Adherence to the European Society of Cardiology guidelines for the treatment of chronic heart failure

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Abstract. Heart failure is a tremendous health problem with significant morbidity and mortality. The treatment of heart failure should be applied appropriately to improve the successful management of patients. This study aims to evaluate the adherence to European Society of Cardiology (ESC) guidelines for the treatment of chronic heart failure and to determine factors associated with guideline adherence. This study is an observational study comprising 97 patients with chronic heart failure with reduced ejection fraction. The guideline adherence was assessed by the use of guideline adherence indicator (GAI), which consider GAI-3 or GAI-5, by calculating the proportion of recommended drugs was prescribed divided by a number of drugs indicated according to the ESC guidelines, in the absence of contraindications. The results showed the use of each indicated drugs were angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (78.4%), beta-blockers (61.9%), mineralocorticoid receptor antagonists (61.9%), diuretics (89.7%), and digitalis (26.8%). Furthermore, the predominant categories of GAI-3 and GAI-5 were moderate. This study demonstrates that the adherence to ESC guidelines for the treatment of chronic heart failure still needs to be improved compared to recent studies. Also, age, etiology of heart failure and comorbidity were associated factors that influence the implementation of ESC guidelines.

1. Introduction
The development of heart failure can result from any cardiac disease that leads to an alteration in left ventricular structure or function, and this is the final and most harmful manifestation.[1,2] The worldwide incidence and prevalence rates of heart failure are high, and they continue to increase with age.[2–4] Moreover, the 5-year survival rate of heart failure is only 35%.[5]

Comprehensive knowledge and experience of the current guidelines are required for the management of heart failure.[6] The purposes of heart failure management are to relieve symptoms and signs (e.g., edema), prevent hospital admission, and improve survival.[7] The management of heart failure should also be performed with appropriate procedures in order to improve the successful treatment of patients.[8]

Studies reported that adherence to the treatment guidelines could improve clinical outcome in patients with heart failure.[9–11] However, adequate management in heart failure patients has not been achieved yet, despite the availability of comprehensive guidelines.[6]

The European Society of Cardiology (ESC) [7] recommends therapy that is necessary to be prescribed, that is angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker
(ARB), beta-blocker, and mineralocorticoid receptor antagonist (MRA) for heart failure management. A diuretic can also be used in conjunction relieve symptoms and signs of congestion.[7] Also, there are certain factors that may influence the treatment of heart failure.[10]

The primary objective of this study is to evaluate the adherence to ESC guidelines for the treatment of chronic heart failure and to determine factors associated with guideline adherence.

2. Materials and Methods

2.1. Study design and study population

This study is an observational study that comprising 97 patients presenting with chronic heart failure with reduced ejection fraction (also known as systolic heart failure) who visited Cardiology Clinic at Haji Adam Malik General Hospital from January 2013 to June 2014. Data were from hospital medical records.

The diagnosis of chronic heart failure was by anamnesis; clinical examination of symptoms and signs of heart failure; echocardiography examination for evaluation of reduced left ventricular ejection fraction with a cut-off value of 40%.

Inclusion criteria were: (i) age over 18 years, (ii) outpatients with chronic heart failure, (iii) left ventricular ejection fraction ≤ 40%. We excluded patients presenting with asthma or symptomatic hypotension (systolic blood pressure < 90 mmHg).

Guideline adherence indicator (GAI) was used, based on the MAHLER survey as described by Komajda et al. [9], to evaluate physician adherence to the ESC guidelines for the treatment of chronic heart failure with reduced ejection fraction. The GAI defined adherence as the proportion of recommended drugs was divided by some medications indicated (range from 0-100%) according to the ESC guidelines, in the absence of contraindications.[7,9] Asthma was considered contraindication for beta-blocker, whereas bradycardia < 50 beats/minute was considered contraindication for both, beta-blockers and digitalis.

The GAI specified into two different groups. GAI-3 consists of ACE-I or ARB, beta-blocker, and MRA, considering the substantial evidence to improve clinical outcome. The GAI-5, in addition to the three pharmacological classes, considered the use of diuretics and digitalis, which predominantly targets improving symptoms. Furthermore, GAI-3 was three categories; these were low adherence (0-33%), moderate adherence (50-67%), and high adherence (100%). In the same way, GAI-5 was three categories; these were low adherence (0-20%), moderate adherence (40-60%), and high adherence (80-100%).

2.2. Statistical analyses

Statistical analyses were by using SPSS (version 22.0, IBM, USA). Continuous variables were as mean ± standard deviation (SD) or median and interquartile range (IQR). Categorical variables were absolute numbers and percentages. Univariate analyses were performed using demographic characteristics, clinical characteristics, and pharmacological characteristics. Bivariate analyses were performed using Chi-square test or Fisher’s exact test, One-way ANOVA test, and Kruskal-Wallis test. A two-sided p-value of < 0.05 was considered statistically significant.

3. Results

The characteristics of patients are in Table 1. The data of 97 consecutive heart failure patients were predominantly male (80.4%), with an average age of the study population was 55.6 years (range of 19-80 years). In more than half of the patients (67%), coronary artery disease was the most common etiology of heart failure, followed by hypertensive heart disease (47.4%). The majority of patients had symptom experience of dyspnea (89.7%). The median left ventricular ejection fraction (LVEF) of the patients was 34%, while the lowest LVEF was 14.8%. Hypertension and atrial fibrillation were predominant-comorbidities of the study population with percentage of 20.6% and 19.6%, respectively.
Table 1. Baseline characteristics of patients.

| Variables                        | Population (n = 97) |
|----------------------------------|---------------------|
| Age (years), mean±SD             | 55.6 ± 11.8         |
| Gender                           |                     |
| Male, n (%)                      | 78 (80.4)           |
| Etiology                         |                     |
| Coronary artery disease (CAD)    | 65 (67)             |
| Hypertensive heart disease (HHD) | 46 (47.4)           |
| Othersa                          | 24 (24.7)           |
| Comorbidity, n (%)               |                     |
| Atrial fibrillation              | 19 (19.6)           |
| Hypertension                     | 20 (20.6)           |
| Othersb                          | 30 (30.9)           |
| Symptom and sign, n (%)          |                     |
| Dyspnea                          | 87 (89.7)           |
| Paroxysmal nocturnal dyspnea     | 31 (32)             |
| Othersc                          | 75 (77.3)           |
| Echocardiography LVEF(%, median (IQR)) | 34 (14.8 – 40) |

aValvular heart disease (n = 15), cardiomyopathy (n = 7), congenital heart disease (n = 2).
bSupraventricular tachycardia (n = 1), history of stroke (n = 3), pericardial effusion (n = 3), left ventricular thrombus (n =2), chronic obstructive pulmonary disease (n = 5), acute kidney injury/chronic kidney disease (n = 5), congestive hepatopathy (n = 1).
cOrthopnoea (n= 20), pulmonary crepitation (n = 20), ankle swelling (n = 18), elevated jugular venous pressure (n = 11), palpitation (n = 6).

The use of pharmacological treatments for heart failure is in Table 2. The prescription rates for ACE-I/ARBs were 78.4%, followed by beta-blockers (61.9%), and MRAs (61.9%). In addition to the three substance classes, the prescription rates diuretic was the highest (89.7%). Also, the most frequently prescribed for heart failure medication was antiplatelets (65.9%), followed by statins (46.4%), organic nitrates (41.2%), and anticoagulants (33%).

Table 2. It is pharmacological treatments for heart failure.

| Medications       | Population (n = 97) |
|-------------------|---------------------|
| Captopril         | 57 (58.8)           |
| Ramipril          | 6 (6.2)             |
| Lisinopril        | 2 (2.1)             |
| Candesartan       | 8 (8.2)             |
| Valsartan         | 3 (3.1)             |
| Bisoprolol        | 60 (61.9)           |
| Spironolactone    | 60 (61.9)           |
| Furosemide        | 87 (89.7)           |
| Digoxin           | 26 (26.8)           |

The GAI was calculated for each group, with predominantly moderate categories for both, GAI-3 (45.4%) and GAI-5 (59.8%). The median values of GAI-3 (67%) and GAI-5(60%) were also calculated to determine the overall quality of pharmacotherapy (Table 3). There were even differences among these groups, GAI-3 and GAI-5. Essential differences included comorbid, age, and etiology of heart failure (Table 4 and Table 5).

Table 3. Guideline adherence indicators.
4. Discussion

The patients enrolled in this study showed similar baseline characteristics as found in other studies.[5,12] Despite that, due to lower life expectancy in Indonesia [13], the average age of the patients is younger compared to the other studies that were in developed countries. For the etiology, CAD was the most common one in this study, which is similar to another study, as CAD is the common cause of heart failure with reduced ejection fraction.[7,14] Heart failure also occurred frequently in patients who have hypertension for a long time, and some studies showed a similar result.[8,11,12,14] Also, this study showed the majority of patients had to experience dyspnea, the sign of congestion, similarly as shown by another study.[15] The median LVEF showed a similar result with another study [12], as this study included patients with systolic heart failure.

ESC guidelines recommend the use of three neurohormonal antagonists for the treatment of chronic heart failure with reduced ejection fraction, that is ACE-I/ARBs, beta-blockers, MRAs.[7] These pharmacological treatments have the anti-remodeling effect and can improve survival.[7,16] In an animal experiment, overexpression of the angiotensin receptor associated with cardiac dysfunction and premature death due to altered cardiac gene expression.[17] Furthermore, it increases sympathetic nervous system and worsening the heart failure.[16] Hyperactivity of adrenergic-β1 receptor provokes cardiac remodeling which is caused by hypertrophic and apoptosis of the ventricle.[16,18,19] However, the prescription rates were not high enough for these three drugs, especially for beta-blockers and MRAs. The prescription rates for ACE-I/ARBs was 78.4%, followed by beta-blockers (61.9%), and MRAs (61.9%). Conversely, diuretics were the most frequently prescribed in this study, with 89.7%, this finding in line with MAHLER survey.[9] Other studies also reported the use of diuretics as the most commonly prescribed drugs.[10,20] In our study, the high prescription rates of diuretics might be due to the majority of patients had experienced dyspnea, which is the sign of congestion.

The adherence to the ESC guidelines was associated with better prognosis, improved clinical outcome, fewer cardiovascular hospitalizations and delayed time to re-hospitalization.[9–11] In this study, we found that the categories of GAI-3 and GAI-5 were lower than other studies.[9,10] The median values of GAI-3 and GAI-5 were also used to evaluate the pharmacotherapy quality [10], and our result in line with Störk et al. [10] for the GAI-3 but not GAI-5. Erhardt et al. [21] explained that the complexity of the guidelines is a significant obstacle to the implementation of the guidelines.

| Low, n (%) | Moderate, n (%) | High, n (%) | Median (IQR) |
|-----------|----------------|-------------|--------------|
| GAI-3     | 25 (25.8)      | 44 (45.4)   | 28 (28.9)    | 67% (33-100%) |
| GAI-5     | 3 (3.1)        | 58 (59.8)   | 36 (37.1)    | 60% (60-80%)  |

Table 4. Patient characteristics by guideline adherence indicator-3.

| Comorbidity, n (%) | Low (n = 25) | Moderate (n = 44) | High (n = 28) | p-value |
|--------------------|--------------|-------------------|--------------|---------|
| Hypertension       | 2 (8)        | 7 (15.9)          | 11 (39.3)    | 0.011*  |

aAnalyzed using Fisher's exact test

| Age (years), mean ± SD | Low (n = 3) | Moderate (n = 58) | High (n = 36) | p-value |
|------------------------|-------------|-------------------|--------------|---------|
| Etiology, n (%)        | 69.3±5.5    | 56.6±12.4         | 52.9±10.1    | 0.041*  |
| Cardiomyopathy         | 0           | 1 (1.7)           | 6 (16.7)     | 0.028a  |

aAnalyzed using One-way ANOVA test
bAnalyzed using Fisher's exact test

4. Discussion

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Availability of heart failure treatment guidelines in a compact and easily accessible format is considered an essential factor in improving the implementation of guidelines.[6,21]

We also found differences among GAI-3 and GAI-5. Patients with high GAI-3 shows a more pronounced to comorbid conditions, particularly hypertension. Furthermore, we found that patients with high GAI-5 tend to have cardiomyopathy as the etiology for heart failure. On the contrary, increasing age-associated with more low category of GAI-5. Our finding consecutive with another study.[22] There were many factors would influence the treatment of heart failure, including age, etiologies of heart failure, and comorbidities.[20] Störk et al. [10] indicated that the treatment in elderly patients seems to be more difficult, as they often suffer from multiple comorbidities.

5. Conclusions
It is the first study to describe the implementation of heart failure guidelines in Indonesia. In our study, the adherence to the ESC guidelines for the treatment of heart failure still needs to be improved compared to recent studies, especially for the prescription of beta-blockers and MRAs. Also, age, etiology of heart failure and comorbidity were associated factors that influence the implementation of ESC guidelines in prescribing heart failure medications.

References
[1] Chatterjee N A and Fifer M A 2011 Heart failure Pathophysiology of heart disease: a collaborative project of medical students and faculty 5th edition ed L S Lilly (Philadelphia: Lippincott Williams & Wilkins) chapter 9 pp 216-43
[2] Mann D L 2012 Management of heart failure patients with reduced ejection fraction Braunwald's heart disease: a textbook of cardiovascular medicine 9th edition ed R O Bonow, et al. (Philadelphia: Saunders) chapter 28 pp 543-69
[3] Go A S, Mozaffarian D, Roger V L, Benjamin E J, Berry J D, Borden W B, Bravata D M, Dai S, Ford E S, Fox C S, et al. 2013 Heart disease and stroke statistics - 2013 update: a report from the American Heart Association Circulation 127 e6-e245
[4] Mosterd A, Hoes A W, de Bruyne M C, Deckers J W, Linker D T, Hofman A and Grobbee D E 1999 Prevalence of heart failure and left ventricular dysfunction in the general population; The Rotterdam study Eur. Heart J. 20 447-55
[5] Bleumink G S, Knetsch A M, Sturkenboom M C J M, Straus S M J M, Hofman A, Deckers J W, Witteman J C M and Stricker B H Ch 2004 Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam study Eur. Heart J. 25 1614-9
[6] Shoukat S, Gowani S A, Taqui A M, Hassan R U, Bhutta Z A, Malik A L, Sherjeel S A, Sheheryar Q and Dhakam S H 2011 Adherence to the European society of cardiology (ESC) guidelines for chronic heart failure - a national survey of the cardiologists in Pakistan BMC Cardiovasc. Disord. 11 1-8
[7] McMurray J J V, Adamopoulos S, Anker S D, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez M A, et al. 2012 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European society of cardiology. Developed in collaboration with the heart failure association (HFA) of the ESC Eur. Heart J. 33 1787-847
[8] Maggioni A P, Anker S D, Dahlström U, Filippatos G, Ponikowski P, Zannad F, Amir O, Chioncel O, Leiro M C, Drozdz J, et al. 2013 Are hospitalized or ambulatory patients with heart failure treated in accordance with European society of cardiology guidelines? Evidence from 12,440 patients of the ESC heart failure long-term registry Eur. J. Heart Fail. 15 1173-84
[9] Komajda M, Lapuerta P, Hermans N, Gonzalez-Juanatey J R, van Veldhuisen D J, Erdmann E, Tavazzi L, Poole-Wilson P and Le Pen C 2005 Adherence to guidelines is a predictor of outcome in chronic heart failure: the MAHLER survey Eur. Heart J. 26 1653-9

[10] Störk S, Hense H W, Zentgraf C, Uebelacker I, Jahns R, Ertrl G and Angermann C E 2008 Pharmacotherapy according to treatment guidelines is associated with lower mortality in a community-based sample of patients with chronic heart failure: a prospective cohort study Eur. J. Heart Fail. 10 1236-45

[11] Yoo B-S, Oh J, Hong B-K, Shin D-H, Bae J-H, Yang D H, Shim W-J, Kim H-S, Kim S-H, Choi J-O, et al. 2014 Survey of guideline adherence for treatment of systolic heart failure in real world (SUGAR): a multi-center, retrospective, observational study PLoS ONE 9 e86596

[12] Peters-Klimm F, Müller-Tasch T, Schellberg D, Remppis A, Barth A, Holzapfel N, Jünger J, Herzog W and Szecsenyi J 2008 Guideline adherence for pharmacotherapy of chronic systolic heart failure in general practice: a closer look on evidence-based therapy Clin. Res. Cardiol. 97 244-52

[13] BPS - Statistics Indonesia 2013 Indonesia population projection: 2010-2035 (Jakarta: BPS - Statistics Indonesia)

[14] Yancy C W, Jessup M, Bozkurt B, Butler J, Casey Jr D E, Drazner M H, Fonarow G C, Geraci S A, Horwich T, Januzzi J L, et al. 2013 2013 ACCF/AHA guideline for the management of heart failure: a report of the american college of cardiology foundation/american heart association task force on practice guidelines Circulation 128 e240-e327

[15] Kelder J C, Cramer M J, Wijgaarden J, Tooren R, Mosterd A, Moons K G M, Lammers J W, Cowie M R, Grobbée D E and Hoes A W 2011 The diagnostic value of physical examination and additional testing in primary care patients with suspected heart failure Circulation 124 2865-73

[16] Triposkiadis F, Karayannis G, Giamouzis G, Skoularigis J, Louridas G and Butler J 2009 The sympathetic nervous system in heart failure: physiology, pathophysiology, and clinical implications J. Am. Coll. Cardiol. 54 1747-62

[17] McMullen J R and Jennings G L 2007 Differences between pathological and physiological cardiac hypertrophy: novel therapeutic strategies to treat heart failure Clin. Exp. Pharmacol. Physiol. 34 255-62

[18] Engelhardt S 2005 β-adrenergic signaling in heart failure Heart failure: A comprehensive guide to diagnosis and treatment ed G W Dec, et al. (New York: Marcel Dekker) chapter 5 pp 75-95

[19] Van Berlo J H, Maillot M and Molkentin J D 2013 Signalling effectors underlying pathologic growth and remodeling of the heart J. Clin. Invest. 123 37-45

[20] Komajda M, Follath F, Swedberg K, Cleland J, Aguilar J C, Cohen-Solal A, Dietz R, Gavazzi A, Van Gilst W H, Hobbs R, et al. 2003 The euro heart failure survey programme - a survey on the quality of care among patients with heart failure in Europe: Part 2: treatment Eur. Heart J. 24 464-74

[21] Erhardt L, Komajda M, Hobbs F D R and Soler-Soler J 2008 Cardiologists’ awareness and perceptions of guidelines for chronic heart failure. The address your heart survey Eur. J. Heart Fail. 10 1020-5

[22] Zugck C, Franke J, Gelbrich G, Frankensteiner L, Scheffold T, Pankuweit S, Duengen H D, Regitz-Zagrosek V, Pieske B, Neumann T, et al. 2012 Implementation of pharmacotherapy guidelines in heart failure: experience from the German competence network heart failure Clin. Res. Cardiol. 101 263-72