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Cardiovascular Safety of Urate Lowering Therapies

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Abstract

Purpose of Review The effect of urate lowering treatment (ULT) on cardiovascular (CV) risk and mortality in gout has been a topic of interest. This review discusses the CV effect of ULT and comparative CV safety among ULT agents.

Recent Findings The mechanism linking gout with CV risk is not fully understood but seems multifactorial involving hyperuricemia, xanthine oxidase (XO), oxidative stress, and chronic inflammation. Conflicting data exist regarding CV benefits of ULT in adults with and without hyperuricemia. Although meta-analyses on randomized controlled trials (RCTs) suggest CV benefits with allopurinol, few high-quality RCTs have examined the CV effect of ULT among patients with hyperuricemia or gout. The recent CARES trial adds new information on comparative CV safety between two XO inhibitors (XOIs), febuxostat and allopurinol, in patients with gout.

Summary It remains unclear whether ULT reduces CV risk in patients with gout or hyperuricemia. Comparative CV safety studies of XOIs suggest that additional mechanisms beyond urate-lowering effect or XO inhibition are likely involved in CV risk modification in patients with gout. Ongoing RCTs of ULT may be able to further determine the effect of ULT on CV risk.

Keywords Gout, hyperuricemia · Cardiovascular · Urate lowering treatment · Allopurinol · Febuxostat

Introduction

Gout is the most common inflammatory arthritis in adults, affecting 3.9% of the US population [1], characterized by recurrent, intense inflammation related to tissue-deposited monosodium urate crystals in patients with hyperuricemia. The prevalence and incidence of hyperuricemia and gout are increasing over time probably due to life style changes, population aging and related comorbidities including obesity, and medications [1, 2].

Many epidemiologic studies support an association between gout and increased risk of diverse cardiovascular (CV) outcomes: ischemic heart disease [3–7] and stroke [6–8], peripheral vascular disease [9], heart failure (HF) [10, 11], chronic kidney disease (CKD) [12•], and all-cause mortality [5, 6, 8]. However, whether gout is an independent CV risk factor is controversial; biological mechanisms linking gout and CV risk are not fully understood. It has been thought that reactive oxygen species and low-grade chronic inflammation associated with hyperuricemia and tophi would, at least in part, lead to an increased CV risk in patients with gout (Fig. 1) [12•]. Reactive oxygen species are induced by xanthine oxidase (XO) during uric acid production and also by intracellular uric acid themselves. The reactive oxygen species impair endothelial NO production, subsequently aggravating CV disease [12•]. Several observations support that subclinical inflammation persists in the affected joints of patients with gout even during the inter-critical phase [13, 14]. The important contribution of persistent inflammation to CV risk has been well appreciated [15]. Based on these findings, it has been hypothesized that urate lowering therapy (ULT) would improve CV outcomes. However, the CV effects of these drugs are still under debate. This review discusses the

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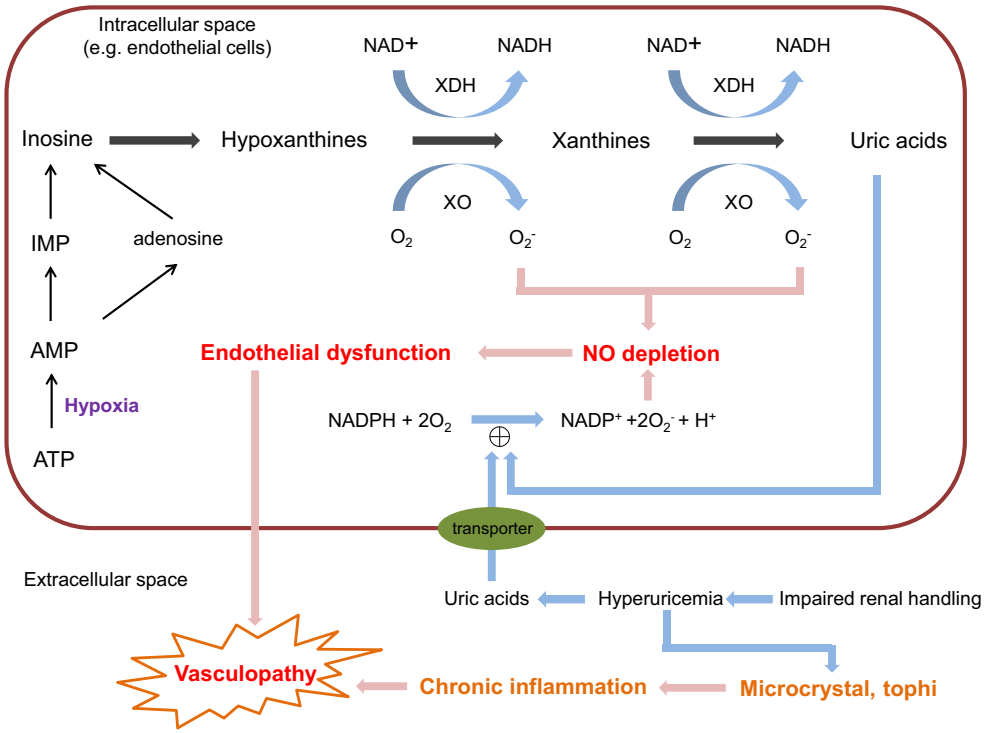

Fig. 1 Mechanisms of increased cardiovascular risk in hyperuricemia or gout. AMP, adenosine monophosphate; ATP, adenosine tri-phosphate; IMP, inosine monophosphate; NADH/NAD^+, reduced/oxidized form of nicotinamide adenine dinucleotide; NADPH/$NADP^+$, reduced/oxidized form of nicotinamide adenine dinucleotide phosphate; NO, nitric oxide; XDH, xanthine dehydrogenase (reduced form of xanthine oxidoreductase); XO, xanthine oxidase (oxidized form of xanthine oxidoreductase)

current evidence on the CV effect of individual urate lowering drugs and their comparative CV safety among patients with gout.

Urate Lowering Treatments

Hyperuricemia is the main cause of gout since uric acid supersaturation is a key preceding event for tissue deposition of monosodium urate crystals. The current therapeutic strategies for reducing serum urate (SU) levels are either inhibition of uric acid production (XO inhibitors, XOIs) or enhancement of renal excretion (uricosuric drugs), aiming at the complete tophi resolution and prevention of future gout flares.

XO Inhibitors

XO catalyzes conversion of hypoxanthine and xanthine into uric acid in the purine metabolic pathway generating reactive oxygen species (Fig. 1) [16]. Since most patients with gout are under-excreters rather than over-producers of uric acid [17], CV effect of the reactive oxygen species derived from uric acid production is uncertain. However, XO activity and uric acid production can be locally enhanced in ischemic tissues due to accelerated ATP degradation (Fig. 1) [18]. Oxidative stress generated under this condition might play a critical role in the development of CV events such as MI or stroke by causing NO depletion, endothelial dysfunction, and ischemia-reperfusion injury in the local hypoxic tissues due to underlying atherosclerotic vasculature. Since XOIs lower both SU levels and XO activity, the CV effect of XOIs has been a topic of interest. However, the effect of XOIs on the oxidative stress is complex because uric acid is also a potent anti-oxidant [19].

Two XOIs, allopurinol and febuxostat, are currently available in the USA. Allopurinol and its metabolite oxypurinol are non-selective XOIs that interfere with other enzymes of purine metabolism [20]. Febuxostat is a selective XOI with no cross-reactivity [21]. The urate lowering effect of daily febuxostat of 40 mg was non-inferior to that of daily allopurinol of 300 mg [22]. Among patients with a mild-to-moderate renal impairment defined as estimated creatinine clearance of 30 to 89 ml/h, febuxostat 40 mg was more likely to achieve SU less than 6.0 mg/dl than reduced doses of allopurinol for impaired renal function [22].

Uricosuric Agents

Uricosuric agents inhibit renal re-uptake of filtered uric acid via urate transporters [23]. Urate transporters are selectively expressed in renal tubules, but endothelial cells were also found to express them [24]. Probenecid and benzbromarone have been the major uricosurics used to treat gout. Lesinurad, an inhibitor of uric acid transporter 1 (URAT1), was approved by the Food and Drug Administration for use in the USA in 2016 but it is no longer available in the USA as of 2019 [25]. Besides urate lowering action, probenecid has exhibited diverse effects

with many affecting CV system [26]. For example, a strong diuretic effect of probenecid in patients with HF has been recognized for a long time [27], as well as of its inotropic effect [28]. Recent studies have shown that probenecid acts as an antagonist of the Cl-/HCO_3- exchanger pendrin [29], and agonist of stimulating transient receptor potential vanilloid 2 (TRPV2) [28] to exert these effects. Furthermore, probenecid has a vasodilator effect via pannexin 1 inhibition and subsequent α-adrenergic inhibition [30].

While the effectiveness of probenecid is limited by impaired renal function [25], benzbromarone is still effective even in patients whose estimated glomerular filtration rate (eGFR) is as low as 30 ml/min/1.73 m^2 [31]. Benzbromarone was not approved in the USA due to potentially severe hepatotoxicity but it is currently used in nearly 20 countries throughout Europe, Asia, and South America [32]. Although the main mechanism of action of benzbromarone is inhibition of urate transporters, in vitro and animal studies have shown that the drug directly reduces intracellular and renal oxidative stress [24, 33, 34].

Cardiovascular Effect of Urate Lowering Treatment

A number of observational and experimental studies have investigated the CV effect of ULT—allopurinol in most studies—in patients with a wide range of clinical conditions including hypertension, HF, CKD, obesity, and/or diabetes.

Effect of XOIs on Endothelial Function

According to a meta-analysis on prospective cohort studies, hyperuricemia was associated with an increased risk for incident hypertension, showing a 1 mg/dl increase in SU level corresponding to a 13% increase of the risk for incident hypertension [35]. Since the link between hypertension and SU is thought to be mediated by oxidative stress and subsequent endothelial dysfunction, several studies investigated the effect of ULT on endothelial function (reflected by endothelium dependent vasodilation). Two RCTs showed that allopurinol improved endothelial function in patients with HF [36•, 37•]. In prior meta-analyses of RCTs comparing the effect of allopurinol versus placebo, allopurinol treatment was associated with a significant improvement in endothelium-dependent vasodilation [38–41] but there was neither dose-response relationship nor any association between SU changes and improvement in endothelial function [40, 41]. A few small RCTs of febuxostat also showed improved endothelial function [42, 43].

Effect of XOIs on Hypertension

Prior animal studies have proposed a specific two-step mechanism that links hyperuricemia to development of hypertension [44]. In rats, pharmacologically induced hyperuricemia resulted in vascular NO depletion, activation of the local renin-angiotensin system, and renal vasoconstriction. During this acute phase, ULT was able to lower blood pressure (BP). After a prolonged period of hyperuricemia, structural alteration of renal afferent arterioles occurred, at which stage the hypertension was no longer sensitive to ULT [44]. If these mechanisms existed in humans, there might be a window of opportunity for ULT to prevent or delay the development of permanent hypertension.

In line with this hypothesis, RCTs on adolescents showed that SU reduction by XOIs was associated with reduced BP [45•, 46] while such benefit was not consistently noted among adults [47–51]. In a UK-based cohort study of older adults with hypertension including 365 in the allopurinol group and 6,678 controls, allopurinol treatment was associated with a small but significant diastolic BP reduction (1.7 mmHg) [52]. However, this positive finding was not reproduced in RCTs, particularly in the elderly [49] or those with comorbidities such as CKD [50] and obesity [51]. Although a recent meta-analysis of RCTs reported that allopurinol treatment was associated with BP reduction [53], the majority of included studies were of small size with a risk of bias, and there was a high heterogeneity in the study populations in terms of age, comorbidity status, and presence of hyperuricemia [53]. To date, it remains uncertain whether ULT is effective in lowering BP in adults with gout or hyperuricemia [54].

Effect of XOIs on Heart Failure

In patients with HF, increased XO activity has been shown to directly correlate with vascular oxidative stress, and the presence of hyperuricemia was negatively associated with survival [55, 56]. However, beneficial effects of XOIs on HF have not been consistently observed.

In a nested case-control study including 25,090 patients with HF, the use of allopurinol was associated with improved HF outcomes (i.e., hospital re-admissions due to HF or all-cause mortality) among a subgroup of patients with gout [57]. However, in a Scottish cohort study of 4,785 patients with HF including 267 incident allopurinol users, 258 prevalent users and 4,260 non-users, incident use of low-dose allopurinol was associated with a higher risk of all-cause death, cardiovascular mortality, and cardiovascular recurrence compared with non-use while incident use of high-dose allopurinol was not associated with such a risk compared with non-use [58]. The discrepancy between these studies could be in part related to different study designs (prevalent user-design versus incident user-design) and residual confounding.

Furthermore, results from RCTs have not consistently found a potential role of ULT in the management of HF. The OPT-CHF study found no clinical benefit of oxypurinol treatment in 405 patients with moderate to severe HF, but a post-hoc subgroup analysis suggested a possible benefit in patients with elevated SU at baseline [59]. In a subsequent EXACT-HF study including 253 patients with moderate to severe HF and hyperuricemia, allopurinol (600 mg/day, > 6 times the bioequivalent dose of oxypurinol used in the OPT-CHF study) did not change clinical status, exercise capacity, quality of life, or left ventricular ejection fraction at 24 weeks [60•]. Taken together, the current available evidence does not support use of allopurinol in patients with HF. Japanese RCTs (LEAF-CHF and EXCITED-UA) are underway to examine the effect of febuxostat [61] and to compare topiroxostat with allopurinol on HF outcomes [62].

Effect of XOIs on Cardiovascular Events and All-Cause Mortality

Some epidemiologic studies have shown an association between use of XOIs and CV disease (i.e., MI, stroke, or CV mortality) or all-cause mortality [63–67]. Table 1 summarizes ten published population-based observational studies that assessed the effect of individual ULT drugs on clinical CV events. In a Danish cohort study of 65,971 hyperuricemic patients, allopurinol was associated with a reduced risk of CV events (by 11%) and of all-cause mortality (by 32%) [63]. In a UK-based study of 4,064 elderly patients with hypertension, use of allopurinol was associated with a reduced risk of stroke by 50% and of cardiac events (MI or acute coronary syndrome) by 39% [64]. In addition, the risk reduction in all-cause mortality by allopurinol versus non-treatment was greater in patients with gout (19%) than in the general population (11%) [65]. Similarly, in studies of US Medicare enrollees, allopurinol initiation was associated with a reduced risk of MI by 15% [66] or of stroke by 9% [67]. However, such CV benefits of allopurinol were not seen among observational studies taking a more rigorous approach for confounding adjustment on gout severity and comorbidities [68, 69].

In a small RCT including 65 patients with stable chronic angina, 6 weeks of allopurinol (600 mg/day) significantly improved exercise capability [70]. In addition, this high-dose allopurinol also induced left ventricular mass regression in patients with ischemic heart disease or with diabetes and left ventricular hypertrophy [71, 72]. In a meta-analysis of RCTs comparing XOIs versus placebo, there was a trend toward beneficial effect of non-selective XOIs on CV events [73]. This meta-analysis also observed a protective effect of non-selective XOIs on the risk of coronary events and hypertension. However, no such benefit was found with selective XOIs in this meta-analysis [73]. As mentioned previously for meta-analyses on other intermediate CV outcomes, the majority of the included trials were relatively small-sized; the quality assessment of individual studies included in the meta-analysis was lacking, and the clinical conditions of study populations (age, presence of hyperuricemia, or comorbidity status) were substantially different across studies [73]. In another meta-analysis of RCTs including only adults with hyperuricemia, there was no significant CV protection by ULT but the data on allopurinol were limited due to the low number of CV outcomes [74]. Overall, there has been no high quality RCT comparing allopurinol versus placebo on clinical CV events. A British RCT (XILO-FIST) is underway to compare post-stroke lesion progression and BP changes between allopurinol versus placebo [75].

In the FEATHER trial (see Table 2), although the study was directed for renal outcomes and relatively small ($n = 467$), there was no difference in the CV risk between febuxostat versus placebo group after 1-year treatment [76]. Likewise, the FREED trial including 1,070 elderly patients with asymptomatic hyperuricemia and one or more CV risk factors, the risk of the cerebral and CV events was comparable between febuxostat (~ 40 mg/day) and non-febuxostat group (allopurinol 100 mg/day in 27.2% and no treatment for the rest) after 3 years of treatment while the risk of the renal events was significantly reduced by 25% in the febuxostat compared to non-febuxostat group [77••]. A Japanese trial (PRIZE) is underway to compare the carotid intima thickness between febuxostat and placebo among patients with asymptomatic hyperuricemia [78], and an ongoing British RCT (ALL-HEART) will provide information on the CV effect of allopurinol versus placebo among patients with ischemic heart disease (see Table 2) [79].

CV Effect of Uricosuric Agents

While in-vitro or animal studies suggested that uricosuric agents provided benefits against vascular dysfunction induced by uric acid exposure [24, 33, 34, 80], only few clinical trials have been conducted to examine the effect of probenecid or benzbromarone on CV outcomes.

In an RCT of 60 adolescents with prehypertension and obesity, both allopurinol (400 mg/day) and probenecid (1 g/day) led to a significant BP reduction [47]. However, probenecid (~ 1 g/day) did not improve endothelial function in adults [81, 82], while it improved echocardiographic parameters at a higher dose (2 g/day) [28]. Considering the unique CV effect of probenecid [27–30], a large RCT of probenecid on clinical CV outcomes is needed. A small RCT that included 14 patients with HF found no significant benefit of benzbromarone on improving brain natriuretic peptide levels and echocardiographic findings [83].

Table 1 Population-based cohort studies to assess or compare the effect of urate lowering drugs on coronary events, stroke, cardiovascular deaths, or all-cause mortality

1st Author, year [Ref]	Database	Sample size	Study population	Treatment	Mean follow-up	CV outcome	CV risk by treatment
Comparison between a urate lowering drug versus placebo							
Dubreuil, 2015 [65]	UK THIN	5927 PS- matched pairs	HUA	Allopurinol	2.9 years	All-cause mortality	Reduced
MacIsaac, 2016 [64]	UK CPRD	2032 PS-matched pairs	Elderly (≥ 65 years old) with hypertension	Allopurinol	77.7 months	Nonfatal stroke and cardiac events (MI or ACS)	Reduced
Larsen, 2016 [63]	Danish Health Care	7127 PS-matched pairs	HUA	Allopurinol	5.08 years	Composite of nonfatal MI/stroke, and CV death. All-cause mortality	Reduced
Singh, 2016 [66]	US Medicare	29,298	Elderly	Allopurinol	NA	Nonfatal MI	Reduced
Singh, 2016 [67]	US Medicare	28,488	Elderly	Allopurinol	NA	Nonfatal stroke	Reduced
Kuo, 2015 [68]	UK CPRD	1016 PS- matched pairs	Incident gout	Allopurinol	Median 10 years	All-cause morality	No difference
Kim, 2015 [69]	US commercial health plan	24,108 PS- matched pairs	Gout	XOIs	1.3 vs.1.4 years	Composite of nonfatal MI, CRV, stroke, and HF	No difference
Comparison between urate lowering drugs							
Zhang, 2018 [88•]	US Medicare	24,936 PS-matched on 74,808	Elderly with gout	Febuxostat vs. allopurinol	1.1 vs. 1.2 years	Composite of nonfatal MI/stroke. All-cause mortality	No difference
Kang, 2019 [89•]	KNHIS	39,640 PS-matched on 9,910	Gout	Allopurinol vs. febuxostat	303 days	Composite of nonfatal MI/stroke, TIA, and CRV. All-cause mortality	No difference
Kim, 2018 [91•]	US Medicare	9722 PS-matched on 29,166	Elderly with gout	Probenecid vs. allopurinol	Median 118 vs. 358 days	Composite of nonfatal MI/stroke.	Reduced by probenecid

ACS, acute coronary syndrome; *CPRD*, clinical practice research database; *CRV*, coronary revascularization; *HUA*, hyperuricemia; *HF*, heart failure; *KNHIS*, Korea National Health Insurance Service; *MI*, myocardial infarction; *NA*, not available; *PS*, propensity score; *TIA*, transient ischemic attack; *THIN*, The Health Improvement Network; *XOI*, xanthine oxidase inhibitor

Table 2 Completed and ongoing clinical trials to assess or compare cardiovascular effect of urate lowering drugs

Trial name [Ref]	Clinical status of study population	Exposure	Comparator	Duration	Outcome	Results
Complete trials						
FEATHER [76]	Stage 3 CKD with aSx HUA	Febuxostat	Placebo	12 months	Serial eGFR change	No change†
FREED [77••]	Elderly patients with aSx HUA	Febuxostat	Non-febuxostat	3 years	Composite of cerebral, CV, and renal events	Renal benefits†
CARES [84••]	Elderly (aged ≥ 65 years) with gout and CV risk factors	Febuxostat	Allopurinol	Median 32 months	Composite of nonfatal MI/stroke, or CV death	Higher risk of CV death and all-cause mortality in febuxostat group
Ongoing trials						
LEAF-CHF [61]	HF with HUA	Febuxostat	Placebo	24 weeks	Plasma BNP change	–
Excited UA [62]	HF with HUA	Topiroxostat	Allopurinol	24 weeks	Serum NT-proBNP change	–
XILO-FIST [75]	Ischemic stroke	Allopurinol	Placebo	2 years	White matter hyper-intensity progression	–
PRIZE [78]	aSx HUA	Febuxostat	Placebo	24 months	Carotid intima-media thickness	–
ALL- HEART [79]	Ischemic heart disease	Allopurinol	Placebo	4 years	Composite of nonfatal MI/stroke, or CV death	–
FAST [90••]	Elderly patients with gout and CV risk factors	Allopurinol	Febuxostat	3 years	Composite of nonfatal MI/stroke, or CV death	–

aSX, asymptomatic; *BNP*, brain natriuretic peptide; *CKD*, chronic kidney disease; *CV*, cardiovascular; *eGFR*, estimated glomerular filtration rate; *HUA*, hyperuricemia; *MI*, myocardial infarction; *NT-proBNP*, N-terminal pro-BNP; *PS*, propensity score; *TIA*, transient ischemic attack; *XOI*, xanthine oxidase inhibitor

† The renal outcomes of interest were different between FEATHER and FREED in that the former assessed eGFR changes and the latter the development of albuminuria or proteinuria. However, both studies were consistent with febuxostat not improving eGFR

Comparative Cardiovascular Risk between Urate Lowering Drugs

Since the main pathophysiologic mechanism that potentially links hyperuricemia to elevated CV risk involves XO-derived oxidative stress [12•], XOIs were thought to exhibit a beneficial CV effect. In particular, some hypothesized that selective XOIs such as febuxostat which has a superior XOI activity than non-selective XOIs (i.e., allopurinol) would have a more favorable CV effect than allopurinol.

Comparative Cardiovascular Risk between Allopurinol and Febuxostat

A recently reported post-marketing cardiovascular outcome trial, CARES, included over 6000 patients with gout at high CV risk and compared the risk of a composite endpoint of CV events (MI, stroke, CV deaths) and all-cause mortality in the febuxostat group versus allopurinol [84••]. After a median follow-up of 32 months, the trial showed a similar risk for non-fatal CV endpoints between the two drugs, but an increased risk for CV and all-cause mortality in the febuxostat group compared to the allopurinol group. The survival curves began to diverge around 30 months, suggesting that the differential risk of mortality in febuxostat users might be more related to the long-term use. Although the allopurinol group had a better survival in the CARES, it was not clear in the study whether febuxostat was more deleterious or allopurinol was more beneficial [85]. Considering the results from the FREED and FEATHER trials [76, 77••], the effect of febuxostat on MI or stroke seems neutral compared to non-treatment, and the result from the CARES could indicate a beneficial CV effect of allopurinol [84••]. However, in CARES, 57% of participants prematurely discontinued treatment and 45% were lost to follow-up [84••]. Although there was no difference in the clinical characteristics between patients who remained versus left the cohort, subsequent post-hoc ascertainment process added more deaths to the allopurinol group than febuxostat (110 versus 89) and nullified the HR, raising a possibility of the association between patient drop-out and study outcomes (i.e., selection bias) [85].

Besides selection bias, other possibilities to explain the results from the CARES trial have been raised. Studies have consistently reported a J-shaped relationship between SU and CV risk with a higher CV mortality among those with lowest SU percentiles [86•]. In light of this relationship, failure to achieve better CV outcomes among those receiving ULT of high efficacy [76, 84••] or at higher dose [60•] might suggest

that profound decrease of SU below a certain level could be hazardous [86•, 87]. Currently, there has been no guide on the optimal lower bound of a target SU level, which should be addressed in future studies.

Two recent large population-based cohort studies of patients with gout showed no difference in the risk of non-fatal CV events and all-cause mortality between febuxostat and allopurinol initiators after rigorous adjustment for baseline confounders [88•, 89•]. However, these cohort studies were limited by potential unmeasured confounding by patients' renal function and other clinical factors and unable to fully determine long-term CV safety of febuxostat versus allopurinol. The ongoing FAST trial may be able to offer more confirmative information on the CV safety of febuxostat [90••].

Comparative Cardiovascular Risk between Allopurinol and Probenecid

To date, no RCT has compared XOIs versus uricosurics on the clinical CV events among adults. A large Medicare-based cohort study has shown a decreased risk of MI, stroke, HF, and mortality associated with probenecid versus allopurinol [91•]. The unique effect of probenecid on pendrin, pannexin1, and TRPV2 [27–30] may potentiate the CV benefit of probenecid versus allopurinol but this finding needs to be confirmed in an RCT setting.

Conclusion

Many epidemiologic studies as well as animal studies consistently suggest an association between hyperuricemia and elevated CV risk [3–11, 12•]. The underlying mechanism is likely to be multifactorial involving hyperuricemia, XO activity, oxidative stress, and chronic inflammation. The lack of benefits on hypertension by ULT, particularly XOIs, in adults unlike in adolescents may indicate a window of opportunity for ULT treatment, suggesting an early treatment in hyperuricemic patients. However, this hypothesis must be proven in large-scale RCTs of adult patients. While the comparative CV risk data from the CARES trial [84••] may suggest an involvement of other mechanisms beyond urate lowering effect or XO inhibition in CV risk modification by XOIs, our knowledge is still scanty on this issue. We eagerly await results from ongoing large-scale RCTs of ULT on various clinical CV outcomes (see Table 2).

Compliance with Ethical Standards

Conflict of Interest Seoyoung C. Kim has received research grants to the Brigham and Women's Hospital from Roche, Pfizer, AbbVie, and Bristol-Myers Squibb for unrelated topics.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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