



Korean guidelines for the management of gout

Jennifer Jooha Lee, M.D., Ph.D.¹, Ji Soo Lee, M.D., Ph.D.², Min Kyung Chung, M.D., Ph.D.², Joong Kyong Ahn, M.D., Ph.D.³, Hyo-Jin Choi, M.D., Ph.D.⁴, Seung-Jae Hong, M.D., Ph.D.⁵, Chong-Hyeon Yoon, M.D., Ph.D.¹, Su-Hyun Kim, M.D., Ph.D.⁶, Kyung-Hwan Jeong, M.D., Ph.D.⁷, Jong-Woo Kim, M.D.⁸, Bo-Yeon Kim, M.D., Ph.D.⁹, Jin-Ho Shin, M.D., Ph.D.¹⁰, Woo Gyu Kim, M.D.¹¹, Soo-Young Kim, M.D., Ph.D.¹², Hyun-Jung Kim, Ph.D.¹³, Jeong-Soo Song, M.D., Ph.D.¹⁴, Jae-Bum Jun, M.D., Ph.D.¹⁵, Hyun-Ah Park, M.D., Ph.D.¹⁶, Shung Chull Chae, M.D., Ph.D.¹⁷, Bum Soon Choi, M.D., Ph.D.¹⁸, Tae Nyun Kim, M.D., Ph.D.¹⁹, Hyun Ah Kim, M.D., Ph.D.²⁰

¹Division of Rheumatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, ²Division of Rheumatology, Department of Internal Medicine, Ewha Womans University School of Medicine, Seoul, ³Division of Rheumatology, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, ⁴Division of Rheumatology, Department of Internal Medicine, Gil Medical Center, Gachon University College of Medicine, Incheon, ⁵Division of Rheumatology, Department of Internal Medicine, Kyung Hee University Hospital, School of Medicine, Kyung Hee University, Seoul, ⁶Division of Nephrology, Department of Internal Medicine, Chung-Ang University School of Medicine, Seoul, ⁷Division of Nephrology, Department of Internal Medicine, Kyung Hee University Medical Center, Seoul, ⁸Department of Family Medicine, Sanggye Paik Hospital, Inje University College of Medicine, Seoul, ⁹Division of Endocrinology & Metabolism, Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Soonchunhyang University College of Medicine, Bucheon, ¹⁰Division of Cardiology, Department of Internal Medicine, College of Medicine, Hanyang University, Seoul, ¹¹Lights & Salt Internal Medicine, Goyang, ¹²Department of Family Medicine, Kangdong Sacred Heart Hospital, Hallym University College of Medicine, Seoul, ¹³Institute for Evidence-Based Medicine, Cochrane Korea, Department of Preventive Medicine, Korea University College of Medicine, Seoul, ¹⁴Division of Rheumatology, Department of Internal Medicine, Chung-Ang University School of Medicine, Seoul, ¹⁵Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, ¹⁶Department of Family Medicine, Seoul Paik Hospital, Inje University College of Medicine, Seoul, ¹⁷Department of Internal Medicine, Kyungpook National University Hospital, Daegu, ¹⁸Division of Nephrology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, ¹⁹Division of Endocrinology and Metabolism, Department of Internal Medicine, Haeundae Paik Hospital, Inje University College of Medicine, Busan, ²⁰Division of Rheumatology, Department of Internal Medicine, Hallym University Sacred Heart Hospital, Anyang, Korea

Gout is the most common form of arthritis, with the prevalence increasing worldwide. The present treatment guidelines provide recommendations for the appropriate treatment of acute gout, management during the inter-critical period, and prevention of chronic complications. The guidelines were developed based on evidence-based medicine and draft recommendations finalized after expert consensus. These guidelines are designed to provide clinicians with clinical evidence to enable efficient treatment of gout.

Keywords: Gout, Guidelines, Treatment

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Corresponding author: Hyun Ah Kim, <https://orcid.org/0000-0002-9318-7446>

Division of Rheumatology, Hallym University Sacred Heart Hospital, 22 Gwanpyeong-ro 170beon-gil, Dongan-gu, Anyang 14068, Korea. **E-mail:** kimha@hallym.ac.kr

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INTRODUCTION

Background

Gout is the most common form of inflammatory arthritis, resulting from hyperuricemia due to abnormalities in purine metabolism or decrease of renal urate excretion. The prevalence of gout and hyperuricemia is rising worldwide because of population aging and changes in diet. The clinical relevance of gout is also increasing because it is closely associated with metabolic syndrome and joint pain. The American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR), as well as European and Japanese professional societies, have published guidelines for the diagnosis and management of gout. There are often substantial differences in diet and lifestyles between Koreans and Westerners, and Koreans have higher risk of gout due to the alcohol drinking culture in the workplace. However, Korean guidelines for gout management have not previously been published. Here, we provide guidelines for the effective treatment of gout that were formulated by consensus drawn from evidence-based medicine reported in the current literature.

Target population, goals, and intended users

The target population of these guidelines includes patients with gout and individuals with hyperuricemia. Our goal is to provide practical guidelines that are appropriate for Korean patients. Patient Intervention Comparatives Outcomes (PICO) questions were generated by the developing and steering committee, and are summarized in Supplementary Material 1. The guidelines are intended to provide clinical information for all clinicians including but not limited to physicians, family medicine doctors, orthopedic surgeons, and primary care doctors. They can be also used to educate medical students and residents. Gout patients who need treatment as well as individuals in the general population may find the information useful. The goal of these guidelines is to provide standards for treatment decisions based on clinical evidence.

Developers

The task force established to develop these guidelines included the chairman and steering committee members of the gout study group at the Korean College of Rheumatology (KCR). The task force appointed a chairperson for the development committee and established a development strategy, for which the

KCR reviewed and approved the budget. The development was financially supported by KCR, which did not affect recommendations. There was no financial support from third parties. The committee consisted of 16 members, including two methodologists and clinicians in various fields (rheumatologists, nephrologists, cardiologists, endocrinologists, family medicine specialists, and orthopedic surgeons). The committee performed literature reviews, retrieved evidence, formulated, and graded the final recommendations (Supplementary Material 2). Two methodologists provided knowledge on literature searches and assessment, evidence retrieval, grading the recommendations, and formulation of agreement on final recommendations to ensure the development was methodologically sound. The guidelines were endorsed by the KCR, Korean Society of Nephrology, Korean Endocrine Society, Korean Society of Hypertension, Korean Orthopedic Association, and Korean Academy of Family Medicine.

Patient value and preferences

No patient panel was included as part of the development team. Instead, we performed structured patient surveys to reflect and consider patient values and preferences regarding disease management. A total of 809 gout patients treated at 16 rheumatology clinics in university-affiliated hospitals were included. Most of the patients (94.8%) were aware of treatment strategies and recognized that gout requires treatment and control indefinitely throughout their lifetimes. About half of the patients (53.6%) preferred combined medication and lifestyle modification, 28.4% of patients preferred urate lowering therapy (ULT) only, and 17.4% of patients preferred lifestyle modification only. Patients who were well aware of treatment strategies, or who preferred ULT medication, showed higher medication compliance (Supplementary Material 3).

Manuscript review

The draft guidelines were generated based on final recommendations formulated by the development committee and underwent a thorough internal review by the steering committee. It was presented in the 2020 annual meeting of KCR for public comment. The clinical practice guidelines committee of KCR reviewed the draft; their comments are summarized in Supplementary Material 4.

Publication and dissemination

The current guidelines are available at the clinical practice guidelines section of the KCR website, which makes them accessible to all healthcare professionals involved in gout treatment. In addition, a summarized leaflet will be disseminated to hospitals, including primary care clinics in order to be easily utilized in daily practice. Paper versions of the leaflets will be released for individuals with difficulty accessing the internet.

Guideline updates

We plan to update the recommendations in five years following the leadership of KCR, allowing time for sufficient evidence to accumulate to impact treatment strategies or for a consensus that revision is required to arise.

Conflict of interest

All members of the development committee disclosed their potential conflicts of interest before the start of the process. Members were asked whether they were hired by or consulted with any company or institution that could affect the guidelines. They were also asked whether they had stocks in or held intellectual properties of any drugs used in gout treatment or received honoraria from certain companies. We obtained signed documentation verifying that there were no conflicts of interest (Supplementary Material 5).

METHODS AND RECOMMENDATIONS

Methods

The current guidelines went through a de novo development process.

1) PICO generation

To formulate PICO questions, the development committee first searched for and reviewed previous guidelines. The members met in person and selected topics that should be addressed in the new guidelines. During the next meeting, the development committee generated and discussed 9 PICO questions that were relevant to the topics to be included (Supplementary Material 1).

2) Literature search and assessment

A systematic literature search was conducted to address each PICO question. Methodologists and members of the development committee selected search terms using Ovid-MEDLINE,

EMBASE, Cochrane Library, KoreaMed, and KMBase during the period from June 2019 to November 2019. Search terms and strategies are described in Supplementary Material 6. Inclusion criteria were as follows: 1) studies conducted among adults, 2) studies written in English or Korean, 3) case reports, observational studies, randomized controlled trials (RCTs), systematic reviews (SRs), and meta-analyses, and 4) appropriate reported results. Exclusion criteria were as follows: 1) studies conducted among children or adolescents, 2) studies for which the results were not properly reported, 3) studies written in languages other than English or Korean, 4) duplicate publications, 5) studies for which it was impossible to obtain the full text, and 6) publications of expert opinions, reviews, or guidelines. A pair of committee members were assigned to each topic, and each team selected articles, through discussion with the development committee if necessary. The literature review process is depicted in a flow chart as suggested by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (Supplementary Material 7).

RCTs were evaluated using the risk of bias (RoB) metric introduced by Cochrane [1], non-randomized studies were evaluated using the risk of bias assessment tool for non-randomized study (RoBANS) [2]. When the results differed between pairs of committee members in the first round, final results were obtained through discussions with the chair of the committee and other members (Supplementary Material 8).

3) Formulation of recommendations: levels of evidence and strength of recommendations

We summarize studies selected through systematic literature review in an evidence table (Supplementary Material 8). Levels of evidence (LoE) and strengths of recommendations (SoR) were determined according to GRADE (The Grading of Recommendations, Assessment, Development and Evaluation) methodology (Table 1) [3]. LoE was categorized into 4 groups according to quality of the study, consistency, and directness. The strength of each recommendation was rated as strong for, conditional for, strong against, or conditional against. The SoR reflects the certainty of evidence indicating the benefits consistently outweigh the risks or are more closely balanced, or no data are available. Determinants of SoR include LoE, size of effect (trade-offs), patient preferences, and availability of resources [4]. Guideline recommendations are summarized in Table 2. We performed patient surveys to incorporate information regarding

patient preferences [5].

4) Consensus building

In-person group consensus was used to formulate the final draft of the recommendations.

5) Final review and approval

The guidelines were reviewed and approved by the clinical practice guideline committee of KCR (Supplementary Material 4).

Gout flare management

1) Choice of anti-inflammatory drug

PICO 1. Should we use non-steroidal anti-inflammatory drugs (NSAIDs) over colchicine/corticosteroids in patients experiencing a gout flare to reduce the duration of the flare?

Recommendation 1.

NSAIDs, colchicine or corticosteroids are conditionally recommended as first-line therapy for gout flares without preference for one agent over another, given similar efficacy in pain relief and flare duration reduction between agents. The choice may be based on comorbidities of individual patients (LoE: low, SoR: weak for)

For acute gouty arthritis, NSAIDs, systemic corticosteroids (oral or parenteral), and colchicine are mainly to alleviate inflammation. The choice is not based upon the effectiveness of each agent, but upon the patient's risk factors for adverse effects or physician preferences. Clinical studies comparing the effectiveness of the 3 drugs included 7 SRs comparing NSAIDs and corticosteroids and 1 RCT comparing NSAIDs and colchicine. Studies comparing colchicine and corticosteroid were not available.

Durations of gouty attacks: Studies comparing the effects of NSAIDs and oral corticosteroids on durations of acute gouty attacks were not available. One quasi-RCT compared treatment with 50 mg of indomethacin three times daily and intramuscular injection of 60 mg of triamcinolone acetonide and found that gouty attacks lasted for 8 and 7 days, respectively. Intramuscular injection of triamcinolone acetonide was found to be equivalent in safety and effectiveness to NSAIDs. An RCT comparing 250 mg of oral naproxen every 8 hours for 7 days and 500 µg of oral colchicine every 8 hours for 4 days showed that the time to complete pain resolution was 5 and 6 days, respectively [6].

Pain: SRs comparing NSAIDs and systemic corticosteroid for effectiveness in relieving pain from acute gouty arthritis found no differences between the drugs within 7 days [7]. A study comparing 250 mg of naproxen every 8 hours for 7 days and 500

Table 1. Level of evidence and strength of recommendations

Explanation	
Class	
High	We are very confident that the true effect lies close to the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
Grade classification	
Strong for	The benefit of intervention is greater than harm with high or moderate level of evidence, and can be strongly recommended in most clinical practice.
Weak for	The benefit and harm of intervention may vary depending on the clinical situation or patient/social value. It is recommended conditionally according to the clinical situation.
Weak against	The benefit and harm of intervention may vary depending on the clinical situation or patient/social value. Intervention may not be recommended in clinical practice.
Strong against	The harm of intervention is greater than benefit with high or moderate level of evidence, and can be strongly recommended against in most clinical practice.
No recommendation	It is not possible to determine the recommendation direction owing to a lack of evidence or discrepancy of results. Thus, further evidence is needed.

Table 2. Recommendations

Recommendation	LoE	SoR
1. Using NSAIDs, colchicine or corticosteroids as first-line therapy for gout flares is conditionally recommended without preference for one agent over another, given similar efficacy in pain relief and flare duration reduction between the agents. Choice may be based on comorbidities of individual patients.	Low	Weak for
2. In patients with gout who are indicated for the initiation of ULT, co-administration of ULT and anti-inflammatory agent during gout flares is conditionally recommended.	Low	Weak for
3. Administering concomitant colchicine prophylaxis therapy when starting ULT is conditionally recommended.	Moderate	Weak for
4. For all patients with gout taking ULT, maintaining a serum urate target of <6 mg/dL is conditionally recommended.	Low	Weak for
5. In order to prevent gout relapse, continuing ULT indefinitely is conditionally recommended.	Very low	Weak for
6. To choose either XOIs or uricosuric agents in chronic tophaceous gout depending on risk/benefit of an individual patient is conditionally recommended.	Very low	Weak for
7. With additional benefits on renal function, ULT is strongly recommended for all patients with gout, unless contraindicated.	High	Strong for

LoE: level of evidence, SoR: strength of recommendation, NSAIDs: non-steroidal anti-inflammatory drugs, ULT: urate lowering therapy, XO: xanthine oxidase inhibitor.

µg of colchicine every 8 hours for 4 days showed that there was no significant difference in the reduction of pain within 7 days [8].

Adverse effects: Compared to NSAIDs, systemic corticosteroids had lower relative risks (RR) of indigestion (0.50, 95% CI 0.27~0.92), nausea (RR 0.25, 95% CI 0.11~0.54), and vomiting (RR 0.11, 95% CI 0.02~0.56). The possibility that systemic corticosteroids are safer than NSAIDs for the treatment of acute gouty arthritis was explored [7]. Compared to an oral naproxen group, an oral colchicine group had higher rates of diarrhea (45.9% vs. 20.0%; OR 3.31; 2.01 to 5.44) and headache (20.5% vs. 10.7%; 1.92; 1.03 to 3.55), and naproxen was therefore recommended as first-line treatment in cases with no contraindications for it [8].

Following the above evidence, there were no differences in the clinical effectiveness of NSAIDs, colchicine, and corticosteroids for the treatment of acute gouty arthritis. Safety was the highest for systemic corticosteroids followed by NSAIDs, and colchicine had the lowest safety. Therefore, we recommend that the choice of specific anti-inflammatory drug should be based upon individual patient risk factors.

2) Initiation of ULT during acute flares

PICO 2. Should clinicians initiate ULT during gout flares vs. after gout flares have resolved?

Recommendation 2.

In patients with gout and indications for the initiation of ULT, co-administration of ULT and anti-inflammatory agents during gout flares is conditionally recommended (LoE: low, SoR: weak for)

There has been concern that commencement of ULT during an acute gout attack is likely to exacerbate the existing flare. There are also expert opinions that complete resolution of existing flares is more important than rapidly lowering serum urate levels in patients suffering acute gouty attacks. We included five studies that analyzed whether commencing ULT during flare episodes aggravated the duration and severity of existing flares. Among these studies, there was a systematic literature review and an observational study [9,10], and three small randomized controlled studies [11-13].

Duration of gout flare: Commencement of ULT during flare seems to extend the duration of the existing flare compared to initiation of ULT following complete resolution of gout flare. However, the evidence showed no significant differences in the duration of existing flares [11].

Severity of gout attack (visual analog scale, VAS): The evi-

dence showed no clinical difference in pain intensity of an existing flare between commencing ULT and placebo during a flare episode [9]. There was no significant difference in VAS scores between ULT group and placebo during the first 14-day observation period of an existing flare [12]. Despite the differences in observation period, the evidence showed no significant differences in pain severity between commencing ULT during a current flare and commencing ULT after complete resolution of a gout flare [11,13].

Recurrence of gout attacks: When comparing commencement of ULT during a current flare to commencement of ULT after a flare has fully resolved, the evidence showed no clinical difference in the risk of gout attacks between two groups [11]. On the other hand, in an observational study, more flares during the first 3 months occurred in the group commencing ULT during a flare episode than the group commencing ULT after the resolution of an existing flare [10].

Taken together, the evidence indicates that commencing ULT during a flare episode did not significantly exacerbate existing gout attacks. Thus, administration of ULT along with anti-inflammatory drugs may be considered during a flare episode. However, further studies to obtain more solid evidence are needed because the evidence low-graded quality studies were included in our review (Supplementary Material 8).

3) Intercritical gout management

PICO 3. Prophylaxis vs. no prophylaxis in patients with gout starting ULT

Recommendation 3.

Administering concomitant colchicine prophylaxis therapy when starting ULT is conditionally recommended (LoE: moderate, SoR: weak for)

There have been concerns that abrupt decreases of serum urate level with the introduction of ULT might result in mobilization flares in gout patients during the intercritical period. Therefore, expert opinion has recommended prescription of concomitant anti-inflammatory drugs for prophylaxis when initiating ULT to decrease the possibility of acute flare. Studies that addressed concomitant anti-inflammatory drugs for prophylaxis included 9 RCTs [14-22] and 2 observational studies [23,24], in which the anti-inflammatory drugs included colchicine, canakinumab, riloncept (Interleukin-1 Trap), and arhalofenate.

Colchicine, the only available drug among these, was used in 3 RCTs [14,16,22]. The frequency of acute flare with prophylactic colchicine was 48/143 (33.6%), which was lower than that with placebo 90/193 (46.6%). Based on these findings, administering concomitant colchicine prophylaxis therapy when starting ULT can be considered to prevent acute flares. However, there are no SRs of this topic, and this conclusion is based on only 3 RCTs with colchicine. Therefore, our recommendations are cautious and cannot be generalized to recommendations of any kind of anti-inflammatory drug. Future research on the use prophylactic use of NSAIDs or low dose corticosteroids is warranted to support the use of concomitant anti-inflammatory drugs for prophylaxis when initiating ULT.

PICO 4. Should ULT be prescribed to achieve serum urate <6 mg/dL in gout in order to prevent gout flares and bone erosion?

Recommendation 4.

For all patients with gout taking ULT, maintaining a serum urate target of <6 mg/dL is conditionally recommended (LoE: low, SoR: weak for)

We conditionally recommend maintaining SU <6 mg/dL in patients with gout receiving ULT. We included a SR of serum urate and the risk of incident gout and a RCT examining whether achieving target serum urate influences structural bone damage. In a SR of the association between serum urate level and gout flares, the rate and frequency of acute gout flares increased as the serum urate level increased, compared to when it was less than 6 mg/dL [25]. Several retrospective studies also demonstrated that maintaining serum urate level below 6 mg/dL was significantly related to fewer gout flares compared to serum urate over 6 mg/dL [26,27]. Maintaining serum target urate level below 6 mg/dL prevented long-term structural damage in a randomized study using dual-energy computed tomography. The progression of CT erosion score after two years was lower in the group treated with targeted ULT to maintain urate less than 6 mg/dL than in the group treated with conventional therapy [28]. Furthermore, subsequent studies using ultrasonography and dual-energy CT have shown that maintaining ULT with a target serum urate level below 6 mg/dL is associated with reductions in size of tophi [28-30]. Based on this evidence, we recommend maintaining the serum urate level below 6 mg/dL

in patients with gout on ULT. There are guidelines that recommend maintaining serum urate level below 5 mg/dL, especially in severe cases based on the notion that the velocity of crystal dissolution depends on the serum urate level [31,32]. However, there are limited systematic literature reviews and randomized clinical studies regarding outcomes according to the specific target serum urate level. Additional evidence on target serum urate levels and outcomes of treat-to-target therapy in ULT is needed (Supplementary Material 8).

PICO 5. Should ULT be stopped vs. continued for patients with gout on ULT?

Recommendation 5.

In order to prevent gout relapse, continuing ULT indefinitely is conditionally recommended (LoE: very low, SoR: weak for)

When ULT is stopped, there is a high chance of relapse. Accordingly, in order to prevent gout relapse, continuing ULT indefinitely is conditionally recommended. This recommendation was derived from 1 SR [33]. Eight small observational studies with varied observational periods ranging from 12 to 96 months were included. The rate of gout relapse after cessation of ULT ranged from 36% to 81%. Patients experienced relapse 1 to 4.5 years after the stopping of ULT. The rate was lower in patients with lower serum urate levels even after stopping ULT. Based on outcomes of gout relapse, 5 observational studies favored continuing ULT over stopping. However, due to the small number of studies and sample size, the LoE is very low. Proper RCTs are warranted.

PICO 6. Should xanthine oxidase inhibitors (XOIs) be prescribed over uricosuric agents in chronic tophaceous gout?

Recommendation 6.

To choose either XOIs or uricosuric agents in chronic tophaceous gout depending on risk/benefit of an individual patient is conditionally recommended (LoE: very low, SoR: weak for)

There were few studies that directly compared treatment outcomes between XOIs and uricosuric agents. One observational study conducted in 63 patients with clinical tophi showed that

the reduction of tophi size was comparable between allopurinol, benzbromarone, and combined treatment groups [34]. Regardless of the medication, patients who achieved lower serum urate levels showed greater tophi size reduction. We found that there was lack of evidence showing superiority of one ULT over another and recommend maintaining low serum urate levels to reduce the size of the tophi and bone erosion.

4) Impact on comorbidities

PICO 7. Should ULT be used in gout patients vs. no treatment in order to preserve renal function?

Recommendation 7.

With additional benefits on renal function, ULT is strongly recommended for all patients with gout, unless contraindicated (LoE: high, SoR: strong for)

Gout is frequently associated with cardiovascular diseases, hypertension, diabetes mellitus, and chronic renal diseases [35]. Hyperuricemia can act as a causal factor for development of these comorbidities [36]. A SR and a meta-analysis evaluating the role of ULT in protecting kidney function showed that ULT (allopurinol, rasburicase, benzbromarone) was associated with decreases in serum creatinine (sCr) and increases in estimated glomerular filtration rate (eGFR) [37]. Therefore, we strongly recommend ULT for all patients with gout, except those who experience side effects or have contraindications for ULT, since ULT has additional renal protective effects. However, evidence for preferring one ULT over another to achieve renal protective effects in patients with gout is currently insufficient. A meta-analysis comparing the renal protective effects of febuxostat and allopurinol showed no significant differences in sCr and eGFR between both drugs, but a significant change in albuminuria favoring febuxostat over allopurinol [38]. This study suggested that febuxostat has better renal protective effects than allopurinol, but more evidence is needed to make a recommendation for selecting one ULT over another to achieve renal protective effects in patients with gout.

PICO 8. Should prescribing ULT be used to improve cardiovascular outcomes in patients with gout vs. no treatment?

Recommendations were not formulated due to a lack of current evidence.

PICO 9. Should prescribing ULT vs. no treatment be used in chronic kidney disease 3,4 patients with asymptomatic hyperuricemia in order to protect renal function?

Recommendations were not formulated because the profile of benefit/harm was not clear.

CONCLUSION

The current guidelines were developed based on up-to-date evidence drawn from the literature in accordance with sound methodology. The recommendations were formulated considering practical situations in Korean clinics, which make them applicable to East Asian countries where lifestyles are similar to those in South Korea. During the development process, we verified that the LoE to which clinicians refer in treatment decisions was not high. Therefore, high quality RCTs are warranted in the future to address controversial topics. Accordingly, we could not find enough evidence regarding the cardiovascular benefits of ULT, and thus recommendations could not be formulated. Likewise, a consensus could not be reached on the question of whether ULT has renal protective effects in patients with asymptomatic hyperuricemia. These are issues of utmost importance and properly designed prospective studies are warranted in the near future.

SUPPLEMENTARY DATA

Supplementary data can be found with this article online at <https://doi.org/10.4078/jrd.2023.0029>.

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CONFLICT OF INTEREST

J.B.J. has been an editorial board member since June 2014, but has no role in the decision to publish this article.

AUTHOR CONTRIBUTIONS

Conceptualization: H.A.K., J.S.S., and J.B.J. Data curation or/ and Analysis: all authors. Writing - original draft: H.A.K., J.J.L., J.S.L., M.K.C., J.K.A., S.J.H., C.H.Y., S.H.K., and J.W.K. Writing - Review & Editing: all authors. All authors read and approved the final manuscript.

ORCID

Jennifer Jooa Lee, <https://orcid.org/0000-0001-6873-6629>
Ji Soo Lee, <https://orcid.org/0000-0001-6279-7025>
Min Kyung Chung, <https://orcid.org/0000-0001-6414-9187>
Joong Kyong Ahn, <https://orcid.org/0000-0003-3246-4435>
Hyo-Jin Choi, <https://orcid.org/0000-0001-5192-6151>
Seung-Jae Hong, <https://orcid.org/0000-0002-9803-529X>
Chong-Hyeon Yoon, <https://orcid.org/0000-0003-2305-4637>
Su-Hyun Kim, <https://orcid.org/0000-0003-3382-528X>
Kyung-Hwan Jeong, <https://orcid.org/0000-0003-1492-8021>
Jong-Woo Kim, <https://orcid.org/0000-0001-7317-8748>
Bo-Yeon Kim, <https://orcid.org/0000-0002-3658-2351>
Jin-Ho Shin, <https://orcid.org/0000-0003-2072-0614>
Woo Gyu Kim, <https://orcid.org/0009-0002-9976-3309>
Soo-Young Kim, <https://orcid.org/0000-0002-3205-9408>
Hyun-Jung Kim, <https://orcid.org/0000-0003-2018-2385>
Jeong-Soo Song, <https://orcid.org/0000-0001-8651-5125>
Jae-Bum Jun, <https://orcid.org/0000-0002-0208-0505>
Hyun-Ah Park, <https://orcid.org/0000-0003-2343-8964>
Shung Chull Chae, <https://orcid.org/0000-0002-9871-6976>
Bum Soon Choi, <https://orcid.org/0000-0002-1412-9951>
Tae Nyun Kim, <https://orcid.org/0000-0001-6568-2469>
Hyun Ah Kim, <https://orcid.org/0000-0002-9318-7446>

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