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Letters to the Editor

Controversy Over the Surrogacy of Proteinuria or Albuminuria for Cardiovascular Outcomes

To the Editor:

We were pleased to read the excellent review by Harrison et al.,[1] recently published in the *Canadian Journal of Cardiology*, entitled "Change in Proteinuria or Albuminuria as a Surrogate for Cardiovascular and Other Major Clinical Outcomes: A Systematic Review and Meta-analysis". The authors declared that "There is ongoing controversy around the surrogacy of proteinuria or albuminuria, particularly for cardiovascular (CV) outcomes"; therefore, the aim of their review article was to assess the surrogacy of changing proteinuria or albuminuria for CV events, end-stage renal disease (ESRD), and all-cause mortality. Results of the study showed inconsistent treatment effects for proteinuria and CV events (20 trials; TER 1.11 [95% confidence interval (CI), 1.01-1.22]). Treatment effects on proteinuria or albuminuria were also inconsistent with the effects on all-cause mortality (21 trials; TER 1.17 [95% CI, 1.07-1.28]), and they concluded that "Change in proteinuria or albuminuria might be a suitable surrogate outcome for ESRD. However, overall treatment effects on these potential surrogates are inconsistent and overestimate the treatment effects on CV events and all-cause mortality." Although the results were interesting, the obtained statistically significant level would be a matter of controversy. Borderline lower limits of 95% CIs made their significance level doubtable, whereas the 95% prediction interval (PI) suggested that the intervention effect could be null or even be in the opposite direction,[2] as PI presents a wider range of interval than CI. Therefore, to evaluate clinical significance, PI was proposed in contrast to statistical significance. To explain further, CI quantifies the accuracy of the mean, whereas PI addresses the actual dispersion of effect sizes, and the 2 measures are not interchangeable. We suggest that the authors calculate the prediction interval for evaluating clinical significances to reach more reliable results.[3]

We would like to mention another statistical issue as well. Meta-analysis uses normal distribution to estimate pooled CI (z-value), whereas relative risk (RR) follows a skewed distribution, which affects the results significantly. To tackle this issue, it would better to log-transform RR and pooled them and then inverse log by an exponential function and report RR instead of log-RR. The review authors did not mention, in the statistical part in the case, whether the process of analysis followed this point. We also assessed the methodological quality of this review using the 16-item **A Mea**surement **T**ool

Table 1. Methodological quality of the included meta-analyses and systematic reviews through AMSTAR 2

	Items	N (%)
1	Did the research questions and inclusion criteria for the review include the components of **PICO** (population, intervention, control group, and outcome)?	Yes
2	Did the report of the review contain an explicit statement that the review methods were established **prior to conduct** of the review, and did the report justify any significant deviations from the **protocol**?	Yes
3	Did the review authors explain their selection of the study designs for **inclusion** in the review?	Yes
4	Did the review authors use a comprehensive literature **search strategy**?	Yes
5	Did the review authors perform **study selection in duplicate**?	Yes
6	Did the review authors perform **data extraction in duplicate**?	Yes
7	Did the review authors provide a list of **excluded studies** and justify the exclusions?	Yes
8	Did the review authors **describe the included studies** in adequate detail?	Yes
9	Did the review authors use a satisfactory technique for assessing the **risk of bias** (RoB) in individual studies that were included in the review?	Yes
10	Did the review authors report on the **sources of funding** for the studies included in the review?	Yes
11	If meta-analysis was justified, did the review authors use appropriate **methods for statistical** combination of results?	Yes
12	If meta-analysis was performed, did the review authors **assess the potential impact of RoB in individual studies on the results** of the meta-analysis or other evidence synthesis?	Yes
13	Did the review authors **account for RoB** in individual studies when interpreting/discussing the results of the review?	Yes
14	Did the review authors provide a satisfactory explanation for—and discussion of—any **heterogeneity** observed in the results of the review?	Yes
15	If they performed quantitative synthesis, did the review authors carry out an adequate investigation of **publication bias** (small study bias) and discuss its likely impact on the results of the review?	Yes
16	Did the review authors report any **potential sources of conflict of interest**, including any funding they received for conducting the review?	Yes
AMSTAR 2 Classification		**High**

AMSTAR, **A Mea**surement **T**ool to **A**ssess Systematic **R**eviews.

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to **A**ssess Systematic **R**eviews (AMSTAR) 2 appraisal tool.[4] According to AMSTAR 2, this study scored 16 items out of 16 (Table 1), so this systematic review provided an accurate and comprehensive summary of the results of the available studies that address the question of interest and is classified as high-quality, although the surrogacy of proteinuria or albuminuria for CV outcomes is still a matter of controversy.

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Disclosures

The authors have no conflicts of interest to disclose.

References

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