Response to: 'Impact of Janus kinase inhibitors on the risk of cardiovascular events in patients with rheumatoid arthritis: systematic review and meta-analysis of randomised controlled trials' by Lee and Song

We would like to thank Drs Lee and Song for their methodological comment¹ on our recent publication.² First, Cochran Q has been widely used for assessing heterogeneity in which p values are obtained by comparing the statistic with a χ^2 distribution. Due to poor power in detecting true heterogeneity, especially in a circumstance of small sample size, the establishment of a cut-off p value is complicated and the cut-off has not been definitively set yet. At present, using a cut-off of 0.1 or 0.05^{3 4} for significance could be considered, although the former is applied more commonly. A cut-off of 0.1 for significance yields the power, however increases the risk of drawing a false-positive conclusion.⁵ In fact, the interpretation of Cochran Q is that the smaller the p value, the less the likelihood that random error can solely explain the inconsistency across studies, and therefore a p value of neither 0.1 nor 0.05 could absolutely or substantially determine the heterogeneity.⁶ In our paper, a preferable approach to quantify heterogeneity, namely I^2 , was also employed, which could be sufficient in investigating heterogeneity across studies, in addition to Cochran Q.⁷ Therefore, whether the p value of 0.1 or 0.05 to be set have no substantial influence on the judgement of heterogeneity in our study. Second, despite a significant heterogeneity observed among tofacitinib, baricitinib and upadacitinib in Jakinibs versus placebo regarding venous thromboembolism events (VTEs) and in dose comparisons regarding all cardiovascular events (CVEs), there is no detectable heterogeneity across included trials for any of individual drugs, which therefore allow using fixed-effects model for tofacitinib, baricitinib and upadacitinib and presenting their corresponding results separately. Actually, one of the sensitivity analyses with random-effects model was performed, but eventually we did not add to our paper because of similar results obtained for Jakinibs overall or individual one in the setting of random-effects model (VTEs: OR=1.08, 95%CI: 0.35 to 3.32 for Jakinibs vs placebo; all CVEs: OR=0.99, 95%CI: 0.52 to 1.88 for low vs high doses of Jakinibs) (figure 1). Considering the generally high level of concordance for study populations among the three kinds of Jakinibs, the most intuitive cause of heterogeneity is inherently different consequences among the three kinds of Jakinibs, as we discussed in detail in Results and Discussion sections. Of note, this interpretation can be challenged due to the relatively small sample size and a low heterogeneity across all included studies (I^2 : 3%, 17%, respectively), rather than subgroups comparison,

and this is why we emphasised further investigations are urgently needed.

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Figure 1 OR of venous thromboembolism events in patients treated with JAK inhibitors compared with placebo (A) and OR of all cardiovascular events in patients treated with different dosages of JAK inhibitors (B) in randomised controlled trials using Mantel-Haenszel random-effects method. JAK, janus kinase; P-Y, patient-year.