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The summary of the 2019 year in heart failure with reduced ejection fraction

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Abstract

The last years it is a good time in heart failure (HF) for innovative therapy. The results of new trials which were published after the last 2016 guidelines for HF need the systematic approach and provide evidence-based guidance for clinical practice. For that reason in the last year 2019 the experts of Heart Failure Association (HFA) European Society of Cardiology published the consensus. The present article summarized the main issues regarding heart failure with reduced ejection fraction together with comment based on the HFA expert consensus.

Key words: heart failure with reduced ejection fraction

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Introduction

Recent years in the heart failure (HF) domain have been marked by significant progress in pharmacotherapy. Since the publication of guidelines of the European Society of Cardiology (ESC) in 2016, several important reports have been published. With this in mind, an expert meeting of the Heart Failure Association (HFA) of the ESC was held last year to summarise the current state of knowledge and procedures in HF. This article presents the most important information regarding heart failure with reduced left ventricular ejection fraction (HFrEF), along with a commentary on the consensus of HFA ESC experts which was published in the "European Journal of Heart Failure" in 2019 [1].

Sodium-glucose co-transporter 2 inhibitors

In the ESC guidelines of 2016, a new concept of pharmacotherapy with sodium glucose co-transporter 2 inhibitors (SGLT2i) appeared for the first time, in connection with the results of the EMPA-REG OUTCOME study. As is known, this study was not dedicated to patients with HF, but the benefits of empagliflozin therapy documented in it contributed to the incorporation of the drug in class IIa recommendation in patients with type 2 diabetes mellitus in order to prevent or delay the onset of HF and to prolong life [2]. Since then, subsequent sub-analyses of the EMPA-REG OUTCOME study have been published, in which empagliflozin has been documented to reduce the risk of a primary endpoint regardless of glycaemic status [3] and baseline cardiovascular risk calculated according to Thrombolysis in Myocardial Infarction (TIMI) Risk Score [4]. Patients from both, high and low risk groups have improved their prognosis. A clinical benefit of empagliflozin therapy has also been documented in terms of life extension in all age groups [5]. However, young patients aged 45 years benefit most, since their improvement in survival is calculated at 4.5 years.

Numerous studies using SGLT2i have appeared in the following years, including, among others, empagliflozin (EMPERIAL, EMPEROR, EMPULSE), dapagliflozin (DECLARE, DAPA-HF) and canagliflozin (CANVAS, CREDENCE). Some of them have already been completed, therefore, in

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the mentioned consensus, information about SGLT2i has been extended to include the use of further flozins (with the recommendation 'should be considered'), *i.e.* canagliflozin and dapagliflozin in patients with type 2 diabetes mellitus and cardiovascular disease or high cardiovascular risk to prevent or delay the onset of HF and hospitalisation for this reason [1]. And the Food and Drug Administration (FDA) in 2019 approved a new indication for dapagliflozin — to reduce the risk of HF hospitalisation in patients with type 2 diabetes mellitus and known cardiovascular disease or with multiple cardiovascular risk factors.

An additional event last year was the announcement of the results of the DAPA-HF study in HFrEF (left ventricular ejection fraction [LVEF] ≤ 40%) at the ESC Congress in Paris, in which about half of the population did not have diabetes mellitus [6]. Participants were randomised into two groups: treated with 10 mg dapagliflozin once daily or receiving placebo. All patients underwent standard HFrEF therapy. The primary composite endpoint was the onset of the first episode of HF intensity (*i.e.* hospitalisation due to this reason or urgent medical intervention requiring intravenous therapy) or cardiovascular death. It should be clarified that the design of the primary endpoint in this study differs from that used in other studies and, apart from hospitalisation for HF, includes a component of outpatient intervention in the form of intravenous drug administration. The analysis of endpoint components showed that taking dapagliflozin reduced the risk of death by 17% and the risk of the first episode of HF intensity by 30% ($p < 0.05$ for both components). In the DAPA-HF population, the primary endpoint occurred in 386 of 2,373 patients (16.3%) in the dapagliflozin group and 502 of 2,373 patients (21.2%) in the placebo group. In the DAPA-HF study, dapagliflozin has been documented to reduce the risk of a primary endpoint by 26% in both, diabetes mellitus patients (hazard ratio [HR] 0.75; 95% confidence interval [CI] 0.63–0.85), as well as non-diabetic patients (HR 0.73; 95% CI 0.60–0.88). The use of this flozin also had a positive effect on the quality of life. The breakthrough in HFrEF therapy with dapagliflozin is that for the first time a hypoglycaemic drug provides the clinical benefit documented in evidence-based medicine (EBM) for patients without concomitant diabetes mellitus. On 5 May this year the FDA approved dapagliflozin in a new indication to reduce the risk of HF death and hospitalisation due to HF in adults with HFrEF in class II–IV according to the New York Heart Association (NYHA) with concomitant type 2 diabetes mellitus and without diabetes mellitus.

Due to mechanism of action of SGLT2i associated with the increase of urinary glucose excretion (glucosuria) by inhibiting its reverse transport in the proximal tubule, which is accompanied by natriuresis, the drugs of this group can be called modern diuretics, although the results of reduced cardiovascular events obtained during SGLT2i therapy indicate significant effects beyond the diuretic effect, of pleiotropic character [7]. It is postulated that SGLT2i reduce heart damage, inhibit the processes of hypertrophy, fibrosis and adverse remodelling by inhibiting the sodium hydrogen pump. This group changes metabolic pathway of a heart muscle cell, using oxidation of energy-richer ketone bodies instead of free fatty acids or glucose, which improves myocardial function and performance. Other beneficial effects of SGLT2i include nephroprotection, weight loss, and lowering of blood pressure. Drugs from this group show weak hypoglycaemic activity, do not pose the risk of hypoglycaemia, and the risk of lowering the estimated glomerular filtration rate (eGFR) is small (3–5 mL/min) and usually occurs at the beginning of therapy. It seems that concomitant use of diuretics and SGLT2i in the long term or with intensive diuretic therapy may promote hyponatraemia, therefore modification of treatment may be necessary. It is also important to remember to follow the rules of hygiene of the intimate area when using SGLT2i and in case of symptoms of ketoacidosis (nausea, vomiting, abdominal pain, anorexia, confusion), which is a possible although rare complication after taking SGLT2i.

ARNI — angiotensin receptor neprilysin inhibitor

Another novelty in HFrEF therapy is **sacubitril/valsartan in pre-discharge period for patients hospitalised due to HF exacerbation.** It is worth recalling that angiotensin receptor neprilysin inhibitors (ARNI) were introduced into HFrEF therapy in 2016, after the breakthrough results of the PARADIGM-HF study in the outpatient population with stable HFrEF [2]. Since then, many subanalyses of the PARADIGM-HF study have been published, in which with respect to sacubitril/valsartan life extension in HFrEF has been documented [8], as well as a lower risk of developing diabetes mellitus requiring insulin therapy [9], a lower risk of severe hyperpotasemia (> 6.0 mmol/L) and deterioration of renal function, compared to treatment with enalapril and angiotensin AT_1 receptor blockers (ARB) and mineralocorticoid receptor antagonists (MRA) [10, 11]. On the other hand, the new studies — TRANSITION [12] and PIONEER-HF [13] — have documented the clinical benefit of ARNI therapy in patients hospitalised due to acute manifestation of HFrEF (*de novo* or chronic exacerbation) in pre-discharge period and in the first weeks after discharge, *i.e.* vulnerable phase. Vulnerable phase is characterised by a high risk of rehospitalisation due to HF exacerbations, deaths and excessive neurohormonal activation. In both studies participated a quite large group of patients with HF *de novo*; in the PIONEER-HF study — 35%, and in the TRANSITION study — 28.9%.

In the TRANSITION and PIONEER-HF studies, it was documented that starting ARNI therapy in pre-discharge period is safe and is associated with early and sustained improvement in reducing the risk of major clinical events

and biomarker levels (N-terminal pro-B-type natriuretic peptide [NT-proBNP], high-sensitivity troponin T [hsTnT), indicating the pathophysiological benefits in population with HFrEF [12, 13].

In the absence of therapies to improve survival in acute HF, the results of the TRANSITION and PIONEER-HF studies have gained significant importance and have been included in the consensus in the form of the following recommendation: **initiation of therapy with sacubitril/valsartan instead of ACEI or ARB may be considered once haemodynamic stability has been achieved in patients hospitalised for acute HF manifestation (*de novo* or chronic exacerbation) in order to improve short-term prognosis and facilitate treatment (avoidance of ACEI treatment with the principle of increasing doses and switching to ARNI)** [1]. For initiation of ARNI therapy in pre-discharge period, the haemodynamic stability criteria, as defined in the above mentioned studies, are significant, *i.e.* lack of intravenous supply of diuretics and vasodilators for at least 6 h, as well as 24 h without administration of intravenous inotropic drugs and systolic blood pressure at least 100 mm Hg without symptomatic hypotension. The drug proved safe in this group of patients.

Pharmacotherapy strategies in HFrEF

The consensus emphasized the role of strategies to improve compliance with guidelines for the use of pharmacotherapy in HF. The suboptimal use of existing pharmacotherapy methods in clinical practice remains an ongoing problem. A large proportion of patients with HFrEF do not undergo adequate pharmacotherapy at adequate doses, and it should be reminded that in case of modifying therapies for HF treatment with proven efficacy, the greatest clinical benefits are achieved when therapeutic target doses are used. In some patients also pharmacotherapy optimisation before the use of electrotherapy is not carried out. What is more, the use of implantable devices is too small, compared to existing needs. The consensus quotes the results of two studies in the area of compliance with pharmacotherapy guidelines — the QUALIFY registry conducted in outpatient patients with stable HFrEF [14, 15] and the BIOSTAT-CHF study in the population with past HF exacerbation [16]. Data on Polish population of the QUALIFY registry were published in "Polskie Archiwum Medycyny Wewnętrznej" ("Polish Archives of Internal Medicine") [17]. It has been documented that compliance with the guidelines at a good level, *i.e.* standard ACEI/beta-adrenolytics/MRA and ivabradine therapy, if recommended, with at least 50% of the recommended target doses, led to improved prognosis (Figure 1).

While, in the BIOSTAT-CHF study [16], which was designed to assess the dose increase of ACEI/ARB and/or beta-adrenolytic, as in QUALIFY, a higher risk of death and/or hospitalisation due to HF was documented in patients taking lower doses, *i.e.* less than 50% of the target therapeutic dose. The results of the above studies clearly indicate that optimisation of therapy is the right way to improve the prognosis and to avoid many hospitalisations in the population with HFrEF.

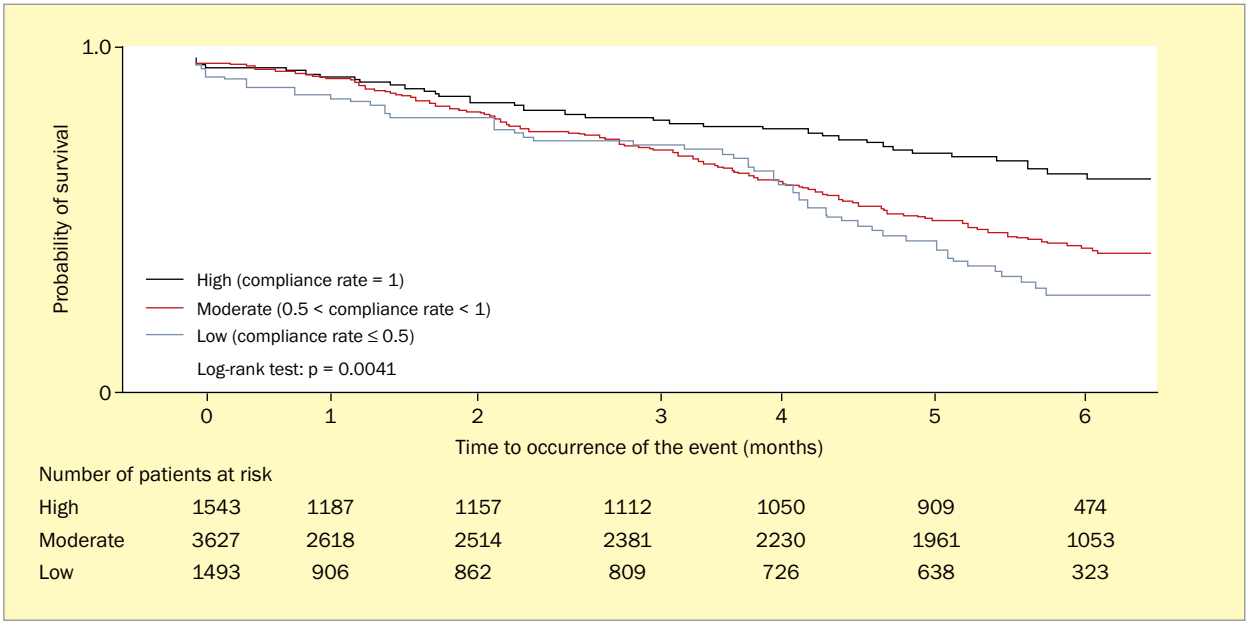

Figure 1. Adherence to pharmacotherapy recommendations in heart failure with reduced left ventricular ejection fraction and survival probability based on the QUALIFY registry (based on [15])

Table 1. The most effective therapies according to the network analysis of Komajda et al. (source [18])

Therapy	Reduction of risk of death [%]	Reduction of risk of cardiovascular death [%]	Reduction of risk of hospitalisation [%]	Reduction of risk of hospitalisation for HF [%]
ARNI + β-adrenolytic + MRA	62	64	42	75
ACEI + β-adrenolytic + MRA + ivabradine	59	59	42	73

ARNI — angiotensin receptor neprilysin inhibitor; MRA — mineralocorticoid receptor antagonists; ACEI — angiotensin-converting enzyme inhibitors

When looking for **the best therapeutic solutions to improve the prognosis of a patient with HFrEF**, the network analysis of Komajda et al. [18] should be mentioned, with the selection of the most effective drug combinations. Table 1 presents treatment regimens and clinical measures for reducing the risk of total mortality, death from cardiovascular causes, hospitalisation for any cause and hospitalisation due to HF. The limitations of this analysis include the lack of analyses of other drug combinations, among which the most interesting seems to include the ARNI + ivabradine combination in the scheme, but this is an issue that requires new research.

Electrotherapy, interventions and other therapies

The consensus [1] also contains information on:

- **implantable cardioverter-defibrillator (ICD) and results of the DANISH study**, which make that the population after 70 years of age with HFrEF of non-ischaemic aetiology and patients with concomitant diseases which increase the risk of death from other causes than sudden cardiac death, are perceived with a greater distance than before in terms of qualification for ICD. The greatest benefit in the DANISH study was achieved by patients with ischaemic aetiology of HFrEF in younger age groups (< 59 years), in whom ICD implantation reduced mortality by nearly half;
- **ablation of atrial fibrillation** (*may be considered*), indicating an invasive treatment strategy (pulmonary vein isolation) as better than pharmacological one in patients with HFrEF and symptoms of paroxysmal arrhythmia, whereas in case of persistent atrial fibrillation, ablation may be considered in patients with HFrEF whose arrhythmia exacerbates HF symptoms, with high probability of maintaining the sinus rhythm and cardiac resynchronisation therapy (CRT) plans or presence of the device. In the CASTLE-AF and CABANA studies, although they are controversial mainly due to their design, there has certainly been evidence of improvements in distance in the 6-minute walk test (6MWT) and quality of life in patients with sinus rhythm after ablation. While, atrioventricular node ablation usually with two-chamber pacing *may be considered* in a situation of ineffective or impossible isolation of pulmonary veins if atrial fibrillation attacks provoke an increase in HF;
- **use of rivaroxaban at a dose of 2 times 2.5 mg added to therapy with acetylsalicylic acid** *may be considered* in outpatient population in NYHA class I–II with EF > 30% to reduce the incidence of strokes or transient ischaemic attack and cardiovascular deaths; no benefit has been reported from this therapy to improve the prognosis in HF or to reduce hospitalisation due to HF (results of the COMMANDER-HF study);
- **functional mitral regurgitation (FMR)** in the light of the results of COAPT and MITRA-FR (MitraClip) and PRIME (sacubitril/valsartan): studies with Mitraclip vary in terms of population and should not be compared, but carrying out these studies allowed to identify patients benefiting from the Mitraclip procedure (COAPT criteria) (*may be considered*), whereas the PRIME study, although conducted on a relatively small population of 118 patients, documented, during ARNI therapy, a beneficial reverse remodelling in echocardiographic assessment with a reduction of effective FMR field. Results of the PRIME study indicate the need to optimise the pharmacotherapy of patients with HFrEF and concomitant FMR, prior to final qualification for invasive activities;
- **potassium-binding drugs** (Patiromer and ZS-9): experts indicate that in patients with HFrEF regardless of concomitant chronic kidney disease, potassium-binding drugs *may be considered* if it is not possible to use MRA and other RAAS inhibitors or to achieve a therapeutic target dose of MRA due to presence of hyperkalaemia. Patiromer is a non-absorbable polymer which has the ability to exchange cations and which, being a counter-ion, contains a calcium-sorbitol complex, instead of sodium, which is present in ZS-9. Patiromer increases faecal potassium excretion by binding potassium in lumen of the gastrointestinal tract. The drug was tested in a group of patients with HF in the PEARL-HF study, which documented that more patients could use 50 mg spironolactone in the new drug group than in the placebo group (91% vs.

74%, p = 0.019). For the possibility of a full HFrEF treatment with disease-modifying drugs, potassium-binding drugs are undoubtedly of significant clinical importance. Research to assess the improvement of prognosis in HFrEF during therapy with this group of drugs is currently underway;

- **myocardial contractility modulation** — a method intended for patients with HFrEF (EF 25–45%) and a narrow QRS below 130 ms (*may be considered*). At the current stage of research, it has been documented that the method improves the quality of life and requires an assessment of the impact on morbidity and mortality. The procedure is not refundable in Poland;
- **ventricular assist devices** — experts point to HeartMate 3 (*should be considered*) instead of HeartMate 2 due to the higher 2-year survival rate and fewer adverse events. However, the availability of this type of therapy in Poland is limited and possible only in the highest reference centres.

Conclusions

To summarise the current state of knowledge, in the next ESC guidelines in 2021 we will probably face a change of standard HFrEF therapy with higher ARNI positioning, incorporation of SGLT2i in the therapeutic algorithm and preference of the most effective combinations of therapy to improve prognosis with respect to compliance with recommendations (target therapeutic doses) and building teams of multi-specialist care. Perhaps new therapies, for which research has now been completed, will also appear in the guidelines.

Conflict of interest

Clinical trials and lectures for Novartis, Boehringer Ingelheim, Servier, Astra.

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