Original Article

The Prevalence and Characteristic of Patients Achieve Target Doses of Medications Used to Treat Heart Failure with Reduced Ejection Fraction at Heart Failure Clinic

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Abstract

OBJECTIVES: To determine the prevalence and characteristics of patients who achieved target doses of angiotensin converting enzyme inhibitors (ACEIs)/ angiotensin II receptor blockers (ARBs), beta-blocker, and mineralocorticoid receptor antagonists (MRAs).

MATERIALS AND METHODS: A retrospective chart review study of heart failure with reduced ejection fraction (HFrEF) patients who received ACEIs/ARBs, beta-blockers, or MRAs and follow-up more than four times at the heart failure outpatient clinic, Chonburi hospital from February 1st, 2017 to February 29th, 2020. Patient data were retrieved from electronic medical records. Two authors collected data into record form (CRF) independently. Achieving target doses was defined by recommended doses according to the ACC/AHA/HFSA Guideline, 2017. The comparison of continuous data was conducted with the Mann-Whitney U test. Pearson Chi-Square and Fisher's exact test were used for the comparison of categorical data.

RESULTS: Patients who achieved target doses of ACEIs/ARBs, beta-blockers and MRAs was 73.3%, 55.3%, and 7.1% respectively. Patients' characteristics of achieved target doses of ACEIs/ARBs were higher baseline left ventricular ejection fractions ($p = 0.026$). Younger age ($p = 0.016$), body mass index (BMI) ≥ 23 kg/m^2 ($p = 0.037$; OR 5.3) and serum creatinine ≤ 2 mg/dL ($p = 0.004$) were the characteristics of patients who achieved target doses of beta-blockers.

CONCLUSION: Most patients in heart failure clinic achieved target doses of ACEIs/ARBs followed by beta-blockers but only a few patients for MRAs. Patient and medical characteristics were different in target doses achievable.

Keywords: heart failure, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, mineralocorticoid receptor antagonists, Target dose

Heart failure (HF), is a global health condition problem with an increasing prevalence and health loss burden every year.[1] Although the exact prevalence of HF in Thailand is unknown, the Asian population living with HF was 1-4.5%.[2] In-hospital mortality rate of HF in Thailand (5.5%) was proportional to other Asian countries.[3]

The treatment goals of HF with reduced ejection fraction (HFrEF) were slow progression of condition, reduced hospital admission, minimizing the risk of death, and improving quality of life. Heart failure medications including ACEIs, ARBs, angiotensin receptor-neprilysin inhibitors (ARNIs), beta-blockers and MRAs reduce hospitalization and mortality. Medications are started at the lowest doses and titrated up slowly, approximately 3-6 months, until the target doses are reached.[4-6] Few patients received target doses of ACEIs/ARBs (16.8%), ARNIs (13.9%), beta-blockers (47.1%) and MRAs (6.3%).[7]

Various factors affect reaching the target dose of heart failure medications. In Change Management of Patients with HF (CHAMP-HF) registry, characteristics that were associated to dose adjustment were age, race, BMI, systolic blood pressure, heart rate, heart failure hospitalization within 1 year, New York Heart Association (NYHA) functional class, left ventricular ejection fraction (LVEF), and comorbidities (hypertension, diabetes mellitus, chronic obstructive pulmonary disease, renal failure, atrial fibrillation, cardiovascular diseases).[8] Similar to the BIOlogy Study to TAilored Treatment in Chronic HF (BIOSTAT-CHF) study, characteristics of patients who did not receive target ACEIs/ARBs doses were female, low estimated glomerular filtration rate (eGFR), low BMI and high level of alkaline phosphatase. Older age, low heart rate and low diastolic blood pressure were the characteristics of those who did not reach target doses of beta-blockers.[9]

In Thailand, there are limited studies on the prevalence and characteristics of HFrEF patients who achieve target doses of medications. Reaching the target doses affects good clinical outcomes. The purpose of the study was to determine characteristics of patients who achieved target doses of ACEIs/ARBs, beta-blockers and MRAs.

Material and Methods

This retrospective chart review study was conducted in adult HFrEF patients (Left ventricular ejection fraction; LVEF ≤ 40%) at the heart failure outpatient clinic, Chonburi hospital, Thailand, from February 1st, 2017 to February 29th, 2020. Patients were being treated with ACEIs, ARBs, beta-blockers, or MRAs and follow-up more than four times were included.

Data collection and Ethical approval

Patient data were retrieved from the electronic medical records, including patient characteristics (sex, age), medical characteristics (NYHA functional class, LVEF, blood pressure, heart rate, serum creatinine, serum potassium, and symptoms of heart failure), and doses of heart failure medications (ACEIs/ARBs, beta-blockers, MRAs). Two authors collect data into record form (CRF) independently. Disagreements were resolved by consulting the third author. The study was approved by the Institutional Review Board of the Chonburi hospital (approval number 96/63/O/h3). Achieving target doses was defined as the recommended doses according to the ACC/AHA/HFSA Guideline, 2017.

Statistical analysis

The statistical software SPSS for windows version 28 (IBM Thailand Co., Ltd., Thailand) was used for analysis. Patient, and medication data were analyzed with descriptive statistics. The comparison of continuous data was conducted with the Mann-Whitney U test since the variance of each group would be unequal and some of the patient groups were very small. Pearson Chi-Square and Fisher's exact test were used for the comparison of categorical data. A $p < 0.05$ is statistically significant.

Results

Of 80 patients who received ACEIs/ARBs, beta-blockers, or MRAs, 41 patients were included in this study (Table 1). At the first visit, their mean LVEF was 26.6 ± 8.5% and this improved at 6 and 12 months. Increasing LVEF to > 40% were 13 (31.7%) patients. After referring to the clinic, patients with symptoms of heart failure decreased. The NYHA classification data are not available for all patients.

Target doses of heart failure medications

Nineteen (46.3%) patients received ACEIs/ARBs, beta-blockers and MRAs concomitantly. Most of the patients were treated with beta-blockers (n = 38; 92.7%). Patients received more ARBs (n = 25) than ACEIs (n = 4). Nine patients received ARNIs instead of ACEIs/ARBs during the study period (Table 1). Patients who received target doses: ACEIs/ARBs (n = 22; 73.3%), beta-blockers (n = 21; 55.3%) and MRAs (n = 2; 7.1%). Most ACEIs/ARBs and MRAs treated patients reached the target doses within 6 months (77.3% and 100.0%, respectively). Fifteen (88.2%) patients received ≥ 50 % target dose of beta-blockers (Figure 1, 2).

Characteristics of patients who achieved target doses of heart failure medications are shown in Table 2. Patients who reached target doses of ACEIs/ARBs had a higher baseline LVEF than non-target doses ($p = 0.026$). The significant different characteristics of patients receiving beta-blockers target doses were younger age ($p = 0.016$), BMI ≥ 23 kg/m^2 ($p = 0.037$; Odd ratio 5.3) and serum creatinine ≤ 2 mg/dL ($p = 0.004$).

Discussion

There are few studies in Thailand that evaluate the number and characteristics of HFrEF patients who were prescribed target doses.[7] This is the one of the studies at a heart failure clinic in Thailand. In our study, most patients received beta-blockers. Consistent with the study of Anupraiwan O et al,[7] most patients continued to receive beta-blockers until the end of study. This was probably due to most of the patients having relatively high heart rate and blood pressure. Optimal resting heart rate in HFrEF patients was 50-60 beats per minute.[10] Blood pressure targets differ in each guideline, blood pressure < 130/80 mmHg or systolic blood pressure 130 mmHg.[11] The number who received ACEIs/ARBs and MRAs were fewer, patients may not tolerate ACEIs/ARBs and MRAs. Accordingly, factors associated with non-use ACEIs/ARBs or MRAs were older age and worsening renal function.[12] Some switched to ARNIs, recommended in HFrEF patients with NYHA class II – III [6].

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Table 1: Patient and medical characteristics of heart failure with reduced ejection fraction (HFrEF) patients (n = 41).

Characteristics	Visit 0	At 6 months	At 12 months
Sex			
Male	24 (58.5)	24 (58.5)	24 (58.5)
Female	17 (41.5)	17 (41.5)	17 (41.5)
Age (years); mean ± SD	58.2 ± 15.6		
BMI (kg/m^2); mean ± SD	24.3 ± 5.7	25 ± 5.8	25.3 ± 5.6
Comorbidities			
Atrial fibrillation	10 (24.4)		
Ischemic heart disease	23 (56.1)		
Hypertension	23 (56.1)		
Dyslipidemia	14 (34.1)		
Diabetes	14 (34.1)		
COPD	3 (7.3)		
Chronic kidney disease	6 (14.6)		
NYHA class*	n = 22		
Class I	7 (17.1)		
Class II	12 (29.3)	16 (39.0)	18 (43.9)
Class III	3 (7.3)	12 (29.3)	7 (17.1)
Unknown class	19 (46.3)	0	1 (2.4)
LVEF (%); mean ± SD	26.6 ± 8.5	13 (31.7)	15 (36.6)
SBP (mmHg); mean ± SD	124.1 ± 19.7	44.9 ± 21.5	52.2 ± 16.9
DBP (mmHg); mean ± SD	74.4 ± 12.2	124.2 ± 17.0	123.3 ± 21.2
Heart rate (bpm); mean ± SD	82.3 ± 15.4	72.9 ± 9.2	72.3 ± 14.3
Serum creatinine (mg/dL); mean ± SD	1.1 ± 0.4	74.9 ± 16.6	74.1 ± 14.8
Serum potassium (mEq/L); mean ± SD	4.1 ± 0.5	1.2 ± 0.5	1.2 ± 0.5
Symptoms of heart failure**	9 (22.0)	4.3 ± 0.4	4.1 ± 0.5
Enalapril	4 (9.8)	7 (17.1)	5 (12.2)
Losartan	23 (56.1)		
Valsartan	2 (4.9)		
Bisoprolol	2 (4.9)		
Carvedilol	34 (82.9)		
Metoprolol tartate	2 (4.9)		
Spironolactone	28 (68.3)		

*Not available in all patients, ** dyspnea, edema, fatigue
ACEIs; Angiotensin converting enzyme inhibitors, ARBs; Angiotensin receptor blockers, BMI; body mass index, COPD; chronic obstructive pulmonary disease, DBP; diastolic blood pressure, LVEF; left ventricular ejection fraction, MRAs; mineralocorticoid receptor antagonists, NYHA; New York Heart Association, SBP; systolic blood pressure

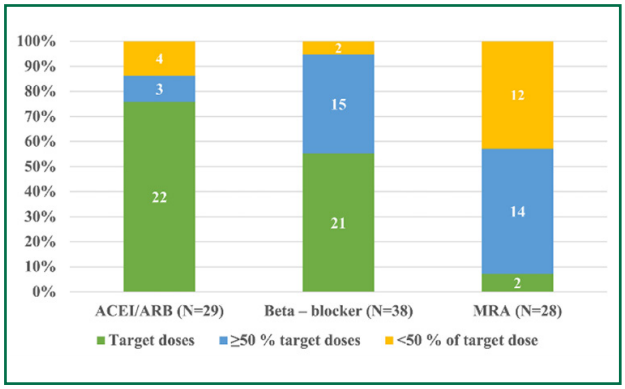

Figure 1: Target doses and non-target doses of angiotensin converting enzyme inhibitors/angiotensin receptor blockers, beta-blockers and mineralocorticoid receptor antagonists.

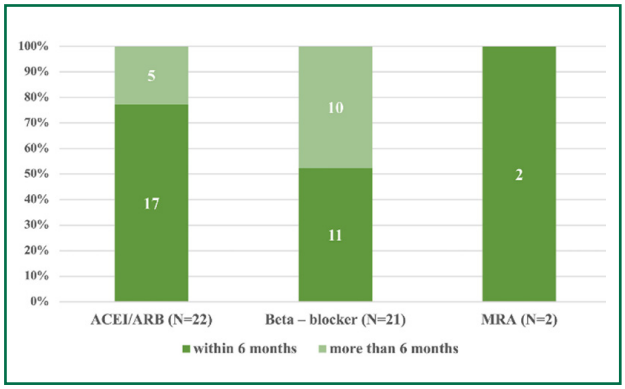

Figure 2: Time to Target doses of angiotensin converting enzyme inhibitors/angiotensin receptor blockers, beta-blockers, and mineralocorticoid receptor antagonists.

Table 2: Characteristics of patients who received target doses and non-target doses of angiotensin converting enzyme inhibitors/ angiotensin receptor blockers, beta-blockers and mineralocorticoid receptor antagonists

Characteristics	ACEIs/ARBs (n = 29)			Beta-blockers (n = 22)			MRAs (n = 28)		
	Target doses (n = 22)	Non-target doses (n = 7)	P-value	Target doses (n = 21)	Non-target doses (n = 17)	P-value	Target doses (n = 2)	Non-target doses (n = 26)	P-value
Sex									
Male	11 (50.0)	3 (42.9)	1.0	10 (47.6)	13 (76.5)	0.1	1 (50.0)	18 (69.2)	1.0
Female	11 (50.0)	4 (57.1)		11 (52.4)	4 (23.5)		1 (50.0)	8 (30.8)	
Age; (years); median ± IQR**	56 ± 20.0	64 ± 27.0	0.273	51 ± 24.0	66 ± 33.0	0.016**	52, 56#	57 ± 26.8	0.664
Comorbidities									
Atrial fibrillation	5 (22.7)	2 (28.6)	1.0	5 (23.8)	5 (29.4)	0.727	1 (50.0)	6 (23.1)	0.44
Ischemic heart disease	12 (54.5)	5 (71.4)	0.665	11 (52.4)	12 (70.6)	0.326	1 (50.0)	13 (50.0)	1.0
Hypertension	14 (63.6)	3 (42.9)	0.403	13 (61.9)	9 (52.9)	0.743	1 (50.0)	16 (6.5)	1.0
Dyslipidemia	6 (27.3)	3 (42.9)	0.642	6 (28.6)	6 (35.3)	0.734	1 (50.0)	8 (30.8)	1.0
Diabetes	5 (22.7)	2 (28.6)	1.0	6 (28.6)	7 (41.2)	0.502	1 (50.0)	9 (34.6)	1.0
COPD	2 (9.1)	0 (0.0)	1.0	2 (9.5)	1 (5.9)	1.0	0.0	3 (11.5)	1.0
Chronic kidney disease	2 (9.1)	0 (0.0)	1.0	1 (4.8)	4 (23.5)	0.152	1 (50.0)	3 (11.5)	0.27
BMI ≥ 23 kg/m^2**	18 (81.8)	6 (85.7)	1.0	18 (85.7)	9 (52.9)	0.037**	2 (100.0)	20 (76.9)	1.0
Baseline LVEF (%); median ± IQR*	30 ± 11.0	18 ± 9.0	0.026*	26 ± 13.0	23 ± 8.6	0.624	22,31#	26 ± 14.0	0.926
LVEF > 40%	12 (54.5)	3 (42.9)	0.682	11 (52.4)	7 (41.2)	0.532	1 (50.0)	13 (50.0)	1.0
SBP ≥ 90 mmHg	22 (100.0)	6 (85.7)	0.241	21 (100.0)	15 (88.2)	0.193	2 (100.0)	24 (92.3)	1.0
DBP ≥ 60 mmHg	20 (90.9)	5 (71.4)	0.238	18 (85.7)	10 (58.8)	0.078	1 (50.0)	22 (84.6)	0.331
HR ≥ 60 bpm	16 (72.7)	7 (100.0)	0.289	17 (81.0)	13 (76.5)	1.0	1 (50.0)	21 (80.8)	0.389
Serum creatinine ≤ 2 mg/dL**	21(95.5)	6 (85.7)	0.431	21 (100.0)	11 (64.7)	0.004**	2 (100.0)	23 (88.5)	1.0
Serum potassium < 5 mEq/L	22 (100.0)	6 (85.7)	0.241	20 (95.2)	16 (94.1)	1.0	2 (100.0)	25 (96.2)	1.0
No symptoms of heart failure	11 (50.0)	5 (71.4)	0.41	14 (66.7)	7 (41.2)	0.19	0 (0.0)	10 (38.5)	0.524

*p < 0.05 for ACEIs/ARBs, ** p < 0.05 for beta-blockers, # individual value report
ACEIs; Angiotensin converting enzyme inhibitors, ARBs; Angiotensin receptor blockers, BMI; body mass index, COPD; chronic obstructive pulmonary disease, DBP; diastolic blood pressure, LVEF; left ventricular ejection fraction, MRAs; mineralocorticoid receptor antagonists, NYHA; The New York Heart Association, HR; heart rate, SBP; systolic blood pressure

Few patients received intermediate – release metoprolol tartrate instead of metoprolol succinate, not available in hospital. The comparison study found that metoprolol tartrate and metoprolol succinate in HF patients had similar benefits in function, exercise and hemodynamics.[13] In the COMET trial, carvedilol reduced the risk of death, cardiovascular hospitalization, and all-cause hospitalization compared to metoprolol tartate.[14]

In our study, a higher percentage of patients achieved target dose of ACEIs/ARBs or beta-blockers than previous studies and fewer patients with target doses of MRAs.[7] A systematic review showed that the proportion of patients reaching target dose of ACEIs/ARBs, beta-blockers and MRAs was 4–55%, 4-60% and 22-80%, respectively.[12] MRAs was usually prescribed after the target dose of ACEIs/ARBs or beta-blockers has been reached. Most patients titrated to ACEIs/ARBs or MRAs target doses within 6 months but about half of beta-blockers target doses. Recommended up-titration was after 2-4 weeks for ACEIs/ARBs, beta-blockers and 4-8 weeks for MRAs. Titration period was approximately 3-6 months.[15,16]

The highest tolerated dose is recommended when target doses cannot be achieved.[6] Most of the patients treated with ACEIs/ARBs or beta-blockers received ≥ 50% of target doses. Patients who were treated with MRAs, about half of patients received ≥ 50% of target doses, more than the study of Anupraiwan O et al.[7] Patients with ACEIs/ARBs or beta-blockers who received <50% of target doses had a higher mortality rate and combined endpoint of death and/or HF hospitalization than ≥100% of target doses. Those who received 50 – 99% of ACEIs/ARBs or beta-blockers target doses had similar risk of combined endpoint of death and/or HF hospitalization compared to ≥100% of target doses.[9]

Achievable target doses depend on various characteristics. Received ACEIs/ARBs target doses was a higher LVEF according to Greene SJ et al, patients with stable target doses of ACEIs/ARBs have higher ejection fraction.[17] Characteristics of patients treated with target doses of beta-blockers were similar to previous studies; younger age, lower serum creatinine and higher BMI.[8,12] No differences were found in patients with MRAs as small numbers achieved MRAs target doses.

There were several limitations of this study, data were not available in retrospective chart review e.g., NYHA functional class, liver function tests, and medication adherence. Small numbers of patients to evaluate factors associated with targeted dose. Target doses of ARNIs and clinical outcome were not evaluated in our study.

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Conclusion

Most patients in heart failure clinics achieve 50-100% of ACEIs/ARBs or beta-blockers target doses, and 100% of target doses achieved was common in beta-blockers. Patients with target doses of ACEIs/ARBs had higher LVEF. Characteristics of patients treated with target doses of beta-blockers were younger age, serum creatinine ≤ 2 mg/dL and BMI ≥ 23 kg/m^2. This is a preliminary study, factors associated with 50 – 100% of targeted doses of HF medications, including ARNIs, and clinical outcomes should be evaluated further in a larger study.

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Conflicts of interest

No conflicts of interest

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