- [4] Huikuri HV, Kervinen K, Niemelä M, et al. Effects of intracoronary injection of mononuclear bone marrow cells on left ventricular function, arrhythmia risk profile, and restenosis after thrombolytic therapy of acute myocardial infarction. *Eur Heart J* 2008;29:2723–32.
- [5] Janssens S, Dubois C, Bogaert J, et al. Autologous bone marrow-derived stem-cell transfer in patients with ST-segment elevation myocardial infarction: double-blind, randomised controlled trial. *Lancet* 2006;367:113–21.
- [6] Li ZQ, Zhang M, Jing YZ, et al. The clinical study of autologous peripheral blood stem cell transplantation by intracoronary infusion in patients with acute myocardial infarction (AMI). *Int J Cardiol* 2007;115:52–6.
- [7] Kang HJ, Lee HY, Na SH, et al. Differential effect of intracoronary infusion of mobilized peripheral blood stem cells by granulocyte colony-stimulating factor on left ventricular function and remodeling in patients with acute myocardial infarction versus old myocardial infarction: the MAGIC Cell-3-DES randomized, controlled trial. *Circulation* 2006;114(1 Suppl):145–51.
- [8] Meluzin J, Mayer J, Groch L, et al. Autologous transplantation of mononuclear bone marrow cells in patients with acute myocardial infarction: the effect of the dose of transplanted cells on myocardial function. *Am Heart J* 2006;152:975.e9–15.
- [9] Schächinger V, Assmus B, Erbs S, et al. Intracoronary infusion of bone marrow-derived mononuclear cells abrogates adverse left ventricular remodelling post-acute myocardial infarction: insights from the reinfusion of enriched progenitor cells and infarct remodelling in acute myocardial infarction (REPAIR-AMI) trial. *Eur J Heart Fail* 2009;11:973–9.
- [10] Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). In: Higgins JP, Green S, editors. *The Cochrane Collaboration*; 2011. Available from www.cochrane-handbook.org
- [11] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
- [12] Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000;56:455–63.
- [13] Beitsnes JO, Gjesdal O, Lunde K, et al. Left ventricular systolic and diastolic function improve after acute myocardial infarction treated with acute percutaneous coronary intervention, but are not influenced by intracoronary injection of autologous mononuclear bone marrow cells: a 3 year serial echocardiographic sub-study of the randomized-controlled ASTAMI study. *Eur J Echocardiogr* 2011;12:98–106.
- [14] Piepoli MF, Vallisa D, Arbasi M, et al. Bone marrow cell transplantation improves cardiac, autonomic, and functional indexes in acute anterior myocardial infarction patients (Cardiac study). *Eur J Heart Fail* 2010;12:172–80.
- [15] Castellani M, Colombo A, Giordano R, et al. The role of PET with ¹³N-ammonia and ¹⁸F-FDG in the assessment of myocardial perfusion and metabolism in patients with recent AMI and intracoronary stem cell injection. *J Nucl Med* 2010;51:1908–16.
- [16] Grajek S, Popiel M, Gil L, et al. Influence of bone marrow stem cells on left ventricle perfusion and ejection fraction in patients with acute myocardial infarction of anterior wall: randomized clinical trial: Impact of bone marrow stem cell intracoronary infusion on improvement of microcirculation. *Eur Heart J* 2010;31:691–702.
- [17] Nogueira FB, Silva SA, Haddad AF, et al. Systolic function of patients with myocardial infarction undergoing autologous bone marrow transplantation. *Arq Bras Cardiol* 2009;93(374–9):367–72.
- [18] Plewka M, Krzemińska-Pakuła M, Lipiec P, et al. Effect of intracoronary injection of mononuclear bone marrow stem cells on left ventricular function in patients with acute myocardial infarction. *Am J Cardiol* 2009;104:1336–42.
- [19] Wöhrle J, Merkle N, Mailänder V, et al. Results of intracoronary stem cell therapy after acute myocardial infarction. *Am J Cardiol* 2010;105:804–12.
- [20] Traverse JH, McKenna DH, Harvey K, et al. Results of a phase 1, randomized, double-blind, placebo-controlled trial of bone marrow mononuclear stem cell administration in patients following ST-elevation myocardial infarction. *Am Heart J* 2010;160:428–34.

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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 as 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 Passaro 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 Passaro 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

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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 in the International Journal of Cardiology (Shewan and Coats 2010;144:1–2).

References

- [1] Passaro D, Fadda G, Maratea D, Messori A. Anti-platelet treatments in acute coronary syndrome: simplified network meta-analysis. *Int J Cardiol* 2011;150:364–7.
- [2] Biondi-Zoccai G, Lotrionte M, Agostoni P, et al. Adjusted indirect comparison meta-analysis of prasugrel versus ticagrelor for patients with acute coronary syndromes. *Int J Cardiol* 2011;150:325–31.
- [3] Salanti G, Kavvoura FK, Ioannidis JP. Exploring the geometry of treatment networks. *Ann Intern Med* 2008;148:544–53.
- [4] Biondi-Zoccai G, Landoni G, Modena MG. A journey into clinical evidence: from case reports to mixed treatment comparisons. *HSR Proc Intensive Care Cardiovascular Anesth* 2011;3:93–6.
- [5] Biondi-Zoccai GG, Agostoni P, Abbate A, et al. Adjusted indirect comparison of intracoronary drug-eluting stents: evidence from a metaanalysis of randomized bare-metal-stent-controlled trials. *Int J Cardiol* 2005;100:119–23.
- [6] Biondi-Zoccai GG, Lotrionte M, Abbate A, et al. Direct and indirect comparison meta-analysis demonstrates the superiority of sirolimus- versus paclitaxel-eluting stents across 5854 patients. *Int J Cardiol* 2007;114:104–5.
- [7] Biondi-Zoccai G, Lotrionte M, Moretti C, et al. Percutaneous coronary intervention with everolimus-eluting stents (Xience V): systematic review and direct-indirect comparison meta-analyses with paclitaxel-eluting stents (Taxus) and sirolimus-eluting stents (Cypher). *Minerva Cardioangiol* 2008;56:55–65.
- [8] Testa L, van Gaal WJ, Biondi-Zoccai GG, et al. Repeat thrombolysis or conservative therapy vs. rescue percutaneous coronary intervention for failed thrombolysis: systematic review and meta-analysis. *QJM* 2008;101:387–95.
- [9] Testa L, Zoccai GB, Porto I, et al. Adjusted indirect meta-analysis of aspirin plus warfarin at international normalized ratios 2 to 3 versus aspirin plus clopidogrel after acute coronary syndromes. *Am J Cardiol* 2007;99:1637–42.
- [10] Fryback DG, Stout NK, Rosenberg MA. An elementary introduction to Bayesian computing using WinBUGS. *Int J Technol Assess Health Care* 2001;17:98–113.
- [11] Meta-analysis and evidence based medicine Training in Cardiology (METCARDIO) indirect meta-analysis tool (ITC). Available from <http://www.metcardio.org/macros/IMT.xls> last accessed on 21 May 2011.