Acta Cardiol Sin 2016;32:397–399
Editorial Comment
doi: 10.6515/ACS20160316A

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

Wei-Hsian Yin

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 $\pm$ 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-

Received: February 16, 2016 Accepted: March 16, 2016
Division of Cardiology, Cheng-Hsin General Hospital, Faculty of Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan.
Address correspondence and reprint requests to: Dr. Wei-Hsian Yin, Division of Cardiology, Cheng-Hsin General Hospital, No. 45, Cheng-Hsin Street, Pei-Tou, Taipei 112, Taiwan. Tel: 886-2-2826-1242; Fax: 886-2-2826-1242; E-mail: yinwh@pchome.com.tw

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.[10] 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.[10] 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*.[11] 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 unacceptably 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.[11-13] 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.[11-13] 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

1. McMurray JJ, Adamopoulos S, Anker SD, et al. 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 J Heart Fail* 2012;14:803-69.
2. Yancy CW, Jessup M, Bozkurt B, et al. 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* 2013;128:e240-327.
3. Wang CC, Chen JH, Yu WC, et al. Guidelines of the Taiwan Society of Cardiology (TSOC) for the Diagnosis and Treatment of Heart Failure. *Acta Cardiol Sin* 2012;28:161-95.
4. Huang CH, Chien KL, Chen WJ, et al. Impact of heart failure and left ventricular function on long-term survival--report of a community-based cohort study in Taiwan. *Eur J Heart Fail* 2007;9:587-93.
5. Tseng CH. Clinical features of heart failure hospitalization in younger and elderly patients in Taiwan. *Eur J Clin Invest* 2011;41(6):597-604.
6. Mao CT, Liu MH, Hsu KH, et al. Effect of multidisciplinary disease management for hospitalized heart failure under a national health insurance programme. *J Cardiovasc Med* 2014;15:1558-2027.
7. Maggioni AP, Anker SD, Dahlström U, et al.; Heart Failure Association of the ESC. 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* 2013;15(10):1173-84.
8. Ambrosy AP, Fonarow GC, Butler J, et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. *J Am Coll Cardiol* 2014;63(12):1123-33.
9. Chang HY, Wang CC, Cherng WJ, et al. TSOC-HFrEF Registry: a registry of hospitalized patients with decompensated systolic heart failure: description of population and management. (in submission)
10. Nguyen E, Weeda ER, White CM. A review of new pharmacologic

treatments for patients with chronic heart failure with reduced ejection fraction. *J Clin Pharmacol* 2015 Dec 2. doi: 10.1002/jcph.677 [Epub ahead of print].
11. Chen CH. Critical questions about PARADIGM-HF and the future. *Acta Cardiol Sin* 2016;32:387-396.
12. Macdonald PS. Combined angiotensin receptor/neprilysin inhibitors: a review of the new paradigm in the management of chronic heart failure. *Clin Ther* 2015;37(10):2199-205.
13. Braunwald E. The path to an angiotensin receptor antagonist-neprilysin inhibitor in the treatment of heart failure. *J Am Coll Cardiol* 2015;65(10):1029-41.