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Finerenone in SGLT-2 Inhibitors Era: Current Positioning in Diabetic Kidney Disease

Renin-angiotensin system blockers (RASB) were the only approved pharmacological agents for the treatment of chronic kidney disease (CKD) in people with type 2 diabetes (T2D) until recently, beside optimal control of blood glucose and blood pressure. Amongst the RASBs, angiotensin II receptor blockers (ARBs) were the first class of pharmacological agents to reduce the progression of diabetic kidney disease (DKD) in two pivotal randomized controlled trials (RCTs), IDNT (Irbesartan) and RENAAL (Losartan) in 2001 [1, 2]. After a wait of nearly two decades, sodium-glucose co-transport-2 inhibitors (SGLT2i), a newer class of antidiabetic agents, become the second pharmacological agents to show a significant reduction in CKD progression through three landmark trials: CREDENCE (Canagliflozin) in 2019, DAPA-CKD (Dapagliflozin) in 2020, and EMPA-KIDNEY (Empagliflozin) in 2022 [3–5]. Additionally, in these dedicated renal endpoint trials, both canagliflozin and dapagliflozin significantly reduced the prespecified secondary cardiovascular (CV) composite of CV death and heart failure hospitalization (HHF), while canagliflozin also reduced the prespecified composite of three-point major adverse cardiovascular events [3P-MACE, including non-fatal myocardial infarction (MI), non-fatal stroke, and CV death] [3, 4]. Furthermore, dapagliflozin also reduced all-cause mortality in DAPA-CKD [4]. Full results for EMPA-KIDNEY are awaited but the top-line results showed positive renal outcomes [5]. Indeed, both canagliflozin and dapagliflozin have already been approved for the treatment of CKD with T2D and additionally, dapagliflozin has also been approved for the treatment of CKD without T2D.

Finerenone (BAY 94-8862) is a novel, selective, non-steroidal mineralocorticoid receptor antagonist (MRA) found to reduce the progression of CKD in people with T2D in large phase 3 trials FIDELIO-DKD (NCT02540993) [6]. Additionally, finerenone also reduced secondary CV composite of four-point MACE including non-fatal MI, non-fatal stroke, CV death, or HHF. Subsequent phase 3 FIGARO-DKD (NCT02545049) study and the pooled FIDELITY analysis of both FIDELIO-DKD and FIGARO-DKD suggested that finerenone reduces the progression of CKD and CV composite in T2D [7, 8]. Indeed, finerenone is the first MRA that has been approved for the treatment of DKD. Although previous steroidal MRA such as spironolactone and eplerenone was associated with a significant reduction in albuminuria in DKD, none of these agents are currently recommended in patients with CKD owing to an increased risk of hyperkalemia, acute kidney injury, and the anticipated reduction in estimated glomerular filtration rate (eGFR) [9]. However, in head-to-head phase 2 studies, finerenone was associated with a significantly lower risk of renal impairment (6.0% vs. 28.6%; $p < 0.0001$) and renal failure (1.5% vs. 7.9%; $p = 0.04$) compared to spironolactone (ARTS, NCT01345656) and a significant 44% less relative risk of cardiovascular death (HR 0.56; 95% CI, 0.34–0.93; $p = 0.02$) compared to eplerenone (ARTS-HF, NCT01807221), despite a similar beneficial effect in reducing N-terminal brain-natriuretic peptide (NT-proBNP) in patients with heart failure with reduced

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ejection fraction (HFrEF) and mild to moderate CKD, with or without T2D [10, 11]. Additionally, finerenone was associated with a lesser risk of hyperkalemia compared with spironolactone (ARTS) or eplerenone (ARTS-HF). Finerenone has been recently approved by the United State Food Drug Administration (FDA) and the European Medicine Agency (EMA) for the treatment of DKD.

Nevertheless, the larger question which is not fully addressed includes:

a) Which agent between SGLT2i and finerenone should be used first in patients with CKD and T2D receiving RASB?
b) How comparable is the renal and CV benefit of finerenone compared to SGLT2i in people with T2D with CKD (in absence of any available head-to-head trial)?
c) What could be the rationale for combining both drugs?
d) Is there any evidence that suggests combination therapy could be additive in renal or CV protection? and,
e) How to position finerenone in patients with CKD with T2D receiving SGLT2i and RASB?

While both FDA and EMA approved finerenone in CKD with T2D on a stable dose of RASB, two international bodies such as Kidney Disease Improving Global Outcomes (KDIGO) 2022 (proposed draft) and the American Diabetes Association and European Association of Studies in Diabetes (ADA-EASD) 2022 updated section 11 (May 31, 2022) recommend SGLT2i as the first-line drug ahead of finerenone for the treatment of CKD in T2D who are on a stable dose of RASB [12, 13]. ADA-EASD also recommends glucagon-like peptide-1 receptor agonists (GLP-1RA) in patients with DKD, if SGLT2i are contraindicated or not tolerated or as an add-on agent after SGLT2i if further HbA1c lowering is required. Similarly, the American Association of Clinical Endocrinology (AACE) updated 2022 clinical practice guideline [14] also suggests using SGLT2i, GLP-1RA, and finerenone in DKD. While KDIGO 2022 issues a strong recommendation for SGLT2i as the first-line drug and recommends adding finerenone when there is persistent albuminuria despite SGLT2i use, both ADA-EASD 2022 and AACE 2022 recommend finerenone for those who are unable to use SGLT2i or where SGLT2i is contraindicated. The reason for choosing SGLT2i ahead of finerenone could be related to:

i) A consistent benefit in all three SGLT2i renal outcome trials (CREDENCE, DAPA-CKD, and EMPA-KIDNEY). Co-incidentally all three SGLT2i renal outcome trials were stopped prematurely by the ethical committee due to excess benefits against placebo. No such premature stoppage was seen for finerenone trials (FIDELIO-DKD and FIGARO-DKD),
ii) Unlike FIDELIO-DKD, composite renal benefits in FIGARO-DKD were insignificant (HR 0.87; 95% CI, 0.76–1.01) [7],
iii) The effect of canagliflozin on kidney failure — perhaps the most important patient-centric renal outcome — was significantly larger in CREDENCE (HR 0.68; 95% CI, 0.54–0.86) unlike FIDELIO-DKD having no significant effect (HR 0.87; 95% CI, 0.72–1.05) [15].
iv) NNT (number needed to treat) to prevent one primary renal outcome was 29 for finerenone (FIDELIO-DKD), 22 for canagliflozin (CREDENCE), and 19 for dapagliflozin (DAPA-CKD). These differences could be related to differences in the inclusion criteria and baseline characteristics of the patients across these trials (DAPA-CKD included CKD without T2D as well), however,
v) Even in a post-hoc analysis that compared the cardiorenal outcomes of a "CREDENCE-like" equivalent cohort (matched baseline albuminuria and eGFR) of FIDELIO-DKD to the CREDENCE trial there was — a. An insignificant benefit with finerenone on kidney failure (HR 0.81; 95% CI, 0.64–1.02) [16]. In the nearly equivalent "Diabetes-cohort" of DAPA-CKD, kidney failure was significantly reduced with dapagliflozin (HR 0.69; 95% CI 0.51–0.92), compared to the placebo [17, 18], b. Cardiovascular risk reduction was less consistent with finerenone in the "CREDENCE-like" cohort of FIDELIO-DKD compared with CREDENCE and "Diabetic-cohort" of DAPA-CKD, and finally, c. mortality reduction (composite of CV death or HHF, and all-cause mortality) was not observed with finerenone ("CREDENCE-like" cohort in FIDELIO-DKD) unlike CREDENCE and "Diabetes-cohort" of DAPA-CKD. Indeed, HHF was insignificant in the "CREDENCE-like" cohort of FIDELIO-DKD compared with CREDENCE and "Diabetes-cohort" of DAPA-CKD. Table 1 summarizes these findings [3, 17, 18].

Mechanistically, the action of SGLT2i and finerenone could be both complementary and synergistic, making this combination pharmacologically attractive and biologically plausible. The reason includes:

i) SGLT2i reduces glomerular hyperfiltration and CV beneficial effects are ascribed to change in hemodynamics, while finerenone reduces inflammation and fibrosis by inhibiting MR, thus it is exciting to believe that both differential mechanisms can complement each other in reducing renal disease progression. Indeed, a pre-clinical study showed empagliflozin and finerenone combination therapy

Table 1. Comparison of Cardio-Renal Outcome in CKD and Type 2 Diabetes with Equivalent Baseline Renal Profile

	"CREDENCE-like" cohort of FIDELIO-DKD, (N = 4,619) [16]	CREDENCE, (N = 4,401) [3, 16]	"Diabetes-cohort" of DAPA-CKD[!], (N = 2,906) [17, 18]
A. Drug studied, doses	Finerenone, 10/20 mg	Canagliflozin, 100 mg	Dapagliflozin, 10 mg
B. HbA1c (mean)	7.7%	8.3%	7.8%
C. Duration of diabetes (mean, year)	16.1	15.8	13.7
D. Inclusion criteria	a. UACR > 300–5000 mg/g b. eGFR 30– < 75 mL/min	a. UACR >300–5000 mg/g b. eGFR 30– < 90 mL/min	a. UACR 200–5000 mg/g b. eGFR 25–75 mL/min
E. Key exclusion criteria	a. Symptomatic HFrEF b. Serum K^+ > 4.8 mmol/L	a. Class IV NYHA HF b. On MRA at baseline c. Serum K^+ > 5.5 mmol/L	a. Class IV NYHA HF
F. Pre-randomization	Optimization of RASB	Optimization of RASB	Optimization of RASB
G. Outcomes			
i. Cardio-renal composite endpoints (kidney failure, eGFR decline ≥ 57% [≥ 50% in DAPA--CKD[!]] and renal or CV death); HR (95% CI)	**0.74 (0.63–0.87)**	**0.70 (0.59–0.82)**	**0.64 (0.52–0.79)**
a) Kidney failure	0.81 (0.64–1.02)	**0.68 (0.54–0.86)**	**0.69 (0.51–0.92)**
b) Sustained decrease in ≥ eGFR of 57% from baseline (≥ 50% decrease in eGFR criteria for DAPA-CKD[!])	**0.65 (0.52–0.80)**	**0.60 (0.48–0.76)**	**0.55 (0.42–0.72)**
c) Renal death	—	—	—
d) CV death	0.90 (0.69–1.18)	0.78 (0.61–1.00)	NR
ii. Kidney-specific composite endpoints (kidney failure, eGFR decline ≥ 57% [≥ 50% in DAPA-CKD[!]] and renal death), HR (95% CI), p-value	**0.69 (0.57–0.84)**	**0.66 (0.53–0.81)**	**0.57 (0.45–0.73)**
iii. All-cause death	0.88 (0.72–1.08)	0.83 (0.68–1.02)	**0.74 (0.56–0.98)**
iv. CV death or HHF	0.86 (0.71–1.05)	**0.69 (0.57–0.83)**	**0.70 (0.53–0.92)**
v. HHF	0.81 (0.68–1.08)	**0.61 (0.47–0.80)**	**0.47 (0.31–0.73)**

[!]DAPA-CKD chose eGFR decline of ≥ 50%
CKD — chronic kidney disease; CV — cardiovascular; eGFR — estimated glomerular filtration rate; HFrEF — heart failure with reduced ejection fraction; HHF — heart failure hospitalization; K^+ — potassium; MRA — mineralocorticoid antagonists; NR — not reported; NYHA — New York heart association; RASB — renin-angiotensin system blockers; UACR — urinary albumin creatinine ratio

had an incremental reduction in albuminuria and was more effective in improving cardiac and renal lesions in hypertension-induced end-organ damage transgenic rats model compared to empagliflozin or finerenone alone [19],

ii) Most evidence (although inconsistent) suggests SGLT2i increases aldosterone levels like other diuretics and thus the addition of finerenone may help to counterbalance this effect [20, 21], but most importantly,

iii) Owing to a reduced potential of hyperkalemia, SGLT2i can counterbalance MRA-induced hyperkalemia including finerenone. To this end,

1) An analysis from CREDENCE found canagliflozin to reduce severe hyperkalemia (> 6.0 mmol/L) by 23% (HR 0.77; 95% CI, 0.61–0.98; p = 0.03) [22]. Similarly, there was a 33% reduction (HR 0.67; 95% CI, 0.47–0.95) in severe hyperkalemia with dapagliflozin in DECLARE-TIMI [22]. Indeed, a recent meta-analysis (6 RCTs of SGLT2i including CREDENCE and DECLARE-TIMI, n = 49,875) showed a 20% reduction (HR 0.80; 95% CI, 0.68–0.93; p = 0.004) in investigator-reported hyperkalemia and 16% lower risk (HR: 0.84; 95% CI, 0.76–0.93; p < 0.001) of severe hyperkalemia (> 6.0 mmol/L) with SGLT2i [23]. Notably, this reduction in severe hyperkalemia with SGLT2i was observed regardless of baseline eGFR, RASB, diuretics, or MRA use, and without any increased risk of hypokalemia.
2) Similar findings were noted in three heart failure trials of SGLT2i [24–26]. Reduction in hyperkalemia was also observed with SGLT2i in DAPA-HF (71% MRA

users at baseline), EMPEROR-Reduced (71% using MRA at baseline), and EMPEROR-Preserved (37.5% using MRA at baseline) vs. placebo. Reduction in severe hyperkalemia (> 6.0 mmol/L) was evidently noticeable with SGLT2i against placebo in MRA users — a 50% relative risk reduction in DAPA-HF (HR 0.50; 95% CI, 0.29–0.85; p = 0.01), 39% relative risk reduction in EMPEROR-Preserved (HR 0.61; 95% CI, 0.40–0.93) and a similar trend noted in EMPEROR--Reduced (HR 0.64; 95% CI, 0.38–1.05).

3) About finerenone, an analysis of FIDELIO-DKD stratified on the baseline SGLT2i use reported a lesser episode of treatment-emergent hyperkalemia in combined SGLT2i plus finerenone users compared to finerenone alone (serum potassium > 5.5 mmol/L, 7% vs. 22%, respectively; and serum potassium > 6.0 mmol/L, 0% vs. 5% respectively) [27].
4) In the pooled FIDELITY analysis, overall hyperkalemia incidence was lower in baseline SGLT2i users vs. non-users in both finerenone (10.3% vs. 14.3% respectively) and placebo arms (2.7% vs. 7.2%, respectively). Similarly, severe hyperkalemia (serum potassium > 6.0 mmol/L) was lower in SGLT2i users vs. non-users in both finerenone (0.9% vs. 3.4% respectively) and placebo arms (0.7% vs. 1.3%, respectively). Moreover, incidences of hyperkalemia events leading to permanent drug discontinuation were lower in SGLT2i users vs. non-users in both finerenone (1.1% vs. 1.7% respectively) and placebo arms (0.7% vs. 0.6%, respectively) [28].

Concerning SGLT2i and finerenone combination therapy on the cardio-renal outcome, we do not have any available evidence to suggest that the combination could be incremental except in one preclinical study [19]. It should be noted that only 4.6% (259/5674) and 8.4% of patients (618/7352) in FIDELIO-DKD and FIGARO-DKD respectively were receiving SGLT-2i at baseline and renal and CV benefits were similar regardless of baseline SGLT2i use. No difference (P interaction = 0.21) in primary renal composite was observed between SGLT-2i users vs. non-users (HR 1.38; 95% CI, 0.61–3.10 and HR 0.82; 95% CI, 0.72–0.92, respectively) in FIDELIO-DKD [27]. Similarly, no difference (P interaction = not reported) in primary CV composite observed between SGLT-2i users vs. non-users (HR 0.49; 95% CI, 0.28–0.86 and HR, 0.89; 95% CI, 0.78–1.01, respectively) in FIGARO-DKD [7]. Indeed, in the pooled FIDELITY (n = 13,026) analysis [6.7% (n = 877) receiving SGLT2i at baseline, and 8.5% (n = 1,113) initiated SGLT2i during the study], no difference in either CV (P interaction = 0.46) or renal composite outcome (P interaction = 0.29) was observed between SGLT2i plus finerenone vs. finerenone alone [28].

Table 2. Renal and Mortality Outcomes with RASB (ACEi or ARBs), SGLT2i, and Non-Steroidal MRA in Patients Having CKD and Type 2 Diabetes (values adapted from [12])

Drug class	Renal outcome (#Doubling serum Cr or ^Composite renal outcome)					Cardiovascular death			All-cause mortality		
	Pooled studies (n)	N	Mean follow--up (months)	RR[!] or HR (95% CI)	Pooled studies (n)	N	Mean follow--up (months)	RR[!] or HR (95% CI)	Pooled studies (n)	N	Mean follow--up (months)	RR[!] or HR (95% CI)
ACEi[#]	9	6,780	27	0.68[!] (0.47–1.00)	1	4,912	4.5	1.07[!] (0.85–1.35)	23	7,515	32	0.93[!] (0.78–1.12)
ARBs[#]	4	3,280	34	**0.84**[!] **(0.72–0.98)**	2	1,714	42	1.62[!] (0.58–4.55)	9	4,179	25	0.99[!] (0.85–1.16)
SGLT2i[^]	8	34,788	36	**0.60** **(0.52–0.70)**	12	46,442	34	**0.90** **(0.83–0.98)**	17	31,523	33	***0.88*** ***(0.82–0.95)***
Non-steroidal MRA[^]	2	13,026	37	**0.84** **(0.77–0.92)**	3	13,318	35	0.88[!] (0.76–1.02)	5	14,138	20	0.90[!] (0.81–1.00)

[#]Doubling of serum creatinine; [^]Composite renal outcome, [!]RR — risk ratio
ACEi — angiotensin-converting enzyme inhibitors; ARBs — angiotensin II receptor blockers; CI — confidence interval; CKD — chronic kidney disease; HR — hazard ratio; MRA — mineralocorticoid receptor antagonists; RASB — renin--angiotensin system blockers; SGLT2i — sodium-glucose cotransporter-2 inhibitors

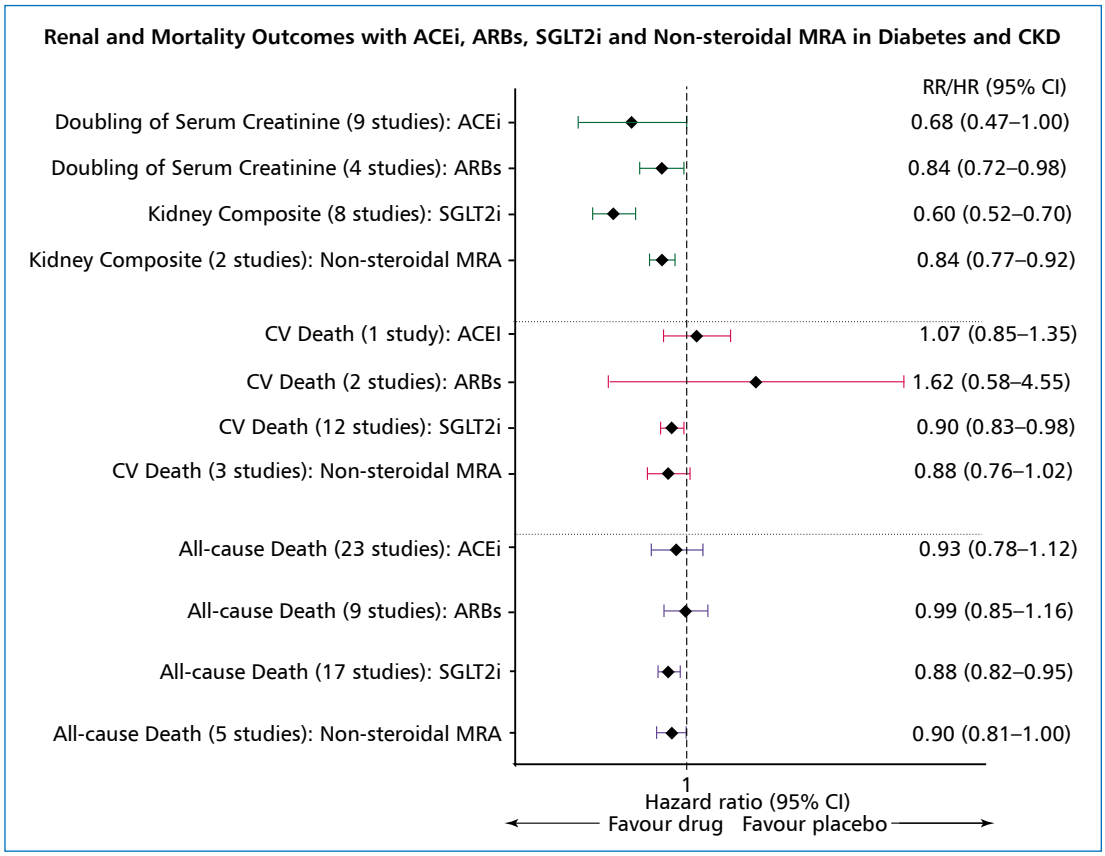

Figure 1. Cardio-Renal Outcomes of ACEi, ARBs, SGLT-2 Inhibitors, and Non-Steroidal MRA in Treatment of Chronic Kidney Disease with Type 2 Diabetes (values adapted from [12])
ACEi — angiotensin-converting enzyme inhibitors, ARBs — angiotensin II receptor blockers; CI — confidence interval; CKD — chronic kidney disease; CV — cardiovascular; HR — hazard ratio; MRA — mineralocorticoid receptor antagonists; RR — risk ratio; SGLT2i — sodium-glucose cotransporter-2 inhibitors

Contrarily, a recent small (n = 46), cross-over, open-label study (ROTATE-3, EU2017-004641-25) suggested that a combination therapy of dapagliflozin 10 mg/day with steroidal MRA eplerenone 50 mg/day had a large UACR reduction (–53%; 95% CI, –61.7 to –42.4%) at week-4 compared to either dapagliflozin (–19.6%; 95% CI, –34.3 to –1.5%) or eplerenone therapy (–33.7%; 95% CI, –46.1 to –18.5%) alone. This greater reduction in UACR was coupled with significantly lesser episodes of hyperkalemia in the dapagliflozin-eplerenone combination arm (4.3%) compared to eplerenone alone (17.4%). No episode of hyperkalemia was noted with dapagliflozin (0%) [29]. An ongoing 6-month (n = 807), double-blind, three-arm study (CONFIDENCE, NCT052-54002) that is currently assessing the efficacy (change in UACR as the primary outcome and changes in eGFR as secondary outcome) and safety (incidence of hyperkalemia) of finerenone (10–20 mg/day) plus empagliflozin (10 mg/day) compared with either finerenone (10-20 mg/day) or empagliflozin (10 mg/day) in participants with CKD (stage 2–3 and UACR of 300–5000 mg/g) and T2DM will further enlighten the relative merits of these agents in near future [30].

Summarily, after two decades of constant endeavors, we finally have three drugs (either as a class or as individuals) RASB, SGLT2i, and finerenone that have shown significant potential to reduce the progression of CKD in T2D [31]. Table 2 summarizes the relative renal and CV benefits of these three classes of drugs derived from the updated meta-analysis of KDIGO 2022 and Figure 1 is a forest plot representation of these outcomes. Both SGLT2i and finerenone have been recommended in people with T2D and CKD with prior RASB optimization. Since SGLT2i and finerenone have nearly comparable renal and cardiac benefits in CKD with T2D but baseline SGLT2i use had notably less frequent hyperkalemia compared to finerenone alone, this suggests prior use of SGLT2i will likely enable less finerenone withdrawal. Although the combination of SGLT2i and MRA has shown an incremental reduction in albuminuria, there is no conclusive evidence yet available that suggests long-term renal or CV benefits

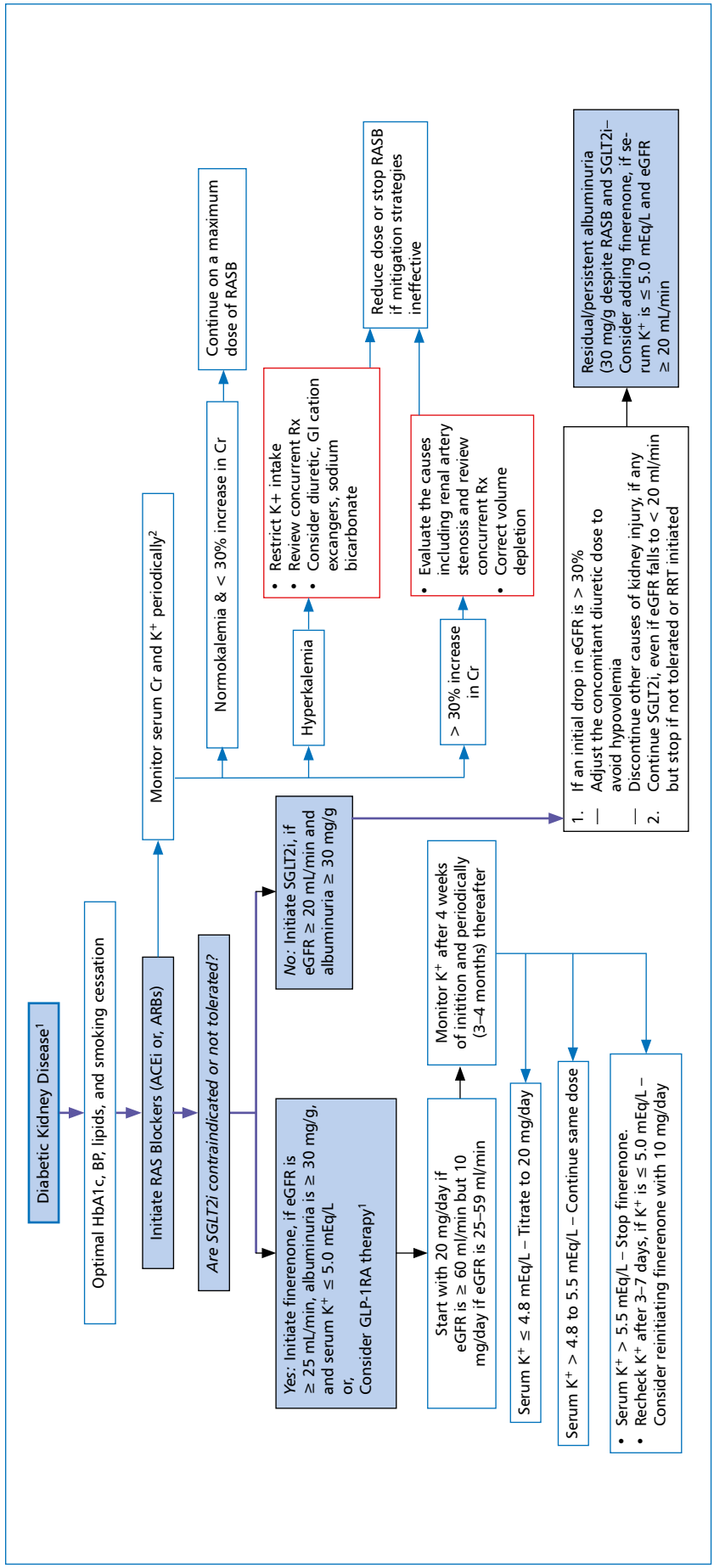

Figure 2. Positioning of RASB, SGLT-2 Inhibitors, and Finerenone in Treatment of Diabetic Kidney Disease
[1]Diabetic kidney disease is defined as albuminuria > 30 mg/g and or reduction in eGFR < 60 mL/min in persons with diabetes
[2]KDIGO 2022 and AACE/ACE 2022 guidelines recommend monitoring serum potassium every 2–4 weeks
[3]Indications and eGFR threshold may vary by region
[4]GLP-1RAs are another class of agent that is recommended in DKD if SGLT2i are contraindicated or not tolerated and also as an add-on agent after SGLT2i if further HbA1c lowering is required
KDIGO — kidney disease and global outcome; AACE — American Association of Clinical Endocrinology; ACEi — angiotensin-converting enzyme inhibitors; ARBs — angiotensin II receptor blockers; BP — blood pressure; CKD — chronic kidney disease; Cr — creatinine; eGFR — estimated glomerular filtration rate; GI — gastrointestinal; RASB — renin-angiotensin system blockers; GLP-1RA — glucagon-like peptide-1 receptor agonists; HbA1c — glycated hemoglobin; K^+ — potassium; Rx — treatment; SGLT2i — sodium-glucose cotransporter-2 inhibitors;

could be incremental with SGLT2i and finerenone combination therapy. Figure 2 is a proposed positioning of all three drugs (class or individual) in the management of CKD and T2D based on the latest (2022) updated guidelines from the KDIGO, ADA-EASD, and the AACE [12–14].

Conflict of interest

Dr. AKS and RS, have nothing to report. Dr. Shah reports receiving research grants through the University of Colorado from NovoNordisk, Insulet, Tandem Diabetes Care, and Dexcom and honoraria from Dexcom, Insulet, LifeScan, DKSH Singapore, and Medscape LLC for consulting and speaking outside the submitted work. Dr. Misra has received speaking honoraria from Bayer.

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