



Letter to the Editor

Letter to the Editor Regarding “Ticagrelor for Asian Patients With Acute Coronary Syndrome in Real-World Practice: A Systematic Review and Meta-analysis of Observational Studies.” The Benefit of Using Person-Year When the Follow-up Period Varies in a Meta-analysis



Sir,

We read with great interest a meta-analysis published in the *Indian Heart Journal* “Ticagrelor for Asian patients with acute coronary syndrome in real-world practice: a systematic review and meta-analysis of observational studies”.¹ We would like to congratulate the authors for their study on the effectiveness of ticagrelor vs clopidogrel in patients with acute myocardial infarction, by considering the data from published observational studies. The study has definitely provided us with better evidence in this field. However, we had the following observations to make:

1. Of the six studies included by the authors in the meta-analysis, each study had a different follow-up period. Also, there is a variation in the follow-up period for different cohorts (ticagrelor vs clopidogrel) within the study. An example for this discrepancy is a study by Lee et al included in the meta-analysis,² in which clopidogrel cohort was recruited and followed up from 2012 to 2014, while the ticagrelor cohort was recruited and followed up from 2013 to 2014. This implies that the first patient recruited in the clopidogrel cohort was followed up for three years unless he had an event of interest, and the first recruit of the ticagrelor cohort was followed up for a total period of two years. By logic, incidence rate of events increases with increase in the duration of follow-up. To avoid such discrepancies, a better method is to use patient-year in the denominator, which is

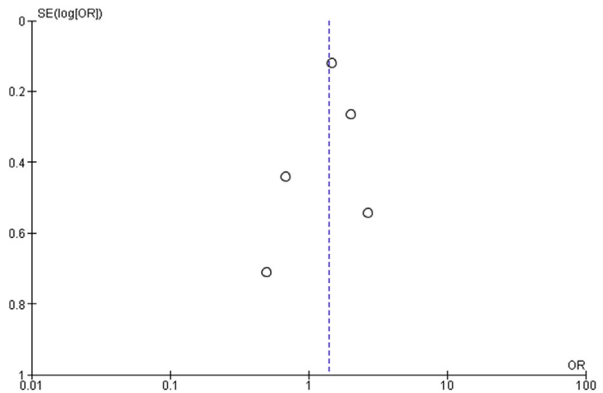


Fig. 2. Funnel plot (major bleeding).

calculated by multiplying the number of cohort recruits with the year of follow-up.³ The pooled odds ratio (OR) of major bleeding for ticagrelor vs clopidogrel considering patient-year in the denominator is 1.40 (95% confidence interval [CI]: 0.92–2.13, $I^2 = 51%$, $p = 0.11$) (Fig. 1) as compared with the OR for major bleeding reported by authors of meta-analysis (OR = 1.11 [95% CI: 0.62–2.00, $I^2 = 75%$, $p = 0.73$].

Study or Subgroup	Ticagrelor		Clopidogrel		Weight	Odds Ratio IV, Random, 95% CI
	Events	Total	Events	Total		
Chen 2016	10	101	14	101	15.4%	0.68 [0.29, 1.62]
Lee 2018	76	2765	779	40919	39.0%	1.46 [1.15, 1.85]
Sim	44	1553	22	1553	26.6%	2.03 [1.21, 3.40]
Wang 2018	8	779	6	1558	11.5%	2.68 [0.93, 7.76]
Xin	5	73	4	31	7.5%	0.50 [0.12, 1.99]
Total (95% CI)		5271		44162	100.0%	1.40 [0.92, 2.13]
Total events	143		825			
Heterogeneity: $\tau^2 = 0.10$; $\chi^2 = 8.12$, $df = 4$ ($P = 0.09$); $I^2 = 51%$						
Test for overall effect: $Z = 1.58$ ($P = 0.11$)						

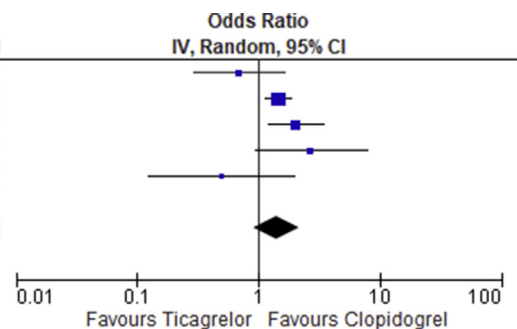


Fig. 1. Pooled odds ratio and 95% confidence intervals (CIs) for major bleeding (total cohort population expressed as person-year) using a random-effects model by the method of inverse variance and heterogeneity assessed with the I^2 measure.

2. Though as a rule of thumb, test for publication bias is to be performed when the number of included studies is more than ten as the power of tests otherwise is too low to distinguish chance from real asymmetry, inclusion of funnel plot in the meta-analysis would help the reader in assessing for any publication or other biases with respect to each outcome.⁴ (Fig. 2)

Source(s) of support

Nil.

Presentation at a meeting

Nil.

Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ihj.2019.04.004>.

References

1. Akhmetzhan Maratovich Galimzhanov, Baurzhan Slymovich Azizov. Ticagrelor for Asian patients with acute coronary syndrome in real-world practice: a systematic review and meta-analysis of observational studies. *Indian Heart J.* 2019;71(1):15–24. <https://doi.org/10.1016/j.ihj.2019.01.003>.
2. Lee C, Cheng C, Yang YK, et al. Cardiovascular and bleeding risks in acute myocardial infarction newly treated with ticagrelor vs. Clopidogrel in Taiwan. *Circ J.* 2018;82:747–775.
3. Guevara JP, Berlin JA, Wolf FM. Meta-analytic methods for pooling rates when follow-up duration varies: a case study. *BMC Med Res Methodol.* 2004;4:17. <https://doi.org/10.1186/1471-2288-4-17>. Published 2004 Jul 12.
4. Sterne Jonathan AC, Sutton Alex J, Ioannidis John PA, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ.* 2011;343:d4002.

Ashish Kumar U*, Mariam Shariff
Department of Critical Care Medicine, St. John's Medical College
Hospital, Bangalore, Karnataka, 560034, India

* Corresponding author. Department of Critical Care Medicine, St. John's Medical College Hospital Bangalore 560034, Karnataka, 560034, India.

E-mail addresses: ashirvadmangalore@gmail.com (A. Kumar U),
Mariam.shariff@gmail.com (M. Shariff).

1 March 2019

Available online 19 April 2019