Cardiovascular Drugs and Therapy
https://doi.org/10.1007/s10557-020-06955-5

LETTER TO THE EDITOR

A Reconciliation Attempt of the Acute Coronary Syndrome Clinical Trials on Clopidogrel, Prasugrel, and Ticagrelor

Wim J. R. Rietdijk[1] · Loes Mandigers[1] · Corstiaan A. den Uil[1]

Dear Editor,

Recently, Schüpke and colleagues performed an investigator-initiated head-to-head trial on prasugrel versus ticagrelor in acute coronary syndrome [1]. We highly commend the authors for performing such study. Certainly, given the earlier trials comparing prasugrel and ticagrelor to clopidogrel [2, 3], which influenced many national guidelines, these trials [2, 3] demonstrated absolute risk reductions of 2% for both ticagrelor and prasugrel versus clopidogrel. It was now shown that prasugrel led to lower primary endpoint (i.e., 12- and 15-month mortality) than ticagrelor. As a thought experiment, we wondered whether the results of the three trials could be reconciled to make a practice recommendation. For this reason, in this letter, we present a reflection of our journey in achieving this purpose.

Sample Size and Power Issue

As a start, we noted that the sample size calculation in Schüpke et al. [1] may be biased and not based on existing literature. The primary endpoint in the prasugrel arm in Wiviott et al. [2] occurred less frequently (~ 9.3%) than assumed by the authors in their power calculation (12.9%), suggesting that the sample size may be too small to effectively estimate a difference. Though, one could have based this assumption on the previous trials, rather than guessing 12.9%. Due to this reason, the study may suffer from a power issue.

Pooling the Data

The power issue gave rise to our direction to attempt to reconcile the three trials by pooling the data. In order to do so, we requested the individual patient data for the respective corresponding authors [2, 3], but unfortunately, this was unavailable for physicians. Therefore, we had to work with the published data in the respective studies. Qualitative inspection of the baseline tables showed that the samples were more or less comparable (see Supplementary Material Table A). This allowed us to pool the data and estimate the odds ratios (OR) and 95% confidence intervals (95% CI). Taken together, the fact that we did not have any information on censoring and the power calculations were done based on chi-square test, we opted for calculating ORs rather than summarizing the hazard ratios.

Interestingly, the pooled estimate of the prevalence of the primary endpoint was not significantly different for prasugrel (9%) and ticagrelor groups (10%, OR = 1.05, 95% CI 0.95–1.16; Table 1), while we can conclude that clopidogrel is inferior to both prasugrel and ticagrelor ($p < 0.05$).

Of course, such pooling comes with limitations. The primary endpoint differed slightly between the trials (1) definitions of events (Schüpke et al. [1]: death from cardiovascular cause, nonfatal myocardial infarction (MI), or nonfatal stroke; Wiviott et al. [2]: death from cardiovascular cause, MI, or stroke; Wallentin et al. [3]: death from vascular cause, MI, or stroke) and (2) the follow-up duration (Wiviott et al. [2]: 15 months and reporting a slightly lower event rate at 12 months; versus 12 months in the other two trials). Though, one may expect with the constant hazard ratio assumption that the proportions are similar at the 1-year mortality cutoff. (3) A major difference

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10557-020-06955-5) contains supplementary material, which is available to authorized users.

✉ Wim J. R. Rietdijk
w.rietdijk@erasmusmc.nl

[1] Department of Intensive Care Medicine, Erasmus MC University Medical Center, Rotterdam, the Netherlands

Published online: 25 March 2020

Table 1 Raw data from each trial separately and the odds ratios based on pooled data

Individual mortality data	Study	Treatment versus control	Treatment		Control		
			Primary endpoint (−)	Primary endpoint (+)	Primary endpoint (−)	Primary endpoint (+)	
	Wiviott et al. (2007)	Prasugrel versus clopidogrel	6170	643	6014	781	
	Wallentin et al. (2009)	Ticagrelor versus clopidogrel	8469	864	8277	1014	
	Schüpke et al. (2019)	Ticagrelor versus prasugrel	1828	184	1869	137	
Pooled estimates			Prasugrel		Clopidogrel		
			Primary endpoint (−)	Primary endpoint (+)	Primary endpoint (−)	Primary endpoint (+)	OR (95% CI)
		Patients	8039	780	14,291	1795	1.29 (1.21–1.38)*
		Mortality rate		9%		11%	
			Clopidogrel		Ticagrelor		
			Primary endpoint (−)	Primary endpoint (+)	Primary endpoint (−)	Primary endpoint (+)	OR (95% CI)
		Patients	14,291	1795	10,297	1048	0.81 (0.75–0.88)*
		Mortality rate		11%		10%	
			Prasugrel		Ticagrelor		
			Primary endpoint (−)	Primary endpoint (+)	Primary endpoint (−)	Primary endpoint (+)	OR (95% CI)
		Patients	8039	780	10,297	1048	1.05 (0.95–1.16)
		Mortality rate		9%		10%	

*Statistically significant at 5% alpha level

between the three trials was the prevalence of STEMI, which varied between 20 and 40%. This may have influenced the results, but unfortunately, we were unable to control for this factor.

To conclude, given the power issue in the Schüpke et al. trial [1], it leads us to pool the primary outcomes for clopidogrel, prasugrel, and ticagrelor. Based on these analyses, we conclude that clopidogrel is inferior to prasugrel and ticagrelor, but the latter two have similar outcomes. Future research, e.g., by means of re-analyzing the existing data, is needed to define sub-groups of acute coronary syndrome and test whether prasugrel (a thienopyridine) or ticagrelor (a cyclo-pentyltriazolo-pyrimidine) is the best treatment option for which of these groups.

References

1. Schüpke S, Neumann F-J, Menichelli M, Mayer K, Bernlochner I, Wöhrle J, et al. Ticagrelor or prasugrel in patients with acute coronary syndromes. N Engl J Med. 2019;381:1524–34.
2. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007;357:2001–15.
3. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361:1045–57.