ARNI: A New Paradigm for the Treatment of Heart Failure in Taiwan?

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Heart failure (HF) is defined as a complex clinical syndrome, and can result from any structural or functional cardiac disorders which impair the ability of ventricles to fill with or eject blood.1-3 The incidence of HF in Taiwan is rising as a result of an ageing population and increasing numbers of patients living longer with chronic cardiovascular disease; HF is one of the leading causes of hospitalization in adults in Taiwan.3,4 There have been considerable advances in the pharmacological management of HF over the past 20 years. Anti-heart failure medications, including beta-blockers, ACEIs (angiotensin-converting enzyme inhibitors), ARBs (angiotensin receptor blockers), and aldosterone antagonists, improve the chances of survival in HF patients. However, even with optimal anti-failure medical treatment, the mortality and morbidity of patients with advanced HF remain high.1-3 This is especially true in Taiwan, and certain recent studies have reported that Taiwanese HF patients have inferior outcomes to those from other countries, with reduced quality of life, more re-hospitalizations, and a greater incidence of cardiovascular death.4-6 Therefore, there is a major unmet need for better therapies for HF in Taiwan.

Traditionally, HF therapy was primarily targeted at relieving symptoms of congestion (pulmonary and peripheral edema) or increasing cardiac contractility (e.g. with diuretics and digoxin, respectively). Current therapy strategies have been designed to counter, additionally, the progression of HF and to improve ‘meaningful’ survival.1-3 However, even though recent guidelines are based on the overwhelming evidence for treatment benefits in HF, reliable data from the developed Western countries have revealed significant underperformance of hospital physicians in HF diagnosis and management, with evidence of underuse and under-dosing of evidence-based therapies.7,8 In Taiwan, most of the available data on physician prescribing patterns for anti-heart failure medications are limited to single-center registries. The HF with reduced ejection fraction registry of the Taiwan Society of Cardiology (TSOC-HFrEF registry) was the first database to include a large sample of hospitalized patients with decompensated HF from different regions in Taiwan. By the end of 2014, a total of 1509 patients over 20 years of age (64 ± 16 years, 72.4% male) with a definitive diagnosis of HFrEF (left ventricular ejection fraction of < 40%), admitted to 21 public or private hospitals, were recruited. The in-hospital mortality affected 2.4% of all patients included. At discharge, the prescription rates of beta-blockers, ACEIs, ARBs, and aldosterone antagonists were 27.5%, 34.6%, 59.6%, and 49.0% respectively, which were significantly lower than those of the Western developed countries.9 At the one-year follow-up mark, there had been no significant changes regarding the prescription rates of those 4 major categories of anti-failure medications, and the mortality rate was 18.6% (data on files). The low rates of prescription of drugs based on evidence suggest that searching for a better therapy for HF is urgently necessary.

Responding to these data on underperformance requires physicians to take positive action in a number of areas within their practices. Enhanced access to diagnostic tests, especially echocardiography, is essential. Not only should they more actively inspect for potential HF in their highest-risk patients (post-myocardial infarction, hypertension, diabetes, etc.) but, once confirmed, their confirmed HF condition should be aggressively managed. The aims of such treatments are not just re-
lieving the symptoms but also improving the overall morbidity and mortality. In HF patients with LV dysfunction, adequate treatment should include evidence-based optimal medical treatment, at an appropriate dose. If we reconsider HF as a condition with similar prognosis to a serious malignancy, our management would then be more timely and appropriate.

Moreover, the observation that HF continues to progress in patients receiving optimal therapy has raised the possibility of other biological pathways contributing to ventricular remodeling and HF. Various pharmacological target sites have been identified and implicated in the pathogenesis of HF. Novel therapies have emerged from an improved understanding of the pathophysiology of HF. Among them, angiotensin receptor/neprilysin inhibitors (ARNIs), described as a “game changer” by cardiologists, have been extensively discussed by Chen in the paper published in this issue of *Acta Cardiologica Sinica*. Based on findings from clinical trials of valsartan/sacubitril (brand name Entresto, previously known as LCZ696), the first drug trial in this class conducted to date, selective neprilysin inhibitors are unlikely to be of any benefit and may be associated with adverse effects when used in isolation in HF. Combining NIs with ACEIs are unsafe because of an acceptably high prevalence of angioedema, which may be mediated by elevated levels of endogenous bradykinin. Combining a NI with an ARB avoids the risk for angioedema. The ARNI valsartan/sacubitril was associated with greater reductions of both mortality and morbidity, compared with those with enalapril in a large-scale, Phase III PARADIGM-HF (Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial in patients with HFrEF. Meanwhile, valsartan/sacubitril may also be beneficial in HF with preserved ejection fraction, and a Phase III clinical trial of valsartan/sacubitril used for this indication is under way. It is likely to replace ACEIs as a core therapeutic component of chronic HF in the near future.

In sum, there have been significant advances in the therapy of HF in recent decades. However, in spite of effective medical interventions, mortality and morbidity rates remain substantial, and recent surveys of practice in Taiwan show a low level of implementation of evidence-based therapies for HF. The development of newer agents such as ARNIs to improve HF therapy may benefit millions of patients living with HF in the future. However, overcoming the possible underlying obstacles facilitating underperformance of HF treatment in Taiwan, including unfamiliarity with the impact of HF and exaggerated concerns over treatment risks and side-effects, etc., remains of paramount importance.

**REFERENCES**

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