September 10, 2020

Dr. Elisa Ferracane, Pharmacist
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RE: CIRCULATION AHA/2020/050472
Comparison of oral P2Y12 inhibitors in acute coronary syndrome: a re-analysis based on the restricted mean survival time.

Dear Dr. Ferracane,

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Title: Comparison of oral P2Y12 inhibitors in acute coronary syndrome: a re-analysis based on the restricted mean survival time.

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Comparison of oral P2Y12 inhibitors in acute coronary syndrome: a re-analysis based on the restricted mean survival time

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Navarese and coworkers\(^1\) have performed a network meta-analyses to compare oral P2Y12 inhibitors in acute coronary syndrome. Twelve randomised trials were studied. The main efficacy end-points included cardiovascular mortality, nonfatal myocardial infarction, all-cause mortality, stroke, and stent thrombosis which were assessed separately. The composite end-point of major cardiovascular events (MACEs) was not included. The hazard ratio (HR) was the outcome measure. As regards efficacy, the results of Navarese et al.\(^1\) showed that ticagrelor and prasugrel reduced cardiovascular mortality compared with clopidogrel. Similar advantages were found for ticagrelor and/or prasugrel concerning most of the other end-points of efficacy. In contrast, ticagrelor and prasugrel increased major bleedings compared with clopidogrel.

A wide literature has recently focused on some important disadvantages of the HR because this parameter frequently violates the proportional hazard model and also because of its nature of relative outcome measure;\(^2,3\) more importantly, the HR tends to overemphasise the difference in favour of the more effective treatment. In contrast, the restricted mean survival time (RMST), an absolute outcome measure quite similar to the median, is increasingly recognized to perform better. In particular, the RMST is more stable than the median and, unlike the median, can be computed from any Kaplan-Meier curve irrespective of the cumulative event frequency reached in the curve.\(^2,3\)

According to the composite end-point of MACEs, we re-analysed the 12 randomised trials of Navarese et al. using the RMST rather than the HR. Three studies were excluded because they did not report any Kaplan-Meier curves. Another was excluded because its follow-up lasted 6 months. The remaining 8 trials (based on clopidogrel, prasugrel or ticagrelor) were re-examined using the
RMST as opposed to the HR. The RMST (estimated from the Kaplan-Meier curves) was applied in its model-independent method.⁵

In a separate report,⁴ we have presented these RMST results including an analysis that ranked the RMSTs across the 16 cohorts. Prasugrel ranked 1st (11.39 months), 3rd (11.32 months), 8th (11.08 months), 9th (10.99 months), and 14th (10.52 months); ticagrelor 4th (11.28 months), 5th (11.15 months), 6th (11.13 months), 7th (11.10 months), and 11th (10.98 months); clopidogrel 2nd (11.36 months), 10th (10.99 months), 12th (10.95 months), 13th (10.86), 15th (10.52 months), and 16th (10.15 months).

The clear message arising from these results is that the 16 cohorts have a nearly identical effectiveness; e.g., the greatest difference across these 16 cohorts is between prasugrel of Schupke’s trial (ranking first with 11.39 months) and clopidogrel of Wang’s trial (ranking last with 10.15 months); this difference is of only 1.2 months.

Although this re-analysis consists of indirect comparisons managed narratively and has lost its linkage with randomization, the overall picture emerging from these RMSTs is a strong message of equivalent effectiveness across clopidogrel, prasugrel, and ticagrelor. In fact, although some pairwise comparisons reached statistical significance, the criterion of clinical relevance guides the interpretation of these results because all pairwise differences are small.

In conclusion, the message based on the HR focused on differences is reinterpreted as a message of equivalent effectiveness based on the RMST.

References

From 12 Randomized Trials. *Circulation* 2020;142(2):150-160. doi:10.1161/CIRCULATIONAHA.120.046786

2. Messori A. Eight major international journals have recently published a paper to highlight the methodological advantages of the restricted mean survival time, *Open Science Framework* [https://osf.io/3gi96/](https://osf.io/3gi96/) published 13 July 2020, doi:10.17605/OSF.IO/DY3UH

