Uric Acid as a Risk Factor for Chronic Kidney Disease and Cardiovascular Disease — Japanese Guideline on the Management of Asymptomatic Hyperuricemia

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REVIEW

Uric Acid as a Risk Factor for Chronic Kidney Disease and Cardiovascular Disease

— Japanese Guideline on the Management of Asymptomatic Hyperuricemia —

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Serum uric acid (UA) is taken up by endothelial cells and reduces the level of nitric oxide (NO) by inhibiting its production and accelerating its degradation. Cytosolic and plasma xanthine oxidase (XO) generates superoxide and also decreases the NO level. Thus, hyperuricemia is associated with impaired endothelial function. Hyperuricemia is often associated with vascular diseases such as chronic kidney disease (CKD) and cardiovascular disease (CVD). It has long been debated whether hyperuricemia is causally related to the development of these diseases. The 2020 American College of Rheumatology Guideline for the Management of Gout (ACR2020) does not recommend pharmacological treatment of hyperuricemia in patients with CKD/CVD. In contrast, the Japanese Guideline on Management of Hyperuricemia and Gout (JGMHG), 3rd edition, recommends pharmacological treatment of hyperuricemia in patients with CKD. In a FREED study on Japanese hyperuricemic patients with CVD, an XO inhibitor, febuxostat, improved the primary composite endpoint of cerebro-cardio-renovascular events, providing a rationale for the use of urate-lowering agents (ULAs). Since a CARES study on American gout patients with CVD treated with febuxostat revealed increased mortality, ACR2020 recommends switching to different ULAs. However, there was no difference in the mortality of Japanese patients between the febuxostat-treated group and the placebo or allopurinol-treated groups in either the FEATHER or FREED studies.

Key Words: Cardio-renal continuum; CARES study; Urate-lowering agent; Uric acid transporter; Xanthine oxidase

Hyperuricemia is defined as a serum uric acid (UA) level >7.0 mg/dL.[1] It occurs in 20% of men and in 5% of women in the entire adult Japanese population.[1] It can be caused by genetic mutations or polymorphisms that accelerate the production of UA or reduce its excretion.[1] In addition, a diverse set of environmental factors contribute to its development. Typical symptomatic complications of hyperuricemia are gout and ureteral calculus, caused by monosodium urate (MSU) crystals. Even in the absence of these complications, asymptomatic hyperuricemia is frequently associated with lifestyle-related diseases. Although it is also associated with vascular diseases such as chronic kidney disease (CKD) and cardiovascular disease (CVD), it remains unclear whether hyperuricemia is causally related to the development of these diseases. The Japanese Guideline on the Management of Hyperuricemia and Gout (JGMHG), 2nd edition,[1] recommends pharmacological treatment of asymptomatic hyperuricemia, whereas Western guidelines such as the 2020 American College of Rheumatology Guideline for the Management of Gout[2] (ACR 2020), do not. In this review, we discuss how hyperuricemia relates to vascular diseases

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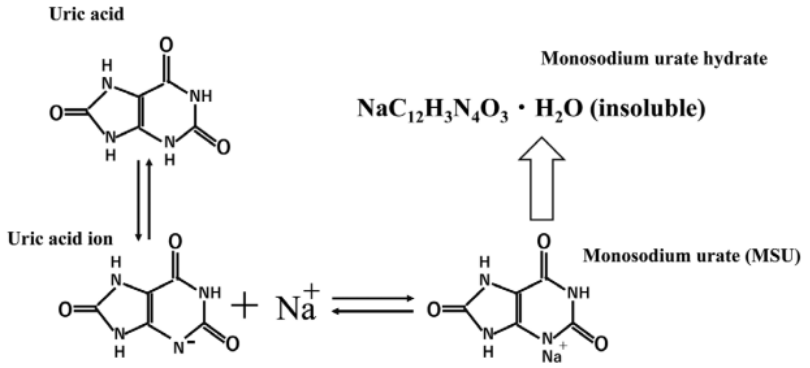

Figure 1. Generation of uric acid ion, monosodium urate and monosodium urate hydrate from uric acid. Uric acid in solution gives rise to uric acid ion with a negative charge. This uric acid ion reacts with Na^+, yields to soluble monosodium urate (MSU), which then gives rise to insoluble monosodium urate hydrate.

and present evidence of the benefit of pharmacological treatment of asymptomatic hyperuricemia, focusing on the difference between the JGMHG 3rd edition[3] and ACR2020.[2]

Definition of Hyperuricemia

Ever since the evolutionary loss of uricase activity, UA has been the end product of the human body's purine metabolism. The ionized forms of UA in solution easily form MSU. When the concentration of MSU exceeds the solubility, MSU binds with water molecules to form crystals as MSU monohydrate (**Figure 1**). Because a 140 mmol/L NaCl solution is saturated with MSU at 6.8 mg/dL at 37°C,[4,5] ACR 2020[2] defines hyperuricemia as serum UA (SUA) >6.8 mg/dL (**Table 1**). And as the solubility of MSU in the serum is slightly higher than the saturation value of 6.8 mg/dL,[6] JGMHG defines hyperuricemia as SUA >7 mg/dL[1,3] (**Table 1**). When the UA level is >7 mg/dL in the joint fluid, MSU crystals are generated and taken up by macrophages, causing gout. Based on the evidence showing that hyperuricemia increases the chance of developing gout,[7] JGMHG[1,3] recommends administration of a urate-lowering agent (ULA) to treat asymptomatic hyperuricemia (**Table 1**). This recommendation was supported by a FEATHER study[8] that followed patients with asymptomatic hyperuricemia for 3 years and revealed a decreased incidence of gout in those treated with febuxostat (2/219: 0.9%) compared to those treated with placebo (13/222: 5.9%). In contrast, because of the limited effect, ACR 2020[2] does not recommend administration of ULAs to patients with asymptomatic hyperuricemia (**Table 1**).

Association of Asymptomatic Hyperuricemia With Lifestyle-Related Diseases, CKD and CVD

As the SUA level is determined by the balance between its production and excretion, the pathophysiological mechanisms of hyperuricemia have been categorized into 3 types; that is, the overproduction type; the renal underexcretion type; and the mixed type.[9] Recently, it was demonstrated that a UA transporter ATP-binding cassette superfamily G member 2 (ABCG2) appeared in the intestine where it transports UA to stool.[10] Loss of function due to mutation of the *ABCG2* gene increases SUA and causes gout.[11] Thus, the reduced extra-renal excretion type was categorized as a novel pathophysiological mechanism.[11]

Asymptomatic hyperuricemia is frequently associated with lifestyle-related diseases such as hypertension,[12] diabetes mellitus,[13] metabolic syndrome[14] and non-alcoholic fatty liver disease,[15] and vascular diseases such as CKD[16] and CVD.[17–19] These diseases are known to be associated with insulin resistance.[20] In renal proximal tubular cells, UA is reabsorbed by the urate transporter 1 (URAT1) localized on the luminal side.[21] Hyperinsulinemia caused by insulin resistance enhances both the activity and protein expression of URAT1,[22] hence facilitating the reabsorption of UA[23] and increasing SUA.

Hyperuricemia and Endothelial Function

Hyperuricemia is associated with vascular diseases. It has long been debated whether hyperuricemia may be causally related to the development of these diseases. The endothelium preserves vascular tone. Vasodilation induced by both acetylcholine administration and sheer stress is attributable to nitric oxide (NO) production of the endothelium.[24] Thus, the impaired vasodilation is characterized as impaired endothelial function.[24,25] Although impaired endothelial function causes CVD and CKD,[26] it is also associated with hyperuricemia.[27] Several lines of evidence support potential links between hyperuricemia and impaired endothelial function.

UA and Endothelial Function

Accumulating evidence indicates that hyperuricemia impairs vasodilation induced by NO production. The flow-mediated vasodilation in the forearm artery by sheer stress was impaired in hyperuricemic patients.[27,28] UA infusion into the brachial artery of healthy volunteers resulted in impaired vasodilation of the forearm artery in response to acetylcholine.[29] UA reduced NO production and inhibited

Table 1. Differences Between JGMHD 3rd Edition and ACR2020 Guidelines

		JGMHD 3rd Edition	ACR2020 Guidelines
Guideline development method	The clinical questions	Determined by voting among Guideline development group based on GRADE approach	Determined by voting among panel members based on GRADE approach
	The systematic review	Guideline development group provide the key words to Japanese Medical Library Association, which collects reports, and then Guideline development group conduct SR	The voting panel conduct SR
	The evaluation of body of evidence	Certainty of balance between benefit and harm based on GRADE approach	Certainty of balance between benefit and harm based on GRADE approach
	The patient contribution	Patients provided the information of their value and preference	Patients participate in voting of recommendation as the voting panel
	The determination of recommendation	Determined by voting among Guideline development group referred to strength of evidence, cost and resources, and value and preference	Determined by voting among voting panel including patients referred to strength of evidence, cost and resources, and value and preference
Statement	Definition of hyperuricemia	SUA >7.0 mg/dL	SUA >6.8 mg/dL
	Target to treat for gout	Below 6 mg/dL	Less than 6 mg/dL
	Asymptormatic hyperuricemia without complication	Considering the use of ULA at SUA ≥9 mg/dL and target to SUA ≤6 mg/dL	Pharmacological treatment of asymptomatic hyperuricemia is not recommended
	Asymptormatic hyperuricemia with complication	Considering the use of ULA at SUA ≥8 mg/dL and target to SUA ≤6 mg/dL	
	Asymptormatic hyperuricemia with renal disease	The use of ULAs to retard the decline in kidney function is conditionally recommended in patients with hyperuricemia and renal disease	The benefit of ULAs in asymptomatic hyperuricemia has yet to be established
	Asymptormatic hyperuricemia with hypertension	The use of ULAs to improve life prognosis and reduce the risk of CVD cannot be conditionally recommended for hypertensive patients with hyperuricemia	
	Asymptormatic hyperuricemia with heart failure	The use of ULAs to improve life prognosis and reduce the risk of CVDs cannot be conditionally recommended for patients with heart failure and hyperuricemia	

ACR2020 Guidelines, 2020 American College of Rheumatology Guideline for the Management of Gout; CVD, cardiovascular disease; JGMHD 3rd edition, Japanese Guideline on Management of Hyperuricemia and Gout, 3rd edition; SR, systematic review; SUA, serum uric acid; ULA, urate-lowering agent.

its vasodilation induced by administration of acetylcholine in rat and mouse aortic arteries.[30,31] This effect of UA is apparently exerted by UA in the intracellular space of endothelial cells, taken up through UA transporters (UATs), because the reduced NO production by UA in endothelial cells was eliminated by UATs inhibitors.[21,32–34] UATs such as URAT1, UA transporter voltage-dependent 1 (URATv1), Monocarboxylate Transporters 9 (MCT9), ABCG2 and Multidrug resistance protein 4 (MRP4) are ubiquitously expressed in tissues including endothelial cells.[35] URAT1, URATv1 and MCT9 belong to the influx transporters that absorb UA, whereas ABCG2 and MRP4 belong to the efflux transporters that secrete UA. Hyperuricemia increases the intracellular level of UA, which was proven by using ^{14}C-labeled UA.[36,37] Of these influx transporters, URAT1 or URATv1 is responsible for absorption of UA by endothelial cells.[32,35,37,38]

Within the endothelial cells, UA reduces the level of NO in response to acetylcholine both by inhibiting its production and accelerating its degradation. NO is generated by endothelial NO synthase (eNOS).[39] Acetylcholine activates the phosphoinositide 3-kinases (PI3 kinase)/Ak strain transforming (Akt) pathway that results in phosphorylated eNOS-Ser^{1177}. This phosphorylated eNOS is the active form that can bind to calmodulin (CaM), resulting in the production of NO from L-arginine.[39] Intracellular UA activates phosphatase and tensin homolog deleted from chromosome 10 (PTEN) and decreases eNOS-Ser^{1177} phosphorylation, and inhibits NO production.[31] Besides, intracellular UA activates protein kinase C (PKC) that phosphorylates eNOS-Thr^{495} and attenuates its binding to CaM, resulting in reduced NO production.[31,40] These inhibitory effects of UA on NO production were attenuated by anti-oxidants, suggesting the involvement of superoxide. In fact, UA facilitates assembly of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase subunits on the membrane, and produces superoxides,[41] which reduces NO level by inhibiting its production and accelerating its degradation (**Figure 2**).

Xanthine Oxidase (XO) and Endothelial Function

Xanthine oxidoreductase (XOR) is the central player in the formation of UA and it also generates superoxide. XOR is composed of 2 components: xanthine dehydrogenase (XDH) and XO. XO is generated from XDH by post-translational modification and catalyses the last 2 steps of reactions that convert hypoxanthine to xanthine, and xanthine to UA. These reactions yield superoxide and

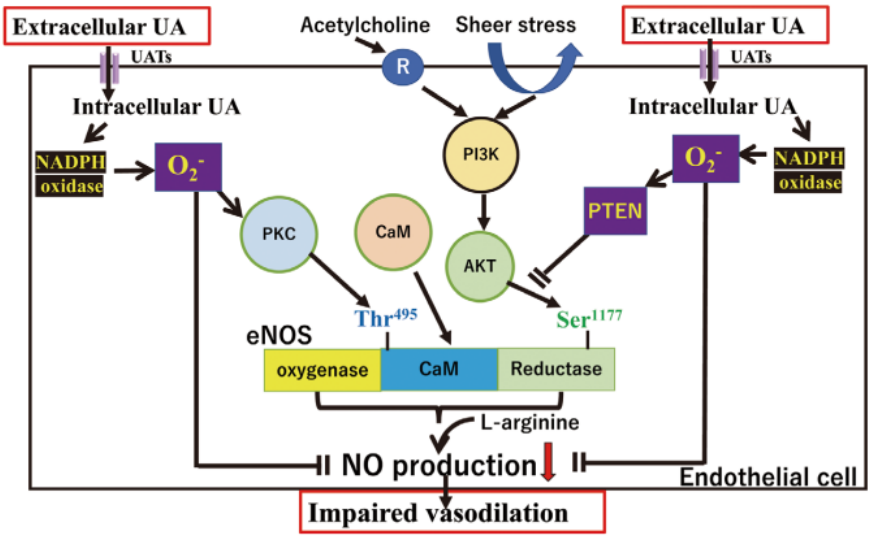

Figure 2. UA and endothelial function. Both acetylcholine and sheer stress activate the PI3K-AKT pathway, by which eNOS-Ser^{1177} is phosphorylated, and its binding to CaM is facilitated. Intracellular UA activates NADPH oxidase, which generates superoxide (O_2^-). O_2^- reacts with NO, and degrades it. O_2^- activates PTEN and dephosphorylates eNOS-Ser^{1177}, reducing NO production. O_2^- also activates PKC and phosphorylates eNOS-Thr^{495}, inhibiting NO production. UATs, uric acid transporters; R, receptors; UA, uric acid; NADPH, nicotinamide adenine dinucleotide phosphate; PI3K, phosphoinositide 3-kinases; AKT, Ak strain transforming; PTEN, phosphatase and tensin homolog deleted from chromosome 10; PKC, protein kinase C; eNOS, endothelial nitric oxide synthase; CaM, calmodulin; NO, nitric oxide; uric acid; Ser, serine; Thr, threonine.

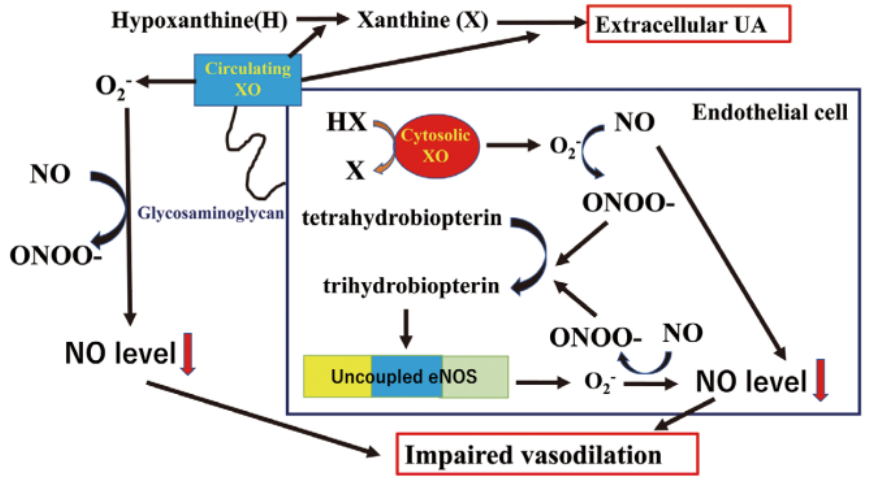

Figure 3. Xanthine oxidase and endothelial function. By converting hypoxanthine to xanthine and UA, circulating and cytosolic XO generates superoxide. O_2^- degrades NO. O_2^- reacts with NO and produces peroxynitrite, reduces tetrahydrobiopterin and converts eNOS to a superoxide-generating enzyme. Both circulating and cytosolic XO can impair vasodilation. eNOS, endothelial nitric oxide synthase; O_2^-, superoxide; NO, nitric oxide; $ONOO^-$, peroxynitrite; XO, xanthine oxidase.

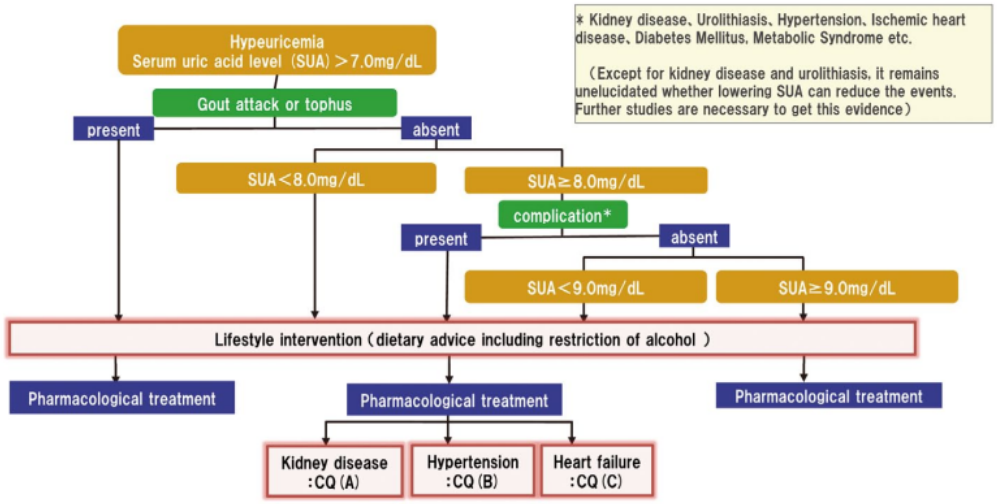

Figure 4. Flowchart for the medical treatment of hyperuricemia and gout. In patients with a SUA ≥8 mg/dL who have complications such as CKD, hypertension, heart failure etc., treatment with ULAs should be considered after life-style modifications. The recommendation by JGMHD 3rd edition on the use of ULAs in patients with CKD, hypertension or heart failure has been described, in part, by clinical questions (CQ) (A), CQ (B) or CQ (C) in the text, respectively. SUA, serum uric acid; CKD, chronic kidney disease; JGMHD 3rd edition, Japanese Guideline on Management of Hyperuricemia and Gout, 3rd edition; ULAs, urate-lowering agent.

hydrogen peroxide.[42] XO is highly active in the liver and small intestine, but it also exists both in the cytoplasm and on the surface of endothelial cells. Superoxide generated by XO reacts directly with NO, resulting not only in decreased NO but also increased peroxynitrite. Peroxynitrite can oxidize and inactivate tetrahydrobiopterin. In the absence of tetrahydrobiopterin, eNOS is converted into a superoxide-generating enzyme.[43] Recently, XO was found to exist in plasma.[44] This circulating XO is believed to be released from XOR-rich organs such as the liver. It binds glycosaminoglycans on the surface of endothelial cells.[45] Superoxide produced by endothelium-bound XO reacts with NO, yields peroxynitrite and attenuates the NO-dependent production of cGMP by smooth muscle cells (**Figure 3**).[46]

UA as an Antioxidant

In the extracellular space, UA is known to be one of the most potent antioxidants. It can scavenge superoxide, hydroxyl radicals and singlet oxygen and can chelate transition metals. It is thought to be responsible for neutralizing more than 50% of the free radicals in human blood.[47] In addition, UA at physiological levels prevents hydrogen peroxide-induced inactivation of superoxide dismutase, an antioxidant enzyme capable of removing superoxide anion radicals.[48] Given the role of SUA as an antioxidant, an extreme reduction could also impair endothelial functions. This was proven by the measurements of the flow-mediated dilatation of the forearm artery,[49] and exercise-induced constriction of the renal artery[50] in renal hypouricemic patients. The J-shaped association between SUA levels and cardiovascular event risks had been observed in epidemiological studies,[51,52] indicating that low levels of SUA are associated with a higher risk of cardiovascular events as much as high levels of SUA.

The Japanese Guideline on the Management of Hyperuricemia and Gout

Despite the lines of evidence for asymptomatic hyperuricemia as a risk factor for CKD and CVD, the use of ULAs is still controversial. The JGMHG 2nd edition[1] recommends ULAs to prevent gout, CKD and CVD. Multinational evidence-based recommendations did not reveal a benefit of pharmacological treatment of asymptomatic hyperuricemisa.[53] ACR 2020[2] stated that, although there are associations between hyperuricemia and other comorbid conditions such as hypertension, CVD and CKD,[54] the benefit of ULA in the absence of gout has yet to be established.[55]

In the JGMHG 3rd edition published in 2018,[3] the rationality of pharmacological treatment has been evaluated based on the GRADE method[56] recommended by Medical Information Network Distribution Services.[57] The flow chart and clinical questions (CQs) for treating hyperuricemia associated with CKD, hypertension or heart failure as CVD are shown in **Figure 4**.

As for the pharmacological treatment of hyperuricemia with CKD (CQ (A): **Table 2**), the beneficial outcome was the "inhibition of decline in renal function". Five randomized control trials (RCTs) examined the change in the estimated glomerular filtration rate (eGFR).[58–62] A meta-analysis, with patients in the ULA intervention group and subjects in the control group, showed a statistically significant improvement in eGFR in the ULA intervention group.[3] Three RCTs assessed another beneficial outcome as the "inhibition of end-stage renal failure". A meta-analysis indicated that all studies found the frequency of end-stage renal failure was significantly low in the ULA intervention

Table 2. Clinical Questions and Recommendations Regarding Pharmacological Treatment of Asymptomatic Hyperuricemia in Patients With CKD, Hypertension or Heart Failure

CQ (A): Can urate-lowering agents be recommended in patients with hyperuricemia and kidney injury over non-medication?		
Recommendation	**Strength of recommendation**	**Certainty in evidence**
The use of urate-lowering agents to retard the decline in kidney function is conditionally recommended in patients with hyperuricemia and kidney injury.	It is conditionally recommended.	B (moderate)
CQ (B): Can urate-lowering agents be recommended for hypertensive patients with hyperuricemia over non-medication treatment?		
Recommendation	**Strength of recommendation**	**Certainty in evidence**
The use of urate-lowering agents to improve life prognosis and reduce the risk of cardiovascular disease cannot be conditionally recommended for hypertensive patients with hyperuricemia.	It is not conditionally recommended.	D (very weak)
CQ (C): Can urate-lowering agents be recommended for patients with heart failure and hyperuricemia over non-medication treatment?		
Recommendation	**Strength of recommendation**	**Certainty in evidence**
The use of urate-lowering agents to improve life prognosis and reduce the risk of cardiovascular disease cannot be conditionally recommended for patients with heart failure and hyperuricemia.	It is not conditionally recommended.	C (weak)

CKD, chronic kidney disease; CQ, clinical question.

group.[3] The harmful outcome of "an increase in adverse effects" was examined in 3 RCTs.[62–64] There was no difference observed in the onset of adverse events between the ULA intervention group and the control group. Thus, ULAs improved the renal function and suppressed the onset of end-stage renal failure in CKD patients, and there was no significant difference in adverse effects between ULA-treatment and placebo groups,[60,63,64] indicating that the benefit of ULAs is over the harm. ULAs are conditionally recommended for use in hyperuricemic patients with CKD because the strength of the evidence was determined to be moderate (B).

As for the pharmacological treatment of hyperuricemia with hypertension (CQ (B): **Table 2**), the beneficial outcome was the "inhibition of cardiovascular events". Two observational studies demonstrated that the risk of cardiovascular events was reduced in patients receiving allopurinol.[65,66] A meta-analysis found that use of allopurinol was associated with a significant reduction in the risk of cardiovascular events. There were no papers from which it was possible to evaluate another beneficial outcome, a "reduction in cardiovascular mortality". A meta-analysis was conducted by the Cochrane Library[67] using 3 prospective interventional studies comparing the effect of allopurinol and placebo to evaluate an "increase in adverse effects". There was no difference in the onset of adverse events between the ULA intervention group and the placebo group. It stated that the use of ULAs to improve patients' prognosis and reduce the risk of CVD cannot be conditionally recommended for hypertensive patients with hyperuricemia because the strength of the evidence was determined to be extremely weak (D).

As for the pharmacological treatment of hyperuricemia with heart failure (CQ (C): **Table 2**), the beneficial outcome was "reduced cardiovascular events". There were 2 RCTs;[68,69] however, neither found a significant difference between the ULA intervention group and the placebo group. Two RCTs evaluated another beneficial outcome, "reduced overall mortality",[68,69] and neither found a significant difference in the overall mortality between the ULA intervention group and the placebo group. There was one RCT[69] that evaluated an "increase in adverse effects" and found no significant difference between the ULA intervention group and the placebo group. It stated that the use of ULAs to improve life prognosis and reduce the risk of CVD cannot be conditionally recommended for patients with heart failure and hyperuricemia because the strength of the evidence was determined to be weak (C).

Further studies are required to verify the rationality of pharmacological treatment of asymptomatic hyperuricemia patients with hypertension or heart failure. Recently, a FREED study[70] reported that febuxostat improved the primary composite endpoint of cerebro-cardio-reno-vascular events in hyperuricemic patients with hypertension, diabetes and cerebro-cardio-reno-vascular disease. This improvement was caused by protecting renal function, indicating that improvement in renal function restores cardiac function (cardio-renal continuum).

ACR2020 Recommendation for the Use of a XO Inhibitor in Patients With Gout and Cardiovascular Events

According to the ACR Guideline 2020,[2] switching from febuxostat to an alternative ULA is conditionally recommended for patients with a history of CVD events. In the CARES trial of febuxostat vs. allopurinol,[71] there was no difference in the primary composite CVD endpoint between the two. However, febuxostat was associated with a higher risk of CVD-related death and all-causes mortality compared with allopurinol. It was not associated with any other secondary CVD outcomes such as non-fatal myocardial infarction, non-fatal stroke, or urgent revascularization for unstable angina. Because of the lack of an untreated control group, the absolute CVD risk related to either febuxostat or allopurinol is unknown. There was a bias of incompleteness because of high dropout rates in both the febuxostat and allopurinol groups. Febuxostat had been reinforced to the maximum dose of 60 mg/day; however,

allopurinol had been increased to a dose less than its maximum value, because 52.8% of enrolled patients had CKD, indicating the impaired validity of this study protocol. A large observational study in the USA did not show an increased risk of CVD or all-causes mortality associated with febuxostat compared with allopurinol.[72] Another study using a managed care database demonstrated a lower risk of a CVD event among febuxostat initiators than allopurinol initiators.[73] Taken together with the FEATHER[8] study and FREED study[70] in Japanese patients, there was not any difference in mortality between the febuxostat group and the placebo or allopurinol groups, thus, it may not be recommended to switch using febuxostat to an alternative oral ULA in patients with a history of CVD. The ongoing FAST trial[74] in Europe serves to confirm the cardiovascular safety of allopurinol and febuxostat in the management of gout.

Although the key issue in the CARES study[71] was the higher CVD death rates and all-causes mortality in Americans treated with febuxostat vs. allopurinol, the data that attracted attention was a drastic increase in major adverse CVD events after quitting these drugs when subjects went "off-drug".[75,76] It has been reported that the mean percentage of CV death in patients was 0.17% and 0.085% per month for 4 years with febuxostat and allopurinol, respectively.[76] This rate increased to 2.19% and 1.56% per month, respectively, during the first 30 off-drug days. A similar trend was observed in subsequent time periods up to 180 days off-drug. The possibility of "XO inhibitor withdrawal syndrome" was proposed, as has β-blocker withdrawal.[77] Although further studies are necessary to confirm "XO inhibitor withdrawal syndrome", it is not recommended to quit either allopurinol or febuxostat once administration to patients has commenced.

Conclusions

Despite the role of UA as an antioxidant, hyperuricemia impairs endothelial function via an accumulation of intracellular UA and XO, which may cause vascular diseases. Recommendations on ULAs differ between the JGMHG 3rd edition and ACR2020. Although both guidelines have been developed based on the GRADE method, the difference is attributable to the different situation of the Medicare systems and patient opinion between the 2 countries. The JGMHG 3rd edition recommends pharmacological treatment of hyperuricemia in patients with CKD, emphasizing the importance of the cardio-renal continuum for treatment of asymptomatic hyperuricemia patients with hypertension and heart failure. In order to reduce mortality in hyperuricemic patients with either hypertension or heart failure, ULAs could be used, when patients agree. Further RCTs are needed to study the rationality of using ULAs to improve the prognosis of hyperuricemic patients with CVD.

Disclosures

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