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# Diuretic dose is a strong prognostic factor in ambulatory patients awaiting heart transplantation

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## Abstract

**Aims** The prognostic value of 'high dose' loop diuretics in advanced heart failure outpatients is unclear. We aimed to assess the prognosis associated with loop diuretic dose in ambulatory patients awaiting heart transplantation (HT).

**Methods and results** All ambulatory patients ( $n = 700$ , median age 55 years and 70% men) registered on the French national HT waiting list between 1 January 2013 and 31 December 2019 were included. Patients were divided into 'low dose', 'intermediate dose', and 'high dose' loop diuretics corresponding to furosemide equivalent doses of  $\leq 40$ , 40–250, and  $> 250$  mg, respectively. The primary outcome was a combined criterion of waitlist death and urgent HT. N-terminal pro-B-type natriuretic peptide, creatinine levels, pulmonary capillary wedge pressure, and pulmonary pressures gradually increased with higher diuretic dose. At 12 months, the risk of waitlist death/urgent HT was 7.4%, 19.2%, and 25.6% ( $P = 0.001$ ) for 'low dose', 'intermediate dose', and 'high dose' patients, respectively. When adjusting for confounders, including natriuretic peptides, hepatic, and renal function, the 'high dose' group was associated with increased waitlist mortality or urgent HT [adjusted hazard ratio (HR) 2.23, 1.33 to 3.73;  $P = 0.002$ ] and a six-fold higher risk of waitlist death (adjusted HR 6.18, 2.16 to 17.72;  $P < 0.001$ ) when compared with the 'low dose' group. 'Intermediate doses' were not significantly associated with these two outcomes in adjusted models ( $P > 0.05$ ).

**Conclusions** A 'high dose' of loop diuretics is strongly associated with residual congestion and is a predictor of outcome in patients awaiting HT despite adjustment for classical cardiorenal risk factors. This routine variable may be helpful for risk stratification of pre-HT patients.

**Keywords** Advanced heart failure; Diuretic; Heart transplant; Congestion; Cardiorenal syndrome

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## Introduction

Loop diuretics are the only group of drugs with a class I recommendation in heart failure (HF), for alleviating HF symptoms, despite a level C recommendation.<sup>1</sup> As advanced HF is characterized by the presence of severe cardiac dysfunction resulting in recurrent hospitalizations for congestive episodes,<sup>2</sup> it could lead to a progressive increase in daily diuretics dose particularly in patients with cardiorenal syndrome. Persisting fluid overload or increased diuretic requirement are criteria requiring referral to an advanced HF centre according to HF guidelines.<sup>1,3</sup> However, the dose of loop diuretic that should prompt a referral is not well defined according to the author of “‘I Need Help’—A Mnemonic to Aid Timely Referral in Advanced Heart Failure’.”<sup>3</sup>

Diuretic resistance has mainly been evaluated in acute settings and is dependent (albeit not exclusively) on transient phenomena such as impaired diuretic absorption, decreased renal blood flow, renal congestion, azotaemia, hypoalbuminaemia, and proteinuria.<sup>4</sup> Diuretic dose has been shown to be a strong prognostic marker in ambulatory patients with HF (e.g. in the EMPHASIS trial<sup>5</sup>). Yet, the prognostic value of daily doses of diuretics has not been extensively studied in ambulatory advanced HF. Indeed, the Seattle Heart Failure Model,<sup>6</sup> which incorporates the daily oral furosemide dose as a continuous variable, was developed based on the PRAISE study<sup>7</sup> published in 1996. In that study, the patients had an average New York Heart Association class of 3.6 and were predominantly treated with digoxin and angiotensin-converting enzyme inhibitors (ACEis). Similarly, Eshaghian *et al.* reported a correlation between diuretic dose and mortality in advanced HF, but their study included patients referred in the 1990s, of whom only 40% were receiving beta-blockers (BBs) and 26% were on mineralocorticoid receptor antagonists (MRAs).<sup>8</sup> Considering that pump dysfunction is a significant characteristic of advanced HF, the prognostic value of diuretic dose may be less significant in this specific patient population. Furthermore, the current era of life-saving HF treatments such as ACEis, BBs, MRAs, and, more recently, angiotensin receptor-neprilysin inhibitors may have diminished the predictive value of diuretic dose.

The aim of the present study was to assess the association between congestion and diuretic dose as well as the prognostic value of daily diuretic doses in contemporary ambulatory patients with advanced HF listed for heart transplantation (HT).

## Methods

### Study population

A total of 2089 patients (18 years or older) without previous solid organ transplants (heart, kidney, liver, or pancreas)

listed on the French national waiting list for HT between 1 January 2013 and 31 December 2019 were deemed eligible. Of the latter, 700 ambulatory patients without intravenous inotrope therapy, mechanical assistance, or dialysis at time of listing were included.

### Furosemide equivalent dose

Only two loop diuretics are available in France, furosemide and bumetanide. A 1 mg dose of bumetanide was considered equivalent to 40 mg of furosemide. Three groups were created according to furosemide dose. Diuretic dosages were categorized based on previous reports<sup>5</sup> and clinically relevant thresholds. A reference ‘low dose’ group was defined as patients with a daily furosemide dose of  $\leq 40$  mg, the ‘high dose’ furosemide group was defined as a daily dose of  $>250$  mg, and the ‘intermediate dose’ group corresponded to patients with a daily furosemide dose between 41 and 250 mg.

### Follow-up and study outcomes

The primary outcome was the combined criteria of the occurrence of waitlist death or urgent HT. Secondary outcomes were components of waitlist mortality, delisting for aggravation, urgent HT, or left ventricular assist device (LVAD) implantation.

Urgent HT was defined by the presence of intravenous inotrope or extracorporeal mechanical assistance at time of transplant.

Follow-up of all study events was maintained up to 12 August 2021. Patients were censored at elective HT or delisting for medical improvement.

### Data collection and variables

This national multicentre study was performed using the data from the French registry (CRISTAL). The registry is administered by the Ministry of Health (Agence de la Biomédecine), which prospectively collects data on all organ transplant candidates in France along with their outcomes. A description of the CRISTAL registry has previously been published.<sup>9</sup> Data were registered in CRISTAL at the time of patient listing and during follow-up as part of routine care. The study was conducted according to French legislation stipulating that anonymized research studies based on the national CRISTAL registry do not require institutional review board or ethics approval.

**Table 1** Patient characteristics, medication use, laboratory, and echocardiographic parameters at time of heart transplant listing according to quartile of furosemide dose

At listing time	Missing (%)	Whole cohort n = 700	Furosemide equivalent dose 0–40 mg (n = 202)	Furosemide equivalent dose 41–250 mg (n = 365)	Furosemide equivalent dose >250 mg (n = 133)	P-value
<b>Demographic data</b>						
Age, years	0 (0)	55 (47 to 61)	54 (41 to 60)	56 (47 to 61)	56 (49 to 62)	0.011
Male sex, n (%)	0 (0)	491 (70)	143 (71)	253 (69)	95 (71)	0.876
<b>Medical history</b>						
Hypertension, n (%)	19 (3)	151 (22)	38 (19)	84 (23)	29 (22)	0.494
Diabetes, n (%)	0 (0)	111 (16)	17 (8)	62 (17)	32 (24)	<0.001
Smoking history, n (%)	16 (2)	398 (55)	104 (53)	204 (57)	70 (54)	0.617
Heart failure duration, days	234 (33)	3202 (688 to 6295)	3543 (993 to 7175)	3273 (650 to 6166)	2386 (600 to 5520)	0.350
<b>Heart failure aetiology, n (%)</b>						
Ischaemic, n (%)	0 (0)	214 (31)	60 (30)	114 (31)	40 (30)	0.969
Dilated cardiomyopathy, n (%)	0 (0)	298 (43)	86 (43)	155 (42)	57 (43)	
Hypertrophic cardiomyopathy	0 (0)	77 (11)	24 (12)	41 (11)	12 (9)	
Furosemide equivalent dose, mg	0 (0)	100 (40 to 250)	40 (20 to 40)	120 (80 to 200)	500 (375 to 750)	<0.001
CRT, n (%)	37 (5)	237 (34)	63 (32)	125 (34)	49 (39)	0.468
ICD, n (%)	6 (1)	596 (85)	168 (83)	320 (88)	108 (82)	0.058
<b>Biological, laboratory data</b>						
Creatinine, µmol/L	1 (0)	106 (87 to 131)	98 (83 to 120)	109 (89 to 136)	112 (89 to 137)	<0.001
eGFR, mL/min/1.73 m <sup>2</sup>	1 (0)	62.2 (48.5 to 81.3)	70.5 (54.1 to 85.3)	60.4 (45.7 to 77.6)	59.6 (46.3 to 79.4)	<0.001
Naatraemia, mmol/L	2 (0)	138 (136 to 140)	139 (137 to 140)	137 (135 to 139)	137 (133 to 138)	<0.001
Total bilirubin, µmol/L	25 (4)	13 (9 to 19)	12 (8 to 17)	13 (9 to 19)	14 (10 to 22)	0.002
BNP, ng/L	480 (69)	574 (332 to 1002)	513 (280 to 983)	620 (353 to 1074)	603 (368 to 1052)	0.294
NT-proBNP, ng/L	264 (38)	2290 (1297 to 4198)	1703 (946 to 2577)	2553 (1482 to 4734)	2769 (1740 to 4993)	<0.001
BNP/NT-proBNP Z-score	59 (8)	-0.30 (-0.54 to 0.15)	-0.44 (-0.61 to -0.11)	-0.24 (-0.50 to 0.26)	-0.22 (-0.45 to 0.26)	<0.001
<b>Echocardiography</b>						
LVEF, %	13 (2)	25 (20 to 33)	25 (20 to 35)	25 (20 to 30)	25 (20 to 37)	0.633
LVEDD, mm	146 (21)	64 (55 to 73)	65 (56 to 75)	64 (56 to 73)	62 (53 to 70)	0.129

BNP, B-type natriuretic peptide; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter-defibrillator; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide. Values are expressed as median (interquartile<sub>25–75%</sub>) or n (%).

## Statistical analysis

All results were first summarized overall and subsequently stratified according to the three groups of furosemide equivalent doses.

Baseline continuous variables are expressed as medians with interquartile 25–75% (IQ<sub>25–75%</sub>) range or as means ( $\pm$  standard deviation). Comparisons of continuous variables were carried out using the Kruskal–Wallis test and *t*-test as required. Categorical variables are expressed as frequencies (percentages) and compared using the  $\chi^2$  test. The two-tailed significance level was set at  $P < 0.05$ . Due to the use of B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) depending on the collection year and centres, a combined BNP or NT-proBNP Z-score value was created.

Survival probabilities are graphically represented as Kaplan–Meier curves. Cox proportional hazard regression was used to examine the association between furosemide equivalent dose groups and primary and secondary outcomes. Competing risk on HT waitlist (non-urgent HT, delisting for aggravation, urgent HT, or LVAD implantation, as appropriate) was taken into account by using cause-specific hazard function introduced by Fine and Gray.<sup>10</sup> To further assess the added value of the diuretic dose on top of other congestion variables, we constructed a multivariable model adjusted for age, gender, estimated glomerular filtration rate (eGFR), bilirubin, and BNP/NT-proBNP Z-score.

All analyses were performed using SPSS Version 27.0.1.0 (IBM SPSS Statistics for Windows, NY: IBM Corp) and R software Version 4.1.2 (R Foundation for Statistical Computing).

## Results

### Baseline characteristics

Among the 700 studied patients, median age was 55 (47–61) years and 70% were men; 43% had dilated cardiomyopathy and 31% had ischaemic cardiomyopathy. The population presented a low level of comorbidities (22% hypertension and 16% diabetes). Median HF duration was 8.7 years, and ejection fraction was 25 (20–33)%. Median eGFR and NT-proBNP were 62.2 (48.5–81.3) mL/min/1.73 m<sup>2</sup> and 2290 (1297–4198) ng/L, respectively (Table 1). Overall diuretic dose was 100 (40–250) mg.

### Association between diuretic dose and congestion variables

NT-proBNP ( $P < 0.001$ ), creatinine ( $P < 0.001$ ), total bilirubin levels ( $P = 0.002$ ), pulmonary artery pressures ( $P < 0.001$ ),

**Table 2** Clinical, functional, and haemodynamic variables at time of heart transplant listing

At listing time	Missing (%)	Whole cohort <i>n</i> = 700	Furosemide equivalent dose 0–40 mg ( <i>n</i> = 202)	Furosemide equivalent dose 41–250 mg ( <i>n</i> = 365)	Furosemide equivalent dose >250 mg ( <i>n</i> = 133)	<i>P</i> -value
Time from RHC to transplant listing, days	25 (4)	66 (28–124)	66 (27–135)	68 (28–124)	67 (32–109)	0.920
Systolic PAP, mmHg	29 (4)	41 (33–52)	36 (28–47)	44 (35–54)	45 (38–54)	<0.001
Mean PAP, mmHg	21 (3)	28 (22–35)	25 (18–33)	29 (23–36)	30 (25–37)	<0.001
Diastolic PAP, mmHg	32 (5)	20 (15–25)	17 (12–23)	20 (15–26)	22 (17–26)	<0.001
PCWP, mmHg	97 (14)	20 (14–25)	17 (11–24)	21 (15–26)	22 (17–26)	<0.001
Cl, L/min/m <sup>2</sup>	41 (6)	2.1 (1.7–2.5)	2.1 (1.8–2.4)	2.0 (1.7–2.5)	2.1 (1.7–2.5)	0.663
PVR, Wood units	34 (5)	2.1 (1.5–3.0)	2.0 (1.4–2.6)	2.2 (1.5–3.0)	2.0 (1.4–3.0)	0.028
<b>Clinical and functional variables</b>						
Systolic blood pressure, mmHg	66 (9)	102 (94–112)	104 (96–114)	102 (94–112)	102 (93–112)	0.222
Diastolic blood pressure, mmHg	65 (9)	67 (60–74)	65 (60–74)	67 (60–74)	67 (60–74)	0.778
Heart rate, b.p.m.	58 (8)	70 (61–79)	65 (60–74)	70 (62–80)	72 (65–81)	<0.001
VO <sub>2</sub> max	185 (26)	12.5 (10.2–15.0)	13.3 (11.0–16.0)	12.2 (10.2–14.8)	11.4 (9.0–14.0)	<0.001
NYHA I	3 (0)	3 (0)	2 (1)	1 (0)	0	0.301
NYHA II	69 (10)	69 (10)	26 (13)	28 (8)	15 (11)	
NYHA III	521 (75)	521 (75)	148 (73)	275 (75)	98 (74)	
NYHA IV	104 (15)	104 (15)	26 (13)	59 (16)	19 (14)	

b.p.m., beats per minute; Cl, cardiac index; NYHA, New York Heart Association; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RHC, right heart catheterization; VO<sub>2</sub> max, maximal oxygen uptake.

pulmonary capillary wedge pressure (PCWP) ( $P < 0.001$ ), and heart rate ( $P < 0.001$ ) gradually increased with diuretic dose (Table 2). Conversely, natraemia, eGFR, and peak  $VO_2$  decreased with diuretic dose ( $P < 0.001$  for all).

## Outcomes on heart transplant waitlist

During a mean follow-up of 278 days, there were 158 composite outcomes of waitlist death or urgent HT: 47 waitlist deaths and 111 urgent HTs.

Overall, 'high dose' patients had the worst prognosis whereas 'low dose' patients experienced the best outcome. At 12 months, waitlist mortality occurred in 2 (1.0%), 19 (5.2%), and 13 (9.8%) patients for 'low dose', 'intermediate dose', and 'high dose' profiles, respectively (log-rank  $P < 0.001$ ; Figure 1). At 12 months, waitlist death or urgent HT occurred in 15 (7.4%), 70 (19.2%), and 34 (25.6%) patients for 'low dose', 'intermediate dose', and 'high dose' patients, respectively (log-rank  $P = 0.001$ ; Figure 1).

## Predictors of primary outcome (waitlist mortality or urgent heart transplantation)

In raw analyses, significant associations with primary outcome were observed for 'intermediate dose' and 'high dose' patients (Table 3). These associations remained significant after adjustment only in 'high dose' patients with a 48% increase for the 'intermediate dose' group [hazard ratio (HR), 95% confidence interval (CI), 1.48, 0.95 to 2.31;  $P = 0.081$ ]

whereas 'high dose' diuretics were associated with a two-fold increase in this outcome (HR 2.23, 1.33 to 3.73;  $P = 0.002$ ).

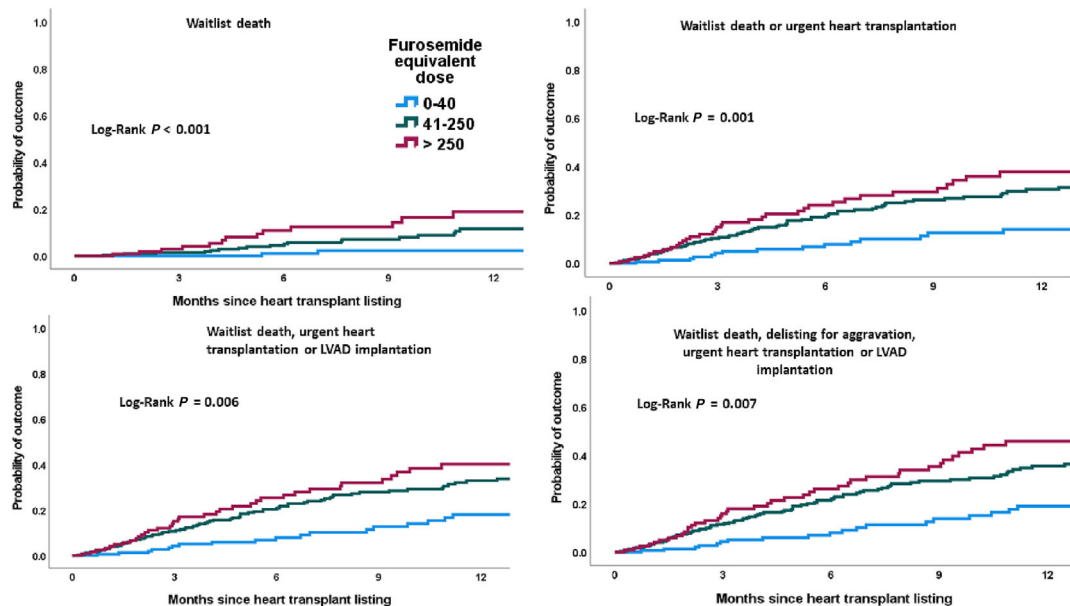
## Predictors of waitlist mortality

In crude analyses, significant associations with waitlist death were observed only for 'high dose' patients (Table 3). A 'high dose' was associated with a six-fold increase in this outcome (HR 5.61, 2.11 to 14.90;  $P < 0.001$ ). In multivariable models adjusting for congestion variables (including total bilirubin and natriuretic peptides), association of 'high dose' with waitlist death was stronger (HR 6.18, 2.16 to 17.72;  $P < 0.001$ ). The intermediate dose was not significantly associated with waitlist death after adjustment (Table 3).

## Predictors of other outcomes on heart transplant waitlist

'High dose' profiles were also associated with the combined outcome of waitlist mortality, urgent HT, or LVAD implantation and with the combined outcome of waitlist mortality, delisting for aggravation, urgent HT, or LVAD implantation in crude analysis (HR 2.06, 1.36 to 3.11;  $P < 0.001$  and HR 2.02, 1.39 to 2.93;  $P < 0.001$ , respectively) and after adjustment including congestion parameters (HR 1.97, 1.23 to 3.15;  $P = 0.004$  and HR 1.99, 1.30 to 3.05;  $P = 0.001$ , respectively).

**Figure 1** Likelihood of different outcomes according to quartiles of furosemide equivalent dose. LVAD, left ventricular assist device.



**Table 3** Unadjusted and adjusted association of furosemide dose groups with outcomes

	Furosemide equivalent dose 0–40 mg (n = 202)	Furosemide equivalent dose 41–250 mg (n = 365)	Furosemide equivalent dose >250 mg (n = 133)
<b>Univariate model</b>			
Waitlist mortality <sup>a</sup>	Ref	2.48 (0.95–6.48) <i>P</i> = 0.064	<b>5.61 (2.11–14.90)</b> <i>P</i> < 0.001
Waitlist mortality or urgent heart transplantation <sup>b</sup>	Ref	<b>1.66 (1.10–2.51)</b> <i>P</i> = 0.017	<b>2.45 (1.56–3.87)</b> <i>P</i> < 0.001
Waitlist mortality, urgent heart transplantation, or LVAD implantation <sup>c</sup>	Ref	<b>1.45 (1.00–2.09)</b> <i>P</i> = 0.047	<b>2.06 (1.36–3.11)</b> <i>P</i> < 0.001
Waitlist mortality, delisting for aggravation, urgent heart transplantation, or LVAD implantation <sup>d</sup>	Ref	1.34 (0.96–1.87) <i>P</i> = 0.084	<b>2.02 (1.39–2.93)</b> <i>P</i> < 0.001
<b>Adjusted model for age, gender, estimated glomerular filtration rate, BNP/NT-proBNP Z-score, and total bilirubin</b>			
Waitlist mortality <sup>a</sup>	Ref	2.45 (0.87–6.92) <i>P</i> = 0.091	<b>6.18 (2.16–17.72)</b> <i>P</i> < 0.001
Waitlist mortality or urgent heart transplantation <sup>b</sup>	Ref	1.48 (0.95–2.31) <i>P</i> = 0.081	<b>2.23 (1.33–3.73)</b> <i>P</i> = 0.002
Waitlist mortality, urgent heart transplantation, or LVAD implantation <sup>c</sup>	Ref	1.35 (0.91–2.01) <i>P</i> = 0.130	<b>1.97 (1.23–3.15)</b> <i>P</i> = 0.004
Waitlist mortality, delisting for aggravation, urgent heart transplantation, or LVAD implantation <sup>d</sup>	Ref	1.29 (0.90–1.86) <i>P</i> = 0.170	<b>1.99 (1.30–3.05)</b> <i>P</i> = 0.001

LVAD, left ventricular assist device.

Bolded values are used to highlight significant results and facilitate reading. Bold highlighting can be removed.

<sup>a</sup>The Fine–Gray subdistribution hazard model with non-urgent heart transplantation, delisting for aggravation, urgent heart transplantation, or LVAD implantation as a competing risk event.

<sup>b</sup>The Fine–Gray subdistribution hazard model with non-urgent heart transplantation, delisting for aggravation, or LVAD implantation as a competing risk event.

<sup>c</sup>The Fine–Gray subdistribution hazard model with non-urgent heart transplantation or delisting for aggravation as a competing risk event.

<sup>d</sup>The Fine–Gray subdistribution hazard model with non-urgent heart transplantation as a competing risk event.

## Sensitivity analysis

The quartile or modified (rounded to 40 mg multiple) quartile analyses revealed a non-significant rise in risk for Quartiles 2 and 3. However, it was only the quartile representing a daily furosemide dose exceeding 250 mg that exhibited a significant association with the outcomes (Supporting Information, *Table S1*).

When dichotomized ( $\leq 20$  and  $> 20$  mmHg), PCWP was added in addition to Model 2, and the results remained statistically significant in the ‘high dose’ group (*P*-value < 0.05 for all), with no significant interaction between diuretic dose and dichotomized PCWP (Supporting Information, *Table S2*).

## Discussion

In the present study, we report the prognostic value of high-dose loop diuretics in a cohort of patients with advanced HF listed for HT. We found a significant and sizeable association between diuretic dose, haemodynamic congestion status, and prognosis on the waitlist in this specific population. This suggests that congestion (and its treatment) remains an important issue in advanced HF. Diuretic dose should be perceived as an important risk stratifier in patients awaiting HT.

## Prognosis of high diuretic dose

The effects of diuretics in chronic HF on morbidity and mortality have yet to be studied in large prospective randomized controlled trials. However, many observational studies have found an association between diuretic prescription and outcome,<sup>5,11–13</sup> indicating that loop diuretics are powerful prognostic markers. In the EMPHASIS trial, loop diuretic use at baseline was associated with the risk of cardiovascular death or HF hospitalization in a stepwise manner, with a doubling of the risk for patients receiving between 1 and 40 mg of furosemide and a three-fold increase for those receiving more than 40 mg.<sup>5</sup> In a post hoc analysis of Studies Of Left Ventricular Dysfunction (SOLVD), loop diuretic treatment was associated with a greater risk of hospitalization or death [risk ratio (RR) = 1.31, 1.09 to 1.57] compared with patients without diuretics.<sup>13</sup> In a propensity match study, Ahmed *et al.* found a 31% increased risk of death in patients with diuretics.<sup>12</sup> The relationship between loop diuretic dose and prognosis was investigated more recently in two different studies using propensity score.<sup>14,15</sup> Dini *et al.* showed that the risk of death increased linearly across quartiles of furosemide dose in a population of HF outpatients (HR 1.38, 95% CI 1.14 to 1.68). The median furosemide dose was 25 mg reflecting a low-risk population. In this latter study, a daily dose of 50 mg was identified as the best threshold value to predict a high risk of death within 3 years. This threshold appears concordant with the threshold set in our study

between 'low dose' patients (furosemide equivalent dose  $\leq 40$  mg) vs. 'intermediate dose' and 'high dose' patients. Similarly, in a population of symptomatic HF of ischaemic aetiology, composite outcomes of cardiovascular death or hospitalization associated with low-, medium-, and high-dose groups were 1.71 (1.41–2.06), 1.99 (1.50–2.64), and 2.94 (1.95–4.41), respectively.<sup>15</sup> In our study, in the specific population of patients awaiting HT, the 'high dose' group was significantly associated with a six-fold increased risk of waitlist death and a two-fold risk of a composite outcome of waitlist death or urgent HT after adjustment for confounding factors. Loop diuretic dose consequently appears as a strong risk marker of outcome in a wide range of HF patients as it is still sizably associated with outcome in extreme profiles such as patients awaiting HT.

### Diuretic dose and congestion in chronic settings

Diuretics have a class I recommendation to alleviate signs and symptoms of congestion.<sup>1</sup> The optimal diuretic dose in chronic settings is unknown and in a recent statement from the Heart Failure Association of the European Society of Cardiology, it is advised to use to the lowest possible dose of diuretics with a need for individual adjustment.<sup>16</sup> In the latest guidelines, the objective of diuretics is to obtain euvolaemia, despite the absence of 'consensual definition'.<sup>1</sup> Indeed, in a recent meta-analysis including 13 studies and over 8000 patients, patients who achieved euvolaemia had a better prognosis even in the presence of worsening renal function (WRF) than those without WRF or decongestion.<sup>17</sup> Our study provides further, novel findings on the relationship between loop diuretic dose and decongestion. Interestingly, congestion increased concomitantly with diuretic dose. Indeed, pulmonary artery pressure, PCWP, and NT-proBNP were progressively higher from the 'low dose' group to the 'high dose' group, hence reflecting the inability of loop diuretics to reach euvolaemia in certain patients in a 'real life' cohort of severe patients awaiting HT. Many strategies have been proposed to obtain euvolaemia in congestive patients under loop diuretics, including an increase in routine loop diuretic dosage, use of adjunct continuous or bolus intravenous diuretics, and addition of thiazide,<sup>18,19</sup> acetazolamide,<sup>20</sup> or tolvaptan.<sup>21</sup> All these combinations were associated with increased natriuresis and diuresis in acute settings, although none of these strategies were assessed in chronic HF. In a recent position statement paper, experts indicated that it may be necessary to increase the treatment dose after an acute decompensation for patients already on loop diuretics at admission.<sup>16</sup> However, in the ASCEND-HF trial, change in dosage at discharge was not associated with improved outcomes compared with no dose change (adjusted odds ratio 0.92, 0.79 to 1.07).<sup>22</sup>

### Risk marker or risk factor

Although the design and purpose of this study were not to assess the toxicity of loop diuretics, a 'high dose' defined by a daily dose of furosemide equivalent  $> 250$  mg was associated with outcomes even after adjusting for other severity parameters. This threshold is close to the experts' definition of diuretic resistance (160 mg twice daily of furosemide or equivalent).<sup>23</sup> Unlike a previous study published by Pellicori *et al.* in a less ill population,<sup>24</sup> we found that diuretic dose was independently associated with outcome even after adjusting for natriuretic peptides, hepatic, and renal functions.

Pathophysiological hypotheses have recently emerged to better understand the role of diuretics in cardiorenal interaction. Indeed, it has been shown that the use of diuretics is associated with a decrease in the excretion of trimethylamine N-oxide causing renal and plasma accumulation.<sup>25</sup> This uraemic toxin is associated with an increased risk for all-cause mortality at 5 years in patients with chronic kidney disease (CKD) and in normal populations<sup>26</sup> as well as the risk of death and/or rehospitalization for HF in patients hospitalized for acute HF.<sup>27</sup> Moreover, all diuretic classes lead to a sustained increase in plasma renin activity with a gradual effect related to their natriuretic and diuretic efficacy (loop diuretics  $>$  thiazide  $>$  MRA).<sup>28</sup> This adaptive compensatory system could potentially participate in the long-term progression of HF and CKD, particularly in advanced HF, when patients are intolerant to drugs blocking the renin-angiotensin-aldosterone system (or treated with a suboptimal dose).

Diuretic dose thus appears to be both a risk factor for the cardiorenal syndrome<sup>29</sup> and a risk marker. Indeed, it integrates cardiovascular risk factors (hypertension and diabetes mellitus), severity of cardiac and renal disease (higher NT-proBNP and lower eGFR and peak  $\text{VO}_2$ ), and congestive state (residual congestion despite high diuretic dose). Nevertheless, the fact that diuretics maintained a significant association with prognosis even after adjusting for these factors suggests that the prognostic value of diuretic dose extends beyond their influence.

### Clinical implications

A 'high diuretic dose' identifies patients with advanced HF featuring a more congestive profile. Such profile may be due to the presence of residual congestion,<sup>30,31</sup> which is associated with worse outcome, rather than the higher diuretic dose itself. Indeed, residual congestion has been shown to be related to worse outcome throughout the patient journey<sup>31</sup> and should consequently be repeatedly evaluated, possibly using ultrasound approaches,<sup>30–32</sup> to adapt congestion treatment. Using wireless pulmonary artery haemodynamic monitoring<sup>33</sup> or ultrasound imaging of inferior vena



cava or renal veins could be of particular interest in this context.<sup>32</sup> Future studies investigating the effects of diuretic 'optimization' based on more advanced assessments of congestion are needed to better ascertain the long-term prognostic effects of loop diuretic exposure. Optimal dosage, the possibility of a decrease in diuretic dose and the use of thiazide or acetazolamide as co-diuretics, in chronic settings should be prospectively assessed in future studies.

Diuretic dose appears as an integrator of cardiorenal risk factors and a strong prognostic marker in patients with severe HF. A furosemide equivalent dose > 250 mg may be propitiously considered as a red flag for adverse cardiovascular outcomes and should encourage close monitoring into tertiary centre. This parameter could also be useful to take into account to optimize access to transplantation and/or the timing of mechanical cardiac support implantation.

## Limitations

The present study was an observational study and loop diuretic dose was only assessed at time of listing for HT as were the proper catheter and biological parameter assessments. First, we noted a median interval of 2 months between right heart catheterization and listing for HT. Given that this study primarily involved outpatients, the probability of a substantial alteration in diuretic dose within this timeframe is minimal. Furthermore, it is important to note that diuretic dose is not a criterion for the graft allocation score, thus ruling out the possibility of adjusting the dose to enhance priority for HT. Second, the inclusion of renal function evolution over time, stratified by furosemide dose, would have been valuable in determining whether patients with higher diuretic doses are at an elevated risk for renal complications. Third, while this is a nationwide study, given that HT implementation differs worldwide, association of diuretic dose with outcome may vary according to geographical context.

## Conclusions

Diuretic dose is a strong predictor of outcome in advanced HF. High-dose furosemide (>250 mg) is associated with waitlist death and a composite of waitlist death or urgent transplantation in ambulatory advanced HF patients awaiting transplantation.

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## Conflict of interest

G.B. reports consulting fees from AstraZeneca, Boehringer-Ingelheim, and Abbott, outside the submitted work. G.C. reports personal fees from Institut de France and Fullbright, outside the submitted work. R.D., C.D., C.G., and J.G. have nothing to disclose. P.G. reports consulting fees or honoraria from Air Liquide Santé International, Abiomed, Amomed, and Abbott and support from Pfizer, outside the submitted work. A.B. has nothing to disclose. M.M. reports honoraria from LFB/Hemosims Cardio, outside the submitted work. E.E., R. G., C.C., K.N., S.P., and V.G. have nothing to disclose. F.B. reports consulting fees or honoraria from Jansen & Jansen, Boehringer, AstraZeneca, and Pfizer, outside the submitted work. E.V., N.O., S.G., and K.B. have nothing to disclose. L.S. reports personal fees or honoraria from Novartis, Vifor, and AstraZeneca, outside the submitted work. K.D. has nothing to disclose. N.G. reports personal fees from AstraZeneca, Bayer, Boehringer, Novartis, and Vifor, outside the submitted work. M.F.S., P.F., and C.A. have nothing to disclose.

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## Supporting information

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

**Table S1:** Primary outcome according to quartile and modified quartile analysis.

**Table S2:** Adjusted association of furosemide dose groups with outcomes.

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