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ORIGINAL ARTICLE

Cardiac Dysfunction, Congestion and Loop Diuretics: their Relationship to Prognosis in Heart Failure

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Abstract
Background Diuretics are the mainstay of treatment for congestion but concerns exist that they adversely affect prognosis. We explored whether the relationship between loop diuretic use and outcome is explained by the underlying severity of congestion amongst patients referred with suspected heart failure.
Method and Results Of 1190 patients, 712 had a left ventricular ejection fraction (LVEF) ≤50 %, 267 had LVEF >50 % with raised plasma NTproBNP (>400 ng/L) and 211 had LVEF >50 % with NTproBNP ≤400 ng/L; respectively, 72 %, 68 % and 37 % of these groups were treated with loop diuretics including 28 %, 29 % and 10 % in doses ≥80 mg furosemide equivalent/day. Compared to patients with cardiac dysfunction (either LVEF ≤50 % or NT-proBNP >400 ng/L) but not taking a loop diuretic, those taking a loop diuretic were older and had more clinical evidence of congestion, renal dysfunction, anaemia and hyponatraemia. During a median follow-up of 934 (IQR: 513–1425) days, 450 patients were hospitalized for HF or died. Patients prescribed loop diuretics had a worse outcome. However, in multi-variable models, clinical, echocardiographic (inferior vena cava diameter), and biochemical (NTproBNP) measures of congestion were strongly associated with an adverse outcome but not the use, or dose, of loop diuretics.
Conclusions Prescription of loop diuretics identifies patients with more advanced features of heart failure and congestion, which may account for their worse prognosis. Further research is needed to clarify the relationship between loop diuretic agents and outcome; imaging and biochemical measures of congestion might be better guides to diuretic dose than symptoms or clinical signs.

Keywords Loop diuretic · Heart failure · Congestion · Prognosis

Introduction

Amongst patients with heart failure, clinical [1, 2], echocardiographic [3–5], or biochemical [6–8] evidence of congestion is associated with an increased rate of hospitalization and higher mortality. Diuretics, especially high-ceiling diuretics acting on the Loop of Henle, are the mainstay of treatment for congestion in order to relieve symptoms and signs, but may activate the renin-angiotensin-aldosterone and sympathetic nervous systems which is thought to contribute to the progression and adverse outcome of heart failure [9, 10].

However, there is a remarkable paucity of data on how diuretics should be best used to improve outcomes in heart failure. Conventional clinical practice is to use sufficient doses to relieve symptoms and signs of congestion. Once established, there is often no attempt to stop diuretic therapy to find out whether chronic daily dosing is required and there is often reluctance to prescribe higher doses to patients with more advanced heart failure [11]. No randomised study has ever demonstrated whether loop diuretics alter mortality in patients with chronic heart failure although clearly they must

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be life-saving for patients with extreme congestion. There is a strong association between the use of loop diuretic agents, especially in higher doses, and worse outcome [12, 13] but this may merely be a barometer of congestion [14]. The observed relationship between diuretic dose, severity of congestion and outcome deserves further investigation.

Accordingly, we compared the relation between diuretic dose, congestion and outcome in patients with chronic heart failure (either with reduced or normal left ventricular ejection fraction), using three different methods for assessing congestion: a clinical congestion scale; a biochemical measurement (natriuretic peptides); and imaging (inferior vena cava diameter).

Methods

Study Population

Out-patients attending a community heart failure clinic with suspected or confirmed heart failure (HF) between November 2008 and May 2013 were enrolled and followed for at least nine months. HF was defined as symptoms or signs of HF, supported by objective evidence of cardiac dysfunction: either a left ventricular ejection fraction (LVEF) ≤50 % at echocardiography or raised plasma concentration of amino-terminal pro-brain natriuretic peptide (NT-proBNP) (>400 ng/l) [15]. Patients were grouped as: those without substantial evidence of cardiac dysfunction (NTproBNP ≤400 ng/l and LVEF >50 %) and, for patients with HF, by the daily dose of loop diuretics taken (none, furosemide or equivalent ≤40 mg/day, >40 to 80 mg/day, > 80 mg/day). Those without objective evidence of cardiac dysfunction were further divided into patients with NT-proBNP <125 ng/l or NTproBNP between 125 ng/l and 400 ng/l [16].

Patients provided a detailed clinical history and had blood tests (including haematology, biochemistry profile and NT-proBNP), ECGs and echocardiograms on the same day. Ischaemic heart disease was defined as a previous history of myocardial infarction or angiographic evidence of significant coronary artery disease (>70 % on epicardial vessels). Diagnoses of hypertension and diabetes were based on prior medical history from medical records obtained from the general practitioner or from information collected at clinical visits. Patients in atrial fibrillation or atrial flutter were grouped as "AF".

A congestion score was constructed, based on lung auscultation (normal, presence of basal, mid-zone or diffuse crepitations), JVP (not visible, raised 1–4 cm, raised to earlobe), peripheral oedema (none, ankles, below or above knees) and liver examination (not palpable, palpable) with one point attributed for each degree of severity and a total possible score of nine [17].

Echocardiographic Measurements

Echocardiography was performed by experienced operators using a Vivid Five, Seven or Nine (GE Health Care, UK) system. Echocardiograms were reviewed by a single operator (PP) blinded to other patient details. LVEF was measured using Simpson's biplane method. LA volume was indexed to body surface area (LAVI). Tricuspid annular plane systolic excursion (TAPSE) was used to assess RV systolic function. The trans-tricuspid systolic gradient was also measured when a suitable Doppler signal was available. With the patient supine, the maximum IVC diameter during the respiratory cycle was measured approximately three centimetres before merger with the right atrium.

Congestion

We used three indices as measures of congestion.

1) Clinical congestion score: Patients with a score of 1 or 2 out of a possible score of nine were defined as mildly congested; those with a score of 3 or more were defined as severely congested [17]
2) Echocardiographic congestion: we used the size of the inferior vena cava to define three groups. Patients with an IVC ≤16 mm were not considered to be congested, those with an IVC 17–20 mm were defined as mildly congested, those with an IVC ≥21 mm were considered severely congested. [18].
3) Biochemical congestion: we used NTproBNP to define three groups, based on current and previous guidelines (Not congested: NTproBNP < 125 ng/l; Possible congestion: 125–400 ng/l; congestion: NTproBNP >400 ng/l; (15, 16)), or by classifying patients according to NTproBNP terciles (tercile 1, least congested; tercile 2: intermediate congestion; tercile 3: most congested).

Data regarding hospitalizations and death were collected from the hospital's electronic systems, supplemented by information from patients and their family doctors. The hospital is the only one in the region offering acute medical services. Outcome was censored at the point of last medical contact in either primary or secondary care. Vital status was confirmed from national records. The primary outcome was a composite of admission for worsening HF or death from all causes. Admission for HF was defined as an admission for worsening of relevant symptoms resulting in substantial intensification of treatment for HF.

The study conforms to the principles outlined in the Declaration of Helsinki and was approved by relevant ethical bodies. All subjects gave their written informed consent for their data to be used at their first clinical visit.

Statistical Methods

Categorical data are presented as number and percentages; normally distributed continuous data as mean ± standard deviation (SD); non-normally distributed variables as median and interquartile range (IQR).

Student t-test or Mann Whitney U test, and one-way analysis of variance and Kruskal-Wallis tests were used to compare continuous variables between groups. Chi-squared tests were used for categorical variables. Associations between variables and prognosis were assessed using Cox proportional hazards models. Multivariable models were tested by progressively excluding the stronger variables associated with outcome in univariable analysis. Kaplan-Meier curves with the log-rank statistic were used to illustrate outcome. Analyses were performed using SPSS and Stata software, and a 2-sided P value <0.05 was considered statistically significant.

Results

Patient Characteristics

Data for the overall population studied (n = 1190) are shown in Table 1; 979 patients (82 %) had evidence of cardiac dysfunction and were considered to have heart failure, whilst 211 (18 %) fulfilled neither imaging nor biomarker criteria for cardiac dysfunction and were considered not to have heart failure.

The proportion of patients with or without heart failure taking loop diuretics was 71 % and 37 % respectively. Patients with heart failure taking loop diuretics had more evidence of congestion, especially those on higher doses. Patients taking higher doses of loop diuretics were also older, more likely to have diabetes, had worse renal function and lower systolic blood pressure, haemoglobin and serum sodium concentration. They also had lower left ventricular ejection fraction, larger left atrial volume, worse right ventricular systolic function, higher systolic pulmonary pressure and greater IVC diameter (Table 1).

For patients who did not fulfil criteria for heart failure whose plasma NTproBNP was 125–400 ng/l, those who were taking loop diuretics had more symptoms and signs of congestion, worse renal function and higher heart rate compared to those who were not taking loop diuretics, but cardiac structure and function on echocardiography were similar (Table 1 supplementary).

Amongst patients with NTproBNP <125 ng/l, those on loop diuretics were more likely to have IHD, had more symptoms and slightly higher natriuretic peptides than those who were not taking loop diuretics but no echocardiographic differences were observed between those on loop diuretics and those who were not.

Loop Diuretics and Outcome

The entire cohort was followed up for a median of 934 (IQR: 513–1425) days. There were 450 events (205 individuals were admitted to hospital with heart failure and 245 died). There was a dose-response relation between daily dose of diuretic and outcome. Compared to patients with HF not taking loop diuretics, those treated with higher doses of loop diuretics (>80 mg furosemide per day or equivalent) had a markedly greater risk of an adverse event (HR: 3.50, 95 % CI: 2.49–4.93) (Kaplan-Meier curve, Fig. 1).

The relationship between loop diuretic use and outcome persisted in patients with heart failure with LVEF below and above 50 % (Figs. 2 and 3).

Increasing clinical, echocardiographic or biochemical evidence of congestion were the major predictors of adverse outcome in patients with HF, rather than increasing doses of diuretics. For patients with heart failure who were not congested, the 1-year outcome was similar regardless of the amount of loop diuretic prescribed, whilst those patients with more evidence of congestion had a worse outcome for any given dose of diuretic. Patients with more severe congestion despite higher doses of loop diuretic agents had the worst outcome (Table 2).

In univariable Cox regression analysis (Table 3), clinical, biochemical and echocardiographic measures of congestion, as well as diuretic dose, predicted adverse outcome.

In multivariable analysis, increases in all three indices of congestion (clinical score, IVC diameter and NT-proBNP) were independent predictors of a worse prognosis (Table 3). By contrast, diuretic dose was not independently associated with outcome and it is only when the six most powerful predictors are removed from the multivariable analysis that dose of diuretic enters the model (Table 4).

Discussion

Prescription of diuretics remains, to a large extent, subjective, relatively evidence-free and therefore a focus for opinion-based medicine [11]. There is a strong relationship between use and dose of loop diuretics and prognosis in patients with chronic heart failure with either reduced or normal LVEF, but this analysis suggests that the relationship reflects the link between diuretic dose and severity of congestion, whether assessed clinically, by echocardiography, or using natriuretic peptides. After adjusting for the severity of congestion, the dose of diuretic taken did not predict outcome. However, diuretic dose can usually be readily obtained from the patient-record and is therefore a practical method of identifying those at greater risk of an adverse outcome in surveys, audits and trials.

Table 1 Characteristics of patients by diagnosis and by amount of loop diuretic taken (only for those with HF)

Variable	Missing	No HF NTproBNP < 125 ng/l	No HF NTproBNP 125-400 ng/l	HF no loop diuretics	HF 10 to 40 mg Furosemide	HF > 40 to 80 mg Furosemide	HF > 80 Furosemide	P between HF groups
Patients – no.	NA	102	109	283	411	177	108	NA
Demographic								
Age - years	0	65 (51–71)	72 (66–79)	73 (64–80)	75 (69–81)	75 (67–81)	77 (67–82)	0.013
Sex (male) – no. (%)	0	62 (61)	61 (56)	209 (74)	279 (68)	126 (76)	82 (76)	0.227
IHD – no. (%)	0	23 (22)	40 (36)	176 (62)	257 (63)	109 (62)	81 (75)	0.078
DM– no. (%)	0	39 (38)	44 (40)	67 (24)	115 (28)	69 (39)	50 (46)	<0.001
HTN– no. (%)	0	65 (64)	84 (77)	170 (60)	216 (53)	85 (48)	50 (46)	0.024
COPD– no. (%)	0	12 (12)	17 (16)	21 (7)	47 (11)	24 (14)	15 (14)	0.116
NYHA class I– no. (%)		61 (60)	46 (42)	87 (31)	63 (15)	14 (8)	3 (3)	<0.001
NYHA class II– no. (%)	0	30 (29)	34 (31)	150 (53)	208 (51)	95 (54)	37 (34)	
NYHA class III– no. (%)		11(11)	29 (27)	46 (16)	140 (34)	68 (38)	68 (63)	
Congested– no. (%)	0	7 (7)	9 (8)	17 (6)	60 (15)	34 (19)	37 (34)	<0.001
AF– no. (%)	0	1 (1)	8 (7)	81 (29)	150 (37)	74 (41)	59 (55)	<0.001
BMI- kg/m^2	0	30.6 (5.6)	32.1 (6.9)	28.7 (5.3)	28.3 (5.8)	29.5 (6.2)	29.6 (6.0)	0.198
SBP – mmHg	0	136 (20)	140 (22)	135 (24)	129 (24)	121 (23)	124 (25)	<0.001
HR- bpm	0	73 (13)	71 (14)	70 (14)	71 (15)	73 (13)	72 (14)	0.159
Blood results								
Haemoglobin - g/dl	1	14.1 (1.4)	13.5 (1.5)	13.7 (1.6)	13.1 (1.7)	12.9 (1.7)	12.6 (1.9)	<0.001
Creatinine - umol/l	0	79 (65–93)	90 (74–110)	90 (79–109)	105 (87–141)	113 (92–143)	131 (100–180)	<0.001
eGFR– ml/min/1.73m^2	0	86 (71–108)	72 (56–90)	72 (58–85)	59 (42–75)	55 (41–71)	46 (31–64)	<0.001
Na – mmol/l	0	139 (2)	138 (3)	138 (3)	138 (3)	138 (3)	137 (4)	0.005
K – mmol/l	5	4.2 (0.4)	4.4 (0.4)	4.4 (0.4)	4.4 (0.5)	4.4 (0.5)	4.3 (0.5)	0.241
NTproBNP– ng/l	2	51 (29–85)	236 (161–291)	794 (381–1596)	1310 (628–2939)	1717 (735–3120)	1966 (1120–4572)	<0.001
Urea – mmol/l	0	4.8 (3.9–5.8)	6.4 (4.7–7.8)	5.8(4.6–7.2)	7.8 (5.9–10.30)	8.8 (6.4–11.8)	11.7 (8.3–16.1)	<0.001
Albumin – g/l	1	40 (3)	39 (3)	39 (3)	38 (3)	38 (3)	37 (4)	<0.001
Bilirubin– umol/l	0	12 (10–15)	13 (11–15)	14 (12–18)	14 (12–18)	15 (12–19)	16 (12–22)	0.028
Treatment								
Beta-blockers– no. (%)	0	32 (31)	58 (53)	222 (78)	332 (81)	151 (85)	82 (76)	0.187
ACE-I or ARB– no. (%)	0	58 (57)	81 (74)	230 (81)	359 (87)	163 (92)	92 (85)	0.009
MRA– no. (%)	0	14 (14)	17 (16)	59 (21)	148 (36)	98 (55)	61 (56)	<0.001
Loop– no. (%)	0	28 (27)	50 (46)	NA	NA	NA	NA	0.006*
Loop >40 mg/day– no. (%)	0	3 (3)	17 (16)	NA	NA	NA	NA	<0.001*
Bendroflumethiazide– no. (%)	0	NA	NA	34 (13)	2 (1)	1 (1)	2 (2)	<0.001
Metolazone– no. (%)	0	NA	NA	0	0	3 (2)	3 (3)	0.001
Echocardiography								
LVEDV – ml	0	100 (78–114)	90 (68–114)	137 (100–178)	158 (111–202)	153 (110–198)	146 (109–197)	0.001
LVEF - %	0	59 (55–63)	59 (55–64)	45 (36–54)	40 (32–51)	40 (31–50)	42 (30–55)	0.003
LVEF ≤ 40 %	0	NA	NA	111 (39)	206 (50)	89 (50)	50 (46)	0.027
LAVI - ml/m^2	0	23 (20–27)	28 (21–35)	37 (29–51)	43 (32–56)	43 (33–58)	51 (37–65)	<0.001

Table 1 (continued)

Variable	Missing	No HF NTproBNP < 125 ng/l	No HF NTproBNP 125-400 ng/l	HF no loop diuretics	HF 10 to 40 mg Furosemide	HF > 40 to 80 mg Furosemide	HF > 80 Furosemide	P between HF groups
TAPSE – mm	2	22 (19–25)	21 (17–24)	20 (16–22)	18 (15–21)	17 (14–20)	16 (13–20)	<0.001
TR gradient – mmHg	39	17 (16–21)	20 (16–25)	25 (20–31)	25 (20–33)	26 (20–37)	31 (22–40)	<0.001
IVC – mm	38	15 (14–17)	15 (14–17)	18 (16–21)	19 (16–23)	19 (17–23)	22 (18–26)	<0.001
E/e'	735	7 (6–9)	9 (7–11)	10 (9–14)	12 (10–17)	13 (9–17)	15 (10–19)	0.002
Events								
Deaths– no. (%)	NA	6 (6)	21 (19)	45 (16)	135 (33)	66 (37)	50 (46)	NA
HF Hospitalizations– no. (%)	NA	5 (5)	11 (10)	34 (12)	81 (20)	50 (28)	24 (22)	NA

List of abbreviation used: *IHD* Ischemic Heart Disease, *DM* Diabetes Mellitus, *COPD* Chronic Obstructive Pulmonary Disease, *HTN* hypertension, *SBP* Systolic Blood Pressure, *HR* heart rate, *BMI* Body Mass Index, *eGFR* estimated Glomerular Filtration Rate, *AF* atrial fibrillation, *NTproBNP* N-terminal B-type natriuretic peptide, *LVEDV* Left Ventricle End Diastolic Volume, *LVEF* Left Ventricular Ejection Fraction, *LAVI* Left Atrial Volume Index, *TAPSE* Tricuspid Annular Plane Systolic Excursion, *TR gradient* Trans-Tricuspid systolic gradient, *IVC* inferior vena cava, *HF* heart failure, *MRA* Mineralocorticoid receptor antagonists, *ACE-I* angiotensin-converting-enzyme inhibitor, *ARB* Angiotensin II receptor blockers, *NA* not applicable

*NTproBNP < 125 vs 125–400

Current guidelines emphasize that diuretics are a treatment for the clinical symptoms and signs of congestion and that there is no evidence of a favourable effect on disease progression. There are theoretical concerns that, whilst relieving congestion, diuretics may cause neuro-endocrine (NE) activation and accelerate disease progression but there is no conclusive evidence that this is true. Moreover, introduction of NE antagonists may have reversed any adverse consequence of diuresis that once existed, especially the risk of hypokalaemia. Relief of congestion may reduce atrial and RV volumes and pulmonary artery pressure [19]. There is evidence that the severity of RV rather than LV dysfunction is more tightly linked to prognosis [3, 5] and increased atrial pressure and volume may provoke AF [17]. Therefore, achieving euvolaemia through adequate diuresis, protected by agents that block NE activation and hypokalaemia, might have favourable effects on disease progression. Indeed, potassium sparing diuretics appear associated with better outcomes in observational studies of diuretics in heart failure [12], perhaps because they prevent hypokalaemia and reduce the propensity of arrhythmias or perhaps because they replete intracellular potassium thereby improving the metabolic function of cells, including skeletal muscle and cardiac myocytes [20].

The effects of diuretics on renal function are complex [21]. In patients with severe oedema, diuretics may reduce renal parenchymal oedema and renal venous pressure without reducing renal arterial perfusion pressure, leading to improved renal function. In patients with less grossly elevated venous pressure, the fall in renal arterial perfusion pressure and complex changes in adenosine, intra-renal haemodynamics and tubulo-glomerular feedback conspire to cause a decline in glomerular filtration rate [21]. Moreover, washout of the medullary concentration gradient and other 'braking' effects may lead to varying degrees of tolerance to diuretic effects. High-dose loop diuretics may also cause hypochloraemia, which may contribute to diuretic resistance, neuro-endocrine activation and an adverse prognosis [22, 23].

Although a meta-analysis including three small randomized trials enrolling 202 patients in total suggested that mortality might be lower for those patients treated with diuretics compared to placebo [24], no randomised prospective study has evaluated the impact of loop diuretics on mortality in patients with chronic heart failure. Given the need to use diuretics to control symptoms of congestion, the low event rates in patients with cardiac dysfunction who do not have congestion and the possibility that diuretics are only safe and effective in patients who have congestion, it is difficult to design definitive outcome studies to address the topic. Clearly, for patients with severe congestion about to die of fluid overload, diuretics must be life-saving.

Retrospective analyses of several RCTs have raised concerns about a possible detrimental effect of long-term loop diuretic therapy. In the Prospective Randomized Amlodipine

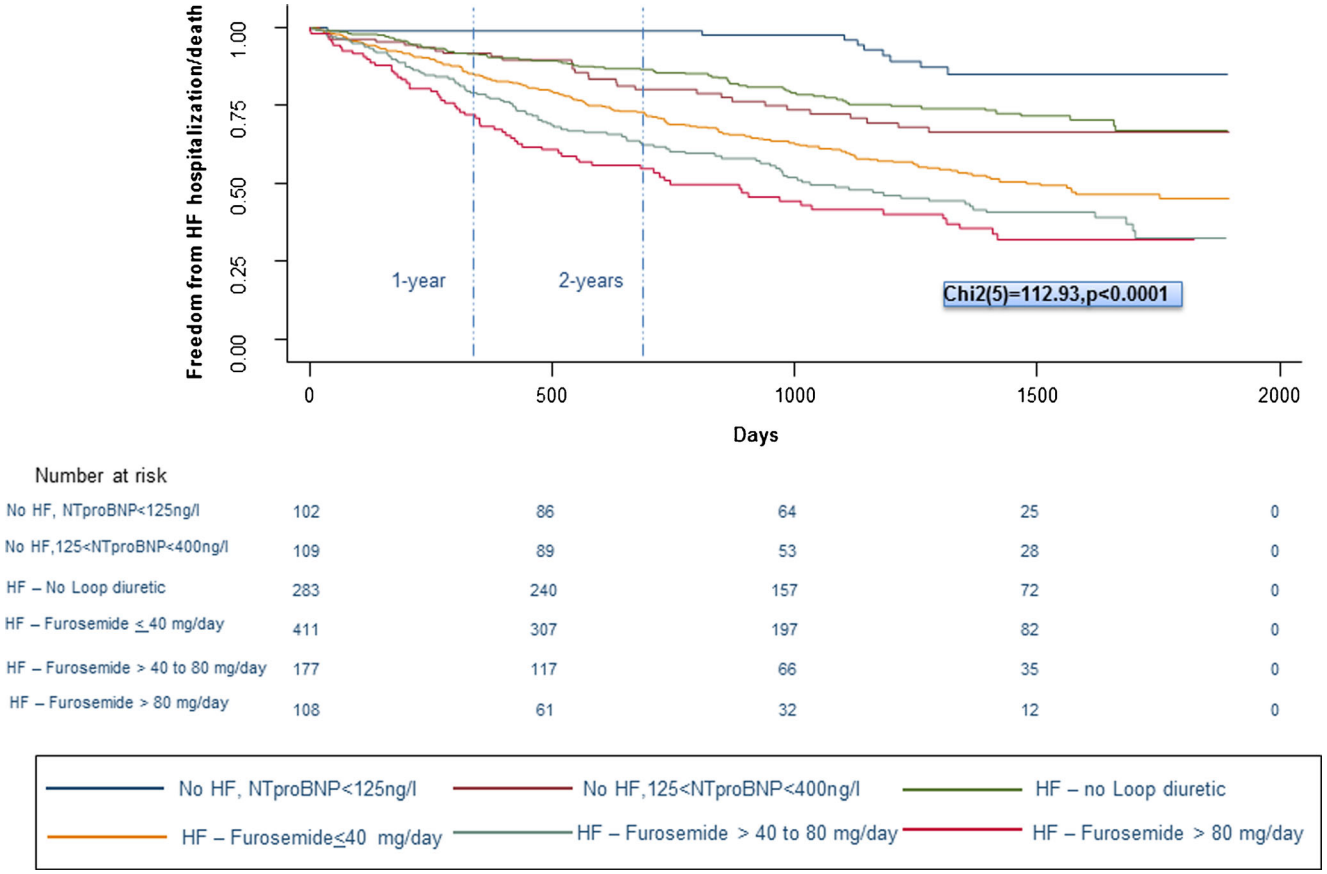

Fig. 1 Kaplan Meier curve for the primary outcome of death from all causes and heart failure hospitalizations in the overall population. Compared to patients with heart failure not taking loop diuretics, those treated with higher doses of loop diuretics (>80 mg furosemide per day) had a markedly greater risk of an adverse event (HR: 3.50, 95 % CI: 2.49–4.93, $p < 0.001$)

Survival Evaluation (PRAISE) trial [13], the use of furosemide ≥80 mg/day (or equivalent dose of other diuretics) or the use of metolazone combined with a loop diuretic, were independent predictors or mortality. In a sub-analysis of the Studies of Left Ventricular Dysfunction (SOLVD) [12], amongst >6000 patients with moderate or severe left

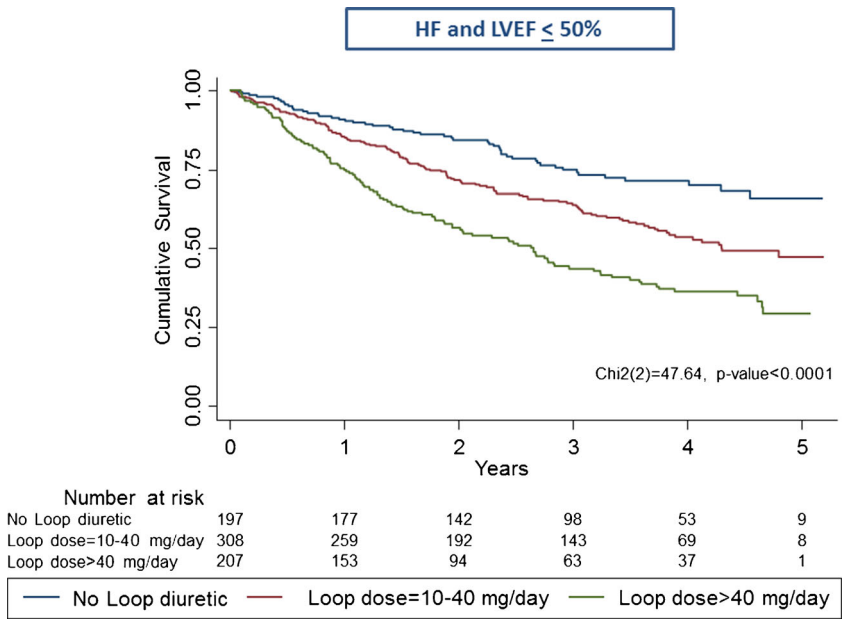

Fig. 2 Kaplan Meier curve for the primary outcome of death from all causes and heart failure hospitalizations in patients with HF and reduced left ventricular ejection fraction (LVEF ≤ 50 %). Compared to patients not taking loop diuretics, those treated with any dose of loop diuretic had a 2-fold increased risk of an adverse event (HR: 2.18, 95 % CI: 1.62–2.95, $p < 0.001$). The risk increased with increasing dose of loop diuretic taken (Dose >40 mg/day vs no diuretic: HR: 2.95, 95 % CI: 2.13–4.10, $p < 0.001$; Dose = 10–40 mg/day vs no diuretic: HR: 1.76, 95 % CI: 1.27–2.43, $p = 0.001$)

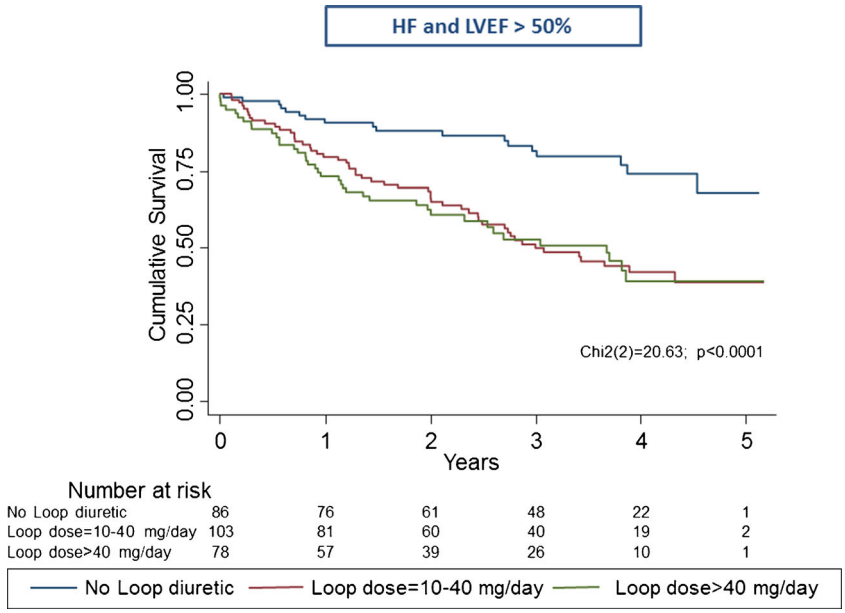

Fig. 3 Kaplan Meier curve for the primary outcome of death from all causes and heart failure hospitalizations in patients with raised NTproBNP (>400 ng/l) and normal LVEF (>50 %). Compared to patients not taking loop diuretics, those treated with any dose of loop diuretic had a 3-fold increased risk of an adverse event (HR: 3.04, 95 % CI: 1.83–5.04, p < 0.001)

Table 2 1-year event free survival. 965 patients with HF were followed-up for at least 365 days unless censored due to an event. During the first 365 days 163 events were recorded. NTproBNP was not available for two patients, for 34 patients IVC diameter was not available. P for significance amongst groups of patients treated with increasing dose of loop diuretics (@) or by increasing clinical, biochemical or echocardiographic congestion (#, highlighted in bold) are reported

1-year event free survival		No loop diuretic	Lower dose loop diuretic (≤40 mg)	Higher dose loop diuretic (>40 mg)	P@
Clinical congestion	Not congested (0)	92 %	87 %	85 %	0.123
	Mild congestion (1-2)	90 %	84 %	76 %	0.062
	Great congestion (≥3)	73 %	71 %	54 %	0.109
P#		**0.054**	**0.009**	**<0.001**	
Biochemical*	Not congested (NTproBNP < 125 ng/l)	100 %	100 %	100 %	1
	Mild congestion (NTproBNP = 125–400 ng/l)	98 %	93 %	100 %	0.267
	Great congestion (NTproBNP >400 ng/l)	88 %	82 %	72 %	<0.001
P#		**0.025**	**0.066**	**0.009**	
Biochemical**	NTproBNP tercile 1	98 %	95 %	90 %	0.048
	NTproBNP tercile 2	91 %	87 %	72 %	0.001
	NTproBNP tercile 3	83 %	70 %	61 %	0.005
P#		**0.002**	**<0.001**	**<0.001**	
Echocardiographic	No congestion (IVC ≤ 16 mm)	95 %	92 %	88 %	0.342
	Mild congestion (IVC 17–20 mm)	92 %	92 %	83 %	0.101
	Great congestion (IVC ≥ 21 mm) ***	82 %	71 %	61 %	0.006
P#		**0.030**	**<0.001**	**<0.001**	

*Median NTproBNP per group: No Loop diuretic 1107 (692–1911) ng/l; Lower dose Loop diuretic: 1526 (857–3325) ng/l; Higher dose Loop diuretic: 1962 (1133–3924) ng/l; p < 0.001

**Median NTproBNP per group: Tercile 1: No Loop diuretic: 224 (143–378)ng/l; Lower dose Loop diuretic: 445 (237–632)ng/l; Higher dose Loop diuretic: 586 (381–846)ng/l, p < 0.001; Tercile 2: No Loop diuretic: 790 (613–1021)ng/l; Lower dose Loop diuretic: 1289 (1088–1623)ng/l; Higher dose Loop diuretic: 1869 (1503–2129)ng/l, $p < 0.001$; Tercile 3: No Loop diuretic 2012 (1573–3266)ng/l; Lower dose Loop diuretic: 4020 (2926–6342)ng/l; Higher dose Loop diuretic: 4837 (3556–8487)ng/l, $p < 0.001$

***Median NTproBNP per group: No Loop 1736 (997–3267) ng/l; Lower dose Loop diuretic: 2877 (1471–4890) ng/l; Higher dose Loop diuretic: 2917 (1663–5506) ng/l; p < 0.001; Median IVC per group: No Loop diuretic 23 (22–24) mm; Lower dose Loop diuretic: 24 (22–27) mm; Higher dose Loop diuretic: 24 (22–27) mm; p = 0.001

Table 3 Univariable and multivariable Cox regression models for the composite endpoint of death or HF hospitalization in patients with HF. The independent predictors of adverse outcome are highlighted in bold

Variables	Univariable analysis			Multivariable analysis		
	HR (95 % CI)	χ^2	p-value	HR (95 % CI)	χ^2	p-value
Age - years	**1.04 (1.03–1.05)**	**73.78**	**<0.001**	**1.03 (1.01–1.04)**	**14.88**	**<0.001**
Sex (men)	0.96 (0.77–1.18)	0.16	0.69			
IHD(yes vs no)	1.10 (0.90–1.35)	0.95	0.33			
DM (yes vs no)	1.07 (0.87–1.31)	0.38	0.54			
HTN(yes vs no)	0.91 (0.75–1.10)	0.95	0.33			
COPD(yes vs no)	1.11 (0.83–1.49)	0.48	0.48			
NYHA class III vs I/II	**2.22 (1.83–2.70)**	**64.94**	**<0.001**	**1.52 (1.21–1.92)**	**12.99**	**<0.001**
Congested (yes vs no)	**2.34 (1.86–2.96)**	**51.55**	**<0.001**	**1.38 (1.01–1.86)**	**4.20**	**0.04**
AF (yes vs no)	1.32 (1.08–1.60)	7.51	0.006			
BMI - kg/m^2	0.96 (0.94–0.98)	19.31	<0.001			
SBP- mmHg	0.99 (0.99–1.00)	4.19	0.041			
HR- bpm	1.01 (1.00–1.01)	3.82	0.051			
Haemoglobin - g/dl	0.81 (0.76–0.85)	57.95	<0.001			
Creatinine - umol/l	1.01 (1.00–1.01)	69.97	<0.001			
eGFR- ml/min/1.73m^2	0.98 (0.97–0.99)	63.72	<0.001			
Na– mmol/l	**0.92 (0.90–0.95)**	**26.36**	**<0.001**	**0.95 (0.92–0.98)**	**9.76**	**0.002**
K– mmol/l	1.27 (1.03–1.58)	4.99	0.026			
LogNTproBNP	**3.87 (3.18–4.72)**	**181.65**	**<0.001**	**1.58 (1.15–2.17)**	**7.93**	**0.005**
Urea- mmol/l	**1.09 (1.08–1.11)**	**127.50**	**<0.001**	**1.06 (1.03–1.09)**	**12.71**	**<0.001**
Albumin – g/l	0.91 (0.88–0.93)	44.88	<0.001			
Bilirubin– umol/l	1.03 (1.01–1.04)	13.32	<0.001			
LD > 80 vs ≤ 80 mg/day	1.96 (1.50–2.55)	24.14	<0.001			
LVEDV- ml	1.01 (1.00–1.01)	10.22	0.001			
LVEF- %	0.99 (0.98–1.00)	9.19	0.002			
LAVI - ml/m^2	1.02 (1.01–1.02)	76.33	<0.001			
TAPSE – mm	0.93 (0.91–0.95)	46.48	<0.001			
TR gradient – mmHg	1.03 (1.03–1.04)	90.36	<0.001			
IVC – mm	**1.11 (1.10–1.11)**	**138.92**	**<0.001**	**1.06 (1.03–1.09)**	**15.15**	**<0.001**

List of abbreviation used: *IHD* Ischemic Heart Disease, *DM* Diabetes Mellitus, *COPD* Chronic Obstructive Pulmonary Disease, *HTN* hypertension, *SBP* Systolic Blood Pressure, *HR* heart rate, *BMI* Body Mass Index, *eGFR* estimated Glomerular Filtration Rate, *AF* atrial fibrillation, *NTproBNP* N-terminal B-type natriuretic peptide, *LD* loop diuretic, *LVEDV* Left Ventricle End Diastolic Volume, *LVEF* Left Ventricular Ejection Fraction, *LAVI* Left Atrial Volume Index, *TAPSE* Tricuspid Annular Plane Systolic Excursion, *TR gradient* Trans-Tricuspid systolic gradient, *IVC* inferior vena cava

ventricular dysfunction, the risk of hospitalization or death due to worsening HF in patients taking non-potassium sparing diuretics alone was greater (risk ratio [RR] 1.31, 95 % CI 1.09 to 1.57; $p = 0.0004$) when compared to those not taking any diuretic. Recently, Damman and coauthors examined the relationship between loop diuretic use and dose with a composite outcome of cardiovascular death or hospitalization for HF by propensity score matching different cohorts of patients with systolic dysfunction enrolled in the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) trial. They also suggested that the use of diuretics was associated with an adverse outcome, particularly a higher risk of admissions for heart failure [25]. Eshaghian and colleagues [14] also found that use of more intense diuretic treatment was associated with a worse outcome. They noted that those who were prescribed higher doses of diuretics (>160 mg of furosemide) had more severe symptoms, lower LV ejection fraction and cardiac index, and higher pulmonary capillary wedge pressure than those not taking, or taking lower doses of loop diuretics. Similar to our results, those taking >160 mg furosemide had an almost 4-fold increased risk of death compared to those taking furosemide 0–40 mg/day.

However, assessing the effect of diuretics on outcome is inevitably confounded by indication: the perceived need to prescribe them to control symptoms and signs of congestion. Propensity matched analyses, unless done before initiation of

Table 4 Multivariable Cox regression models

Variable	LogNTproBNP removed	LogNTproBNP & IVC removed	LogNTproBNP & IVC & Urea removed	LogNTproBNP & IVC & Urea & TR grad removed	LogNTproBNP & IVC & Urea & TR grad & LAVI removed	LogNTproBNP & IVC & Urea & TR grad & LAVI & Creatinine removed	LogNTproBNP & IVC & Urea & TR grad & LAVI & Creatinine & Congested removed
Age - years	X	X	X	X	X	X	X
NYHA class III vs I/II	X	X	X	X	X	X	X
Congested – yes vs not	X						
AF– yes vs not							
BMI- kg/m^2							
SBP - mmHg							
HR- bpm							
Haemoglobin - g/dl						X	X
Creatinine- umol/l			X				
Na– mmol/l	X	X	X	X	X	X	X
K– mmol/l							
Urea- mmol/l	X	X					
Albumin – g/l				X	X	X	X
Bilirubin– umol/l					X	X	X
LD > 80 vs ≤ 80 mg/day						X	X
LVEDV- ml					X	X	X
LVEF- %							
LAVI- ml/m^2		X	X	X			
TAPSE– mm				X	X	X	X
TR gradient– mmHg	X	X	X				
IVC– mm	X						

Different multivariable Cox regression models for the composite endpoint of death or HF hospitalization in patients with HF were tested. All the variables on the left column have been included, and then we consecutively excluded the strongest variable(s) in the univariable analysis (those excluded are reported above each column from each model). X identifies variables that entered the multivariable models tested with a $P < 0.05$. List of abbreviation used: *SBP* Systolic Blood Pressure, *BMI* Body Mass Index, *eGFR* estimated Glomerular Filtration Rate, *HR* heart rate, *AF* atrial fibrillation, *NTproBNP* N-terminal B-type natriuretic peptide, *LD* loop diuretic, *LVEDV* Left Ventricle End Diastolic Volume, *LVEF* Left Ventricular Ejection Fraction, *LAVI* Left Atrial Volume Index, *TAPSE* Tricuspid Annular Plane Systolic Excursion, TR gradient Trans-Tricuspid systolic gradient, *IVC* inferior vena cava

diuretics, are systematically biased and irrevocably confounded, since diuretics influence many key prognostic variables such as blood pressure, electrolytes and renal function resulting in systematic error that is likely to match patients on diuretics to patients who have a very different intrinsic prognosis. Multi-variable analysis, as presented in this paper, is less likely to be confounded than other statistical approaches to this issue.

The relationship between diuretic dose and severity of congestion deserves further consideration. In one sense, being congested whilst taking a loop diuretic can be considered treatment failure, since diuretics are being used in an attempt to control congestion but have failed to do so adequately. This may reflect over-cautious use. Alternatively, continuing congestion despite administration of diuretics could reflect a deleterious drug effect accelerating disease progression. More aggressive treatment with higher doses of loop diuretics might have reduced congestion but may aggravate renal dysfunction with uncertain effects on symptoms and prognosis. There is perhaps more evidence addressing the question than is immediately apparent. A series of RCTs has investigated whether treatment guided by natriuretic peptides, a biomarker of

congestion, improves outcomes. The results of these studies have been inconclusive, but often because the treatment strategy failed to reduce natriuretic peptides [26, 27]. In some successful studies, the key intervention that reduced NP was higher doses of diuretics [28, 29]. Implanted haemodynamic monitoring devices also suggest that appropriate intensification of diuretic doses improves well-being and outcome [30]. Thus, one interpretation of these trials is that treating persisting congestion with higher doses of diuretics improves outcome.

Despite the general belief that achieving the lowest tolerated dose, or even withdrawal, of loop diuretics, might be beneficial for patients with heart failure, our study suggests that it might not be appropriate due to the risk of recurrent congestion, since congestion rather than diuretic dose was more strongly linked to outcome. Many patients diagnosed with heart failure, some probably erroneously, can tolerate prolonged withdrawal of diuretic therapy but it is not clear whether withdrawal improves symptoms or outcome and it does put patients at increased risk of decompensation [31, 32]. On the other hand, treating patients who do not have overt clinical evidence of congestion with loop diuretics cannot improve symptoms but may cause NE activation [33].

Loop diuretics are commonly prescribed for breathlessness or oedema in the absence of evidence of substantial cardiac dysfunction. Such patients in our study had an adverse outcome compared to those not taking loop diuretics, although this might reflect the higher prevalence of comorbidities, such as ischaemic heart disease. Alternatively, diuretics may have reduced plasma concentrations of NT-proBNP and left atrial volume, thereby masking evidence of cardiac dysfunction. Although diuretics might be discontinued in many of these patients, further trials to demonstrate the safety and tolerability of diuretic withdrawal are needed.

Limitations

There is no universally accepted definition of heart failure. Of patients with LVEF ≤50 %, 36 (5 %) had an NT-proBNP <125 ng/L and some might consider these patients did not have heart failure. Many would not accept elevation of NT-proBNP alone as diagnostic of heart failure. Of patients with an NT-proBNP >400 ng/L and LVEF >50 %, 166 (60 %) were in AF, 22 (8 %) had eGFR <30 ml/min, only 67 (25 %) had a normal LA volume (LAVI < 34 mL/m^2 (18)) and 181 (68 %) were taking loop diuretics. Thus, very few patients with NT-proBNP >400 ng/L had no other evidence of major cardiac dysfunction. On the other hand, loop diuretics may have concealed underlying cardiac dysfunction, normalizing NT-proBNP and atrial volumes. Withdrawal of diuretics is likely to have revealed evidence of cardiac dysfunction in some patients.

Conclusions

The presence of congestion assessed either clinically, by echocardiography or by plasma concentrations of natriuretic peptides, identifies patients with chronic heart failure at high risk of an adverse outcome whether or not they are taking loop diuretics. Diuretics are more likely to be a marker of, rather than a cause of, a worse prognosis in patients with heart failure receiving contemporary therapy with NE antagonists that prevent hypokalaemia. However, further research is needed to clarify the relationship between loop diuretic agents and outcome; imaging and biochemical measures of congestion might be better guides to diuretic dose than symptoms or clinical signs.

Compliance with Ethical Standards

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Conflict of Interest Dr. Cleland reports grants and personal fees from Amgen, grants and personal fees from Novartis, grants from Roche, grants and personal fees from Servier, grants and personal fees from Stealth Biopharmaceuticals, personal fees from Trevena, outside the submitted work. Dr. Clark reports personal fees from Novartis, grants and personal fees from Servier, outside the submitted work.

Ethical Approval All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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