The case for evidence-based medicine for the association between hyperuricaemia and CKD

Stefanie Steiger, Qiuyue Ma and Hans-Joachim Anders

We write in response to the Perspectives article by Y. Sato et al. (The case for uric acid-lowering treatment in patients with hyperuricaemia and CKD. *Nat. Rev. Nephrol.* **15**, 767–775; 2019)[1], which advocated treating asymptomatic hyperuricaemia to attenuate the progression of chronic kidney disease (CKD), based on small randomized control trials (RCTs) categorized as either 'interpretable' or 'non-interpretable'. The majority of interpretable RCTs suggested a treatment effect, whereas non-interpretable RCTs did not. The authors concluded that "treatment of so-called asymptomatic hyperuricaemia to slow or delay the progression of CKD should be a key management strategy"[1]. We have several objections to this statement.

First, 5 of 14 'interpretable' studies that reported positive results were not retrievable via Pubmed, Medline or Google Scholar and were only available from one Chinese repository of research literature. Q.M., who is a native Chinese speaker, analysed these publications and found variations between the full text and the English abstract — for example, urate-lowering therapy (ULT) with benzbromarone was mentioned in the English abstract but not in the full text of one study[2], which might lead to misinterpretation of the study. By contrast, a post-hoc analysis of two replicate phase III RCTs that was published open access in English and fulfilled the interpretable criteria established by the authors but reported negative results[3] was omitted from their analysis[1], suggesting a selection bias towards the concept proposed by the authors.

Second, the analysis by the authors is flawed because the threshold criteria change in estimated glomerular filtration rate (eGFR) and/or change in creatinine clearance in controls, which were used to identify interpretable studies, were not corrected in the control group for trial length (range 1–84 months). This normalization for trial length should be a mandatory criterion when assessing whether a study of CKD progression is interpretable. Moreover, the authors included trial outcome as a selection criterion for classifying a study as interpretable, which implies a self-fulfilling prophecy[4].

Third, 9 of 14 'interpretable' RCTs were either underpowered, reported an improvement in eGFR in the control arm, were single-centre RCTs and/or were not registered in clinicaltrials.gov before publication. In our opinion, collectively, these studies do not provide sufficient evidence for changes in treatment recommendations[5]; regulatory authorities only consider well-powered multi-centre RCTs[4] for this purpose.

Since publication of the article by Sato et al., preliminary results from two large multicentre RCTs have been reported[6,7] and consistently failed to show a causal link between asymptomatic hyperuricaemia and CKD progression (Supplementary information). Furthermore, as acknowledged by the authors[1], two large Mendelian randomization studies[8,9] had shown no significant causal relationship between serum uric acid level and risk of CKD.

After revising the analysis according to the aforementioned points, a meta-analysis of all single-centre RCTs suggests a small treatment effect size of 10% (overall odds ratio (OR) 0.90). By contrast, a meta-analysis of multi-centre RCTs demonstrates that ULT does not attenuate CKD progression (overall OR 1.0) (Supplementary information). In the case of asymptomatic hyperuricaemia and CKD, the best available scientific evidence does not support the use of ULT in patients with asymptomatic hyperuricaemia and CKD, at least not with the purpose of attenuating CKD progression.

There is a reply to this letter by Sato, Y. et al. *Nat. Rev. Nephrol.* https://doi.org/10.1038/s41581-020-0289-2 (2020)

Stefanie Steiger, Qiuyue Ma and Hans-Joachim Anders
Department of Medicine IV, University Hospital, LMU Munich, Munich, Germany.
e-mail: hjanders@med.uni-muenchen.de

https://doi.org/10.1038/s41581-020-0288-3

1. Sato, Y. et al. The case for uric acid-lowering treatment in patients with hyperuricaemia and CKD. *Nat. Rev. Nephrol.* **15**, 767–775 (2019).
2. Tan, Y., Fu, J., Liang, M., Lin, Z. & Huang, J. Clinical observation of the effect of allopurinol to protect renal function in patients with diabetic nephropathy. *Mod. Hosp.* **11**, 36–38 (2011).
3. Yood, R. A., Ottery, F. D., Irish, W. & Wolfson, M. Effect of pegloticase on renal function in patients with chronic kidney disease: a post hoc subgroup analysis of 2 randomized, placebo-controlled, phase 3 clinical trials. *BMC Res. Notes* **7**, 54 (2014).
4. Downing, N. S., Aminawung, J. A., Shah, N. D., Krumholz, H. M. & Ross, J. S. Clinical trial evidence supporting FDA approval of novel therapeutic agents, 2005–2012. *JAMA* **311**, 368–377 (2014).
5. Djulbegovic, B. & Guyatt, G. H. Progress in evidence-based medicine: a quarter century on. *Lancet* **390**, 415–423 (2017).
6. Badve, S. et al. Effect of allopurinol on the progression of CKD: the CKD-FIX study[abstract TH-PO1198]. *ASN Kidney Week* https://www.asn-online.org/education/kidneyweek/2019/program-abstract.aspx?controlId=3261360 (2019).
7. Doria, A., Gelecki, A., Spino, C. & Maurer, M. Preventing Early Renal Loss in Diabetes (PERL) study: outcome of a 3-year trial of serum uric acid reduction with allopurinol [abstract FR-OR137] *ASN Kidney Week* https://www.asn-online.org/education/kidneyweek/2019/program-abstract.aspx?controlId=3274268 (2019).
8. Ahola, A. J. et al. The serum uric acid concentration is not causally linked to diabetic nephropathy in type 1 diabetes. *Kidney Int.* **91**, 1178–1185 (2017).
9. Jordan, D. M. et al. No causal effects of serum urate levels on the risk of chronic kidney disease: a Mendelian randomization study. *PLoS Med.* **16**, e1002725 (2019).

Acknowledgements
This work was supported by the Deutsche Forschungsgemeinschaft (STE2437/2-1 and AN372/24-1) and by LMUexcellent initiative (S.S.). Q.M. was supported by the Chinese Scholarship Council.

Competing interests
The authors declare no competing interests.

Supplementary information
Supplementary information is available for this paper at https://doi.org/10.1038/s41581-020-0288-3.

Reply to 'The case for evidence-based medicine for the association between hyperuricaemia and CKD'

Yuka Sato, Daniel I. Feig, Austin G. Stack, Duk-Hee Kang, Miguel A. Lanaspa, A. Ahsan Ejaz, L. Gabriela Sánchez-Lozada, Masanari Kuwabara, Claudio Borghi and Richard J. Johnson

In our Perspectives article (The case for uric acid-lowering treatment in patients with hyperuricaemia and CKD. *Nat. Rev. Nephrol.* **15**, 767–775; 2019)[1] we proposed that individuals with hyperuricaemia and chronic kidney disease (CKD) with worsening kidney function should be considered for urate-lowering therapy (ULT) to

slow progression of CKD[1]. When reviewing the literature, we argued that a trial was only interpretable if the control group showed clinically meaningful worsening of kidney function, which we defined as a reduction in estimated glomerular filtration rate (eGFR) of at least 4–5 ml/min/1.73 m^2. In their Correspondence article (The case for evidence-based medicine for the association between hyperuricaemia and CKD. *Nat Rev. Nephrol.* https://doi.org/10.1038/s41581-020-0288-3 (2020))[2], Steiger and colleagues state that we omitted a post-hoc analysis of two negative randomized clinical trials (RCTs)[3] but these trials would be considered to be 'non-interpretable' by our criteria (ΔeGFR 2.7 ml/min/1.73 m^2 in controls)[3]. Steiger et al. also expressed concerns about our inclusion of five RCTs published in peer-reviewed Chinese journals, which were summarized in a systematic review and meta-analysis[4]. Although one of these articles contained an error in the English abstract[5], we contend that their data should not be ignored simply because they are not indexed in PubMed.

Steiger et al. also argue that CKD progression should be evaluated according to the rate of eGFR decline rather than the absolute change in eGFR during the trial. However, we believe that absolute changes in ΔeGFR are most relevant to clinicians. Our study was not 'self-fulfilling' as it was based on whether the controls progressed. Indeed, it is self-fulfilling to report that a study is negative when it is inconclusive.

Preliminary data from two randomized placebo-controlled studies — CKD-FIX and PERL — indicated that treatment with allopurinol did not prevent worsening of CKD. Full reports from these trials are pending but these studies were not designed to test whether allopurinol is beneficial in patients with CKD and hyperuricaemia as patients with normal serum urate were included in each study. Both studies were intention-to-treat analyses in which large numbers of patients (19% in CKD-FIX and 30% in PERL) stopped treatment yet were included in the final analysis. Although this approach might be statistically correct for the analysis of a specific treatment effect, the inclusion of individuals in the treatment group who were non-compliant with therapy and therefore had persistent hyperuricaemia, or of treated individuals with normouricaemia, is scientifically incongruous with testing the hypothesis that ULT can slow eGFR decline in patients with hyperuricaemia and progressive CKD.

Evidence-based medicine should evaluate the totality of evidence available and all approaches carry assumptions that deserve scrutiny[6,7]. A clinical trial can be well designed but uninterpretable. For example, an anti-hypertensive cannot be deemed ineffective if tested in patients who are normotensive. The effects of a drug used to treat hyperuricaemia cannot be tested in individuals with normal uric acid levels, and a clinical trial cannot be interpreted as having failed if no patient in either group gets the disease. Alas, the problem with evidence-based medicine is not the evidence, but the interpretation, especially if the underlying assumptions are not recognized.

Yuka Sato[1], Daniel I. Feig[2], Austin G. Stack[3,4], Duk-Hee Kang[5], Miguel A. Lanaspa[1], A. Ahsan Ejaz[6], L. Gabriela Sánchez-Lozada[7], Masanari Kuwabara[8], Claudio Borghi[9] and Richard J. Johnson[1,10]

[1]Division of Renal Diseases and Hypertension, University of Colorado Anschutz Medical Campus, Aurora, CO, USA.
[2]Division of Pediatric Nephrology, University of Alabama, Birmingham, AL, USA.
[3]Division of Nephrology, Department of Medicine, University Hospital Limerick, Limerick, Ireland.
[4]Graduate Entry Medical School, University of Limerick, Limerick, Ireland.
[5]Division of Nephrology Department of Internal Medicine, Ewha Womans University College of Medicine Ewha Medical Research Center, Seoul, Korea.
[6]Division of Nephrology, Hypertension and Renal Transplantation, University of Florida, Gainesville, FL, USA.
[7]Dept. Cardio-Renal Physiopathology, INC Ignacio Chavez, Mexico City, Mexico.
[8]Department of Cardiology and Intensive Care Unit, Toranomon Hospital, Tokyo, Japan.
[9]Department of Medicine, University of Bologna, Bologna, Italy.
[10]Rocky Mountain Regional VA Medical Center, Aurora, CO, USA.
✉*e-mail: richard.johnson@cuanschutz.edu*

https://doi.org/10.1038/s41581-020-0289-2

1. Sato, Y. et al. The case for uric acid-lowering treatment in patients with hyperuricaemia and CKD. *Nat. Rev. Nephrol.* **15**, 767–775 (2019).
2. Steiger, S., Ma, Q. & Anders, H.-J. The case for evidence-based medicine for the association between hyperuricaemia and CKD. *Nat Rev. Nephrol.* https://doi.org/10.1038/s41581-020-0288-3 (2020).
3. Yood, R. A., Ottery, F. D., Irish, W. & Wolfson, M. Effect of pegloticase on renal function in patients with chronic kidney disease: a post hoc subgroup analysis of 2 randomized, placebo-controlled, phase 3 clinical trials. *BMC Res. Notes* **7**, 54 (2014).
4. Liu, X. et al. Effects of uric acid-lowering therapy on the progression of chronic kidney disease: a systematic review and meta-analysis. *Ren. Fail.* **40**, 289–297 (2018).
5. Tan, Y., Fu, J., Liang, M., Lin, Z. & Huang, J. Clinical observation of the effect of allopurinol to protect renal function in patients with diabetic nephropathy. *Mod. Hosp.* **11**, 36–38 (2011).
6. Johnson, R. J. Finding the truth: multivariable analysis and the assassination of Abraham Lincoln. *J. R. Coll. Physicians Edinb.* **48**, 153–154 (2018).
7. Johnson, R. J. Finding the truth: blind faith and the lemming phenomenon. *J. R. Soc. Med.* **111**, 175–176 (2018).

Competing interests

A.G.S. has had an unrestricted educational grant from Menarini International Operations Luxemburg and has consulted for Menarini and Grunenthal Pharma. G.S.-L. has had funding from Relburn Metabolomic and Danone Research Foundation; R.J.J. has equity with XORT Therapeutics, which is developing novel xanthine oxidase inhibitors, is an inventor on several patents on the role of uric acid in hypertension, metabolic syndrome and diabetic nephropathy that resulted from research (US Patent No. 7,799,794; US Patent No. 8,236,488; US Patent No. 8,557,831; US Patent No. 9,155,740 B), and has consulted for Danone Research Foundation, Horizon Pharmaceuticals and Astra Zeneca.