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 Sections of the Polish Cardiac Society

Marcin Grabowski[1], Krzysztof Ozierański[1], Paweł Balsam[1], Rafał Dąbrowski[2], Michał M. Farkowski[2], Andrzej Gackowski[3], Ewa Jędrzejczyk-Patej[4], Zbigniew Kalarus[4], Przemysław Leszek[5], Jadwiga Nessler[3], Maciej Sterliński[6], Grzegorz Opolski[1], Andrzej Przybylski[7]

1 1st Department of Cardiology, Medical University of Warsaw, Warsaw, Poland
2 2nd Department of Coronary Artery Disease, The Cardinal Stefan Wyszyński Institute of Cardiology, Warsaw, Poland
3 Department of Coronary Disease and Heart Failure, Jagiellonian University Medical College, Institute of Cardiology, John Paul II Hospital, Kraków, Poland
4 Clinical Department of Cardiology, Department of Cardiology, Congenital Heart Disease and Electrotherapy, Silesian Center for Heart Diseases, Zabrze, Poland
5 Department of Heart Failure and Transplantology, The Cardinal Stefan Wyszyński Institute of Cardiology, Warsaw, Poland
6 Department of Arrhythmia, The Cardinal Stefan Wyszyński Institute of Cardiology, Warsaw, Poland
7 Faculty of Medicine, University of Rzeszów, Rzeszów, Poland

KEY WORDS
angiotensin receptor–neprilysin inhibitor, heart failure, sacubitril/valsartan, sudden cardiac death, ventricular arrhythmia

ABSTRACT
Exacerbation of chronic heart failure (HF) is the most common cause of hospitalization in adults, which is associated with high morbidity and mortality rates, mainly due to HF exacerbation or sudden cardiac death (SCD). A novelty in the treatment of HF with reduced left ventricular ejection fraction (HFrEF) in recent years has been the approval of sacubitril/valsartan, a drug belonging to angiotensin receptor–neprilysin inhibitors (ARNIs). Sacubitril/valsartan significantly reduces the severity of HF symptoms as well as the risk of hospitalization and death and is characterized by a good safety profile. Therefore, it has a strong position in the guidelines of international cardiac societies. However, the precise mechanism underlying the beneficial effects of ARNIs on cardiovascular mortality is unknown. The advantages of ARNIs are likely to result from improved left ventricular ejection fraction, reduced myocardial remodeling, and increased natriuretic peptide availability. Therefore, sacubitril/valsartan may exhibit antiarrhythmic properties and reduce the risk of ventricular arrhythmias and SCD in patients with HFrEF. Importantly, the improvement of the function and electrical stabilization of cardiomyocytes may translate into a reduced risk of appropriate and inappropriate implantable cardioverter-defibrillator interventions and improvement in the percentage of biventricular pacing. In this expert opinion of the Heart Rhythm and Heart Failure Sections of the Polish Cardiac Society, we summarize and discuss the current knowledge on the effect of sacubitril/valsartan on the occurrence of ventricular arrhythmias and the risk of SCD in patients with chronic HFrEF.

Correspondence to:
Paweł Balsam, MD, PhD, 1st Department of Cardiology, Medical University of Warsaw, ul. Banacha 1a, 02-097 Warszawa, Poland, phone: +48 22 599 19 58, email: pawel.balsam@wum.edu.pl
Received: September 16, 2019.
Accepted: September 17, 2019.
Published online: September 17, 2019.
Kardiol Pol. 2019; 77 (10): 987-993
doi:10.33963/KP.14972

Introduction Current trends show that the prevalence of heart failure (HF) is still increasing.[1] Decompensated HF is the most frequent cause of hospitalization in adults, which results in high morbidity and mortality as well as poor quality of life.[1,2] Patients with HF with reduced left ventricular ejection fraction (HFrEF) have a high risk of sudden

cardiac death (SCD).[2] It is estimated that approximately 40% of deaths in patients with HFrEF are related to SCD caused mainly by ventricular arrhythmia.[3] Numerous studies have shown that the risk of SCD in HFrEF is lower with optimal medical treatment using angiotensin-converting enzyme inhibitors (ACEIs), β-blockers, and mineralocorticoid receptor antagonists (MRAs). According to the guidelines, the use of angiotensin receptor blockers (ARBs) should be limited to patients with intolerance to ACEIs. Cardiac device therapies such as implantable cardioverter-defibrillator (ICD) implantation and cardiac resynchronization therapy (CRT) are also recommended in selected patients to further reduce morbidity and mortality.[2] According to recent European registries, the use of ICD implantations and CRT has been increasing, with the current rates of 10% to 24% and 7% to 14% of patients, respectively.[4-6]

Considering the above data, HF constitutes a considerable financial burden for the health care system and patients.[7] Therefore, continuous efforts are needed to optimize the management of HF, including an improvement in pharmacologic treatment, cardiac device therapy, and outpatient care. An important novelty in the treatment of HFrEF in recent years has been the approval of a new medicinal product containing a combination of valsartan and sacubitril, belonging to angiotensin receptor–neprilysin inhibitors (ARNIs). In the PARADIGM-HF study (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure), sacubitril/valsartan compared with enalapril significantly reduced the risk of hospitalization and death for HF, providing a real chance for further improvement in medical treatment of HF.[3] The first published data on the use of sacubitril/valsartan in Polish outpatients with HFrEF showed a significant reduction of HF symptoms, improved exercise tolerance, a reduction in natriuretic peptide levels, and good tolerance of the drug.[8]

In this position paper, we review the current knowledge on the effect of sacubitril/valsartan on the occurrence of ventricular arrhythmia and the risk of SCD in patients with HFrEF. Our aim was to discuss the potential antiarrhythmic properties of sacubitril/valsartan and their implication for improving the quality of life and prognosis of these patients.

Pathophysiological and clinical reasons for using angiotensin receptor–neprilysin inhibitors in the prevention of sudden cardiac death Despite years of research, investigators have not found strong predictive factors of ventricular arrhythmia and SCD in patients with HFrEF. The strongest association with SCD was shown for reduced left ventricular ejection fraction (LVEF). Therefore, LVEF is the only parameter used as an indication for ICD implantation for primary prevention of SCD.[9] It is increasingly difficult to identify patients who will benefit from ICD implantation, especially among patients with nonischemic cardiomyopathy. Therefore, an important strategy to reduce the risk of SCD may be a further intensification of pharmacological treatment. This may be achieved with sacubitril/valsartan, currently the only representative of the new class of ARNIs. The precise mechanism by which ARNIs affect cardiovascular mortality is unknown. Sacubitril/valsartan acts simultaneously on the 2 main pathways activated in HF: it blocks the angiotensin II receptor (valsartan) and inhibits neprilysin (sacubitril). Stimulation of the angiotensin II type-2 (AT2) receptor, a component of the renin–angiotensin–aldosterone axis, results in increased sympathetic activity, cardiac hypertrophy, reverse remodeling, fibrosis, and coagulability disorders. Finally, it leads to cardiomyocyte dysfunction, which in turn contributes to the proarrhythmic effect. Therefore, by blocking the AT2 receptor, valsartan reverses many of those unfavorable effects. Neprilysin is an enzyme that degrades natriuretic peptides, bradykinin, adrenomedullin, and other vasoactive peptides. Heart failure is associated with increased neprilysin activity, resulting in a higher degradation of natriuretic peptides whereby they no longer exert their beneficial effects. Inhibition of neprilysin by sacubitril has a positive impact on the cardiovascular system by a vasodilating action and improvement in the availability of natriuretic peptides, which in turn leads to an increase in natriuresis and diuresis as well as a reduction of left ventricular and vascular remodeling.[10,11]

The PARADIGM-HF trial included patients with an LVEF of 40% or less (mean, 29%; interquartile range, 25%–34%). In a multivariate analysis, LVEF was a significant and independent predictor of all study outcomes. Importantly, sacubitril/valsartan was shown to be effective in reducing cardiovascular death and hospitalization for HF across the LVEF spectrum.[12] The ongoing PARAGON-HF trial (Prospective Comparison of ARNI with ARB Global Outcomes in HF With Preserved Ejection Fraction; clinicaltrials.gov, NCT01920711) should clarify whether patients with preserved LVEF will also benefit from the use of sacubitril/valsartan. In the PARADIGM-HF study, patients treated with sacubitril/valsartan were also less likely to require a cardiac device implantation or cardiac transplant (hazard ratio [HR], 0.78; 95% confidence interval [CI], 0.60–1.02; $P = 0.07$).[3]

Natriuretic peptides are one of the promising predictors of SCD.[9] The levels of N-terminal fragment of the prohormone brain natriuretic peptide (NT-proBNP) were shown to correlate

with beneficial effects of treatment; therefore, their measurement is recommended for monitoring and adjustment of HF therapy.[1,13] Patients treated with sacubitril/valsartan, compared with those receiving enalapril, showed an early (within 30 days) and sustained reduction of NT-proBNP and troponin levels, while brain natriuretic peptide (BNP) levels increased due to neprilysin inhibition.[3] Elevated NT-proBNP levels were reported to correlate with the number of premature ventricular contractions (PVC) and ICD shocks due to ventricular arrhythmia.[14]

A reduction in the risk of ventricular arrhythmia in the PARADIGM-HF trial might result from intensification of HF treatment by combining the 2 molecules—sacubitril and valsartan. A reduction of preload and afterload, an improvement of left ventricular function due to neprilysin inhibition, and a reduction of myocardial fibrosis, myocardial ischemia, and sympathetic tone (shown in preclinical studies)[15] might play an important role in modification of the fatal ventricular arrhythmia substrate.

Current status of angiotensin receptor–neprilysin inhibitors in the guidelines on the treatment of heart failure and ventricular arrhythmias In patients with HFrEF, a simultaneous treatment with an ACEI (or ARB if ACEI is not tolerated or contraindicated) and a β-blocker should be initiated to reduce the risk of HF hospitalization and death. In symptomatic patients with an LVEF of 35% or lower, MRAs are recommended to further reduce the risk.[2] These medications should be gradually uptitrated to target or maximum tolerated doses to achieve adequate inhibition of the sympathetic system activity. However, observational studies have shown that the majority of HF patients receive suboptimal doses of the recommended drugs,[4,16] which directly correlates with worse prognosis.[17]

The 2016 European Society of Cardiology (ESC) guidelines on HF recommended the use of sacubitril/valsartan instead of ACEIs (or ARBs) in ambulatory patients with HFrEF (LVEF ≤35%) who remain symptomatic (NYHA functional class II—IV) despite optimal treatment with an ACEI (or ARB), a β-blocker, and an MRA to further reduce the risk of death and HF hospitalization (class of recommendation I, level of evidence B). According to the inclusion criteria defined in the PARADIGM-HF study, patients should have elevated natriuretic peptide levels (plasma BNP ≥150 pg/ml or plasma NT-proBNP ≥600 pg/ml, or BNP ≥100 pg/ml or NT-proBNP ≥400 pg/ml if the patient was hospitalized for HF in the last 12 months) and should tolerate ACEI doses equivalent to enalapril 10 mg twice daily.[2] On the other hand, the guidelines developed by the American College of Cardiology, American Heart Association Task Force on Clinical Practice Guidelines, and the Heart Failure Society of America recommend the use of ARNIs in patients with similar characteristics but with an LVEF of 40% or lower and a NYHA class II–III.[13] Finally, the 2017 Canadian Cardiovascular Society guidelines recommend the use of ARNIs instead of ACEIs (or ARBs) in patients with HFrEF (LVEF ≤40%) treated with target or maximally tolerated doses of an ACEI (or ARB if ACEI intolerant), β-blockers, and MRAs who remain symptomatic (NYHA class II–IV).[18]

The 2015 ESC guidelines for the management of ventricular arrhythmias and prevention of SCD (before sacubitril/valsartan was approved) confirmed the antiarrhythmic effects of ACEIs, ARBs, β-blockers, MRAs, and implantable cardiac devices, and recommended the use of ablation or surgery for SCD prevention.[9] However, none of the available antiarrhythmic drugs had been proved to effectively reduce the risk of life-threatening ventricular arrhythmias and SCD.[9] In the 2016 ESC guidelines on HF, treatment with ACEIs, β-blockers, MRAs, and sacubitril/valsartan was recommended particularly in patients with HFrEF and ventricular arrhythmias in order to reduce the risk of SCD (class of recommendation I, level of evidence A).[19] International guidelines on the use of ARNIs in patients with HFrEF are summarized in TABLE 1.

Practical guidance on the implementation and monitoring of the effects of sacubitril/valsartan was published previously in a position paper of the Heart Failure Working Group of the Polish Cardiac Society.[20] Preliminary clinical experience with the use of ARNIs in Poland has also been reported.[8]

Ventricular arrhythmias: results of the PARADIGM-HF study Briefly, PARADIGM-HF was a double-blind study including 8442 patients with chronic HF (NYHA classes II–IV) and an LVEF of 40% or lower, treated with guideline-recommended medical therapy. Patients were randomized in a 1:1 ratio to enalapril, 10 mg twice daily, or sacubitril/valsartan, 200 mg twice daily.[3] Patients were on potentially optimal medical treatment with high rates of using guideline-recommended medications: ACEIs, 100%; β-blockers, 93%; and MRAs, 55%. The PARADIGM-HF study was terminated prematurely (median follow-up, 27 months) due to the clear benefits of sacubitril/valsartan compared with enalapril. The study showed a reduction in all-cause and cardiovascular mortality, incidence of SCD, mortality and hospitalizations due to HF, and the severity of HF symptoms. Patients in the sacubitril/valsartan group more often had hypotension, but they had a lower risk of hyperkaliemia, renal impairment, and cough than patients in the enalapril group. The main findings of the PARADIGM-HF trial and post-hoc analyses are summarized in TABLE 2.

Patients with implantable cardiac devices were underrepresented in the PARADIGM-HF study: approximately 15% of patients had

TABLE 1 Summary of guidelines on the use of sacubitril / valsartan in patients with heart failure with reduced left ventricular ejection fraction

Recommendations	Class of recommendation	Level of evidence
2016 ESC guidelines[2]		
Sacubitril / valsartan is recommended as an alternative to an ACEI 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 ACEI, a β-blocker, and an MRA.[a]	I	B
Treatment with a β-blocker, an MRA, and sacubitril / valsartan reduces the risk of sudden death and is recommended for patients with HFrEF and ventricular arrhythmias (like for other patients).	I	A
2017 ACC / AHA / HFSA guideline update[13]		
Inhibition of the renin–angiotensin–aldosterone system with ARNIs in conjunction with β-blockers and MRAs in selected patients is recommended for patients with chronic HFrEF (LVEF ≤40%; NYHA class II–III) to reduce morbidity and mortality.	I	B-R
In patients with chronic symptomatic HFrEF (NYHA class II or III) who tolerate an ACEI or ARB, switching to an ARNI is recommended to further reduce morbidity and mortality.	I	B-R
ARNIs should not be administered simultaneously with ACEIs or within 36 hours since the last dose of an ACEI.	III	B-R
ARNIs should not be administered to patients with a history of angioedema.	III	C-EO
2017 CCS guideline update[18]		
An ARNI is recommended instead of an ACEI or ARB in patients with HFrEF (LVEF ≤40%; NYHA class II–IV) who remain symptomatic despite optimal guideline-directed medical therapy to reduce the risk of cardiovascular death, rate of hospitalizations for HF, and severity of HF symptoms.	Strong	High

a In patients with elevated natriuretic peptide levels (plasma BNP ≥150 pg/ml or NT-proBNP ≥600 pg/ml, or plasma BNP ≥100 pg/ml or NT-proBNP ≥400 pg/ml in the case of HF hospitalization within the last 12 months) and who tolerate enalapril at a dose of 10 mg twice daily.

Abbreviations: ACC, American College of Cardiology; ACEI, angiotensin-converting enzyme inhibitor; AHA, American Heart Association; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; B-R, moderate level of evidence from 1 or more randomized clinical trials; CCS, Canadian Cardiovascular Society; C-EO, consensus of expert opinion; ESC, European Society of Cardiology; HF, heart failure; HFrEF, heart failure with reduced left ventricular ejection fraction; HFSA, Heart Failure Society of America; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association

an ICD, and 7%, CRT.[3] The rate of SCD did not differ between patients with or without an ICD.[21] The benefits of a lower SCD risk were observed mainly in patients with mild-moderate symptoms of HF (NYHA class I–III), while mortality in patients with NYHA class IV HF was mainly related to HF worsening. Optimization of pharmacological therapy with ACEIs, β-blockers, MRAs, and sacubitril / valsartan is expected to reduce the risk of SCD.[9] Implantation of an ICD within 40 days after myocardial infarction was shown to offer no benefits. It is recommended only after optimization of pharmacological therapy (3–9 months) if LVEF is maintained at a level of 35% or lower.[2,22] After the diagnosis of HF, the therapy should be adjusted not more often than once in 2 weeks and uptitrated to target (or maximally tolerated) doses within 3 to 6 months.[13] In patients with HFrEF, MRAs are recommended before the introduction of ARNIs to improve outcomes, but it is not obligatory.[13] Three months after achieving optimal therapy, left ventricular function should be assessed to evaluate indications for ICD or CRT. Importantly, the beneficial effects of sacubitril / valsartan were maintained even after dose reduction (HR, 0.80; 95% CI, 0.70–0.93; P <0.001) and were similar to those observed in patients without dose reduction (HR, 0.79; 95% CI, 0.71–0.88; P <0.001).[23] However, each 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).

An important limitation of the PARADIGM-HF study is that the antiarrhythmic effect of sacubitril / valsartan was not the primary endpoint, which reduces the statistical reliability as well as raises concerns regarding the accurate assessment of outcomes observed for the reduction of SCD risk. Moreover, because enalapril was used in the control group, it is not possible to determine whether the potential antiarrhythmic effect was exerted by valsartan or sacubitril.

Other studies on angiotensin receptor–neprilysin inhibitors and ventricular arrhythmia In a meta-analysis of 12 clinical trials involving over 40 000 patients with HFrEF, Shen et al[18] showed that the risk of SCD in this group decreased almost by half in the last 2 decades due to progress in pharmacotherapy. During the 90-day follow-up, the overall mortality rate was 2.4% in the RALES study (the first of the series of trials) to 1% in the PARADIGM-HF study (the most recent trial) and doubled over

TABLE 2 Main outcomes of the PARADIGM-HF trial and post hoc analyses comparing sacubitril/valsartan with enalapril in patients with heart failure with reduced left ventricular ejection fraction[3,21]

Outcome	HR (95% CI)
All-cause mortality	0.84 (0.76–0.93)
Cardiovascular mortality	0.80 (0.71–0.89)
Sudden death	0.80 (0.68–0.94)
Death from HF exacerbation	0.79 (0.64–0.98)
Cardiovascular mortality or first hospitalization for HF exacerbation	0.80 (0.73–0.87)
Noncardiovascular mortality	1.09 (0.84–1.41)
First hospitalization for HF exacerbation	0.79 (0.71–0.89)
Total number of HF hospitalizations	0.77 (0.67–0.89)
Intensification of outpatient therapy[a]	0.84 (0.74–0.94)
ED visit due to HF exacerbation[b]	0.66 (0.52–0.85)
Use of intravenous positive inotropic drugs	0.69 (0.57–0.85)
Total number of cardiovascular hospitalizations	0.84 (0.76–0.92)
Total number of hospitalizations for any reason	0.84 (0.78–0.91)
Need for cardiac resynchronization, left ventricular assist device implantation, or cardiac transplant	0.78 (0.60–1.02)

a Use of intravenous diuretics or an increase in the use of diuretics for >1 month

b Treatment in the ED and discharge before hospital admission

Abbreviations: CI, confidence interval; ED, emergency department; HR, hazard ratio; others, see TABLE 1

the next 90 days. The high-risk group included older people, men, as well as patients 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 chronic) and overall mortality.

Considering the effectiveness of the analyzed drugs in reducing the overall mortality, a careful selection is needed when referring patients with HFrEF for cardiac device therapy in the primary prevention of SCD. The DANISH study emphasized the need to identify a subgroup of high-risk patients in whom ICD implantation will be most beneficial as well as the subgroups of patients in whom intensive medical treatment will be sufficient.[24] In most patients, the current guidelines recommend the use of intensive medical treatment for at least 3 months, with repeat assessment of LVEF prior to a cardiac device implantation. However, it may take even up to 12 months to reduce the left ventricular volume and increase LVEF after the start of treatment. Therefore, a period of 3 months may be too short to observe a sufficient improvement in left ventricular function to avoid cardiac device therapy.

In 2017, a study was published that assessed the effect of ARNIs in 120 patients meeting the following criteria: HF in NYHA classes II–IV, LVEF of less than 40%, and an implanted ICD with the possibility of telemonitoring.[14] Patients were followed for 18 months: during the first 9 months, they were treated with an ACEI (ramipril) or ARB (valsartan) only, and during the subsequent 9 months, with an ARNI (sacubitril/valsartan). They were simultaneously treated with β-blockers and MRAs. Most patients in the study were men (76%), and the mean age of the study group was 70 years. Almost 82% of the patients had HF of ischemic etiology. The mean LVEF was 30%. The use of sacubitril/valsartan was associated with an improvement in NYHA functional class, reduction of NT-proBNP levels, and a decrease in blood pressure. Moreover, it was related to fewer ICD shocks. Patients receiving the ARNI experienced 1 appropriate and 1 inappropriate ICD shock during 9 months, as compared with 8 appropriate and 3 inappropriate ICD shocks in patients receiving the ACEI or ARB. The new drug also reduced the risk of sustained ventricular tachycardia (VT) (0.8% vs 6.7%) and nonsustained VT (mean 5.4 vs 15 episodes per patient, respetively). No data on mortality were reported, so presumably several or no deaths occurred during the 18-month follow-up. However, the most important finding was that the reduction of ventricular arrhythmias with ARNI therapy was the main reason for lowering the risk of SCD. Potential mechanisms underlying the reduction of VT are not fully understood. Of note, the potassium concentration was significantly higher in patients treated with ARNI, but there were no

significant differences in the blood potassium concentration between patients with or without ventricular arrhythmias. The main limitation of this study is that all patients were first treated with the ACEI or ARB alone and were then switched to the ARNI. The improvement in terms of HF and the risk of ventricular arrhythmias may be partly related to the optimization of treatment and strict patient monitoring.

In a retrospective study, a cohort of 151 patients with HFrEF and with an implanted ICD or CRT with remote telemonitoring were switched from an ACEI or ARB to sacubitril/valsartan.[25] After the introduction of sacubitril/valsartan, the authors observed a decrease in the burden of ventricular arrhythmias (VT/ventricular fibrillation, nonsustained VT, PVCs), resulting in reduced occurrence of appropriate therapy. An improvement in the rate of resynchronization therapy was also observed in patients with a low percentage of biventricular pacing (<90%) at baseline. At the same time, no difference was observed in the severity of atrial fibrillation after switching to sacubitril/valsartan.[25]

Another small single-center registry study, SUMA (Sacubitril/Valsartan Used in Outpatients in Madrid), recruited 108 outpatients on the day of starting sacubitril/valsartan therapy. Electrical storm (defined as ≥2 episodes of sustained ventricular arrhythmia or defibrillation within 24 hours) requiring therapy discontinuation occurred in 6 patients (5.6%) shortly after introducing sacubitril/valsartan. The total number of days of sacubitril/valsartan administration was 5, 6, 44 (8 since titration), 84, 93, and 136 (105 since titration), respectively.[26] However, because of the study design and a small number of patients, the presented data were not sufficient to suggest a potential relationship between sacubitril/valsartan and an increased risk of electrical storm. Further studies are needed to elucidate the potential proarrhythmic effect of sacubitril/valsartan.

The results of the above studies emphasize that intensive pharmacological treatment should be the first step in the treatment of patients with HFrEF and an increased risk of ventricular arrhythmias, while further research should clarify whether sacubitril/valsartan has antiarrhythmic properties.

Influence of angiotensin receptor–neprilysin inhibitors on the effectiveness of resynchronization therapy Currently, there are no reliable data to support the potential benefits of switching from routine ACEI or ARB to ANRI in the primary prevention of SCD. This interesting and controversial issue requires further research. Still little is known about the potential impact of ARNIs on the optimization of CRT. Mechanical dyssynchrony induced by left bundle branch block results in increased severity of HF symptoms, adverse left ventricular remodeling, and worsening of prognosis. The use of CRT is recommended in symptomatic patients with HFrEF with left bundle branch block to reduce the symptoms of HF as well as morbidity and mortality.[2]

In the study by de Diego et al,[14] patients receiving sacubitril/valsartan were shown to have a lower prevalence of PVCs than patients on ramipril or valsartan (mean [SD], 33 [12] vs 78 [15]; P <0.003). They also showed a trend towards a reduction in the incidence of paroxysmal atrial tachycardia and atrial fibrillation. Prior to the study, cardiac rhythm monitoring was optimized in patients with atrial fibrillation. All patients with known permanent or paroxysmal atrial fibrillation associated with impaired biventricular pacing underwent percutaneous atrioventricular node radiofrequency ablation.[14] The reduction in the number of PVCs and atrial arrhythmias was associated with a higher percentage of biventricular pacing (mean [SD], 95% [6%] vs 98.8% [1.3%]; P <0.02). According to current knowledge, morbidity and mortality rates increase with the reduction in the percentage of biventricular pacing. The main reasons for the loss of CRT pacing are atrial tachyarrhythmias, particularly atrial fibrillation and PVCs. It is estimated that numerous PVCs account for approximately 20% of cases of a reduced percentage of biventricular pacing.[27]

Summary: recommendations In summary, a reduction in mortality during sacubitril/valsartan treatment is strongly associated with a modified risk of SCD and death due to exacerbation of HF. The addition of ARNIs (instead of ACEIs) to the current optimal medical treatment, regardless of the presence of an implantable device, may or not offer additional benefits, including a reduction in the risk of SCD. Optimization of medical treatment with ARNIs in patients with an ICD or CRT may reduce the risk of appropriate and inappropriate ICD shocks as well as increase the rate of biventricular pacing, thus improving the quality of life and prognosis of these patients. Finally, the role of ARNIs in the treatment of supraventricular arrhythmias as well as in establishing the indications for ICD or CRT implantation for primary prevention of SCD is not fully elucidated.

SUPPLEMENTARY MATERIAL

Polish version of the paper is available as supplementary material at www.mp.pl/kardiologiapolska.

ARTICLE INFORMATION

CONTRIBUTION STATEMENT All authors contributed to the writing and design of the manuscript. MG, KO, PB, and GO reviewed the literature and wrote the manuscript. RD, MMF, AG, EJ-P, ZK, PL, JN, and AP contributed to critical revision of the manuscript. All authors edited the manuscript and approved its final version.

CONFLICT OF INTEREST KO, PB, and GO received lecture fees from Novartis and participated in Novartis clinical trials. MMF received lecture and consultancy fees from Medtronic, Abbott, Boston Scientific, and Zoll; AG received lecture fees

from Novartis. EJ-P received lecture and consultancy fees from Medtronic, Biotronik, Abbott, and Boston Scientific. The remaining authors do not declare any conflicts of interest.

HOW TO CITE Grabowski M, Ozierański K, Balsam P, et al. 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 Sections of the Polish Cardiac Society. Kardiol Pol. 2019; 77: 987-993. doi:10.33963/KP.14972

REFERENCES

1 Yancy CW, Januzzi JL Jr, Allen LA, et al. 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol. 2018; 71: 201-230.

2 Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure [in Polish]. Kardiol Pol. 2016; 74: 1037-1147.

3 McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014; 371: 993-1004.

4 Komajda M, Anker SD, Cowie MR, et al. Physicians' adherence to guideline-recommended medications in heart failure with reduced ejection fraction: data from the QUALIFY global survey. Eur J Heart Fail. 2016; 18: 514-522.

5 Balsam P, Tyminska A, Kaplon-Cieslicka A, et al. Predictors of one-year outcome in patients hospitalised for heart failure: results from the Polish part of the Heart Failure Pilot Survey of the European Society of Cardiology. Kardiol Pol. 2016; 74: 9-17.

6 Maggioni AP, Anker SD, Dahlstrom U, et al. 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: 1173-1184.

7 Czech M, Opolski G, Zdrojewski T, et al. The costs of heart failure in Poland from the public payer's perspective. Polish programme assessing diagnostic procedures, treatment and costs in patients with heart failure in randomly selected outpatient clinics and hospitals at different levels of care: POLKARD. Kardiol Pol. 2013; 71: 224-232.

8 Kaluzna-Oleksy M, Kolasa J, Migaj J, et al. Initial clinical experience with the first drug (sacubitril/valsartan) in a new class - angiotensin receptor neprilysin inhibitors in patients with heart failure with reduced left ventricular ejection fraction in Poland. Kardiol Pol. 2018; 76: 381-387.

9 Priori SG, Blomstrom-Lundqvist C, Mazzanti A, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death [in Polish]. Kardiol Pol. 2015; 73: 795-900.

10 Nessler J, Straburzynska-Migaj E, Windak A, et al. Expert consensus on the usefulness of natriuretic peptides in heart failure [in Polish]. Kardiol Pol. 2018; 76: 215-224.

11 Mills J, Vardeny O. The role of neprilysin inhibitors in cardiovascular disease. Curr Heart Fail Rep. 2015; 12: 389-394.

12 Solomon SD, Claggett B, Desai AS, et al. Influence of ejection fraction on outcomes and efficacy of sacubitril/valsartan (LCZ696) in heart failure with reduced ejection fraction: the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) Trial. Circ Heart Fail. 2016; 9: e002744.

13 Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol. 2017; 70: 776-803.

14 de Diego C, Gonzalez-Torres L, Nunez JM, et al. Effects of angiotensin-neprilysin inhibition compared to angiotensin inhibition on ventricular arrhythmias in reduced ejection fraction patients under continuous remote monitoring of implantable defibrillator devices. Heart Rhythm. 2018; 15: 395-402.

15 von Lueder TG, Wang BH, Kompa AR, et al. Angiotensin receptor neprilysin inhibitor LCZ696 attenuates cardiac remodeling and dysfunction after myocardial infarction by reducing cardiac fibrosis and hypertrophy. Circ Heart Fail. 2015; 8: 71-78.

16 Opolski G, Ozieranski K, Lelonek M, et al; on behalf of the Polish Qualify Investigators. Adherence to the guidelines on the management of systolic heart failure in ambulatory care in Poland. Data from the international QUALIFY survey. Pol Arch Intern Med. 2017; 127: 657-665.

17 Komajda M, Cowie MR, Tavazzi L, et al. Physicians' guideline adherence is associated with better prognosis in outpatients with heart failure with reduced ejection fraction: the QUALIFY international registry. Eur J Heart Fail. 2017; 19: 1414-1423.

18 Ezekowitz JA, O'Meara E, McDonald MA, et al. 2017 Comprehensive update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure. Can J Cardiol. 2017; 33: 1342-1433.

19 Dickstein K, Normand C, Auricchio A, et al. CRT Survey II: a European Society of Cardiology survey of cardiac resynchronisation therapy in 11 088 patients-who is doing what to whom and how? Eur J Heart Fail. 2018; 20: 1039-1051.

20 Straburzynska-Migaj E, Nessler J, Gruchala M, et al. Sacubitril/valsartan for treatment of chronic heart failure with reduced ejection fraction. Can all patients benefit? A position statement paper of experts of the Heart Failure Working Group of the Polish Cardiac Society. Kardiol Pol. 2017; 75: 286-293.

21 Desai AS, McMurray JJ, Packer M, et al. Effect of the angiotensin-receptor-neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients. Eur Heart J. 2015; 36: 1990-1997.

22 Ganga HV, Maan A, Kevin Heist E. Should primary prevention ICDs still be placed in patients with non-ischemic cardiomyopathy? A review of the evidence. Curr Cardiol Rep. 2018; 20: 31.

23 Vardeny O, Claggett B, Packer M, et al. Efficacy of sacubitril/valsartan vs. enalapril at lower than target doses in heart failure with reduced ejection fraction: the PARADIGM-HF trial. Eur J Heart Fail. 2016; 18: 1228-1234.

24 Kober L, Thune JJ, Nielsen JC, et al. Defibrillator implantation in patients with nonischemic systolic heart failure. N Engl J Med. 2016; 375: 1221-1230.

25 Martens P, Nuyens D, Rivero-Ayerza M, et al. Sacubitril/valsartan reduces ventricular arrhythmias in parallel with left ventricular reverse remodeling in heart failure with reduced ejection fraction. Clin Res Cardiol. 2019; 108: 1074-1082.

26 Vicent L, Juarez M, Martin I, et al. Ventricular arrhythmic storm after initiating sacubitril/valsartan. Cardiology. 2018; 139: 119-123.

27 Cheng A, Landman SR, Stadler RW. Reasons for loss of cardiac resynchronization therapy pacing: insights from 32 844 patients. Circ Arrhythm Electrophysiol. 2012; 5: 884-888.