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Efficacy of Sacubitril/Valsartan for the Treatment of Heart Failure with Moderately Reduced and Preserved Ejection Fraction

Jabbarov O. O., Aminova G. A., Najmiddinov A. Sh.
Tashkent medical academy.

Maxmusayev E. J.
Samarkand State Medical University

Abstract: Heart failure with mildly reduced ejection fraction and heart failure with preserved ejection fraction are associated with significant morbidity and mortality, as well as growing economic burden. This review describes recent studies on the use of sacubitril/valsartan in heart failure patients with mildly reduced or preserved ejection fraction.

Keywords: sacubitril/valsartan, heart failure, heart failure with mildly reduced ejection fraction, heart failure with preserved ejection fraction, worsening heart failure.

Heart failure (HF) is a multifaceted life-threatening syndrome characterized by significant morbidity and mortality, low functional status and quality of life of patients, as well as high costs of the healthcare system. Most randomized clinical trials (RCTs), evidence-based which have improved the survival rate of patients with HF, including patients with HF with left ventricular ejection fraction (EF LV) ≤35 or ≤40%. Patients with HF with LVEF >40% have no less serious prognosis, but the evidence base is carrying effective treatment for this group of patients currently limited. It is important to note that the period after decompensation, HF is most vulnerable to re-hospitalization and death. Sacubitril/valsartan is a combination of neprilysin inhibitor and angiotensin II receptor blocker (BRA). The review provides a description of the results of the latest of these studies on the use of this drug in patients with HF with moderately reduced or reserved EF[2,3,4].

Classification of HF according to LVEF

LVEF remains the main parameter for diagnostic, phenotyping, determining prognosis and selection treatment tactics for heart failure. According to modern recommendations distinguish patients with reduced LVEF (HFrEF– LVEF≤40%), moderately reduced LVEF (HFmEF – LVEF 41–49%) and preserved LVEF (HFpEF – LVEF≥50%). In addition, they distinguish patients with improved EF (LVEF>40%), who previously had LVEF≤40%, but subsequently their LVEF exceeded strength 40%. Patients with HFpEF, unlike patients with HFrEF, are more older people, more often women, more often have arterial hypertension (AH), atrial fibrillation (AF), renal dysfunction and non-cardiac associated diseases, are less likely to suffer from coronary heart disease (CHD) and have lower levels of natriuretic peptides. HFmEF has some intermediate similarities between HFrEF and HFpEF, but more pronounced clinical and therapeutic similarities are noted between HFmEF and HFrEF, which justifies the term HF with “moderately reduced” EF. Compared to patients with HFpEF general characteristics of HFmEF and HFrEF are younger, more often male, ischemic etiology of HF and lower prevalence of AF. In the ESC Heart Failure Long-Term Registry (ESC-HF-LT) patients with HFmEF were less symptomatic (more low class according to the classification of severity of chronic HF of the New York Heart Association - NYHA), were less likely to receive diuretics and had less overall comorbidities than patients with HFpEF or HFrEF. A potential explanation for these results may be that some patients with HFmEF end up with improved LVEF during treatment[1].

Treatment of HFrEF and HFpEF

Special studies on patient treatment was not carried out with HFmEF. Based on subanalyses previously performed studies are recommended to be look at the possibility of assigning allowed β-blockers (β-blockers), blockers of renin-angiotensin-aldosterone system (angiotensin converting enzyme inhibitors - ACEI, or ARBs, or sacubitril/valsartan), mineralocorticoid antagonists receptors (AMPR) and sodium inhibitors glucose cotransporter type 2 (iNGLT-2) to reduce risk of cardiovascular death and hospitalization due to about worsening heart failure. According to American recommendations, the appointment of sacubitril/valsartan is recommended to be considered in patients with HFmEF or HFpEF with greatest effect when LVEF is lower norms (LVEF<60%)[1-4].

Sacubitril/valsartan for HFmEF and HFpEF

The first RCT to study sacubitril/valsartan in patients with HFpEF and HFmEF became a phase II PARAMOUNT study (n=301, patients with LVEF≥45%). In the current 12 weeks of observation in the sacubitril/valsartan group there was a statistically significant decrease in the level N-terminal propeptide of natriuretic hormone (NT-proBNP) compared with the valsartan group (relative change compared to the initial level 0,77, 95% confidence interval – CI 0,64–0,92; p=0,005).

Subsequently, in the phase III **PARAGON-HF** study the effectiveness of sacubitril/valsartan was assessed in compared with valsartan therapy in 4822 patients with EF LV≥45%. Patients with ADHF were not included in the study. As a combined primary endpoint hospitalization for HF or death from cardiovascular causes. During the observation period (median 35 months) in the sacubitril/valsartan group compared with the valsartan group, there was a reduction in the risk of achievement of the primary endpoint by 13%, however did not reach statistical significance (ratio risks – RR 0,87, 95% CI 0,75–1,01; p=0,0587). It is important to note that the greatest benefit from sacubitril/valsartan therapy was observed in patients with less LVEF or equal to the median (median LVEF in the study – 57%). In this subgroup, the prescription of sacubitril/valsartan was associated with a significant reduction in risk achievement of the primary endpoint by 22% (RR 0,78, 95% CI 0,64–0,95). Women were also found a significant reduction in the primary endpoint by 27% (RR 0,73, 95% CI 0,59–0,90). In addition, it has been shown that patients with LVEF≥45% sacubitril/valsartan has a high security profile. In the PARAGON-HF study safety assessment of sacubitril/valsartan were consistent with the PARADIGM-HF study estimates, where the effectiveness of sacubitril/valsartan was compared with enalapril in patients with HFrEF. In accordance with the results of the PARAGON-HF study sacubitril/valsartan is recommended for the treatment of patients with HFmEF/ HFpEF with a note that benefits are greatest in patients with LVEF below normal (LVEF<60[1,4,6]

In the period after an exacerbation of HF, patients are most vulnerable for readmission and death. In retrospective analysis of PARAGON-HF in patients with recent hospitalization for HF, risk of re-hospitalization and death from cardiovascular diseases turned out to be 2–3 times higher compared to patients without long-term hospitalization. In the study 622 (13% of total number randomized) patient at least 1 time hospitalized for ADHF within 30 days before inclusion in the study. In the valsartan group, the frequency achieving the primary endpoint (hospitalization for HF or death from cardiovascular causes) among patients with a recent exacerbation of HF was 26,7 events per 100 patient-years compared to 7,9 events rate per 100 patient-years in patients without recent hospitalization. It is important to note that the effectiveness of treatment sacubitril/valsartan versus valsartan was higher in patients with recent hospitalization about HF. Absolutely reduced risk of achieving primary endpoint in patients included in the study follow-up for 30 days after hospitalization was 6,4% in the sacubitril/valsartan group compared with valsartan group. This effect decreased as time since last hospitalization increased[3-6].

ADHF in patients with HFmEF/HFpEF is usually associated with increasing the level of brain natriuretic peptide (BNP) and NT-proBNP, which decrease after adequate treatment and stabilization of the condition. Similar to data PARAGON-HF in the I-PRESERVE study (Irbesartan in Heart Failure with Preserved Ejection Fraction Study) patients with recent hospitalization for HF and increased NT-

proBNP levels (>360 pg/ml) had a higher risk cardiovascular death and readmission regarding HF. Decrease in BNP levels during treatment associated with improved clinical outcomes[1,5].

In the study PIONEER-HF assessed the effect of therapy sacubitril/valsartan initiated after stabilization of the condition during hospitalization for ADHF compared with enalapril in patients with HFrEF. The PIONEER-HF study showed that sacubitril/valsartan therapy was associated with a large decrease NT-proBNP concentration was safe and good tolerable and is associated with a significant decrease in the composed end point (death or re-hospitalization for heart failure, or implantation of ventricular assist powerful device, or being placed on a waiting list for heart transplantation) by 46% (RR 0,54, 95% CI 0,37–0,79)[1,2,5].

In this regard, assessing the effectiveness of therapeutic strategies that can lead to decreased levels BNP, in patients with HFmEF/HFpEF and recent ADHF is an important task. Based on the data described the PARAGLIDE-HF study was planned.

Results of the PARAGLIDE-HF study

Prospective comparison of ARNI with ARB Given following stabiLization In DEcompensated HFpEF (PARAGLIDE-HF) – multicenter, double-blind randomized controlled trial to study the effectiveness, safety and tolerability of sacubitril/valsartan versus valsartan for HFmEF and HFpEF (LVEF >40%) in patients with recent deterioration HF. Inclusion criteria were age older 18 years old, diagnosed with HF (previously established or diagnosed for the first time) with LVEF>40% (over the last 3 months) and level NT-proBNP≥500 pg/ml (or BNP≥150 pg/ml) for patients in sinus rhythm (NT-proBNP≥1000 pg/ml or BNP 300≥pg/ml for AF)[1-3].

Patients were randomized in a 1:1 ratio to sacubitril/valsartan group with titration to target doses 200 mg (102,8 mg + 97,2 mg) 2 times a day and group valsartan titrated to 160 mg 2 times a day as tolerated. The starting dose of the study drug is determined divided based on the clinical situation. In patients who have not previously taken ACE inhibitors/ARBs or have taken these drugs in low doses, as well as in patients with level of GFR>20 and <30 ml/min/1,73 m2 therapy is started first level dose [sacubitril/valsartan 50 mg (25,7 mg + 25,3 mg) 2 times a day or valsartan 40 mg 2 times in a day][1-4].

The study included 467 patients, among 52% of them are female, average age is 70±12 years (mean ± SD), median body mass index was 33 (IQR 27–40) kg/m2. Median LVEF – 55% (IQR 50–60%), 23% of patients with HFmEF (LVEF 41–49%), 24% pain patients had LVEF>60%. Median NT-proBNP on screening was 2009 (IQR 1291–3813) pg/ml, median BNP – 517 (IQR 350–911) pg/ml. Ischemic etiology of HF detected only in 18% of patients. Most patients suffered from hypertension – 95,9%, AF - in 58,5% of patients, diabetes – 48,6%. At baseline, 77,1% of patients received ACEi/ARBs, β-AB – 75,8%, AMKR – 28,9%, NGLT-2 – 12%. Over time during the observation period 39% of patients received the study drug at the first level dose, 21% at the second level dose and in 40% of patients it was possible to achieve the target dose of the study of the drug, data between the sacubitril/valsartan and valsartan were not significantly different[1,2].

In light of similar research findings PARAGON-HF PARAGLIDE-HF data provides additional support for clinical benefits sacubitril/valsartan in patients with HFmEF/HFpEF, especially among those with LVEF below normal (LVEF<60%)[1-6].

Pooled Analysis of PARAGLIDE-HF and PARAGON-HF

The main goal of PARAGLIDE-HF was to assess the changes differences in BNP levels, the study was not powered to assess clinical outcomes. The larger PARAGON-HF study included a subgroup of patients with recent worsening of HF, similar to patients PARAGLIDE-HF studies. Pooled analysis PARAGLIDE-HF and PARAGON-HF were previously planned in the PARAGLIDE-HF statistical analysis for a more complete assessment of therapeutic effects sacubitril/valsartan on cardiovascular and renal outcomes. The primary analysis included 1088 patients: participants in the PARAGLIDE-HF

study (n=466) and PARAGON-HF study group (n=622, patients who were hospitalized for HF within 30 days before randomization)[1,3].

Combined analysis of PARAGLIDE-HF and PARAGONHF shows the effectiveness of early administration of sacubitril/valsartan after an episode of exacerbation of heart failure in a patients with HFmEF or HFpEF. Combined analysis of all participants showed the benefits of treatment with sacubitril/valsartan, regardless of how long ago the HF worsened. Greater power made it possible to increase accuracy and justify positive effect of treatment with acubitril/valsartan in relation to cardiovascular an-d renal outcomes in patients with HFmEF or HFpEF.

Conclusion

Combined analysis of PARAGLIDE-HF and PARAGONHF showed a reduction in the risk of hospitalization for HF and cardiovascular mortality, cardiovascular and renal complications when using sacubitril/valsartan in patients with HFmEF or HFpEF. Most The greatest benefit was observed in patients with LVEF below normal (LVEF <60%). Sacubitril/valsartan is effective as in patients with stable HF and in patients after recent decompensation[1-6].

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