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Analysis of Clinical Evidence and Latest Fantastic Four Guidelines in Heart Failure Management

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ABSTRACT

Heart failure with reduced ejection fraction (HFrEF) is a leading global cause of illness and death. Although treatments exist, recurrence and mortality rates remain high. The Fantastic Four therapy—combining ARNI, beta-blockers, MRAs, and SGLT2 inhibitors—has proven effective in improving outcomes. However, its implementation faces challenges such as clinical, regulatory, and access barriers, as well as limited understanding among healthcare providers. This research aims to analyze the latest clinical evidence underlying the recommendation for using the Fantastic Four in heart failure management, as well as to evaluate its suitability and implications for clinical practice. The research method used is a qualitative approach through literature review, with analysis stages including data screening, data presentation, and conclusion drawing. Research findings indicate that all four classes of medications are highly effective in reducing cardiovascular mortality and hospitalization rates in patients with HFrEF. The latest guidelines from the ESC 2021 and ACC/AHA/HFSA 2022 recommend initiating this therapy simultaneously from the time of diagnosis. However, implementation in practice, including in Indonesia, remains inconsistent. Lack of clinician understanding and the absence of these therapies in the JKN scheme pose additional barriers. Patient compliance issues, drug interactions, and monitoring of side effects also present challenges. Therefore, systematic strategies, education, and evidence-based policies are needed to ensure effective implementation of these therapies. These findings support the need for adaptation of global guidelines and the development of evidence-based policies to support the implementation of modern combination therapy for heart failure patients.

Keywords: *Heart failure, HFrEF, Fantastic Four, clinical guidelines, therapy implementation*

INTRODUCTION

Heart failure is a severe or end-stage manifestation of various heart diseases and has become a major challenge in global public health (Roger, 2021). This is due to the high mortality rate as well as the significant frequency of readmission (Bozkurt et al., 2021; Ran et al., 2025). A report from the Global Burden of Disease (GBD) shows that the prevalence of heart failure continues to increase along with increasing life expectancy and the rising prevalence of other cardiovascular diseases such as hypertension, ischemic heart disease, and diabetes mellitus. The 2019 GBD study estimated the prevalence and years of life with disability (YLD) due to heart failure globally, covering 369 diseases and injuries in 204 countries and 21 GBD regions from 1990 to 2019 (Yan et al., 2023).

In response to the growing burden of disease, several global heart failure associations have regularly updated and released guidelines for the diagnosis and treatment of heart failure

to provide up-to-date guidance for clinical practice (Heidenreich et al., 2022; Ran et al., 2025). In the last decade, major advances in pharmacological therapies have changed approaches to heart failure management, particularly in cases with reduced ejection fraction (HFrEF). One of the latest therapeutic approaches that has received widespread attention in the cardiology community is a combination of therapies known as the Fantastic Four. This approach includes four main types of treatment, namely Angiotensin Receptor-Neprilysin Inhibitor (ARNI), beta-blockers, Mineralocorticoid Receptor Antagonists (MRAs), and Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2i), which have been shown to synergistically improve clinical outcomes in heart failure patients (Butler et al., 2020; Severino et al., 2024).

Previous research has extensively documented the efficacy of these therapeutic agents. For instance, Vaduganathan et al. (2020) demonstrated that comprehensive disease-modifying therapies significantly extend lifetime benefits for HFrEF patients. Similarly, McDonagh et al. (2021) highlighted the substantial reduction in cardiovascular mortality and hospitalization rates with the use of ARNI, beta-blockers, MRAs, and SGLT2 inhibitors. Bauersachs (2021) further reinforced these findings, noting the critical role of these four pillars in modern heart failure management. The PARADIGM-HF and DAPA-HF trials, among others, have provided robust evidence supporting the simultaneous initiation of these therapies rather than a sequential approach (Docherty et al., 2022; Chen et al., 2023).

In response to the clinical evidence, the latest guidelines from the European Society of Cardiology (ESC, 2021) and the American Heart Association (AHA, 2022) have recommended the use of these four therapies as a mainline treatment. This recommendation marks an important shift in the treatment paradigm, where therapy is no longer given gradually as in the conventional approach but is recommended to be started simultaneously from the beginning of diagnosis to provide maximum benefit to the patient. Furthermore, the update in the 2023 ESC Guidelines suggests a more intensive strategy, namely initiating and rapidly increasing the dose of evidence-based treatment before patients are discharged from the hospital. This strategy is based on results from trials showing great potential benefits even without the complete four-pillar approach (Severino et al., 2024).

However, although the Fantastic Four approach has been shown to be effective in lowering mortality and hospitalization in patients with decreased ejection fraction heart failure (HFrEF), its implementation in everyday clinical practice still faces various challenges. These barriers include limited access to recommended medications, potential side effects, and low acceptance rates from patients and health workers regarding the implementation of this therapeutic strategy (Risalah, 2022). This situation demands a more in-depth analysis of the latest clinical evidence and guidelines to understand the effectiveness, safety aspects, and most appropriate implementation strategies in various healthcare contexts.

This research aims to review the current clinical evidence that forms the basis for recommendations for the use of the Fantastic Four approach in the management of heart failure. In addition, this study evaluates the extent to which clinical guidelines can be adapted and implemented effectively in clinical practice in Indonesia. The results of this study are expected to strengthen clinicians' understanding of the effectiveness of the Fantastic Four approach, as well as provide a scientific basis for the revision or update of heart failure management guidelines at the national level. Furthermore, these findings are also expected to serve as strategic considerations for policymakers in efforts to expand access to evidence-based

therapies and integrate them into the National Health Insurance (JKN) system. In terms of academic benefits, this research contributes significantly as a scientific reference for further studies on the application of comprehensive therapy at various levels of health facilities in Indonesia.

METHOD

The research method used in this study was a qualitative approach, focusing on an in-depth understanding of phenomena, experiences, and meanings rather than quantitative measurements. The data consisted of secondary sources obtained from various reliable literature, including scientific articles, clinical guidelines, and official publications relevant to heart failure management and the Fantastic Four therapy. Data collection was conducted through literature review to gather comprehensive information.

Data analysis involved three main activities: data reduction, which filtered and focused on relevant information to make it concise and clear; systematic data presentation to clarify relationships and patterns; and drawing conclusions by interpreting the analysis results to achieve a valid and accountable understanding of the phenomenon. This approach enabled the study to generate in-depth and contextual insights regarding the implementation and effectiveness of Fantastic Four therapies in heart failure management.

RESULTS AND DISCUSSION

Heart failure is a condition when the heart is unable to perform its role optimally in carrying oxygen-rich blood to all tissues of the body. This disorder can be caused by damage to the structure of the heart or a disturbance in its mechanical function. In clinical practice, heart failure is characterized not only by symptoms such as shortness of breath, fatigue, and swelling, but also by objective findings that indicate the presence of anatomical abnormalities or heart function, even when the body is at rest. This combination of subjective symptoms, physical signs, and diagnostic evidence strengthens the identification of heart failure as a complex syndrome that requires comprehensive treatment (Airlangga & Wulandari, 2023).

Heart failure often develops quietly and can worsen quickly, causing many patients to experience serious complications or even death before the diagnosis is accurately established. This makes early diagnosis and intervention a major challenge in clinical practice (Korczyk & Kaye, 2022). Chronic heart failure (CHF), especially with decreased ejection fraction (HFrEF), is a condition whose prevalence is significantly increasing and continues to be a major burden on the healthcare system (Stolfo et al., 2022). Therefore, clinical guideline-based therapy started early has proven to be the only effective way to reduce mortality and hospitalization due to CHF.

Studies such as the SHIFT trial show that the sooner CHF therapy is given after the onset of symptoms, the better the clinical outcomes the patient achieves. Delays in the initiation of therapy, especially in patients whose symptoms have lasted a long time or have entered the stage of severe decompensation, are associated with the need for invasive interventions such as mechanical circulation support and with poorer clinical outcomes. So time is a key factor, and any delay in diagnosis and treatment increases the risk of therapy failure (Abdin et al., 2021).

The Fantastic Four Heart Failure Project is presented as an innovative solution in the treatment of heart failure with reduced ejection fraction (HFrEF) through the use of four main

classes of drugs that have been shown to significantly reduce mortality and hospitalization due to heart failure. The four therapies include ARNI (Angiotensin Receptor-Neprilysin Inhibitor), beta blockers, MRA (Mineralocorticoid Receptor Antagonist), and SGLT2i (Sodium-Glucose Cotransporter-2 Inhibitor). ARNIs such as sacubitril/valsartan function in place of ACE inhibitors and provide vasodilating and natriuretic effects. Beta blockers such as bisoprolol and carvedilol inhibit sympathetic activity and improve heart function. MRAs such as spironolactone reduce sodium retention and fibrosis, while SGLT2i such as dapagliflozin have been shown to lower the risk of cardiovascular death even in non-diabetic patients (Bauersachs, 2021). This approach is recommended by international guidelines (ESC 2021 and ACC/AHA/HFSA 2022) to be administered simultaneously from the beginning of diagnosis because it has a synergistic effect. Although proven effective, the implementation of this therapy still faces challenges such as limited clinical knowledge, drug access, and cost, especially in developing countries (Taslima et al., 2024).

The Fantastic Four Heart Failure Project is a strategic initiative designed to address key challenges in heart failure management, particularly in patients covered by the Northern Interior Rural Division (NIRD) (Campbell-William, 2025). The project reinforces a cross-disciplinary collaborative approach, focusing on the management of the four main pillars of heart failure therapy, known clinically as the "four main therapies" (ACE inhibitors/ARNI, beta blockers, MRA, and SGLT2 inhibitors) (Chen et al., 2023). By engaging a PCN pharmacist, patients can receive more rigorous treatment monitoring and faster dose adjustments, something that is often an obstacle in rural or remote areas due to limited access to specialists (Wang et al., 2024).

Four-pillar therapy for heart failure with decreased ejection fraction (HFrEF) consists of RAAS inhibitors (ACE inhibitors or ARNIs), beta-blockers, mineralocorticoid receptor antagonists (MRAs), and sodium-glucose co-transporter 2 inhibitors (SGLT2i). These four classes of drugs have been consistently proven in various clinical trials to reduce mortality from cardiovascular disease and reduce the rate of recurrent hospitalization in HFrEF patients (Docherty et al., 2022). Therefore, recent international guidelines, such as those from the European Society of Cardiology (ESC) 2021 and the combined American College of Cardiology (ACC), American Heart Association (AHA), and Heart Failure Society of America (HFSA) 2022, recommend that these four therapies be administered simultaneously from the beginning of diagnosis, rather than gradually as in previous conventional approaches (Coisne et al., 2023).

Although the effectiveness of this therapy has been recognized globally, its implementation in the field, especially in developing countries such as Indonesia, still faces various obstacles. One of the biggest challenges is the lack of understanding by some clinicians of the urgency of using this therapy completely and early. In addition, limitations in the national health financing system, such as not fully including these four drugs in the list covered by the National Health Insurance (JKN), also limit patients' access to recommended therapies.

On the other hand, the issue of patient adherence to treatment is also an important concern. The simultaneous use of four types of drugs often raises concerns among patients, both due to the large amount of medication that must be taken and because of the potential for side effects (Piña et al., 2021). The interaction between drugs and the need for routine monitoring of clinical parameters, such as renal function and electrolyte levels, add to the complexity of managing these therapies, especially in primary care facilities with limited resources. Therefore, a

systematic and integrated approach is needed that includes health worker training, integration of evidence-based policies into the health financing system, and ongoing education to patients. A team-based approach, such as that pursued by the Fantastic Four Heart Failure Project, can be an ideal model in ensuring that these four-pillar therapies are not only prescribed appropriately, but also run consistently, closely monitored, and tailored to each patient's condition. With this strategy, the clinical benefits of modern HFrEF therapy can be felt equally across all walks of life.

CONCLUSION

The latest clinical evidence and guidelines from ESC 2021 and ACC/AHA/HFSA 2022 support the simultaneous use of the Fantastic Four—SGLT2 inhibitors, ARNI, beta-blockers, and MRAs—in reducing mortality and hospitalizations in patients with heart failure with reduced ejection fraction (HFrEF). Despite their proven effectiveness, implementation challenges remain, particularly in developing countries like Indonesia, due to limited access, gaps in clinical knowledge, and inconsistent integration within the national health insurance system. Future research should explore strategies to overcome these barriers, focusing on improving accessibility, healthcare provider education, and policy integration to enhance the adoption of this comprehensive therapy in diverse clinical settings.

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