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ORIGINAL ARTICLE

Real-world safety of neurohormonal antagonist initiation among older adults following a heart failure hospitalization

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Abstract

Aims To optimize guideline-directed medical therapy for heart failure, patients may require the initiation of multiple neurohormonal antagonists (NHAs) during and following hospitalization. The safety of this approach for older adults is not well established.

Methods and results We conducted an observational cohort study of 207 223 Medicare beneficiaries discharged home following a hospitalization for heart failure with reduced ejection fraction (HFrEF) (2008–2015). We performed Cox proportional hazards regression to examine the association between the count of NHAs initiated within 90 days of hospital discharge (as a time-varying exposure) and all-cause mortality, all-cause rehospitalization, and fall-related adverse events over the 90 day period following hospitalization. We calculated inverse probability-weighted hazard ratios (IPW-HRs) with 95% confidence intervals (CIs) comparing initiation of 1, 2, or 3 NHAs vs. 0. The IPW-HRs for mortality were 0.80 [95% CI (0.78–0.83)] for 1 NHA, 0.70 [95% CI (0.66–0.75)] for 2, and 0.94 [95% CI (0.83–1.06)] for 3. The IPW-HRs for readmission were 0.95 [95% CI (0.93–0.96)] for 1 NHA, 0.89 [95% CI (0.86–0.91)] for 2, and 0.96 [95% CI (0.90–1.02)] for 3. The IPW-HRs for fall-related adverse events were 1.13 [95% CI (1.10–1.15)] for 1 NHA, 1.25 [95% CI (1.21–1.30)] for 2, and 1.64 [95% CI (1.54–1.76)] for 3.

Conclusions Initiating 1–2 NHAs among older adults within 90 days of HFrEF hospitalization was associated with lower mortality and lower readmission. However, initiating 3 NHAs was not associated with reduced mortality or readmission and was associated with a significant risk for fall-related adverse events.

Keywords Heart failure; Guideline-directed medical therapy; Older adults; Adverse drug events; Polypharmacy

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Introduction

The use of multiple neurohormonal antagonists (NHAs) including beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs) represents the hallmark of guideline-concordant heart failure with reduced ejection fraction (HFrEF) treatment.[1,2] Initiating these therapies prior to or around hospital discharge would seem to be an excellent opportunity to ensure guideline adherence given patient access and patient receptiveness to medication changes.[3] However, the short-term benefits of this approach are mixed—whereas a landmark study from over a decade ago showed that initiation of an NHA at the time of hospital discharge was associated with improved outcomes among individuals hospitalized with decompensated

HF,[4] an inpatient cohort of almost 20 000 HF patients revealed little correlation between NHA initiation and clinical outcomes like readmissions and mortality, at least in the short term.[5] These observations, coupled with data showing that efforts to reduce readmissions may have increased mortality,[6–8] underscore the importance of exploring whether the routine practice of NHA initiation at or soon after hospital discharge may be causing harm.

Data from the Get With the Guidelines (GWTG) Registry have revealed that almost 25% of adults hospitalized with HF require the addition of ≥2 medications at hospital discharge to comply with guideline recommendations[9]; most of these include NHAs. When coupled with the high burden of comorbidity among older adults with HF,[10] adding multiple NHAs to a regimen can lead to a total medication count that exceeds 10.[11] This is cause for concern, as a high number of medications are known to be associated with adverse clinical outcomes[12,13] including falls,[14–17] disability,[18–20] and hospitalizations.[21–23] This may be especially relevant during the post-hospitalization period, when concurrent geriatric conditions like cognitive impairment[24,25] can lead to challenges when medication regimens are altered.[26] Indeed, adverse drug events are common following a hospitalization.[27] NHAs represent a particularly high-risk class of agent for older adults given age-related alterations in pharmacokinetics and pharmacodynamics[28] and maladaptive physiological changes to the cardiovascular system,[29] predisposing them to falls and low blood pressure. This is an important issue to consider, as falls represent a major cause of morbidity and mortality among older adults[30–33]; and low on-treatment blood pressure has been linked to increased mortality among older frail adults,[34,35] as well as those with HF based on recent data from a Korean cohort.[36] Taken together, these observations reflect a critical need to evaluate whether the initiation of multiple NHAs among older adults at or soon after hospital discharge is safe, which we sought to address in a cohort of older adults hospitalized for HF in the United States.

Methods

Study oversight

This study was approved by the Dartmouth Institutional Review Board, which waived informed consent.

Study design and data source

This is a retrospective cohort study that used national data from a 100% sample of Medicare fee-for-service (FFS) beneficiaries enrolled in both Medicare Parts A (inpatient coverage) and B (outpatient coverage) and a random 40% sample enrolled in Part D (prescription drug coverage). Medicare is a federal health insurance programme in the United States that provides coverage to ~80% of adults with HF in the United States.[37] Medicare claims data provide patient-level information on demographics, health plan enrolment, health service use, diagnoses and procedures documented in inpatient and outpatient settings, and medication dispensing.

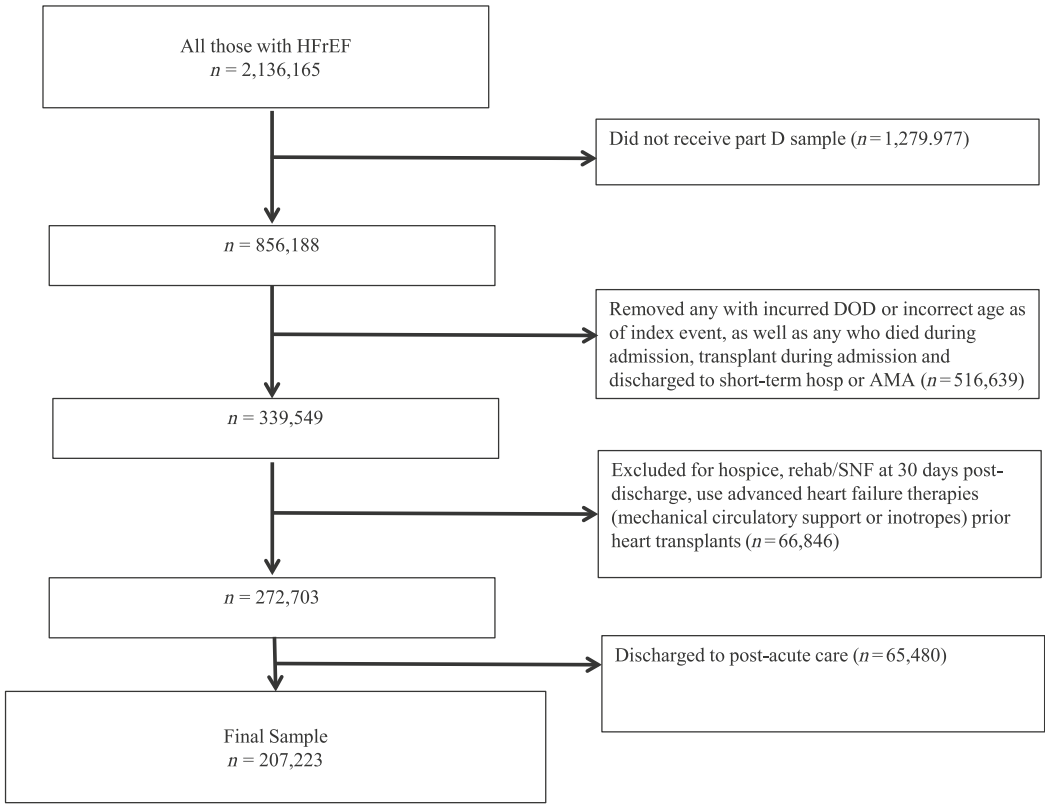
Study population

The study population included patients aged 66 years or older in Medicare FFS who were discharged alive to home following a hospitalization for HFrEF with an admission date between 1 January 2008 and 31 December 2015. For inclusion in the cohort, we required at least 12 months of continuous Parts A and B FFS enrolment and at least 3 months of continuous Part D enrolment immediately prior to the index HFrEF hospitalization admission date and required at least 12 months of continuous Parts A and B FFS enrolment and continuous Part D enrolment during the 12 months after index HFrEF hospitalization discharge date or until death. We excluded individuals who were discharged to post-acute care settings instead of home and excluded individuals who were receiving hospice in the 7 days before the index hospitalization or admitted to hospice within 7 days after discharge. This cohort was previously developed to study medication patterns in older adults with HFrEF and has previously been described.[38,39] Briefly, we sampled the first hospitalization for each beneficiary during the study period, regardless of whether the hospitalization was an incident HF event or not. HFrEF was defined based on an algorithm (eMethods) that incorporates International Classification of Diseases (ICD) Version 9 and 10 codes used in prior work.[40,41] Cohort entry was the day of hospital discharge. Many patients with *advanced* HF do not tolerate NHAs due to low blood pressure and/or low cardiac output, and there are limited data on its efficacy in advanced HF.[42] Therefore, we excluded patients with advanced HF, defined as those who required durable mechanical circulatory support within the prior year or during the index hospitalization, and excluded those discharged with home inotropes. We also excluded individuals who received cardiac transplantation in the prior year because the benefit of NHAs is not established for this condition. The patient eligibility cascade is shown in *Figure 1*.

Exposure

The exposure was the number of NHAs initiated during the 90 day post-hospitalization period, measured as a time-varying variable. In other words, we determined counts for each day of the 90 day post-hospitalization period for each

Figure 1 Flowchart of eligibility for inclusion in the study, 2008–2015 Medicare fee-for-service. AMA, against medical advice; DOD, date of death; HFrEF, heart failure with reduced ejection fraction; SNF, skilled nursing facility.



patient. NHAs included the following four classes: beta-blockers, ACEIs, ARBs, and MRAs. Because angiotensin receptor-neprilysin inhibitors (ARNIs) were only approved in mid-2015 and rarely used during the study period, we did not consider these agents in our exposure definition. Initiation of each drug class was defined as the first dispensing of each class in Medicare Part D claims in the 90 days after hospital discharge without dispensings in the 90 days prior to the index hospital admission. We used a time-varying exposure definition whereby individuals' exposure group could be reclassified on each day of follow-up during the 90 days after hospital discharge if NHAs were newly prescribed or discontinued.

Start and end of follow-up

The start of follow-up (baseline or time zero) for each individual was the date of discharge for the index hospitalization (the time of first eligibility). The end of follow-up was death, disenrollment from Medicare Parts A, B, and D, or administrative end of follow-up (31 December 2016 or 30 days, 90 days, or 1 year, depending upon the follow-up period examined), whichever was earliest. To reduce the risk of misclassification of follow-up time and outcomes, individuals were censored on any date on which their exposure status changed through the addition or subtraction of one or more new NHAs (e.g. if an individual had already initiated one NHA before Day 21 of follow-up and then initiated a second NHA on Day 21, their events and person-time contributed to the one NHA exposure group would be censored and they would begin contributing outcome events and person-time to the two NHAs exposure group from Day 21 forward in time).[43]

Outcomes

The primary outcome was 90 day all-cause mortality measured using the date of death in the Medicare Master Beneficiary Summary file. We also examined 90 day all-cause rehospitalization, which was defined based on MedPAR inpatient claims. Finally, we examined rehospitalization, emergency departments visits, or outpatient healthcare professional encounters due to a composite of fall-related adverse events that included dizziness, hypotension, syncope, and falls-related injuries[44] based on ICD codes documented in any coding position on inpatient, Part B, or outpatient claims (eMethods).

Baseline characteristics

Characteristics that could potentially confound the relationship between NHA count and outcomes were prespecified and all measured at or prior to hospital discharge. These covariates included socio-demographics (age, sex, race, dual-eligibility status, multiple zip code tabulation area-level variables, including per cent poverty, per cent with a bachelor's degree, and geographic region), comorbid conditions based on Elixhauser, the severity of illness (implantable cardioverter-defibrillator as a marker of HF severity, intensive care unit stay, and hospitalization in prior year), total medication burden based on unique prescription drugs filled over the 90 days before the index HF hospitalization, geriatric conditions from the prior year (including the presence of frailty-based score of at least 0.25[45,46] and the presence of Alzheimer's disease or related dementias[47]), use of post-acute care in a skilled nursing facility in the year[48] before the index HF hospitalization, and year of hospitalization.

Causal contrast

Our causal contrast of interest was the per-protocol effect: the effect that would have been observed if all individuals had actually adhered to the number of NHAs that they were observed to have initiated (i.e. an 'as-treated' estimate).

Statistical analyses

We adjusted for potential confounding by baseline covariates of the relationship between the number of NHAs initiated and outcomes by estimating propensity scores using multinomial logistic regression models that included 38 baseline characteristics, as previously described. The propensity scores were used to construct stabilized inverse probability of treatment weights (IPTWs). Standardized mean differences were used to evaluate covariate balance between NHA exposure groups before and after IPTW.

We estimated hazard ratios (IPW-HRs) with 95% confidence intervals (CIs) using IPTW cause-specific discrete-time hazards regression models to account for the competing risk of death when examining all-cause rehospitalization and fall-related adverse events. For mortality, we used IPTW discrete-time hazards regression models. Treatment was the only covariate in the models. We did not test the proportional hazards assumption because we interpreted our estimates as a weighted average of the time-varying hazard ratios over the entire follow-up period in accordance with recent guidance.[49]

Risk differences between NHA exposure groups were estimated at selected time points between baseline and the end of follow-up, including at 30 and 90 days.[50] We computed 95% CIs via a non-parametric bootstrap based on 200 resamplings. The corresponding number needed to treat (NNT) [and number needed to harm (NNH)] was also calculated at each selected time point.

We used SAS Version 9.4 (SAS Institute, Cary, NC, USA) for both data processing and analyses. Our analyses were conducted from 1 November 2019 to 30 November 2021.

Stability and sensitivity analyses

To examine the robustness of our findings to alternate study design and analytic decisions, we conducted a stability analysis. For all three outcomes (mortality, readmission, and fall-related adverse events), we added covariates with absolute standardized differences of 0.10 or greater after IPW into the outcome estimation model to examine whether the results differed from those of the main analyses after accounting for the residual covariate imbalance across NHA exposure groups.

To assess how robust our findings were to potential unmeasured or residual confounding, we conducted a sensitivity analysis using the E-value.[51] The E-value is the minimum strength of association, on the risk ratio (RR) scale, that an unmeasured confounder would need to have with both NHA use and an outcome to fully explain away the observed treatment effect estimate (i.e. if there truly was no effect).

Results

Overall study population

We examined 207 223 eligible patients. The mean [standard deviation (SD)] age was 78.8 (7.9) years, 50% were female, and 82% were non-Hispanic White (*Table 1*). The most common comorbid conditions were hypertension (58%), chronic pulmonary disease (19%), and diabetes without chronic complications (18%). The mean (SD) number of unique prescription drugs filled over the 90 days before the index HF hospitalization was 8.7 (4.8). Prior to the hospitalization, 25.4% took 0 NHAs, 37.8% took 1, 32.4% took 2, and 4.4% took 3. The most common NHAs were beta-blockers (54.3%), followed by ACEIs and ARBs (51.8%), and, finally, MRAs (9.8%). Approximately 21% were frail and 8.9% had Alzheimer's disease or related dementia. The mean (SD) length of stay for the index hospitalization was 4.5 (3.5) days, and approximately 34% required the intensive care unit. Nearly half (49%) of the study population experienced a hospitalization during the prior year [mean (SD): 1 (1.5)], and 9% spent at least 1 day in a skilled nursing facility prior to the index hospitalization. Differences in baseline characteristics were attenuated following inverse probability weighting (Supporting Information, *Figures S1–S7*).

Table 1 Baseline characteristics of patients in the study population, 2008–2015 Medicare fee-for-service, stratified by the number of neurohormonal antagonists initiated during the 90 day period following hospitalization

Characteristics	All (N = 207 223)	NHA initiation count			
		0 (n = 122 510)	1 (n = 57 929)	2 (n = 22 347)	3 (n = 4437)
Socio-demographics, *n* (%)					
Age, mean (SD)	78.8 (7.9)	79.1 (8.0)	78.9 (7.9)	78 (7.8)	76.6 (7.4)
Age subgroup					
66–74 years	69 894 (33.7)	40 001 (32.7)	19 381 (33.5)	8526 (38.2)	1986 (44.8)
75–84 years	82 858 (40.0)	49 011 (40)	23 413 (40.4)	8717 (39)	1717 (38.7)
85+ years	54 471 (26.3)	33 498 (27.3)	15 135 (26.1)	5104 (22.8)	734 (16.5)
Female sex	103 066 (49.7)	61 168 (49.9)	28 788 (49.7)	10 946 (49)	2164 (48.8)
Race					
Black non-Hispanic	20 327 (9.8)	12 004 (9.8)	5588 (9.6)	2261 (10.1)	474 (10.7)
White non-Hispanic	168 818 (81.5)	99 740 (81.4)	47 372 (81.8)	18 142 (81.2)	3564 (80.3)
Hispanic	11 859 (5.7)	7126 (5.8)	3229 (5.6)	1253 (5.6)	251 (5.7)
Other	5864 (2.8)	3441 (2.8)	1639 (2.8)	647 (2.9)	137 (3.1)
Unknown	355 (0.2)	199 (0.2)	101 (0.2)	44 (0.2)	11 (0.2)
Dual eligibility with Medicaid	62 949 (30.4)	38 610 (31.5)	16 803 (29)	6330 (28.3)	1206 (27.2)
Area-level variables based on zip code					
Under the poverty line, mean (SD)	16.0 (9.4)	16.1 (9.4)	15.9 (9.3)	15.9 (9.4)	15.6 (9.1)
Bachelor's degree education, mean (SD)	26.5 (15.6)	26.3 (15.6)	26.7 (15.6)	26.8 (15.6)	27.2 (15.5)
Geographic region					
Midwest	52 324 (25.3)	30 593 (25)	14 753 (25.5)	5781 (25.9)	1197 (27)
Northeast	40 554 (19.6)	24 699 (20.2)	11 096 (19.2)	4087 (18.3)	672 (15.1)
South	85 443 (41.2)	50 979 (41.6)	23 826 (41.1)	8923 (39.9)	1715 (38.7)
West	28 902 (13.9)	16 239 (13.3)	8254 (14.2)	3556 (15.9)	853 (19.2)
Comorbid conditions, *n* (%)					
Valvular disease	4924 (2.4)	3628 (3.0)	1041 (1.8)	234 (1.0)	21 (0.5)
Pulmonary circulation disease	1057 (0.5)	767 (0.6)	248 (0.4)	[a]	[a]
Peripheral vascular disease	13 673 (6.6)	8593 (7.0)	3825 (6.6)	1093 (4.9)	162 (3.7)
Hypertension	120 708 (58.3)	73 950 (60.4)	34 217 (59.1)	10 825 (48.4)	1716 (38.7)
Paralysis	1112 (0.5)	723 (0.6)	288 (0.5)	[a]	[a]
Other neurological disorders	6108 (2.9)	3822 (3.1)	1622 (2.8)	565 (2.5)	99 (2.2)
Chronic pulmonary disease	38 719 (18.7)	23 932 (19.5)	10 585 (18.3)	3546 (15.9)	656 (14.8)
Diabetes without chronic complications	37 092 (17.9)	22 429 (18.3)	10 616 (18.3)	3479 (15.6)	568 (12.8)
Diabetes with chronic complications	7581 (3.7)	4846 (4.0)	2121 (3.7)	549 (2.5)	65 (1.5)
Hypothyroidism	23 624 (11.4)	14 429 (11.8)	6685 (11.5)	2135 (9.6)	375 (8.5)
Renal failure	32 949 (15.9)	22 454 (18.3)	8533 (14.7)	1791 (8.0)	171 (3.9)
Liver disease	1046 (0.5)	613 (0.5)	313 (0.5)	101 (0.5)	19 (0.4)
Lymphoma	1856 (0.9)	978 (0.8)	554 (1.0)	255 (1.1)	69 (1.6)
Metastatic cancer	1357 (0.7)	711 (0.6)	433 (0.7)	178 (0.8)	35 (0.8)
Solid tumour without metastasis	2433 (1.2)	1386 (1.1)	725 (1.3)	263 (1.2)	59 (1.3)
Rheumatoid arthritis/collagen vascular disease	4406 (2.1)	2521 (2.1)	1308 (2.3)	476 (2.1)	101 (2.3)
Coagulopathy	2410 (1.2)	1564 (1.3)	622 (1.1)	192 (0.9)	32 (0.7)
Obesity	7473 (3.6)	4782 (3.9)	1987 (3.4)	607 (2.7)	97 (2.2)
Weight loss	1209 (0.6)	723 (0.6)	313 (0.5)	135 (0.6)	38 (0.9)
Fluid and electrolyte disorders	15 358 (7.4)	9762 (8.0)	4216 (7.3)	1185 (5.3)	195 (4.4)
Chronic blood loss anaemia	319 (0.2)	227 (0.2)	77 (0.1)	15 (0.1)	0 (0.0)
Deficiency anaemias	22 559 (10.9)	14 500 (11.8)	6204 (10.7)	1619 (7.2)	236 (5.3)
Alcohol abuse	300 (0.1)	172 (0.1)	87 (0.2)	[a]	[a]
Drug abuse	85 (0.0)	52 (0.0)	21 (0.0)	[a]	[a]
Psychosis	1133 (0.5)	692 (0.6)	282 (0.5)	132 (0.6)	27 (0.6)
Depression	5414 (2.6)	3329 (2.7)	1448 (2.5)	528 (2.4)	109 (2.5)
Disease severity, *n* (%)					
Prior ICD	32 033 (15.5)	22 000 (18.0)	7855 (13.6)	1916 (8.6)	262 (5.9)
ICU stay	71 033 (34.3)	39 221 (32.0)	21 193 (36.6)	8799 (39.4)	1820 (41.0)
Hospitalization in prior year	102 167 (49.3)	66 598 (54.4)	26 739 (46.2)	7659 (34.3)	1171 (26.4)
Geriatric conditions					
Count of medications filled 90 days prior to index hospitalization, *n* (%)					
0–4	37 104 (17.9)	13 423 (11.0)	11 658 (20.1)	9493 (42.5)	2530 (57.0)
5–7	49 997 (24.1)	27 564 (22.5)	15 784 (27.2)	5666 (25.4)	983 (22.2)
8–9	36 747 (17.7)	23 131 (18.9)	10 360 (17.9)	2863 (12.8)	393 (8.9)
10–12	42 642 (20.6)	28 808 (23.5)	10 979 (19.0)	2539 (11.4)	316 (7.1)
13+	40 733 (19.7)	29 584 (24.1)	9148 (15.8)	1786 (8.0)	215 (4.8)
Frailty, *n* (%)	44 056 (21.3)	29 118 (23.8)	11 309 (19.5)	3186 (14.3)	443 (10.0)
Alzheimer's and related disease, *n* (%)	18 503 (8.9)	11 722 (9.6)	4939 (8.5)	1615 (7.2)	227 (5.1)
Post-acute SNF care in prior year, *n* (%)	19 137 (9.2)	12 336 (10.1)	5058 (8.7)	1525 (6.8)	218 (4.9)

ICD, implantable cardioverter-defibrillator; ICU, intensive care unit; NHA, neurohormonal antagonist; SD, standard deviation; SNF, skilled nursing facility.
[a]Cell size too small to report per Medicare Data Use Agreement policies.

Characteristics by treatment group

Table 1 also displays baseline characteristics according to the number of NHAs initiated during the 90 day period following hospitalization, prior to applying IPTW. By the end of the 90 day post-hospitalization follow-up period, 122 510 people were initiated on 0 NHAs, 57 929 were initiated on 1, 22 347 were initiated on 2, and 4437 were initiated on 3. The most common NHAs initiated were beta-blockers (24.1%), followed by ACEIs and ARBs (19.5%), and, finally, MRAs (12.4%).

All absolute standardized mean differences in baseline characteristics were <0.10 after IPTW, with the following exceptions: When comparing NHA count of 0 to 3, standardized mean differences exceeded 0.10 for hypertension (0.13), peripheral vascular disorders (0.12), hospitalization in the prior year (0.11), and frailty (0.10); when comparing NHA count of 1 to 3, standardized mean differences exceeded 0.10 for hypertension (0.13), peripheral vascular disorders (0.12), hospitalization in the prior year (0.11), and frailty (0.10); and when comparing NHA count of 1 to 3, standardized mean differences exceeded 0.10 for peripheral vascular disorders (0.10). The minimum of the IPW was 0.08, the maximum was 28.53, and the mean of the IPW was 1.01.

Mortality

As shown in *Figure 2*, mortality was greatest among those with NHA count of 0. Compared with a count of 0 NHAs initiated during the post-discharge period, the IPW-HR for mortality for 1 NHA was 0.80 [95% CI (0.78–0.83), $P < 0.001$], IPW-HR for 2 was 0.70 [95% CI (0.66–0.75), $P < 0.001$], and IPW-HR for 3 was 0.94 [95% CI (0.83–1.06), $P = 0.31$]. At 30 days, risks of mortality for NHA initiation count of 0 were 0.7% higher than a count of 1 and 1.1% higher than a count of 2. The corresponding NNTs at 30 days were 141 for an NHA count of 1 and 93 for a count of 2. At 90 days, the risks of mortality for NHA initiation count of 0 were 1.8% higher than a count of 1 and 2.8% higher than a count of 2. The corresponding NNTs at 90 days were 55 for an NHA count of 1 and 36 for a count of 2. E-value calculations indicated that an unmeasured confounder of both the exposure and outcome would need to have RRs of 1.79 to fully attenuate the association observed for an NHA count of 1 and 2.20 to fully attenuate the association for NHA count of 2. In a stability analysis that included covariates with post-weighting standard error > 0.10, IPW-HRs were similar to the main model (Supporting Information, *Table S1*).

Rehospitalizations

Figure 3 shows that readmission was greatest among those with NHA count of 0. Compared with a count of 0 NHAs initiated during the post-discharge period, the IPW-HR for readmission for 1 NHA was 0.95 [95% CI (0.93–0.96), $P < 0.001$], IPW-HR for 2 was 0.89 [95% CI (0.86–0.91), $P < 0.001$], and IPW-HR for 3 was 0.96 [95% CI (0.90–1.02), $P = 0.19$]. At 30 days, the risks of readmission for NHA initiation count of 0 were 0.9% higher than a count of 1 and 2.0%

Figure 2 Survival curves for neurohormonal antagonist (NHA) initiation count and mortality.

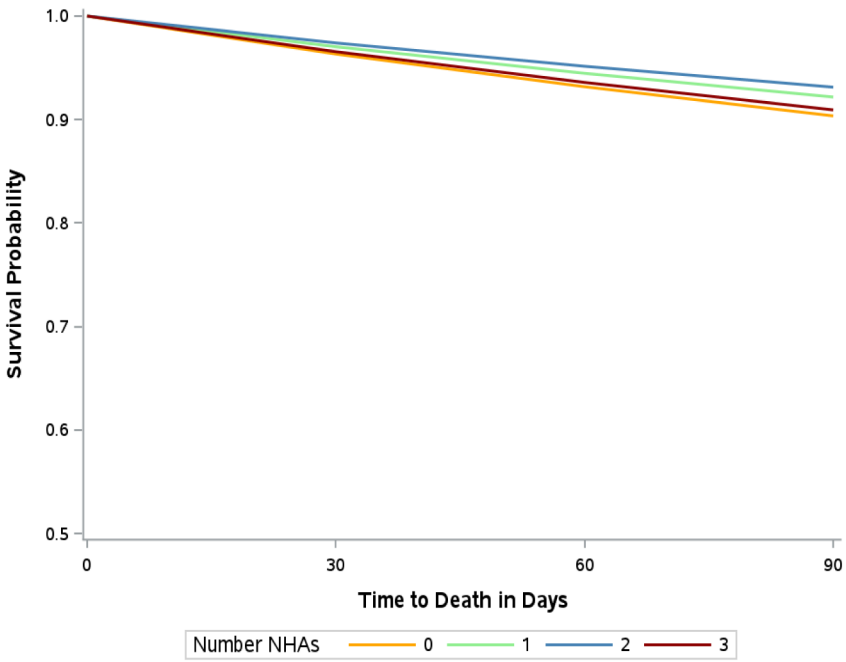
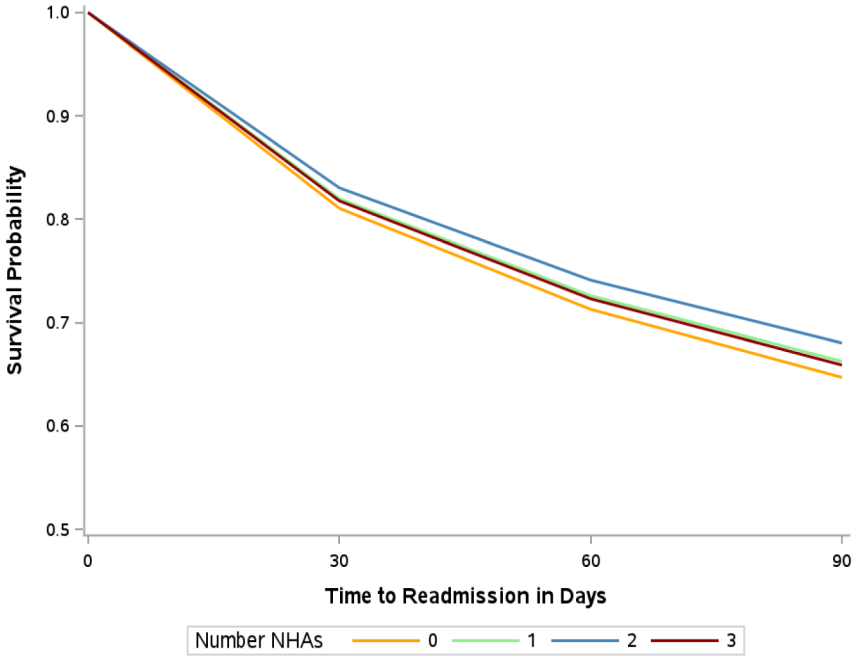


Figure 3 Survival curves for neurohormonal antagonist (NHA) initiation count and readmission.



higher than a count of 2. The corresponding NNTs at 30 days were 107 for an NHA count of 1 and 50 for a count of 2. At 90 days, the risks of mortality for NHA initiation count of 0 were 1.6% higher than a count of 1 and 3.3% higher than a count of 2. The corresponding NNTs at 90 days were 65 for an NHA count of 1 and 30 for a count of 2. E-value calculations indicated that an unmeasured confounder of both the exposure and outcome would need to have IPW-HRs of 1.24 to fully attenuate the association observed for an NHA count of 1 and 1.40 to fully attenuate the association for NHA count of 2. In a stability analysis that included covariates with post-weighting standard error $>$ 0.10, findings were similar (Supporting Information, *Table S1*).

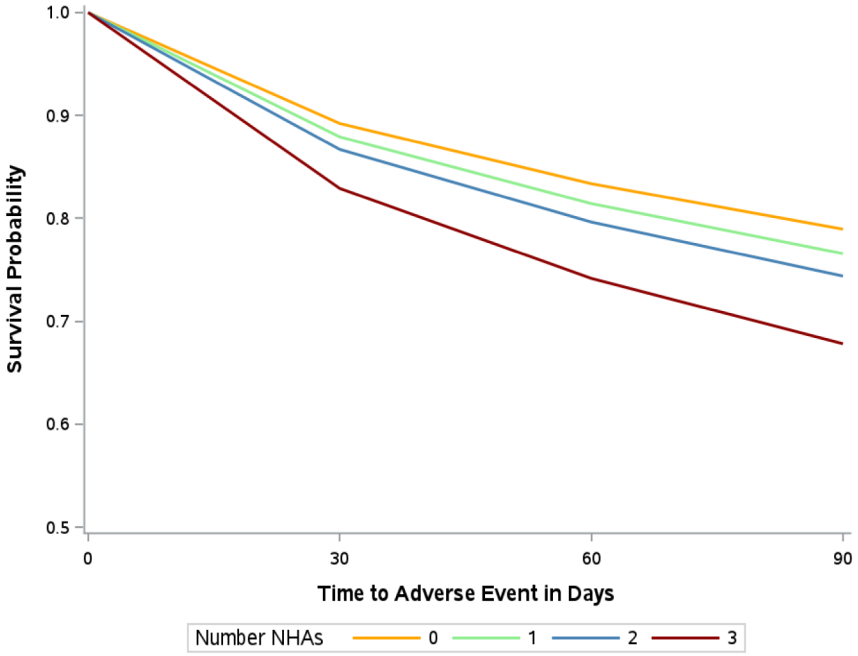
Fall-related adverse events

Figure 4 shows that hazard for fall-related adverse events increased in a graded fashion with increasing NHA initiation count. Compared with a count of 0 NHAs initiated during the post-discharge period, the IPW-HR for fall-related adverse events for 1 NHA was 1.13 [95% CI (1.10–1.15), $P < 0.001$], IPW-HR for 2 was 1.25 [95% CI (1.21–1.29), $P < 0.001$], and IPW-HR for 3 was 1.64 [95% CI (1.54–1.76), $P < 0.001$]. At 30 days, the risks of falls-related adverse events for NHA initiation count of 0 were 1.3% lower than a count of 1, 2.5% lower than a count of 2, and 6.3% lower than a count of 3. The corresponding NNHs at 30 days were 77 for an NHA count of 1, 40 for a count of 2, and 16 for a count of 3. At 90 days, the risks of falls-related adverse event for NHA initiation count of 0 were 2.4% lower than a count of 1, 4.6% lower than a count of 2, and 11% lower than a count of 3. The corresponding NNHs at 90 days were 42 for an NHA count of 1, 22 for a count of 2, and 9 for a count of 3. E-value calculations indicated that an unmeasured confounder of both the exposure and outcome would need to have RRs of 1.51 to fully attenuate the association observed for an NHA count of 1, 1.81 to fully attenuate the association for NHA count of 2, and 2.67 to fully attenuate the association for NHA count of 3. In a stability analysis that included covariates with post-weighting standard error $>$ 0.10, findings were similar (Supporting Information, *Table S1*).

Discussion

This analysis from a real-world population of older adults enrolled in FFS Medicare demonstrated that the initiation of 1–2 NHAs during the post-hospitalization period was inversely associated with 90 day mortality and readmission, albeit at an increased risk for fall-related adverse events. Our findings also showed that initiation of 3 NHAs during the post-hospitalization period was not associated with a meaningful reduction in either 90 day mortality or readmission but was associated with a significantly increased risk of fall-related adverse events. These findings have important implications for optimal approaches to prescribing guideline-directed medical therapy (GDMT), especially as the number of GDMT agents for HF continues to increase.

Figure 4 Survival curves for neurohormonal antagonist (NHA) initiation count and fall-related adverse events.



An important strategy for optimizing GDMT is the initiation of therapy at the time of a hospitalization.[3] Because hospitalization for HF represents a heralding event with implications on overall prognosis,[52] initiation of therapy that can alter the natural history of the disease at the time of the event seems logical. However, results have been mixed with regard to improvement in short-term outcomes such as readmission or mortality.[4,5] Moreover, to achieve maximal GDMT, it is frequently necessary to concurrently initiate multiple agents. Indeed, almost 25% of patients require initiation of ≥2 medications at hospital discharge in order to comply with guideline recommendations.[9] There is theoretical concern about harm that can result from concurrently initiating multiple agents in an older population that is intrinsically at higher risk for adverse events[11] at a time when adverse drug events are especially common.[27] Yet, given the long-term benefits of GDMT,[53] the approach of initiating multiple GDMT agents at the time of hospitalization has largely been embraced. Our observations here are reassuring for the initiation of 1–2 NHAs in the post-discharge period and support this strategy given improvements in both mortality and readmission.

In contrast, our study showed that initiation of 3 NHAs was not associated with either reduced mortality or reduced readmission. Moreover, we found that initiation of three agents was associated with a significantly increased risk of fall-related adverse events, with NNHs of 16 at 30 days post-discharge and 9 at 90 days post-discharge. Concerns about adverse events in the setting of initiation of multiple NHAs stem from prior work in the non-HF population that indicates that the falls risk following hospitalization is high,[54] especially when initiating medications that can lower blood pressure.[55] Our findings here raise a concern about initiating too many medications around the same time, which could synergistically have a negative impact on patients. Experts in the field have advocated for the initiation of quadruple therapy prior to hospital discharge.[56] This strategy includes beta-blockers, ARNIs, MRAs, and sodium-glucose co-transporter-2 (SGLT-2) inhibitors. Although we did not formally include ARNIs in our count, it is reasonable to infer at least as much of an effect on fall-related adverse events given shared features with ARBs and ACEIs. To be clear, these data do not alter the notion that quadruple therapy (and more generally, GDMT) can have substantial benefits on long-term mortality, hospitalization, and even quality of life. However, data here should increase awareness about the concurrent initiation of multiple NHAs during the post-hospitalization period, which is well known to be a particularly vulnerable period marked by subclinical impairments in reserve and resilience.[57] Future work is warranted to better understand patterns observed here. For example, it is not known whether certain medication combinations are riskier than others; it is also not known whether certain subpopulations have a higher risk than others. Further examination of these issues would also benefit from examination in a population with substantial use of newer agents such as ARNIs and SGLT-2 inhibitors.

Our findings support the importance of integrating nuance when initiating GDMT. Although the potential benefits of mortality and readmission appeared to outweigh the risks of fall-related adverse events among those who experienced

NHA initiation of 1–2, patients' values must be incorporated to determine the best course of action for each patient. Falls and related injuries can be a particularly devastating event for many patients, with consequences that most notably include loss of independence and potential placement into a nursing home.[31] Accordingly, many patients may prefer to minimize the risk of falls, even at the sacrifice of short-term mortality benefits. It may be reasonable to initiate these therapies in the outpatient setting after recovery from hospitalization. The problem with this approach has been that the rate of outpatient initiation of GDMT is low.[58] Data here suggesting potential harm from current practice lend further support to the urgent need for novel strategies in the ambulatory setting to rectify this long-standing issue. Future work should build upon emerging ideas such as integrating advanced professional practitioners into dedicated GDMT clinics[59] and leveraging telemedicine for the purposes of safe and effective remote GDMT initiation and titration.[60]

There are many strengths to this analysis. This includes real-world population, large sample size, and an array of important covariates. There are also some limitations. First, because this was an observational study using administrative data, findings may reflect the presence of residual confounding rather than true causal relationships. For example, we did not have data on echocardiographic parameters (such as left ventricular ejection fraction), HF aetiology (such ischaemic vs. non-ischaemic), the severity of comorbid conditions, objective vital sign measures (such as heart rate or blood pressure), or other clinical data that affect medication prescribing decisions. We also did not have data on diuretic dosage and did not adjust for the baseline number of NHA taken prior to hospitalization due to data convergence issues. Covariate imbalance across NHA exposure groups warrants caution in causal inferences. Future work that can examine chart-level data to determine whether adverse drug events contributed to the outcome using formalized criteria like Naranjo criteria would be beneficial.[61] Relatedly, differentiating types and severity of fall-related adverse events will be important to understand the risks of certain prescribing patterns. Second, although Medicare recipients represent a large proportion of the US population with HF (>75% of hospitalizations in the United States),[37] generalizability may be limited for individuals without Medicare. Third, although we used a time-varying exposure, we did not adjust for time-varying confounders because we believed that there were few measured covariates that would meaningfully change over our 90 day follow-up period. We also did not use inverse probability weighting to adjust for potential selection bias related to censoring when individuals switched from one NHA exposure group to another.[62] If there is marked residual confounding and/or selection bias, our as-treated analysis may not have succeeded at validly estimating the per-protocol effect of interest. Fourth, we leveraged claims-based measures to identify diagnoses including HF, comorbid conditions, and fall-related adverse events. Although we used validated algorithms, there are inherent limitations to the accuracy of claims-based measures of diagnoses, including the potential for an underestimation of the true prevalence (i.e. insufficient sensitivity).

Conclusions

Among older adults hospitalized for HF, we reassuringly found that initiating 1–2 NHAs in the post-discharge period following an HF hospitalization was associated with lower 90 day mortality and lower 90 day readmission. However, initiation of 3 NHAs was not associated with improved mortality or readmission and was associated with a significant risk for fall-related adverse events. These data indicate that caution should be exercised when initiating 3 NHAs in the post-discharge period of an HF hospitalization.

Conflict of interest

P.G. is supported by the American Heart Association (grant number 20CDA35310455) and the National Institute on Aging (grant number K76AG064428), receives personal fees for medicolegal consulting related to heart failure, and has received honoraria from Akcea Therapeutics Inc. and Bionest Inc. A.R.Z. was supported, in part, by the National Institute on Aging (grant numbers R01AG045441, R01AG065722, R21AG061632, R01AG061221, R24AG064025) and receives grant funding support paid directly to Brown University for research on the epidemiology of vaccinations and infections among nursing home residents and infants. M.M.S. has received research support from Amgen. L.A.A. has received grant support from the American Heart Association, the National Institutes of Health, and the Patient-Centered Outcomes Research Institute and consultant fees from ACI Clinical, Amgen, Boston Scientific, Cytokinetics, and Novartis. E.B.L. has received research support from Amgen. L.G. was supported by the National Heart Lung and Blood Institute (grant numbers K23HL142835, K23HL142835-S1). M.J.K. receives grant funding support from the National Institute on Aging (grant number 1R24AG064025) and personal consult fee from Endocrine and Diabetes Plus Clinic of Houston. The remaining authors have nothing to disclose.

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Supporting information

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

Table S1. Stability analysis with adjustment for covariates* with post-weighting standardized mean differences >0.10.
Figure S1. Distribution of original weights by neurohormonal antagonist initiation count.
Figure S2. Standardized mean differences for 0 vs. 1 neurohormonal antagonist initiation count.
Figure S3. Standardized mean differences for 0 vs. 2 neurohormonal antagonist initiation count.
Figure S4. Standardized mean differences for 0 vs. 3 neurohormonal antagonist initiation count.
Figure S5. Standardized mean differences for 1 vs. 2 neurohormonal antagonist initiation count.
Figure S6. Standardized mean differences for 1 vs. 3 neurohormonal antagonist initiation count.
Figure S7. Standardized mean differences for 2 vs. 3 neurohormonal antagonist initiation count.

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