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RESEARCH ARTICLE

Association between loop diuretic dose changes and outcomes in chronic heart failure: observations from the ESC-EORP Heart Failure Long-Term Registry

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Aims Guidelines recommend down-titration of loop diuretics (LD) once euvolaemia is achieved. In outpatients with heart failure (HF), we investigated LD dose changes in daily cardiology practice, agreement with guideline recommendations, predictors of successful LD down-titration and association between dose changes and outcomes.

Methods and results We included 8130 HF patients from the ESC-EORP Heart Failure Long-Term Registry. Among patients who had dose decreased, successful decrease was defined as the decrease not followed by death, HF hospitalization, New York Heart Association class deterioration, or subsequent increase in LD dose. Mean age was 66 ± 13 years, 71% men, 62% HF with reduced ejection fraction, 19% HF with mid-range ejection fraction, 19% HF with preserved ejection fraction. Median [interquartile range (IQR)] LD dose was 40 (25–80) mg. LD dose was increased in 16%, decreased in 8.3% and unchanged in 76%. Median (IQR) follow-up was 372 (363–419) days. Diuretic dose increase (vs. no change) was associated with HF death [hazard ratio (HR) 1.53, 95% confidence interval (CI) 1.12–2.08; $P = 0.008$] and nominally with cardiovascular death (HR 1.25, 95% CI 0.96–1.63; $P = 0.103$). Decrease of diuretic dose (vs. no change) was associated with nominally lower HF (HR 0.59, 95% CI 0.33–1.07; $P = 0.083$) and cardiovascular mortality (HR 0.62,

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95% CI 0.38–1.00; $P = 0.052$). Among patients who had LD dose decreased, systolic blood pressure [odds ratio (OR) 1.11 per 10 mmHg increase, 95% CI 1.01–1.22; $P = 0.032$], and absence of (i) sleep apnoea (OR 0.24, 95% CI 0.09–0.69; $P = 0.008$), (ii) peripheral congestion (OR 0.48, 95% CI 0.29–0.80; $P = 0.005$), and (iii) moderate/severe mitral regurgitation (OR 0.57, 95% CI 0.37–0.87; $P = 0.008$) were independently associated with successful decrease.

Conclusion Diuretic dose was unchanged in 76% and decreased in 8.3% of outpatients with chronic HF. LD dose increase was associated with worse outcomes, while the LD dose decrease group showed a trend for better outcomes compared with the no-change group. Higher systolic blood pressure, and absence of (i) sleep apnoea, (ii) peripheral congestion, and (iii) moderate/severe mitral regurgitation were independently associated with successful dose decrease.

Keywords Loop diuretics • Furosemide • Drug titration • Chronic heart failure • Prognosis • Mortality

Introduction

Loop diuretics (LD) represent the mainstay of treatment for relieving congestion in patients with heart failure (HF).[1,2] Approximately 80% of chronic HF (CHF) patients are treated with a diuretic, consistently in both HF with reduced (HFrEF) and preserved ejection fraction (HFpEF).[3–5] Although diuretics have a class I recommendation in the guidelines, for patients with signs and symptoms of congestion, the level of evidence is 'B'.[6] One meta-analysis of small randomized trials suggests diuretics may improve outcomes,[7,8] but observational studies have suggested a significant dose-dependent association between LD use and adverse outcome in CHF.[9–11] Higher LD doses may represent a marker of disease severity rather than a true risk factor,[12] though this has also been identified in a small randomized study.[13]

In addition, inappropriately high doses of LD might hamper up-titration of guideline-directed medical therapy (GDMT) and result in electrolyte disturbances, further neurohormonal activation, accelerated kidney function decline and symptomatic hypotension.[14,15] Importantly, a post-hoc analysis of the CHAMPION trial indicated that mainly increases but also decreases in LD dose were the most common therapy changes related to improved outcome.[16] Therefore, it is advised to use the lowest possible dose of diuretics and to adjust to individual needs, but in reality, often patients are kept on the same dosages for a long period of time.[17,18] If patients are asymptomatic, the use of a LD could be discontinued in up to 60% of (selected) stable HF patients.[19,20]

Nonetheless, data on real-world use of LD in patients with CHF and the extent that clinicians adhere to guideline recommendations are lacking.[21] Moreover, although LD dose decrease is recommended, clinical data supporting that this strategy is feasible and beneficial are relatively limited.[13,16,19,22] Finally, no clinical or laboratory predictors of LD down-titration success, possibly able to guide this process, have been recognized to date.[20]

Thus, in outpatients with CHF we assessed: (i) LD dose changes in daily cardiology practice, (ii) the association between LD dose changes and GDMT changes, (iii) the agreement between daily cardiology practice and guideline recommendations regarding LD titration depending on volume status, (iv) the association between clinical characteristics and successful LD down-titration at baseline visit, and (v) the association between LD dose changes and 1-year outcomes.

Methods

Study design

The European Society of Cardiology Heart Failure Long-Term (ESC-HF-LT) Registry was a prospective, multinational, multicentre, observational study of HF patients, conducted by the EURObservational Research Programme (EORP) in 337 cardiology centres from 33 ESC member countries. Data on subsequent hospital admissions and mortality were obtained at 12 months. The registry was approved by local ethical review boards according to the regulations of each participating country. All patients enrolled in the survey signed an informed consent, unless exempt by the local ethics committee. Further details on the ESC-EORP-HF-LT Registry are provided elsewhere.[23,24]

In brief, site selection targeted a sample of hospitals of different levels of complexity, focusing on building up a network of centres representative of European reality. The number of centres in each country varied according to its size. Patients were managed according to the diagnostic and therapeutic interventions currently performed in each centre for patients with HF. No specific protocols or recommendations were provided during this observational study. Current guidelines for the management of HF were discussed during Investigator meetings, and doctors participating in the registry were encouraged to adhere to them. Several training meetings were organized for national coordinators and study investigators to assure consistency in data collection among participating centres. Furthermore, in each participating country, data sources were subjected to verification for a random sample of 5% of enrolled patients, by EORP monitors.

For this analysis, outpatients with HF seen at the participating clinics between 22 March 2011 and 30 November 2016 were included. The index date was defined as the baseline outpatient visit where baseline characteristics and diuretic dose changes were assessed: data on diuretics were recorded both prior to and after the index outpatient visit. Patients were included in the analysis if they received diuretics prior to and at end of the index visit, and excluded if they were missing data on diuretics at baseline or were receiving only a non-loop type diuretic (i.e. a diuretic other than furosemide, torasemide or bumetanide). LD doses were converted to equivalents of furosemide (20 mg of torasemide = 1 mg of bumetanide = 40 mg of furosemide). The decision to exclude from the analysis patients that were not receiving a diuretic but were started on one during the index visit was based on the inability to recognize patients with first diagnosis of HF. We believe that these patients represent a different population compared with patients who are already receiving a LD. We take the same stance in regard to patients who were receiving LD prior to index

visit and had their diuretic discontinued. Therefore, we only included patients who were receiving a LD both at beginning and end of index visit.

Study parameters and outcome measures

Loop diuretic dose change during baseline index visit was calculated based on the equation: LD dose after minus LD dose prior to index visit. LD dose change >0 was defined as dose increase, LD dose change <0 as dose decrease and LD dose change =0 as no change of dose. GDMT included beta-blockers, angiotensin converting enzyme inhibitors (ACEi) and/or angiotensin receptor blockers (ARBs) and mineralocorticoid receptor antagonists (MRAs). Beta-blockers doses are depicted in carvedilol equivalents. Other beta-blockers were transformed to carvedilol equivalents based on the equation: 50 mg carvedilol = 10 mg bisoprolol = 200 mg metoprolol = 10 mg nebivolol; ACEi/ARB doses are depicted in captopril equivalents. Other ACEi/ARBs were transformed to captopril equivalents based on the equation: 150 mg captopril = 10 mg ramipril = 40 mg enalapril = 40 mg lisinopril = 4 mg trandolapril = 16 mg perindopril = 40 mg fosinopril = 32 mg candesartan = 320 mg valsartan = 150 mg losartan. MRA doses are depicted in spironolactone/eplerenone equivalents.

Clinical stability was defined as the presence of all of the following: (i) symptoms corresponding to New York Heart Association (NYHA) classes I or II, and (ii) no history of HF hospitalization during the previous 6 months, and (iii) lack of all physical signs of congestion or hypoperfusion captured in the registry (pulmonary rales, S3 gallop, jugular venous pressure > 6 cm, pleural effusion, cold extremities, hepatomegaly, peripheral oedema) for which data were available. When information for each of these signs was not provided, the respective sign was considered absent.

The outcomes studied were: (i) all-cause mortality, (ii) cardiovascular (CV) mortality, (iii) HF mortality, and (iv) HF hospitalization during 1-year following index outpatient visit. A visit 12 months after the entry visit was mandatory per registry protocol in order to collect information on morbidity and mortality. A phone call could replace the clinical visit, in case of impossibility for the patient to reach clinical centres. Patients failing to attend clinical or phone visit were denoted as lost to follow-up, as no other method, such as administrative data or other registries, was used for patient status acquisition.

Furthermore, rates of and predictors of successful LD dose decrease at index visit were studied. Successful LD decrease was defined as the decrease of LD during index visit not followed by the composite of (i) death, (ii) HF hospitalization, (iii) NYHA class deterioration, or (iv) subsequent increase in LD dose during 12-month follow-up.

Statistical analysis

Baseline characteristics according to loop diuretic dose change

Baseline characteristics of patients with LD dose decrease vs. increase vs. no-change were presented as means ± standard deviation (SD), median (25th–75th percentile), or counts (percentage) and compared with the Kruskal–Wallis test (non-parametric) for continuous variables, and with the chi-square test or Fisher's exact test (if chi-square was not applicable) for categorical variables.

Guideline-directed medical therapy according to loop diuretic dose change

Proportions of patients with LD dose decrease vs. increase vs. no-change (i) receiving GDMT for HF and (ii) having GDMT initiated or up-titrated were presented as counts (percentage) and compared with the chi-square test. To investigate the association between LD and GDMT dose changes, a univariable logistic regression analysis was performed using GDMT changes as the dependent variable.

Associations between baseline characteristics and successful loop diuretic dose decrease

To identify independent predictors of successful LD decrease, univariable and multivariable logistic regressions were performed using successful LD dose decrease as the dependent variable. The 31 baseline variables tested as independent variables are marked with * in *Table 1*. The eight variables that were statistically significant in univariable analysis are marked with # in *Table 1* and were included in the multivariable model to identify independent predictors of successful LD dose decrease.

Associations between loop diuretic dose change at index visit and subsequent outcomes

Plots of Kaplan–Meier curves for time to event for the three LD change groups were compared using the log-rank test. In each analysis, subjects without the event were censored at the date of last contact or at a competing event. For time to CV death and time to HF death, subjects with unknown cause of death were not taken into account. To identify independent predictors of the study outcomes, univariable and multivariable Cox regression models were performed using study outcomes as the dependent variable. Baseline covariates which were significant at a level <0.05 and had at least 80% of available data were entered in a stepwise selection. Covariates remaining at the last step were included in the multivariable model. LD dose changes were entered in all multivariable models. Patients lost to follow-up were not considered for Cox models and Kaplan–Meier curves.

A two-sided *P*-value of <0.05 was considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

From March 2011 to November 2016, 10 845 outpatients with CHF were included in the ESC-EORP-HF-LT Registry. After excluding 2715 patients who met the pre-defined exclusion criteria, 8130 outpatients were analysed (*Figure 1*). The baseline characteristics of the patients that were excluded from the analysis are depicted in *Table 1*.

Baseline characteristics and patterns of loop diuretic dose change

Mean age was 66 ± 13 years, with 71% men. Mean left ventricular ejection fraction was 37 ± 14% (62% HFrEF, 19% HF with mid-range ejection fraction, 19% HFpEF). Mean ± SD and median [interquartile range (IQR)] daily dose of LD was 61 ± 81 and 40 (25–80) mg, respectively, and 3168 (40%) were stable and 4800

Table 1 Baseline characteristics of heart failure outpatients enrolled in the ESC Heart Failure Long-Term Registry, stratified by diuretic dose change

Variable	Excluded patients ($n = 2715$)	% Missing	Diuretic dose increased ($n = 1279$, 16%)	Stable diuretic dose ($n = 6180$, 76.0%)	Diuretic dose decreased ($n = 671$, 8.3%)	*P*-value**	*P*-value pairwise***
Clinically stable[a] (%)	1495 (57)	0.0	270 (21)	2614 (43)	284 (43)	<0.001	0.78
Age (years)*#	63.0 ± 13.7	0.0	65.7 ± 13.6	66.4 ± 12.7	64.2 ± 14.1	0.003	<0.001
Male sex*	185 (71)	0.0	899 (70)	4433 (72)	474 (71)	0.52	0.55
BMI (kg/m^2)*	27.6 ± 4.8	1.0	28.7 ± 5.7	28.2 ± 5.2	27.7 ± 5.1	0.008	0.10
Systolic BP (mmHg)*#	127.7 ± 21.3	0.2	127.1 ± 22.8	122.9 ± 20.1	121.5 ± 21.2	<0.001	0.051
Diastolic BP (mmHg)*	75.7 ± 12.4	0.5	74.8 ± 13.4	72.9 ± 11.6	72.2 ± 12.1	<0.001	0.06
Heart rate (bpm)*	71.3 (15.5)	0.1	79.5 ± 20.0	72.2 ± 14.2	72.4 ± 15.0	<0.001	0.66
Peripheral congestion*#	191 (8.2)	1.5	481 (38)	1084 (18)	127 (19)	<0.001	0.43
Pulmonary congestion*	371 (58.2)	60.4	565 (76)	1325 (61)	200 (66)	<0.001	0.13
Peripheral hypoperfusion*	60 (2.6)	0.0	79 (6.2)	174 (2.8)	36 (5.4)	<0.001	<0.001
HF history with previous hospitalization*	898 (35)	0.1	540 (43)	2954 (48)	362 (54)	<0.001	0.004
HF history >12 months*	1314 (72)	4.5	535 (52)	3282 (60)	286 (46)	<0.001	<0.001
Primary HF aetiology*		0.0				<0.001	<0.001
Dilated cardiomyopathy	679 (26)		309 (24)	1821 (30)	244 (36)		
Hypertension	261 (10)		121 (9.5)	455 (7.4)	59 (8.8)		
Ischaemic heart disease	1052 (41)		545 (43)	2737 (44)	244 (36)		
Other	580 (23)		304 (24)	1166 (19)	124 (19)		
CRT*	176 (7.5)	0.1	114 (9.1)	983 (16)	92 (14)	<0.001	0.21
ICD*	400 (17)	0.1	235 (19)	1735 (28)	137 (21)	<0.001	<0.001
Smoking status*	350 (14)	0.0	168 (13)	617 (10)	76 (11)	0.003	0.27
Diabetes*	595 (23)	0.0	460 (36)	2120 (34)	231 (34)	0.52	0.95
COPD*	258 (9.8)	0.0	184 (15)	945 (15)	108 (16)	0.59	0.57
Sleep apnoea*#	77 (3.3)	0.3	80 (6.3)	351 (5.8)	33 (5.0)	0.48	0.37
Prior stroke/TIA*	216 (8.2)	0.0	119 (9.3)	606 (9.8)	60 (8.9)	0.69	0.47
Chronic kidney dysfunction*#	244 (9.3)	0.0	304 (24)	1325 (22)	155 (23)	0.13	0.33
Hepatic dysfunction*	48 (2.0)	0.0	63 (4.9)	217 (3.5)	31 (4.6)	0.03	0.15
Depression*	164 (6.3)	0.0	107 (8.4)	449 (7.3)	52 (7.8)	0.35	0.65
Atrial fibrillation/flutter*#	409 (17)	6.1	365 (30)	1340 (23)	134 (21)	<0.001	0.14
NYHA class		0.0				<0.001	
I–II	2141 (82)		718 (56)	4528 (73)	483 (72)		
III–IV	463 (18)		561 (44)	1649 (27)	187 (28)		
LVEF (%)*	41.2 ± 12.9	3.2	37.7 ± 13.9	36.7 ± 13.6	36.0 ± 13.6	0.015	0.14
Mitral regurgitation*# moderate/severe	406 (21)	14.5	500 (43)	1681 (33)	179 (29)	<0.001	0.09
Haemoglobin (g/dL)*#	13.7 ± 1.8	15.9	12.8 ± 1.9	13.3 ± 1.8	13.2 ± 1.9	<0.001	0.33
S-creatinine (mg/dL)*	1.2 ± 0.9	9.4	1.3 ± 0.7	1.3 ± 2.3	1.5 ± 4.4	0.30	0.26
eGFR (mL/min/1.73 m^2)*	74.2 ± 30.9	11.3	61.6 ± 23.6	62.7 ± 26.8	62.3 ± 26.0	0.69	0.73
NT-proBNP (pg/mL)[b]	816 [302–1995]	67.0	2381 [849–4970]	1467 [592–3605]	1516 [604–4250]	<0.001	0.50
Beta-blockers*	1945 (83)	0.0	872 (68)	5411 (88)	573 (85)	<0.001	0.11

Table 1 (Continued)

Variable	Excluded patients ($n = 2715$)	% Missing	Diuretic dose increased ($n = 1279$, 16%)	Stable diuretic dose ($n = 6180$, 76.0%)	Diuretic dose decreased ($n = 671$, 8.3%)	*P*-value**	*P*-value pairwise***
Beta-blockers dose change at index visit (mg/day)	–	–	3.4 ± 10.5	1.8 ± 7.2	4.1 ± 11.0	<0.001	<0.001
Beta-blockers dose change from index visit to 12-month FU (mg/day)	–	–	2.8 ± 14.5	1.7 ± 13.3	3.6 ± 25.6	0.002	0.136
ACEi and/or ARBs*	1978 (84)	0.0	912 (71)	5312 (86)	579 (86)	<0.001	0.79
ACEi and/or ARBs dose change at index visit (mg/day)	–	–	10.7 ± 31.2	3.5 ± 19.4	4.8 ± 30.0	<0.001	0.013
ACEi and/or ARBs dose change from index visit to 12-month FU (mg/day)		–	7.2 ± 41.4	2.3 ± 37.8	7.2 ± 37.1	<0.001	0.001
MRAs*	758 (29)	0.0	521 (41)	3820 (62)	430 (64)	<0.001	0.25
MRA dose change at index visit (mg/day)	–	–	5.7 ± 14.5	0.7 ± 7.0	0.2 ± 11.3	<0.001	0.051
MRA dose change from index visit to 12-month FU (mg/day)		–	3.1 ± 18.5	1.2 ± 15.2	0.9 ± 14.4	0.042	0.955
Diuretics							
Dose diuretics prior to visit (mg/day)	–	0.0	55.5 ± 73.7	59.1 ± 80.2	75.7 ± 88.6	<0.001	<0.001
Dose diuretics after visit (mg/day)	–	0.0	74.6 ± 87.9	59.1 ± 80.2	48.9 ± 67.9	<0.001	<0.001
Diuretic dose change at index visit (mg/day)	–	0.0	43.2 ± 44.9 40 [20–40]	0.0 ± 0.0 0 [0–0]	−37.6 ± 47.4 −25 [−40; −20]	<0.001	<0.001

Values are presented as means ± standard deviation, median [25th–75th percentile], or *n* (%). Data are at the beginning of the visit, i.e. prior to any medication changes.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; FU, follow-up; HF, heart failure; ICD, implantable cardioverter-defibrillator; LD, loop diuretic; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; TIA, transient ischaemic attack.

Beta-blockers doses are depicted in carvedilol equivalents. Other beta-blockers were transformed to carvedilol equivalents based on the equation: 50 mg carvedilol = 10 mg bisoprolol = 200 mg metoprolol = 10 mg nebivolol. ACEi/ARB doses are depicted in captopril equivalents. Other ACEi/ARBs were transformed to captopril equivalents based on the equation: 150 mg captopril = 10 mg ramipril = 40 mg enalapril = 40 mg lisinopril = 4 mg trandolapril = 16 mg perindopril = 40 mg fosinopril = 32 mg candesartan = 320 mg valsartan = 150 mg losartan. MRA doses are depicted in spironolactone/eplerenone equivalents.

LD dose change during baseline index visit was calculated based on the equation: LD dose after minus LD dose prior to index visit. LD dose change >0 was defined as dose increase, LD dose change <0 as dose decrease and LD dose change =0 as no change of dose.

[a]Patients were considered as clinically stable if they fulfilled *all* of the following: (i) HF symptoms corresponding to NYHA functional classes I or II, (ii) no history of HF hospitalization during the previous 6 months, and (iii) lack of all physical signs of congestion or hypoperfusion captured in the registry (pulmonary rales, S3 gallop, jugular venous pressure > 6 cm, pleural effusion, cold extremities, hepatomegaly, peripheral oedema).

[b]NT-proBNP values were available in 33% of patients.

*Baseline variables tested in univariable model.

#Statistically significant variables in univariable analysis used for the multivariable model to identify predictors of successful LD dose decrease.

***P*-value for comparison between diuretic dose increased, stable and decreased groups. Patients included vs. excluded from the analysis differed significantly regarding all baseline characteristics except for sex distribution and use of beta-blockers and ACEi and/or ARBs.

****P*-value for comparison between diuretics dose stable and decreased groups.

Table 2 Loop diuretic dosing and clinical stability

	Clinically stable	Not clinically stable	Stability not reported	Total
LD dose decrease	284 (9.0)	380 (7.9)	7 (4.3)	671 (8.3)
LD dose increase	270 (8.5)	1003 (21)	6 (3.7)	1279 (16)
LD dose stable	2614 (83)	3417 (71)	149 (92)	6180 (76)
Total	3168 (100)	4800 (100)	162 (100)	8130 (100)

Values are presented as *n* (%).
LD, loop diuretic.
Stability is defined as the presence of (i) New York Heart Association functional class I or II, (ii) no history of heart failure hospitalization during the previous 6 months, and (iii) lack of physical signs of congestion or hypoperfusion captured in the registry (pulmonary rales, S3 gallop, jugular venous pressure >6 cm, pleural effusion, cold extremities, hepatomegaly, peripheral oedema).

Table 3 Incidence of the components of failed/unsuccessful loop diuretic dose decrease during 1-year follow-up among 671 patients with loop diuretic dose decrease at baseline

Variable	Patients with missing data	Patients with event
All-cause death	21 (3.1)	51 (7.8)
HF hospitalization	47 (7.0)	83 (13)
NYHA deterioration	112 (17)	93 (17)
LD dose increase	112 (17)	187 (34)
Composite of death, HF hospitalization, NYHA deterioration, or LD dose increase	112 (17)	288 (52)

Values are presented as *n* (%).
HF, heart failure; LD, loop diuretic; NYHA, New York Heart Association.

(60%) were unstable. During the index visit, 16% had dose of LD increased. Diuretic dose was increased in a significantly higher proportion of unstable compared with stable patients ($P < 0.001$; *Table 2*). The general tendency was to keep the dose of LD unchanged (76%), but even more so in stable than in unstable patients ($P < 0.001$). LD dose was reduced in few patients (8.3%), without, however, dose decrease showing interaction with clinical stability ($P = 0.098$; *Table 2*).

Baseline clinical characteristics according to loop diuretic dose change

Baseline characteristics per LD dose change are shown in *Table 1*. Patients in the LD dose increase group had significantly higher systolic blood pressure but otherwise had characteristics consistent with more severe HF compared with patients in the LD decrease and no-change groups (*Table 1*). There was no difference in estimated glomerular filtration rate, but the LD increase group had higher left ventricular ejection fraction and higher rates of moderate/severe mitral and tricuspid valve regurgitation. Peripheral hypoperfusion was more common in the increase and decrease groups than in the no-change group.

Guideline-directed medical therapy according to loop diuretic dose change

At the beginning of index visit GDMT was less often used among patients who had LD dose increased compared with patients with LD maintenance and decrease ($P < 0.001$; *Table 1*). Surprisingly, GDMT was up-titrated slower (both at index visit and between index visit and follow-up) in patients with unchanged LD dose compared not only with patients with decreased LD dose but also with patients with increased LD dose ($P < 0.001$ for all comparisons; *Table 1*).

GDMT was initiated and/or up-titrated in a significantly higher proportion of patients with LD dose increase at index visit compared with patients with LD dose decrease or maintenance ($P < 0.001$; online supplementary *Table S1*), finding which was constant across patients in all ejection fraction groups (online supplementary *Table S1*). In univariable logistic regression, LD dose decrease [odds ratio (OR) 2.444, 95% confidence interval (CI) 2.074–2.880] and increase (OR 3.929, 95% CI 3.468–4.452) were both associated with increased probability of GDMT initiation/up-titration compared with LD dose maintenance ($P < 0.001$; online supplementary *Table S2*).

Predictors of successful loop diuretic dose decrease among patients with dose decrease at index visit

Among 671 patients (8.3%) who had LD dose decreased, outcomes are reported in *Table 3*. Overall, in 271/559 patients (48%) LD dose decrease was successful. Higher systolic blood pressure (OR per 10 mmHg change 1.11, 95% CI 1.01–1.22; $P = 0.032$) and absence of (i) sleep apnoea (OR 0.24, 95% CI 0.09–0.69; $P = 0.008$), (ii) moderate/severe mitral valve regurgitation (OR 0.57, 95% CI

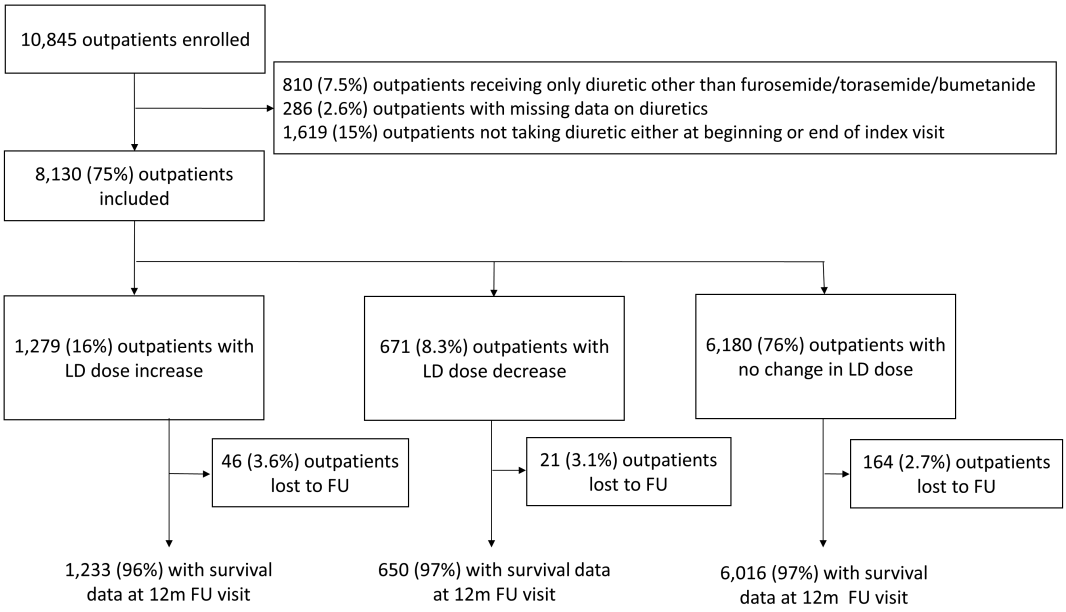

Figure 1 Flow-chart of patient selection. FU, follow-up; LD, loop diuretic.

0.37–0.87; $P = 0.008$), and notably (iii) peripheral congestion (OR 0.48, 95% CI 0.29–0.80; $P = 0.005$) were associated with the LD dose decrease being successful (*Table 4*).

Association between diuretic dose change and outcomes

During a median (IQR) follow-up of 372 (363–419) days, outcomes were available for 7899/8130 patients (97%), with 757 deaths (9.6%) [385 CV deaths (51% of all), 257 HF deaths (34% of all)], 2344 patients rehospitalized at least once (30%), and 1095 rehospitalized at least once for HF (15%). Detailed information on data availability and outcomes in the overall cohort and across the three LD groups is shown in online supplementary *Table S3*. The cumulative rate of all-cause death was 14% for LD dose increase, 7.8% for LD dose decrease and 8.9% for no-change LD dose groups ($P < 0.001$; *Figure 2A*). The respective rates of CV death were 7.3%, 3.2% and 4.7% ($P < 0.001$; *Figure 2B*), of HF death 5.4%, 2.2% and 3.1% ($P < 0.001$; *Figure 2C*) and of the composite of all-cause death or HF hospitalization 26.6%, 17.7% and 19.0% ($P < 0.001$; *Figure 2D*).

The adjusted hazard ratios (HR) for 1-year outcomes are depicted in *Figure 3*, whereas the results of the multivariable Cox regression analyses for all study outcomes in online supplementary *Table S4*. LD dose increase (vs. no change) was associated with increased risk for HF death (HR 1.53, 95% CI 1.12–2.08; $P = 0.008$) and nominally with increased risk of CV death (HR 1.25, 95% CI 0.96–1.63; $P = 0.103$). These associations were pronounced and statistically significant among patients with HFpEF (HR 2.472, 95% CI 1.188–5.143; $P = 0.015$ for HF death; and HR 2.037, 95% CI 1.090–3.810; $P = 0.026$ for CV death; online supplementary *Table S5*). Conversely, decrease of diuretic dose (vs. no change) was nominally associated with a lower CV (HR 0.620, 95% CI 0.38–1.00; $P = 0.052$) and HF mortality (HR 0.59, 95% CI 0.33–1.07; $P = 0.083$).

Loop diuretic dose increase (vs. decrease) was independently associated with a twofold risk of CV death (HR 2.01, 95% CI 1.19–3.39; $P = 0.009$), a 2.6 times higher risk of HF death (HR 2.57, 95% CI 1.37–4.83; $P = 0.003$), and nominally with HF hospitalization (HR 1.31, 95% CI 0.99–1.73; $P = 0.063$).

Discussion

In this large population of HF patients across 33 ESC countries, (i) LD dose at an outpatient visit was down-titrated in only 8.3% overall and in only 9% of clinically stable patients; (ii) LD dose increase and decrease were associated with increased probability of GDMT initiation/up-titration both at index visit and during follow-up compared with LD dose maintenance; (iii) overall, increase of LD dose was associated with increased risk of CV and especially HF events, while decrease of LD dose was associated with decreased risk for CV and HF events; (iv) among patients with LD dose decrease, this was 'successful' in half, and (v) higher systolic blood pressure, and absence of sleep apnoea, peripheral congestion and moderate/severe mitral regurgitation independently predicted successful LD dose decrease.

Patterns of loop diuretic dose change

The rate of LD dose decrease was disappointingly low but in line with previous smaller studies,[12,25] highlighting a discordance between 'real-world' HF patterns and guidelines. This is potentially attributable to the paucity of evidence guiding use of diuretics in HF.

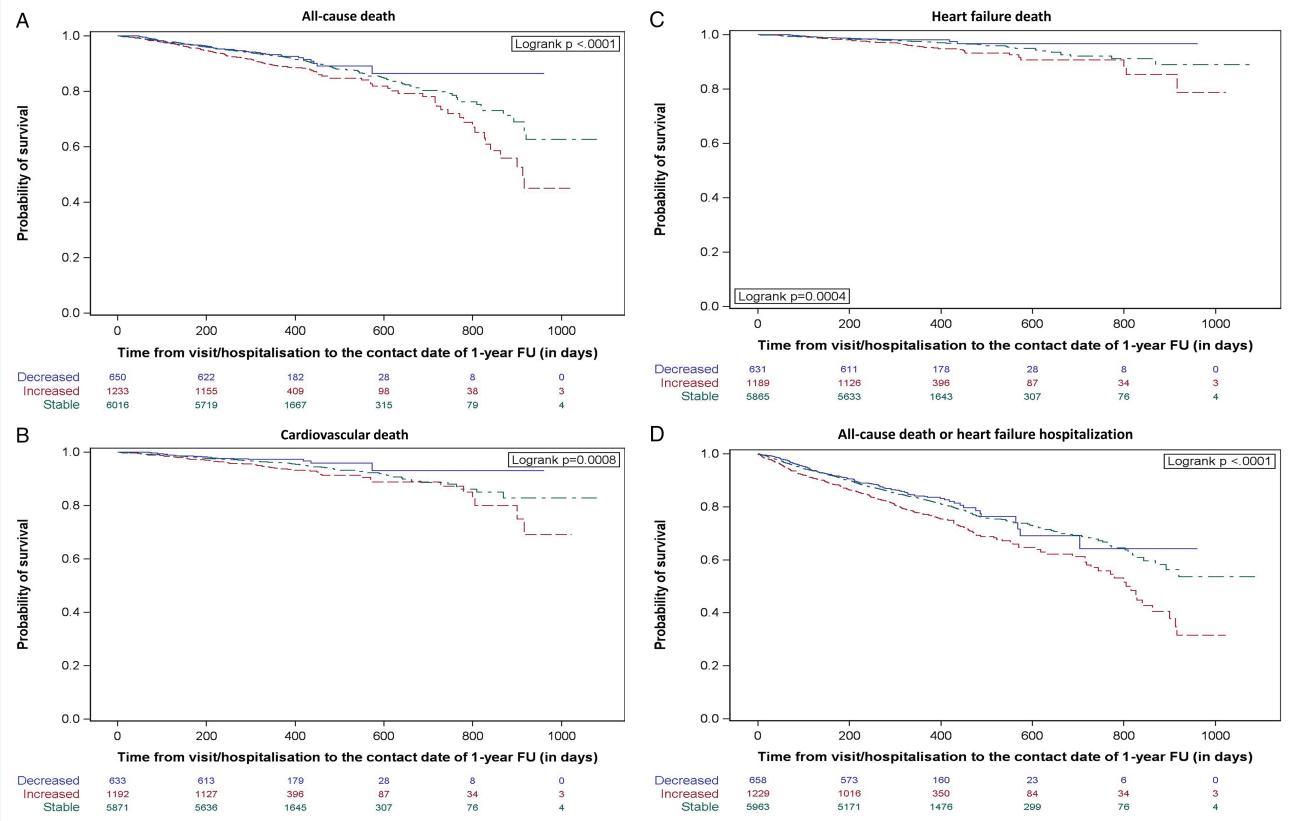

Figure 2 Kaplan–Meier curves for the three study groups with (*A*) all-cause death, (*B*) cardiovascular death, (*C*) heart failure death, and (*D*) all-cause death or heart failure hospitalization as the endpoint. FU, follow-up.

Guideline-directed medical therapy according to loop diuretic dose change

At baseline patients in the LD increase group had higher rates of clinical instability (higher NYHA classes, more signs/symptoms of congestion, higher levels of natriuretic peptides) and lower rates of receipt of GDMT, findings which are expected and in line with current knowledge.[26,27] The surprising finding of our analysis was that LD dose increase did not seem to hinder GDMT initiation and/or up-titration. Contrary, in our analysis LD dose maintenance was associated with less frequent and slower up-titration of GDMT (both at index visit and between index visit and follow-up) compared not only with patients with decreased LD dose but also with patients with increased LD dose. Interestingly, patients with LD dose increase were also more likely to have GDMT initiation and/or up-titration even compared with patients with LD dose decrease. These results seemingly contradict recently published findings from the BIOSTAT-CHF study, according to which higher doses of LD hinder up-titration of ACEi in HFrEF patients.[28] However, a reasonable explanation for this difference lies in the design of the two studies: BIOSTAT-CHF was a prospective study aiming at achieving optimal GDMT among HFrEF patients who were undertreated, while ESC-HF-LT is merely a registry which captures patterns of HF medication use in a real-life setting. In this direction, our findings strongly indicate, though do not prove, that clinicians' inertia rather than patient's intolerability or volume status is the main barrier to GDMT optimization in HF outpatients in real life.

Association between diuretic dose change and outcomes

Loop diuretic increase was associated with worse, whereas decrease with better clinical outcomes compared to maintenance. This of course may be simply a risk marker of greater HF severity among patients who have dose increased and/or kept stable, but uniquely the registry contains extensive data on variables that may affect both diuretic dosing and outcomes, including data on left and right-sided congestion, perfusion, clinical stability, HF severity and comorbidities, and clinical and laboratory variables. We performed extensive adjustment for these and other variables, and the risk associated with LD dose increase (vs. maintenance) remained approximately 50% higher for HF death and approximately 10–25% increased for other outcomes. On the other hand, LD dose decrease (vs. maintenance) also presented with a trend for 40% lower CV and HF death. This magnitude of risk excess after extensive adjustment suggests that it is likely, although not proven, that increase as well as maintenance of LD dose are risk markers for more severe HF but *also* true risk factors for worse outcomes.

Table 4 Associations between clinical characteristics and successful dose decrease among chronic heart failure outpatients with loop diuretic dose decrease at baseline

Variable (potential predictor of successful diuretic dose decrease)	Univariable		Multivariable	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age (per year)	0.99 (0.98–1.00)	0.03		
Systolic BP (per 10 mmHg)	1.11 (1.02–1.21)	0.02	1.11 (1.01–1.22)	0.032
Peripheral congestion (yes vs. no)	0.46 (0.30–0.73)	<0.001	0.48 (0.29–0.80)	0.005
Pulmonary congestion (yes vs. no)	0.94 (0.56–1.59)	0.83		
Peripheral hypoperfusion (yes vs. no)	0.77 (0.35–1.70)	0.51		
HF history with previous hospitalization (yes vs. no)	0.97 (0.70–1.36)	0.88		
HF history >12 months (yes vs. no)	0.81 (0.57–1.14)	0.23		
Primary aetiology (IHD vs. non-IHD)	0.89 (0.63–1.25)	0.50		
Diabetes (yes vs. no)	0.75 (0.53–1.07)	0.11		
Sleep apnoea (yes vs. no)	0.38 (0.16–0.92)	0.03	0.24 (0.09–0.69)	0.008
Chronic kidney dysfunction (yes vs. no)	0.65 (0.44–0.97)	0.04		
Rhythm atrial fibrillation/flutter vs. sinus	0.53 (0.34–0.83)	0.005		
EF (%)	1.00 (0.99–1.02)	0.43		
Mitral regurgitation moderate/severe (yes vs. no)	0.53 (0.36–0.78)	0.001	0.57 (0.37–0.87)	0.008
Haemoglobin (g/dL)	1.12 (1.01–1.23)	0.03		
Beta-blockers (prior to visit) (yes vs. no)	1.30 (0.80–2.11)	0.29		
ACEi and/or ARBs (prior to visit) (yes vs. no)	1.52 (0.93–2.47)	0.09		
MRAs (prior to visit) (yes vs. no)	1.24 (0.88–1.76)	0.22		

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CI, confidence interval; EF, ejection fraction; IHD, ischaemic heart disease; HF, heart failure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; OR, odds ratio.
An OR > 1.0 means the variable was associated with successful dose decrease.
Cohort size: *n* = 559 patients with complete data on variables to assess success of dose decrease. All variables tested in the univariable logistic regression analysis are depicted with * in *Table 1*.

These findings are consistent with previous reports that high LD doses are associated with increased risk for death and other adverse outcomes.[9–12,29–33] Interestingly, Mielniczuk *et al.*[12] observed that the association between LD and adverse outcome was rendered insignificant after adjustment for clinical stability; however, in our study the associations between dose change and outcomes were independent of clinical stability and other factors. Furthermore, a major limitation of previous analyses was that LD doses and not dose change were studied. Apart from a single retrospective study,[25] and a small randomized study, in which HF patients were randomly assigned to either maintenance or dose decrease,[13] the association between LD dose change and outcomes is here for the first time studied and reported in such a large population of unselected HF outpatients.

Successful loop diuretic dose decrease and its predictors

Loop diuretic dose decrease was successful through 1-year follow-up in half of patients in whom it was attempted. That it was unsuccessful in the other half does not mean it should not be attempted given the more favourable outcomes of patients with LD decrease overall. Previous smaller studies suggest that down-titration of LD dose in selected stable patients is feasible in 58–95%, but these did not include all patients at outpatient visits and are less generalizable.[13,18,22,34,35] Furthermore, previous small studies could not identify independent predictors of successful dose decrease.[18,20,35] Understanding such predictors may inform the selection of the appropriate patient for dose decrease, thus increasing this potentially beneficial intervention. Thus, importantly, for the first time, we have demonstrated independent predictors for successful LD dose decrease: higher blood pressure and absence of sleep apnoea, peripheral congestion and moderate/severe mitral valve regurgitation. Volume overload in HF leads to left ventricular dilatation, progressive remodelling, and aggravates the severity of secondary mitral regurgitation and impairs left atrial function, while decongestion may lead to relative reversal of these phenomena.[36,37] Thus, LD dose reduction in patients with more severe secondary mitral regurgitation may be more difficult to achieve. Notably, absence of peripheral congestion was strongly and independently associated with successful LD dose decrease (adjusted HR 0.48), whereas absence of pulmonary congestion, hypoperfusion, and other markers of HF severity were not. A recent analysis from the ESC-HF-LT Registry showed that 31% of HF patients had residual congestion at hospital discharge, and that this was associated with a 46% increased risk of death post-discharge.[38] Taken together, our findings suggest that LD dose decrease should be attempted more often in general but should be done with caution or not at all in patients with residual peripheral congestion. Thus, in euvolaemic patients with HF we should perhaps use *less* diuretics, whereas in patients with peripheral congestion we should perhaps use *more* diuretics. In the light

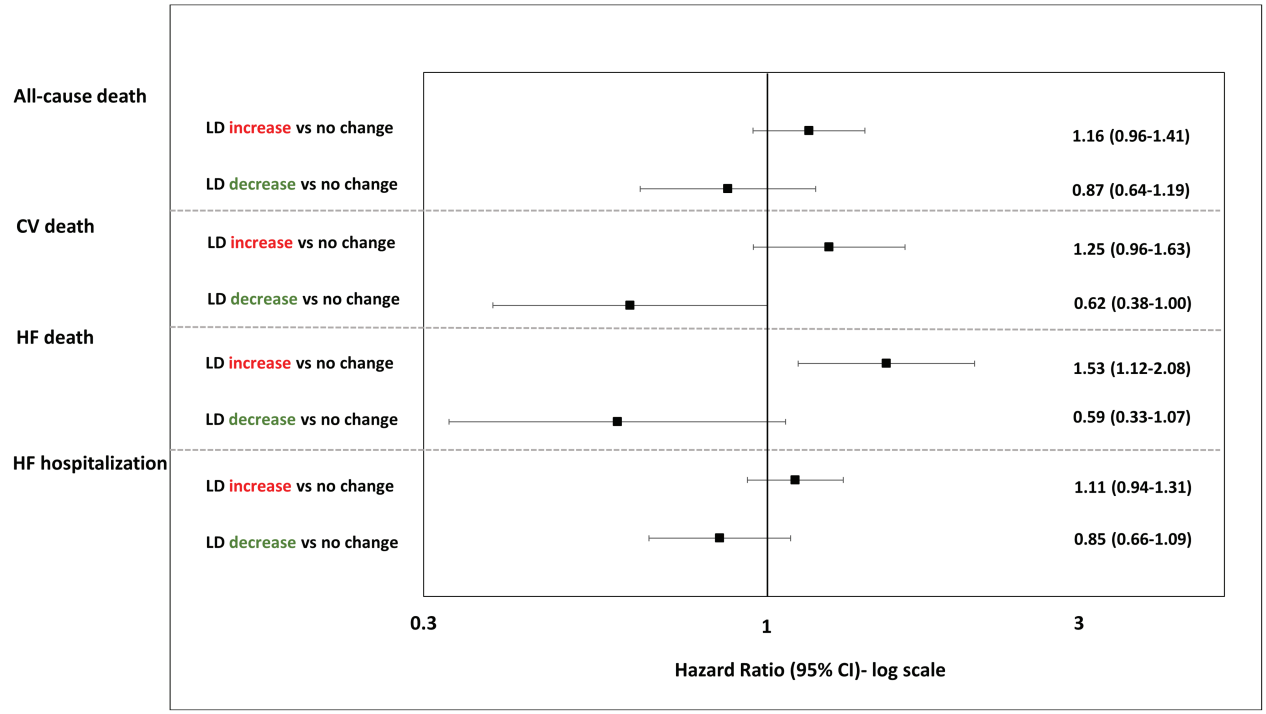

Figure 3 Among all patients, adjusted hazard ratios for all-cause death, cardiovascular (CV) death, heart failure (HF) death and HF hospitalization according to loop diuretic (LD) dose change. CI, confidence interval.

of the favourable effects that sodium–glucose co-transporter-2 inhibitors and sacubitril/valsartan demonstrate in the outcomes of patients with HF,[39,40] combined with their postulated mechanisms of action and their potential to mediate LD dose decrease,[41,42] their use must be encouraged in all suitable HF patients. In any case, the paucity of strong evidence guiding diuretic treatment in HF is unequivocal, and the design and execution of studies to test the feasibility and effects of different diuretics and different dosing regimens are urgently needed.

Limitations

The study included patients seen in cardiology units only. HF diagnosis and cause of death were based on treating physicians and not adjudicated. LD use is a marker of LD need, which is a marker of HF severity. Thus, the association between LD changes and outcomes is expected. We excluded patients enrolled in the registry at HF hospitalization but cannot exclude that LD increases were appropriate interventions for worsening HF and congestion in the outpatient setting. While signs and symptoms are subjective and unreliable, they add important clinical information and are rarely available in registry and cohort studies. We included all patients with diuretics at baseline, but clinically, the LD increase group likely represents a phenotype with a clear worsening of HF, whereas LD decrease and LD unchanged are likely more similar. Furthermore, due to the complexity of the analyses, the multiple comparator groups, and the lack of information on non-CV outcomes, we were not able to perform sensitivity or consistency analyses using for example propensity scores or falsification outcomes (e.g. non-CV 'negative control' outcomes). Thus, the outcome analyses should be interpreted with caution. Nevertheless, we do raise the possibility that some of the reduced risk with LD decrease and increased risk with LD increase actually represent, at least in part, a causal harmful effect of conventional LD, such as through neurohormonal activation. Furthermore, the reasons underlying changes or lack of change in LD dose are unknown and can only be postulated. Finally, LD dose change was studied at a single time-point and not over time. This means that we have captured data on two time points, which notably are far apart from each other, therefore dynamic changes over time could not be accounted for. This is an important limitation, as we do not know if and how many changes patients had. Moreover, the fact that outcome data were only available at 1 year after the index visit – when LD dose changes were recorded – also weakens the associations between LD dose change and outcomes. A relatively small, but clinically meaningful, proportion of patients (~3%) were lost to follow-up. Nevertheless, this is the largest and most rigorously adjusted study of diuretic dosing to date.

Conclusion

At HF outpatient visits, LD dose was down-titrated in only 8.3% overall and in only 9.0% of clinically stable patients, unchanged in 76% and up-titrated in 16% overall. Maintenance of LD dose was

associated with decreased likelihood of initiating and/or up-titrating GDMT compared with LD dose increase and decrease, possibly denoting clinicians' inertia as the reason for sub-optimal GDMT dosing in real life. Increase of LD dose was associated with worse outcomes, while LD dose decrease with better outcomes. After rigorous adjustment for multiple factors, a strong association remained, suggesting, but not proving, that failure to appropriately reduce diuretic dose among outpatients may potentially be causing worse outcomes. However, residual confounding cannot be excluded. Among patients who underwent LD dose decrease, this was 'successful' in half. Higher systolic blood pressure independently predicted successful diuretic dose decrease. In contrast, peripheral (but not pulmonary) congestion as well as sleep apnoea and mitral regurgitation independently predicted unsuccessful LD dose decrease. Taken together, these findings suggest that LD dose decrease should be attempted more often in stable euvolaemic patients, whereas in patients with peripheral congestion, LD should not be reduced and perhaps increased. This hypothesis warrants testing in randomized trials.

Supplementary Information

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

Table S1. Rates of loop diuretic dose changes among patients with guideline-directed medical therapy changes. Data presented in overall cohort and stratified by ejection fraction group (HFrEF, HFmrEF and HFpEF).

Table S2. Univariable logistic regression analysis with increase/initiation in guideline-directed medical therapy as dependent and diuretic dose change as independent variables.

Table S3. Data availability and rates of 12-month study outcomes among the overall study cohort and across the three groups of loop diuretic dose change.

Table S4. Multivariable Cox regression analyses for study outcomes.

Table S5. Multivariable Cox regression analyses for the study outcomes stratified by ejection fraction group.

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Appendix

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