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ORIGINAL RESEARCH ARTICLE

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Evidence-based pharmacotherapies used in the postdischarge phase are associated with improved one-year survival in senior patients hospitalized with heart failure

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Summary

Aim: Hospitalized heart failure (HF) patients have a poor prognosis postdischarge. We determined whether renin-angiotensin system inhibitors (RASI) and β-blockers dispensed to patients within 60 days post-HF hospital discharge are associated with improved 1-year survival.

Methods: A retrospective population-based study was conducted in 4897 seniors, aged 65-84 years, alive at 60 days postindex HF hospitalization in Western Australia over 2003-2008. Dispensing of RASI and β-blocker dispensing was identified from the Pharmaceutical Benefits Scheme claims database linked to hospital admission and death records.

Results: At 1-year posthospital discharge, the all-cause mortality and all-cause death or HF rehospitalization rate was 13.5% (n = 663) and 24.4% (n = 1193), respectively. Postdischarge RASI and β-blocker were dispensed in 77.4% and 53.0% of patients, respectively. Their use was associated with a lower inverse probability treatment weighted (IPTW) HR for 1-year mortality of 0.70, 95% CI 0.61-0.81 and 0.79, 95% CI 0.68-0.92, respectively (both $P < 0.0001$), with a survival advantage most evident in the subgroup (70.1%) of patients with ischemic HF. In the overall cohort, these therapies were also associated with reduced IPTW HRs for all-cause death or HF rehospitalization (both $P < 0.005$) but not for HF rehospitalization exclusively. Use of a β-blocker was associated with a reduced IPTW HR for HF rehospitalization in the ischemic HF subgroup only.

Conclusions: In a cohort of senior patients hospitalized with HF, dispensing of a RASI or β-blocker within 60 days postdischarge is associated with a 1-year survival benefit. Early postdischarge support programs after recent HF hospitalization should include measures to optimize adherence to evidence-based medications.

KEYWORDS
heart failure, hospitalization, renin-angiotensin system inhibitor, survival, β-blocker

Xiwen Qin and Joseph Hung are equal first co-authors.

1 | INTRODUCTION

Hospitalization for heart failure (HF) is associated with a poor prognosis with a high postdischarge mortality and rehospitalization rate that has barely improved in the recent era despite available evidence-based therapies.[1-4] The early postdischarge care of patients after acute HF hospitalization is now recognized as an important management issue in both the European and US guidelines.[5,6] Renin-angiotensin system inhibitors (RASI) and β-blockers are proven prognostic treatments for HF with reduced ejection fraction (HFrEF), and current practice guidelines recommend that these therapies are initiated or maintained during HF hospitalization unless contraindicated or not tolerated.[5,6] Observational studies have reported that RASI[7-9] and/or β-blocker dispensing[8-11] at hospital discharge are independently associated with a lower risk of 1-year all-cause mortality. However, to our knowledge, previous studies have not examined if persistence to these oral therapies in the early postdischarge period is associated with improved medium-term survival. The early postdischarge phase after acute HF hospitalization is often described as a "vulnerable period"[12] during which persistence and adherence to treatment regimens may be suboptimal without ongoing clinical surveillance and multidisciplinary support.[13,14] We therefore examined if dispensing of a RASI or β-blocker to patients within a 60-day postdischarge window following HF hospitalization was independently associated with a lower risk of subsequent all-cause death or HF rehospitalization in a retrospective population-based cohort study of seniors, aged 65-84 years, with hospitalized HF.[15]

2 | METHODS

2.1 | Data sources

This study used statutory government-held administrative databases audited for quality to create person-linked health records as described in the study protocol.[15] Briefly, the Hospital Morbidity Data Collection (HMDC) from the WA Data Linkage System[16] was used to identify patients with hospitalization for HF from 2003 to 2008 and linked to matching death records from the WA mortality registry. The national Pharmaceutical Benefits Scheme (PBS) claims data were used to identify all matching records of medications dispensed from June 1, 2002, to June 30, 2011.[15]

2.2 | Study population

We identified a cohort of 4897 seniors, aged 65-84 years, with an index (first in period) hospitalization in 2003-2008 for HF as a principal diagnosis or HF as a secondary diagnosis and ischemic heart disease (IHD) as a principal diagnosis, and who were alive at 60 days following the date of discharge. Patients with a history of valvular heart disease or dialysis were excluded. The methodology used to identify the cohort and the codes used to identify HF and other comorbidities have been previously described.[15]

2.3 | Data collection

Demographic data were identified based on patients' index HF admission. Medical and surgical history was identified from the HMDC using a fixed 20-year look-back period from 60 days postdischarge (ie landmark date) and prevalent HF cases were defined on the basis of a HF hospitalization prior to index admission.[15] The reason we used 60 days postdischarge as the landmark date was to allow sufficient time for patients to exhaust previous drug supplies and get their scripts refilled from community pharmacies after seeing their health practitioner. Individual medications including RASI and β-blockers dispensed in the 6 months prior to index admission and between the date of hospital discharge and 60 days later were identified from the PBS data by their Anatomical Therapeutic Chemical (ATC) code.[15] We compared patients who were supplied with any RASI or β-blocker within 60 days of discharge to those who had no supplies in this period.

2.4 | Study outcomes

We used the landmark analysis method to evaluate the association between dispensed HF therapies (RASI and β-blocker) between hospital discharge and 60 days later (landmark date) and outcomes to 1 year after HF discharge.[17] Use of the landmark analysis method overcomes immortal time bias that may occur with observational studies and avoids the complexity of time-dependent analyses.[17] The primary outcome was time from landmark to all-cause mortality censored at 1 year of follow-up. Secondary outcomes were time to rehospitalization for HF as a principal diagnosis or a composite of all-cause mortality or HF rehospitalization, whichever event occurred first.

2.5 | Statistical analysis

Descriptive statistics were presented as a mean with SD for continuous variables and frequency (%) for categorical variables. We tested the differences between groups using a chi-square test for categorical variables and the *t* test for continuous variables or Wilcoxon rank-sum test for nonparametric variables. Time to outcomes were plotted using a cumulative incidence function and Gray's test was used to assess differences between the groups.[19] Initially, unadjusted and covariate-adjusted Cox proportional hazards regression models were fitted to estimate the associations between treatment within 60-days postdischarge and the study outcomes. Covariates included in the regression models were selected from the available variables up to landmark date based on potential associations with treatments and/or study outcomes (Table 1). These included demographic characteristics (sex, age, Aboriginal status, and Accessibility and Remoteness Index of Australia plus (ARIA+) classification); hospital group (metro, rural, private); medical and surgical history from 20-year look-back period (prior HF, ischemic heart disease (IHD), hypertension, atrial

TABLE 1 Baseline characteristics of patients stratified by RASI vs no RASI and β-blocker vs no β-blocker dispensed within 60 days postdischarge after index heart failure hospitalization

		RASI			β-Blocker		
Characteristics	**Total cohort**	**Yes**	**No**	***P*-value**	**Yes**	**No**	***P*-value**
Total n (%)	4897	3790 (77.4)	1107 (22.6)		2596 (53.0)	2301 (47.0)	
Male	2778 (56.7)	2178 (57.5)	600 (54.2)	0.06	1546 (60.0)	1232 (53.5)	<0.0001
Age (mean ± SD)	76.6 ± 5.5	76.5 ± 5.5	77.1 ± 5.5	0.001	76.1 ± 5.5	77.2 ± 5.4	<0.0001
Age group							
65-74 years	1786 (36.5)	1424 (37.6)	362 (32.7)	0.003	1062 (40.9)	724 (31.5)	<0.0001
75-84 years	3111 (63.5)	2366 (62.4)	745 (67.3)		1534 (59.1)	1577 (68.5)	
Aboriginal patients (n, %)	103 (2.1)	62 (1.6)	41 (3.7)	<0.0001	38 (1.5)	65 (2.8)	0.0009
ARIA + classification (n, %)							
Major city	2244 (45.8)	1763 (46.5)	481 (43.5)	<0.0001	1230 (47.4)	1014 (44.1)	<0.0001
Inner regional	1441 (29.4)	1133 (29.9)	308 (27.8)		812 (31.3)	629 (27.3)	
Outer regional	514 (10.5)	408 (10.8)	106 (9.6)		254 (9.8)	260 (11.3)	
Remote	221 (4.5)	169 (4.5)	52 (4.7)		92 (3.5)	129 (5.6)	
Very remote	154 (3.1)	87 (2.3)	67 (6.1)		61 (2.4)	93 (4.0)	
Missing data	323 (6.6)	230 (6.1)	93 (8.4)		147 (5.7)	176 (7.7)	
Hospital group (n, %)							
Metro teaching	1634 (33.4)	1315 (34.7)	319 (28.8)	<0.0001	941 (36.3)	693 (30.1)	<0.0001
Metro nonteaching	1049 (21.4)	822 (21.7)	227 (20.5)		617 (23.8)	432 (18.8)	
Rural hospitals	1031 (21.1)	749 (19.8)	282 (25.5)		441 (17.0)	590 (25.6)	
Private hospitals	1183 (24.2)	904 (23.9)	279 (25.2)		597 (23.0)	586 (25.5)	
Length of stay (Median, IQR)	5 (2, 9)	5 (2, 8)	5 (2, 10)	0.25	5 (2, 8)	5 (2, 9)	0.36
Medical history (n, %)							
Prevalent HF	1621 (33.1)	1257 (33.2)	364 (32.9)	0.86	849 (32.7)	772 (33.6)	0.53
IHD	3434 (70.1)	2749 (72.5)	685 (61.9)	<0.0001	2070 (79.7)	1364 (59.3)	<0.0001
Hypertension	3691 (75.4)	2946 (77.7)	745 (67.3)	<0.0001	2061 (79.4)	1630 (70.8)	<0.0001
AF	2284 (46.6)	1782 (47.0)	502 (45.4)	0.33	1251 (48.2)	1033 (44.9)	0.02
Diabetes	1985 (40.5)	1607 (42.4)	378 (34.2)	<0.0001	1141 (44.0)	844 (36.7)	<0.0001
COPD	1584 (32.4)	1181 (31.2)	403 (36.4)	0.001	603 (23.2)	981 (42.6)	<0.0001
CKD	1537 (31.4)	1165 (30.7)	372 (33.6)	0.07	893 (34.4)	644 (28.0)	<0.001
PVD	1022 (20.9)	776 (20.5)	246 (22.2)	0.20	556 (21.4)	466 (20.3)	0.32
Stroke	609 (12.4)	459 (12.1)	150 (13.6)	0.20	322 (12.4)	287 (12.5)	0.94
Cancer	1660 (33.9)	1271 (33.5)	389 (35.1)	0.32	847 (32.6)	813 (35.3)	0.06
Dementia	266 (5.4)	182 (4.8)	84 (7.6)	0.0003	94 (3.6)	172 (7.5)	<0.0001
Depression	413 (8.4)	281 (7.4)	132 (11.9)	<0.0001	176 (6.8)	237 (10.3)	<0.0001
Charlson score (mean ± SD)	3.2 ± 2.8	3.2 ± 2.8	3.4 ± 2.9	0.10	3.3 ± 2.8	3.2 ± 2.8	0.11
History of procedure							
PCI	843 (17.2)	691 (18.2)	152 (13.7)	0.0005	562 (21.7)	281 (12.2)	<0.0001
CABG	802 (16.4)	629 (16.6)	173 (15.6)	0.44	510 (19.7)	292 (12.7)	<0.0001
Prior medications used (n, %)							
RASI	3086 (63.0)	2729 (72.0)	357 (32.3)	<0.0001	1776 (68.4)	1310 (56.9)	<0.0001
β-Blocker	1647 (33.6)	1342 (35.4)	305 (27.6)	<0.0001	1346 (51.9)	301 (13.1)	<0.0001

(Continues)

TABLE 1 (Continued)

Characteristics	Total cohort	RASI			β-Blocker		
		Yes	No	*P*-value	Yes	No	*P*-value
MRA	233 (4.8)	181 (4.8)	52 (4.7)	0.91	126 (4.9)	107 (4.7)	0.31
Digoxin	348 (7.1)	277 (7.3)	71 (6.4)	0.31	174 (6.7)	174 (7.6)	0.24
Concurrent medications used within 60 days postdischarge (n, %)							
RASI	3790 (77.4)	—	—	NA	2218 (85.4)	1572 (68.3)	<0.0001
β-Blocker	2596 (53.0)	2218 (58.5)	378 (34.2)	<0.0001	—	—	NA
MRA	893 (18.2)	770 (20.3)	123 (11.1)	<0.0001	569 (21.9)	324 (14.1)	<0.0001
Digoxin	706 (14.4)	575 (15.2)	131 (11.8)	0.005	415 (16.0)	291 (12.7)	0.0009
Loop diuretic	2926 (59.8)	2447 (64.6)	479 (43.3)	<0.0001	1665 (64.1)	1261 (54.8)	<0.0001
Antiarrhythmic	469 (9.6)	395 (10.4)	74 (6.7)	0.0002	258 (9.9)	211 (9.2)	NS
Warfarin	1088 (22.2)	906 (23.9)	182 (16.4)	<0.0001	667 (25.7)	421 (18.3)	<0.0001
Statin	2757 (56.3)	2312 (61.0)	445 (40.2)	<0.0001	1756 (67.6)	1001 (43.5)	<0.0001
Calcium antagonist	770 (15.7)	593 (15.7)	177 (16.0)	0.78	342 (13.2)	428 (18.6)	<0.0001

Abbreviation: ARIA+, Accessibility and Remoteness Index of Australia plus classification; IHD, ischemic heart disease; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; PVD, peripheral vascular disease; PCI, percutaneous coronary intervention, CABG, coronary artery bypass graft; RASI, renin-angiotensin- system inhibitor; MRA, mineralocorticoid receptor antagonist; NA, not applicable.

fibrillation (AF), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), peripheral vascular disease (PVD), stroke, cancer, dementia, depression, coronary artery bypass graft surgery (CABG) or percutaneous coronary intervention (PCI), and a derived Charlson comorbidity index); medication history in the 6 months prior to the index HF admission (RASI, β-blocker, mineralocorticoid receptor antagonist, digoxin), and concomitant use of medications 60-day post-HF discharge (mineralocorticoid receptor antagonist, digoxin, loop diuretics, antiarrhythmic agents, warfarin, statins, and calcium antagonists).

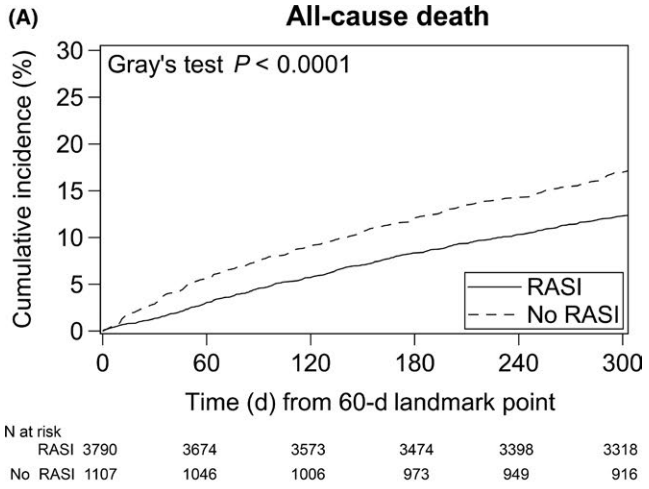
We then carried out a propensity score (PS) analysis using the inverse probability treatment weighting (IPTW) method to adjust for potential bias in the allocation of treatments.[18] The PS was estimated using a logistic regression model which included all of the above-mentioned covariates as predictors for treatment with a RASI in the 60-day postdischarge period and likewise a separate model to predict treatment with β-blockers. A weight was then calculated for each patient as 1/PS for patients in the treated group and 1/1-PS for those in the untreated group. Extreme weight values were truncated at the 5th and 95th percentile ends of the distribution. We confirmed that the IPTW method (through weighting) has adequately balanced the covariate profile of the two groups by comparison of the unweighted and weighted standardized difference in means/proportions for each of the covariates.[18] Finally, we used weighted-Cox regression models that included only the treatment group variable for comparing RASI vs no RASI, and a separate model for β-blocker vs no β-blocker.

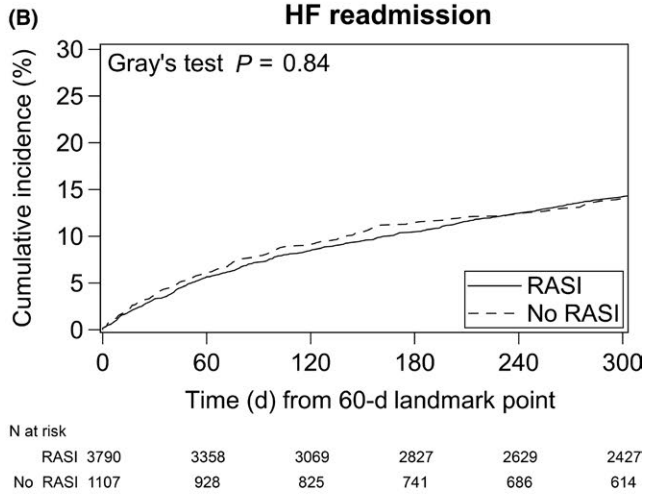
We expressed results as hazard ratios (HR) and 95% confidence intervals (95% CI). The Akaike information criterion was used to assess the model fit, and the proportional hazards assumptions for the Cox regression models were tested and showed no violation for models (global test $P > 0.05$). For the outcome of time to HF rehospitalization, we considered death as a competing risk and fitted proportional hazards models that provided the subdistribution hazard ratio (sHR).[19] Tests of the interaction between treatment (RASI or β-blocker) and sex, age group, and IHD history were conducted. We also performed a prespecified subgroup analysis in patients with prior IHD on the basis that patients with ischemic HF are more likely to have left ventricular systolic dysfunction (LVSD) and therefore HFrEF.[20] Further, RASIs and β-blockers are proven therapies for secondary prevention in IHD, particularly with associated heart failure.[21] All statistical analyses were performed with SAS version 9.4 (SAS Institute, Inc. Cary, NC).

3 | RESULTS

3.1 | Baseline characteristics

Table 1 shows the baseline characteristics of the total cohort, and RASI or β-blocker user subgroups alive at 60 days postdischarge. The cohort comprised 4897 patients, with mean age 76.6 years and 56.7% being male. A prevalent history of HF occurred in 33.1% and IHD in 70.1%. Other common comorbidities included hypertension, AF, diabetes, COPD, CKD, and PVD. The use of a RASI or β-blocker within 60-days postdischarge was recorded in 77.4% and 53.0% of patients, respectively. Among these patients, 84.8% and 83.2% of survivors maintained their medications at 1-year follow-up. Positive associates of RASI and β-blocker use were younger age, a major city or inner regional accessibility (ARIA+) classification, and a history of IHD, hypertension, diabetes, or PCI/CABG, while negative associates were being an Aboriginal and history of COPD, depression or dementia (Table 1). Female gender was a negative associate for β-blocker use only and CKD a positive associate of β-blocker use only.





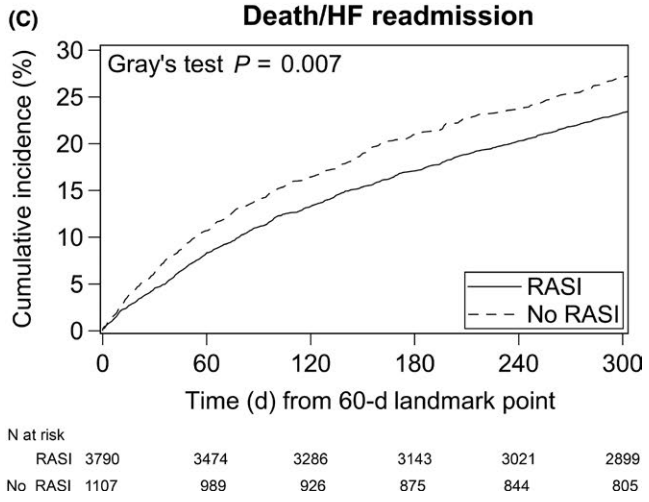
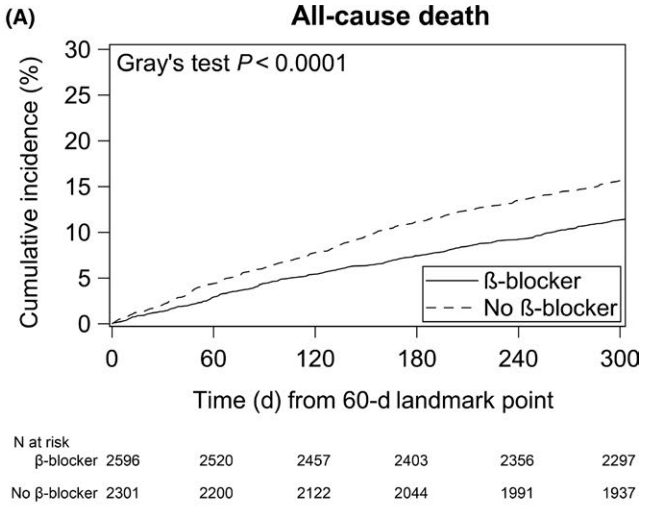
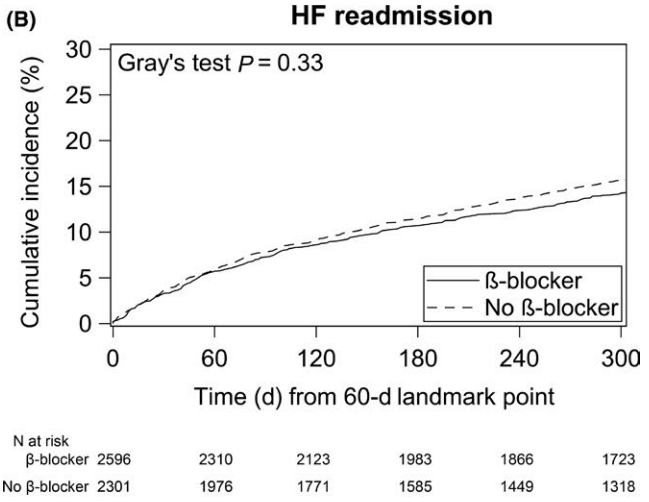


FIGURE 1 Cumulative incidence function curves for (A) all-cause death, (B) HF readmission, and (C) all-cause death or HF readmission in patients with a RASI use within 60 days postdischarge after HF hospitalization (solid line) and those not using a RASI (dashed line). HF, heart failure; RASI, renin-angiotensin system inhibitor; N, number





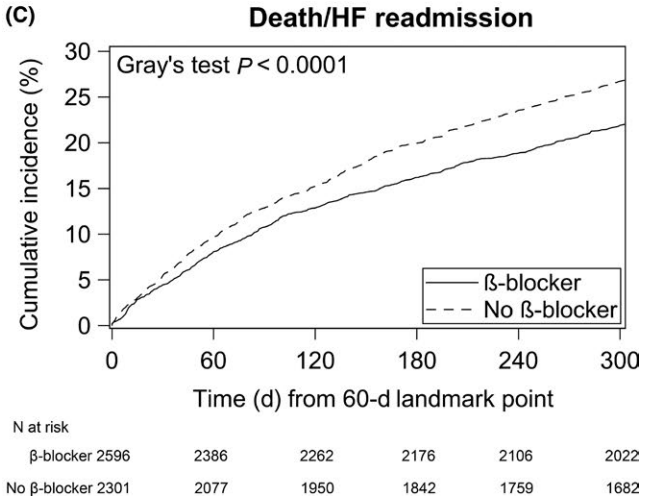


FIGURE 2 Cumulative incidence function curves for (A) all-cause death, (B) HF readmission, and (C) all-cause death or HF readmission in patients with β-blocker use within 60 days postdischarge after HF hospitalization (solid line) and those not using a β-blocker (dashed line). HF, heart failure; N, number

TABLE 2 Unadjusted, covariate-adjusted and IPTW hazard ratios from Cox regression models for 1-year outcomes after hospitalized heart failure according to use of postdischarge medications for RASI vs no RASI group and β-blocker vs no β-blocker group

	Number (%)				Number (%)			
1-year outcomes	RASI (n = 3790)	No RASI (n = 1107)	HR (95% CI)	*P* value	β-Blocker (n = 2596)	No β-Blocker (n = 2301)	HR (95% CI)	*P* value
All-cause mortality	472 (12.5)	191 (17.3)			299 (11.5)	364 (15.8)		
Unadjusted			0.70 (0.59, 0.83)	<0.0001			0.71 (0.61, 0.83)	<0.0001
Covariate-adjusted[a]			0.81 (0.68, 0.97)	0.006			0.76 (0.63, 0.92)	0.02
IPTW			0.70 (0.61, 0.81)	<0.0001			0.79 (0.68, 0.92)	<0.0001
HF rehospitalization[b]	543 (14.3)	155 (14.0)			358 (13.8)	340 (14.8)		
Unadjusted			0.99 (0.83, 1.19)	0.93			0.91 (0.78, 1.05)	0.20
Covariate-adjusted[a]			0.89 (0.74, 1.06)	0.28			0.89 (0.73, 1.08)	0.18
IPTW			0.92 (0.79, 1.06)	0.92			0.92 (0.79, 1.07)	0.26
All-cause mortality or HF rehospitalization	891 (23.5)	302 (27.3)			574 (22.1)	619 (26.9)		
Unadjusted			0.84 (0.73, 0.95)	0.007			0.80 (0.71, 0.89)	0.0001
Covariate-adjusted[a]			0.84 (0.74, 0.96)	0.02			0.83 (0.72, 0.96)	0.01
IPTW			0.81 (0.72, 0.90)	0.0002			0.84 (0.75, 0.94)	0.002

Abbreviations: RASI, renin-angiotensin- system inhibitor; HR, hazard ratio; CI, confidence interval; IPTW, inverse probability treatment weight; HF, heart failure.

[a]Adjusted for age, gender, indigenous status, hospital group, ARIA+ classification, prevalent HF, other medical comorbidities, coronary revascularization procedures, and prior or concurrent use of other cardioactive medications.

[b]The hazard ratio for HF rehospitalization is subdistribution HR treating death as a competing risk event.

3.2 | Postdischarge outcomes by RASI or β-blocker use

In the total cohort at 1-year after HF discharge, observed all-cause mortality was 13.5% (n = 663), HF rehospitalization 14.3% (n = 698), and all-cause death or HF rehospitalization in 24.4% (n = 1193). Figures 1 and 2 show the cumulative incidence function curves with Gray's test for significance and Table 2 the unadjusted and adjusted hazard ratios of 1-year outcomes for RASI vs no RASI and β-blocker vs no β-blocker groups. There was no significant interaction between treatments and sex and age groups. Use of RASI and β-blocker was each independently associated with a better survival and lower unadjusted and adjusted HR for all-cause mortality and the composite of death or HF rehospitalization at 1-year (Table 2). However, neither RASI nor β-blocker use was associated with a lower sHR for HF rehospitalization. In IPTW analysis, RASI users had a significantly lower HR for 1-year all-cause death (0.70, 95% CI, 0.61-0.81) as did β-blocker users (0.79, 95% CI, 0.68-0.92) compared to nonusers. In general, the IPTW analysis did not materially change the estimated HRs from the standard covariate adjustment models but narrowed the width of the 95% CIs (Table 2).

3.3 | Postdischarge outcomes in subgroups according to ischemic heart disease

Postdischarge dispensing of a RASI was higher in patients with ischemic vs nonischemic HF (80.0% vs 71.1%) and also for β-blockers (60.3% vs 35.9%). In the ischemic HF subgroup, use of RASI and β-blocker were each associated with a lower unadjusted and covariate-adjusted HR for all-cause mortality (Table S1). Compared to nonusers, RASI and β-blocker users had a reduced IPTW HR for all-cause death of 0.71, 95% CI, 0.60-0.85 and 0.79, 95% CI, 0.66-0.95, respectively, and also all-cause death/HF rehospitalization (Table S1). The test for interaction between RASI or β-blocker use and IHD history was not significant ($P > 0.5$) for all-cause mortality. However, there was a significant interaction between β-blocker use (but not RASI) and IHD history for HF readmission ($P = 0.02$) and all-cause death/HF rehospitalization ($P = 0.04$). In the ischemic HF subgroup only, β-blocker use was associated with a reduced IPTW sHR for HF rehospitalization (0.83, 95% CI 0.70-0.99) and all-cause death/HF rehospitalization (0.79, 95% CI 0.69-0.91).

4 | DISCUSSION

To our knowledge, this is the first study to show that in a "real-world" cohort of senior patients hospitalized with HF, dispensing of a RASI or β-blocker within 60-days postdischarge was independently associated with a lower 1-year mortality. Our cohort contained predominantly patients with ischemic HF, who are also more likely to have LVSD and HFrEF,[20] and are therefore also more likely to have a survival benefit from these HF therapies. Our findings extend observational studies that showed dispensing of a RASI or β-blocker at discharge from HF hospitalization is associated with an improved medium-term survival.[7-11] However, this study highlights the importance of persistence to proven HF therapies posthospital discharge

and represents an important opportunity to improve longer term outcomes.

Our study was population-based in seniors, aged 65-84 years, who had an index hospitalization for HF in WA and comprised the full spectrum of HF patients with reduced, mid-range, and preserved ejection fraction.[15] Even though we excluded those who died within the first 60 days postdischarge, their subsequent 1-year mortality (13.6%) and risk of death or HF rehospitalization (24.4%) emphasize the poor medium-term prognosis of even stable survivors after hospitalized HF. Due to the senior age of our cohort, there was a generally higher prevalence of comorbidities than reported in other hospitalized HF cohorts.[1-4] In particular, IHD prevalence was high (70.1%), and in these patients, use of both RASI and β-blocker is indicated for treating systolic HF and for secondary cardiac prevention. The overall use of a RASI (77.4%) and particularly β-blocker (53.0%) postdischarge appears suboptimal, and a more recent (2013) prospective audit of consecutive patients admitted with acute HF to participating Australian hospitals showed that the rate of discharge prescription of a RASI or β-blocker has not improved in the current era.[22] The ideal medication uptake cannot be ascertained without knowledge of the actual proportion of cases with HFrEF and those who were intolerant or had contraindications to these drugs. However, previous studies have highlighted that suboptimal HF pharmacotherapy is prevalent and there is often a risk-treatment mismatch where elderly patients at greatest risk of death after hospitalized HF are also less likely to receive a RASI or β-blocker.[23,24] Almost one-third of our cohort had a history of COPD which is the most powerful predictor of underuse of β-blockers in HF,[25] even though cardioselective β-blockers can be safely used in the majority of HF patients with COPD with the same mortality benefits.[26]

4.1 | Survival effect

Some,[7-9] but not all,[27] observational studies have shown that use of a RASI at discharge after HF hospitalization is independently associated with improved 1-year survival. Similarly, use of a β-blocker at discharge has been associated with a more favorable 1-year mortality.[8,9,11] In one study, the survival benefit of β-blockers extended to HF patients with preserved EF (HFpEF)[9] but it was negative in another study.[11] We have extended these studies to show that patients who used a RASI or β-blocker after hospital discharge had a 20%-30% lower adjusted hazards of 1-year all-cause mortality. Use of these drugs was also associated with a similar significant reduction in hazards of subsequent death or HF rehospitalization but the effect was mostly through reduced mortality. It is not surprising that the same relative survival benefit with use of RASI and β-blocker was found in our patients with ischemic HF given that they are also more likely to have systolic HF. However, we found no evidence of heterogeneity in treatment effect between the ischemic and nonischemic HF subgroups for all-cause mortality even though cases with HFpEF are more likely in the latter subgroup. However, the intercontinental GREAT registry study reported a favorable association of RASSi and β-blocker use at discharge with 1-year mortality which extended to patients with HFpEF as well as HFrEF.[9] It is possible that RASIs and β-blockers can have a beneficial effect in patients with HFpEF through other clinical indications such as IHD, hypertension, or diabetes.

4.2 | Effect on HF rehospitalization

Despite significant mortality benefits, we found that RASSi or β-blocker use postdischarge was not associated with a significantly lower hazard of HF rehospitalization, with the exception of β-blockers in patients with ischemic HF. Other studies of RASI or β-blocker use at HF discharge have also reported no association with the risk of HF readmission.[10,28] The lack of effect on HF rehospitalization in unselected HF cohorts could be due to inclusion of a substantial proportion (≈50%) of patients with HFpEF.[11] The precipitating factors for HF hospitalization are also diverse and include noncardiovascular causes (eg respiratory infection, renal failure), and noncompliance/inappropriate decrease in HF therapy may represent only a minority among cardiovascular causes.[29-31] We observed a favorable association of β-blocker use with HF rehospitalization in ischemic HF patients and this is probably because myocardial ischemia is a common precipitant of HF.[29-31] These findings highlight that management strategies to reduce HF rehospitalization will need to include diverse HF precipitants in addition to compliance with evidence-based HF therapies.[12]

4.3 | Limitations

The present study has several limitations. Being an observational study, a causal association between treatment and outcomes cannot be proven. We included only seniors aged 65-84 years although this older age group is more representative of the "real-world" cohort of hospitalized HF patients than those usually included in randomized clinical trials. We are unable to exclude patients with HFpEF without echocardiography data, but their inclusion would if anything have biased our results toward a null treatment effect. We adjusted for demographics and concomitant comorbidity and treatment factors that may confound the association between treatments and outcomes. Adjustment for propensity to receive specific medications should further reduce the risk of bias due to nonrandom allocation of treatments. However, there may be other important unmeasured confounders and even with propensity adjustment, a healthy user bias cannot be ruled out. Changes in treatment regimen (eg initiation, discontinuation) after the landmark point might confound the 1-year mortality outcomes although the majority of survivors dispensed a RASI or β-blocker within 60 days postdischarge remained on these therapies after 1 year. Our PBS dataset contains dispensing data but not the dosages prescribed so we are unable to assess a dose-response relationship. Use of proven HF pharmacotherapies may have improved in the current era but we found no evidence this has occurred in the Australian context.[22] A major strength of the study is the complete follow-up and capture of outcomes using the individual-based linked administrative data.

5 | CONCLUSION

In a cohort of senior patients hospitalized with HF, use of RASI and β-blocker within 60 days postdischarge is associated with a 1-year survival benefit predominantly in patients with ischemic HF. Early postdischarge support programs after HF hospitalization should include measures to optimize adherence to evidence-based medications.

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CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

XQ performed the analyses and cowrote the first draft of the manuscript with JH. The study was conceived by FMS and JH, statistical support was provided by MK and FMS, and all authors contributed to the study design. FMS, JH, and TB secured funding for the project, and FMS obtained the linked administrative datasets. All authors provided input into interpretation of results and critical revision of article and approved the final manuscript.

ETHICS

Ethics approval was obtained from Western Australian Department of Health, Human Research Ethics Committee, October 21, 2014 (ref 2014/11), Western Australian Aboriginal Health Ethics Committee, June 19, 2014 (ref 572), and The University of Western Australia, Human Research Ethics Committee, February 2, 2016 (ref RA/4/1/8065).

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SUPPORTING INFORMATION

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

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