SGLT2i in Diabetes, Cardiovascular Disease, and Kidney Disease

Subjects: Cardiac & Cardiovascular Systems

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Sodium glucose cotransporter 2 inhibitor (SGLT2i) is a class of drugs that were originally intended for decreasing blood glucose in diabetes. However, recent trials have shown that there are other beneficial effects. Recent major SGLT2i landmark trials have demonstrated benefits for cardiovascular disease (reduce major adverse cardiovascular events (heart attack, stroke, cardiovascular death), hospitalization for heart failure, all-cause death), and renal disease (delay the onset of dialysis) regardless of diabetic status.

SGLT2 inhibitor | cardiorenal disease | cardiovascular disease | renal disease | diabetes

1. Introduction

Diabetes, cardiovascular disease, and renal disease are all clinically related disease states. Diabetes is a major cause of chronic kidney disease and renal failure. Diabetes increases the risk for cardiovascular disease and death [1]. The top cause of death in diabetes is cardiovascular disease. In renal disease, a low estimated glomerular filtration rate (eGFR) is associated with higher mortality [2].

The origin of sodium glucose cotransporter 2 inhibitors (SGLT2i) is traced back to phlorizin, which is an organic compound first discovered and extracted from apple tree bark in 1835 by De Koninck and Stas [3]. It has played a role in diabetes research through its action of renal glucosuria and inhibition of glucose reabsorption. Originally intended for treating diabetes, SGLT2i has since intersected the fields of endocrinology, cardiology, and nephrology. In 2008, the United States Food and Drug Administration mandated the inclusion of cardiovascular outcomes in diabetes trials. Since this era of cardiovascular outcome trials, more benefits from SGLT2i have been discovered. The convergence of the treatment of diabetes, cardiovascular disease, and renal disease is a paradigm shift.

2. Sodium Glucose Cotransporter 2 Inhibitor Trials in Type 2 Diabetes

The initial large clinical trials were focused on patients with type 2 diabetes, the main inclusion criterion.

The EMPA-REG OUTCOME trial was the earliest SGLT2i cardiovascular outcome trial and showed major cardiovascular benefits [4]. The trial studied 7020 patients with type 2 diabetes and patients received either empagliflozin or placebo. There was a reduction in major adverse cardiovascular events (MACE) (myocardial

infarction, stroke, cardiovascular death) in the empagliflozin group (HR, 0.86; 95% CI, 0.74–0.99; p = 0.04 for superiority). Additionally, a reduction in hospitalization for heart failure was observed in patients receiving empagliflozin (HR, 0.65; 95% CI, 0.50–0.85; p = 0.002). This trial was the first positive cardiovascular outcome trial in type 2 diabetics.

The CANVAS Program trial compared canagliflozin to placebo in 10,142 patients with type 2 diabetes. A reduction in major adverse cardiovascular event was observed in the canagliflozin group (HR, 0.86; 95% CI, 0.75–0.97; p = 0.02 for superiority) [5][6]. Additionally, hospitalization for heart failure and cardiovascular death was reduced in the canagliflozin group (HR 0.78; 95% CI, 0.67–0.91). There was an increased risk of amputation, specifically at the toe or metatarsal in those that received canagliflozin.

The DECLARE-TIMI 58 trial evaluated dapagliflozin compared to placebo in 17,160 patients with type 2 diabetes [7][8]. There was a reduction in heart failure-related death and hospitalization (HR, 0.83; 95% CI, 0.73–0.95; p = 0.005). Notably, dapagliflozin did not reduce the rate of major adverse cardiovascular event (HR, 0.93; 95% CI, 0.84–1.03; p = 0.17). Renal events occurred less frequently in the dapagliflozin group (HR, 0.76; 95% CI, 0.67 to 0.87).

The TIMI Study Group performed a meta-analysis which included the EMPA-REG OUTCOME, CANVAS Program, and DECLARE-TIMI 58 trials with a total of 34,322 patients [9]. SGLT2i reduced hospitalization for heart failure (HR, 0.77; 95% CI 0.71–0.84; $p < 0.0001$) and progression of renal disease (HR, 0.55; 95% CI 0.48–0.64, $p < 0.0001$) in patients with or without cardiovascular disease or history of heart failure.

These trials showed the benefits of SGLT2i in reducing cardiovascular events in patients with type 2 diabetes (**Table 1**). This led to trials focusing on primarily examining cardiovascular benefits.

Table 1. Sodium glucose cotransporter 2 inhibitors (SGLT2i) trials in type 2 diabetes.

Trial (Medication)	Main Outcome HR (95% CI) (*p*-Value)	Key Summary
EMPA-REG OUTCOME [4] (empagliflozin 10 or 25 mg)	↓ MACE, 0.86 (0.74–0.99) (p = 0.04) ↓ HHF ↓ All cause death	This was the first SGLT2i trial showing reduction of CV events.
CANVAS Program [5][10] (canagliflozin 100 or 300 mg)	↓ MACE 0.86 (0.75–0.97) (p = 0.02)	Canagliflozin reduced CV events and HHF.
DECLARE-TIMI 58 [7] (dapagliflozin 10 mg)	↓ CV death or HHF 0.83 (0.73–0.95) (p = 0.005)	Dapagliflozin reduced CV death and HHF. MACE was not reduced.

Trial (Medication)	Main Outcome HR (95% CI) (*p*-Value)	Key Summary
VERTIS CV [11] (ertugliflozin 5 or 15 mg)	MACE 0.97 (0.75–1.03) ($p < 0.001$ for noninferiority)	Ertugliflozin is non-inferior to placebo in reducing MACE.

After observing such major cardiovascular benefits from SGLT2i in patients with type 2 diabetes, researchers decided to evaluate the potential cardiovascular benefits from SGLT2i therapy in patients without type 2 diabetes.

CV, cardiovascular; eGFR, estimated glomerular filtration rate; HHF, heart failure for hospitalization; MACE, major adverse cardiovascular event.

The DAPA-HF trial included 4744 heart failure reduced ejection fraction (HFrEF) patients receiving dapagliflozin versus placebo [12]. Dapagliflozin reduced the occurrence of the composite outcome of worsening heart failure or cardiovascular mortality (HR, 0.74; 95% CI 0.65–0.85; $p < 0.001$). Additionally, both hospitalization for heart failure (HR, 0.70; 95% CI 0.59–0.83) and cardiovascular mortality (HR, 0.82; 95% CI, 0.69–0.98) were reduced by dapagliflozin regardless of diabetic status.

The EMPEROR-Reduced trial compared empagliflozin to placebo in 3730 HFrEF patients [13]. The primary composite outcome of hospitalization for heart failure or cardiovascular death was reduced by empagliflozin (HR, 0.75; 95% CI, 0.65–0.86; $p < 0.001$). Empagliflozin reduced the number of hospitalizations for heart failure (HR, 0.70; 95% CI, 0.58–0.85; $p < 0.001$). The benefits of empagliflozin in reducing cardiovascular death and worsening heart failure was observed regardless of diabetic status.

The EMPEROR-Preserved trial compared empagliflozin to placebo in 5988 patients with heart failure with preserved ejection fraction (HFpEF) (ejection fraction above 40%) [14]. The primary outcome of hospitalization for heart failure or cardiovascular death was reduced by empagliflozin (HR, 0.79; 95% CI 0.69–0.90; $p < 0.001$) in both patients with or without diabetes. This result was mainly driven by the lowered risk of hospitalization for heart failure in those receiving empagliflozin.

The SOLOIST-WHF trial evaluated sotagliflozin and placebo in 1222 patients hospitalized for worsening heart failure, which included both HFrEF and HFpEF patients [15]. Interestingly, sotagliflozin is both a sodium glucose cotransporter 2 (SGLT2) inhibitor and sodium glucose cotransporter 1 (SGLT1) inhibitor. Sotagliflozin reduced cardiovascular death and hospitalization (HR, 0.67; 95% CI, 0.52–0.85; $p < 0.001$). This trial demonstrated that SGLT2i therapy can be started safely and effectively in patients even after an episode of decompensation [16]. Initiation of sotagliflozin before or after discharge significantly lowered cardiovascular death and urgent visits for heart failure.

The EMPULSE trial included 530 hospitalized patients with diagnosis of acute de novo or decompensated chronic heart failure regardless of left ventricular ejection fraction [17]. Patients were randomized to receive either empagliflozin or placebo. The primary outcome was a composite of death, number of heart failure events, time to first heart failure event, or a 5-point or greater change in the Kansas City Cardiomyopathy Questionnaire Total Symptom Score. Patients that received empagliflozin experienced greater benefit compared to the placebo group (stratified win ratio, 1.36; 95% CI, 1.09–1.68; $p = 0.0054$). The effectiveness of empagliflozin was observed in both

acute de nove and decompensated chronic heart failure, regardless of ejection fraction or diabetic status. These clinical benefits could be observed in the 90 days after treatment initiation. The EMPULSE trial demonstrated that empagliflozin can be safely initiated in hospitalized patients for acute heart failure.

The DELIVER trial studied the role of dapagliflozin compared to placebo in 6263 heart failure patients [18]. This trial is the most inclusive heart failure trial. Namely, the trial included both hospitalized patients and outpatients with an ejection fraction of 40% or greater or an improved ejection fraction (previously EF < 40%). Dapagliflozin was shown to reduce the primary composite endpoint of cardiovascular death or worsening heart failure (HR, 0.82; 95% CI 0.73–0.92; $p < 0.001$). Those receiving dapagliflozin experienced lower total events and symptoms compared to the placebo group.

A pooled meta-analysis of the DAPA-HF and DELIVER trials demonstrated that dapagliflozin reduced the risk of cardiovascular death (HR, 0.86; 95% CI 0.76–0.97; $p = 0.01$), hospitalization for heart failure (RR, 0.71; 95% CI 0.65–0.78; $p < 0.001$), and major adverse cardiovascular event (HR, 0.90; 95% CI 0.81–1.00; $p = 0.045$), across a whole spectrum of left ventricular ejection fractions from ejection fraction of 25% to 65% [19]. This has widened the indications for SGLT2i.

These SGLT2i cardiovascular trials show the effective reduction of hospitalization for heart failure and cardiovascular death (**Table 2**). SGLT2i indications for cardiovascular disease continue to expand with subsequent cardiovascular outcome trial.

Table 2. SGLT2i trials in cardiovascular disease.

Trial (Medication)	Main Outcome HR (95% CI) (*p*-Value)	Key Summary
DAPA-HF [12] (dapagliflozin 10 mg)	↓ composite of CV death and HHF 0.74 (0.65–0.85) ($p < 0.001$)	Dapagliflozin reduced the risk of worsening HF or CV death in HFrEF patients, regardless of diabetic status.
EMPEROR-Reduced [13] (empagliflozin 10 mg)	↓ composite of CV death and HHF 0.75 (0.65–0.86) ($p < 0.001$)	Empagliflozin shown to reduce HHF and CV death in HFrEF, regardless of diabetic status.
EMPEROR-Preserved [14] (empagliflozin 10 mg)	↓ CV death or HHF 0.79 (0.69–0.90) ($p < 0.001$)	Empagliflozin reduced CV death or HHF in HFpEF patients.
SOLOIST-WHF [15] (sotagliflozin 200 or 400 mg)	↓ CV death and HHF 0.67 (0.52–0.85) ($p < 0.001$)	This was the first major trial of SGLT1/SGLT2 inhibitor in hospitalized patients.

Trial (Medication)	Main Outcome HR (95% CI) (*p*-Value)	Key Summary
EMPULSE [17] (empagliflozin 10 mg)	↓Death, HF events, time to first HF event, ≥5 change in KCCQ score stratified win ratio, 1.36 (1.09–1.68) ($p = 0.0054$)	Empagliflozin is effective and can be safely initiated in hospitalized patients.
DELIVER [18]/Meta-analysis of DELIVER and DAPA-HF [19] (dapagliflozin 10 mg)	↓ CV death or worsening HF 0.82 (0.73–0.92) ($p < 0.001$)	Patients with HF with mildly reduced or preserved ejection fraction. Dapagliflozin benefits extend to all HF patients across a whole spectrum of EF.

CV, cardiovascular; EF, ejection fraction; HF, heart failure; HHF, hospitalization for heart failure; HFrEF, heart failure reduced ejection fraction; HFpEF, heart failure preserved ejection fraction; KCCQ, Kansas City Cardiomyopathy Questionnaire Total Symptom Score.

4. Sodium Glucose Cotransporter 2 Inhibitor Trials in Renal Disease

Renal benefits were signaled in various SGLT2i trials, leading to the following trials examining the role of SGLT2i in renal disease.

The CREDENCE trial examined the use of canagliflozin and placebo in 4401 patients with type 2 diabetes and chronic kidney disease (CKD) [20]. The primary outcome of end-stage kidney disease, doubling of baseline serum creatinine, renal mortality, or mortality was reduced in patients on canagliflozin (HR, 0.70; 95% CI, 0.59–0.82; $p = 0.00001$). The secondary outcomes of cardiovascular death or hospitalization for heart failure were also reduced by canagliflozin (HR, 0.69; 95% CI, 0.57–0.83; $p < 0.001$). The CREDENCE trial showed that canagliflozin offers both cardiovascular and renal protection to patients with type 2 diabetes and chronic kidney disease patients. Adverse effect rates were comparable among the canagliflozin and placebo groups.

The DAPA-CKD trial studied 4304 patients with chronic kidney disease, regardless of diabetic status, receiving dapagliflozin [21]. The primary outcome (decline of estimated glomerular filtration rate (eGFR), new end-stage renal disease (ESRD), renal mortality, or cardiovascular mortality) was reduced in those receiving dapagliflozin (HR 0.61; 95% CI 0.51–0.72; $p < 0.001$). Additionally, dapagliflozin reduced hospitalization for heart failure and cardiovascular mortality (HR 0.71; 95% CI 0.55–0.92; $p = 0.009$). Importantly, the benefits of dapagliflozin extended to both patients with and without diabetes. Both dapagliflozin and placebo groups had a similar incidence of adverse effects.

The positive results from the CREDENCE and DAPA-CKD trials are timely since the RENAAL trial from two decades ago was the last positive trial involving chronic kidney disease patients [22].

The EMPA-KIDNEY trial studied 6609 patients chronic kidney disease with an estimated glomerular filtration rate between 20 and 45 mL/min per 1.73 m^2 who received either empagliflozin or placebo [23]. The primary outcome of

'Keeffe, L.M.; Gao, P.; Wood, A.M.; Burgess, S.; et al. Association of Cardiometabolic Multimorbidity With Mortality. JAMA 2015, 314, 52.
2. Mahmoodi, B.K.; Matsushita, K.; Woodward, M.; Blankestijn, P.J.; Cirillo, M.; Ohkubo, T.; Rossing, P.; Sarnak, M.J.; Stengel, B.; Yamagishi, K.; et al. Associations of Kidney Disease Measures with Mortality and End-Stage Renal Disease in Individuals with and without Hypertension: A Meta-Analysis. Lancet 2012, 380, 1649–1661.
3. Ehrenkranz, J.R.; Lewis, N.G.; Kahn, C.R.; Roth, J. Phlorizin: A Review. Diabetes Metab. Res. Rev. 2005, 21, 31–38.
4. Zinman, B.; Wanner, C.; Lachin, J.M.; Fitchett, D.; Bluhmki, E.; Hantel, S.; Mattheus, M.; Devins, T.; Johansen, O.E.; Woerle, H.J.; et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N. Engl. J. Med. 2015, 373, 2117–2128.
5. Rådholm, K.; Figtree, G.; Perkovic, V.; Solomon, S.D.; Mahaffey, K.W.; de Zeeuw, D.; Fulcher, G.; Barrett, T.D.; Shaw, W.; Desai, M.; et al. Canagliflozin and Heart Failure in Type 2 Diabetes Mellitus: Results from the CANVAS Program. Circulation 2018, 138, 458–468.
6. Neal, B.; Perkovic, V.; Matthews, D.R.; Mahaffey, K.W.; Fulcher, G.; Meininger, G.; Erondu, N.; Desai, M.; Shaw, W.; Vercruysse, F.; et al. Rationale, Design and Baseline Characteristics of the CANagliflozin CardioVascular Assessment Study–Renal (CANVAS-R): A Randomized, Placebo-controlled Trial. Diabetes Obes. Metab. 2017, 19, 387–393.
7. Wiviott, S.D.; Raz, I.; Bonaca, M.P.; Mosenzon, O.; Kato, E.T.; Cahn, A.; Silverman, M.G.; Bansilal, S.; Bhatt, D.L.; Leiter, L.A.; et al. The Design and Rationale for the Dapagliflozin Effect on Cardiovascular Events (DECLARE)–TIMI 58 Trial. Am. Heart J. 2018, 200, 83–89.
8. Wiviott, S.D.; Raz, I.; Bonaca, M.P.; Mosenzon, O.; Kato, E.T.; Cahn, A.; Silverman, M.G.; Zelniker, T.A.; Kuder, J.F.; Murphy, S.A.; et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N. Engl. J. Med. 2019, 380, 347–357.
9. Zelniker, T.A.; Wiviott, S.D.; Raz, I.; Im, K.; Goodrich, E.L.; Bonaca, M.P.; Mosenzon, O.; Kato, E.T.; Cahn, A.; Furtado, R.H.M.; et al. SGLT2 Inhibitors for Primary and Secondary Prevention of

the progression of kidney disease (ESRD, decline in estimated glomerular filtration rate, and death from renal causes) and cardiovascular death was reduced in the empagliflozin group (HR 0.72; 95% CI 0.64–0.82; $p < 0.001$). Importantly, these results were consistent regardless of diabetic status. Aside from renal benefits, patients receiving empagliflozin had lower hospitalization than the placebo group (HR 0.86; 95% CI 0.78–0.95; $p = 0.003$).

The CREDENCE, DAPA-CKD, and EMPA-KIDNEY trials unequivocally show that SGLT2i dramatically delays the need for renal replacement therapy and reduces death from renal causes (**Table 3**).

Table 3. SGLT2i trials in renal disease.

Trial (Medication)	Main Outcome HR (95% CI) (*p*-Value)	Key Summary
CREDENCE [20] (canagliflozin 100 mg)	↓ ESRD, doubling of sCr, renal death, or CV death 0.70 (0.59–0.82) ($p = 0.00001$)	CREDENCE was the first trial in more than two decades in improving kidney endpoints.
DAPA-CKD [21] (dapagliflozin 10 mg)	↓ Decline in eGFR, new ESRD, renal death, or CV death 0.61 (0.51–0.72) ($p < 0.001$)	Dapagliflozin reduced the risk of eGFR decline, ESRD, and renal or CV death in CKD patients, regardless of diabetic status.
EMPA-KIDNEY [23] (empagliflozin 10 mg)	↓ ESRD, decrease in eGFR, renal death or CV death 0.72 (0.64–0.82) ($p < 0.001$) ↓ Hospitalization 0.86 (0.78–0.95) ($p = 0.003$)	Empagliflozin reduced ESRD, eGFR decline, and renal or CV death in CKD patients, regardless of diabetic status.

5. Discussion

Aside from the major outcome benefits in type 2 diabetes, various recent SGLT2i trials have consistently shown cardiovascular and renal benefits regardless of diabetic status [24]. There is strong and consistent evidence showing the benefits of SGLT2i medications in diabetes, cardiovascular disease, and renal disease. With these three diseases having overlapping pathology, SGLT2i are a unique treatment strategy to manage all three chronic diseases. SGLT2i medications are safe, with infrequent and manageable minor side effects such as genital mycotic infections [25].

New clinical guidelines have now adopted SGLT2i therapy after the release of the promising benefits of SGLT2i medications [26][27][28]. In type 2 diabetes, SGLT2i are second-line medications after metformin; however, recently, guidelines have started to recommend SGLT2i earlier in the course of treatment in high risk patients [29]. In heart failure, SGLT2i therapy is now first-line therapy in patients with or without diabetes [26]. With the recent DELIVER and DAPA-HF trials, SGLT2i are shown to be effective across all left ventricular ejection fractions. In renal disease and diabetes, SGLT2i and metformin are recommended as first-line therapy in patients with an estimated glomerular filtration rate equal to or over 30 mL/min per 1.73 m^2 [30]. As additional landmark trials continue to be released, additional approved indications for SGLT2i should continue to arise.

Cardiovascular and Renal Outcomes in Type 2 Diabetes: A Systematic Review and Meta-Analysis of Cardiovascular Outcome Trials. Lancet 2019, 393, 31–39.
10. Neal, B.; Perkovic, V.; Mahaffey, K.W.; de Zeeuw, D.; Fulcher, G.; Erondu, N.; Shaw, W.; Law, G.; Desai, M.; Matthews, D.R. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N. Engl. J. Med. 2017, 377, 644–657.
11. Cannon, C.P.; Pratley, R.; Dagogo-Jack, S.; Mancuso, J.; Huyck, S.; Masiukiewicz, U.; Charbonnel, B.; Frederich, R.; Gallo, S.; Cosentino, F.; et al. Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. N. Engl. J. Med. 2020, 383, 1425–1435.
12. ... .; ... with
13. ... rma, S.; ... n in
14. ... cca, H.- ... with a
15. ... Riddle, M.C.; Voors, A.A.; Metra, M.; et al. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. N. Engl. J. Med. 2020, 384, 117–128.
16. Docherty, K.F.; McMurray, J.J.V. SOLOIST-WHF and Updated Meta-analysis: Sodium–Glucose Co-transporter 2 Inhibitors Should Be Initiated in Patients Hospitalized with Worsening Heart Failure. Eur. J. Heart Fail. 2021, 23, 27–30.
17. Voors, A.A.; Angermann, C.E.; Teerlink, J.R.; Collins, S.P.; Kosiborod, M.; Biegus, J.; Ferreira, J.P.; Nassif, M.E.; Psotka, M.A.; Tromp, J.; et al. The SGLT2 Inhibitor Empagliflozin in Patients Hospitalized for Acute Heart Failure: A Multinational Randomized Trial. Nat. Med. 2022, 28, 568–574.
18. Solomon, S.D.; McMurray, J.J.V.; Claggett, B.; de Boer, R.A.; DeMets, D.; Hernandez, A.F.; Inzucchi, S.E.; Kosiborod, M.N.; Lam, C.S.P.; Martinez, F.; et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. N. Engl. J. Med. 2022, 387, 1089–1098.
19. Jhund, P.S.; Kondo, T.; Butt, J.H.; Docherty, K.F.; Claggett, B.L.; Desai, A.S.; Vaduganathan, M.; Gasparyan, S.B.; Bengtsson, O.; Lindholm, D.; et al. Dapagliflozin across the Range of Ejection Fraction in Patients with Heart Failure: A Patient-Level, Pooled Meta-Analysis of DAPA-HF and DELIVER. Nat. Med. 2022, 28, 1956–1964.

Future research continues to examine the use of SGLT2i in type 1 diabetes and pre-diabetes. Currently, there are limited studies on SGLT2i use in type 1 diabetes [30]. Ongoing research continues to study the safety of SGLT2i use in estimated glomerular filtration rate under 30 mL/min per 1.73 m^2. Future trials can further explore SGLT2i's ability in lowering blood pressure. The EMPACT-MI trial is currently studying the use of empagliflozin in patients who had an acute myocardial infarction and examining the possibility in reducing the risk of heart failure and death.

The mechanism of actions pertaining to the cardiovascular benefits of SGLT2i is still under investigation. Proposed mechanisms include improved cardiac energy metabolism [31]. Continued research will help to better understand the impressive benefits of SGLT2i medications.

Overall, SGLT2i consistently shows effectiveness in type 2 diabetes, heart failure, and chronic kidney disease and safety in various trials.

6. Conclusions

Major SGLT2i clinical trials have consistently shown both cardiovascular and renal benefits in addition to the glucose lowering effects of SGLT2i.

SGLT2i medications have shown major clinical benefits in three main patient groups:

- Patients with type 2 diabetes;
- Heart failure patients with any ejection fraction;
- Patients with chronic kidney disease.

20. Perkovic, V.; Jardine, M.J.; Neal, B.; Bompoint, S.; Heerspink, H.J.L.; Charytan, D.M.; Edwards, R.; Agarwal, R.; Bakris, G.; Bull, S.; et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N. Engl. J. Med. 2019, 380, 2295–2306.
21. Heerspink, H.J.L.; Stefánsson, B.V.; Correa-Rotter, R.; Chertow, G.M.; Greene, T.; Hou, F.-F.; Mann, J.F.E.; McMurray, J.J.V.; Lindberg, M.; Rossing, P.; et al. Dapagliflozin in Patients with Chronic Kidney Disease. N. Engl. J. Med. 2020, 383, 1436–1446.
22. Brenner, B.M.; Mitch, W.E.; Zhang, Z. Effects of Losartan on Renal and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Nephropathy. N. Engl. J. Med. 2001, 345, 861–869.
23. The EMPA-KIDNEY Collaborative Group. Empagliflozin in Patients with Chronic Kidney Disease. N. Engl. J. Med. 2022, 388, 117–127.
24. Chan, J.C.H.; Chan, M.C.Y. Novel Drugs for Diabetes Also Have Dramatic Benefits on Hard Outcomes of Heart and Kidney Disease. Curr. Cardiol. Rev. 2022, 18, e110522204572.
25. McGill, J.B.; Subramanian, S. Safety of Sodium-Glucose Co-Transporter 2 Inhibitors. Am. J. Med. 2019, 132, S49–S57.e5.
26. McDonald, M.; Virani, S.; Chan, M.; Ducharme, A.; Ezekowitz, J.A.; Giannetti, N.; Heckman, G.A.; Howlett, J.G.; Koshman, S.L.; Lepage, S.; et al. CCS/CHFS Heart Failure Guidelines Update: Defining a New Pharmacologic Standard of Care for Heart Failure with Reduced Ejection Fraction. Can. J. Cardiol. 2021, 37, 531–546.
27. Heidenreich, P.A.; Bozkurt, B.; Aguilar, D.; Allen, L.A.; Byun, J.J.; Colvin, M.M.; Deswal, A.; Drazner, M.H.; Dunlay, S.M.; Evers, L.R.; et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2022, 145, e895–e1032.
28. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int. 2022, 102, S1–S127.
29. Type 2 Diabetes in Adults: Management; NCIE: London, UK, 2022; ISBN 978-1-4731-1477-7.
30. de Boer, I.H.; Caramori, M.L.; Chan, J.C.N.; Heerspink, H.J.L.; Hurst, C.; Khunti, K.; Liew, A.; Michos, E.D.; Navaneethan, S.D.; Olowu, W.A.; et al. KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int. 2020, 98, S1–S115.
31. Lopaschuk, G.D.; Verma, S. Mechanisms of Cardiovascular Benefits of Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitors. JACC Basic Transl. Sci. 2020, 5, 632–644.