Review Article

The Use of SGLT2i and GLP-1 RA in Patients with Type 2 Diabetes in Thailand: Evidence Review and Recommendations

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Background: Cardiovascular (CV) and renal comorbidities are common among type 2 diabetes (T2D) patients, and significantly increase the cost and burden of care. Both sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1 RA) improve key outcomes including major CV events, hospitalization for heart failure, and renal outcomes, albeit to varying degrees in different T2D populations.

Materials and Methods: The authors reviewed evidence from GLP-1 RA and SGLT2i CV outcomes trials and real-world studies in Thailand and elsewhere.

Results: The authors formulated recommendations to guide selection of anti-diabetes medication based on patients' clinical characteristics and CV or renal risk profile.

Conclusion: These recommendations could help guide management of CV/renal comorbidities and risk alongside glucose-lowering therapy for individual patients.

Keywords: Type 2 diabetes mellitus; Cardiovascular diseases; Chronic kidney disease; Clinical outcomes; SGLT2i; GLP-1 RA

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Amongst all the chronic diseases affecting the world's population today, type 2 diabetes (T2D) represents one of the largest healthcare burdens because of the high rate of associated comorbidities, especially cardiovascular (CV) and renal complications. T2D management places a high demand on resources, both human and financial[1]. In a study of 24,501 participants in Thailand, the average annual medical cost of care for a diabetic patient was 551 USD[2]. When including the indirect non-medical costs, an average of 881 USD is spent per year on every patient with diabetes, which is approximately a fifth of the annual per capita income in Thailand. Older age and comorbidities were key contributors towards increased cost of care.

Conditions such as hypertension, dyslipidemia, and obesity are more common in people with diabetes than in normal glucose tolerance[3,4]. According to the Thai National Health Examination Survey, 2004 to 2014, nearly 48% of men and women with diabetes suffered from hypertension[5]. Elevated levels of low-density lipoprotein cholesterol (LDL-C) were seen in up to 71% of diabetic patients, and body mass index of 30 kg/m² or more in almost a fifth of diabetic patients[5]. These conditions are significant risk factors for major adverse CV events or MACE, which is a composite of CV death, non-fatal stroke,

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and non-fatal myocardial infarction (MI), heart failure (HF), and renal complications. Nationwide estimates for prevalence of ischemic heart disease in Thai diabetic patients ranged from 3.5% to 8%[6,7]. In a retrospective study in a tertiary center in Bangkok, nearly a third of diabetic patients had CV disease[8]. In a 5-year longitudinal Thai cohort study, up to 10% of deaths in patients with CV disease were attributed to diabetes[9]. Furthermore, among HF trial patients, those of the Asian races were three times more likely to have diabetes than the Caucasian patients, despite younger age and lower obesity rates[10-12]. The impact of diabetes on hospitalizations due to heart failure (hHF) was also more pronounced in Asian patients than their Caucasian counterparts[10]. Amongst HF patients in Thailand, diabetes was the second most common comorbidity reported at 31% of HF patients[13].

T2D is also the most common cause of chronic kidney disease (CKD) and end stage renal disease (ESRD)[14]. It is estimated that approximately one out of every four patients with T2D will develop CKD[15,16]. According to the Annual Thailand Renal Replacement Therapy 2015 report, diabetes was the foremost cause of dialysis and ESRD leading to renal replacement therapy, accounting for nearly 39% of the cases[17]. According to a single center study in Bangkok and a nation-wide multi-center cross-sectional study, around 40% of Thai diabetic patients have nephropathy[8,18]. In a multi-center cross-sectional study of diabetes patients across Thailand, decreased glomerular filtration rate was significantly correlated with higher incidence of cerebrovascular diseases, ischemic stroke, and peripheral neuropathy[19], and was independently associated with increased diabetic retinopathy, severe diabetic retinopathy, and severe visual impairment[20]. Nephropathy resulting in CV complications is a major cause of morbidity and mortality in diabetes patients. In a 4-year prospective observational study of the Thai T2D patients, diabetic nephropathy was strongly associated with all-cause mortality (hazard ratio [HR] 1.75; 95% confidence interval [CI] 1.12 to 2.75)[21].

Effective long-term treatment of diabetes entails not only controlling blood glucose levels, but also addressing the related comorbidities and their risk factors. Addressing CV and renal risk factors have been shown to reduce morbidity and mortality in diabetic patients[22]. Unfortunately, some of the older anti-hyperglycemic medications were found to have poor outcomes with relation to diabetic comorbidities, particularly CV and renal systems[23]. As a result, CV outcome trials (CVOTs) were made mandatory since 2008 for the approval of anti-hyperglycemic medications by the U.S. Food and Drug Administration (FDA)[24]. Amongst the various classes of anti-hyperglycemic medications, sodium glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1 RA) have shown promising effects on CV and renal complications in both clinical trials and real-world studies. Here, the authors presented consensus-based recommendations and a treatment algorithm to help prevent or delay onset of CV and renal complications in T2D patients in Thailand.

Overview of SGLT2i

The SGLT2is are oral anti-hyperglycemic agents that reduce plasma glucose by increasing urinary excretion of glucose. Their glucose-lowering efficacy is dependent on kidney function, and presently are not approved for patients whose estimated glomerular filtration rate (eGFR) is less than 45 mL/minute/1.73m^2[25]. However, the renoprotective effects of SGLT2i have been observed consistently across different levels of kidney function[26,27]. SGLT2is also increase insulin sensitivity and glucose uptake by muscle cells, decrease gluconeogenesis, and improve first-phase insulin release from pancreatic beta cells. The reported mean reduction in HbA1c with SGLT2i is 0.5% to 1%[28,29] and their efficacy is comparable in Asian and non-Asian patients[30]. SGLT2i reduce weight, blood pressure, plasma triglycerides, and increase high density cholesterol[25,29,31]. The reported average reduction in systolic and diastolic blood pressure is in the range of 2 to 4 mmHg and 1 to 2 mmHg, respectively[28,29]. Weight loss of up to 2 kg has been observed.

SGLT2is are generally well tolerated and have a low risk of hypoglycemia. Notable adverse events (AEs) include diabetic ketoacidosis (DKA), volume depletion, and urogenital infections[32]. Some SGLT2is are associated with increased risk for bone fractures[33,34]. DKA is potentially the most life-threatening of the SGLT2i-associated AEs, but the number of cases reported has been low. It may be precipitated by risk factors such as infection, low carbohydrate diet, reduced calorie intake, alcohol consumption, dose reduction/discontinuation of insulin or oral insulin secretagogue therapy[28]. Interruption of SGLT2i therapy may be considered during periods of prolonged fasting due to illness or surgery, low carbohydrate diet, stress, or change in insulin or insulin secretagogue medication[28].

Patient selection and counseling can help avoid DKA. Mycotic genital infections are usually mild to moderate and easily managed by standard therapy[28]. In Asian patients, the risk of urinary infections with SGLT2i was no more than with placebo[30]. It is advisable to check if patients had a history of urogenital infections before initiating SGLT2i therapy.

The first SGLT2i to be introduced in Thailand was dapagliflozin in 2014, followed by other members of the class. The efficacy of SGLT2i in Thai patients was confirmed in a retrospective, real-world, observational study in diabetic patients at a specialized diabetes center[35]. One hundred fifty-one patients that continued with the treatment for at least six months were included in the analysis. After six months, the mean (±SD) HbA1c was reduced from 8.8% (±1.5) to 7.9% (±1.3) and mean weight was reduced from 78.2 kg (±18.0) to 75.9 kg (±17.5). On the average, glycemic control was maintained for up to 18 months, but body weight gradually increased again towards the baseline value. At the last follow-up, at a median of 16 months, the median reduction in HbA1c and weight from baseline were 1% and 1.5 kg, respectively. Frequently reported AEs were polyuria (2.1%), volume depletion related events (1.6%), urinary tract infection (UTI) (2.1%), genital infections (2.6%), and hypoglycemia (7.9%) [35]. UTI and genital infections were more frequent in women than in men, and responded to standard treatment, typically without having to discontinue SGLT2i therapy. No cases of DKA were reported in the present study. SGLT2i exhibited up to 18 months durability as monotherapy or as add-on to other oral anti-hyperglycemic agents or insulin treatment. The findings of the present study were comparable with the results from meta-analysis of dapagliflozin randomized controlled trials (RCTs)[36].

A recent healthcare database analysis on adults treated with SGLT2is as dapagliflozin, empagliflozin, and canagliflozin, in Thailand, indicated that, under real-world conditions, the effect of SGLT2i treatment were similar to those documented in RCTs. On the average, reductions in HbA1c (0.7%), body weight (2.5 kg), and blood pressure with systolic blood pressure (SBP) 3.5 mmHg, diastolic blood pressure (DBP) 2.4 mmHg[37] were within the range observed across RCTs[29]. The estimated incidence of AEs of interest with genital tract infections at 2.8%, UTIs at 2.2%, and major hypoglycemic events at 0.9%, were relatively low, and the observed trends were generally consistent with findings from meta-analysis of RCTs[29,38].

SGLT2is are most commonly introduced as an add-on therapy for uncontrolled on metformin monotherapy. Meta-analysis of the studies on the cost-utility of SGLT2i versus DPP4 inhibitors (DPP4i) and sulfonylureas, which is also commonly used as second-line agents after metformin failure, suggested that SGLT2s may be cost-effective compared with sulfonylureas but not compared with DPP4i[39]. The estimated total incremental net benefit (TINB) for SGLT2i was 3,675.09 USD (95% CI 1656.46 to 5,693.71) versus sulfonylureas, and 164.95 USD (95% CI 534.71 to 864.61) versus DPP4i[39].

The results of a cost-utility analysis focusing on dapagliflozin added to standard treatment in Thai patients with heart failure and reduced ejection fraction (HFrEF) indicated that add-on dapagliflozin had 87% probability of being cost-effective at a willingness-to-pay (WTP) threshold of 160,000 THB/QALY or 5,131 USD/QALY[40]. Considering that this WTP level is similar to the Thai GDP per capita of approximately 160,000 THB, this suggests that add-on dapagliflozin may be a cost-effective strategy in the context of the Thai healthcare system.

In the setting of the COVID-19 pandemic, interest in the organ-protective effects of SGLT2i has motivated the DARE trial [Dapagliflozin in Respiratory Failure in Patients with COVID-19 (DARE-19, NCT04350593)] on the effects of adding dapagliflozin to standard care in COVID-19 patients with cardiometabolic risk factors for COVID-19 complications[41]. Although SGLT2is have been shown to have favorable effects on processes such as inflammation, oxidative stress, and energy metabolism, which are implicated in COVID-19-associated respiratory and multi-organ failure, it remains to be seen whether there is a positive benefit-risk balance of SGLT2i treatment in diabetic patients with COVID-19[42].

Overview of GLP-1 RA

GLP-1 RA are subcutaneously injected medications that stimulate insulin secretion and reduce glucagon secretion in a glucose-dependent manner. Although all GLP-1 RA agents target the same receptor, they are quite distinct in structure and pharmacokinetics, which translates into varying pharmacodynamics and clinical effects. Because of these differences, some GLP-1 RA agents are administered daily, and others are on a weekly schedule[43].

In clinical trials, HbA1c reduction was in the range of 0.7% to 1.9%, and weight reduction in

the range of 1 to 3 kg(43). In a meta-analysis of randomized clinical trials of GLP-1 RA in Asian patients, the overall standardized mean difference (SMD) for HbA1c change from baseline was –0.81% (95% CI –0.99 to –0.62)[44]. SMD for change from baseline in free plasma glucose was –0.51 mmol/L (95% CI –0.70 to –0.33) and for weight loss from baseline was –0.31 kg (95% CI –0.47 to –0.15). In another meta-analysis, in which most patients were Asian, the weighted mean difference in HbA1c from baseline was –1.16% (95% CI to 1.48 to –0.85)[45]. This analysis suggested that GLP-1 RA agents have higher anti-hyperglycemic efficacy in Asian patients than in non-Asian patients, but this observation requires independent confirmation. GLP-1 RA also improved satiety, decreased blood pressure, LDL-C, total cholesterol, and triglycerides[46,47].

Gastrointestinal events such as nausea, vomiting, and diarrhea, are the most common AEs with GLP-1 RA. Nausea is mostly mild-to-moderate, and decreases over time[43]. Gastrointestinal events are less common with agents that are administered weekly compared with those administered daily. The risk of hypoglycemia has been consistently low because of their glucose-dependent mechanism of action. However, hypoglycemia risk may be increased when GLP-1 RAs are used in combination with sulfonylureas or insulin. There may be a rare association between incidence of pancreatitis and GLP-1 RA therapy. However, the data are limited, unclear, and await further confirmation. In Asian patients, gastrointestinal events are the most prominent AE[44]. Compared with other anti-hyperglycemic medications, GLP-1 RA showed slightly lower incidence of hypoglycemia[44].

Meta-analysis of the cost-effectiveness studies on GLP-1 RA indicated that, in high-income countries, GLP-1 RAs were significantly more cost-effective than insulins, but not significantly more cost-effective than DPP4i, sulfonylureas, or thiazolidines[48].

A recent cost-benefit analysis of liraglutide and sitagliptin in Thai T2D patients concluded that the clinical benefits of liraglutide relative to sitagliptin in controlling T2D where HbA1c is lower than 7%, without hypoglycemia or weight gain can partly offset its higher cost. When CV benefit, meaning a reduction in major CV events, was considered in the evaluation, liraglutide treatment was associated with cost savings of 20,085 THB per 100 patients per year, relative to sitagliptin[49].

As SGLT2i and GLP-1 RA act through complementary mechanisms, there has been considerable interest in the potential benefits of SGLT2i + GLP-1 RA combination therapy, particularly its early initiation[50]. Combinations of SGLT2i and GLP-1 RA have been investigated in controlled and observational clinical studies, and suggest additive effects on body weight, partially additive effects on HbA1c, as well potentially synergistic effects on BP. However, dedicated studies are needed to determine benefit of such combinations in terms of longer-term CV and/or renal outcomes[50].

CV outcomes of SGLT2i and GLP-1 RA treatment

Three SGLT2i agents, empagliflozin, dapagliflozin and canagliflozin, show evidence of protective effects against MACE and hHF (Table 1). Several GLP-1 RA agents are available, for which reduced risk of MACE, but not hHF, was observed with liraglutide, semaglutide, albiglutide, and dulaglutide (Table 2).

SGLT2i

The first major trial with SGLT2i to demonstrate positive CV outcomes was the Empagliflozin CV Outcome Event Trial in T2D Mellitus Patients (EMPA-REG OUTCOME) trial[51]. The study enrolled T2D patients with existing atherosclerotic CVD (ASCVD). In comparison with placebo, empagliflozin reduced the risk of MACE by 14%. Empagliflozin treatment also significantly reduced death from CV causes, hHF, and from any cause (Table 1). The cardioprotective effect of empagliflozin was maintained even in patients with concomitant ASCVD and renal dysfunction[52].

In this trial, 21.6% of patients were of Asian race. CV outcomes for this sub-group were similar to the overall population[53]. HR for MACE was 0.68 (95% CI 0.48 to 0.95), hHF 0.70 (95% CI 0.37 to 1.33), and death from any causes 0.64 (95% CI 0.40 to 1.01). Thus, empagliflozin improves CV outcomes in Asian patients to a similar extent as in Caucasian races.

The Canagliflozin CV Assessment Study (CANVAS) program, showed improvement in CV outcomes with canagliflozin versus placebo[54]. In the present study, approximately two-thirds of the participants had established ASCVD, while the remainder had multiple CV risk factors (MRF). Canagliflozin significantly reduced MACE (HR 0.86; 95% CI 0.75 to 0.97) compared with placebo, but the difference in CV death was not significant. The risk of hHF was significantly reduced with canagliflozin compared with placebo (Table 1), and benefit was observed both for patients with MRF and those with

Table 1. Key results from SGLT2i cardiovascular and cardiorenal outcomes trials

Name of trial (No. of participants)	Intervention (dose)	Population	Median follow-up (years)	Primary outcome; HR (95% CI)	CV death; HR (95% CI)	hHF; HR (95% CI)	Renal outcome; HR (95% CI)	Asian sub-group; n, primary outcome; HR (95% CI)	NNT for primary outcome[d,e,g,i]
EMPA-REG OUTCOME (n=7,020)	Empagliflozin (10 mg or 25 mg/day) vs. placebo	T2D patients with ASCVD (100%)	3.1	MACE, 0.86 (0.74 to 0.99)	0.62 (0.49 to 0.77)	0.65 (0.50 to 0.85)	0.61 (0.53 to 0.70)	1,517, 0.68 (0.48 to 0.95)	153
CANVAS Program (n=10,142)	Canagliflozin (100 mg or 300 mg/day) vs. placebo	T2D patients with ASCVD (65.6%) or CV risk factors[a] (34.4%)	2.4	MACE, 0.86 (0.75 to 0.97)	0.87 (0.72 to 1.06)	0.67 (0.52 to 0.87)	0.60 (0.47 to 0.77)	1,284, 1.08 (0.72 to 1.64)	217
DECLARE (n=17,160)	Dapagliflozin (10 mg/day) vs. placebo	T2D patients with ASCVD (40.6%) or CV risk factors[b] (59.4%)	4.2	MACE, 0.93 (0.84 to 1.03) CV death or hHF, 0.83 (0.73 to 0.95)	0.98 (0.82 to 1.17)	0.73 (0.61 to 0.88)	0.53 (0.43 to 0.66)	2,303, NR	MACE (ns); CV death or hHF 111
VERTIS-CV (n=8,246)	Ertugliflozin (5 mg or 15 mg/day) vs. placebo	T2D patients with ASCVD (100%)	3.5	MACE, 0.97 (0.85 to 1.11)	0.92 (0.77 to 1.11)	0.70 (0.54 to 0.90)	0.81 (0.63 to 1.04)	497, 0.89 (0.51 to 1.56)	MACE (ns)
SCORED (n=10,584)	Sotagliflozin (200 mg with increase to 400 mg/day) vs. placebo	T2D patients with CKD (25 to 60 mL/minute/1.73m^2) and CV risk factors[c]	1.33	Primary composite[d], 0.74 (0.63 to 0.88)	0.90 (0.73 to 1.12)	0.67 (0.55 to 0.82)	0.71 (0.46 to 1.08)	682, NR	54
DAPA-HF (n=4,744)	Dapagliflozin (10 mg/day) vs. placebo	HFrEF patients with T2D (45%) or no T2D (55%)	1.5	Primary composite[d], 0.74 (0.65 to 0.85)	0.82 (0.69 to 0.98)	0.70 (0.59 to 0.83)	0.71 (0.44 to 1.16)	1,116, 0.64 (0.49 to 0.86)	21
EMPEROR-REDUCED (n=3,730)	Empagliflozin (10 mg/day) vs. placebo	HFrEF patients with T2D (50%) or no T2D (50%)	1.33	Primary composite[e], 0.75 (0.65 to 0.86)	0.92 (0.75 to 1.12)	0.69 (0.59 to 0.81)	0.50 (0.32 to 0.77)	672, NR 0.57 (0.41 to 0.78)	19
SOLOIST-WHF (n=1,222)	Sotagliflozin (200 mg with increase to 400 mg/day) vs. placebo	T2D patients recently hospitalized for worsening HF	0.75	Primary composite[d], 0.67 (0.52 to 0.85)	0.84 (0.58 to 1.22)	0.64 (0.49 to 0.83)	NR	15, NR	4
CREDENCE (n=4,401)	Canagliflozin (100 mg/day) vs. placebo	T2D patients with CKD[f] (100%)	2.62	Primary composite[g], 0.70 (0.59 to 0.82)	0.78 (0.61 to 1.00)	0.61 (0.47 to 0.80)	0.66 (0.53 to 0.81)	877, 0.66 (0.46 to 0.95)	22
DAPA-CKD (n=4,304)	Dapagliflozin (10 mg/day) vs. placebo	CKD patients[h] with T2D (67.5%) or no T2D (32.5%)	2.4	Primary composite[i], 0.61 (0.51 to 0.72)	0.81 (0.58 to 1.12)	0.31 (0.10 to 0.94) without ASCVD 0.54 (0.35 to 0.82) with ASCVD	0.56 (0.45 to 0.68)	1,467, NR 0.66 (0.46 to 0.93)	19

T2D=type 2 diabetes; ASCVD=atherosclerotic cardiovascular disease; CV=cardiovascular; HR=hazard ratio; HFrEF=heart failure with reduced ejection fraction; MACE=major cardiovascular events; MI=myocardial infarction; hHF=hospitalization for heart failure; NNT=number needed to treat; NR=not reported; ns=not significant

[a] ≥50 years of age and ≥2 among the following: duration of diabetes ≥10 years; systolic blood pressure >140 mmHg on ≥1 antihypertensive agent; current smoker; micro- or macroalbuminuria; high density lipoprotein cholesterol <1 mmol/L

[b] Men ≥55 years/women ≥60 years and ≥1 amongst the following: hypertension; low density cholesterol >130 mg/dL or use of lipid lowering therapies; use of tobacco

[c] ≥18 years with ≥1 major CV risk factor (hHF during previous 2 years, EF ≤40%, LVH, CAC ≥300, NT-proBNP ≥400 pg/mL, hsTnT >15 pg/mL, hsCRP >3 mg/L, UACR ≥300 mg/g) or ≥55 years with ≥2 minor risk factors (BMI ≥35 kg/m2, LDL >130 mg/dL, HDL <40 or <50 mg/dL (men or women), current smoking, SBP/DBP >140/90 mmHg, CAC >100 to <300, UACR ≥30 to <300 mg/g

[d] Primary composite: CV death or worsening heart failure (Hospitalization or an urgent visit for heart failure)

[e] Primary composite: CV death or hospitalization for heart failure

[f] eGFR between 30 to <90 mL/minute/1.73m2, and albuminuria (UACR between >300 to 5,000)

[g] Primary composite: doubling of serum creatinine level, ESRD, renal or CV death

[h] eGFR between 25 to 75 mL/minute/1.73m2, and albuminuria (UACR between 200 to 5,000)

[i] Primary composite: decline in eGFR ≥50%, end stage kidney disease, renal or CV death

Table 2. Key results from GLP-1 RA cardiovascular outcomes trials

Name of trial (No. of participants)	Intervention	Population	Median follow-up (years)	Primary outcome; HR (95% CI)	CV death; HR (95% CI)	hHF; HR (95% CI)	Renal outcome; HR (95% CI)	Asian sub group; n, MACE; HR (95% CI)
ELIXA (n=6,068)	Lixisenatide (10 µg or 20 µg/day) vs. placebo	T2D patients with acute coronary syndrome (100%)	2.1	MACE, 1.02 (0.89 to 1.17)	0.98 (0.78 to 1.22)	0.96 (0.75 to 1.23)	0.82 (0.67 to 1.00)	NR
LEADER (n=9,340)	Liraglutide (1.8 mg/day) vs. placebo	T2D patients with ASCVD (81.3%) or CV risk factors[a] (18.7%)	3.8	MACE, 0.87 (0.78 to 0.97)	0.78 (0.66 to 0.93)	0.87 (0.73 to 1.05)	0.78 (0.67 to 0.92)	936, 0.87 (0.57 to 1.27)
SUSTAIN-6 (n=3,297)	Semaglutide (0.5 mg or 1 mg/week) vs. placebo	T2D patients with ASCVD or CKD (83%) or CV risk factors[b] (17.0%)	2.1	MACE, 0.74 (0.58 to 0.95)	0.98 (0.65 to 1.48)	1.11 (0.77 to 1.61)	0.64 (0.46 to 0.88)	NR
EXSCEL (n=14,782)	Exenatide (2 mg/week) vs. placebo	T2D patients with (73.1%) or without (26.9%) ASCVD	3.2	MACE, 0.91 (0.83 to 1.00)	0.86 (0.77 to 0.97)	0.94 (0.78 to 1.13)	0.85 (0.73 to 0.98)	1,452, 0.81 (0.57 to 1.14)
REWIND (n=9,901)	Dulaglutide (1.5 mg/week) vs. placebo	T2D patients with ASCVD (31.5%) or CV risk factors[c] (69.5%)	5.4	MACE, 0.88 (0.79 to 0.99)	0.91 (0.78 to 1.06)	0.93 (0.77 to 1.12)	0.85 (0.77 to 0.93)	NR
HARMONY (n=9,643)	Albiglutide (30 mg or 50 mg/week) vs. placebo	T2D patients with ASCVD (100%)	1.6	MACE, 0.78 (0.68 to 0.90)	0.93 (0.73 to 1.19)	0.85 (0.70 to 1.04)[d]	NR	470, NR
PIONEER 6 (n=3,183)	Semaglutide (14 mg/day) vs. placebo	T2D patients with ASCVD or CKD (84.7%) or CV risk factors[b] (15.3%)	1.3	MACE, 0.79 (0.57 to 1.11)	0.49 (0.27 to 0.92)	0.86 (0.48 to 1.55)	NR	NR

T2D=type 2 diabetes; ASCVD=atherosclerotic cardiovascular disease; CVOT=cardiovascular outcomes trial; CV=cardiovascular events; hHF=hospitalization for heart failure; HR=hazard ratio; MACE=major cardiovascular events; MI=myocardial infarction; NR=not reported

[a] Men ≥55 years/women ≥60 years and ≥1 amongst the following: hypertension; low density cholesterol >130 mg/dL or use of lipid lowering therapies; use of tobacco

[b] Age ≥60 years and ≥1 amongst the following: persistent microalbuminuria or proteinuria; hypertension and left ventricular hypertrophy; left ventricular systolic or diastolic dysfunction; ankle/brachial index <0.9

[c] Age ≥60 years and ≥2 amongst the following: tobacco use; dyslipidemia; hypertension; abdominal obesity

[d] Composite of CV death and hH

established ASCVD. In the present study, less than 13% of the participants were of Asian origin. Sub-group analyses did not show a decrease in the relative risk of MACE in Asian participants (Table 1), unlike other groups[55]. Additional studies are required to clarify the CV effects of canagliflozin treatment in Asian patients.

CV outcomes with dapagliflozin were studied in the Dapagliflozin Effect on CV Events - Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial[32]. The risk of poor CV and renal outcomes was lower in the present study than the previous trials, because fewer participants (40%) had established ASCVD, while the remainder had MRF. Patients were also followed up for a longer duration than in the previous trials. The risk of MACE with dapagliflozin was non-inferior to placebo but was lower for hHF (HR 0.73; 95% CI 0.61 to 0.88) (Table 1). Protection from HF was observed in patients with established ASCVD, or with MRF.

A meta-analysis of pooled data from five CVOTs (EMPA-REG, CANVAS, DECLARE-TIMI 58, CREDENCE, VERTIS-CV)[27,32,51,55,56] indicated that, as a class, SGLT2is have a moderate positive effect on MACE (HR 0.90; 95%CI 0.85, 0.95)[57]. Although most MACE outcomes occurred in the subset of patients with ASCVD, the presence or absence of ASCVD was not found to modify the effect on MACE (HR 0.89; 95% CI, 0.84, 0.95 and HR 0.94; 95% CI, 0.83, 1.07; P=0.63 for interaction). Consistent across the trials, reduction in hHF was large and significant (HR 0.68; 95% CI 0.61, 0.76), regardless of the presence or absence of ASCVD[57]. Meta-analyses of the pooled Asian cohort from three trials showed benefit in composite of CV death or hHF (HR 0.75; 95% CI 0.60, 0.93), but none in MACE (HR 0.84; 95% CI 0.67, 1.05)[58].

Consistent with clinical trial findings, results from the two real-world studies that included more than 800,000 patients indicated that use of SGLT2i was clearly associated with lower risk of death (HR range 0.49 to 0.51) and hHF (HR range 0.61 to 0.64), compared with other glucose-lowering drugs[59,60]. In one of the studies, the outcome was independent of ASCVD status at baseline[60]. Analysis of data from a Swedish healthcare registry showed that dapagliflozin

lowered the risk of hHF or CV death by 21% (HR 0.79; 95% CI 0.69, 0.92) compared with other glucose-lowering drugs, but the risk of MACE was not affected[61]. Being real-world observations, these studies add value to the data obtained from the RCTs, which have the limitation of highly controlled settings and study populations.

GLP-1 RA

The CV outcomes of liraglutide were tested in the Liraglutide Effect and Action in Diabetes: Evaluation of CV Outcome Results (LEADER) trial[62]. Patients with MRF or established ASCVD were enrolled. Liraglutide significantly reduced the relative risk of MACE (HR 0.87; 95% CI 0.78, 0.97) and CV death compared with placebo. There was a non-significant decrease in hHF with liraglutide compared with placebo (Table 2).

CV safety has been demonstrated for oral and subcutaneous formulations of semaglutide. In Semaglutide in Subjects with T2D (SUSTAIN-6), risk of MACE was significantly lower with subcutaneous semaglutide compared with placebo (Table 2)[63]. Amongst the participants, 83% had established ASCVD or CKD or both. In the Peptide Innovation for Early Diabetes Treatment (PIONEER) 6 trial, the CV risk profile of oral semaglutide was non-inferior to placebo[64]. The outcomes were independent of the presence of ASCVD, CKD, or MRF.

The HARMONY trial or Effect of Albiglutide, when added to standard blood glucose-lowering therapies, recruited participants with T2D and ASCVD[65]. The relative risk of MACE was significantly lower with albiglutide than with placebo (HR 0.78; 95% CI 0.68 to 0.90), although the decline in death from CV causes was very robust (Table 2). A composite secondary endpoint composed of CV death or hHF was less with albiglutide, but non-significant.

In the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA)[66] and Exenatide Study of CV Event Lowering (EXSCEL)[67] trials, lixisenatide and exenatide did not display any additional cardioprotective effect, although they were non-inferior to placebo (Table 2). Researching CV Events with a weekly Incretin in Diabetes (REWIND) trial had a long follow-up period of 5.4 years[68]. Among the participants, 69% did not have ASCVD at baseline. The relative risk of MACE was lower with dulaglutide than with placebo (HR 0.88; 95% CI 0.79 to 0.99), but there was no effect on hHF (Table 2). The risk of MACE was independent of established ASCVD or MRF.

In a meta-analysis of GLP-1 RA trials (LEADER, SUSTAIN-6, HARMONY, EXSCEL, ELIXA) data from 42,920 patients were pooled[69]. GLP-1 RA reduced the relative risk of MACE by 12% but the effect was restricted to patients with established ASCVD and not seen in MRF patients. Unlike SGLT2i, there was no reduction in relative risk of hHF with GLP-1 RA.

In the LEADER, SUSTAIN-6, and EXSCEL trials, 6% to 12% of participants enrolled were of Asian race. A meta-analysis of data pooled together for this subpopulation exhibited statistically greater efficacy in MACE outcomes (HR 0.35; 95% CI 0.09 to 1.32) compared to Caucasian (HR 0.92; 95% CI 0.84 to 1.01)[70]. It was not entirely clear why the CV benefit of GLP-1 RA appeared greater in Asian patients. The findings warrant further exploration in studies focusing on Asian populations.

In summary, data from placebo-controlled CVOTs have clearly established that SGLT2i modestly reduced the relative risk of MACE in patients with established ASCVD, and substantially reduced the risk of hHF. In MRF patients, clear benefit is seen for hHF but not for MACE. Some variation in MACE reduction has been observed across SGLT2i class members, but the underlying reasons are unclear. Amongst the CVOTs for SGLT2i, the EMPA-REG OUTCOME trial enrolled patients with the highest morbidity and mortality risk in terms of ASCVD and baseline renal function (Figure 1A), yet, the observed cardioprotective effects of SGLT2i were the most pronounced in the present study (Table 1). For MACE, the estimated number needed to treat (NNT) in the EMPA-REG OUTCOME trial (empagliflozin) was lower than the NNT calculated for canagliflozin treatment in the CANVAS program, or dapagliflozin treatment in the DECLARE trial (Table 1). In the VERTIS CV study, which also enrolled T2D patients with baseline ASCVD, MACE, reduction with ertugliflozin was modest and non-inferior versus placebo. However, as with other SGLT2i, significant hHF reduction was seen regardless of baseline ASCVD status[56].

Likewise, the GLP-1 RA CVOTs enrolled a high proportion of patients with established ASCVD (Figure 1B). GLP-1 RA reduced the relative risk of MACE compared with placebo in patients with established ASCVD, but not in MRF patients. However, not all GLP-1 RA significantly improved MACE, liraglutide, semaglutide, albiglutide, and dulaglutide were superior to placebo, whereas

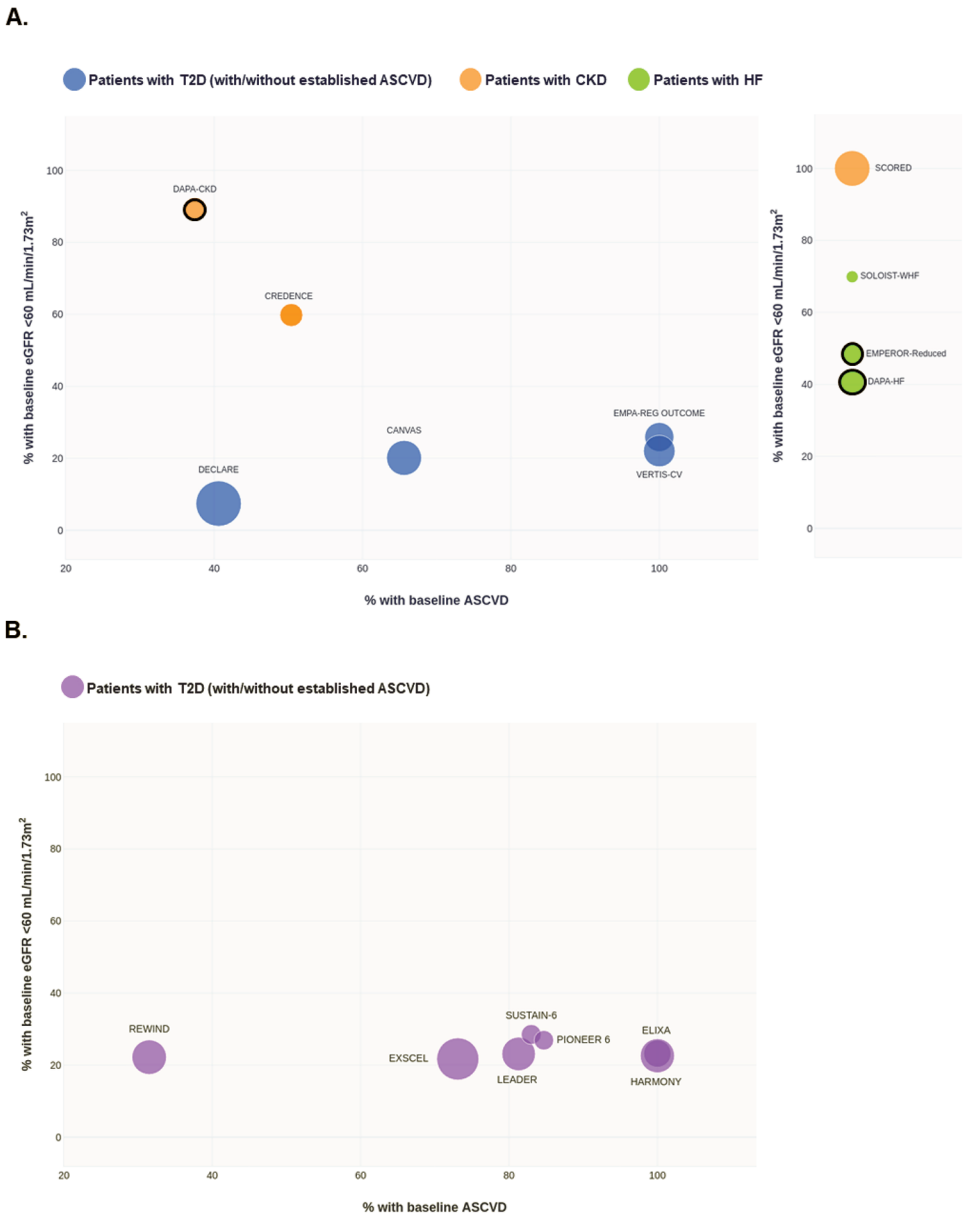

Figure 1. Baseline cardiovascular and renal risk profile in SGLT2i and GLP-1 RA cardiovascular or cardiorenal outcomes trial populations.

X axis: Cardiovascular risk (% with baseline ASCVD); Y axis: renal function (% with eGFR <60 mL/minute/1.73m2). Each bubble in the plot represents one trial, the bubble with thick band represents trials that included both T2D and non T2D patients, and the size of bubble represents the number of patients enrolled.

A. SGLT2i cardiovascular/cardiorenal outcomes trials. Blue bubbles: trials that enrolled T2D patients with or without established ASCVD. Orange bubbles: trials that enrolled CKD patients. Green bubbles: trials that enrolled HF patients. Trials that did not report the percentage of patients with baseline ASCVD are shown to the right of the main plot.

B. GLP-1 RA cardiovascular outcomes trials. All trials enrolled T2D patients with or without established ASCVD.

ASCVD, atherosclerotic cardiovascular disease; T2D, type 2 diabetes; eGFR, estimated glomerular filtration rate, SGLT2i, sodium-glucose cotransporter 2 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist

lixisenatide and exenatide were non-inferior to placebo[62,63,65-67]. Reduction in relative risk of hHF was not seen with any of the GLP-1 RA members. The data for GLP-1 RA in Asian patients are limited because of the small number of Asian patients included in these trials.

Renal outcomes of SGLT2i and GLP-1 RA treatment

Many anti-diabetic medications require dose adjustments in patients with renal impairment. Renal outcomes were analyzed in the CVOTs designed for SGLT2i and GLP-1 RA to test their durability in T2D patients with renal disease (Table 1, 2). However, these analyses have limitations, because in most of these CVOTs, renal evaluations were secondary outcome, and the patient populations were not specifically selected according to kidney function. Three SGLT2i agents, empagliflozin, canagliflozin, and dapagliflozin, improved renal outcomes in diabetic patients compared with placebo. All GLP-1 RA agents including liraglutide, semaglutide, dulaglutide, albiglutide, lixisenatide, and exenatide, exhibited varying degrees of renoprotective effects in diabetic patients. The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial was the first to specifically enroll T2D patients with albuminuria CKD to examine renal outcomes with canagliflozin[27]. Subsequently, the DAPA-CKD trial was the first to examine cardiorenal outcomes in CKD patients with or without T2D[71].

SGLT2i

In the EMPA-REG OUTCOME trial[72], 17.8% of patients had eGFR between 45 to 59 mL/minute/1.73m², and 7.7% of patients had eGFR of 30 to 44 mL/minute/1.73m². Microalbuminuria was recorded in 28.7% of patients, and macroalbuminuria in 11% of patients. The progression of kidney disease was slower with empagliflozin than with placebo and the HR for incident or worsening nephropathy was 0.61 (95% CI 0.53 to 0.70)[72]. Empagliflozin decreased the relative risk of doubling of serum creatinine or renal replacement therapy by 44% and 55%, respectively. Similar to the overall population, the Asian sub-population had a HR of 0.64 (95% CI 0.49 to 0.83) for incident or worsening of nephropathy with empagliflozin compared with placebo[73]. The relative risk of doubling of serum creatinine, initiation of renal replacement therapy, or renal death was also lesser with empagliflozin (HR 0.48; 95% CI 0.25 to 0.92).

Canagliflozin had positive renal outcomes with respect to progression of albuminuria (HR 0.73; 95% CI 0.67 to 0.79), and a composite of sustained 40% reduction in eGFR, which is for renal replacement therapy or death from renal causes (Table 1)[55]. A sub-analysis of CANVAS program data in which patients were grouped according to baseline eGFR levels did not impact the protective effect of canagliflozin on CV and renal systems[74]. In fact, favorable outcomes were observed in patients with eGFR as low as 30 mL/minute/1.73m².

Dapagliflozin reduced the relative risk of ESRD or renal death (HR 0.41; 95% CI 0.20 to 0.82) and sustained decline in eGFR (Table 1) compared with placebo[75]. Renal outcomes were independent of established ASCVD, CV risk factors, or baseline eGFR.

The CREDENCE trial enrolled patients with T2D and CKD[27]. At baseline, mean baseline eGFR was 56.2±18.2 mL/minute/1.73m², and median urinary albumin-to-creatinine ratio (UACR) 927 with an interquartile range of 463 to 1,833. The primary outcome was a composite of ESRD, doubling of serum creatinine level, or death from renal or CV causes, which was decreased by 30% with canagliflozin compared with placebo (Table 1). The relative risk of the renal-specific outcome as ESRD, doubling of serum creatinine, or death from renal causes, was 34% lower with canagliflozin than with placebo (Table 1).

In a meta-analysis of the EMPA-REG OUTCOME, CANVAS, DECLARE, CREDENCE and VERTIS CV trials[57], SGLT2i treatment was associated with significant reduction in the hazard for progression of kidney disease as the HR for kidney composite outcomes for SGLT2i versus placebo was 0.62 (95% CI 0.56 to 0.70), although there was moderate heterogeneity across the trials. The improvements seen were equally robust regardless of the presence of established ASCVD, or history of HF[57]. Another meta-analysis of 40 RCTs comprising 29,954 patients compared renal outcomes with SGLT2i versus placebo[76]. The renoprotective effect of SGLT2i was consistently demonstrated via decrease in albuminuria, and slower progression to macroalbuminuria. Furthermore, the risk of worsening of renal impairment, initiation of kidney transplant, and death from renal disease were lower with SGLT2i. These effects were observed irrespective of presence or absence of baseline renal impairment. Another review of 10 published studies also concluded that the renoprotective effect of SGLT2i is independent of baseline renal function[77].

CVD-REAL 3 was a multinational observational cohort study of renal outcomes in more than 65,000 patients initiating SGLT2i and other glucose-lowering drugs. Dapagliflozin and empagliflozin were the most frequently initiated SGLT2i with 57.9% and 34.1% of initiation episodes, respectively. With a mean

follow-up time of 14.9 months, this analysis showed that initiation of SGLT2i therapy was associated with a reduced rate of eGFR decline and lower risk of major kidney events as composite outcome of 50% eGFR decline or ESRD, than initiation of other glucose-lowering drugs[78]. These findings indicated that the benefits of SGLT2i therapy on renal outcomes in clinical trials may be generalizable to real-world clinical practice.

GLP-1 RA

A composite of new-onset persistent macroalbuminuria, persistent doubling of serum creatinine level, ESRD, or death due to renal disease occurred in fewer patients treated with liraglutide compared with placebo (Table 2)[79]. Likewise, the rate of new or worsening nephropathy were lower with semaglutide compared with placebo (Table 2)[63]. Relative risk of renal outcome such as new macroalbuminuria, sustained decline in eGFR, or chronic renal replacement therapy, was lower with dulaglutide than with placebo (HR 0.85; 95% CI 0.77 to 0.93)[80]. This effect was more prominent for new macroalbuminuria (HR 0.77; 95% CI 0.68 to 0.87) than for the other two outcomes.

Lixisenatide reduced the progression of UACR in patients who were macroalbuminuric at baseline as compared with placebo adjusted least squares mean in UACR at baseline of –68.53 and at week 108 of –9.84[81]. The risk of new-onset macroalbuminuria was also lower with lixisenatide after adjustment for baseline and on-trial HbA1c (Table 2). Exenatide reduced the composite of renal outcomes with a 40% decline in eGFR, renal replacement, renal death, or new macroalbuminuria, compared with placebo (Table 2)[82].

In the meta-analyses of LEADER, SUSTAIN-6, ELIXA, and EXSCEL trials, a broad composite of renal outcomes as seen with worsening of eGFR, ESRD, new-onset macroalbuminuria, or renal death, was significantly reduced by 18% by GLP-1 RA versus placebo (HR 0.82; 95% CI 0.75 to 0.89)[69]. However, this effect was mainly attributed to reduction in macroalbuminuria, and the renoprotective effect of GLP-1 RA was not significant.

In summary, SGLT2i agents such as empagliflozin, dapagliflozin, and canagliflozin improve renal outcomes by decreasing the relative risk of worsening of eGFR, ESRD, renal death, and macroalbuminuria to different degrees[27,32,34,55,72]. These renoprotective effects appear to be independent of baseline renal function. GLP-1 RA agents such as liraglutide, semaglutide, dulaglutide, lixisenatide, and exenatide, also improve renal outcomes, but their efficacy is attributed largely to reduction in progression of macroalbuminuria[69].

Putting knowledge into practice, expert recommendations for management of T2D with comorbidities

The treatment pathway in Figure 2 summarizes the authors' recommendations for management of T2D in patients with CV or renal comorbidities.

T2D with multiple risk factors

For patients who present with T2D with multiple risk factors for CV diseases, early add-on treatment with SGLT2i should be considered to reduce hHF and renal complications.

T2D patients with MRF are defined as being 50 years or older with more than one of the following, hypertension, elevated LDL-C of more than 130 mg/dL, abdominal obesity, micro- or macroalbuminuria, and use of tobacco. Data from the DECLARE[32,75] and CANVAS[54,74] trials suggest the benefits of SGLT2i in decreasing hHF and renal complications in T2D patients with MRF. Real-world studies[59,60] and meta-analysis[57] of clinical trials also support the same observation. There is no clear indication that SGLT2i reduce MACE in these patients.

T2D with established CV disease

For patients with T2D and established atherosclerotic CV disease, treatment with:

- SGLT2is are recommended to reduce MACE, hHF and worsening of renal outcomes.
- GLP-1 RAs are recommended to reduce MACE and worsening of renal outcomes.

SGLT2is have demonstrated reduction in CV (MACE and HF) and renal outcomes in patients with established ASCVD[27,32,51,54,55,72,75]. Results from meta-analyses[57] and real-world studies[59,60] also support these benefits of SGLT2i.

To date, CV and cardiorenal outcomes with SGLT2i have been studied in a number of partially overlapping patient populations (Table 1) such as T2D patients with or without established ASCVD or multiple risk factors (DECLARE, CANVAS, EMPA-REG OUTCOME, VERTIS CV), as well as HF patients (EMPEROR-Reduced, SOLOIST-WHF, DAPA-HF), and CKD patients (DAPA-CKD, CREDENCE, SCORED) (Figure 1A). Of note, some data on CV and cardiorenal outcomes are available for non-T2D populations as well. The DAPA-CKD

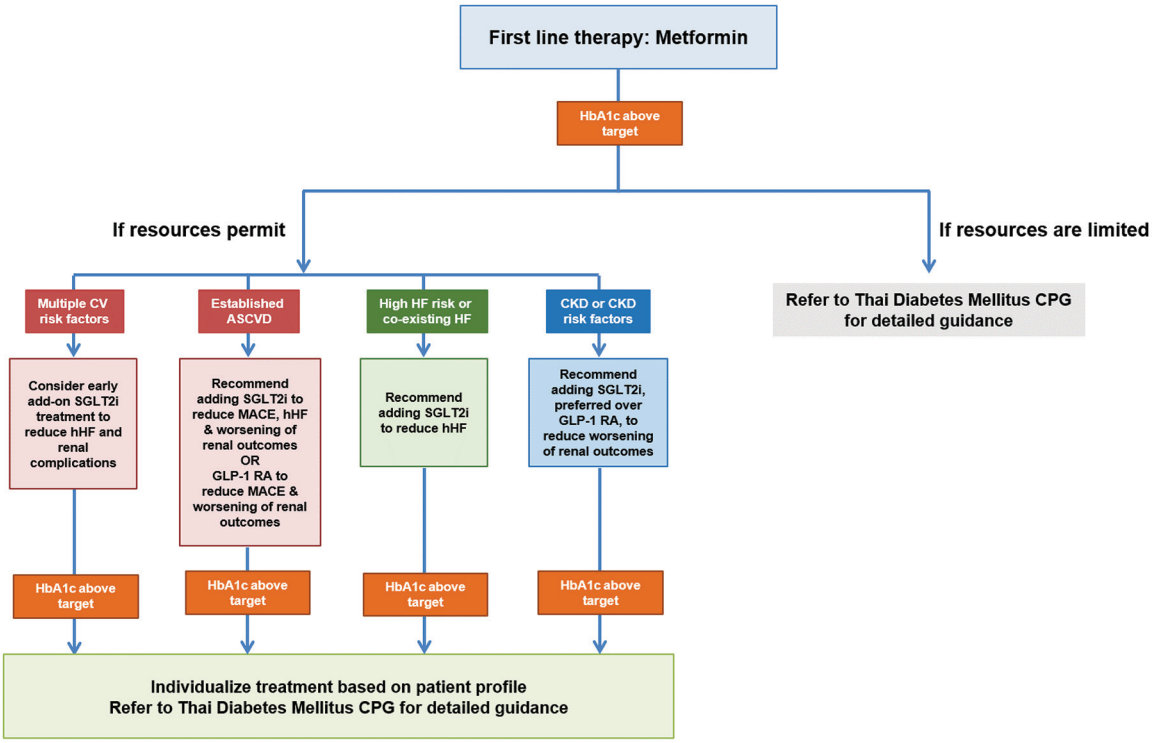

Figure 2. Recommendations for management of T2D in patients with cardiovascular or renal comorbidities.

ASCVD, atherosclerotic cardiovascular disease; CPG, clinical practice guidelines; CKD, chronic kidney disease; hHF, hospitalization for heart failure; SGLT2i, sodium-glucose cotransporter 2 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin A1c; T2D, type 2 diabetes

trial included CKD patients both with and without T2D, and the DAPA-HF and EMPEROR-Reduced trials included HF patients with and without T2D. Differences in patient population profiles may partly explain the variation seen across the trials in terms of positive outcomes, since CV benefit was more prominent among patients with established ASCVD. For example, less pronounced CV benefit was observed in the DECLARE study, which included a lower proportion of T2D patients with ASCVD, than in EMPA-REG OUTCOME that had 100% with baseline ASCVD, and CANVAS that had 65.6% with baseline ASCVD. In the VERTIS CV study, MACE reduction with ertugliflozin in T2D patients with baseline ASCVD was modest and non-inferior to placebo. However, as with other SGLT2i, significant hHF reduction was seen regardless of baseline ASCVD status.

Amongst the GLP-1 RA, liraglutide[62], semaglutide[63], dulaglutide[68], and albiglutide[65] reduce the risk of MACE in patients with established ASCVD. GLP-1 RA also improve renal outcomes, although the benefits are mostly restricted to reduction in the progression of macroalbuminuria[69].

T2D with heart failure

For T2D patients at high risk of HF, SGLT2i are recommended to reduce hHF[32,51,52,54,56,83].

For T2D patients with HF, SGLT2i are recommended to reduce CV death or hHF[84-86]. In HF patients without T2D, SGLT2i also reduce CV death or hHF.

The majority of the T2D patients enrolled in SGLT2i outcome trials (DECLARE, EMPA-REG OUTCOME, CREDENCE, CANVAS) did not have HF at baseline, but were at high risk due to presence of risk factors such as hypertension, ASCVD, diabetes, obesity, metabolic syndrome (stage A), or left ventricular hypertrophy (stage B)[87]. The combined findings from outcomes trials clearly demonstrate that SGLT2i reduce hHF in the range of 35% to 39% in patients at risk of HF[27,32,51,54]. For patients with established HF, clinical trials have demonstrated the benefits of SGLT2i in reducing hHF[71,84,86].

T2D with CKD

For patients with T2D and CKD, the use of SGLT2i is preferred over GLP-1 RA to reduce worsening of renal outcomes.

CKD is defined as eGFR of less than 60 mL/minute/1.73m², and albuminuria as UACR of more than 30 mg/g[26,27]. Clinical trials and meta-analyses with SGLT2i have consistently shown decrease in renal composite outcomes consisting of macroalbuminuria, slower decline in eGFR, decrease in need for renal replacement therapy, ESRD, or death from renal causes compared with placebo[27,32,34,55,72,74,76]. Of note, the CREDENCE trial, which was specifically designed and powered to examine renal outcomes of canagliflozin treatment in T2D patients with CKD, showed 30% risk reduction in the renal composite outcome. In the DAPA-CKD trial, which enrolled CKD patients with or without T2D, dapagliflozin was associated with a 39% risk reduction in the renal composite outcome for a sustained eGFR decline of 50% or more, ESRD onset, or death from CV or renal causes, compared with placebo[26]. Likewise, GLP-1 RA also exhibit improved renal composite outcomes compared with placebo[63,79,81,82]. Results of a meta-analysis[69] suggest that GLP-1 RA may have a larger effect on macroalbuminuria than on other renal outcomes.

Conclusion

A substantial proportion of T2D patients in Thailand have diabetes-related complications or comorbidities, notably CKD or HF. In addition, diabetes is a common comorbid condition among both CKD and HF patients in Thailand. An estimated 8% to 14% of the Thai population have CKD[88,89], and 28.5% of CKD patients also have T2D[89,90]. Diabetes is the primary cause of ESRD in up to 40% of Thai patients receiving dialysis therapy[17]. Similarly, diabetes is one of the most common comorbidities among HF patients in Thailand with 31% of the patients[13].

Since these conditions often coexist, resulting in increased burden and cost of care, it is preferable to utilize treatments that address multiple aspects of these coexisting diseases, if resources permit. For T2D patients, it is important to manage CV as well as renal comorbidities and risk, in tandem with optimizing anti-hyperglycemic therapy. Regardless of HbA1c levels, selection of anti-hyperglycemic agent(s) should be guided by knowledge of their effects on other hypoglycemia, body weight, and CV or renal parameters. Based on published evidence and patterns of T2D and its complications/comorbidities among patients in Thailand, the authors' key recommendations are as follows:

- For T2D patients with MRF, early add-on of SGLT2i therapy is recommended to reduce hHF and renal complications.
- For T2D patients with established ASCVD
  - SGLT2i are recommended to reduce MACE, hHF, and worsening of renal outcomes
  - GLP-1 RA are recommended to reduce MACE and worsening of renal outcomes
- For T2D patients with HF or at increased HF risk, SGLT2i are recommended to reduce hHF.
- For T2D patients with CKD, use of SGLT2i is preferred over GLP-1 RA to reduce worsening of renal outcomes.

What is already known on this topic?

Clinical evidence in cardiorenal protective effect of SGLT2i and GLP-1 RA is extensive at present. There is major question regarding the optimal application of these new diabetes drugs particularly in Thais. The authors have summarized and consolidated current literature and Thai data on the cardiorenal benefits of SGLT2i and GLP-1 RA in T2D patients to produce clinical recommendations for physicians.

What this study adds?

Physicians should add SGLT2i early in T2D patients with MRF or increased HF risk. This study recommends SGLT2i or GLP-1 RA in T2D patients with established ASCVD and recommends SGLT2i over GLP-1 RA in T2D patients with CKD.

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Authors' contributions

All authors contributed to drafting and revising the manuscript for intellectual content and accuracy. All authors read and approved the final manuscript.

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Conflicts of interest

Krittayaphong R has received honoraria from AstraZeneca and Boehringer Ingelheim. All other authors declare that they have no competing interests.

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