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Comparison of Oral P2Y12 Inhibitors in Acute Coronary Syndrome

Q1 Syndrome

Baldetti et al.1 have performed a network meta-analysis to compare oral P2Y12 inhibitors (clopidogrel, prasugrel, ticagrelor) in acute coronary syndrome. Seven randomized trials, along with some observational studies, were analyzed. The main efficacy endpoint was a composite of major adverse cardiovascular events (MACE) at 12 months including cardiovascular death, myocardial infarction, and stroke (Table 5). Other end points of efficacy (e.g., all-cause death at 1 year) were also evaluated. The odds ratio (OR) was the outcome measure. As regards 1-year all-cause death, the results of this network meta-analysis favored prasugrel and ticagrelor compared with clopidogrel; prasugrel also reduced myocardial infarction rate compared with clopidogrel (Table 4). The other end points of efficacy (e.g., the MACE composite end-point) showed no significant differences among the 3 agents.

Q2 A wide literature has recently focused on some important disadvantages of both the hazard ratio and the OR (which are both relative outcome measures) particularly because, in pairwise comparisons, they tend to overemphasize the difference in favor of the more effective treatment.2,3 Network meta-analyses are known to accentuate this tendency of OR.

Q3 In a separate report,4 we have presented the narrative results that we obtained by analyzing the same 7 randomized trials assessed by Baldetti et al.5 (15 patient cohorts; data from page 17 of the Supplementary Appendix). Our rankings in effectiveness (based on event-free rates at 12 months; event = MACE) were estimated by simple arithmetic ordering. Since these results separately rely on the 15 patient cohorts, they lost their linkage with the inclusion criteria of the 7 trials and with the effects of randomisation.

The results in these 15 cohorts were the following: prasugrel ranked 1st, 4th, 6th, 9th and 13th; clopidogrel ranked 2nd, 7th, 8th, 14th and 15th; ticagrelor ranked 3rd, 5th, 10th, and 12th. The message arising from these results is that the effectiveness of clopidogrel, prasugrel, and ticagrelor has clearly a random distribution; hence, a network meta-analysis is unable to provide any meaningful information beyond the one provided by this narrative analysis. It should be noted that the assumptions of our reanalysis (e.g., transitivity of outcomes) are the same as those implicitly adopted by Baldetti et al.1 in their network meta-analysis.

As pointed out by Westafer and Schrigger,5 all network meta-analyses are based on the transitivity property and therefore assume that participants and trials are similar enough so that patients could have been randomized to any of the treatment arms. This allows the direct and indirect comparison to be made in any combination of between-treatment comparisons. Although meta-analyses are sometimes considered the ultimate form of evidence, the results are only as good as the underlying studies. Ideally, any meta-analysis would include only those studies that are conducted on similar populations and use similar interventions; this is particularly important in network meta-analysis for the treatment effects to be transitive and determine reliable indirect estimates.

Coherence and/or network consistency is a unique component to evaluation of a network meta-analysis. So, network meta-analyses must be scrutinized for inconsistency, heterogeneity of trials and potential sources of bias.

The overall picture emerging from our narrative analysis (in particular, our rankings) is a message of heterogeneous effectiveness across clopidogrel, prasugrel, and ticagrelor thus emphasizing the potential inconsistencies of these 7 randomized trials. Although Baldetti et al presented a conclusion about comparative effectiveness favoring prasugrel, this conclusion is not supported by our results. In our view, our narrative analysis is simpler and more reliable than the unavoidably complex network meta-analysis that suffers from the methodological biases typical of this statistical technique.

Declaration of interests

The authors declare no conflicts of interests.


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