A SELECTION OF TEN READINGS ON TOPICS RELATED TO PUTTING A STOP TO CKD

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Selection of readings made by A/Prof Goh Lee Gan

READING 1 – SGLT2I IMPROVE CARDIORENAL OUTCOME OF IHD PATIENTS

Chen S,[1,2] He Y,[1,2] Huang Z,[1,2] Wang B,[1,2] Li Q,[1,2] Wei W,[1,2,3,4] Liu J,[1,2,4] Huang H,[1,2,4] Xu X,[5] Guo D,[5] Chen J,[1,2,4,6] Tan N,[1,2,4,6] Liu Y,[1,2,4,6] Chen H.[4,7] Sodium Glucose Cotransporter Type 2 Inhibitors Improve Cardiorenal Outcome of Patients With Coronary Artery Disease: A Meta-Analysis. Front Endocrinol (Lausanne). 2022 Mar 7;13:850836. PMID: 35330914.

URL: doi: 10.3389/fendo.2022.850836. PMID: 35330914. (Free full text).

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ABSTRACT
OBJECTIVE: Sodium glucose cotransporter type 2 inhibitors (SGLT-2i) are beneficial for cardiorenal outcomes in patients with type 2 diabetes mellitus (T2DM), heart failure (HF), or chronic kidney disease (CKD). However, whether or not the patients with coronary artery disease (CAD) have prognostic benefit from SGLT-2i treatment has not been fully studied. The purpose of this meta-analysis is to determine the prognostic benefit of SGLT-2i administration in CAD patients.

METHODS: We searched the PubMed, Embase, and Cochrane Library from inception until 15 October 2021. We included randomised controlled trials (RCTs) reporting the effect of SGLT-2i on major adverse cardiovascular event (MACE), hospitalisation for heart failure (HHF), cardiovascular (CV) death, and cardiorenal parameters in CAD patients. Hazard ratio (HR) with 95 percent confidence interval (CI) and mean difference (MD) from trials were meta-analysed using fixed-effects models.

RESULTS: Nine trials enrolling 15,301 patients with CAD were included in the analyses. Overall, SGLT2i were associated with a reduced risk of MACE (HR: 0.84; 95 percent CI 0.74-0.95; I2=0 percent), HHF (HR: 0.69; 95 percent CI 0.58-0.83; I2=0 percent) and a composite of CV death or HHF (HR: 0.78; 95 percent CI 0.71-0.86; I2=37 percent) in CAD patients. Compared with the control group, estimated glomerular filtration rate (eGFR) level decreased less in SGLT-2i group (mean difference [MD] = -3.60, 95 percent CI, -5.90 to -1.30, p=0.002; I2=0 percent).

CONCLUSIONS: SGLT-2i can improve cardiorenal outcomes in CAD patients. Further RCTs and real-world studies are need to investigate the effect of SGLT2i on CAD patients.

READING 2 – SGLT2I IN NON-DIABETIC KIDNEY DISEASE

Tesař V[1] SGLT2 inhibitors in non-diabetic kidney disease. Adv Clin Exp Med. 2022 Feb;31(2):105-107. PMID: 35077036.

URL: doi: 10.17219/acem/145734. PMID: 35077036 (Free full text).

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ABSTRACT
There is an accumulating evidence demonstrating the renoprotective and cardioprotective role of sodium-glucose cotransporter 2 (SGLT2) inhibitors in early to advanced diabetic kidney disease. Data from recently published Dapagliflozin and Prevention of Adverse Outcomes in the Chronic Kidney Disease (DAPA-CKD) trial clearly show that dapagliflozin is similarly renoprotective in non-diabetic chronic kidney disease in a wide range of estimated glomerular filtration rate (eGFR) of 25-75 mL/min/1.73 m^2 (0.42-1.25 mL/s/1.73 m^2) and albumin/creatinine ratio 200-5,000 mg/g (approx. 20-500 mg/mmol). Patients with type 1 diabetes, autosomal dominant polycystic kidney disease, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, and lupus nephritis were excluded from the study, but, on the other hand, prespecified subanalysis demonstrated that dapagliflozin should be renoprotective also in patients with immunoglobulin A (IgA) nephropathy. The renoprotective effect of SGLT2 inhibitors is additive to the renoprotection conferred with blockers of renin-angiotensin system, including both inhibitors of angiotensin converting enzyme (ACEI), or angiotensin receptor blocker (ARB). These promising data will be hopefully confirmed by the ongoing the Study of Heart and Kidney Protection With Empagliflozin (EMPA-KIDNEY) trial, the results of which are expected later in 2022.

READING 3 – CVD AND KIDNEY OUTCOMES WITH FINERENONE IN PATIENTS WITH T2DM AND CKD

Agarwal R,[1] Filippatos G,[2] Pitt B,[3] Anker SD,[4] Rossing P,[5,6] Joseph A,[7] Kolkhof P,[8] Nowack C,[9] Gebel M,[10] Ruilope LM,[11,12,13] Bakris GL[14]; FIDELIO-DKD and FIGARO-DKD investigators. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. Eur Heart J. 2022 Feb 10;43(6):474-484. PMID: 35023547

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Comment in Eur Heart J. 2022 Feb 10;43(6):485-487.

ABSTRACT
AIMS: The complementary studies FIDELIO-DKD and FIGARO-DKD in patients with type 2 diabetes and chronic kidney disease (CKD) examined cardiovascular and kidney outcomes in different, overlapping stages of CKD. The purpose of the FIDELITY analysis was to perform an individual patient-level prespecified pooled efficacy and safety analysis across a broad spectrum of CKD to provide more robust estimates of safety and efficacy of finerenone compared with placebo.

METHODS AND RESULTS: For this prespecified analysis, two phase III, multicentre, double-blind trials involving patients with CKD and type 2 diabetes, randomised 1:1 to finerenone or placebo, were combined. Main time-to-event efficacy outcomes were a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for heart failure, and a composite of kidney failure, a sustained ≥57 percent decrease in estimated glomerular filtration rate from baseline over ≥4 weeks, or renal death. Among 13,026 patients with a median follow-up of 3.0 years (interquartile range 2.3-3.8 years), the composite cardiovascular outcome occurred in 825 (12.7 percent) patients receiving finerenone and 939 (14.4 percent) receiving placebo [hazard ratio (HR), 0.86; 95 percent confidence interval (CI), 0.78-0.95; P=0.0018]. The composite kidney outcome occurred in 360 (5.5 percent) patients receiving finerenone and 465 (7.1 percent) receiving placebo (HR, 0.77; 95 percent CI, 0.67-0.88; P=0.0002). Overall safety outcomes were generally similar between treatment arms. Hyperkalaemia leading to permanent treatment discontinuation occurred more frequently in patients receiving finerenone (1.7 percent) than placebo (0.6 percent).

CONCLUSION: Finerenone reduced the risk of clinically important cardiovascular and kidney outcomes versus placebo across the spectrum of CKD in patients with type 2 diabetes.

KEY QUESTION: Does finerenone, a novel selective, nonsteroidal mineralocorticoid receptor antagonist, added to maximum tolerated renin-angiotensin system inhibition reduce cardiovascular disease and kidney disease progression over a broad range of chronic kidney disease in patients with type 2 diabetes?

KEY FINDING: In a prespecified, pooled individual-level analysis from two randomised trials, we found reductions both in cardiovascular events and kidney failure outcomes with finerenone. Because 40 percent of the patients had an estimated glomerular filtration rate of >60 mL/min/1.73m^2, they were identified solely on the basis of albuminuria.

TAKE-HOME MESSAGE: Finerenone reduces the risk of clinical cardiovascular outcomes and kidney disease progression in a broad range of patients with chronic kidney disease and type 2 diabetes. Screening for albuminuria to identify at-risk patients among patients with type 2 diabetes facilitates reduction of both cardiovascular and kidney disease burden.

READING 4 – INCREASED MORTALITY RISK IN EARLY STAGES OF TYPE 2 DIABETES MELLITUS

Kadowaki T,[1] Komuro I,[2] Morita N,[3] Akiyama H,[3] Kidani Y,[3] Yajima T.[4] Manifestation of Heart Failure and Chronic Kidney Disease are Associated with Increased Mortality Risk in Early Stages of Type 2 Diabetes Mellitus: Analysis of a Japanese Real-World Hospital Claims Database. Diabetes Ther. 2022 Feb;13(2):275-286. PMID: 34979961.

URL: doi: 10.1007/s13300-021-01191-y. PMID: 34979961 (Full free text).

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ABSTRACT
INTRODUCTION: To assess the initial manifestation of comorbidities and their impact on mortality risk in patients with type 2 diabetes mellitus (T2DM) without a history of cardiovascular or renal complications (i.e., in the early stages of T2DM) compared with patients without T2DM.

METHODS: We performed a retrospective cohort study using a Japanese hospital claims database. The incidence rates of comorbidities (chronic kidney disease [CKD], heart failure [HF], myocardial infarction [MI], peripheral arterial disease [PAD], and stroke) and mortality risk were compared between patients with T2DM and age-/sex-matched patients without T2DM (matched 1:2).

RESULTS: Among the comorbidities assessed in this study, CKD and/or HF was the most frequent initial manifestation in the patients with T2DM (n=426,186) with an incidence rate 2.02 times greater than that in matched patients without T2DM (n=1,018,609). The mortality risk was also greater in patients with T2DM than in patients without T2DM with a hazard ratio of 1.73. In both patients with and without T2DM, the presence of CKD or HF was associated with greater mortality risks compared with the presence of MI, PAD, or stroke.

CONCLUSIONS: The high incidence of CKD or HF manifestation can contribute to the augmented mortality risk in patients in the early stages of T2DM compared with patients without T2DM. These findings highlight the importance of early interventions for preventing/treating CKD and HF to improve the prognosis of patients with T2DM.

READING 5 – HYPERTENSION AND RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM BLOCKADE IN ADULTS

Banerjee D,[1] Winocour P,[2] Zac-Varghese S,[2] Chowdhury TA,[3] De P,[4] Wahba M,[5] Montero R,[6] Fogarty D,[7] Frankel AH,[8] Karalliedde J,[9] Mark PB,[10] Patel DC,[11] Pokrajac A,[12] Sharif A,[13] Bain S,[14] Dasgupta I[15]; Association of British Clinical Diabetologists and The Renal Association. **Management of hypertension and renin-angiotensin-aldosterone system blockade in adults with diabetic kidney disease: Association of British Clinical Diabetologists and the Renal Association UK guideline update 2021. BMC Nephrol. 2022 Jan 3;23(1):9. PMID: 34979961**

URL: doi: 10.1186/s12882-021-02587-5. PMID: 34979961 (Free full text).

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ABSTRACT
People with type 1 and type 2 diabetes are at risk of developing progressive chronic kidney disease (CKD) and end-stage kidney failure. Hypertension is a major, reversible risk factor in people with diabetes for development of albuminuria, impaired kidney function, end-stage kidney disease, and cardiovascular disease. Blood pressure control has been shown to be beneficial in people with diabetes in slowing progression of kidney disease and reducing cardiovascular events. However, randomised controlled trial evidence differs in type 1 and type 2 diabetes and different stages of CKD in terms of target blood pressure. Activation of the renin-angiotensin-aldosterone system (RAAS) is an important mechanism for the development and progression of CKD and cardiovascular disease. Randomised trials demonstrate that RAAS blockade is effective in preventing/slowing progression of CKD and reducing cardiovascular events in people with type 1 and type 2 diabetes, albeit differently according to the stage of CKD. Emerging therapy with sodium glucose cotransporter-2 (SGLT-2) inhibitors, non-steroidal selective mineralocorticoid antagonists, and endothelin-A receptor antagonists have been shown in randomised trials to lower blood pressure and further reduce the risk of progression of CKD and cardiovascular disease in people with type 2 diabetes. This guideline reviews the current evidence and makes recommendations about blood pressure control and the use of RAAS-blocking agents in different stages of CKD in people with both type 1 and type 2 diabetes.

READING 6 – SGLT2I FOR HEART FAILURE IN PATIENTS WITH AND WITHOUT TYPE 2 DIABETES

Giaccari A,[1] Pontremoli R,[2] Perrone Filardi P.[3] SGLT-2 inhibitors for treatment of heart failure in patients with and without type 2 diabetes: A practical approach for routine clinical practice. Int J Cardiol. 2022 Mar 15;351:66-70. PMID: 34979145.

doi: 10.1016/j.ijcard.2021.12.050. PMID: 34979145 (Free full text).

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Comment in Int J Cardiol. 2022 Apr 1;352:102-103.

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

READING 7 – CARDIOVASCULAR OUTCOMES OF GLUCOSE-LOWERING THERAPY IN CKD PATIENTS

Kamdar A,[1] Sykes R,[1,2] Morrow A,[1,2] Mangion K,[1,2,3] Berry C.[1,2,3] Cardiovascular outcomes of glucose lowering therapy in chronic kidney disease patients: a systematic review with meta-analysis. Rev Cardiovasc Med. 2021 Dec 22;22(4):1479-1490. PMID: 34957787.

URL. doi: 10.31083/j.rcm2204152. PMID: 34957787 (Free full text).

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ABSTRACT
Chronic kidney disease (CKD) and cardiovascular disease share common risk factors such as hypertension, diabetes mellitus, and dyslipidaemia. Patients with CKD carry a high burden of cardiovascular disease and may be excluded from clinical trials on the basis of safety. There are an increasing number of clinical trials that predefine sub-group analysis for CKD. This systematic review with fixed-effect meta-analysis investigates glucose-lowering therapy and cardiovascular outcomes in relation to CKD. We included randomised controlled trials (RCT) of glucose-lowering treatments performed in adults (aged ≥18 years), humans, with no restriction on date, and English-language restriction in patients with pre-existing CKD regardless of diabetes status. Embase & Ovid Medline databases were searched up to April 2021. Risk of bias was assessed according to Revised Cochrane risk-of-bias tool. We included seven trials involving a total of 48,801 participants. There were four sodium-glucose cotransporter-2 inhibitors (SGLT2i), 2 glucagon-like peptide-1 receptor (GLP-1R) agonists and 1 Dipeptidyl-peptidase 4 (DPP4) inhibitor identified. SGLT2i (relative risk (RR)=0.90, 95 percent confidence interval (CI) [0.79-1.02]) and GLP-1R agonists (RR=0.83, 95 percent CI [0.72-0.96]) were associated with a reduction in cardiovascular

death. SGLT2i (RR=0.69, 95 percent CI [0.63-0.75]) are also associated with a reduction in hospitalisation for heart failure. In summary, this meta-analysis of large, RCTs of glucose-lowering therapies has demonstrated that treatment with SGLT2i or GLP-1R agonists may improve 3-point-MACE and cardiovascular outcomes in patients with chronic renal failure compared with placebo. This systematic review was registered with the PROSPERO network (registration number: CRD42021268563) and follows the PRISMA guidelines on systematic reviews and metanalysis.

READING 8 – SGLT2I AND RENAL OUTCOMES ACCORDING TO BASELINE ALBUMINURIA

Delanaye P,[1] Wissing KM,[2] Scheen AJ.[3] Sodium-glucose cotransporter 2 inhibitors: renal outcomes according to baseline albuminuria. Clin Kidney J. 2021 Jun 11;14(12):2463-2471. PMID: 34950459.

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ABSTRACT
Sodium-glucose co-transporter 2 inhibitors (SGLT2is) reduce albuminuria and hard renal outcomes (decline of renal function, renal replacement therapy, and renal death) in patients with/without type 2 diabetes at high cardiovascular or renal risk. The question arises whether baseline albuminuria also influences renal outcomes with SGLT2is as reported with renin-angiotensin-aldosterone system inhibitors. Post hoc analyses focusing on albuminuria and renal outcomes of four cardiovascular outcome trials [EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients), CANVAS (Canagliflozin Cardiovascular Assessment Study), DECLARE-TIMI 58 (Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events-Thrombolysis in Myocardial Infarction 58), and VERTIS CV (Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial)] and some renal data from two heart failure trials [Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) and EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction)] showed renal protection with SGLT2is without significant interaction ($P > 0.10$) when comparing renal outcomes according to baseline levels (A1, A2, and A3) of urinary albumin:creatinine ratio (UACR), a finding confirmed in a dedicated meta-analysis. Two trials [CREDENCE (Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy) and DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease)] specifically recruited patients with CKD and UACRs of 200-5,000 mg/g. A post hoc analysis of CREDENCE that distinguished three subgroups according to UACR (300-1,000, 1,000-3,000, and >3,000 mg/g) showed a greater relative reduction in UACR in patients with lower baseline albuminuria levels (P for interaction = 0.03). Patients with a UACR >1,000 mg/g showed a significantly greater reduction in absolute (P for interaction < 0.001) and a trend in relative (P for interaction = 0.25) risk of renal events versus those with lower UACR levels. In conclusion, baseline UACR levels do not significantly influence the nephroprotection by SGLT2is, yet the greater protection in patients with very high UACRs in CREDENCE deserves confirmation. The underlying mechanisms of renal protection with SGLT2is might be different in patients with or without (high) UACR.

READING 9 – DIABETES MANAGEMENT IN CHRONIC KIDNEY DISEASE: SYNOPSIS 2020 KDIGO CPG

Navaneethan SD,[1] Zoungas S,[2] Caramori ML,[3] Chan JCN,[4] Heerspink HJL,[5] Hurst C,[6] Liew A,[7] Michos ED,[8] Olowu WA,[9] Sadusky T,[10] Tandon N,[11] Tuttle KR,[12] Wanner C,[13] Wilkens KG,[14] Lytvyn L,[15] Craig JC,[16] Tunnicliffe DJ,[17] Howell M,[17] Tonelli M,[18] Cheung M,[19] Earley A,[19] Rossing P,[20] de Boer IH,[21] Khunti K.[22] Diabetes Management in Chronic Kidney Disease: Synopsis of the 2020 KDIGO Clinical Practice Guideline. Ann Intern Med. 2021 Mar;174(3):385-394. PMID: 33166222.

URL: doi: 10.7326/M20-5938. Epub 2020 Nov 10 PMID: 33166222 (Free full text).

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ABSTRACT

DESCRIPTION: The Kidney Disease: Improving Global Outcomes (KDIGO) organisation developed a clinical practice guideline in 2020 for the management of patients with diabetes and chronic kidney disease (CKD).

METHODS: The KDIGO Work Group (WG) was tasked with developing the guideline for diabetes management in CKD. It defined the scope of the guideline, gathered evidence, determined systematic review topics, and graded evidence that had been summarised by an evidence review team. The English-language literature searches, which were initially done through October 2018, were updated in February 2020. The WG used the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach to appraise evidence and rate the strength of the recommendations. Expert judgement was used to develop consensus practice points supplementary to the evidence-based graded recommendations. The guideline document underwent open public review. Comments from various stakeholders, subject matter experts, and industry and national organisations were considered before the document was finalised.

RECOMMENDATIONS: The guideline includes 12 recommendations and 48 practice points for clinicians caring for patients with diabetes and CKD. This synopsis focuses on the key recommendations pertinent to the following issues: comprehensive care needs, glycaemic monitoring and targets, lifestyle interventions, antihyperglycemic therapies, and educational and integrated care approaches.

READING 10 – EXECUTIVE SUMMARY 2020 KDIGO DIABETES MANAGEMENT IN CKD GUIDELINE

de Boer IH,[1] Caramori ML,[2] Chan JCN,[3] Heerspink HJL,[4] Hurst C,[5] Khunti K,[6] Liew A,[7] Michos ED,[8] Navaneethan SD,[9] Olowu WA,[10] Sadusky T,[11] Tandon N,[12] Tuttle KR,[13] Wanner C,[14] Wilkens KG,[15] Zoungas S,[16] Lytvyn L,[17] Craig JC,[18] Tunnicliffe DJ,[19] Howell M,[19] Tonelli M,[20] Cheung M,[21] Earley A,[21] Rossing P,[22] 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.

URL: 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 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.