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Original Article

Gap between guidelines and clinical practice in heart failure with reduced ejection fraction: Results from TSOC-HFrEF registry

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Abstract

Background: Heart failure (HF) is a global health problem. Guidelines for the management of HF have been established in Western countries and in Taiwan. However, data from the Taiwan Society of Cardiology-Heart Failure with reduced Ejection Fraction (TSOC-HFrEF) registry showed suboptimal prescription of guideline-recommended medications. We aimed to analyze the reason of non-prescription and clinical outcomes as a result of under-prescription of medications.

Methods: A total of 1509 patients hospitalized for acute HFrEF were recruited in 21 hospitals in Taiwan by the end of October 2014. Prescribed guideline-recommended medications and other relevant clinical parameters were collected and analyzed at discharge and 1 year after index hospitalization.

Results: At discharge, 62% of patients were prescribed with either angiotensin-converting enzyme-inhibitors (ACEI) or angiotensin receptor blockers (ARB); 60% were prescribed with beta-blockers and 49% were prescribed with mineralocorticoid receptor antagonists (MRA). The proportions of patients at ≥50% of the target dose for ACEI/ARB, beta-blockers and MRA were 24.4%, 20.6%, 86.2%, respectively. At 1-year follow-up, dosages of ACEI/ARB and MRA were up-titrated in about one-fourth patients, and dosages of beta-blocker were up-titrated in about 40% patients. One-year mortality rate was lowest in patients who received at least 2 classes of guideline-recommended medications with ≥50% of the target dose, and highest in those who received 0 or 1 class of medications.

Conclusion: The TSOC-HFrEF registry demonstrated the under-prescription of guideline-recommended medications and reluctance of physicians to up-titrate medications to target dose. Action plan needs be formulated in order to improve physician's adherence to HF guidelines.

Keywords: Adherence; Beta-blocker; Guidelines; Heart failure; Renin-angiotensin blockade; Taiwan

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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1. Introduction

Heart failure (HF) is a leading cause of morbidity and mortality worldwide and it is a major burden for the global health-care system. At least 1−2% of the adult populations in developed countries are affected by heart failure. Moreover, as a result of the rapidly aging population and improving survival of patients suffered from acute myocardial infarction and various heart diseases, the HF population is increasing rapidly worldwide.[1−3]

Over-activation of neurohumoral systems is a central mechanism to the pathophysiology of HF. The use of the neurohumoral antagonists, such as angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs) and cardio-selective beta-blockers have been associated with significant improvement of clinical outcomes in large randomized controlled studies.[4−10]

Twenty years ago, guidelines for diagnosis and management of HF were first published by the European Society of Cardiology and the American Heart Association. These guidelines have been further revised in subsequent updates.[11,12] In 2012, the Heart Failure Committee of the Taiwan Society of Cardiology published its own Guideline for the Diagnosis and Treatment of Heart Failure.[13] However, implementation of guideline-recommended management into clinical practice takes time. Observational survey showed that the utilization of guideline directed therapies remained suboptimal.[14,15] Underutilization of guideline-recommended medications and suboptimal 1-year outcome have been reported in the Taiwan Society of Cardiology-Heart Failure with reduced Ejection Fraction (TSOC-HFrEF) registry.[16,17] The purposes of the study were firstly to evaluate physicians' prescription pattern according to current HF guidelines; and secondly to evaluate patient characteristics in those who did not receive the guideline recommended therapy. We aim to generate meaningful data that help with policy planning in future HFrEF patient management.

2. Methods

2.1. Study designs, patients, and data management

The TSOC-HFrEF registry was a prospective, multicenter, observational survey of patients presenting to 21 hospitals in Taiwan for acute decompensated systolic HF from May 2013 to October 2014. Institutional Review Board of each hospital agreed to participate in the registry. The enrollment of patients, the characteristics of patient population, and the management during index hospitalization had been completely described in previous manuscript.[16] Data were collected during index hospitalization beginning with the initial point of care and ending with discharge or death. Laboratory data at baseline (either at emergency room or at admission) were collected for analysis, except for serum creatinine level, which was collected prior to discharge. Outpatient visits were arranged after discharge. Prescribed guideline-recommended medications and other relevant clinical parameters were collected and analyzed at discharge and 1 year after index hospitalization. Data were collected centrally using an electronic, standardized case report form and sent electronically to the data collection center.

2.2. Assessment of guideline-recommended therapies

The rate of prescription and the prescribed dosage of ACEIs, ARBs, beta-blockers and MRAs were collected separately. For those patients who received ACEIs treatment, doses of captopril, enalapril and ramipril were analyzed whether ≥50% target doses were achieved, since these medications were the most frequently-prescribed ACEIs in the TSOC-HFrEF registry and evidence-based doses of these medications are available from guidelines.[11,13] Doses of candesartan, valsartan and losartan were analyzed in patients who received ARBs and doses of spironolactone and eplerenone were analyzed in patients who received MRAs. For the patients treated with beta-blockers, dosages of bisoprolol, carvedilol and metoprolol succinate were analyzed. Novel guideline-recommended therapies (I*f*-channel blocker and angiotensin receptor neprilysin inhibitor) had not been widely available in Taiwan during the study period and their data were not collected in the current study.

2.3. Statistical analysis

The quantitative data were expressed as the mean value ± standard deviation or as median and inter-quartile range (IQR); categorical variables were reported as percentages. Descriptive summaries were presented for all patients, and for subgroups of patients. Student's *t*-test or the Mann−Whitney U-test was used for the comparisons between the continuous data, and Chi-square test was used for the comparisons between the categorical data. A Kaplan−Meier survival analysis was used to present the survival curves. Multivariate Logistic regression analysis with forward selection was performed to assess predictability of variables on the prescription of guideline-recommended medications, presented as odds ratios (OR) and 95% confidence intervals (CI) using $P < 0.05$ in univariate analyses for inclusion. A P-value of <0.05 was considered statistically significant. All testes were two-sided. The statistical analyses were performed using SPSS Statistics 17.0 software (Chicago, IL, USA).

3. Results

3.1. Index hospitalization

A total of 1509 hospitalized patients (age 63.9 ± 16.1 years, 72.4% male) were included in the TSOC-HFrEF registry from May 2013 to October 2014. The patient characteristics and the management during index hospitalization have been completely described in previous manuscript.[16] The most common etiology of HF was ischemic cardiomyopathy (44.1%), followed by dilated cardiomyopathy (32.9%), and valvular heart disease

(7.9%). In-hospital mortality rate was 2.4% and a total of 1473 patients discharged from index hospitalization were finally analyzed for pharmacological treatments.

3.2. Guideline-recommended medications at discharge

The rate of prescription of renin-angiotensin system (RAS) blockade was moderate (62.1%) at discharge after index hospitalization. The rate of prescription of ACEIs was 27.5%, which was slightly fewer than the prescription rate of ARBs (34.6%). At discharge, 59.6% of patients were treated with beta-blockers and 49% were treated with MRAs. Baseline pharmacological treatments, dosages, and the proportion of patients at ≥50% of the target dose for evidence-based HF medications and within each class are shown in Table 1. The proportions of patients at ≥50% of the target dose for ACEIs, ARBs, beta-blockers and MRAs were 27.1%, 22.3%, 20.6%, 86.2%, respectively. The proportions of patients achieved the target dose for RAS blockades, beta-blockers and MRAs were 5%, 3.6%, 21.6%, respectively.

Ramipril was the most commonly prescribed ACEIs (33.8%). The proportion of ≥50% of the target dose of ramipril was also the highest among patients treated with ACEIs (34.6%). Candesartan was the most commonly prescribed ARBs (39.7%), but the proportions of ≥50% of the target dose of candesartan was only 14.4%. The proportion of ≥50% of the target dose among patients treated with ARBs was higher in patients receiving valsartan (39%). Bisoprolol was the most frequently prescribed beta-blocker (59.7%). The proportions of ≥50% of the target dose of beta-blockers were only 20% and were similar among different types of beta-blockers. Almost all prescriptions in patients treated with MRAs were spironolactone, and the proportions of ≥50% of the target dose were both high in patients treated with spironolactone or eplerenone.

3.3. One-year outcome

One-year outcome of the TSOC-HFrEF registry had been completely described in previous manuscript.[17] In brief, all-cause mortality rates were 9.5% and 15.9% and CV mortality rates were 6.8% and 10.5% at 6 and 12 months after hospital discharge, respectively. Re-hospitalization rates for HF were 31.9% and 38.5% at 6 and 12 months after index hospitalization, respectively.

Multivariate analysis in the previous published manuscript showed that prescription of less than 2 types of guideline-directed medical therapy (HR 1.59, 95% CI 1.07–2.38, $p = 0.023$) could independently predict the all-cause mortality.[17] In current study, we further analyzed the effects of drug dosing on mortality. A total of 10.9% patients received two or three classes of guideline-recommended medications with ≥50% of the target dose. These patients had a better prognosis than those who received less than 50% of the target dose and those who received less than 2 classes of guideline-recommended medical therapy (Fig. 1).

3.4. Factors associated with guideline-recommended medications prescription

To explore the reasons for non-prescription of guideline-recommended therapies in the TSOC-HFrEF registry, univariate and multivariate analyses were performed for the prescription of three classes of guideline-recommended medications and are shown in Table 2. Old age was universally associated with non-prescription of each class of guideline-

Table 1
Type and doses of guideline-recommended medications for the treat of heart failure over time.

	At discharge			At 12 months		
	Rate of use	Dose (mg/day)	≥50% of target dose	Rate of use	Dose (mg/day)	≥50% of target dose
RAS blockers	**62.1%**		**24.4%**	**57.7%**		**24.3%**
ACEIs	27.5%		27.1%	16.9%		36.2%
Ramipril	33.8%	4.5 ± 4.2	34.6%	44.2%	4.6 ± 4.4	36.1%
Captopril	30.3%	29.0 ± 22.9	14.8%	15.3%	31.1 ± 20.8	12.0%
Enalapril	23.6%	8.1 ± 8.9	31.6%	20.2%	12.3 ± 11.9	54.5%
Others	12.2%			20.2%		
ARBs	34.6%		22.3%	40.8%		20.0%
Candesartan	39.7%	7.2 ± 5.0	14.4%	32.9%	6.8 ± 5.2	10.0%
Valsartan	35.0%	114.1 ± 62.0	39.0%	40.3%	112.4 ± 61.8	34.4%
Losartan	16.4%	41.4 ± 29.1	6.0%	16.5%	40.5 ± 18.8	4.6%
Others	8.9%			10.3%		
Beta-blockers	**59.6%**		**20.6%**	**66.2%**		**26.3%**
Bisoprolol	57.9%	2.5 ± 2.0	21.7%	62.0%	2.7 ± 1.9	27.4%
Carvedilol	37.5%	13.6 ± 14.1	20.7%	33.7%	15.0 ± 13.5	25.3%
Metoprolol	1.3%	40.0 ± 26.2	18.2%	2.8%	48.6 ± 36.1	27.8%
MRAs	**49.0%**		**86.2%**	**40.8%**		**86.6%**
Spironolactone	98.7%	28.9 ± 14.2	86.0%	99.5%	32.8 ± 29.3	86.6%
Eplerenone	1.3%	52.8 ± 19.5	100%	0.5%	75.0 ± 35.4	100%

ACEI: Angiotensin-converting enzyme inhibitors.
ARB: Angiotensin receptor blockers.
MRA: Mineralocorticoid receptor antagonist.
RAS: Renin-angiotensin system.

recommended therapies. The prescription rate of MRAs was higher in patients with lower blood pressure and lower left ventricular ejection fraction at discharge, and the prescription rate of beta-blockers was higher in patients with lower discharge heart rate. The prescription rates of ACEIs/ARBs and beta-blockers were higher when the patients were heavier. Higher serum creatinine level was associated with non-prescription of ACEIs/ARBs and MRAs, where as asthma or chronic obstructive pulmonary disease (COPD) was associated with non-prescription of beta-blockers.

3.5. Guideline-recommended medications at one-year follow-up

Right column of Table 1 shows the type and doses of guideline-recommended medications at one-year follow-up. The prescription rates of RAS blockade decreased from 62.1% at discharge to 57.5% at 1-year. The prescription rates of ACEIs decreased from 27.5% to 16.8% whereas the prescription rates of ARB increased from 34.6% to 40.8%. Fig. 2 shows the prescription pattern of guideline-recommended medications at one year after discharge. Among patients treated with RAS blockade, 63.1% of patients were prescribed with the same medications within one-year but the dosage remained similar or had been reduced. 11.1% of patients changed their prescription from ACEIs to ARBs or vice versa without up-titration of equivalent dosages. Only 23.3% of patients received up-titration with same medications and 2.5% of patients received up-titration of equivalent dosages after shifting medications between ACEIs and ARBs within one-year.

Prescribing rates of beta-blockers increased from 59.6% of the patients at discharge to 66.2% of the patients at 12-month. Bisoprolol remained the most commonly prescribed beta-blocker at one-year follow-up. Among patients treated with beta-blockers, 52.8% of patients were prescribed with same medications within one-year but the dosage remained similar or had been reduced. Approximately 40% of patients received either up-titration with same medications or after shifting different types of beta-blockers within one-year. The proportions of patients at ≥50% of the target dose for beta-blockers increased from 20.6% of the patients at discharge to 26.3% of the patients at 1-year.

Prescribing rates of MRAs decreased from 49% of the patients at discharge to 40.8% of the patients at 12-month. The proportions of patients at ≥50% of the target dose for MRAs were similar between baseline and one-year follow-up. Among patients treated with MRAs, dosages were up-titrated in 25% of patients within one-year and remained the same in 63.9% of patients.

4. Discussion

The TSOC-HFrEF registry is the first large-scale, prospective multicenter database of patients hospitalized for

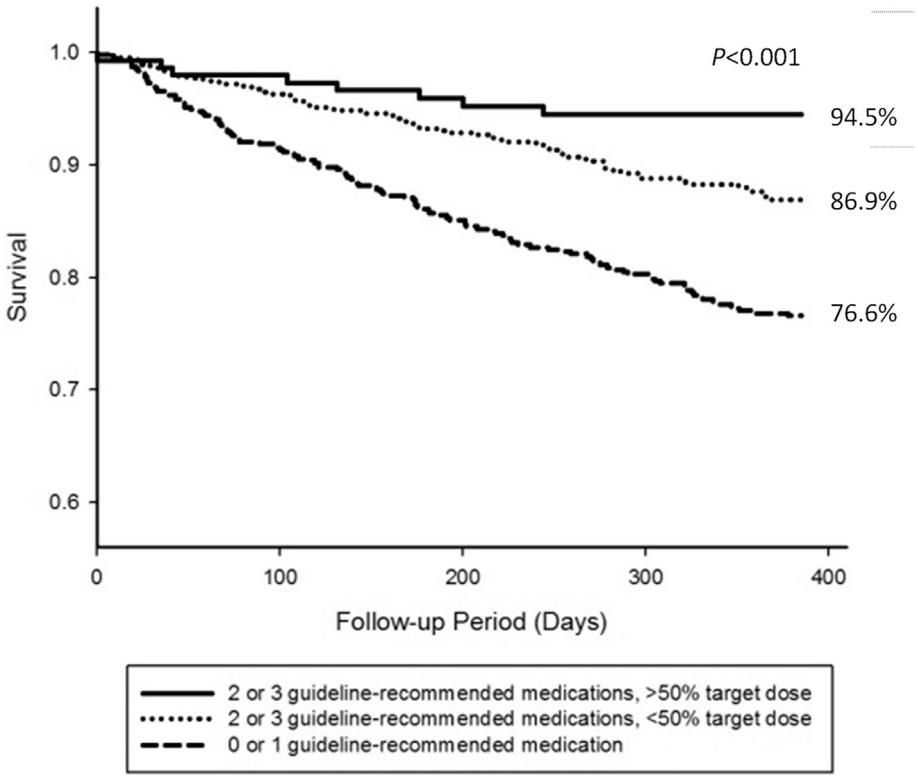

Fig. 1. Kaplan–Meier survival curves in the registry patients presenting with different types and dosages of guideline-recommended medications.

Table 2
Univariate and multivariate analysis of guideline-recommended medications prescription at discharge.

Univariate	RAS blocker			Beta blocker			MRA		
	Yes	No	*p*	Yes	No	*p*	Yes	No	*p*
Age (y/o)	61.6 ± 15.9	67.4 ± 14.9	<0.001	61.6 ± 16.0	67.2 ± 14.9	<0.001	60.6 ± 18.4	66.9 ± 14.5	<0.001
Male	74.2%	69.5%	0.048	72.8%	71.8%	NS	75.1%	69.8%	0.022
Body mass index (kg/m^2)	25.9 ± 5.3	24.2 ± 4.5	<0.001	25.9 ± 5.3	24.2 ± 4.5	<0.001	25.8 ± 5.4	24.7 ± 4.7	<0.001
Admission SBP (mmHg)	133.7 ± 28.1	127.6 ± 25.2	0.031	133.9 ± 28.4	127.7 ± 24.8	0.001	130.4 ± 27.5	132.3 ± 26.8	NS
Admission HR (bpm)	92.8 ± 22.0	92.5 ± 22.6	NS	93.8 ± 23.0	91.1 ± 20.8	0.061	93.5 ± 22.2	92.0 ± 22.2	NS
Discharge SBP (mmHg)	120.4 ± 18.8	118.6 ± 17.9	NS	120.4 ± 18.6	118.7 ± 18.1	NS	116.9 ± 17.9	122.4 ± 18.5	<0.001
Discharge SBP≤100 mmHg	13.5%	13.4%	NS	12.8%	14.5%	NS	16.6%	10.5%	0.001
Discharge HR (bpm)	80.4 ± 14.7	80.4 ± 14.8	NS	79.2 ± 14.3	82.1 ± 15.2	<0.001	81.2 ± 15.0	79.6 ± 14.4	0.03
Discharge HR ≥ 100 bpm	10.9%	9.7%	NS	8.3%	13.6%	0.001	11.7%	9.3%	NS
Creatinine (mg/dL)	1.6 ± 1.6	2.3 ± 2.0	<0.001	1.9 ± 1.9	1.9 ± 1.6	NS	1.4 ± 0.9	2.4 ± 2.3	<0.001
Creatinine≥2.5 mg/dL	9.4%	26.3%	<0.001	14.8%	17.6%	NS	6.5%	25.2%	<0.001
eGFR (mL/min/m^2)	64.1 ± 43.1	42.7 ± 29.6	<0.001	60.3 ± 39.2	49.3 ± 39.8	<0.001	65.9 ± 42.9	46.0 ± 33.8	<0.001
eGFR≤30 mL/min/m^2	17.7%	40.2%	<0.001	22.8%	31.5%	<0.001	14.1%	38.3%	<0.001
Serum sodium (mEq/L)	138.1 ± 4.2	137.2 ± 4.7	0.054	137.9 ± 4.3	137.5 ± 4.6	0.05	137.6 ± 4.4	137.9 ± 4.5	NS
Serum potassium (mEq/L)	4.0 ± 0.6	4.1 ± 0.7	0.003	4.0 ± 0.6	4.0 ± 0.7	NS	4.0 ± 0.6	4.1 ± 0.7	0.001
Asthma/COPD	10.3%	11.6%	NS	7.3%	15.9%	<0.001	9.9%	11.7%	NS
LVEF (%)	27.9 ± 8.2	28.6 ± 8.2	NS	28.0 ± 8.1	28.4 ± 8.3	NS	26.0 ± 8.2	30.2 ± 7.7	<0.001
Use of RAS blocker	–	–	–	66.1%	55.3%	<0.001	67.2%	56.4%	<0.001
Use of beta blocker	63.9%	52.9%	<0.001	–	–	–	59.8%	59.5%	NS
Use of MRA	53.3%	42.0%	<0.001	49.1%	48.8%	NS	–	–	–

Multivariate	RAS blocker			Beta blocker			MRA		
	Odds ratio	95% CI	*p*	Odds ratio	95% CI	*p*	Odds radio	95% CI	*p*
Age (per ↑ 1 y/o)	0.985	0.977–0.993	<0.001	0.983	0.975–0.991	<0.001	0.981	0.973–0.989	<0.001
Discharge SBP (per ↑ 1 mmHg)	–	–	–	–	–	–	0.992	0.985–0.999	0.02
Discharge HR (per ↑ 1bpm)	–	–	–	0.982	0.974–0.990	<0.001	–	–	–
Body mass index (per ↑ 1 kg/m^2)	1.052	1.025–1.080	<0.001	1.041	1.015–1.068	0.002	–	–	–
Creatinine (per ↑ 1 mg/dL)	0.824	0.772–0.880	<0.001	–	–	–	0.646	0.574–0.727	<0.001
LVEF (per ↑ 1%)	–	–	–	–	–	–	0.950	0.935–0.964	<0.001
Asthma/COPD	–	–	–	0.531	0.371–0.760	0.001	–	–	–
Use of RAS blocker	–	–	–	1.400	1.115–1.759	0.004	–	–	–
Use of beta blocker	1.454	1.157–1.827	0.001	–	–	–	–	–	–

ACEI: Angiotensin-converting enzyme inhibitors.
ARB: Angiotensin receptor blockers.
COPD: Chronic obstructive pulmonary disease.
GFR: Glomerular filtration rate.
HR: Heart rate.
LVEF: Left ventricular ejection fraction.
MRA: Mineralocorticoid receptor antagonist.
RAS: Renin-angiotensin system.
SBP: Systolic blood pressure.

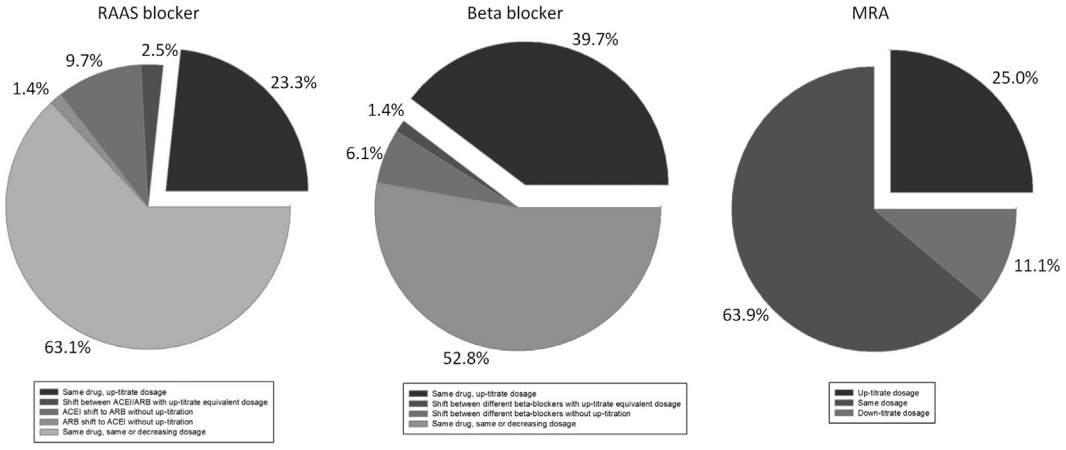

Fig. 2. Treatment patterns of guideline-recommended medications at one year after discharge.

HFrEF in Taiwan. It provided important information of the patient characteristics, treatment modalities and clinical outcomes. The results revealed significant gaps between guideline recommendations and real world practice in Taiwan. Although there are many international registries aimed to investigate the clinical practice in patients with heart failure, there have been no reports in Taiwanese. Our data study was novel for Taiwanese HFrEF patients.

4.1. Patient-related factors for non-prescription of guideline-recommended therapies

A number of reasons for the underutilization of guideline-recommended therapies have been proposed.[15,18,19] These reasons affect each other and the issues are complex to be resolved. Patient factors including old age, frailty and comorbidities, could directly lead to drug intolerance or contraindications to prescribed medications. Elderly are more fragile, and therefore experience greater incidence of side effects and intolerability from guideline-recommended therapies. Old age was a universal factor associated with non-prescription of guideline-recommended therapies in the TSOC-HFrEF registry.

In the current registry, higher body weight was associated with increased prescription rates of RAS blockades and beta-blockers. Low body weight HF patients are generally weaker because of loss of fat tissue, bone tissue as well as impaired muscle quality.[20] Similar to the elderly patients, low body weight HF patients are more fragile and therefore, guideline-directed medical therapies appear to be less tolerable in these patients.

Two comorbidities were found to be independently associated with the non-prescription of guideline-recommended medical therapies in this study. Renal dysfunction was associated with underutilization of RAS blockades and MRAs, whereas COPD and/or asthma were associated with underutilization of beta-blockers. The prevalence of renal impairment and end-stage renal disease patients in Taiwan is very high. Report from Taiwan Renal Registry Data System demonstrated the prevalence of renal replacement therapy was 2926 per million of the population in 2012.[21] In our current registry, the prevalence of chronic renal failure was 31.5%,[16] which was much higher than the data reported in the previous European and Asian national surveys.[22–25]

The prevalence of COPD and/or asthma in current registry was 11%, which was lower than that in the ADHERE[26] and EHFS-II[22] registries (31% and 19%, respectively). But the prescription rate of beta-blockers was 59.6% which was unexpectedly lower than that in the ADHERE and EHFS-II registries (62.6% and 61.4%, respectively). The results indicate that COPD and/or asthma were not the only factor for beta-blockers non-adherence. Indeed, one finding in the current registry showed that patients with higher heart rate at discharge were less likely to receive beta-blocker treatment. This finding seemed paradoxical since elevated heart rate at hospital discharge predicts higher hospital readmission as well as one-year mortality, and beta blockers should be used to lower heart rate.[27] However, an increase resting heart rate per se is also a marker of severe HF status. Patient with elevated discharge heart rate might be in a more severe state of HF, and fear of further contractility worsening could be an explanation that beta-blockers were not initiated in these patients. Similar finding was noted in the Swedish Heart Failure Registry: 92.8% of patients with heart rate less than 70 bpm received beta-blockers, whereas 87.3% of patients with heart rate between 70 and 100 bpm and 79.3% of patients with heart rate more than 100 bpm received beta-blockers ($p < 0.001$).[28]

We observed a higher prescription of MRAs in current registry comparing to the data published in previous studies.[22–26] More than 85% of patients treated with MRAs achieved at least 50% of target dosages. Interestingly, patients with lower blood pressure at discharge were more likely to receive MRAs treatment. Together with the relatively lower prescription rates of RAS blockade and beta-blockers, we postulated that both patients and physicians concerned about the adverse effect of hypotension. Physicians omitted RAS blockade and/or beta-blockers and used MRAs to avoid hypotension since MRA has less blood pressure lowering effect than the other drugs. A total of 7.4% patients in the registry received MRAs alone without RAS blockade and beta-blockers. This modified treatment is a compromise according to patients' condition; unfortunately, MRA stand-alone treatment resulted in poorer prognosis during follow-up, as depicted in Fig. 1. Physicians should thoroughly explain the benefit of guideline-recommended therapies to patients in order to improve patient's acceptance and adherence to medications.

4.2. Physician-related factors for non-prescription of guideline-recommended therapies

Physician-related factors include lack of awareness of treatment goals, focusing on symptom relief rather than reduction of mortality, or fear of adverse effects. In some healthcare systems, general practitioners and cardiologists co-manage HF patients, but general practitioners were less likely to prescribe guideline-directed medications.[29,30] This reflects a lower risk of mortality or readmission of HF patients managed by cardiologists than noncardiologists.[31] This would not be an issue in TSOC-HFrEF registry, as all HF patients were treated by cardiologists in hospital and outpatient clinic. However, given the high proportion of underutilization guideline-recommended medications, establishing educational program for cardiologists to optimize drug treatment of HFrEF would be helpful in improving clinical outcome.

Fear of adverse effects during initiation or dose escalation of guideline-recommended medications could be an important factor. However, current registry did not record the reason of non-prescription, so the percentage of adverse effect was unknown. We observe that the prescribing rate of ACEI decreased over time whereas that of ARB increased from discharge to one-year follow-up. This trend could be explained by patients not tolerating side effects of cough or angioedema

from ACEI and had therapy switched from ACEI to ARB. As mentioned above, patients with COPD and/or asthma were associated with underutilization of beta-blockers. However, COPD is not an absolute contraindication for beta-blocker use unless worsening symptoms developed after beta-blocker treatment. Our current registry could not to elucidate the fact whether the under-usage of beta-blockers was due to deterioration of pulmonary condition or the fear of side effects.

4.3. Underdosing of guideline-recommended therapies

Many previous studies had demonstrated the dose-dependent manner of guideline-recommended medical therapies: In ATLAS study, lisinopril at high dose significantly decreased death or hospitalization for any cause by 12% ($p = 0.002$) compared with that at low dose.[32] In HEAAL study, again, losartan at high dose reduced death or hospitalization for HF in patients with HFrEF, compared with losartan at low dose (hazard ratio 0.90, 95% CI 0.82−0.99; $p = 0.027$).[33] Even in patients aged more than 70 y/o, the high dose (>50% target dose) of RAS blockades was associated with a better survival than the low dose (<50% target dose) (HR = 0.35; 95% CI 0.19−0.67; $p = 0.001$).[34] According to current guideline, these neurohormonal inhibitors should be up-titrated to maximum tolerated evidence-based doses in order to reduce mortality and morbidity in patients with HFrEF.[11−13]

However, in current registry, the proportion of patients at target dose and ≥50% of target dose was low (5% and 24.4% for RAS blockades, 3.6% and 20.6% for beta-blockers, and 21.6% and 86.2% for MRAs). Our data indicated that the prescribed dosage of recommended HFrEF medications in Taiwan was less than that in the recent QUALIFY global survey,[35] which showed the proportion of patients at target dose and ≥50% of target dose was 27.9% and 63.3% for ACEIs, 14.8% and 51.8% for beta-blockers, and 70.8% and 99.1% for MRAs, respectively. Although only a few patients in current registry achieved optimal dose of two or three guideline-recommended therapies, their one-year mortality rate was significantly low. This finding emphasized the importance of optimal dosing. A rigorous plan for dose uptitration should be established in daily practice.

4.4. Study limitations

There are several limitations which should be acknowledged in the present study. First, the design was an observational, prospective survey which included only hospitalized patients with reduced ejection fraction. Despite covariate adjustment, other measured or unmeasured factors might also affect outcomes. Second, the reasons for failure to initiate or up-titrate guideline-recommended medical therapy were not collected in current registry, therefore, we could not provide a detailed explanation for underutilization of these medications, and the percentage of "real under-utilization" of guide-recommended therapy could not be calculated.

In conclusion, the TSOC-HFrEF registry is the largest national database to-date involving acute decompensated HFrEF patient in Taiwan. This registry demonstrated the underutilization of guideline-recommended medications at discharge and suboptimal up-titration of guideline drugs during follow-up. Our data was novel for Taiwanese HFrEF patients and indicates that rigorous and effective plans should be initiated for further improvement of HF care.

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