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Review

Acute renal injury events in diabetic patients treated with SGLT2 inhibitors: A comprehensive review with a special reference to RAAS blockers

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ABSTRACT

Renin-angiotensin-aldosterone system (RAAS) blockers and sodium-glucose cotransporter type 2 inhibitors (SGLT2is) are two pharmacological classes that proved a remarkable nephroprotective effect, yet a risk of acute kidney injury (AKI) was also pointed out. In 2016, the US Food and Drug Administration recommended caution with the concomitant use of these medications. While the literature devoted to RAAS blockers remained surprisingly limited, numerous articles were published in recent years with SGLT2is. Safety analyses of large prospective cardiorenal trials showed a reduced rather than an increased number of AKI events in patients with type 2 diabetes treated with SGLT2is compared with those treated with placebo, despite the fact that a majority of patients received RAAS blockers at baseline. Interestingly, retrospective observational studies confirmed these reassuring findings in real-life conditions in more heterogeneous and possibly more frailty populations also commonly treated with RAAS blockers by showing a reduced risk of AKI with SGLT2is compared with other glucose-lowering drugs. Currently, there are no evidence of an increased risk of AKI with RAAS blocker-SGLT2i combinations in absence of haemodynamic instability. Several underlying mechanisms could explain a decreased rather than an increased risk of AKI with SGLT2is, including in patients treated with RAAS blockers.

Introduction

Acute kidney injury (AKI) is an increasing complication in the general population [1] and the risk of this serious adverse event is further increased among patients with type 2 diabetes mellitus (T2DM) [2], and even more so in those individuals with chronic kidney disease (CKD) [3]. Observational studies showed that higher glycated haemoglobin levels were associated with AKI episodes in adults with T2DM and CKD, suggesting that improving glycaemic control may reduce the risk of AKI [4]. Large observational databases linking kidney function and other routine patient health data were used to study AKI and demonstrated the progression of this adverse event in clinical practice and its overall burden [5]. AKI should not be considered as a benign and completely reversible condition [2]. Indeed, AKI episodes are associated with a higher cardiovascular risk [6] and with a greater risk of later chronic deterioration of kidney function [7], including an almost twofold increase in mortality [8]. In fact, AKI and CKD may be viewed as interconnected syndromes [9]. Because the treatment of AKI is still challenging, prevention represents a major objective [1, 10-12].

Two pharmacological classes have demonstrated their potential to reduce glomerular hyperfiltration and improve renal (and cardiovascular as well) outcomes, first renin-angiotensin-aldosterone system (RAAS) blockers already in the late eighties [13, 14], second sodium-glucose cotransporter type 2 inhibitors (SGLT2is) in the last decade [15–17]. Besides the overall nephroprotective effect, the risk of AKI with RAAS inhibitors is recognised since their clinical use. Such increased risk of AKI is emphasised in international guidelines [18], even if rather poorly documented [19, 20]. Furthermore, there is a possible confusion of language for clinicians because of an imprecise terminology (so-called “nephrotoxic drugs”) [21]. In 2016, the U.S. Food and Drug Administration (FDA) also warned of the risk of AKI

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Table 1
Similarities and differences between RAAS inhibitors and SGLT2is.

Effects	RAAS inhibitors	SGLT2is
Reduction of glomerular hyperfiltration	Yes	Yes
Change in intra-renal haemodynamics	Predominant efferent arteriole dilation	Efferent arteriole dilation and afferent arteriole constriction
Reduction in arterial blood pressure	Yes	Yes (but to a lesser degree)
Improvement prognosis in heart failure	Yes (if reduced LVEF)	Yes (with reduced or preserved LVEF)
Reduction in microalbuminuria/proteinuria	Yes Prognostic marker for further nephroprotection	Yes Prognostic marker for further nephroprotection
Improvement of renal prognosis, including the risk of ESRD	Yes (if albuminuria)	Yes (with or without albuminuria)
Risk of hyperkalaemia	Yes	No
Initial dip in GFR	Yes (functional and reversible) Prognostic marker for further nephroprotection	Yes (functional and reversible)
Risk of AKI	Poorly documented (especially in monotherapy)	Reduced in RCTs and observational studies
Caution to reduce AKI	Avoid dehydration Stop the drug if haemodynamic instability Stop the drug if high risk of AKI (serious surgery, contrast product injection in CKD, etc.)	Avoid dehydration Stop the drug if haemodynamic instability Stop the drug if high risk of AKI (serious surgery, contrast product injection in CKD, etc.)

AKI: acute kidney injury. CKD: chronic kidney disease. ESRD: end-stage renal disease. GFR: glomerular filtration rate. LVEF: left ventricular ejection fraction. RCTs: randomised controlled trials.

for two SGLT2is, canagliflozin and dapagliflozin [22]. The FDA drug safety communication required that AKI be listed as a potential side effect of SGLT2is along with cautious prescription of these drugs with other medications, RAAS inhibitors and diuretics being mentioned in the list besides nonsteroidal anti-inflammatory drugs (NSAIDs) [22]. Surprisingly, whereas the literature is rather scarce regarding the risk of AKI with RAAS inhibitors [19, 20], this concern has been extensively covered for SGLT2is in recent years [23].

The main objective of this comprehensive review is to analyze the available data of the literature regarding the risk of AKI with SGLT2is. However, there is a close connection between SGLT2is and RAAS inhibitors, both concerning intra-renal haemodynamic changes and potential dual effects on renal outcomes (Table 1). Furthermore, these two pharmacological classes are widely used as combined therapy in clinical practice. Therefore, a focus of the risk of AKI with RAAS inhibitors will first be briefly developed and a final discussion about a potential interference between RAAS blockers and SGLT2is regarding the risk of AKI will be analysed.

Heterogeneity of AKI definitions

One major limitation when analysing the literature derives from the heterogeneity in the definition of AKI between studies [24]. Some studies used the MedDRA ("Medical Dictionary for Regulatory Activities") terminology, which brings together a variety of sometimes confusing terms. Some authors used ICD ("International Classification of Diseases") score to define hospitalization for AKI (yet, with some differences between scores considered across studies: ICD-9 and/or ICD-10). Others used the definition recommended by the KDIGO (for "Kidney Disease: Improving Global Outcomes") 2012 guidelines based on laboratory data (stage 1 being defined as an increase in serum creatinine by > 0.3 mg/dl within 48 h or increase in serum creatinine by >1.5 times baseline value within seven days) [1]. This heterogeneity may explain the differences in the incidence of AKI events across studies, besides the influence of different characteristics of the recruited populations. It also makes it difficult to compare results between interventional trials with pharmacotherapies such as RAAS inhibitors and SGLT2is. The diversity of the definitions of AKI contrasts with the more homogeneous definition of the primary renal composite outcome used in prospective cardiovascular/renal outcome trials with SGLT2is, i.e. sustained reduction in renal function, progression to end-stage renal disease or renal death [15] (even if the reduction in renal function may be estimated with either doubling of serum creatinine or ≥40% decline in estimated glomerular filtration rate (eGFR) [25]).

AKI with RAAS inhibitors

Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are largely prescribed among patients with T2DM, especially those with microalbuminuria/proteinuria, arterial hypertension, cardiovascular disease and heart failure [18, 26]. These agents were among the first drugs that demonstrated a significant improvement of overall cardiovascular [27] and renal [28, 29] prognosis in patients with T2DM. Because a change in intrarenal haemodynamics, an initial dip of eGFR is commonly observed after the initiation of RAAS inhibitors and a stenosis of renal artery should be suspected in case of a marked (> 30%) increase in serum creatinine [26, 30]. Of note, however, a strong positive association exists between acute increases in serum creatinine of up to 30% that stabilize within the first two months of ACEI therapy and long-term preservation of renal function [31, 32]. Nevertheless, RAAS inhibitors have been recognised to be associated with an increased risk of AKI, yet this remains a matter of debate, at least in monotherapy and beyond any other cause of blood volume reduction [19]. Despite the lack of clear evidence, several guidelines recommend to withhold RAAS inhibitor usage under acute complications (hypovolaemia, hypotension, sepsis) [26, 33]. The KDIGO guidelines on CKD "recommend temporary discontinuation of potentially nephrotoxic and renally excreted drugs in people with a GFR < 60 ml/min/1.73 m^2 (GFR categories G3a-G5) who have serious intercurrent illness that increases the risk of AKI. These agents include, but are not limited to RAAS blockers" (guideline 4.4.3) [34].

Increased risk

RAAS blockers cause vasodilation of the renal efferent arteriole, which results in reduction of intraglomerular filtration pressure [35]. During hypovolaemia, this mechanism still lowers GFR and ultimately can promote AKI [26]. However, the concern that the use of RAAS inhibitors leads to the precipitation of AKI is poorly substantiated in the scientific literature. In randomised controlled trials (RCTs), the incidence of AKI associated with the use of ACEIs/ARBs is poorly documented due to uncertain definitions of renal adverse events and lack of studies with kidney-related severe outcomes [36]. Of note, few clinical studies have been conducted to compare the

incidence of AKI in patients using ACEIs or ARBs versus non-users of RAAS blockers. Some studies reported a higher risk of AKI with the concomitant use of RAAS blockers with diuretics and NSAIDs [37, 38]. In contrast to ARBs, mainly excreted by the liver, the dosage of ACEIs, cleared by the kidney, must be adapted to account for renal clearance in patients with CKD to avoid AKI. It has been suggested that the risk of AKI might be lower with ARBs than with ACEIs in patients with impaired renal function, especially in the elderly population [39]. The risk of AKI in emergency medical admissions has been shown to be higher among users of ACEIs/ARBs at target or above target dosages so that physicians should adjust RAAS blockade according to eGFR [40]. The best evidence emerges from several studies that demonstrated an escalated risk of AKI linked with combined ACEI/ARB prescription as compared to monotherapy in patients with diabetic nephropathy [41, 42], which led to a recommendation of discontinuation or strict limitation of this dual therapy.

Higher rates of AKI on ACEI or ARB therapy were not reported in any of the landmark RCTs that demonstrated the benefits of these drugs in slowing progression of diabetic kidney disease but, once again, this could at least partly due to the fact that these trials were conducted in an era before agreement on a uniform definition of AKI [33]. Of note, however, a subgroup analysis of data from the EMPA-REG OUTCOME trial by baseline background medications found a slightly increased risk of AKI in patients on RAAS inhibitors compared to patients not taking these drugs, both in patients treated with placebo (7% versus 5.2%) and in patients treated with empagliflozin (5.3% versus 4.5% in the subgroup empagliflozin 10 mg and 5.9% versus 2.7% in the subgroup empagliflozin 25 mg) [43].

In the absence of clear-cut RCT data, information on the link between RAAS inhibitors and AKI comes from observational studies. Most of them were undertaken among hospitalised patients exposed to potential well-known biases inherent to observational studies [33]. In an ecological analysis, up to 15% of the increase in AKI admissions in England over a 4-year time period (2007−2011) was potentially attributable to increased prescribing of ACEIs and ARBs. However, these findings are limited by the lack of patient level data such as indication for prescribing and patient characteristics [44]. The most robust observational evidence comes from population-based cohort studies where baseline comorbidities and co-medications can be accounted for. There are only a few studies of this type and they have shown only weak or no association between ACEi/ARB use and AKI: hazard ratio (HR) 1.12 (95% confidence interval (CI) 1.07−1.17) in hypertensive patients [20], unadjusted odds ratio (OR) 1.93 (1.81−2.06) falling to 1.11 (1.02−1.20) when adjusted for several potential confounders in a large cohort of patients registered with UK general practitioners [45], HR 1.14 (1.02−1.29) in patients with coronary artery disease [46], no increase in relative risk among users of ACEIs/ARBs compared with users of other antihypertensive agents following different infections [47]. In a meta-analysis of retrospective studies of patients undergoing cardiovascular surgery, preoperative use of RAS blockers was associated with borderline increased odds of postoperative AKI (OR 1.17; 95% CI, 1.01−1.36; p = 0.04) [48]

If RAAS inhibitors could be potentially associated with AKI, the degree of increased risk varies between patient groups depending on individual characteristics [20]. In a study that used routine clinical data to quantify risk factors for AKI in ACEI/ARB users [49], patients with increasing comorbidity were at highest risk of AKI, with many conditions associated with increased risk of AKI, including diabetes mellitus, heart failure and CKD, where there is high-grade evidence for using RAAS blockers in accordance with international guidelines [18, 26]. A study examined the association between ACE/ARB use and AKI by evidence-based indication. Although RAAS blockade increases the risk of AKI overall, in patients with an evidence-based indication, the majority of the effect was explained by underlying co-morbidities. In contrast, in people without an evidence-based indication, prescription of RAAS blockers was found to be an independent predictor of AKI [45].

Decreased risk

The role of the RAAS in renal physiology and pathophysiology is highly complex, which may result in contrasted results [19, 33]. A systematic review that analysed the impact of exposure to ACEIs/ARBs in patients experiencing AKI showed that exposure to RAAS blockers after AKI is associated with lower risks of all-cause mortality, recurrent AKI, and progression to incident CKD [50]. This was confirmed in a recent retrospective cohort of veterans where the use of RAAS blockers among survivors of moderate-to-severe AKI was associated with little to no difference in risk for recurrent AKI but was associated with improved survival [51]. The conclusion was that reinitiating or starting RAAS inhibitors among patients with strong indications is warranted but should be balanced with individual overall risk for recurrent AKI and with adequate monitoring [51]. Continued use of RAAS inhibitors has been proposed among three strategies to preserve kidney function and minimize further kidney injury in patients with 'incipient AKI' [52]. A meta-analysis of studies with propensity score analysis evaluated the risk of postoperative AKI in patients who received preoperative RAAS inhibitors. It demonstrated that the pooled relative risk of AKI in patients receiving RAAS inhibitors was slightly decreased (HR 0.92, 95% CI: 0.85−0.99) [53].

Overall, it has been proposed that healthcare providers will have to use clinical reasoning rather than guideline-based reflex attitudes to decide whether ACE/ARB therapy should be stopped in response to a small increase in serum creatinine level and even following an AKI event in patients for whom there is a strong evidence-based indication for long-term use of RAAS blockers [33].

AKI with SGLT2is

SGLT2is have a specific innovative mode of action by inhibiting tubular glucose reabsorption, which results in a glucose-lowering effect independently of insulin [54]. Furthermore, glucosuria is accompanied by osmotic diuresis and at least transient natriuresis [55], all effects that result in some weight loss, lowering of arterial blood pressure and reduction in fluid overload. Several large prospective placebo-controlled cardiovascular and renal outcome trials have shown the potential of this pharmacological class to reduce rates of hospitalization for heart failure and progression of renal disease [56, 57]. SGLT2is are increasingly used among patients with T2DM [56]. They are now considered as a first-choice glucose-lowering drug (or a second-choice after metformin) in individuals with renal disease or heart failure and as an alternative choice to GLP-1 receptor agonists in patients with atheromatous cardiovascular disease in recent international guidelines issued by endocrinologists, cardiologists and nephrologists [18, 58, 59]. Overall, nephroprotection has been consistently reported with SGLT2is, yet a possible risk of AKI has been suspected in some patients. Of note, the risk of AKI with SGLT2is varied according to the source of data published in the literature, but most results from RCTs and observational retrospective studies are reassuring.

Case reports

SGLT2is have been associated with the occurrence of AKI events in several case reports [60–64]. Kidney biopsies were performed in most of these patients and showed the following histological findings: extensive vacuolisation with foamy appearance and epithelial cell injury with cytoplasmic swelling of proximal tubular cells suggestive of osmotic nephropathy [60, 61], acute tubular necrosis with extensive cytoplasmic vacuolisation and areas of tubulitis [64],

marked acute tubulointerstitial nephritis with lymphocytic infiltrates and eosinophils in the interstitium and focal tubulitis [62].

Nevertheless, the renal safety or SGLT2is is overall reassuring [65–67]. It has been hypothesized [68] that the early onset of AKI events with SGLT2is in some post-marketing reports might reflect the acute changes in eGFR attributable to the known renal haemodynamic effects of SGLT2 inhibition (initial dip), to some extent close to those well known for RAAS inhibitors, as discussed below (Table 1) [16].

Pharmacovigilance reports

In 2016, the U.S. Food and Drug Administration (FDA) Adverse Events Reporting System (FAERS) collected over 100 cases of AKI for canagliflozin and dapagliflozin since their approval. The proportion of cases with AKI among reports with SGLT2is was almost three-fold higher compared to reports without these drugs (relative OR 2.88, 95% CI 2.71–3.05, $p < 0.001$) [69]. In a more recent Chinese study published in 2019 based on the related data in the US FAERS, the reporting odds ratio (ROR) values of AKI events associated with all SGLT2is was 2.84 (95% CI 2.71–2.98) in patients with diabetes. When SGLT2is were combined with RAAS blockers, the corresponding ROR was even higher, reaching 4.05 (3.66–4.48). Of note, these ROR values were slightly higher when SGLT2is were combined with diuretics (ROR 6.07, 5.27–7.00) or with NSAIDs (ROR 4.66, 3.79–5.74) [70].

More reassuring data were recorded in the Japanese Adverse Drug Event Report database (JADER) (4322 adverse events of interest that involved SGLT2is between April 2014 and February 2019); indeed, the ROR for acute renal failure with SGLT2is versus other glucose-lowering drugs was calculated as 1.0 (95% CI 0.9–1.2) [71].

Of note, post marketing surveillance of suspected adverse drug reactions through spontaneous reporting is challenging and exposed of potential reporting biases [72].

R&D phase 3 trials

In phase 3 RCTs that were published before cardiovascular and renal outcome trials, AKI episodes were reported in 10 trials (7 with placebo and 3 with an active comparator). The number of AKI adverse events was very low in these trials and pooled estimate was non-significant (relative risk 0.48; 95% CI 0.14–1.64) [73].

Cardiorenal outcome trials

When considering the safety results with canagliflozin, dapagliflozin and empagliflozin in cardiovascular/renal outcome trials, several meta-analyses reported statistically significant 25 to 35% reductions in AKI events in patients treated with SGLT2is compared to placebo: HR 0.66 (95% CI 0.54–0.80) [74], risk ratio 0.75 (95% CI 0.66–0.85) [75], HR 0.74 (95% CI 0.64–0.85) [76].

Post-hoc analyses of major outcome trials confirmed positive results with SGLT2is. In DECLARE-TIMI 58, serious adverse events of AKI were reported by 0.8% of patients in the dapagliflozin group versus 1.2% in the placebo group (HR 0.64, 95% CI 0.47–0.88, $p = 0.005$). This reduction was consistent across all subgroups considered [77]. When focusing on elderly patients, AKI was reported at higher rates with increasing age ($P = 0.0001$), but AKI events were overall fewer with dapagliflozin versus placebo, with no age-based treatment interaction ($P = 0.6922$) [78]. A trend for a reduction in AKI incidence was also reported in two landmark studies carried out in patients with CKD and albuminuria. In CREDENCE (a trial where all patients were treated with a RAAS inhibitor), the event rate of AKI was 1.7 per 100 patient-years in the canagliflozin 100 mg group compared with 2.0 per 100 patient-years in the placebo group (HR 0.85, 95% CI 0.64–1.13, $P = 0.30$), without heterogeneity across the different subgroups considered, including the use versus no-use of diuretics (p for interaction = 0.50); a similar trend was observed when considering AKI related serious adverse events (HR 0.79, 95% CI 0.52–1.19), $P = 0.26$) [79]. In DAPA-CKD, AKI-related serious adverse events were not significantly different and occurred in 52 (2.5%) and 69 (3.2%) participants in the dapagliflozin 10 mg and placebo groups, respectively (HR 0.77, 95% CI 0.54–1.10) [80].

In a meta-analysis that included 10 eligible RCTs with a total of 71,553 participants, the use of SGLT2i was associated with reduced risks of AKI (risk ratio 0.84, 95% CI 0.77–0.91) and hyperkalaemia (RR 0.84, 95% CI 0.72–0.99) [81]. In a network meta-analysis of 18 trials with a total of 2051 AKI events (range: 1–300) among 156,690 patients with T2DM, SGLT2is were associated with a lower risk of AKI compared with placebo (OR 0.76; 95% CI 0.66- 0.88). Even more interesting from a clinical point of view, SGLT2is were significantly associated with a lower risk in AKI than both DPP-4 inhibitors (OR 0.68; 95% CI 0.54–0.86). and GLP-1 receptor agonists (OR 0.79; 95% CI 0.65–0.97) [82].

Finally, in a detailed analysis of 47 (35 of them judged as of low quality) quantitative systematic reviews assessing SGLT2i safety, none of the agents investigated in these publications (canagliflozin, dapagliflozin, empagliflozin) were associated with an increased risk of AKI [83]

Observational real-life studies

In a meta-analysis of 4 observational studies with 5 cohorts ($n = 83,934$), 777 AKI events were reported. The odds of suffering AKI were reduced in patients receiving SGLT2is (OR 0.40, 95% CI 0.33–0.48, $P < 0.001$) [84]. The low OR is most probably explained by the fact that one large study (only available as an abstract) included in this meta-analysis considered “hospitalization for kidney disease” instead of true AKI. In another recent systematic review [85], a numerical reduction in AKI events associated with SGLT2i exposure was noticed in 4 observational studies published in 2017–2019 (point estimates ranging from 0.40 to 0.72) [86–88], although the confidence intervals were wide and all crossed unity, suggesting that these studies may be underpowered with a too short follow-up.

In a recent updated meta-analysis of 9 cohorts from 8 observational studies worldwide (North America, Europe, Asia) [86–93], the relative risk of AKI was significantly reduced (HR 0.61, 95% CI 0.55–0.67, $P < 0.0001$) in SGLT2i users (725 AKI events/68,802 patients) compared with non-users (treated with other glucose-lowering agents, including incretin-based compounds: 977 AKI events/67,458 patients), yet with a certain degree of between-study heterogeneity ($I^2 = 70\%$) [94].

A lower incidence of AKI events was also reported in two recent studies, a small-size study in patients with T2DM and heart failure [95] and a cohort study using US Medicare data [96]. The latter observational retrospective study (the largest one published so far) that compared 90,094 propensity score-matched T2DM patients >/= 66 years old found fewer AKI events in SGLT2i users compared with GLP-1 RA users (HR 0.85 0.79–0.92) [96].

Even if most observational studies used propensity-score matching to compare SGLT2i users versus non-users, this statistical method does not eliminate possible biases of sample selection due to different prescriptions by physicians according to patient profiles [97]. A second limitation of the published observational studies was the rather short (< 1 year in most studies) follow-up. However, in case reports of AKI, the adverse events occurred within the first few weeks-months after the initiation of SGLT2i therapy [60–64]. A final limitation was the use of different definitions of AKI between studies [24], yet the results appear consistent whatever the definition used [94].

Thus, as for the recognized nephroprotective effects [98], patient data from routinely collected medical records complement evidence from outcome trials and overall showed a reduced risk of AKI with SGLT2is. Because of the consistent results of a reduction rather an increase of the risk of AKI in patients treated with SGLT2is, one can

endorse the conclusion that "we can finally stop worrying about SGLT2is and AKI" [99]. Whether there may be some differences between the various SGLT2is regarding the protection across AKI remains a matter of discussion, even it has been suggested that empagliflozin may exert a stronger effect compared with dapagliflozin and canagliflozin [100, 101].

AKI with RAAS blocker-SGLT2i combined therapy

In the warning by the FDA in 2016 regarding a possible increased risk of AKI with SGLT2is, caution was recommended about the combination with RAAS inhibitors [22]. Interestingly, cases of AKI were four times more likely to report concomitant use of RAAS inhibitors and diuretics, compared to cases with SGLT2is reporting other adverse events [69]

From a haemodynamic point of view, a combination of pre-glomerular arteriole constriction through SGLT2is and post-glomerular arteriole dilation under RAAS inhibition would be expected to cause an increased risk of AKI [102]. However, a large majority (> 75%) of patients recruited in the cardiovascular and renal outcome trials received RAAS inhibitors, yet a reduction rather than an increase in AKI events was reported in patients treated with an SGLT2i compared to those treated with a placebo [74–76]. Similarly, in the observational studies considered in a recent meta-analysis [94], most patients receiving an SGLT2i were also treated with a RAAS inhibitor.

In a nationwide Japanese retrospective cohort study that aimed to identify factors associated with an increased risk of AKI in patients with T2DM treated with SGLT2is, the use of RAAS inhibitors was more frequent among patients who developed AKI (307/476 = 64.5%) compared to the cohort of patients without AKI (93,781/171,146 = 54.8%, $P < 0.001$). Of note, an even more pronounced difference was noticed for diuretic use (52.5% versus 19.8%, respectively, $P < 0.001$) [103]. A retrospective survey over 12 months examined whether the effect of SGLT2is on eGFR may be influenced by concomitant medications. Under background therapy with RAAS inhibitors, the initial drop in eGFR observed with SGLT2is was only marginally greater than in patients not using RAAS inhibitors ($P = 0.059$) [104]. In a subgroup analysis of the CVD-REAL 3 multinational observational cohort study, the annual rate of eGFR decline in patients treated with SGLT2is was only slightly greater in the group receiving RAAS blockers compared to the group without RAAS blockers: −1.04 (−1.22 to −0.86) versus −0.75 (−1.04 to −0.45) ml/min/1.73 m^2) [105].

A post-hoc analysis evaluated the effects of dapagliflozin 10 mg/day over 12–24 weeks across 13 placebo-controlled studies in T2DM patients with a urinary albumin-to-creatinine ratio (UACR) ≥ 30 mg/g treated with or without RAAS inhibitors at baseline. Overall, adverse events were more common in patients with RAAS inhibitors, presumably because these patients were older and had a longer duration of T2DM, compared with patients without RAAS inhibitors. However, among patients with RAAS inhibitor treatment, the adverse event profile, including renal adverse events, was similar in the placebo and dapagliflozin treatment groups [106].

A subgroup analysis of data from the EMPA-REG OUTCOME trial by baseline background medications found a slightly increased risk of AKI in patients on RAAS inhibitors compared to patients not taking these drugs in both placebo and empagliflozin groups, but the risk of AKI with RAAS inhibitor use tended to be lower in patients also taking empagliflozin (5.3% with the dose 10 mg and 5.9% with the dose of 25 mg versus 7% with placebo) [43]. In DECLARE TIMI 58, AKI events were less frequent in the dapagliflozin group than in the placebo group, a finding consistent across all subgroups, including in users versus non-users of RAAS inhibitors and diuretics [77].

In a recent systematic review and meta-analysis of eight RCTs, aggregate published data suggested that the combination of SGLT2is and RAAS inhibitors in the treatment of patients with T2DM may be similar in efficacy and safety if not superior to SGLT2is alone. However, specific data on AKI events were not mentioned in this paper [107].

Of note, a re-examination of US FAERS data, combined with Japan observations, indicated that the signal of AKI with SGLT2is tends to be reduced in patients with concomitant use of a RAAS inhibitor, yet this conclusion requires further confirmation [108]. Thus, overall, combined therapy with SGLT2is and RAAS inhibitors appears safe from a renal point of view, at least in the absence of haemodynamic instability [109, 110].

Underlying mechanisms

Why a focus on AKI with SGLT2is?

The role of RAAS inhibitors in AKI, when used in monotherapy and beyond any episode of hypovolaemia, has been debated. Most recommendations are still to stop RAAS inhibitors in case of AKI [26], even if some data argue for a beneficial effect of these drugs in this condition by different mechanisms [2, 19, 33]. More obviously, AKI is frequently observed in clinical practice when RAAS inhibitors are used in combination with NSAIDs [37, 38]. Indeed, both drugs decrease intra-glomerular pressure, RAAS inhibitors by acting on the efferent arteriole (vasodilatation) [26] and NSAIDs by acting on the afferent arteriole (vasoconstriction) [111]. The risk of AKI is still increased in every clinical situation of volume depletion (diarrhea, cirrhosis, nephrotic syndrome etc.). Such a volume depletion can also be due to diuretics, and indeed, epidemiological studies have showed a significant increase of AKI with the triple combination of NSAIDs, RAAS inhibitors and diuretics [38].

The risk of AKI was logically examined and dreaded with SGLT2is. Indeed, in parallel to the mechanism of RAAS inhibitors, the positive effect of SGLT2is on albuminuria and renal outcomes is explained, at least in part, by a reduction of the intra-glomerular pressure [112–114]. On the other hand, the positive effect of SGLT2is on hospitalization for heart failure is also explained, at least in part, by a diuretic effect [55]. Therefore, because the vast majority of patients included in RCTs were still treated by RAAS inhibitors, the potentially harmful triad was present: RAAS inhibitors, together with a drug with diuretic activity, combined with an additional and independent effect on glomerular haemodynamics. During particular medical circumstances (injection of contrast-product), and in association with usual co-medications (NSAIDs, high-dose diuretics), particularly if baseline glomerular filtration rate is decreased, patients treated with SGLT2i may be at risk of AKI, thus warranting caution when prescribed [115]. Of note, as with RAAS blockers [31, 32], the initial dip in eGFR observed soon after the initiation of SGLT2i therapy should not be viewed as a nephrotoxic effect of the drug. On the contrary, it most probably reflects the protective mechanism of action of this pharmacological class and should not lead to any safety concern, especially a fear of AKI development [116].

Besides intra-renal haemodynamic changes, another potential deleterious mechanism concerns changes in renal energy metabolism [117]. The reabsorption of glucose by the proximal tubules, which is enhanced in diabetic patients, is dependent on the electrochemical gradient of sodium established by the Na^+/K^+ co-transporter, consuming adenosine triphosphate generated by oxidation [118]. The kidney of the diabetic patient is thus a high consumer of oxygen, which could lead to chronic renal hypoxaemia, itself promoting inflammation and fibrosis [118, 119]. Data from animal models have suggested that inhibition of this transport by SGLT2is could reduce oxygen consumption by 30% [120], and preliminary data in humans (oxygenation of the cortex being assessed by magnetic resonance) go in the same direction [121]. The glucose reabsorption could, however, be shifted to the late proximal tubule and the ascending limb of the loop of Henle, where oxygen consumption is increased [117]. SGLT2 could then induce hypoxia in the medulla, which will lead to

secretion of erythropoietin but could also theoretically increase the sensitivity of the medulla to ischaemic insults [102, 118, 122].

Finally, other hypotheses including increased intratubular uric acid concentrations or increased production of sorbitol and fructose have been evoked to participate in AKI risk with SGLT2is [102, 123].

But the risk of AKI is low (and maybe reduced) with SGLT2is

Several hypotheses can be advanced to explain the reassuring and often favourable results regarding the risk of AKI reported in both RCTs and real-life studies.

Back to the haemodynamic effects of SGLT2is in the glomerulus, by blocking the reabsorption of glucose and sodium, SGLT2is lead to more delivery of sodium to the macula densa, a condition that restores the tubuloglomerular feedback, and finally decreases the intra-glomerular pressure. Once again, this mechanism is one of the explanations for the renal benefit of these drugs, but also for the early dip in GFR observed at the initiation of the therapy [17]. The subtle mechanisms leading to the decrease of the intra-glomerular pressure are more debated. Cherney et al. suggested that SGLT2is have a vasoconstrictive effect on the afferent arteriole [18], whereas van Bommel et al. favoured an vasodilatory effect of SGLT2is on the efferent arteriole. Of importance, in the last study, most patients were also treated with RAAS inhibitors [6]. As discussed by these authors, the fact that preglomerular perfusion is relatively preserved (contrary to the action of NSAIDs) could be one explanation of the low risk of AKI with SGLT2is [6].

The diuretic component of SGLT2is is also a part of the story about the theoretical risk of AKI. However, the diuretic action of SGLT2is could be a bit different from other diuretics, and the overall contribution of their diuretic effect, due to an osmotic or natriuretic component, to better cardiorenal outcomes is still debated [55]. Contrary to classical diuretics, SGLT2is seem to have several advantages: no increased sympathetic activity, no or few ionic disturbances, and a favourable metabolic profile (in terms of insulin resistance, glycaemic control, lipid profile and serum uric acid) [55]. Furthermore, as previously discussed [55], the diuretic effect of SGLT2is could specifically act on the extravascular, interstitial volume [124–126]. Thus, SGLT2is could be this ideal diuretic which acts on lung overload and/or lower limb oedemas, but maintains the efficient intra-vascular volume. If such an action is confirmed, it may be an elegant explanation of the low risk of AKI reported with this pharmacological class.

Other mechanisms of action have been described to explain the neutral (and most probably beneficial) effect of SGLT2is regarding AKI. One of the main clinical effects of SGLT2is is doubtless the outstanding results on hospitalization for heart failure [127]. The connection between kidneys and the heart is well-known, with the description of the cardio-renal syndrome [128, 129]. AKI is a classical complication of acute heart failure [130]. If a drug, such as SGLT2is, is preventing hospitalization for heart failure, it may be expected that it could be also associated with a decreased in AKI episodes.

Other potential mechanisms of protection against AKI have been proposed in fundamental research. We already discussed the potential role of SGLT2s on the hypoxaemic status of the medulla. Recently, this observation has been suggested to potentially have beneficial effects [102]. Indeed, ex vivo dapagliflozin was associated with increased expression of hypoxaemia-inducible factors, which have been shown to decrease ischaemia-reperfusion tubular injury [102, 131]. Other authors have proposed in a rodent model of ischaemia-reperfusion that SGLT2is induce a reduction of glucose uptake and stimulate the expression of vascular endothelial growth factor-A, which could maintain neoangiogenesis in AKI [132]. Of note, however, all these mechanisms remain hypothetical.

Conclusion

As with RAAS inhibitors, there has been concern about use of SGLT2is in patients with T2DM and increased risk of AKI, as suggested by several case reports and post-marketing pharmacovigilance surveys (FAERS). However, the current evidence points in the opposite direction, i.e. that SGLT2is appear to be associated with a reduction in AKI events as shown both in large prospective placebo-controlled outcome trials and in retrospective observational cohort studies in real-life. A reduction in AKI with SGLT2is was also observed in subgroups of T2DM patients commonly recognised as being at higher risk such as elderly people, individuals with CKD and proteinuria and patients treated with RAAS blockers and diuretics. One limitation of all these clinical observations is the heterogeneity of definitions used to ascertain the presence or not of AKI, so that comparison between studies may be hazardous. The literature is rather poor regarding the risk of AKI with RAAS inhibitors despite the widespread use of these agents for many years while it is already extensive for SGLT2is after a few years of commercialization. This may reflect an increasing fear of side effects with new drugs, especially by regulatory agencies, in recent years compared to the common situation 30 years ago. Overall, these reassuring findings do not preclude that AKI may occur in patients treated with SGLT2is. However, most probably this adverse event results from other underlying conditions that favour marked dehydration or the co-administration of other potentially nephrotoxic agents.

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