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Editorial

Improving patient outcomes : The pivotal role of guideline directed medical treatment

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ABSTRACT

Guideline directed medical therapy (GDMT) continues as the main pillar of management for heart failure with reduced ejection fraction (HFrEF). Numerous positive landmark trials and emergence of novel drugs provide strong evidence supporting the capability of GDMT in reducing cardiovascular mortality, hospitalization due to heart failure (HHF), and advancement of renal impairment. The introduction of a four-pill regimen comprising five specific pharmacological agents represents a major shift in disease-modifying care, significantly slowing symptomatic decline and improving long-term survival outcomes. Despite strong clinical recommendation, there is a huge gaps in the implementation of clinically-proven pharmacological strategies for eligible patients that further linked to relatively persistently flat mortality curves of HfrEF patients. Effective adherence to HF guidelines is often hindered by a multifaceted interplay of patient-related hurdles, clinical inertia, and systemic healthcare limitations. These challenges are further compounded by age-related complexities and multimorbidity, where concerns over pill burden and inadequate disease literacy frequently lead to suboptimal therapeutic outcomes.

In the current landscape of heart failure with reduced ejection fraction (HFrEF), phenotypic-driven strategies reinforce the indispensable role of guideline-directed medical therapy (GDMT) as the cornerstone of clinical intervention (see Figure 1).[1] The 2023 International Society for Heart and Lung Transplantation (ISHLT) updates further solidify this clinical priority, specifying that comprehensive GDMT and device optimization are fundamental requirements for the candidacy evaluation of individuals undergoing durable mechanical circulatory support.[2] Current empirical data indicates that adopting a quadruple therapy regimen which integrating a β-blocker, ARNI, MRA, and SGLT2 inhibitor, offers a substantial survival advantage over traditional ACE-i/ARB and β-blocker combinations. Projections suggest an extension of event-free survival (freedom from cardiovascular mortality or first HHF) ranging from 2.7 years in octogenarians to 8.3 years in 55-year-old patients, with overall life expectancy increasing by up to 6.3 years in the younger cohort. Nevertheless, previous study suggests that even conventional dual therapy can reduce mortality hazards by 43–53%.[3] In addition to survival benefits, GDMT frequently facilitates favorable reverse remodelling of both side of the heart, particularly in cases of de novo HF. Research by Ramandi et al demonstrated that achieving optimal therapeutic dosages of β-blocker, MRA, and ACE-i/ARB leads to significant right ventricular (RV) functional improvement within a 9-month follow-up period following the index HF episode. This is a critical clinical outcome, as the presence of RV dysfunction is a known independent predictor of increased mortality.[4] Thus, in Indonesian clinical context, despite economic constraints regarding the accessibility of SGLT2 inhibitor, clinicians should remain confident that optimizing the three pillars (ACE-i/ARB, β-blocker, and MRA) referred to Indonesian local guidelines will still yield substantial clinical benefit for the patients (see Figure 2).[5] The fundamental priority remains early implementation and rapid optimization of GDMT, a strategy that has been already supported by STRONG-HF trial, which reported significant reductions in all-cause mortality and HHF.[6] These findings provide robust randomized evidence that a high-intensity approach to initiating and optimizing therapy, coupled with close clinical follow-up, is superior to standard practice. Consequently, these results reinforce the essential role of specialized HF clinics and the pivotal contribution of HF nurses in monitoring patients during the dose-up titration phase.

HF nurses possess specialized competencies essential for the longitudinal management of chronic disease. They are specialized in position to recognize and mitigate gaps in clinical care, making them ideal role in coordinating the GDMT optimization programs. Their comprehensive expertise regarding the HF disease progression, symptoms, self-care management, and dietary requirements is fundamental to improving patient outcomes. Additionally, their knowledge of the predicted benefits and side effects of the four pillars therapy is important in encouraging patient adherence and therapeutic success. Therefore, each conversation between HF nurses and patients, whether conducted via teleconsultation or clinic visit, serves as an important opportunity to strengthen the long-term adherence of GDMT.[7]

Unfortunately, current real-world registries highlight a concerning prevalence of failure to achieve optimal therapy recommendation, even though many patients are already eligible for the recommended therapy regimens. Even in cases where no intolerance and contraindication is present, this negligence occurs and pointing out systemic limitation in optimizing heart failure care. While patients with established HFrEF face a serious risk of disease progression, hospitalization, and mortality, they are oftenly misunderstood as having

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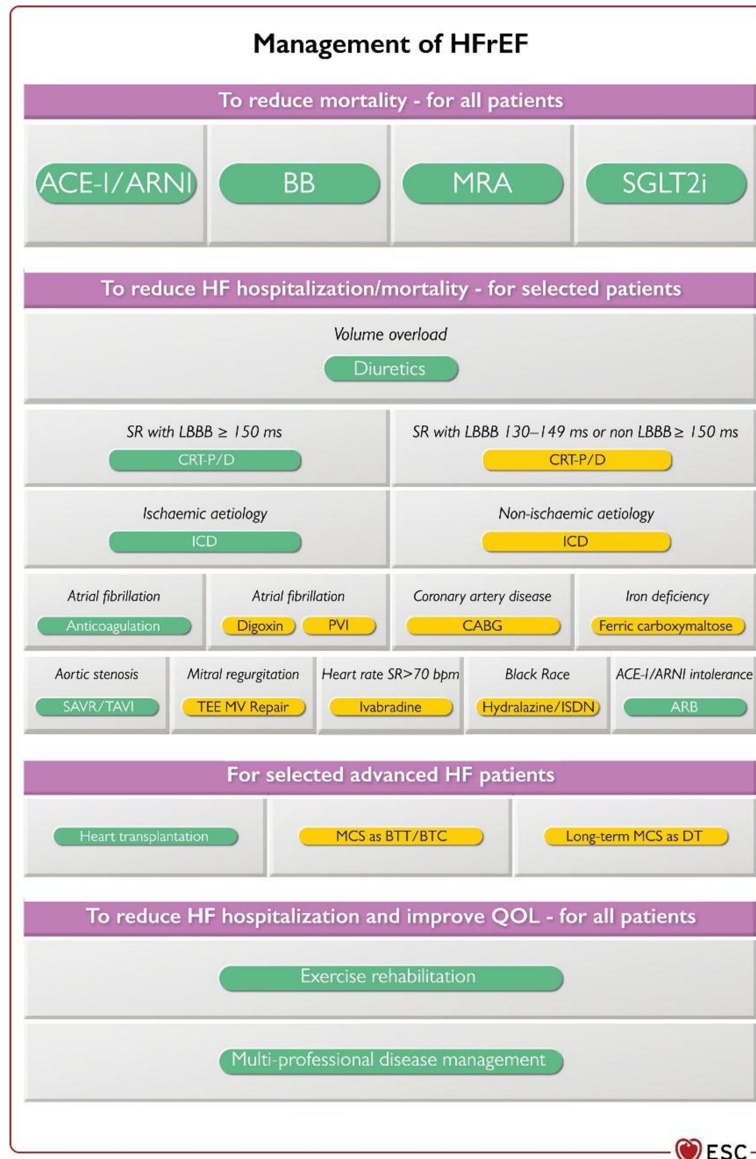

Figure 1. Phenotypic-based management algorithm for heart failure with reduced ejection fraction (HFrEF). HF (heart failure); HFrEF (heart failure with reduced ejection fraction); ACE-i (angiotensin-converting enzyme inhibitor); ARNI (angiotensin receptor-neprilysin inhibitor); BB (β -blocker); MRA (mineralocorticoid receptor antagonist); SGLT2i (sodium-glucose co-transporter 2 inhibitor); SR (sinus rhythm); LBBB (left bundle branch block); CRT-P/D (cardiac resynchronization therapy pacemaker/defibrillator); ICD (implantable cardioverter-defibrillator); PVI (pulmonary vein isolation); CABG (coronary artery bypass graft); SAVR (surgical aortic valve replacement); TAVI (transcatheter aortic valve implantation); TEE (transoesophageal echocardiography); MV (mitral valve); ISDN (isosorbide dinitrate); ARB (angiotensin receptor blocker); MCS (mechanical circulatory support); BTT (bridge to transplantation); BTC (bridge to candidacy); DT (destination therapy); QOL (quality of life)[1]

"chronic stable" condition due to the presence of only mild to moderate symptoms. This perspective, which focuses on relative measurements over absolute annual incidence rates, may lead to prolonged exposure to hazardous risks that eventually compromise patients' survival. In reality, patients who clinically classified as having 'stable' HfrEF are often fall into the high-risk category for cardiovascular mortality or HHF.[8] Apart from medication availability, some factors contribute to the clinician reluctance such as those related to the overlapping hemodynamic problems associated with hypotension, hyperkalemia, and the progression of renal dysfunction.[9] Otherwise, the combined therapeutic benefits of GDMT are synergistic with each component providing cumulative benefits that build on the clinical efficacy of the other drugs. Clinical trial data indicate that both ARNI and SGLT2 inhibitor shown a protective effect against hyperkalemia when compared to ACE-i or placebo. This benefit is especially pronounced in patients receiving concomitant MRA therapy, where these agents help mitigate the risk of electrolyte imbalances.[9]

Another inertia is worrisome of hypotension that will be found in 10-15% ambulatory chronic HFrEF.[10] The etiology of low blood pressure (BP) in the context of HFrEF is typically multifactorial. Beyond the primary deficit in cardiac output, factors such as secondary hypovolemia from aggressive diuresis, treatment-induced changes in vascular tone, and dysfunctional vasoreactivity associated with metabolic comorbidities play pivotal roles in limiting systemic pressure. Particularly, ARNI efficacy is independent of baseline hemodynamics. Patients with lower BP, even on reduced dosages, derive survival benefits comparable to those with higher baseline pressure.[10] Thus, asymptomatic low BP should not avoid the up titration of the GDMT. Significant reductions in BP during the initiation of HF therapy do not appear to diminish the clinical efficacy of the treatment. This suggests that the acute hypotensive response is effectively offset by long-term systemic improvements, indicating that the survival benefits of these agents are independent of their immediate hemodynamic impact.[10,11] Even ESC 2021 addendum clarifies that if a patient experienced dizziness or light headedness with ARNI, it is common and often improves with time and should be met with patient reassurance rather than immediate treatment discontinuation.[1]

Despite the significant benefit of GDMT, approximately 5-10% of HFrEF patients will eventually progress to advanced heart failure. This stage is fundamentally described as having marked HF manifestations with frequent hospitalizations even after tries to optimize GDMT and devices ideally. Conventional clinical perspectives suggest that patients with end-stage HF exhibit reduced physiological resilience. This indicates increased sensitivity to pharmacological interventions, mainly

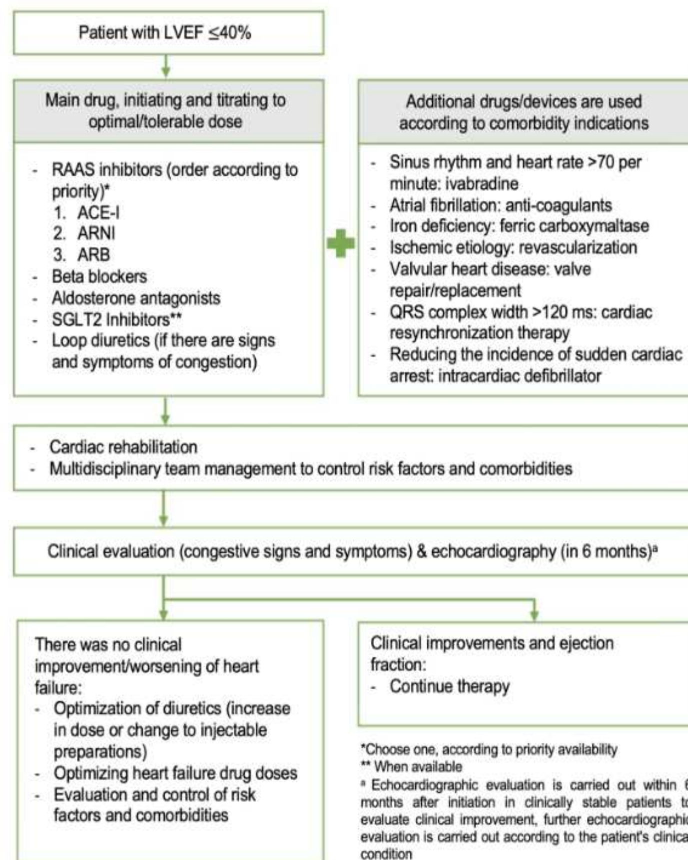

Figure 2. Algorithm of HFrEF management by the Indonesian Heart Association (PERKI). LVEF (left ventricular ejection fraction); ACE-i (angiotensin-converting enzyme inhibitor); ARNI (angiotensin receptor-neprilysin inhibitor); ARB (angiotensin II receptor blocker); RAAS (renin-angiotensin-aldosterone system); SGLT2 (sodium-glucose co-transporter 2)[5]

driven by hemodynamic instability and the complex nature of frailty. Despite the lack of evidence regarding GDMT in advanced HF, it is important to recognize that we have entered a modern era of therapy with new agents such as SGLT2 inhibitor that only affect blood pressure and may offer superior tolerability in this high-risk population. Clinical strategies for improving drug tolerance involve a methodical approach that start with lower therapeutic doses followed by gradual and careful dose increases. The key interventions are including gradual drug administration to avoid peak-effect hypotension, focusing on volumetric stabilization before starting β-blocker, and utilizing the potassium-sparing effects of SGLT2 inhibitor before introducing MRA in patients with renal impairment. Additionally, β-blocker therapy should be delayed until after device implantation is done in cases of symptomatic bradycardia, with a plan to restart therapy after temporary contraindications have resolved.[12] The primary strategy should remain to optimize all pillars of therapy, even though the titration process is longer than in Stage C HF, because comprehensive therapy consistently associated with better clinical outcomes.[12] Finally, management in advanced HF must be tailored to hemodynamic profiles, where the specific sequence of drug initiation is decided by the patient's clinical phenotype.

Conflict of Interest

There is no conflict of interest.

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