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Loop Diuretic Prescription and 30 Day Outcomes in Older Patients With Heart Failure

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Abstract

BACKGROUND—Heart failure (HF) is a major source of morbidity and mortality. Fluid retention and shortness of breath are its cardinal manifestations for which loop diuretics are used.

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Although their usefulness is well accepted, less is known about their role in improving clinical outcomes.

OBJECTIVES—To determine the relationship between loop diuretics and clinical outcomes in patients with HF.

METHODS—Of the 25,345 older patients hospitalized for HF in Medicare-linked OPTIMIZE-HF registry, 9,866 (39%) received no pre-admission diuretics. We excluded 1,083 patients receiving dialysis and 847 discharged on thiazide diuretics. Of the remaining 7,936 patients, 5,568 (70%) were prescribed loop diuretics at discharge. Using propensity scores for receipt of loop diuretics estimated for each of the 7,936 patients, we assembled a matched cohort of 2,191 pairs of patients, balanced on 74 baseline characteristics. Hazard ratios (HRs) and 95% confidence intervals (CIs) for outcomes were estimated in the matched cohort.

RESULTS—Matched patients (N=4,382) had a mean age of 78 years, 54% were women, and 11% African American. 30-day all-cause mortality occurred in 4.9% (107/2,191) and 6.6% (144/2,191) of patients in the loop diuretic and no loop diuretic groups, respectively (HR when the use of loop diuretics was compared to their nonuse, 0.73; 95% CI, 0.57–0.94; p=0.016). Patients in the loop diuretic group had a significantly lower risk of 30-day HF readmission (HR, 0.79; 95% CI, 0.63–0.99; p=0.037) but not of 30-day all-cause readmission (HR, 0.89; 95% CI, 0.79–1.01; p=0.081). None of the associations was statistically significant during 60 days of follow-up.

CONCLUSION—Hospitalized older patients not taking diuretics prior to hospitalization for HF decompensation who received a discharge prescription for loop diuretics had significantly better 30-day clinical outcomes than those not discharged on loop diuretics. These findings provide new information about short-term clinical benefits associated with loop diuretic use in HF.

Tweet:

Discharge prescription of loop diuretics is linked to improved 30-day outcomes in hospitalized patients with heart failure.

Condensed Abstract:

Loop diuretics improve fluid retention and dyspnea and are essential for the management of heart failure (HF). However, less is known about the association between loop diuretic use and clinical outcomes. Findings from the current propensity score-matched study suggest that in hospitalized older patients not taking diuretics prior to hospitalization for HF decompensation, loop diuretic prescription at discharge is associated with a lower risk of 30-day mortality and readmission.

Keywords

Heart failure; Loop diuretics; Outcomes

Heart failure (HF) is a major cause of morbidity and mortality and is a leading cause for hospitalization (1). Fluid retention is central to the pathophysiology of HF and underlies the cardinal manifestations of HF which are shortness of breath and edema (2). Loop diuretics frequently are the only drugs that can adequately control fluid retention in HF (1,3). According to the American College of Cardiology Foundation / American Heart

Association (ACCF/AHA) HF guideline, "*diuretics have been shown to improve symptoms and exercise tolerance in patients with heart failure*", however, "*diuretic effects on morbidity and mortality are not known*" (1). The objective of the current study was to examine the association between loop diuretics and clinical outcomes in patients with HF with reduced and preserved ejection fraction (HFrEF and HFpEF).

Methods

Data Source and Study Population

We used data from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry for the current analysis. OPTIMIZE-HF is a web-based registry of 48,612 HF hospitalizations in 259 hospitals from 48 states between March 1, 2003 and December 31, 2004 (4–8). Extensive baseline data were collected, and data on long-term outcomes were later obtained for 26,376 unique patients by linking with the Medicare data (Figure 1) (9). Of the 26,376 patients, 25,345 were discharged alive. The OPTIMIZE-HF protocol was approved by each participating center's institutional review board (RB) or by a central IRB (5). Data used for the current analysis was approved by the IRB and Research and Development Committee of the Veterans Affairs Medical Center, Washington, DC.

Assembly of an Inception Cohort

To minimize prevalent-user bias, we assembled an inception cohort by excluding 15,479 patients who were taking diuretics prior to hospitalization for HF decompensation (10,11). We then excluded 728 patients with a history of dialysis and 355 who received dialysis during hospitalization (Figure 1). Because thiazide diuretics have less diuretic effect, have a different mechanism of action, and may augment the effect of loop diuretics (1,12), we excluded 847 patients discharged on thiazide diuretics (Figure 1). Thus, our study sample included 7,936 patients. Of the 7,936 patients, 5,568 received a discharge prescription for loop diuretics and 2,368 did not.

Assembly of a Balanced Cohort

In a randomized controlled trial (RCT) of diuretics, all patients will have a 50% probability of receiving the drug regardless of whether one received it or not. The probability of receiving a prescription for diuretics in the clinical practice setting, however, would be influenced by measured and unmeasured baseline characteristics and would vary between 0 and 100%. This conditional probability, also known as a propensity score (13,14), can be estimated to assemble a matched cohort in which patients receiving and not receiving a prescription for diuretics will be balanced on measured baseline characteristics. This balance is measured as an absolute standardized difference, and baseline characteristics with values <10% are considered balanced (0% implies no bias). Although within a matched pair patients receiving and not receiving a prescription for diuretics may not have the same baseline characteristics, they will have a similar probability of receiving the drug (15–17). Thus, like randomization, propensity score matching is a study design tool. As in an RCT, the process of assembling a propensity score-matched cohort is outcome blinded (18,19), but unlike in an RCT, it may not balance unmeasured baseline characteristics. However,

sensitivity analysis (described later) can determine their impact on observed significant associations.

We used a non-parsimonious multivariable logistic regression model to estimate propensity scores for the receipt of loop diuretics for each of the 7,936 patients. We used 74 baseline patient and care characteristics listed in Supplemental Figure 1 as covariates in the model. Using a greedy matching algorithm described elsewhere in detail (6–8,20), we matched 2,191 patients receiving a prescription for loop diuretics with 2,191 patients not receiving one based on their propensity scores. Among the 4,382 matched patients, those receiving and not receiving a prescription for loop diuretics had the same 67% probability of receiving those drugs (mean propensity score, 0.67; ±standard deviation, 0.13 for both study groups; p=0.950). We then estimated absolute standardized differences for all 74 baseline characteristics to assess their post-match balance.

Outcomes Data—Our outcomes of interest were HF readmission, all-cause readmission, and all-cause mortality. We also examined two combined endpoints of either readmission or mortality. We examined these outcomes at 30 and 60 days after hospital discharge. Data on all events and time to events were collected from the Medicare data (9).

Statistical Analyses—Descriptive analyses were conducted using the Pearson chi-square and Wilcoxon rank sum tests. All outcome analyses were conducted in the matched cohort in which patients receiving and not receiving a prescription for loop diuretics were balanced on 74 baseline characteristics. Kaplan-Meier survival analysis were used to generate plots for all-cause mortality and HF readmission. Cox regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) associated with loop diuretic use. Because patients in the matched cohort were balanced on 74 baseline characteristics, the Cox regression model was not adjusted for these variables. Assumption of the proportional hazard was assessed by visual examinations of the log (minus log) curves. Formal sensitivity analyses were conducted using Rosenbaum's approach (21) described elsewhere in detail (6,7). All outcomes were analyzed separately among patients with HFrEF and HFpEF, defined as EF <45% and ≥45%, respectively. Additional subgroup analyses were conducted to determine the homogeneity of the association in other clinically relevant subgroups. All statistical tests were 2-tailed, and a p value <0.05 was considered significant. SPSS for Windows version 26 (IBM Corp., Armonk, NY) and SAS for Window version 9.2 (Cary, NC) were used for data analyses.

Results

Baseline Characteristics

Patients in the propensity score-matched cohort (n=4,382) had a mean (±standard deviation) age of 78 (±10) years, 54% were women, and 11% were African American. Before matching, patients in the loop diuretic group were older and had a higher prevalence of signs and symptoms of HF (Table 1). After propensity score matching, all 74 baseline characteristics had an absolute standardized difference <5%, 56 had values <2%, and 41 had values <1% (0% indicates no residual bias; Supplemental Figure 1).

30-Day All-Cause Mortality

Among the 2,191 pairs of propensity score-matched patients who were not taking diuretics prior to hospitalization for HF decompensation, 30-day all-cause mortality occurred in 4.9% (107/2,191) and 6.6% (144/2,191) of the patients receiving and not receiving a discharge prescription for loop diuretics, respectively (HR when receipt of a discharge prescription for loop diuretics was compared with its non-receipt, 0.73; 95% CI, 0.57–0.94; p=0.016; Table 2, Central Illustration). Findings of the formal sensitivity analysis are presented in Table 2 (footnote). The association between discharge prescription for loop diuretics and mortality attenuated during 60 days of follow-up and lost statistical significance (Table 2, Central Illustration).

30-day all-cause mortality occurred in 5.7% (62/1,084) and 6.6% (78/1,075) of the patients with HFrEF receiving and not receiving loop diuretics, respectively (HR, 0.78; 95% CI, 0.56–1.09; P=0.147), and 4.1% (45/1,107) and 5.9% (66/1,116) of the patients with HFpEF receiving and not receiving loop diuretics, respectively (HR, 0.68; 95% CI, 0.46–0.99; p=0.043; p for interaction=0.582; data not presented). The associations were not different when EF was used as a continuous variable (p for interaction=0.889).

30-Day Readmissions

Among the 2,191 pairs of propensity score-matched patients, 30-day HF readmission occurred in 6.2% (135/2,191) and 7.7% (168/2,191) of the patients in the loop diuretic and no loop diuretic groups, respectively (HR associated with loop diuretic prescription, 0.79; 95% CI, 0.63–0.99; p=0.037; Table 2, Central Illustration). Findings of the formal sensitivity analysis are presented in Table 2 (footnote). Loop diuretic prescription had no significant association with 30-day non-HF readmission (HR, 0.84; 95% CI, 0.63–1.13; p=0.729; data not presented in Table 2) and 30-day all-cause readmission (HR, 0.89; 95% CI, 0.79–1.01; p=0.081; Table 2). The association of loop diuretic prescription at discharge had no significant association with HF or all-cause readmissions during 60 days of follow-up (Table 2).

30-day HF readmission occurred in 6.4% (69/1,084) and 8.2% (88/1,075) of HFrEF patients receiving and not receiving loop diuretics, respectively (HR, 0.76; 95% CI, 0.56–1.04; p=0.090), and 6.0% (66/1,107) and 7.2% (80/1,116) of HFpEF patients receiving and not receiving loop diuretics, respectively (HR, 0.81; 95% CI, 0.59–1.12; p=0.210; data not presented). The associations were not different between HFrEF versus HFpEF (p for interaction=0.937) or when EF was used as a continuous variable (p for interaction=0.909).

30-Day Combined Endpoints

The combined endpoint of 30-day HF readmission or all-cause mortality occurred in 11% (233/2,191) and 14% (299/2,191) of the patients receiving and not receiving loop diuretics, respectively (HR associated with loop diuretic prescription, 0.76; 95% CI, 0.64–0.91; p=0.002; Table 2, Figure 2). There was also an associated lower risk for the combined endpoint of 30-day all-cause readmission or all-cause mortality (Table 2). Findings of the formal sensitivity analysis are presented in Table 2 (footnote). Associations with

both combined endpoints were attenuated during 60 days of follow-up and lost statistical significance (Table 2).

Among patients with HFrEF, the combined endpoint of 30-day HF readmission or all-cause mortality occurred in 11.6% (126/1,084) and 15.1% (162/1,075) of the patients in the loop diuretic and no loop diuretic groups, respectively (HR, 0.76; 95% CI, 0.60–0.95; p=0.019; Figure 2). Among patients with HFpEF, these events occurred in 9.7% (107 /1,107) and 12.3% (137/1,116) of the patients in the loop diuretic and no loop diuretic groups, respectively (HR, 0.77; 95% CI, 0.60–0.99; p=0.042; p for interaction=0.956; Figure 2).

Subgroup Analyses

Findings from other subgroup analyses of the combined endpoint of 30-day HF readmission or all-cause mortality are displayed in Figure 2. The association of discharge prescription for loop diuretics with the combined endpoint of 30-day HF readmission or all-cause mortality was generally homogeneous in other clinically relevant subgroups except that it was significantly stronger in subgroups with admission pulmonary rales and lower extremity edema (Figure 2). HRs (95% CIs) for the combined endpoint in subgroups with and without pulmonary rales were 0.62 (0.50–0.77; p<0.001) and 1.08 (0.81–1.43; p=0.604), respectively (p for interaction=0.003; Figure 2). This association was also significantly different between subgroups with and without lower extremity edema (p for interaction=0.001; Figure 2).

Discussion

Findings from the current study demonstrate that a loop diuretic prescription at discharge was associated with a significant albeit modest reduction in the risk of 30-day HF readmission in older patients hospitalized for HF decompensation who were not taking diuretics prior to hospitalization (Central Illustration). A loop diuretic prescription was also associated with a lower risk of 30-day all-cause mortality as well as of the combined endpoint of 30-day HF readmission or all-cause mortality. We also observed that these associations were homogeneous in subgroups with reduced and preserved EF. All associations attenuated during 60 days of follow-up and were no longer statistically significant (Central Illustration). To the best of our knowledge, this is the first report on the association between loop diuretic prescription and improved 30-day clinical outcomes in patients with HFrEF and HFpEF. These results suggest that the clinical benefits associated with loop diuretic use in patients with HF may extend beyond mere symptom alleviation to improved clinical outcomes.

Loop diuretics increase urinary sodium excretion in the loop of Henle by inhibiting the sodium-potassium-chloride cotransporter 2 (22). Findings from small RCTs with short follow-up suggest that loop diuretics may improve signs and symptoms of fluid retention in patients with HF (23–26). These findings may in part explain the lower risk of 30-day HF readmission observed in our study. This is supported by the findings from our subgroup analysis that suggest diuretic-associated clinical benefits were greater in subgroups with evidence of congestion such as pulmonary rales and lower extremity edema. This is also supported by our observation that the use of loops diuretics was not associated with a lower risk of non-HF related readmissions. The lower risk of 30-day all-cause mortality in the

diuretic group is intriguing but may be mediated by improved HF symptoms and lower HF readmission risk. Continued congestion and hospitalization after discharge have been shown to be associated with a higher risk of death in patients with HF (27–30).

Several observations from our study suggest that the associations observed in our study may be an underestimation of the true associations of outcomes with loop diuretics. Because patients in our study were hospitalized for decompensated HF, presumably all were initiated on loop diuretics during hospitalization, which likely attenuated between-group differences in congestive symptoms and signs before discharge. Patients in the loop diuretics group also had a higher burden of congestion before admission (Table 1). Even though these and other measured baseline characteristics were balanced after matching, residual confounding and unmeasured confounding may have further attenuated the true associations. Finally, if some patients were restarted on loop diuretics due to congestion during the first 30 days, then the resultant misclassification would even further dilute the true associations. If more patients were restarted on diuretics during the second month that may explain the loss of significance of the 60-day associations. Taken together, the inpatient use of loop diuretics in all patients, the post-discharge resumption of loop diuretics in the no-diuretic group, and the potential residual/unmeasured confounding by a higher disease/symptom burden of the loop diuretic group suggest that the actual associations of loop diuretics with 30-day outcomes may be even greater than those detected in our study.

Information provided by the current study has practical implications for clinicians involved in HF care. Despite the general impression that most clinicians would use loop diuretics to relieve symptoms in nearly all patients with HF, findings from our study suggest that many patients hospitalized for HF decompensation were not receiving diuretics before hospitalization. Furthermore, a substantial portion of these patients was discharged without a loop diuretic prescription. A potential explanation for this is that HF symptoms of these patients appeared resolved, and loop diuretics were not considered necessary as these drugs are currently recommended only for improving symptoms (1). HF remains a leading cause for 30-day hospital readmission for older adults. The new message from our study is that prescription of loop diuretics at discharge may be associated with a lower risk of short-term rehospitalizations and mortality in these patients. These findings are expected to clarify the role of loop diuretics in HF and strengthen the evidence for the guideline recommendation on loop diuretics.

Limitations

Several limitations of our study need to be acknowledged. Even though patients receiving and not receiving a discharge prescription for loop diuretics were balanced on 74 measured characteristics at the time of the prescription (at study baseline) it is possible that as discussed above, observed significant associations are underestimated by residual and unmeasured confounding. The findings of our sensitivity analyses suggest that significant 30-day associations observed in our study may be sensitive to an unmeasured confounder. However, sensitivity analysis cannot determine whether an unmeasured confounder exists or not. Further, such a confounder would need to be a near-perfect predictor of the outcomes of the significant 30-day associations and also not have strong associations with any of the

74 measured baseline characteristics used in our study. We did not have access to data on loop diuretic doses or start/ re-start/ discontinuation after hospital discharge. Prior studies have suggested frequent adjustment of diuretics after hospital discharge (1). Like other guideline-recommended therapies, it is not only their use that may be important but also attention to adequate dosing at discharge, titration after discharge, and close monitoring. Although the management of HF has evolved in the past several decades, the role of loop diuretics has not. Our study is based on fee-for-service Medicare beneficiaries, which may limit generalizability. Findings from the current study may not be generalized to patients with renal failure requiring dialysis.

Conclusions

Among older patients hospitalized for decompensated heart failure who were not taking diuretics before hospitalization, a loop diuretic prescription at discharge is associated with a significantly lower risk of 30-day all-cause mortality and heart failure readmission. These findings provide new information that may strengthen guideline recommendations and improve short-term clinical outcomes in patients with heart failure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

EF	ejection fraction
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
OPTIMIZE-HF	Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure
RCT	randomized controlled trial

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Perspectives

Competency in Patient Care: For older patients hospitalized with decompensated heart failure not taking diuretics prior to admission, prescription of a loop diuretic at discharge is associated with a lower 30-day risk of re-admission and mortality.

Translational Outlook: Future studies should examine the relationship of loop diuretic dosage at discharge and titration after discharge with longer-term clinical outcomes.

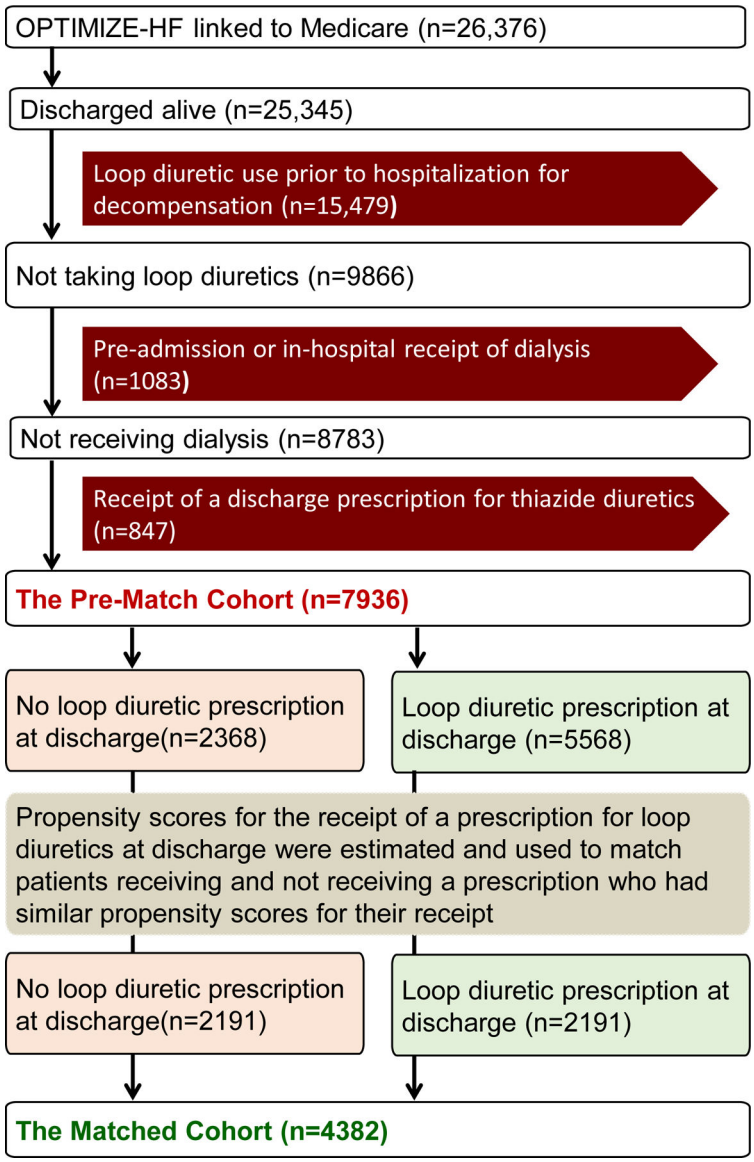


Figure 1. Assembly of the Study Cohort.

Flow chart displaying assembly of a propensity score-matched cohort of older patients hospitalized for heart failure decompensation who were not taking diuretics prior to hospitalization, by loop diuretic prescription at discharge. OPTIMIZE-HF = Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure.

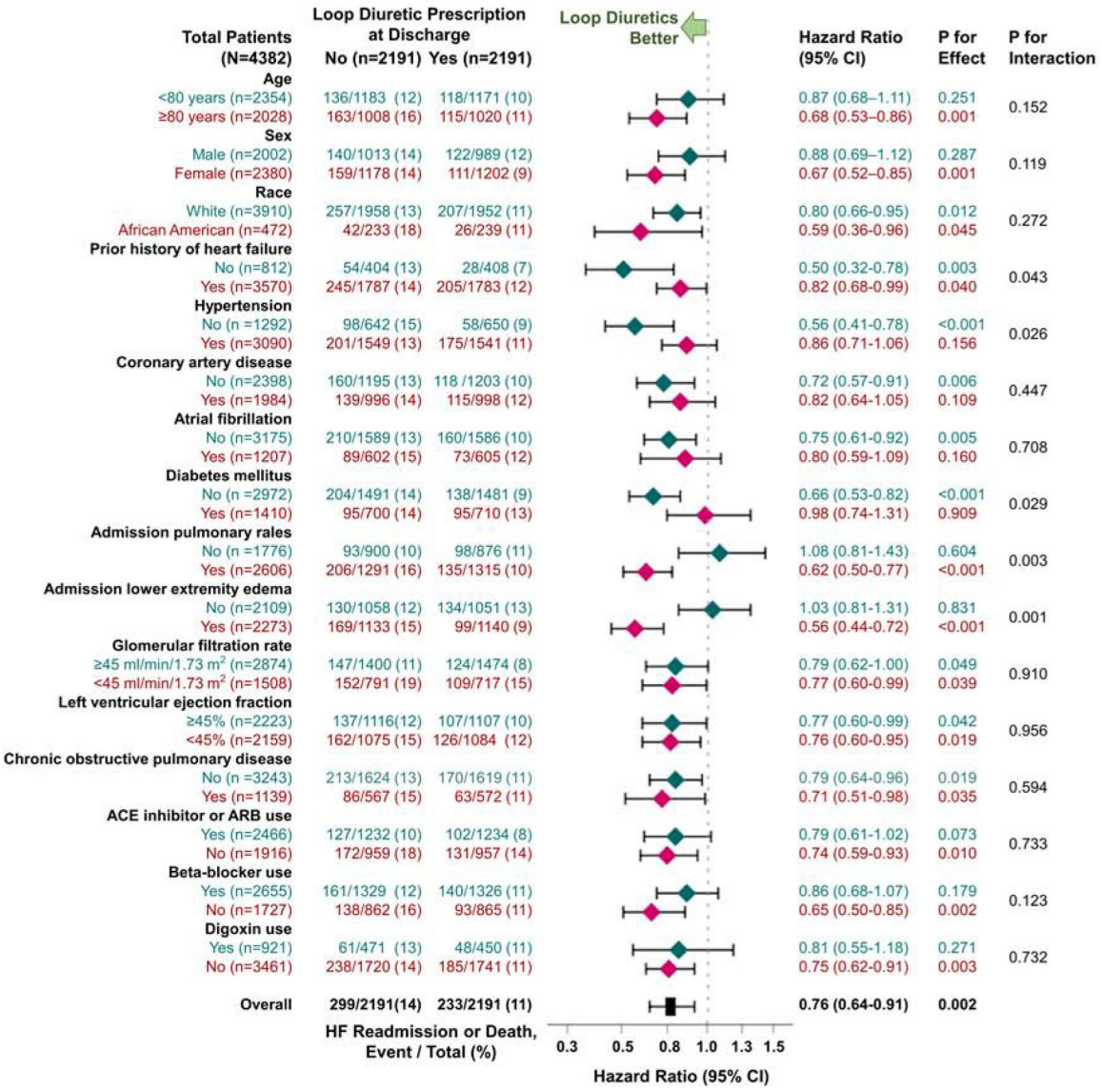
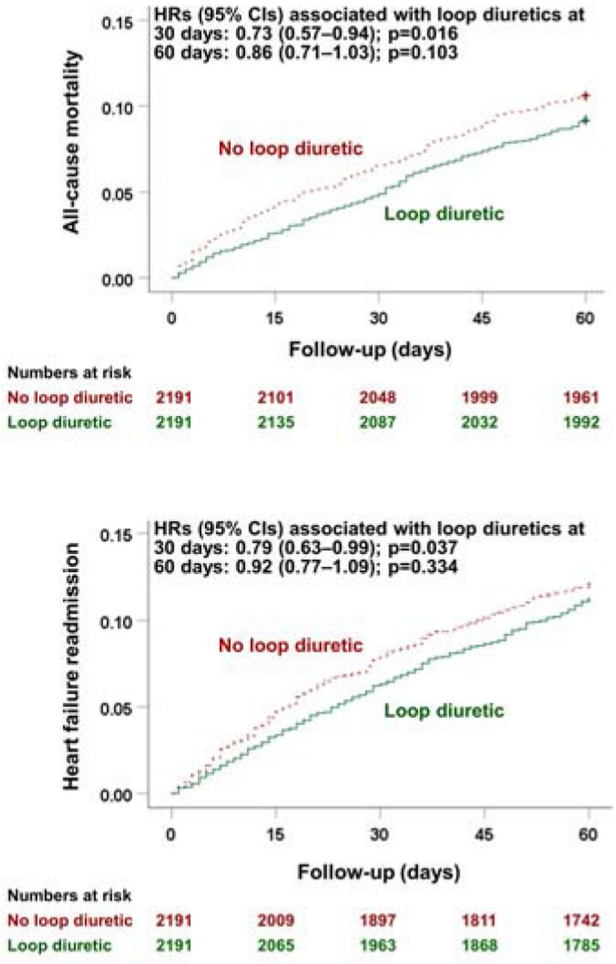


Figure 2: Forest Plots for Subgroup Analyses by Loop Diuretic Initiation.

In all subgroups analyzed, older patients hospitalized for heart failure decompensation who were not taking diuretics prior to hospitalization, those who received a prescription for loop diuretics at discharge had a lower risk of the combined endpoint of heart failure readmission or all-cause mortality during the first 30 days of follow-up after hospital discharge compared with patients who did not receive a loop diuretic prescription, except by history of prior heart failure, hypertension, diabetes mellitus admission pulmonary rales, and admission lower extremity edema. Note: Results of subgroup analyses need to be interpreted with caution as they may be false positive due to multiple comparisons and false negative due to inadequate power. ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker, CI = confidence interval.



Central Illustration: Kaplan-Meier Plots by Loop Diuretic Prescription

This study assessed the relationship of prescription of loop diuretics at the time of hospital discharge with all-cause mortality (top panel) and heart failure readmission (bottom panel) in 2191 pairs of propensity score-matched older patients hospitalized for heart failure decompensation who were not taking diuretics prior to hospitalization. During the first 30 days of follow-up after hospital discharge, a discharge prescription for loop diuretics was associated with a significantly lower risk of both outcomes. Both associations lost statistical significance during 60 days of follow-up. CI = confidence interval; HR = hazard ratio.

Table 1.

Baseline Characteristics by Discharge Prescription for Loop Diuretics in Older Patients With Heart Failure not Taking Diuretics Prior to Hospitalization for Heart Failure Decompensation

	Before propensity score matching (n=7,936)			After propensity score matching (n=4,382)		
	Discharge prescription of loop diuretics		P value	Discharge prescription of loop diuretics		P value
	No (n=2,368)	Yes (n=5,568)		No (n=2,191)	Yes (n=2,191)	
Age, yrs	77.7 (±10.7)	78.3 (±10.2)	0.010	77.9 (±10.4)	77.8 (±10.5)	0.841
Age ≥70 years	1504 (64%)	3729 (67%)	0.003	1114 (65%)	1444 (66%)	0.341
Women	1274 (54%)	3061 (55%)	0.336	1178 (54%)	1202 (55%)	0.467
African American	242 (10%)	632 (11%)	0.141	233 (11%)	239 (11%)	0.770
Past medical history						
HF diagnosis before admission	1934 (82%)	4467 (80%)	0.136	1787 (82%)	1783 (81%)	0.876
HF hospitalization (prior 6 mos.)	288 (12%)	632 (11%)	0.301	263 (12%)	277 (13%)	0.520
Hypertension	1676 (71%)	3969 (71%)	0.649	1549 (71%)	1541 (70%)	0.791
Myocardial infarction	510 (22%)	1199 (22%)	0.997	470 (21%)	479 (22%)	0.741
Diabetes mellitus	769 (32%)	1862 (33%)	0.403	700 (32%)	710 (32%)	0.746
Peripheral vascular disease	307 (13%)	684 (12%)	0.402	280 (13%)	283 (13%)	0.892
Atrial fibrillation	641 (27%)	1658 (30%)	0.015	602 (27%)	605 (28%)	0.919
COPD	614 (26%)	1346 (24%)	0.097	567 (26%)	572 (26%)	0.863
Acute kidney insufficiency	66 (3%)	94 (2%)	0.001	57 (3%)	52 (2%)	0.628
Admission symptoms and signs						
Dyspnea on exertion	1351 (57%)	3530 (63%)	<0.001	1275 (58%)	1265 (58%)	0.760
Orthopnea	474 (20%)	1420 (26%)	<0.001	459 (21%)	449 (20%)	0.709
Paroxysmal nocturnal dyspnea	259 (11%)	797 (14%)	<0.001	250 (11%)	249 (11%)	0.962
Dyspnea at rest	951 (40%)	2434 (44%)	0.003	895 (41%)	890 (41%)	0.878
JVP elevation	499 (21%)	1501 (27%)	<0.001	478 (22%)	472 (22%)	0.826
Third heart sound	150 (6%)	445 (8%)	0.010	141 (6%)	138 (6%)	0.853
Pulmonary rales	1362 (58%)	3641 (65%)	<0.001	1291 (59%)	1315 (60%)	0.460
Lower extremity edema						
None to trace	1536 (65%)	2924 (53%)		1387 (63%)	1393 (64%)	
Mild to moderate (1+ to 2+)	659 (28%)	2002 (36%)	<0.001	635 (29%)	628 (29%)	0.973
Severe (3+ to 4+)	173 (7%)	642 (12%)		169 (8%)	170 (8%)	
Other admission clinical findings						
Weight (kilogram)	75 (±18)	76 (±18)	0.100	75 (±18)	75 (±18)	0.348
Heart rate, beat/min	89 (±22)	88 (±22)	0.394	88 (±22)	88 (±22)	0.378

	Before propensity score matching (n=7,936)			After propensity score matching (n=4,382)		
	Discharge prescription of loop diuretics		P value	Discharge prescription of loop diuretics		P value
	No (n=2,368)	Yes (n=5,568)		No (n=2,191)	Yes (n=2,191)	
Systolic blood pressure, mmHg	147 (±32)	147 (±31)	0.466	147 (±32)	148 (±32)	0.910
Diastolic blood pressure, mmHg	76.5 (±16.4)	77.4 (±16.0)	0.022	76.8 (±16.3)	76.9 (±15.9)	0.847
Admission laboratory findings						
Serum creatinine, mg/dL	1.4 (±0.6)	1.3 (±0.5)	<0.001	1.3 (±0.6)	1.3 (±0.6)	0.358
Serum sodium, mEq/L	138 (±5)	138 (±5)	0.111	138 (±5)	138 (±5)	0.922
Serum hemoglobin, g/dL	12 (±2)	12 (±2)	0.905	12 (±2)	12 (±2)	0.747
Serum pro-BNP, pg/mL	1035 (507–1173)	1053 (556–1273)	0.011	1039 (509–1179)	1034 (517–1220)	0.763
Serum troponin level elevation	458 (19%)	1027 (18%)	0.349	411 (19%)	430 (20%)	0.466
LVEF, %	43 (±14)	42 (±15)	0.013	43 (±14)	43 (±15)	0.945
LVEF ≤40%	1027 (43%)	2641 (47%)		943 (43%)	963 (44%)	
LVEF 41–49%	386 (16%)	789 (14%)	0.002	354 (16%)	350 (16%)	0.828
LVEF ≥50%	955 (40%)	2138 (38%)		894 (41%)	878 (40%)	
In-hospital medications and interventions						
Dobutamine parenteral infusion	59 (2%)	127 (2%)	0.570	52 (2%)	58 (3%)	0.562
Dopamine parenteral infusion	75 (3%)	120 (2%)	0.008	57 (3%)	58 (3%)	0.925
Nesiritide parenteral infusion	166 (7%)	494 (9%)	0.006	154 (7%)	168 (8%)	0.418
Mechanical ventilation	68 (3%)	130 (2%)	0.161	63 (3%)	62 (3%)	0.928
Discharge medications						
ACE inhibitors or ARBs	1241 (52%)	3781 (68%)	<0.001	1232 (56%)	1234 (56%)	0.951
Beta blockers	1369 (58%)	3662 (66%)	<0.001	1329 (61%)	1326 (61%)	0.926
Aldosterone antagonists	147 (6%)	604 (11%)	<0.001	145 (7%)	147 (7%)	0.904
Digoxin	483 (20%)	1418 (25%)	<0.001	471 (21%)	450 (21%)	0.436
Amlodipine	175 (7%)	398 (7%)	0.703	167 (8%)	163 (7%)	0.819
Anti-arrhythmic drugs	252 (11%)	659 (12%)	0.127	242 (11%)	237 (11%)	0.809
Warfarin	456 (19%)	1347 (24%)	<0.001	451 (21%)	448 (20%)	0.911
Aspirin	1069 (45%)	2838 (51%)	<0.001	1031 (47%)	1064 (49%)	0.318
Discharge instructions						
Diet	1909 (81%)	4928 (89%)	<0.001	1850 (84%)	1826 (83%)	0.324
Medications	2005 (85%)	5182 (93%)	<0.001	1952 (89%)	1927 (88%)	0.236
Worsening symptoms	1442 (61%)	3729 (67%)	<0.001	1391 (63%)	1377 (63%)	0.661
Weight monitoring	1007 (43%)	2994 (54%)	<0.001	986 (45%)	994 (45%)	0.808
Follow-up	1979 (84%)	5044 (91%)	<0.001	1916 (87%)	1913 (87%)	0.891
Hospital length of stay, days	4 (2–7)	4 (3–7)	0.243	4 (2–7)	4 (3–7)	0.762

	Before propensity score matching (n=7,936)			After propensity score matching (n=4,382)		
	Discharge prescription of loop diuretics		P value	Discharge prescription of loop diuretics		P value
	No (n=2,368)	Yes (n=5,568)		No (n=2,191)	Yes (n=2,191)	
Hospital academic center	977 (41%)	2353 (42%)	0.408	905 (41%)	915 (42%)	0.759

Values are mean ±SD, n (%), or median (interquartile range). The p values comparing medians are based on nonparametric independent sample median test. ACE = Angiotensin Converting Enzyme; ARB = Angiotensin Receptor Blocker; BNP = B-type Natriuretic Peptide; COPD = Chronic Obstructive Pulmonary Disease; HF = Heart Failure; JVP = Jugular Venous Pressure; LVEF = Left Ventricular Ejection Fraction

Table 2.

Outcomes by Discharge Prescription for Loop Diuretics in 4,382 Propensity Score-Matched Older Patients with Heart Failure Not Taking Diuretics Prior to Hospitalization for Heart Failure Decompensation

Outcomes by event type and follow-up duration	Events (%), by discharge prescription of loop diuretics		Hazard ratio associated with initiation of loop diuretics (95% confidence interval); p value
	No (n=2,191)	Yes (n=2,191)	
30 days			
All-cause mortality *	144 (6.6%)	107 (4.9%)	0.73 (0.57–0.94); p=0.016
Heart failure readmission †	168 (7.7%)	135 (6.2%)	0.79 (0.63–0.99); p=0.037
All-cause readmission	509 (23%)	468 (21%)	0.89 (0.79–1.01); p=0.081
HF readmission or all-cause mortality ‡	299 (14%)	233 (11%)	0.76 (0.64–0.91); p=0.002
All-cause readmission or all-cause mortality §	604 (28%)	530 (24%)	0.85 (0.76–0.96); p=0.008
60 days			
All-cause mortality	232 (11%)	201 (9%)	0.86 (0.71–1.03); p=0.103
Heart failure readmission	251 (12%)	236 (11%)	0.92 (0.77–1.09); p=0.334
All-cause readmission	712 (33%)	693 (32%)	0.94 (0.85–1.05); p=0.267
HF readmission or all-cause mortality	455 (21%)	410 (19%)	0.88 (0.77–1.00); p=0.057
All-cause readmission or all-cause mortality	827 (38%)	782 (36%)	0.92 (0.83–1.01); p=0.080

Because formal sensitivity analyses can only be conducted when associations are significant in the matched cohort, only the results for significant 30-day associations are presented below:

* For 30-day all-cause mortality, in 11% (242/2,191) of matched pairs we were able to determine which patients within a pair clearly had longer 30-day survival, and in 58% (140/242) of those pairs, these patients belonged to the loop diuretic group (p=0.015). This significant association could be explained away by a hidden covariate that is a near-perfect predictor of 30-day mortality, if it increased the odds of a discharge prescription for loop diuretics by 6.4%.

† For 30-day HF readmission, in 13% (279/2,191) of matched pairs we were able to determine which patients within a pair clearly had a longer 30-day event-free survival, and in 56% (157/279) of the pairs, these patients belonged to the loop diuretics group (p=0.036). An unmeasured confounder that is a near-perfect predictor of 30-day HF readmission could explain away this association if it also increased the odds of a discharge prescription for loop diuretic by 1.6%.

‡ For the combined endpoint of 30-day HF readmission or death, in 23% (496/2,191) of matched pairs we were able to determine which patients within a pair clearly had a longer 30-day event-free survival, and in 57% (283/ 496) of the pairs, these patients belonged to the loop diuretics group (p=0.002). An unmeasured confounder that is a near-perfect predictor of 30-day HF readmission could explain away this association if it also increased the odds of a discharge prescription for loop diuretic by 11.3%.

§ For the combined endpoint of 30-day total readmission or death, in 45% (976/2,191) of matched pairs we were able to determine which patients within a pair clearly had a longer 30-day event-free survival, and in 54% (522/ 976) of the pairs, these patients belonged to the loop diuretics group (p=0.030). An unmeasured confounder that is a near-perfect predictor of 30-day HF readmission could explain away this association if it also increased the odds of a discharge prescription for loop diuretic by 1.4%.