WHAT WILL BE THE IMPACT OF SACUBITRIL/VALSARTAN IN CLINICAL PRACTICE?

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Abstract

The Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbility in Heart Failure Trial (PARADIGM-HF) has shown a reduction in the risk of death and hospitalizations for heart failure-with sacubitril/valsartan, compared with enalapril, in patients with heart failure and reduced ejection fraction. Guidelines now recommend the substitution of ACEI or ARBs with sacubitril/valsartan in the patients who remain symptomatic despite ongoing optimal treatment. The clinical impact of these indications remains uncertain. Based on the inclusion criteria of PARADIGM-HF, sacubitril/valsartan is not indicated in the patients with heart failure and preserved ejection fraction, although they are the majority of the patients with heart failure. The trial enrolled ambulatory patients and thus start of sacubitril/valsartan is not indicated in those hospitalized for heart failure. Drug's tolerability may be limited by hypotension with, however, a lower rate of renal dysfunction, compared with enalapril. Cost of the new treatment is also an issue. Thus, similar to what occurred when other neurohormonal antagonists have been introduced in clinical practice, increased awareness of poor heart failure outcomes and better patient's management programs may be of outmost importance for the implementation of this new agent.

The Prospective Comparison of ARNI (Angiotensin Receptor-Neprilysin Inhibitor) with ACEI (Angiotensin-Converting-Enzyme Inhibitor) to Determine Impact on Global Mortality and Morbility in Heart Failure Trial (PARADIGM-HF) compared the ARNI sacubitril/valsartan with enalapril in ambulatory patients with symptomatic Heart Failure (HF), reduced Left Ventricular (LV) Ejection Fraction (HFrEF), ≤40%, changed to ≤35% during the study, el-

evated Brain Natriuretic Peptides (BNP) plasma levels (BNP ≥150 pg/mL) or NT-proBNP ≥600 pg/mL or, if they had been hospitalized for HF in the previous 12 months, BNP ≥100 pg/mL or NT-proBNP ≥400 pg/mL, and an estimated glomerular filtration rate (eGFR)≥30 mL/min/1.73 m^2 of Body Surface Area (BSA). Patients had to be able to tolerate separate treatments periods with enalapril (10 mg b.i.d.) and sacubitril/valsartan (97/103 mg b.i.d.) during a run-in period [1]. In this study, sacubitril/valsartan, compared with enalapril, reduced the rate of the primary endpoint, combined cardiovascular mortality or HF hospitalizations, as well as cardiovascular deaths and HF hospitalizations alone, by 20%, p<0.001 in all cases, all-cause mortality alone, by 16%, emergency visits for outpatient worsening HF by 34%, cardiovascular hospitalizations, all-cause hospitalizations, intensive care unit admissions, all p<0.001 [1,2].

The results of PARADIGM-HF are extremely consistent. Both sudden cardiac death and worsening HF death were reduced by 20% and 21%, p=0.008 and p=0.038, respectively [3]. The effects on outcomes were similar across all pre-specified subgroups, different ages, Left Ventricular Ejection Fraction (LVEF) values, HF severity scores, diabetics versus non diabetics. Early rehospitalizations and recurrent HF hospitalizations were also reduced by sacubitril/valsartan versus enalapril [4,5]. Even splitting of PARADIGM-HF into two separate trials, based on the time of enrolment, gave similar results [5].

Compared with enalapril, the new drug was well tolerated in PARADIGM-HF. The rate of hypotensive episodes was higher but that of increases in serum creatinine and of hyperkaliemia was lower with sacubitril/valsartan versus enalapril. Angioedema, the serious adverse effect that had caused the withdrawal of the combined ACEI neprilysin inhibitor omapatrilat, occurred in only 0.2% of the patients on sacubitril/valsartan, including also the mild cases, with only a 0.1% rate of cases requiring catecholamines or glucorticoids, versus 0.1% in both cases, with enalapril [1].

PARADIGM-HF therefore showed the efficacy and safety of neurohormonal modulation with increased levels of vasodilating peptides, in addition to blockade of angiotensin II receptors, in patients with chronic HFrEF. Based on these results, sacubitril/valsartan is now indicated in the guidelines as a substitute to ACEI or Angiotensin Receptor Blockers (ARB) in the ambulatory patients with HFrEF who remain symptomatic despite optimal medical treatment with ACEI or ARB, beta-blockers and mineralcorticoid antagonists [6,7].

Now, with such impressive results, can we expect that the new drug will be administered to all the patients with a potential indication? Which factors may limit its implementation into clinical practice? Some of these variables are listed in the table I and their discussion will be the focus of the next paragraphs of this article.

Patients' characteristics

It is well known that the characteristics of the patients included in the randomized clinical trials are poorly related with those of the patients treated in clinical practice [8]. This may be true also for PARADIGM-HF [9]. Similar to all the successful efficacy trials in patients with HF, also PARADIGM-HF included patients with HFrEF. This is a well characterized group of patients.

Table I - Potential limitations to sacubitril/valsartan use in clinical practice.

Patient's characteristics
- Ambulatory
- HFrEF
- eGFR ≥30 mL/min/1.73 m^2 BSA
Side effects
- Hypotension
- Angioedema
Long-term effects
- Kidney function
- Cognitive function
Costs of treatment

However, unfortunately for the success of sacubitril/valsartan, the number of patients with HFrEF has remained stable, if not decreased, in these years, because of the decline in coronary artery disease, whereas we are facing a steady increase in the proportion of patients with HF and preserved LVEF (HFpEF) [10]. Although sacubitril/valsartan was effective, compared with valsartan, in a preliminary trial, the large outcome trial in HFpEF patients is still ongoing [11]. Second, severe kidney dysfunction was an exclusion criterion in PARADIGM-HF and the drug is not indicated in these patients despite its importance as a major comorbility of HF [12].

A further complication is that PARADIGM-HF was limited to outpatients and the current guidelines, consistently, reserve their indication only to ambulatory patients. There are no data about the patients recently hospitalized for HF. On the other hand, HF decompensation is the clinical event which better shows the insufficiency of current HF treatment and therefore may prompt the substitution of an ACEI/ARB with sacubitril/valsartan. Initiation during the hospitalization might also allow better titration and easier treatment of side effects. We must think of our patients as oncologists are used to do: HF is a condition of increased risk, independently from the symptoms and treatment, and must be optimized independently from symptom's severity but just based on the poor patient's prognosis [13,14]. The favourable effects on outcomes of sacubitril/valsartan, compared with enalapril, were numerically larger in New York Heart Association (NYHA) class II, compared with NYHA class III patients, in PARADIGM-HF [1].

Side effects

The incidence of side effects was rather small during the PARADIGM-HF trial. Serum creatinine increase >2.5 mg/dl occurred only in 3.3% of the patients on sacubitril/valsartan versus 4.5% of those on enalapril, and ≥3.0 mg/dl occurred in only 1.5% and 2.0% of the patients, respectively. Hypotension was more frequent in the patients on sacubitril/valsartan but, again, with a relatively low rate of 14.0% on sacubitril/valsartan versus 9.2% on enalapril and with a rate of symptomatic hypotension with systolic blood pressure <90 mm Hg of 2.7% versus 1.4%, respectively [1]. Notwithstanding, it is difficult to predict what will be the real impact of these adverse events in clinical practice and

how much it may limit the implementation of the new drug. The main reason is that PARADIGM-HF had two run-in phases during which patients received single-blind treatment with enalapril 10 mg bid for 2 weeks followed by single-blind treatment with sacubitril/valsartan, first 100 mg bid and then 200 mg bid, for 4-6 weeks. During these two run-in phases 1.102/10.513 patients (10.4%) and 977/9.419 patients (10.4%), respectively, were excluded, mainly for adverse events [1]. It is therefore difficult to predict the proportion of patients who will not be able to tolerate sacubitril/valsartan in clinical practice.

It is likely that, as in many other cases, the drug will be administered at lower doses than those used in the clinical trial. It is at least reassuring that, even at lower doses, valsartan/sacubitril is more effective than enalapril with, however, poorer outcomes in these patients than when maintained at full doses [15]. Different modalities of drug titration have also been studied and shown to be similarly effective as those used in PARADIGM-HF [16].

Long-term effects

Long-term events are always an issue when the results of clinical trials are translated into clinical practice. Clinical trials last for a relatively short interval. The median duration of follow-up was 27 months in PARADIGM-HF. What can be the long-term effects of this treatment, beyond those of the current study? Renal function seems protected to a larger extent by sacubitril/valsartan compared with enalapril. However, an increase in albuminuria has been found in an analysis from the Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioNfracTion (PARAMOUNT) trial [11]. Although the association between albuminuria and long-term changes in kidney function is controversial, these data deserve further studies.

Neprilysin is also responsible of the degradation of beta-amyloid and a greater accumulation and deposition of beta-amyloid peptide in the brain during long-term sacubitril/valsartan administration has been hypothesised [17].

However, many different pathways are responsible of beta-amyloid degradation, in addition to neprilysin, no increase of beta-amyloid concentration in the cerebrospinal fluid has been noted after sacubitril/valsartan administration to normal subjects and no increase in cognitive defects has been found in PARADIGM-HF with no difference compared with other trials with ACEI [5,18]. Long-term data, beyond the duration of the trial, will be, however, collected from proper registries.

Costs of treatment

Drug development is an extremely expensive process. Most of the drugs tested in clinical trials are then shown to be ineffective. It has no sense hoping that companies can support clinical trials with no revenues. However, a proper balance between drug's costs and the capacity of the healthcare system to afford such costs must be found. If the treatment is too expensive, it will not be implemented in clinical practice. This may be even more critical with a new drug for ambulatory patients who often look clinically stable during their outpatient's visits. The cost efficacy of sacubitril/valsartan has been recently analysed and an

acceptable incremental cost effectiveness ratio has been shown. However, the benefits are time dependent and greater with longer duration of treatment [19].

Conclusions

PARADIGM-HF is a landmark clinical trial bound to change our clinical practice. However, translating the results of one trial into clinical practice is always a challenge (tab. II). In the case of sacubitril/valsartan, we will have to take care of specific aspects. Implementation of a new drug in ambulatory patients with side effects that may require close monitoring will require increased awareness with regards of the poor prognosis of also these patients. Treatment must be based on the improvement in outcomes, rather than simply on symptoms. The same can be said with respect to its early initiation and its costs. Scientific societies and patient's organizations will likely have to play a pivotal role for the implementation of sacubitril/valsartan in clinical practice.

Table II - Issues and possible actions to increase the impact of the new agent sacubitril/valsartan in clinical practice.

Issue	*Action needed*	*Subject*
Indicated ONLY in patients with - Chronic HF - Low EF - Ambulatory	Increase awareness when visiting outpatients	Cardiologists Primary care physicians, Scientific societies; Patients' organizations
Adverse events (hypotension)	Close follow-up when started	Cardiologists Primary care physicians, Scientific societies; Patients' organizations
Long-term efficacy and safety	Registry data	All prescribers Scientific societies regulatory bodies
Better cost efficacy with longer treatment	Earlier initiation of treatment	Same as above

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