Position Statement of SGLT-2 inhibitors & CKD

CKD CPG Development Group
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1. In individuals with proteinuric diabetic kidney disease and type 2 DM, renoprotection is seen with canagliflozin, dapagliflozin and empagliflozin.
2. In individuals with non-diabetic proteinuric CKD, renoprotection is seen with dapagliflozin and empagliflozin.
3. Cardiovascular protective benefits are seen regardless of the diabetic status and stages of CKD, although data is scarce for patients who are on dialysis and transplant.

SUMMARY

1. Renal outcome trials (CREDENCE, DAPA-CKD and EMPA-KIDNEY)) showed consistent finding that SGLT-2 inhibitors reduce risk of renal progression and reduce proteinuria in CKD patients with/without diabetes, over and above the renoprotection provided by RAAS blockade.

2. Renal protection was seen even in CKD 4 patients with eGFR as low as eGFR 20 ml/min per 1.73 m^2. However, the evidence is lacking for patients with polycystic kidney disease, patients with glomerulonephritis treated with immunosuppression, transplant recipients or patients with ESKD. Future studies are required to evaluate the safety and effectiveness of SGLT2i–in these CKD subpopulations.

3. In CVOT trials (EMPA-REG, CANVAS, DECLARE-TIMI and VERTIS-CV), SGLT-2 inhibitors consistently showed positive impact on kidney outcomes except ertugliflozin.

4. In HF trials (DAPA-HF, EMPEROR-REDUCED, EMPEROR-PRESERVED and SOLOIST-WHF), SGLT-2 inhibitors consistently showed positive impact on kidney outcomes, in addition to improving cardiovascular outcomes. DAPA-HF did not reach statistical significance for secondary kidney outcomes.

5. The CV benefits from studies in atherosclerotic cardiac disease and heart failure were seen irrespective of diabetic status and level of renal impairment.

SGLT-2 inhibitors Renal Outcome Trials

	CREDENCE [1]	DAPA-CKD [2]	EMPA-KIDNEY [3]
Drug	Canagliflozin	Dapagliflozin	Empagliflozin
N	4,401	4304	6609
Median follow-up, year	2.6	2.4	2.0
ACE inhibitor/ARB,(%)	4395 (99)	4224 (98.1)	5613 (84.9)
DM, (%)	100%	67%	48%
Baseline eGFR, ml/min/1.73m^2			
eGFR (ml/min per 1.73 m2) (mean ±SD)	30-90 (56.2±18.2)	25-75 (43.1 ±12.4)	20-90 (37.5 ±14.8)
eGFR categories (%)			
≥45 ml/min per 1.73 m2	3035 (69)	1782 (41.4)	1424 (22)
≥30–44 ml/min per 1.73 m2	1191 (27.1)	1898 (44.1)	2905 (44)
<30 ml/min per 1.73 m2	174 (3.9)	624 (14.5)	2280 (34)
Baseline urine ACR, n(%)			
UACR(mg/g) {Median IQR}	300-5000 mg/g {927 (463–1833)}	200-5000 mg/g 949.3	- {412 (94–1190)}
UACR categories, n(%)			
<300mg/g	-	-	3194(48)
≥300mg/g	-	-	3451(52)
Primary kidney disease (%)			
Diabetic kidney disease	4401 (100)	2510 (58.3)	2057 (31)
Ischemic/hypertensive nephropathy	-	687 (16)	1445 (22)
Glomerular disease	-	695 (16.1)	1669 (25)
IgA nephropathy	-	270 (6.3)	817 (12)
Focal segmental glomerulosclerosis	-	115 (2.7)	195 (3.0)
Membranous nephropathy	-	43 (1.0)	96 (1.0)
Minimal change disease	-	11 (0.3)	14 (<1)
Other glomerular disease	-	256 (5.9)	547 (8.0)
Unknown	-	214 (5)	630 (10)
Other	-	198 (4.6)	808 (12)
Outcomes, HR (95% CI)			
Primary composite outcome *	**0.70 (0.59–0.82)**	**0.61 (0.51–0.72)**	**0.72 (0.64-0.82)**
Doubling of serum creatinine level/ Sustained ≥50% decline in eGFR / Sustained ≥40% decline in eGFR	0.60 (0.48–0.76)	0.53 (0.42–0.67)	0.70 (0.61-0.81)
End-stage kidney disease	0.68 (0.54–0.86)	0.64 (0.50–0.82)	0.69 (0.56-0.85)
Renal death	NA	NA	0.90 (0.22-3.66)
Cardiovascular death	0.78 (0.61–1.00)	0.81 (0.58–1.12)	0.84 (0.60-1.19)

** Footnote - Primary composite outcomes definitions:*

(a) CREDENCE: Sustained doubling of creatinine, sustained eGFR <15, ESKD, or death from renal or CV causes.

(b) DAPA-CKD: Sustained ≥50% decline in eGFR, sustained eGFR <15, ESKD, or death from renal or CV causes.

(c) EMPA-KIDNEY: Sustained ≥40% decline in eGFR, sustained eGFR <10, ESKD, or death from renal or CV causes.

Highlights:

1. All the 3 SGLT-2 inhibitors Renal Outcome Trials, i.e. CREDENCE, DAPA-CKD and EMPA-KIDNEY, have showed consistent positive results on primary composite outcome in patient with diabetic kidney disease.

2. Up to 33% of patients in DAPA-CKD and 54% in EMPA-KIDNEY were non-diabetic kidney disease. The effects on kidney outcomes were consistent between DKD and non-DKD.

3. DAPA-CKD and EMPA-KIDNEY studied the effect of SGLT2 in patients with lower eGFR. In DAPA-CKD, about 14% of patients had baseline eGFR 25 to 30 ml/min per 1.73m^2 whereas about 35% in EMPA-KIDNEY had eGFR <30 ml/min per 1.73m^2. The beneficial effects of SGLT-2 inhibitors in those with stage 4 CKD were consistent with results from the overall trial.

4. Although evidence for kidney-related end points remains limited for patients with eGFR <20 ml/min per 1.73 m^2, it should be emphasized that SGLT2 inhibitors may be continued until patients are on dialysis.

5. DAPA-CKD and EMPA-KIDNEY included 270 and 817 participants with IgA nephropathy respectively. In DAPA-CKD prespecified analysis of IgA nephropathy participants, the primary composite kidney outcome was lower for patients with dapagliflozin (HR 0.29, 95% CI 0.12–0.73) with a mean annual rate of eGFR decline of 3.5ml/min/1.73 m^2 with dapagliflozin and 4.7ml/min/ 1.73 m^2 with placebo. Dapagliflozin also resulted in a 26% reduction in albuminuria in comparison to placebo.

6. In non-diabetic patients, SGLT2 inhibitors were well tolerated with no cases of major hypoglycemia or diabetic ketoacidosis.

SGLT-2 inhibitors Cardiovascular Outcome Trials (CVOTs)

	EMPA-REG [4] (2015)	CANVAS [5] (2017)	DECLARE-TIMI [6] (2019)	VERTIS-CV [7] (2020)
Drug	Empagliflozin	Canagliflozin	Dapagliflozin	Ertugliflozin
N	7,020	10,142	17,160	8,238
Median follow-up, year	3.1	2.4	4.2	3.5
Duration of DM, year mean±SD or median(IQR)	57% had T2D >10 years	13.5±7.8	11 (6–16)	12.9±8.3
ACE inhibitor/ARB, %	81	80	81	81
Baseline established CVD, n (%)	6964 (99)	7324 (72)	6974 (41)	8236 (99)
Baseline eGFR, ml/min/1.73m^2				
eGFR(lower limit)	≥30	≥30	≥60	≥30
Baseline eGFR	74	76	85	76
Baseline eGFR, <60 mL/min/1.73 m^2, %	26	25	7.4	22
Baseline urine ACR, n(%)				
<30mg/g	4,239 (60)	7,116 (69)	11,962 (69)	5,677 (69)
30-300mg/g	2,012 (29)	2266 (23)	4029 (24)	2486 (30)
>300mg/g	769 (11)	760 (8)	1169 (7)	75 (0.1)
Outcomes, HR (95% CI)				
Composite CV outcomes *1	**0.86 (0.74–0.99)**	**0.86 (0.75–0.97)**	0.93 (0.84–1.03)	0.97 (0.85-1.11)
Composite Kidney outcomes	**0.54 (0.40–0.75)**	**0.60 (0.47–0.77)**	**0.53 (0.43–0.66)**	0.81 (0.63-1.04)

* 1 - Cardiovascular death, nonfatal MI, or nonfatal stroke

** Footnote - Composite kidney outcomes definitions:*

(a) EMPA-REG: Doubling of serum creatinine, initiation of kidney replacement therapy, or death caused by kidney disease.

(b) CANVAS: 40% decrease in eGFR, death resulting from kidney disease, or kidney replacement therapy requirement.

(c) DECLARE-TIMI: 40% decrease in eGFR, ESKD, or death caused by kidney disease.

(d) VERTIDS-CV: Doubling of serum creatinine, dialysis/transplant or kidney death.

Highlights:

1. All 4 SGLT-2 inhibitors CVOTs included composite renal outcomes as pre-specified secondary outcome. The definitions of the composite renal outcomes have minor differences among the trials.

2. Approximately 80% of subjects in these CVOTs were on RAS blockers at baseline.

3. Generally, less than 25% of study subjects had significant CKD, as defined by eGFR<60ml/min/1.73m^2. Of note, only 7.4% of subjects in DECLARE-TIMI had eGFR<60ml/min/1.73m^2. Up to 60 to 69% of study subjects had albuminuria <30mg/g at baseline.

4. In these CVOTs, SGLT-2 inhibitors consistently showed positive impact on kidney outcomes except ertugliflozin where the hazard ratio (0.81) was not statistically significant.

SGLT-2 inhibitors Heart Failure (HF) trials

	DAPA-HF [8] (2019)	EMPEROR-REDUCED [9] (2020)	EMPEROR-PRESERVED [10] (2021)	SOLOIST-WHF [11] (2021)
Drug	Dapagliflozin	Empagliflozin	Empagliflozin	Sotaglifozin
N	4744	3730	5988	1222
Median follow-up, months	18	16	26	9
DM, %	42	50	49	100
ACE inhibitor/ARB, %	84	71	81	82
MRA, %	71	70	37	64
ARNI, %	11	19	2	17
Baseline ejection fraction, %	31	27	54	35
Baseline eGFR, ml/min/1.73m^2				
eGFR(lower limit)	≥30	≥20	≥20	≥30
Baseline eGFR, mL/min/1.73 m^2	66	62	61	50
Baseline eGFR, <60 mL/min/1.73 m^2, %	41%	48%	50%	NA
Outcomes, HR (95% CI)				
Composite CV outcomes [*1]	**0.74 (0.65–0.85)**	**0.75 (0.65-0.86)**	**0.79 (0.69–0.90)**	**0.67 (0.52 to 0.85)**
Composite Kidney outcomes	0.71 (0.44–1.16)	**0.52 (0.29-0.92)**	**1.36 (1.06–1.66)** [*2]	−0.16 (−1.30 to 0.98) [*3]

*1 - composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or death from cardiovascular causes.

*2 – eGFR slope change per year (mL/min/1.73 m^2) : −1.25 ± 0.11 in Empagliflozin vs −2.62 ± 0.11 in Placebo

*3 – Difference in mean change in eGFR

** Footnote - Composite kidney outcomes definitions:*

(a) DAPA-HF: Sustained decline in the eGFR of ≥50%, ESKD, dialysis, or kidney transplantation

(b) EMPEROR-REDUCED: Time to first occurrence of any of the components of 50% or higher sustained decline in eGFR, ESKD, or renal death.

(c) EMPEROR-PRESERVED: eGFR (CKD-EPI) mean slope change per year.

(d) SOLOIST-WHF: Mean change in estimated GFR.

Highlights:

1. SGLT-2 inhibitor HF trials recruited patients with or without DM, in which patients with DM constituted 42 to 50% of study population. SOLOIST-WHF recruited 100% diabetic patients but was under-powered because of early termination due to loss of funding from the sponsor.

2. Generally, SGLT-2 inhibitor HF trials recruited more CKD (eGFR<60 mL/min/1.73 m^2) patients, approximately 41 to 50% of study population, as compared to SGLT-2 inhibitors CVOTs.

3. In these HF trials, SGLT-2 inhibitors consistently showed positive impact on kidney outcomes, in addition to improving cardiovascular outcomes. Of note, DAPA-HF did not reach statistical significance for secondary kidney outcomes.

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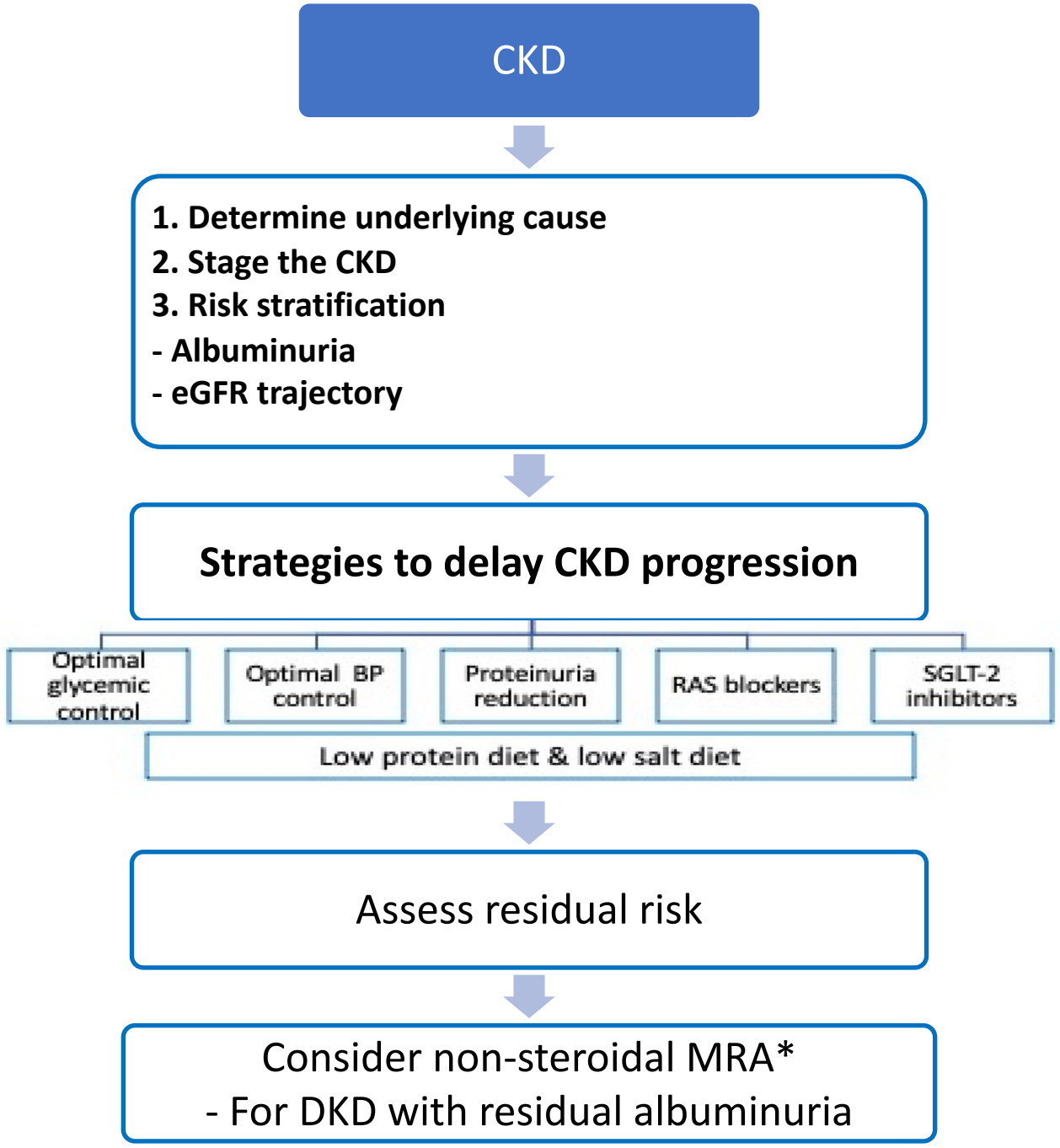
Comparison among SGLT-2 inhibitors (available in Malaysia)

	Canagliflozin	Empagliflozin	Dapagliflozin	Ertugliflozin	Luseogliflozin
Absorption(hrs)	1-2	1.5	2	1	2.25
Bioavailability	65%	78%	78%	100%	78%
Protein bound	99%	86%	91%	93.6%	96%
Elimination	52% (faeces) 33% (urine)	41% (faeces) 54% (urine)	21% (faeces) 75% (urine)	41% (faeces) 50% (urine)	56% (faeces) 44% (urine)
T ½ (hrs)	10.6(100mg) 13.1(300mg)	12.4	12.9	11.2	17
SGLT-2:SGLT-1 specificity	200 times	2500 times	1200 times	2235 times	1770 times
eGFR (for initiation based on PI*)	≥60	≥30 (for T2DM) ≥20 (for HF)	≥25	≥30	≥60
Renal Outcome Trial	CREDENCE (2019)	EMPA-KIDNEY (2022)	DAPA-KIDNEY (2020)	NA	NA
Indications as per PI* (Malaysia), as of 31st Dec 2022	1. T2DM 2. Diabetic kidney disease	1. T2DM 2. Heart failure	1. T2DM 2. Heart failure 3. CKD	T2DM	T2DM

* PI = Prescription Information

Updated on 08/01/2023



** Mineralocorticoids Receptor Antagonist*