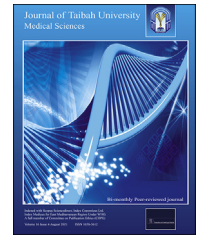Taibah University

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Original Article

Aggressive beta-blocker titration in stabilized acute heart failure patients with low left ventricular ejection fraction

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الملخص

أهداف البحث: ينبغي البدء باستعمال مانع بيتا مع المرضى الذين يعانون من فشل القلب الحاد المستقر. وينبغي إجراء معايرة بعد فترة أسبوعين من استعمال مانع بيتا. ولا تزال فوائد معايرة مانع بيتا الدقيقة غير واضحة. تهدف هذه الدراسة إلى التحقيق في نتائج المعايرة لمانع بيتا الدقيقة لدى مرضى القلب الحاد المستقر مع انخفاض كسر طرد البطين الأيسر.

طرق البحث: في هذه الدراسة الأترابية الاستعادية، قمنا بتحليل البيانات السريرية من سجل قصور القلب. تم تقسيم مرضى فشل القلب الحاد الذين يعانون من انخفاض كسر طرد البطين الأيسر<٤٠٪ إلى مجموعتين، مجموعة معايرة مانع بيتا الدقيقة ومجموعة موجهة حسب المبادئ التوجيهية. تم تعريف النتائج الأولية على أنها مجموعة من ارتفاع تفاقم قصور القلب، وعدم انتظام ضربات القلب البطينية، والوفيات أثناء دخول المستشفى. وقد اعتبرنا النتائج الثانوية مكونات للنتائج الأولية وكذلك النتائج خلال المتابعة التي تستغرق ٩٠ يوما بعد الخروج من المستشفى، بما في ذلك إعادة التنويم بقصور القلب والوفيات.

النتائج: لم تكن النتائج الأولية بين المجموعتين مختلفة بشكل كبير (١٢.٣٪ مقابل ٢٤.٤٪؛ المخاطر النسبية ٠.٥١). ومع ذلك، فإن معايرة مانع بيتا الدقيقة خفضت عدم انتظام ضربات القلب البطينية (٥.٧٪ مقابل ١٧.٨٪؛ ٠.٣٢). ومعدل إعادة التنويم بقصور القلب (٢.٦٪ مقابل ٧.٥٪؛ ٠.٣٥) ومعدل الوفيات (٤.٣٪ مقابل ٥٪؛ ٠.٨٧)، ولم يتم العثور على اختلاف بشكل ملحوظ في الوفيات بين المجموعتين.

الاستنتاجات: بالمقارنة مع معايرة مانع بيتا حسب توجيهات المبادئ التوجيهية، كانت معايرة مانع بيتا الدقيقة أكثر أمانا في مرضى فشل القلب الحاد المستقر وانخفاض كسر طرد البطين الأيسر الذين تم تثبيت حالتهم سابقا. بالإضافة إلى ذلك، فإن معايرة مانع بيتا الدقيقة قللت بشكل فاعل من أحداث عدم انتظام ضربات القلب البطينية.

الكلمات المفتاحية: المعايرة الدقيقة؛ مانع بيتا؛ فشل القلب الحاد؛ انخفاض الجزء الأيسر من قذف البطين؛ عدم انتظام ضربات القلب البطينية

Abstract

Objectives: A beta-blocker should be initiated in patients with stable acute heart failure (AHF). Beta-blocker titration should be conducted after a two-week interval. The benefits of aggressive beta-blocker titration are still unclear. This study aimed to investigate the aggressive beta-blocker titration outcomes in stabilized AHF patients with low left ventricular ejection fraction (LVEF).

Methods: In this retrospective cohort study, we analysed clinical data from the heart failure (HF) registry. AHF Patients with LVEF <40% were divided into aggressive and guideline-directed beta-blocker titration groups. The composite of worsening HF, ventricular arrhythmia, and mortality during hospitalization were defined as the primary outcomes. We considered secondary outcomes as the components of primary outcomes and also the outcomes during a 90-day follow-up after hospital discharge, including HF readmission and mortality.

Results: The primary outcomes between both groups were not significantly different (12.3% vs 24.4%; relative risk [RR] 0.51; 95% confidence interval [CI] 0.25−1.01; $p = 0.055$). However, the aggressive beta-blocker titration reduced ventricular arrhythmia events (5.7% vs 17.8%;

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RR 0.32; 95% CI 0.12−0.84; $p = 0.016$). The 90-day HF readmission rate (2.6% vs 7.5%; RR 0.35; 95% CI 0.07 −1.66; $p = 0.179$) and mortality rate (4.3% vs 5%; RR 0.87; 95% CI 0.18−4.31; $p = 1.000$) between both groups were not found to be significantly different.

Conclusion: Compared to the guideline-directed beta-blocker titration, the aggressive beta-blocker titration was safe in low LVEF AHF patients who have been previously stabilized. Additionally, aggressive beta-blocker titration effectively reduced ventricular arrhythmia events.

Keywords: Acute heart failure; Aggressive titration; Beta-blocker; Low left ventricular ejection fraction; Ventricular arrhythmia

Introduction

Heart failure (HF) is defined as the complex clinical syndrome that results from any structural or functional impairment of ventricular ejection or filling of blood.[1,2] It is currently estimated that approximately 64.34 million people worldwide have HF.[3] Along with the global population aging, the prevalence of HF continues to increase as time goes by. Among hospitalized HF patients, around 50% of them had HF with reduced ejection fraction (HFrEF).[4] HFrEF is a progressive disease which has various clinical courses. Some HFrEF patients are still clinically stable without any symptoms, while others will develop an acute heart failure (AHF) episode that requires hospital admission.[5,6] Congestion is the most common clinical presentation in AHF patients.[7] Around 17% of patients develop worsening heart failure (WHF) within 1.5 years, on average, after initial HFrEF diagnosis. The two-year mortality rate of HFrEF is 22.5%.[8] However, the administration of neurohormonal antagonists such as beta-blockers, angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), mineralocorticoid receptor antagonists (MRA), and angiotensin receptor−neprilysin inhibitors (ARNI) could improve the prognosis of HFrEF patients.[9] Therefore, several guidelines recommend the neurohormonal-antagonists for the treatment of HFrEF patients.[1,2,10,11]

Several randomized controlled trials (RCTs) revealed that beta-blockers effectively improved survival, reduced hospitalisation,[12−17] and improved the New York Heart Association (NYHA) functional class in HFrEF patients.[14] However, those RCTs included stable chronic HFrEF patients in outpatient settings,[12−17] and not AHF patients who were already stabilized. In AHF patients, a beta-blocker should be initiated cautiously once the patients have been stabilized without congestion and hypoperfusion. According to the guideline, the beta-blocker should be started with a low dose. The beta-blocker dose should be doubled after at least a two-week interval.[2,11] However,

sometimes in daily clinical practice, more aggressive beta-blocker titration is performed by physicians. A previous study demonstrated that intermediate and high doses of beta-blockers provided better ventricular tachyarrhythmias protection.[18] To date, the evidence of the risk or benefit of aggressive beta-blocker dose titration in stabilized AHF patients is not available. Our study aimed to investigate the aggressive beta-blocker titration outcomes in stabilized AHF patients with low left ventricular ejection fraction (LVEF).

Materials and Methods

Study design and participants

We have conducted the HF registry in the Saiful Anwar General Hospital, Malang, Indonesia, since 2017. This registry was approved by the Ethical Committee of Saiful Anwar General Hospital and conformed with the principles outlined in the Declaration of Helsinki. All AHF patients who were hospitalized and who gave their informed consent were registered. All data on the participants' (1) demographic characteristics, (2) AHF signs and symptoms, (3) cardiovascular disease (CVD) risk factors, (4) comorbidities, (5) electrocardiography, (6) chest x-ray, (7) laboratory findings, (8) echocardiography, (9) treatment, and (10) clinical outcomes were obtained. By 2020, we had registered 1, 146 AHF patients.

In this retrospective cohort study, we evaluated the effect of differential titrations of beta-blockers among patients, using data from the HF registry. The inclusion criteria included (1) AHF patients with NYHA functional class IV, (2) aged ≥18 years old, and (3) with an LVEF of <40%. Patients with one or more the following criteria: (1) not received beta-blocker during hospitalization; (2) contraindications for beta-blocker administration such as asthma, second or third-degree atrioventricular (AV) block, critical limb ischemia, or known allergic reaction; (3) incomplete data; (4) loss to follow-up; or (5) stage 4 or 5 chronic kidney disease (CKD) were excluded from the data analysis. In the end, 167 patients were included in the data analysis.

Exposures and outcomes

The exposure in this research was the way beta-blocker titration was conducted. Patients were divided into two groups: the aggressive beta-blocker titration group and the guideline-directed beta-blocker titration group. Aggressive beta-blocker titration is defined as the doubling of the beta-blocker dose that was conducted earlier than what is recommended in the guidelines. In this group, the doubling of the beta-blocker dose was performed at less than two weeks (14 days). While in the guideline-directed beta-blocker titration group, the doubling of the beta-blocker dose was conducted according to the guideline recommendations[1,2,11] − after a two-week interval, at least. Beta-blocker initiation (for the patients without previous beta-blocker medication) and/or beta-blocker up-titration (for the patients with or without previous beta-blocker medication) were conducted during hospitalization, when the patients had already been stabilized. In this study, we used bisoprolol. For patients without a previous

history of beta-blocker medication, the initial bisoprolol dose was 1.25 mg.

The primary outcome of this retrospective cohort study was a composite of worsening HF (acute pulmonary edema or cardiogenic shock), ventricular arrhythmia (documented ventricular fibrillation or ventricular tachycardia), and mortality during hospitalization. Data on the primary outcomes were available in the HF registry database. Secondary outcomes were all components of the primary outcomes and outcomes during a 90-day follow-up after hospital discharge, including HF readmission and mortality. The phone calls were conducted to obtain data about the 90-day HF readmission and mortality.

Data analysis

The data analysis process was conducted using the IBM Statistical Package for Social Science (SPSS version 25.0). Categorical data were presented using numbers and percentages. The mean and standard deviation (SD) were used to present normally distributed continuous data, while the median and interquartile range (IQR; 25th percentile [0.25 quantile] and the 75th percentile [0.75 quantile]) were used to present non-normally distributed continuous data. We used the Kolmogorov−Smirnov test and the Shapiro−Wilk test to assess continuous data normality. The comparison between two continuous variables was tested using the independent t-test for normally distributed data and the Mann Whitney test for not normally distributed data. The comparison between

two categorical variables was tested using the Chi-squared test or Fisher's exact test. The primary and secondary outcomes were calculated along with the relative risks (RR) and associated 95% confidence intervals (95% CI). The 90-day HF readmission and mortality also were analysed using the Kaplan−Meier curve. The comparison of the two survival curves was compared using the Log-rank criterion. In all analyses, a p-value of <0.05 was considered statistically significant.

Results

Baseline characteristics of patients

Out of the 1146 AHF patients registered in the HF registry starting from 2017, 285 patients had LVEF $<40\%$. We excluded 118 patients because they had one or more of the following exclusion criteria: (1) loss to follow-up (n = 62); (2) not received beta-blocker during hospitalization (n = 21); (3) incomplete data (n = 25); and (4) stage 4 or 5 CKD (n = 10). Around 167 AHF with LVEF $<40\%$ patients received beta-blockers during hospitalization. A total 122 (73.1%) patients received aggressive beta-blocker titration and 45 (26.9%) patients received guideline-directed beta-blocker titration. The study flowchart is summarized in Figure 1.

Male patients comprised 67.7% of the participants included in this retrospective study. Prior HF hospitalization was experienced by 36.5% of patients. The most common
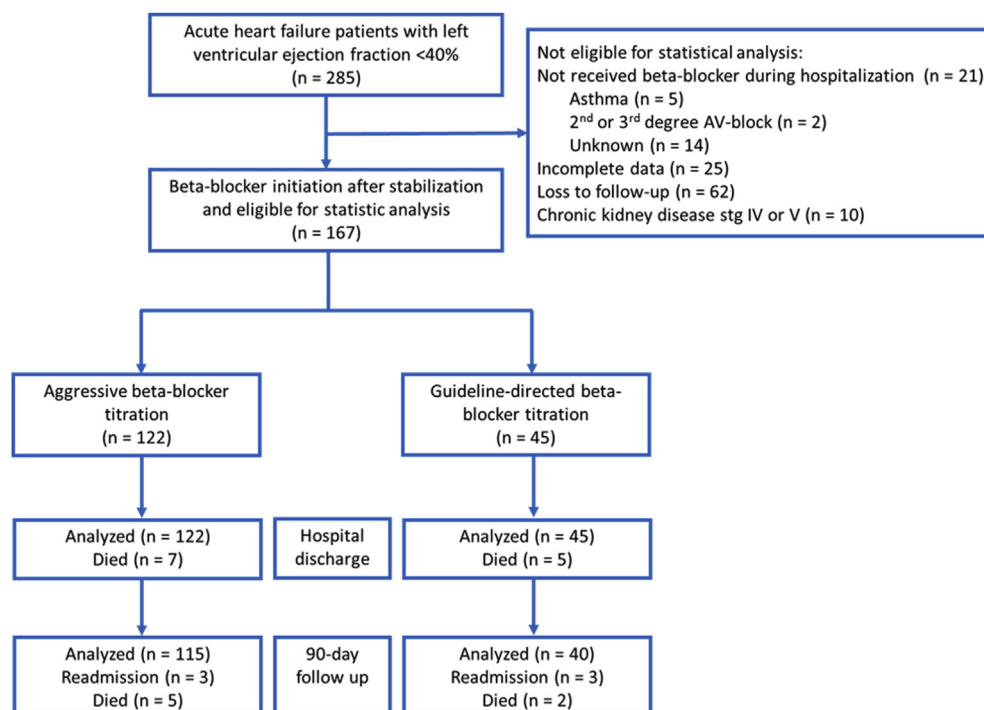

Figure 1: Study flowchart.

Table 1: Baseline characteristic at hospital admission.

Parameters	Aggressive beta-blocker titration (n = 122)	Guideline directed beta-blocker titration (n = 45)	p-value
Age, years	57 (50 - 63)	57 (49.5 - 64)	0.773[#]
Sex, male	81 (66.4)	32 (71.1)	0.563*
Precipitating factors			
ACS	42 (34.4)	18 (40)	0.505*
Arrhythmia	9 (7.4)	3 (6.7)	0.875**
Infection	22 (18.0)	11 (24.4)	0.356*
Poor compliance	29 (23.8)	7 (15.6)	0.295*
Others	20 (16.4)	6 (13.3)	0.628*
Prior HF hospitalization	41 (33.6)	20 (44.4)	0.197*
Comorbid conditions			
Current smoker	23 (18.9)	10 (22.2)	0.628*
Diabetes	41 (33.6)	12 (26.7)	0.393*
Hypertension	41 (33.6)	18 (40.0)	0.443*
Ischemic heart disease	85 (69.7)	32 (71.1)	0.857*
Atrial fibrillation	14 (11.5)	2 (4.4)	0.240**
Stroke or TIA	8 (6.6)	3 (6.7)	1.000**
Previous use of medications			
ACEI or ARB	24 (19.7)	6 (13.3)	0.344*
Beta-blocker	61 (50)	15 (33.3)	0.055*
MRA	38 (31.1)	10 (22.2)	0.258*
Diuretic	53 (43.4)	17 (37.8)	0.510*
SBP, mmHg	125.0 (110.0 - 140.0)	138 (105.0 − 150.0)	0.371[#]
DBP, mmHg	80.0 (70.0 - 90.0)	80.0 (70.0 - 90.0)	0.516*
Heart rate, bpm	88.0 (75.8 -100.0)	98.0 (83.0 -112.0)	0.025[#]
Creatinine level, mg/dL	1.2 (1.0 - 1.6)	1.2 (0.9 - 1.5)	0.350[#]
eGFR (MDRD), mL/min/1.73m^2	59.7 (45.8 - 81.7)	64.9 (47.5 - 87.8)	0.409[#]
Sodium level, mEq/L	137.0 (134.0 - 139.0)	136.0 (130.0 - 139.0)	0.292[#]
Potassium level, mEq/L	3.9 ± 0.6	3.8 ± 0.7	0.315[##]
Ejection fraction, %	28.6 ± 5.8	28.0 ± 6.2	0.586[##]
Length of stay, days	5.5 (4.0 - 7.0)	5.0 (5.0 - 7.0)	0.571[#]

Values are expressed as mean ± SD, median (IQR), or n (%). ACS = acute coronary syndrome; ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HF = heart failure; IQR = interquartile range; MDRD = modification of diet in renal disease; MRA = mineralocorticoid receptor antagonists; n = number; SBP = systolic blood pressure; SD = standard deviation; TIA = transient ischemic attack.

[#] Mann-Whitney test
[##] Independent t-test
* Chi-squared test
** Fisher's exact test.

precipitating factor was acute coronary syndrome (ACS), followed by poor compliance with HF medications and infection. The most common etiology and comorbid conditions among the study participants was ischemic heart disease. Some patients had received previous HF treatment. Generally, the baseline characteristics of patients at hospital admission between both groups were not significantly different. At hospital admission heart rate in aggressive beta-blocker titration groups was lower (88.0 [75.8−100.0] bpm vs 136.0 [130.0−139.0] bpm; p = 0.025). The baseline characteristics of patients at hospital admission are summarized in Table 1. During hospitalization, the HF drug regimen between the aggressive beta-blocker titration group and the guideline-directed beta-blocker titration group was not significantly different. All patients were treated using ACEI/ARB and diuretic. The use of mineralocorticoid receptor antagonist, nitrate, and digoxin were 56.9%, 35.3%, and

13.2%, respectively. The treatment during hospitalization is summarized in Table 2. The highest bisoprolol dose during hospitalization was 5 mg daily.

In both groups, baseline characteristics were generally the same except for heart rate during hospital admission. Treatment between the two groups also did not differ significantly. We did not see any potential confounders. Therefore, we did not conduct a data adjustment.

Primary outcome

We wanted to know the overall benefit of aggressive beta-blocker titration in stabilized AHF patients. Therefore, our primary outcome was the composite of worsening HF (acute pulmonary edema or cardiogenic shock), ventricular arrhythmia (documented ventricular fibrillation or ventricular tachycardia), and mortality

Table 2: Treatment during hospitalization.

Parameters	Aggressive beta-blocker titration (n = 122)	Guideline directed beta-blocker titration (n = 45)	p-value
ACEI or ARB	122 (100.0)	45 (100.0)	- *
MRA	68 (55.7)	27 (60.0)	0.622*
Diuretic	122 (100.0)	45 (100.0)	- *
Nitrate	42 (34.4)	17 (37.8)	0.688*
Digoxin	19 (15.6)	3 (6.7)	0.196**

Values are expressed as n (%). ACEI = angiotensin-converting enzyme inhibitors, ARB = angiotensin receptor blockers, MRA = mineralocorticoid receptor antagonists; n = number.
 * Chi-squared test.
 ** Fisher's exact test.

Table 3: Clinical outcomes during hospitalization.

Parameters	Aggressive beta- blocker titration (n = 122)	Guideline directed beta-blocker titration (n = 45)	Relative Risk (95% CI)	p-value
Composite endpoint	15 (12.3)	11 (24.4)	0.51 (0.25−1.01)	0.055*
Worsening HF	11 (9.0)	5 (11.1)	0.81 (0.30−2.21)	0.768*
Ventricular arrhythmia	7 (5.7)	8 (17.8)	0.32 (0.12−0.84)	0.016*
Mortality	7 (5.7)	5 (11.1)	0.52 (0.17−1.54)	0.309*

Values are expressed as n (%). HF = heart failure; n = number.
 * Chi-squared test.

Table 4: Clinical outcomes during 90-day follow-up after hospital discharge.

Parameters	Aggressive beta- blocker titration (n = 115)	Guideline directed beta-blocker titration (n = 40)	Relative Risk (95% CI)	p-value
HF readmission	3 (2.6)	3 (7.5)	0.35 (0.07−1.66)	0.179**
Mortality	5 (4.3)	2 (5)	0.87 (0.18−4.31)	1.000**

Values are expressed as n (%). HF = heart failure; n = number.
 ** Fisher's exact test.

during hospitalization. Between both groups, the primary outcomes were different though not statistically different (12.3% vs 24.4%; relative risk [RR] 0.51; 95% confidence interval [CI] 0.25−1.01; p = 0.055) (Table 3).

Secondary outcomes

The incidence of worsening HF (9.0% vs 11.1%; RR 0.81; 95% CI 0.30−2.21; p = 0.768) and mortality rate (5.7% vs 11.1%; RR 0.52; 95% CI 0.17−1.54; p = 0.309) during hospitalization between both groups were not different significantly. However, the aggressive beta-blocker titration reduced ventricular arrhythmia events (5.7% vs 17.8%; RR 0.32; 95% CI 0.12−0.84; p = 0.016) (Table 3). We also assessed the outcomes in the 90 days following the participant's hospital discharge. The 90-day HF readmission (2.6% vs 7.5%; RR 0.35; 95% CI 0.07−1.66; p = 0.179) and mortality rate (4.3% vs 5%; RR 0.87; 95% CI 0.18−4.31; p = 1.000) between the aggressive titration group and the guideline-directed titration group were not significantly different (Table 4). The Kaplan−Meier curve analysis also revealed a similar result − that there was no significant different in 90-day of HF readmission and mortality free survival (Figure 2).
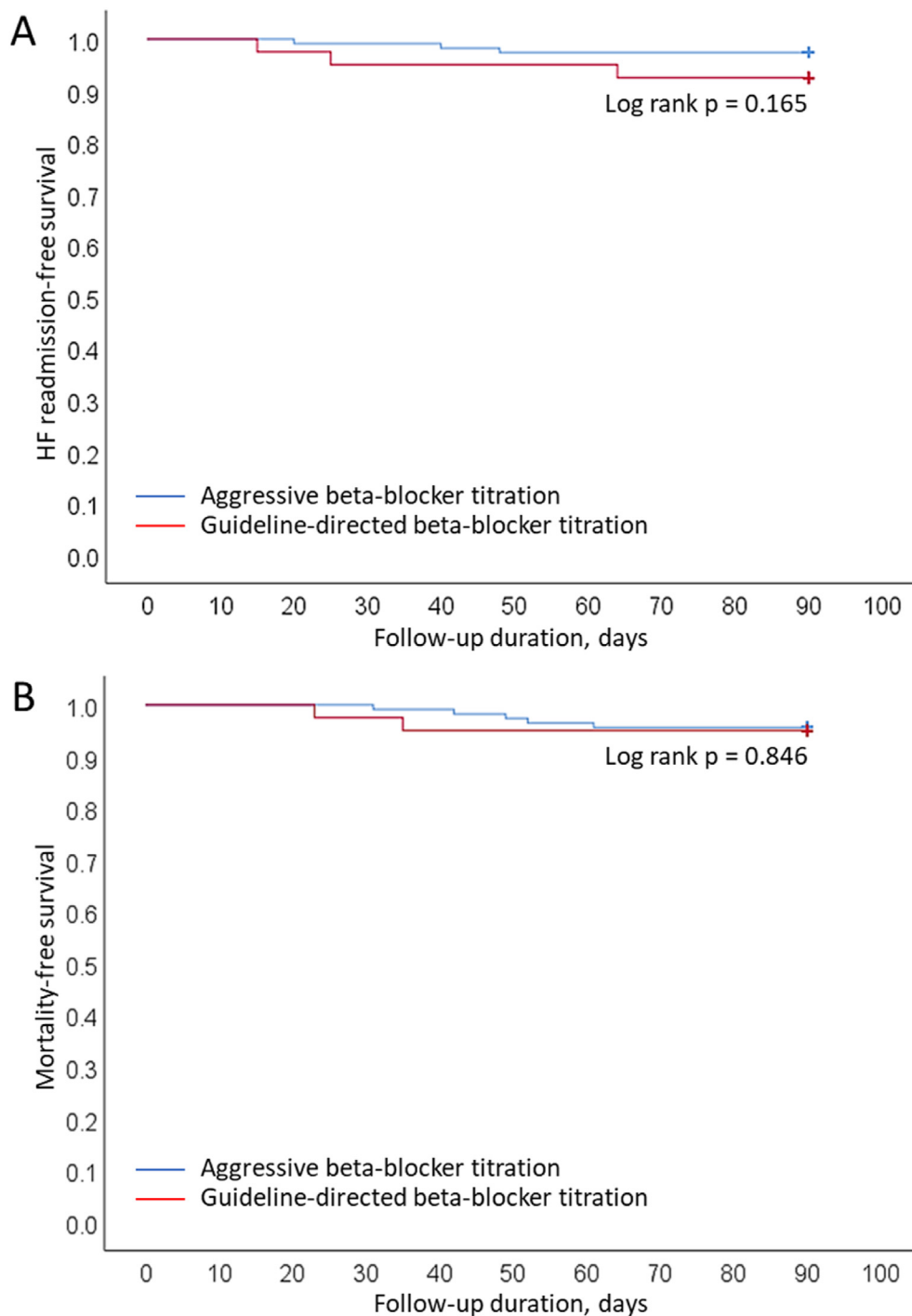
Figure 2: Kaplan Meier survival curves for (A) HF readmission-free survival and (B) mortality-free survival during the 90-day follow up period. HF = heart failure.

Discussion

Compared to guideline-directed beta-blocker titration, aggressive beta-blocker titration in stabilized AHF patients demonstrated a similar composite of worsening HF (acute pulmonary edema or cardiogenic shock), ventricular arrhythmia (documented ventricular fibrillation or ventricular tachycardia), and mortality during hospitalization. Interestingly, in the subgroup analysis, we found that aggressive beta-blocker titration effectively reduced ventricular arrhythmias incidence. During the 90-day follow-up period, both groups revealed no significantly difference with regard to readmission and mortality rate.

Generally, HF is defined as a clinical syndrome with symptoms and signs caused by the inability of the ventricle to pump at a normal pressure because of functional or

structural heart disease. HF with LVEF <40% is classified as HFrEF.[1,2,10,11] The understanding of the pathophysiological concept of HF has evolved. In the past, HF was reported to be due to myocardial injury and/or hemodynamic disturbances that included increased preload, increased afterload, and impaired contractility.[6] However, in recent decades, there has been evidence that the neurohormonal system has a significant role in HF pathophysiology. The neurohormonal systems involved in response to HFrEF are the sympathetic nervous system (SNS), renin-angiotensin-aldosterone system (RAAS), and arginine vasopressin system, which have the primary role of vasoconstrictor, antinatriuretic, and antidiuretic, and lead to the ventricular remodelling process. Ventricular remodelling strongly correlates with the development and progression of ventricular dysfunction, arrhythmia, and bad prognosis in HF patients. Another neurohormonal system includes the natriuretic peptide system (NPS), nitric oxide system, prostaglandin system, and dopaminergic system, which plays the central role of vasodilator and natriuretic.[19−24] For HFeEF patients, several guidelines have recommended drugs which modify the neurohormonal system, such as ACEI, ARB, beta-blocker, MRA, or ARNI, because they can improve the prognosis.[1,2,10,11] So far, RCTs that support the benefits of beta-blocker initiation and up-titration in HFrEF patients have been performed in stable chronic heart failure patients in outpatient clinical settings.[12−17]

The initiation and/or up-titration of beta-blockers in a recently stabilized AHF patient with low LVEF is a double-edged sword. Because of its negative chronotropic and inotropic nature, hemodynamic deterioration is always possible during beta-blocker initiation or up-titration.[25,26] The previous studies reported that the beta-blocker discontinuation was closely correlated with increased mortality than the beta-blocker continuation.[27−30] In this study, approximately 45.5% of the patients had received beta-blocker before they suffered from AHF episodes with NYHA functional class IV. In this study, all patients received bisoprolol because it is a beta-blocker that has been proven to be beneficial for HFrEF patients and is included in the universal health coverage system in Indonesia. Treatment of congestion with diuretics and/or vasodilators was the main priority.[31,32] Therefore, all patients in this study received diuretic and ACEI/ARB, as recommended by the guidelines.[1,2,10,11] Some cardiovascular physicians decided to stop giving beta-blockers while the patient was still in congestion and then initiated a low dose beta-blocker when the congestion was resolved and the patient was hemodynamically stable. In contrast, some other cardiovascular physicians chose to continue with beta-blockers. The decision to up-titrate beta-blocker dose depended on the cardiovascular physician, according to each patient's clinical conditions.

We wanted to compare aggressive and guideline-directed beta-blocker titration in stabilized AHF patients with LVEF <40% through this retrospective study. Most RCTs involving beta-blockers for HFREF used a two-week interval, at least, before increasing or doubling the beta-blocker dose.[12−16] The study of the effects of nebivolol intervention on outcomes and rehospitalization in seniors with heart failure (SENIORS) was the only RCT that used one-to-two-week interval beta-blocker dose up-titration.[17]

However, again, in those RCTs, beta-blocker dose titration was conducted in an outpatient setting. Our study revealed no significant difference in the primary outcome, which included the composite of worsening HF (acute pulmonary edema or cardiogenic shock), ventricular arrhythmia (documented ventricular fibrillation or ventricular tachycardia), and mortality during hospitalization in both groups. The incidence of worsening HF and mortality during hospitalization were also not significantly different. The possible explanations are that (1) all patients received vasodilator (ACEI or ARB) dan diuretic (furosemide), and (2) all patients had been already stabilized and were free from congestion during beta-blocker initiation or up-titration. Our study also showed that the 90-day HF readmission rate and mortality rate between both groups were not significantly different. Those results were probably because (1) all patients received ACEI/ARB and beta-blockers according to the guideline recommendation; (2) all patients were discharged without congestion; and (3) the biggest challenge was beta-blocker titration during hospitalization when the AHF patient had been recently stabilized during hospitalization, not in the outpatient setting in a stable condition.

Myocardial remodelling and fibrosis in HFrEF are well known as the source of ventricular arrhythmia.[33,34] Grupo de estudio de la sobrevida en la insuficiencia cardiaca en Argentina (GESICA) trial showed that non sustained ventricular tachycardia was the independent predictor for increased sudden death and overall mortality in patients with left ventricular systolic dysfunction.[35] The result from the antiarrhythmics versus implantable defibrillators (AVID) trial revealed that beta-blockers have independently improved the survival rate in HFrEF patients who suffered from the episode of ventricular fibrillation or symptomatic ventricular tachycardia and did not receive the specific antiarrhythmic drugs.[36] However, our study demonstrated the important lesson that aggressive beta-blocker titration decreased the incidence of ventricular arrhythmia during hospitalization in HFrEF patients. The antiarrhythmic properties of beta-blockers are related to their ability to protect the heart from catecholamine over-stimulation by inhibiting catecholamine binding to beta-adrenergic receptors on myocardial cells.[33,34,37] Through aggressive beta-blocker titration, adequate blood/plasma beta-blocker concentrations will be rapidly achieved so that the optimum therapeutic effect occurs immediately.

In this study, there was no loss to follow-up because, since the beginning, before conducting data analysis, we had excluded patients who had lost to follow-up and were not completely registered. To the best of our knowledge, our study is the only study that provides data on the outcomes between aggressive and guideline-directed beta-blocker titration in AHF patients who are already stabilized. However, several drawbacks were found in our study. First, as in the other observational studies, confounders could not be avoided totally, especially for the treatment regimen given by the cardiovascular physicians and the several factors that lead to hospital readmission and mortality during the 90-day follow-up after hospital discharge. Second, there was a small number of study participants. Third, our study follow-up period was shorter than that of earlier studies.[12−17,36] Fourth, the drug regimen and dose during the 90-day follow-up period

were not recorded; this was our major limitation. Due to these drawbacks, an RCT with better design, a larger number of participants, and longer follow-up is required.

Conclusion

In conclusion, aggressive beta-blocker titration was safe for AHF patients with low LVEF who have been previously stabilized with diuretic and vasodilator (ACEI/ARB). Aggressive beta-blocker titration effectively reduced ventricular arrhythmia in stabilized low LVEF AHF patients. Our study provided preliminary data on the safety and efficacy profile of aggressive beta-blocker titration in stabilized AHF patients with low LVEF.

Recommendations

Aggressive beta-blocker titration may be considered in stabilized AHF patients with low LVEF. Resolving congestion with adequate diuretic and vasodilator treatment is required before aggressive beta-blocker titration in this population.

Source of funding

Conflict of interest

The authors have no conflict of interest to declare.

Ethical approval

Ethical approval for heart failure (HF) registry was obtained from the Ethical Committee of Saiful Anwar General Hospital, Malang, Indonesia (No: 400/188/K.3/302/2017), dated November 29th 2017.

Authors contributions

Idea/concept was by YW; Design was by YW/MSR; Control/supervision by MSR; Data collection/processing by YW/DS/IJA; Analysis/interpretation by YW/DS/IJA; Literature review by YW/MSR/DS/IJA; Writing the article was done by YW/MSR; Critical review by YW/MSR. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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References

1. Yancy CW, Jessup M, Bozkurt B. 2013 ACCF/AHA guideline for the management of heart failure. **J Am Coll Cardiol 2013**; 62(16): e147–e239. https://doi.org/10.1016/j.jacc.2013.05.019.

2. Ponikowski P, Voors AA, Anker SD. 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 Heart J 2016**; 37(27): 2129–2200. https://doi.org/10.1093/eurheartj/ehw128.

3. Lippi G, Sanchis-Gomar F. Global epidemiology and future trends of heart failure. **AME Med J 2020**; 5(15): 1–6. https://doi.org/10.21037/amj.2020.03.03.

4. Virani SS, Alonso A, Benjamin EJ, et al. Heart disease and stroke statistics—2020 update: a report from the American heart association. **Circulation 2020**; 141(9). https://doi.org/10.1161/CIR.0000000000000757.

5. Butler J, Djatche LM, Sawhney B, et al. Clinical and economic burden of chronic heart failure and reduced ejection fraction following a worsening heart failure event. **Adv Ther 2020**; 37(9): 4015–4032. https://doi.org/10.1007/s12325-020-01456-1.

6. Arrigo M, Jessup M, Mullens W, et al. Acute heart failure. **Nat Rev Dis Primer 2020**; 6(16): 62–69. https://doi.org/10.1038/s41572-020-0151-7.

7. Lala A, McNulty SE, Mentz RJ, et al. Relief and recurrence of congestion during and after hospitalization for acute heart failure: insights from diuretic optimization strategy evaluation in acute decompensated heart failure (DOSE-AHF) and cardiorenal rescue study in acute decompensated heart failure (CARESS-HF). **Circ Heart Fail 2015**; 8(4): 741–748. https://doi.org/10.1161/CIRCHEARTFAILURE.114.001957.

8. Butler J, Yang M, Manzi MA, et al. Clinical course of patients with worsening heart failure with reduced ejection fraction. **J Am Coll Cardiol 2019**; 73(8): 935–944. https://doi.org/10.1016/j.jacc.2018.11.049.

9. Burnett H, Earley A, Voors AA, et al. Thirty years of evidence on the efficacy of drug treatments for chronic heart failure with reduced ejection fraction: a network meta-analysis. **Circ Heart Fail 2017**; 10(1):e003529. https://doi.org/10.1161/CIRCHEARTFAILURE.116.003529.

10. Yancy CW, Jessup Mariell, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the€Management of heart failure. **J Am Coll Cardiol 2017**; 70(6): 776–803. https://doi.org/10.1016/j.jacc.2017.04.025.

11. McDonald MA, Abrams H, Chan M, et al. 2017 comprehensive update of the Canadian cardiovascular society guidelines for the management of heart failure. **Can J Cardiol 2017**; 33: 1342–1433. https://doi.org/10.1016/j.cjca.2017.08.022.

12. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: metoprolol CR/XL randomised intervention trial in congestive heart failure (MERIT-HF). **Lancet 1999**; 353(9169): 2001–2007. https://doi.org/10.1016/S0140-6736(99)04440-2.

13. CIBIS-II Investigators and Committees. The cardiac insufficiency bisoprolol study II (CIBIS-II): a randomised trial. **Lancet 1999**; 353(9146): 9–13. https://doi.org/10.1016/S0140-6736(98)11181-9.

14. Hjalmarson Å, Goldstein S, Fagerberg B. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure the metoprolol CR/XL randomized intervention trial in congestive heart failure (MERIT-HF). **J Am Med Assoc 2000**; 283(10): 1295–1302. https://doi.org/10.1001/jama.283.10.1295.

15. Packer M, Krum H, Castaigne A. Effect of carvedilol on survival in severe chronic heart failure. **N Engl J Med 2001**; 344(22): 1651–1658. https://doi.org/10.1056/NEJM200105313442201.

16. Packer M, Fowler MB, Roecker EB, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. **Circulation 2002**; 106(17): 2194–2199. https://doi.org/10.1161/01.CIR.0000035653.72855.BF.

17. Flather MD, Shibata MC, Coats AJS, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). **Eur Heart J 2005**; 26(3): 215−225. https://doi.org/10.1093/eurheartj/ehi115.

18. Ruwald A-C, Kutyifa V, Ruwald MH, et al. The association between biventricular pacing and cardiac resynchronization therapy-defibrillator efficacy when compared with implantable cardioverter defibrillator on outcomes and reverse remodelling. **Eur Heart J 2015**; 36(7): 440−448. https://doi.org/10.1093/eurheartj/ehu294.

19. Hartupee J, Mann DL. Neurohormonal activation in heart failure with reduced ejection fraction. **Nat Rev Cardiol 2017**; 14(1): 30−38. https://doi.org/10.1038/nrcardio.2016.163.

20. Goldsmith SR. Arginine vasopressin antagonism in heart failure: current status and possible new directions. **J Cardiol 2019**; 74(1): 49−52. https://doi.org/10.1016/j.jjcc.2019.03.001.

21. Polónia J, Gonçalves FR. The historical evolution of knowledge of the involvement of neurohormonal systems in the pathophysiology and treatment of heart failure. **Rev Port Cardiol Engl Ed 2019**; 38(12): 883−895. https://doi.org/10.1016/j.repce.2020.02.006.

22. Borovac JA, D'Amario D, Bozic J, Glavas D. Sympathetic nervous system activation and heart failure: current state of evidence and the pathophysiology in the light of novel biomarkers. **World J Cardiol 2020**; 12(8): 373−408. https://doi.org/10.4330/wjc.v12.i8.373.

23. Pugliese NR, Masi S, Taddei S. The renin-angiotensin-aldosterone system: a crossroad from arterial hypertension to heart failure. **Heart Fail Rev 2020**; 25(1): 31−42. https://doi.org/10.1007/s10741-019-09855-5.

24. Azevedo PS, Polegato BF, Minicucci MF, Paiva SAR, Zornoff LAM. Cardiac remodeling: concepts, clinical impact, pathophysiological mechanisms and pharmacologic treatment. **Arq Bras Cardiol 2016**; 106(1): 62−69. https://doi.org/10.5935/abc.20160005.

25. Funck-Brentano C. Beta-blockade in CHF: from contraindication to indication. **Eur Heart J Suppl 2006**; 8(suppl_C): C19−C27. https://doi.org/10.1093/eurheartj/sul010.

26. Bhatt AS, DeVore AD, DeWald TA, Swedberg K, Mentz RJ. Achieving a maximally tolerated β-blocker dose in heart failure patients. **J Am Coll Cardiol 2017**; 69(20): 2542−2550. https://doi.org/10.1016/j.jacc.2017.03.563.

27. Metra M, Torp-Pedersen C, Cleland JGF, et al. Should beta-blocker therapy be reduced or withdrawn after an episode of decompensated heart failure? Results from COMET. **Eur J Heart Fail 2007**; 9(9): 901−909. https://doi.org/10.1016/j.ejheart.2007.05.011.

28. Fonarow GC, Abraham WT, Albert NM, et al. Influence of beta-blocker continuation or withdrawal on outcomes in patients hospitalized with heart failure. **J Am Coll Cardiol 2008**; 52(3): 190−199. https://doi.org/10.1016/j.jacc.2008.03.048.

29. Orso F, Baldasseroni S, Fabbri G, et al. Role of beta-blockers in patients admitted for worsening heart failure in a real world setting: data from the Italian Survey on Acute Heart Failure†. **Eur J Heart Fail 2009**; 11(1): 77−84. https://doi.org/10.1093/eurjhf/hfn008.

30. Abi Khalil C, Sulaiman K, Mahfoud Z, et al. Non-withdrawal of beta blockers in acute decompensated chronic and de novo heart failure with reduced ejection fraction in a prospective multicentre study of patients with acute heart failure in the Middle East. **BMJ Open 2017**; 7(7):e014915. https://doi.org/10.1136/bmjopen-2016-014915.

31. Mebazaa A, Yilmaz MB, Levy P, et al. Recommendations on pre-hospital and early hospital management of acute heart failure: a consensus paper from the heart failure association of the European society of cardiology, the European society of emergency medicine and the society of academic emergency medicine − short version. **Eur Heart J 2015**; 36(30): 1958−1966. https://doi.org/10.1093/eurheartj/ehv066.

32. Mebazaa A, Tolppanen H, Mueller C, et al. Acute heart failure and cardiogenic shock: a multidisciplinary practical guidance. **Intensive Care Med 2016**; 42(2): 147−163. https://doi.org/10.1007/s00134-015-4041-5.

33. Massare J, Berry JM, Luo X, et al. Diminished cardiac fibrosis in heart failure is associated with altered ventricular arrhythmia phenotype. **J Cardiovasc Electrophysiol 2010**; 21(9): 1031−1037. https://doi.org/10.1111/j.1540-8167.2010.01736.x.

34. Grandi E, Ripplinger CM. Antiarrhythmic mechanisms of beta blocker therapy. **Pharmacol Res 2019**; 146: 104274. https://doi.org/10.1016/j.phrs.2019.104274.

35. Doval HC, Nul DR, Grancelli HO, et al. Nonsustained ventricular tachycardia in severe heart failure: independent marker of increased mortality due to sudden death. **Circulation 1996**; 94(12): 3198−3203. https://doi.org/10.1161/01.CIR.94.12.3198.

36. Exner DV, Reiffel JA, Epstein AE, et al. Beta-blocker use and survival in patients with ventricular fibrillation or symptomatic ventricular tachycardia: the antiarrhythmics versus implantable defibrillators (AVID) trial. **J Am Coll Cardiol 1999**; 34(2): 325−333. https://doi.org/10.1016/S0735-1097(99)00234-X.

37. Lymperopoulos A, Rengo G, Koch WJ. Adrenergic nervous system in heart failure: pathophysiology and therapy. **Circ Res 2013**; 113(6): 739−753. https://doi.org/10.1161/CIRCRESAHA.113.300308.