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Editorial

Practical considerations on the introduction of sacubitril/valsartan in clinical practice: Current evidence and early experience

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ABSTRACT

The combination of neprilysin inhibitor sacubitril with the angiotensin II receptor 1 blocker valsartan is the first agent from the angiotensin receptor neprilysin inhibitors (ARNI) class authorized for clinical use in heart failure (HF) patients with reduced ejection fraction (HFrEF). Sacubitril/valsartan resulted in 20% reduction in the incidence rate of death or HF hospitalization compared to enalapril in symptomatic HFrEF patients in the seminal PARADIGM-HF trial. As a result, the recently updated European and American HF guidelines granted this agent a class IB indication for the treatment of ambulatory/chronic symptomatic HFrEF patients. However, translating the positive results of trials into true clinical benefit is often challenging. This is particularly true in the case of sacubitril/valsartan, as HF is a heterogeneous syndrome including many severely ill patients who are prone to decompensation, while this new agent comes to replace a cornerstone of current evidence-based HF therapy. In the present paper, we address a number of practical issues regarding the introduction of sacubitril/valsartan and propose an algorithm based on available evidence and early clinical experience.

1. Introduction

Heart failure (HF) is a modern epidemic affecting 26 million individuals worldwide, with an expected increase in prevalence over the following years [1]. The prognosis of HF patients is dismal, with approximately 50% of patients dying at 5 years from diagnosis. Current guideline-recommended therapy with neurohormonal inhibitors combined with device therapy produce an incremental reduction of mortality in HF patients with reduced ejection fraction (HFrEF) [2]. However, survival improvement reaches a plateau after the combination of 4–5 HF therapies thus leaving a residual mortality that needs to be addressed [2]. In addition, no therapy has yet proved effective in improving survival in HF with preserved ejection fraction (HFpEF), while recurrent hospital admissions remain a significant burden being associated with particularly adverse outcomes and huge financial expenditures [3]. As a result, there is a partially unmet need for novel HF drugs to improve survival and reduce hospitalization-associated burden.

The combination of neprilysin inhibitor sacubitril with the angiotensin II receptor 1 blocker valsartan was the first agent from the class of angiotensin receptor neprilysin inhibitors (ARNI) that went through broad clinical testing and subsequently authorization for clinical use in HF with reduced ejection fraction (HFrEF) [4]. The seminal study of sacubitril/valsartan in HFrEF, the PARADIGM-HF trial that enrolled 8442 patients with symptomatic HFrEF and increased levels of natriuretic peptides, showed that sacubitril/valsartan, when compared with the angiotensin converting enzyme inhibitor enalapril, a cornerstone of HFrEF therapy, resulted in 20% reduction in the incidence rate of death or HF hospitalization (primary endpoint), along with a 16% reduction in the incidence rate of all-cause death at 3.5 years [5,6]. Based on the results of this study, the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) approved sacubitril/valsartan for the treatment of symptomatic chronic HFrEF patients in November 2015 and July 2015, respectively. Subsequently, the European Society of Cardiology (ESC) and the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for HF, both published in late May 2016, granted a class I, level of evidence B recommendation for the use of sacubitril/valsartan in HFrEF [7,8].

The introduction of novel agents in clinical practice is generally challenging and often requires careful steps in order to translate the positive results of trials into true clinical benefit. This is particularly true in the case of sacubitril/valsartan for two main reasons. First, HF is a severe condition with dismal prognosis and HF populations are much more heterogeneous than those studied in trials, including many seriously ill patients who are prone to decompensation or other complications with treatment changes. Second, the PARADIGM-HF trial introduced sacubitril/valsartan not by adding it on top of standard

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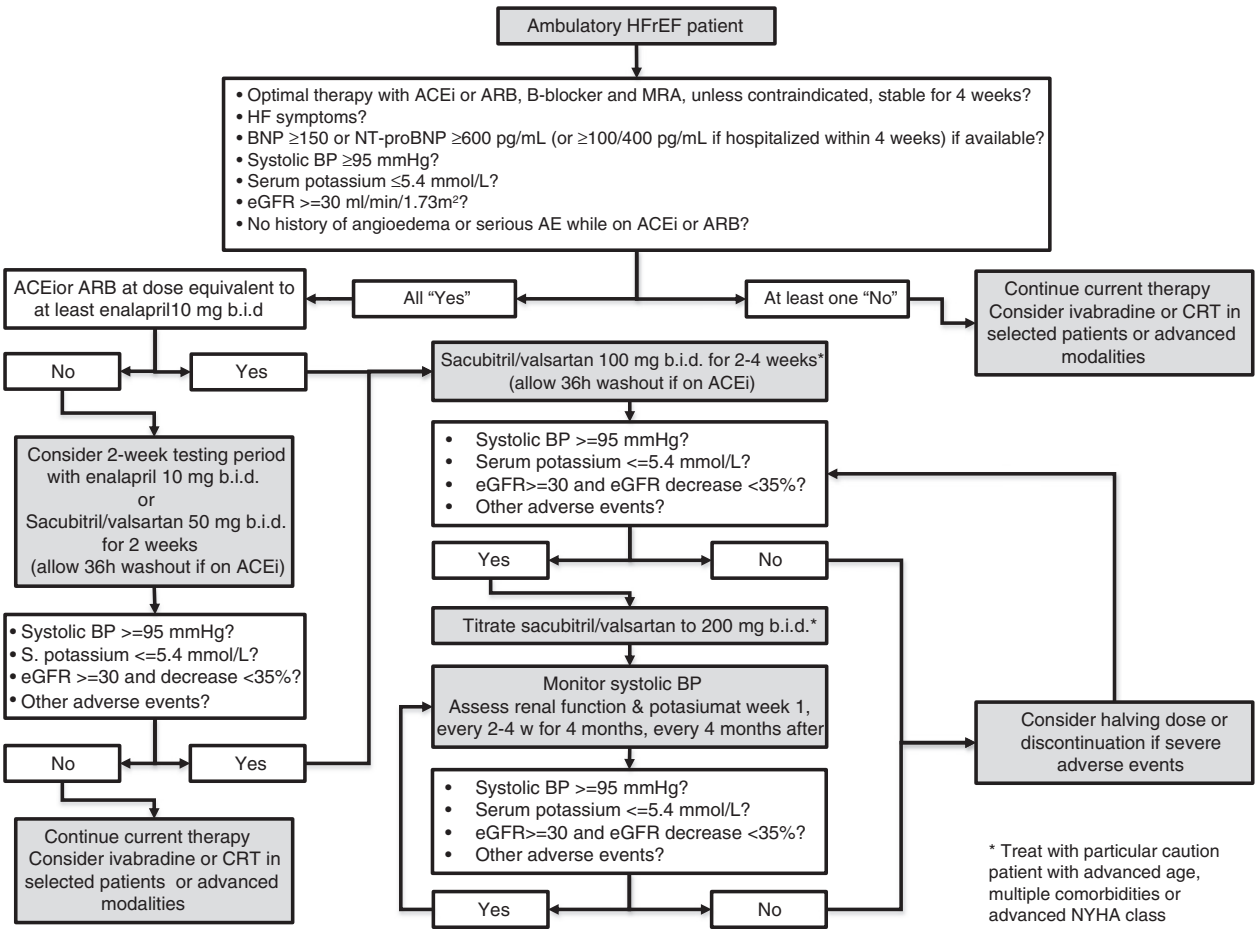

Fig. 1. A proposed algorithm for the introduction of sacubitril/valsartan in clinical practice (HFrEF: heart failure with reduced ejection fraction; BNP: B-type natriuretic peptide; NT-proBNP: N-terminal proBNP; BP: blood pressure; eGFR: estimated glomerular filtration rate; ACEi: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blocker; MRA: mineralocorticoid receptor antagonist; b.i.d.: bis in die, twice daily; CRT: cardiac resynchronization therapy; NYHA: New York Heart Association).

care, according to the common practice, but by substituting angiotensin converting enzyme inhibitors (ACEi), a cornerstone of current evidence-based HF therapy [9].

In the present paper, we address a number of practical issues regarding the introduction of sacubitril/valsartan into clinical practice and propose an algorithm that incorporates the available evidence derived by clinical trials, as well as on our experience in treating the first HFrEF patients with this agent within specialized HF centers.

2. How to use: evidence-based practical considerations

2.1. Who to treat

The best way to ensure translation of positive results reported by trials into clinical benefit is to treat as similar patients as possible to those studied in trials. PARADIGM-HF included symptomatic patients with HFrEF with New York Heart Association (NYHA) class II to IV symptoms and with elevated levels of natriuretic peptides [B-type natriuretic peptide (BNP) ≥ 150 pg/mL or N-terminal (NT)-proBNP ≥ 600 pg/mL or, in case of HF hospitalization during the previous 12 months, BNP ≥ 100 pg/mL or NT-proBNP ≥ 400 pg/mL] [5,6]. Pretreatment with an ACEi or ARB and a B-blocker was allowed in case it had been stable for 4 weeks before screening and ACEi or ARB had been being received at a dose equivalent to at least 10 mg of enalapril daily. Between screening and randomization, there were two run-in phases, one with enalapril 10 mg twice daily for 2 weeks followed by another of sacubitril/valsartan at 100 mg twice daily titrated to 200 mg twice daily for 4–6 weeks. PARADIGM-HF excluded patients with symptomatic hypotension, a low systolic blood pressure (<100 mmHg at screening or <95 mmHg at randomization), an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 or a decrease in eGFR >35% between screening and randomization, a serum potassium level >5.2 mmol/L at screening (or >5.4 mmol/L at randomization), or a history of angioedema or other unacceptable side effects resulting from treatment with ACEi or ARB [5].

The recent ESC guidelines for HF recommend sacubitril/valsartan as a replacement for an ACEi in ambulatory HFrEF patients, who remain symptomatic with NYHA class II to IV symptoms despite optimal treatment with an ACEi, a beta-blocker and a mineralocorticoid receptor antagonist (MRA), to further reduce the risk of death and HF hospitalization [7]. In addition, the ESC guidelines also require that candidate patients are able to tolerate ACEi or ARB at doses equivalent to enalapril 10 mg twice daily and have increased levels of natriuretic peptides, as previously defined [7]. The recently updated version of the ACC/AHA guidelines for HF recommend sacubitril/valsartan for symptomatic chronic HFrEF patients with NYHA II or III symptoms who tolerate an ACEi or ARB, as a replacement for ACEi or ARB to further reduce morbidity and mortality [8]. It seems that the ACC/AHA recommendation is more relaxed as it does not clearly state the need for beta-blockers and MRA pretreatment or the need for increased levels of natriuretic peptides, but, on the other hand, excludes patients with NYHA IV symptoms [8].

Bearing in mind the above, the ideal patient for sacubitril/valsartan seems to be an ambulatory symptomatic HFrEF patient on optimal treatment with an ACEi or ARB (at a dose equivalent to at least