Japanese Society of Gout and Uric & Nucleic Acids 2019
Guidelines for Management of Hyperuricemia
and Gout 3rd edition

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Abstract

[Background] Accumulated evidences suggested that hyperuricemia may be risk for renal failures, cardiovascular disease and lifestyle related disease since the 2nd edition of the guideline for the management of hyperuricemia and gout published in 2010, while hyperuricemia is a definitive risk of gout and urolithiasis. Besides, the novel non-purine xanthine oxidoreductase inhibitors have been developed recently. However, it remains unclear whether pharmacological treatment for asymptomatic hyperuricemia may be recommended to protect from gout arthritis and renal and cardiovascular disease. [Objects] Japanese guideline for the management of hyperuricemia and gout the 3rd edition tend to be developed to prevent patients, from asymptomatic hyperuricemia and gout. [Methods] After setting the important clinical issues on hyperuricemia and gout, seven clinical questions accompanied by advantage and disadvantage outcomes have been selected. Using the systematic reviews on reports related to outcome of each clinical question, bias risk of each evidence has been estimated. Taken together with the estimation of body of evidence, patients’ opinions and medical economics, the recommendation for each clinical question has been determined. [Results] 1) NSAIDs, glucocorticoid and colchicine are equally recommended to be use for gout attack, 2) Lowering serum urate less than 6mg/dL is recommended to treat tophus, 3) Long term colchicine cover is recommended to treat gout patients after administration of urate lowering agents (ULAs) than short period colchicine cover, 4) ULAs are partially recommended to use for hyperuricemic patients with hypertension in order to suppress the deterioration of renal function, 5) ULAs are not partially recommended to use for hyperuricemic patients with hypertension in order to improve the prognosis and suppress the cardiovascular events, 6) ULAs is not partially recommended to use for hyperuricemic patients with heart failure in order to improve the prognosis and to suppress the cardiovascular events, 7) Dietary education including restriction of alcohol abuse is recommended for management of hyperuricemia. The Japanese version was published on December in 2018. This guideline has been translated into English. [Conclusion] This guideline is expected to cover the decision making against the important clinical issues on hyperuricemia and gout.

1) Introduction

Westernization of the Japanese diet has resulted in a yearly increase in the number of hyperuricemia patients in Japan, with 20–25 % of adult males presenting with hyperuricemia in 2010. Hyperuricemia has been reported to occur in 20 % of men and in 5 % of women in the entire population. The prevalence of gout, which is caused by hyperuricemia, is estimated to exceed 1 % of men aged 30 years and older, and the number of gout patients is estimated to be in excess of 1 million nationwide as of 2016 based on the Comprehensive Survey of Living Conditions Reports, including various surveys in Japan, indicated that this number is currently rising. In terms of the age distribution of gout patients, the highest numbers of patients are in their 60s, followed by an equal number of patients in their 50s and 70s. The reason for the decrease in the number of gout patients after the age of 60 is unclear. The initial age at onset is most commonly in the 30s, followed by the 40s and 50s. Hyperuricemia is defined based on the solubility of uric acid as a serum urate concentration exceeding 7.0 mg/dL, irrespective of gender. Hyperuricemia itself does not reveal any subjective symptoms. Single and multi-gene defects related to nucleic acid metabolism-related enzymes, and urate transporters that trigger accelerated uric acid production or reduce renal excretion of uric acid, have been suggested as the cause of hyperuricemia. A diverse range of environmental factors, including lifestyle habits such as diet, alcohol consumption, and exercise, is strongly associated with the onset of hyperuricemia. Hyperuricemia is broadly divided into the overproduction of uric acid, underecretion of uric acid, and mixed types, and recently the existence of a renal load type, including reduced extrarenal excretion of uric acid type and the overproduction of uric acid, has also been proposed.

Persistent hyperuricemia increases the uric acid pool in the body, and the monosodium urate (MSU) precipitates into the joints and renal tract as crystals. The MSU crystals that precipitate into the joints are phagocytosed by leukocytes, which secrete cytokines that trigger inflammation, causing gouty arthritis. MSU crystals can also cause ureteral calculus, while hyperuricemia and hyperuricosuria can result in serious kidney failure caused by chronic interstitial nephritis. Hyperuricemia is associated with a high incidence of lifestyle diseases and organ involvement, including cerebral and cardiovascular events, however, it remains to be elucidated whether...
Asymptomatic hyperuricemia should be handled as either a marker or as a risk factor for lifestyle diseases and organ involvement. As stated above, the common diseases of hyperuricemia and gout require a guideline to enable provision of standardized medical treatment. The first edition of the Guideline for the Treatment of Hyperuricemia and Gout was established in treatment of gouty arthritis. The second edition showed methods to handle asymptomatic hyperuricemia and proposed the possibility that hyperuricemia may be either a risk factor or a marker for lifestyle diseases and organ involvement. Furthermore, the existing urate lowering drugs cannot be solely used for the treatment of asymptomatic hyperuricemia, however, novel xanthine oxidoreductase (XOR) inhibitors such as febuxostat and topiroxostat have been developed that can be used for the treatment of asymptomatic hyperuricemia alone.

Furthermore, there are arguments with regards to hyperuricemia being a risk factor for organ involvement, and it remains undetermined how best to handle asymptomatic hyperuricemia in routine clinical practice. Moreover, the level of awareness about hyperuricemia is still low among even medical personnel, and currently, the condition is not being appropriately treated and preventive measures are not being adopted.

Overseas guidelines define identification of MSU crystals as the diagnosis of gouty arthritis. Low-dose colchicine, nonsteroidal anti-inflammatory drugs (NSAIDs), and steroid therapy are used to treat acute gouty arthritis as the 1st line medication, with these guidelines setting the control target for serum uric acid levels as < 6.0 mg/dL for gouty arthritis and < 5.0 mg/dL if there were tophi present. Allopurinol is the 1st-line drug to control uric acid level. Kidney function and evaluation of cardiovascular disease risk are recommended in patients with hyperuricemia and/or gout, however, the pharmacological treatment for asymptomatic hyperuricemia is not recommended to prevent gout, kidney impairment, and cardiovascular events. Thereby, there are differences between the Japanese and Western guidelines on recommendation such as pharmacological treatment for gouty arthritis, the uric acid control target for tophi, the pros and cons of controlling serum uric acid level for hyperuricemia with organ involvement, and the pros and cons of dietary advice. Accordingly, the Guideline for the Treatment of Hyperuricemia and Gout 3rd edition was developed to clarify these differences.

2) Aim and target of this guideline
This guideline is mainly to be used during medical treatment, including general practice and medical examinations in hospitals, clinics, care and health check facilities, etc., by physicians, nurses, pharmacists, healthcare public health nurses, physical therapists, patients and patients’ families in Japan. It will also be available to the general public via the website. This guideline should be used for decision-making regarding treatment strategy and the development of consensus between patients and physicians.

3) Topics associated with hyperuricemia and gout
Extraction of key clinical issues and treatment algorithm
We extracted 5 key clinical issues based on the characteristics of hyperuricemia and gout, and their epidemiology and development of their general diagnostic flow. [Gouty arthritis]: The first-line drug to be used for treating gouty arthritis has not been determined. Neither whether colchicine cover should be used short-term or long-term to prevent frequent gouty flares. [Tophi]: The target for controlling serum urate concentration in patients with tophi has not been determined. [Hyperuricemia in patients with renal impairment and/or cardiovascular disease]: It has not been determined whether uric acid lowering agents should be used for organ protection and to improve the prognosis of hyperuricemia patients in renal impairment, hypertension, and/or heart failure. [Improvement of lifestyle diseases in asymptomatic hyperuricemia]: It has not been determined whether dietary advice is effective in reducing serum uric acid concentration and protecting against development of gouty arthritis in asymptomatic hyperuricemia patients.

The algorithm on the management of hyperuricemia and gout was created to address the above key clinical issues as shown in Figure 1.

4) Guideline development method
Organizational structure
In April 2016, 10 people were requested to form the guideline executive committee and 32 people were requested to become guideline development group on behalf of Japanese Society of Gout and Uric & Nucleic Acids. A steering group (secretariat of guideline development) was
formed from the guideline revision committee to ensure close contact with the society secretariat. For each clinical question (CQ), 2 people were assigned to be responsible for the scope of the systematic review (SR) as SR supervisors (14 people in total), and 4 people were assigned to be responsible for each SR (28 people in total). Members of the Japan Medical Library Association (JMLA) were requested to act as collaborators to conduct SRs. The guideline revision committee implemented revision work for creating the 7 CQ recommendations, based on the Medical Information Distribution Service (Minds) Manual for Clinical Practice Guideline Development 201712). Moreover, 2 experts, a nephrologist and cardiologist, were requested to perform an external review. Three experts were consigned as collaborators to assess pharmaceutical information and medical economics. A liaison committee commissioned 14 people to coordinate with related associations on the treatment manual for hyperuricemia and gout. The member of guideline development group is described in Table 8.

Funding for development of the guidelines
This guideline was developed with the operating costs of the Japanese Society of Gout and Uric & Nucleic Acids. A research grant of JPY 600,000 was also received in the 2016 fiscal year from the Gout and Uric Acid Research Foundation. The two offices of the guideline control committee and guideline development group are not held concurrently, and the opinions of the founding agencies have not affected the content of the guideline. Based on the above information, the Japanese Society of Gout and Uric & Nucleic Acids has not received any support from specific organizations or corporations in the development of this guideline. The revision committee for this guideline has not received any funding or other support from corporations such as pharmaceutical companies.

Conflicts of interest (COI)
Conflicts of interest of the revision committee for this guideline are managed and disclosed in accordance with the following criteria based on the Policy of Conflict of Interest in Clinical Research of Japanese Society of Gout and Uric & Nucleic Acids13).

a) The revision committee for this guideline shall disclose COI in the following circumstances relating to the pharmaceuticals with product names (hereinafter referred to as applicable pharmaceutical) stated in this guideline during any of the one-year periods during which the guideline revision committee was active (fiscal years 2016, 2017, and 2018).

• When research funding for the applicable pharmaceutical exceeds JPY 1 million per single

Figure 1: Flowchart for medical treatment of hyperuricemia and gout

* Kidney disease, Urolithiasis, Hypertension, Ischemic heart disease, Diabetes Mellitus, Metabolic syndrome etc. (Except of kidney disease and urolithiasis, it remains unelucidated whether lowering SUA can reduce the events. Further study is necessary to get these evidence)
company
• When the total amount of payment for lecture fees, consultancy fees, manuscript fees, and other forms of remuneration associated with the applicable pharmaceutical exceeds JPY 1 million per single company
• When income from company shares or other such sources associated with the applicable pharmaceutical exceeds JPY 1 million
• When a committee member is in an employment relationship with a company associated with the applicable pharmaceutical

b) The disclosure will be presented as a list of company names voluntarily declared by each member of the guideline revision committee in accordance with the aforementioned criteria.

Any members of the guideline revision committee to whom conflicts of interest are applicable based on the aforementioned criteria are listed below.


Although 11 of the 32 guideline development group members were found to have COI, the number of members with COI does not exceed half of the total. Meeting deliberations and decisions are governed by the rules of participation. Scenarios where deliberations and decisions were specifically required during the guideline development process were compliant with Policy of Conflict of Interest in Clinical Research, Japanese Society of Gout and Uric & Nucleic Acids. According to the rules of participation, depending on the amount of money received by the committee member, any member who receives an amount exceeding JPY 5 million per year from an individual company associated with the applicable pharmaceutical, even once within the last 3 years, cannot participate in deliberation on the related pharmaceutical. Moreover, any member who receives an amount of money exceeding JPY 500,000 but less than JPY 5 million can participate in deliberation, but cannot participate in voting. A committee member who does not participate in deliberation will exercise voting rights in advance at the discretion of the committee chair. Deliberation and voting on bills where the chair has a COI, shall be performed by the vice-chair in their place.

Deciding on the CQ and the benefit and harm outcomes
Key clinical issues on the treatment of hyperuricemia and gout were converted to a PICO (patients, intervention, comparison, outcome) format by the Japanese Society of Gout and Uric & Nucleic Acids councilor and a public appeal was launched as key clinical issues based on GRADE approach\(^{14,15}\). A total of 155 key clinical issues converted to PECO/PICO format were collected by June 11\(^{th}\), 2016 (including duplications). The guideline steering team removed duplications, organized the key clinical issues in accordance with the PICO format PIC, and formulated 27 key clinical issues classified into 6 categories: acute gouty arthritis, chronic gouty arthritis, asymptomatic hyperuricemia associated with renal impairment, cardiovascular disease, and other. To decide on the CQ, the person responsible for scope refined the issues by removing the following items: ① Issues for specialist doctors, ② Issues not directly related to treatment, ③ Issues that already have an established treatment, and ④ Issues with only a small number of randomized controlled trials (RCT). The importance of the 27 types of PIC format CQ was scored twice by the guideline development committee using the Delphi technique. Each CQ formulated with PIC was scored from 1 to 9 using the Delphi technique (7-9: Critical for decision-making, 4-6: Important for decision-making, but not critical, 1-3: Not important for patients).

The outcomes for each benefit and harm were voted on
twice with the Delphi technique and scored from 1 to 9, and items selected as critical (7–9 points), and important, but not critical, (4–6 points) were adopted as outcomes.

The ordered PIC format CQs and the outcomes for each CQ were distributed in advance and seven important PIC format CQs and three outcomes of benefit and harm for each CQ, were selected by the guideline committee on November 12, 2016 (supplement 13). Next, the SRs were performed. Questionnaires about the CQs were sent to patient groups to call for patient input.

Primary and secondary screening of literature searches for systematic review

The person in charge of scope decided on the SR teams, and English and Japanese literature searches were conducted in collaboration with librarians from the JMLA to conduct the SRs, which has been instructed by the JMLA in February 2017.

① Keywords were selected by the person in charge of scope to be sent to librarians from the JMLA who established the search strategy based on each CQ. Next, a comprehensive search was conducted on literature in PubMed, Ichushi Library (Japan Medical Abstract Society Library), and the Cochrane Library (CDSR and CCRCT) from 1966 to March 31st, 2017, with the cooperation of the JMLA.

② Primary screening was conducted with all 4 members of each CQ SR team separately, selecting the necessary literature from the subject heading, abstract, and search words of the same literature lists, matching the results, and making decisions through SR team discussions on any literature where the rejection and adoption decisions of the different members failed to match.

③ The SR team was divided into 2 people responsible for 2 beneficial outcomes (O), and 2 people responsible for 1 harmful outcome. Each group of two people independently read the main text of literature selected through the primary screening process to conduct a secondary screening process, selecting reference literature for each of the outcomes. This process has been followed by GRADE method16-24.

Evaluation and integration of body of evidence (August 1 – October 31, 2017)

Each SR team completed the forms regarding either interventional studies or observational studies as well as overall evidence for each of the beneficial and harmful outcomes in each CQ using Minds Manual for Clinical Practice Guideline Development 201717,21.

① Two people independently evaluated forms for either interventional study or observational study for each of the outcomes, then each opinion was integrated to complete the evaluation. The evaluation was conducted regarding the risk of bias, indirectness, and number of patients at risk.

② The SR team used form for meta-analysis and form for qualitative review when not conducting a meta-analysis.

Then, the person responsible for scope evaluated the overall evidence for each outcome using a cross-sectional approach, and the evaluation on body of evidence was completed by two people cross-matching the results. Evaluation of the strength (certainty) of the body of evidence was conducted based on factors of domains such as Risk of bias, Inconsistency, Imprecision, Indirectness, and Others (Publication bias etc). Evaluation of the certainty in body of evidence followed the method proposed by GRADE working group14-20, with the certainty in body of evidence ultimately graded into 4 grades: A (strong), B (moderate), C (weak), and D (very weak)24. In evaluation of RCTs, the certainty in body of evidence started from A (strong), and the grade was then adjusted through evaluation of factors of domains that reduce the grade, including risk of bias, inconsistency, indirectness, imprecision, and publication bias. Non-RCTs were also evaluated for three factors that reduce the grade14-24. The definitions of risk of bias, inconsistency, indirectness, imprecision, and publication bias used for evaluation were consistent with those of GRADE guidelines14, 17-21.

The person responsible for scope described the SR report summaries (evidence summary), and formulated recommendation drafts based on those summaries. Views on patient values and preferences for the testimonial draft were requested in advance from hyperuricemia and/or gout patient representatives and included in the recommendation draft. The person responsible for scope also sought opinions on medical economics and included that information, mainly focused on the drug price from the viewpoint of insurance coverage, in the recommendation draft. The recommendation draft was summarized for each of the 4 factors such as overall
evidence across outcomes, certainty of the balance between benefit and harm, consistency and certainty (or diversity) in the values, preferences, and burden of patients, and the net benefit sufficiently balanced with the cost and resource use to determine the recommendation.

**Basic policies for determining recommendations**

When formulating the recommendation, the strength and direction of recommendation were determined from the perspective of certainty in body of evidence, certainty of benefit and harm balance, diversity of patients’ values and preferences, and burden, cost, and available resources.

The drafts recommendations were made as of December 17, 2017.

**Procedures for determining recommendations**

Determining the recommendations was based on deliberations by the development group, and recommendations were determined by vote.

i) **Panel meeting**

The panel meeting was held in the Conference Room B, 3rd Floor of the World Trade Center Building from 10 am to 5 pm on December 17, 2017. A total of 26 committee members had voting rights. Decisions on each of the 4 factors for recommendation were conducted in the meeting using the summarized recommendation drafts, the SR report summaries, the overall evidence tables evaluated for each outcome, and the patient questionnaires. The person responsible for the scope of each CQ first presented the recommendation draft and explained the associated evidence summary; the matters were then thoroughly deliberated and the recommendations were determined with a vote. The strength of the recommendations were determined through voting with a raising hand to determine which of the following 4 grades shown in the Minds guideline development method.

Recommendations with 70% or more of the valid number of votes were accepted, and if 70% was not reached, the second highest option was deliberated and voting was conducted again. Based on the preliminary evaluation of COI, all guideline development committee members were able to participate in deliberation, however, members with COI related to voting did not participate in voting, and hence COI did not affect the recommendations.

The content of recommendations was determined by the panel meeting; the related explanations were checked by the guideline revision control committee, and corrections were made only to the wording of the explanation.

ii) **Viewpoint of recommendations**

The recommendations have 3 elements: direction of recommendation, strength of the recommendation and strength (certainty) of evidence, and recommendations were expressed using combinations of these. The direction of recommendation refers to whether the recommendation will be implemented. Strength of recommendation refers to whether the recommendation is strong or weak, while the strength of evidence corresponds to one of A (strong), B (moderate), C (weak/low), or D (very weak/low) according to the GRADE approach. The strength of recommendation is divided into four parts based on the combination, and it must be noted that this does not imply that there are four types of recommendations, but simply means that the extent of the strength of the direction and strength of the recommendation lays on a continuum.

iii) **Patient values and preferences**

This guideline called for opinions on the values and preferences of patients with hyperuricemia and/or gout through questionnaires distributed to patient groups visiting hospitals on an outpatient basis, and the recommendations were determined based on the input from these patients. Opinions were sought on the key clinical issues to be adopted into the CQ using questionnaires to elicit opinions from 5 subjects in a patient group of 11 subjects, and this input was considered when deciding on the CQ. Opinions were also sought at the recommendation draft stage using questionnaires to elicit opinions from 6 subjects in a patient group of 11 subjects, and this input was incorporated as the values and preferences of patients. The values and preferences were shown in the recommendation draft as factors to consider for the strength of the recommendation. This input was presented at the panel meeting, deliberated, and incorporated into the formulation of the recommendations.

**Items relating to finalization and publication**

i) **Finalization**

A broad range of opinions were sought by the Japanese Society of Gout and Uric & Nucleic Acids members, and the documents were revised accordingly. Next, an external review was done by expert of cardiology and nephrology...
who were not members of the present guideline committees, and Minds conducted an external review on the guideline development method. Public comments were sought using the Minds GUIDE system and the Japanese Society of Gout and Uric & Nucleic Acids website, and these public comments and the actions responding to their comments were reflected in the final version.

ii) Specific methods and approach to external review

The guideline underwent Minds external review based on the Appraisal of Guidelines for Research & Evaluation (AGREE II)\(^{27}\) to improve the development method quality, and this input was reflected in the document. An external review committee assessed the guideline development methods based on AGREE II, and comments were collected from nephrologists and cardiologists as the experts for evaluation of renal impairment and cardiovascular diseases that occur as complications of hyperuricemia and gout. The guideline revision committee then deliberated the necessity of altering the guideline with respect to each comment and decided on the optimal approach. The same approach was taken regarding the public comments.

Way of using this guideline

• We envision that this guideline will be used by patients with hyperuricemia and/or gout and medical personnel, including non-specialists on hyperuricemia and gout. The recommendations in this guideline are applicable to adult patients with hyperuricemia and gout. These guidelines don’t restrict clinicians’ expertise. The information provided in this guideline indicates general treatment methods and may not always be suitable for specific individual patients. The final judgment requires consultation between the attending physician and the patient. Hyperuricemia and gout can have organ involvement, hence, specialists in the respective fields should be consulted as needed.

[Clinical Question 1]

Can NSAIDs, glucocorticoids, and colchicine be recommended for patients with acute gouty arthritis (gout attacks) over no pharmacological treatment?

Recommendation - NSAIDs, glucocorticoids, and colchicine (low dose) are conditionally recommended for patients with acute gouty arthritis (gout attacks) over no pharmacological treatment.

PICO format for CQ1 is shown in table 1.

1. Recommendation determinants

1) Strength of evidence: B (moderate)

A systematic literature review identified only 2 studies that used placebos.

Most studies compared one kind of NSAID to another NSAID, or glucocorticoids to one of conventional NSAIDs. In case of these 2 studies, colchicine was reported to be more effective than the placebo. The case definition, the measurement methods and time points of efficacy or adverse events, differed between the studies. The NSAID doses identified in these studies were higher than the approved NSAID dose in Japan, and no reports provided evidence on whether NSAIDs, glucocorticoids, or colchicine should be the first-line treatment. Taken together, the strength of evidence for the recommendation was generalized as B (moderate).

In regard to NSAIDs, none of the identified studies demonstrated the superiority of one NSAID over another. Adverse events associated with the use of indomethacin were significantly high in some studies, however, differences in the study methods needed to be taken into consideration. Colchicine in high dose has a high incidence of adverse events (including severe ones), indicating that this administration method should be avoided. Low-dose colchicine can be recommended in clinical practice. Glucocorticoids can be taken orally and can also be administered via intraarticular or intramuscular injections. Although few studies examined these methods of administration, they were determined as viable treatment options in clinical practice.

2) Balance between benefit and harm

In the NSAID studies the identified comparators were classical NSAIDs, mainly indomethacin, diclofenac and naproxen, and the doses in these studies were larger than those approved in Japan. High-dose colchicine treatment
is effective for gouty arthritis but has a high incidence of adverse events. Therefore high-dose colchicine is not recommended. Low-dose colchicine treatment has a good balance between benefit and harm, but this was based on a single paper. Glucocorticoids have an equivalent effect as NSAIDs, and the reports indicated that there were lower, or the same number of adverse reactions observed. Furthermore, it should be noted that these studies excluded cases where NSAIDs or glucocorticoids were contraindicated, and also NSAID doses in the studies were higher than those approved in Japan.

3) Patient values and preferences
It is concerning that the drug doses evaluated were higher than the doses used in Japan. To decrease pain, it is important to use the drugs as early as possible. However, it remains unclear which drug should be used first.

4) Cost and resources
The period of administration of oral glucocorticoids, NSAIDs, or colchicine for acute gouty arthritis was generally considered to be up to 14 days and these drugs are not expensive. Therefore, these treatments are not considered to be financially burdensome.

2. Process of deciding on the recommendation
A comparative study of low-dose and high-dose celecoxib demonstrated significantly superior pain reduction effects with the high-dose treatment\(^{28}\). Oral glucocorticoids had an equivalent efficacy to NSAIDs\(^{29-32}\), and colchicine had a greater effect than the placebo\(^{33,34}\). Therefore, NSAIDs, glucocorticoids and colchicine were estimated to have a superior effect for improving gouty arthritis compared to the placebo.

Given that no evidence was obtained on the superiority or inferiority of these three drugs, the selection of these drugs should be based on the patient’s comorbidities and concomitant medication. In particular, it should be noted that colchicine should not be administered in high doses. The efficacy of colchicine has been investigated in patients within 12 hours of the onset of acute gouty arthritis. High dose colchicine is associated with an increased incidence of gastrointestinal adverse events such as diarrhea\(^7\), and hence colchicine should be used in low doses.

3. Other
The pain associated with acute gouty arthritis is severe and markedly reduces the quality of life in affected patients. Drug administration is only conditionally recommended in view of the small number of papers comparing medication to placebo, the differences in case definition, the

Table 1: PICO format for CQ1

<table>
<thead>
<tr>
<th>Components of CQ</th>
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<tbody>
<tr>
<td><strong>P (Patients, Problem, Population)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Sex</td>
<td>(Not specified) Male / Female</td>
<td>Age</td>
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<tr>
<td>Disease/clinical condition</td>
<td>Patients with attacks of acute gouty arthritis</td>
<td>Geographic constrains</td>
</tr>
<tr>
<td>List of I (Interventions) / C (Comparisons, Controls, Comparators)</td>
<td></td>
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<tr>
<td>NSAIDs, steroids, colchicine / control: non-medication</td>
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<tr>
<td>List of O (Outcomes)</td>
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<tr>
<td>Outcomes</td>
<td>Benefit or Harm</td>
<td>Importance</td>
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<tr>
<td>O₁</td>
<td>Gouty arthritis improved</td>
<td>(Benefit or Harm)</td>
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<tr>
<td>O₂</td>
<td>Adverse events increased</td>
<td>(Benefit or Harm)</td>
</tr>
<tr>
<td>O₃</td>
<td>Acute inflammatory response substances decreased</td>
<td>(Benefit or Harm)</td>
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measurement of efficacy or the adverse events. However, in clinical settings, starting pharmacological treatment for acute gouty arthritis as quickly as possible is the principle, and this has not been changed from previous guidelines.

Selection of the aforementioned three drugs should be decided based on the clinical course of gouty arthritis (including the time from onset), the patient’s comorbidities, and concomitant medications. An adequate dose of NSAIDs should be used. In the identified studies, the administered dose of NSAIDs was generally higher than the dose approved in Japan, although in case of some NSAIDs, relatively higher doses have been approved in Japan for the treatment for gouty arthritis by the insurance providers. NSAIDs should be avoided in patients with gastric ulcers or in those patients taking anticoagulants, and be used with caution in patients with a history of chronic kidney disease or cardiovascular events. A 1.0 mg dose of colchicine should be administered within 12 hours of arthritis onset, followed by 0.5 mg one hour later\(^4\). There were no studies in regard to the treatment for any residual pain the day after taking the initial doses of colchicine, but colchicine can be continued at a dose of 0.5-1.0 mg/day depending on the severity of the pain until the arthritis was improved. An increased incidence of gastrointestinal complication such as diarrhea was observed with the higher doses of colchicine. Caution is also needed in patients with liver and/or kidney dysfunction and in drug interactions. In case of glucocorticoids, oral prednisolone doses of 30–35 mg/day for 5 days were administered in the identified studies\(^ {29-32} \) but a dose of 20–30 mg/day will be considered adequate in Japan. Caution is needed when prescribing glucocorticoids in patients with diabetes, infections, postoperative patients, glaucoma, and so on. Glucocorticoids can also be administered via intraarticular or intramuscular injection.

When there are no factors limiting the use of the aforementioned three drugs, then it will be appropriate to select drugs based on the patient’s preference or the physician’s experience. Medical treatment should be stopped promptly once the symptoms have resolved or sufficiently improved.

4. Voting results

Number of voters: 26; valid votes: 26

(1) Recommend “use drugs for treatment”: 5 votes; (2) Conditionally recommend “use drugs for treatment”: 21 votes; (3) Conditionally recommend “do not use drugs for treatment”: 0 votes; (4) Recommend “do not use drugs for treatment”: 0 votes.

Thus, (2) conditionally recommend “use drugs for treatment” was adopted.

5. Summary of evidence

1) Outline of search results

A total of 40 studies that conducted RCTs were selected from the 150 English and Japanese papers extracted from the search. Next, studies examining drugs that were not currently available or drugs that were not currently used to treat gout were excluded, and ultimately, we investigated 17 papers on NSAIDs, glucocorticoids, and colchicine. We conducted a systematic review, and “gouty arthritis is improved,” “acute inflammatory reaction substances are reduced,” and “adverse events are increased” were selected as outcomes. The following was considered in evaluating the strength of the evidence.

- The definition of gouty arthritis (i.e., evidence of MSU crystals, use/non-use of classification criteria, number of affected joints, and time from onset to incorporation) differed depending on the studies.
- There were only two papers that compared active treatment with placebo.
- “Gouty arthritis is improved” was analyzed using the improvement of pain from the baseline based on the patient’s evaluation of pain as the index. However, the pain evaluation method and the timing of measurement differed depending on the paper.
- There were only two papers that compared active treatment with placebo.
- “Gouty arthritis is improved” was analyzed using the improvement of pain from the baseline based on the patient’s evaluation of pain as the index. However, the pain evaluation method and the timing of measurement differed among the studies. There was only one paper using NSAIDs that examined “reduction of acute inflammatory substances” and it was unable to evaluate that point. All adverse events were used as indices for “adverse events are increased.” Factors such as the definition of adverse events and the timing of evaluation differed depending on the studies, and it was vital to note the exclusion of cases where the drug used was contraindicated.
- The results of the meta-analysis required careful interpretation because of a small number of target papers and the differences in measurements of efficacy and adverse events.
- The examined papers were all from overseas, where the dose of NSAIDs was larger than the approved dose in Japan, and some of the NSAIDs were not approved in Japan.
2) Outcome 1: Gouty arthritis is improved; Outcome 2: Adverse events are increased

(1) NSAID

No placebo-controlled trials were identified, but a comparison of six types of interventional drugs versus control drugs (one of indomethacin, naproxen, or diclofenac) was available. There was no difference observed in the efficacy between the interventional drugs and the control drugs, and the strength of evidence of “no difference was found in efficacy on gouty arthritis of NSAIDs used as the study drug compared to indomethacin, naproxen, or diclofenac” was set as B (moderate). Meta-analysis of the eight papers that used indomethacin as the control drug found the overall risk of adverse events (risk ratio, RR) was 0.73 [95% confidence interval: 0.56–0.96], and the risk was significantly higher in the indomethacin group. The strength of evidence showing “the NSAIDs used as the study drugs have a lower incidence of adverse events than indomethacin, naproxen, and diclofenac” was set as C (weak).

(2) Glucocorticoids

There were no placebo-controlled trials, so the examination focused on the four RCT papers that compared oral prednisolone with indomethacin or naproxen. There was no difference observed in the pain improvement effect between oral prednisolone and NSAIDs (pain improvement standardized mean difference = -0.09 [-0.26–0.08]), so the strength of evidence of “there is no difference in the improvement effect on gouty arthritis between oral glucocorticoids and indomethacin and naproxen” was set as B (moderate). In the three papers that used indomethacin as the control, adverse events were significantly reduced in the prednisolone administration group (RR = 0.37 [0.25–0.54]) but considering the differences in case definition or measurement of efficacy/adverse events, the strength of evidence of “oral glucocorticoids have a lower incidence of adverse events than indomethacin and naproxen” was set as C (weak).

(3) Colchicine

Two placebo-controlled RCTs were extracted from the search. High-dose colchicine was more effective than a placebo treatment, but notably more adverse events were reported, including serious events. Therefore, the certainty in evidence about “high-dose colchicine notably increases the incidence of adverse events compared to placebo” was set as A (strong).

There was only one paper on a study conducted in the US involving low-dose colchicine treatment (oral colchicine 1.2 mg within 12 hours of onset of gouty arthritis and 0.6 mg one hour later). The effect of low-dose colchicine was significantly higher than a placebo (RR = 2.44 [1.25–4.76]), while no difference was reported with high-dose colchicine treatment (RR = 1.18 [0.73–1.93]). Therefore, the certainty in evidence of “low-dose colchicine has greater improvement effect on gouty arthritis than placebo, and there is no change in adverse events compared to placebo” was set as B (moderate).

Based on the above information, the overall level of evidence was determined to be B (moderate).

3) Outcome 3: Acute inflammatory reaction substances are reduced

There was only one paper on NSAIDs so this point could not be considered.

6. Degree of consensus

21 of the 26 people (81%) conditionally recommend “use drugs for treatment.”

7. Literature retrieval method

Search DB: Ichushi Web (Japan Medical Abstracts Society)
Search date: 7 March 2017
Search DB: PubMed
Search date: 7 March 2017

[Clinical Question 2]
Can urate lowering agents be recommended in patients with hyperuricemia and kidney injury over non-medication?

Recommendation - The use of urate lowering agents to retard the decline in kidney function is conditionally recommended in patients with hyperuricemia and kidney injury.

PICO format for CQ2 is shown in table 2.

1. Recommendation determinants

1) Strength of evidence: B (moderate)

Five papers were extracted and used to set the amount of
change in the estimated glomerular filtration rate (eGFR) as a beneficial outcome\(^{45-49}\). A meta-analysis, with 255 patients in the drug intervention group and 239 subjects in the control group, showed a statistically significant difference in the amount of change determined as 4.12 mL/min/1.73 m\(^2\) [95% confidence interval: 3.69–4.56] (p < 0.001), but there was a substantial heterogeneity (I\(^2\) = 87%). Three RCT papers that set the onset of renal event as a beneficial outcome were extracted from the search\(^{49-51}\). A meta-analysis, with 134 patients in the drug intervention group and 106 subjects in the control group, resulted in a risk ratio of 0.51 [95% confidence interval 0.35–0.76], indicating a statistically significant difference among groups (p < 0.001), but with a moderate heterogeneity (I\(^2\) = 45%). The renal event was defined as a 40% elevation in the serum creatinine or a decline of more than 10% in the eGFR. Furthermore, it was considered limitation that the adverse events were not consistent, that is, set either as a serum creatinine reaching 1.5 mg/dL or increasing to ≥ 0.3 mg/dL. Moreover, given the short observation period, the small patient cohort, and heterogeneities in the study results and drug selection, the strength of evidence was reported as B (moderate).

2) Balance of benefit and harm

Three RCTs were extracted that mentioned the adverse effects of the intervention\(^{47,51,52}\). Based on a meta-analysis with 1,064 patients in the drug intervention group and 226 subjects in the control group, the risk ratio was calculated as 1.10 [95% confidence interval: 0.48–2.56], indicating no statistically significant difference (p = 0.82). There was a moderate heterogeneity (I\(^2\) = 33%) and reporting bias. It was unlikely that the incidence of adverse events increased with the administration of urate lowering agents, which made it easier to determine the balance of benefit and harm when using urate lowering agents. However, when administering allopurinol to patients with moderate or greater decline in kidney function (C\(_{Cr}\) < 50 mL/min), the precautions for dose reduction should be taken into consideration. Furthermore, when using the novel urate lowering agents such as febuxostat and topiroxostat, it is essential to note that the package inserts stated that these drugs should be administered with caution in patients with severe renal function impairment, since there is little use experience and safety has not been established.

3) Patient values and preferences

Many supporting opinions from patients were given to the present statement of the CQ2. Further issues whether uricosuric drugs are similarly effective as uric acid production inhibitors examined during this time were provided. There were also questions about the target values

### Table 2: PICO format for CQ2

<table>
<thead>
<tr>
<th>Components of CQ</th>
<th>P (Patients, Problem, Population)</th>
<th></th>
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<td>Sex</td>
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<tr>
<td>Disease/clinical condition</td>
<td>Patients with hyperuricemia and renal impairment</td>
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<td>List of I (Interventions) / C (Comparisons, Controls, Comparators)</td>
<td>Urate lowering agents / control: non-medication</td>
<td></td>
</tr>
<tr>
<td>List of O (Outcomes)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>Benefit or Harm</td>
<td>Importance</td>
</tr>
<tr>
<td>O₁ Inhibits decline in kidney function</td>
<td>(Benefit or Harm)</td>
<td>7.86</td>
</tr>
<tr>
<td>O₂ Inhibits end-stage renal failure</td>
<td>(Benefit or Harm)</td>
<td>7.21</td>
</tr>
<tr>
<td>O₃ Increased adverse events</td>
<td>(Benefit or Harm)</td>
<td>6.34</td>
</tr>
</tbody>
</table>
of serum uric acid and concerns about the adverse drug reactions when used for a long period of time. Further clinical research with larger numbers of patients and longer observation periods is expected.

4) Cost and resources

Allopurinol also has generic versions and the drug price ranges from JPY 462–693/month (using 200–300 mg/day, as of November 2017). Thus, there was no financial issue associated with the use of this drug as medical treatment was covered by insurance (please note that the indication for allopurinol is “hypertension with hyperuricemia and gout”). However, considering an increased likelihood of selecting febuxostat and topiroxostat as the urate lowering agents for patients with hyperuricemia and renal impairment, the medical costs would be increased.

2. Process of deciding on the recommendation

When starting the systematic review, the screening process included not only interventional studies, but also observational studies. However, considering potential bias, it was decided to restrict the selection to RCTs. The beneficial outcome was set as “inhibition of decline in renal function,” but depending on the paper, serum creatinine, creatinine clearance, or eGFR were examined. Considering the gender differences in serum creatinine levels, the differences in measurement methods, and considering the latest trends, RCTs that conducted evaluation with eGFR were selected. Five papers were extracted, and the results were described as above. Only 3 papers examined the onset of end-stage renal failure (renal event) for assessment of another beneficial outcome, i.e., “inhibition of end-stage renal failure (renal event)”. All of the studies found a statistically significant difference. Given the small patient cohort, the short observation period, and extent of heterogeneity, the strength of evidence was determined to be B (moderate).

The harmful outcome was examined and, although there were only 3 papers, the number of examined cases exceeded 1200 people. There was no difference observed in the onset of adverse events with the control group. As a result, it was better to consider the pros and cons of administering urate lowering agents based on the beneficial aspect, rather than being concerned about the harmful aspects. This result contributed to increasing the recommendation level but based on the limitations described in the beneficial outcomes, the recommendation level was determined to be B (moderate).

3. Other

Bose et al. (2014) and Kanji et al. (2015) are existing meta-analysis reports. The report by Bose et al. extracted 4 RCT papers and the amount of change in eGFR was 3.1 mL/min/1.73 m² [95% confidence interval: 0.9–7.1], indicating no significant difference (p = 0.13). The report by Kanji et al. extracted 5 RCT papers and the amount of change in eGFR was 3.2 mL/min/1.73m² [95% confidence interval: 0.16–6.2], indicating a significant difference (p = 0.039). The problem with their meta-analysis is that since the older papers reported results based on serum creatinine values, the meta-analysis was performed by recalculations using the mean serum creatinine value to calculate eGFR. If those two papers were excluded, then the significant difference disappeared with a result of 2.6 mL/min/1.73m² [95% confidence interval: 1.5–6.6], (p = 0.21). Therefore, the present meta-analysis was conducted based on the results of the RCTs reported from 2014 onwards.

Another point that should be mentioned here is that this investigation did not consider exercise-induced acute kidney injury (EIAKI) associated with a reduction in serum uric acid levels induced by the administration of urate lowering agents. This is due to the lack of reports with a large number of EIAKI cases related to CQ2, which made the clarification of this issue difficult. EIAKI is common in children, so the collaboration with a specialist in pediatric kidney disease are necessary. However, this condition has been increasingly encountered recently in adults who exercise regularly. In this guideline, we would like to simply point out that onset of EIAKI is an important point involved in developing the target serum uric acid levels for treatment.

4. Voting results

Number of voters: 18; Valid votes: 18
(1) Recommend to “use drugs for treatment”: 0 votes; (2) Conditionally recommend to “use drugs for treatment”: 17 votes; (3) Conditionally recommend to “do not use drugs for treatment”: 1 vote; (4) Recommend to “do not use drugs for treatment”: 0 votes.

Thus, (2) Conditionally recommend to “use drugs for treatment” was decided.
5. Summary of evidence

1) Outline of search results

A comprehensive search of systematic reviews, RCTs, and observational studies from literature that included the three items of hyperuricemia or gout, kidney or renal disease, and urate lowering agents (including the drug names) was carried out using the following literature retrieval methods. The retrieved literature was screened and those papers comparing the use of urate lowering agents with non-medication treatment in patients with hyperuricemia or gout complicated by renal impairment for any of the outcomes of “Inhibits decline in kidney function”, “Inhibits end-stage renal failure (renal events),” or “Increased adverse events” were selected. In the secondary screenings that considered differences between observational studies and drug intervention studies, bias risk, and heterogeneity of the research methods, the extracted papers were limited to RCTs on patients with severe hyperuricemia and stage 3 or worse chronic kidney disease (CKD).

2) Outcome 1: Inhibits decline in kidney function

Five RCT papers were adopted\(^{45-49}\). The weight of the results of Goicoechea et al\(^{45}\), was the highest at 77 %, followed by Hosoya et al\(^{46}\), at 13 %. The difference in the amount of change in eGFR in the drug intervention group was 4.12 mL/min/1.73 m\(^2\) [95% confidence interval: 3.7–4.6], indicating a better result than the control group and a statistically significant difference (p < 0.001). The observation period ranged from 22 weeks to 3 years and the heavier weighted investigation by Goicoechea et al\(^{55}\), lasted 2 years, so it had a comparatively high strength of evidence.

3) Outcome 2: Inhibits end-stage renal failure (renal events)

Five RCT papers were used\(^{49-51}\). The result of meta-analysis indicated that the risk ratio of a renal event with drug intervention was 0.51 [95% confidence interval: 0.35–0.76], showing a statistically significant difference (p < 0.001). However, Sicar et al\(^{49}\), set end-stage renal failure (renal event) as a decline in eGFR of > 10%, which cannot be described as a sufficient outcome.

4) Outcome 3: Adverse events are increased

A meta-analysis of adverse events was conducted using literature\(^{47,51,52}\). As a result, the risk ratio of onset of an adverse event was 1.10 [95% confidence interval: 0.48–2.56], which did not indicate a significant difference (p = 0.82). In the report by Hosoya et al\(^{47}\), adverse events were observed in 68 % of subjects in both groups, with nasopharyngitis being the most common adverse event at 21 %, followed by gout attack and liver impairment. There was a statistically significant high incidence of elevated transaminase (ALT) over 1.5 times the upper limit. Schumacher et al\(^{52}\), compared the incidence of adverse events in the febuxostat group (80, 120, or 240 mg), the allopurinol group (300 or 100 mg for patients with reduced kidney function), and the placebo group. The incidence of diarrhea and dizziness was high in the 240 mg febuxostat group but the maximum dose available in Japan is 60 mg, so these results cannot be applied directly to Japan.

Based on the above information, drug intervention showed no increase in the occurrence of adverse events, and it was valid to determine the propriety of drug intervention based on the beneficial aspects of treatment. However, the liver function should be monitored.

6. Degree of consensus

17 of the 18 committee members (94%) conditionally recommend “use drugs for treatment”.

7. Literature retrieval method

Search DB: Ichushi Web (Japan Medical Abstracts Society)

Search date: 11 March 2017

Search DB: PubMed

Search date: 11 March 2017

[Clinical Question 3]

Can urate lowering agents be recommended for hypertensive patients with hyperuricemia over non-medication treatment?

Recommendation – The use of urate lowering agents to improve life prognosis and reduce the risk of cardiovascular disease cannot be actively recommended for hypertensive patients with hyperuricemia.

PICO format for CQ3 is shown in table 3.

1. Recommendation determinants

1) Strength of evidence: D (extremely weak)

The evidence supporting the use of urate lowering agents
to improve life prognosis and inhibit cardiovascular events in hypertensive patients with hyperuricemia is extremely weak. There were only a small cohort for adverse events, and it had a small number of adverse events. Moreover, there was also no information on serious adverse events such as Stevens–Johnson syndrome, so the safety-related evidence was extremely weak.

2) Balance between benefit and harm

It is possible that there may be a benefit of reducing the risk of cardiovascular disease but there is a high degree of uncertainty. Furthermore, while it is possible that there may be few adverse reactions, this claim also has a high degree of uncertainty. Therefore, the balance between benefit and harm is unclear.

3) Patient values and preferences

Individual patients had diverse values and preferences. There were opinions supporting the recommendation of this treatment considering the low risk of adverse events, the lack of evidence that denies the effect, and the low medical cost burden. Conversely, there were also opinions advising caution when using drugs with little evidence in cardiovascular disease prevention. Furthermore, there were also opinions supporting the inclusion of this treatment in guidelines as expert opinion if experts prefer using urate lowering agents for this purpose, even if there is little evidence to support these claims. There was also the opinion that if these drugs were administered to prevent gout, then this CQ is pointless.

4) Cost and resources

In terms of the cost of urate lowering agents, the generic version of allopurinol can be used if the treatment is covered by insurance (please note that the indication for allopurinol is “hypertension with hyperuricemia and gout”) and the drug price ranges from JPY 462–693/month (using 200–300 mg/day, as of November 2017). Therefore, this drug was considered inexpensive.

2. Process of deciding on the recommendation

The only drugs used in the literature in this investigation were uric acid production inhibitors (allopurinol); however, the term “urate lowering agents” was stated. The extremely weak evidence for the inhibition of cardiovascular events was greatly emphasized when creating the recommendation. Also, while a meta-analysis indicated no apparent increase in the adverse events, the number of events was small and the information relating to serious events was unclear. Thus, as a result of consultation, it was determined that there was insufficient rationale to recommend the use of urate lowering agents in terms of benefit compared to the high uncertainty of harm.

Table 3: PICO format for CQ3

<table>
<thead>
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<th>Components of CQ</th>
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<td>Urate lowering agents / control: non-medication</td>
</tr>
<tr>
<td>List of O (Outcomes)</td>
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<tr>
<td>Outcome:</td>
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<tr>
<td>Benefit or Harm: (Benefit or Harm)</td>
</tr>
<tr>
<td>Importance:</td>
</tr>
<tr>
<td>Adopt or not:</td>
</tr>
<tr>
<td>O₁: Inhibits cardiovascular events</td>
</tr>
<tr>
<td>7.32</td>
</tr>
<tr>
<td>Acceptable</td>
</tr>
<tr>
<td>O₂: Inhibits cardiovascular mortality</td>
</tr>
<tr>
<td>7.00</td>
</tr>
<tr>
<td>Acceptable</td>
</tr>
<tr>
<td>O₃: Increased adverse events</td>
</tr>
<tr>
<td>6.54</td>
</tr>
<tr>
<td>Acceptable</td>
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</table>
of the balance of benefit and harm. Based on the above information, it was decided to set the statement as “The use of urate lowering agents to improve life prognosis and reduce the risk of cardiovascular disease cannot be actively recommended for hypertensive patients with hyperuricemia.”

3. Other
1) Points to note when applying this treatment to clinical practice
The increased risk of cardiovascular events in hypertensive patients also exhibiting hyperuricemia has been demonstrated in a large number of observational studies. Thus, urate lowering agents have been expected to mitigate the risk. However, there have been no prospective interventional studies on the effect of urate lowering agents on improving life prognosis and reducing the risk of cardiovascular disease in hypertensive patients with hyperuricemia. Currently, there have been only two observational studies on the use of urate lowering agents in patients with hypertension, which demonstrated that the risk of cardiovascular disease was lowered in patients who received uric acid production inhibitor allopurinol than in patients who did not use this drug. There was no reported research on uricosuric drugs. Given the special characteristics of these patients, it is difficult to apply the findings from these two studies on allopurinol to all hypertensive patients with hyperuricemia across the board. The results of analysis limited to correction including use of both renin–angiotensin inhibitors and low-dose allopurinol (<300 mg/day) treatment found no significant difference and, given the prescription situation in Japan, it would be difficult to apply this treatment to clinical practice. The newly developed non-purine–analogue uric acid production inhibitors are widely used in clinical practice in Japan, but there are no findings yet showing that these urate lowering agents are related to improved life prognosis or having an inhibitory effect on cardiovascular events. Based on the above information, it must be said that the evidence related to the efficacy of urate lowering agents in improving life prognosis and exerting an inhibitory effect on cardiovascular events in hypertensive patients with hyperuricemia, is extremely weak.

In contrast, while it has been demonstrated in a meta-analysis, albeit a small-scale analysis, that there was no apparent increase in adverse events caused by urate lowering agents in these patients, the small number of events is problematic in terms of certainty in evidence. Although the incidence is low, allopurinol has been associated with the onset of serious adverse events such as Stevens–Johnson syndrome. Thus, this drug cannot be described as extremely safe.

2) Practical approach considering the clinical background and priorities of individual patients
Many hypertensive patients with hyperuricemia also present with many risk factors for cardiovascular disease, including diabetes, dyslipidemia, etc. These patients have an even greater risk for developing cardiovascular disease. Thus, it is important to carefully manage each risk factor. When these patients wish to proactively take urate lowering agents to further inhibit the onset of cardiovascular events, it is advisable to consider administration of these drugs after fully explaining to the patient that the efficacy has not been sufficiently clarified, and the rare but serious adverse drug reactions exists. Allopurinol is inexpensive, but it is vital to carefully consider the use of urate lowering agents in patients taking multiple medications (polypharmacy) and in cases where doubts about the efficacy or concerns about adverse events outweighs the expected therapeutic effect. Thus, refraining from administration is also a valid option.

4. Voting results
Number of voters: 18; Valid votes: 18
(1) Recommend “use drugs for treatment”: 0 votes; (2) Conditionally recommend “use drugs for treatment”: 2 votes; (3) Conditionally recommend “do not use drugs for treatment”: 14 votes; (4) Recommend “do not use drugs for treatment”: 2 votes.
Thus, (3) Conditionally recommend “do not use drugs for treatment” was adopted.

5. Summary of evidence
1) Outline of search results
A comprehensive search of systematic reviews, RCTs, and observational studies from literature that included the three items of hyperuricemia or gout, heart failure or heart disease, and urate lowering agents (including the drug names) was carried out using the following literature retrieval methods. The retrieved literature was screened, and two observational studies and one meta-analysis were selected.
2) Outcome 1: Inhibits cardiovascular events

No prospective interventional studies have been implemented for hypertensive patients with hyperuricemia. The two observational studies demonstrated that the risk of cardiovascular disease was reduced in patients receiving allopurinol. The result of the meta-analysis implemented independently by the systematic review team, based on the results of both studies, found that use of allopurinol was associated with a significant reduction in the risk of cardiovascular disease compared with non-use of allopurinol \[RR = 0.57, 95\% \text{ confidence interval} : 0.41 - 0.73\]. The study by Terawaki et al.\(^{56}\) was a retrospective observational study following patients from Japan who presented with hypertensive nephrosclerosis (mean age = 71 ± 11.8 years, men = 61.2 \%) with moderate or higher kidney impairment (mean eGFR = 25.8 ± 11.7 \text{mL/min/1.73 m}^2) and used allopurinol (n = 67) or did not use allopurinol (n = 111) for a mean period of 19.8 ± 10.9 months. The patients who used allopurinol had a lower tendency of the primary endpoint risk, which comprised the overall mortality and cardiovascular events (i.e., angina pectoris, acute myocardial infarction, congestive heart failure, and hemorrhagic and ischemic stroke), than patients who did not use allopurinol (10.4 \% vs. 18.9 \%, p = 0.13, log-rank test). A Cox proportional hazards model adding confounding factors such as gender, history of cardiovascular disease, and use of diuretics demonstrated that use of allopurinol was associated with a significant reduction in the primary endpoint (RR = 0.34, p = 0.04, standard deviation = 0.53). However, when the results are corrected with a propensity score, including renin–angiotensin (RA) inhibitors, the significant difference disappeared. The other observational study was a large-scale cohort study\(^{57}\) implemented in the UK, which retrospectively observed elderly hypertensive patients aged ≥ 65 years who used allopurinol (n = 2032) or did not use allopurinol (n = 2032) for a 10–year period and had been matched with a propensity score. The use of allopurinol was associated with a significantly reduced risk of stroke overall, compared to patients who did not use allopurinol \[RR = 0.50, 95\% \text{ confidence interval} : 0.32 - 0.80\], and the same was found with cardiac events (myocardial infarction, acute coronal syndrome) \[RR = 0.63, 95\% \text{ confidence interval} : 0.44 - 0.89\]. However, analysis by dose indicated that the risk of any event was not significantly reduced in the low-dose allopurinol group (<300 mg/day) compared to the non-use group.

In summary, in both observational studies, there may have been control group patients who did not have hyperuricemia and, as no significant difference was found with a correction including RA inhibitors and low-dose allopurinol, it would be difficult to apply this treatment to clinical practice given the prescription situation in Japan. Based on the above information, it was determined that the evidence relating to the benefit of urate lowering agents is extremely weak.

3) Outcome 2: Inhibits cardiovascular mortality

There were no papers from which it was possible to evaluate the outcome based on cardiovascular mortality alone. In the aforementioned study by Terawaki et al.\(^{56}\), overall mortality was included in the primary outcome but there was no separate discussion on the cardiovascular mortality, and hence it could not be evaluated.

4) Outcome 3: Increased adverse events

A meta-analysis was conducted by the Cochrane Library\(^{58}\) using three studies which allowed to evaluate adverse events of prospective interventional studies comparing the urate lowering effect of allopurinol and placebo in hypertensive patients with hyperuricemia or normal hypertensive patients. The results showed that adverse events that required the discontinuation of treatment were observed in 5 of the 131 patients using allopurinol, while adverse events were observed in 2 of the 110 patients in the placebo group. Thus, it was demonstrated that there was no apparent increase in adverse events associated with use of allopurinol \[RR = 1.86, 95\% \text{ confidence interval} : 0.43 - 8.1\]. However, the evidence was determined to be extremely weak due to significant problems with certainty in evidence, including the small number of patients and small number of adverse events.

6. Degree of consensus

14 of the 18 people (77 \%) conditionally recommend “do not use drugs for treatment.”

7. Literature retrieval method

Search DB: Ichushi Web (Japan Medical Abstracts Society)
Search date: 4 March 2017
Search DB: PubMed
Search date: 4 March 2017
Can one recommend maintaining the serum urate concentration at ≤ 6.0 mg/dL with pharmacotherapy for patients with tophi?

Recommendation - It can be recommended to maintain the serum urate concentration at ≤ 6.0 mg/dL with pharmacotherapy for patients with tophi.

PICO format for CQ4 is shown in table 4.

1. Recommendation determinants
   1) Strength of evidence: C (weak)
      Since there is little investigation with a high strength of evidence, the evidence for the recommendation is weak. Treatment and improvement of tophi was investigated as a secondary outcome in the RCTs and in post hoc analysis during development of the three drugs, and in a number of cohort studies.

   2) Balance between benefit and harm
      Maintaining the serum urate concentration at ≤ 6.0 mg/dL with pharmacological treatment for patients with tophi can be expected to reduce the size or completely eliminate the tophi. There was no acquired evidence to indicate that establishing a target management level for serum urate concentration increased gout attacks in the treatment process as a harmful outcome.

   3) Patient values and preferences
      When an opinion was requested from patient’s representatives, concerns that controlling the serum urate concentration at ≤ 6.0 mg/dL may increase gout attacks or require increased drug doses were stated. However, setting the serum urate concentration target to ≤ 6.0 mg/dL in patients suffering from gout with tophi was already written in previous guidelines (2nd edition). In treatments where a target is not set or the target is set at around 7.0, urate concentration would probably often exceed 7.0, which would prolong the elimination of the tophi and the normalization of the urate pool. During this period, gout attacks were likely to continue.

      A rapid reduction in uric acid levels when starting therapy with uric acid lowering agents increased the risk of gout attacks, and the drug information provided by febuxostat also stated that target levels should be achieved by gradually increasing the dose, while checking the serum urate concentration. Therefore, if the same methods of administration were applied to other uric acid lowering agents, these concerns should be allayed. Conversely, in the febuxostat clinical study, the number of attacks reported one year after treatment was lower in the group with lower uric acid levels. Therefore, it is essential to be aware that an insufficient reduction of the uric acid levels can result in an increased risk of gout attacks over the long term.

Table 4: PICO format for CQ4

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<td>Geographic constraints Not specified Other Not specified</td>
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</table>

List of I (Interventions) / C (Comparisons, Controls, Comparators)
Maintain the serum urate concentration at ≤ 6.0 mg/dL with pharmacotherapy / control: none

List of O (Outcomes)

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<thead>
<tr>
<th>Outcomes</th>
<th>Benefit or Harm</th>
<th>Importance</th>
<th>Adopt or not</th>
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<tr>
<td>O₁</td>
<td>Improves tophi (Benefit or Harm)</td>
<td>7.62</td>
<td>Acceptable</td>
</tr>
<tr>
<td>O₂</td>
<td>Increases gout attacks (Benefit or Harm)</td>
<td>6.31</td>
<td>Acceptable</td>
</tr>
<tr>
<td>O₃</td>
<td>Inhibits decline in kidney function (Benefit or Harm)</td>
<td>6.24</td>
<td>Acceptable</td>
</tr>
</tbody>
</table>
4) Cost and resources
The determination of which uric acid lowering agents is to be prescribed to maintain the serum urate concentration at ≤ 6.0 mg/dL can be decided during the medical examination, and based on which treatment is covered by medical insurance.

2. Process of deciding on the recommendation
The initial CQ4 was “Can it be recommended to maintain the serum urate concentration at ≤ 6.0 mg/dL with pharmacotherapy for patients with tophi compared with not setting a target level for serum urate concentration?” However, through the process of the systematic review, there were no RCTs that matched this CQ PICO. In the panel meeting held in December 2017, consensus could not be reached on the recommendation decision in regard to this CQ. Hence, a new CQ draft was presented excluding C of the PICO, which would not affect the systematic review that had already been implemented. Accordingly, the current CQ of “Can it be recommended to maintain the serum urate concentration at ≤ 6.0 mg/dL with pharmacological treatment for patients with tophi?” was adopted. In the voting for this CQ draft, there was consensus to strongly recommend the proposed CQ.

3. Other
There tended to be marked improvement of tophi when the uric acid levels were kept at ≤ 6.0 mg/dL in the post hoc analysis of febuxostat. In the RCT for pegloticase, the tophi disappeared within 12 months in responders with uric acid levels maintained around 2.0–4.0 mg/dL.

The longer the mean value of uric acid was kept at a lower level using uric acid lowering agents, the greater the rate of reduction in the size of the tophi, since a cohort study on febuxostat demonstrated that the tophi disappeared over a longer period of time.

In terms of the target uric acid level, all of the RCTs set the primary outcome as ≤ 6.0 or < 6.0 mg/dL and given that tophi improved with uric acid levels of ≤ 6.0 mg/dL and did not improve with uric acid levels of ≥ 6.0 mg/dL in a cohort study using joint echography, ≤ 6.0 mg/dL was incorporated into the target for controlling serum uric acid level for CQ4 despite the weak evidence. Although the size-reduction and elimination of tophi are promoted when the uric acid levels are maintained at a lower level, this required higher doses of medication, which may suggest the increased occurrence of adverse events. The presence of tophi also suggested the excess urate pools and the higher possibility of gout attacks. The greater the reduction in uric acid after treatment, the greater the risk of gout flares. Thus, an extremely low target of uric acid level was also considered unsuitable. Since in clinical setting, there are often cases where the uric acid lowering agent is administered without monitoring serum urate concentration, the target level for treating tophi was clarified in CQ4.

The maintenance of the uric acid level at ≤ 6.0 mg/dL is thought to reduce the size of tophi with certainty. Given that the previous guideline (Version 2) has stated “cases with recurrent gouty arthritis and cases with tophi are indicated for pharmacotherapy, and it is preferable to maintain the serum urate concentration at ≤ 6.0 mg/dL,” there was consensus that the strength of recommendation was “implement treatment.”

4. Voting results
The draft recommendation “Maintaining the serum urate concentration at ≤ 6.0 mg/dL with pharmacological treatment for patients with tophi can be recommended over not setting a target level for serum urate concentration.” was presented for the initial CQ4 “Can it be recommended to maintain the serum urate concentration at ≤ 6.0 mg/dL with pharmacotherapy for patients with tophi?” In the first round of voting on the recommendation level the results were: (1) Recommend “treatment”: 5 votes; (2) Conditionally recommend “treatment”: 11 votes; (3) Conditionally recommend “do not use treatment”: 2 votes; (4) Recommend “do not use treatment”: 0 votes; which did not achieve a 70 % concordance rate. After another vote on (1) and (2), the results were (1) 6 votes and (2) 12 votes, which again was less than 70 %, and consensus was not reached.

Next, two revised proposals for the CQ draft were presented, and “Can it be recommended to maintain the serum urate concentration at ≤ 6.0 mg/dL with pharmacotherapy for patients with tophi?” was adopted and voting was conducted.

Number of voters: 18; valid votes: 18
(1) Recommend “treatment”: 14 votes; (2) Conditionally recommend “treatment”: 4 votes; (3) Conditionally recommend “do not use treatment”: 0 votes; (4) Recommend “do not use treatment”: 0 votes
Thus, (1) Recommend “treatment” was adopted.

5. Summary of evidence

1) Outline of search results

The initial statement was “Maintaining the serum urate concentration at ≤ 6.0 mg/dL with pharmacotherapy for patients with tophi can be recommended over not setting a target level for the serum urate concentration” and a systematic review was attempted with “Does it improve tophi?”, “Inhibits decline in kidney function by reducing uric acid level” as the benefit, and “Increases gout attacks” as the harm.

However, there were no reports that matched the PICO of the initial CQ. Therefore, we searched for reports on tophi and changes in uric acid levels following uric acid reduction therapy.

There was a report on the intervention for tophi in the 2014 Cochrane Database Scientific Review but the listed RCT was only report that had already been adopted in this review. Therefore, a meta-analysis was not carried out.

There were no RCTs that matched this CQ, but in the RCTs during the development of febuxostat, pegloticase, and lesinurad, the primary outcome was to reduce uric acid levels to ≤ 6.0 or < 6.0 mg/dL, and the improvement of tophi was investigated as the secondary outcome and in the post hoc analysis. The number of patients were 762, 225, and 607, respectively, but only some of those patients reported the presence of tophi. Furthermore, although the number of patients with tophi was stated at the baseline, this information was not clearly stated in the final evaluation. Given that the administration method and therapeutic effect of oral medication and pegloticase significantly differ, the differences in the observation period among studies, the unknown number of patients with tophi, and the unknown changes in uric acid levels, it was impossible to conduct a meta-analysis.

The febuxostat RCT evaluated the reduction rate in tophi and the number of tophi between the febuxostat group and the allopurinol group. Although no difference was found among two groups, in the post hoc analysis, the group with a mean serum urate concentration of ≤ 6.0 mg/dL had a larger reduction rate in tophi than the group that did not achieve this reduction in the serum urate concentration (p=0.06). In a quasi RCT that analyzed data from the two febuxostat RCTs, the factors that influenced the size of tophi were analyzed with linear regression for 1832 patients but there was no description of the number of patients with tophi and the changes in uric acid levels and tophi.

In the pegloticase RCT, 40 % (21/52) of the patients in every 2 week pegloticase administration group and 21 % (11/52) of patients in every 4 week pegloticase administration group had a complete response of tophi (defined as disappearance of at least one tophus registered at baseline), which was a significant improvement compared to the placebo group (7 %, 2/27) (p = 0.02 and p = 0.20). There were two quasi RCT reports including an open label extension after the pegloticase RCT. Responders were defined as the group that maintained uric acid levels at ≤ 6.0 mg/dL at ≥ 80 % of the observation points during the RCT period. There were more reported patients with complete response of tophi in the responder group, but was not a significant difference. The uric acid levels were reduced to around 2 mg/dL during the RCT period in responders in every 2 week pegloticase administration group and the tophi was thought to have improved in a short period of time.

Contrastingly, in the lesinurad RCT, either lesinurad 200 mg, 400 mg or placebo were added to allopurinol, and a significant reduction in uric acid was seen in the lesinurad addition group but no significant difference in tophi improvement was detected between both groups. This was due to the reduction in uric acid with lesinurad being smaller than the reduction achieved with pegloticase. Furthermore, it was highly likely that a one-year observation period was too short to see an improvement in tophi.

In a cohort study, uric acid lowering therapy was implemented for 63 patients with tophi and the results demonstrated that the lower the mean uric acid level after treatment, the higher the reduction rate of the tophi maximum diameter (r = 0.62, r2 = 0.48, p < 0.05). There was no target uric acid level set, but if the mean level was < 7.0 mg/dL, there was at least a difference in the uric acid level and all patients had a reduction in tophi. In a 5-year treatment with febuxostat, 26 of the 116 patients with gout had tophi and the tophi disappeared in 18 of these patients (69 %) but the differences in uric acid levels between the group where tophi disappeared and the group where tophi did not disappear were not examined. The intraarticular micro nodules and double contour findings in 16 patients with gout were observed with joint echography and 12 out of 12 patients who reached a serum urate concentration of < 6.0 mg/dL with 6 months of uric acid reduction therapy.
acid reducing therapy showed disappearance or reduction of the tophi on echo. Contrastingly, the 4 patients who did not achieve this reduction had no improvement in tophi\(^{27}\). However, this study did not examine clinical tophi.

2) Outcome 1: Improves tophi
   Improvement of tophi was demonstrated in RCT, quasi RCT, and cohort studies that set the primary outcome as maintaining uric acid levels to ≤ 6.0 mg/dL for tophi, but it was difficult to calculate the effect estimates and confidence interval\(^{10,11}\).

3) Outcome 2: Increases gout attacks; Outcome 3: Inhibits decline in kidney function
   There was no evidence corresponding to increased gout attacks or inhibition of a decline in kidney function.

6. Degree of consensus
   14 of the 18 people (77 %) recommend “treatment”.

7. Literature retrieval method
   Search DB: Ichushi Web (Japan Medical Abstracts Society)
   Search date: 9 March 2017
   Search DB: PubMed
   Search date: 9 March 2017

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**[Clinical Question 5]**

Can urate lowering agents be recommended for patients with heart failure and hyperuricemia over non-medication treatment?

**Recommendation** – The use of urate lowering agents to improve life prognosis and reduce the risk of cardiovascular disease cannot be actively recommended for patients with heart failure and hyperuricemia.

PICO format for CQ5 is shown in table 5.

1. **Recommendation determinants**
   1) Strength of evidence: C (weak)
   Only two of the adopted RCTs looked into secondary outcomes. Both had short observation periods of 6 months and a small sample size. There was little bias risk but there were differences in the study target, drug intervention, and outcome measurements. Based on the above information, the evidence was determined to be weak.

   2) Balance between benefit and harm
   The benefit from the two RCTs was small, and given that the harm in one RCT was also small, it was not possible to state that there is a certain balance between benefit and harm.

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**Table 5: PICO format for CQ5**

<table>
<thead>
<tr>
<th>Components of CQ</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
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</tr>
<tr>
<td><em>(Not specified) / Male / Female</em></td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td><em>(Not specified) / ________________________________</em></td>
</tr>
<tr>
<td>Disease/clinical condition</td>
</tr>
<tr>
<td>Patients with heart failure and hyperuricemia</td>
</tr>
<tr>
<td>Geographic constraints</td>
</tr>
<tr>
<td>Not specified</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Not specified</td>
</tr>
<tr>
<td>List of I (Interventions) / C (Comparisons, Controls, Comparators)</td>
</tr>
<tr>
<td>Urate lowering agents / control : non-medication</td>
</tr>
<tr>
<td>List of O (Outcomes)</td>
</tr>
<tr>
<td>Outcomes</td>
</tr>
<tr>
<td>Benefit or Harm</td>
</tr>
<tr>
<td>Importance</td>
</tr>
<tr>
<td>Adopt or not</td>
</tr>
<tr>
<td><strong>O₁</strong> Reduced cardiovascular mortality (Benefit or Harm) 7.31 Acceptable</td>
</tr>
<tr>
<td><strong>O₂</strong> Reduced overall mortality (Benefit or Harm) 6.59 Acceptable</td>
</tr>
<tr>
<td><strong>O₃</strong> Increased adverse events (Benefit or Harm) 6.41 Acceptable</td>
</tr>
</tbody>
</table>
3) Patient values and preferences

There was the opinion that, generally, treatment can be received with the main treatment being for hyperuricemia and gout rather than for improving heart failure. In contrast, there was also the opinion that there are significant issues in clinical practice with respect to the outcomes with weak evidence, and that high-quality research should be conducted in Japanese patients, even if the sample size is small. There was also the opinion that there was no point in raising this issue as a CQ because using xanthine oxidoreductase (XOR) inhibitors was the obvious treatment for hyperuricemia, even in patients with heart failure. Finally, there was the opinion that the use of urate lowering agents was acceptable, provided that there were few adverse events.

4) Cost and resources

Allopurinol also has generic versions and the drug price ranges from JPY 462–693 /month (using 200–300 mg/day, as of November 2017), hence there were no financial issues associated with the use of this drug as medical treatment was covered by insurance (please note that the indication for allopurinol is “hypertension with hyperuricemia or gout”).

2. Process of deciding on the recommendation

Xanthine oxidoreductase (XOR) inhibitors were the only drugs whose use was reported in the reviewed literature. There was no improvement in the life prognosis including overall mortality and cardiovascular mortality seen in patients with heart failure and hyperuricemia treated with urate lowering agents. Thus, it was determined that the administration of urate lowering agents cannot be recommended. In contrast, while there was no difference in harm compared to placebo and reports indicating that the complication of hyperuricemia is a poor prognostic factor in patients with heart failure, there were limited high-quality intervention studies. Hence, it was determined that administration of urate lowering agents cannot be actively recommended.

3. Other

It is widely known that the use of diuretics and beta-blockers to improve the prognosis of heart failure tend to cause hyperuricemia. Inhibiting a decline in the kidney function and gout attacks are important clinical challenges with hyperuricemia irrespective of whether or not a patient presents with heart failure. Moreover, a decline in kidney function, particularly in patients with heart failure, can affect the body fluid balance and it is known to be intimately related to the deterioration of heart failure (cardio-renal syndrome).

Based on the above information, we proposed that an investigation was implemented on the appropriateness of urate lowering treatments in these cases by evaluating serum urate concentration, body fluid balance (or effective circulating blood volume), and kidney function on the premise that the main aim is to inhibit the declining kidney function and gout attacks in patients with heart failure.

4. Results of voting

Number of voters: 18; valid votes: 18
(1) Recommend “treatment”: 0 votes; (2) Conditionally recommend “treatment”: 1 vote; (3) Conditionally recommend “do not use treatment”: 15 votes; (4) Recommend “do not use treatment”: 2 votes
Thus, (3) Conditionally recommend “do not use treatment” was adopted.

5. Summary of evidence

1) Outline of search results

The search involved a comprehensive assessment of systematic reviews, RCTs, and observational studies from literature that included the three items of hyperuricemia or gout, heart failure or heart disease, and urate lowering agents (including the drug names), using the following literature retrieval methods. The retrieved literature was screened, and papers that presented evidence of examining any of the outcomes of “Reduced cardiovascular mortality”, “Reduced overall mortality”, and “Increased adverse events” comparing the use of urate lowering agents with non-medication treatment for patients with hyperuricemia or gout complicated by heart failure, were selected.

Three RCTs and four observational studies were selected from PubMed. The observational studies were mainly retrospective investigations, and there were many issues with obtaining answers to this CQ, including the target patients, adherence evaluation, and setting of outcomes. Thus, there was little information that would enable a conclusion to be reached.

2) Outcome 1: Reduced cardiovascular mortality

Two RCTs were adopted, but neither found a
significant difference in cardiovascular mortality between the drug intervention group and the placebo group.

Both papers had short observation periods of 6 months and small sample sizes (both the drug intervention group and the placebo group had around 200 to 400 patients). Furthermore, there were differences between the two papers in terms of the definition of heart failure (heart failure patients with moderate or worse severity – NYHA III–IV, patients with systolic dysfunction, etc.) and the administered drug (allopurinol or oxipurinol at a dose of 300–600 mg/day).

Both papers were considered to have a low level of bias, and examined secondary outcomes. Additionally, integrating and evaluating only these two papers was difficult and the evaluation of inconsistency was also not possible. Therefore, the strength of evidence was determined to be weak.

3) Outcome 2: Reduced overall mortality

Two RCTs were adopted, but neither found a significant difference in overall mortality between the drug intervention group and the placebo group.

For the reason stated in Outcome 1, integrating and evaluating these two papers was difficult and the evaluation of inconsistency was also not possible. Thus, the strength of evidence was determined to be weak.

4) Outcome 3: Increased adverse events

Aggregation of the number of patients with adverse events was only possible with the RCT by Givertz et al. and there was no significant difference. The RCT by Xiao et al. examined changes in laboratory values related to intravascular function and cardiac contractility, but there was no description of the randomization method for patients with heart failure not associated with hyperuricemia. Therefore, it was thought there was a high risk of bias and the paper was not adopted.

Based on the above information, the RCT indicates that there is no increase in adverse events through drug intervention. However, it is difficult to evaluate the outcome with only one paper, so it was determined that the strength of evidence is weak.

6. Degree of consensus

15 of the 18 people (83%) conditionally recommend “do not use drugs for treatment.”

7. Literature retrieval method

Search DB: Ichushi Web (Japan Medical Abstracts Society)
Search date: 11 March 2017
Search DB: PubMed
Search date: 11 March 2017

[Clinical Question 6]

Can long-term colchicine use be recommended over short-term use to prevent gout attacks in gout patients after initiating urate lowering therapy?

Recommendation – Long-term colchicine use to prevent gout attacks can be conditionally recommended for gout patients when starting urate lowering therapy.

PICO format for CQ6 is shown in table 6.

1. Recommendation determinants

1) Strength of evidence: C (weak)

Only two RCTs have been adopted in this investigation. One was a small sample size trial with a high risk of bias, and the other examined secondary outcomes, including the use of NSAIDs. Therefore, the evidence quality was evaluated as weak.

2) Balance between benefit and harm

From the two RCTs, it was considered that long-term colchicine use is effective, although it increased the incidence of liver damage. However, it would be too hasty to determine whether long-term colchicine use is beneficial or harmful, since the number of RCTs used in this CQ was too small.

3) Patient values and preferences

Patient values and preferences were diverse. While there were opinions that regarded the effect of colchicine to prevent gout attacks as important and agreed with the long-term colchicine use, there were also other opinions that were concerned about the severity of liver damage and not preferred the long-term use of colchicine.

4) Cost and resources

The cost of colchicine (JPY 7.8 per tablet) was JPY 1404 per 6 months (with a 30% tax = JPY 421, using 0.5 mg/day, as of November 2017), and hence no significant financial
burden was considered even if taken for 6 months.

2. Process of recommendation decision

Febuxostat is generally sold in high dosage forms, such as 40 or 80mg tablets in most countries. Therefore, if the urate lowering therapy was started with febuxostat, there was an increased risk of gout attacks owing to the rapid decline in the serum urate concentration. Thus, colchicine co-administration may be needed to prevent gout attacks. In the post hoc analysis that examined the three RCTs, the starting dose of febuxostat was high, for example 40, 80, and 120 mg\(^2\), thus necessitating the long-term administration of colchicine. However, given that the incidence of liver damage was higher with long-term rather than with short-term colchicine co-administration, and the different clinical circumstances in Japan where low dose febuxostat is usually used after the initiation of urate lowering therapy, long-term colchicine use was conditionally recommended.

3. Other

Gout attacks often developed when the serum urate concentration rapidly decreased after initiating the urate lowering therapy. Thus, prophylactic administration of NSAIDs or colchicine was recommended, when initiating urate lowering therapy\(^7,8\). Colchicine inhibits the activation of IL-1β which mediates MSU crystal-NLRP3-inflammasome by phagocytosis of macrophages, which is considered to be the early stage of a gout attack\(^5\). Thus, colchicine is a suitable drug for preventing gout attacks. The starting dose of urate lowering agents overseas had to be high because their dosage choice in limited, therefore colchicine co-administration was useful. On the contrary, in Japan, urate lowering agents were started with a minimal dose (10 mg tablet is available) and increased gradually, so colchicine co-administration may not be necessary. Furthermore, even if colchicine co-administration was needed provisionally, it could be stopped once the serum urate concentration reached the therapeutic target level. Therefore, long-term administration, for example 6 months, may be unnecessary. However, according to an investigation by Borstad et al., a 6-month colchicine administration was effective even in severe cases with high urate pool volumes, such as in patients with chronic gout\(^8\), for whom allopurinol was started at the low dose of 100 mg and gradually increased. Therefore, when colchicine is co-administered with urate lowering agents, it is preferable to decide the period of administration by taking into account the morbidity period of gout in each patient.

4. Voting results

Number of voters: 26; valid votes: 26

Table 6: PICO format for CQ6

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<tr>
<th>Components of CQ</th>
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<th></th>
</tr>
</thead>
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<tr>
<td>Sex</td>
<td>(Not specified)</td>
<td>Male / Female</td>
<td>Age</td>
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<td>Disease/clinical conditions</td>
<td>Patients with frequent gout attacks</td>
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<td>Geographic constraints</td>
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<td>Other</td>
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<td></td>
<td>List of I (Interventions) / C (Comparisons, Controls, Comparators)</td>
<td>Long-term colchicine administration / control: short-term colchicine administration</td>
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<tr>
<td>List of O (Outcomes)</td>
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<tr>
<td>Benefits or Harm</td>
<td>Importance</td>
<td>Adopt or not</td>
<td></td>
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<tr>
<td>O₁</td>
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<td>(Benefit or Harm)</td>
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<td>Increased adverse events</td>
<td>(Benefit or Harm)</td>
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<tr>
<td>O₃</td>
<td>Improved QOL</td>
<td>(Benefit or Harm)</td>
<td>6.45</td>
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(1) Recommend “colchicine co-administration”: 0 votes; (2) “Conditionally recommend colchicine co-administration”: 19 votes; (3) Conditionally recommend “do not treat with colchicine co-administration”: 6 votes; (4) Recommend “do not treat with colchicine co-administration”: 1 vote

Thus, (2) “Conditionally recommend colchicine co-administration” was adopted.

5. Summary of evidence

1) Outline of search results

A comprehensive search of treatment guidelines, systematic reviews, and RCTs from literature that included the items hyperuricemia or gout treatment, therapy or prevention, and colchicine, was carried out using the following literature retrieval methods. The retrieved literatures were screened and the articles that presented evidence examining any of the outcomes of “Prevents gout attacks”, “Increased adverse events” and “Improved QOL” were selected. Although two RCTs were selected from PubMed, one RCT compared the short-term administration with the long-term administration in the same subjects, and was thus excluded. Additionally, the Cochrane Library was searched and another RCT was selected.

2) Outcome 1: Prevents gout attacks

In a study that compared colchicine 1 mg/day administered for 3 to 6 months as the short-term administration group and the same dose administered for 7 to 9 months as the long-term administration group, gout attacks occurred in 34 of the 63 patients (54 %), and in 17 of 62 patients (27.4 %) in the short- and long-term administration group, respectively, reducing the incidence of gout attacks by 50%. Thus, prophylactic administration of colchicine for 7 to 9 months was considered preferable \[RR = 1.58, 95\% confidence interval : 1.16-2.15\]\(^{75}\).

A post hoc analysis of the 3 Phase-III RCTs, FACT [Febuxostat Versus Allopurinol Controlled Trial], APEX [Allopurinol- and Placebo-Controlled, Efficacy Study of Febuxostat], and CONFIRMS [a phase III, randomized, multicenter, double-blind, allopurinol-controlled study assessing the efficacy and safety of oral febuxostat in subjects with gout]\(^{76}\), was carried out after discussion among the persons in charge of the scope and the SR team.

The FACT and APEX studies, where prophylactic colchicine was administered for 8 weeks (colchicine 0.6 mg once a day or naproxc 250 mg twice a day), were set as short-term treatment groups, while the CONFIRMS study, in which the same drugs were administered for 6 months, was set as a long-term treatment group. The incidence of gout attacks immediately after withdrawing the prophylactic treatment in the FACT and APEX studies (8–12 weeks), and the CONFIRMS study (24–28 weeks) was compared using the number of patients experiencing gout attacks in the respective trials\(^{60,81,82}\). In the short-term treatment group, 611 of the 1823 patients (33.5%) had gout attacks compared to only 90 of the 2268 patients (4%) in the long-term treatment group. Therefore, the prophylactic administration of colchicine for 6 months seemed preferable \[RR = 1.45, 95\% confidence interval : 1.40-1.52\]\(^{76}\). However, since both colchicine and naproxen were used concomitantly for the prophylaxis of gout attacks in these investigations, long-term colchicine co-administration cannot be concluded as preferable.

3) Outcome 2: Increased incidence of adverse events

Karimzadeh et al. reported an elevation in the transaminase (ALT, AST) levels by ≤ 2 times the reference value in 8 out of 63 patients (4.8 %) receiving colchicine for 3 to 6 months (short-term treatment group), and in 5 out of 62 patients (8.1 %) receiving colchicine for 7 to 9 months (long-term treatment group), indicating a 1.69 times higher incidence of liver dysfunction in the long-term treatment group. However, elevation of liver function was observed only temporarily and the values normalized even in cases of continuous use of colchicine\(^{75}\). Overall adverse events induced by NSAIDS and colchicine were noted in 547 of 993 subjects (55.1 %) in the short-term colchicine co-administration groups (FACT, APEX) and in 996 of 1807 subjects (55.1 %) in the long-term colchicine co-administration group (CONFIRMS), indicating no differences in the rate of adverse events between the trials. However, 140 of 1807 subjects (7.7 %) in the long-term colchicine co-administration group reported liver damage compared to 25 of 993 subjects (2.5 %) in the short-term colchicine co-administration groups, indicating an incidence 3.08 times higher in the long-term colchicine co-administration group. A meta-analysis including these two RCTs disclosed that the incidence of liver damage was significantly higher in the long-term colchicine co-administration group than in the short-term colchicine co-administration group \[RR = 2.93, 95\% confidence interval : 1.96-4.68\].
4) Outcome 3: Improved QOL

There were no RCTs that mentioned QOL, concerning colchicine use. We considered the study by Borstad et al.\(^{80}\), which compared the severity of gout attacks with colchicine co-administration to no administration, using VAS (visual analog scale) as a substitute for QOL. However, this study reported that the VAS in the colchicine co-administration group, 6 months after starting the urate lowering therapy, was 3.64, which was milder than the 5.08 in the placebo group. Hence, it was not possible to determine the merit or demerit of the period of the colchicine co-administration based on these results.

6. Degree of consensus

Nineteen of 26 people (73%) conditionally recommend “treatment.”

7. Literature retrieval method

Search DB: Ichushi Web (Japan Medical Abstracts Society)
Search date: 3 March 2017
Search DB: PubMed
Search date: 3 March 2017

[Table 7: PICO format for CQ7]

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<tr>
<td>Disease/clinical conditions</td>
</tr>
<tr>
<td>Geographic constraints</td>
</tr>
</tbody>
</table>

| List of I (Interventions) / C (Comparisons, Controls, Comparators) |
| Dietary advice (including alcohol advice) / control; no dietary advice |

<table>
<thead>
<tr>
<th>List of O (Outcomes)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcomes</strong></td>
</tr>
<tr>
<td>O(_1) Reduced uric acid levels</td>
</tr>
<tr>
<td>O(_2) Inhibits gout</td>
</tr>
<tr>
<td>O(_3) Increased incidence of new gout attacks</td>
</tr>
</tbody>
</table>

Can dietary advice be recommended over not providing dietary advice to patients with asymptomatic hyperuricemia?

Recommendation – Dietary advice is recommended over not providing dietary advice to patients with asymptomatic hyperuricemia.

1. Recommendation determinants

1) Strength of evidence: C (weak)

We were unable to collect evidence that compared the provision of dietary advice (including drinking habits) and the non-provision of dietary advice with the outcomes of “Reduced uric acid levels”, “Inhibits gout”, and “Increased incidence of new gout attacks” in subjects with asymptomatic hyperuricemia. When we collected evidence with dietary advice considered as the individual diet content, the diet content was significantly involved in “Reduced uric acid levels”, “Inhibits gout”, and “Increased incidence of new gout attacks”, and it was demonstrated that patients should take note of their dietary content. However, many of these studies, excluding literature on alcohol consumption and hyperuricemia, were implemented outside Japan. Furthermore, there were no studies targeting patients with only asymptomatic hyperuricemia, and many reports were missing outcomes depending on diet content.
Therefore, the certainty in evidence is low. In addition, although evidence was collected regarding the influence of sugar and alcohol in elevating uric acid levels and that of alcohol, sugar, meat, and seafood increasing the incidence of gout, no evidence was collected on the reduction of uric acid or the inhibition of gout through the limited intake of these food groups.

From the perspective of diets, the common element of increasing the amount of fruit and vegetables in the diet and decreasing the amount of meat and fat was observed between the Dietary Approaches to Stop Hypertension (DASH) diet (diet with increased consumption of fruits, vegetables, and low-fat dairy products, and decreased consumption of saturated fat, total fat, and cholesterol), the Mediterranean diet (diet with high consumption of olive oil, legumes, fruits, nuts, seafood, and saffritto, and low consumption of red meat, high-fat food, pastries, snacks, etc.), and the fruit and soy diet (diet with high consumption of fruit and soy). The results of diet seemed to support the results with individual foods (vitamin C, meat). The collected evidence suggested the usefulness of dietary advice in considering the diet content and individual foods, and in addition to eliminating obesity and excess weight. However, the importance of the outcomes differed depending on the diet content, and the quantity of intake may differ from the standard intake in Japan. Therefore, the certainty in the evidence was set as C (weak).

2) Balance between benefit and harm
Dietary advice is considered to be associated with a low incidence of harmful events (increase of new gout attacks). In contrast, there were diet contents that induced benefits (reduced uric acid levels and inhibition of gout) but the evidence based on dietary advice could not be collected, making it challenging to evaluate the size of the benefit of dietary advice.

3) Patient values and preferences
Even when the importance of dietary advice is understood, the effect cannot be fully grasped. There was also the opinion that the correction of obesity should suffice. The strength of recommendation is weak based on patient values and preferences.

4) Cost and resources
The cost for one session of nutritional advice was JPY 780 as the fee for nutritional dietary advice (cost with 30% tax burden, as of November 2017), and hence was not considered to be expensive.

2. Process of deciding on the recommendation
We debated on “Can dietary advice be recommended over not providing dietary advice to patients with asymptomatic hyperuricemia?” in the recommendation preparation panel meetings based on the systemic review report.

Based on the evidence collected for this CQ, the results demonstrated the usefulness of dietary advice with regards to the diet content and individual foods, although the certainty in evidence is C (weak). One of the main aims of dietary advice is to eliminate obesity and excess weight, as it is clear that these are involved in a risk as hyperuricemia and gout. We recognized that the evidence collected for this CQ demonstrated the usefulness of dietary advice with regards to the diet content and individual foods, in addition to the elimination of obesity and excess weight. Therefore, 24 of 26 people voted to “recommend provision of dietary advice”, and 2 of 26 people voted to “conditionally recommend provision of dietary advice”. There was also a debate whether to phrase the expression in the CQ7 as “dietary advice” or “dietary therapy”, and “dietary advice” was established based on 22 of 26 people voting for “dietary advice” and 4 of 26 people voting for “dietary therapy”.

3. Other
Obesity, particularly accumulation of visceral fat, demonstrated a positive correlation with serum urate concentration and a negative correlation with the uric acid clearance. Furthermore, it has been observed that weight loss increased uric acid clearance and reduced the serum urate concentration. Therefore, adjusting the intake energy was the first role of dietary advice, as one of the main aims of dietary advice for asymptomatic hyperuricemia is to eliminate obesity and excess weight. Reports indicated that the serum urate concentration was elevated and the incidence of gout increased with increased alcohol consumption, and hence advice to limit alcohol intake also played an important role in dietary advice.

When we collected evidence on the content of each diet, we observed that excessive consumption of sugar elevated the serum urate concentration, while the excessive consumption of sugar, meat, and seafood increased the incidence of gout attacks. Furthermore, the collected
evidence demonstrated that the intake of vitamin C reduced serum urate concentration, and the intake of dairy products and coffee inhibited gout attacks. In contrast, no association was detected between coffee intake and the serum urate concentration, nor between the tea intake and serum urate concentration or gout. From the perspective of diets, we observed that the DASH diet, the Mediterranean diet, and the fruit and soy diet were associated with a reduction in the serum urate concentration. Thus, the provision of dietary advice with regards to the content of these diets and individual foods, in addition to adjusting the energy intake and the restriction of alcohol intake, was recommended.

However, when providing dietary advice, it was essential to be aware of the dissimilarities in patient awareness, motivation, and ideas. It was also challenging to consider adjusting energy intake as a useful dietary advice in non-obese patients. Therefore, although providing dietary advice with regards to the dietary content and individual foods is recommended, it is also essential to evaluate the cause of hyperuricemia.

The fee for a single session of nutritional dietary advice was JPY 780, and hence was not considered expensive. Furthermore, the harm that could occur from dietary advice (increase of new gout attacks) is considered to be limited, and it was also clarified that the dietary content resulted in beneficial outcomes (reduced uric acid levels and inhibition of gout). However, the stage at which the diet content can be presented specifically and numerically has not yet been reached.

Additional notes have been included below regarding the association of vitamin C with urinary tract stones, and that of purine intake and uric acid levels with the onset of gout, which was one of the topics raised in the panel discussion. There is insufficient evidence that excess intake of vitamin C is related to the onset or recurrence of urinary tract stones via the increased excretion of oxalate through the urine in gout, but patients with urinary tract stones should remain cautious. Sufficient evidence could not be collected on the association between purine intake with the uric acid levels, and onset of gout.

4. Voting results

Number of voters: 26; valid votes: 26
(1) Recommend “provision of advice”: 24 votes; (2) Conditionally recommend “provision of advice”: 2 votes, (3) Conditionally recommend “do not provide advice”: 0 votes; (4) Recommend “do not provide advice”: 0 votes
Thus, (1) recommend “provision of advice” was adopted.

5. Summary of evidence

1) Outline of search results

We attempted to collect evidence that compared provision of dietary advice (including drinking habits) with the non-provision of dietary advice in patients with asymptomatic hyperuricemia, with the outcomes of “Reduced uric acid levels”, “Inhibits gout”, and “Increased incidence of new gout attacks”. However, we failed to collect the required evidence.

Next, we conducted an exhaustive search of literature on dietary advice, taken as the individual diet content, with the outcomes of “Reduced uric acid levels”, “Inhibits gout”, and “Increased incidence of new gout attacks”, and collected 1308 papers. Primary screening excluded 1203 papers, and 105 papers were adopted. Secondary screening excluded 92 papers, and 13 papers were adopted. The selection criteria for secondary screening were studies that were interventional studies with an intervention period of roughly 30 days or more, observational studies with roughly 1000 subjects or more, and observational studies with an observation period of 3 years or more. Among the 13 papers adopted through secondary screening, Paper 1 was a meta-analysis that investigated the effect of coffee intake on uric acid levels and onset of gout, similar to Paper 2, and there was no variance in the content of the evidence, so Paper 1 was eliminated after the process of secondary screening. The 12 papers adopted as a result of this literature search were then evaluated, and the following results were obtained.

2) Outcome 1: Reduced uric acid levels

In a meta-analysis investigating the association between coffee intake and uric acid levels in 38,639 people, no association was observed between coffee intake and uric acid levels, even in a comparison between the group with the highest coffee intake and the group with the lowest intake (−0.1 [95% CI: −0.23 to −0.05] mg/dL). The strength of evidence was set as B (moderate). Vitamin C supplementation significantly reduced uric acid levels according to the meta-analysis of the RCTs (556 people, median value 30 days) (−0.35 [(95% confidence interval (CI)): −0.66 to −0.03] mg/dL). The strength of evidence was set as B (moderate).
The DASH diet (30 days) significantly reduced uric acid levels compared to the control (-0.35 [95% CI: -0.65 to -0.05] mg/dL). However, the strength of evidence was set as C (weak) based on the study subjects being hypertensive patients, the difficulty in blinding, and the protocol changing the salt intake partway through the study86).

In a 5-year observational study on the Mediterranean diet, the group with good adherence to the Mediterranean diet had a significantly greater extent of reduction in uric acid levels compared to the group with poor adherence to the Mediterranean diet (1.73 [95% CI: 1.04 to 2.89] times). The strength of evidence was set as C (weak) based on the study subjects being elderly patients with a high cardiovascular risk and the evaluation being based on good or bad adherence87).

In an RCT that compared the intake of sugar (cola) and water, a significant relative increase in uric acid levels in the sugar intake group (15%, p = 0.009) was observed. However, the strength of evidence was set as C (weak) based on the study subjects being obese with a BMI of > 30 kg/m² and the excessive intake of cola set at 1L/day88).

Two observational studies assessed in Japanese males reported that alcohol intake increased the risk of developing hyperuricemia. The studies targeted only males without hyperuricemia, and the outcomes were not uric acid levels per se. However, the results were dose-dependent, and the study was a large-scale investigation, with a total of 11,407 subjects. Therefore, the strength of evidence was set as B (moderate)89,90.

An RCT that compared a fruit and soy diet with a standard therapeutic diet (subjects were 187 Chinese patients with asymptomatic hyperuricemia) found no significant difference in the uric acid levels (6.61 mg/dL vs 6.62 mg/dL). However, given that the uric acid levels were significantly reduced in both groups after completion of the interventional study and there was no comparison with a normal diet, the strength of evidence was set as C (weak)91).

In a meta-analysis investigating the association between tea intake and the inhibition of gout, the group with the highest coffee intake compared to the group with the lowest intake (0.43 [0.31 to 0.59] times). The strength of evidence was set as B (moderate) based on the large scale of the study, the lack of heterogeneity and the results being high effectiveness indicators93).

In a meta-analysis of an observational study investigating the association between coffee intake and inhibition of gout in 135,302 people, coffee was significantly inhibited in the group with the highest coffee intake compared to the group with the lowest intake (0.43 [0.31 to 0.59] times). The strength of evidence was set as B (moderate) based on the large scale of the study and the results being high effectiveness indicators99,900.

In a systematic review of studies investigating the association between tea intake and the inhibition of gout in 42,924 people, a significantly higher incidence of gout attacks was observed in the group with the highest tea intake and the group with the lowest intake (0.82 [95% CI: 0.38 to 1.75] times). The intake of tea as reported may differ to the intake of tea by the Japanese people, but the strength of evidence was set as B (moderate) based on the large scale of the study92).

4) Outcome 3: Increased incidence of new gout attacks

In a meta-analysis investigating the association between alcohol intake and gout attacks in 42,924 people, a significantly higher incidence of gout attacks was observed in the group with the highest alcohol intake than in the group with no intake/social drinkers (1.98 [95% CI: 1.52 to 2.58] times). The strength of evidence was set as B (moderate) based on the large scale of the study, and the results being high effectiveness indicators94).

In an observational study investigating the association between sugar intake and onset of gout in 125,299 people, a significantly higher incidence of gout was observed in the group with the highest intake of sugar (quintile) than in the low intake group (1.62 [95% CI: 1.28 to 2.03] times). The strength of evidence was set as B (moderate) based on the large scale of the study, the results being high effectiveness indicators95).

In a 12-year observational study investigating the association between meat intake and the onset of gout in 47,150 men, a significantly higher incidence of gout was reported in the group with the highest intake of dairy products (quintile) than in the group with the lowest intake (0.56 [0.42 to 0.74] times). The strength of evidence was set as B (moderate) based on the large scale of the study and the results being high effectiveness indicators96).

3) Outcome 2: Inhibits gout

In 12-year observational study on 47,150 men, investigating the association between the intake of dairy products and the inhibition of gout, a significantly lower rate of gout was reported in the group with the highest intake of dairy products (quintile) than in the group with the lowest intake (0.56 [0.42 to 0.74] times). The strength of evidence was set as B (moderate) based on the large scale of the study and the results being high effectiveness indicators97).
was reported in the group with the highest intake of meat (quintile) than in the low intake group (1.41 [95% CI: 1.07 to 1.86] times). The strength of evidence was set as B (moderate) based on the large scale of the study, and the results being high effectiveness indicators.

In a 12-year observational study investigating the association between seafood intake and onset of gout in 47,150 men, a significantly higher incidence of gout was observed in the group with the highest intake of seafood (quintile) than in the low intake group (1.51 [95% CI: 1.17 to 1.95] times). The strength of evidence was set as B (moderate) based on the large scale of the study, and the results being high effectiveness indicators.

6. Degree of consensus
24 of 26 people (92%) recommended “provision of advice.”

7. Literature retrieval method
Search DB: Ichushi Web (Japan Medical Abstracts Society)
Search date: 2 March 2017
Search DB: PubMed
Search date: 2 March 2017 (first search)
Search DB: PubMed
Search date: 13 March 2017 (second search)

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<td>Department of Community-based Family Medicine, Tottori University Faculty of Medicine</td>
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<td>Department of Cardiovascular Regeneration and Medicine, Research Institute for Radiation Biology and Medicine, Hiroshima University</td>
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<td>Ikako Masuda</td>
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<td>Hiroko Morisaki</td>
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| Einosuke Mizuta   | Department of Cardiology, Sanin Rosai Hospital                               | Chief of Department          | Yonago   | Hypertension, Cardiovascular diseases, genetics  | 1. The Japanese Society of Internal Medicine  
2. The Japanese Circulation Society  
3. The Japanese Society of Hypertension  
4. The Japan Society of Human Genetics  
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| Shigetaka Yoshida | Atami Oceanview Hospital                                                     | Director of dialysis center  | Shizuoka | Nephrology and Dialysis                          | Japanese Society of Nephrology, The Japanese Society for Dialysis Therapy, Japanese Society of Internal Medicine | Systematic review                  |
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**Societies and Organizations:**
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- The Japanese Circulation Society
- The Japanese Society of Hypertension
- The Japanese Society of Hematology
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