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The effect of sacubitril/valsartan on the occurrence of ventricular arrhythmia and the risk of sudden cardiac death in patients with chronic heart failure with reduced left ventricular ejection fraction. Expert opinion of the Heart Rhythm and Heart Failure Associations of the Polish Cardiac Society

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Abstract:

Exacerbation of chronic heart failure (HF) is the most common cause of hospitalization in adults, which is associated with high morbidity and mortality, mainly in the mechanism of exacerbation of chronic HF or sudden cardiac death (SCD). A novelty in the treatment of HF with reduced left ventricular ejection fraction (HFrEF) in recent years has been registration of sacubitril/valsartan - a drug belonging to the angiotensin II receptor and neprilysin inhibitors (ARNI). Sacubitril/valsartan significantly reduces the severity of HF symptoms, the risk of hospitalization and death and is characterized by a good safety profile, due to which it has a strong position in the guidelines of international cardiac societies. However, the precise mechanism in which ARNI has a beneficial effect on cardiovascular mortality is not known. The advantages of ARNI are likely to result from improvement of left ventricle ejection fraction, reduced myocardial remodeling and increased natriuretic peptide availability. Therefore, sacubitril/valsartan may potentially exhibit anti-arrhythmic properties and reduce risk of ventricular arrhythmias and SCD in patients with HFrEF. What is important, the improvement of the function and the electrical stabilization of cardiomyocytes may translate to decrease of the risk of adequate and inadequate interventions of cardioverter defibrillator and
an improvement of biventricular pacing of resynchronization systems. The following expert opinion of the Heart Rhythm and Heart Failure Sections of the Polish Cardiac Society presents a summary and interpretation of current knowledge regarding the influence of sacubitril/valsartan on the occurrence of ventricular arrhythmias and the risk of SCD in patients with chronic HFrEF.

**Key words:** angiotensin receptor neprilysin inhibitor, entresto, heart failure, sudden cardiac death, ventricular arrhythmia,

**Introduction**

Current trends show that the prevalence of heart failure (HF) is still increasing (1). Decompensated HF is the most frequent cause of hospitalization of adults resulting in high morbidity, mortality and poor quality of life (1, 2). Patients with HF with reduced left ventricle ejection fraction (HFrEF) are also at high risk of sudden cardiac death (SCD) (2). It is estimated that approximately 40% of deaths in HFrEF are related to SCD caused mainly by ventricular arrhythmia (3). The risk of SCD in HFrEF has been previously shown to be reduced with optimal medical treatment with angiotensin converting enzyme inhibitors (ACE-I), beta-blockers and mineralocorticoid receptor antagonists (MRA). According to the guidelines use of angiotensin-receptor blockers (ARB) should be restricted to patients unable to tolerate of ACE-I. Treatment with device therapies like an implantable cardioverter defibrillator (ICD) and a cardiac resynchronization therapy (CRT) are also recommended in selected patients in order to reduce morbidity and mortality (2). Basing on data from recent European registries use of ICD and CRT is constantly increasing approximately up to 10-24% and 7-14% of real-life HF patients, respectively (4-6).

Compounding this, HF is a great driver of health care costs for national payers and patients themselves (7). Hence, there is a need for continuous efforts towards optimization of
HF therapy, including improvement in pharmacotherapy, devices and ambulatory disease management. An important novelty in the treatment of HFrEF in recent years was registration of a new medicinal product containing a combination of valsartan and sacubitril, belonging to the angiotensin receptor neprilysin inhibitors (ARNI). In PARADIGM-HF (Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor With an Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure) study sacubitril/valsartan comparing with enalapril significantly reduced the risks of hospitalization and death for HF giving a real chance for further improvement in HF therapy (3). First published data on practical use of sacubitril/valsartan in ambulatory HFrEF patients in Poland showed significant reduction of HF symptoms, improved exercise tolerance and drop in natriuretic peptides concentrations, as well as good drug tolerance (8).

This position paper presents the collection and interpretation of the current state of knowledge on the influence of sacubitril-valsartan on the occurrence of ventricular arrhythmias and SCD risk in patients with HFrEF. The aim of the authors of this document is to discuss the potential anti-arrhythmic properties of sacubitril-valsartan and their importance in improving the quality of life and prognosis of patients with HFrEF.

The pathophysiological and clinical reasons for the use of ARNI in prevention of sudden cardiac death

Despite decades of research investigators have not found strong predictive factors of ventricular arrhythmia and SCD in patients with HFrEF. The strongest association with the SCD occurrence was shown for reduced left ventricle ejection fraction (LVEF), and therefore LVEF is the only indicator of ICD use for the primary prevention of SCD (9). Identification of patients who will benefit from ICD implantation becomes more difficult, especially in patients with non-ischemic cardiomyopathy. Therefore, an important pathway to decrease the risk of
SCD may be a further intensification of the pharmacotherapy, what can be achieved with sacubitril/valsartan, currently the only representative of the ARNI group. The precise mechanism by which ARNI influences cardiovascular mortality is uncertain. Sacubitril/valsartan acts on two main pathways being activated in HF - blocks the angiotensin II receptor (valsartan) and inhibits neprilysin (sacubitril) simultaneously. Stimulation of the AT2 receptor, as a part of the renin-angiotensin-aldosterone (RAAS) axis, provokes increased sympathetic activity, cardiac hypertrophy, reverse remodelling, fibrosis and coagulability disorders. Finally, it results in cardiomyocytes dysfunction which contributes to pro-arrhythmogenic effect. Therefore, valsartan through blocking AT2 receptor, reverse many of those adverse effects. Neprilysin is an enzyme that degrades natriuretic peptides, bradykinin, adrenomedullin, and other vasoactive peptides. HF is associated with increased neprilysin activation resulting in intensified degradation of natriuretic peptides, and therefore abolition of their positive effects. Inhibition of neprilysin, by sacubitril, causes beneficial effects on cardiovascular system through vasodilating effect and increasing the availability of natriuretic peptides, which in turn leads to growth natriuresis and diuresis, as well as reduction of left ventricular and vascular remodelling (10, 11).

The PARADIGM-HF trial included patients with LVEF <40%, average LVEF was 29% (interquartile range, 25-34). In multivariate analyses LVEF was a significant and independent predictor of all study outcomes. What is important, sacubitril/valsartan was showed to be effective at reducing all endpoints across the LVEF spectrum (12). There is ongoing PARAGON-HF trial (clinicaltrials.gov NCT01920711) analysing whether patients with preserved LVEF would also benefit from sacubitril/valsartan. In the PARADIGM-HF study patients treated with sacubitril/valsartan were less likely to need an implantation of cardiac device or cardiac transplantation (HR 0.78, 95%CI 0.60–1.02, p=0.07) (3).
Among promising variables for predicting SCD occurrence are natriuretic peptides (9). Concentrations of NT-proBNP were also showed to be parallel with the treatment benefits and therefore are recommended for monitoring and adjusting of the HF therapy (1, 13). Patients treated with sacubitril/valsartan, comparing with enalapril, have early (within 30- days) and sustained reduction in NT-proBNP and troponins concentrations, while BNP levels increases due to neprilsin inhibition (3). Elevated concentrations of NT-proBNP correlates with number of premature ventricular contractions and ventricular arrhythmia ICD events (14).

Reduction of the risk of ventricular arrhythmia in the PARADIGM-HF trial might result from intensification of HF treatment through connection of these two molecules – sacubitril and valsartan. Reduction of preload and afterload, improvement of the left ventricular function obtained by neprilsin inhibition, as well as reduction of myocardial fibrosis, myocardial ischemia and sympathetic tone, (shown in preclinical studies (15)), might play an important role in modification of the substrate for fatal ventricular arrhythmias.

**Current position of ARNI in guidelines for treatment of heart failure and ventricular arrhythmias.**

In HFrEF patients an ACE-I (or ARB if ACE-I is not tolerated/contraindicated) and a beta-blocker should be initiated simultaneously to reduce the risk of HF hospitalization and death. In patients with LVEF ≤35% and who remain symptomatic to further reduce risk of mortality and HF hospitalizations MRA should be added (2). These medications should be gradually up-titrated to target or maximum tolerated doses to achieve adequate inhibition of the sympathetic system. However, there is evidence from real-life data that majority of patients receive suboptimal doses (4, 16), which directly correlates with worse prognosis of HF patients (17).
The recent HF guidelines of the European Society of Cardiology (ESC) recommended use of a new compound sacubitril/valsartan instead of ACE-I (or ARB) in ambulatory patients with HFrEF (LVEF ≤35%) who remain symptomatic (NYHA functional class II-IV) despite optimal treatment with an ACE-I (or ARB), a beta-blocker and a MRA to further reduce the risk of death and HF hospitalization (class I, level of evidence B). According to the PARADIGM-HF study inclusion criteria, patients should have increased natriuretic peptides (plasma BNP ≥150 pg/mL or plasma NT-proBNP ≥600 pg/mL; or BNP ≥100 pg/mL or NT-proBNP ≥400 pg/mL if occurred HF hospitalization within the last 12 months) and be able to tolerate ACE-I doses equivalent to enalapril 10 mg b.i.d. (2). While, the American guidelines’ (ACC/AHA/HFSA) algorithm allows for use of ARNI in patients with similar characteristics but with LVEF ≤ 40% and NYHA class II-III (13). Canadian Cardiovascular Society guidelines published in 2017 recommend use of ARNI instead of ACE-I (or ARB) in HFrEF (LVEF ≤40%) patients treated with target/maximally tolerated doses of ACE-I (or ARB if ACE-I intolerance), beta-blockers and MRA, who are still symptomatic (NYHA class II-IV) (18).

The ESC guidelines for the management of ventricular arrhythmias and prevention of SCD published in 2015 (therefore before sacubitril/valsartan was registered) supported anti-arrhythmic efficacy of an ACE-I, an ARB, a beta-blocker, a MRA and implantable devices, as well as recommended use of ablation or surgery for SCD prevention (9). However, among anti-arrhythmic drugs none have been proven to effectively reduce the risk of life-threatening ventricular arrhythmias and SCD (9). In the 2016 ESC HF guidelines treatment with an ACE-I, a beta-blocker, a MRA, and sacubitril/valsartan was especially strongly advised for patients with HFrEF and ventricular arrhythmias in order to reduce the risk of SCD (class I, level of evidence A) (19). Table 1 presents summary of guidelines of international societies on use of ARNI in patients with HFrEF.
Practical guidance on implementation and monitoring of effects of sacubitril/valsartan was presented previously in position paper of the Heart Failure Working Group of the Polish Cardiac Society (20). There are also available first insights of initial clinical experience with ARNI in Poland (8).

**Results of PARADIGM-HF study in the field of ventricular arrhythmias and sudden cardiac death**

Briefly, the PARADIGM-HF was a double-blind study which randomized (1:1) 8,442 patients with chronic HF (New York Heart Association classes II–IV) and left ventricular ejection fraction ≤ 40%, who were treated with guideline-recommended medical therapy, to enalapril 10 mg twice daily or sacubitril/valsartan 200 mg twice daily (3). Patients had potentially optimal pharmacotherapy with high utilization of guidelines-recommended medications – ACE-I (100%), beta-blockers (93%) and MRA (55%). The PARADIGM-HF study was terminated ahead of time (after median 27 months of observation) because of observed clear benefits of sacubitril/valsartan compared to enalapril. The study showed a decrease in all-cause mortality, cardiovascular mortality, SCD, HF mortality, HF hospitalizations, and symptoms of HF. In the study group more commonly occurred hypotension, but was a lower risk of hyperkaliemia, renal impairment and cough, than in the enalapril group. Summary of main results of the PARADIGM-HF trial and post-hoc analyses are showed in table 2.

In the PARADIGM-HF study patients with implanted cardiac devices were underrepresented – approximately 15% had ICD and 7% CRT (3). Rate of SCD did not differ in patients with or without ICD (21). The benefit from reduction of SCD risk is especially observed in patients with mild-moderate symptoms of HF (NYHA class I-III), while mode of death in NYHA class IV is mainly related to HF worsening. Optimization of pharmacological therapy with ACE-I, beta-blockers, MRA and sacubitril/valsartan is expected to reduce the risk
of SCD (9). Implantation of ICD within 40 days after myocardial infarction was showed to have no benefits. It is recommended only after optimization of pharmacotherapy (3-9 months), when LVEF is still ≤35% (2, 22). After HF diagnosis, the therapy should be adjusted no more frequently than every two weeks and up-titrated to target (or maximally tolerated) doses within 3-6 months (13). In HFrEF patients, before introduction of ARNI, use of MRA is recommended to further improve outcomes, but is not mandatory (13). Three-months after achievement of optimal therapy reassessment of ventricular function should occur, to determine the need for ICD or CRT. What is important, the advantages of treatment with sacubitril/valsartan persists even after need for dose reduction (HR 0.80, 95% CI 0.70–0.93, P < 0.001) and are similar to that observed in patients without any dose reduction (HR 0.79, 95% CI 0.71–0.88, P < 0.001) (23). However, still any dose reduction in the PARADIGM-HF trial was associated with an increased risk of the primary endpoint (cardiovascular death or HF hospitalization) (HR 2.5, 95% CI 2.2–2.7, P < 0.001).

It should be noted that an important limitation of the results of the PARADIGM-HF study is that the antiarrhythmic effect of sacubitril/valsartan was not the primary endpoint of the study, which reduces the statistical reliability and the possibility of a reliable interpretation of the results obtained in the reduction of SCD risk. Moreover, the use of enalapril in the control group does not allow to determine whether the potential antiarrhythmic effect was more due to the properties of valsartan or sacubitril.

Other research data on ARNI and ventricular arrhythmia

Shen et al. in a meta-analysis of 12 clinical trials involving over 40,000 patients with HFrEF showed that the risk of sudden death in this group decreased almost by half in the last
two decades due to the progress in pharmacotherapy (18). During the 90-day follow-up, the overall mortality rate was 2.4% in the RALES study (the earliest from the studies) to 1.0% in the PARADIGM-HF study (the latest from the studies) and doubled over the next 90 days. Among the high-risk patients were: older people, men, people with low LVEF, low systolic blood pressure, renal failure, myocardial infarction in the past or diabetes. However, there was no correlation between the duration of HF (newly diagnosed vs. long-term) and general mortality.

Taking into account the effectiveness of the analyzed drugs in reducing the overall mortality, cautious qualification to electrotherapy in the primary prevention of SCD in patients with HFrEF is necessary. The DANISH study emphasized the need to identify a subgroup of high-risk patients in whom ICD implantation will be most beneficial and subgroups of patients who are sufficiently treated with intensive pharmacotherapy only (24). In accordance with current guidelines, the majority of patients are required to use intensive pharmacotherapy for at least 3 months, with re-measurement of LVEF prior to implantation of the cardiac device. However, reducing the volume of the left ventricle and increasing LVEF may take up to 12 months after the start of treatment. Therefore, 3 months may be too short time to see if there is sufficient improvement in the left ventricle function to avoid the need for electrostimulation.

In order to further investigate the effect of ARNI therapy, a study was carried out on a group of 120 patients meeting the following criteria: HF in the II-IV class according to NYHA, LVEF <40% and implanted ICD with the possibility of telemonitoring (14). Patients were followed for 18 months: the first 9 months during treatment with ACE-I (ramipril) or ARB (valsartan) only, and the next 9 months with ARNI (sacubitril/valsartan). Patients were also treated with beta-blockers and MRA. The majority of patients (76%) in the study were men, the average age was 70 years. In almost 82% of the subjects there was an ischemic etiology of HF. The mean value of LVEF in the subjects was 30%. The use of ARNI was associated with
improvement in NYHA functional class, reduction of NT-proBNP concentration and decrease in blood pressure. It is worth noting that fewer ICD shocks were observed in the ARNI group. Patients receiving ARNI experienced one adequate and one inadequate ICD shock for nine months, while patients receiving ACE-I or ARB experienced eight adequate and three inadequate ICD shocks. The new drug also reduced the risk of persistent ventricular tachycardia (VT) (0.8% versus 6.7%), non-sustained VT (nsVT) (mean 5.4 vs 15 episodes per patient). The authors of the study did not provide any data on mortality, so presumably several deaths occurred during the 18-month follow-up or there were no deaths at all. However, the most important is the fact that reduction of ventricular arrhythmias with ARNI therapy was the main factor reducing the risk of SCD. Potential mechanisms to reduce this arrhythmia are not fully understood. It is worth noting that the potassium concentration was significantly higher in the group of patients treated with ARNI, but there were no significant differences in the concentration of potassium in the blood between patients with or without ventricular arrhythmias. The main weakness of this study is that initially all patients were treated with ACE-I or ARB alone, after which they were switched to ANRI. The improvement of parameters both in HF and the risk of ventricular arrhythmias may be partly related to the optimization of treatment and strict control of patients.

In a retrospective analysis, a cohort of 151 HFrEF patients with ICD or CRT with remote telemonitoring and treated with ACE-I or ARB were switched to sacubitril/valsartan. After the introduction of sacubitril/valsartan the percentage of ventricular arrhythmias (VT/ventricular fibrillation (VF), nsVT, premature ventricular complexes (PVC)) and adequate therapy of the device decreased. An improvement in the percentage of the resynchronization therapy was also observed in patients with an initial low percentage (<90%) of biventricular stimulation. At the same time, after changing to sacubitril/valsartan no difference in the burden of atrial fibrillation was observed in relation to the initial treatment with ACE-I or ARB (25).
In another small single-center registry SUMA (Sacubitril/Valsartan Used in Outpatients in Madrid) 108 outpatient patients were recruited on the day of initiation of the treatment with sacubitril/valsartan. Electric storm (defined as ≥ 2 episodes of sustained ventricular arrhythmia or defibrillations within 24 hours) requiring discontinuation of the therapy occurred in 6 (5.6%) patients within a short time after switching to sacubitril/valsartan. The total number of days of administration of sacubitril/valsartan was 5.6, 44 (8 on titration), 84, 93 and 136 (105 on titration), respectively (26). The data presented, due to the nature of the study and the small number of patients, are not sufficient to suggest a potential relationship of sacubitril/valsartan with an increased risk of electric storm episodes. Further studies are needed regarding the potential proarrhythmic effect of sacubitril/valsartan.

The presented research results emphasize that intensive pharmacotherapy should be the first step in the treatment of patients with HFrEF and increased risk of ventricular arrhythmias, while the potential anti-arrhythmic effect of sacubitril/valsartan still requires further research.

**Influence of ARNI on the effectiveness of resynchronization therapy**

Currently, no reliable data is available, whether routine ACE-I or ARB conversion to ANRI can be beneficial in the primary prevention of SCD, which is an intriguing and controversial question requiring further research. Still little is known about the potential impact of ARNI on the optimization of CRT. Induced by left bundle branch block (LBBB) mechanical dyssynchrony affects the severity of HF symptoms, adverse left ventricle remodeling and worsening of prognosis. The use of CRT is the method recommended in symptomatic HFrEF patients with LBBB to reduce the symptoms of HF and reduce morbidity and mortality (2).

In the de Diego et al. study in the sacubitril/valsartan group, a reduction in the prevalence of PVC was observed (33 ± 12 vs 78 ± 15, p <0.003 respectively) and a trend towards a reduction in the incidence of episodes of paroxysmal atrial tachycardia and atrial
fibrillation in comparison to treatment with ramipril or valsartan (14). Prior to the study, cardiac rhythm control was optimized in patients with atrial fibrillation. All patients with known permanent or paroxysmal atrial fibrillation associated with impaired biventricular pacing underwent percutaneous radiofrequency ablation of atrioventricular node (14). The reduction in the number of PVC and atrial arrhythmias observed in the study translated into a statistically significant higher percentage of biventricular pacing (95% ± 6 vs 98.8% ± 1.3, p <0.02) (14). According to current knowledge, morbidity and mortality increases with the reduction in the percentage of biventricular pacing. The main causes of loss of ventricular pacing are atrial tachyarrhythmia, mainly atrial fibrillation and PVC. It is estimated that many PVCs account for approximately 20% of cases of patients with a reduced rate of biventricular pacing (27).

**Conclusions - recommendations**

– Reduction in mortality when using sacubitril/valsartan (ARNI) is strongly associated with a modification of the risk of SCD and death due to an exacerbation of HF.

– Adding ARNI (in exchange for ACE-I) to the current optimal pharmacotherapy, regardless of the presence of an implantable device, may bring additional benefits, including a reduction in the risk of SCD.

– Optimization of pharmacotherapy with ARNI in patients with ICD or CRT may translate into a reduction in the risk of adequate and inadequate device interventions and an improvement in the rate of biventricular pacing of the resynchronisation systems and improvement of the quality of life and prognosis.

– The role of ARNI in the treatment of supraventricular arrhythmias and the determination of indications for ICD or CRT implantation as part of the primary prevention of SCD is currently not clearly established.


**Contribution statement**

All the authors contributed significantly to the creation and design of the manuscript. MG, KO, PB and GO carried out a literature review and wrote the manuscript. RD, MMF, AG, EJP, ZK, PL, JN, and AP carried out a critical revision of the manuscript. All the authors critically corrected the manuscript. All authors finally approved the manuscript.

**Conflict of interest**

KO - lecture fees from Novartis, participation in Novartis clinical trials;

PB - lecture fees from Novartis, participation in Novartis clinical trials;

RD - lack;

MMF - lecture and consultancy fees: Medtronic, Abbott, Boston Scientific, Zoll;

AG - lecture fees from Novartis;

EJP - lecture and consultancy fees from Medtronic, Biotronik, Abbott, Boston Scientific;

ZK -
Table 1. Summary of guidelines on use of sacubitril/valsartan in patients with HFrEF. Based on the references: (2, 13, 18).

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ESC 2016 guidelines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sacubitril/valsartan is recommended as a replacement for an ACE-I to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF (LVEF ≤35%) NYHA class II-IV, who remain symptomatic despite optimal treatment with an ACE-I, a beta-blocker and an MRA.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Treatment with beta-blocker, MRA, and sacubitril/valsartan reduces the risk of sudden death and is recommended for patients with HFrEF and ventricular arrhythmias (as for other patients).</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td><strong>2017 ACC/AHA/HFSA guidelines update</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The clinical strategy of inhibition of the renin-angiotensin system with ARNI in conjunction with beta blockers, and MRA in selected patients, is recommended for patients with chronic HFrEF (LVEF ≤40%) NYHA class II-III to reduce morbidity and mortality.</td>
<td>I</td>
<td>B-R</td>
</tr>
</tbody>
</table>
In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE-I or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality. | I | B-R |
---|---|---|
ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor. | III | B-R |
ARNI should not be administered to patients with a history of angioedema. | III | C-EO |

**2017 CCS guidelines update**

We recommend that an ARNI be used in place of an ACE-I or ARB, in patients with HFrEF (LVEF ≤40%) NYHA class II-IV, who remain symptomatic despite treatment with appropriate doses of GDMT to decrease cardiovascular death, HF hospitalizations, and symptoms. | Strong | High |

ACC – American College of Cardiology, ACE-I - angiotensin converting enzyme inhibitors, AHA – American Heart Association, ARB - angiotensin-receptor blockers, ARNI - angiotensin receptor neprilysin inhibitors, CCS - Canadian Cardiovascular Society, ESC – European Society of Cardiology, GDMT - guideline-directed medical therapy, HF – heart failure, HFrEF – heart failure with reduced left ventricle ejection fraction, HFSA - Heart Failure Society of America, MRA - mineralocorticoid receptor antagonists

B-R randomized trials,

C-EO – consensus of expert opinion,

a Patient should have elevated natriuretic peptides (plasma BNP ≥150 pg/mL or plasma NT-proBNP ≥600 pg/mL, or if HF hospitalization within the last 12 months, plasma BNP ≥100 pg/mL or plasma NT-proBNP ≥400 pg/mL) and able to tolerate enalapril 10 mg b.i.d.
Table 2. Summary of main outcomes from the PARADIGM-HF trial and post-hoc analyses comparing sacubitril/valsartan with enalapril in patients with HFrEF. Based on the references: (3, 21).

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death</td>
<td>0.84 (0.76-0.93)</td>
</tr>
<tr>
<td>Death from CV causes</td>
<td>0.80 (0.71-0.89)</td>
</tr>
<tr>
<td>Sudden death</td>
<td>0.80 (0.68-0.94)</td>
</tr>
<tr>
<td>Death from HF worsening</td>
<td>0.79 (0.64-0.98)</td>
</tr>
<tr>
<td>Death from CV causes or first hospitalization for HF worsening</td>
<td>0.80 (0.73-0.87)</td>
</tr>
<tr>
<td>Non-CV death</td>
<td>1.09 (0.84-1.41)</td>
</tr>
<tr>
<td>First hospitalization for HF worsening</td>
<td>0.79 (0.71-0.89)</td>
</tr>
<tr>
<td>Total number of HF hospitalizations</td>
<td>0.77 (0.67-0.89)</td>
</tr>
<tr>
<td>Intensification of outpatient therapy&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.84 (0.74-0.94)</td>
</tr>
<tr>
<td>ED visit for HF worsening&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.66 (0.52-0.85)</td>
</tr>
<tr>
<td>Receiving of IV positive inotropic drugs</td>
<td>0.69 (0.57-0.85)</td>
</tr>
<tr>
<td>Total number of CV hospitalizations</td>
<td>0.84 (0.76-0.92)</td>
</tr>
<tr>
<td>Total number of hospitalizations for any reason</td>
<td>0.84 (0.78-0.91)</td>
</tr>
<tr>
<td>Patients requiring cardiac resynchronization, ventricular assist device implantation, or cardiac transplantation</td>
<td>0.78 (0.60–1.02)</td>
</tr>
</tbody>
</table>

CI – confidence interval, CV – cardiovascular, ED – emergency department, HF – heart failure, HR – hazard ratio,

<sup>a</sup> i.v. or an increase in daily diuretics for >1 month

<sup>b</sup> treated in the emergency department and discharged before hospital admission