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SGLT-2 inhibitors for treatment of heart failure in patients with and without type 2 diabetes: A practical approach for routine clinical practice

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ABSTRACT

Sodium-glucose cotransporter-2 inhibitors (SGLT-2i), initially studied and approved for the treatment of diabetes, are now becoming a promising class of agents to treat heart failure (HF) and chronic kidney disease (CKD), even in patients without diabetes. While the potential benefits in several diseases (usually treated by different medical specialties) is amplifying the interest in these drugs, their use in frail patients with multiple pathologies and on polypharmacy can be complex, requiring a composite multidisciplinary approach. Following a brief overview of the evidence supporting the benefits of SGLT-2i in patients with HF or CKD, we herein provide guidance for prescribing SGLT-2i in daily practice using a multidisciplinary approach. A shared treatment algorithm is presented for initiating an SGLT-2i in patients already being treated for diabetes and HF. Tools to prevent hypoglycemia, blood pressure drop, genital infections, euglycemic diabetic ketoacidosis and eGFR dip are also provided. It is hoped that this practical, multidisciplinary guidance for initiating SGLT-2i in patients with HF and/or CKD, whatever therapy they are currently on, can help to offer SGLT-2i to the largest population of patients possible to provide the most therapeutic benefit.

1. Introduction

Heart failure (HF) affects millions of patients globally, and due to the increased aging of the population is expected to further increase in the future [1]. While current treatments have led to a reduction in mortality, at least in patients with HF with reduced ejection fraction (HFrEF), prognosis remains poor and new therapeutic alternatives are needed [1]. In this regard, sodium-glucose cotransporter-2 (SGLT-2) inhibitors (SGLT-2i) are a promising class of agents to treat HF. Already approved for type 2 diabetes (T2D), and with a prominent role in current guidelines [2], some of these drugs have been recently approved for the treatment of HF and CKD. By inhibiting SGLT-2, these agents lead to excretion of glucose in urine with subsequent lowering of plasma glucose and other profound changes in substrate utilization [3]. However, it is unlikely that the observed benefits in HF can be explained by glucose-lowering alone. Indeed, multiple mechanisms have been proposed to explain the beneficial cardio- and reno-protective effects, including hemodynamic, anti-inflammatory, anti-fibrotic, antioxidant, and metabolic effects [4–6].

Herein, we briefly overview the supporting evidence documenting the benefits of SGLT-2i in patients with HF or CKD, with or without diabetes. This will be followed by the main objective of this publication, i.e., to provide guidance for prescribing SGLT-2i in daily practice using a multidisciplinary approach, especially in frail patients.

2. SGLT-2i in heart failure

Four major cardiovascular (CV) outcome trials (CVOTs) – EMPA-REG (empagliflozin), CANVAS (canagliflozin), DECLARE-TIMI 58 (dapagliflozin), and VERTIS CV (ertugliflozin), have assessed the CV benefits of SGLT-2i in patients with T2D [7–10]. Reductions of 30%, 33%, 27%, and 35% respectively were seen in the relative risk for hospitalizations for HF (hHF), in these four trials [7–10]. A meta-analysis of CVOTs on over 34,000 patients reported that SGLT-2i reduced the risk of major adverse CV events (MACE; including CV death, myocardial infarction, and stroke) by 11%, with benefits only for patients with atherosclerotic CV disease [11].

Based on these results, dedicated trials in patients with HF were initiated. In DAPA-HF, 4744 patients with New York Heart Association class II, III, or IV HF and an ejection fraction (EF) of ≤40% were

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randomized to either dapagliflozin or placebo [12]. Dapagliflozin was superior to placebo in preventing the primary composite endpoint of cardiovascular death, hospitalization for heart failure or urgent heart failure visit (HR 0.74 [95% CI 0.65, 0.85], $p < 0.0001$). These results prompted the EMA to include the indication for dapagliflozin in the treatment of HFrEF [13]. The EMPEROR-Reduced trial randomized 3730 patients with the same major enrolment criteria used for DAPA-HF to receive empagliflozin or placebo [14]. The primary outcome was a composite of CV death or hHF. After a median of 16 months, the primary outcome was seen in 19.4% of patients receiving empagliflozin vs. 24.7% for placebo (HR 0.75; $p < 0.001$). A meta-analysis of these two trials [15] suggested a class effect.

Additional evidence for this prospect was recently demonstrated in the SOLOIST-WHF trial in 1222 patients who were hospitalized for worsening heart failure and randomized to sotagliflozin or placebo. Sotagliflozin reduced the primary endpoint (CV death and hospitalizations or urgent visits for heart failure) with an HR of 0.67 ($p < 0.001$) [16]. Interestingly, benefits were seen in patients regardless of whether left ventricular EF was reduced [<50%] or preserved [≥50%]. The EMPEROR-Preserved trial recently reported that empagliflozin significantly decreased the combined risk of CV death or hHF in patients with HF and preserved EF, irrespective of the presence of T2D [17], with an HR of 0.79 ($p < 0.001$). A similar study with dapagliflozin (DELIVER; NCT03619213) is still ongoing. It has been postulated that mechanisms for the benefits of SGLT-2 inhibition involve enhanced renal glucose excretion, which promotes weight loss, improved myocardial function, and decreases in uric acid [16]. While reduction in blood pressure may have some effects, it is unclear what role the slight reduction in blood pressure may have in these patients.

3. SGLT-2i in chronic kidney disease

Several CVOTs have shown that SGLT-2i have reno-protective effects. Following the CANVAS trials [18], the CREDENCE study randomized 4401 patients with T2D, an eGFR of 30 to <90 ml/min/ 1.73 m^2 and substantial albuminuria to canagliflozin 100 mg or placebo [19]. Of note, the annual decline in eGFR was slower with canagliflozin (−1.72 vs. -4.33 ml/min/1.73 m^2) and the absolute benefits on renal outcomes were most prominent in patients with lower eGFR at baseline [19].

In the VERTIS CV trial, 8246 patients with type 2 diabetes and established atherosclerotic CV disease were randomized to ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo as add-on therapy [20]. The exploratory kidney composite outcome of sustained 40% reduction from baseline in eGFR, chronic kidney dialysis/transplant, or renal death was lower with ertugliflozin than placebo, HR 0.66 ($p < 0.01$) [20].

SGLT-2i benefits on renal function were particularly interesting in the DAPA-CKD study, as 32.5% of studied patients did not have diabetes at enrollment. This trial randomized 4304 patients with eGFR of 25 to 75 ml/min/1.73 m^2 and UACR of 200–5000 to dapagliflozin 10 mg or placebo [21]. The primary outcome was a composite of sustained decline in eGFR of at least 50%, end-stage kidney disease, or death from renal or CV causes. Dapagliflozin was superior to placebo in preventing the primary composite endpoint of ≥50% sustained decline in eGFR, reaching end-stage kidney disease, cardiovascular or renal death with a HR of 0.61 (95% CI 0.51, 0.72; $p < 0.0001$). The composite endpoint of death from CV causes or hHF also favored dapagliflozin (HR 0.71; $p = 0.009$) and there were also fewer deaths among those treated with dapagliflozin (4.7% vs. 6.8%; HR 0.69; $p = 0.004$). Importantly, benefits were seen in patients both with and without T2D. These results prompted the EMA to include the indication for dapagliflozin in the treatment of CKD [13].

4. Practical guidance for daily practice

4.1. Initiating an SGLT-2i in patients being treated for T2D

There are currently few recommendations for the use of SGLT-2i in patients with HFrEF with or without type 2 diabetes, although the Canadian Cardiovascular Society (CCS) guidelines have provided some general guidance in such patients [22] as have the Association of British Clinical Diabetologists (ABCD) and Diabetes UK [23]. In addition, the updated ESC guidelines on HF have indicated that SGLT-2i are to be considered to have Level IA evidence for their use in HF patients with reduced EF, even if no specific recommendations were made regarding their initiation [24]. Very recently, the American College of Cardiology also issued guidelines on optimizing the decision pathway for patients with HFrEF [25]. However, none of these guidelines provides support for initiating an SGLT-2i for HFrEF in a patient already taking medicines for diabetes.

Though sharing SGLT-2i initiation with the endocrinologist or general practitioner who is already caring for the diabetic patient is fundamental, the interaction may take time. Our purpose is therefore to provide a few but important suggestions on how to initiate an SGLT-2i in a diabetic patient with HFrEF, especially when frailty is present. Beyond the possible (although rare) risk of euglycemic diabetic ketoacidosis (eDKA) described below, the major risk in patients with diabetes is induction of hypoglycemia, usually associated with higher mortality rates [26]. Non-endocrinologists should therefore carefully evaluate a series of parameters before initiation of another medicine for diabetes which might induce a significant adverse event. As seen in Table 1 and Fig. 1, after an accurate targeted anamnesis, the first check should regard the diabetes medicines already in use. Since sulfonylurea receptor agonists (SURa: sulfonylureas and glinides) and insulin are the only diabetes medicines able to induce hypoglycemia, their absence in the diabetes treatment plan might ensure the absence of this risk, independently of the other medicines already present in the treatment plan (metformin, DPP-4is, GLP-1 RAs, pioglitazone, acarbose, alone or in combination). On the contrary, if SURa or insulin are present, the risk of inducing hypoglycemia is possible, and caution should be taken, especially in frail patients. The possible risk of hypoglycemia induced by the initiation of an SGLT-2i depends on several parameters, including efficacy, starting glucose control, and the patient's current risk of hypoglycemia, which should be explored in depth with a specific anamnesis (including possible signs suggesting hypoglycemic episodes). Since SGLT-2i mostly lose their glucose-lowering effect when eGFR is lower than 45 ml/min/ 1.73 m^2 (below this threshold these medicines must be suspended if prescribed "only" for diabetes), the addition of an SGLT-2i is not expected to further lower glucose levels and is therefore safe, unless the patient is already experiencing hypoglycemic episodes. The second important parameter to be monitored is glucose control, namely, HbA_{1c}. Since SGLT-2i are expected to lower HbA_{1c} by not more than 0.8%, their addition in patients already treated with other medicines but with an $HbA_{1c} \geq 7.5\%$ can be considered safe. The most important parameter that should be verified before initiating an SGLT-2i is the presence of hypoglycemic episodes. The evaluation of reported self-monitored blood glucose (SMBG) is fundamental before initiating treatment. In case of hypoglycemic episodes, even if anamnestically collected, glucose lowering medications should be reduced by up to 50%. This reduction

Table 1
Parameters to be checked before initiating an SGLT-2i in a patient with diabetes who is already treated with glucose-lowering medication to avoid hypoglycemia.

- Type of medications (for diabetes)
- eGFR
- HbA_{1c}
- Self-Monitored Blood Glucose

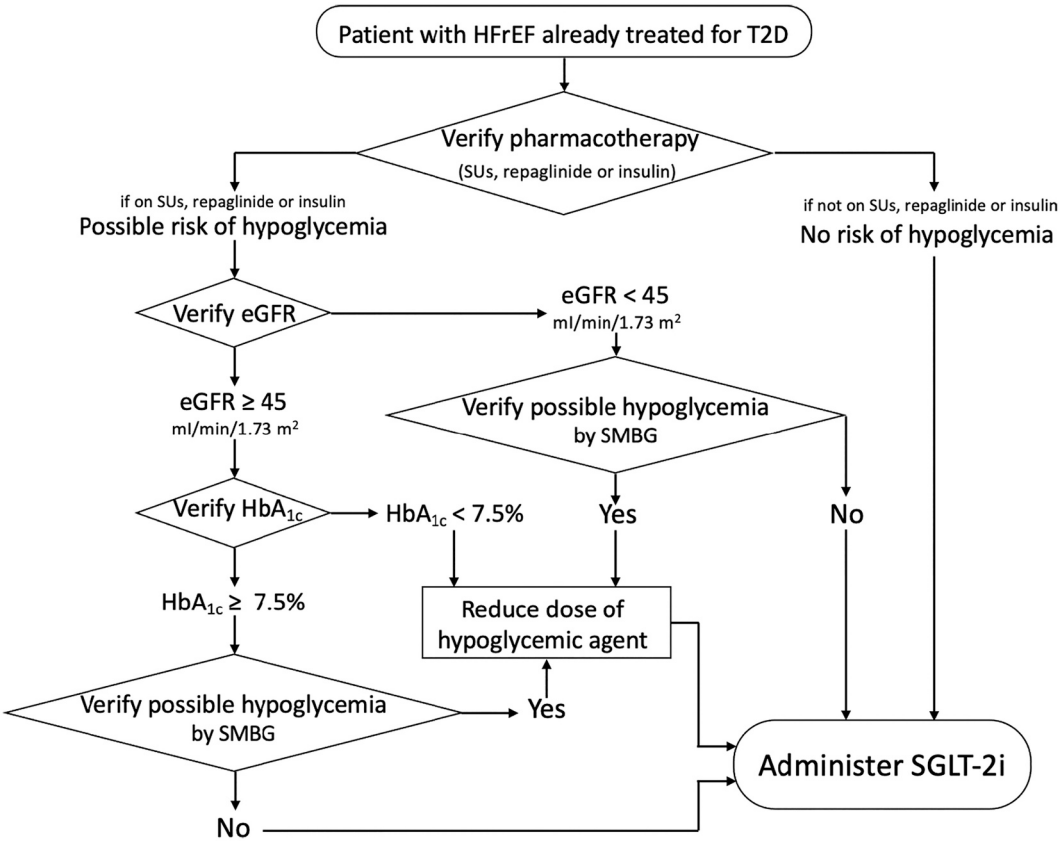

Fig. 1. Proposed algorithm for initiating SGLT-2i in patients with HF and already treated for T2D. Accurate anamnesis for previous genital infections, frailty and previous hypoglycemic episodes should always precede SGLT-2i initiation. SMBG, self-monitoring of blood glucose.

should also be applied to patients taking SURa and/or insulin with an eGFR higher than 45 ml/min/1.73 m^2 and HbA_{1c} < 7.5% even if there are no hypoglycemic episodes. A simple algorithm that summarizes the above information is shown in Fig. 1. Collaboration with the endocrinologist or general practitioner in prescribing diabetes therapy, is obviously essential.

4.2. Initiating an SGLT-2i in patients receiving treatment for HF

When considering initiating an SGLT-2i in patients already receiving treatment for HF (with or without diabetes), the main factor to consider is blood pressure/volume control. If blood pressure is already at or above the desired value (95–100 mmHg), then an SGLT-2i can be initiated immediately. However, if blood pressure is lower, which may be the case in patients receiving multiple renin-angiotensin-aldosterone system (RAAS) inhibitors (RAAS-i) and diuretics, then down titration of diuretic or other antihypertensive medication should be considered to allow initiation of an SGLT-2i, especially in frail patients.

4.3. Diuretics

A sub-analysis of DAPA-HF has examined the effects of no diuretic and dose of loop diuretic equivalent to furosemide <40, 40, and > 40 mg daily [27]. Dapagliflozin was seen to reduce the composite risk of cardiovascular death, worsening heart failure events, and all-cause death across all subgroups, including those receiving no diuretic. Volume depletion was highest in those receiving a dose of furosemide >40 mg/day, while patients not receiving a diuretic had a lower risk of volume depletion. Overall, the use of dapagliflozin in patients also receiving a loop diuretic was considered safe and was well tolerated.

4.4. Avoiding the risk of an eGFR dip

Given the mechanism of action on the kidney, SGLT-2i are associated with a transient decrease in eGFR, also known as the eGFR dip; an eGFR dip ≥10% is seen in 28–45% of diabetic patients receiving an SGLT-2i [28]. Data from randomized trials and real-world studies has strongly suggested that eGFR dip is not uncommon in patients initiating a SGLT-2i and that it is a functional and reversible phenomenon that should be distinguished from acute kidney injury [29]. eGFR dip has also been associated with a reduced risk of adverse renal and cardiovascular outcomes [29].

Diuretic use and more severe renal impairment at baseline have also been associated with eGFR dip. eGFR dip has thus been attributed to the protective mechanism of action of SGLT-2i and is not usually a cause for safety concerns since it is transient. However, if the decline in eGFR is substantial (e.g. >30% from baseline), then the clinician should be aware that a dose reduction may be necessary [25]. If a patient with an eGFR dip is concomitantly initiating a RAAS-i/diuretic and SGLT-2i, then caution may be warranted. In such cases, it may be prudent to initiate one drug (class) at a time, possibly giving preference to the antihypertensive medication [25] and monitor the patient's eGFR after a minimum period of two weeks. If the eGFR is ≥25 ml/min/1.73 m^2t, then the other agent can be initiated. If eGFR remains low, then an additional period of wait and see is needed. It should also be noted that in the DAPA-CKD trial, patients were enrolled with an eGFR as low as 25 ml/min/1.73 m^2. Accordingly, the lower threshold for initiating an SGLT-2i, even for HF, should be 25 ml/min/1.73 m^2. (≥ 30 ml/min/1.73 m^2 for empagliflozin).

4.5. Genital infections

Since SGLT-2i result in significant glucosuria, patients, at least those with type 2 diabetes, are at increased risk for severe genital infections, with a hazard ratio of 4.45 in women and 3.30 in men for patients over the age of 60 years [30]; though a full analysis in non-diabetic patients has not been published yet, preliminary data based on SAEs in EMPEROR-Reduced [14] and DAPA-CKD [21] seem to suggest that the risk of genital infections is reduced but not abolished. To circumvent the risk, common precautionary measures should be taken. An accurate targeted anamnesis on possible previous episodes of genital infections and/or presence of risk factors are obviously mandatory. Patients should then receive recommendations for increased genital hygiene, with abundant rinsing, rather than the use of additional antimicrobial soaps [4]. In addition, over prescription of antibiotics should be avoided, especially in women with frequent genital infections (e.g., once a month). Discontinuation of therapy is usually not needed.

4.6. Euglycemic diabetic ketoacidosis

Diabetic ketoacidosis (DKA) is considered as the triad of hyperglycemia, metabolic acidosis, and ketosis [31]. Euglycemic DKA (eDKA) is defined when patients present with DKA and blood glucose levels <200 mg/dl [31]. While rare, eDKA has been associated with the use of SGLT-2i [32]. The most common symptoms of eDKA are the same as DKA, namely nausea, vomiting, and abdominal pain [33]. Since eDKA has been related to glucosuria, leading to low serum glucose, the clinician should consider suspending the SGLT-2i whenever the patient is fasting, for whatever reason. The Phase 3 DARE-19 study examined the use of dapagliflozin in patients with cardiometabolic risk factors, hospitalized with COVID-19 and confirmed the good safety profile of dapagliflozin in patients with respiratory insufficiency [34].

In the presence of any dehydrating illness, such as nausea or vomiting, the 'sick day' rule should be applied, namely the SGLT-2i should be suspended during the time of illness [22]. The CCS guidelines further recommend that an SGLT-2i be withheld in the presence of concomitant infection, trauma, surgery, or any other major physiological stressor [22]. In all the above cases, all the antihyperglycemic medications that the patient is receiving should be maintained and only the SGLT-2i should be temporarily suspended. Insulin should not be suspended unless recommended by the consulting diabetologist.

5. The importance of a multidisciplinary approach

The SGLT-2i are a relatively new class of antihyperglycemic agents whose benefits go well beyond glucose lowering. Given their benefits on multiple clinical outcomes, their use in patients with HF is likely to increase substantially in the next few years, with increasing prescriptions by cardiologists. In this light, it is important to consider the advantages of a multidisciplinary approach to managing difficult-to-treat patients with multiple comorbidities, such as the typical patient with HF. A multidisciplinary approach is currently considered the gold standard for management of patients with HF [35]. Furthermore, in the patient with T2D, a diabetologist should be considered as an essential member of the multidisciplinary team including the heart failure specialist, nephrologists, general practitioner, and other specialists. If the patient has CKD or is being administered a SGLT-2i, the presence of a nephrologist should also be taken into consideration [36]. A multidisciplinary approach will have undoubted benefits on the patient's overall management and care.

6. Conclusions

The optimal standard of care for patients with HF is constantly evolving and choosing the best therapy for these patients is not always straightforward. Currently, four classes of drugs are to be considered as disease modifiers, including beta blockers, RAAS/ARNI blockers, mineralocorticoid antagonists and, more recently, SGLT-2i. These classes of drugs have demonstrated a reduction in mortality and morbidity in patients with HF and reduced EF. Optimization of therapy, aiming at including administration of all classes in patients with HF and reduced EF is projected to confer a substantial mortality/morbidity benefit [37]. SGLT-2i will be more widely adopted in the future, and while diabetologists are familiar with these drugs, cardiologists are only just gaining experience. Indeed, SGLT-2i are now considered as first-line therapy for patients with HF and diabetes [38]. Clinicians will nonetheless strive to make the best clinical judgements and decisions based on their experience. Herein, we have provided practical guidance and tips for initiating SGLT-2i in patients with HF. With this approach, it is hoped that SGLT-2i can be offered to the broadest possible population of patients with HF in order to receive the maximal benefits from these drugs.

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Availability of data and materials

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Authors' contributions

All the authors had an equal role in the conception and drafting of the manuscript.

Declaration of Competing Interest

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References

[1] D. Berliner, J. Bauersachs, Current drug therapy in chronic heart failure: the new guidelines of the european Society of Cardiology (ESC), Korean Circ. J. 47 (2017) 543–554.
[2] C.M. Otto, R.A. Nishimura, R.O. Bonow, B.A. Carabello, J.P. Erwin 3rd, F. Gentile, et al., 2020 ACC/AHA guideline for the Management of Patients with Valvular Heart Disease: a report of the american College of Cardiology/American Heart Association joint committee on clinical practice guidelines, Circulation 143 (2021) e72–e227.
[3] A. Giaccari, Sodium-glucose co-transporter inhibitors: medications that mimic fasting for cardiovascular prevention, Diabetes Obes. Metab. 21 (2019) 2211–2218.
[4] V.V. Garla, J. Butler, L.F. Lien, SGLT-2 inhibitors in heart failure: guide for prescribing and future perspectives, Curr. Cardiol. Rep. 23 (2021) 59.

[5] P. Grubic Rotkvic, M. Cigrovski Berkovic, N. Bulj, L. Rotkvic, I. Celap, Sodium-glucose cotransporter 2 inhibitors' mechanisms of action in heart failure, World J. Diabetes 11 (2020) 269–279.
[6] S. Verma, J.J.V. McMurray, SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review, Diabetologia 61 (2018) 2108–2117.
[7] C.P. Cannon, R. Pratley, S. Dagogo-Jack, J. Mancuso, S. Huyck, U. Masiukiewicz, et al., Cardiovascular outcomes with ertugliflozin in type 2 diabetes, N. Engl. J. Med. 383 (2020) 1425–1435.
[8] B. Neal, V. Perkovic, K.W. Mahaffey, D. de Zeeuw, G. Fulcher, N. Erondu, et al., Canagliflozin and cardiovascular and renal events in type 2 diabetes, N. Engl. J. Med. 377 (2017) 644–657.
[9] S.D. Wiviott, I. Raz, M.P. Bonaca, O. Mosenzon, E.T. Kato, A. Cahn, et al., Dapagliflozin and cardiovascular outcomes in type 2 diabetes, N. Engl. J. Med. 380 (2019) 347–357.
[10] B. Zinman, C. Wanner, J.M. Lachin, D. Fitchett, E. Bluhmki, S. Hantel, et al., Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes, N. Engl. J. Med. 373 (2015) 2117–2128.
[11] T.A. Zelniker, S.D. Wiviott, I. Raz, K. Im, E.L. Goodrich, M.P. Bonaca, et al., SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials, Lancet 393 (2019) 31–39.
[12] J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi, L. Kober, M.N. Kosiborod, F. A. Martinez, et al., Dapagliflozin in patients with heart failure and reduced ejection fraction, N. Engl. J. Med. 381 (2019) 1995–2008.
[13] Dapagliflozin, Summary of Product Characteristics. 2021.
[14] M. Packer, S.D. Anker, J. Butler, G. Filippatos, S.J. Pocock, P. Carson, et al., Cardiovascular and renal outcomes with empagliflozin in heart failure, N. Engl. J. Med. 383 (2020) 1413–1424.
[15] F. Zannad, J.P. Ferreira, S.J. Pocock, S.D. Anker, J. Butler, G. Filippatos, et al., SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-reduced and DAPA-HF trials, Lancet 396 (2020) 819–829.
[16] D.L. Bhatt, M. Szarek, P.G. Steg, C.P. Cannon, L.A. Leiter, D.K. McGuire, et al., Sotagliflozin in patients with diabetes and recent worsening heart failure, N. Engl. J. Med. 384 (2021) 117–128.
[17] S.D. Anker, J. Butler, G. Filippatos, J.P. Ferreira, E. Bocchi, M. Bohm, et al., Empagliflozin in heart failure with a preserved ejection fraction, N. Engl. J. Med. 385 (2021) 1451–1461.
[18] V. Perkovic, D. de Zeeuw, K.W. Mahaffey, G. Fulcher, N. Erondu, W. Shaw, et al., Canagliflozin and renal outcomes in type 2 diabetes: results from the CANVAS program randomised clinical trials, Lancet Diabetes Endocrinol. 6 (2018) 691–704.
[19] M.J. Jardine, Z. Zhou, K.W. Mahaffey, M. Oshima, R. Agarwal, G. Bakris, et al., Renal, cardiovascular, and safety outcomes of canagliflozin by baseline kidney function: a secondary analysis of the CREDENCE randomized trial, J. Am. Soc. Nephrol. 31 (2020) 1128–1139.
[20] D.Z.I. Cherney, B. Charbonnel, F. Cosentino, S. Dagogo-Jack, D.K. McGuire, R. Pratley, et al., Effects of ertugliflozin on kidney composite outcomes, renal function and albuminuria in patients with type 2 diabetes mellitus: an analysis from the randomised VERTIS CV trial, Diabetologia 64 (2021) 1256–1267.
[21] H.J.L. Heerspink, B.V. Stefansson, R. Correa-Rotter, G.M. Chertow, T. Greene, F. F. Hou, et al., Dapagliflozin in patients with chronic kidney disease, N. Engl. J. Med. 383 (2020) 1436–1446.
[22] E. O'Meara, M. McDonald, M. Chan, A. Ducharme, J.A. Ezekowitz, N. Giannetti, et al., CCS/CHFS heart failure guidelines: clinical trial update on functional mitral regurgitation, SGLT2 inhibitors, ARNI in HFpEF, and tafamidis in amyloidosis, Can. J. Cardiol. 36 (2020) 159–169.
[23] U. Dashora, R. Gregory, P. Winocour, K. Dhatariya, S. Rowles, A. Macklin, et al., Association of British Clinical Diabetologists (ABCD) and Diabetes UK joint position statement and recommendations for non-diabetes specialists on the use of sodium glucose co-transporter 2 inhibitors in people with type 2 diabetes (January 2021), Clin. Med. (Lond.) 21 (2021) 204–210.
[24] Heart Failure Associated of thge ESC, 2021, 29 June-1 July.
[25] C. Writing, T.M. Maddox, J.L. Januzzi Jr., L.A. Allen, K. Breathett, J. Butler, et al., 2021 update to the 2017 ACC expert consensus decision pathway for optimization of heart failure treatment: answers to 10 pivotal issues about heart failure with reduced ejection fraction: a report of the american College of Cardiology Solution set Oversight Committee, J. Am. Coll. Cardiol. 77 (2021) 772–810.
[26] S.M. Pearson, B. Whittam, K. Kulavarasalingam, A. Mitchell-Gears, C. James, R. A. Ajjan, Reduction in cardiovascular mortality following severe hypoglycemia in individuals with type 2 diabetes: the role of a pragmatic and structured intervention : structured intervention for community hypoglycemia, Cardiovasc. Diabetol. 20 (2021) 18.
[27] A.M. Jackson, P. Dewan, I.S. Anand, J. Belohlavek, O. Bengtsson, R.A. de Boer, et al., Dapagliflozin and diuretic use in patients with heart failure and reduced ejection fraction in DAPA-HF, Circulation 142 (2020) 1040–1054.
[28] H.J.L. Heerspink, D.Z.I. Cherney, Clinical implications of an acute dip in eGFR after SGLT2 inhibitor initiation, Clin. J. Am. Soc. Nephrol. 16 (2021) 1278–1280.
[29] Y. Xie, B. Bowe, A.K. Gibson, J.B. McGill, G. Maddukuri, Z. Al-Aly, Clinical implications of estimated glomerular filtration rate dip following sodium-glucose Cotransporter-2 inhibitor initiation on cardiovascular and kidney outcomes, J. Am. Heart Assoc. 10 (2021), e020237.
[30] C.V. Dave, S. Schneeweiss, E. Patorno, Comparative risk of genital infections associated with sodium-glucose co-transporter-2 inhibitors, Diabetes Obes. Metab. 21 (2019) 434–438.
[31] P. Rawla, A.R. Vellipuram, S.S. Bandaru, Raj J. Pradeep, Euglycemic diabetic ketoacidosis: a diagnostic and therapeutic dilemma, Endocrinol. Diabetes Metab. Case Rep. 2017 (2017).
[32] K.R. Burke, C.A. Schumacher, S.E. Harpe, SGLT2 inhibitors: a systematic review of diabetic ketoacidosis and related risk factors in the primary literature, Pharmacotherapy 37 (2017) 187–194.
[33] A. Diaz-Ramos, W. Eilbert, D. Marquez, Euglycemic diabetic ketoacidosis associated with sodium-glucose cotransporter-2 inhibitor use: a case report and review of the literature, Int. J. Emerg. Med. 12 (2019) 27.
[34] M.N. Kosiborod, R. Esterline, R.H.M. Furtado, J. Oscarsson, S.B. Gasparyan, G. G. Koch, et al., Dapagliflozin in patients with cardiometabolic risk factors hospitalised with COVID-19 (DARE-19): a randomised, double-blind, placebo-controlled, phase 3 trial, Lancet Diabetes Endocrinol. 9 (2021) 586–594.
[35] G. Morton, J. Masters, P.J. Cowburn, Multidisciplinary team approach to heart failure management, Heart 104 (2018) 1376–1382.
[36] M.G. Shlipak, S.L. Tummalapalli, L.E. Boulware, M.E. Grams, J.H. Ix, V. Jha, et al., The case for early identification and intervention of chronic kidney disease: conclusions from a kidney disease: improving global outcomes (KDIGO) controversies conference, Kidney Int. 99 (2021) 34–47.
[37] M. Vaduganathan, B.L. Claggett, P.S. Jhund, J.W. Cunningham, J. Pedro Ferreira, F. Zannad, et al., Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials, Lancet 396 (2020) 121–128.
[38] N. Kumowski, N. Marx, K. Schutt, Treating heart failure in patients with diabetes: the view of the cardiologist, Diabetes Res. Clin. Pract. 176 (2021), 108852.