Original Research Article

INTEGRATING SGLT-2 INHIBITORS INTO THE CLINICAL MANAGEMENT OF TYPE 2 DIABETES MELLITUSAND CHRONIC KIDNEY DISEASE: CURRENT EVIDENCE AND FUTURE OUTLOOK

ABSTRACT

Objective and background: The prevalence of type 2 diabetes mellitus (T2DM) is steadily increasing globally. A significant complication of T2DM is diabeticnephropathy, which contributes to the progression of kidney disease and increased morbidity. Sodium-Glucose Co-Transporter-2 (SGLT2) inhibitors are a class of oral antidiabetic agents that not only effectively lower blood glucose levels but also provide protective benefits for kidney health**Methods:**A comprehensive review of studies was conducted focusing on the use of SGLT2 inhibitors in patients with T2DM, including those with chronic kidney disease (CKD), defined as a glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2. The studies evaluated clinical outcomes such as cardiovascular events, kidney disease progression, and mortality.**Results:**Research findings demonstrate that SGLT2 inhibitors significantly reduce the risk of hospitalization due to heart failure, myocardial infarction, and stroke. Additionally, these medications lower the incidence of cardiovascular-related and all-cause mortality. Renal-specific benefits include slowing the progression of albuminuria, reducing the decline in GFR, lowering the need for renal replacement therapy, and decreasing kidney-related deaths

1. INTRODUCTION

Type 2 diabetes mellitus is one of the major health issues worldwide, affecting more than 90% of individuals with diabetes. According to data from the International Diabetes Federation (IDF), the prevalence of diabetes mellitus continues to rise year by year. The global prevalence of diabetes among adults aged 20-79 years was estimated to be 537 million in 2021, projected to increase to approximately 643 million by 2030, and 783 million by 2045. In Indonesia, the prevalence of diabetes mellitus ranks 5th globally, with 19.5 million cases in 2021, expected to rise to 28.6 million by 2045. Indonesia also ranks 3rd in the world with 14.3 million individuals living with undiagnosed diabetes mellitus (73% of the population).[1]

The increased expression of Sodium-Glucose Co-Transporter-2 (SGLT-2) in the proximal tubules of the kidneys is one of the pathophysiological mechanisms of hyperglycemia in patients with diabetes mellitus, as well as hyperfiltration in diabetic kidney disease. Various mechanisms of SGLT-2 inhibitors can provide renal protection.[1,4]

Several studies on SGLT-2 inhibitors (such as canagliflozin, dapagliflozin, and empagliflozin) in patients with type 2 diabetes mellitus, including EMPA-REG OUTCOME, CANVAS/CANVAS-R, DECLARE-TIMI 58, CREDENCE, DAPA-CKD, and EMPA-KIDNEY, have focused on cardiovascular and renal outcomes[5,6]

Comment [AMC1]: Diabetic kidney disease.

Comment [AMC2]:

Comment [AMC3]: Diabetic kidney disease (DKD)

Comment [AMC4]:

Comment [AMC5]: And/or albumin excretion rate = or > 30 mg/gr creatinine

Comment [AMC6]: This definition is incompleted. Authors may add " and/or urine albumin/creatinine ratio = or> 30 mg alb/gr creatinine

Comment [AMC7]:

Comment [AMC8]: Authors please, you can actualise the data according to the last publication in The Lancet Nov 2024

Comment [AMC9]: Authors please complete all the references.

2. METHODS.

Comment [AMC10]: Authors need to include a flow chart with the studies included and rejected for this review.

This review article examines the integration of Sodium-Glucose Co-Transporter-2 (SGLT2) inhibitors into the clinical management of type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD). A systematic approach was employed to analyze peer-reviewed studies, clinical trials, and meta-analyses published in the last decade. Key databases such as PubMed, Scopus, and clinical trial registries were searched using keywords including "SGLT2 inhibitors," "type 2 diabetes," "chronic kidney disease," "renal protection," and "cardiovascular outcomes."[4,9]

The inclusion criteria were studies involving adult patients with T2DM and/or CKD, reporting on the efficacy and safety outcomes of SGLT2 inhibitors. Data extracted included effects on glycemic control, renal outcomes (e.g., progression of albuminuria, glomerular filtration rate decline, need for renal replacement therapy), and cardiovascular endpoints (e.g., heart failure hospitalization, stroke, and myocardial infarction). Additional focus was placed on subgroup analyses involving patients with varying degrees of CKD.[3,7]

A narrative synthesis was conducted to summarize the current evidence, emphasizing the clinical benefits, mechanisms of action, and future implications of SGLT2 inhibitors in these patient populations. Limitations of existing studies and areas for future research were also identified to guide clinical decision-making and research priorities.[2,8]

3. ~~RESULTS~~MECHANISMS INVOLVED IN THE PATHOGENESIS OF DKD.

Type 2 ~~diabetes mellitus~~DM is a type of diabetes that occurs due to progressive loss of insulin secretion, not caused by autoimmunity. Patients typically have a background of insulin resistance and metabolic syndrome.[11] The pathogenesis of hyperglycemia in type 2 ~~diabetes mellitus~~DMcan include beta-cell pancreatic failure, pancreatic alpha-cell dysfunction, fat cell resistance to insulin's antilipolytic effects, impaired insulin action in muscle cells, increased glucose production by the liver, increased food intake due to insulin resistance in the brain, changes in the gut microbiota composition, glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) deficiencies, decreased amylin levels, low-grade systemic inflammation, and increased expression of Sodium-Glucose Co-Transporter-2 (SGLT-2), which causes increased glucose reabsorption in the renal tubules.[8,10]

Type 2 ~~diabetes mellitus~~DMcan lead to macrovascular complications such as coronary artery disease, stroke, peripheral artery disease, heart failure, and microvascular complications including neuropathy, retinopathy, and nephropathy.[12]

Diabetic kidney disease (DKD)is a clinical diagnosis defined by the presence of chronic kidney disease characterized by persistent (at least 3 months) urinary albumin excretion (albumin-to-creatinine ratio [ACR] ≥ 30 mg/g) and/or low estimated glomerular filtration rate (< 60 mL/min/1.73 m²) in patients with diabetes mellitus. Diabetic nephropathy, on the other hand, is based on histological changes in the glomerulus (glomerular basement membrane thickening, mesangial expansion with or without nodular sclerosis/Kimmelstiel–Wilson

Comment [AMC11]: Authors may add that there are forms of DKD without albuminuria or proteinuria that can progress to advanced CKD.

lesions, podocyte loss, endothelial damage) observed in kidney biopsies.[14] Diabetic kidney disease can occur in nearly half of patients with type ~~2 diabetes mellitus~~DMthroughout their lifetime. Approximately 20% of patients with type 2 diabetes will have an estimated glomerular filtration rate < 60 mL/min/1.73 m², and 28% will develop albuminuria.[15] If type 2 diabetes occurs at ages 15-24 years, the risk of developing moderate albuminuria is nearly 100%. Globally~~, diabetic kidney disease~~ DKD is the leading cause of chronic kidney disease and end-stage kidney disease (ESKD). [16]According to the 2018 Indonesian Renal Registry data, diabetic kidney disease/nephropathy ranks second, accounting for 27%, as the cause of CKD~~chronic kidney disease~~ stage 5, following hypertensive kidney disease which accounts for 36%.[12]

The pathogenesis of ~~diabetic kidney disease~~DKDin patients with type 2 ~~diabetes mellitus~~DMbegins with the presence of hyperglycemia and dyslipidemia, which act as promoters of glomerular hyperfiltration and hyperperfusion. Glomerular hyperfiltration, an increase above the physiological value of glomerular filtration rate (120-180 mL/min/1.73 m²), is estimated to occur in 40-50% of patients with type 2 DM~~diabetes mellitus~~. [17]The mechanisms underlying glomerular hyperfiltration are not fully understood, but one considered mechanism is the increased glucose reabsorption in the proximal tubules through Sodium-Glucose Co-Transporter-2 (SGLT2), which reduces solute levels in the distal tubules, particularly sodium chloride at the macula densa. The decrease in tubuloglomerular feedback can lead to the dilation of the afferent arteriole, increasing glomerular perfusion. Simultaneously, activation of the renin-angiotensin system leads to an increase in local angiotensin II production at the efferent arteriole, causing vasoconstriction (Figure 1).[16]

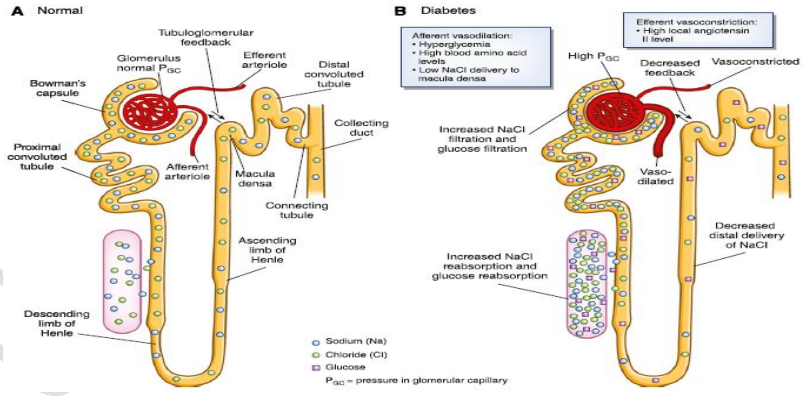

Figure 1. Renin-Angiotensin System Activation and Its Effect on Efferent Arteriole Vasoconstriction

In addition, there is an increase in endothelin-1, a vasoconstrictor of the efferent arteriole, which, similar to the renin-angiotensin- system, plays a role in hypertension, endothelial dysfunction, inflammation, and activation of receptors that directly increase glomerular

Comment [AMC12]: -Aldosterone...

permeability and fibrosis. [15]Other factors contributing to the development of ~~diabetic kidneydisease~~ DKDinclude an increase in the production of advanced glycation end products, reactive oxygen species, intracellular nicotinamide adenine dinucleotide hydrogen, and transforming growth factor-β. [14]Additionally, there is an increase in pro-fibrotic factors such as connective tissue growth factor and vascular endothelial growth factor, which play a role in the survival of endothelial cells, podocytes, and mesangial cells. These various factors can activate intracellular signaling pathways, such as protein kinase C, janus kinase/signal transducers and activators of transcription (JAK/STAT), and NF-κB. [17]

Protein kinase C increases levels of prostaglandin E2 and nitric oxide, causing vasodilation of the afferent arteriole, amplifying the effects of angiotensin II on the efferent arteriole, and increasing vascular endothelial growth factor, transforming growth factor-β, and connective tissue growth factor. [11]Janus kinase 2 is activated by reactive oxygen species and is linked to mesangial cell hypertrophy. NF-κB, a transcription factor, regulates various genes associated with inflammation, immunity, and apoptosis. The activation of NF-κB correlates with the occurrence of proteinuria and interstitial cell infiltration in the kidneys. Proteinuria contributes to the stimulation of NF-κB, and like a cycle, it can lead to persistent proteinuria. [12]

The pathophysiology of diabetic kidney disease in patients with type 2~~diabetes~~DMis more complex, as cardiovascular risk factors such as hypertension, obesity, and hyperuricemia also contribute to the development of microvascular damage. Systemic hypertension and obesity can lead to glomerular hyperfiltration through increased systemic blood pressure passing through the glomerulus and glomerular hypertrophy. [14]Additionally, in patients with ~~diabetes mellitus~~DMand obesity, there is reduced autophagic activity (a mechanism that maintains homeostasis during oxidative stress) in podocytes and proximal tubular epithelial cells in the kidneys. This makes patients more vulnerable to kidney injury. Increased uric acid contributes to diabetic kidney disease through endothelial dysfunction, enhanced renin-angiotensin activity, induction of the inflammatory cascade, and the production of cytokines such as transforming growth factor-β. [11]

4. ~~DISCUSSION~~. Mechanisms of action of SGLT2 inhibitors and Results of different recent studies.

Sodium-Glucose Co-Transporter-2 (SGLT-2) is a membrane protein located in the renal tubule cells that simultaneously transports sodium and glucose for reabsorption. SGLT-2 is predominantly found in the first and second segments of the proximal tubules of the kidneys, where it plays a crucial role in the reabsorption of approximately 90% of the filtered glucose. Any remaining glucose is reabsorbed through the Sodium-Glucose Co-Transporter-1 (SGLT-1) in the distal segment of the proximal tubule. [10]In individuals with normal glomerular filtration rate (GFR) ~~and plasma glucose levels~~, all glucose is reabsorbed in the proximal renal tubules. However, in cases of hyperglycemia, such as in patients with ~~diabetes mellitus~~DM, a greater-than-normal amount of glucose is filtered into the proximal renal tubules, leading to increased glucose reabsorption. This process is associated with an upregulation of both SGLT-2 and SGLT-1 expression. [19] SGLT-2 inhibitors are oral anti-diabetic medications that work by inhibiting glucose reabsorption in the proximal renal

tubules, thus promoting the excretion of glucose through urine. By blocking the SGLT-2 transporter, these medications help lower blood glucose levels in patients with type 2 and provide additional benefits such as weight loss, improved blood pressure control, and kidney protection. [11]

The kidney protection effects of Sodium-Glucose Co-Transporter-2 (SGLT-2) inhibitors are attributed to several mechanisms, including: (1) Reduction of renal glucose and sodium reabsorption in the proximal renal tubules: This leads to a decrease in hyperfiltration by increasing sodium transport to the macula densa, thereby activating the tubuloglomerular feedback and causing vasoconstriction of the afferent arteriole. (2) Lower blood glucose levels: This reduces the potential for glucose toxicity to the kidneys (such as hypertrophy, inflammation, and injury) and other organs, thereby helping to protect kidney function. (3) ~~Blood pressure reduction:~~Due to a decrease in plasma volume and sodium, as well as weight loss, SGLT-2 inhibitors contribute to lowering blood pressure. (4) Sodium-Glucose Co-Transporter-2 and Na+/H+ exchanger 3 (NHE3) co-expression: Inhibition of SGLT-2 leads to natriuresis, which contributes to a reduction in blood pressure and other beneficial renal effects. (5) Increased glucagon levels This causes vasodilation and increases renal blood flow, glomerular filtration rate, and electrolyte excretion. At the same time, a reduction in insulin levels leads to increased lipolysis and gluconeogenesis. (6). A reduction of kidney injury due to ischemia~~: This~~occurs through the increased activation of transcription factors, particularly those induced by hypoxia, which are involved in kidney repair processes. (7) Reduction in arterial stiffness, vascular resistance, uric acid levels: SGLT-2 inhibitors also modulate the renin-angiotensin-aldosterone system, contributing to improved kidney function and cardiovascular protection. These mechanisms work synergistically to protect kidney function and provide broader cardiovascular benefits for patients with diabetes and chronic kidney disease.[11, 14, 15]

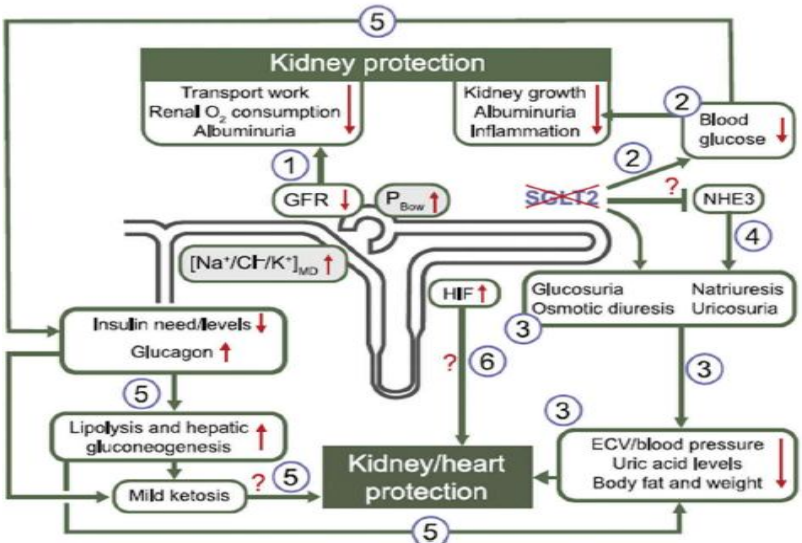

Figure 2. Mechanism of Kidney Protection by Sodium-Glucose Co-Transporter-2 Inhibitors

Source: Davidson JA. SGLT2 inhibitors in patients with type 2 diabetes and renal disease: overview of current evidence.Postgrad Med. 2019

Various studies on Sodium-Glucose Co-Transporter-2 (SGLT-2) inhibitors in patients with type 2 ~~diabetes mellitus~~ DMhave been conducted. The Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) study, involving 7,020 patients with type 2 diabetes, showed that administering 10 mg/25 mg of empagliflozin compared to placebo resulted in a lower risk of death from cardiovascular causes (hazard ratio 0.62; 95% CI 0.49-0.77; p<0.001), death from all causes (hazard ratio 0.68; 95% CI 0.57-0.82; p<0.001), and hospitalization for heart failure (hazard ratio 0.65; 95% CI 0.50-0.85; p=0.002). Similarly, the Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes (CANVAS/CANVAS-R) study involving 10,142 patients with type 2 diabetes at high cardiovascular risk found….[4] that the~~The~~administration of 100 mg/300 mg canagliflozin, compared to placebo, was associated with a lower risk of death from cardiovascular causes, myocardial infarction, and stroke (hazard ratio 0.86; 95% CI 0.75-0.97; p<0.001), progression of albuminuria (hazard ratio 0.73; 95% CI 0.67-0.79), a 40% decline in glomerular filtration rate, the need for renal replacement therapy, and death from renal causes (hazard ratio 0.60; 95% CI 0.47-0.77) in the Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes (CANVAS/CANVAS-R) study with 10,142 patients with type 2 diabetes at high cardiovascular risk. [3,4]

Comment [AMC13]:

In the Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes (DECLARE-TIMI 58) study, involving 17,160 patients, the administration of 10 mg dapagliflozin, compared to placebo, showed a lower risk for hospitalization due to heart failure (hazard ratio 0.73; 95% CI 0.61-0.88), a 40% decline in glomerular filtration rate, the occurrence of end-stage kidney disease, and death from renal causes (hazard ratio 0.76; 95% CI 0.67-0.87). [1,5]

The Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy (CREDENCE) study involving 4,401 patients with type 2 diabetes and a mean glomerular filtration rate of 56 mL/min/1.73 m², demonstrated that 100 mg of canagliflozin, compared to placebo, was associated with a lower risk of end-stage kidney disease, doubling of serum creatinine, and death from renal causes (hazard ratio 0.66; 95% CI 0.53-0.81; p<0.001), as well as cardiovascular death, myocardial infarction, and stroke (hazard ratio 0.80; 95% CI 0.67-0.95; p=0.01), and hospitalization due to heart failure (hazard ratio 0.61; 95% CI 0.47-0.80; p<0.001) [6, 9]

The Dapagliflozin in Patients with Chronic Kidney Disease (DAPA-CKD) study, involving 4,304 patients with a glomerular filtration rate of 25-75 mL/min/1.73 m², of which 67.5% had type 2 diabetes, showed that the administration of 10 mg dapagliflozin, compared to placebo, resulted in a lower risk for a ≥50% decline in glomerular filtration rate, end-stage kidney disease, and death from renal causes (hazard ratio 0.56; 95% CI 0.45-0.68; p<0.001), as well as death from cardiovascular causes or hospitalization due to heart failure (hazard ratio 0.71; 95% CI 0.55-0.92; p=0.009). [10, 14]

The Empagliflozin in Patients with Chronic Kidney Disease (EMPA-KIDNEY) study, which involved 6,609 patients with a glomerular filtration rate of 20-45 mL/min/1.73 m² or 45-90 mL/min/1.73 m² with albumin-to-creatinine ratio ≥200, and 46% of whom had type 2 diabetes, demonstrated that the administration of 10 mg empagliflozin, compared to placebo, resulted in a lower risk of progression of kidney disease or death from cardiovascular causes (hazard ratio 0.72; 95% CI 0.64-0.82; p<0.001). These results were consistent in both patients with diabetes and those without diabetes. [11,15]

CONCLUSION

Sodium-glucose co-transporter 2 (SGLT-2) inhibitors are oral antidiabetic medications with potential renal protective effects. The administration of SGLT-2 inhibitors in patients with type 2 diabetes ~~is expected to~~has demonstrated to reduce the risk of cardiovascular and renal complications. These medications work by inhibiting glucose reabsorption in the kidneys, promoting glucose excretion through urine, and improving glycemic control. Additionally, SGLT-2 inhibitors have been shown to offer benefits beyond glucose control, such as reducing the risk of heart failure, slowing the progression of chronic kidney disease, and lowering the risk of cardiovascular events [11, 13, 16]

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

The authors hereby state that no generative AI tools such as large language models (ChatGPT, COPILOT, etc.) or text-to-image generators were utilized in the creation or editing of this work.

DATA AVAILABILITY

All relevant data are included in the paper and its supporting information files. This study aims to inform researchers identify integrating SGLT-2 Inhibitors into the Clinical

REFERENCES

1 Dysted MP, Esztergalyos B, Gautam S, Helman B, Pinkepank M, Randi A, et al. IDF diabetes atlas. 10th ed. Belgium: International Diabetes Federation; 2021. p. 6

2 Tim Penyusun. Pedoman pengelolaan dan pencegahan diabetes mellitus tipe 2 di Indonesia 2021. 1st ed. Jakarta: PB Perkeni; 2021. p. 6.

3 Davidson JA. SGLT2 inhibitors in patients with type 2 diabetes and renal disease: overview of current evidence. Postgrad Med. 2019;131(4):251-60

4 Davidson JA. SGLT2 inhibitors in patients with type 2 diabetes and renal disease: overview of current evidence. Postgrad Med. 2019;131(4):251-60

5 Giorgino F, Vora J, Fenici P, Solini A. Renoprotection with SGLT2 inhibitors in type 2 diabetes over a spectrum of cardiovascular and renal risk. Cardiovasc Diabetol. 2020;19(1):196

6 Krishnan A, Shankar M, Lerma EV, Wiegley N. Sodium Glucose Cotransporter 2 (SGLT2) Inhibitors and CKD: Are You a #Flozinator? Kidney Med. 2023;5(4):1-7

7 ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. Classification and diagnosis of diabetes. Diabetes Care. 2023;46(1):S19–S40

8 Hoogeveen EK. The epidemiology of diabetic kidney disease. Kidney Dial. 2022;2(3):433–42

9 Tim Penyusun. Report Of Indonesian Renal Registry. 11th ed. Jakarta: Pernefri; 2018. p. 14

10 Toth-Manikowski S, Atta MG. Diabetic kidney disease: pathophysiology and therapeutic targets. J Diabetes Res. 2015;6(5):1-16*y*

11 Jalal DI, Maahs DM, Hovind P, Nakagawa T. Uric acid as a mediator of diabetic nephropathy. Semin Nephrol. 2011;31(5):459-65

12 Margonato D, Galati G, Mazzetti S, Cannistraci R, Perseghin G, Margonato A, et al. Renal protection: a leading mechanism for cardiovascular benefit in patients treated with SGLT2 inhibitors. Heart Fail Rev. 2021;26(2):337-45.

13 Bailey CJ, Day C, Bellary S. Renal protection with SGLT2 Inhibitors: effects in acute and chronic kidney disease. Curr Diab Rep. 2022;22(1):39-52

14 Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373(22):2117-28

15 Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al.

Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377(7):644–57

16 Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019;380(4):347–57

17 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;380(24):2295–306

18 Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou F-F, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383:1436-1446.

19 The EMPA-KIDNEY Collaborative Group, Empagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2023;388:117-27.