Early Recognition of Type 2 Diabetes Complications and Use of SGLT2i in Multidisciplinary Approach: Indonesian Perspective - An Expert Opinion

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ABSTRACT

Indonesia ranks seventh with the highest number of cases of type 2 diabetes mellitus (T2DM). T2DM is associated with major undesirable complications including cardiovascular disease and chronic kidney disease. Kidneys play a major role in maintaining glucose homeostasis, leading the development of sodium glucose transporter inhibitors (SGLT2i). These inhibitors block renal sodium and glucose reabsorption. Several cardiovascular trials proved that SGLT2i have cardioprotective and renoprotective roles and have been suggested as a drug of choice in primary and secondary prevention and management of cardiorenal complications associated with T2DM. This review highlights the need for a multidisciplinary recommendation for T2DM management in Indonesian population. Additionally, it is vital to provide the perspective of Indonesian medical experts in terms of screening, diagnosis and treatment as the outcome differs geographically.

An expert panel of 6 members from Indonesia was convened to review the existing literature and develop an expert-based review/ summary on this topic. Members were chosen for their proficiency in diabetes, kidney disease and cardiovascular disease. The experts opined that the early use of SGLT2i will be effective in preventing and minimising the progression of cardiorenal complications. Moreover, a consistent multidimensional approach is necessary for improved outcomes.

Keywords**:** *Type 2 diabetes mellitus, SGLT2i, cardiorenal complications.*

INTRODUCTION

Diabetes mellitus (DM) is a metabolic condition that affects 537 million adults worldwide, with the number estimated to increase to 783 million by 2045.[1] DM in Indonesia is a major health problem and has been a cause of serious concern since the 1980s.[2] Indonesia is ranked seventh among the top 10 countries with

the highest number of diabetics.[3] The prevalence of diabetes in Indonesian adults (20–79 years) is estimated to be 10.7 million, increasing to 13.7 and 16.6 million by 2030 and 2045, respectively.[4] According to DiabCare 2008 study in Indonesia, 97.5% of patients had type 2 DM (T2DM), of which 67.9% had poor glycemic control with HbA1c being in the range of 8.1 ± 2.0%.[5] In addition, the DISCOVER study, presented in Lisbon, Portugal during EASD, Indonesia had the highest mean HbA1c levels (9.2± 2%) among other participating countries. Despite the initiation of second-line therapy, the mean HbA1c levels in 70% of patients were >8%.[6]

T2DM is the central factor in the development and progression of CVD and kidney disease, which can lead to atherosclerotic CVD (ASCVD) and heart failure (HF).[7,8] A review by Asian experts from 9 different countries found that the prevalence of HF is approximately identical to global estimates i.e., 1% to 3%. Asian HF patients were observed to spend between 5 (Indonesia) to 12.5 days (Taiwan) in the hospital with a 3 to 15% readmission rate within 30 days due to HF.[8]

A vicious circle exists between T2DM, heart failure, and kidney disease, with the prevalence of HF increasing as CKD progresses.[9] A higher risk of cardiovascular disease (CVD) is associated with T2DM, which is estimated to be 1.6 to 2.6%.[4] Worldwide, CVD affects 32.2% of T2DM patients and it's the leading cause of morbidity and mortality in diabetic population.[10] According to a retrospective cohort study (n=1085) conducted from 2011 -2018, the incidence of cardiovascular events among the prediabetic and diabetic Indonesian population was 9.7% over a six-year period. In addition, age ≥ 45 years and hypertension were the predictors of cardiovascular events.[3]

Following the confluence of CVD and diabetes, CKD adds a layer of complexity.[11] Diabetic kidney disease affects 40% of the diabetic population and is the leading cause of end-stage kidney disease (ESKD). The prevalence of ESKD is 10 times higher in individuals with diabetes that ranges from 10% to 67%.[12] Comorbidities trigger a sudden decline in renal functioning of CKD patients. In Indonesia, the most common underlying disease in CKD patients is hypertension and diabetic kidney disease.[13] As per the Indonesian renal registry 2019, 26% patients with CKD stage 5 patients had an etiological diagnosis of diabetic kidney disease.[13,14] According to the statistics presented at 'the 14th national congress meeting of the Indonesian Society of Nephrology' hypertension (35%) and diabetic nephropathy (29%) are the two key etiological variables observed in CKD 5 patients.[15]

The guidelines of Indonesian Society of Endocrinology 2011, recommend diabetes screening for high-risk groups including individuals with hypertension, dyslipidaemia, coronary artery disease and obese people having sedentary lifestyle. They also recommend that, high risk individuals obtaining a negative result should be tested annually and people >45 years should be screened every 3 years.[16,17] A cross sectional survey of 15,332 urban Indonesians aged between 18-55 years, reported 4.6% of diabetes mellitus prevalence with instances of 1.1% previously diagnosed and 3.5% undiagnosed cases. In addition, prevalence of hypertension and dyslipidemia among previously diagnosed and undiagnosed cases was found to be 41.4% and 50%; 49.4% and 50%, respectively.[18]

To lessen the risk of nephropathy progression, the PERKENI 2021 guidelines recommend, optimising glucose levels and hypertension control. In patients (non-pregnant) with moderate (30-299 mg/24hr) to severe albuminuria (>300/24 hr), therapy with angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers with regular monitoring of serum creatinine and serum potassium levels is suggested, but not to be used as a primary prevention. Furthermore, nephrologist intervention is recommended, if serum creatinine is ≥ 2.0 mg/dL, or difficulty persist in determining the etiology, management, or in advance renal failure cases.[19]

The intersection of diabetes, kidney disease, ASCVD, and HF necessitates the emergence of diabetic treatment modalities that are both safe and effective[7] and simultaneously provide primary prevention from cardiorenal complications associated with T2DM. Newer glucose-lowering

agents have generated a possibility to influence the history of T2DM and cardiorenal complications. Sodium–glucose cotransporter 2 inhibitors (SGLT2i) are the new class of drugs approved for the management of T2DM. Dapagliflozin, empagliflozin, canagliflozin, and ertugliflozin have been investigated in cardiovascular outcome trials (CVOTs) and approved by the European Medicines Agency and Food and Drug Administration (FDA) either as monotherapy or as an adjunct to other antidiabetic agents.[20,21] SGLT2i are a relatively new addition to the armament of T2DM therapeutic modalities. When evaluated in conjunction with other oral medications or insulin, all SGLT2i demonstrate similar reductions in HbA1c.[22–25] Although the short-term HbA1c reduction seen with SGLT2i is comparable to that attained with sulfonylureas and dipeptidyl peptidase-4 inhibitor (DPP-IV), the glycemic effect appears to be more durable with SGLT2i.[26,27] Several meta-analyses reported improvement in glycemic control with the use of SGLT2i.[28,29] In addition to glycemic effects, SGLT2i exerts several extra-glycemic effects, including weight loss, blood pressure reduction, lipid level regulation, CV risk reduction, renoprotective impact, and reduction in macro- and micro-vascular events, as well as lowering the risk of hypoglycaemia.[22] Evidence in line, stating SGLT2i having glycemic and extra glycemic effects, indicates that SGLT2i may be used in primary and secondary prevention of cardiorenal complications in T2DM patients.[20]

This review emphasises on the burden of diabetes in Indonesia and to make recommendations for early screening, diagnosis, and treatment to prevent cardio-renal complications. There is need for a multidisciplinary recommendation for T2DM management in the Indonesian population as there is no data regarding the official guidelines or recommendations. Additionally, the objective of this review is to justify the beneficial role of SGLT2i in primary and secondary prevention of cardiorenal complications associated with T2DM, wherein primary prevention is described as prevention of occurrence of cardiorenal complication and secondary prevention is to reduce the worsening of cardiorenal complication in T2DM patients.

METHODOLOGY

The need for comprehensive review of the early recognition of T2DM complications and its prevention and management using SGLT2i in Indonesian population was identified by the Indonesian medical specialists from various fields. An expert panel of 6 members (four from university hospitals, and two from public sector) from Indonesia was convened to review the existing literature and develop an expert-based review/ summary on this topic. Members were chosen for their proficiency in diabetes, kidney disease and cardiovascular disease. Series of teleconferences and web-based communications were held from June to August 2021. A manuscript outline was developed, with individual sections assigned to the authors as per their expertise. All the authors had continuous access to the working document to provide input and each section was critically reviewed and revised.

In preparation, an extensive literature search was conducted using key words - diabetes mellitus, “type 2 diabetes” “diabetes Indonesia” “chronic kidney disease”, “cardiovascular disease”, “microvascular complications”, “HbA1c”, “SGLT2 inhibitors”, “EMPA”, “DAPA” and “CANA” in, MEDLINE, Cochrane Library and Science Direct databases, to identify relevant articles. In addition, experts recommended articles outside the scope of formal searches, and findings from conference proceedings and relevant online data sources were also reviewed. **(Figure 1)**

A total of 68 articles were identified out of which 54 were shortlisted. A total of 52 full text articles (meta-analysis, reviews, and randomized controlled trials) published in English and in peer-reviewed and indexed journals from 2005-2021 were selected and the studies with only abstract were excluded. Articles published before the start search date provided conceptual content only.

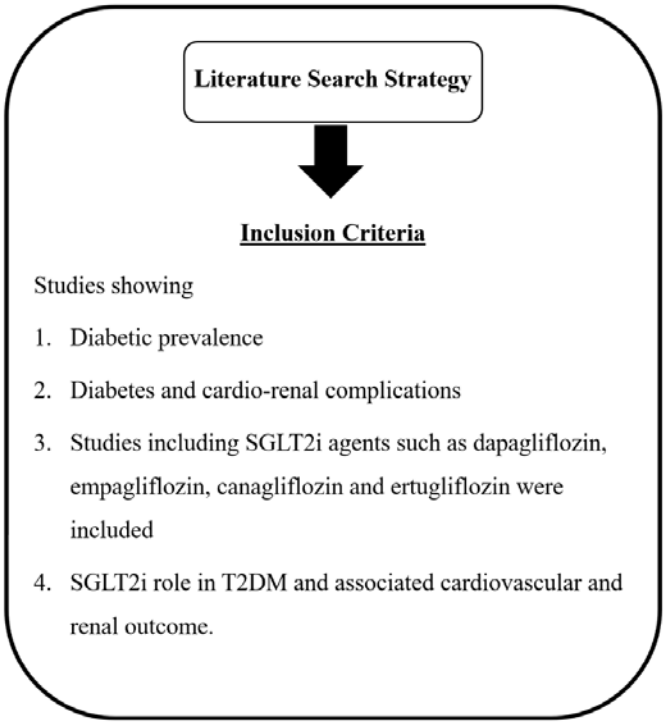

Figure 1. Literature search strategy.

DISCUSSION

Among several SGLT2 inhibitors, empagliflozin has the highest SGLT2 receptor selectivity, and the other agents have intermediate selectivity (dapagliflozin and canagliflozin).[20] The relative specificities of different SGLT2i to various SGLT receptors contribute to modest variances in their clinical characteristics. The mechanism of action of SGLT2i is presented in **Figure 2.**[21]

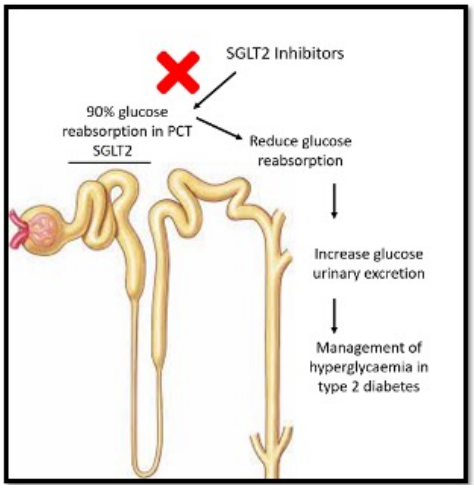

Figure 2. Mechanism of action of sodium glucose transporter 2 inhibitors.

SGLT2i and T2DM

SGLT2i mediates the reabsorption of 90% of filtered glucose and inhibits glucose reabsorption at the level of the proximal convoluted tubule (PCT), resulting in enhanced glucosuria, osmotic diuresis, and natriuresis, thereby managing the hyperglycemia with reduced risk of hypoglycemia.[30] Furthermore, SGLT2i have added benefits of persistent calorie reduction leading to weight loss, reduced β-cell stress, increased rate of insulin secretion, and insulin sensitivity. Sequentially, all these mechanisms regulate blood glucose levels despite β cell dysfunction or insulin resistance. Additionally, they are effective in advanced stages of T2DM due to their insulin-independent mechanism.[21]

Efficacy and safety of SGLT2i in T2DM patients were investigated in a systematic review and meta-analysis that included 38 trials (n=23,997). SGLT2i (canagliflozin, dapagliflozin, and empagliflozin) lowered glycated hemoglobin levels (HbA1C) (–0.6% to –0.9%), fasting blood glucose (FBG) (–1.1 to –1.9 mmol/L), blood pressure (BP) (systolic –4.9 to –2.8 mmHg; diastolic – 2.0 to –1.5 mmHg), and body weight (–1.6 to –2.5 kg) when compared with placebo.[28]

In line with the evidence, a systematic review including three trials of dapagliflozin and two each for canagliflozin and empagliflozin reported that monotherapy with SGLT2i significantly improved glycemic control, induced weight loss, and reduced blood pressure. The common adverse events reported were an increase in urinary tract infections (4–9%) and genital tract infections.[28] Similarly, another systematic review and network meta-analysis including 39 randomized controlled trials (RCTs) (n=25,468) reported that SGLT2i was superior to placebo in terms of glycemic control, weight loss, and reduction of systolic and diastolic BP.[31]

Drug intensification is often required in T2DM patients who are on stable metformin therapy. SGLT2i are potential candidates for combination therapy as they have shown promising outcomes. A meta-analysis, including six RCTs, compared the efficacy and safety of SGLT2i with non-SGLT2 combinations (glimepiride, linagliptin, sitagliptin, glipizide) as an add on to metformin treatment. The study reported that SGLT2i+metformin therapy significantly reduced HbA1c% more than the non-SGLT2i combination after 52 weeks and as well as after 104 weeks of therapy (p<0.00001). Moreover, reduction in FPG, weight, and BP was significantly more in the SGLT2i group (p<0.00001) and the incidence of hypoglycemia was also reported to be lower with SGLT2i.[32–34]

Primary and Secondary Prevention

CVOTs distinguished T2DM patients without established CVD (primary prevention) and patients with established CVD (secondary prevention).[20] Thus, it can be inferred that primary prevention is refers to preventing cardiorenal complications in diabetic patients, whereas secondary prevention refers to the diabetic patients who have experienced an acute ischemic event and to prevent the aforementioned complications from worsening. SGLT2i have shown the possibility of being cardioprotective by demonstrating relative risk reduction of major adverse cardiovascular events (MACE). Several meta-analyses have reported in favour of SGLT2i, highlighting its renoprotective and cardioprotective effects.[35,36] Outcome was reported as significant reduction in MACE in empagliflozin and canagliflozin trials, whereas dapagliflozin showed reduction in CV mortality and hHF.[7,37,38] Studies determining the role of SGLT2i in primary and secondary prevention are presented in **Table 1 and 2** [7,37–43] Glycemic and extraglycemic effects of SGLT2i are presented in **Figure 3.**[21]

SGLT2i and CVOT

T2DM confers a two-to-three-fold increased risk of coronary artery disease, including angina, myocardial infarction (MI), stroke, and HF in patients with or without established cardiovascular illness.[30] SGLT2i has demonstrated the potential of being cardioprotective by exhibiting relative risk (RR) reduction of 3 Point (non-fatal stroke, non-fatal myocardial infarction and CV death)-MACE.[7] The Empagliflozin Cardiovascular Outcome Event Trial (EMPA-REG OUTCOME) was the first trial to demonstrate the CV benefits of SGLT2i. Over a median of 3.1 years. the risk of CV and all-cause mortality reduced in the SGLT2i group by 38% and 32%, respectively, with no significant difference in the risk of non-fatal heart attack or stroke. Empagliflozin was also found to be effective in secondary prevention.[37] Similarly, DECLARE and CANVAS trials have also demonstrated the cardioprotective effects of SGLT2i in multiple risk populations.[7,38,44] DECLARE-TIMI 58, is the largest, longest and broadest SGLT2i trial compared the efficacy and safety of dapagliflozin in 17,160 patients with T2DM over a median of 4.2 years. The study showed risk reduction for both the primary endpoints i.e., MACE and hHf/ CV was insignificant. The renal outcome was 4.3% in dapagliflozin group vs. 5.6% in the placebo group due to the reduced rate of hospitalization for HF, regardless of the previous history of ASCVD and HF.[7] Therefore, it can be stated that dapagliflozin has provided beneficial effects in both primary and secondary prevention.[7,36,45]

SGLT2i and Heart Failure

T2DM is a prevalent co-morbidity in patients with HF and a major prognostic factor in patients with established HF. Chronic HF is the major cause of hospitalization in patients over 65 years, with a 10% 30-day and 50% 1-year mortality.

Table 1. Effect of SGLT2 Inhibitors on Cardiovascular Outcome

Cardiovascular Outcomes	EMPA-REG outcome	CANVAS	DECLARE-TIMI 58	CREDENCE	VERTIS CV	DAPA HF	RWE
	Empagliflozin vs Placebo	Canagliflozin vs Placebo	Dapagliflozin vs Placebo	Canagliflozin vs Placebo Events/1000 patients	Ertugliflozin vs Placebo	Dapagliflozin vs Placebo	Dapagliflozin vs Glucose lowering Drugs Events/1000 patients
Death from CV causes, non-fatal MI or non-fatal stroke HR (95% CI)	10.5% vs 12.1% 0.86 (0.74-0.99)	26.9% vs 31.5% 0.86 (0.75 - 0.97)	8.8% vs 9.4% 0.93 (0.84 - 1.03)	38.7 vs 48.7 0.80(0.67 - 0.95)	11.9% vs 11.9 % 0.97 (0.85-1.11)	----	----
CV death HR (95% CI)	3.7% vs 5.9 % 0.62 (0.49 – 0.77)	11.6% vs 12.8% 0.87 (0.72 – 1.06)	2.9% vs 2.9% 0.98 (0.82 – 1.17)	19.0 vs 24.4 0.78 (0.61 – 1.00)	6.2% vs 6.7% 0.92 (0.77 – 1.11)	9.6% vs 11.5% 0.82 (0.69 – 0.98)	6.1 vs 8.1 0.75 (0.57 – 0.97)
Hospitalization for heart failure HR (95% CI)	2.7% vs 4.1% 0.65 (0.50 – 0.85)	5.5% vs 8.7 % 0.67 (0.52 – 0.87)	2.5% vs 3.3% 0.73 (0.61 – 0.88)	15.7 vs 25.3 0.61 (0.47 – 0.81)	2.5% vs 3.6% 0.70 (0.54 – 0.90)	9.7% vs 13.4% 0.70 (0.59 – 0.83)	15.5 vs 19.6 0.79 (0.67 – 0.93)
Non-fatal MI HR (95% CI)	4.5% vs 5.2% 0.87 (0.70 – 1.09)	9.7% vs 11.6% 0.85 (0.69 – 1.05)	4.6% vs 5.1% 0.89 (0.77 – 1.01)	----	5.6% vs 5.4% 1.04 (0.86 – 1.27)	----	10.3 vs 11.3 0.91 (0.74 – 1.11
Non-fatal stroke HR (95% CI)	3.2% vs 2.6% 1.24 (0.92 – 1.67)	7.1% vs 8.4% 0.90 (0.71 – 1.15)	2.7% vs 2.7% 1.01 (0.84 – 1.21)	----	2.9% vs 2.8% 1.00 (0.76 – 1.32)	----	----

CANVAS: Canagliflozin Cardiovascular Assessment Study Program; CREDENCE: Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation; CVD: cardiovascular disease; DAPA CKD: Dapagliflozin in patients with chronic kidney disease; DECLARE-TIMI 58: Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58; EMPA-REG:, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose; VERTISCV: Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease;
eGFR: estimated glomerular filtration rate; ESKD: End stage kidney disease; HR: Hazard Ratio

Table 2. Effect of SGLT2 Inhibitors on Kidney Outcomes.

Renal Outcomes	CANVAS	DECLARE-TIMI 58	CREDENCE	VERTIS CV	DAPA CKD
	CANA vs Placebo	DAPA vs Placebo	CANA vs Placebo	Ertugliflozin vs Placebo	DAPA vs Placebo
Renal composite outcome description	40% reduction in eGFR, renal replacement therapy or renal death	≥ 40% decrease in eGFR to <60 ml/ min/1.73 m2, ESKD, or death from renal cause	Doubling of serum creatinine, ESKD, renal death	Death form renal causes, renal replacement therapy or doubling of serum creatinine level	≥ 50% decline in eGFR, ESKD, renal death
Renal composite outcome HR (95% CI)	5.5% vs 9.0% 0.60 (0.47 – 0.77)	1.5% vs 2.8% 0.53 (0.43 – 0.66)	43.2 vs 61.2 0.70 (0.59 – 0.82)	3.2% vs 3.9% 0.81 (0.63 – 1.04)	9.2% vs 14.5% 0.61 (0.51 – 0.72)

CANVAS: Canagliflozin Cardiovascular Assessment Study Program; CREDENCE: Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation; CVD: cardiovascular disease; DAPA CKD: Dapagliflozin in patients with chronic kidney disease; DECLARE-TIMI 58: Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58; EMPA-REG:, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose; VERTISCV: Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease;
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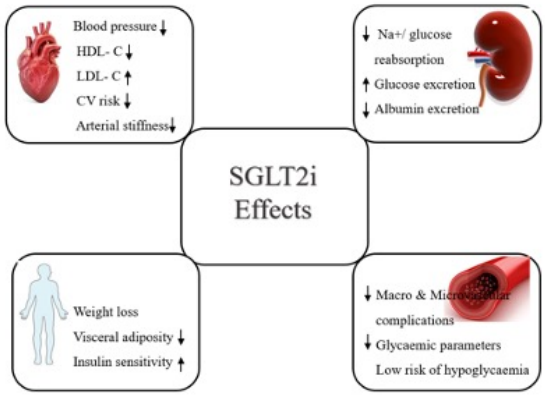

Figure 3. Effects of sodium glucose transporter 2 inhibitors.

According to their ejection fraction (EF), patients with T2DM may develop three distinct types i.e., HF with reduced EF (HFrEF), HF with mildly reduced EF (HFmrEF) and HF with preserved EF (HFpEF).[30]

A meta-analysis including six large trials of >46,000 patients with T2DM reported that SGLT2i was associated with a significant reduction of hHF (HR: 0.68; 95%CI: 0.61–0.76), Benefits on the risk of hHF and its related outcomes are independent of baseline ASCVD and prior HF.[46] Further, DAPA HF trial[41], determined the efficacy of dapagliflozin (10 mg/ day) in 4,744 patients with symptomatic HF and reduced EF (<40%). Over a median follow-up of 18.2 months, the primary outcome (worsening HF or cardiovascular death) occurred in 16.3% in the dapagliflozin group vs. 21.2% in the placebo group. Only 42% had significant T2DM. The magnitude of clinical benefits of dapagliflozin on the primary outcome was similar in patients with or without T2DM and with or without ischemic heart disease.[41] The EMPEROR reduced trial,[47] evaluated the efficacy of empagliflozin (10mg/ day) against placebo or indicated therapy in 3730 patients with heart failure and 40% EF. The primary outcome occurred in 19.4% in the empagliflozin group with lowered number of hHF and 24% of the placebo group.[47] These observations provide a strong basis for the guidelines and recommendations supporting the use of SGLT2i.

SGLT2i and CKD

Despite efforts being made to achieve optimal glycemic and blood pressure control, patients with CKD still have a high risk of progressing to ESKD, highlighting the need for additional renoprotective therapies to preserve the estimated glomerular filtration rate (eGFR) and prevent ESKD. The renoprotective effects of SGLT2i were first demonstrated in DECLARE-TIMI 58 trial[7], and CANVAS study[39], although the renal outcomes reported from these studies

were the secondary outcome measures.[7,38] In a meta-analysis of three CVOTs, SGLT2i reduced the composite of worsening kidney function by 45% (0.55 [0.48–0.64]), with a similar effect in those with and without ASCVD.[38] As per European society of cardiology guidelines, treatment with an SGLT2i is recommended at eGFR of 30 - <90 ml/min/1.73 m^2.[45]

The CREDENCE trial[39], evaluated the renoprotective effects of canagliflozin in 4,401 patients with T2DM, CKD, and macroalbuminuria. Patients with eGFR>30 and <90 mL/min/1.73 m^2 and urine albumin-to-creatinine ratio (UACR) >300–5000 mg/g and all patients receiving renin–angiotensin system blockade were included. The primary outcome risk measure was a composite of ESKD, doubling of the serum creatinine level, or renal or cardiovascular deaths which was reduced by 30% in the canagliflozin group relative to the placebo group. The canagliflozin group also reported a lower risk of cardiovascular death, myocardial infarction, or stroke.[39]

Determination of UACR may help in early recognition of renal complications. A prespecified analysis of DAPA-CKD trial,[48] was conducted and the primary outcome was composite of sustained decline in eGFR to at least 50%, ESKD, kidney-related or CV-related death. 68% of patients had T2DM, of which 14% had CKD. The relative risk of primary and secondary outcome with dapagliflozin was consistent in a patient with T2DM, diabetic kidney disease, glomerulonephritis, and ischemic or hypertensive CKD, concluding that dapagliflozin reduces the risk of major adverse kidney and CV events and all-cause mortality in diabetic and non-diabetic CKD.[48]

Indonesian Perspective

The aim in formulating this paper is to emphasise the existing diabetes burden in Indonesia and measures that can be taken to curb its prevalence. Diabetes related consequences are devastating, and it is vital to provide the Indonesian medical experts perspective with regards to screening, diagnosis, and treatment. Thus, timely screening and management of the disease is critical. The root of this article signifies that T2DM care necessitates multidimensional approach including cardiology, endocrinology, and nephrology, as it unfortunately leads to cardiorenal complications affecting the community at large.

For policy makers to consider: The purpose is to focus on improving primary healthcare (PHC) settings in terms of diabetes prevention, screening and early intervention. Enabling these adjustments will help to reduce the ongoing

Table 3. Recommendations for SGLT2 Inhibitors Therapy.

Recommendations for SGLT2i	
American Diabetes Association [50]	Type 2 diabetes patients with established ASCVD or high risk established kidney disease, or heart failure- SGLT2i or GLP 1 r agonist with demonstrated CVD benefit is recommended as part of the glucose lowering regimen independent of HbA1C and in consideration of patient specific factors
Asian Pacific Society of Nephrology (2020) [50]	Recommends SGLT2i in adult patient with type 2 diabetes and eGFR ≥ 30ml/min/1.73m2, who have CVD or diabetic kidney disease
European Society of Cardiology (ESC) and European Association for the Study of Diabetes (2019) [45]	Empagliflozin, Canagliflozin or Dapagliflozin are recommended in patients with type 2 diabetes and CVD, or at very high/high CV risk to reduce CV events
	Empagliflozin is recommended in T2DM and CVD patients to reduce risk of death
	SGLT2i are recommended to lower risk of hospitalization for heart failure in T2DM patients
	SGLT2i is recommended if eGFR is 30 - <90ml/min/1.73 m2 and is associated with lower risk of renal endpoints
Kidney Disease Improving Global Outcomes (2020) [51]	Recommends SGLT2i in treating patients with T2DM, CKD and eGFR ≥ 30ml/min/1.73m2
PERKENI 2021[19]	Recommends SGLT2i for T2DM patients with ASCVD/ high risk, heart failure or CKD

T2DM prevalence and its implementation may prove beneficial given the vast number of people that visit the PHC.

For Doctors and Patients: According to American Diabetes Association (ADA), asymptomatic adults should be screened for prediabetes and type 2 diabetes using an informal assessment of risk factors. Furthermore, annual monitoring of prediabetic patients is recommended. Regardless of medication, urinary ACR and eGFR must be assessed atleast once a year in these patients. Optimal timely referral to nephrologist allows instituting preventive and therapeutic measures designed to retard progression of kidney complications, preparing kidney replacement therapy and enhance the quality of life.[49]

Patients should be referred for evaluation by a nephrologist if they have an eGFR <30 mL/min/1.73m^2 or in the condition of uncertainty in determining etiology of kidney disease, difficult management issues, and rapidly progressing kidney disease. Lastly, all the patients should receive general preventive self-care education.[49] According to PERKENI 2021 guidelines, patients should be referred to an endocrinologist, if they are found to have DM related chronic complications such as diabetic retinopathy/ nephropathy, symptoms of unstable angina, and unresolved hyperglycaemia, persisting even after treatment i.e., FBG > 130mg/dL, post prandial blood glucose >180mg/dL or HbA1c >7% with ≥3 months of therapy. It is also recommended that patients should be educated about their disease condition with the help of educational materials as a part of prevention.[19]

CONCLUSION

Early recognition of T2DM complications and its management with appropriate therapy is the need of the hour. In line of evidence, glycemic and extraglycemic effects of SGLT2i have been thoroughly characterised. They have been found to be beneficial in controlling the HbA1c levels in T2DM patients. According to the facts and literature, it can be stated that SGLT2i are useful in providing primary and secondary prevention of cardiovascular and kidney-related complications in T2DM patients. Dapagliflozin has shown benefit for both primary and secondary prevention, whereas empagliflozin have been proven to be effective in secondary prevention, however its role in primary prevention is yet to be established. Therefore, it can be suggested that the early use of SGLT2i will be effective in preventing and minimising the progression of cardiorenal complications.

According to experts, a coordinated and multidisciplinary management of the patient with T2DM, with earlier implementation of guidelines and clinical recommendations, are the key factors for the comprehensive diabetic care and prevention.

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CONFLICT OF INTEREST

There is no conflict of interest

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