New approach to heart failure in diabetes mellitus

Nowe spojrzenie na niewydolność serca z towarzyszącą cukrzycą

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Abstract

Despite the introduction of complex pharmacological approaches, heart failure (HF) is still a therapeutic challenge, especially when it is associated with type 2 diabetes mellitus (T2DM). Recently, large clinical trials have shown multiple benefits from using sodium-glucose co-transporter-2 inhibitors and glucagon-like peptide-1 agonists not only in the field of diabetes but also as agents reducing the risk of cardiovascular events and the frequency of hospitalisation due to HF deterioration. This has been reflected in the recent American Heart Association (ACC) 2018 guidelines for risk reduction in patients with T2DM and cardiovascular diseases, and in the ACC/American Heart Association (AHA) 2019 guidelines for primary prevention of cardiovascular diseases.

Key words: heart failure, diabetes, pharmacotherapy

Folia Cardiologica 2019; 14, 4: 411–417

Introduction

Heart failure (HF) continues to be a significant clinical and socio-economic problem, despite an increased understanding of its causes and diverse treatment approaches. Although many new compounds have appeared promising in the treatment of HF, most have proved ineffective. Owing to economic factors, existing compounds have been studied with the aim of using them for novel indications.

The co-occurrence of HF with type 2 diabetes mellitus (T2DM) worsens a patient's prognosis and increases the risk of cardiovascular events and hospitalisation due to an exacerbation of HF. Additionally, HF alone increases the risk of being affected by diabetes by around four times, while patients with diabetes are at a 2.5-fold higher risk of developing HF [1]. Interestingly, patients with diabetes have a 75% higher risk of death due to a cardiovascular event than the general population [1]. This indicates that diabetes and HF reciprocally induce each other's development and worsen one another's prognosis. Because of this, HF therapy has focused on the available drugs used in the treatment of diabetes and their potentially positive effect on the vascular system.

Diabetic cardiomyopathy

Diabetes affects the heart via several mechanisms. One of these is diabetic microangiopathy, which causes coronary artery disease and reduced blood flow to the heart muscle. Co-occurrence of diabetes in patients with HF worsens the diastolic function of the left ventricle (LV) by increasing its stiffness and mass. Diastolic dysfunction correlates with markers of insulin resistance, such as fasting glucose levels, glycated haemoglobin and body mass index (BMI) [1].

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Diabetic cardiomyopathy is further classified into two types: restrictive cardiomyopathy, occurring more often in patients with type 2 diabetes and obesity, and dilated cardiomyopathy, which is more common with type 1 diabetes. Predisposing factors for restrictive cardiomyopathy can be hyperglycaemia, hyperinsulinemia and lipotoxicity, while autoimmunological processes accompany dilated cardiomyopathy.

The effect of diabetes on heart muscle metabolism

The heart muscle generates most of its energy from free fatty acids (FFAs) and glucose. However, due to the Randle cycle, the heart possesses a metabolic elasticity and is able to adapt to the body's current metabolic abilities. In HF, the initial uptake of glucose and FFAs by cardiomyocytes increases, but their oxidation within mitochondria is decreased, leading to an accumulation of metabolic intermediates in the cytosol. In T2DM, increased levels of FFAs stimulate the proliferation of peroxisomes and elevated insulin resistance [1]. This minimises the use of glucose, thus reducing the metabolic elasticity of the heart muscle. The dominant use of FFAs in the hearts of diabetic patients contributes to a drop in effective energy production. This happens firstly because FFA oxidation requires higher amounts of oxygen than it would for glucose, and additionally because FFAs induce the expression of uncoupling protein, leading to a loss of effective production of adenosine triposphate (ATP).

In diabetes, calorific need is estimated for elevated levels of FFAs and glucose. By contrast, in HF, sympathetic activation induces lipolysis and the release of FFAs from adipose tissue into the plasma. Elevated levels of FFAs are associated with worsened diastolic dysfunction.

Ketone bodies increase in response to energy depletion or starvation, due to their function as an alternative energetic substrate. They are not directly available from the diet, but are instead produced by the liver over the course of incomplete oxidation of FFAs. Enzymes inducing the metabolic transformation of ketone bodies display an increased activity in HF, while those that inhibit this process remain scarce [1]. When this occurs, the failing heart oxidises ketone bodies as its main source of energy, while remaining metabolic pathways become compromised. Interestingly, ketone bodies induce the transport of FFAs to the adipose tissue, thus decreasing the concentration of circulating FFAs. This in turn increases the uptake of glucose by cardiomyocytes, therefore increasing the efficiency of energy production.

Heart failure and insulin resistance

Insulin resistance, or the impaired ability of cells to take up glucose from circulation in response to insulin, is associated with lipolysis, lipogenesis and gluconeogenesis, increasing the supply of metabolic substrates to the heart muscle. However, overloading of the heart with these substrates decreases the efficiency of their oxidation, leading to metabolic insufficiency, followed by myocardial failure due to lipotoxicity and glucotoxicity [1]. In this case, insulin resistance of the heart muscle may serve as a kind of adaptive mechanism to reduce overloading with metabolic substrates.

Existing approaches to pharmacotherapy in patients with heart failure accompanied by diabetes

European Society of Cardiology (ESC) guidelines from 2016 indicated only **metformin** as a treatment for patients with HF, but not due to functions improving the patients' prognosis, but rather because metformin does not cause exacerbation of HF in this patient group. Metformin is a first-line treatment for type 2 diabetes, despite its mechanism of action not being fully known. It slows downs the process of gluconeogenesis by inhibiting respiratory enzymes. In addition to these metabolic changes, animal studies have shown that metformin prevents heart damage following ischaemia, limiting the extent of a stroke and weakening post-ischaemic myocardial remodelling [1]. In addition, metformin improves endothelial function by limiting the production of peroxides and increasing the bioavailability of nitric oxide. It also strengthens the anti-inflammatory effect, weakening myocardial fibrosis. In one randomised trial, metformin reduced mortality and the incidence of ischaemic heart disease in diabetic patients, and these results were confirmed through a cohort study and a meta-analysis [1]. However, to date there have been no prospective studies raising the issue of using metformin in patients with both HF and diabetes. ESC guidelines from 2016 suggesting metformin as a first-line treatment in this patient group were based solely on a series of cohort studies which showed a slowed progression of HF and a smaller proportion of incidents of lactic acidosis in this patient group [2]. However, accompanying metformin therapy was not associated with a reduction in ischaemic area in the myocardium, or with improved diastolic ventricular function in diabetics with acute coronary syndromes.

On the other hand, the use of exogenous **insulin** stimulates the activity of the autonomic nervous system and causes an increase in vascular resistance, and hypertrophy of the myocardium and vasculature [3]. Moreover, over the course of using insulin, endothelial dysfunction occurs. The aforementioned changes are accompanied by a progression of HF and an increased risk of mortality. Insulin also retains sodium and causes water retention, which in HF patients can cause exacerbation of the illness and oedema [4].

Glitazones have similar side effects — especially in combination with insulin, they cause fluid retention, oedemas, and increase in body mass (in 15% of those treated, this occurs within a week of commencing treatment, and may reach a 5 kg increase in body mass over six months) and pathologic fractures. During glitazone therapy, one can observe a temporary drop in haemoglobin concentration, a direct toxic effect on myocytes, and an unfavourable effect on the remodelling phenomenon [4]. Despite the literature containing data on the favourable effects of glitazones in patients with HF, such as the fact that they reduce vascular insulin resistance, lead to a reduction in afterload and additionally improve endothelial and myocardial function through improved glucose usage at the cost of decreasing the usage of FFAs, and lead to a regression in the hypertrophy of the heart muscle, their use in this patient group is highly risky [5].

Sodium-glucose co-transporter-2 inhibitors and glucagon-like peptide-1 agonists — a new approach in the cardiac patient population

In 2018, American College of Cardiology (ACC) recommendations for the first time positioned sodium-glucose co-transporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) agonists as drug classes that exhibit significant benefits in patients with HF and diabetes [5]. It was shown that the use of these compounds reduces negative cardiovascular effects in patients with diabetes, which initiated the development of a new treatment model not only in managing diabetes, but also in expanding this strategy into preventing cardiovascular events, which are the main cause of death in patients from this group. A similar position is presented by the American Heart Association (AHA). In the ACC/AHA guidelines for primary prevention of cardiovascular diseases published in 2019, SGLT2 inhibitors and GLP-1 agonists may be consider for adults with diabetes type 2 and additional cardiovascular risk factors, who require glucose-lowering therapy despite initial lifestyle modifications and metformin to improve glycemic control and reduce cardiovascular risk [6].

SGLT-2 inhibitors are known as relatively new orally administered antidiabetic drugs used in the pharmacotherapy of type 2 diabetes. Large randomised clinical studies conducted in patients with diabetes and accompanying cardiovascular disease showed that two drugs from this group — empagliflozin and kanagliflozin — reduce the frequency of cardiovascular events and the number of hospitalisations due to heart failure (Table 1) [5]. Beyond the effects on blood glucose levels, these drugs cause increased excretion of sodium in urine and potentiate diuresis, reduce body mass, and decrease systolic blood pressure. This may be a result of their effects on the sympathetic nervous system and inhibition of sodium-hydrogen pumps, most likely reducing damage to the heart, hypertrophy, fibrosis, remodelling and systolic dysfunction [5]. This group may use an alternative metabolic pathway of the myocardium, using the oxidation of energetically richer ketone bodies instead of FFAs or glucose, which improves the functioning and efficiency of the heart muscle. It is also worth mentioning the recently published results of the DECLARE study [7]. This analysed the cardiovascular benefits in diabetic patients of using a different SGLT-2 inhibitor — dapagliflozin. It turned out that dapagliflozin did not affect the risk of cardiovascular events (MACE, defined as cardiovascular death, myocardial infarction or stroke), but did reduce mortality due to cardiovascular causes. A lower frequency of hospitalisations due to aggravations was also recorded [7].

When it comes to therapy using SGLT-2 inhibitors, side effects must be taken into account. One effect that is not very threatening, but causes more of a nuisance, is an increased risk of fungal infection. These are usually not very severe and are easily treated with antifungals. The literature has also described individual cases of an increased risk of ketoacidosis, which is why patients using SGLT-2 inhibitors are instructed that if they experience symptoms such as nausea, vomiting or abdominal pain, they should immediately stop taking the drugs and seek specialist advice [5]. This is also the case for empagliflozin, kanagliflozin and dapagliflozin, which is confirmed by the DECLARE study [7].

GLP-1 agonists have also demonstrated benefits for patients with HF and diabetes. In addition to lowering glucose levels by intensifying glucose-dependent insulin secretion and weakening glucagon production, and by slowing down stomach emptying, this drug group — as shown by the majority of clinical studies — reduces the risk of cardiovascular events (Table 2). This pertains mostly to long-acting GLP-1 agonists such as liraglutide. It has been documented that they lower systolic blood pressure from 1 to 6 mm Hg and reduce low-density lipoprotein (LDL) concentration. In animal studies, drugs from this group reduced the extent of ischaemia in acute coronary syndromes and improved myocardial function following reperfusion and decreased post-ischaemic remodelling of the LV. They improved LV function in HF patients mainly through increasing glucose consumption by cardiomyocytes. In another study, these drugs decreased blood pressure by releasing atrial natriuretic peptide [5]. Positive cardiovascular effects were observed primarily in patients with a positive history of circulatory ailments, which is why they are recommended as a secondary prevention mechanism.

The main side effects relate to the digestive system — nausea and vomiting. A solution in this situation is to start with small doses of the drug and incrementally increase

Table 1. Summary of clinical trials of sodium-glucose co-transporter-2 inhibitors

Parameter	EMPA-REG OUTCOME	CANVAS/CANVAS–R	DECLARE
Number of patients	N = 7,020	N = 10,142	N = 17,160
Drug	Empagliflozin	Kanagliflozin	Dapagliflozin
Dosage	10 or 25 mg p.o. daily	100 or 300 mg p.o. daily	10 mg p.o. daily
Mean observation time [years]	3.1	2.4	4.2
Baseline HbA$_{1c}$ [%]	8.1	8.2	8.3
Mean duration of diabetes [years]	N/A*	13.5	10.5
Taking metformin [%]	74	77	82
Taking statin [%]	77	75	75
Incidence of cardiovascular disease [%]	> 99	66	41
Primary endpoint** [HR (95% CI)]	0.86 (0.74–0.99)	0.86 (0.75–0.97)	0.83 (0.73–0.95)
Death due to CV [HR (95% CI)]	0.62 (0.49–0.77)	0.87 (0.72–1.06)	0.98 (0.82–1.17)
Episode of ACS (irrespective of consequences) [HR (95% CI)]	0.87 (0.70–1.09)	0.89 (0.73–1.09)	0.89 (0.77–1.01)
Stroke (irrespective of consequences) [HR (95% CI)]	1.18 (0.89–1.56)	0.87 (0.69–1.09)	1.01 (0.84–1.21)
Overall mortality [HR (95% CI)]	0.68 (0.57–0.82)	0.87 (0.74–1.01)	0.93 (0.84–1.03)
Hospitalisation due to HF [HR (95% CI)]	0.65 (0.50–0.85)	0.67 (0.52–0.87)	0.73 (0.61–0.88)

*57% of patients with diabetes lasting > 10 years; **death due to CV causes, myocardial infarction not leading to death (excluding silent ischaemia); stroke not leading to death; p.o. — per os; HbA$_{1c}$ — glycated haemoglobin; HR — hazard ratio; CI — confidence interval; CV — cardiovascular; ACS — acute coronary syndrome; HF — heart failure

Table 2. Summary of clinical trials of glucagon-like peptide-1 agonists in the context of cardiovascular effects

Parameter	LEADER	SUSTAIN-6	EXS-CEL	ELIXA
Number of patients	9,340	3,297	14,752	6,068
Drug	Liraglutide	Semaglutide	Exenatide QW	Lixisenatide
Dosage	1.8 mg or the maximal tolerate dose per day	0.5 mg or 1 mg weekly	2 mg weekly	10 μg or 20 μg daily
Mean observation time [years]	3.8	2.1	3.2	2.1
Baseline HbA$_{1c}$ [%]	8.7	8.7	8.0	7.7
Mean duration of diabetes [years]	12.8	13.9	12	9.3
Taking metformin [%]	76	73	77	66
Taking statin [%]	72	73	74	93
Incidence of cardiovascular disease	81/18	72/24	73.1/16.2	100/22
Primary endpoint* [HR (95% CI)]	0.87 (0.78–0.97)	0.74 (0.58–0.95)	0.91 (0.83–1.00)	1.02 (0.89–1.17)
Death due to CV [HR (95% CI)]	0.78 (0.66–0.93)	0.98 (0.65–1.48)	0.88 (0.76–1.02)	0.98 (0.78–1.22)
Episode of ACS (irrespective of consequences) [HR (95% CI)]	0.86 (0.73–1.00)	0.74 (0.51–1.08)	0.97 (0.85–1.10)	1.03 (0.87–1.22)
Stroke (irrespective of consequences) [HR (95% CI)]	0.86 (0.71–1.06)	0.61 (0.38–0.99)	0.85 (0.70–1.03)	1.12 (0.79–1.58)
Overall mortality [HR (95% CI)]	0.85 (0.74–0.97)	1.05 (0.74–1.50)	0.86 (0.77–0.97)	0.94 (0.78–1.13)
Hospitalisation due to HF [HR (95% CI)]	0.87 (0.73–1.05)	1.11 (0.77–1.61)	0.94 (0.78–1.13)	0.96 (0.75–1.23)

*Death due to CV causes, myocardial infarction not leading to death (excluding silent ischaemia), stroke not leading to death; QW — quaque; HbA$_{1c}$ — glycated haemoglobin; HR — hazard ratio; CI — confidence interval; CV — cardiovascular; ACS — acute coronary syndrome; HF — heart failure

Table 3. Recommended doses and indications for sodium-glucose co-transporter-2 inhibitors based on American College of Cardiology (ACC) 2018 experts' statement [5] and ACC/American Heart Association (AHA) guidelines 2019 [6]

Parameter	Empagliflozin	Kanagliflozin	Dapagliflozin [7]
Doses	10 mg p.o. daily 25 mg p.o. daily	100 mg p.o. daily May be increased to 300 mg daily	10 mg p.o. daily
Indications approved by the FDA	Improved control of glycaemia in patients with DM2 Reduction in risk of death due to cardiovascular causes in adult with DM2 and CV disease	Improved control of glycaemia in patients with DM2	Improved control of glycaemia in patients with DM2
Dose modification	eGFR ≥ 45 mL/min/1.73 m^2 — no change eGFR < 45 — do not increase dosage, discontinue if eGFR is stable low	eGFR ≥ 60 mL/min/1.73 m^2 — no change eGFR 45–59 — do not exceed 100 mg per day eGFR < 45 — do not increase dosage, discontinue if eGFR continues to fall	eGFR < 60 mL/min/1.73 m^2 — discontinue the drug therapy

p.o. — per os; FDA — Food and Drug Administration; DM2 — type 2 diabetes; CV — cardiovascular; eGFR — estimated glomerular filtration rate

Table 4. Recommended doses and indications for glucagon-like peptide-1 agonists

Parameter	Liraglutide	Semaglutide	Lixisenatide	Exenatide QW
Doses	Initially 0.6 mg s.c. daily Slowly increase to 1.8 mg or maximal tolerated dose	Initially 0.25 mg s.c. weekly Slowly increase to maximal tolerated dose	10 µg s.c. daily Increase, if tolerated, to 20 µg daily	2 mg s.c. weekly
Indications approved by the FDA	Improved control of glycaemia in patients with DM2 Reduced risk of MI, CVA and death due to CV in patients with DM2 and CV disease	Improved control of glycaemia in patients with DM2	Improved control of glycaemia in patients with DM2	Improved control of glycaemia in patients with DM2
Dose modification	Increase slowly to reduce nausea and vomiting Discontinue if pancreatitis is suspected No need to change dosage in the case of impaired kidney or liver function	Increase slowly to reduce nausea and vomiting Discontinue if pancreatitis is suspected No need to change dosage in the case of impaired kidney or liver function	Increase slowly to reduce nausea and vomiting Discontinue if pancreatitis is suspected CrCL ≥ 30 mL/min — do not change dosage CrCL 15–29 — monitor kidney function CrCL < 15 — do not use	Discontinue if pancreatitis is suspected CrCL ≥ 60 mL/min — do not change dosage CrCL 30–59 — close observation CrCL < 30 — do not use

s.c. — subcutaneously; FDA — Food and Drug Administration; DM2 — type 2 diabetes; MI — myocardial infarction; CVA — cerebrovascular accident; CV — cardiovascular; CrCL — creatinine clearance

the dosage, while educating the patient about the size of consumed meals. GLP-1 agonists can also increase the incidence of cholecystitis, acute pancreatitis or pancreatic cancer. However, to date a definitive correlation between the use of these drugs and the mentioned conditions has not been proven [5].

A new therapeutic model for patients with HF and diabetes mellitus

Based on the update on HF 2019 is SGLT2 inhibitors should be consider in patients with cardiovascular disease and in patients with high cardiovascular risk to prevent or delay the
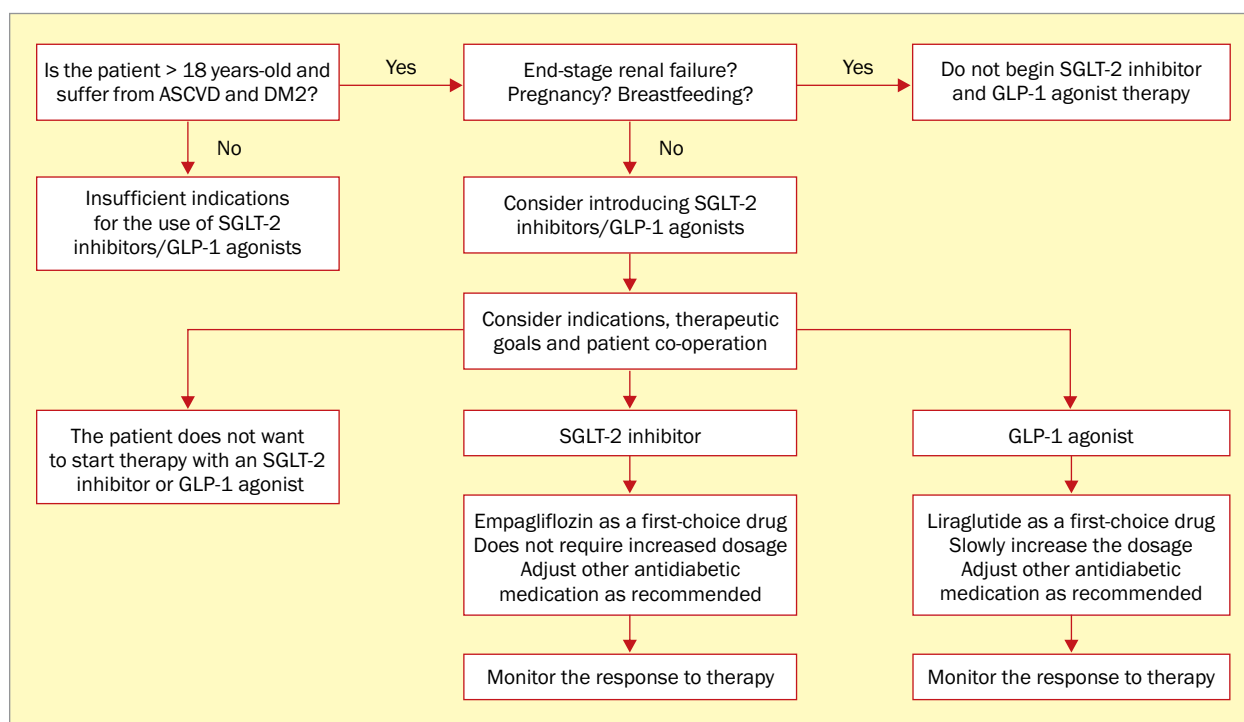
Figure 1. Treatment protocol according to American College of Cardiology (ACC) 2018 for antidiabetic drug therapy (based on [5]); ASCVD — atherosclerotic cardiovascular disease; DM2 — type 2 diabetes; SGLT-2 — sodium-glucose co-transporter-2; GLP-1 — glucagon-like peptide-1

onset of HF or HF hospitalization [8]. When commencing therapy with SGLT-2 inhibitors, in which the most recommended drug is currently empagliflozin, treatment should begin with lowest available dose. Increasing the dosage is not necessary to maintain a favourable cardiovascular effect, however it should be noted that it can be increased due to non-cardiac causes (Table 3). Among GLP-1 agonists, the currently most promising drug in clinical trials is liraglutide. Therapy with this drug should be started with a minimal dose, which should be incrementally increased to a maximum tolerated dose, bearing in mind that the therapeutic concentration for the reduction of cardiovascular risk is 1.18 mg per day (Table 4).

Patients starting SGLT-2 inhibitor therapy should be informed about the previously mentioned side effects. In addition, due to increased diuresis, which may be exacerbated by any simultaneously used loop diuretics, patients must monitor for symptoms of dehydration, such as orthostatic hypotension. SGLT-2 inhibitors can also decrease eGFR levels, which is why it is worthwhile to control for kidney function in the first few weeks of introducing the drug. Patients commencing therapy with

GLP-1 agonists should be informed about possible digestive symptoms, such as nausea and vomiting, which do not indicate a pathology, but become self-limiting over time (Figure 1) [5].

Summary

The development of pharmacotherapy in diabetes and additional positive effect on the cardiovascular system of two drug groups — SGLT2 inhibitors and GLP-1 agonists — give completely new look on the population with heart failure and co-existing diabetes. The current challenge for specialists is to implement the therapy according to the ACC 2018 scheme. The new antidiabetic drugs are in the 2019 ACC//AHA guidelines for primary prevention for cardiovascular diseases. It should be emphasize many trials with SGLT2 inhibitors are ongoing in HF with and without diabetes as co-existing disease.

Conflict(s) of interest

Participation in the Emperial study.

Streszczenie

Niewydolność serca (HF), mimo wprowadzenia złożonych modeli farmakoterapii, wciąż stanowi wyzwanie terapeutyczne, zwłaszcza gdy współtowarzyszy jej cukrzyca. W ostatnim czasie wyniki dużych badań klinicznych wykazały liczne korzyści ze stosowania inhibitorów kotransportera glukozowo-sodowego 2 i analogów glukagonopodobnego peptydu 1 jako leków nie tylko przeciwcukrzycowych, ale i obniżających ryzyko wystąpienia zdarzeń sercowo-naczyniowych oraz częstość hospitalizacji z powodu zaostrzeń HF. Znalazło to odzwierciedlenie w ostatnich wytycznych *American College of Cardiology* (ACC) z 2018 roku dotyczących ryzyka u pacjentów z cukrzycą i chorobami układu sercowo-naczyniowego oraz najnowszych wytycznych ACC/*American Heart Association* (AHA) z 2019 roku poświęconych prewencji pierwotnej chorób układu sercowo-naczyniowego.

Słowa kluczowe: niewydolność serca, cukrzyca, farmakoterapia

Folia Cardiologica 2019; 14, 4: 411–417

References

1. Maack C, Lehrke M, Backs J, et al. Heart failure and diabetes: metabolic alterations and therapeutic interventions: a state-of-the-art review from the Translational Research Committee of the Heart Failure Association — European Society of Cardiology. Eur Heart J. 2018; 39(48): 4243–4254, doi: 10.1093/eurheartj/ehy596, indexed in Pubmed: 30295797.

2. Ponikowski P, Voors A, Anker S, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Kardiol Pol. 2016: 1037–1147, doi: 10.5603/kp.2016.0141, indexed in Pubmed: 27748494.

3. MacDonald M, Petrie M, Fisher M, et al. Pharmacologic management of patients with both heart failure and diabetes. Curr Heart Fail Rep. 2009; 6(2): 126–132, doi: 10.1007/s11897-009-0019-3.

4. Banasiak W, Ponikowski P. Niewydolność serca u chorych na cukrzycę. Choroby Serca Naczyn. 2006; 3(1): 7–12.

5. Das SR, Everett BM, Birtcher KK, et al. 2018 ACC Expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes and atherosclerotic cardiovascular disease: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol. 2018; 72(24): 3200–3223, doi: 10.1016/j.jacc.2018.09.020, indexed in Pubmed: 30497881.

6. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the primary prevention of cardiovascular disease. Circulation. 2019 [Epub ahead of print]: CIR0000000000000678, doi: 10.1161/ /CIR.0000000000000678, indexed in Pubmed: 30879355.

7. Wiviott S, Raz I, Bonaca M, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019; 380(4): 347–357, doi: 10.1056/nejmoa1812389.

8. Seferovic PM, Ponikowski P, Anker SD, et al. Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of The Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2019 [Epub ahead of print], doi: 10.1002/ejhf.1531, indexed in Pubmed: 31129923.