Pharmacotherapy of heart failure A.D. 2023. Expert opinion of Working Group on Cardiovascular Pharmacotherapy, Polish Cardiac Society

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DOI: 10.33963/KP.a2023.0110

Received:
April 21, 2023

Accepted:
April 21, 2023

Early publication date:
May 2, 2023

ABSTRACT

Heart failure (HF) remains one of the most common causes of hospitalization and mortality among Polish patients. The position of the Section of Cardiovascular Pharmacotherapy presents the currently applicable options for pharmacological treatment of HF based on the latest European and American guidelines from 2021–2022 in relation to Polish healthcare conditions. Treatment of HF varies depending on its clinical presentation (acute/chronic) or left ventricular ejection fraction. Initial treatment of symptomatic patients with features of volume overload is based on diuretics, especially loop drugs. Treatment aimed at reducing mortality and hospitalization should include drugs blocking the renin-angiotensin-aldosterone system, preferably angiotensin receptor antagonist/neprilysin inhibitor, i.e. sacubitril/valsartan, selected beta-blockers (no class effect — options include bisoprolol, metoprolol succinate, or vasodilatory beta-blockers — carvedilol and nebivolol), mineralocorticoid receptor antagonist, and sodium-glucose cotransporter type 2 inhibitor (flozin), constituting the 4 pillars of pharmacotherapy. Their effectiveness has been confirmed in numerous prospective randomized trials. The current HF treatment strategy is based on the fastest possible implementation of all four mentioned classes of drugs due to their independent additive action. It is also important to individualize therapy according to comorbidities, blood pressure, resting heart rate, or the presence of arrhythmias. This article emphasizes the cardio- and nephroprotective role of flozins in HF therapy, regardless of ejection fraction value. We propose practical guidelines for the use of medicines, profile of adverse reactions, drug interactions, as well as pharmacoeconomic aspects. The principles of treatment with ivabradine, digoxin, vericiguat, iron supplementation, or antiplatelet and anticoagulant therapy are also discussed, along with recent novel drugs including omecamtiv mecarbil, tolvaptan, or coenzyme Q10 as well as progress in the prevention and treatment of hyperkalemia. Based on the latest recommendations, treatment regimens for different types of HF are discussed.

Key words: ACC/AHA/HFSA guidelines, ESC guidelines, heart failure, pharmacoeconomics, pharmacotherapy

Table 1. Definitions of heart failure with lowered, mildly reduced, and preserved left ventricular ejection fraction [2]

Type HF	HFrEF	HFmrEF	HFpEF
	Symptoms ± signs	Symptoms ± signs	Symptoms ± signs
	LVEF ≤40%	LVEF 41%–49%	LVEF ≥50%
	—	Recognition more likely in the presence of structural abnormalities of the heart or impaired filling of LV	Features of structural and/or functional abnormalities, corresponding to diastolic dysfunction of LV, increased filling pressure of LV, increased concentration of natriuretic peptides

Abbreviations: HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LV, left ventricle; LVEF, left ventricular ejection fraction

INTRODUCTION

There are approximately 1.2 million patients with symptomatic heart failure (HF) in Poland, i.e. 3.2% of the population of our country, and around 140 000 patients die annually. Up to 40% of patients with HF die within 5 years of diagnosis [1]. These historic data may no longer be true with optimal HF therapy, yet HF remains a very frequent cause of death. The goal of HF treatment is primarily to reduce mortality and morbidity (relieve symptoms, improve quality of life, decrease the need for hospital treatment) and prevent the progression of the disease. Most of hospital admissions, frequent in this group, are associated with deterioration in the clinical condition of the patient, which often results from inadequate disease control, including suboptimal pharmacotherapy — the primary method of HF treatment. The degree of implementation of existing treatment recommendations for HF patients is influenced by many different factors, such as the education of doctors, patient characteristics (e.g. age, concomitant diseases), and socioeconomic factors, including specific costs and availability of medicines and other treatments.

This expert opinion represents a consensus of experts designated by the Working Group on Cardiovascular Pharmacotherapy of the Polish Society of Cardiology (SFSN PTK) commenting upon the latest guidelines of the European Society of Cardiology (ESC, 2021) [2] and American scientific societies (American Heart Association [AHA], American College of Cardiology [ACC], Heart Failure Society of America — 2022 [HFSA]), and taking into account specific features of the Polish healthcare system [3]. We present characteristics of groups of drugs currently used in HF therapy, recommended in the guidelines, paying particular attention to practical aspects — possible problems during the inclusion of individual groups of drugs, monitoring after initiation of treatment, contraindications to treatment, and recommendations for the patient receiving specific therapies.

DEFINITIONS OF HEART FAILURE AND DIFFERENCES IN THERAPEUTIC RECOMMENDATIONS

Heart failure is a complex clinical syndrome resulting from any structural or functional impairment of ventricular filling or ejection, including symptoms (e.g. dyspnea, decreased exercise tolerance) that may be accompanied by signs (e.g. peripheral edema, pulmonary rales, or crackles). HF most often results from myocardial dysfunction, which can be systolic and/or diastolic. Other causes or factors contributing to HF may include abnormalities of the valves, pericardium, and endocardium, as well as arrhythmias or cardiac conduction disorders. There are usually two clinical forms of HF: chronic heart failure (CHF) and acute heart failure (AHF). The diagnosis of CHF refers to patients who have previously been diagnosed with heart failure or who have developed symptoms gradually. The term AHF refers to the rapid or gradual development of signs or symptoms of HF that are so severe that the patient requires urgent medical attention, initiation or intensification of treatment, including intravenous therapy or surgical procedures. AHF may be the first manifestation of HF (*de novo* HF) or result from acute decompensation of CHF.

The latest ESC [2] and American AHA/ACC/HFSA guidelines [3] introduced a new HF classification depending on left ventricular ejection fraction (LVEF) values (Table 1):

- HF with reduced LVEF (≤40%) — HFrEF (heart failure with reduced ejection fraction);
- HF with mildly reduced LVEF (41%–49%) — HFmrEF (heart failure with mildly reduced ejection fraction);
- HF with preserved LVEF (≥50%) — HFpEF (heart failure with preserved ejection fraction).

Pharmacotherapy is the basis for the treatment of HFrEF and aims to reduce mortality, prevent re-hospitalization due to HF severity and improve clinical condition and physical performance. Importantly, therapeutic recommendations vary from type to type of HF. The broadest set of studies concerns HFrEF, and the scientific evidence for the effectiveness of therapies of other types comes from recently completed studies. Importantly, HFrEF patients who improve ejection fraction even to values ≥50% should continue effective HFrEF pharmacotherapy and are categorized as HFimpEF (heart failure with improved EF). The dynamic development of research led to the situation where the ESC 2021 guidelines did not represent the current state of knowledge (with regard to use of flozins) as early as on the day of their presentation.

In order to achieve symptomatic improvement in patients with any type of HF and fluid overload features, diuretics (most often loop diuretics) are necessary (at least at certain stages of treatment) — although they are not categorized as prognosis-improving drugs when used long-term.

In order to reduce the risk of death or hospitalization for HF (improvement of prognosis) in HFrEF, each patient should possibly receive the following four groups of drugs:

- Renin-angiotensin-aldosterone (RAA) axis inhibitors (RAASi) — optimally sacubitril-valsartan, i.e. an angiotensin receptor antagonist in combination with a neprilysin inhibitor, which prevents the breakdown of endogenous natriuretic peptides (ARNI, angiotensin receptor-neprilysin inhibitor). These were previously preferred in HFrEF as a class of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs). They are acceptable in the case of ACEI intolerance but offer a lower degree of protection.
- Beta-blockers (BB) tested in the treatment of HFrEF (4 drugs — bisoprolol, carvedilol, extended-release metoprolol, nebivolol — a class effect is not accepted)
- Mineralocorticoid receptor antagonists (MRA) — spironolactone or eplerenone.
- Flozin (sodium-glucose cotransporter type 2 inhibitor [SGLT2i]), with evidence of benefit in the treatment of HF independently of coexisting diabetes mellitus and/or chronic kidney disease — i.e. empagliflozin or dapagliflozin.

Doses of HF medications (except flozins, having only one dose level) should be gradually increased to the doses used in clinical trials (or, if this is not possible, to the maximum tolerated doses). ARNI, originally recommended as a replacement for ACEI in stable symptomatic patients, should now be considered a first-line treatment, instead of ACEI, also after hospitalization for exacerbated HFrEF, preferably with initiation in the pre-discharge period.

In patients with HFmrEF and HFpEF, SGLT2i (dapagliflozin or empagliflozin) have become the most recommended drug class, which reduces the risk of death or hospitalization for heart failure, regardless of the coexistence of diabetes. In HFmrEF, drugs typical of HFrEF, i.e. RAASi, BB, and MRA can be used with a lower class of recommendations. Since many patients with HFmrEF/HFpEF also have chronic coronary syndrome, hypertension, or atrial fibrillation, they are still candidates for drugs from the above groups, as optimal treatment of the above-mentioned diseases is essential. According to the American recommendations, ARNI can also be used across the spectrum of heart failure.

It should be emphasized, that HF patients with EF improvement — HFimpEF (HF with improved EF) who meet the HFrEF criteria, regardless of the current LVEF value that increased thanks to typical HFrEF therapy, should absolutely continue the HFrEF treatment regimen. This group was analyzed in a targeted way by the DELIVER study, confirming the beneficial effects of dapagliflozin [4].

New strategy for the treatment of heart failure — rapid implementation of comprehensive pharmacotherapy

The conventional approach to HFrEF treatment based on initiating a single drug therapy and increasing the dose to the maximum tolerated/target before adding another drug, was based solely on the historic in which these 4 groups of drugs were tested in prospective randomized clinical trials. Unfortunately, this strategy took 6 to 12 months, during which HF progressed. Currently, a different approach is recommended, leading to the fastest possible initiation and rapid escalation of ARNI, BB, and MRA dosage, simultaneously with the initial optimal dose of SGLT2i. Each of these four drug classes provides independent and additive benefits, obtained early after starting treatment. It is the responsibility of the members of the multidisciplinary HF Team to ensure the rapid and safe implementation of these four basic treatments for HFrEF [2]. The ESC guidelines outline a treatment strategy to reduce mortality, indicating drugs and non-pharmacological therapies of first choice in HFrEF patients, taking into account the HF etiology. The new strategy for the implementation of treatment for HFrEF patients and the shift towards an individual approach to treatment depending on the clinical profile of the patient is recommended by this writing group [5] (Figure 1).

The experts' proposal for the use of the main HFrEF therapies assumes the four groups of recommended drugs ("pillars of HF therapy", "drugs of the first step", "the big four") should be optimally initiated at the same time or, alternatively, stepwise — depending on the clinical profile of the patient, but within a period not exceeding 4 weeks. The American ACC/AHA/HFSA guidelines specify that one can start treatment simultaneously or sequentially. The crucial practical recommendations are as follows:

- Simultaneous initiation takes place at the initial (low) doses recommended for HFrEF (except for SGLT2i, which are dosed from the beginning at the optimal dose), assuming monitoring of potency and side effects (including kidney function).
- Alternatively, drugs can be switched on sequentially, depending on clinical or other factors, without having to reach the target dose before starting the next drug — the priority is to complete the "four pillars of therapy" **as soon as possible**.
- Drug doses should be increased to target values according to tolerability.
- Doses of drugs can be increased faster in the hospital setting than in outpatients.
- The initiation of all four therapies is prioritized before the full dose escalation of any single "pillar".

Proper treatment of HF patients should, therefore, mainly take into account the pursuit of maximum or maximally tolerated doses of included drugs, appropriate control of drug-specific biochemical parameters, and the possibility of individualization of therapy depending on coexisting loads (this does not apply to SGLT2 inhibitors, as they are used in a single dose). The sequence can be adapted to the patient's profile and the doctor's experience.

It is suggested that beta-blockers should be included after compensation (i.e. the patient's "dry and warm" pro-

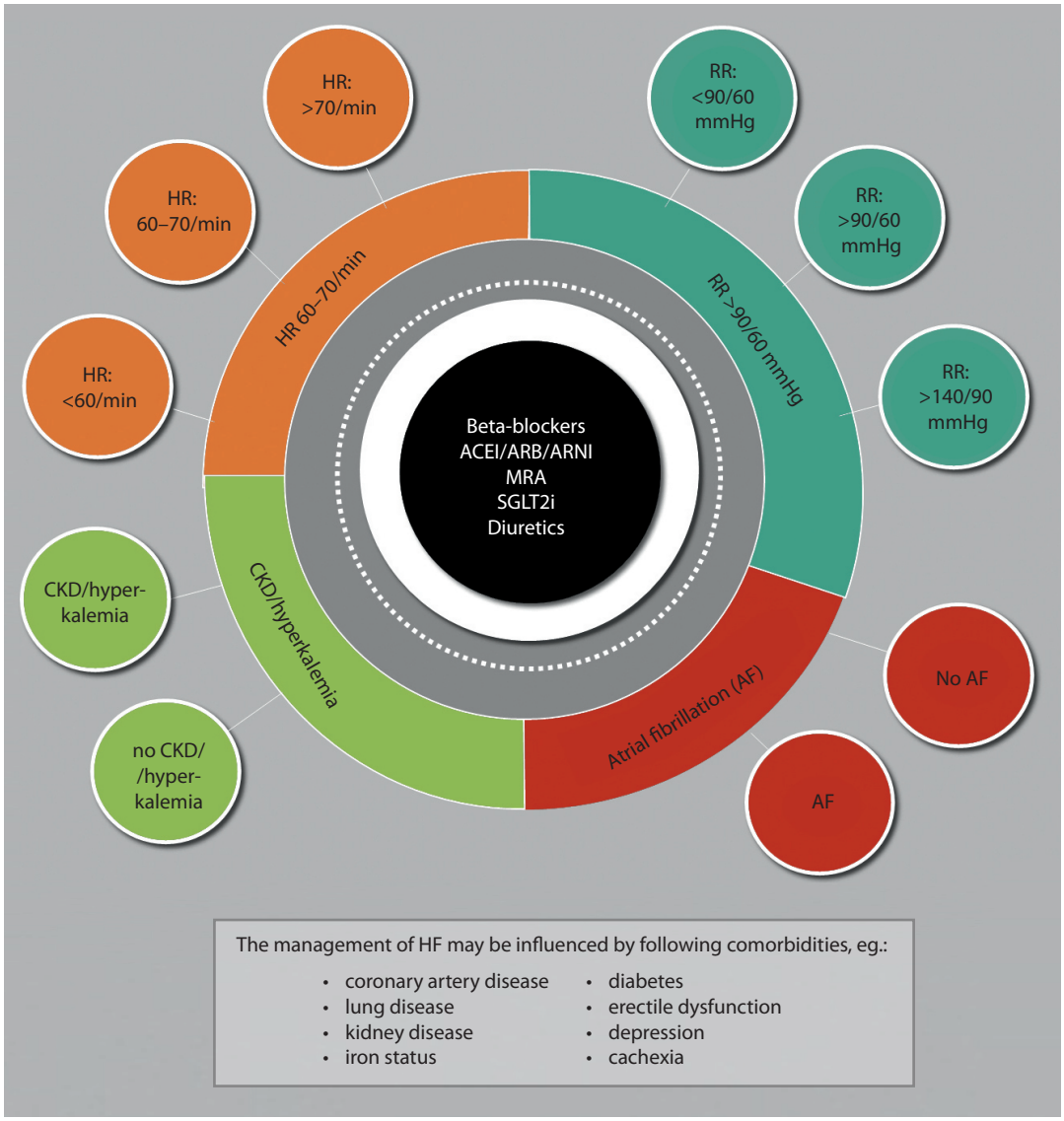

Figure 1. Profiling HFrEF treatment depending on clinical characteristics of the patient. Modified according to [4]
Abbreviations: AF, atrial fibrillation; CKD, chronic kidney disease; other — see Table 1

file), and other of the above-mentioned drugs even during a period of incomplete cardiac compensation [2]; however, the prerequisite is still the stabilization of volume status and arterial pressure.

The guidelines emphasize the superior efficacy of sacubitril/valsartan over ACEI, and the selection of appropriate therapy requires patients in New York Heart Association (NYHA) class II–III to convert from a classic RAA blockade to ARNI use to reduce mortality. The indications for use of ARNI have been significantly expanded, also with regard to hospital initiation without prior ACEI/ARB treatment, including patients hospitalized as a result of acute, decompensated HFrEF after hemodynamic stabilization [6, 7]. In addition, compared to ACEI alone, sacubitril/valsartan reduces the rate of deterioration in renal function over time, and this, together with the observation that ARNI and SGLT2i reduce the risk of hyperkalemia and improve MRA tolerance, means that the use of these two drugs in patients may increase the likelihood of safe introduction and long-term use of MRA.

Due to the unique mechanism of action of SGLT2i, these drugs can be safely initiated in most patients without end-stage renal failure. SGLT2i studies assumed prior use of RAASi/MRA/BB [2] although the benefits appear to be independent of other first-line drugs. In some patients with newly-diagnosed HFrEF, e.g. in the case of low blood pressure and impaired renal function, flozins may be initiated early to facilitate the subsequent introduction of other class I recommended drugs [8].

It is extremely important to provide the patient (and often also his/her family) with reliable information about the available possible HF pharmacotherapy with costs per month of therapy and to discuss with the patient what amount of money from the household budget can be allocated to medicines. In good communication practice, the doctor informs the patient about the indication for a given

treatment. If the recommended drug is not reimbursed, the patient should be informed about the price, without emotional interpretation, and then the patient's decision as to the possibility of buying drugs should be noted in the medical documentation. It is also important to explain to the patient that the pharmacological therapy of HF will not last one month only but will be long-term. Special issues related to treatment modifications requiring a dedicated explanation include, for example, the principles of safe conversion from ACEI to ARNI (36-hour interval before the first dose) or dose equivalence (e.g. torasemide vs. furosemide).

BLOCKADE OF THE RENIN-ANGIOTENSIN-ALDOSTERONE AXIS

Excessive activation of the renin-angiotensin-aldosterone (RAA) system is one of the main pathophysiological mechanisms of HF. Drugs that correct this pathological mechanism work by inhibiting the activity of the angiotensin-converting enzyme (ACEI), blocking the AT1 receptor for angiotensin II (ARB) or mineralocorticoid receptor (MRA, see paragraph 6) [9]. They improve survival provided that they are used continuously and at the recommended maximum tolerated doses. The latest 2021 ESC guidelines for the management of heart failure clearly strengthen the indication for sacubitril/valsartan (the only representative of ARNI to date) [2]. It is recommended for all symptomatic HFrEF patients as a first-line treatment in place of the ACEI recommended earlier. It is extremely important to explain to the patient the potential benefits of switching from the current ACEI/ARB treatment to ARNI, e.g. greater improvement in quality of life, and reduction in risk of rehospitalization for HF exacerbation, or cardiovascular death. At the same time, the patient should be informed about an increase in the cost of therapy.

Practical advice for using ARNI

1. Switching on the drug can be started in stable outpatients, as well as in patients during the stabilization period (after cardiovascular decompensation) during hospitalization — with systolic RR ≥100 mm Hg and potassium concentration ≤5.4 mmol/l;
2. Before starting treatment, kidney and liver function, serum potassium concentration, blood pressure, and volume status should be assessed; contraindications to ARNI are very similar to those to ACEI.
3. A 36-hour interval should be maintained between the last dose of ACEI (but not ARB if previously used) and the first dose of sacubitril/valsartan when switching from one drug to another; the drug can be administered with or without food;
4. As standard, the starting dose should be 49 mg/51 mg twice daily; it is possible to start with a dose of 24 mg/26 mg twice daily when the patient has not been previously treated with ACEI/ARB, has taken low doses of ACEI/ARB, or presents with systolic pressure of 100–110 mm Hg, moderate or severe renal impairment (glomerular filtration rate [GFR] below 60 ml/min/1.73 m^2) or moderate hepatic impairment;
5. If well tolerated, the initial dose of the drug should be doubled after 2-4 weeks until the target dose is reached;
6. Control of serum potassium and creatinine 1–2 weeks after the onset of treatment and after reaching the target dose, subsequent control every 4 months;
7. A slight increase in urea, creatinine, and potassium levels after therapy inititation is not uncommon; the indication for dose reduction or discontinuation may be intolerable hypotension, less frequently, clinically significant hyperkalemia or renal impairment;
8. Monitoring of treatment should be based on the determination of plasma concentration of NT-proBNP, but not BNP.

Practical guidance on the use of ACEI/ARB

Angiotensin-converting enzyme inhibitors should be used in all patients with HFrEF who have not received ARNI — the class effect is accepted in relation to improved prognosis although only some molecules have controlled prospective studies in this area. They should also be used in asymptomatic HFmrEF/HFrEF. The use of angiotensin receptor antagonists (ARBs) is recommended as an alternative treatment in patients with HFrEF who are intolerant to ACEI and ARNI to reduce the risk of hospitalization and cardiovascular death. It is worth noting that both the guidelines and the Summary of Product Characteristics allow only the use of candesartan or valsartan in this indication. Conversion from previous ARB/ACEI therapy to ARNI should be proposed to all symptomatic HFrEF patients (the benefits with EF ≥40% are poorly documented) — in Poland, a significantly higher cost of therapy represents a practical problem:

- the use of the drug should be started in stable outpatients and also in patients during the period of stabilization after decompensation of the circulatory system during hospitalization;
- kidney function and electrolyte concentration should be assessed before starting treatment and excessive diuretic treatment should be avoided;
- to minimize the risk of hypotension, treatment can be started in the evening, before bedtime;
- urea, creatinine, and serum potassium should be measured 1–2 weeks after starting treatment and 1–2 weeks after escalation of the dose; subsequent control tests should be performed every 4 months (more often in patients with renal impairment and/or a tendency to electrolyte disturbances);
- do not discontinue ACEI too hastily due to reported cough — it rarely excludes the use of the drug. It is important to consider alternative causes (pulmonary congestion, smoking, lung disease); determination of intolerance should be preceded by a few weeks of discontinuation followed by rechallenge and testing ACEI with a lower coughing potential (e.g. imidapril, perindopril, zofenopril)

Contraindications to the use of ACEI/ARB are:

- history of angioedema (absolute — for ACEI, as well as ARNI)
- bilateral renal artery stenosis
- stenosis of the renal artery of the only active or dominant kidney
- pregnancy or planned pregnancy.

BETA-BLOCKERS

Beta-blockers (BBs) are an important component of HF pharmacotherapy. Excessive activation of the sympathetic system in the course of HF and related stimulation of β1 receptors triggers a number of molecular processes leading to the activation of apoptotic processes in the heart muscle. Although the use of this group of drugs in HF pharmacotherapy was initially avoided, the effectiveness of 4 drugs in the class in HF treatment was documented in controlled prospective clinical studies (the class effect is not accepted) [10]. The efficacy of bisoprolol, carvedilol (the only non-cardioselective BB used in HF), and prolonged-release metoprolol succinate has been demonstrated, as included in both the European and American guidelines. Results of randomized BB trials in HF patients showed a reduction in the risk of death by more than a third compared to placebo, also in patients in NYHA class IV. The use of BB in HF is beneficial from the pharmacological and economic point of view. The fourth BB with proven efficacy in HF therapy, exerting (like carvedilol) a vasodilatory effect, is nebivolol. In the SENIORS trial, the benefit of nebivolol (reduced risk of composite endpoint defined as all-cause mortality or cardiovascular hospital admission, albeit without statistically significant reduction in mortality alone) has been demonstrated in patients ≥70 years of age with HF regardless of the ejection fraction value [11].

Treatment of HF with BB requires gradual escalation of doses with control of, among others, the chronotropic effect and arterial pressure — typical dose ranges are:

- Bisoprolol 1 × 1.25 mg → 1 × 10 mg
- Carvedilol 2 × 3.125 mg → 2 × 25 mg (in patients >85 kg — 2 × 50 kg)
- Metoprolol succinate 1 × 12.5 mg → 1 × 200 mg
- Nebivolol 1 × 1.25 mg → 1 × 10 mg

When deciding to start treatment with BB in HF patients, several important contraindications to their use should be taken into account. In clinical practice, these will most often be all conditions of exacerbation of HF symptoms, occurring with decompensation of the circulatory system and atrioventricular fluid overload disorders. When using BB, the patient requires monitoring of heart rate values, especially in combination with anti-arrhythmic drugs or digitalis glycosides and arterial blood pressure values. The most common side effects are due to a blockage of the sympathetic system and include mainly bradycardia and arterial hypotension, as well as an increase in exercise intolerance in the initial period of use. Depending on other risk factors, co-morbidity, hemodynamic status, and tolerance of such treatment, HF patients should ultimately achieve an average heart rate (HR) over the course of a day in the range of 60–69/min.

MINERALOCORTICOID RECEPTOR ANTAGONISTS

MRAs (eplerenone and spironolactone) are recommended in all patients with HFrEF as one of the four pillars of pharmacotherapy alongside beta-blockers, SGLT2 and ARNI (or ACEI/ARB). Their use is associated with a reduction in HF symptoms, risk of hospitalization for HF, and mortality. In contrast to the previous 2016 guidelines, which recommended the inclusion of MRAs in those patients with HFrEF which persisted despite ACEI and BB treatment, the current 2021 ESC guidelines assume that therapy with the above four drug groups (with class I recommendations) should be initiated concurrently or directed towards the rapid achievement of the "four pillars" in stages, depending on the clinical profile of the patient if possible. After 4–8 weeks, it is recommended to optimize the dose (for both drugs, the initial dose is 25 mg, and the target — 50 mg) before considering other forms of pharmacotherapy or implantable devices. In the HFmrEF group, both ESC and AHA/ACC/HFSA guidelines recommend MRA in class IIb in combination therapy. In HFpEF patients, the AHA/ACC/HFSA guidelines recommend MRA in class IIb in combination therapy, while the ESC guidelines do not provide any recommendations for this group of patients. In HFpEF, MRAs appear to be more effective in patients with lower EF (closer to 50%). In TOPCAT, spironolactone was associated with a reduction in the risk of hospitalization for HF in patients with HF and EF >45%. Eplerenone is more specific for blocking aldosterone-binding mineralocorticoid receptors than spironolactone (100–1000 times lower affinity for androgen-binding receptors and progesterone) and, therefore, less likely to cause gynecomastia/mastodynia (0.5% vs. 10%) in males and genital bleeding in females. In Poland, spironolactone is reimbursed and cheaper for the patient than eplerenone.

The new non-steroidal selective MRA — finerenone — reduced the risk of cardiovascular events in the group of patients with renal failure and type 2 diabetes [12, 13]. The analysis of the results of the available studies provided promising evidence of a reduction in the risk of HF diagnosed for the first time, reduction in hospitalization for HF, and cardiovascular mortality [14]. Further studies are needed to assess its effectiveness and safety in the treatment of patients with HF — the drug has no recommendations in this regard.

Practical recommendations for the use of MRA are mainly related to kidney function control. Particular caution should be exercised in patients with renal impairment and hyperkalemia:

- It is advisable to perform control tests for creatinine and electrolytes at 1 and 4 weeks after starting treatment or increasing the dose at 8 and 12 weeks, 6, 9, and 12 months, and then every 4 months.

- When estimated GFR ≤30 ml/min/1.73 m^2 or potassium ≥5.0 mEq/l, initiation of MRA therapy is contraindicated.
- In the case of potassium >5.5 mmol/l or creatinine >221 µmol/l (2.5 mg/dl)/estimated GFR <30 ml/min/1.73 m^2, the MRA dose should be reduced by half, and the patient should be carefully monitored. In the case of potassium >6.0 mmol/l or creatinine >310 µmol/l (3.5 mg/dl)/estimated GFR <20 ml/min/1.73 m^2, MRA should be withheld immediately.
- Other agents likely to increase serum potassium (e.g. potassium-sparing diuretics such as triamterene and amiloride, trimethoprim/trimethoprim-sulfamethoxazole, salt substitutes with high potassium content) are nephrotoxic agents (e.g. NSAIDs) and potent CYP3A4 inhibitors such as ketoconazole, itraconazole, nefazodone, telithromycin, clarithromycin, ritonavir, and nelfinavir (when eplerenone is used), which should be avoided during treatment.

FLOZINS — INHIBITORS OF SODIUM-GLUCOSE COTRANSPORTER TYPE 2

Inhibitors of sodium-glucose cotransporter type 2 (SGLT2i, flozins) are a new group of drugs of critical importance in the pharmacotherapy of HF patients. The multidirectional mechanism of action of SGLT2i consists in reducing glucose reabsorption and lowering the renal threshold for glucose and thus increasing glucose excretion, nephroprotective effect, and reduction of the pre- and post-load of the left ventricle due to increased osmotic diuresis, reduced plasma volume, and blood pressure. Recently, numerous non-renal SGLT2i signaling pathways with potential cardioprotective significance have been identified — related, among others, to the processes of inflammation, fibrosis, apoptosis, and cardiomyocyte energetics [15].

According to the current guidelines [2, 3], 2 SGLT2i drugs – dapagliflozin or empagliflozin – are strongly recommended (class I) in patients with heart failure (NYHA class II-IV) with reduced left ventricular ejection fraction (LVEF ≤40%) to reduce the risk of hospitalization for heart failure and death. At the moment, only the newer AHA/ACC/HFSA guidelines extend this recommendation to all categories of HF according to the current state of knowledge, taking into account the reduction in the risk of deaths or hospitalization caused by HF (as well as nephroprotective effects) also in patients with HFmrEF and HFpEF.

The DAPA-HF trial evaluated the long-term prognosis in patients with heart failure in NYHA class II-IV with reduced LVEF (≤40%). In the DAPA-HF trial, patients treated with dapagliflozin showed a 30% reduction in the risk of worsening of heart failure/hospitalization for heart failure, a 17% reduction in the relative risk of all-cause death, and an improvement in patients' quality of life and reduced severity of HF symptoms compared to placebo [16]. The clinical benefit of dapagliflozin was observed independently of the diagnosis of type 2 diabetes mellitus. The EMPEROR-Reduced study also demonstrated a beneficial effect of the SGLT2-empagliflozin inhibitor on the prognosis of patients with symptoms in NYHA class II–IV with reduced LVEF (≤40%). Empagliflozin, regardless of the diagnosis of type 2 diabetes mellitus, reduced the incidence of cardiovascular death or hospitalization for heart failure by 25% (primary endpoint) and the first and subsequent hospital admissions for heart failure by 30% (secondary endpoint) [17]. The results of both studies are consistent, suggesting the effect of SGLT2i to improve survival in HFrEF patients.

Since May 2022, dapagliflozin and empagliflozin have become reimbursed in Poland (at the level of 30% of costs), which will probably improve the availability of these drugs for HF patients. The reimbursement indications refer to patients with CHF with reduced LVEF (≤40%) regardless of the co-occurrence of diabetes mellitus who remain in NYHA class II–IV despite the use of beta-adrenolytic-based therapy, ACEI/ARB/ARNI and, if such treatment is indicated, mineralocorticoid receptor antagonists. From a practical point of view, it is important that reimbursed treatment with SGLT2 inhibitors may be initiated by a physician of any specialty who takes care of an HF patient.

Practical advice for the use of SGLT2 inhibitors in patients with HF:

- the use of dapagliflozin or empagliflozin (at doses of 1 × 10 mg/day, without the need for adjustment) is beneficial when taking other medicines recommended for the treatment of HFrEF;
- no dose adjustment is necessary due to renal impairment; however, the use in the treatment of HF in patients with eGFR <20 ml/min/1.73 m^2 (empagliflozin) and <25 ml/min/1.73 m^2 (dapagliflozin) is contraindicated;
- in the initial phase of treatment, a temporary increase in renal parameters can be observed, which is transient — the SGLT2i class is characterized by long-term nephroprotective effect; however, this effect may add up with a similar effect of initiating or escalating other drugs, e.g. ACEI/ARB — the decision on simultaneous or rapid sequential implementation of the "4 pillars of therapy" should be individualized;
- SGLT2i increases the risk of fungal infections (most commonly Candida albicans) of the external genitourinary organs of mild or moderate severity, and if they occur, SGLT2i treatment needs not be discontinued; recurrences of this complication are rare; SGLT2i initiation, however, make it imperative to instruct patients about the importance of perineal hygiene;
- due to increased osmotic diuresis and natriuresis, it may be necessary to increase fluid supply and modify the dose of loop diuretics [1], and in patients treated with insulin or sulphonylureas – to adjust the strength of hypoglycemic drugs.

IVABRADINE

Ivabradine is a drug that slows down spontaneous depolarization in the sinoatrial node of the cardiac conduction system by blocking the flow of ions through channels I_f, acting as a negative chronotropic agent only in patients with sinus rhythm. The unique mechanism of action, its metabolic neutrality, absence of negative inotropic effect or the effect on preload or afterload result in the lack of adverse decrease in myocardial contractility and blood pressure. Slowing the heart rate causes a beneficial hemodynamic effect in patients with HFrEF through improved coronary perfusion, better filling of the left ventricle, increased systolic deformation, and expansion of the aortic wall. The negative chronotropic effect is proportional to the baseline sinus rhythm rate, and the recommended doses typically reduce the heart rate by 10 beats/min. In the current guidelines [2, 3], we find a recommendation for its use in patients with HFrEF and a sinus rhythm rate of ≥70 beats/min based on the results of the SHIFT study [18]. In this study, ivabradine was added to optimal background therapy for HF in patients with symptomatic HFrEF (EF ≤ 35%), NYHA class II–IV, and sinus rhythm ≥70/min, resulting in a reduction in cardiovascular mortality and subsequent hospitalization for HF over 12 months of follow-up.

Ivabradine is recommended in two clinical situations:

- consideration should be given to its use in symptomatic patients with LVEF ≤35%, sinus rhythm, and resting heart rate ≥70 beats/min despite the use of optimal background therapy including BB at maximum tolerated dose, ACEI (or ARNI), and MRA (recommendation class IIa/B);
- and for these patients who are intolerant to or have contraindications to BB, they should receive ACEI (or ARNI) and MRA (Class IIa/C recommendation) concomitantly.

Activation of ivabradine may occur in a patient with stable HFrEF in class II–IV, (with extreme caution in patients in NYHA class IV and with worsening symptoms of the disease, e.g. within fewer than 4 weeks of hospitalization for HF decompensation). It is very important that the patient receives standard, guideline-compliant background therapy, including BB at the maximum tolerated dose. The dose of BB should be optimized first, not stopping at the initial dose of therapy — the optimal dose for the patient should be determined within a month, after which the resting heart rate should be checked — and ivabradine should be added if the value exceeds 70/min.

When starting treatment with ivabradine, it is important to remember the differences in Polish reimbursement indications (lump sum). They concern HF with systolic dysfunction, NYHA class II–IV, with a documented ECG-confirmed sinus rhythm ≥75/min (rather than ≥70/min, in the guidelines) with or without the concomitant use of standard therapy, with or without beta-blocker, when its use is contraindicated or intolerable. This heart rate was approved by the European Medicines Agency (EMA) for improved survival (decrease in overall mortality) in the SHIFT HF subgroup in patients with HR ≥75/min.

Starting treatment with ivabradine at a dose of 5 mg twice a day (in patients over 75 years of age up to 2.5 mg twice a day), one should be aiming at a target dose of 7.5 mg twice a day. The dose should be optimized in intervals no shorter than 2 weeks, and the dose is left unchanged if HR is within the range of 50–60/min. The dose of ivabradine must be reduced with HR less than 50/min or with symptomatic bradycardia, and the possibility of adverse interactions should be rechecked if new drugs are used. If atrial fibrillation occurs, ivabradine should be discontinued (although the medicine may still be of benefit in patients with paroxysmal atrial fibrillation [AF], who spend most of their time in sinus rhythm).

Contraindications to the use of ivabradine [2] are any conditions of circulatory instability, atrial fibrillation, pregnancy, and breastfeeding (due to the potential risk of fetal harm), severe liver or kidney dysfunction (no pharmacokinetic and safety data at creatinine clearance <15 ml/min), and adverse or allergic reactions.

Situations requiring special attention during ivabradine therapy, apart from NYHA class IV discussed above, are a resting heart rate < 50/min, moderate liver damage, and chronic retinal diseases (a typical fully reversible effect after discontinuation of the drug are visual disturbances — "phosphenes" usually presenting as flashes provoked by sudden changes in ambient light intensity). Possible drug interactions should be considered when related to the risk of bradycardia and QT prolongation (concomitant use of verapamil, diltiazem, amiodarone, digoxin, and ranolazine) and strong inhibitors of the hepatic isoenzyme CYP 3A4, which are involved in the metabolism of ivabradine in the liver and intestines (antifungal agents such as ketoconazole, macrolide antibiotics including clarithromycin, HIV protease inhibitors, and nefazodone).

DIURETICS

Diuretics are considered the foundation of treatment for HF patients with exacerbation of symptoms, edema, or pulmonary congestion. In everyday clinical practice, they are the drugs of choice for the treatment of acute HF. The effectiveness of loop diuretics in reducing mortality and hospitalization rates has been confirmed in many non-randomized studies, most recently in the analysis of the OPTIMIZE-HF registry [19]. Depending on the mechanism of action and the gripping point, diuretic drugs can be divided into several classes, shown in Figure 2 (modified according to [20]).

Loop diuretics are essential for HF patients. The results of the recently published TRANSFORM-HF study [21] did not confirm differences in overall mortality of HF patients treated with furosemide and torasemide. It should be remembered that, unlike furosemide, torasemide is used once a day (despite doses covering a wide range of 5–200 mg/day) thanks to better bioavailability and longer

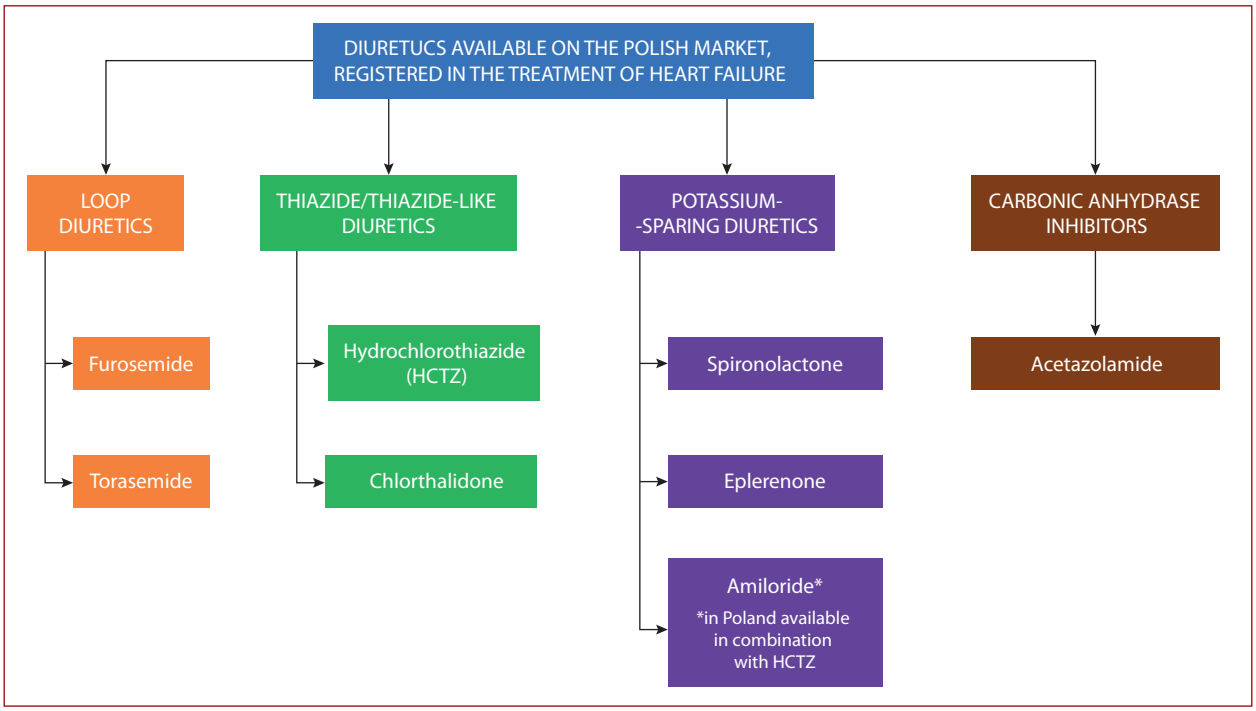

Figure 2. Practical classification of diuretic drugs registered in Poland in the treatment of heart failure (developed on the basis of Ali S et al. [20]). Sodium-glucose cotransporter 2 inhibitors are not shown as they are not used as a typical diuretic although they induce osmotic diuresis. Similarly, the purpose of mineralocorticoid receptor use is different from diuretic effect). Thiazide-like diuretics indapamide and clopamide available in Poland are not registered for HF

Abbreviations: HCTZ, hydrochlorothiazide

duration of action (which reduces the burden of therapy and improves the quality of life compared to furosemide). In patients with HF, one tablet of furosemide (40 mg) usually corresponds to 15–20 mg of torasemide.

The recently completed ADVOR study demonstrated the efficacy of three-day intravenous administration of 500 mg/day of acetazolamide during the initial phase of treatment with intravenous loop diuretics in HF patients with exacerbation in achieving a faster resolution of fluid overload [22]. In Poland, only the orally administered form of the drug is available, which also ensures good bioavailability.

Thiazide/thiazide-like diuretics can also be used in HF as monotherapy (especially when GFR is preserved) or in combination with loop diuretics. Such combination therapy is particularly useful in cases of resistance to loop diuretics, observed in 20% to even 50% of hospitalized patients [23].

In diuretic therapy, patients with HF should be primarily monitored for blood pressure (risk of hypotension, especially in combination with other drugs used in HF — ACEI, ARNI), electrolyte levels (especially potassium), and renal parameters (the possibility of exacerbation of renal failure, e.g. in the pre-renal mechanism). Particular caution should be exercised in patients with concomitant liver disease or chronic kidney disease while in people taking chronic non-steroidal anti-inflammatory drugs, the effect of diuretics may be weakened [2].

TREATMENT OF IRON DEFICIENCY

Anemia is a common comorbidity in HF patients. Its presence indicates a more advanced stage of the disease and the occurrence of additional concomitant diseases. It is clearly and closely linked to a worse prognosis. Its occurrence in HF does not depend on the age or the value of left ventricular ejection fraction. Sideropenia, or iron deficiency, has been treated for many years almost as a synonym of anemia and is seen as the underlying cause in HF patients. Today, we know that this concept is much complex and also includes situations where iron deficiency is accompanied by normal hemoglobin concentration. The function of iron in the body is not limited to the formation of hemoglobin — it is an essential element of a number of cellular processes, and its deficiency strongly worsens the prognosis in HF. The importance of the problem is now better understood in the current ESC guidelines — the treatment of iron deficiency is already determined by three recommendations, resulting from the FAIR-HF [24], CONFIRM-HF [25], and AFFIRM-AHF studies [26]. The first (class I) concerns the appropriateness of active screening for anemia and iron deficiency in all HF patients. The second (class IIa) recommends considering intravenous iron administration as an iron-carboxymaltose complex to reduce symptoms and improve exercise capacity and quality of life in symptomatic patients with HF and ejection fraction <45% and iron deficiency (defined as plasma ferritin <100 µg/l or ferritin 100–299 µg/l with

Table 2. Definitions of iron management disorders in the context of HF

	Description	Desirable values in patients with heart failure	Values indicative of sideropenia in heart failure
Anemia	Hemoglobin levels in whole blood below normal	>12.0 g/dl in women >13.0 g/dl in men	—
Ferritin	Liver protein storing iron ions	In plasma: 100–400 µg/l in women 100–200 µg/l in men	In plasma: <100 µg/l In plasma: 100–299 µg/l concomitant TSAT<20%
Transferrin	Primary plasma iron carrier	15–50 µmol/l	
TIBC — total iron binding capacity	The maximum amount of iron required for complete saturation of transferrin,	250–400 µmol/l	
TSAT — iron saturation of transferrin	(Iron/TIBC total iron binding capacity) × 100%	>20%	

transferrin saturation <20%). The third recommendation (class IIa), going one step further, increases the target group by patients with EF<50%, recently hospitalized for heart failure, thus covering not only the entire HFrEF group but also HFmrEF. It is worth noting that the cut-off points for ferritin and iron saturation of transferrin as an indication for iron administration have remained unchanged since 2016 — the basic definitions are presented in Table 2. The US 2022 guidelines approach this issue similarly, formulating one simple recommendation — in patients with HFrEF and iron deficiency, regardless of anemia, intravenous iron administration is justified for improving the functional state and quality of life.

It should be added that administration of erythropoietin alone is not recommended to reduce morbidity and mortality in HF. Oral iron substitution is ineffective, as demonstrated in the IRON-OUT study [27] — the only recommended form of iron supplementation remains the the intravenous form. The iron-carboxymaltose complex in this form is available in Poland, it is administered both in hospitals and in outpatient conditions, and the occurrence of adverse symptoms is extremely rare. The beneficial effect of reducing the risk of cardiovascular hospitalization and improving the quality of life is obtained after a single or double administration of the drug, and this effect lasts for many months or even years. These benefits only apply to the intravenous form and are not observed with oral iron administration preparations. It should be added that the results of the IRONMAN study announced at the end of 2022 [28] document a similar range of benefits in over two and a half years of follow-up (however, without a significant decrease in hospitalization for HF confirmed in AFFIRM-HF) with intravenous administration of iron complex with derisomaltose, a drug also available in Poland.

DIGOXIN

Digoxin is a cardiac glycoside, isolated from the woolly foxglove, affecting the heart muscle, striated and smooth muscles, renal tubules, and the vagus nerve center, already known in ancient Greece and Egypt.

In HFrEF therapy, digoxin can be considered, in accordance with the European guidelines, as an adjunct in symptomatic patients with HFrEF (NYHA class II–IV despite treatment with ACEI or ARNI, BB, and MRA) at sinus rhythm to reduce the risk of hospitalization (both for all causes and because of HF) — this is a low class IIb/B recommendation. It is mainly based on the DIG study (the Digitalis Investigation Group, using digoxin vs. placebo, in patients treated concomitantly with ACEI and a diuretic) published in 1997 [29], with a different standard of primary HF treatment. The American guidelines allow the use of digoxin (recommendation class IIb) in symptomatic HFrEF class II–III according to NYHA, and it is not possible to use the original therapy due to its poor tolerance. In clinical practice, the use of digoxin in this indication is rare. The justification for the low class of recommendations for digoxin is the fact that only one randomized trial produced no mortality reduction, demonstrating a moderate reduction in the risk of a composite endpoint (mortality or hospitalization rates, along with symptom reduction), which is also consistent with the results of the meta-analyses of clinical trials [30].

A common and widely accepted indication for digoxin is symptomatic heart failure or decompensation of heart failure, caused/exacerbated by the rapid rate of ventricular rhythm in the course of AF. Digoxin should be considered in AF patients with rapid ventricular function (>110 bpm) despite beta-blocker use, in the absence of hemodynamic instability, and administered in 0.25–0.5 mg boluses intravenously, if not previously used. The dose of the drug should be adjusted taking into account the narrow therapeutic window, especially in patients with factors affecting its metabolism, such as chronic kidney disease, elderly age, female sex, frailty syndrome, hypokalemia, malnutrition, and possible drug interactions. To determine the correct maintenance dose, the concentration of digoxin in the serum should be determined — the optimal concentration in the serum is 0.5–0.9 ng/ml. The concentration of 1.2 ng/ml should not be exceeded, as the risk of death increases linearly at higher values.

Digoxin is also a useful drug for achieving the recommended control of ventricular frequency in AF [2, 31] — initial lenient rare control (<110/min) with the use of beta-blockers before digoxin, used as an alternative or auxiliary drug, is allowed. Strict control of ventricular

function (<80/min at rest and <110/min at moderate exercise) should be sought in the following days of therapy if symptoms persist or if cardiac dysfunction is likely to be associated with tachycardia (tachycardia induced cardiomyopathy). Optimal heart rate control is also a strategy for patients with atrial fibrillation and hemodynamically stable heart failure — it should be obtained using beta-blockers, digoxin, or amiodarone. In the absence of clinical improvement, performing procedures such as electrical or pharmacological cardioversion, atrial fibrillation ablation, or modification of the atrioventricular junction in patients not responding to pharmacotherapy should be considered. The strategy of maintaining sinus rhythm with the use of ablation is gaining importance [3] in the light of newer studies and their meta-analyses, showing the advantage of the procedure based on ablation of atrial fibrillation consisting in improving the prognosis: reduction of mortality from all causes (reduction of risk by 49%), hospitalization frequency (reduction of risk by 56%), improvement of left ventricular function and quality of life [32]. This may further reduce the role of digoxin in the treatment of HF in the near future.

VERICIGUAT

The new molecule recommended for the treatment of HF is vericiguat — a drug registered in the European Union in 2021 (tablets: 2.5, 5, and 10 mg), which can be considered in selected HFrEF patients who have experienced a deterioration in HF while using first-line therapies (RAA system inhibitor/ARNI, BB, and MRA). In the case of the ESC guidelines, this recommendation has an IIbB class and in the case of the AHA/ACC/HFSA guidelines — 2bR-B.

Vericiguat is a soluble guanylate cyclase (sGC) stimulator. A drug with a similar mechanism of action, riociguat, is already used in thromboembolic therapy and primary pulmonary hypertension (as part of drug programs), but in the case of HF, the NO-sGC-cGMP pathway is a completely new point of reference for pharmacotherapy [33]. In the course of heart failure, the function of the NO-sGC-cGMP pathway is impaired. An increase in sGC activity inhibits the processes of fibrosis and cell hypertrophy, reduces inflammation, and relaxes smooth muscle cells. In turn, an increase in cGMP activity through activation of phosphodiesterase 2 also reduces excessive cAMP activity, which can stimulate the sympathetic system, RAA system, and, in consequence, pathological cardiac remodeling [34].

The clinical benefit of vericiguat (a significant 10% reduction in the risk of death or rehospitalization for HF) was demonstrated in the VICTORIA study in patients with recent HF exacerbation (EF <45%, NYHA class II–IV). However, it is noteworthy that vericiguat was added to the HFrEF pharmacotherapy conducted in accordance with the guidelines available during the design phase, i.e. not including the flozins. Only 60% of patients received "standard pharmacotherapy" at that time, and only 15% used ARNI. The effect on the primary endpoint became noticeable after approximately 4 months of therapy. At the time of writing of this article, vericiguat already has Polish-language characteristics of the medicinal product (MPCh), but it is not available in pharmacies and its price is not known. Although the idea of including a new neurohormonal pathway in the therapy is very interesting and it is worth following the results of subsequent clinical trials taking into account the use of this molecule, in practice it is difficult to predict whether adding vericiguat to the current quadruple regimen (ACEI/ARA/ARNI+BB+MRA+SGLT2i) will provide similar benefits. Based on the data from the MPCh (www.ema.europa.eu/en/documents/product-information/verquvo-epar-product-information_en.pdf), it is worth remembering that the drug has a half-life of approximately 30 hours in HF patients, it is administered orally with a meal at a dose of 1 × 2.5 mg once a day, doubling every 3 weeks to the target dose of 1 × 10 mg per day. Specific contraindications are pregnancy and breast-feeding, hypotension <100 mm Hg SBP, and a significant reduction in renal function (eGFR <15 ml/min/1.73 m^2). It must not be co-administered with riociguat or nitrates. Typical side effects are hypotension, anemia, dyspepsia or gastroesophageal reflux disease, and dizziness or headache.

ANTIPLATELET AND ANTICOAGULANT DRUGS

The current HF guidelines, both the 2021 ESC document and the 2022 AHA/ACC/HFSA document, do not comment in any new way on antiplatelet therapy — so one should assume that the recommendations described in the documents dedicated to such entities, such as chronic coronary syndromes, peripheral atherosclerosis, or stroke are to be followed.

In the HF documents, there is some new content on the principles of anticoagulation (affecting the plasma coagulation system) used for the prevention of stroke and venous thromboembolic disease or in situations where we find the presence of blood clots in the vessels. An important subgroup of HF patients includes those with coexisting AF. In such a situation, the very fact of diagnosing heart failure implies at least 1 point on the CHA_2DS_2-VaSC scale — anticoagulant treatment should, therefore, at least be considered, and in the vast majority of cases it will be indicated. The American guidelines emphasize that the risk of thromboembolic complications of AF in HF patients, as the only additional risk factor, is several times higher than without it. The American guidelines also point out that the use of anticoagulants is a reasonable course of action for patients with AF and amyloidosis of the heart, regardless of the CHA_2DS_2-VaSC score. The principles of prophylaxis in HF-associated AF do not deviate from the general principles with a preference for non-vitamin K antagonist oral anticoagulant (NOAC) due to higher effectiveness and better safety profile in the context of intracranial bleeding. The decisions in this matter are individual and must take into account, among others, the financial capabilities of the

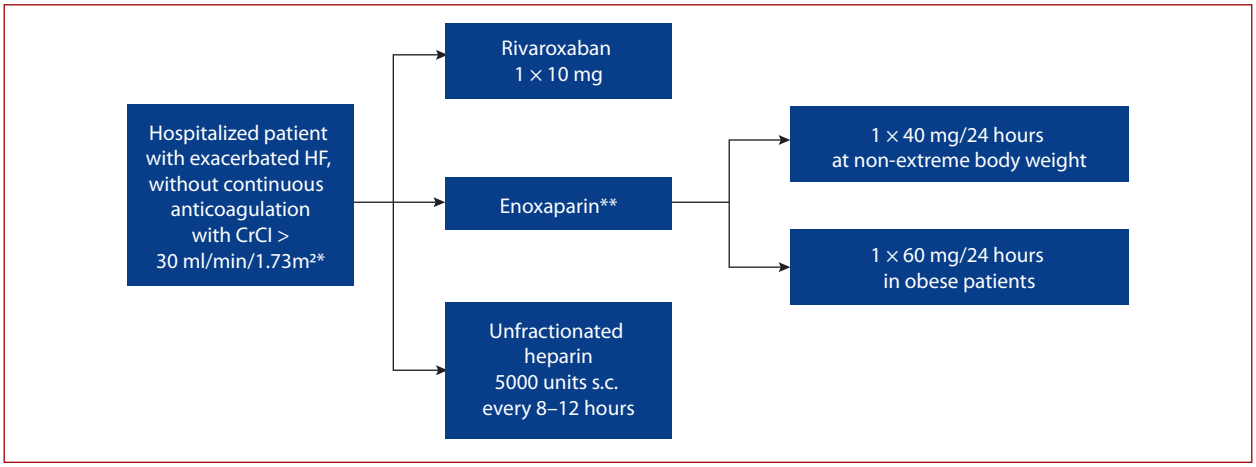

Figure 3. The strategy for the prevention of thromboembolic complications in patients hospitalized for heart failure exacerbation according to the American guidelines

*The American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA) guidelines indicate that data on efficacy of various thromboembolic complication prevention strategies are derived from randomized trials in patients with creatinine clearance (CrCl) >30 ml/min. The US guidelines do not provide management recommendations for patients with CrCl ≤30 ml/min. **The European Society of Cardiology guidelines suggest using low molecular weight heparin, without further specific recommendations

patient — in the case of NOAC in Poland, the refund applies only to prevention or deep vein thrombosis (30%/S), so it can be used by HF patients with a history of pulmonary embolism or venous thromboembolic disease, but not with AF as an indication.

According to the 2022 ESC guidelines for heart failure, anticoagulation with low molecular weight heparin (LMWH) is recommended as part of the management of acute heart failure (IA) if the patient does not have contraindications or does not use chronic anticoagulants for other indications. The American guidelines also confirm this indication, however, allowing not only the use of LMWH but also fondaparinux or NOAC. Suggestions for the principles of anticoagulation prophylaxis in the case of hospitalization of patients with HF exacerbation, not using anticoagulants for other indications, are presented in Figure 3.

It should be emphasized that both European and American guidelines do not recommend the use of anticoagulants in HF patients without accompanying typical indications for this treatment. The issue of the appropriateness of using vitamin K antagonists (VKA) or NOAC in patients with HFrEF without confirmed AF, which was discussed for many years, has been resolved. In the randomized, prospective COMMANDER study evaluating the effects of complementing the standard pharmacotherapy regimen in patients with HFrEF, a concomitant coronary heart disease but without rivaroxaban AF at a dose of 2 × 2.5 mg, it was not shown that such a course of action was associated with a reduction in the risk of stroke, heart attack, or death [35]. A systematic review in the Cochrane database finds no evidence that the use of anticoagulants in HF patients without AF is associated with any clinical benefits [36].

PHARMACOTHERAPY IN HFMREF

Treatment of patients diagnosed with HF with mildly reduced left ventricular ejection fraction (41%–49%) is largely similar to treatment of HFrEF. Symptomatic treatment in patients with fluid overload/congestion features is based on diuretics, currently in the first class of European and American recommendations. Prognosis-enhancing therapies have lower classes of recommendation in HFmrEF, with the notable exception of SGLT2i — empagliflozin and dapagliflozin — which tested positive in large prospective trials involving patients with HFmrEF and HFpEF. These were the first drugs, the studies on which achieved the expected endpoints in the HFmrEF/HFpEF prognosis, and the obtained benefits were consistent in those subgroups of patients.

The results of the EMPEROR-Preserved and DELIVER studies confirmed similar efficacy of empagliflozin and dapagliflozin in both patients with preserved and mildly [36] reduced ejection fraction [37] (in the case of DELIVER — also patients with HFimpEF [37]). A statistically significant reduction in the incidence of the primary endpoint in the form of worsening [38, 39] of HF symptoms or cardiovascular mortality compared to the placebo group was achieved. These studies allowed SGLT2i to be placed in recommendation class 2a as the most strongly recommended class of drugs improving prognosis in HFmrEF [3]. The scheme HFmrEF recommendations by the ACC/AHA/HRSA [3] are presented in Figure 4.

Therefore, considering the available evidence, the standard pharmacotherapy of HFmrEF should include one of the above-mentioned flozins, and an increase in their class of recommendations is expected soon (due to two successful prospective studies). Their high position in the

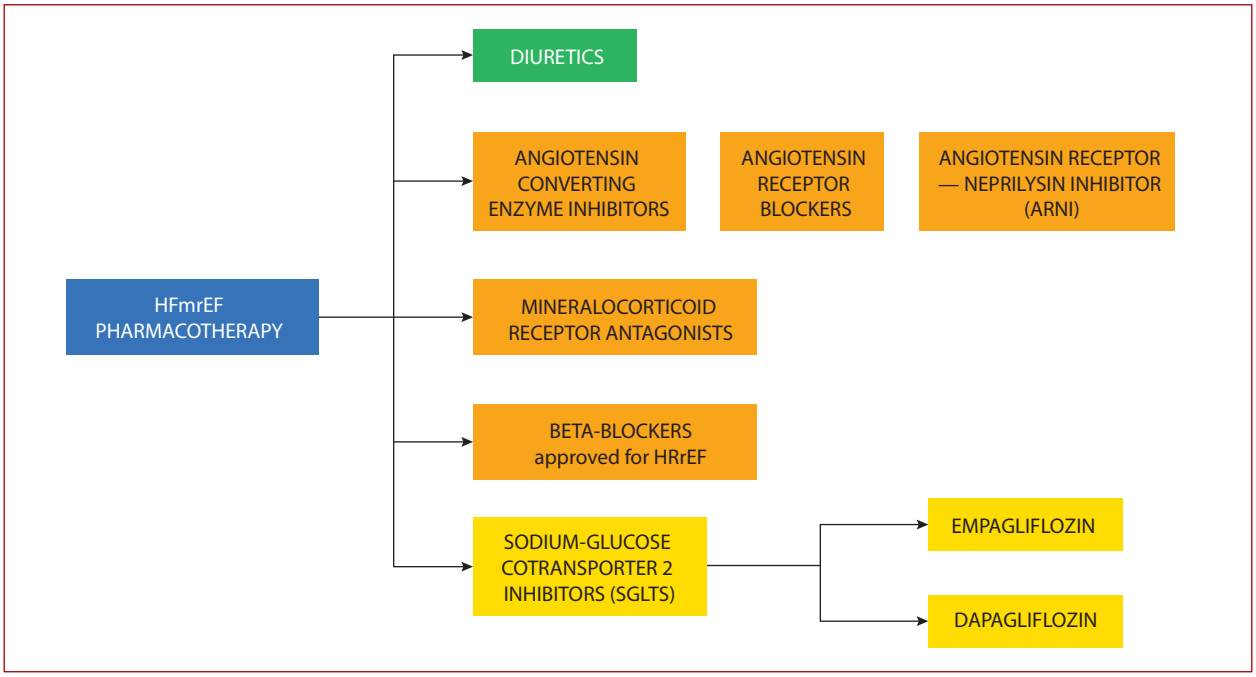

Figure 4. Pharmacotherapeutic regimen for HFmrEF proposed in the American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA) [3] guidelines (colors correspond to the classes of recommendations: green — recommended drugs; yellow — drugs to be considered for use; orange — drugs that can be considered in therapy). The level of recommendations for sodium glucose cotransporter 2 inhibitors is likely to increase due to the consistent, favorable results of two prospective trials

Abbreviations: see Table 1

recommendations proves the considerable effectiveness and, importantly, safety of this group of drugs.

PHARMACOTHERAPY IN HFPEF

The 2021 ESC guidelines do not include recommendations for modifying the course of HFpEF because they were created before the announcement of the groundbreaking positive results of the EMPEROR-Preserved [37] and DELIVER trials [36]. Screening for risk factors and conditions associated with HFpEF and their treatment are recommended, as well as treatment aimed at reducing the symptoms of fluid retention with diuretics — loop diuretics are preferred. The authors of the 2021 ESC guidelines emphasize that the US Food and Drug Administration (FDA) has approved the use of sacubitril/valsartan and spironolactone in HFpEF patients. In a subgroup analysis of the PARAGON-HF study, a reduction in the incidence of hospitalization for heart failure was shown among patients with LVEF <57%. In a meta-analysis of the PARADIGM-HF and PARAGON-HF studies, a reduction in the incidence of cardiovascular death and hospitalization for heart failure was demonstrated [40].

According to the newer guidelines published in 2022 [3] (after the presentation of EMPEROR-Preserved), the use of SGLT2i should be considered in HFpEF patients to reduce cardiovascular mortality and the risk of hospitalization (class IIa). The use of ARBs, ARNI, and MRAs to reduce the risk of hospitalization (class IIb) may also be considered. It is emphasized that the clinical benefits of ARB, ARNI, and MRA are greatest for patients in whom LVEF is close to 50% [3].

The success of studies with empagliflozin and dapagliflozin [36, 37] allowed for the first time to include in the recommendations drugs that reduce the risk of death and hospitalization caused by exacerbation of HF in HFpEF. In the EMPEROR-Preserved study published in 2021, it was shown that in patients with HF and LVEF >40%, NT-proBNP concentration above 300 pg/ml (>900 pg/ml in the case of AF) and GFR not lower than 20 ml/min/1.73 m^2, joining the standard empagliflozin treatment (vs. placebo) reduced the risk of cardiovascular death or hospitalization for heart failure over 26 months and was associated with a lower rate of deterioration in renal function. A reduction in the risk of the main endpoint was observed both in the subgroup of patients with diabetes and patients without diabetes [41]. Similarly, the DELIVERY study presented at the 2022 ESC Heart Failure Congress in Madrid (therefore, not available when the guidelines were developed) showed that dapagliflozin significantly reduced the risk of cardiovascular death or HF exacerbation in patients with HFpEF/HFmrEF. Patient inclusion criteria were very similar (LVEF>40%, NT-proBNP concentration above 300 pg/ml and >600 pg/ml for AF and GFR not lower than 25ml/min/1.73 m^2, HFimpEF patients were also accepted [41]). Both studies also showed benefits in terms of quality of life for patients treated with flozin. These consistent results of key [42] conceptually similar studies allow us to expect recommendations for flozins in HFpEF and HFmrEF in the upcoming guidelines of higher classes. Therefore, dapagliflozin or empagliflozin treatment is a key treatment method available to Polish patients in

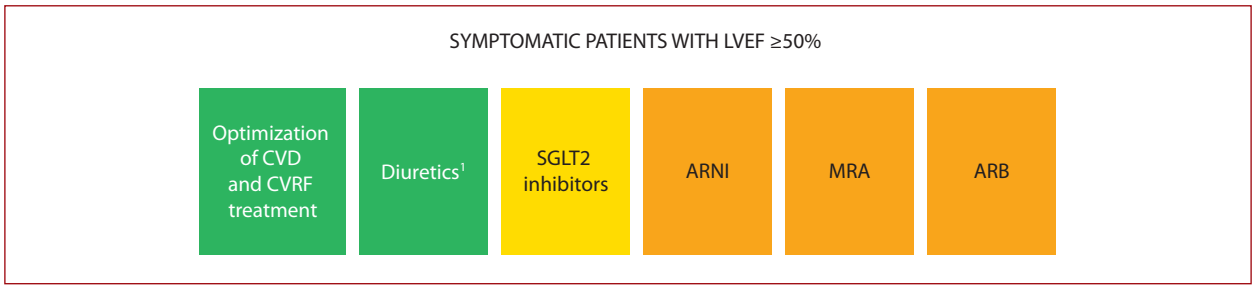

Figure 5. Basic principles of pharmacotherapy in patients with HFpEF (modified according to [3]) — the order according to the decreasing classes of recommendations; the class of recommendations SGLT2i is likely to increase

[1]In patients with congestion/fluid overload features

Abbreviations: ARNI, angiotensin receptor-neprilysin inhibitor; ARB, angiotensin II receptor blockers; CVD, cardiovascular diseases underlying HFpEF; CVRF, cardiovascular risk factors; MRA, mineralocorticoid receptor antagonists; SGLT2i, sodium glucose cotransporter 2 inhibitors

these numerous patient populations in which we have not yet had clearly effective treatment methods.

Recently a beneficial effect of SGLT2i independent of the EF value was also observed in patients with exacerbated HF recruited to the EMPULSE study [43]. Patients receiving empagliflozin for 9 days of follow-up had a 36% reduction in the risk of cardiovascular death, hospitalization for heart failure, and improved quality of life (Figure 5).

KEY ELEMENTS OF AHF PHARMACOTHERAPY

According to the ESC guidelines, the pharmacotherapy strategy for acute heart failure should depend on its clinical form:

- In patients with acute decompensated heart failure (ADHF) who gradually accumulate sodium and water, therapy should be based on diuretics (with the addition of inotropes/vasoconstrictors in cases of coexistence of peripheral hypoperfusion/hypotension);
- In patients with pulmonary edema, who are predominantly affected by rapid redistribution of pulmonary circulation fluid, often due to increased subsequent load, vasodilators are used in addition to diuretics,
- In patients with cardiogenic shock, inotropes/vasoconstrictors are indicated;
- In patients with isolated right ventricular failure, as in ADHF, mainly diuretics are used along with inotropes/vasoconstrictors in the case of arterial hypotension.

In the American guidelines, AHF therapy is also based on assessment of congestion and perfusion. Similarly, in both documents, therapy priorities include the search for reversible causes of AHF and their treatment.

Although there is still no breakthrough in the available pharmacotherapy of AHF, the presented regimens are helpful in the care of AHF patients. The main novelty is the practical algorithm for the use of diuretics in AHF (referring to the algorithm proposed by the Heart Failure Association ESC [44] in 2019 — see below).

The guidelines clarify selected recommendations for AHF pharmacotherapy:

- Diuretics (ESC, AHA/ACC/HFSA: recommendation class I). Treatment with loop diuretics should be initiated intravenously with furosemide 20–40 mg or torasemide 10–20 mg (dosage for patients not previously treated with diuretics). For patients previously treated with diuretics, a dose equal to or doubling the long-term daily oral dose of the loop diuretic should be administered.
- The assessment of the efficacy of the therapy should be based on the evaluation of natriuresis (efficacy criterion: sodium concentration in a single urine sample at 2 hours ≥50–70 mmol/l) and/or diuresis (efficacy criterion: hourly diuresis at 6 hours ≥100–150 ml/hour). In the case of insufficient response to treatment, the dose of loop diuretic should be doubled with subsequent re-evaluation.
- A combination of a loop diuretic with thiazide (recommendation class IIa) or acetazolamide should be considered. In the recently published ADVOR study, the addition of acetazolamide (3 days, 500 mg/day intravenously) to loop diuretics in patients with AHF increased the effectiveness of diuretic treatment and shortened hospitalization time [22]. An alternative may be the use of flozins (SGLT2i). Such a strategy, the so-called "sequential nephron blockade" by drugs inhibiting sodium resorption at different levels of the nephron (SGLT2 inhibitors and acetazolamide — in the proximal tubule, thiazides, and aldosterone antagonists — in the distal tubule), may help overcome the so-called "resistance to loop diuretics" [44].
- Vasodilators: nitrates or sodium nitroprusside (ESC, AHA/ACC/HFSA: recommendation class IIb) may be considered as initial therapy in patients with systolic blood pressure (SBP) >110 mm Hg to reduce congestion symptoms.
- Inotropic drugs (ESC: recommendation class IIb, AHA/ACC/HFSA: recommendation class I) may be considered in patients with SBP <90 mm Hg and features of hypoperfusion who do not respond to standard therapy including fluid administration.

- Vasoconstrictors (ESC: recommendation class IIb) may be considered in patients with cardiogenic shock; noradrenaline is preferred.
- Opioids (ESC: recommendation class III). ESC 2021 guidelines do not recommend routine opioid use except for severe/persistent pain or anxiety.

Both ESC and US guidelines emphasize the importance of discharging a patient from the hospital without residual congestion, initiation and optimization of pharmacotherapy to improve prognosis, and scheduling a follow-up visit 1–2 weeks after discharge. Most patients with AHF in Poland are treated in internal disease wards. Hospitals of lower referentiality may not have access to the full range of diagnostic tests or therapeutic procedures, which may lead to differences in AHF procedures among Polish hospitals [45], e.g. in many centers, no determination of urine sodium concentration is performed (despite the low cost of the test).

PRACTICAL ADVICE FOR HANDLING AHF

Below is the most important practical advice for the treatment of acute heart failure (medicines available in Poland).

Recommendations for the use of diuretics:

- Dosage — usually initiated i.v. with a subsequent switch to the oral route;
- Loop diuretics — initially an intravenous bolus in diuretic naive patients:
  - Furosemide — starting dose: 20–40 mg, typical chronic daily dose: 40–240 mg; can be administered as 2–3 boluses per day or in a continuous infusion — efficacy is similar; maximum daily dose 400–600 mg (up to 1000 mg in patients with severe renal insufficiency),
  - Torasemide — usually parenteral initiation switched to the oral form – starting dose: 10–20 mg, typical chronic daily dose: 10–20 mg in one dose; maximum daily dose 200–300 mg;
- Thiazide diuretics:
  - Hydrochlorothiazide — starting dose: 25 mg, usual dose: 12.5–100 mg;
- Carbonic anhydrase inhibitor:
  - Acetazolamide — starting dose: 250–375 mg, usual dose: 500 mg (recommended in ADVOR study for 3 days i.v. – in Poland only oral formulation is available);
- Once an evident negative fluid balance has been achieved, the dose of diuretics should be gradually reduced;
- The switch from intravenous to oral therapy should be initiated after the patient has achieved stable clinical status and continued at the lowest possible dose to avoid signs of congestion;
- The most common side effects of diuretics:
  - hypokalemia, hyponatremia, and metabolic alkalosis,
  - hypomagnesemia, hypocalcemia, and hyperuricemia,
  - hypovolemia, hypotension, and renal dysfunction;
- Monitoring of the therapy: clinical signs of congestion, fluid balance, urine sodium, blood pressure, serum blood urea/nitrogen, creatinine, sodium, potassium, and calcium,
- Recommendations for the use of vasodilators:
  - May be considered at systolic blood pressure >110 mm Hg,
  - Administration of these drugs can be started with small doses, which are then gradually increased to achieve clinical improvement and control of blood pressure;
- Dosage:
  - Nitroglycerin — initially 10–20 μg/min, can be increased to 200 μg/min,
  - Sodium nitroprusside — initially 0.3 μg/kg/min, can be increased to 5 μg/kg/min;
- Hypotension resulting from excessive reduction of preload and afterload should be avoided;
- Caution should be exercised in patients with left ventricular hypertrophy and/or severe aortic valve stenosis.
- Nitroglycerin tolerance and cross-tolerance to other nitrate and nitrite preparations may occur. In order to avoid the phenomenon of tolerance, the lowest effective doses of the drug, asymmetrical dosage, and periodic administration of nitroglycerin alternately with other vasodilators should be used;
- Adverse reactions: hypotension, headache, tachycardia, nausea, and vomiting;
- Monitoring of therapy: blood pressure measurements, ECG;
- Rules for the use of inotropic and vasospasmodic drugs. Dosage:
  - Dobutamine — 2–20 μg/kg/min (beta-adrenergic effect),
  - Dopamine — 3–5 μg/kg/min: inotropic effect (beta-adrenergic effect),
  - >5 μg/kg/min: inotropic (beta-adrenergic effect) and vasospasmodic (alpha-adrenergic effect),
  - Milrinon — 0.375–0.75 μg/kg/min,
  - Levosimendan — 0.1 μg/kg/min, dose range: 0.05–0.2 μg/kg/min,
  - Noradrenaline — 0.2–1.0 μg/kg/min — a drug preferred in severe arterial hypotension,
  - Adrenaline — 0.05–0.5 μg/kg/min;
- Adverse reactions: tachycardia, arrhythmias, myocardial ischemia, sympathetic system stimulation symptoms, hypotonia, hypertension, and peripheral tissue ischemia;
- Monitoring: ECG, blood pressure measurements, gasometry.

FUTURE PERSPECTIVES OF THE HEART FAILURE TREATMENT

Omecamtiv mecarbil (oral tablets used twice a day in doses of 25–50 mg) is a new, selective activator of cardiac myosin for patients with HF and with impaired fraction of

the left ventricle. It is not registered in Europe, the procedure of its registration in the US is ongoing. The drug can be classified as an inotropic substance, but unlike most of them, strengthening muscle contraction is not associated with greater energy, oxygen demand, or an increase in the heart rate. The drug supports stronger binding of myosin to the actin filament, which translates into an increase in the number of these bonds and an increase in the strength of myofibrillar contraction. In the GALACTIC-HF trial, in more than 8 000 patients with symptomatic HF and LVEF ≤35% adding omecamtiv to standard therapy reduced the relative risk of HF patients' decompensation by 10% over 2 years (absolute risk reduction of 2.1%) [46]. A slightly stronger effect in patients with the lowest EF values is worth pointing out. However, the GALACTIC-HF study did not meet the modern requirements of basic optimal HF therapy due to the lack of standard use of flozins. The drug is mentioned once in the latest ESC guidelines for heart failure and is currently unavailable.

Tolvaptan (once-daily tablets in doses of 7.5, 15, and 30 mg — higher registered doses for people with polycystic kidney disease) is a selective vasopressin type 2 receptor antagonist. It is registered for the treatment of hyponatremia in the course of chronic HF, cirrhosis of the liver, polycystic kidney disease, and Schwartz-Bartter syndrome (inappropriate release of vasopressin syndrome); it has been available commercially for many years in the US and Europe. The latest 2021 ESC guidelines list tolvaptan as therapy to be considered for persistent hyponatremia with stagnation but recall the lack of results of randomized clinical trials indicating clear cardiovascular benefits in this patient group [47].

The HF guidelines omit a substance that improves prognosis for heart failure as indicated in a randomized prospective double-blind placebo-controlled trial. This substance is coenzyme Q10. In the Q-SYMBIO study involving 420 patients with heart failure in NYHA class III-IV, high doses of coenzyme Q10 3 × 100 mg daily were used. In a two-year follow-up, coenzyme Q10 reduced the risk of cardiovascular events in this group by 50% (11% absolute risk reduction), the relative risk reductions were: 43%, 42%, and 41% for cardiovascular mortality, total mortality, the need for hospitalization for heart failure, respectively. [48]. The above results were confirmed in the analysis of a subgroup of Europeans participating in the Q-SYMBIO study [49]. The problem with using coenzyme Q10 lies in the fact that only in some countries it is registered in such large doses as a drug, while in many countries it is simply an ingredient in dietary supplements, in several times smaller doses. In the QSYMBIO study, ubiquinone was used, but some preparations sold on the Polish pharmaceutical market contain ubiquinol. In the Q-SYMBIO study, a dose of 3 × 100 mg per day was deliberately used because the bioavailability of ubiquinone is so low that similar effective serum concentrations (concentrations above 2.5 mcg/ml) are not achieved using a single daily dose of 300 mg. However, the Q-SYMBIO study identifies an easily available, relatively inexpensive drug for adjuvant chronic HF therapy [50]. Further studies are awaited to precisely define its clinical benefits in HF patients.

Except for the medications shown in Figure 6, no other novel oral drugs of interest in HF are mentioned in the current guidelines. Recently, however, significant progress has been made in the pharmacotherapy of hyperkalemia, through the introduction of modern potassium-binding drugs. So far, none of these drugs has specified registered indications for use in hyperkalemia in chronic HF, but knowledge of these therapeutic options for doctors dealing with NS patients may be important — hyperkalemia is a typical problem precluding the administration of full doses of RAA blocking drugs, including MRA. These drugs bind potassium in the digestive tract, reducing its absorption. These include medicines as old as sodium or calcium polystyrene sulphonate introduced to the pharmaceutical markets 70 years ago and newer ones — zirconium cyclo-silicate introduced in 2018 and patiromer introduced in 2015 in the US and in 2017 in Europe. Patiromer — a medicine in the form of sachets containing 8.4,16.8, or 25.2 g of this agent is currently the only one with a clinical trial in the population of people with NS and hyperkalemia. The results of the DIAMOND study involving nearly 900 patients with chronic HFrEF, announced in 2022, showed that patiromer reduced the risk of significant hyperkalemia (>5.5 mmol/l) by 37% compared to placebo and the need to reduce the dose of the aldosterone antagonist by 38% [51].

Since there are currently no registered indications for the treatment of chronic hyperkalemia in this patient population, this can only be done "off label" — apart from the registered indications – based on the results of the DIAMOND study. Thus one can consider such treatment in adult patients with NS in NYHA class II-IV, with LVEF fraction ≤40%, who have laboratory-detected hyperkalemia (>5.0 mmol/l) or are currently characterized by normokalemia during such treatment. However, last year there were episodes where hyperkalemia caused the need for dose reduction or prevented the inclusion/optimization of a dose of a drug that inhibits the renin-angiotensin system, regardless of the drug class (ACE inhibitor, sartan, sacubitril/valsartan, MRA). The criteria for exclusion from the DIAMOND study were chronic kidney disease with GFR <30 ml/min/1.73 m^2, hypotension <90 mmHg, and general poor prognosis due to comorbidities.

WHAT'S NEW? WHAT ARE THE CHALLENGES IN THE POLISH HEALTHCARE SYSTEM

The latest guidelines for HF pharmacotherapy — both European from 2021 and American from 2022 — are groundbreaking for clinical practice. They introduce not only new key drug groups but also new pharmacotherapy regimens based on the principle of phenotyping in HFrEF and take into account new populations of HF patients for whom therapeutic effectiveness has been documented.

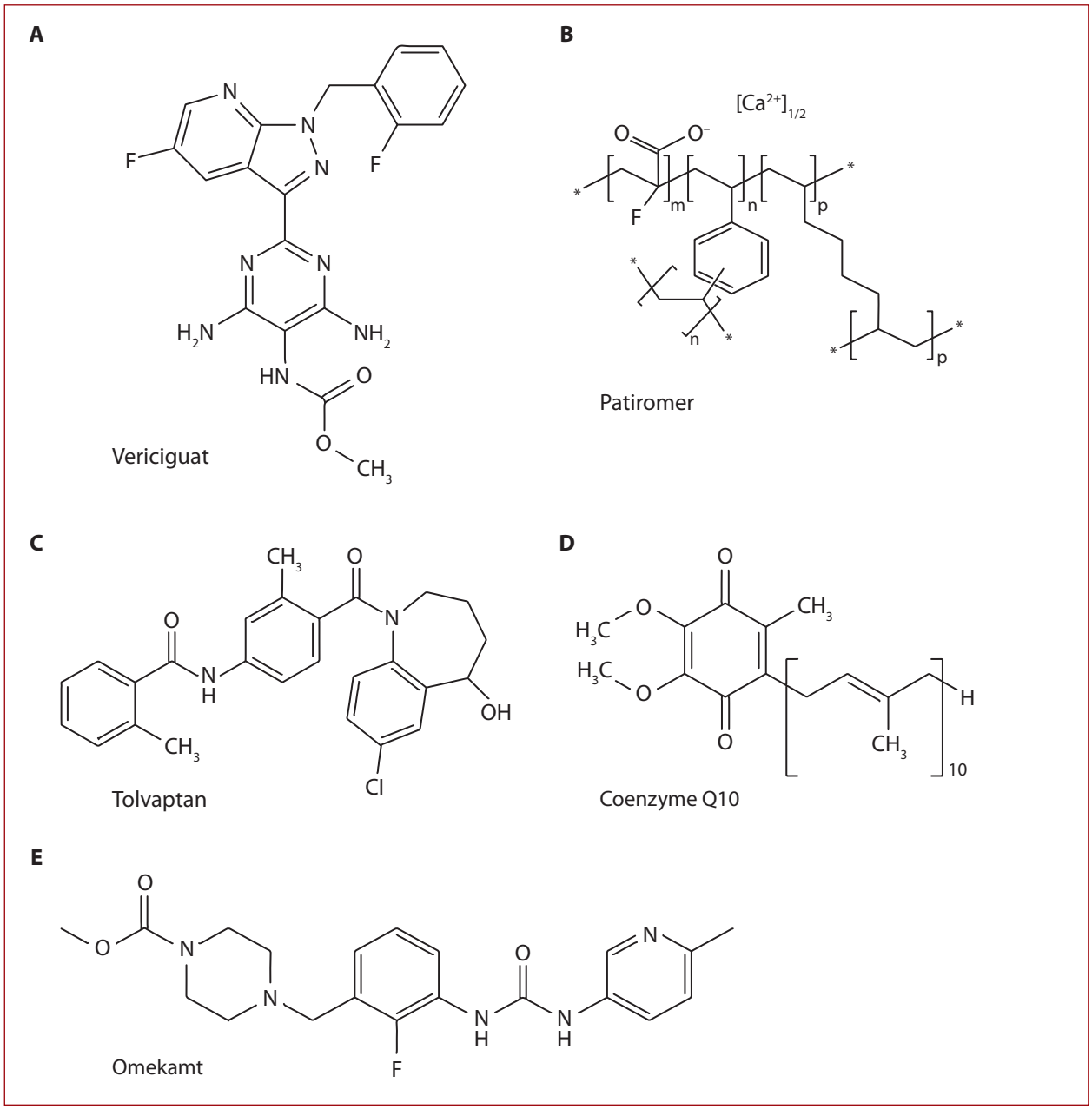

Figure 6. Structural formulas of new drugs with potential usefulness in heart failure: vericiguat (**A**), patiromer (**B**), tolvaptan (**C**), coenzyme Q10 (**D**), omecamtiv (**E**)

After many years of research in the field of HF with EF >40%, we have seen recommendations for HFmrEF and HFpEF. Similar progress concerns patients hospitalized for acute HF, for whom discharge from the hospital is a key moment for the implementation of evidence-based treatment, enabling the improvement of the prognosis of this group of patients. Recommendations for the discharge period, formulated through the prism of national circumstances, were prepared by the Polish Heart Failure Association (ANS) experts of the Polish Cardiac Society (PTK) in cooperation with the College of Family Physicians and the Polish Society of Family Medicine [7]. This document discusses a number of important aspects of the management in the discharge period, including the importance of iron deficiency.

The 2022 ACC recommendations were the first to consider SGLT2i for patients with HFmrEF and HFpEF. ARNI and MRA were also recommended in HFpEF and HFmrEF, with a slightly lower positioning. It is worth emphasizing here that at the time of publication of the ACC 2022 recommendations, the results of the DELIVER study were not available. Currently, we have data that allow using SGLT2i (empagliflozin and dapagliflozin [52]) in HF regardless of EF, i.e. across the entire HF spectrum [41].

We support the proposed current scheme and recommend, in Polish conditions, therapy based on pillars improving prognosis with clinically effective drugs highly positioned in the guidelines. Importantly, we recommend acting quickly to bring benefits already in the first month

of use. Modern pharmacotherapies also have a very well-documented beneficial effect on the quality of life. The current document does not cover new drugs that change the prognosis and quality of life in specific forms of HF, e.g. in cardiac amyloidosis (e.g. tafamidis) or hypertrophic cardiomyopathy (mavacamten), but they have become available outside clinical research programs and progress in the development of such therapies also falls within the broadly-understood contemporary HF pharmacotherapy.

But as usual, novelties are expensive, and not all currently recommended modern drugs are reimbursed for Polish patients. However, it is noteworthy that the introduction of dapagliflozin and empagliflozin reimbursement for HFrEF in May 2022 improved access to these drugs. Extension of reimbursement (July 2022) for patients with chronic kidney disease (CKD) (at the moment only for dapagliflozin) allows implementing the reimbursed drug in those HFmrEF and HFpEF patients in whom CKD coexists and the conditions for reimbursement for CKD are met. Similarly, HFpEF/HFmrEF patients may benefit from empagliflozin and dapagliflozin reimbursement options after modifications to SGLT2i reimbursement terms in the treatment of diabetes. In order to meet the needs of clinical practice, ANS experts have prepared a document on patient identification in accordance with the requirements of reimbursement for SGLT2 inhibitor therapy [53]. Unfortunately, there is still no refund for sacubitril/valsartan for Polish patients. However, thanks to the reduction in the price of this drug by the manufacturer, it has become more accessible to patients with HFrEF, and a shared decision on its inclusion should be made in each patient with symptomatic HF, taking into account his/her economic possibilities.

The problem in Poland is not only the limited availability of treatment with modern drugs but also the organization of HF patient care, which creates barriers to implementation of optimal pharmacotherapy with the possibility of achieving target doses, patient monitoring, and initiation of therapy based on the evidence-based medicine (EBM). This is of particular prognostic importance for patients after hospitalization for the acute manifestation of HF, i.e. for a patient in the "post-discharge sensitive phase". Long waiting times for a visit to a cardiologist, inertia of doctors, or economic aspects are classic barriers that the patient encounters during his/her illness. For effective treatment of HF, the following elements are also necessary: education of the patient and his/her family, the ability to self-control, including weight monitoring, and patient knowledge of the basic elements of pharmacotherapy (diuretic treatment) as well as the long-term adherence and compliance with the treatment. The 2021 ESC guidelines emphasize the role of the heart failure nurse in the care of HF patients. In Poland, since 2021, an education platform for nurses has been launched (www.edu.slabeserce.pl), addressed to those who would like to become educators for HF patients. The Education and Certification Program was created under the auspices of PTK, ANS PTK, and the Supreme Chamber of Nurses and Midwives.

The 2021ESC guidelines also refer, in the first class of recommendations, to multi-specialty care programs for HF patients. Including HF patients in this model of care has been shown to reduce HF mortality by as much as 25%, hospitalization for HF by 26%, and the total number of hospital admissions by 19% [54]. In Poland, such solutions do not work, and the developed KONS comprehensive care program has not been implemented. Expectations for new solutions included in the National Cardiac Care Network, currently in the pilot phase, must therefore be high, especially as it assumes unlimited financing for the treatment of heart failure.

Article information

Conflict of interest: JDK: lecture honoraria, grants, advisory boards: Adamed, AstraZeneca, Bausch Health, Bayer, Berlin-Chemie Menarini, Boehringer Ingelheim, Ewopharma, Novartis, Novo Nordisk, Pfizer, Polpharma, Sandoz, TEVA, Servier. IGG: lecture honoraria: Bayer, Boehringer Ingelheim, Krka, NovoNordisk, Promed. MB: lecture honoraria: Adamed, Aurovitas Pharma, Bausch Health, Bayer, Biofarm, Bioton, Boehringer Ingelheim, Egis, Gedeon Richter, Krka, Merck, MSD, Pfizer, Polfarmex, Ranbaxy, Recordati, Sandoz, Sanofi, Servier, USP Zdrowie, Viatris, Zentiva. JD: lecture honoraria, grants, institutional sponsoring- AstraZeneca, Bayer, Berlin-Chemie Menarini, Boehringer Ingelheim, Novartis, Vifor. KJF: lecture honoraria, grants, advisory boards: Adamed, AstraZeneca, Bausch Health, Bayer, Boehringer Ingelheim, Krka, Mundipharma, Mylan, Novartis, Sandoz, Servier. AKC: lecture honoraria: Angelini Pharma, Astra Zeneca, Bayer, Bausch Health, Boehringer Ingelheim, Krka, Pfizer, Polpharma, Servier. ML: lecture honoraria, grants, advisory boards: Amgen, AstraZeneca, Bausch Health, Bayer, Boehringer Ingelheim, Ewopharma, Novartis, Novo Nordisk, Servier. AM: lecture honoraria: Adamed, AstraZeneca, Aurovitas Pharma, Bayer, BerlinChemie Menarini, Boehringer Ingelheim, Celon, Egis, Gedeon Richter, Krka, Lilly, MSD, Novo Nordisk, Pfizer, Polpharma, Promed, Recordati, Sandoz, Sanofi, Servier, USP Zdrowie, Viatris, Zentiva. FMS: lecture honoraria: Astra Zeneca, Adamed, Boehringer Ingelheim, Krka, Recordati, Zentiva. MW: lecture honoraria: Adamed, Apotex, AstraZeneca, Aurovitas, Bayer, Berlin-Chemie Menarini, Boehringer Ingelheim, Egis, Krka, Novartis, NovoNordisk, Pfizer, Polpharma PromedSandoz, SanofiAvensis, Servier, Teva. BWK: lecture honoraria, advisory boards: Adamed, Astra Zeneca, Bausch Health, Bayer, Berlin-Chemie Menarini, Boehringer Ingelheim, Egis, Krka, Novartis, Pfizer, Sandoz, Sanofi. Other authors declare no conflict of interest.

Funding: None.

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