Editorial

Uric acid lowering therapy for prevention of cardiovascular disease requires further evidence to be validated

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It has been observed since the late 19th century that gout is associated with hypertension, diabetes, kidney disease and cardiovascular disease (1). In 1897, Dr. Davis suggested that hypertension in gout might partly be due to hyperuricemia which increases arteriolar tonus (1). In 1951, Gertler *et al.* observed the association between serum uric acid (SUA) and coronary heart disease (2). In 1966, Cannon *et al.* showed the association between hyperuricemia and primary as well as renal hypertension (3). Since then, many epidemiological studies have been reported regarding associations between SUA and cardiovascular diseases including coronary heart disease (4), stroke (5), childhood hypertension (6), metabolic syndrome (7,8) and kidney disease (9,10). However, these observations do not clarify causal relationships. Culleton *et al.* examined whether elevated SUA is an independent risk factor of incident coronary heart disease, death from cardiovascular disease and death from all causes (11). They concluded that SUA is not an independent risk factor of coronary heart disease, death from cardiovascular disease or death from all causes and that any apparent association between SUA and these outcomes is probably due to the association between SUA and other cardiovascular risk factors (11). Thus, major academic societies have not considered SUA as an independent risk factor of cardiovascular diseases (12,13). It was argued that associations between SUA and cardiovascular diseases are either confounded by other risk factors such as obesity and hypertension or are representative of reverse causality (14). These controversial opinions led to a shift of interest away from SUA, and asymptomatic hyperuricemia was not considered as an indication for SUA lowering treatment in patients with cardiovascular and renal diseases (15). However, experimental, epidemiological, and clinical studies provocatively suggested that SUA may contribute to the development of hypertension (16), metabolic syndrome (17), and kidney disease (18). Recent epidemiological studies have explored associations of SUA with a wide range of conditions and some intermediate phenotypes or biomarkers (19). In an attempt to understand the possible underlying mechanisms, laboratory studies have been carried out and found that uric acid is potentially involved in multiple biological processes, including oxidative stress, systemic inflammation and intrahepatic fructose metabolism, all mechanisms that could be associated with the development of cardiovascular diseases and metabolic disorders (20,21). Alternatively, SUA levels may only present a marker of high oxidative stress associated with increased xanthine oxidase activity, instead of being an active agent in the pathogenic processes (22). SUA levels in human are considerably higher than those in other primates because human cells do not express urate oxidase which catabolizes uric acid. Urate oxidase expression was lost in early primate evolution and uric acid is the end product of purine metabolism in humans. In addition, nearly 90% of uric acid is re-absorbed along the renal tubules. Thus, some human individuals suffer from gout due to hyperuricemia. On the other hand, uric acid is considered an important antioxidant for humans. Low levels of SUA have been associated with neurodegenerative disorders such as Parkinson's disease (23) and Alzheimer's disease (24). Taking into account the antioxidant properties of uric

acid, its potential anti-pathogenic roles in cardiovascular diseases may also be considered (25). In view of the complex potential roles of uric acid in cardiovascular diseases, assessing the credibility of the observed evidence may have implications both for clinical practice and public health. It is recognized that different types of studies have specific strengths and weaknesses that can be complementary. Therefore, an umbrella review, which collects and evaluates evidence from multiple resources systematically, might help clarify the composite literature.

Li *et al.* carried out such an umbrella review of meta-analyses of observational studies and randomized controlled trials, and Mendelian randomization studies on associations between SUA and multiple health outcomes (26). In particular, they summarized the range of related health outcomes, presented the magnitude, direction, and significance of the reported associations and effects, assessed the potential biases, and identified which associations and effects have the most convincing evidence. Their comprehensive umbrella review will help investigators to judge the relative priority of health outcomes related to SUA for future research and clinical management of disease. In summary, despite a few hundred systematic reviews, meta-analyses, and Mendelian randomization studies exploring 136 unique health outcomes, convincing evidence of a clear role of SUA level only exists for gout and nephrolithiasis. Concordant evidence between observational studies and randomized controlled trials existed for hypertension and chronic kidney disease, but a potential causal role of SUA level for these outcomes has not been verified by current Mendelian randomization studies and even for these two outcomes not all meta-analyses of randomized controlled trials are concordant among themselves and with observational evidence. Therefore, the available evidence does not support any change in the existing clinical recommendations in relation to hyperuricemia (26). Current recommendations on the drug treatment of hyperuricemia are related to gout or nephrolithiasis (14). Li *et al.* raised large uncertainty about the potential therapeutic benefits of an expansion of SUA lowering therapy. Although they identified some highly suggestive associations from observational studies, there was a lack of concordance with clinically relevant endpoints from randomized controlled trials or surrogate endpoints from Mendelian randomization studies, and therefore evidence is insufficient to support any SUA lowering drug intervention for these outcomes other than gout or nephrolithiasis (26).

In some countries, SUA lowering therapy in the management of non-gout diseases is already recommended. However, there is no consistent definition of hyperuricemia and much remains unknown about the causal role of SUA in these non-gout diseases. In addition, recent evidence suggests that asymptomatic hyperuricemia may be an independent risk factor for the potentially fatal allopurinol hypersensitivity syndrome (27). In order to understand the role of SUA lowering therapy for asymptomatic hyperuricemia, adequately powered clinical trials with clinically relevant end points are essential to carefully examine the benefits and risks of such a strategy. It is not sufficient to use observational data alone to support interventions for asymptomatic biochemical abnormalities in clinical practice, noting the frequent lack of concordance between observational studies and randomized controlled trials. A key question for studies examining the role of SUA lowering therapy in asymptomatic hyperuricemia is whether the benefits of preventing the outcome outweigh the risks of long-term SUA lowering therapy, particularly when SUA lowering therapy can be associated with life-threatening complications, albeit rarely. Key issues that need to be addressed with regard to treating "non-gout diseases" include the appropriate patient population and age group. Whether there is a "target SUA level" or a specific drug dose, as well as the duration of SUA lowering therapy for each clinically relevant end point will need to be carefully defined through a clinical trial program. Whether xanthine oxidase inhibitors and uricosuric agents have similar effects suggesting that SUA reduction per se is what is required rather than xanthine oxidase inhibition also needs to be clarified. Until such clinical trials are completed and conclusively demonstrate benefit over risk of treatment, SUA lowering therapy for asymptomatic hyperuricemia cannot be supported (27).

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Footnote

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