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

OBJECTIVES The purpose of this study was 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 the Medicare-linked OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) registry, 9,866 (39%) received no pre-admission diuretics. The study 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, a matched cohort of 2,191 pairs of patients was assembled 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% were African American. The 30-day all-cause mortality occurred in 4.9% (107 of 2,191) and 6.6% (144 of 2,191) of patients in the loop diuretic and no loop diuretic groups, respectively (HR when the use of loop diuretics was compared with nonuse: 0.73; 95% CI: 0.57 to 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 to 0.99; p = 0.037) but not of 30-day all-cause readmission (HR: 0.89; 95% CI: 0.79 to 1.01; p = 0.081). None of the associations was statistically significant during 60 days of follow-up.

CONCLUSIONS 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. (J Am Coll Cardiol 2020;76:669–79) Published by Elsevier on behalf of the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

EF = ejection fraction

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

RCT = randomized controlled trial

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 (ACCF)/American Heart Association (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 heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF).

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METHODS

DATA SOURCE AND STUDY POPULATION. We used data from the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) 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 (IRB) 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 who were not taking diuretics prior to hospitalization for HF decompensation. Of these 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

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC* author instructions page.

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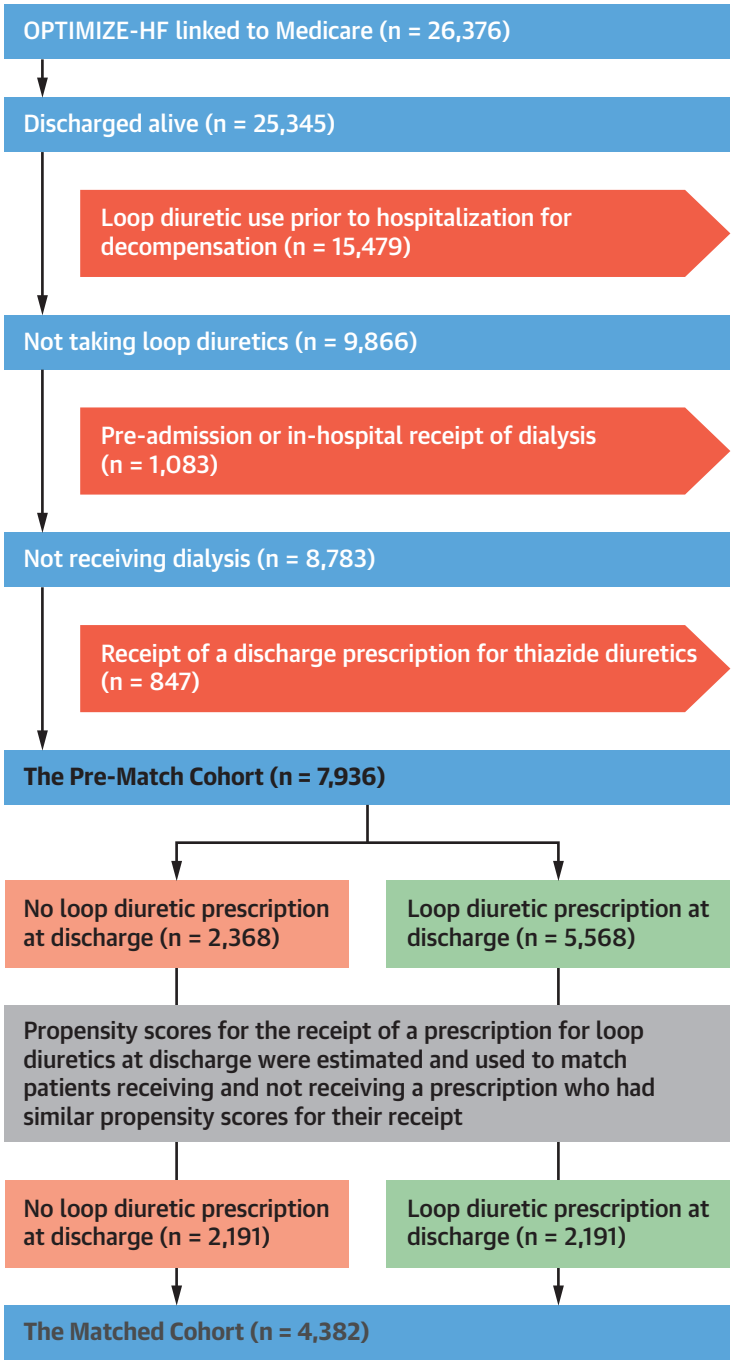
FIGURE 1 **Assembly of the Study Cohort**



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.

not balance unmeasured baseline characteristics. However, sensitivity analysis (described in the following text) can determine their impact on observed significant associations.

We used a nonparsimonious 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

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			Discharge Prescription of Loop Diuretics		
	No (n = 2,368)	Yes (n = 5,568)	p Value	No (n = 2,191)	Yes (n = 2,191)	p Value
Age, yrs	77.7 ± 10.7	78.3 ± 10.2	0.010	77.9 ± 10.4	77.8 ± 10.5	0.841
Age ≥70 yrs	1,504 (64)	3,729 (67)	0.003	1,114 (65)	1,444 (66)	0.341
Women	1,274 (54)	3,061 (55)	0.336	1,178 (54)	1,202 (55)	0.467
African American	242 (10)	632 (11)	0.141	233 (11)	239 (11)	0.770
Past medical history						
HF diagnosis before admission	1,934 (82)	4,467 (80)	0.136	1,787 (82)	1,783 (81)	0.876
HF hospitalization (prior 6 months)	288 (12)	632 (11)	0.301	263 (12)	277 (13)	0.520
Hypertension	1,676 (71)	3,969 (71)	0.649	1,549 (71)	1,541 (70)	0.791
Myocardial infarction	510 (22)	1,199 (22)	0.997	470 (21)	479 (22)	0.741
Diabetes mellitus	769 (32)	1,862 (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)	1,658 (30)	0.015	602 (27)	605 (28)	0.919
COPD	614 (26)	1,346 (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	1,351 (57)	3,530 (63)	<0.001	1,275 (58)	1,265 (58)	0.760
Orthopnea	474 (20)	1,420 (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)	2,434 (44)	0.003	895 (41)	890 (41)	0.878
JVP elevation	499 (21)	1,501 (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	1,362 (58)	3,641 (65)	<0.001	1,291 (59)	1,315 (60)	0.460
Lower extremity edema						
None to trace	1,536 (65)	2,924 (53)		1,387 (63)	1,393 (64)	
Mild to moderate (1+ to 2+)	659 (28)	2,002 (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, kg	75 ± 18	76 ± 18	0.100	75 ± 18	75 ± 18	0.348
Heart rate, beats/min	89 ± 22	88 ± 22	0.394	88 ± 22	88 ± 22	0.378
Systolic blood pressure, mm Hg	147 ± 32	147 ± 31	0.466	147 ± 32	148 ± 32	0.910
Diastolic blood pressure, mm Hg	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 proBNP, pg/ml	1,035 (507–1,173)	1,053 (556–1,273)	0.011	1,039 (509–1,179)	1,034 (517–1,220)	0.763
Serum troponin level elevation	458 (19)	1,027 (18)	0.349	411 (19)	430 (20)	0.466
LVEF, %	43 ± 14	42 ± 15	0.013	43 ± 14	43 ± 15	0.945
LVEF ≤40%	1,027 (43)	2,641 (47)		943 (43)	963 (44)	
LVEF 41%–49%	386 (16)	789 (14)	0.002	354 (16)	350 (16)	0.828
LVEF ≥50%	955 (40)	2,138 (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

Continued on the next page

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 ± SD, 0.67 ± 0.13 for both study groups;

TABLE 1 Continued

	Before Propensity-Score Matching (n = 7,936)			After Propensity-Score Matching (n = 4,382)		
	Discharge Prescription of Loop Diuretics			Discharge Prescription of Loop Diuretics		
	No (n = 2,368)	Yes (n = 5,568)	p Value	No (n = 2,191)	Yes (n = 2,191)	p Value
Discharge medications						
ACE inhibitors or ARBs	1,241 (52)	3,781 (68)	<0.001	1,232 (56)	1,234 (56)	0.951
Beta-blockers	1,369 (58)	3,662 (66)	<0.001	1,329 (61)	1,326 (61)	0.926
Aldosterone antagonists	147 (6)	604 (11)	<0.001	145 (7)	147 (7)	0.904
Digoxin	483 (20)	1,418 (25)	<0.001	471 (21)	450 (21)	0.436
Amlodipine	175 (7)	398 (7)	0.703	167 (8)	163 (7)	0.819
Antiarrhythmic drugs	252 (11)	659 (12)	0.127	242 (11)	237 (11)	0.809
Warfarin	456 (19)	1,347 (24)	<0.001	451 (21)	448 (20)	0.911
Aspirin	1,069 (45)	2,838 (51)	<0.001	1,031 (47)	1,064 (49)	0.318
Discharge instructions						
Diet	1,909 (81)	4,928 (89)	<0.001	1,850 (84)	1,826 (83)	0.324
Medications	2,005 (85)	5,182 (93)	<0.001	1,952 (89)	1,927 (88)	0.236
Worsening symptoms	1,442 (61)	3,729 (67)	<0.001	1,391 (63)	1,377 (63)	0.661
Weight monitoring	1,007 (43)	2,994 (54)	<0.001	986 (45)	994 (45)	0.808
Follow-up	1,979 (84)	5,044 (91)	<0.001	1,916 (87)	1,913 (87)	0.891
Hospital length of stay, days	4 (2–7)	4 (3–7)	0.243	4 (2–7)	4 (3–7)	0.762
Hospital academic center	977 (41)	2,353 (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.

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 2 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 analyses 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, New York) and SAS for Windows version 9.2 (Cary, North Carolina) were used for data analyses.

RESULTS

BASELINE CHARACTERISTICS. Patients in the propensity score-matched cohort (n = 4,382) had a mean 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 of 2,191) and 6.6% (144 of

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)	0.016
Heart failure readmission†	168 (7.7)	135 (6.2)	0.79 (0.63–0.99)	0.037
All-cause readmission	509 (23.2)	468 (21.4)	0.89 (0.79–1.01)	0.081
HF readmission or all-cause mortality‡	299 (13.6)	233 (10.6)	0.76 (0.64–0.91)	0.002
All-cause readmission or all-cause mortality§	604 (27.6)	530 (24.2)	0.85 (0.76–0.96)	0.008
60 days				
All-cause mortality	232 (10.6)	201 (9.2)	0.86 (0.71–1.03)	0.103
Heart failure readmission	251 (11.5)	236 (10.8)	0.92 (0.77–1.09)	0.334
All-cause readmission	712 (32.5)	693 (31.6)	0.94 (0.85–1.05)	0.267
HF readmission or all-cause mortality	455 (20.8)	410 (18.7)	0.88 (0.77–1.00)	0.057
All-cause readmission or all-cause mortality	827 (37.7)	782 (35.7)	0.92 (0.83–1.01)	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 of 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 of 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 of 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 of 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 diuretics by 1.6%. ‡For the combined endpoint of 30-day HF readmission or death, in 23% (496 of 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 of 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 this combined endpoint could explain away this association if it also increased the odds of a discharge prescription for loop diuretics by 11.3%. §For the combined endpoint of 30-day total readmission or death, in 45% (976 of 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 of 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 this combined endpoint could explain away this association if it also increased the odds of a discharge prescription for loop diuretics by 1.4%.

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 nonreceipt: 0.73; 95% CI: 0.57 to 0.94; p = 0.016) (**Table 2, Central Illustration**). Findings of the formal sensitivity analysis are presented in the **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**).

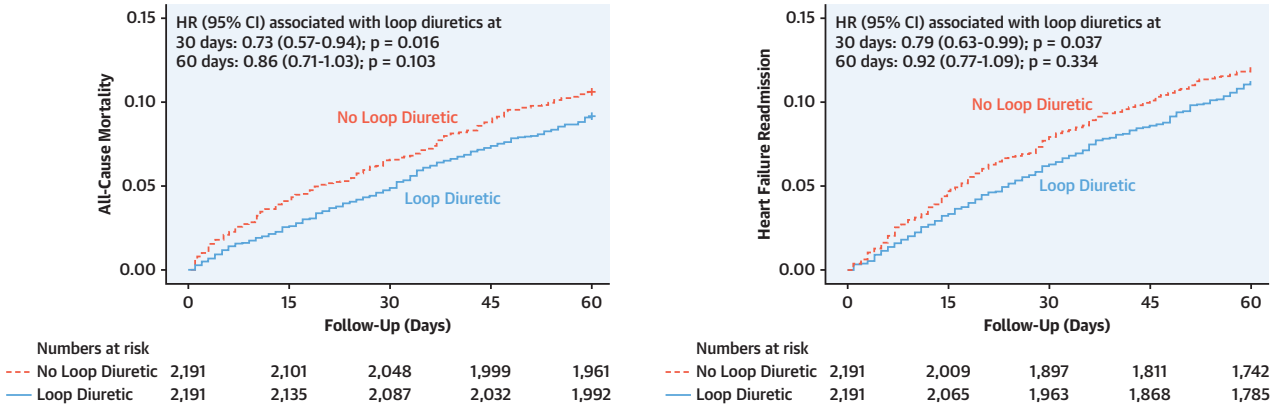
The 30-day all-cause mortality occurred in 5.7% (62 of 1,084) and 6.6% (78 of 1,075) of the patients with HFrEF receiving and not receiving loop diuretics, respectively (HR: 0.78; 95% CI: 0.56 to 1.09; p = 0.147), and 4.1% (45 of 1,107) and 5.9% (66 of 1,116) of the patients with HFpEF receiving and not receiving loop diuretics, respectively (HR: 0.68; 95% CI: 0.46 to 0.99; p = 0.043; p for interaction = 0.582; data not presented in Tables or Figures). 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 of 2,191) and 7.7% (168 of 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 to 0.99; p = 0.037) (**Table 2, Central Illustration**). Findings of the formal sensitivity analysis are presented in the **Table 2** footnote. Loop diuretic prescription had no significant association with 30-day non-HF readmission (HR: 0.84; 95% CI: 0.63 to 1.13; p = 0.729; data not presented in **Table 2**) and 30-day all-cause readmission (HR: 0.89; 95% CI: 0.79 to 1.01; p = 0.081) (**Table 2**). The association of loop diuretic prescription at discharge had no significant association with HF readmission or all-cause readmission during 60 days of follow-up (**Table 2, Central Illustration**).

The 30-day HF readmission occurred in 6.4% (69 of 1,084) and 8.2% (88 of 1,075) of HFrEF patients receiving and not receiving loop diuretics, respectively (HR: 0.76; 95% CI: 0.56 to 1.04; p = 0.090), and 6.0% (66 of 1,107) and 7.2% (80 of 1,116) of HFpEF patients receiving and not receiving loop diuretics, respectively (HR: 0.81; 95% CI: 0.59 to 1.12; p = 0.210; data not presented in Tables or Figures). 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 of 2,191) and 14%

CENTRAL ILLUSTRATION **Kaplan-Meier Plots by Loop Diuretic Prescription**



Faselis, C. et al. J Am Coll Cardiol. 2020;76(6):669-79.

This study assessed the relationship of prescription of loop diuretics at the time of hospital discharge with all-cause mortality **(left)** and heart failure readmission **(right)** in 2,191 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.

(299 of 2,191) of the patients receiving and not receiving loop diuretics, respectively (HR associated with loop diuretic prescription: 0.76; 95% CI: 0.64 to 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 the 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 of 1,084) and 15.1% (162 of 1,075) of the patients in the loop diuretic and no loop diuretic groups, respectively (HR: 0.76; 95% CI: 0.60 to 0.95; p = 0.019) (Figure 2). Among patients with HFpEF, these events occurred in 9.7% (107 of 1,107) and 12.3% (137 of 1,116) of the patients in the loop diuretic and no loop diuretic groups, respectively (HR: 0.77; 95% CI: 0.60 to 0.99; p = 0.042; p for interaction = 0.956) (Figure 2).

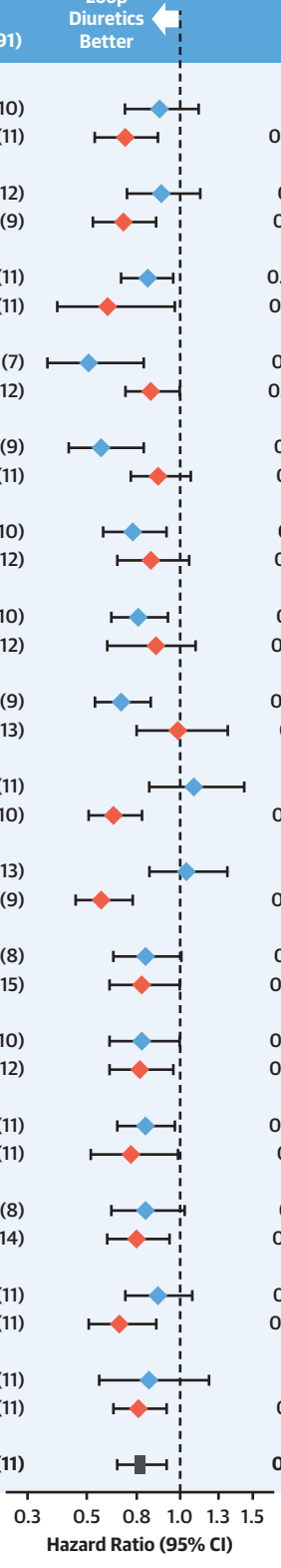
SUBGROUP ANALYSES. Findings from other subgroup analyses of the combined endpoint of 30-day HF readmission or all-cause mortality are displayed in Figure 2. The association of discharge prescription for loop diuretics with the combined endpoint of 30-day HF readmission or all-cause mortality was generally homogeneous in other clinically relevant subgroups, except it was significantly stronger in subgroups with admission pulmonary rales and lower extremity edema (Figure 2). The HRs for the combined endpoint in subgroups with and without pulmonary rales were 0.62 (95% CI: 0.50 to 0.77; p < 0.001) and 1.08 (95% CI: 0.81 to 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

FIGURE 2 Forest Plots for Subgroup Analyses by Loop Diuretic Prescription

Total Patients (N = 4,382)	Loop Diuretic Prescription at Discharge: No (n = 2,191)	Loop Diuretic Prescription at Discharge: Yes (n = 2,191)	Hazard Ratio (95% CI)	p for Effect	p for Interaction
Age					
<80 years (n = 2,354)	136/1,183 (12)	118/1,171 (10)	0.87 (0.68-1.11)	0.251	0.152
≥80 years (n = 2,028)	163/1,008 (16)	115/1,020 (11)	0.68 (0.53-0.86)	0.001	
Sex					
Male (n = 2,002)	140/1,013 (14)	122/989 (12)	0.88 (0.69-1.12)	0.287	0.119
Female (n = 2,380)	159/1,178 (14)	111/1,202 (9)	0.67 (0.52-0.85)	0.001	
Race					
White (n = 3,910)	257/1,958 (13)	207/1,952 (11)	0.80 (0.66-0.95)	0.021	0.272
African American (n = 472)	42/233 (18)	26/239 (11)	0.59 (0.36-0.96)	0.045	
Prior history of heart failure					
No (n = 812)	54/404 (13)	28/408 (7)	0.50 (0.32-0.78)	0.003	0.043
Yes (n = 3,570)	245/1,787 (14)	205/1,783 (12)	0.82 (0.68-0.99)	0.040	
Hypertension					
No (n = 1,292)	98/642 (15)	58/650 (9)	0.56 (0.41-0.78)	<0.001	0.026
Yes (n = 3,090)	201/1,549 (13)	175/1,541 (11)	0.86 (0.71-1.06)	0.156	
Coronary artery disease					
No (n = 2,398)	160/1,195 (13)	118/1,203 (10)	0.72 (0.57-0.91)	0.006	0.447
Yes (n = 1,984)	139/996 (14)	115/998 (12)	0.82 (0.64-1.05)	0.109	
Atrial fibrillation					
No (n = 3,175)	210/1,589 (13)	160/1,586 (10)	0.75 (0.61-0.92)	0.005	0.708
Yes (n = 1,207)	89/602 (15)	73/605 (12)	0.80 (0.59-1.09)	0.160	
Diabetes mellitus					
No (n = 2,972)	204/1,491 (14)	138/1,481 (9)	0.66 (0.53-0.82)	<0.001	0.029
Yes (n = 1,410)	95/700 (14)	95/710 (13)	0.98 (0.74-1.31)	0.909	
Admission pulmonary rales					
No (n = 1,776)	93/900 (10)	98/876 (11)	1.08 (0.81-1.43)	0.604	0.003
Yes (n = 2,606)	206/1,291 (16)	135/1,315 (10)	0.62 (0.50-0.77)	<0.001	
Admission lower extremity edema					
No (n = 2,109)	130/1,058 (12)	134/1,051 (13)	1.03 (0.81-1.31)	0.831	0.001
Yes (n = 2,273)	169/1,133 (15)	99/1,140 (9)	0.56 (0.44-0.72)	<0.001	
Glomerular filtration rate					
≥45 ml/min/1.73 m^2 (n = 2,874)	147/1,400 (11)	124/1,474 (8)	0.79 (0.62-1.00)	0.049	0.910
<45 ml/min/1.73 m^2 (n = 1,508)	152/791 (19)	109/717 (15)	0.77 (0.60-0.99)	0.039	
Left ventricular ejection fraction					
≥45% (n = 2,223)	137/1,116 (12)	107/1,107 (10)	0.77 (0.60-0.99)	0.042	0.956
<45% (n = 2,159)	162/1,075 (15)	126/1,084 (12)	0.76 (0.60-0.95)	0.019	
Chronic obstructive pulmonary disease					
No (n = 3,243)	213/1,624 (13)	170/1,619 (11)	0.79 (0.64-0.96)	0.019	0.594
Yes (n = 1,139)	86/567 (15)	63/572 (11)	0.71 (0.51-0.98)	0.035	
ACE inhibitor or ARB use					
Yes (n = 2,466)	127/1,232 (10)	102/1,234 (8)	0.79 (0.61-1.02)	0.073	0.733
No (n = 1,916)	172/959 (18)	131/957 (14)	0.74 (0.59-0.93)	0.010	
Beta-blocker use					
Yes (n = 2,655)	161/1,329 (12)	140/1,326 (11)	0.86 (0.68-1.07)	0.179	0.123
No (n = 1,727)	138/862 (16)	93/865 (11)	0.65 (0.50-0.85)	0.002	
Digoxin use					
Yes (n = 921)	61/471 (13)	48/450 (11)	0.81 (0.55-1.18)	0.271	0.732
No (n = 3,461)	238/1,720 (14)	185/1,741 (11)	0.75 (0.62-0.91)	0.003	
Overall	**299/2,191 (14)**	**233/2,191 (11)**	**0.76 (0.64-0.91)**	**0.002**	



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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 loop 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**). Although 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, it 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.

STUDY LIMITATIONS. Although 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 in the previous text, 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

FIGURE 2 Continued

In all subgroups analyzed, in 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 that the 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.

74 measured baseline characteristics used in our study. We did not have access to data on loop diuretic doses or start/restart/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 HF 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 HF readmission. These findings provide new information that may strengthen guideline recommendations and improve short-term clinical outcomes in patients with HF.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: For older patients hospitalized with decompensated HF not taking diuretics prior to admission, prescription of a loop diuretic at discharge is associated with a lower 30-day risk of readmission 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.

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KEY WORDS heart failure, loop diuretics, outcomes

APPENDIX For a supplemental figure, please see the online version of this paper.