

**A SELECTION OF TEN READINGS ON TOPICS RELATED TO  
UPDATES IN DM AND CKD MANAGEMENT:  
"ARE SGLT2 INHIBITORS THE ANSWER?"**

**Some are available as free full text, and some require payment**

**Selection of readings made by A/Prof Goh Lee Gan**

**READING 1. RENOPROTECTION WITH SGLT2 INHIBITORS IN TYPE 2 DIABETES**

**Giorgino F,<sup>1</sup> Vora J,<sup>2</sup> Fenici P,<sup>3</sup> et al. Renoprotection with SGLT2 inhibitors in type 2 diabetes over a spectrum of cardiovascular and renal risk. *Cardiovasc Diabetol*. 2020 Nov 22;19(1):196. PMID: 33222693.**

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**ABSTRACT**

Approximately half of all patients with type 2 diabetes (T2D) develop a certain degree of renal impairment. In many of them, chronic kidney disease (CKD) progresses over time, eventually leading to end-stage kidney disease (ESKD), requiring dialysis and conveying a substantially increased risk of cardiovascular morbidity and mortality. Even with widespread use of renin-angiotensin system blockers and tight glycaemic control, a substantial residual risk of nephropathy progression remains. Recent cardiovascular outcomes trials investigating sodium-glucose cotransporter 2 (SGLT2) inhibitors have suggested that these therapies have renoprotective effects distinct from their glucose-lowering action, including the potential to reduce the rates of ESKD and acute kidney injury. Although patients in most cardiovascular outcomes trials had a higher prevalence of existing cardiovascular disease compared with those normally seen in clinical practice, the proportion of patients with renal impairment was similar to that observed in a real-world context. Patient cardiovascular risk profiles did not relevantly impact the renoprotective benefits observed in these studies. Benefits were observed in patients across a spectrum of renal risk, but were evident also in those without renal damage, suggesting a role for SGLT2 inhibitors in the prevention of CKD in people with T2D. In addition, recent studies such as CREDENCE and DAPA-CKD offer a greater insight into the renoprotective effects of SGLT2 inhibitors in patients with moderate-to-severe CKD. This review outlines the evidence that SGLT2 inhibitors may prevent the development of CKD and prevent and delay the worsening of CKD in people with T2D at different levels of renal risk.

**READING 2 – EFFECTS OF CANAGLIFOZIN IN PATIENTS WITH EGFR LESS THAN 30 ML/MIN PER 1.73 M<sup>2</sup>.**

**Bakris G,<sup>1</sup> Oshima M,<sup>2,3</sup> Mahaffey KW,<sup>4</sup> et al. Effects of Canagliflozin in Patients with Baseline eGFR <30 ml/min per 1.73 m<sup>2</sup>: Subgroup Analysis of the Randomized CREDENCE Trial. *Clin J Am Soc Nephrol*. 2020 Dec 7;15(12):1705-1714. PMID: 33214158.**

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Comment in *Clin J Am Soc Nephrol*. 2020 Nov 19.

## ABSTRACT

**BACKGROUND AND OBJECTIVES:** The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CRENCE) trial demonstrated that the sodium glucose cotransporter 2 (SGLT2) inhibitor canagliflozin reduced the risk of kidney failure and cardiovascular events in participants with type 2 diabetes mellitus and CKD. Little is known about the use of SGLT2 inhibitors in patients with eGFR <30 ml/min per 1.73 m<sup>2</sup>. The participants in the CRENCE study had type 2 diabetes mellitus, a urinary albumin-creatinine ratio >300-5000 mg/g, and an eGFR of 30 to <90 ml/min per 1.73 m<sup>2</sup> at screening. This post hoc analysis evaluated participants with eGFR <30 ml/min per 1.73 m<sup>2</sup> at randomisation.

**DESIGN, SETTING, PARTICIPANTS, & MEASUREMENTS:** Effects of eGFR slope through week 130 were analysed using a piecewise, linear, mixed-effects model. Efficacy was analysed in the intention-to-treat population, on the basis of Cox proportional hazard models, and safety was analysed in the on-treatment population. At randomisation (an average of 29 days after screening), 174 of 4,401 (4 percent) participants had an eGFR <30 ml/min per 1.73 m<sup>2</sup> (mean [SD] eGFR, 26 [3] ml/min per 1.73 m<sup>2</sup>).

**RESULTS:** From weeks 3 to 130, there was a 66 percent difference in the mean rate of eGFR decline with canagliflozin versus placebo (mean slopes, -1.30 versus -3.83 ml/min per 1.73 m<sup>2</sup> per year; difference, -2.54 ml/min per 1.73 m<sup>2</sup> per year; 95 percent confidence interval [CI], 0.90 to 4.17). Effects of canagliflozin on kidney, cardiovascular, and mortality outcomes were consistent for those with eGFR <30 and ≥30 ml/min per 1.73 m<sup>2</sup> (all P interaction >0.20). The estimate for kidney failure in participants with eGFR <30 ml/min per 1.73 m<sup>2</sup> (hazard ratio, 0.67; 95 percent CI, 0.35 to 1.27) was similar to those with eGFR ≥30 ml/min per 1.73 m<sup>2</sup> (hazard ratio, 0.70; 95 percent CI, 0.54 to 0.91; P interaction=0.80). There was no imbalance in the rate of kidney-related adverse events or AKI associated with canagliflozin between participants with eGFR <30 and ≥30 ml/min per 1.73 m<sup>2</sup> (all P interaction >0.12).

**CONCLUSIONS:** This post hoc analysis suggests canagliflozin slowed progression of kidney disease, without increasing AKI, even in participants with eGFR <30 ml/min per 1.73 m<sup>2</sup>. Copyright © 2020 by the American Society of Nephrology.

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## READING 3. SLOWING CKD PROGRESSION WITH SGLT2 INHIBITORS

**Wheeler DC,<sup>1</sup> James J,<sup>2</sup> Patel D,<sup>1</sup> et al. SGLT2 Inhibitors: Slowing of Chronic Kidney Disease Progression in Type 2 Diabetes. *Diabetes Ther.* 2020 Dec;11(12):2757-2774. PMID: 32996085.**

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## ABSTRACT

Diabetic kidney disease (DKD) is a topic of increasing concern among clinicians involved in the management of type 2 diabetes mellitus (T2DM). It is a progressive and costly complication associated with increased risk of adverse cardiovascular (CV) and renal outcomes and mortality. Ongoing monitoring of the estimated glomerular filtration (eGFR) rate alongside the urine albumin-to-creatinine ratio (ACR) is recommended during regular T2DM reviews to enable a prompt DKD diagnosis or to assess disease progression, providing an understanding of adverse risk for each individual. Many people with DKD will progress to end-stage kidney disease (ESKD), requiring renal replacement therapy (RRT), typically haemodialysis or kidney transplantation. A range of lifestyle and pharmacological interventions is recommended to help lower CV risk, slow the advancement of DKD, and prevent or delay the need for RRT. Emerging evidence concerning sodium-glucose co-transporter-2 inhibitor (SGLT2i) agents suggests a role for these medicines in slowing eGFR decline, enabling regression of albuminuria and reducing progression to ESKD. Improvements in renal end points observed in SGLT2i CV outcome trials (CVOTs) highlighted the possible impact of these agents in the management of DKD. Data from the canagliflozin CRENCE trial (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) have since demonstrated the effectiveness of this medicine in reducing the risk of kidney failure and CV events in a population comprising individuals with T2DM and renal disease. CRENCE was the first SGLT2i study to examine renal outcomes as the primary end point. Real-world studies have reaffirmed these outcomes in routine clinical practice. This article summarises the evidence regarding the use of SGLT2i medicines in slowing the progression of DKD and examines the possible mechanisms underpinning the renoprotective effects of these agents. The relevant national and international guidance for monitoring and treatment of DKD is also highlighted to help clinicians working to support this vulnerable group.

#### READING 4. DAPAGLIFOZIN IN PATIENTS WITH CKD

Heerspink HJL,<sup>1</sup> Stefánsson BV,<sup>1</sup> Correa-Rotter R,<sup>1</sup> et al. Dapagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med.* 2020 Oct 8;383(15):1436-1446. PMID: 32970396.

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##### Comment in:

*Kidney Int.* 2020 Dec;98(6):1387-1389; *Nat Rev Nephrol.* 2021 Apr;17(4):223-224; *N Engl J Med.* 2021 Jan 28;384(4):388-389; *N Engl J Med.* 2021 Jan 28;384(4):389; *Ann Intern Med.* 2021 Feb;174(2):JC20.

##### ABSTRACT

**BACKGROUND:** Patients with chronic kidney disease have a high risk of adverse kidney and cardiovascular outcomes. The effect of dapagliflozin in patients with chronic kidney disease, with or without type 2 diabetes, is not known.

**METHODS:** We randomly assigned 4,304 participants with an estimated glomerular filtration rate (GFR) of 25 to 75 ml per minute per 1.73 m<sup>2</sup> of body-surface area and a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of 200 to 5,000 to receive dapagliflozin (10 mg once daily) or placebo. The primary outcome was a composite of a sustained decline in the estimated GFR of at least 50 percent, end-stage kidney disease, or death from renal or cardiovascular causes.

**RESULTS:** The independent data monitoring committee recommended stopping the trial because of efficacy. Over a median of 2.4 years, a primary outcome event occurred in 197 of 2,152 participants (9.2 percent) in the dapagliflozin group and 312 of 2,152 participants (14.5 percent) in the placebo group (hazard ratio, 0.61; 95 percent confidence interval [CI], 0.51 to 0.72; P<0.001; number needed to treat to prevent one primary outcome event, 19 [95 percent CI, 15 to 27]). The hazard ratio for the composite of a sustained decline in the estimated GFR of at least 50 percent, end-stage kidney disease, or death from renal causes was 0.56 (95 percent CI, 0.45 to 0.68; P<0.001), and the hazard ratio for the composite of death from cardiovascular causes or hospitalisation for heart failure was 0.71 (95 percent CI, 0.55 to 0.92; P=0.009). Death occurred in 101 participants (4.7 percent) in the dapagliflozin group and 146 participants (6.8 percent) in the placebo group (hazard ratio, 0.69; 95 percent CI, 0.53 to 0.88; P=0.004). The effects of dapagliflozin were similar in participants both with and without type 2 diabetes. The known safety profile of dapagliflozin was confirmed.

**CONCLUSIONS:** Among patients with chronic kidney disease, regardless of the presence or absence of diabetes, the risk of a composite of a sustained decline in the estimated GFR of at least 50 percent, end-stage kidney disease, or death from renal or cardiovascular causes was significantly lower with dapagliflozin than with placebo.

## READING 5. SGLT2 INHIBITORS AND NEPHROPROTECTION

Piperidou A,<sup>1</sup> Loutradis C,<sup>1</sup> Sarafidis P.<sup>2</sup> SGLT-2 inhibitors and nephroprotection: current evidence and future perspectives. *J Hum Hypertens*. 2021 Jan;35(1):12-25. PMID: 32778748.

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### ABSTRACT

Chronic kidney disease (CKD) is a major public health issue and an independent risk factor for cardiovascular and all-cause mortality. Diabetic kidney disease develops in 30 to 50 percent of diabetic patients and it is the leading cause of end-stage renal disease in the Western world. Strict blood pressure control and renin-angiotensin system (RAS) blocker use are the cornerstones of CKD treatment; however, their application in everyday clinical practice is not always ideal and in many patients CKD progression still occurs. Accumulated evidence in the past few years clearly suggests that sodium-glucose co-transporter-2 (SGLT-2) inhibitors present potent nephroprotective properties. In clinical trials in patients with type 2 diabetes mellitus, these agents were shown to reduce albuminuria and proteinuria by 30 to 50 percent and the incidence of composite hard renal outcomes by 40 to 50 percent. Furthermore, their mechanism of action appears rather solid, as they interfere with the major mechanism of proteinuric CKD progression, i.e., glomerular hypertension and hyperfiltration. The present review summarises the current evidence from human trials on the effects of SGLT-2 inhibitors on nephroprotection and discusses their position in everyday clinical practice.

## READING 6. KDIGO GUIDELINE 2020 – DM MANAGEMENT IN CKD

de Boer IH,<sup>1</sup> Caramori ML,<sup>2</sup> Chan JCN,<sup>3</sup> et al. Executive summary of the 2020 KDIGO Diabetes Management in CKD Guideline: evidence-based advances in monitoring and treatment. *Kidney Int*. 2020 Oct;98(4):839-848. PMID: 32653403.

doi: 10.1016/j.kint.2020.06.024. Epub 2020 Jul 10. PMID: 32653403 (Free full text).

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### ABSTRACT

Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease represents the first KDIGO guideline on this subject. The guideline comes at a time when advances in diabetes technology and therapeutics offer new options to manage the large population of patients with diabetes and chronic kidney disease (CKD) at high risk of poor health outcomes. An enlarging base of high-quality evidence from randomised clinical trials is available to evaluate important new treatments offering organ protection, such as sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists. The goal of the new guideline is to provide evidence-based recommendations to optimise the clinical care of people with diabetes and CKD by integrating new options with existing management strategies. In addition, the guideline contains practice points to facilitate implementation when insufficient data are available to make well-justified recommendations or when additional guidance may be useful for clinical application. The guideline covers comprehensive care of patients with diabetes and CKD, glycaemic monitoring and targets, lifestyle interventions, antihyperglycemic therapies, and self-management and health systems approaches to management of patients with diabetes and CKD.

## READING 7. PATHOPHYSIOLOGIC MECHANISMS IN DIABETIC KIDNEY DISEASE

**Barrera-Chimal J,<sup>1</sup> Jaisser F.<sup>2,3,4</sup> Pathophysiologic mechanisms in diabetic kidney disease: A focus on current and future therapeutic targets. *Diabetes Obes Metab.* 2020 Apr;22 Suppl 1:16-31. PMID: 32267077.**

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### ABSTRACT

Diabetic kidney disease (DKD) is the primary cause of chronic kidney disease around the globe and is one of the main complications in patients with type 1 and 2 diabetes. The standard treatment for DKD is drugs controlling hyperglycaemia and high blood pressure. Renin angiotensin aldosterone system blockade and sodium glucose cotransporter 2 (SGLT2) inhibition have yielded promising results in DKD, but many diabetic patients on such treatments nevertheless continue to develop DKD, leading to kidney failure and cardiovascular comorbidities. New therapeutic options are urgently required. We review here the promising therapeutic avenues based on insights into the mechanisms of DKD that have recently emerged, including mineralocorticoid receptor antagonists, SGLT2 inhibitors, glucagon-like peptide-1 receptor agonist, endothelin receptor A inhibition, anti-inflammatory agents, autophagy activators, and epigenetic remodelling. The involvement of several molecular mechanisms in DKD pathogenesis, together with the genetic and epigenetic variability of this condition, makes it difficult to target this heterogeneous patient population with a single drug. Personalised medicine, taking into account the genetic and mechanistic variability, may therefore improve renal and cardiovascular protection in diabetic patients with DKD.

## READING 8. MECHANISMS OF CARDIORENAL EFFECTS OF SGLT2 INHIBITORS

**Zelniker TA,<sup>1</sup> Braunwald E.<sup>2</sup> Mechanisms of Cardioresenal Effects of Sodium-Glucose Cotransporter 2 Inhibitors: *JACC State-of-the-Art Review.* *J Am Coll Cardiol.* 2020 Feb 4;75(4):422-434. PMID: 32000955.**

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Erratum in *J Am Coll Cardiol.* 2020 Sep 22;76(12):1505.

### ABSTRACT

Sodium-glucose cotransporter 2 inhibitors (SGLT2i), a new drug class approved for treatment of diabetes, have been shown to possess a favourable metabolic profile and to significantly reduce atherosclerotic events, hospitalisation for heart failure, cardiovascular and total mortality, and progression of chronic kidney disease. Although initially considered to be only glucose-lowering agents, the effects of SGLT2i have expanded far beyond that, and their use is now being studied in the treatment of heart failure and chronic kidney disease, even in patients without diabetes. It is therefore critical for cardiologists, diabetologists, nephrologists, and primary care physicians to be familiar with this drug class. This first part of this two-part review provides an overview of the current understanding of the mechanisms of the cardio-metabolic-renal benefits of SGLT2i. The second part summarises the recent clinical trials of SGLT2i.

## READING 9. SGLT2 INHIBITORS IN RENOPROTECTION IN DM

**Gonzalez DE,<sup>1</sup> Foresto RD,<sup>1</sup> Ribeiro AB.<sup>2</sup> SGLT-2 inhibitors in diabetes: a focus on renoprotection. *Rev Assoc Med Bras* (1992). 2020 Jan 13;66Suppl 1(Suppl 1):s17-s24. PMID: 31939531.**

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### ABSTRACT

Type 2 diabetes mellitus is an important public health problem, with a significant impact on cardiovascular morbidity and mortality and an important risk factor for chronic kidney disease. Various hypoglycaemic therapies have proved to be beneficial to clinical outcomes, while others have failed to provide an improvement in cardiovascular and renal failure, only reducing blood glucose levels. Recently, sodium-glucose cotransporter-2 (SGLT2) inhibitors, represented by the empagliflozin, dapagliflozin, and canagliflozin, have been showing satisfactory and strong results in several clinical trials, especially regarding the reduction of cardiovascular mortality, reduction of hospitalisation due to heart failure, reduction of albuminuria, and long-term maintenance of the glomerular filtration rate. The benefit from SGLT2 inhibitors stems from its main mechanism of action, which occurs in the proximal tubule of the nephron, causing glycosuria, and a consequent increase in natriuresis. This leads to increased sodium intake by the juxtaglomerular apparatus, activating the tubule glomerular feedback and, finally, reducing intraglomerular hypertension, a frequent physiopathological condition in kidney disease caused by diabetes. In addition, this class of medication presents an appropriate safety profile, and its most frequently reported complication is an increase in the incidence of genital infections. Thus, these hypoglycaemic agents have gained space in practical recommendations for the management of type 2 diabetes mellitus and should be part of the initial therapeutic approach to provide, in addition to glycaemic control, cardiovascular outcomes, and the renoprotection in the long term.

## READING 10. KIDNEY OUTCOMES ASSOCIATED WITH SGLT2 INHIBITOR USE IN REAL-WORLD CLINICAL PRACTICE

**Heerspink HJL,<sup>1</sup> Karasik A,<sup>2</sup> Thuresson M,<sup>3</sup> et al. Kidney outcomes associated with use of SGLT2 inhibitors in real-world clinical practice (CVD-REAL 3): a multinational observational cohort study. *Lancet Diabetes Endocrinol*. 2020 Jan;8(1):27-35. PMID: 31862149.**

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### ABSTRACT

**BACKGROUND:** Cardiovascular and kidney outcome trials have shown that sodium-glucose co-transporter-2 (SGLT2) inhibitors slow progression of chronic kidney disease in patients with type 2 diabetes with or without chronic kidney disease. The aim of this study was to assess whether these benefits extend to patients with type 2 diabetes treated in routine clinical practice.

**METHODS:** CVD-REAL 3 was a multinational observational cohort study in which new users of SGLT2 inhibitors and other glucose-lowering drugs with measurements of estimated glomerular filtration rate (eGFR) before and after (within 180 days) initiation were identified via claims, medical records, and national registries in Israel, Italy, Japan, Taiwan, and the UK. Propensity scores for SGLT2 inhibitor initiation were developed in each country, with 1:1 matching with initiators of other glucose-lowering drugs. Propensity score included (in addition to other clinical and demographic variables) baseline eGFR and eGFR slope before SGLT2 inhibitor or other glucose-lowering drug initiation. The main outcome measure was rate of eGFR decline (slope) calculated with a linear mixed regression model. Differences in eGFR slope between SGLT2 inhibitors and other glucose-lowering drugs were calculated and pooled. We also assessed a composite outcome of 50 percent eGFR decline or end-stage kidney disease.

**FINDINGS:** After propensity matching, there were 35,561 episodes of treatment initiation in each group, from 65,231 individual patients. Dapagliflozin, empagliflozin, canagliflozin, ipragliflozin, tofogliflozin, and luseogliflozin accounted for 57.9 percent, 34.1 percent, 5.7 percent, 1.4 percent, 0.5 percent, and 0.4 percent of SGLT2 inhibitor initiation episodes, respectively. At baseline, 29,363 (41.3 percent) of 71,122 initiations were in women, mean age was 61.3 years, mean HbA1c was 72 mmol/mol (8.71 percent), and mean eGFR was 90.7 mL/min per 1.73 m<sup>2</sup>. During follow-up, SGLT2 inhibitor initiation was associated with reduced eGFR decline (difference in slope for SGLT2 inhibitors vs other glucose-lowering drugs 1.53 mL/min per 1.73 m<sup>2</sup> per year, 95 percent CI 1.34-1.72, p<0.0001). During a mean follow-up of 14.9 months, 351 composite kidney outcomes occurred: 114 (3.0 events per 10,000 patient-years) among initiators of SGLT2 inhibitors and 237 (6.3 events per 10,000 patient-years) among initiators of other glucose-lowering drugs (hazard ratio 0.49, 95 percent CI 0.35-0.67; p<0.0001). These findings were consistent across countries (pheterogeneity 0.10) and prespecified subgroups.

**INTERPRETATION:** In this large, international, real-world study of patients with type 2 diabetes, initiation of SGLT2 inhibitor therapy was associated with a slower rate of kidney function decline and lower risk of major kidney events compared with initiation of other glucose-lowering drugs. These data suggest that the benefits of SGLT2 inhibitors on kidney function identified in clinical trials seem to be largely generalisable to clinical practice.