The evolution of guideline-directed medical therapy among decompensated HFrEF patients in sacubitril/valsartan era: Medical expenses and clinical effectiveness

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Abstract

Background: Over recent years, new evolution in guideline-directed medical therapy (GDMT) contributes to clinical benefits in patients with heart failure and reduced ejection fraction (HFrEF). The additional medical expenditure may be a concern due to the current financial constraint. This study aimed to investigate the medical costs and clinical effectiveness of contemporary GDMT in recently hospitalized HFrEF patients.

Methods: Acutely decompensated hospitalized HFrEF patients from two multicenter cohorts of different periods were retrospectively analyzed. A propensity score matching was performed to adjust the baseline characteristics. Annual medication costs, risks of mortality, and recurrent heart failure hospitalizations (HFH) were compared.

Results: Following 1:2 propensity score matching, there were 426 patients from the 2017-2018 cohort using sacubitril/valsartan, while 852 patients from 2013 to 2014 did not use so at discharge. Baseline characteristics were similar, whereas the sacubitril/valsartan users were more likely to receive beta-blockers, ivabradine and mineralocorticoid receptor antagonists at discharge (79.3% vs 60.4%, 23.2% vs 0%, and 64.1% vs 49.8%, $p < 0.001$). The 2017-2018 cohort produced more medication costs by 1277 United States dollar (USD) per person per year, while it resulted in lower rates of HFH and all-cause mortality (10.3 vs 20.3 and 48.8 vs 79.9 per 100 person-year, $p < 0.001$). Costs of preventing a mortality event and a HFH event with contemporary treatments were 15 758 USD (95% confidence interval [CI] 10 436-29 244) and 5317 USD (95% CI 3388-10 098), respectively.

Conclusion: The higher adoption of GDMT was associated with greater medical expenses but better clinical outcomes in recently decompensated HFrEF patients.

Keywords: Cost-effectiveness; Heart failure; Hospitalization; Mortality; Sacubitril/valsartan

1. INTRODUCTION

Heart failure (HF) is a global problem for healthcare systems because of the substantial amounts of resources it consumes. Despite advances in HF treatment, re-hospitalization rates and mortality remain high, and these adverse events give rise to substantial social and economic burdens.[1–3] Deaths and repeated hospitalizations for HF often occur during the early post-discharge period. Therefore, the latest European Society of Cardiology (ESC) HF guideline recommended that oral disease-modifying HF therapy be continued or initiated after hemodynamic stabilization in patients hospitalized for acute

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HF.[4,5] Nevertheless, in real-world practice, the prescription rates of guideline-directed medical therapy remain suboptimal. The ESC Heart Failure Long-Term Registry (ESC-HF-LT-R) showed that prescription rates of renin-angiotensin system inhibitors and beta-blockers ranged between 60.5% to 80.3% and 51.0% to 80.3%, respectively, among acute HF patients from various European regions.[6] In a recently published United States Registry involving more than 10 000 patients, the utilization rates of standard-of-care therapies before and after the onset of worsening HF were low. In contrast, the re-hospitalization rate within 30 days following the worsening HF event was 56%.[7] These results highlight the importance of effective optimization of existing guideline-recommended therapy and novel pharmacologic strategies during hospitalization.

The PIONEER-HF study (Comparison of Sacubitril–Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode) demonstrated that the initiation of sacubitril/valsartan (SAC/VAL) therapy produced a more significant reduction in the N-terminal pro-brain natriuretic peptide (NT-proBNP) concentration than enalapril therapy in HF with reduced ejection fraction (HFrEF) patients hospitalized for acute decompensation.[8] The PIONEER-HF study's 8-week study period was relatively short because the vulnerable phase following HF hospitalization might last up to 6 months post-discharge.[9] Evolution of pharmacotherapy and elevation of HF awareness may improve outcomes in HFrEF patients. Following hospitalizations for HFrEF, contemporary treatment strategies, including the adoption of SAC/VAL and widely use guideline-directed medical therapy, increases medical expenses; however, it remains unclear whether this action improves outcome. Therefore, we utilized two Taiwanese multicenter HF cohorts to determine the effects and the costs of SAC/VAL and additional HF medications prescribed before discharge among HFrEF patients hospitalized for acute decompensations.

2. METHODS

2.1. Study design and patient characteristics

The current study analyzed data from two multicenter HF cohorts in Taiwan: (1) the TSOC-HFrEF registry (Taiwan Society of Cardiology—Heart Failure with reduced Ejection Fraction registry) was initiated by the Taiwan Society of Cardiology. It was a prospective multicenter observational survey of 1509 patients with HFrEF who recently admitted for HF to 21 hospitals between 2013 and 2014;[10,11] (2) the TAROT-HF study (Treatment with Angiotensin Receptor neprilysin inhibitor for Taiwan Heart Failure patients study) was a principal investigator-initiated multicenter retrospective HF study, enrolling symptomatic HFrEF patients from ten hospitals who had started SAC/VAL treatment between 2017 and 2018.[12] The TAROT-HF study consisted of both outpatients with chronic HFrEF and those who admitted to hospital for acute HFrEF; however, only patients who started SAC/VAL during the HF hospitalization were enrolled for the current analysis. The definition of HFrEF included HF symptoms defined in the New York Heart Association (NYHA)—Functional Classes II, III, or IV, and left ventricular ejection fraction (LVEF) <40%. The protocols of the two HF cohorts were similar. We collected 50 variables per patient in both cohorts during index HF hospitalization, including age, sex, body mass index, HF etiologies, systolic blood pressure, heart rate, length of stay, NYHA-Functional class, LVEF, estimated glomerular filtration rate (eGFR), comorbidities, drug therapy, laboratory data, and the use of cardiac devices. The study complied with the Declaration of Helsinki's ethical principles and was approved by the institutional ethics committee of each hospital. Informed consent was obtained from every patient in the TSOC-HFrEF registry; however, no informed consent was obtained in the TAROT-HF study because of its retrospective design. This post hoc analysis study was approved by the Institutional Review Board [Approval number (853)109-02: The evolution in HF management over recent years.]

The inclusion criteria for current analysis included (1) male or female symptomatic HFrEF patients of age >20 years old; and (2) discharge for acute decompensated HF. The exclusion criteria included (1) refusal of medical advice or loss to follow-up; and (2) SAC/VAL treatment was permanently discontinued within 6 months post-discharge (for the TAROT-HF study patients). Propensity score matching was performed for patients from both cohorts. The study flowchart is shown in Fig. 1.

2.2. Study outcomes

We identified three clinical outcomes as follows: death from cardiovascular causes, all-cause mortality, and hospital readmissions due to HF. Since the TSOC-HFrEF cohort had only 1 year of follow-up data, all patients were censored when meeting the outcome events of cardiovascular death and all-cause mortality or balancing the follow-up period. First HF rehospitalization event and total events of HF rehospitalization within 1 year following the index HF hospitalization were collected.

2.3. Medication costs

Prescribed medications and their dosages, including angiotensin-converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), SAC/VAL, beta-blocker, mineralocorticoid receptor antagonist (MRA), ivabradine, digoxin, diuretic, nitrate, and oral anticoagulant, were noted at discharge, at 6 months, and at 12 months postdischarge. Target doses of guideline-directed medical therapy were adopted from the 2016 ESC HF guideline.[5] Medication costs were calculated based on the 2018 Taiwan National Health Insurance price. If the medications and dosages changed at any time points, alteration of price was estimated from the midpoint between time points. Total 1-year medication costs following index hospitalization were calculated. Medication costs were calculated using the New Taiwan dollar and were expressed as United States dollar (USD) with a currency rate of 30 New Taiwan dollars to 1 USD.

2.4. Statistical analysis

The continuous variables were expressed as mean value ± SD; categorical variables were reported as percentages. We performed propensity score matching to adjust for confounding effect on interesting outcomes. The propensity was estimated using a logistic regression model with covariates as follows: age, gender, body mass index, systolic blood pressure at discharge, heart rate at discharge, NYHA-Functional Class at discharge, length of stay, LVEF, eGFR, HF etiology, and nine co-morbidities, including hypertension, diabetes mellitus, dyslipidemia, peripheral arterial disease, atrial fibrillation, chronic obstructive pulmonary disease or asthma, sleep apnea, history of stroke, and prior history of myocardial infarction. Each patient in the SAC/VAL-treated group was matched to two patients in the non-SAC/VAL group (1:2 matching) because more patients did not receive SAC/VAL. In the matching process, we used the greedy, nearest-neighbor method without replacement and with a caliper of 0.01 of the propensity score.

Differences in baseline characteristics and clinical parameters were tested using the chi-square test for categorical variables. The student's *t*-test or the Wilcoxon rank-sum test was used for the comparisons of continuous data. The risks of cardiovascular death and all-cause mortality were analyzed using survival analysis with the Kaplan-Meier method and log-rank test. Univariate and multivariate Cox regression models were

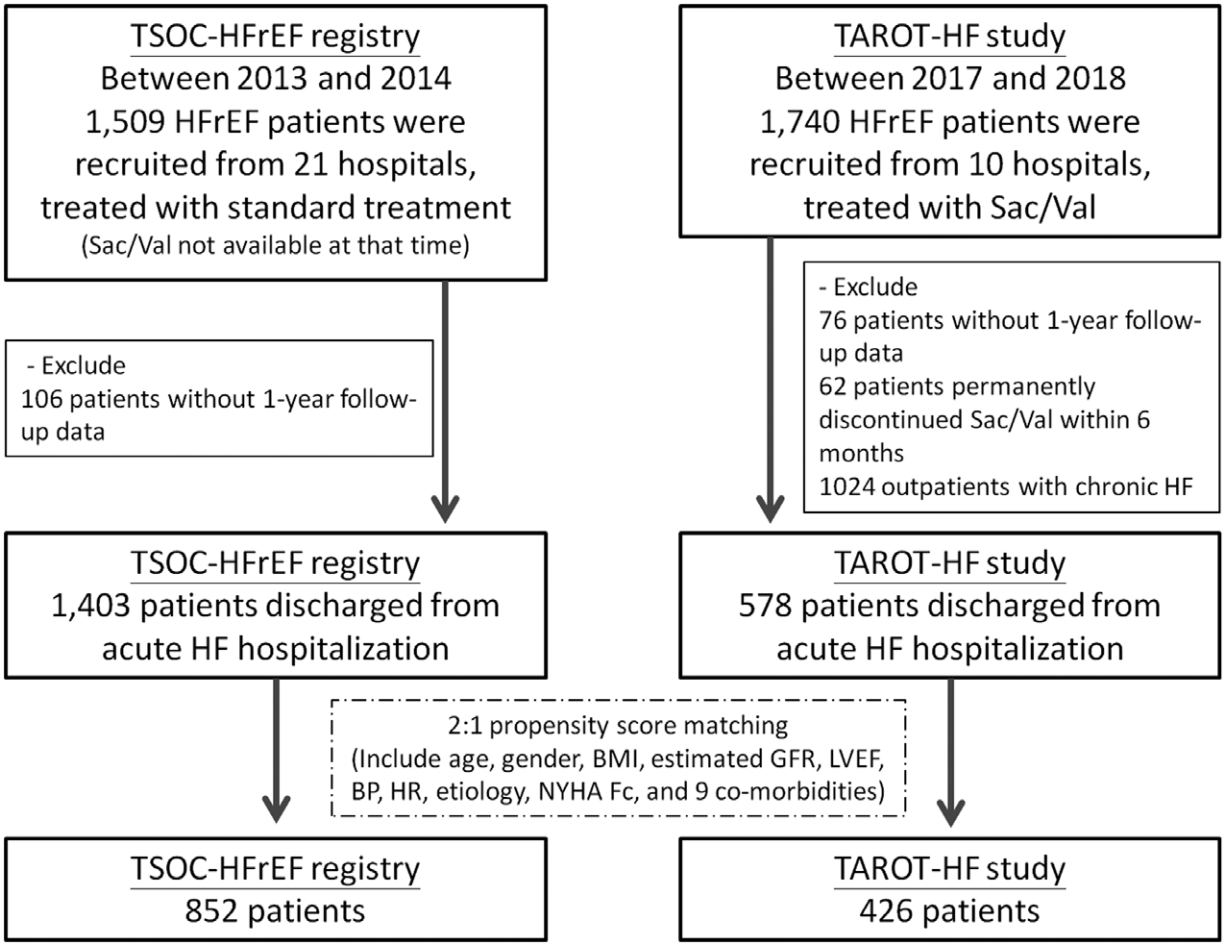

Fig. 1 The flowchart of the current study.

used to compare hazard ratios (HRs) of all-cause mortality with 95% confidence intervals (CIs) between the groups. The HR was adjusted for the following variables: age, gender, HF etiology, body mass index, systolic blood pressure, eGFR, NYHA-functional class at discharge, history of HF hospitalization, LVEF, atrial fibrillation, hypertension, diabetes, chronic obstructive pulmonary disease, peripheral arterial disease, hyperuricemia, prior stroke, prescriptions of HF medications at discharge, including beta-blocker, MRA, ivabradine, digoxin, nitrate, diuretic, and anticoagulant. CIs were estimated for the SAC/VAL treatment for cost-effectiveness ratios: nontreatment ratios by nonparametric bootstrapping. A p-value of <0.05 was considered statistically significant. The statistical analyses were performed using IBM SPSS Statistics 24.0 software (IBM SPSS; IBM Corp, Armonk, NY).

3. RESULTS

3.1. Baseline characteristics

After applying the inclusion and exclusion criteria, 1981 HFrEF patients discharged from acute decompensated HF were included. Among these patients, 578 receiving SAC/VAL at discharge were from the TAROT-HF study, and 1403 patients who did not receive SAC/VAL at discharge were from the TSOC-HFrEF registry. Before propensity score matching, patients from the TAROT-HF study had more severe HF symptoms, had higher discharge heart rates, lower discharge eGFR, and tended to have a history of atrial fibrillation and dyslipidemia. After 1:2 propensity score matching, a total of 1278 patients were included in the final analysis. The mean age of the study cohorts was 64.3 years, and the mean LVEF was 28.6%. Overall, the two matched cohorts were well balanced. Table 1 displays detailed baseline characteristics of both cohorts before and after propensity score matching.

3.2. Prescribed medications and medication costs

Table 2 summarizes the medications prescribed at discharge. All patients from the TAROT-HF cohort were treated with SAC/VAL, whereas 60.8% of the patients from the TSOC-HFrEF cohort were treated with ACEi or ARB at discharge. Patients from the TAROT-HF cohort were more likely to receive beta-blockers (79.3% vs 60.4%, $p < 0.001$) and MRA (64.1% vs 49.8%, $p < 0.001$) but less likely to receive diuretics other than MRA (65.3% vs 71.9%, $p = 0.014$) and nitrate (21.8% vs 39.9%, $p < 0.001$) at discharge. The prescription rates of digoxin and oral anticoagulants were similar between the two cohorts. A total of 23.2% of patients from the TAROT-HF cohort received ivabradine at discharge.

Prescription rates and patterns of guideline-directed medical therapies among two cohorts during a 1-year follow-up were shown in Fig. 2. Among the TAROT-HF cohort patients, up-titration of SAC/VAL was noted ($p < 0.001$). In contrast, the prescription doses of beta-blocker, MRA, and ivabradine were numerically greater but not statistically significant during

Table 1

Baseline characteristics between different study cohorts

	Before propensity score matching			After propensity score matching		
	TAROT-HF 2017-2018 (N = 578)	TSOC-HFrEF 2013-2014 (N = 1403)	*P*	TAROT-HF 2017-2018 (N = 426)	TSOC-HFrEF 2013-2014 (N = 852)	*p*
Age (y)	63.5 ± 15.0	63.9 ± 15.7	0.617	64.0 ± 15.2	64.5 ± 15.6	0.574
Male gender, n (%)	430 (74.4)	1014 (72.3)	0.334	313 (73.5)	630 (73.9)	0.857
Ischemic etiology, n (%)	262 (45.3)	633 (45.1)	0.932	189 (44.4)	398 (46.7)	0.427
BMI (kg/m^2)	25.5 ± 4.9	25.2 ± 4.9	0.385	25.3 ± 4.6	25.2 ± 5.0	0.665
LVEF (%)	28.1 ± 7.3	28.5 ± 8.1	0.300	28.1 ± 7.9	28.8 ± 7.5	0.143
Length of stay	11.8 ± 10.6	12.5 ± 14.5	0.199	11.7 ± 10.3	12.2 ± 12.6	0.475
NYHA Functional class at discharge						
II	237 (41.0)	977 (69.6)	<0.001	203 (47.7)	439 (51.5)	0.192
III/IV	341 (59.0)	426 (30.4)		223 (52.3)	413 (48.5)	
SBP at discharge (mmHg)	118.2 ± 21.4	119.6 ± 18.4	0.158	120.6 ± 21.1	118.6 ± 18.9	0.088
Heart rate at discharge (bpm)	82.9 ± 16.0	80.5 ± 14.7	0.004	82.3 ± 15.6	80.6 ± 14.2	0.058
eGFR at discharge (mL/min/1.73m^2)	57.2 ± 36.8	62.3 ± 35.4	0.005	58.5 ± 40.3	59.2 ± 33.5	0.772
Comorbidities						
Diabetes mellitus	252 (43.6)	617 (44.0)	0.877	187 (43.9)	371 (43.5)	0.905
Hypertension	323 (55.9)	718 (51.2)	0.057	245 (57.5)	455 (53.4)	0.164
Prior myocardial infarction	161 (27.9)	353 (25.2)	0.214	113 (26.5)	228 (26.8)	0.929
PAD	39 (6.7)	94 (6.7)	0.969	24 (5.6)	56 (6.6)	0.514
Previous stroke/TIA	69 (11.9)	130 (9.3)	0.072	48 (11.3)	92 (10.8)	0.800
Atrial fibrillation	215 (37.2)	369 (26.3)	<0.001	157 (36.9)	278 (32.6)	0.133
Dyslipidemia	233 (40.3)	479 (34.1)	0.009	170 (39.9)	334 (39.2)	0.808
COPD/asthma	72 (12.5)	151 (10.8)	0.278	51 (12.0)	103 (12.1)	0.952
Sleep apnea	15 (2.6)	38 (2.7)	0.887	10 (2.3)	25 (2.9)	0.545

BMI = body mass index; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PAD = peripheral arterial disease; SBP = systolic blood pressure; TAROT-HF = Treatment with Angiotensin Receptor neprilysin inhibitor for Taiwan Heart Failure patients; TIA = transient ischemic attack; TSOC-HFrEF = The Taiwan Society of Cardiology—Heart Failure with reduced Ejection Fraction.

Table 2

Types of medications for heart failure treatment at discharge and medication costs (USD) per person within 1-year after discharge

	TAROT-HF 2017-2018 (N = 426)	TSOC-HFrEF 2013-2014 (N = 852)	Mean difference (SE)	*p*
At discharge, n (%)				
ACEi/ARB	0 (0.0)	518 (60.8)		<0.001
ARNI	426 (100)	0 (0.0)		<0.001
Beta-blocker	338 (79.3)	515 (60.4)		<0.001
MRA	273 (64.1)	424 (49.8)		<0.001
Ivabradine	99 (23.2)	0 (0.0)		<0.001
Digoxin	96 (22.5)	209 (24.5)		0.430
Diuretics	278 (65.3)	613 (71.9)		0.014
Nitrate	93 (21.8)	340 (39.9)		<0.001
Oral anticoagulant	110 (25.8)	193 (22.7)		0.213
Medication cost per patient, USD (SE)				
Total	1,443 (35)	166 (7)	1,277 (36)	<0.001
ACEi/ARB	2 (0)	31 (1)	–29 (1)	0.005
ARNI	1,097 (29)	0 (0)	1097 (29)	<0.001
Beta-blocker	31 (1)	16 (0)	15 (1)	<0.001
MRA	30 (3)	13 (1)	17 (3)	<0.001
Ivabradine	116 (10)	0 (0)	116 (10)	<0.001
Digoxin	3 (0)	4 (0)	–1 (0)	<0.001
Diuretics	11 (11)	16 (1)	–5 (1)	0.004
Nitrate	19 (3)	36 (2)	–16 (4)	<0.001
Oral anticoagulant	134 (14)	52 (6)	83 (15)	<0.001

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; MRA = mineralocorticoid receptor antagonist; TAROT-HF = Treatment with Angiotensin Receptor neprilysin inhibitor for Taiwan Heart Failure patients; TSOC-HFrEF = The Taiwan Society of Cardiology—heart failure with reduced ejection fraction.

follow-up. Among the TSOC-HFrEF cohort patients, up-titration of beta-blocker and down-titration of MRA were noted during follow-up.

Overall, the mean difference of medication cost per person within 1 year between the two cohorts was 1277 (SE 36) USD. The costs for SAC/VAL, beta-blocker, MRA, ivabradine, and oral anticoagulants were significantly higher in the matched TAROT-HF cohort patients than those of the TSOC-HFrEF cohort. On the other hand, the costs of ACEi/ARB, digoxin, diuretic, and nitrate were significantly higher in the matched TSOC-HFrEF cohort patients than those of the TAROT-HF cohort. Table 2 and Fig. 3 display the comparisons of medication costs between the study cohorts.

3.3. Clinical outcomes

At follow-up, the incidences of all-cause mortality were 10.3 per 100-person years and 20.3 per 100-person years for the matched TAROT-HF and the TSOC-HFrEF registry cohorts, respectively (Fig. 4A, $p < 0.001$). After multivariate analysis (Table 3), prescriptions of SAC/VAL and beta-blocker at discharge were both independently associated with lower risks of 1-year all-cause mortality (HR 0.54, 95% CI 0.38-0.76, $p = 0.001$ for SAC/VAL; HR 0.59, 95% CI 0.46-0.75, $p < 0.001$ for beta-blocker). The incidences of cardiovascular death were 7.6 per 100-person year and 13.0 per 100-person year for the matched TAROT-HF and the TSOC-HFrEF registry cohorts, respectively ($p = 0.011$, Fig. 4B).

During 1 year following index HF hospitalization, 801 readmissions for HF occurred in 450 patients. A total of 26.8% and 39.4% of patients in the matched TAROT-HF and the TSOC-HFrEF registry cohorts experienced at least one time of HF rehospitalization within 1 year following index hospitalization, respectively ($p < 0.001$). The total HF rehospitalization

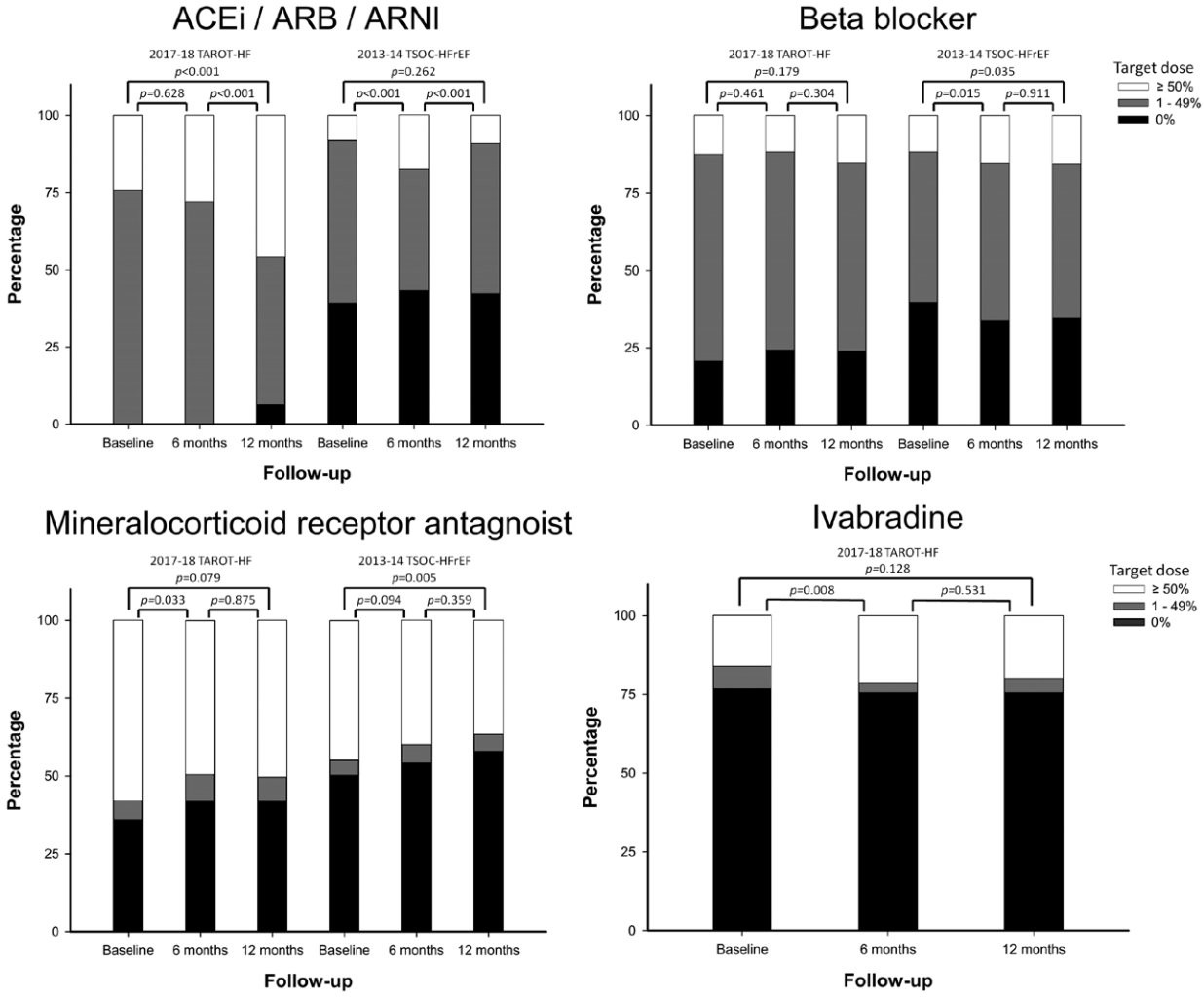

Fig. 2 Prescription types and doses of guideline-recommended medications within 1 year following the index hospitalization for heart failure.

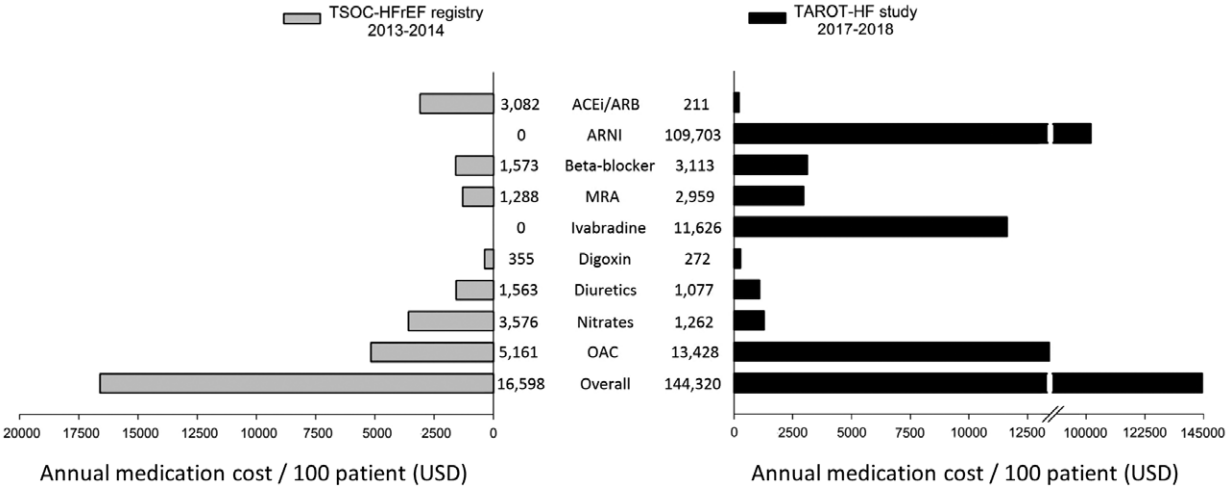

Fig. 3 The comparisons of medication cost within 1 year following the index hospitalization for heart failure between two cohorts.

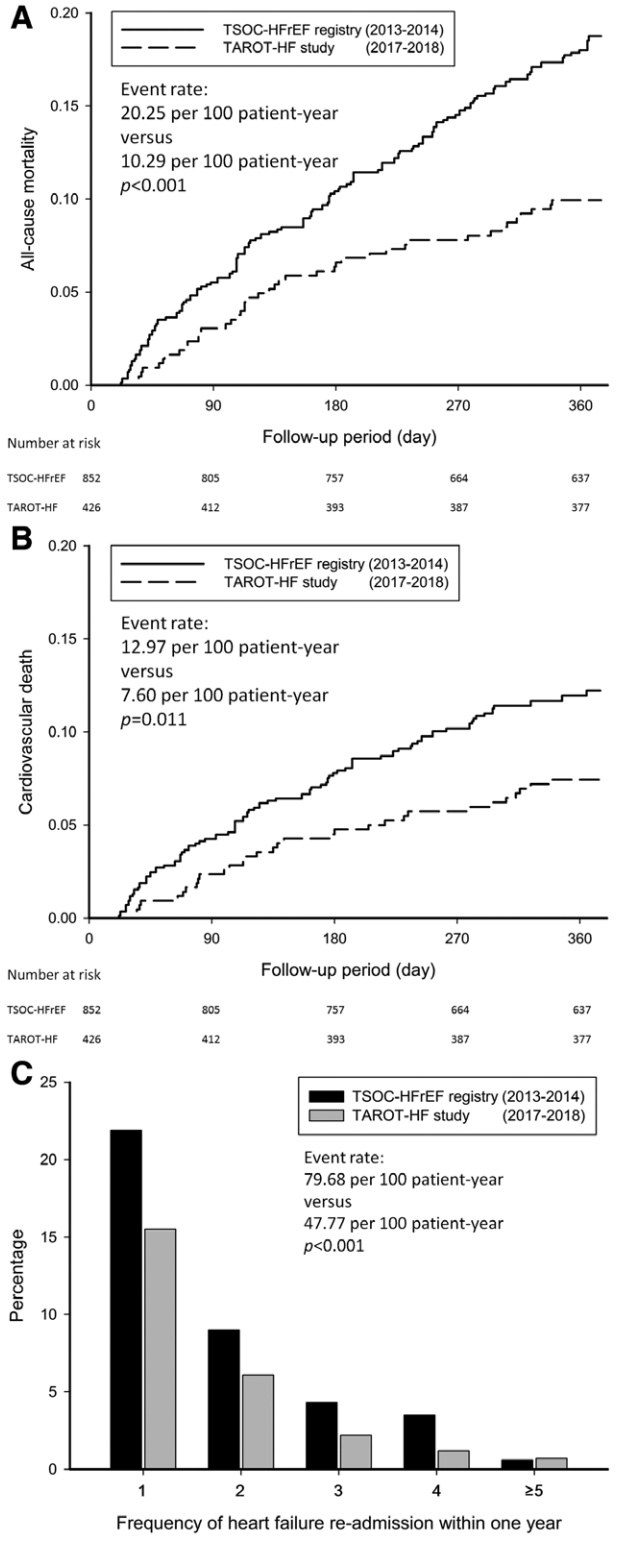

Fig. 4 A, Kaplan-Meier survival curves for all-cause mortality; (B) Kaplan-Meier survival curves for cardiovascular mortality; and (C) Frequencies of heart failure readmission within 1 year following the index hospitalization for heart failure among two cohorts.

incidences were 48.8 per 100-person years and 79.7 per 100-person years for the matched TAROT-HF and the TSOC-HFrEF registry cohorts, respectively (risk ratio 0.76, 95% CI 0.60-0.88, $p < 0.001$, Fig. 4C). Table 4 summarizes the overall clinical events within 1 year after discharge. Comparing to the matched TSOC-HFrEF cohort, 8.1 (SE 2.0) mortality events and 24.0 (SE 5.1) HF rehospitalization events were avoided per 100 patients in the matched TAROT-HF cohort. The cost of avoiding a mortality event was estimated to be 15 758 USD (95% CI 10 436-29 244). The cost of avoiding one HF rehospitalization event was estimated to be 5317 USD (95% CI 3388-10 098).

4. DISCUSSION

Adverse events frequently occurred after acute decompensated HF. In this study, 35.2% of patients suffered from HF readmission, and 15.3% of patients died from any cause within 1 year after index HF hospitalization. Many factors may be attributed to such poor outcomes, including cardiac factors, noncardiac comorbidities, patient-related factors, and system-based factors.[13] Optimizations of guideline-recommended therapy before discharge were shown to prevent adverse events during the vulnerable phase.[7,9]

The PIONEER-HF trial showed that SAC/VAL reduced NT-proBNP levels to a greater degree than enalapril among HFrEF patients admitted with acute decompensated HF.[8] The PIONEER-HF trial demonstrated that 8.0% of patients in the SAC/VAL arm and 13.8% in the enalapril arm were readmitted for HF at 8 weeks (HR 0.56, 95% CI 0.37-0.84). In the present real-world study, we also showed that patients treated with SAC/VAL at discharge would have a significantly lower risk for HF readmission at 1 year than those without SAC/VAL treatment. Although the duration of the PIONEER-HF trial was too short to demonstrate a difference in mortality, the survival curves in the current study showed the benefits of SAC/VAL could be observed soon within 2 to 3 months after discharge, suggesting that appropriate treatment should be delivered in a timely fashion to these high-risk patients.

Following the treatment course of acute HF hospitalization, persistent but subclinical congestion was not uncommon at discharge.[9] Failure to relieve congestion progressively increases left ventricular filling pressure and results in myocardial damage, reflected by abnormalities in biomarkers such as cardiac troponin and natriuretic peptide. In addition to the goal of reaching euvolemia, it is also essential to initiate or up-titrate disease-modifying pharmacological therapies during hospitalization for HF.[5] Unfortunately, numerous randomized controlled trials and HF registries had demonstrated the suboptimal prescription and dosing of guideline-directed medical therapy upon discharge.[14–17] Even in the recently published PIONEER-HF study, baseline prescription rates of ACEi/ARB, beta-blocker, and MRA were only 47.9%, 59.6%, and 10.0%, respectively.[8] In this real-world observational study, in addition to the differences in SAC/VAL utilization, prescription rates of beta-blocker and MRA were also significantly higher in the 2017/18 TAROT-HF cohort than those in the 2013/14 TSOC-HFrEF cohort. This finding suggests that awareness of HF care gradually increased over time. Ivabradine was not available at the TSOC-HFrEF registry, whereas, among the TAROT-HF cohort patients, 23.2% were treated with ivabradine. The prescription rate of ivabradine in the TAROT-HF cohort was higher than those in the acute HF subgroup of the ESC-HF-LT registry (3.2%), the CHAMP registry (1%),[18] and the DAPA-HF study (5%).[19] Because the benefits of disease-modifying pharmacological therapies are believed to be incremental,[20] comprehensive therapy with SAC/VAL, beta-blocker, MRA, and ivabradine in the TAROT-HF cohort may result in better outcomes compared with conventional therapy in the TSOC-HFrEF registry.

In a model-based analysis, Gaziano et al[21] suggested that SAC/VAL initiation during hospitalization in patients with recently

Table 3

Multivariate analysis for factors associated with 1-year all-cause mortality following index heart failure hospitalization

	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% confidence interval	*p*	Hazard ratio	95% confidence interval	*p*
Sacubitril/valsartan	0.51	0.36-0.72	<0.001	0.54	0.38-0.76	0.001
Beta-blocker	0.46	0.36-0.59	<0.001	0.59	0.46-0.75	<0.001
MRA	0.80	0.69-0.93	0.003	NS	NS	NS
Ivabradine	1.11	0.76-1.63	0.593			
Digoxin	1.17	0.85-1.61	0.323			
Nitrate	1.36	1.02-1.81	0.035	NS	NS	NS
Diuretics	1.20	0.88-1.65	0.248			
Anticoagulant	1.06	0.77-1.47	0.705			

Multivariate analysis was adjusted for age, gender, heart failure etiology, body mass index, systolic blood pressure, estimated glomerular filtration rate, New York Heart Association functional class at discharge, history of heart failure hospitalization, left ventricular ejection fraction, atrial fibrillation, hypertension, diabetes, chronic obstructive pulmonary disease, peripheral arterial disease, hyperuricemia, prior stroke, and prescriptions of heart failure medications at discharge.
MRA = mineralocorticoid receptor antagonist.

Table 4

Clinical events within 1 year after discharge

	TAROT-HF, 2017-2018 (N = 426)	TSOC-HFrEF, 2013-2014 (N = 852)	Ratio (95% CI)	Events avoid per 100 patient (SE)	*p*
Events, n (per 100 patient-year)					
All-cause mortality	42 (10.3)	153 (20.3)	0.51 (0.36-0.72)	8.1 (2.0)	<0.001
Cardiovascular death	31 (7.6)	98 (13.0)	0.60 (0.40-0.69)	4.2 (1.7)	0.011
HF readmission, first	114 (27.9)	336 (44.5)	0.56 (0.44-0.72)	12.7 (2.7)	<0.001
HF readmission, total	199 (48.8)	602 (79.7)	0.76 (0.60-0.88)	24.0 (6.1)	<0.001

CI = confidence interval; HF = heart failure; TAROT-HF = Treatment with Angiotensin Receptor neprilysin inhibitor for Taiwan Heart Failure patients; TSOC-HFrEF = The Taiwan Society of Cardiology—heart failure with reduced ejection fraction.

decompensated HFrEF would be cost-effective compared with the long-term use of enalapril, with a cost per quality-adjusted life-years of 21 532 USD. However, as mentioned above, the integrative effects of new therapies in real-world practice with four types of disease-modifying medications could not be represented by this model. Medical circumstances in Taiwan are much different from those in other countries. Taiwan National Health Insurance is a single-payer, and universal-coverage national healthcare system,[22] and this system deals with the financing of healthcare and reimbursement of all medical claims.[23] With these advantages, drug prices and affordability are usually lower than in other countries. For example, 100 mg SAC/VAL costs 9.5 USD in the United States but only 2.5 USD in Taiwan. Assuming a similar scenario to that of the current study in the United States, the mean difference per person within 1 year between the two groups might increase to 4000 USD. The cost of avoiding death might increase to 57 000 USD. Although we did not conduct a cost-effectiveness analysis due to lack of quality-adjusted life-years data, we demonstrated that a new treatment strategy, including the prescription of SAC/VAL along with higher utilization of beta-blocker and MRA before discharge, saved one life with an additional cost of less than the gross domestic product per capita in Taiwan.

This study had several limitations. First, the sample size was relatively small. An ongoing HF registry in Taiwan expecting to enroll >3500 recently decompensated HF patients may soon rectify this limitation. Second, although propensity matching was performed, some confounders may still exist and may influence the clinical outcomes. Third, we only enrolled patients receiving SAC/VAL treatment during hospitalization for HF and did not assess the effect of SAC/VAL initiation postdischarge. Quality-adjusted life-years are used in cost-effectiveness analysis; however, assessment tools such as the Euro-QoL 5D score were not available during the current study.

In conclusion, in these real-world Taiwanese populations with acute decompensated HFrEF from different periods, adopting a new treatment strategy was associated with more significant medical expenses but a lower risk of all-cause mortality, cardiovascular death, and HF rehospitalizations within 1 year. Costs of preventing a mortality event and a repeated HF hospitalization event with contemporary treatments were 15 758 USD (95% CI 10 436-29 244) and 5317 USD (95% CI 3388-10 098), respectively.

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REFERENCES

1. Sakata Y, Shimokawa H. Epidemiology of heart failure in Asia. *Circ J* 2013;77:2209–17.

2. Cleland JG, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, et al; Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The EuroHeart Failure survey programme– a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. *Eur Heart J* 2003;**24**:442–63.
3. Shimokawa H, Miura M, Nochioka K, Sakata Y. Heart failure as a general pandemic in Asia. *Eur J Heart Fail* 2015;**17**:884–92.
4. Gheorghiade M, Vaduganathan M, Fonarow GC, Bonow RO. Rehospitalization for heart failure: problems and perspectives. *J Am Coll Cardiol* 2013;**61**:391–403.
5. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al; Authors/Task Force Members; Document Reviewers. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;**18**:891–975.
6. Crespo-Leiro MG, Anker SD, Maggioni AP, Coats AJ, Filippatos G, Ruschitzka F, et al; Heart Failure Association (HFA) of the European Society of Cardiology (ESC). European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. *Eur J Heart Fail* 2016;**18**:613–25.
7. Butler J, Yang M, Manzi MA, Hess GP, Patel MJ, Rhodes T, et al. Clinical course of patients with worsening heart failure with reduced ejection fraction. *J Am Coll Cardiol* 2019;**73**:935–44.
8. Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, et al; PIONEER-HF Investigators. Angiotensin-neprilysin inhibition in acute decompensated heart failure. *N Engl J Med* 2019;**380**:539–48.
9. Greene SJ, Fonarow GC, Vaduganathan M, Khan SS, Butler J, Gheorghiade M. The vulnerable phase after hospitalization for heart failure. *Nat Rev Cardiol* 2015;**12**:220–9.
10. Wang CC, Chang HY, Yin WH, Wu YW, Chu PH, Wu CC, et al. TSOC-HFrEF registry: a registry of hospitalized patients with decompensated systolic heart failure: description of population and management. *Acta Cardiol Sin* 2016;**32**:400–11.
11. Chang HY, Wang CC, Wu YW, Chu PH, Wu CC, Hsu CH, et al. One-Year outcomes of acute decompensated systolic heart failure in Taiwan: lessons from TSOC-HFrEF Registry. *Acta Cardiol Sin* 2017;**33**:127–38.
12. Lee YH, Chiou WR, Hsu CY, Lin PL, Liang HW, Chung FP, et al. Different left ventricular remodeling patterns and clinical outcomes between non-ischemic and ischemic etiologies in heart failure patients receiving sacubitril/valsartan treatment [published online ahead of print October 29, 2020]. *Eur Heart J Cardiovasc Pharmacother*. Doi: 10.1093/ehjcvp/pvaa125.
13. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, et al; OPTIMIZE-HF Investigators and Hospitals. Factors identified as precipitating hospital admissions for heart failure and clinical outcomes: findings from OPTIMIZE-HF. *Arch Intern Med* 2008;**168**:847–54.
14. DeVore AD, Mi X, Mentz RJ, Fonarow GC, Van Dyke MK, Maya JF, et al. Discharge heart rate and β-blocker dose in patients hospitalized with heart failure: findings from the OPTIMIZE-HF registry. *Am Heart J* 2016;**173**:172–8.
15. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, et al; SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010;**376**:875–85.
16. Albert NM, Yancy CW, Liang L, Zhao X, Hernandez AF, Peterson ED, et al. Use of aldosterone antagonists in heart failure. *JAMA* 2009;**302**:1658–65.
17. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, et al; OPTIMIZE-HF Investigators and Hospitals. Association between performance measures and clinical outcomes for patients hospitalized with heart failure. *JAMA* 2007;**297**:61–70.
18. Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI, et al. Medical therapy for heart failure with reduced ejection fraction: the CHAMP-HF Registry. *J Am Coll Cardiol* 2018;**72**:351–66.
19. McMurray JJV, DeMets DL, Inzucchi SE, Køber L, Kosiborod MN, Langkilde AM, et al; DAPA-HF Committees and Investigators. The Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure (DAPA-HF) trial: baseline characteristics. *Eur J Heart Fail* 2019;**21**:1402–11.
20. Vaduganathan M, Claggett BL, Jhund PS, Cunningham JW, Pedro Ferreira J, Zannad F, et al. Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. *Lancet* 2020;**396**:121–8.
21. Gaziano TA, Fonarow GC, Velazquez EJ, Morrow DA, Braunwald E, Solomon SD. Cost-effectiveness of sacubitril-valsartan in hospitalized patients who have heart failure with reduced ejection fraction. *JAMA Cardiol* 2020;**5**:1236–44.
22. Wu TY, Majeed A, Kuo KN. An overview of the healthcare system in Taiwan. *London J Prim Care (Abingdon)* 2010;**3**:115–9.
23. Hsing AW, Ioannidis JP. Nationwide population science: lessons from the Taiwan National Health Insurance Research Database. *JAMA Intern Med* 2015;**175**:1527–9.