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CKJ REVIEW

Sodium-glucose cotransporter 2 inhibitors for diabetic kidney disease: a primer for deprescribing

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ABSTRACT

Chronic kidney disease (CKD) is a critical global public health problem associated with high morbidity and mortality, poorer quality of life and increased health care expenditures. CKD and its associated comorbidities are one of the most complex clinical constellations to manage. Treatments for CKD and its comorbidities lead to polypharmacy, which exponentiates the morbidity and mortality. Sodium-glucose cotransporter 2 inhibitors (SGLT2is) have shown remarkable benefits in cardiovascular and renal protection in patients with type 2 diabetes mellitus (T2DM). The pleiotropic effects of SGLT2is beyond glycosuria suggest a promising role in reducing polypharmacy in diabetic CKD, but the potential adverse effects of SGLT2is should also be considered. In this review, we present a typical case of a patient with multiple comorbidities seen in a CKD clinic, highlighting the polypharmacy and complexity in the management of proteinuria, hyperkalemia, volume overload, hyperuricemia, hypoglycemia and obesity. We review the cardiovascular and renal protection effects of SGLT2is in the context of clinical trials and current guidelines. We then discuss the roles of SGLT2is in the management of associated comorbidities and review the adverse effects and controversies of SGLT2is. We conclude with a proposal for deprescribing principles when initiating SGLT2is in patients with diabetic CKD.

Keywords: chronic kidney disease, deprescribing, diabetic kidney disease, polypharmacy, sodium-glucose cotransporter 2

CASE PRESENTATION

A 67-year-old morbidly obese male with a history of hypertension, type 2 diabetes mellitus (T2DM), systolic heart failure and hyperuricemia was followed in the renal clinic for chronic kidney disease (CKD) Stage 3a with nephrotic-range proteinuria. He had a recent kidney biopsy for increasing proteinuria and serum creatinine, which revealed diabetic nephropathy with chronic active interstitial nephritis. He was previously taken off a blocker of the renin–angiotensin–aldosterone system (RAAS) because of multiple episodes of hyperkalemia. Despite being on a low potassium diet, furosemide and patiromer, his potassium remained >5 mEq/L, which precluded reintroduction of the RAAS blockade medications. Also, his endocrinologist had recently intensified his diabetic regimen with insulin due to poor hemoglobin A1c control, and since then he has experienced

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weight gain and more frequent episodes of hypoglycemia. He also required up-titration of furosemide due to fluid retention in the lower extremities. The higher dose of furosemide precipitated a gout attack in his right knee, for which he took a course of steroids and was started on allopurinol. He reported persistent right knee pain from the gout attack, which severely limited his mobility and ability to exercise and left him feeling overwhelmed by his growing medication list. In the renal clinic, he expressed frustration that his renal function had declined further despite all his efforts to adhere to the medical advice of his multiple health care providers.

INTRODUCTION

CKD is a critical global public health problem associated with high morbidity and mortality, poorer quality of life and increased health care expenditures [1]. Comorbid conditions like diabetes, hypertension, hyperlipidemia, hyperuricemia, heart failure and cardiovascular disease are highly prevalent in CKD [2, 3] and associated with increased mortality [4, 5]. This constellation of conditions can be difficult to manage, often leading to polypharmacy in an attempt to manage comorbidities and mitigate the progression of CKD [6–8]. Indeed, as kidney function declines, patients experience additional complications, including anemia, bone mineral disorders, acidosis, hypervolemia and cardiovascular complications, all of which often require medication therapy. Most CKD patients take an average of 8–13 medications [9]. The number of prescribed medications is a recognized predictor of prescribing problems, including inappropriate dosage, drug–drug interactions and drug–disease interactions [10]. The use of multiple complex medication regimens in CKD increases drug-related problems [11] and inappropriate drug use is associated with 40% higher mortality in patients with CKD compared with those with preserved kidney function [12].

Our index case highlights a prescribing cascade, a process whereby the side effects of drugs result in more prescriptions, which causes additional side effects and unanticipated drug interactions [13]. Prescribing cascades similar to the example above are not uncommon in managing diabetic kidney disease.

Balancing the management of CKD, including associated comorbidities and complications, with the minimization of necessary and appropriate medications is challenging. However, the nephrologist now has sodium-glucose cotransporter 2 inhibitors (SGLT2is), a novel class of diabetic medications with many potentially helpful uses. Large clinical trials of SGLT2is have demonstrated remarkable benefit among patients with T2DM in reducing the risk of cardiovascular death, heart failure hospitalization and progression of renal disease [14]. The pleiotropic effects of SGLT2is beyond glycosuria suggest a promising role in managing multiple problems with a single once-daily pill, yet the efficacy and safety profile in moderate CKD is less clear. In this review we present a typical case of a patient with multiple comorbidities seen in CKD clinic, highlighting the complexity in management and resultant polypharmacy. We discuss the current evidence and guidelines for the use of SGLT2is in patients with diabetic CKD. We review the roles that SGLT2is may play in mitigating CKD complications, managing comorbidities and decreasing medication burden in this population, as well as the potential adverse effects of SGLT2is. We conclude with a proposal for safer deprescribing methods when initiating SGLT2is in the renal clinic.

Cardiovascular and renal protective effects of SGLT2is and current guideline recommendations

The US Food and Drug Administration (FDA) approved the use of SGLT2is for T2DM and cardiovascular risk reduction in patients with an estimated glomerular filtration rate (eGFR) >45mL/min/1.73 m^2. The characteristics of the study populations and the cardiovascular and renal outcomes of the pivotal trials of SGLT2is [15–18] are summarized in Table 1. The study population typically represented a group of obese patients with long-standing, poorly controlled T2DM and with various degrees of preexisting cardiovascular and renal disease who were receiving the standard of care for the management of diabetes and cardiovascular disease. Notably, the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA-REG) and Canagliflozin Cardiovascular Assessment Study (CANVAS) study populations had high cardiovascular disease burden, the Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy (CREDENCE) trial population had high renal disease burden and the Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI58) had the lowest cardiovascular and renal disease burdens. The EMPA-REG, CANVAS and CREDENCE trials demonstrated reduced major adverse cardiovascular events (MACEs), whereas the DECLARE-TIMI58 did not, probably reflecting less severe cardiovascular burden in the study population. Unequivocally, all four trials showed reduced heart failure hospitalizations irrespective of cardiovascular disease burden. All three SGLT2is reduced the renal composite outcomes compared with placebo. The CREDENCE trial observed the highest renal event rates and absolute risk reduction, followed by the EMPA-REG, CANVAS and DECLARE-TIMI58 trials, which is a downtrend likely corresponding to the degree of renal disease burden. In summary, SGLT2is are effective in the prevention of heart failure hospitalizations and progression of CKD and reducing cardiovascular events in patients with high cardiovascular risk.

The 2019 American Diabetes Association (ADA) guidelines recommend SGLT2is as the preferred class of agents to be added after metformin in patients with T2DM and a history of heart failure or CKD, if eGFR is >30 mL/min/1.73 m^2 [19, 20]. SGLT2is are also recommended as one of the two preferred agents (the other is GLP-1 receptor agonists) to be added after metformin in patients with atherosclerotic cardiovascular disease (ASCVD). Furthermore, clinicians should consider switching from other diabetes agents without cardiovascular or renal benefit to SGLT2is, even in patients who are currently at their target hemoglobin A1c level. In addition, the ADA recommends prescribing SGLT2is in patients who would benefit clinically from weight loss and to minimize the risk of hypoglycemia. The ADA also acknowledges that in those without established cardiovascular disease or CKD, SGLT2is are the last recommended class of agents for use because of the high drug price. The cost-effectiveness of SGLT2is compared with other oral hypoglycemic drugs in patients with cardiovascular disease, heart failure or CKD is yet to be determined.

The pleiotropic effects of SGLT2is on polypharmacy in diabetic CKD

The highly prevalent comorbidities and associated polypharmacy highlight the complexity of care for patients with diabetic

Table 1. Summary of key study population characteristics and outcomes in the pivotal clinical trials of SGLT2is

Characteristics	EMPA-REG	CANVAS	DECLARE-TIMI58	CREDENCE
Study drug	Empagliflozin	Canagliflozin	Dapagliflozin	Canagliflozin
Sample size	7020	10 142	17 160	4401
eGFR inclusion criteria (mL/min/1.73 m^2)	>30	>30	>60	30–90
Albuminuria inclusion criteria (mg/g)	NA	NA	NA	300–5000
Average age (years)	63	63	64	63
Duration of diabetes (years)	14	14	11	16
Percent with prior cardiovascular disease	100	66	40	51
Percent with preexisting heart failure	10	14	10	15
Body mass index (kg/m^2)	31	32	32	31
Blood pressure (mmHg)	135/77	137/78	135/85	140/78
Glycated hemoglobin (%)	8.1	8.2	8.3	8.3
Baseline eGFR (mL/min/1.73 m^2)	74	76	85	56
Percent with eGFR <60 mL/min/1.73 m^2	26	21	7	41
Percent with albuminuria	40	31	NA	99
Percent on metformin	74	77	82	58
Percent on insulin	48	50	41	66
Percent on sulfonylurea	43	43	43	29
Percent on ACEi or ARB	81	80	81	100
Percent on diuretics	44	44	41	47
Percent on statin	77	75	75	69
Outcomes (placebo versus experiment, rate/1000 patient-year)				
Progression of proteinuria[a]	118 versus 104*	129 versus 89*	NA	NA
Renal composite outcomes[b]	11.5 versus 6.3*	9.0 versus 5.5*	7.0 versus 3.7*	40.4 versus 27.0*
Three-point MACE[c]	43.9 versus 37.4*	31.5 versus 26.9*	24.2 versus 22.6	48.7 versus 38.7*
Hospitalization for Heart failure	14.5 versus 9.4*	8.7 versus 5.5*	8.5 versus 6.2*	25.3 versus 15.7*

*$P < 0.05$.

[a]Incident albuminuria or a 30% increase in albuminuria or progression to macroalbuminuria.

[b]Doubling of serum creatinine level accompanied by eGFR ≤45 mL/min/1.73 m^2, initiation of renal replacement therapy or death from renal disease (EMPA-REG); 40% reduction in eGFR, renal replacement therapy or renal death (CANVAS); ≥40% decrease in eGFR to <60 mL/min/1.73 m^2, ESRD or death from renal cause (DECLARE-TIMI58).

[c]Death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke.

Table 2. The prescribing cascade in the management of CKD

Medications	Used for	Unintended consequence	Added medication burden
ACEi/ARB/spironolactone	Proteinuria, hypertension, heart failure	Hyperkalemia	Patiromer, diuretics
Loop and thiazide diuretics	Hypertension, heart failure, hyperkalemia	Hyperuricemia	Urate-lowering agents
		Hyperglycemia	Diabetic agents
Insulin/insulinotropic agents	Diabetes	Weight gain	Weight reduction medications
		Sodium retention	Diuretics, antihypertensives
		Hypoglycemia	Not applicable

CKD (Table 2) [21]. The pleiotropic effects of SGLT2is show great promise in addressing these complex polypharmacy issues in diabetic CKD, including the management of proteinuria, hyperkalemia, volume overload, hyperuricemia, hypoglycemia, obesity and anemia (Table 3).

SGLT2is as an add-on or rescue therapy to RAAS blockers for proteinuria. The angiotensin-converting enzyme inhibitors (ACEis) and angiotensin II receptor blockers (ARBs) are the cornerstone classes of medications to reduce proteinuria and slow CKD progression. However, the rate of hyperkalemia from RAAS blockade is 3-fold higher in patients with CKD than in those without CKD [26]. Incident hyperkalemia is associated with a dose reduction or discontinuation of RAAS blockers [27], increased emergency room visits [27] and higher mortality [26]. The trend of ACEi/ARB usage rates in patients with diabetes and CKD has decreased since the early 2000s [28, 29], possibly due to resultant hyperkalemia. Dietary consultation on low potassium diets and coprescribing of kaliuretic diuretics and intestinal potassium binders are the current potassium-lowering strategies to allow reintroduction of ACEis/ARBs.

The efficacy of proteinuria reduction of SGLT2is is ∼30–40% in proteinuric diabetic kidney disease with the eGFR range from 30 to 90 mL/min/1.73 m^2 [30, 31], which is comparable to ACEi/ARB or spironolactone monotherapy [22, 32]. A 30% reduction in proteinuria is associated with a reduced incidence of CKD and end-stage renal disease (ESRD) [33, 34]. In the SGLT2i clinical trials, 80–100% of patients were on an ACEi or ARB agent and the addition of an SGLT2i further reduced the rate of incident or worsening nephropathy by 30–45% [15–18], suggesting that SGLT2is should be used as an add-on agent to treat diabetic kidney disease. In patients who are intolerant of RAAS blockade, SGLT2is represent alternative renoprotective agents with less incident hyperkalemia in the clinical trials

Table 3. The pleiotropic effects of SGLT2is

Clinical indication	Current therapy	Possible benefits when combining or substituting with SGLT2is besides cardiac and renal protection	Optimization Strategy
Prevent adverse renal and cardiovascular events	ACEi/ARB, spironolactone [22, 23]	Synergy in proteinuria reduction Reduce hyperkalemia from RAAS blockers	Coprescribe
Secondary hyperparathyroidism	Active vitamin D analogs [24]	Mitigate the SGLT2i-mediated up-regulation of FGF23 and suppression of 1,25-dihydroxyvitamin D [25]	Coprescribe if indicated
Volume overload	Loop and thiazide diuretics	Synergy in natriuresis Less metabolic derangement	Coprescribe if indicated with dose adjustment
Glucose control	GLP-1 RAs	Additional glycemic control with low risk of hypoglycemia	Coprescribe if indicated
	DPP-4 inhibitors	Additional glycemic control with low risk of hypoglycemia	Coprescribe if indicated
	Thiazolidinediones	Avoid sodium retention and exacerbation of heart failure	Deprescribe
	Insulin/insulinotropic agents	Weight loss, less sodium retention and lower hypoglycemic risk	Deprescribe
Prevent hyperkalemia	Loop and thiazide diuretics	Less metabolic derangement	Deprescribe
	Patiromer	Lower medication cost and simpler dosing schedule	Deprescribe
Hypertension	CCB, α1-blocker, clonidine	No	Deprescribe

BP, blood pressure; CCB, calcium channel blocker; ESA, EPO-stimulating agent.

[15, 35–37], even in patients with moderate renal insufficiency [15, 18, 38]. SGLT2i-induced natriuresis in the proximal tubule [39] and the induction of aldosterone [40, 41] promote kaliuresis from the distal tubule, but a clinically relevant potassium-lowering effect was not demonstrated in clinical trials [36].

Besides the potassium-neutral proteinuria reduction effect, SGLT2is raised the hematocrit by 2–3% [40, 42] in both CKD and non-CKD patients [35]. This observation is attributed not only to its hemoconcentration effect, but also erythropoiesis [40] due to increased endogenous erythropoietin (EPO) production [43], which may be related to mitigation of renal cortex hypoxia and improvement of pericyte function [44].

SGLT2i as an add-on to overcome diuretic resistance. Diuretic resistance is commonly seen in CKD patients and leads to poor outcomes. Poor drug absorption due to intestinal edema, reduced effective drug concentration due to proteinuria and impaired tubular secretion and compensatory sodium reabsorption from unblocked sodium transporters (such as Na^+/H^+ exchanger 3, Na-Cl cotransporter and SGLT2) all contribute to diuretic resistance [45]. Many strategies to overcome diuretic resistance have been attempted, but none have demonstrated long-term clinical benefit [46]. Loop diuretics are the most commonly used drugs for decongestion in CKD. Chronic loop diuretic use increases distal nephron sodium retention via the Na-Cl cotransporter. The combination of thiazide diuretics and loop diuretics has been shown to promote natriuresis and decongestion in loop diuretic–resistant patients, but long-term benefit in reducing cardiovascular mortality remains uncertain and metabolic and electrolytes disorders are common [47].

Multiple large clinical trials have demonstrated that SGLT2is significantly reduce heart failure hospitalizations regardless of a history of ASCVD or existing heart failure [14]. A recent study demonstrated a mutually adaptive synergy between SGLT2is and loop diuretics, and combination therapy was superior to either drug alone in promoting natriuresis [39]. Interestingly, despite diminished blood glucose–lowering effects of SGLT2is as renal function worsens, the antihypertensive and cardioprotective effects persisted across all eGFR groups [48, 49], suggesting that SGLT2is maintain natriuresis in patients with reduced eGFR despite lower drug delivery to the proximal tubules. Studies are currently under way examining SGLT2is [50] or thiazide diuretics [51] in combination with loop diuretics on heart failure outcomes and mortality. In euvolemic patients who are on a stable diuretic regimen, the addition of SGLT2i may require down-titration or discontinuation of existing diuretics to avoid overdiuresis.

SGLT2is mitigate hyperuricemia and hyperglycemia from loop and thiazide diuretics. Loop and thiazide diuretics are commonly used for salt-sensitive hypertension, volume management or hyperkalemia. Loop and thiazide diuretics cause increased uric acid net absorption from the proximal tubules by direct effects on urate transporters [52, 53] and by the indirect effect on volume contraction. Compared with nondiuretic antihypertensives, the use of diuretics increases the serum uric acid level by 0.7–0.9 mg/dL [54, 55] and increases the risk of gout attacks [55], which can potentially lead to worse cardiovascular and renal outcomes [56]. Also, loop and thiazide diuretics are associated with insulin resistance [57] and dose-dependent increased risk of incident diabetes [58, 59], probably related to compensatory sodium reabsorption coupled with increased glucose reabsorption via SGLT2 [39]. Since hyperuricemia, metabolic syndrome and diabetes are closely related and coexist in patients with CKD, the frequent use of loop or thiazide diuretics for blood pressure and volume management places CKD patients at risk for developing new comorbidities.

SGLT2i-induced glycosuria improves hyperglycemia and modulates the urate transporter GLU9 to promote uric acid excretion [60] and reduce serum uric acid level by ∼0.8 mg/dL [61]. Substituting thiazide diuretics with an SGLT2i can improve metabolic derangements without affecting blood pressure control [62]. Therefore the addition of an SGLT2i could mitigate the

metabolic derangements of loop and thiazide diuretics and allow for deprescribing of uric acid–lowering agents.

SGLT2is as diabetic agents with low hypoglycemic risk and weight reduction effect. Insulin and sulfonylureas are well-known to cause hypoglycemia [19, 63–66], especially in patients with CKD [67], whereas the newer classes of glucose-lowering agents, such as SGLT2i, glucagon-like peptide-1 receptor agonists (GLP-1 RA) and dipeptidyl peptidase 4 inhibitors pose a lower risk of hypoglycemia but are underprescribed in CKD patients [68]. Diabetes and CKD together compound the risk for incident hypoglycemia, which is associated with excess mortality [69].

The higher incidence of hypoglycemia in CKD patients is likely related to reduced insulin clearance and renal gluconeogenesis as renal function declines [70]. Moreover, insulin directly suppresses gluconeogenesis in the proximal tubules, while inhibition of SGLT2 enhances gluconeogenesis via activation of sirtuin1/peroxisome proliferator-activated receptor γ coactivator-1α [71], thus providing mechanistic insights into the higher risk of hypoglycemia seen with insulin and sulfonylureas, especially in patients with CKD, and justification for substituting them with SGLT2is. SGLT2is have been used in patients with eGFR >30 mL/min/1.73 m^2 in clinical trials [15, 17, 18] and have shown a low risk of hypoglycemia [72]. As an add-on to insulin-based or sulfonylurea-based glucose-lowering regimens, SGLT2is improved glycemic control with a lower risk of hypoglycemia [73, 74].

Weight reduction improves cardiovascular and renal risk factors [75, 76] and independently improves renal outcomes [77]. Insulin and sulfonylureas cause weight gain, which often leads to serial escalations in the treatment of diabetes, joint pain, hypertension, hyperlipidemia or proteinuria. SGLT2is can reduce weight by 2–4 kg on average [72] due to total body water reduction upon initiation and then by increasing fat metabolism with chronic use [78]. The weight loss effect is maintained in mild to moderate CKD [49] and attenuated in moderate to severe CKD [79].

The adverse effects of SGLT2is

While SGLT2is have demonstrated great promise for cardiovascular and renal protection, the potential adverse effects of SGLT2is should not be overlooked. The common adverse effects include osmotic diuresis, volume depletion and genital fungal infections. Less common adverse effects that have been reported in some clinical trials but not seen in meta-analyses [38, 72] include urinary tract infection, diabetic ketoacidosis, lower extremities amputation and bone fracture. Diabetic ketoacidosis was only seen in the CREDENCE and DECLARE-TIMI58 trials and the lower extremities amputation was only seen in the CANVAS trial, but not in the CREDENCE, EMPA-REG or DECLARE-TIMI58 trials. Last but not least, 55 cases of necrotizing fasciitis of the perineum were reported in case series [80] but not seen in clinical trials.

Of note, the risk of bone fracture is controversial. In both healthy volunteers [25] and T2DM patients with moderate CKD [81], canagliflozin increased serum phosphate, which stimulated fibroblast growth factor 23 (FGF23) and decreased 1,25-hydroxyvitamin D [25] and accelerated the loss of hip bone mineral density [82]. A higher risk of bone fracture was seen in the CANVAS trial. However, the risk of bone fracture was neither higher in the SGLT2i arm in the CREDENCE, EMPA-REG or DECLARE-TIMI58 trials [15, 16, 18] nor in the meta-analysis of the safety profile of SGLT2is in CKD patients [38]. The magnitude and variability of bone mineral adverse effects of SGLT2is are yet to be determined in the postmarket safety surveillance. It is advisable to monitor patient's parathyroid hormone (PTH) level while on SGLT2is and treat with active vitamin D analogs if the PTH level uptrends above the goal.

In summary, starting SGLT2is in a highly select group of CKD patients after meticulously weighing the risks and benefits and frequent monitoring of volume status, genital and foot hygiene, electrolytes, kidney function and bone mineral biomarkers are the keys to ensuring the safety of patients on SGLT2is.

The controversy around using SGLT2is for renoprotection in moderate to severe diabetic CKD

The glucose-lowering effect of SGLT2is when the eGFR is <45 mL/min/1.73 m^2 is almost negligible. At present, the FDA does not recommend the use of canagliflozin, empagliflozin and dapagliflozin when the eGFR is <45 mL/min/1.73 m^2. However, diabetic patients with moderate to severe proteinuric CKD have a very high risk of progression to ESRD despite the current standard of care, which is a substantial unmet medical need. The CREDENCE trial and the subgroup analysis of the EMPA-REG and CANVAS trials showed that the cardiovascular risk reduction, heart failure hospitalization reduction and composite renal outcome reduction were maintained in patients with an eGFR of 30–45 mL/min/1.73 m^2 and the safety profile was similar to the patients with preserved renal function, which argues for the 'off-label' use of SGLT2is in T2DM patients with proteinuria and an eGFR of 30–45 mL/min/1.73 m^2. The most updated ADA guidelines in June 2019 recommend the use of SGLT2is in diabetic CKD patients with an eGFR >30 mL/min/1.73 m^2 [20]. Other clinical trials of SGLT2is that target cardiovascular and renal outcomes in both diabetic and nondiabetic CKD patients are currently under way [EMPA-Kidney (The Study of Heart and Kidney Protection With Empagliflozin; NCT03594110) and DAPA-CKD (A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease; NCT03036150)].

Deprescribing principles when using SGLT2is in patients with diabetic CKD

The pleiotropic effects of SGLT2is can potentially break the prescribing cascade that contributes to polypharmacy (Figure 1). The following proposed deprescribing principles for SGLT2i use are intended only for diabetic kidney disease.

The first principle is to 'think SGLT2i first'. Adding an SGLT2i or switching to an SGLT2i is recommended in type 2 diabetic patients with an eGFR >30 mL/min/1.73 m^2 and with established ASCVD, heart failure or CKD [19, 20]. For CKD patients with adequate glycemic control who are seen in a CKD clinic, initiation of or switching to an SGLT2i by the treating nephrologist may reduce the likelihood of polypharmacy and hypoglycemia, providing more individualized diabetes and renal care.

The second principle is to 'coprescribe other agents for synergy or mitigation of side effects' (Table 3). For example, coprescribing RAAS blockers has synergy in proteinuria reduction and renal protection and mitigates the hyperkalemia caused by RAAS blockers; coprescribing active vitamin D analogs mitigates the induction of FGF23 and suppression of 1,25-dihydroxyvitamin D by SGLT2is [25].

The third principle is to 'deprescribe less desirable agents when possible'. The less desirable agents may have a similar

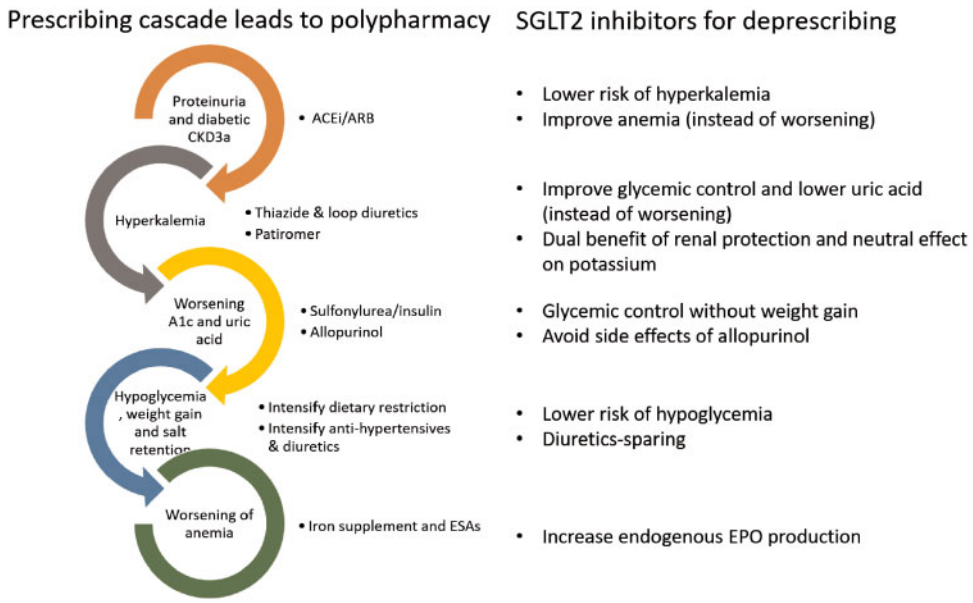

FIGURE 1: Prescribing cascade in CKD and SGLT2is for deprescribing. A hypothetical prescribing cascade after prescribing ACEi/ARB for proteinuria in a diabetic CKD3a patient. The multifaceted effects of SGLT2is show great promise in the management of diabetic CKD and its comorbidities. ESAs, EPO-stimulating agents.

Table 4. Practical considerations for when to defer initiation or withhold SGLT2is

Clinical conditions	Concerns	Recommended actions
Cognitive impairment	Unable to follow instructions for surveillance and medication titration; at risk for dehydration	Avoid SGLT2is; assess cognitive impairment
Poorly controlled hyperglycemia and a history of diabetic ketoacidosis	Poor adherence; risk of hyperglycemia-induced dehydration; risk of ketoacidosis	Avoid SGLT2is; referral to diabetologist
Unhealed diabetic foot wound	Risk of amputation	Avoid SGLT2is; referral to podiatry
History of frequent urinary tract infections, indwelling urinary catheter or self-catheterization	Risk of urinary tract infection	Avoid SGLT2is
Frequent vaginal candidal infections or unable to maintain genital hygiene for medical (e.g. phimosis) or social (e.g. insecure housing) reasons	Risk of genital fungal infection	Avoid SGLT2is
Peripheral vascular disease	Risk of amputation	Use with caution; frequent foot exam while on SGLT2is; referral to vascular surgery
Osteoporosis or renal osteodystrophy	Risk of bone fracture	Use with caution; monitor PTH and total vitamin D levels; referral to osteoporosis specialist for fracture risk assessment
Dynamic volume status (poor oral intake, diarrhea) or labile blood pressure	Dehydration and hypotension	Use with caution; deprescribe other diuretics and antihypertensives
Frequent nocturia	Patient intolerant of polyuria	Reduce dose or withhold

treatment effect but less desirable features, such as diabetic agents with no cardiovascular or renal protection benefit, dyssynergy with existing treatment, safety concerns or agents that may yield poor adherence due to regimen complexity or side effects (Table 3). From our experience, empagliflozin initiation necessitated adjustments to diabetes, hypertension and diuretic regimens in almost all patients. Whether SGLT2i use reduces the medication burden warrants further investigation. The deprescribing process requires careful planning, active surveillance and interdisciplinary communications [83].

The final principle is that 'when taking a holistic approach to medication management, safety comes first'. This principle requires the establishment of individualized treatment goals and consideration of the whole patient at the time of prescription or deprescription [67, 84]. Monitor closely for adverse effects when starting or stopping medications. We provide a list of practical considerations (Table 4) in the decision-making process of medication management in patients with CKD, specifically related to the use of SGLT2is.

The outcome of the index clinical case

After the introduction of empagliflozin to the patient's medication regimen, he experienced significant diuresis in the first 4 weeks and his serum creatinine increased from 1.21 (eGFR = 62 mL/min/1.73 m^2) to 1.58 mg/dL (eGFR = 45 mL/min/1.73 m^2) and potassium fell <4 mEq/L. We discontinued his

patiromer and reduced the furosemide dose. His serum creatinine returned to baseline and his potassium stabilized at 4.0–4.8 mEq/L. His proteinuria decreased significantly from 7.8 to 3.8 g and we successfully reintroduced a low-dose ARB. His uric acid level was 2.1 mg/dL at the 6-month follow-up visit and allopurinol was discontinued. Over 6 months, he lost 11 kg and his insulin dose was reduced, with hemoglobin A1c remaining at the goal. In response to an increase in his PTH level, we started him on low-dose calcitriol. In summary, after the introduction of empagliflozin, we discontinued or reduced four medications, reintroduced one renoprotective medication and initiated one medication for bone health. The patient tolerated the SGLT2i well and was thankful for the reduction in his proteinuria as well as the number of medications.

CONCLUSION

Diabetic CKD is complex to manage because of the high prevalence of comorbidities and resultant polypharmacy. The pleiotropic effects of SGLT2is show remarkable cardiovascular and renal benefits and great promise to address polypharmacy issues in diabetic CKD. Meticulous patient selection, individualized treatment plans and careful surveillance for adverse effects are the keys to ensure safety in patients on SGLT2is. SGLT2is are recommended in appropriate patients even when glycemic control is adequate. Further study on whether SGLT2is decrease medication burden for patients with diabetic kidney disease is warranted.

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CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this article have not been published previously in whole or part, except in abstract format.

REFERENCES

1. Xie Y, Bowe B, Mokdad AH *et al*. Analysis of the Global Burden of Disease study highlights the global, regional, and national trends of chronic kidney disease epidemiology from 1990 to 2016. *Kidney Int* 2018; 94: 567–581
2. Stevens LA, Li S, Wang C *et al*. Prevalence of CKD and comorbid illness in elderly patients in the United States: results from the Kidney Early Evaluation Program (KEEP). *Am J Kidney Dis* 2010; 55: S23–S33
3. Patel N, Golzy M, Nainani N *et al*. Prevalence of various comorbidities among veterans with chronic kidney disease and its comparison with other datasets. *Ren Fail* 2016; 38: 204–208
4. Fraser SDS, Roderick PJ, May CR *et al*. The burden of comorbidity in people with chronic kidney disease stage 3: a cohort study. *BMC Nephrol* 2015; 16: 193
5. Tonelli M, Wiebe N, Guthrie B *et al*. Comorbidity as a driver of adverse outcomes in people with chronic kidney disease. *Kidney Int* 2015; 88: 859–866
6. Schmidt IM, Huebner S, Jennifer Nadal SIT *et al*. The burden of polypharmacy in patients with CKD: the GCKD study. *J Am Soc Nephrol* 2018; 29: 399
7. Hayward SJ, Hole BD, Rachel Denholm PRD *et al*. Polypharmacy in older patients developing advanced CKD in 6 European countries: results from the EQUAL study. *J Am Soc Nephrol* 2018; 29: 399
8. Fasipe O, Akhideno P, Ibiyemi-Fasipe O *et al*. The burden of polypharmacy and pattern of comorbidities among chronic kidney disease patients in clinical practice. *Arch Med Health Sci* 2018; 6: 40
9. Stengel B, Metzger M, Combe C *et al*. Risk profile, quality of life and care of patients with moderate and advanced CKD: the French CKD-REIN Cohort study. *Nephrol Dial Transplant* 2018; 34: 277–286
10. Steinman MA, Miao Y, Boscardin WJ *et al*. Prescribing quality in older veterans: a multifocal approach. *J Gen Intern Med* 2014; 29: 1379–1386
11. Njeri LW, Ogallo WO, Nyamu DG *et al*. Medication-related problems among adult chronic kidney disease patients in a sub-Saharan tertiary hospital. *Int J Clin Pharm* 2018; 40: 1217–1224
12. Quintana-Bárcena P, Lord A, Lizotte A *et al*. Prevalence and management of drug-related problems in chronic kidney disease patients by severity level: a subanalysis of a cluster randomized controlled trial in community pharmacies. *J Manag Care Spec Pharm* 2018; 24: 173–181
13. Rochon PA, Gurwitz JH. Optimising drug treatment for elderly people: the prescribing cascade. *BMJ* 1997; 315: 1096–1099
14. Zelniker TA, Wiviott SD, Raz I *et al*. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet* 2018; 6736: 1–9
15. Wanner C, Inzucchi SE, Lachin JM *et al*. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 2016; 375: 323–334
16. Wiviott SD, Raz I, Bonaca MP *et al*. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019; 380: 347–357
17. Neal B, Perkovic V, Mahaffey KW *et al*. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017; 377: 644–657
18. Perkovic V, Jardine MJ, Neal B *et al*. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019; 380: 2295
19. Davies MJ, D'Alessio DA, Fradkin J *et al*. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2018; 41: 2669–2701
20. American Diabetes Association. 11. Microvascular complications and foot care: standards of medical care in diabetes—2019. *Diabetes Care* 2019; 42 (Suppl 1): S124–S138
21. Tonelli M, Wiebe N, Manns BJ *et al*. Comparison of the complexity of patients seen by different medical subspecialists in a universal health care system. *JAMA Netw Open* 2018; 1: e184852
22. Selvaraj S, Claggett B, Shah SJ *et al*. Prognostic value of albuminuria and influence of spironolactone in heart failure with preserved ejection fraction. *Circ Hear Fail* 2018; 11: 1–10
23. Navaneethan SD, Nigwekar SU, Sehgal AR *et al*. Aldosterone antagonists for preventing the progression of chronic kidney disease: a systematic review and meta-analysis. *Clin J Am Soc Nephrol* 2009; 4: 542–551

24. de Borst MH, Hajhosseiny R, Tamez H *et al*. Active vitamin D treatment for reduction of residual proteinuria: a systematic review. *J Am Soc Nephrol* 2013; 24: 1863–1871
25. Blau JE, Bauman V, Conway EM *et al*. Canagliflozin triggers the FGF23/1, 25-dihydroxyvitamin D/PTH axis in healthy volunteers in a randomized crossover study. *JCI Insight* 2018; 3: doi: 10.1172/jci.insight.99123
26. Einhorn LM, Zhan M, Hsu VD *et al*. The frequency of hyperkalemia and its significance in chronic kidney disease. *Arch Intern Med* 2009; 169: 1156
27. Chang AR, Sang Y, Leddy J *et al*. Antihypertensive medications and the prevalence of hyperkalemia in a large health system. *Hypertension* 2016; 67: 1181–1188
28. Centers for Disease Control and Prevention. *Chronic Kidney Disease Surveillance System—United States*. http://www.cdc.gov/ckd (12 November 2018, date last accessed)
29. Murphy DP, Drawz PE, Foley RN. Trends in angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker use among those with impaired kidney function in the United States. *J Am Soc Nephrol* 2019; 30: 1314–1321
30. Cherney D, Lund SS, Perkins BA *et al*. The effect of sodium glucose cotransporter 2 inhibition with empagliflozin on microalbuminuria and macroalbuminuria in patients with type 2 diabetes. *Diabetologia* 2016; 59: 1860–1870
31. Heerspink HJL, Johnsson E, Gause-Nilsson I *et al*. Dapagliflozin reduces albuminuria in patients with diabetes and hypertension receiving renin-angiotensin blockers. *Diabetes Obes Metab* 2016; 18: 590–597
32. Kunz R, Friedrich C, Wolbers M *et al*. Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin angiotensin system on proteinuria in renal disease. *Ann Intern Med* 2008; 148: 30–48
33. Coresh J, Heerspink HJL, Sang Y *et al*. Change in albuminuria and subsequent risk of end-stage kidney disease: an individual participant-level consortium meta-analysis of observational studies. *Lancet Diabetes Endocrinol* 2019; 7: 115–127
34. Sumida K, Molnar MZ, Potukuchi PK *et al*. Changes in albuminuria and subsequent risk of incident kidney disease. *Clin J Am Soc Nephrol* 2017; 12: 1941–1949
35. Wanner C, Lachin JM, Inzucchi SE *et al*. Empagliflozin and clinical outcomes in patients with type 2 diabetes mellitus, established cardiovascular disease, and chronic kidney disease. *Circulation* 2018; 137: 119–129
36. Yavin Y, Mansfield TA, Ptaszynska A *et al*. Effect of the SGLT2 Inhibitor dapagliflozin on potassium levels in patients with type 2 diabetes mellitus: a pooled analysis. *Diabetes Ther* 2016; 7: 125–137
37. Filippatos TD, Tsimihodimos V, Liamis G *et al*. SGLT2 inhibitors-induced electrolyte abnormalities: an analysis of the associated mechanisms. *Diabetes Metab Syndr Clin Res Rev* 2018; 12: 59–63
38. Jun M, Heerspink HL, Toyama T *et al*. Effect of SGLT2 inhibitors on cardiovascular, renal and safety outcomes in patients with type 2 diabetes mellitus and chronic kidney disease: a systematic review and meta-analysis. *Diabetes Obes Metab* 2019; 21: 1237–1250
39. Wilcox CS, Shen W, Boulton DW *et al*. Interaction between the sodium-glucose-linked transporter 2 inhibitor dapagliflozin and the loop diuretic bumetanide in normal human subjects. *J Am Heart Assoc* 2018; 7: e007046
40. Lambers Heerspink HJ, de Zeeuw D, Wie L *et al*. Dapagliflozin a glucose-regulating drug with diuretic properties in subjects with type 2 diabetes. *Diabetes Obes Metab* 2013; 15: 853–862
41. Cherney DZI, Perkins BA, Soleymanlou N *et al*. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. *Circulation* 2014; 129: 587–597
42. Thewjitcharoen Y, Yenseung N, Malidaeng A *et al*. Effectiveness of long-term treatment with SGLT2 inhibitors: real-world evidence from a specialized diabetes center. *Diabetol Metab Syndr* 2017; 9: 1–8
43. Ferrannini E, Baldi S, Frascerra S *et al*. Renal handling of ketones in response to sodium-glucose cotransporter 2 inhibition in patients with type 2 diabetes. *Dia Care* 2017; 40: 771–776
44. Sano M, Takei M, Shiraishi Y *et al*. Increased hematocrit during sodium-glucose cotransporter 2 inhibitor therapy indicates recovery of tubulointerstitial function in diabetic kidneys. *J Clin Med Res* 2016; 8: 844–847
45. Hoorn EJ, Ellison DH. Diuretic resistance. *Am J Kidney Dis* 2017; 69: 136–142
46. Ellison DH, Felker GM. Diuretic treatment in heart failure. *N Engl J Med* 2017; 377: 1964–1975
47. Jentzer JC, Dewald TA, Hernandez AF. Combination of loop diuretics with thiazide-type diuretics in heart failure. *J Am Coll Cardiol* 2010; 56: 1527–1534
48. Cherney DZI, Cooper ME, Tikkanen I *et al*. Pooled analysis of phase III trials indicate contrasting influences of renal function on blood pressure, body weight, and HbA1c reductions with empagliflozin. *Kidney Int* 2018; 93: 231–244
49. Petrykiv S, David Sjöström C, Greasley PJ *et al*. Differential effects of dapagliflozin on cardiovascular risk factors at varying degrees of renal function. *Clin J Am Soc Nephrol* 2017; 12: 751–759
50. Mordi NA, Mordi IR, Singh JS *et al*. Renal and cardiovascular effects of sodium-glucose cotransporter 2 (SGLT2) inhibition in combination with loop diuretics in diabetic patients with chronic heart failure (RECEDE-CHF): protocol for a randomised controlled double-blind cross-over trial. *BMJ Open* 2017; 7: e018097
51. Trullàs JC, Morales-Rull JL, Casado J *et al*. Rationale and design of the "Safety and Efficacy of the Combination of Loop with Thiazide-type Diuretics in Patients with Decompensated Heart Failure (CLOROTIC) Trial:" a double-blind, randomized, placebo-controlled study to determine the effect of combined diuretic therapy (loop diuretics with thiazide-type diuretics) among patients with decompensated heart failure. *J Card Fail* 2016; 22: 529–536
52. Hagos Y, Stein D, Ugele B *et al*. Human renal organic anion transporter 4 operates as an asymmetric urate transporter. *J Am Soc Nephrol* 2007; 18: 430–439
53. El-Sheikh AAK, van den Heuvel J, Koenderink JB *et al*. Effect of hypouricaemic and hyperuricaemic drugs on the renal urate efflux transporter, multidrug resistance protein 4. *Br J Pharmacol* 2009; 155: 1066–1075
54. Savage PJ, Pressel SL, Curb JD *et al*. Influence of long-term, low-dose, diuretic-based, antihypertensive therapy on glucose, lipid, uric acid, and potassium levels in older men and women with isolated systolic hypertension: the Systolic Hypertension in the Elderly Program. *Arch Intern Med* 1998; 158: 741–751
55. McAdams DeMarco MA, Maynard JW, Baer AN *et al*. Diuretic use, increased serum urate levels, and risk of incident gout in a population-based study of adults with hypertension: the Atherosclerosis Risk in Communities cohort study. *Arthritis Rheum* 2012; 64: 121–129

56. Johnson RJ, Kang DH, Feig D *et al*. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? *Hypertension* 2003; 41: 1183–1190
57. Eriksson JW, Jansson PA, Carlberg B *et al*. Hydrochlorothiazide, but not candesartan, aggravates insulin resistance and causes visceral and hepatic fat accumulation: the Mechanisms for the Diabetes Preventing Effect of Candesartan (MEDICA) study. *Hypertension* 2008; 52: 1030–1037
58. Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. *Lancet* 2007; 369: 201–207
59. Andersson C, Norgaard ML, Hansen PR *et al*. Heart failure severity, as determined by loop diuretic dosages, predicts the risk of developing diabetes after myocardial infarction: a nationwide cohort study. *Eur J Heart Fail* 2010; 12: 1333–1338
60. Chino Y, Samukawa Y, Sakai S *et al*. SGLT2 inhibitor lowers serum uric acid through alteration of uric acid transport activity in renal tubule by increased glycosuria. *Biopharm Drug Dispos* 2014; 35: 391–404
61. Zhao Y, Xu L, Tian D *et al*. Effects of sodium-glucose cotransporter 2 (SGLT2) inhibitors on serum uric acid level: a meta-analysis of randomized controlled trials. *Diabetes Obes Metab* 2018; 20: 458–462
62. Kimura T, Sanada J, Shimoda M *et al*. Switching from low-dose thiazide diuretics to sodium–glucose cotransporter 2 inhibitor improves various metabolic parameters without affecting blood pressure in patients with type 2 diabetes and hypertension. *J Diabetes Investig* 2018; 9: 875–881
63. Ben-Ami H, Nagachandran P, Mendelson A *et al*. Drug-induced hypoglycemic coma in 102 diabetic patients. *Arch Intern Med* 1999; 159: 281–284
64. Gangji AS, Cukierman T, Gerstein HC *et al*. A systematic review and meta-analysis of hypoglycemia and cardiovascular events: a comparison of glyburide with other secretagogues and with insulin. *Diabetes Care* 2007; 30: 389–394
65. Holman RR, Farmer AJ, Davies MJ *et al*. Three-year efficacy of complex insulin regimens in type 2 diabetes. *N Engl J Med* 2009; 361: 1736–1747
66. Monami M, Dicembrini I, Kundisova L *et al*. A meta-analysis of the hypoglycaemic risk in randomized controlled trials with sulphonylureas in patients with type 2 diabetes. *Diabetes Obes Metab* 2014; 16: 833–840
67. Triantafylidis LK, Hawley CE, Perry LP *et al*. The role of deprescribing in older adults with chronic kidney disease. *Drugs Aging* 2018; 35: 973–984
68. Boye KS, Botros FT, Haupt A *et al*. Glucagon-like peptide-1 receptor agonist use and renal impairment: a retrospective analysis of an electronic health records database in the U.S. population. *Diabetes Ther* 2018; 9: 637–650
69. Moen MF, Zhan M, Hsu VD *et al*. Frequency of hypoglycemia and its significance in chronic kidney disease. *Clin J Am Soc Nephrol* 2009; 4: 1121–1127
70. Neumiller JJ, Alicic RZ, Tuttle KR. Therapeutic considerations for antihyperglycemic agents in diabetic kidney disease. *J Am Soc Nephrol* 2017; 28: 2263–2274
71. Sasaki M, Sasako T, Kubota N *et al*. Dual regulation of gluconeogenesis by insulin and glucose in the proximal tubules of the kidney. *Diabetes* 2017; 66: 2339–2350
72. Zhang X, Zhu Q, Chen Y *et al*. Cardiovascular safety, long-term noncardiovascular safety, and efficacy of sodium–glucose cotransporter 2 inhibitors in patients with type 2 diabetes mellitus: a systemic review and meta-analysis with trial sequential analysis. *J Am Heart Assoc* 2018; 7: e007165
73. Rosenstock J, Jelaska A, Frappin G *et al*. Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled type 2 diabetes. *Diabetes Care* 2014; 37: 1815–1823
74. Goring S, Hawkins N, Wygant G *et al*. Dapagliflozin compared with other oral anti-diabetes treatments when added to metformin monotherapy: a systematic review and network meta-analysis. *Diabetes Obes Metab* 2014; 16: 433–442
75. Wing RR, Lang W, Wadden TA *et al*. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. *Diabetes Care* 2011; 34: 1481–1486
76. Bolignano D, Zoccali C. Effects of weight loss on renal function in obese CKD patients: a systematic review. *Nephrol Dial Transplant* 2013; 28: iv82–iv98
77. Scirica BM, Bohula EA, Dwyer JP *et al*. Lorcaserin and renal outcomes in obese and overweight patients in the CAMELLIA-TIMI 61 trial. *Circulation* 2019; 139: 366–375
78. Ferrannini E, Muscelli E, Frascerra S *et al*. Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. *J Clin Invest* 2014; 124: 499–508
79. Pollock C, Stefánsson B, Reyner D *et al*. Albuminuria-lowering effect of dapagliflozin alone and in combination with saxagliptin and effect of dapagliflozin and saxagliptin on glycaemic control in patients with type 2 diabetes and chronic kidney disease (DELIGHT): a randomised, double-blind, plac. *Lancet Diabetes Endocrinol* 2019; 2: 1–13
80. Bersoff-Matcha SJ, Chamberlain C, Cao C *et al*. Fournier gangrene associated with sodium-glucose cotransporter-2 inhibitors: a review of spontaneous postmarketing cases. *Ann Intern Med* 2019; 170: 764
81. Weir MR, Kline I, Xie J *et al*. Effect of canagliflozin on serum electrolytes in patients with type 2 diabetes in relation to estimated glomerular filtration rate (eGFR). *Curr Med Res Opin* 2014; 30: 1759–1768
82. Bilezikian JP, Watts NB, Usiskin K *et al*. Evaluation of bone mineral density and bone biomarkers in patients with type 2 diabetes treated with canagliflozin. *J Clin Endocrinol Metab* 2016; 101: 44–51
83. Scott IA, Hilmer SN, Reeve E *et al*. Reducing inappropriate polypharmacy: the process of deprescribing. *JAMA Intern Med* 2015; 175: 827–834
84. Whittaker CF, Miklich MA, Patel RS *et al*. Medication safety principles and practice in CKD. *Clin J Am Soc Nephrol* 2018; 13: 1738–1746