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USE OF SODIUM-GLUCOSE TRANSPORT PROTEIN 2 (SGLT2) INHIBITORS IN DIABETIC KIDNEY DISEASE (DKD)

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Abstract

SGLT2 inhibitors have emerged as a major disease-modifying therapy for preventing the development of chronic kidney disease (CKD). These agents can be used to prevent the decline in renal function through the reduction of glomerular hypertension mediated through tubuloglomerular feedback apart from their effects on glycemic control. The indications for SGLT2 inhibitors have evolved based on growing evidence from randomized controlled trials and broadly fit into five categories, including: glycemic control/metabolic risk, reduced ASCVD, heart failure, diabetic kidney disease with albuminuria, and nondiabetic CKD with albuminuria. . The initial trial was performed in patients with relatively good overall renal function, although sub-analyses suggest that the beneficial effect may extend to patients with CKD. SGLT2 inhibitors block glucose reabsorption in the renal tubules and are effective in reducing glucose levels based on the amount of glucose filtered, thereby increasing the glomerular filtration rate. The greatest transport burden on the diabetic kidney is in the early proximal tubule. SGLT2 inhibitors make the transport load more evenly distributed between the tubular segments. In addition, the total tubular transport load is reduced by lowering GFR. The SGLT2 inhibitory effect helps maintain mitochondrial function and tubular cell metabolism which can maintain tubular function and GFR in the long term.

Kata kunci: *Diabetic kidney disease; Glomerular filtration rate; SGLT2 inhibitors; Sodium*

INTRODUCTION

Hyperglycemia caused by insulin secretion, action, or both is called diabetes mellitus (DM). Diabetic chronic hyperglycemia damages, dysfunctions, and fails glands, especially the eyes, kidneys, nerves, heart, and blood vessels.[1] Because diagnosis standards vary, DM prevalence is hard to estimate. 10.2 million Americans have DM. In Indonesia, 1.5-2.3% of people over 15 have DM, and 6.1% in Manado. Women have more Type 2 DM than men.[2–4] Type 2 diabetes mellitus causes hyperglycemia due to insulin resistance, insufficient insulin production, and excessive or incorrect glucagon secretion. Type 2 diabetes causes microvascular, macrovascular, and neuropathic problems.[5]

Persistent hyperglycemia in uncontrolled DM can cause several complications, both acute and chronic.[6] Diabetes is not only a prominent cause of chronic renal disease but also a substantial contributor to the development of cardiovascular disease (CVD).[7] Diabetic nephropathy, often known as DKD, affects 40% of type 2 diabetics. Between 1990 and 2012, DKD deaths rose 94%. By 2030, the World Health Organization expects diabetes-related fatalities to double. Notably, cardiovascular disease mortality is the main risk.[8–10]

Controlling hyperglycemia, blood pressure, lipids, and lifestyle can decrease DKD progression, as with other diabetes-related issues. Despite indications that renin-angiotensin-aldosterone system (RAS) inhibition slows diabetic kidney disease (DKD),[11] Recent cardiovascular outcome trials and renal specific trials have shown the additional benefits of sodium-glucose cotransporter-2 inhibitors (SGLT2i) in lowering DKD progression and cardiovascular risk. This study examines the evidence-based method for diabetic kidney protection.[12–14]

SGLT2 inhibitors are a significant disease-modifying treatment for CKD prevention. Apart from glycemic management, these medicines reduce glomerular hypertension via tubuloglomerular feedback to preserve renal function.[13,15] SGLT2 inhibitor clinical trials have rapidly expanded their authorized clinical uses beyond diabetic mellitus (DM). SGLT2 inhibitors are now indicated for heart failure with or without reduced ejection fraction, stage 4 CKD, and chronic glomerulonephritis, according to studies.[16–18]

The EMPA-KIDNEY trial was recently terminated early because it demonstrated that SGLT2 inhibitors could be readily indicated for patients with CKD without albuminuria.[19] SGLT2 inhibitors should be prescribed by acutely reducing the estimated glomerular filtration rate (eGFR) at beginning, commencing at the lowest dose utilized in clinical studies, evaluating volume status, and mitigating adverse effects.[14] This article examines the use of SGLT-2 inhibitors for the treatment of diabetic kidney disease (often known as DKD).

METHODS

Protocol

The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 checklist served as the foundation for the development of the rules governing the conduct of this systematic review.

Eligibility Criteria

This systematic review was developed to analyze papers on "SGLT-2 inhibitor" and "Diabetic Kidney Disease". These are the subjects that were mentioned in the evaluated studies. The following requirements must be met in order for your work to be considered: 1) Articles must be available in their full online; 2) Articles must be written in English; and 3) Articles must have been published between 2012 and the time this systematic review is prepared. The following kind of textual submissions will under no circumstances be accepted: 1) Editorial letters, 2) contributions without a Digital Object Identifier (DOI), and 3) article reviews and similar submissions.

Search Strategy

The search for studies to be included in the systematic review was carried out from April 7th, 2023 using the PubMed and SagePub databases by inputting the words: "SGLT-2 inhibitor" and "Diabetic Kidney Disease". Where *("sodium glucose transporter 2 inhibitors"[Pharmacological Action] OR "sodium glucose transporter 2 inhibitors"[MeSH Terms] OR "sodium glucose transporter 2 inhibitors"[All Fields] OR "sglt 2 inhibitor"[All Fields]) AND ("diabetic nephropathies"[MeSH Terms] OR ("diabetic"[All Fields] AND "nephropathies"[All Fields]) OR "diabetic nephropathies"[All Fields] OR ("diabetic"[All Fields] AND "kidney"[All Fields] AND "disease"[All Fields]) OR "diabetic kidney disease"[All Fields])* is used as search keywords.

Data retrieval

Following the completion of a literature search, in which the titles and abstracts of previously published studies were read, the author revised the criteria for what should be included and what should be excluded from the study. Only the studies that were able to meet all of the requirements were taken into consideration for inclusion in the systematic review.

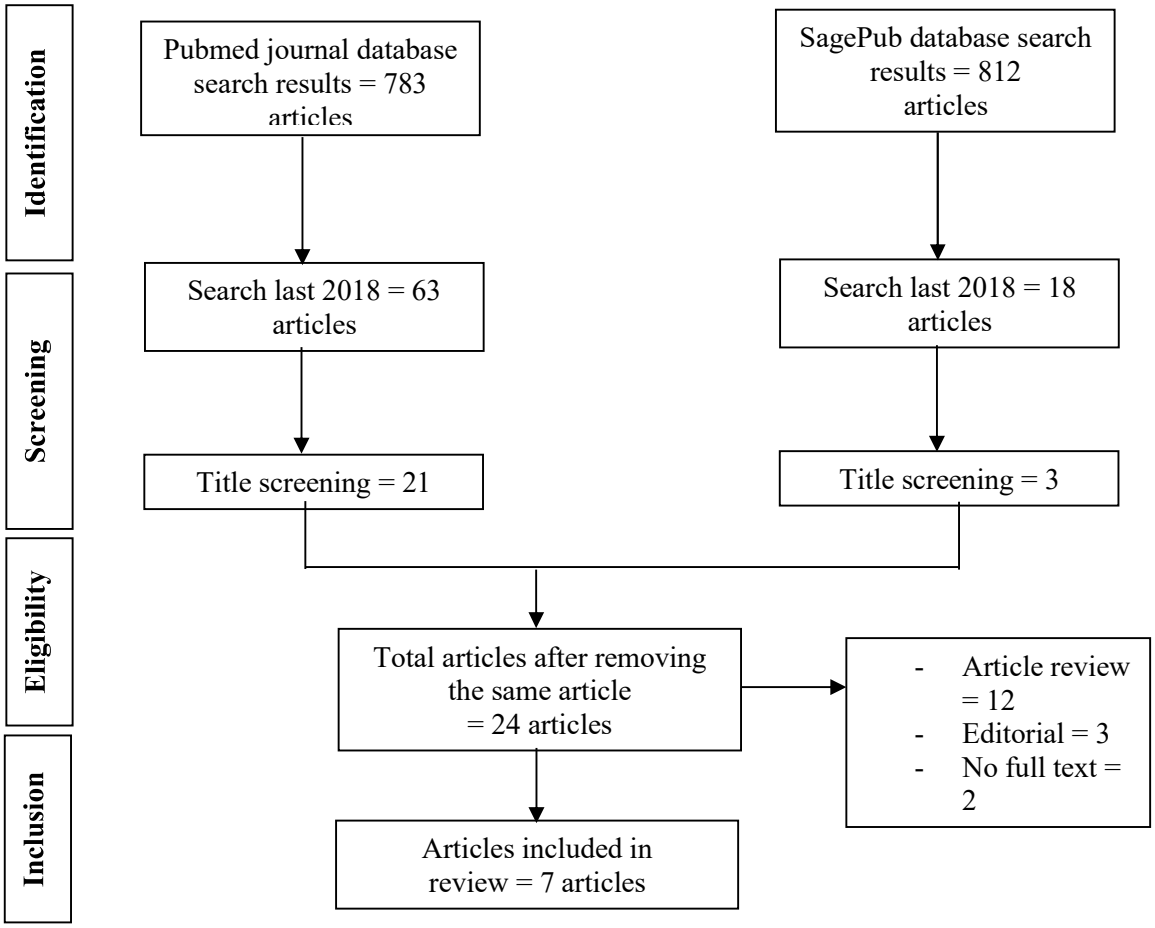

Figure 1. Article search flowchart

It is possible to collect information in the form of a title, author, publication date, origin of study location, research study design, and research variables in each individual study. This information is laid out in a particular format for your perusal.

Quality Assessment and Data Synthesis

To determine which studies might be eligible for consideration, the authors conducted their own independent reviews of a selection of the studies found in the articles' titles and abstracts. Following this, the full texts of the studies that qualify for inclusion in the systematic review will be read in order to determine which studies can be used as final inclusions for the purpose of the review.

RESULT

Wheeler, et al (2021)[20] showed effect of dapagliflozin on the primary outcome was consistent across patients with diabetic nephropathy (n = 2510; HR = 0.63, 95% CI = 0.51-0.78), glomerulonephritides (n = 695; 0.43, 0.26-0.71), ischaemic or hypertensive chronic kidney disease (n = 687; 0.75, 0.44-1.26), and CKD of other or unknown cause (n = 412; 0.58, 0.29-1.19; $P_{interaction}$=0.53). Those with and without type 2 diabetes showed similar rates of major adverse events or study drug discontinuation in the dapagliflozin and placebo groups.

Second study showed the hazard ratio (HR) for the composite of a sustained decline in estimated GFR of at least 50%, end-stage kidney disease, or death from renal causes was 0.56 (95% CI = 0.45-0.68; P<0.001), and the composite of death from cardiovascular causes or heart failure hospitalization was 0.71 (95%, 0.55-0.92; P = 0.009). 101 dapagliflozin patients (4.7%) and 146 placebo patients (6.8%) died (hazard ratio, 0.69; 95% CI, 0.53 to 0.88; P = 0.004). Dapagliflozin had equal results in type 2 diabetics and non-diabetics. Dapagliflozin's safety was proven.[21]

Table 1. The litelature include in this study

Author	Origin	Method	Agent Therapy	Sample Size	Result
Wheeler, 2021[20]	Australia	Multicentre, double-blind, placebo-controlled, randomised trial	Dapagliflozin	4,304 participants	In patients with diabetic and non-diabetic chronic kidney disease, treatment with dapagliflozin lowers the risk of significant adverse kidney and cardiovascular events, as well as the chance of death from any cause.
Heerspink, 2020[21]	UK, US	Multicentre, double-blind, placebo-controlled, randomised trial	Dapagliflozin	4,304 participants	In patients who had chronic kidney disease, taking dapagliflozin resulted in a statistically significant

					reduction in the risk of a composite outcome that included a sustained decrease in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes. This was the case regardless of whether or not the patients also had diabetes.
Perkovic, 2019[22]	UK, US, Australia	Multicentre, double-blind, placebo-controlled, randomised trial	Canagliflozin	4,401 patients	The risk of kidney failure and cardiovascular events was lower in the canagliflozin group than it was in the placebo group after a median follow-up of 2.62 years in patients who had type 2 diabetes and renal disease.
Jongs, 2021[23]	US, UK, Netherland, Denmark, Australia	Multicentre, double-blind, placebo-controlled, randomised trial	Dapagliflozin	4,304 patients	Dapagliflozin significantly reduced albuminuria in patients with chronic kidney disease, both in those patients who also had type 2 diabetes and in those patients who did not have type 2 diabetes. The relative reduction in albuminuria was higher in those patients who had type 2 diabetes.
Wheeler, 2020[24]	UK, US, Sweeden, Ukraine, Argentina, Peru, Brazil, Canada	Multicentre, double-blind, placebo-controlled, randomised trial	Dapagliflozin	4,304 patients	In the DAPA-CKD experiment, participants have been recruited with a wide variety of underlying renal disorders. These participants are also getting treatment that blocks the renin-angiotensin system. The patients in the trial will have CKD Stages 2-4 and elevated albuminuria, and either type 2 diabetes or not. The researchers will investigate the efficacy and safety of dapagliflozin.
Bhatt, 2021[25]	UK	Multicentre, double-blind, placebo-controlled, randomised trial	Sotagliflozin	19,188 patients	Sotagliflozin resulted in a lower risk of the composite of deaths from cardiovascular causes, hospital-izations for heart failure, and urgent visits for heart failure in patients with diabetes and chronic kidney disease, with or without albuminuria. However, sotagliflozin was associated with adverse events. Patients with diabetes and chronic kidney disease with or without albuminuria were studied.
Agarwal, 2022[26]	USA, UK, Spain, Germany	Multicentre, double-blind, placebo-controlled, randomised trial	Canagliflozin	5,674 patients	The shortcomings of making direct comparisons between trials are brought to light by this research. When fundamental variations in the way the trials were designed are taken into account, the cardiorenal advantages demonstrated by FIDELIO-DKD and CREDENCE are comparable in magnitude.

Jongs, et al (2021)[23] showed dapagliflozin reduced stage advancement in 3,820 patients with UACR less than 3000 mg/g at baseline (0·41, 0·32 to 0·52). Larger UACR decreases at day 14 following dapagliflozin treatment were linked with reduced eGFR decline during follow-up (β per log unit UACR change -3·06, 95% CI -5·20 to -0·90; p=0·0056). Participants with a wide range of underlying kidney diseases receiving renin-angiotensin system blocking therapy have been enrolled in the DAPA-CKD trial. The trial will examine the efficacy and safety of dapagliflozin in participants with CKD Stages 2-4 and increased albuminuria, with and without T2D.[24]

Perkovic, et al (2019)[22] showed the canagliflozin had an incident rate of 43.2 per 1000 patient-years, compared to 61.2 in the placebo group (HR = 0.70; 95% CI = 0.59-0.82; P = 0.00001). The relative risk (RR) of the renal-specific composite of end-stage kidney disease, a doubling of creatinine, or death from renal causes was 34% lower (HR = 0.66; 95% CI = 0.53-0.81; P<0.001), and the relative risk of end-stage kidney disease was 32% lower (HR = 0.68; 95% = 0.54-0.86; P =

0.002). Sotagliflozin reduced the composite of cardiovascular deaths, heart failure hospitalizations, and urgent heart failure visits compared to placebo but was associated with adverse events.[25]

DISCUSSION

Canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin are drugs that have been approved by the Food and Drug Administration (FDA) as agents for treating adult patients with type 2 diabetes mellitus (DM). The four agents are SGLT2 inhibitor class agents by acting on proteins. SGLT-2 is expressed in the proximal tubule of the kidney. This can cause a decrease in filtered glucose reabsorption, lower the renal threshold for glucose (RTG), and increase glucose excretion in the urine.[27]

Canagliflozin was the first SGLT-2 inhibitor to receive FDA approval on March 29, 2013. This agent is indicated in adult type 2 DM patients to improve blood glucose control in addition to using diet and exercise therapy. This agent is also indicated to reduce the risk of cardiovascular side effects in type 2 DM subjects with cardiovascular disease and minimize the risk of end stage renal disease (ESRD), cardiovascular mortality, hospitalization for heart failure, and increased serum creatinine in type 2 DM patients with diabetic nephropathy. as well as albuminuria.[14,27]

Dapagliflozin was FDA-approved in January 2014. This agent, like dapagliflozin, reduces heart failure-related hospitalizations in type 2 DM patients with underlying cardiovascular disease or multiple cardiovascular risk factors. In progressive CKD patients, this drug reduces the risk of reduced eGFR, ESRD, cardiovascular mortality, and heart failure hospitalization. Empagliflozin became the third FDA-approved SGLT2-inhibitor in August 2014. This agent has the same indications as the prior two. Ertugliflozin was the 2017 FDA-approved drug.[14,20,27]

Sotagliflozin reduced the composite of cardiovascular deaths, heart failure hospitalizations, and urgent heart failure visits compared to placebo but was associated with adverse events.[25] SGLT2 inhibitors can increase the output of patients with renal and cardiovascular disease in T2DM patients.[28] The first trial was in patients with good renal function, however sub-analyses suggest that CKD patients may benefit. SGLT2 inhibitors prevent renal tubule glucose reabsorption, lowering glucose levels and raising glomerular filtration rate. SGLT2 inhibitors are not currently recommended for advanced CKD T2DM patients.[29]

Canagliflozin vs. placebo was compared for renal and secondary cardiovascular outcomes in T2DM patients with albuminuric CKD in the CREDENCE study. 4401 patients with an eGFR of 30-90ml/min/1.73 m2 and albuminuria (albumin-creatinine ratio 300-5000 mg/g) were followed for 2.62 years. Standard treatment was a RAS blocker. Canagliflozin reduces ESRD risk by 30%.[30] Canagliflozin reduces cardiovascular mortality, myocardial infarction, stroke, and heart failure hospitalizations. Their findings are similar to systematic reviews and meta-analyses of SGLT2 inhibitor-treated T2DM and CKD patients in randomized controlled trials.[30,31]

The CREDENCE study approved canagliflozin for treating diabetic nephropathy and lowered the incidence of heart failure hospitalization in T2DM patients. CKD patients' elevated glucose load at the single nephron level keeps SGLT2 inhibitors' natriuretic and diuretic effects. Due to elevated blood glucose levels and single nephron hyperfiltration in the remaining nephrons, paracellular sodium release in the proximal tubule induces natriuretic, kaliuretic, and diuretic effects.[32]

A recent meta-analysis also reported that SGLT2 inhibitors were associated with strong and consistent reductions in acute kidney injury (AKI).[33] In T2DM patients, dapagliflozin lowers urine indicators of glomerular and tubular damage. In a preliminary investigation using a bilateral renal artery clamp model, SGLT2 gene-knockout mice did not influence ischemia-reperfusion damage or GFR recovery. Nespoux *et al.*[14] demonstrated that gene-knockout of SGLT1 did not affect early-stage kidney injury, but improved renal recovery in this model.

Diabetics' early proximal tubules carry the most. SGLT2 inhibitors balance tubular segment transport burden. Lowering GFR also reduces tubular transit load. SGLT2 inhibits mitochondrial function and tubular cell metabolism to preserve tubular function and GFR throughout time. Early studies demonstrated that SGLT2-I restored the urine lactate-pyruvate ratio in Akita DMT1 rats and DMT2 patients due to mitochondrial oxidative metabolism to glycolysis.[14]

CONCLUSION

SGLT2 inhibitors have emerged as a key therapy for preventing the development of DKD and CKD in albuminuric patients with and without diabetes including patients with IgA nephropathy, FSGS, and heart failure. While SGLT2 inhibitors have been shown to have cardiorenal benefits, there is still a large unmet need to reduce the remaining risk in patients with DKD and CKD.

REFERENCES

[1]. International Diabetes Federation. Diabetes. Brussels: IDF; 2017.
[2]. Evans K. Diabetic ketoacidosis: update on management. Clin Med. 2019 Sep;19(5):396–8.
[3]. Association AD. 15. Diabetes Care in the Hospital: Standards of Medical Care in Diabetes—2019. Diabetes Care [Internet]. 2018 Dec 7;42(Supplement_1):S173–81. Available from: https://doi.org/10.2337/dc19-S015
[4]. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 2016;62–9.

[5]. Soelistijo SA, Lindarto D, Decroli E, et al. Pedoman Pengelolaan dan Pencegahan Diabetes Melitus Tipe 2 Dewasa di Indonesia. Jakarta: PB Perkeni; 2021.
[6]. Patoulias D, Papadopoulos C, Stavropoulos K, et al. Prognostic value of arterial stiffness measurements in cardiovascular disease, diabetes, and its complications: The potential role of sodium-glucose co-transporter-2 inhibitors. J Clin Hypertens. 2020;22(4):562–71.
[7]. Inker LA, Astor BC, Fox CH, Isakova T, Lash JP, Peralta CA, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. Am J kidney Dis Off J Natl Kidney Found. 2014 May;63(5):713–35.
[8]. Alicic RZ, Rooney MT, Tuttle KR. Diabetic kidney disease: challenges, progress, and possibilities. Clin J Am Soc Nephrol. 2017;12(12):2032–45.
[9]. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095–128.
[10]. Sacks FM, Hermans MP, Fioretto P, Valensi P, Davis T, Horton E, et al. Association between plasma triglycerides and high-density lipoprotein cholesterol and microvascular kidney disease and retinopathy in type 2 diabetes mellitus: a global case–control study in 13 countries. Circulation. 2014;129(9):999–1008.
[11]. Stephens JW, Brown KE, Min T. Chronic kidney disease in type 2 diabetes: Implications for managing glycaemic control, cardiovascular and renal risk. Diabetes Obes Metab. 2020 Apr;22 Suppl 1:32–45.
[12]. Ni L, Yuan C, Chen G, Zhang C, Wu X. SGLT2i: beyond the glucose-lowering effect. Cardiovasc Diabetol. 2020 Jun;19(1):98.
[13]. Liu B, Wang Y, Zhang Y, Yan B. Mechanisms of Protective Effects of SGLT2 Inhibitors in Cardiovascular Disease and Renal Dysfunction. Curr Top Med Chem. 2019;19(20):1818–49.
[14]. Nespoux J, Vallon V. Renal effects of SGLT2 inhibitors: an update. Curr Opin Nephrol Hypertens. 2020 Mar;29(2):190–8.
[15]. Li H-L, Lip GYH, Feng Q, Fei Y, Tse Y-K, Wu M-Z, et al. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) and cardiac arrhythmias: a systematic review and meta-analysis. Cardiovasc Diabetol. 2021 May;20(1):100.
[16]. Peng X, Li L, Zhang M, Zhao Q, Wu K, Bai R, et al. Sodium-Glucose Cotransporter 2 Inhibitors Potentially Prevent Atrial Fibrillation by Ameliorating Ion Handling and Mitochondrial Dysfunction. Front Physiol. 2020;11:912.
[17]. Verma S, McMurray JJ V. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. Diabetologia. 2018 Oct;61(10):2108–17.
[18]. Voors AA, Angermann CE, Teerlink JR, Collins SP, Kosiborod M, Biegus J, et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. Nat Med. 2022 Mar;28(3):568–74.
[19]. Wanner C, Lachin JM, Inzucchi SE, Fitchett D, Mattheus M, George J, et al. Empagliflozin and Clinical Outcomes in Patients With Type 2 Diabetes Mellitus, Established Cardiovascular Disease, and Chronic Kidney Disease. Circulation. 2018 Jan;137(2):119–29.
[20]. Wheeler DC, Stefánsson B V, Jongs N, Chertow GM, Greene T, Hou FF, et al. Effects of dapagliflozin on major adverse kidney and cardiovascular events in patients with diabetic and non-diabetic chronic kidney disease: a prespecified analysis from the DAPA-CKD trial. lancet Diabetes Endocrinol. 2021 Jan;9(1):22–31.
[21]. Heerspink HJL, Stefánsson B V, Correa-Rotter R, Chertow GM, Greene T, Hou F-F, et al. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2020 Oct;383(15):1436–46.
[22]. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med. 2019 Jun;380(24):2295–306.
[23]. Jongs N, Greene T, Chertow GM, McMurray JJ V, Langkilde AM, Correa-Rotter R, et al. Effect of dapagliflozin on urinary albumin excretion in patients with chronic kidney disease with and without type 2 diabetes: a prespecified analysis from the DAPA-CKD trial. lancet Diabetes Endocrinol. 2021 Nov;9(11):755–66.
[24]. Wheeler DC, Stefansson B V, Batiushin M, Bilchenko O, Cherney DZI, Chertow GM, et al. The dapagliflozin and prevention of adverse outcomes in chronic kidney disease (DAPA-CKD) trial: baseline characteristics. Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc. 2020 Oct;35(10):1700–11.
[25]. Bhatt DL, Szarek M, Pitt B, Cannon CP, Leiter LA, McGuire DK, et al. Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease. N Engl J Med. 2021 Jan;384(2):129–39.
[26]. Agarwal R, Anker SD, Filippatos G, Pitt B, Rossing P, Ruilope LM, et al. Effects of canagliflozin versus finerenone on cardiorenal outcomes: exploratory post hoc analyses from FIDELIO-DKD compared to reported CREDENCE results. Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc. 2022 Jun;37(7):1261–9.
[27]. Lytvyn Y, Bjornstad P, Udell JA, Lovshin JA, Cherney DZI. Sodium Glucose Cotransporter-2 Inhibition in Heart Failure: Potential Mechanisms, Clinical Applications, and Summary of Clinical Trials. Circulation. 2017 Oct;136(17):1643–58.
[28]. Kluger AY, Tecson KM, Barbin CM, Lee AY, Lerma E V, Rosol ZP, et al. Cardiorenal Outcomes in the CANVAS, DECLARE-TIMI 58, and EMPA-REG OUTCOME Trials: A Systematic Review. Rev Cardiovasc Med. 2018;19(2).
[29]. Neuen BL, Young T, Heerspink HJL, Neal B, Perkovic V, Billot L, et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. lancet Diabetes Endocrinol. 2019;7(11):845–54.
[30]. Tian L, Cai Y, Zheng H, Ai S, Zhou M, Luo Q, et al. Canagliflozin for Prevention of Cardiovascular and Renal Outcomes in Type2 Diabetes: a Systematic Review and Meta-Analysis of Randomized Controlled Trials. Front

Pharmacol. 2021;12:691878.
[31]. Toyama T, Neuen BL, Jun M, Ohkuma T, Neal B, Jardine MJ, et al. Effect of SGLT2 inhibitors on cardiovascular, renal and safety outcomes in patients with type 2 diabetes mellitus and chronic kidney disease: a systematic review and meta-analysis. Diabetes, Obes Metab. 2019;21(5):1237–50.
[32]. Layton AT, Vallon V. Renal tubular solute transport and oxygen consumption: insights from computational models. Curr Opin Nephrol Hypertens. 2018;27(5):384–9.
[33]. Castellana M, Procino F, Sardone R, Trimboli P, Giannelli G. Generalizability of sodium-glucose co-transporter-2 inhibitors cardiovascular outcome trials to the type 2 diabetes population: a systematic review and meta-analysis. Cardiovasc Diabetol. 2020;19(1):1–10.