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Agreement between adjusted indirect comparison and simplified network meta-analyses on prasugrel and ticagrelor (Reply to Passaro et al. — Int J Cardiol 2011) ☆

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We thank Passaro and colleagues for their interesting simplified network meta-analysis, [1] stemming from our recent adjusted indirect comparison meta-analysis comparing prasugrel versus ticagrelor in patients with acute coronary syndromes [2].

Indeed, network meta-analyses (i.e. mixed treatment comparisons) and adjusted indirect comparison meta-analysis are very closely related, as the latter may be considered a simplified network meta-analysis with a star shape [3]. Thus, the fact that Passaro et al. largely confirm the direction and magnitude of effect of our own analysis, thus supporting its precision, accuracy, and validity, comes a no major surprise, but rather testifies the consistency of these innovative statistical approaches (Table 1) [4]. We have already endeavored in this type of research study design in the past, focusing on first generation drug-eluting stents, [5,6] second generation drug-eluting stents, [7] mechanical coronary recanalization after failed thrombolysis, [8] and antithrombotic agents for atrial fibrillation, [9] and so far none of our findings have been disproved by later trials or analyses.

The discrepancy reported by Passero et al. in comparison to our findings on the safety end-point of major bleeding (odds ratio 0.70 [95% confidence interval 0.54–0.91] in our work versus risk ratio 0.72 [0.50–1.04] in Passero et al.) might depend more on the definitions used than on the statistical method. Indeed, we employed the stringent albeit insensitive Thrombolysis in Myocardial Infarction

☆ Conflicts of interest: Dr. Biondi-Zoccai has lectured for Astra Zeneca, Bristol Myers Squibb, Sanofi-Aventis; he has consulted for Astra Zeneca and Eli Lilly.

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Table 1
Comparison of statistical results from Biondi-Zoccai et al.'s adjusted indirect comparison meta-analysis [2] and Passero et al.'s network meta-analysis [1], both comparing prasugrel and ticagrelor in patients with acute coronary syndromes.*

End-point	Biondi-Zoccai et al.'s adjusted indirect comparison meta-analysis [2]	Passero et al.'s simplified network meta-analysis [1]
Death, myocardial infarction or stroke	OR = 1.02 (0.88–1.16)	RR = 1.04 (0.90–1.19)†
Death	OR = 0.83 (0.65–1.05)	RR = 0.82 (0.65–1.04)
Myocardial infarction	OR = 1.12 (0.94–1.33)	NA
Stroke	OR = 1.18 (0.75–1.81)	NA
Stent thrombosis	OR = 1.59 (1.08–2.32)	NA
Major bleeding	OR = 0.70 (0.54–0.91)	RR = 0.72 (0.50–1.04)
Major non-CABG-related bleeding	OR = 0.95 (0.69–1.32)	NA
Major CABG bleeding	OR = 0.23 (0.09–0.58)	NA
Major or minor bleeding	OR = 0.79 (0.65–0.96)	NA
Minor bleeding	OR = 0.93 (0.69–1.27)	NA
Drug discontinuation	OR = 0.98 (0.84–1.13)	NA

*Reported with 95% confidence intervals, with values < 1.0 favoring ticagrelor, and > 1.0 favoring prasugrel; †death from cardiovascular causes; CABG = coronary artery bypass grafting; NA = not available; OR = odds ratio; RR = risk ratio.

(TIMI) definition, and also distinguished coronary artery bypass grafting (CABG)-related major bleeding from non-CABG-related major bleeding [2]. Conversely, they did not specify which definition was chosen for their analysis, and moreover it is unclear whether they distinguished CABG-related from non-CABG-related major bleeding [1]. Thus, we cannot definitively address the purported discrepancy between their findings and our own for major bleeding.

They also appear to have overlooked other key end-points, including stent thrombosis, which remains in our opinion of utmost importance, and which appeared significantly less likely with prasugrel than with ticagrelor (odds ratio 0.63 [0.43–0.93], p=0.020 in our work) [2]. In addition, we could not find details on the statistical methods used to build their analytical network nor the statistical package employed for computations. We guess they used Bayesian methods with non-informative priors and the WinBUGS package, [10] whereas we used fixed-effect frequentist methods and a freeware package developed by the Meta-analysis and Evidence based medicine Training in Cardiology (METCARDIO) group [11]. The aforementioned differences, as well as the simple impact of multiple testing and the use of risk ratios versus odds ratios might easily explain apparent discrepancies between the analyses.

In conclusion, we remain positive that advanced statistical approaches, including adjusted indirect comparison meta-analyses and mixed treatment comparisons, will play an ever increasing role in shaping clinical research and practice. Thus, this scholarly debate on our recent adjusted indirect comparison meta-analysis comparing prasugrel and ticagrelor in acute coronary syndromes is more than welcome and stands as further proof of the need for external repetition and validation of any research endeavor.

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing inthe International Journal of Cardiology (Shewan and Coats 2010;144:1–2).

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