Treatment of Asymptomatic Hyperuricemia for the Prevention of Gouty Arthritis, Renal Disease, and Cardiovascular Events: A Systematic Literature Review

Ophir Vinik, Mihir D. Wechalekar, Louise Falzon, Rachelle Buchbinder, Désirée M. van der Heijde, and Claire Bombardier

ABSTRACT. ***Objective.*** To systematically review available literature on treatment of hyperuricemia (HU) as a measure of preventing gouty arthritis, renal disease, or cardiovascular events in asymptomatic patients.

Methods. A systematic literature search was conducted in the Cochrane Library, Medline, Embase, clinical trials registries of the World Health Organization and the US National Institutes of Health, and abstracts from American College of Rheumatology/European League Against Rheumatism meetings, for interventional studies involving adults with no history of gouty arthritis, who were treated for HU. Outcomes of interest included gouty arthritis, renal disease (i.e., renal insufficiency, urate nephropathy, nephrolithiasis), and cardiovascular events (i.e., myocardial infarction, heart failure, ischemic stroke).

Results. A total of 3 studies met the inclusion criteria, 2 studies assessing the prevention of renal disease and 1 study evaluating the potential for delaying progression of preexisting renal disease. In hyperuricemic patients without renal disease, treatment resulted in increased estimated glomerular filtration rate. In hyperuricemic patients with preexisting renal disease, treatment resulted in no significant elevation of serum creatinine over a 1-year followup. However, differences in renal function between the treatment and no-treatment groups were not statistically significant in any of the identified studies.

Conclusion. Very limited data are available on the treatment of HU in asymptomatic patients. There is currently insufficient empiric evidence to suggest that lowering serum uric acid level in asymptomatic patients with HU can prevent gouty arthritis, renal disease, or cardiovascular events. (J Rheumatol Suppl. 2014 Sept; 92:70–4; doi:10.3899/jrheum.140465)

Key Indexing Terms:
HYPERURICEMIA ASYMPTOMATIC GOUTY ARTHRITIS PREVENTION

This article is part of the 3e (Evidence, Expertise, Exchange) Initiative on Diagnosis and Management of Gout[1]. The objective of the current work was to systematically review the available literature concerning 1 of the 10 selected questions as an evidence base for generating the recommendations. This review relates to the question: Can we prevent gouty arthritis, renal disease, and cardiovascular events by lowering serum uric acid levels in patients with asymptomatic hyperuricemia? If yes, what should be the target levels?

From the Division of Rheumatology, University of Toronto, Toronto, Ontario, Canada; Rheumatology Research Unit, Repatriation General Hospital, Daw Park; Flinders University, Bedford Park, South Australia, Australia; Center for Behavioral Cardiovascular Health, Columbia University Medical Center, New York, NY, USA; Monash Department of Clinical Epidemiology, Cabrini Hospital, Malvern, Victoria; Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Malvern, Victoria; Rheumatology Department, Leiden University Medical Center, Leiden, The Netherlands; Division of Rheumatology and Institute of Health Policy, Management, and Evaluation, University of Toronto; and Toronto General Research Institute, University Health Network; and Institute for Work and Health, Mount Sinai Hospital, Toronto, Ontario, Canada.

The authors acknowledge the work of all members of the 3e scientific committees and all participants in the national meetings. This article is derived from the 3e Gout program, which was sponsored by AbbVie Inc. Margaux Orange, Paris, France, provided logistical and administrative support for the 3e Gout meetings; this work was funded by AbbVie Inc. AbbVie employees were present during the 3e meetings, but did not influence the scientific discussions. AbbVie did not review the content or have influence on this manuscript.

O. Vinik, MD, FRCPC, Division of Rheumatology, University of Toronto; M.D. Wechalekar, MD, FRACP, Rheumatology Research Unit, Repatriation General Hospital; and Flinders University; L. Falzon, PGDipInf, Center for Behavioral Cardiovascular Health, Columbia University Medical Center; R. Buchbinder, MBBS (Hons), MSc, PhD, FRACP, Director, Monash Department of Clinical Epidemiology, Cabrini Hospital, and Professor, Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University; D.M. van der Heijde, MD, PhD, Professor of Rheumatology, Rheumatology Department, Leiden University Medical Center; C. Bombardier, MD, FRCPC, Professor, Division of Rheumatology and Institute of Health Policy, Management, and Evaluation, University of Toronto; and Toronto General Research Institute, University Health Network; Institute for Work and Health, Mount Sinai Hospital.

Address correspondence to Dr. O. Vinik, Division of Rheumatology, University of Toronto, 60 Murray Street, Toronto, Ontario M5T 3L9, Canada; E-mail: ophir.vinik@utoronto.ca

The clinical significance of elevated serum uric acid as a harbinger of various diseases is unclear. Large observational cohort studies have demonstrated an association between hyperuricemia (HU) and an increased risk of gout, although the number of affected patients in these studies was generally small, and their uric acid levels very high[2,3]. An association with adverse renal and cardiovascular (CV) outcomes has also been suggested. Specifically, HU has been shown to have a predictive and prognostic value as a marker in patients with hypertension[4,5], heart failure[6], cardiovascular disease[7], cerebrovascular disease[8], metabolic syndrome[9], and renal disease[10,11]. However, it remains unclear whether treatment of HU can prevent its associated adverse outcomes of gouty arthritis, renal disease, or CV events in asymptomatic patients. A systematic review of the literature was conducted to address this question as an evidence base for developing clinical practice recommendations.

MATERIALS AND METHODS

The research question was used to generate the PICO (Population, Intervention, Comparison, Outcome), a concept suggested by the Cochrane Collaboration as a tool in conducting systematic literature reviews. The target population was defined as adults (age > 18 years) with elevated serum uric acid level but without history of gouty arthritis. The intervention of interest included any uric acid-lowering therapy, and comparators could be no treatment or placebo. The included outcomes were gouty arthritis (including tophi), renal disease, encompassing renal insufficiency, urate nephropathy and nephrolithiasis, and CV events, including myocardial infarction, heart failure and ischemic cerebrovascular stroke. Included study types were randomized controlled trials, case controlled studies, cohort studies, and case series. Studies involving congenital, malignant, or iatrogenic causes of HU were excluded. Articles written in a language other than English or a language in which at least 1 member of the 3e bibliographic group was fluent (Dutch, German, French, and Spanish) were excluded.

A systematic search was conducted using the Cochrane Library, OVID Medline (1948 to October 2011), and Embase (1980 to October 2011). The search strategy was devised with the help of an experienced librarian (LF) (for the complete search strategy, see online supplementary data available from www.3egout.com). Clinical trials registries of the World Health Organization (WHO) and the US National Institutes of Health (NIH), as well as abstracts from the American College of Rheumatology (ACR) and European League Against Rheumatism meetings (EULAR) (2010–2011) were also searched. Search results were reviewed by 2 reviewers (OV, MW), who also extracted the relevant data. Risk of bias was assessed using the Cochrane Collaboration risk of bias tool[12].

RESULTS

A total of 1683 articles were identified as well as 4 abstracts from the ACR and EULAR meetings and 7 entries from the clinical trials registries of the WHO and NIH (Figure 1). After detailed review, only 3 studies met the inclusion criteria, none of which pertained to the prevention of gouty arthritis or CV events (Table 1). Two studies[13,14] assessed the prevention of renal disease by treating HU in asymptomatic patients, and 1 study[15] evaluated the potential for delaying progression of renal disease by treating HU in patients with preexisting renal dysfunction. The limited number of identified studies precluded a subsequent metaanalysis. All 3 studies were deemed to have high risk of bias based on lack of allocation concealment and lack of blinding of both participants and outcome assessors (for more details see online supplementary data available from www.3egout.com).

Kanbay, *et al* (2007)[13] conducted an open single-arm trial in which 48 patients with HU and normal renal function were treated with a xanthine oxidase inhibitor (allopurinol 300 mg per day) for 3 months. Their renal function and plasma urate levels were monitored and compared to a group of 21 non-HU patients. A total of 10 patients dropped out of the study, of which 1 was due to rash in the treatment group. After 3 months of treatment there was a significant decrease in the mean serum uric acid level in the HU group compared to baseline (8.0 ± 0.76 mg/dl to 5.5 ± 1.2 mg/dl; $p < 0.05$). The mean estimated glomerular filtration rate (eGFR) of patients on treatment increased (79.2 ± 31.9 ml/min to 92.9 ± 36.8 ml/min; $p < 0.05$) with an associated decrease of their serum creatinine (1.24 ± 0.36 mg/dl to 1.14 ± 0.32 mg/dl; $p < 0.05$). There was no significant change in urine protein excretion in the treatment group compared to baseline. At 3 months there were no statistically significant differences between the treatment and no-treatment groups with respect to eGFR, serum creatinine, and urine protein excretion.

In a subsequent open-label randomized trial by Kanbay, *et al* (2011)[14], 72 HU patients with normal renal function were randomized to either a xanthine oxidase inhibitor (allopurinol 300 mg per day) or to no treatment and were followed for 4 months with monitoring of renal function. No adverse outcomes were reported. At the end of 4 months there was a significant reduction in uric acid level in those treated with the xanthine oxidase inhibitor (8.3 ± 1.1 mg/dl to 5.8 ± 1.5 mg/dl; $p < 0.05$) compared to baseline. The mean eGFR in the treatment group increased (86.3 ± 19.4 ml/min to 89.6 ± 12.6 ml/min; $p = 0.001$), but with no significant change in urine protein excretion compared to baseline. There was also no statistically significant difference between the treatment and no-treatment groups with respect to these variables.

The third included study, Siu, *et al* (2006)[15], recruited patients with HU who had a baseline renal disease defined as serum creatinine between 120 and 400 μmol/l and/or 24-h urine protein excretion > 0.5 g. Their definition of HU was uric acid > 7.6 μmol/l (compared to 7 μmol/l in the other 2 studies). This was an open-label, randomized study in which 54 patients were randomized to receive either xanthine oxidase inhibitor (allopurinol, dosed at 200 mg per day when serum creatinine was ≤ 150 μmol/l, and 100 mg per day if serum creatinine was > 150 μmol/l) or no treatment. They were followed at 12 months with measurement of renal function. Other medications such as antihypertensive and lipid-lowering agents were allowed to be adjusted during the study at clinician's discretion. They reported 1

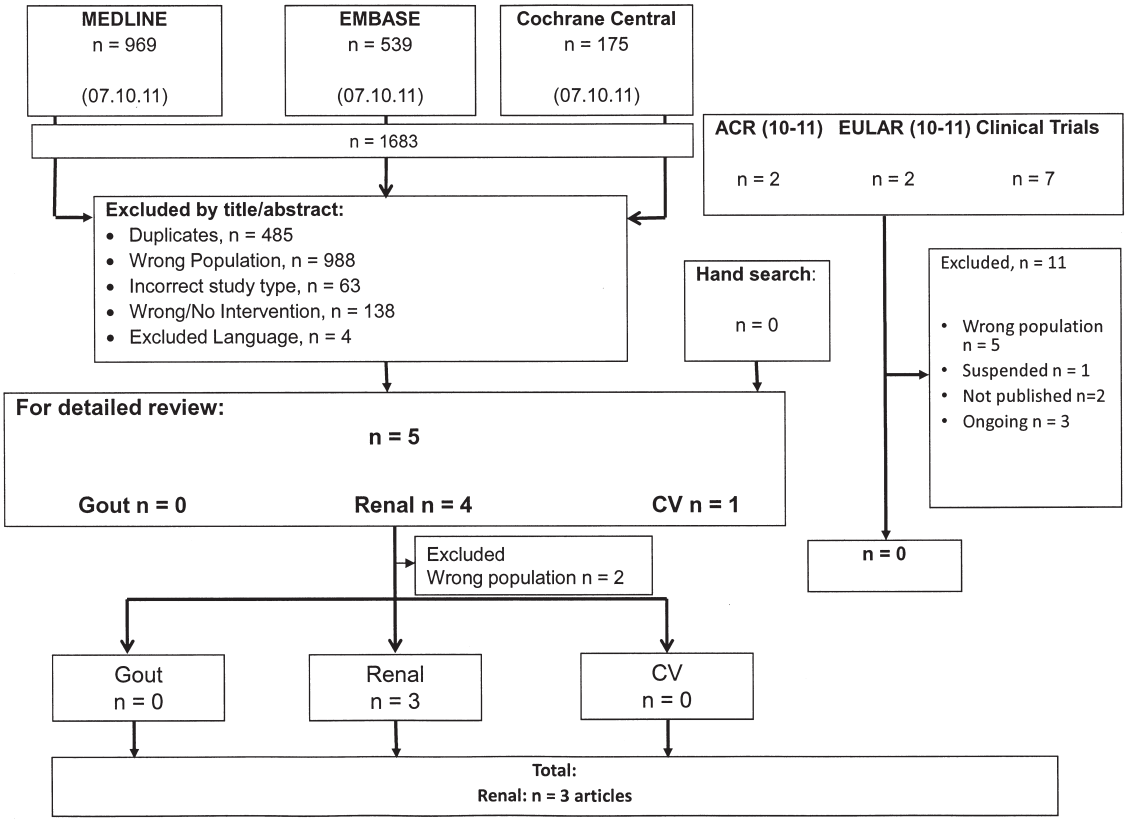

Figure 1. Literature search results: of 1683 identified articles, 5 were selected for detailed review, of which 3 met all inclusion criteria. ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; CV: cardiovascular.

Table 1. Summary of included studies.

Study	Total N/Renal Function	Urate Level, mg/dl (μmol/l)	Duration, mo	Design	Intervention (n)	Comparator (n)	Risk of Bias
Kanbay, *et al*, 2007[13]	69/normal	> 7 (> 420)	3	Interventional	Allopurinol 300 mg/day (n = 48)	No treatment (non-HU, n = 21)	High
Kanbay, *et al*, 2011[14]	72/normal	> 7 (> 420)	4	Random open-label	Allopurinol 300 mg/day (n = 32)	No treatment (HU, n = 40)	High
Siu, *et al*, 2006[15]	54/serum Cr: 120–400 μmol/l; and/or 24 h urine protein > 0.5 g	> 7.6 (> 452)	12	Random open-label	Allopurinol (n = 26): Cr ≤ 150 μmol/l: 200 mg/day; Cr > 150 μmol/l: 100 mg/day	No treatment (HU, n = 28)	High

Cr: creatinine; HU: hyperuricemia.

dropout from the treatment group due to a skin reaction. After 12 months of treatment, patients receiving a xanthine oxidase inhibitor had a significant reduction in uric acid level (9.75 ± 1.18 mg/dl to 5.88 ± 1.01 mg/dl; $p < 0.05$). There was no significant change in serum creatinine in the treatment group compared to baseline (1.64 ± 0.63 mg/dl to 1.99 ± 0.92 mg/dl; $p > 0.05$), while in the no-treatment group there was a significant increase (1.86 ± 0.69 mg/dl to 2.89 ± 0.96 mg/dl; $p < 0.05$) suggesting worsening renal function. There was no significant change in urine protein excretion in either of the 2 groups compared to baseline. Comparing the 2 groups at 12 months, there were no statistically significant differences with respect to serum creatinine and urine protein excretion.

DISCUSSION

This systematic review summarizes and evaluates the existing evidence on treating HU in patients with no history

of gouty arthritis. Combined with expert opinion from the panel of rheumatologists taking part in the 3e Initiative, these results served as an evidence base for generating 1 of the 10 clinical recommendations on the management of gout.

The findings of this systematic review highlight the paucity of empiric data relating to the treatment of HU as a measure of preventing its previously identified clinical associations with gouty arthritis, renal disease, and CV events. It also illustrates the lack of a uniform definition of HU in the medical literature. This, to some extent, likely reflects the difficulty of establishing an epidemiologically-based reference distribution of uric acid levels in a population because levels appear to change over time and vary among different populations and geographic locations[16].

The definition of asymptomatic HU was a topic of some debate among the 3e group participants. In principle, primary prevention of a disease in an asymptomatic person implies the absence of any history of this disease in the individual. Thus, from a purist perspective, patients with history of any associated sequela of HU should be excluded from the definition of asymptomatic HU. However, since the prevention and management of gout was the main objective of the 3e working group, the eventual agreed-upon definition was limited to patients with HU but no history of gouty arthritis. Patients with preexisting CV or renal disease were included in the definition of asymptomatic HU.

The 3 identified studies related only to the prevention of renal insufficiency. However, the duration of these studies (12 months or less) is likely too short to properly assess the target outcomes, and the small sample sizes are most likely underpowered for their specified outcomes. Although the Kanbay, *et al* studies[13,14] demonstrated an increase in eGFR with xanthine oxidase inhibitor in patients with HU, these were patients with no preexisting renal dysfunction and a normal baseline eGFR. The increase in eGFR in this context is of unclear clinical significance, particularly considering the short study duration.

The study by Siu, *et al*[15], while demonstrating no significant increase in serum creatinine after 1 year treatment with xanthine oxidase inhibitor in patients with preexisting renal disease, was also limited by small sample size and short followup duration. Results were also confounded by the noncontrolled use of other medications with potential renal as well as uric acid effects on metabolism, such as antihypertensive and lipid-lowering agents.

Finally, it must be emphasized that the treatment of HU carries risks of potential adverse events, some of which are not inconsequential[17]. Some of the uric acid-lowering medications carry the specific warning that they are not recommended for the treatment of asymptomatic hyperuricemia[18,19]. This is highlighted in other recent recommendations for the management of gout[20]. Citing the paucity of empiric data, the 2012 ACR guidelines for management of gout did not address the pharmacological management of asymptomatic HU[21].

Notwithstanding the lack of empiric evidence for pharmacological treatment of asymptomatic HU, experts in the 3e group suggested that lifestyle advice on diet, weight loss, and exercise could still be part of the management of these patients. This suggestion is based on the existing evidence for the health benefits of these nonpharmacological interventions, including their effect on uric acid levels and gout[22,23,24].

In summary, HU has been associated with an increased risk of gouty arthritis in large observational studies, although the number of affected patients in these studies is generally small and their uric acid level is significantly elevated. In addition, an associated risk of renal disease and CV events has also been described. However, the available interventional data on treating HU in asymptomatic patients is extremely sparse and fraught with limitations. Therefore, pharmacological treatment of asymptomatic hyperuricemia cannot be recommended at present for the prevention of gouty arthritis, renal disease, or CV events. Further interventional studies are required to determine the potential clinical benefits of this preventive approach.

REFERENCES

1. Sivera F, Andrés M, Carmona L, Kydd AS, Moi J, Seth R, et al. Multinational evidence-based recommendations for the diagnosis and management of gout: Integrating systematic literature review and expert opinion of a broad panel of rheumatologists in the 3e initiative. Ann Rheum Dis 2014;73:328-35.
2. Campion E, Glynn R, DeLarby L. Asymptomatic hyperuricemia: Risk and consequences in the Normative Aging Study. Am J Med 1987;82:421-8.
3. Hall AP, Barry PE, Dawber TR, McNamara PM. Epidemiology of gout and hyperuricemia. A long-term population study. Am J Med 1967;42:27-37.
4. Verdecchia P, Schillaci G, Reboldi G, Santeusanio F, Porcellati C, Brunetti P. Relation between serum uric acid and risk of cardiovascular disease in essential hypertension. The PIUMA study. Hypertension 2000;36:1072–8.
5. Høieggen A, Alderman MH, Kjeldsen SE, Julius S, Devereux RB, De Faire U, et al. The impact of serum uric acid on cardiovascular outcomes in the LIFE study. Kidney Int 2004;65:1041–9.
6. Anker SD, Doehner W, Rauchhaus M, Sharma R, Francis D, Knosalla C, et al. Uric acid and survival in chronic heart failure: Validation and application in metabolic, functional, and hemodynamic staging. Circulation 2003;107:1991–7.
7. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality: The NHANES I epidemiologic follow up study, 1971-1992. JAMA 2000;283:2404-10.
8. Weir CJ, Muir SW, Walters MR, Lees KR. Serum urate as an independent predictor of poor outcome and future vascular events after acute stroke. Stroke 2003;34:1951–6.
9. Gonçalves JP, Oliveira A, Severo M, Santos AC, Lopes C. Cross-sectional and longitudinal associations between serum uric acid and metabolic syndrome. Endocrine 2012;41:450-7.
10. Domrongkitchaiporn S, Sritara P, Kitiyakara C, Stitchantrakul W, Krittaphol V, Lolekha P, et al. Risk factors for development of decreased kidney function in a southeast Asian population: A

12-year cohort study. J Am Soc Nephrol 2005;16:791–9.
11. Hsu CY, Iribarren C, McCulloch CE, Darbinian J, Go AS. Risk factors for end-stage renal disease: 25-year follow-up. Arch Intern Med 2009;169:342–50.
12. Higgins JPT, Altman DG, Sterne JAC, editors. Ch. 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions, Version 5.1.0 (updated March 2011). The Cochrane Collaboration; 2011. Available from: www.cochrane-handbook.org
13. Kanbay M, Ozkara A, Selcoki Y, Isik B, Turgut F, Bavbek N, et al. Effect of treatment of hyperuricemia with allopurinol on blood pressure, creatinine clearance, and proteinuria in patients with normal renal functions. Int Urol Nephrol 2007;39:1227-33.
14. Kanbay M, Huddam B, Azak A, Solak Y, Kadioglu GK, Kirbas I, et al. A randomized study of allopurinol on endothelial function and estimated glomular filtration rate in asymptomatic hyperuricemic subjects with normal renal function. Clin J Am Soc Nephrol 2011;6:1887-94.
15. Siu YP, Leung KT, Tong MK, Kwan TH. Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. Am J Kidney Dis 2006;47:51-9.
16. Johnson RJ, Titte S, Cade JR, Rideout BA, Oliver WJ. Uric acid, evolution and primitive cultures. Semin Nephrol 2005;25:3-8.
17. Roujeau JC, Kelly JP, Naldi L, Rzany B, Stern RS, Anderson T, et al. Medication use and the risk of Stevens–Johnson syndrome or toxic epidermal necrolysis. N Engl J Med 1995;333:1600-7.
18. Uloric [package insert]. Deerfield, IL: Takeda Pharmaceuticals, North America, Inc; 2009; [Internet. See: Prescribing information. Accessed July 3, 2014.] Available from: http://www.uloric.com
19. US Food and Drug Administration. Allopurinol. Updated 2013 Feb. [Internet. See: Indications and usage. Accessed July 3, 2014.] Available from: http://www.drugs.com/pro/allopurinol.html
20. Hamburger M, Baraf HS, Adamson TC 3rd, Basile J, Bass L, Cole B, et al. Recommendations for the diagnosis and management of gout and hyperuricemia. Postgrad Med 2011;123 Suppl 1:3-36.
21. Khanna D, Fitzgerald JD, Khanna PP, Bae S, Singh MK, Neogi T, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: Systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res 2012;64:1431–46.
22. Choi HK, Liu S, Curhan G. Intake of purine-rich foods, protein, and dairy products and relationship to serum levels of uric acid: The Third National Health and Nutrition Examination Survey. Arthritis Rheum 2005;52:283-9.
23. Choi HK, Atkinson K, Karlson EW, Curhan G. Obesity, weight change, hypertension, diuretic use, and risk of gout in men: The health professionals follow-up study. Arch Intern Med 2005;165:742-8.
24. Choi HK, Atkinson K, Karlson EW, Willett W, Curhan G. Alcohol intake and risk of incident gout in men: A prospective study. Lancet 2004;363:1277-81.