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Актуализация позиций глифлозинов в алгоритмах лечения пациентов с сердечной недостаточностью: хронология успеха

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АННОТАЦИЯ

Введение. Несмотря на усилия кардиологических сообществ по внедрению подходов к лечению сердечной недостаточности (СН), основанных на доказательствах высшего уровня, СН остается одной из самых «больших неудовлетворенных потребностей в терапии сердечно-сосудистых заболеваний» по причине широкой распространенности, неблагоприятного прогноза и недостаточного применения методов лечения с клинически доказанной эффективностью. В статье рассматривается хронология изучения и внедрения в клиническую практику ингибиторов натрий-глюкозного котранспортера (син.: глифлозинов) 2-го типа (иНГКТ-2) с момента создания первого препарата группы — флоризина — и далее, поэтапно по мере смены терапевтической парадигмы как результата проведенных клинических исследований. Так, исследования EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58 продемонстрировали, что иНГКТ-2 не только оказывают глюкозурическое действие, но также снижают развитие и прогрессирование СН и увеличивают продолжительность жизни пациентов с сахарным диабетом 2-го типа (СД2) и сниженной фракцией выброса (ФВ) левого желудочка (ЛЖ). Исследования DAPA-HF, EMPEROR-Reduced доказали возможность улучшения исходов у пациентов с СН со сниженной ФВ ЛЖ независимо от наличия или отсутствия СД2, тем самым значительно расширив потенциальную целевую группу для иНГКТ-2. Исследование EMPEROR-Preserved — единственное исследование иНГКТ-2 на сегодняшний день (исследуемый препарат — эмпаглифлозин), продемонстрировавшее высокую эффективность в профилактике сердечно-сосудистой смертности и госпитализаций по причине СН, по-видимому, независимо от ФВ ЛЖ и наличия СД2. В результате, 9 сентября 2021 г. FDA (Food and Drug Administration, США) присвоило препарату Jardiance® (эмпаглифлозин) статус «прорывной терапии» (англ.: «*breakthrough therapy*») для лечения СН с сохраненной ФВ ЛЖ. Исследования EMPA-REG OUTCOME, DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, DAPA-CKD показали, что иНГКТ-2 замедляют развитие терминальной стадии хронической болезни почек. Наконец, основным результатом исследования EMPULSE, завершившегося в 2022 г., стала доказанная клиническая польза эмпаглифлозина у госпитализированных и стабилизированных пациентов с острой декомпенсацией СН вне зависимости от статуса СН и наличия СД2.

Заключение. С момента внедрения в клиническую практику иГНКТ-2 они успешно и достаточно быстро прошли путь от противодиабетических препаратов второй линии, для которых было достаточно только не ухудшать прогноз серьезных сердечно-сосудистых осложнений, до самостоятельного и эффективного класса препаратов в лечении СН (с классом рекомендаций I и IIa). Совокупность клинических исследований эмпаглифлозина свидетельствует, что пока это единственный препарат из группы иГНКТ-2, доказавший безопасность и клиническую эффективность, в т. ч. по влиянию на прогноз, у пациентов с СН независимо от статуса ФВ ЛЖ, наличия или отсутствия СД2, при назначении амбулаторно и стабилизированным пациентам в стационаре.

Ключевые слова: *ингибиторы натрий-глюкозного котранспортера 2 типа; иГНКТ-2; сердечная недостаточность; прогноз; фракция выброса; эмпаглифлозин*

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Actualization of Positions of Gliflozins in Treatment Algorithms for Patients with Heart Failure: Chronology of Success

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ABSTRACT

INTRODUCTION: Despite the efforts of the cardiologic communities to introduce approaches to treatment of heart failure (HF) based on the highest level of evidence, HF remains one of the "least satisfied demands in the therapy of cardiovascular diseases" due to high prevalence, poor prognosis and insufficient use of treatment methods with clinically proven effectiveness. The article considers chronology of study and introduction of sodium-glucose cotransporter 2 inhibitors (syn.: *gliflozins*; SGLT2is) in clinical practice from the moment of creation of the first drug of this group — florizin — and further, stepwise with the change of the therapeutic paradigm as the result of performed clinical trials. Thus, EMPAREG OUTCOME, CANVAS, DECLARE-TIMI 58 studies demonstrated that SGLT2is not only produce a glucosuric effect, but also reduce the development and progression of HF and increase the life expectancy of patients with type 2 diabetes mellitus (DM2) and with reduced left ventricular ejection fraction (LFEF). DAPA-HF, EMPEROR-Reduced studies proved a possibility of improving the outcomes for patients with HF with reduced LVEF irrespective of the presence or absence of DM2, thereby significantly expanding the potential target group for SGLT2is. EMPEROR-Preserved study is the only study of SGLT2is to date (the study drug — empagliflozin) that has demonstrated high effectiveness of the drug in prevention of cardiovascular mortality and hospitalizations for HF, probably irrespective of LVEF and the existence of DM2. In result, on September 9, 2021, FDA (Food and Drug Administration, USA) assigned the "breakthrough therapy" status to Jardiance® (empagliflozin) drug for treatment of HF with preserved LFEF. EMPA-REG OUTCOME, DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, DAPA-CKD studies have shown SGLT2is to slow down the development of the terminal stage of chronic kidney disease. Finally, the main result of EMPULSE study completed in 2022, was the proven clinical benefit of empagliflozin in hospitalized and stabilized patients with acute HF decompensation irrespective of HF status and existence of DM2.

CONCLUSION: From the moment SGLT2is have been introduced in the clinical practice, they rapidly and successfully passed the way from the second-line antidiabetic drugs for which it was just enough not to worsen the prognosis for serious cardiovascular complications, to independent and effective class of drugs for treatment of HF (with class I and IIa recommendations). The totality of clinical trials of empagliflozin showed that empaflorizin is so far the only drug of the SGLT2is group with the proven safety and clinical effectiveness including the influence on the prognosis, in patients with HF irrespective of the LVEF status, presence or absence of DM2, for use in outpatient treatment and in stabilized patients in hospital.

Keywords: *sodium glucose cotransporter-2 inhibitor; SGLT2i; heart failure; prognosis; ejection fraction; empagliflozin*

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ECO•VECTOR

LIST OF ABBREVIATIONS

ACE — angiotensin-converting enzyme
ARB — angiotensin receptor blocker
ARNi — angiotensin receptor-neprilysin inhibitors
βB — β-blocker
CHF — congestive heart failure
CI — confidence interval
DM2 — type 2 diabetes mellitus
EF — ejection fraction
EMA — European Medicine Agency
FDA — Food and Drug Administration
HFmrEF — heart failure with moderately reduced ejection fraction
HFpEF — heart failure with preserved ejection fraction
HFrEF — heart failure with reduced ejection fraction
HR — hazard ratio
LV — left ventricle
MCRA — mineralocorticoid receptor antagonist
NYHA — New York Heart Association
RCT — randomized clinical trial
SGLTi — sodium-glucose cotransporter inhibitor
SGLT1i — sodium-glucose cotransporter 1 inhibitor
SGLT2i — sodium-glucose cotransporter 2 inhibitor
USA — United States of America

Seventy years ago, in the spring of 1952, as a medical student ..., I was given the opportunity to assist in the management of patients with heart failure. Treatment was quite limited at the time, consisting of a low salt diet (which was rarely followed), digitalis (now of questionable value), and meralluride (mercuhydrin), a relatively weak organomercurial diuretic which required painful intramuscular injection. Following hospital discharge patients with heart failure returned to the outpatient clinic for weekly injections of meralluride... Few patients survived for more than 3 months after hospital discharge, and the patients 'drowning' in their pulmonary oedema often caused death...

E. Braunwald

In: "Heart failure: a 70 year Odyssey", May 2022 [1]

Beginning of history

The beginning of history of glucose cotransporter inhibitor (SGLTi, syn.: *gliflozins*) can probably be considered 1835, when a French chemist C. Petersen isolated phlorizin, $C_{21}H_{24}O_{10}$ (Figure 1) from the root cortex of apple tree, a solid white substance, that was first used for treatment for malaria [2]. Only 50 years later, in 1886, von Mering, a German professor of medicine, discovered *glucosuric* and, as a consequence, hypoglycemic effect of phlorizin [2, 3].

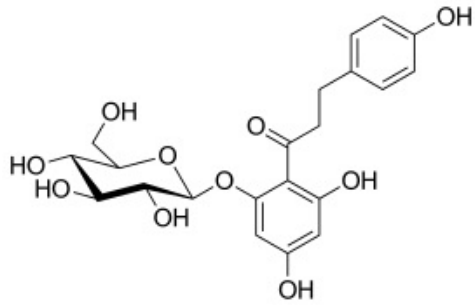

Fig. 1. Chemical structure of phlorizin.

In the first half of the XXth century, it was found that glucose, *being filtered* at the first stage in renal glomeruli, is subsequently almost completely reabsorbed in the proximal renal tubules, which probably is evolutionarily

reasonable. In the 1960s, it was proved that, firstly, glucose reabsorption requires *active* transport and, secondly, it occurs together with transport of sodium [2], which requires a special molecule — cotransporter. In 1962, F. C. Alvarado and R. K. Crane found out that phlorizin is a competing inhibitor of this cotransporter [2, 4] and can reduce the level of plasma glucose in diabetic animals [5].

Phlorizin is currently known to be an inhibitor of sodium-glucose cotransporter 1 and 2 (SGLT1i and SGLT2i, respectively) competing with D-glucose for binding with these types of carriers. The main problem that had limited its clinical use, is poor absorption in the gastrointestinal tract. Therefore, further on, an active search for *analogs* with more optimal pharmacokinetic parameters was undertaken.

In 1996, researchers from Kyoto University and Tanuba Seiygyu Co. (Japan) developed analogs to Phlorizin — first *chemically created* SGLT [2,6].

Chronology of clinical trials

In the period from 2012 to 2015, European Medicine Agency (EMA) and Food and Drug Administration (FDA) of the United States of America (USA) approved three SGLT2 inhibitors: *dapagliflozin, canagliflozin and empagliflozin* — for reduction of plasma glucose level in patients with type 2 diabetes mellitus (DM2). The preceding randomized clinical trials (RCT) with these drugs showed that at the appropriate doses, SGLT2i reduced the level of HgbA1c by ≈0.6% in absolute terms, caused moderate reduction of the body mass and arterial pressure and in general were well tolerated. They were considered to be quite effective *second-level* antidiabetic agents and were recommended as addition to metformin or sulfonylurea derivatives [2].

An important digression should be made here. Prior to the development of SGLT2i, hypoglycemic therapy often had an *unfavorable* or, at best, neutral effect on cardiovascular events, including the course of heart failure (HF) [7]. For this reason, in 2008, FDA expressed concern about the increased cardiovascular risk of new antidiabetic drugs [8], and shortly thereafter EMA followed suit [2, 9]. In accordance with the requirements of these regulatory authorities, initial trials of SGLT2 inhibitors in patients with DM2 were designed primarily to assess their *cardiovascular safety* [10, 11]. However, such a radical change in the concept of studying antidiabetic drugs predetermined a very serious, in fact, historical, change of the therapeutic paradigm not only in diabetology, but in cardiology as well.

So, already in 2015, the results of the first major RCT of empagliflozin — EMPA-REG OUTCOME — in patients with DM2, cardiovascular diseases with reduced left ventricular ejection fraction (LVEF) were published [12]. Quite unexpectedly, empagliflozin was found to reduce the primary combined (cardiovascular death, non-fatal myocardial infarction or stroke) endpoint by 14%. Even more impressive was 32% reduction of mortality from any cause and 35% reduction of the frequency of hospitalizations for HF. Both the cardiology and endocrinology communities were somewhat puzzled by such favorable results: at that time there was no convincing pathogenetic explanation of them, especially in view of the fact that most patients (both in the empagliflozin group and in the placebo group) received adequate antihypertensive and hypolipidemic therapy and achieved the target respective parameters, which caused a certain distrust of the results of the study [2, 12]...

However, the results were soon confirmed in RCT of canagliflozin (Canagliflozin Cardiovascular Assessment Study, CANVAS) [13, 14] and dapagliflozin (DECLARE-TIMI 58) [15], which led to the first change in the existing therapeutic paradigm (Figure 2A) [2].

Then there were two RCTs in patients with HF and reduced LVEF (HFrEF): with dapagliflozin (*DAPA-HF*) [16] and empagliflozin (*EMPEROR-Reduced*) [17]. The studies have demonstrated the same benefit from application of these SGLT2i *both in patients with and without DM2* and led to the second change in the therapeutic paradigm (Figure 2B) [2].

In 2020, *SOLIST* study in patients with DM2 showed that sotagliflozin reduces severity of HF throughout the entire range of LFEF including a *small subgroup* of patients with HF with preserved LVEF (HFpEF) [18].

On August 27, 2021, at the Congress of the European Society of Cardiology, the results of the *EMPEROR-Preserved* study dedicated to the effect of empagliflozin on prognosis (cardiovascular mortality, hospitalization rate, frequency of first and repeated hospitalizations, decreased kidney function) in patients with chronic HF and LVEF more than 40%, *regardless of the presence/absence of DM2*, were first presented [19]. The main result of the *EMPEROR-Preserved* study was 21% reduction (hazard ratio (HR) 0.79; 95% confidence interval (CI) 0.69–0.90; $p < 0.001$) of the risk of a confirmed case of cardiovascular death or confirmed hospitalization for HF during treatment with empagliflozin. Moreover, the homogeneity of the obtained result was observed in the analysis of subgroups of patients. Empagliflozin reduced the risk of first or repeated hospitalizations for HF by 27% (HR 0.73; 95% CI 0.61–0.88; $p < 0.001$). For the secondary endpoint — the angular coefficient of change in the estimated glomerular filtration rate compared to the initial level — a positive result was also obtained: an increase by 1.36 ml/min x 1.73 m^2 per year with empagliflozin compared to placebo ($p < 0.001$) [19, 20].

Thus, *EMPEROR-Preserved* study was the *first successful* study in the world practice, specially planned for patients with HF and LVEF > 40%. These results confirm a high risk of cardiovascular death and hospitalizations due

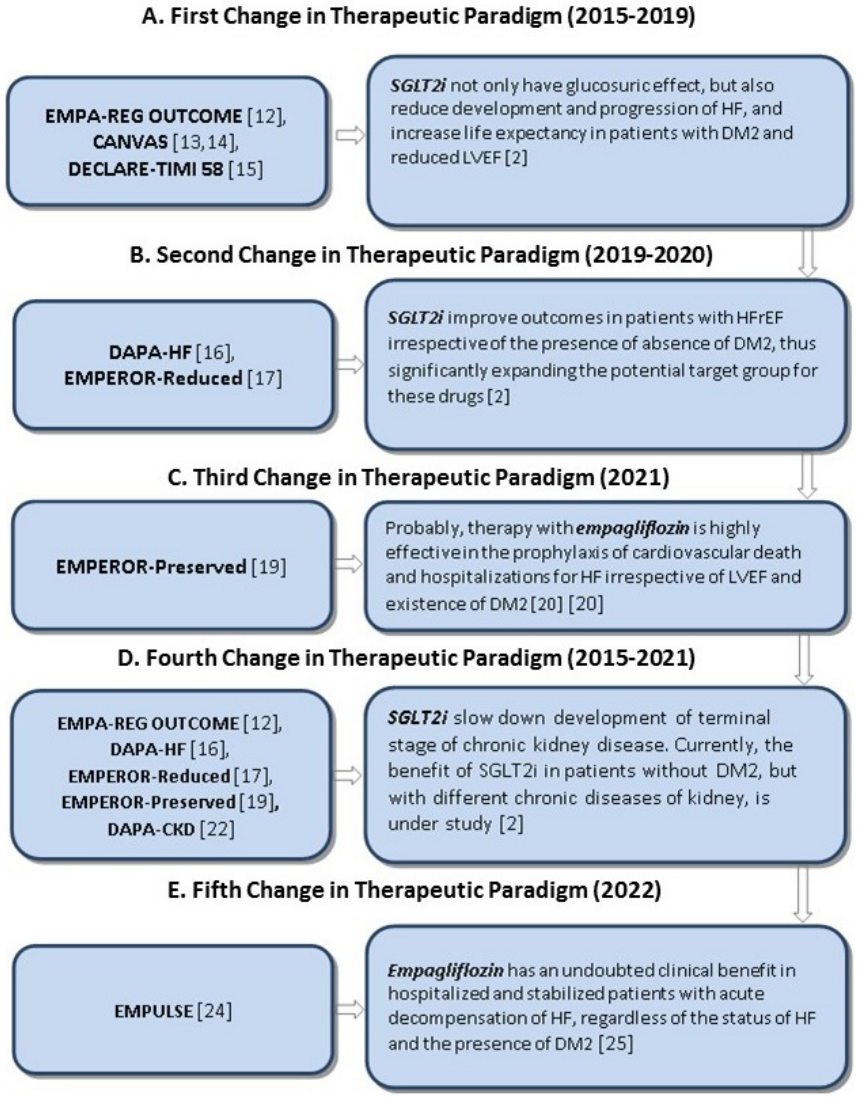

Fig. 2. Main chronological milestones of changes of therapeutic paradigm in result of clinical study of SGLT2i group.
Notes: SGLT2i — sodium-glucose cotransporter 2 inhibitor, HF — heart failure, DM2 — type 2 diabetes mellitus, EF — ejection fraction, LV — left ventricle, HFrEF — heart failure with reduced left ventricular ejection fraction.

to HF in the studied population of patients, while use of empagliflozin at a dose of 10 mg/day can radically change the course of the disease, that was reflected in one more change in the therapeutic paradigm (Figure 2C) [2, 20].

To note, RCT was also conducted for dapagliflozin in patients with HFpEV (*PRESERVED-HF*). Its results showed that 12-week treatment with dapagliflozin can improve *symptoms of HF* that were reported by the patients, reduce *the extent of physical limitations*, *improve physical activity*, however, the improvement of prognosis was not studied [21], therefore, it is unreasonably to speak about comparability of the results of *EMPEROR-Preserved* and *PRESERVED-HF* studies.

The mentioned RCTs in patients with DM2 and HFrEF [12, 16, 17] in combination with two RCTs in patients with chronic kidney disease including patients without DM2, [22, 23], also demonstrated significant renoprotection in these categories of patients due to intake of SGLT2i, which resulted in the fourth change in the therapeutic paradigm (Figure 2D) [2].

The aim of recently completed *EMPULSE* study was evaluation of the clinical benefit and safety of administration of empagliflozin in hospitalized and stabilized (during hospitalization) patients with acute decompensation of HF. This RCT compared the use of empagliflozin (10 mg once a day) and placebo in hospital. The unique aspects of

EMPULSE design were "inclusion window" and duration of follow-up [24, 25]. Thus, the patients were included in the study regardless of the LVEF and the presence/absence of DM2, and were randomized during hospitalization after stabilization of their condition (from 24 hours to 5 days after admission), treatment with empagliflozin lasted up to 90 days. As part of treatment, patients received angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs; in total 70%), mineralocorticoid receptor antagonists (MCRA, 57%), loop diuretics (87%) [24].

The results of EMPULSE study for the primary endpoint are characterized by stable statistical significance of clinical benefits of empagliflozin in the studied sample and their homogeneity in subgroups: with and without DM2, in young or elderly patients, in men or women, among representatives of any region participating in the study. Besides, clinical benefits of empagliflozin did not depend on the LVEF status (preserved or reduced), presence of absence of chronic kidney disease and/or of atrial fibrillation, the level of N-terminal cerebral natriuretic peptide. Divergence of Kaplan-Meier curves (time before lethal outcome) did not show any statistical significance because of small amount of recorded events, but there was an evident trend repeating that of *EMPEROR-Preserved* and *EMPEROR-Reduced* studies, with manifestations of benefit of empagliflozin as early as at the beginning of therapy [24, 25].

Thus, the results of *EMPULSE* study show safety of empagliflozin (so far the only representative of SGLTi) and its clinical advantages in comparison with placebo in hospitalized and stabilized patients with acute decompensation of HF regardless of HF status (Figure 2E) [25].

Significance of results of clinical trials for cardiologic practice

At present, a convincing evidence base has been obtained confirming clinical effectiveness of four classes of medical drugs (inhibitors of renin-angiotensin-aldosterone system including angiotensin receptor-neprilysin inhibitors (ARNi), beta-blockers (βB), MCRA and SGLT2i) in reduction of morbidity and mortality of patients with HFpEF. The necessity of combined four-component therapy (in case of good tolerance) capable of producing multicomponent influence on the mechanisms of development of HF, is out of doubt [28, 29].

The question about *sequencing of administration and titration of these four classes of medical drugs* to achieve a well-tolerated four-component therapy, remains unsolved. In real practice, patients with indications for all four groups of components, often receive only one or two of them, or achievement of the optimal four-component treatment regimen of HF is protracted for a long time [28, 30]. Use of incomplete/sub-optimal therapeutic regimens leads to lethal outcomes, hospitalizations and progression of HF, which could be avoided at present, with the availability of the necessary therapeutic "tools" [28].

In view of the above, of great interest is the scheme proposed by J. J. McMurray and M. Packer in 2020 for accelerated sequence of selection of drug treatment for HF taking into account the results of the entire complex of RCTs on this problem (Figure 3) [28, 31].

Besides, in the current 2022, the professional communities of the USA were the first to present significantly updated Clinical Guidelines for the management of HF. According to them, drug therapy for *HFrEF* should include 4 classes of drugs, including SGLT2i, and a possible first step may be any of the following groups:

- ARNi in II-III functional class HF according to classification of New York Heart Association (NYHA), ACE inhibitors or ARB — in II-IV FC HF according to NYHA (recommendation class I)
- βB (recommendation class I);
- MCRA (recommendation class I);
- SGLT2i (recommendation class I);
- diuretics — *if necessar*y (recommendation class I).

To note, in these Clinical recommendations, only two representatives of iNGKT2 are included in the therapeutic regimens for *HFrEF: empagliflozin and dapagliflozin* (the initial dose for both is 10 mg 1 time per day, the target dose is 10 mg 1 time per day).

For HF with moderately reduced LVEF (*HFmrEF*), SGLTi have recommendation class IIa: "*in patients with HFmrEF, SGLTi may be useful in reducing hospitalizations for HF and mortality from cardiovascular diseases*". A lower recommendation class (IIb) in this category of patients was assigned by experts to the groups of ARNi, ACE inhibitors, ARB, MCRA and βB.

For *HFrEF*, SGLTi also have a high class of recommendations — IIa: "*they can be useful in reducing hospitalizations with HF and mortality from cardiovascular diseases*", whereas MCRA, ARNi, ARB have class IIb. The need for the treatment of hypertension in this population was assigned recommendation class I, treatment of atrial fibrillation — class IIa, regular use of nitrates or phosphodiesterase inhibitors-5 — recommendation class III (no benefit) [32].

As part of the preparation of the next revision of domestic Clinical guidelines for the management of HF, the leading Russian cardiologists also formulated an expert consensus opinion in the form of two documents [20, 25]. Below the most important positions are given:

1) Despite the efforts of the cardiologic communities of the developed countries to introduce top level evidence-based approaches to the treatment of chronic HF, there exists clinical inertia in prescribing combinations of drugs and optimal doses of drugs for the treatment of HF. The international manifesto of endocrinologists published in 2020 states that insufficient use of SGLT2i "*does not*

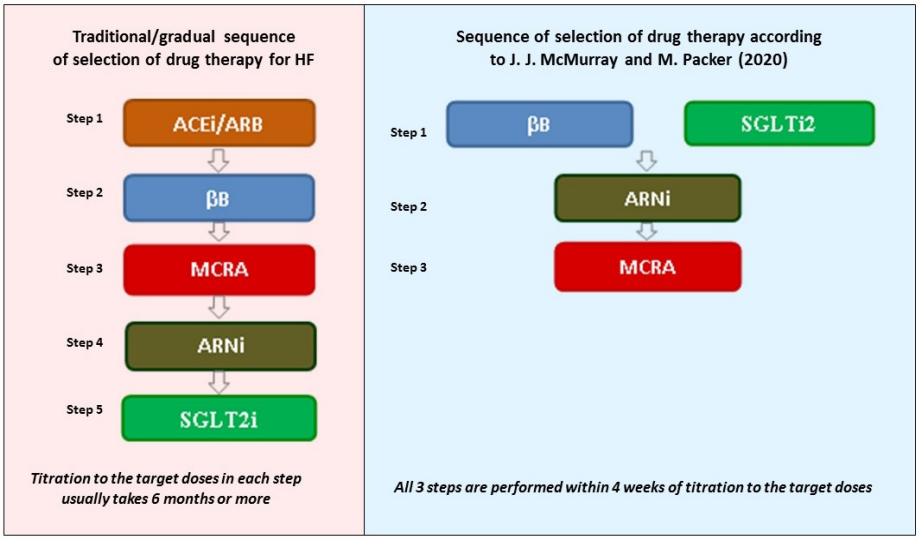

Fig. 3. The sequence of selection of drug therapy for HF according to J. J. McMurray and M. Packer (2020) in comparison with traditional therapy [28, 31].

Notes: ACEi — angiotensin converting enzyme inhibitor, ARB — angiotensin receptor blocker, βB — beta-blocker, MCRA — mineralocorticoid receptor antagonist, ARNi — angiotensin receptor-neprilysin inhibitor, SGLT2i — sodium-glucose co-transporter 2 inhibitor.

allow patients with DM to receive vital treatment, and also exposes them to a greater risk of hospitalization for HF and progression of renal failure" [20];

2) Taking into account the unfavorable prognosis for patients with chronic HF in the absence of the adequate treatment, it is necessary to develop a plan to overcome clinical inertia as soon as possible. This will speed up the process of introducing evidence-based medicine data into real clinical practice [20, 25];

3) Making changes to clinical recommendations will permit to speed up introduction of this treatment in clinical practice, and therefore affect the prognosis of patients with HF at the population level [20, 25].

CONCLUSION

Thus, since the introduction of gliflozins in clinical practice, these drugs have successfully and quickly passed the way from *second-line* antidiabetic drugs, for which it was enough not to worsen the prognosis of serious cardiovascular complications, to an *independent effective* class of drugs for the treatment of heart failure (with recommendation class I and IIa). Convincing grounds have been obtained to consider gliflozins as a *first-line* therapy, a "*cornerstone*" in formation of the drug strategy for the treatment of chronic heart failure.

It is not surprising that in recent years the range of absolute indications for this group have considerably increased, not only and not so much in endocrinological practice, which would be expected, but also in cardiologic practice and, which is especially demonstrative, by primary healthcare (Figure 4) [33]. Nevertheless, to date, heart failure remains one of the "*least satisfied needs in the treatment of cardiovascular diseases*" due to its widespread prevalence, unfavorable prognosis and insufficient use of treatment methods with clinically proven effectiveness.

The range of studies included in the empagliflozin trial program shows that this is the only drug of the group of sodium-glucose cotransporter type 2 inhibitors that has proven clinical effectiveness (including its effect on prognosis) and safety in patients with heart failure irrespective of the status of the left ventricular ejection fraction, the presence/absence of type 2 diabetes mellitus, in various clinical scenarios (in outpatient or stabilized hospitalzed patients). So, on September 9, 2021, the FDA (Food and Drug Administration, USA) assigned Jardiance® (empagliflozin) with the status of "*breakthrough therapy*" for the treatment of heart failure with preserved left ventricular ejection fraction [34, 35].

ADDITIONAL INFORMATION

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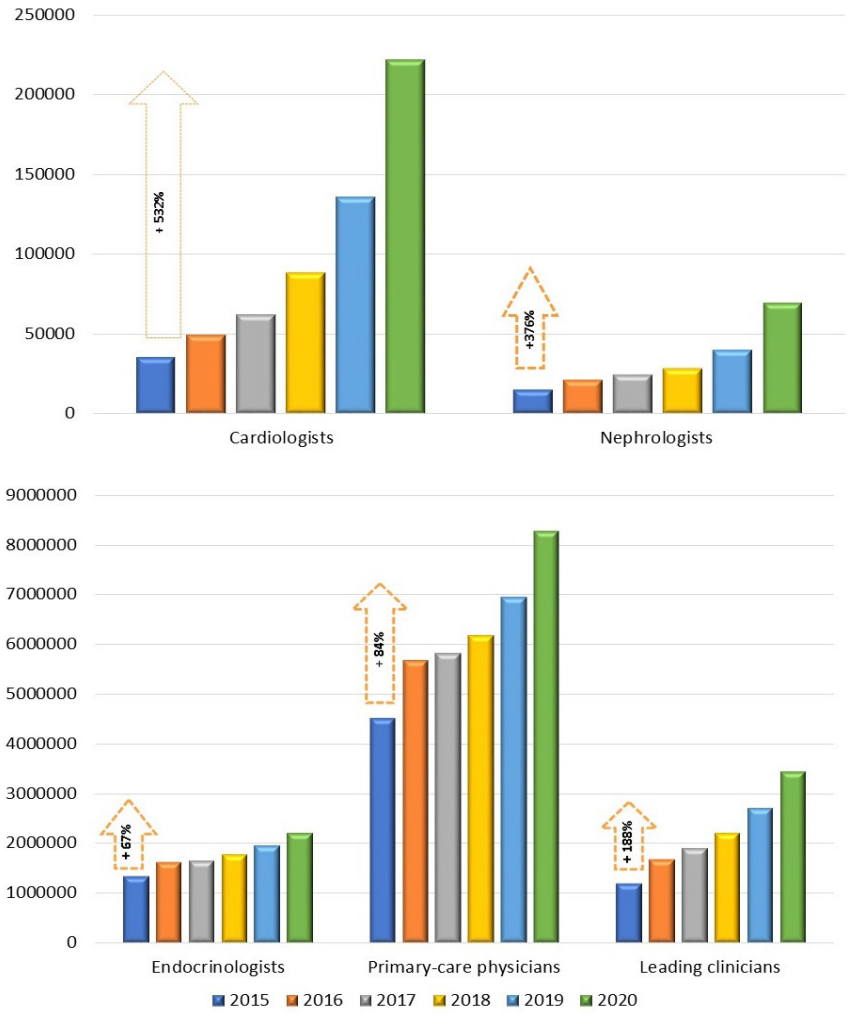

Fig. 4. Dynamics of absolute quantity of administrations of iSGL-2 in the USA in 2015–2022 according to IQVIA's National Prescription Audit data base [33].
Note: iSGLT-2 — sodium-glucose cotransporter-2 inhibitor, USA — the United States of America.

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