

SUPPLEMENT

Supplementary Table 1. Rates of LD dose changes among patients with guideline-directed medical treatment changes. Data presented in overall cohort and stratified by ejection fraction group (HFrEF, HFmrEF and HFpEF)

Variable	Modality	Total (N=8130)	ACEi ARB BB or MRA Start or increase (N=2439)	ACEi ARB BB and MRA no change (or one is incr and another decr) (N=5213)	ACEi ARB BB or MRA Stop or decrease (N=470)	P- value
Diuretic dose status among all patients	Diuretic dose decreased	671/8130 (8.3%)	287/2439 (11.8%)	281/5213 (5.4%)	101/470 (21.5%)	<0.001
	Diuretic dose increased	1279/8130 (15.7%)	700/2439 (28.7%)	498/5213 (9.6%)	81/470 (17.2%)	
	Stable diuretic dose	6180/8130 (76.0%)	1452/2439 (59.5%)	4434/5213 (85.1%)	288/470 (61.3%)	
Diuretic dose status among all patients with available data on HF Status	Diuretic dose decreased	659/7874 (8.4%)	283/2365 (12.0%)	274/5042 (5.4%)	100/459 (21.8%)	<0.001
	Diuretic dose increased	1239/7874 (15.7%)	674/2365 (28.5%)	488/5042 (9.7%)	77/459 (16.8%)	
	Stable diuretic dose	5976/7874 (75.9%)	1408/2365 (59.5%)	4280/5042 (84.9%)	282/459 (61.4%)	
Diuretic dose status among HFrEF patients	Diuretic dose decreased	414/4879 (8.5%)	199/1566 (12.7%)	152/3033 (5.0%)	61/274 (22.3%)	<0.001
	Diuretic dose increased	726/4879 (14.9%)	403/1566 (25.7%)	281/3033 (9.3%)	42/274 (15.3%)	
	Stable diuretic dose	3739/4879 (76.6%)	964/1566 (61.6%)	2600/3033 (85.7%)	171/274 (62.4%)	
Diuretic dose status among HFmrEF patients	Diuretic dose decreased	121/1493 (8.1%)	51/463 (11.0%)	55/954 (5.8%)	15/74 (20.3%)	<0.001
	Diuretic dose increased	245/1493 (16.4%)	152/463 (32.8%)	78/954 (8.2%)	15/74 (20.3%)	
	Stable diuretic dose	1127/1493 (75.5%)	260/463 (56.2%)	821/954 (86.1%)	44/74 (59.5%)	
Diuretic dose status among HFpEF patients	Diuretic dose decreased	124/1502 (8.3%)	33/336 (9.8%)	67/1055 (6.4%)	24/111 (21.6%)	<0.001
	Diuretic dose increased	268/1502 (17.8%)	119/336 (35.4%)	129/1055 (12.2%)	20/111 (18.0%)	
	Stable diuretic dose	1110/1502 (73.9%)	184/336 (54.8%)	859/1055 (81.4%)	67/111 (60.4%)	

Supplementary Table 2. Univariable logistic regression analysis with increase/initiation in guideline-directed medical treatment (GDMT) as dependent and diuretics dose change as independent variables

Description	Statistics	Results
Sample size	n/N	8109/8117
Diuretic change Effect	P value	<0.001 (S)
-Diuretic change decrease vs stable	OR (95% CI)	2.444 (2.074;2.880)
-Diuretic change increase vs stable	OR (95% CI)	3.929 (3.468;4.452)
-Diuretic change increase vs decrease	OR (95% CI)	1.608 (1.331;1.942)
-Diuretic change stable vs decrease	OR (95% CI)	0.409 (0.347;0.482)

* GDMT includes beta-blockers, ACEi/ARBs and MRAs. GDMT increase/initiation is defined as: Yes if increase of dose or start of at least one of the 3 drug categories without decrease or stop in any other category. No otherwise i.e. no change in any of the three or decrease/stop in any of the 3 drugs and increase/start of another category. Patients receiving the optimal GDMT for all 3 drugs both prior and during baseline are excluded

Supplementary Table 3. Data availability and rates of 12-month study outcomes among the overall study cohort and across the three groups of LD dose change

Variable	Modality	All (N=8130)	Diuretic dose increased (N=1279)	Stable diuretic dose (N=6180)	Diuretic dose decreased (N=671)	P-value
Death	No	7142/7899 (90.4%)	1064/1233 (86.3%)	5479/6016 (91.1%)	599/650 (92.2%)	<0.001
	Yes	757/7899 (9.6%)	169/1233 (13.7%)	537/6016 (8.9%)	51/650 (7.8%)	
	ND	231	46	164	21	
CV Death	No	7311/7696 (95.0%)	1105/1192 (92.7%)	5593/5871 (95.3%)	613/633 (96.8%)	<0.001
	Yes	385/7696 (5.0%)	87/1192 (7.3%)	278/5871 (4.7%)	20/633 (3.2%)	
	ND	434	87	309	38	
HF Death	No	7428/7685 (96.7%)	1125/1189 (94.6%)	5686/5865 (96.9%)	617/631 (97.8%)	<0.001
	Yes	257/7685 (3.3%)	64/1189 (5.4%)	179/5865 (3.1%)	14/631 (2.2%)	
	ND	445	90	315	40	
CV Death among dead	No	169/554 (30.5%)	41/128 (32.0%)	114/392 (29.1%)	14/34 (41.2%)	0.310
	Yes	385/554 (69.5%)	87/128 (68.0%)	278/392 (70.9%)	20/34 (58.8%)	
	ND	203	41	145	17	
HF Death among dead	No	286/543 (52.7%)	61/125 (48.8%)	207/386 (53.6%)	18/32 (56.3%)	0.589
	Yes	257/543 (47.3%)	64/125 (51.2%)	179/386 (46.4%)	14/32 (43.8%)	
	ND	214	44	151	19	
HF Hospitalization	No	6445/7540 (85.5%)	933/1152 (81.0%)	4971/5764 (86.2%)	541/624 (86.7%)	<0.001
	Yes	1095/7540 (14.5%)	219/1152 (19.0%)	793/5764 (13.8%)	83/624 (13.3%)	
	ND	590	127	416	47	
Death/Rehospitalization due to HF for KM	No	6497/8130 (79.9%)	939/1279 (73.4%)	5006/6180 (81.0%)	552/671 (82.3%)	<0.001
	Yes	1633/8130 (20.1%)	340/1279 (26.6%)	1174/6180 (19.0%)	119/671 (17.7%)	
	ND	0	0	0	0	

* ND: not determined

Supplementary Table 4. Multivariable Cox regression analyses for study outcomes

Covariable	All-cause mortality		CV mortality		HF mortality		HF hospitalization	
	HR (95% CI)	P-value	HR (95% CI)	P-value HR	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (in years)	1.026 (1.018;1.033)	<0.001	1.027 (1.017;1.037)	<0.001	1.028 (1.016;1.040)	<0.001	NA	NA
Atrial fibrillation	NA	NA	NA	NA	NA	NA	1.299 (1.138;1.483)	<0.001
BMI	0.963 (0.945;0.980)	<0.001	0.936 (0.912;0.961)	<0.001	0.933 (0.904;0.963)	<0.001	NA	NA
Chronic kidney dysfunction	1.761 (1.484;2.091)	<0.001	1.720 (1.356;2.182)	<0.001	2.181 (1.645;2.892)	<0.001	1.730 (1.500;1.995)	<0.001
Depression	1.390 (1.082;1.786)	0.010	1.574 (1.126;2.200)	0.008	1.809 (1.245;2.630)	0.002	1.258 (1.008;1.569)	0.042
Diabetes	1.262 (1.065;1.494)	0.007	1.336 (1.058;1.688)	0.015	NA	NA	1.321 (1.154;1.513)	<0.001
HF history with previous hospitalization	1.252 (1.065;1.472)	0.006	1.554 (1.235;1.957)	<0.001	1.597 (1.205;2.118)	0.001	1.694 (1.478;1.941)	<0.001
Mitral regurgitation moderate-severe	1.305 (1.108;1.536)	0.001	1.390 (1.111;1.740)	0.004	1.400 (1.067;1.837)	0.015	1.245 (1.087;1.426)	0.002
NYHA III/IV	1.692 (1.426;2.007)	<0.001	2.050 (1.624;2.589)	<0.001	2.537 (1.917;3.359)	<0.001	1.928 (1.679;2.214)	<0.001
Elevated JVP	NA	NA	NA	NA	NA	NA	1.327 (1.125;1.566)	<0.001
Peripheral edema	1.410 (1.176;1.691)	<0.001	1.466 (1.149;1.870)	0.002	NA	NA	NA	NA
Primary Etiology Ischemic heart disease	1.194 (1.012;1.408)	0.035	NA	NA	NA	NA	NA	NA
Pulmonary rales	1.263 (1.039;1.534)	0.019	NA	NA	NA	NA	NA	NA
Male Sex	1.251 (1.032;1.517)	0.023	1.366 (1.048;1.780)	0.021	NA	NA	1.250 (1.071;1.459)	0.005
Systolic BP (per 10mmHg)	0.837 (0.801;0.873)	<0.001	0.763 (0.716;0.813)	<0.001	0.726 (0.671;0.786)	<0.001	0.895 (0.865;0.926)	<0.001
Dose decreased	0.874 (0.642;1.190)	0.394	0.620 (0.383;1.005)	0.052	0.593 (0.328;1.070)	0.083	0.849 (0.662;1.089)	0.197
Dose increased	1.162 (0.955;1.414)	0.135	1.248 (0.956;1.628)	0.103	1.525 (1.119;2.080)	0.008	1.108 (0.936;1.311)	0.232

Supplementary Table 5. Multivariable Cox regression analyses for the study outcomes mortality stratified by ejection fraction group

	HF _r EF		HF _{mr} EF		HF _p EF	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
All-cause mortality						
LD Dose decreased	0.890 (0.606;1.306)	0.550	0.845 (0.405;1.761)	0.653	1.149 (0.571;2.309)	0.697
LD Dose increased	1.242 (0.974;1.584)	0.080	0.923 (0.585;1.457)	0.732	1.223 (0.766;1.953)	0.399
CV mortality						
LD dose decreased	0.625 (0.347;1.127)	0.118	0.553 (0.169;1.815)	0.329	1.108 (0.388;3.167)	0.848
LD dose increased	1.168 (0.836;1.632)	0.364	0.980 (0.521;1.843)	0.949	2.037 (1.090;3.810)	0.026
HF mortality						
LD dose decreased	0.583 (0.283;1.198)	0.142	0.321 (0.043;2.408)	0.269	1.743 (0.589;5.159)	0.316
LD dose increased	1.398 (0.949;2.060)	0.090	1.397 (0.660;2.956)	0.382	2.472 (1.188;5.143)	0.015
HF hospitalization						
LD dose decreased	0.758 (0.556;1.034)	0.080	1.452 (0.839;2.514)	0.183	0.973 (0.547;1.732)	0.926
LD dose increased	1.140 (0.929;1.398)	0.209	1.235 (0.811;1.879)	0.326	0.970 (0.646;1.458)	0.884