the difference of a much longer follow-up period (one year in our study).

By contrast, another RCT that assessed loop diuretic omission in stable outpatients showed a clear diuretic response phase in chronic patients taking loop diuretics.[8] In that trial, diuretic cessation caused a 50% drop in natriuresis and a 31% fall in urine output, underlining the risk of sodium and water retention, especially for patients with high N-terminal pro-BNP (NT-proBNP) such as those in that study. However, as pointed out in the study, while natriuresis has an important role in assessing acute HF diuretic response, it is not studied for diuretic discontinuation in chronic patients. Our study did not measure NT-proBNP but BNP, which was the NP available at our center at that time. Our patients had low median BNP at discontinuation, so the results cannot be extrapolated to patients with high NP levels. Results from the present study raise questions as to whether these changes in natriuresis and urine output seen in the acute phase really have a meaningful clinical impact in the chronic phase, as discontinuation of diuretics was possible without significant relapse of congestion.

Another RCT on diuretic discontinuation in elderly patients[31] concluded that withdrawing diuretic therapy in HF would do more harm than good in most patients, as a significant number of patients in the withdrawal group needed to restart diuretics, as well as suffering a significant increase in blood pressure. However, in that trial, of the 102 patients in the withdrawal group, only 46 (45%) were prescribed diuretics with the specific indication of treating HF, with 42 patients taking diuretics to control hypertension, and only 31 patients (30.4%) were taking a loop diuretic (and combinations with other diuretics were included in this number), with most taking thiazides. The characteristics of HF patients in that trial were also not specified, and overall HF treatment was very different, as the article dates from 1997. Overall, it is possible that these results might not apply directly to loop diuretic discontinuation in euvolemic patients with HFREF.[31]

The study we conducted succeeded in collecting some novel information on a topic for which previous evidence is scarce, a strong point that can make it clinically and scientifically relevant. Following loop diuretic discontinuation patients for one year has not been achieved in the literature to date and is also noteworthy. The association we were able to establish between loop diuretic discontinuation and a small number of HF events in a particular subset of patients and conditions may be useful in clinical decision-making for similar patients and conditions. The data presented on patient characteristics and their clinical course until discontinuation and during follow-up, in a population in whom loop diuretic discontinuation could be achieved safely, may also be helpful when designing future studies on this topic.

This study has several limitations that should be considered, and its findings should be interpreted with caution. First and foremost, its observational and retrospective nature has inherent limitations, such as the availability of the desired information in EMRs, leading to missing data, which limits the interpretation of results. The collection of data from a single medical center is another potential source of bias. The absence of a control group is another clear limitation of our work. The small size of the sample considered also limits the statistical power to accurately compare patients with and without events and draw valid associations. Moreover, the study recorded inclusion appointments which occurred in different years, as did the subsequent discontinuation appointment and follow-up period, which impairs the comparability of the data. Notwithstanding, there were no major changes in HF treatment during the period of our study. Only three patients were taking torasemide, and thus our study cannot directly establish that its conclusions would be applicable to loop diuretics other than furosemide.

External validity is limited by the above patient characteristics. There is a need for more studies to better understand whether diuretic discontinuation would also be possible in different subsets of patients (such as older patients or those with impaired kidney function).

Conclusion

Loop diuretic discontinuation in a cohort of stable, euvolemic outpatients with HFREF was associated with a low number of episodes of diuretic resumption and WHF events, supporting the idea that loop diuretic discontinuation is possible in selected patients and conditions. Multicenter randomized controlled studies focused on loop diuretic discontinuation in euvolemic ambulatory patients, with larger sample sizes and prospective in nature, are needed to gather more conclusive evidence.

Conflicts of interest

The authors have no conflicts of interest to declare.

Ethics in publishing

1. Does your research involve experimentation on animals?:

No

2. Does your study include human subjects?:

Yes

If yes; please provide name of the ethical committee approving these experiments and the registration number. :

Approved in September 2022 (No. 239-22) by the Ethics Comittee (CES) of São João University Hospital Centre.

If yes; please confirm authors compliance with all relevant ethical regulations. :

Yes

If yes; please confirm that written consent has been obtained from all patients. :

Yes

3. Does your study include a clinical trial?:

No

4. Are all data shown in the figures and tables also shown in the text of the Results section and discussed in the Conclusions?:

Yes

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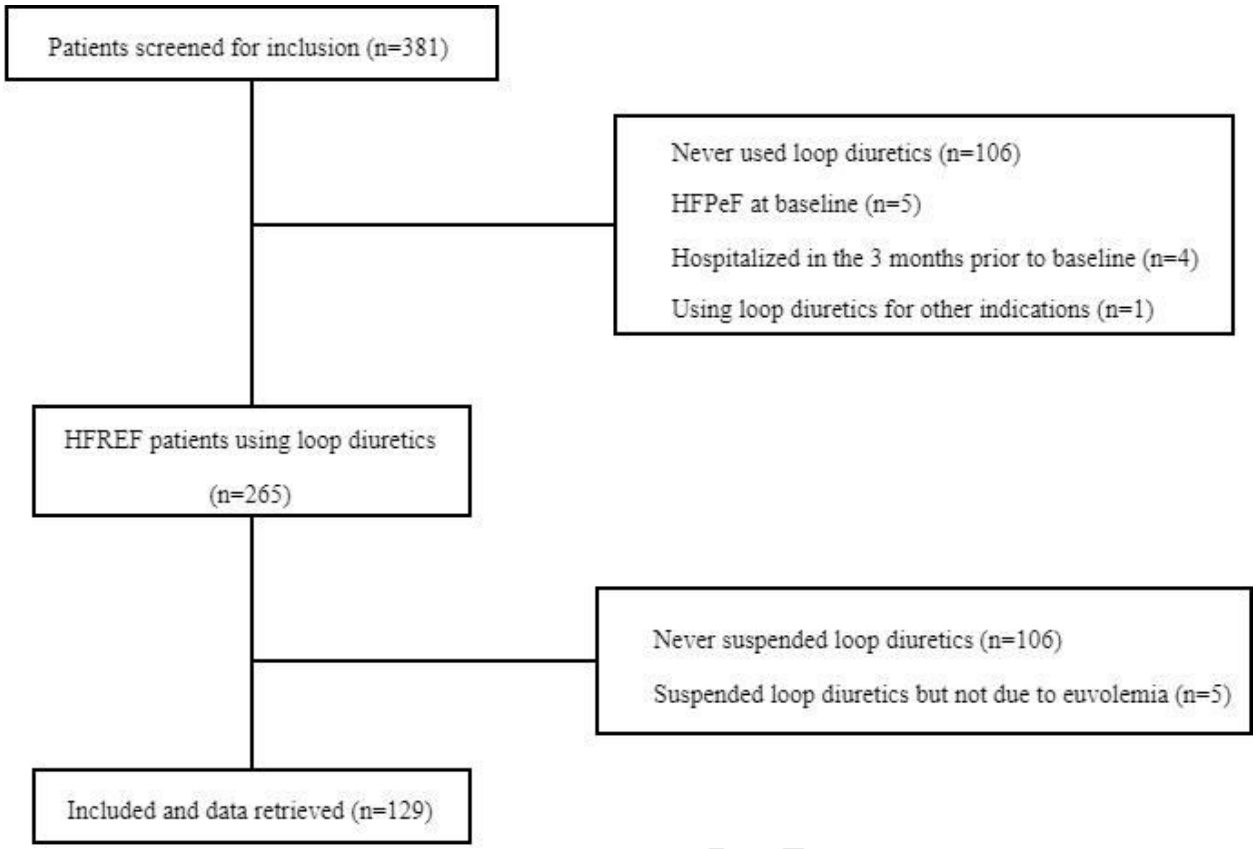

Figure 1 Flow diagram of patient inclusion. HFPEF: heart failure with preserved ejection fraction; HFREF: heart failure with reduced ejection fraction.

Appendix 1

Supplementary Table S1 Completely recovered ejection fraction and events at one year.

		Events at one year		p[a]
		Yes (n=18)	No (n=104)	
LVEF at discontinuation	≥50% (n=19)	4 (21.0)	15 (79.0)	0.399
	Other patients (n=103)	14 (13.6)	89 (86.4)	

LVEF: left ventricular ejection fraction.
[a] Pearson's chi-square test.

Supplementary Table S2 Cardiac resynchronization therapy devices and left ventricular ejection fraction.

	CRT device at discontinuation		p[a]
	Yes	No	
LVEF at discontinuation, median (IQR)	34.5 (30.3-44.8) (n=16)	39.5 (29.0-49.0) (n=72)	0.387

CRT: cardiac resynchronization therapy; IQR: interquartile range; LVEF: left ventricular ejection fraction.
[a] Mann-Whitney U test; significance for $p<0.05$.