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Observational Study

Prescribing Inertia or Not? Quantitative Investigation of Loop Diuretics Prescribing after Palliative Care Consultation among Patients with Heart Failure

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Abstract

Purpose: Loop Diuretics (LD) are the first-line pharmacotherapy to address Heart Failure (HF)-associated edema and dyspnea. However, LD causes frequent urinary, resulting in inconvenience and possibly undermining the quality of life. While prescription adjustment is an essential part of Palliative Care Consultation (PCC), it remains unclear how PCC affects the deprescribing of diuretics for adults with HF.

Methods: We conducted a pre-post analysis of the percentage of HF patients who were prescribed LD in a national Electronic Health Record (EHR) database 12 months before and after the first PCC. The difference in prescription rates between the periods was determined. Adjusted associations of post-PCC LD prescription with pre-PCC LD prescription and patient's characteristics, insurance, provider type, and clinical factors were quantified.

Results: From 2010 to 2018, 5,969 patients with newly diagnosed HF received at least one PCC, among whom 2,539 (42.5%) were prescribed LD before and 1,552 (26.0%) after their first PCC. Despite a decrease in LD prescription rate encompassing the date of PCC, post-PCC LD prescribing was strongly associated with pre-PCC prescribing (aOR[95%CI] 3.2[2.8,3.7]) and varied by age at first PCC, year of HF diagnosis (aOR[95%CI] 2.1[1.9,2.4]) and months from HF diagnosis to first PCC. While our finding demonstrates reduced polypharmacy associated with PCC, the strong association between pre- and post-PCC indicates reverse therapeutic inertia. Future research should investigate the benefits and costs of polypharmacy among specific patient groups to help develop personalized treatment for HF.

More Information

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Keywords: Heart failure; Polypharmacy; Palliative care; Deprescribing; Diuretics; Clinical inertia

Introduction

Despite significant advancement in the clinical management of Heart Failure (HF), this illness remains a progressive, potentially terminal illness. Patients may suffer big symptom burdens of HF due to the precipitant cardiovascular disease and cardiac dysfunction [1,2]. Because fluid retention is central to the pathophysiology of HF, edema, and dyspnea are prevalent among symptoms of HF, affecting more than 90% and 70% of patients, respectively [3,4]. Loop Diuretics (LD) are often the only medications administered to address these common, quality-compromising symptoms [4,5] However, it can be complex and challenging to appropriately prescribe LD to patients with HF since these patients can have multiple morbidities and have been taking other medications contraindicating the use of LD [6]. Thus, deprescribing and reduction of dose are needed on some occasions [6,7].

Yet, it is not always feasible to adjust prescriptions in the management of chronic diseases. Since more than twenty years ago, several clinicians have described "clinical inertia", or "therapeutic inertia", which is the "failure of clinicians to initiate or intensify therapy when indicated" [8-10]. This concept is expanded to include deprescribing and reducing the dose of therapies, to the extent that reverse therapeutic inertia is a failure to reduce or change therapy when no longer needed or indicated [8] Several studies analyzed the clinical inertia and reverse inertia in the pharmacotherapies for chronic diseases, such as diabetes, chronic kidney disease, and heart failure [8,11-13]. Particularly, LD should be carefully

prescribed to patients with advanced HF to prevent adverse effects in the context of polypharmacy [6]. In this way, some patients might experience clinical inertia when their LD prescriptions need adjustment.

Because HF is highly symptomatic, the recent guidelines by the American Heart Association and the European Society of Cardiology recommend Palliative Care (PC) for all patients with HF on a need basis [4,14] For patients with potentially fatal illnesses, PC aims to assess the patient's need and wish for treatment, ensure treatment in the way that patients prefer, and improve the quality of care [1,2,15]. Among the components of PC is the prescription review, wherein prescription and dose adjustments are conducted [4,16]. However, it remains unclear whether Palliative Care Consultation (PCC) can facilitate deprescribing. In this study, we explored the prescription rate of LD, a commonly used medication in patients with HF, before and after the patient's first PCC for HF, and analyzed why the prescribing changed.

Methods

Study data and design

We conducted a pre-post comparison in a retrospective cohort of patients with HF using a random sample of a national all-payer Electronic Health Record (EHR) database. This database contained de-identified records between 2010 and 2018 from a random sample of 5 million adults (age ≥ 18 years) from more than 200 regional non-institutional health systems in the United States. This database included records of inpatient and outpatient services, associated diagnoses, vital signs, laboratory results, procedures, and medication (administered and prescribed) that occurred in the captured health systems during the coverage period. Saint Louis University Internal Review Board granted exempt status for this study.

We created a cohort of adults with newly diagnosed HF, regardless of Ejection Fraction, between 2011 and 2018. To identify individuals with HF, we required 2 separate outpatient encounters within 12 months or 1 inpatient stay with an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), or ICD-10-CM codes for HF (**Table S1**) [17]. To define the index HF, we required 12 months of activity in the database preceding the dates of the initial HF diagnosis. We examined the database for the initial encounter of PCC using ICD-9-CM V66.7 and ICD-10-CM Z51.5. These codes were validated in the Veterans Health Administration (VHA) database and some single-center cancer samples, which demonstrated reasonably good sensitivity and high specificity [18-20]. We used this method in our previously published studies [21].

Inclusion and exclusion criteria

We included adult patients who had index diagnoses of HF, per the algorithm stated in the cohort definition, in 2011 and 2018. Exclusion criteria were: 1) a patient had an activity in the EHR database for less than 12 months before the date of the index HF; 2) the age at the time of index HF diagnosis was younger than 18; and 3) patients received heart transplantations before their first PCC or before end of observation.

Outcome

We extracted prescriptions of furosemide, bumetanide, torsemide, and etacrynic acid in the records of administered and prescribed medications. The outcome of interest was prescriptions of LD in the 12 months after the initial PCC ("pre-PCC").

Explanatory variables

The predictor was prescriptions of LD in the 12 months before the first PCC ("pre-PCC"). Confounders to control were year of HF diagnosis, demographic characteristics, US census region of residence, ZIP-level average household incomes and percentage of college graduates, primary insurance payer, type of provider where PCC occurred, and Charlson-Devo comorbidity index (excluding HF; CCI) at the time of PCC [22,23]. Non-HF CCI was classified in the intervals of 0 to 2, 3 to 5, and greater than 5. Diagnosis codes used to define variables were demonstrated in **Table S1**.

Statistical analysis

We determined the percentage of patients who were

Table S1: Diagnosis and procedural codes for common medical conditions and treatments for individuals with heart failure.

Diagnosis	Diagnosis and Procedural Codes	Other Indicator
Heart failure	ICD-9-CM: 398.91, 402.11, 402.91, 404.11, 404.13, 404.91, 404.93, 428. x; ICD-10-CM: I09.81, I11.0, I13.0, I13.2, I50.x	
Palliative care encounter/consultation [18-20]	ICD-9-CM: V66.7; ICD-10-CM: Z51.5	
Depression [36, 39, 40]	ICD-9-CM: 296.2x, 296.3x, 311; ICD-10-CM: F32.0-F32.5, F32.9, F33.0-F33.3, F33.4x, F33.9	
Generalized anxiety and panic disorder[39, 40]	ICD-9-CM: 300.02, 300.01; ICD-10-CM: F41.1, F41.0	
Diabetes Type II	ICD-9-CM: 250.x0, 250.x2, 357.2, 362.0x, 366.41; ICD-10-CM: E11.x, E08.42, E09.42, E13.42, E08.36, E09.36, E13.36	
Diabetes Type I	ICD-9-CM: 250.x1, 250.x3; ICD-10-CM: E10.x	
Hypertension	ICD-9-CM: 401.x; ICD-10-CM: I10.x	
Chronic pulmonary disease [41, 42]	ICD-9-CM: 491.x, 492.x, 493.2, 496.x; ICD-10-CM: J41.x - J44.x	
Cancer	ICD-9-CM: 140.x-209.x; ICD-10-CM: C00.x to D09.x	
Cerebrovascular disease	ICD-9-CM: 430.x-438.x; ICD-10-CM: I60 – I69, G45, G46	
Dementia	ICD-9-CM: 290.x,294.1,331.2; ICD-10-CM: F00.x - F03.x, F05.1, G30.x, G31.1	

Abbreviations: Current Procedural Terminology (CPT), Healthcare Common Procedure Coding System (HCPCS), International Classification Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), International Classification Diseases, Tenth Revision, Clinical Modification (ICD-10-CM).

prescribed LD in the pre-PCC and the post-PCC periods and calculated the rate difference in the prescription rate of LD. Kappa statistics were used to indicate concordance between pre- and post-PCC LD prescriptions. Baseline characteristics were compared between patients who were prescribed LD pre-PCC and those who were not using the Chi-square test. Multiple logistic regression was conducted to quantify the effects of pre-PCC LD prescription, year of diagnosis, patient characteristics, payer, type of provider, and CCI. The adjusted odds ratio with 95% confidence intervals was reported. All tests were two-tailed with an alpha set at 0.05. Data management and analysis were performed using SAS 9.4 (SAS Institute, Cary, NC, USA) [24].

Results

Between January 2010 and December 2018, 173,445 individuals with HF diagnosis were identified in The Integrated data set. After excluding individuals having less than 12 months of activity before the HF diagnosis, 127,712 individuals with NDHF were included in the study (Figure 1). Following the HF diagnosis, 16,918 patients had at least one PCC, and 5,969 of them had at least a year's activity in both pre-and post-PCC periods. These patients were mostly age 75 years or older when their HF was diagnosed, non-Hispanic, White in race, slightly more in female, residing in ZIP codes with average annual household income under $46,000 and college education among 35% or less of the residents, and having Charlson's comorbidity index (excluding heart failure) less than 6 (Table 1).

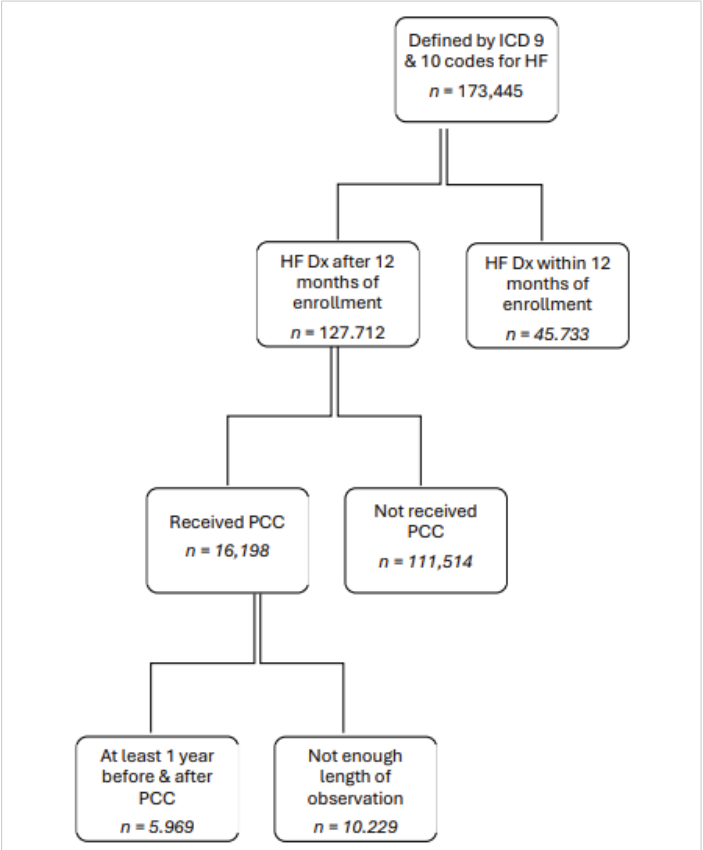

Figure 1: Cohort creation and sample size.

Table 1: Patient characteristics, health service, and clinical factors associated with pre-PCC LD Prescription.

	Overall	No LD before the first PCC	Using LD before the first PCC	
	N = 5969	N = 3430	N = 2539	
	%	%	%	*p* - value
Age of first PCC, years				0.1263
<45 years	1.6	1.7	1.5	
45-64 years	14.3	15.1	13.2	
65-74 years	18.9	18.4	19.6	
>=75 years	65.3	64.8	65.8	
Gender				0.544
Female	55.0	55.6	54.2	
Male	44.9	44.3	45.7	
Unknown	0.1	0.1	0.1	
Race				0.0004
Caucasian	82.5	81.4	84.0	
African American	10.0	10.0	10.1	
Hispanic	2.9	3.2	2.4	
Asian	1.0	1.0	1.1	
Other	3.6	4.4	2.4	
Income per ZIP (as of 2018)				0.2838
<$45999	64.8	64.9	64.6	
$46000-$58999	27.7	27.1	28.6	
>=$59000	3.0	3.2	2.6	
Unknown	4.5	4.8	4.2	
College education per ZIP				0.4493
<=35%	86.4	86.0	87.0	
>35%	9.2	9.5	8.9	
Unknown	4.4	4.6	4.1	
Region of patient's residence				<.0001
Midwest	54.7	50.8	59.9	
Northeast	10.6	11.6	9.2	
Other/Unknown	3.3	3.4	3.2	
South	22.2	23.9	19.9	
West	9.2	10.2	7.9	
Year of HF diagnosis				<.0001
2010-2013	62.8	56.7	70.9	
2014-2018	37.2	43.3	29.1	
Primary Payer (within the year before PCC)				<.0001
Medicare	68.3	66.6	70.6	
Medicare/Medicaid dual	14.1	14.4	13.7	
Commercial	10.0	9.4	10.8	
Medicaid only	2.6	2.7	2.4	
Uninsured/Other	0.9	1.2	0.4	
Unknown	4.2	5.7	2.2	
Any visits to academic facilities (within the year before PCC)	22.5	19.7	26.1	<.0001
Non-HF Charlson's Comorbidity Index around the first PCC				<.0001
0 to 2	52.7	48.2	58.8	
3 to 5	41.2	44.8	36.5	
>5	6.1	7.1	4.7	

LD: Loop Diuretics; PCC: Palliative Care Consultation

We found a decrease of 16.5% in the percentage of patients who were prescribed LD after the first PCC, from 42.5% to 26.0%. The pre-and post-PCC prescriptions of LD were associated (Kappa: 0.2150, $p < 0.0001$; Table 2). When patients' characteristics, payer, provider, and CCI were controlled, we found that patients who were prescribed with LD pre-PCC were three times as likely to be prescribed afterward (aOR[95%CI] 3.22[2.79,3.71]). Age at first PCC was negatively related to the chance of receiving post-PCC loop diuretics (aOR[95%CI] for age < 45 years 2.00[1.24,3.24] and for 45 years - 64 years 1.52[1.21,1.90]) but such trend became minimal when age at first PCC was 75 years or older. Patients residing in the Midwest and who were diagnosed with HF after 2013 were more likely to receive post-PCC loop diuretics (aOR[95%CI] 1.27[1.01,1.59] and 2.12[1.85,2.43]). Patients having visits to academic facilities were marginally associated with increases in prescribed loop diuretics (aOR[95%CI] 1.14[0.98,1.32]). Patients receiving the first PCC after 6 to 12 months of the index HF diagnosis were 1/3 less likely to receive post-PCC loop diuretics (aOR[95%CI] 0.66[0.53,0.83]). However, neither payer type nor Charlson's Comorbidity Index (CCI) was associated with prescribing post-PCC loop diuretics (Table 3, Figure 2).

Discussion

In this study, we found, in patients with newly diagnosed HF, a significant decrease in the percentage of patients who were prescribed loop diuretics following their initial palliative care consultations. However, post-PCC LD prescription was associated with a prescription of LD before the consultation. Patients' age at the initial PCC was inversely associated with the likelihood of prescription. Interestingly, we did not find associations between the comorbidity index and post-PCC prescription of LD.

Loop diuretics are a basic medication to reduce the symptom burden of patients with HF [3-5]. It is widely used for HF because fluid retention affects more than 70% of these patients [5,25]. A national registry even showed that 81% of the HF with reduced ejection fraction (HFrEF) were treated with LD [7]. In fact, existing evidence showed that LD may maintain kidney function and reduce HF mortality and readmissions [5,26]. So it seems counterintuitive to find deprescribing following PCC. However, it can be complicated to appropriately prescribe and adjust the dose of LD for some patients when they have been prescribed concomitant medications. For instance, when patients with HF present hypotension, continued use of LD can worsen the situation [9]. Adverse effects when LD interacts with other medications, including such palliative care medication as barbiturates, opioids, and carbamazepine, can also be a concern [6]. Therefore, prescribing LD and dose adjustment should be very careful and thoughtful, which can be challenging for providers [9,12]. Our findings of reduced LD prescription reflect such challenges in the pharmacotherapy of fluid retention related to HF. Among other adjustments of treatment, pharmacotherapy has been shown critically subject to the complexity of care for patients with multiple chronic conditions, especially those under palliative care; the complexity often results in therapeutical inertia and reverse inertia [8,27-30]. This phenomenon is not rare and has become a major issue to

Table 2: Prescription of loop diuretic therapy before and after the initial PCC.

	Pre-PCC	Post-PCC	Rate Difference	Kappa
	N (%))	N (%)	(95% CI)	(95% CI)
Prescription of LD	2539 (42.5%)	1552 (26.0%)	-0.1654 (-0.1821, -0.1486)	0.2150 (0.1912, 0.2388)
P value			<.0001	<.0001

CI: Confidence Interval; LD: Loop Diuretics; PCC: Palliative Care Consultation

Table 3: Association of post-PCC loop diuretic therapy with pre-PCC loop diuretic therapy.

	aOR (95% CI)	*p* - value
Using Loop Diuretics before the first PCC	3.22 (2.79,3.71)	<.0001
Age at first PCC, years		
45-64 years *vs.* 65-75 years	1.52 (1.21,1.90)	0.1035
<45 years *vs.* 65-75 years	2.00 (1.24,3.24)	0.0172
>=75 years *vs.* 65-75 years	0.99 (0.85,1.17)	0.0002
Gender		
Male *vs.* Female	0.88 (0.78,1.00)	0.7709
Unknown *vs.* Female	1.10 (0.11,11.44)	0.8933
Race		
African American *vs.* Caucasian	1.09 (0.89,1.33)	0.2122
Asian *vs.* Caucasian	0.89 (0.47,1.68)	0.826
Hispanic *vs.* Caucasian	1.06 (0.73,1.53)	0.4919
Other/Unknown *vs.* Caucasian	0.72 (0.49,1.08)	0.137
Income per ZIP (as of 2018)		
Unknown *vs.* $46000-$58999	0.51 (0.10,2.54)	0.4309
<$45999 *vs.* $46000-$58999	0.98 (0.84,1.14)	0.4293
>=$59000 *vs.* $46000-$58999	0.93 (0.63,1.39)	0.626
College education per ZIP		
<=35% *vs.* >35%	0.96 (0.75,1.23)	0.2887
Unknown *vs.* >35%	2.33 (0.42,13.03)	0.3183
Region of patient's residence		
Midwest *vs.* Northeast	1.27 (1.01,1.59)	0.0431
Other/Unknown *vs.* Northeast	0.87 (0.44,1.74)	0.4543
South *vs.* Northeast	1.08 (0.83,1.39)	0.9622
West *vs.* Northeast	1.18 (0.87,1.60)	0.3842
Year of HF diagnosis		
2014-2018 *vs.* 2010-2013	2.12 (1.85,2.43)	<.0001
Primary Payer (within the year before PCC)		
Commercial *vs.* Medicare	0.90 (0.72,1.12)	0.1906
Medicaid only *vs.* Medicare	1.17 (0.79,1.72)	0.018
Medicare/Medicaid dual *vs.* Medicare	0.91 (0.76,1.09)	0.1438
Uninsured/Other *vs.* Medicare	0.93 (0.46,1.88)	0.5437
Unknown *vs.* Medicare	0.24 (0.14,0.42)	<.0001
Any visits to academic facilities (within the year before PCC)	1.14 (0.98,1.32)	0.0852
Non-HF Charlson's Comorbidity Index around the first PCC		
3 to 5 *vs.* 0 to 2	0.99 (0.86,1.12)	0.6305
>5 *vs.* 0 to 2	0.90 (0.68,1.17)	0.4426
Months from HF diagnosis to first PCC		
6-12 months *vs.* <6 months	0.66 (0.53,0.83)	<.0001
>12 months *vs.* <6 months	1.05 (0.90,1.23)	0.001

AOR, adjusted odds ratio. CI, confidence interval. HF, heart failure. LD, loop diuretics. PCC, palliative care consultation.

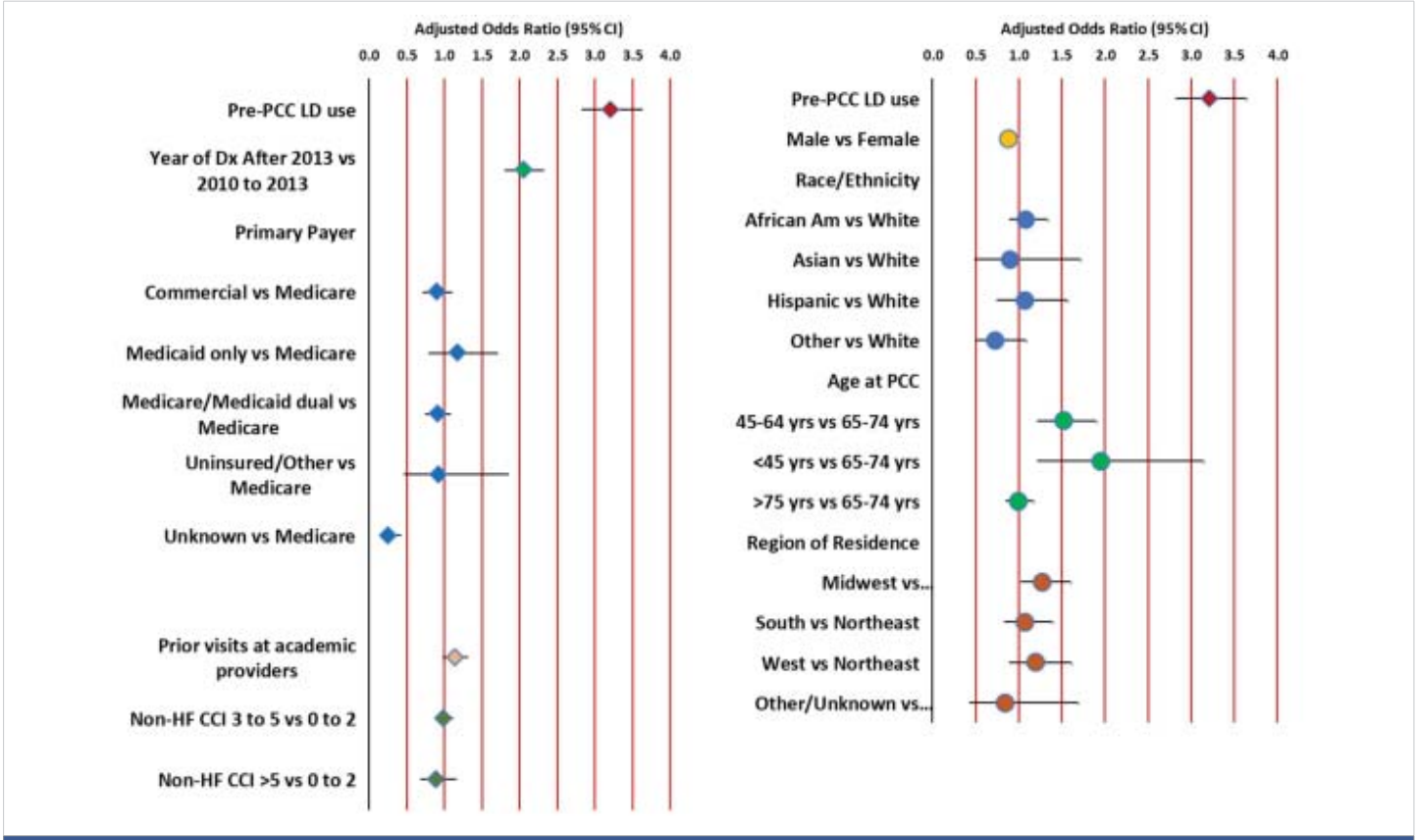

Figure 2: Forest plot of adjusted association between pre-PCC and post-PCC prescriptions of loop diuretics.

tackle in the management of HF [12]. For example, most physicians were familiar with the ESC guidelines but only 25% adhered to treatment recommendations in practice [31]. In the Heart Failure Adherence Retention Trial (HART) cohort, in only 41% of the HF cases did physicians and patients both adhere to the guideline-recommended prescribing and taking of the medications [32]. All these poor adherence can be perceived as therapeutical inertia [8,12,30]. Moreover, the overall decrease in LD prescriptions could be attributed to the prescription review and adjustment that is a component of PC consultation. PCC aims to reduce polypharmacy and unnecessary treatment [2,15,33,34]. According to Granger et al's trial, in which trial that 100% of the enrolled patients with advanced HF experienced polypharmacy at baseline and the number of prescribed medications increased overtime in the 24-week PC intervention, patients who received palliative care consultation had much lower average number of medications by end of intervention, compared to those who received the standard treatment alone [27]. Thus, the beneficial deprescribing associated with PCC should be highlighted.

Interestingly, we found a very strong correlation between the pre-PCC and post-PCC prescriptions of LD (aOR 3.22), and the effect was independent of Charlson's comorbidity index, a predictor of adverse outcomes. Considering these contradictions, we thought that there could be reverse therapeutic inertia in the management of HF as we demonstrated in our cohort, and that the inertia may be attributed, at least partially, to the complexity of care when PCC was called. Understandably, providers would stay with existing treatment plans when prescription adjustment might negatively affect symptom management or even lead to unnecessary adverse effects. Therefore, we saw deprescribing of LD in some patients while there was a strong correlation between the pre-and post-PCC prescribing. It is complicated to address clinical inertia in the management of chronic illnesses since challenges have been identified at the physician, patient, and system levels [9,12]. For example, as reported in the ADDress your Heart study, most physicians were familiar with the ESC guidelines but only 25% adhered to treatment recommendations in practice [31]. Poor adherence in patients and patients' poor awareness of HF burden also undermined physicians' adherence to conduct Guidelines-Directed Medical Therapy (GDMT) [9,12]. Related to health care systems, adjustments of therapy are delayed or undermined due to limited access to cardiology services and disease management programs [9]. A systemic reform of coordinated care for HF patients is necessary to meet the need for prescription adjustments to respond to the complexity and uncertainty of HF.

Last, we think the inconvenience related to LD use also affects the prescription of LD. Particularly, older patients can be even more affected by frequent urination compared to younger patients, given that younger patients were more likely to reconcile the life living with LD, compared to patients

older than 65 years at the time of PCC. Since inconvenience as an adverse effect may be assessed in PCC, it is reasonable to that LD is reduced or paused.

Limitations

This study has a few limitations. First, studies using administrative databases can be affected by the miscoding of diagnoses and prescriptions. To improve precision, we adopted the "2-outpatient-1-patient" method to verify diagnoses [35,36], and cited the definitions of comorbidity used in published studies [17,23]. To reduce missing prescription records, we examined records of both administered and prescribed medications. Second, we were unable to determine Ejection Fraction (EF), HF stage, or functional status because they were not available in the administrative database like what we used. We understand that HF type in terms of EF, functional status, and HF stage are often considered in the current practice of PC referral [37,38], we do not think is critically relevant to our cohort because the current AHA and ESC guidelines recommend PC referral for all patients, whereas the purpose of PC might vary by patient's condition including HF stage and EF [4,14,16]. Third, we did not investigate the impact of concomitant medications to the prescribing of LD. We would like to depict the pattern of concomitant medications around the time of PCC. To our knowledge, the medication list of these patients could be intense. We have decided to investigate the polypharmacy issue in our future research using an EHR database with pharmacy records within a regional health system. Last, we cannot determine if pre-PCC and post-PCC LD prescriptions were causally related due to the study design. However, the associations shed light on the directions of our future investigations on the effects of PCC on polypharmacy, adverse effects, and medication adherence.

Conclusion

We demonstrated in a cohort of newly diagnosed HF that the use of loop diuretics is reduced following the initial palliative care consultation. Our finding indicated that PCC could reduce polypharmacy to help avoid unnecessary adverse effects. However, reverse therapeutic inertia in the clinical management of HF may exist, which could undermine the benefit of deprescribing and treatment adjustment. Future research should be invested in observational studies using a health system-based database to investigate the impact of patient's functional status, HF stage, and concomitant medications on the pharmacological management of symptoms, and mortality and QOL outcomes associated with prescription adjustment following palliative care consultation.

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