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# Authors' reply to the letter regarding "Ticagrelor for Asian patients with acute coronary syndrome in real-world practice: A systematic review and meta-analysis of observational studies"

We thank Kumar and Shariff[1] for their great interest in our meta-analysis entitled as "Ticagrelor for Asian patients with acute coronary syndrome in real-world practice: a systematic review and meta-analysis of observational studies."[2] In response to the observations by Kumar and Shariff, we have the following statements to mention.

First, we generally have the same opinion with Kumar and Shariff in relation to the fact that variable follow-up periods of the included studies should be considered in calculation of summary statistics. Odds ratio only demonstrates the difference between treatments arms at some point in time. Given the fact that treatment arms might differ significantly in terms of duration of follow-up, serious misinterpretations could arise with odds ratio chosen as an effect estimate.[3] To avoid this bias, it is highly recommended to extract time-to-event (survival) data from the studies and compute hazard ratio as summary statistics.[3,4] Of note, Kumar and Shariff calculated pooled odds ratio of major bleeding for ticagrelor versus clopidogrel with patient year data in the denominator.[1] As we know, odds ratio is mainly used with dichotomous outcomes, not time-to-event ones. In this light, the Cochrane Handbook for Systematic Reviews of Interventions recommends estimation of the hazard ratio to deal with survival data.[4] To minimize possible bias, we provided odds ratios and hazard ratios for all the study endpoints, which readers could find in the original text of the meta-analysis.[2] Another important point to be mentioned is that hazard ratios were derived from multivariate Cox proportional models with adjustment for potential confounders. Propensity score matching was also applied in most studies. These statistical approaches are considered essential in reducing selection bias in pooled analyses of observational studies.[4] The results are presented in Fig. 1. In addition, we performed standard leave-one-out sensitivity analyses, which proved the robustness of our findings. After excluding the study conducted by Chen et al, Lee et al, Nur'amin et al, Sim et al, and Wang et al one-by-one, hazard ratios for major adverse cardiac events were 0.79 [95% confidence interval (CI): 0.70–0.90], 0.74 (95% CI: 0.56–0.99), 0.79 (95% CI: 0.71–0.89), 0.76 (95% CI: 0.67–0.85), and 0.77 (95% CI: 0.64–0.94), respectively.

Second, in response to the study by Kumar and Shariff, we could provide a Funnel plot for major adverse cardiac and cerebrovascular events (Fig. 2). However, we must underscore the notion that publication bias assessment is unreliable with a small number of the included studies.[4]

## Conflict of interest

The authors have nothing to disclose.

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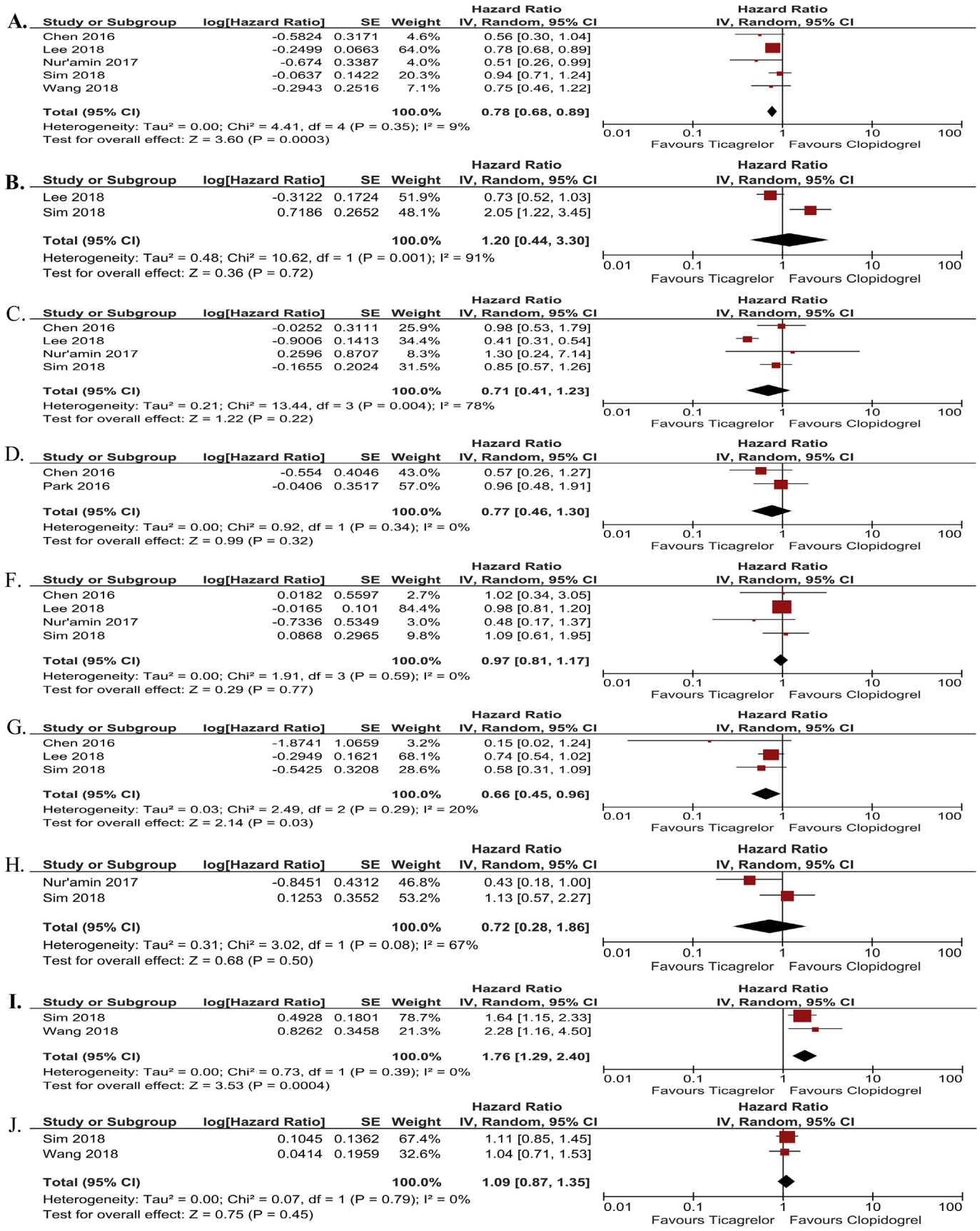


**Fig. 1.** Forest plot of ticagrelor versus clopidogrel for (A) major adverse cardiac and cerebrovascular events, (B) major bleeding, (C) all-cause mortality, (D) cardiovascular mortality, (F) myocardial infarction, (G) stroke, (H) target vessel revascularization, (I) major or minor bleeding, and (J) net adverse clinical and cerebrovascular events in Asian patients with acute coronary syndrome. SE, standard error; IV, inverse variance; CI, confidence interval.

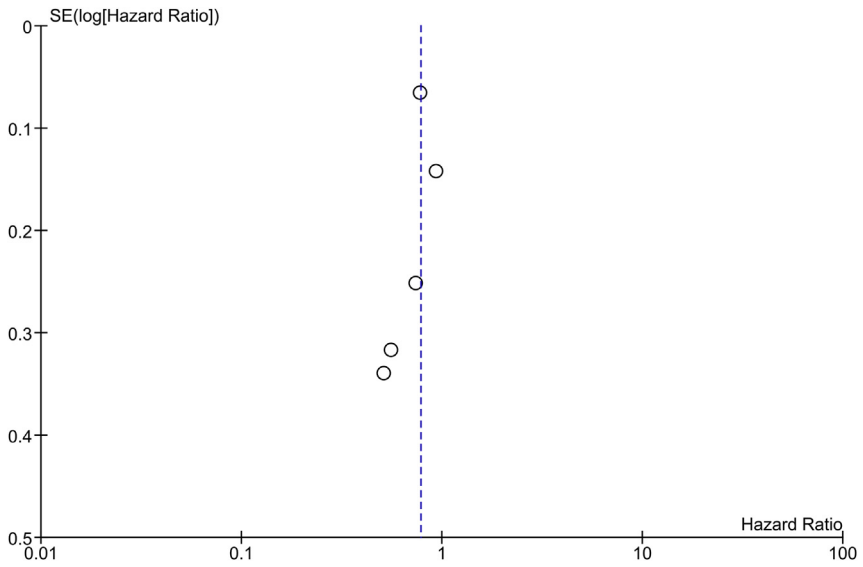


**Fig. 2.** Funnel plot for major adverse cardiac and cerebrovascular events. SE, standard error.