

Current pharmacological treatment of heart failure: What is new in the 2021 ESC guidelines?

Heart failure (HF) is a complex of clinical symptoms and signs caused by structural and/ or functional abnormalities of the heart. The specific pathology underlying it determines subsequent treatment. The latest guidelines of the European Society of Cardiology (ESC) have been revised and structured according to the current classification of HF types, with the term "heart failure with mid-range ejection fraction" replaced by "heart failure with mildly reduced ejection fraction (HFmrEF).

The main purpose of this article is to briefly review the drug classes used in patients with HF. The presented guidelines primarily introduce a new, individualized approach to pharmacotherapy. In patients with heart failure and reduced left ventricular ejection fraction (HFrEF), pharmacotherapy is based on three main goals:

1. reduction in mortality;
2. to prevent re-hospitalization due to worsening HF;
3. improvement of the clinical, functional and quality of life condition.

In this group of patients, pharmacotherapy is the mainstay of treatment and should be initiated before other methods, including device therapy. So far, of course, heart failure has also been treated in relation to comorbidities, but now we have the opportunity and need to consider important clinical features when making therapeutic decisions. The intervention relates not only to the etiology of the disease, but also to important clinical elements such as blood pressure, heart rate, the presence of atrial fibrillation, the presence of chronic kidney disease, hyperkalemia, and finally the presence of congestion. A profiled look allows us to choose the available therapy in the best possible way.

The current standard of care for patients with HFrEF is the use of a drug that blocks or modifies the renin-angiotensin-aldosterone (RAA) system, i.e. angiotensin-converting enzyme (ACEI) / angiotensin receptor -neprilysin inhibitor (ARNI), beta-blocker (BB), mineralocorticoid receptor antagonist (MRA) and a new class of drugs, sodium-glucose co-transporter 2 inhibitors (SGLT2i), irrespective of the coexistence of diabetes mellitus.

Among the latter, two molecules - dapagliflozin and empagliflozin - obtained registration and approval in HFrEF. The current guidelines still recommend the use of ARNI in patients who have persistent symptoms despite the combination of ACEI, BB and MRA, however it is allowed to include ARNI in the first line instead of ACEI. Sartans (ARBs), another group of drugs that affect the function of the RAA system, retained their importance in patients intolerant to ACEI or ARNI.

Thus, there are four main classes of drugs that form the basis of HFrEF treatment. The concept of using these drugs is also new. Previous treatment options required titration, slow addition of subsequent groups of drugs and increasing doses until maximum values were reached. It took many months. The new guidelines propose a simultaneous entry with fundamental therapies, of course taking into account the patient's profile. Within a month, if successful, four groups of drugs needed to stop the progression of the disease should be added and only then doses should be titrated to the doses used in clinical trials, or, if this is impossible, to the maximum tolerated dose.

For the first time, the guidelines recommend pharmacotherapy in patients with HFmrEF. ACEI, BB, MRA and ARNI are in class of recommendation IIb, meaning "their use may be considered". In addition, the indications for the use of intravenous iron in a complex with carboxymaltose were extended with the recommendation to actively seek patients with iron deficiency. There is also a new molecule that appears for the first time in the therapeutic algorithm - vericiguat (soluble guanylate cyclase stimulator), a drug with vasodilating effects, for patients at high risk of adverse events related to heart failure.

Unfortunately, the new European guidelines did not introduce any changes to the management of heart failure patients with preserved left ventricular ejection fraction (HFpEF). The guidelines still talk about the use of diuretics for symptoms of overhydration in these patients and about the optimal treatment of comorbidities, both cardiovascular and non-cardiovascular. However, there is still no dedicated pharmacotherapy for these patients

A detailed overview of the groups of drugs recommended for patients with heart failure is provided below and its

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Received: 12.09.2021 **Accepted:** 13.09.2021

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recommendations in Table 2.

ACEI: ACEI are first-line drugs to reduce mortality and morbidity, and to reduce symptoms.

BB: in combination with ACEI and a diuretic B-blocker therapy reduce mortality and morbidity, and ameliorate symptoms. BB should be initiated at least together with the ACEI and diuretic in clinically stable patients with euolemia. In patients with acute heart failure, the initiation of therapy should be implemented in a hospital setting, with the dose being gradually increased to the recommended dose.

MRA: Spironolactone or eplerenone are indicated in combination with ACEI and BB in all patients to reduce mortality number of hospitalization and ameliorate symptoms. The use of eplerenone compared to spironolactone is associated with a significant lower percentage of induced gynecomastia.

ARNI: ARNI therapy in place of ACEI / ARB shows superiority in reducing the number of hospitalizations due to worsening HF, cardiovascular and general mortality. Additional benefits include improving quality of life, reducing the progression of kidney disease and the risk of hyperkalaemia. ARNI also allow you to reduce the dose of diuretics used. A significantly more frequent complication of ARNI administration is symptomatic hypotension despite maintaining clinical benefits.

SGLT2 inhibitors: In the SGLT2i group, dapagliflozin and empagliflozin showed benefits of their use in patients with HF in combination with standard therapy, regardless of the diagnosis of diabetes. Diuretic-natriuretic properties bring additional benefits in terms of dose reduction of loop diuretics. The dark side of SGLT2i therapy is the increased risk of recurrent genital fungal infections.

Diuretics: Diuretics, especially loop diuretics, are recommended to alleviate symptoms. Their effect on mortality has not been investigated in randomized clinical trials. Their use improves exercise tolerance and reduces the number of hospitalizations. When selecting the appropriate dose, the diuretic effect of other drug groups (ARNI, MRA, SGLT2i) should be taken into account.

If- channel inhibitor: Ivabradine is the only representative of this group of drugs. Ivabradine slows the heart rate by affecting the sinus node and therefore its use should be limited to patients with sinus rhythm ≥ 70 beats/min who cannot tolerate or has contraindications to BB, or has heart rate ≥ 70 beats/min despite optimal BB dose. In symptomatic patients with HFrEF, after joining the standard therapy, Ivabradine reduces cardiovascular mortality and the number of hospitalizations. It should be remembered that before starting Ivabradine, the target dose of BB should be reached.

Digoxin: Digoxin has a very narrow therapeutic window, therefore serum levels should be monitored regularly. In the group of patients with HFrEF and sinus rhythm, digoxin reduces the risk of hospitalization, however, the routine effect of combined therapy with BB has not been assessed. Despite

conflicting results regarding the effect on mortality in patients with HF and atrial fibrillation in symptomatic patients, digoxin may be used to slow down the high ventricular rate.

New groups of drugs studied in the HF patients are Vericiguat and Omecamtiv mecarbil. Vericiguat is an oral soluble guanylate cyclase receptor stimulator. According to the results of VICTORIA study (2) it may be considered, in addition to standard therapy for HFrEF, to reduce the risk of cardiovascular mortality and hospitalizations for HF. Omecamtiv mecarbil is a selective activator of myosin in the heart and studies to date have shown an improvement in cardiac function in patients with HFrEF (GALACTIC-HF study) (3). In the future it may be added to standard therapy to reduce the risk of hospitalization and cardiovascular mortality.

Conclusions:

The current guidelines are a breakthrough in the approach to heart failure not only because of new therapies, but mainly because of the approach to treatment. The newest recommendations mark the beginning of an era in which personalization of implemented therapies comes to the fore. Targeted management of the group of patients discharged from the hospital is also extremely important. It is made clear that patients should be discharged with effective, optimal, oral treatment. It should also be considered whether there is a need to implement iron supplementation.

During a short-term follow-up, the physician should check the patient's condition, pharmacological treatment should be quickly optimized and modified.

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Peer-review: Internal

Conflict of interest: None to declare

Authorship: A.S.

Acknowledgement and funding: None to declare

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Sunset reflection in the Vah river, Liptov region, Slovakia. Ljuba Bacharova, Bratislava, Slovakia.