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Editorial Comment

EDITORIAL COMMENT

The dirty little secret of urate-lowering therapy: useless to stop chronic kidney disease progression and may increase mortality

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ABSTRACT

Hyperuricaemia is frequent in chronic kidney disease (CKD). Observational studies have shown an association with adverse outcomes and acquired hyperuricaemia (meaning serum urate levels as low as 1.0 mg/dL) in animal models induces kidney injury. This evidence does not justify the widespread use of urate-lowering drugs for asymptomatic hyperuricaemia in CKD. However, promising results from small, open-label studies led some physicians to prescribe urate-lowering drugs to slow CKD progression. Two recent, large, placebo-controlled trials (CKD-FIX and PERL) showed no benefit from urate lowering with allopurinol on the primary endpoint of CKD progression, confirming prior negative results. Despite these negative findings, it was still argued that the study population could be optimized by enrolling younger non-proteinuric CKD patients with better preserved glomerular filtration rate (GFR). However, in these low-risk patients, GFR may be stable under placebo conditions. Additionally, the increased mortality trends already identified in gout trials of urate-lowering therapy were also observed in CKD-FIX and PERL, sending a strong safety signal: 21/449 (4.7%) and 10/444 (2.2%) patients died in the combined allopurinol and placebo groups, respectively [chi-squared P-value 0.048; relative risk 2.07 (95% CI 0.98–4.34); P = 0.06]. Given the absent evidence of benefit in multiple clinical trials and the potentially serious safety issues, the clear message should be that urate-lowering therapy should not be prescribed for the indication of slowing CKD progression. Additionally, regulatory agencies should urgently reassess the safety of chronic prescription of urate-lowering drugs for any indication.

Keywords: allopurinol, asymptomatic hyperuricaemia, chronic kidney disease, febuxostat, gout, mortality, urate

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WHY IS LOWERING SERUM URATE BEING EXPLORED AS A TREATMENT FOR CKD?

Chronic kidney disease (CKD) is defined as a decrease in renal function, assessed as estimated glomerular filtration rate (eGFR), to <60 mL/min/1.73 m^2 or evidence of kidney damage (even in the presence of normal GFR), such as increased albuminuria [urinary albumin:creatinine ratio (UACR) >30 mg/g], abnormal urinary sediment, structural abnormalities detected by ultrasound or other abnormalities, persisting for >3 months that have implications for health [1]. CKD is associated with an increased risk of acute kidney injury (AKI), CKD progression to end-stage kidney disease (ESKD) and death (all-cause and cardiovascular) [1]. Since the progressive nature is intrinsic to the definition of CKD and the global burden of CKD is increasing and expected to become one of the top five causes of death in the near future [2, 3], novel approaches to prevent CKD progression are needed. Hyperuricaemia is frequent in CKD and severe hyperuricaemia may cause AKI. Observational studies have shown an association of hyperuricaemia with adverse outcomes and acquired hyperuricaemia in experimental animals induces kidney injury [4–6]. Thus the hypothesis was put forward that urate lowering, or treatment of asymptomatic hyperuricaemia, may slow CKD progression.

WHAT DOES HYPERURICAEMIA MEAN?

The first stumbling block for treating hyperuricaemia is that there is no universally accepted definition of hyperuricaemia or asymptomatic serum urate thresholds that merit treatment. Many clinical laboratories use a statistical definition based on prevalence to define hyperuricaemia, as is done for most biochemical variables. In our centre, this is >5.7 mg/dL for females and >7.0 mg/dL for males [7]. However, this makes little pathophysiological sense. It would imply that urate solubility or negative pathophysiological impact differs for males and females, which has not been demonstrated in humans, although indeed serum urate levels are higher in males than in females and severe kidney disease requiring renal replacement therapy is also more frequent in males [8, 9]. A physicochemical definition of hyperuricaemia based on the solubility limit of urate in body fluids would be a serum urate threshold >7.0 mg/dL as measured by current automated enzymatic methods. Some have proposed an even lower value of 6.0 mg/dL based on observational estimations of the lifelong risk for clinical consequences of hyperuricaemia [10]. However, the concept of 'clinical consequences of hyperuricemia' is unclear, since the only one with a clear cause-and-effect relationship is gout. The confusion regarding the definition of hyperuricaemia is reflected in inclusion criteria [e.g. 7.1–10.0 mg/dL in FEATHER (Febuxostat Versus Placebo Randomized Controlled Trial Regarding Reduced Renal Function in Patients With Hyperuricemia Complicated by Chronic Kidney Disease Stage 3), ≥4.5 mg/dL in PERL (Preventing Early Renal Loss in Diabetes), no specific threshold in CKD-FIX (Controlled trial of slowing of Kidney Disease progression From the Inhibition of Xanthine oxidase)] and target levels of serum urate in clinical trials of nephroprotection [11–13]. To complicate matters further, no information on specific serum urate thresholds can be derived from the most commonly used animal models of hyperuricaemia. Thus, unlike humans, rodents have uricase, which degrades uric acid, and hyperuricaemia is achieved by inhibiting uricase. In rats, adverse kidney effects have been described for serum urate levels as low as 1.0 mg/dL, questioning the clinical relevance of any rat study [14].

THERE IS CLEAR EVIDENCE THAT HYPERURICOSURIA CAUSES KIDNEY DISEASE, BUT IT IS UNCLEAR WHETHER HYPERURICAEMIA CAUSES KIDNEY DISEASE IN HUMANS

While there is clear evidence that hyperuricosuria causes kidney disease, it is less clear whether hyperuricaemia in the absence of hyperuricosuria causes kidney disease. Thus acute severe hyperuricaemia induces kidney injury through the intratubular precipitation of uric acid filtered by glomeruli; a condition known as acute uric acid nephropathy [15]. A classic example is tumour lysis syndrome. However, acute uric acid nephropathy does not require hyperuricaemia. The isolated presence of hyperuricosuria may cause nephropathy, as seen in genetic defects of tubular urate transport (e.g. loss of function SLC22A12 or SLC2A9 mutations) characterized by hypouricaemia and even in users of serum urate-lowering uricosuric drugs such as lesinurad [16]. The cause-and-effect relationship between excess urine uric acid and acute uric acid nephropathy is well established, since preventing uric acid synthesis or increasing uric acid degradation with drugs like allopurinol and rasburicase, respectively, prevented or accelerated the recovery from acute uric acid nephropathy in clinical trials [17]. In the literature, a distinction should be noted regarding the terms 'urate' and 'uric'. At pH 7.40, 98% of serum uric acid is ionized as urate, mainly monosodium urate. However, urine acidification shifts the balance towards uric acid, which tends to precipitate. Thus acute uric acid nephropathy confirms the nephrotoxicity of increased uricosuria but does not provide information on the potential pathogenic role of hyperuricaemia for kidney disease [18].

However, acute uric acid nephropathy is outside the scope of the current report on chronic asymptomatic hyperuricaemia and its association with the development and/or progression of CKD. This association has been suggested by multiple observational studies [19–22]. Association studies are limited by the fact that hyperuricaemia may be an early manifestation of CKD that may precede the observed decrease in eGFR. Thus a decrease in GFR will lead to a decrease in the glomerular filtration of urate and to an increased serum urate. However, the relationship between the magnitude of GFR decrease and the magnitude of serum urate increase depends on multiple confounding factors, including genetic determinants of serum urate, which explain 60% of serum urate concentration variability and may lead to an increase in serum urate above the expected values for the degree of GFR reduction or muscle mass variability that may alter eGFR values calculated by serum creatinine-based equations [e.g. Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)] that assume a fixed muscle mass for individuals of similar sex, age and ethnicity [23]. Additionally, certain genetic nephropathies, such as autosomal dominant tubulointerstitial kidney disease, as well as acquired nephropathies such as lead intoxication, which are underdiagnosed, are also associated with hyperuricaemia [24–26]. Thus the concept of an expected increase in serum urate levels for a certain decrease in GFR is unclear.

Chronic urate nephropathy is the term used to describe a chronic tubulointerstitial nephropathy that occurs in patients with hyperuricaemia and is characterized by sodium urate

crystal deposition in the medullary interstitium because of hyperuricaemia itself, with the potential participation of intratubular precipitation of uric acid [15]. Chronic urate nephropathy is frequently a diagnosis of exclusion, made in the presence of criteria such as CKD, mild proteinuria, unremarkable urinary sediment and hyperuricaemia, while many authors feel that it cannot be diagnosed in the absence of a kidney biopsy [27]. The difficulty of the diagnosis is compounded by the frequent poor representation of the medulla in kidney biopsies, which are intended to sample the cortex. The authors believe that, additionally, the diagnosis cannot be made unless lead intoxication and autosomal dominant tubulointerstitial kidney disease have been excluded. These new criteria would render meaningless the older literature on chronic urate nephropathy and identify a research need to redefine chronic urate nephropathy. Only after there is agreement on the concept of chronic urate nephropathy can studies be designed to address its pathophysiology and therapy. In any case, the focus of the present article is not chronic urate nephropathy, but the use of serum urate-lowering drugs to prevent the progression of CKD from other causes.

WHY RODENT STUDIES ARE NOT RELEVANT FOR THE ROLE OF URATE IN HUMAN CKD?

A large body of evidence on the nephrotoxicity of hyperuricaemia derives from studies in rats or mice in which uricase was inhibited to cause hyperuricaemia. As an example, rat serum urate levels are low (0.5–2.5 mg/dL) and 'hyperuricemia' means serum urate levels of 1.0–5.4 mg/dL [14, 28, 29]. Thus the rat is not a suitable model to study the impact of hyperuricaemia on the human kidney. Any impact of serum urate levels of 1.0–5.4 mg/dL in rat kidneys will be meaningless for humans who have normal serum urate levels of 3.5–6.0 mg/dL. Clearly, rodent physiology is not adapted to those levels of serum urate, while human physiology is. Furthermore, rat data are not consistent and pathways for kidney disease identified in rats are already targeted by the current standard therapy for CKD in humans, so even if they did apply to humans, no additional benefit from serum urate lowering can be expected. Thus it has been hypothesized that in rats, 'hyperuricemic' kidney injury is caused by kidney ischaemia and hypertension resulting from renin–angiotensin system (RAS) activation, endothelial nitric oxide release inhibition, glomerular arteriole injury and changes in glomerular arteriole resistance [14, 28, 30]. However, the results obtained in repeated experiments and the impact of urate-lowering therapy have not been consistent [14, 28, 30] (Figure 1). Recent reports in humans do not resemble rat data, as a wide range of serum urate values was not associated with changes in calculated efferent arteriole resistance, while there was a U-shaped relationship between serum urate and glomerular afferent arteriole resistance [31]. Thus serum urate in the 3.5–6.0 mg/dL range was not associated with changes in afferent arteriole resistance and the highest values of serum urate reached in rats were not associated with altered glomerular arteriole resistance in humans [31]. Furthermore, if indeed, as suggested by rat studies, RAS activation was a key contributor to hyperuricaemia-induced kidney injury, then chronic urate nephropathy would be expected to respond to the current standard of therapy for CKD (i.e. RAS blockade), rendering the specific therapy of hyperuricaemia potentially useless as a nephroprotective strategy. Indeed, some RAS blockers decrease serum urate by increasing uric acid excretion in urine [32]. Furthermore, sodium–glucose cotransporter-2 (SGLT2) inhibitors have emerged as novel nephroprotective agents that further decrease hard kidney and cardiovascular outcomes on top of RAS blockade in diabetic and non-diabetic individuals with CKD [33–36]. It is likely that the new standard of therapy for CKD will be the combination of RAS blockade with SGLT2 inhibitors. Among other potentially beneficial effects, SGLT2 inhibitors decrease serum urate by increasing urine uric acid excretion [37]. This further decreases the probability that any significant impact of urate-lowering therapy on kidney outcomes can be demonstrated in future clinical trials. Additionally, nephroprotection by SGLT2 inhibitors, as confirmed by multiple clinical trials, would argue against a deleterious effect for kidneys at the urine uric acid levels found in CKD patients, as drugs that mildly increase urine uric acid excretion, such SGLT2 inhibitors, are nephroprotective.

In summary, so far, evidence linking hyperuricaemia to CKD progression is weak, as observational studies cannot demonstrate causality and rat studies are not representative of the human condition [12, 38]. Thus definite proof that hyperuricaemia contributes to CKD progression and targeting hyperuricaemia slows CKD progression requires clinical trials demonstrating that lowering serum urate prevents CKD progression.

POTENTIAL RISKS OF TOO MUCH URATE LOWERING: INCREASED ALL-CAUSE MORTALITY

A further issue to be considered is the safety of urate-lowering strategies. Potential risks include adverse effects of the drugs employed to lower urate as well as the potential negative impact of excessive urate lowering, as discussed extensively in prior articles [16, 39, 40]. Thus allopurinol poses a risk of allergic reaction that increases as eGFR decreases. Moreover, seven recent placebo-controlled trials of urate-lowering drugs with different mechanisms of action (uricosuric: lesinurad; xanthine oxidase inhibition: febuxostat; uricase: pegloticase) observed higher mortality or trends towards higher mortality in gout patients with the largest decreases in serum urate [16]. In the largest of these gout trials, the CARES (Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities) trial exploring the cardiovascular safety of febuxostat or allopurinol in 6190 patients with gout and major cardiovascular disease, all-cause and cardiovascular mortality were significantly higher with febuxostat than with allopurinol {hazard ratio [HR] for all-cause death 1.22 [95% confidence interval (CI) 1.01–1.47], HR for cardiovascular death 1.34 [95% CI 1.03–1.73]} [41]. Febuxostat achieved lower serum urate levels and differences in mortality were most evident in patients with lower baseline urate levels [41]. These observations were in line with the U-shaped association of urate with mortality in some observational studies (reviewed in Perez-Gomez *et al.* [16]). Figure 2 [12, 41–44] shows data for achieved urate lowering from the largest placebo-controlled trials in gout, in which a numerical or statistically significant association of more profound urate lowering with mortality was observed, and compares them with the magnitude of urate lowering in recent CKD trials. In this regard, addressing safety as assessed by the impact on mortality should be a key part of the analysis of any drug prescribed for serum urate lowering.

WHAT WAS KNOWN SO FAR?

Several clinical trials have addressed the hypothesis that lowering serum urate levels may delay CKD progression. However,

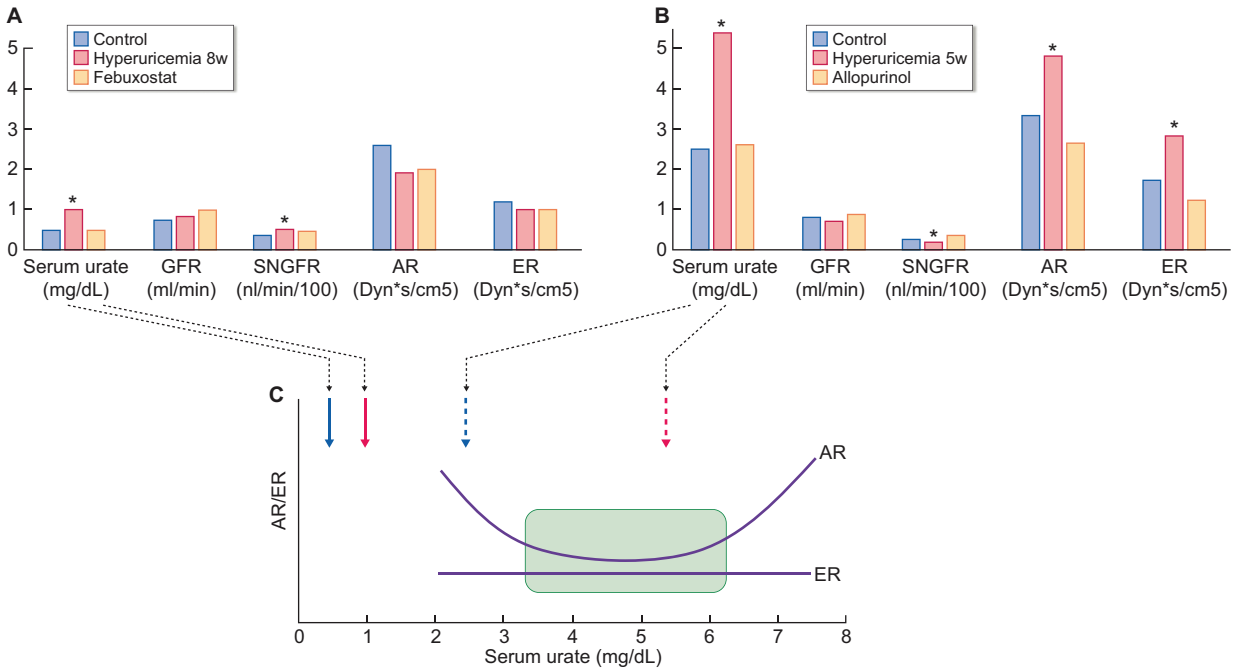

FIGURE 1: Lack of relevance of rat studies for human serum urate pathophysiology. (**A** and **B**) Results from rat studies. (A) Inhibition of rat uricase resulted in hyperuricaemia of ~1.0 mg/dL that was lowered by febuxostat [14]. (B) Inhibition of rat uricase resulted in hyperuricaemia of ~5.4 mg/dL that was lowered by allopurinol [28]. Note that although not all changes observed were statistically significant, the numerical changes associated with hyperuricaemia in different haemodynamic parameters go in opposite directions in both studies, as does the impact of urate lowering, which ranges from no impact to restoring the values found in normouricaemic animals (normouricaemia meaning serum urate 0.5 and 2.5 mg/dL, respectively). The timing of the assessment (5 weeks versus 8 weeks) does not justify opposite findings. (C) Results from human studies. Schematic representation of results from Uedono *et al.* [31]. In humans, afferent arteriolar resistance (AR) but not efferent arteriolar resistance (ER) was associated with serum urate, but the curve was U shaped: both hypo- and hyperuricaemia were associated with similar changes. The arrows denote serum urate values for the normo- and hyperuricaemia rats from (A) (continuous arrows) and (B) (broken arrows), with blue representing normouricaemic controls and red representing hyperuricaemic rats. In (A) and (B), units for the vertical axis are shown in the labels of the horizontal axis. No units are shown in the vertical axis of (C) since this is a conceptual image and numbers for AR and ER are quite different. SNGFR, single-nephron GFR. *Statistically significant difference with normouricaemic rats.

some of these trials were either open label and not controlled by placebo or small studies (Table 1) [12, 44–49]. They mostly recruited patients with established CKD, defined as eGFR <60 mL/min/1.73 m^2, only occasionally considering other CKD criteria such as proteinuria or albuminuria [47, 48, 50]. However, only two trials supported a potential benefit of urate-lowering therapy. Unfortunately they were open-label studies under clinical practice conditions and lacking a placebo control arm, and in one of them the kidney benefit was observed in secondary endpoints or *post hoc* analyses [50].

Goicoechea *et al.* [50] performed a randomized, open-label trial with a routine care (not placebo) control group that randomized 57 of 113 patients with eGFR <60 mL/min/1.73 m^2 to allopurinol 100 mg once daily. Serum urate was not an inclusion criterion. The main finding was that allopurinol decreased the risk of the primary endpoint, i.e. cardiovascular events ($P = 0.039$). There was no difference for another primary endpoint, ESKD requiring dialysis therapy, at 24 months (one patient from each group reached this endpoint). In a further analysis, during the initial 24-month follow-up, eGFR remained stable in the allopurinol group (40.8 ± 11.2 to 42.2 ± 13.2 mL/min/1.73 m^2), but decreased in the control group (39.5 ± 12.4 to 35.9 ± 12.3 mL/min; $P = 0.000$ between groups). Numerically, eGFR increased in the allopurinol group and decreased in the control group (+1.3 ± 1.3versus −3.3 ± 1.2 mL/min/1.73 m^2 after

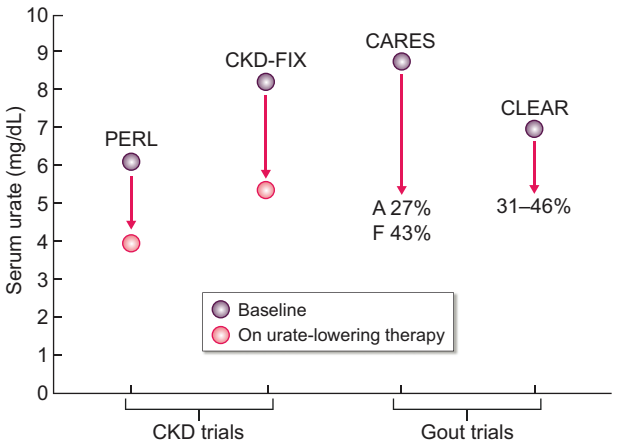

FIGURE 2: Impact of therapy on serum urate levels in key trials that send a safety signal regarding mortality for urate-lowering drugs. RCTs for urate-lowering drugs for CKD (allopurinol) or gout [allopurinol (A) versus febuxostat (F) in CARES, different doses of lesinurad on top of xanthine oxidase inhibitors in CLEAR1 and CLEAR2, which are shown together] [12, 41–44]. Data are taken from the original publication: while CKD trials reported mean achieved serum urate levels, gout trials reported the percentage of patients achieving certain thresholds of serum urate levels and the percentage of patients achieving a serum urate level <5.0 mg/dL is shown. The two numbers for CLEAR correspond to increasing lesinurad doses of 200 and 400 mg. The 400-mg dose was tested in clinical trials but is not supported by regulatory authorities.

Table 1. Key RCTs with primary endpoints referred to kidney function

Control	Author/phase (reference)	Drug	Primary endpoint	Total, *N*	RAS blockade (%)	Baseline eGFR (mL/min/1.73 m^2), (mean (SD range)	Baseline UACR (mg/g), mean (SD range)	Baseline serum urate (mg/dL)	Target urate	Cause of CKD	Follow-up (months)
No placebo control	Goicoechea *et al.*/ND [45]	Allopurinol 100 mg/day	Change in eGFR	113	78	Control 39.5 (27–52) Allopurinol 41 (29–52)	Control 35 (11–436) Allopurinol 36 (15–356)	Control 7.3 ± 1.6 Allopurinol 7.9 ± 2.1	ND	Multiple	24 (extended to 84)
	Siu *et al.*/ND [46]	Allopurinol 100–300 mg/day	>40% increase in serum creatinine, dialysis or death	51	82	Not reported	Control 2.4 ± 2.2[a] Allopurinol 2.4 ± 2.9[a]	Control 9.7 ± 1.2 Allopurinol 9.9 ± 1.7	Normal range	Multiple	12
Placebo controlled	Golmohammadi *et al.*/ND [47]	Allopurinol 100 mg/day	Change in eGFR? Not clearly specified	196	ND	44.5 (40–49)	ND	7.8 ± 1.3	ND	ND	12
	Sircar *et al.*/ND [48]	Febuxostat 40 mg/day	Percent of patients with >10% decrease in eGFR	108	57	Placebo 33 (21–44) Febuxostat 31 (18–45)	Measured qualitatively	Placebo 8.2 ± 1.1 Febuxostat 9 ± 2	ND	ND	6
	FEATHER/2 [49]	Febuxostat 40 mg/day	eGFR slope (mL/min/1.73m^2/year)	443	78	Placebo 45 (35–55) Febuxostat 45 (36–55)	Placebo 120 (17–517) Febuxostat 124 (19–525)	Placebo 7.8 ± 0.9 Febuxostat 7.8 ± 0.9	ND	ND	24
	PERL/3 [44]	Allopurinol 100–400 mg/day	Baseline-adjusted eGFR	530	90	Placebo 74 (55–93) Allopurinol 75 (57–94)	Placebo 60 (13–277)[b] Allopurinol 58 (11–302)[b]	Placebo 6.1 ± 1.5 Allopurinol 6.1 ± 1.5	ND	DM 1	38
	CKD-FIX/3–4 [12]	Allopurinol 100–300 mg/day	Change in eGFR	363	76	Placebo 32 (19–44) Allopurinol 32 (20–43)	Placebo 717 (246–1857) Allopurinol 717 (237–1947)	Placebo 8.2 ± 1.7 Allopurinol 8.2 ± 1.8	ND	Multiple	24

[a]Urinary protein:creatinine ratio in g/g.
[b]Transformed from mg/24 h on a 1:1 basis.
ND, no data.

Table 2. Key patient characteristics in the PERL and CKD-FIX Phase 3 placebo-controlled trials [12, 44]

Characteristics	PERL	CKD-FIX
N	530	363
Age (years), mean ± SD	51 ± 11	62 ± 13
Female sex, *n* (%)	179 (34)	135 (37)
DM (%)	100	58
Baseline serum urate (mg/dL), mean ± SD	6.1 ± 1.5	8.2 ± 1.8
Serum urate achieved on allopurinol (mg/dL)[a]	3.9	5.3 (95% CI 5.1–5.6)
eGFR exclusion criterion (mL/min/1.73 m^2)	<40 or ≥100	<15 or ≥60
Baseline eGFR (mL/min/1.73 m^2), mean ± SD	75 ± 19	32 ± 12
Baseline median UACR (mg/g)	58[b]	717

[a]In both trials, serum urate decreased by ~35–36% from baseline.
[b]Original data in μg/min were converted into mg/24 h and mg/24 h were assumed to be equivalent to mg/g.

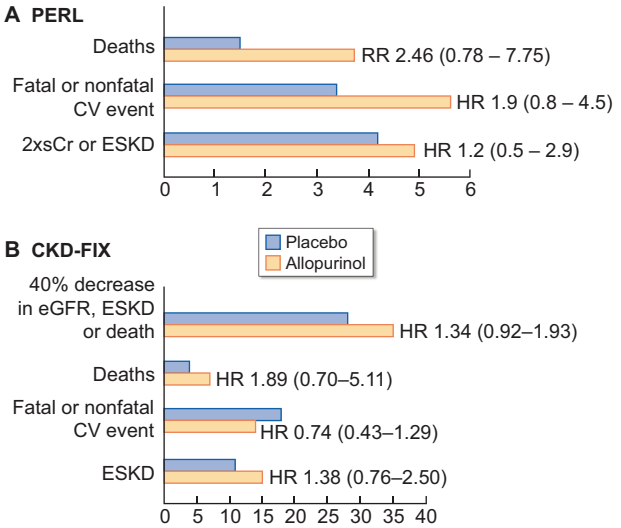

FIGURE 3: Key secondary endpoint events and safety data from the (A) PERLand (B) CKD-FIXtrials of allopurinol versus placebo in CKD patients. Note the different scale of the horizontal axis that shows the percentage of patients with events in both panels. PERL enrolled younger patients (51 versus 62 years) with type 1 diabetes, better preserved eGFR (75 versus 32 mL/min/1.73 m^2) and lower baseline serum urate values (6.1 versus 8.2 mg/dL) [12, 44]. HR or RR and 95% CIs are shown. HR was taken from the original publication while RR was calculated from deaths reported as adverse events. None of the differences was significant; however, trials were not designed to have enough power to detect statistical differences for these safety or secondary outcomes. In our opinion, a worrying safety signal emerges from these data. Note that the RR/HR for death hovers around 2 in the two trials, although the numerical difference is larger for PERL, which achieved lower steady-state serum urate levels on allopurinol.

24 months; P = 0.018) for an annualized change of eGFR of 0.65 and −1.65 mL/min/1.73 m^2/year, respectively [50]. In an extension study for five additional years (n = 56 of 107 patients on allopurinol, median total follow-up 7 years), eGFR decreased significantly less in the allopurinol than in the control group (−6.5 ± 1.6 and −13.3 ± 5.0 mL/min/1.73 m^2, respectively; P = 0.001) for an annualized decrease in eGFR in the more recent 5 years of follow-up of −1.56 and −2.00 mL/min/1.73 m^2/year, respectively [45]. Thus the between-treatment difference was 2.30 mL/min/1.73 m^2/year in the first 2 years and 0.44 mL/min/1.73 m^2/year in the next 5 years. In the extension study, a *post hoc* analysis used a different definition of renal event (starting dialysis therapy and/or doubling serum creatinine and/or ≥50% decrease in eGFR). The risk of a renal event was decreased for allopurinol patients after adjustments [HR 0.32 (95% CI 0.15–0.69), P = 0.004; adjusted for age, sex, baseline kidney function, uric acid level and renin–angiotensin–aldosterone system (RAAS) blockers]. Interpretation of the data is limited by crossover between study groups; nearly 20% of participants randomized to allopurinol stopped the drug and 20% of those randomized to untreated control started allopurinol.

Siu *et al.* [46] performed a randomized controlled trial (RCT) without a placebo arm in 51 asymptomatic hyperuricaemic (>7.6 mg/dL) CKD (proteinuria >0.5 g/day or serum creatinine 1.35–4.50 mg/dL) patients assigned to allopurinol 100–300 mg/day (n = 25) or usual therapy (n = 26) for 12 months with a primary endpoint of a >40% increase in serum creatinine, dialysis or death. The endpoint was reached in 4/25 (16%) allopurinol patients and in a surprisingly high number [12/26 (46%)] of usual therapy patients (P < 0.01) [46]. While allopurinol had a dramatic effect on systolic blood pressure (−13 mmHg), there were no significant differences in serum creatinine at the end of follow-up, which was surprising given the definition of the primary endpoint. Data on eGFR were not reported.

Golmohammadi *et al.* [47] performed a placebo-controlled trial of allopurinol 100 mg once daily for CKD patients (eGFR 15–60 mL/min/1.73 m^2) with asymptomatic hyperuricaemia (uric acid >6.0 mg/dL). Unfortunately, the data are difficult to interpret for several reasons: the study design (randomized or double-blinded), primary endpoint, pre-specified analysis plan or intention-to-treat results are unclear from the article. Patients with CKD Stages G3 and G4 were analysed separately. In any case, eGFR remained stable at 12 months in the 100 patients on placebo and there were no significant differences in eGFR at 12 months between placebo and allopurinol (n = 96) [47].

Sircar *et al.* [48] performed a double-blind, randomized, placebo-controlled trial of febuxostat 40 mg for asymptomatic hyperuricaemia (≥7.0 mg/dL) in patients with CKD Stages 3 and 4 for a primary endpoint of percentage of patients showing a >10% decrease in eGFR from baseline within 6 months. Surprisingly 15/54 (28%) patients randomized to febuxostat did not have eGFR data at the end of the study (6 months of follow-up). This was also the case for 5/54 (15%) placebo patients. Contrary to the article claim of statistical significance, a chi-square analysis of the results [>10% decrease in eGFR: placebo, 26/48 (54%); febuxostat, 17/45 (38%)] did not disclose statistically significant differences in the primary endpoint (P-value 0.11) [48].

The FEATHER trial was the largest trial until the publication in 2020 of CKD-FIX and PERL results. FEATHER randomized 443 patients with Stage 3 CKD and asymptomatic hyperuricaemia (7.0–10.0 mg/dL) to febuxostat or placebo for 9 months. Baseline serum urate was 7.8 ± 0.9 mg/dL and it plateaued at 4.2 mg/dL in the febuxostat group. The primary endpoint was the eGFR slope and there was no significant difference between groups (febuxostat 0.23 ± 5.26 mL/min/1.73 m^2/year versus placebo −0.47 ± 4.48 mL/min/1.73 m^2/year). Of note, eGFR loss did not differ from the expected age-associated eGFR loss in placebo patients. In the subgroup analysis, there was a significant difference favouring febuxostat in patients without proteinuria (P = 0.005) or in those with serum creatinine concentration below the median (P = 0.009), but there were no differences in patients in the CKD Stage G3a category, representing those with more preserved kidney function (P = 0.06). However, in these subgroups, eGFR was stable in placebo patients [49]. Specifically, eGFR loss in placebo patients without proteinuria

Table 3. Key ongoing RCTs with primary endpoints referred to kidney function

Control	Name/phase (reference)	Drug	Primary endpoint	Total N	Baseline eGFR (mL/min/1.73 m^2)	Baseline UACR (mg/g)	Baseline serum urate (mg/dL)	Target urate	Follow-up (months)
No placebo control	Uric acid reduction as a novel treatment for pediatric chronic kidney disease/2/ NCT03865407	Allopurinol	eGFR change	41	>15	ND	>5.5	3.0–5.0	6
	Compare the renal protective effects of febuxostat and benzbromarone in CKD Chinese patients/ND/NCT02944214	Febuxostat 10–80 mg/ Benzbromarone 12.5–100 mg	Serum creatinine, eGFR	800	20–60	ND	>8.0	ND	12
Placebo controlled	A study of verinurad and allopurinol in patients with chronic kidney disease and hyperuricaemia (SAPPHIRE)/2b/ NCT03990363	Verinurad 3–7.5–12 mg/ Allopurinol 100–200–300 mg	UACR	725	>25	30–5000	>6.0	ND	6

A search for CKDs and (urate or uric acid or allopurinol or febuxostat) was performed in ClinicalTrials.gov on 29 July 2020.
ND, no data.

or with better renal function (Stage G3a) was −0.10 and −0.14 mL/min/1.73m^2/year, respectively [49, 51]. Mortality was low at <0.5% (one patient from each group). The dose was progressively increased over 8 weeks to a maintenance dose of 40 mg/day febuxostat.

RECENT DEVELOPMENTS REGARDING EFFICACY OF NEPHROPROTECTION BY URATE-LOWERING DRUGS

Recently, two placebo-controlled randomized trials were published addressing the impact on CKD progression of lowering serum urate levels with allopurinol: the PERL trial and the Australia–New Zealand CKD-FIX trial [12, 13].

PERL enrolled 530 patients with type 1 diabetes mellitus (DM), with a mean DM duration of 35 years, serum urate ≥4.5 mg/dL, eGFR 40–100 mL/min/1.73 m^2 and evidence of diabetic kidney disease, defined as UACR ≥30 mg/g or a decease in eGFR ≥3 mL/min/1.73 m^2/year over the previous 3–5 years [13]. The primary endpoint was the baseline-adjusted measured GFR (mGFR; measured with iohexol) after 3 years plus a 2-month washout period. Allopurinol was uptitrated to 400 mg according to the eGFR. The mGFR should be able to detect subtler changes in GFR than the CKD-EPI or Modification of Diet in Renal Disease equations and is free from interference from changes in muscle mass or drugs that modulate tubular creatinine transport [52, 53]. The mean serum urate level decreased from 6.1 to 3.9 mg/dL with allopurinol and remained at 6.1 mg/dL with placebo. After 3 years of follow-up there were no differences in mGFR or UACR: after washout, the between-group difference in the primary endpoint was 0.001 mL/min/1.73 m^2 (P = 0.99). The mean decrease in mGFR was −3.0 mL/min/1.73 m^2/year with allopurinol and −2.5 mL/min/1.73 m^2/year with placebo [between-group difference −0.6 mL/min/1.73 m^2/year (95% CI −1.5–0.4)]. The mean urinary albumin excretion rate after washout was 40% (95% CI 0–80) higher with allopurinol than with placebo [13]. There were no significant differences in event secondary endpoints, although numerically the HR did not favour allopurinol: serum creatinine doubling or progression to ESKD, HR 1.2 (95% CI 0.5–2.9); fatal or non-fatal cardiovascular event, HR 1.9 (95% CI 0.8–4.5) (Figure 3A) [12, 44].

CKD-FIX enrolled 369 of 620 intended patients and the trial was stopped prematurely because of slow enrolment [12]. Patients had CKD Stages G3 and G4 (eGFR 15–60 mL/min/1.73 m^2) and either UACR ≥265 mg/g or eGFR had decreased at least 3 mL/min/1.73m^2 during the previous year, but there was no serum urate level criterion. Patients were randomized to placebo or allopurinol, starting at 100 mg once daily and uptitrated to 300 mg if they fulfilled specific criteria regardless of serum urate levels [12]. Mean serum urate levels in the allopurinol group decreased to 5.1 mg/dL at 12 weeks and remained at 5.3 mg/dL throughout, while it was 8.2 mg/dL in placebo patients. The primary endpoint was the change in eGFR from randomization to Week 104 calculated with the serum creatinine CKD-EPI equation. After a mean of 2 years of follow-up, there were no differences in eGFR change between groups [allopurinol −3.33 mL/min/1.73 m^2/year (95% CI −4.11 to −2.55) and placebo −3.23 mL/min/1.73 m^2/year (95% CI −3.98 to −2.47); mean difference −0.10 mL/min/1.73 m^2/year (95% CI −1.18–0.97); P = 0.85] [12]. There was also no significant difference in secondary outcomes of composite kidney events, although numerically the HR did not favour allopurinol: 40% decrease in eGFR, ESKD or death from any cause [HR 1.34 (95% CI 0.92–1.93)]

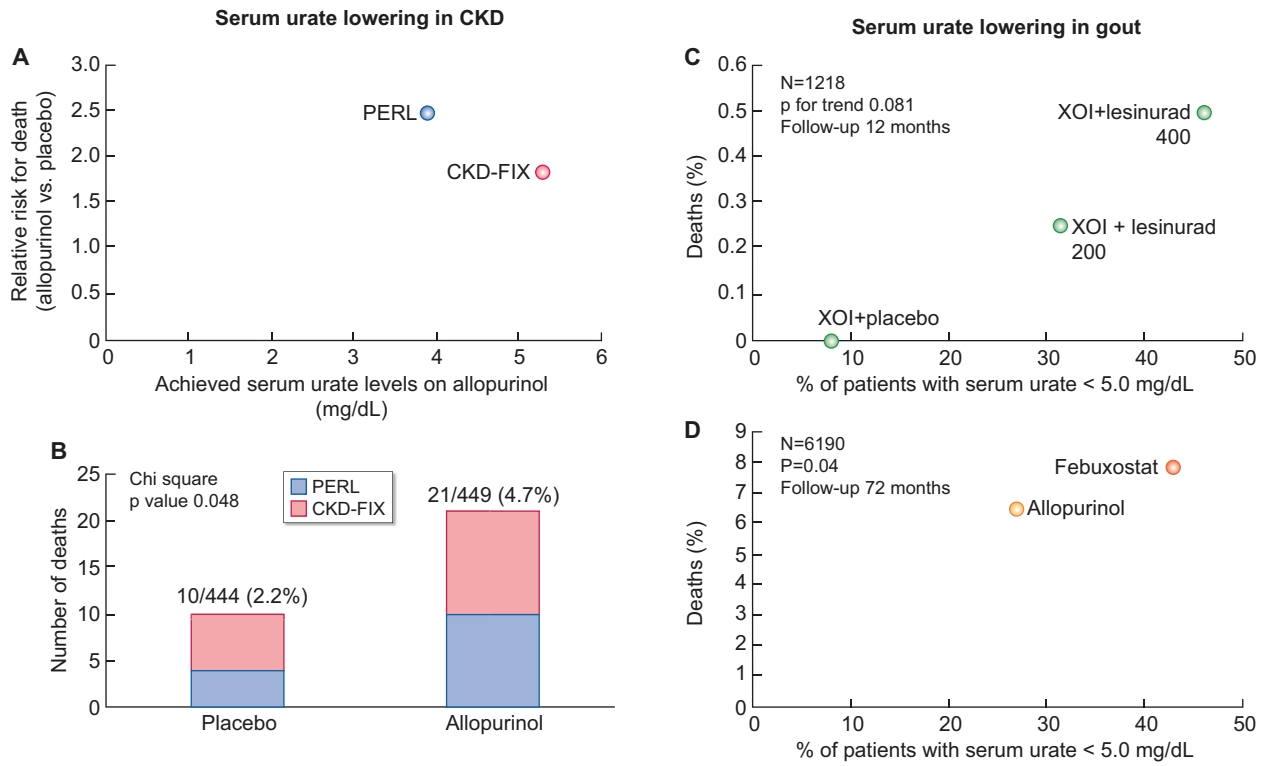

FIGURE 4: Serum urate-lowering therapy is associated with higher mortality in both CKD and gout: impact of achieved serum urate levels. Randomized, placebo-controlled trials for urate-lowering drugs for CKD (allopurinol in PERL and CKD-FIX) or gout (allopurinol versus febuxostat in CARES, different doses of lesinurad [42] on top of xanthine oxidase inhibitors in CLEAR 1 and CLEAR 2, which are shown together) [12, 41, 43, 44]. Data are taken from the original publication, while CKD trials reported mean achieved serum urate levels (**A**), gout trials reported the percentage of patients achieving certain thresholds of serum urate levels (**B, C**). Thus data relating mortality to magnitude of serum urate reduction are visualized as trending in opposite directions in the CKD and gout panels, although in both cases, lower achieved serum urate levels (to the left of the horizontal axis in A and to the right of the horizontal axis in C and D) were associated with numerically and/or statistically significant higher mortality in both the CKD and the gout environments. The increase in mortality associated with serum urate lowering in CKD reached statistical significance when CKD-FIX and PERL data were combined (combined $n = 893$) (**B**), while for gout studies there was a clear trend for higher mortality with decreasing serum urate levels for the combined CLEAR studies (combined $n = 1218$) (**C**) that was statistically significant for the CARES trial of allopurinol versus febuxostat ($n = 6190$) (**D**). In (**D**), $P = 0.04$ refers to the comparison in the number of deaths between allopurinol and febuxostat.

or 30% decrease in eGFR, ESKD or death from any cause [HR 1.23 (95% CI 0.90–1.69)] (Figure 3B). There were also no significant between-group differences in UACR or systolic or diastolic blood pressure.

Both trials differed in several aspects (Table 2). GFR was measured (iohexol) in PERL but estimated from serum creatinine (CKD-EPI) in CKD-FIX. Additionally, baseline serum urate levels were lower (6.1 versus 8.2 mg/dL) and kidney disease less severe in PERL than in CKD-FIX: eGFR 75versus 32 mL/min/1.73 m^2 and median UACR 60 versus 717 mg/g in PERL and CKD-FIX, respectively [12, 13]. Another difference relates to the use of RAAS blockade: 90% in PERL versus 76% in CKD-FIX, where UACR was 12-fold higher [12, 13]. Despite these differences, which cover a wide range of CKD presentations, neither study observed a beneficial effect of allopurinol on the rate of eGFR loss [12, 13].

Some critics pointed out that patients in the PERL trial enrolled patients with mild CKD and minimal proteinuria [54] while, conversely, others emphasized that efficacy should be tested in further RCTs enrolling patients with mild CKD and minimal proteinuria [55, 56]. Furthermore, both trials also enrolled normouricaemic individuals and CKD-FIX was considered to have inadequate power and a high percentage of participants who discontinued the trial regimen (25–30%) [54]. However, futility analysis suggested that chances of finding a statistically significant result by continuing recruitment were at the 1 in 1000 range [57]. It was also pointed out that allopurinol may acutely reduce the eGFR and later stabilize eGFR, as described for RAS blockers and SGLT2 inhibitors [54]. However, this suggestion was based on a study that did not disclose a statistically significant impact of allopurinol on eGFR at any time point [58]. Furthermore, no evidence for an acute effect of allopurinol on eGFR was observed in the first 16 weeks [mean between-group difference −0.89 mL/min/1.73 m^2 (95% CI −2.15–0.37)] of CKD-FIX [57]. Indeed, experience from other trials and a recent meta-analysis suggest that the difference in eGFR between the urate-lowering and control groups decreases rather than increases over time [45, 59].

INCREASED MORTALITY IS A SERIOUS SAFETY SIGNAL IN PERL AND CKD-FIX

The safety of urate-lowering therapy as the focus of current research was further questioned by PERL and CKD-FIX results [16, 60]. While no differences in adverse effects were found in either trial, the safety data were not totally reassuring, especially regarding mortality [12, 13] (Figure 3). In PERL, fatal serious adverse events, though uncommon, were numerically more frequent in allopurinol than in placebo patients [$n = 10$ (3.8%) versus $n = 4$ (1.5%) deaths]. In CKD-FIX, again, fatal serious

adverse events were numerically higher in allopurinol [$n = 11$ (6%)] than in placebo [$n = 6$ (3%)] patients. Overall, 21/449 (4.7%) and 10/444 (2.2%) patients died in the combined allopurinol and placebo groups in PERL and CKD-FIX, respectively (chi-square P-value = 0.048) (Figure 4B [12, 41–44]). A safety signal regarding mortality was also pointed out by others that estimated a combined relative risk of death of 2.07 (95% CI 0.98–4.34; P = 0.06) [61]. This overall difference and the observation of the same trend in both studies cause concern. Ominously, these data fit well with prior observations from controlled clinical trials with a variety of urate-lowering agents for gout that observed higher mortality or trends towards higher mortality in gout patients with the largest decreases in serum urate [16]. Indeed, the numerical difference in mortality was larger for PERL than for CKD-FIX, coinciding with lower serum urate on allopurinol in PERL (3.9 versus 5.3 mg/dL steady-state levels, respectively) [12, 13] (Figure 4A), following the same trend observed for pegloticase, lesinurad, allopurinol and febuxostat in gout trials [16]. In gout trials, a higher numerical mortality approached statistical significance or achieved statistical significance in the larger trials, mortality being higher for lower achieved serum urate: a dose–response numerical association with mortality was observed for lesinurad in the CLEAR (Combining Lesinurad With Allopurinol in Inadequate Responders) 1 and 2 RCTs ($n = 1218$, P for trend = 0.081) and indeed the dose of 400 mg lesinurad was not approved by regulatory authorities [42, 43] (Figure 4C). Further, the difference in mortality between febuxostat and allopurinol was statistically significant in the CARES trial ($n = 6190$): HR for all-cause death 1.22 (95% CI 1.01–1.47) and for cardiovascular death 1.34 (95% CI 1.03–1.73) [41] (Figure 4D).

WILL THERE BE ANY ADDITIONAL INFORMATION AVAILABLE IN THE NEAR FUTURE?

A search of ClinicalTrials.gov on 29 July 2020 did not disclose any ongoing trial that has a similar or more rigorous design than PERL or CKD-FIX (Table 3). Thus three ongoing trials are testing urate-lowering drugs in CKD patients with a primary kidney endpoint. However, none of them is placebo controlled with a primary endpoint of GFR and follow-up (≤12 months) is suboptimal to assess efficacy on kidney function endpoints or safety regarding mortality. The primary endpoint for the lone placebo-controlled trial is albuminuria. Thus no major advances in the field are expected in the next few years.

Another approach to obtain further information is meta-analysis of already available trials. A recent meta-analysis that includes both PERL and CKD-FIX as well as 26 additional trials concluded that urate-lowering therapy did not show benefits on major adverse cardiovascular events [risk ratio (RR) 0.93 (95% CI 0.74–1.18)] and all-cause mortality [RR 1.04 (95% CI 0.78–1.39)] or kidney failure [RR 0.97 (95% CI 0.61–1.54)], thus confirming the futility of urate lowering on hard endpoints [59]. It should be noted that the meta-analysis was not limited to CKD patients or to trials with a kidney function primary endpoint. In this regard, the meta-analysis also concluded that urate-lowering therapy attenuated the decline in the slope of GFR [weighted mean difference 1.18 mL/min/1.73 m^2/year (95% CI 0.44–1.91)]. However, this appears to be mainly driven by older, smaller and short follow-up studies in which the standard of care may have been obsolete. Thus, in addition to the CKD trials PERL, CKD-FIX and FEATHER, the other recent (2019) large (1070 patients) trial that provided eGFR data was the Febuxostat for Cerebral and CaRdiorenovascular Events PrEvention StuDy (FREED) in Japan [62]. In FREED, which enrolled patients with and without CKD, the incidence of renal impairment events, which was a secondary endpoint, was reduced [febuxostat 16.2%, non-febuxostat 20.5%; HR 0.745 (95% CI 0.562–0.987), P = 0.041]. However, in the 3 years of follow-up, there was no significant difference in the mean eGFR slope between the febuxostat and non-febuxostat groups [−0.37 (95% CI −2.32–1.44) versus −0.69 (95% CI −2.63–1.39) mL/min/1.73 m^2; P = 0.606], which both had stable eGFR slopes that did not differ from the age-associated loss of eGFR. Overall, the meta-analysis reported a 0.68 mL/min/1.73 m^2/year (95% CI 0.16–1.20)difference in eGFR slope for trials with a follow-up of at least 2 years (seven studies, $n = 2734$), but did not report on slope under control conditions and whether this was different from the age-associated loss of eGFR or even a negative slope [59]. Interestingly, the futility analysis in CKD-FIX considered a clinically meaningful difference to be 0.6 mL/min/1.73 m^2/year [57].

KEY TAKEAWAYS

The key takeaways from recent trials are that urate-lowering treatments do not preserve kidney function in CKD and additionally have a clear safety signal regarding mortality that is in line with observations from gout trials.

Thus the conclusion of the 2012 Kidney Disease: Improving Global Outcomes guidelines for CKD regarding the insufficient evidence to support or refute the use of agents to lower serum uric acid concentrations in people with CKD and either symptomatic or asymptomatic hyperuricaemia in order to delay progression of CKD [63] should be updated to indicate that there is conclusive evidence for the lack of benefit from lowering serum uric acid concentrations to delay CKD progression. Indeed, despite some encouraging results from early trials lacking a placebo arm, the putative kidney benefits were not confirmed in larger placebo-controlled studies. We believe that the case is now closed and there are no trials on the horizon that will change the current knowledge. Although it was suggested that trials in younger or earlier CKD patients as potential beneficiaries of urate lowering should be pursued [55], the low-risk (high eGFR, low albuminuria) population suggested may not lose renal function at all above the age-associated eGFR loss and future trials are unlikely to demonstrate an improvement over an already stable GFR [51].

However, the main issue with urate-lowering therapy for either CKD or gout is safety, which has not been conclusively demonstrated. Moreover, red flags have been raised. Specifically, a mortality red flag was identified. Numerically more patients died in both allopurinol arms of the two recent CKD trials. Mortality reached significance in the combined analysis of these trials. This follows similar trends observed in prior urate-lowering trials for gout [16].

THE WAY FORWARD

What further avenues might urate-lowering research take? A key unmet need is confirming and eventually understanding the pathophysiological basis for the safety signal on mortality. Additionally, for those who still want to pursue a pathogenic role of urate in kidney disease, there are several issues to address.

First, a consensus definition of hyperuricaemia is needed. This will be difficult to achieve since current animal models are not relevant for humans and observational associations

between higher serum urate levels and outcomes may not reflect causality, as clearly demonstrated for CKD progression by recent clinical trials.

Second, for those still thinking that uric acid may be deleterious to the kidney, there is the possibility to focus on uricosuria. Serum urate levels increase linearly with decreasing GFR, thus increasing the urate burden of single nephrons. The loss of urine concentration ability as CKD progresses may partially compensate, limiting the increase in urinary uric acid concentration. However, the hypothesis that an increased urine uric acid burden may lead to both increased urine uric acid concentrations and increased uric acid reabsorption by tubules in individual nephrons that could trigger tubular injury and interstitial inflammation may be explored. Therefore a potentially novel inclusion criterion in any future clinical trial could be hyperuricosuria or estimates of single-nephron uric acid burden, independent of serum urate levels, and a goal may be to decrease hyperuricosuria and test the impact of achieving this goal on kidney function.

Third, since both CKD-FIX and PERL tested allopurinol, some may feel compelled to test additional urate-lowering drugs for nephroprotection. Based on the safety data from gout trials, we would advise against this, as safety data for febuxostat and lesinurad are even more concerning than those of allopurinol. Specifically, lesinurad would not be a good candidate for nephroprotection studies given that it may be nephrotoxic, especially when used at higher-than-authorized doses [40].

Fourth, any future trial should compare urate lowering in CKD with the current standard of therapy. This standard, following recent trials with SGLT2 inhibitors in diabetic and non-diabetic CKD, consists of RAS blockade plus SGLT2 inhibition [33–36]. Given the minimal impact, if any, of urate-lowering drugs on CKD progression, the lower residual kidney risk in patients on the SGLT2 inhibitor–RAS blocker combination and the fact that SGLT2 inhibitors and some RAS blockers already lower serum urate, the likelihood of success is minimal and it is unlikely that these trials will ever be performed.

CONCLUSION

In conclusion, given the absent evidence of benefit and the potentially serious safety issues identified by RCTs, the clear message should be that urate-lowering therapy is not currently indicated to slow CKD progression. It is highly unlikely that any future evidence will change this message. Deprescription should be considered for patients on these drugs for kidney protection. A careful reassessment by regulatory agencies of the impact on mortality of the chronic prescription for any indication of urate-lowering drugs is urgently needed. This should be based on evidence from clinical trials in populations at risk of mortality with a sufficient follow-up, otherwise any impact on mortality may be diluted by trials enrolling healthier individuals or lacking enough follow-up to assess mortality.

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CONFLICT OF INTEREST STATEMENT

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