GERIATRYCZNE PROBLEMY KLINICZNE/GERIATRICS CLINICAL PROBLEMS
Otrzymano/Submitted: 15.05.2022 • Zaakceptowano/Accepted: 20.05.2022

Hiperkaliemia i zaburzenia czynności nerek po jednoczesnym zastosowaniu sakubitrylu, walsartanu i dapagliflozyny – opis przypadku i przegląd piśmiennictwa

Hyperkalemia and renal dysfunction after simultaneous the use of sacubitril, valsartan and dapagliflozin – case report and literature review

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Summary

Background. Hyperkalemia is a potentially life-threatening disorder associated with cardiac arrhythmias and sudden cardiac death. It occurs when serum potassium level exceeds 5.5 mmol/l. The risk of hyperkalemia increases with age and in case of renal failure, diabetes, dehydration, a diet with the high potassium content and drug therapy. Some drugs known to increase the risk of hyperkalemia are renin-angiotensin-aldosterone system inhibitors (RAASi). Although the therapy with these drugs reduce morbidity and mortality in heart failure (HF) with reduced ejection fraction, it also poses a therapeutic dilemma considering the adverse reaction in the form of hyperkalemia. ***Material and methods.*** We describe a case report of a 91-year-old female patient treated for heart failure who reported severe weakness during the follow-up visit in April 2022. History of STEMI anterior wall infarction treated with LAD coronary angioplasty with DES stent implantation. After myocardial infarction, the patient used carvedilol, perindopril, indapamide, torasemide, eplerenone, acetylsalicylic acid and atorvasterol. In December 2021, the patient was admitted to the hospital with signs of exacerbation of chronic heart failure, with pulmonary edema. The patient had swelling of the lower legs. From December 2021, the patient was taking sacubitril, valsartan, dapagliflozin, bisoprolol, acetylsalicylic acid, atorvasterol and eplerenone. Laboratory tests showed increased levels of potassium, uric acid, creatinine urea and decreased eGFR. ***Results.*** Valsartan, sacubitril and flozin were discontinued. For five days, the patient received 0.9% NaCl and 20 mg furosemide/day intravenously, which improved the patient's health. The patient's treatment was modified – ramipril was introduced 2.5 mg/day, and the remaining pharmacotherapy was continued. At the follow-up visit after 14 days, the patient did not report dyspnoea, edema or weakness. ***Conclusions.*** The described case confirms the risk of hyperkalemia and impaired kidney function which could have occurred as a result of drug interactions recommended in the pharmacotherapy of heart failure. *Geriatria 2022;16:171-178. doi: 10.53139/G.20221618*

Keywords: hear failure, hyperkalemia, RAASi, flozins

Streszczenie

Wstęp. Hiperkaliemia jest potencjalnie zagrażającym życiu zaburzeniem prowadzącym do występowania zaburzeń rytmu serca i nagłego zgonu sercowego. Występuje, gdy poziom potasu w surowicy przekracza 5,5 mmol/l. Ryzyko hiperkaliemii wzrasta wraz z wiekiem oraz w przypadku niewydolności nerek, cukrzycy, odwodnienia, diety o wysokiej zawartości potasu i terapii pewnymi lekami. Jednymi z leków, które zwiększają ryzyko hiperkaliemii są inhibitory układu renina-angiotensyna-aldosteron (RAASi). Chociaż terapia tymi lekami zmniejsza zachorowalność i śmiertelność w niewydolności serca (HF) z obniżoną frakcją wyrzutową, to biorąc pod uwagę działanie niepożądane w postaci hiperkaliemii przywodzi również dylemat terapeutyczny. ***Materiał i metody.*** Przedstawiamy przypadek 91-letniej pacjentki leczonej z powodu niewydolności serca, która zgłosiła silne osłabienie podczas wizyty kontrolnej w kwietniu 2022 roku. W wywiadzie zawał serca STEMI ściany przedniej leczony angioplastyką wieńcową LAD z implantacją stentu DES. Po zawale serca chora stosowała carvedilol, perindopril, indapamid, torasemid, eplerenon, kwas acetylosalicylowy i atorwasterol. W grudniu 2021 pacjentka trafiła do

szpitala z cechami zaostrzenia przewlekłej niewydolności serca, z obrzękiem płuc. U pacjentki występowały obrzęki podudzi. Pacjentka stosowała od grudnia 2021 sakubitryl, walsartan, dapagliflozynę, bisoprolol, kwas acetylosalicylowy, atorwasterol i eplerenon. W badaniach laboratoryjnych odnotowano zwiększone stężenie potasu, kwasu moczowego, mocznika, kreatyniny oraz obniżony eGFR. ***Wyniki.*** Odstawiono walsartan, sakubitryl oraz flozynę. Przez pięć dni chora otrzymywała 0,9 % NaCl i dożylnie 20 mg furosemidu /dobę, co wpłynęło na poprawę stanu zdrowia pacjentki. Zmodyfikowano leczenie chorej – włączono ramipryl 2,5 mg /dobę, kontynuując pozostałą farmakoterapię. Podczas wizyty kontrolnej po 14 dniach pacjentka nie zgłaszała duszności, obrzęków i osłabienia. ***Wnioski.*** Opisany przypadek potwierdza ryzyko wystąpienia hiperkaliemii i zaburzenia funkcji nerek, do której mogło dojść w wyniku interakcji pomiędzy stosowanymi przez pacjentkę lekami zalecanymi w farmakoterapii niewydolności serca. *Geriatria 2022;16:171-178. doi: 10.53139/G.20221618*

Słowa kluczowe: niewydolność serca, hyperkaliemia, RAASi, flozyny

Introduction

Disturbances in the electrolyte balance, especially in potassium, are among the most common abnormalities in clinical practice [1-2]. Potassium is the most abundant cation in the human body – 2% (3.5 and 5.0 mM) is extracellular while 98% (120–140 mM) is intracellular, located mainly in skeletal muscle cells [3,4]. It is an essential element responsible for proper cellular function – it contributes to the regulation of cell volume and intracellular pH, enzymatic functions, and protein and glycogen synthesis [4]. A complex interplay of multiple factors, including renal and gastrointestinal function, medications, supplements, diet, neurohormonal status, and acid-base balance, has an impact on the content and distribution of potassium among the body compartments. The alterations in potassium regulation can result in neuromuscular, gastrointestinal, or cardiac abnormalities [3]. Hyperkalemia, a potentially life-threatening disorder associated with cardiac arrhythmias and sudden cardiac death, occurs when serum potassium level exceeds 5.5 mmol/l [5,6]. According to the RALES study, an increased mortality risk occurs when serum potassium levels rise above 5.5 mEq/L (5.5 mmol/L) [7]. This state may be caused by increased potassium intake, a decrease in excretion, and a shift of this ion from the intracellular to the extracellular space. Hyperkalemia is diagnosed primarily in hospitalized patients (1-10%), while in outpatients over 55 years of age, this disorder occurs less frequently (0.2-0.7%) due to irregular monitoring of electrolyte parameters. The factors increasing the risk of hyperkalemia include age (after 40 years of age, on average, 1 ml/min/year GFR decreases; faster in men), renal failure, diabetes (the main cause of hypoaldosteronism, impairing renal potassium excretion), dehydration, drug therapy and a diet with the high potassium content. The spectrum of clinical symptoms of hyperkalemia is vast – from oligosymptomatic syndromes to death. However, due to the efficient mechanisms of potassium homeostasis (mainly cation excretion by the kidneys), this disorder is rarely observed in people with normal kidney function [1]. In patients suffering from diseases such as chronic kidney disease (CKD), heart failure (HF), and diabetes mellitus (DM), the risk of hyperkalemia is increased 2 to 3 times [1,8,9]. According to the recent data, in patients with the abovementioned conditions (or a combination of these), there is a U-shaped curve of increased mortality associated with serum potassium values above or below 4.0-5.0 mEq/L (normokalemia-K+ ~ 3.5-5 mEq/L). Hence, over-correction of this condition (serum K^+ < 4.0 mEq/L) should be avoided at all costs in this patient group, while hyperkalemia is of concern [6,10]. Apart from pathological conditions, medications used by the patient may also play an essential role in the pathomechanism of these changes. Some drugs known to increase the risk of hyperkalemia (in individuals with cardiovascular disease) are renin-angiotensin-aldosterone system inhibitors (RAASi) – disease-modifying drugs in heart failure with reduced ejection fraction, that also have a positive impact in other cardiovascular conditions. RAASi include angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, mineralocorticoid receptor antagonists, and angiotensin receptor-neprilysin inhibitors [1,5,9]. It has been observed, that the incidence of hyperkalemia in patients with cardiovascular disease (CVD) receiving RAASi in real-world clinical practice exceeds that observed in clinical trials [11]. In patients with HF and concomitant CKD and/or DM,

the risk of RAASi-induced hyperkalemia is exceptionally high – approximately half of these patients experience two or more recurrences of hyperkalemia within one year [9-10]. In addition, even mild hyperkalemia has been independently associated with a significantly increased risk of mortality in this population [10]. Although RAASi represent life-saving therapy, it also entails a therapeutic dilemma, as patients who benefit most from the therapy with drugs from this group are typically those at the greatest risk of associated, severe hyperkalemic events [6].

Case

A 91-year-old female patient treated for heart failure reported severe weakness during the follow-up visit in April 2022. From December 2021, after hospitalization, the patient was treated with a daily regimen: sacubitril 24 mg, valsartan 26 mg, dapagliflozin 10 mg, bisoprolol 2.5 mg, acetylsalicylic acid 75 mg, atorvasterol 20 mg, eplerenone 25 mg and periodically iron preparations. The family doctor ordered laboratory tests, which showed increased levels of potassium, uric acid, creatinine urea and decreased eGFR (estimated glomerular filtration rate) (Table I).Valsartan, sacubitrile and dapagliflozin were discontinued. The patient had been treated with 0.9% NaCl (500 ml) and intravenously 20 mg furosemide/day for five days, which improved the patient's health and the results of laboratory tests. The treatment was modified – ramipril 2.5 mg/day was introduced, and the remaining pharmacotherapy was continued. At the follow-up visit after 14 days, the patient did not report dyspnea, edema or weakness. The patient's history involves STEMI myocardial infarction in the anterior wall (treated with LAD coronary angioplasty with DES stent implantation in 2019), arterial hypertension, post-acute pancreatitis, post-cholecystectomy, post-left nephrectomy (1982). After myocardial infarction, the patient used the daily treatment regimen: carvedilol 25 mg, perindopril 10 mg, indapamide 1.5 mg, torasemide 10 mg, eplerenone 50 mg, acetylsalicylic acid 75 mg and atorvasterol 20 mg. In December 2021, the patient was admitted to the hospital with signs of exacerbation of chronic heart failure with pulmonary edema. The patient was allo- and autopsychically oriented. Auscultation revealed bilateral crackles to the angles of the scapulae, soft heart sounds accentuated correctly, and an audible systolic murmur over the aortic valve and at Erb's point. The patient had edema of the lower legs. The performed ECG showed: normal sinus rhythm 75/min, left axis deviation, left anterior hemiblock (LAH) and Q wave in I, aVL, and V2-3. Echocardiography revealed: unexpanded heart cavities, LK wall thickness 10 mm each, second-degree pulmonary valve regurgitation, systolic dysfunction – akinesia of the apex and adjacent segments of the PMK, lateral and anterior walls, EF 45%, no evidence of fluid in the pericardium. During hospitalization, the following daily doses were included: valsartan 26 mg, sacubitril 24 mg and dapagliflozin 10 mg. Dyspnoea, edema and pulmonary congestion resolved during the treatment. Laboratory examination showed: Pro-BNP 2938.9 pg/ml when admitted, Pro-BNP 1443.0 pg/ml when discharged (reference values <450.0 pg/ml, for patients with chronic heart failure, it is recommended to maintain the Pro-BNP value of approx. 1000 pg/ml).

Discussion

Heart failure (HF) has a worldwide diffusion, and it has been the subject of sustained interest since it was designated as a new epidemic 25 years ago due to an exponential increase in hospitalizations of patients with HF, which generated a hypothesis examined in several epidemiological investigations. However, it has been demonstrated that in White populations there was no increase in the incidence of HF since the

Table I. Test results before, after and after discontinuation of sacubitril, valsartan and dapagliflozin
Tabela I. Wyniki badań laboratoryjnych przed, po włączeniu i po wycofaniu z terapii sakybitrylu, walsartanu i dapagliflozyny

Parameter	Before starting the medications	90 days after starting the medications	After discontinuation of the medications	Reference value
K+	4,1 mmol/l	6,1 mmol/l	4,69 mmol/l	3,5-5,1 mmol/l
Urea	39 mg/dl	139 mg/dl	40 mg/dl	15-40 mg/dl
Creatinine	0,81 mg/dl	1,62 mg/dl	1.09mg/dl	0,57-1,11 mg/dl
eGFR	60ml/min/1,73m^2	23ml/min/1,73m^2	36ml/min/1,73m^2	≥60ml/min/1,73m^2

middle of the 20th century. The observed increase in hospitalizations was an outcome of the improvement in survival after the HF diagnosis that led to an increase in the number of individuals living with HF requiring further hospitalizations [12]. The frequency of HF depends on age. In the general adult population, it is 1-2%, but its frequency increases rapidly after the age of 75, and in people aged 70-80, it reaches up to 20%. Based on epidemiological data, it is estimated that there are about 1 million HF sufferers in Poland [13]. The evidence-based medical therapies reduce heart failure (HF) hospitalizations, improve survival and quality of life for patients with HF and reduced ejection fraction (HFrEF) with mild to moderate symptoms. In patients with HFrEF and advanced symptoms, evidence for the use of medical therapy is less comprehensive insofar as it is often difficult to achieve the dose(s) of a neurohormonal antagonist because of dose-limiting symptomatic hypotension or worsening renal function, or both. Therefore, contemporary guidelines for advanced HFrEF do not concentrate on medical therapy and recommend that these patients should be considered for mechanical circulatory support, cardiac transplantation, or palliative care [14]. Due to the growing population of patients with HF and poor prognosis (about 50% of 5-year mortality), new therapeutic solutions (both non-invasive and invasive) are sought in order to treat patients more and more effectively [15].

It is known that the long-term morbidity and mortality in patients with heart failure with reduced ejection fraction (HFrEF) are improved by treatments that target the renin-angiotensin-aldosterone system (RAAS) [16]. The HF guidelines from 2016 introduced a new product to the treatment regimen of patients with HF-LCZ696. This product combines the action of an angiotensin II receptor inhibitor (valsartan) and a neprilysin inhibitor (sacubitril). Sacubitril/valsartan (S/V), a first-in-class angiotensin receptor neprilysin inhibitor (ARNI), simultaneously suppresses RAAS activation through blockade of angiotensin II type 1 receptors and enhances vasoactive peptides, including natriuretic peptides (NPs) through inhibition of the enzyme responsible for their degradation- neprilysin [16]. The clinical effects of the combination of S/V are manifested by vasodilation and lowering blood pressure, increasing urinary sodium excretion and diuresis, inhibiting the RAA (renin-angiotensin-aldosterone) system and sympathetic nervous system activity and preventing unfavorable remodeling of the heart muscle [15]. The global PARADIGM-HF (Prospective Comparison of Angiotensin II Receptor Blocker Neprilysin Inhibitor With Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure) randomized trial compared S/V with enalapril in ambulatory patients with HFrEF. The cardiovascular mortality or hospitalization rates for patients with HF were reduced thanks to S/V therapy by a relative 20% and all-cause mortality by a relative 16% [17,18]. According to actuarial estimates, it was evaluated that treatment with sacubitril/valsartan would result in a projected benefit of 1 to 2 years of increased life expectancy and survival free from heart failure for patients with HFrEF, across a wide range of age groups [19]. Srivastava et al. reported that the 5-year estimated number needed to treat (NNT) was 14 when S/V was compared to enalapril for the primary outcome of CV death or HF hospitalization [20]. Based on these findings, the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) approved S/V for treatment of HFrEF in 2015 [14]. The guidelines published in 2016 by the European Society of Cardiology (ESC) informed about giving the class I, evidence level B, to the recommendation of the use of S/V instead of an angiotensin-converting enzyme (ACE) inhibitor in order to further reduce the risk of death and hospitalization due to HF in outpatients with stable HF and documented LVEF ≤ 35%, in whom the symptoms in grade II – IV according to NYHA persist despite optimal treatment with an ACE inhibitor (or an antagonist of the AT1 receptor for angiotensin II [ARB, angiotensin receptor blocker]), beta-blocker and mineralocorticoid receptor antagonist (MRA) [5]. Clinical trials and clinical practice indicate that sacubitril/valsartan is safe and well-tolerated by patients. In fact, there are many other comorbidities in patients with HF. They often require physicians who change the therapy or dosage of drugs. The most common comorbidities are renal failure and diabetes. Particular attention should be paid to kidney function parameters to select the drug dose and safely conduct the therapy appropriately. Attention should also be paid to blood glucose levels in diabetic patients treated with metformin, as therapy with S/V may lower blood glucose levels. Less common diseases in this patient group are liver function disorders or renal artery stenosis. Parameters such as blood pressure and potassium concentration require special attention as both low BP values and elevated serum potassium levels are common in HF patients [21].

Drugs from the group of sodium-glucose co-transporter-2 (SGLT-2) inhibitors (flozins) that have been used in the treatment of diabetes were recently discovered to improve and prevent HF. These drugs help reduce hyperglycemia (antidiabetic effect), body weight, and blood pressure. The outcome trials have been shown to reduce hospitalizations for HF in patients with type 2 DM treated with SGLT2 inhibitors. The protective cardiovascular mechanisms of flozins are complex, multifactorial, and not entirely understood. Apart from the diuretic-like function, these drugs may mitigate glycemic-related toxicity, improve cardiac metabolism and bioenergetics by elevating the production of ketones, increase hematocrit, improve tissue oxygen delivery and exert antihypertrophic, antifibrotic, and antiremodeling properties [22,23]. The clinical efficacy of dapagliflozin in the treatment of HFrEF was documented in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) study – a multicenter, prospective, randomized phase III placebo-controlled trial to evaluate the efficacy and safety of dapagliflozin in comparison with placebo [24]. Based on the results of the DAPA-HF study, the EMA and the FDA approved dapagliflozin in 2020 for treating patients with symptomatic chronic HFrEF [25]. The conducted clinical trials, observations of RWE (real-world evidence) and several years of experience show that dapagliflozin is a safe drug. Adverse events (AEs), serious AEs, and those leading to discontinuation of dapagliflozin treatment are rare and at a similar frequency as in the placebo group [24].

During the last few years, several studies have been performed to scrutinize the effects of sacubitril/valsartan and dapagliflozin on renal function and potassium levels to estimate the risk of hyperkalemia. Yavin et al. analyzed fourteen randomized, placebo-controlled, double-blind studies including patients with type 2 diabetes mellitus (T2DM): pooled data from thirteen studies of ≤24 weeks' duration (dapagliflozin 10 mg, N = 2360; placebo, N = 2295); and one 52-week moderate renal impairment study in patients with baseline eGFR ≥30 to <60 mL/min/1.73 m^2 (dapagliflozin 10 mg, N = 85; placebo, N = 84). Central laboratory serum potassium levels were determined at each study visit. There were no reports of clinically relevant mean changes from baseline in serum potassium ≤24 weeks for dapagliflozin 10 mg [-0.05 mmol/L; 95% confidence interval (CI) -0.07, -0.03] versus placebo (-0.02 mmol/L; 95% CI -0.04, 0.00) in the pooled population or in the renal impairment study (-0.03 mmol/L; 95% CI -0.14, 0.08 vs. -0.02 mmol/L; 95% CI -0.13, 0.09, respectively). In the pooled population, the incidence rate ratio for serum potassium ≥5.5 mmol/L over 24 weeks for dapagliflozin 10 mg versus placebo was 0.90 (95% CI 0.74, 1.10). Slightly more patients receiving dapagliflozin 10 mg had serum potassium ≤3.5 mmol/L versus placebo (5.2% vs. 3.6%); however, no instances of serum potassium ≤2.5 mmol/L were reported. There was a conclusion that in patients with T2DM dapagliflozin is not associated with an increased risk of hyperkalemia or severe hypokalemia [26]. However, there was a report of a T2DM patient with potential mineralocorticoid deficiency who developed hyperkalemia after administration of dapagliflozin. The patient developed hyperkalemia (6.5 mEq/L) with increased plasma renin activity of 53.1 ng/mL/h after starting treatment with dapagliflozin [27]. In the DAPA-HF (Dapagliflozin And Prevention of Adverse outcomes in Heart Failure) trial, 4,744 patients with heart failure with reduced ejection fraction (HFrEF) were randomized to placebo or dapagliflozin 10 mg daily. The researchers aimed to assess the efficacy and safety of dapagliflozin in patients taking or not taking an mineralocorticoid receptor antagonist (MRA). Only small changes in mean potassium between baseline and 8 months occurred in each MRA subgroup, but it did not differ between dapagliflozin and placebo. Mild hyperkalemia (K+ >5.5 mmol/l) occurred in 180 of 1,632 patients (11.0%) in the dapagliflozin group and 204 of 1,625 patients (12.6%) in the placebo group within the MRA-treated group. In the group of patients not treated with MRA the corresponding numbers were 63 of 660 (9.6%) and 57 of 682 (8.4%). Moderate/severe hyperkalemia (potassium >6.0 mmol/l) occurred in 21 of 1,683 (1.3%) patients treated with dapagliflozin and in 40 of 1,666 (2.4%) patients treated with placebo in the patients treated with MRA, while in the group without MRA, the corresponding numbers were 13 of 675 (1.9%) and 11 of 695 (1.6%). The results showed lower rates of hyperkalaemia with dapagliflozinin the subgroup of individuals treated with MRAs and suggested that dapagliflozin was similarly efficacious and safe in patients with HFrEF taking or not taking an MRA, supporting the use of both drugs together [28]. Although this observation has not been confirmed in EMPEROR-Reduced, results showed fewer discontinuation of MRAs among patients prescribed with empagliflozin [29]. An important piece of informa-

tion in the context of standard HFrEF therapy is that dapagliflozin may lower the risk of moderate/severe hyperkalemia in patients receiving MRA [30]. Reduced rates of hyperkalemia with SGLT2 inhibitors have also been observed in clinical trials focused on patients with CKD [31]. A trial by Heerspink et al. revealed that among patients with CKD, regardless of the presence or absence of diabetes, the risk of a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal cause was 0.56 (95% CI, 0.45 to 0.68; P<0.001)- significantly lower with dapagliflozin than with placebo [32]. A randomized control trial by McMurray et al., which purpose was to investigate the effects of dapagliflozin in CKD patients, with and without HF, enrolled a total of 4,304 participants (with CKD, with and without type 2 diabetes) randomized to dapagliflozin 10 mg daily or placebo. The primary composite endpoint was >/50% decline in estimated GFR, end-stage kidney disease, or kidney/cardiovascular death; other endpoints were a kidney composite (primary endpoint minus cardiovascular death), the composite of cardiovascular death/HF hospitalization, and all-cause death. Rates of prespecified adverse events were low overall and were generally similar in the HF and no HF subgroups. The adverse event rates were similar in patients assigned to dapagliflozin and placebo, irrespective of history of HF. Regarding the individuals with HF, serious adverse events attributed to acute kidney injury were reported in 8 (3.4%) patients assigned to dapagliflozin and 10 (4.3%) assigned to placebo; HR: 0.72 (95% CI: 0.28-1.82). The corresponding results in patients without HF were 46 (2.4%) and 59 (3.1%); HR: 0.78 (95% CI: 0.53-1.14), (P interaction ¼ 0.87) [33].

Renal dysfunction and hyperkalemia are factors limiting target doses of RAS antagonists. Both renal dysfunction (serum creatinine ≥2.5 mg/dl [221 μmol/l]) and severe hyperkalemia (>6mmol/l) occurred less frequently with sacubitril/valsartan, compared with enalapril in PARADIGM-HF [34]. Damman et al. evaluated the renal effects of sacubitril/valsartan in patients with heart failure and reduced ejection fraction. They found that the decline in eGFR over time was attenuated with sacubitril/valsartan, compared to enalapril, despite a small increase in urinary albumin/creatinine ratio (UACR) with neprilysin inhibition. Furthermore, patients with CKD at baseline (at particularly high risk of adverse outcomes) had a similar relative risk reduction with S/V compared with enalapril and, thus, a large absolute benefit from adding a neprilysin inhibitor to RAS blockade [35]. The risk of hyperkalemia is increased in case of a combination of an MRA with a RAS blocker. According to the PARADIGM-HF, patients on an MRA at baseline who were randomly assigned to enalapril experienced severe hyperkalemia at higher rates than those randomized to sacubitril/valsartan, suggesting that the addition of neprilysin inhibition to dual RAAS blockade may reduce the risk of hyperkalemia associated with this combination [36] [34]. In work by Solomon et al., one can find the data informing that patients on the sacubitril–valsartan were more likely to have hypotension (S/V 15.8 % vs valsartan 10.8%) but less likely to have increases in the creatinine and potassium levels than those taking valsartan [37]. A multicenter, randomized, double-blind trial by Berg et al. scrutinized in-hospital initiation of sacubitril/valsartan (n = 440) versus enalapril (n = 441) in patients stabilized during hospitalization for acute decompensated HF. The composite of cardiovascular death or rehospitalization due to HF was assessed. Safety outcomes included worsening renal function, symptomatic hypotension and hyperkalemia. In each high- versus low-risk subgroup, the risks of renal function worsening, symptomatic hypotension, and hyperkalemia with sacubitril/valsartan versus enalapril were also consistent. Treatment with S/V after initial stabilization conferred a consistent reduction in cardiovascular death or rehospitalization for HF and was well tolerated in high-risk subpopulations admitted for acute decompensated HF [38]. In case of impaired renal function, no dose adjustment is necessary for patients with mild (eGFR 60-90 ml/min/1.73 m^2) symptoms. In patients with moderate renal impairment (eGFR 30-60 ml/min/1.73 m2) an initial dose of 24 mg/26 mg twice daily should be considered. As clinical experience in patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2) is limited, S/V should be used with caution and a starting dose of 24 mg/26 mg twice daily is recommended. There is no experience with the use of S/V in patients with end-stage renal disease; therefore, the use of this drug in these patient groups is not recommended [39]

Conclusion

The described case confirms the risk of adverse reactions to drugs the patient applies. The safety data of the preparation containing valsartan and neprilysin indicate the possibility of, i.a., high blood potassium

levels, low blood pressure and impaired renal function. The recommendations for dapagliflozin point out that special care should be taken in the elderly due to the greater risk of renal failure. Monitoring serum potassium concentration and renal function parameters is reasonable not only before initiating these two drugs into therapy, especially in elderly patients. Observation of renal function and potassium concentration is also necessary during the therapy because incorrect values of these determinations may force the reduction of doses of drugs or their discontinuation.

Conflict of interest
None

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