European Journal of Cardio-Thoracic Surgery 52 (2017) 454–455
doi:10.1093/ejcts/ezx224 Advance Access publication 10 July 2017

EDITORIAL COMMENT

Cite this article as: Piccolo R, Windecker S, Kolh P. Geographical differences in the ratio of percutaneous and surgical myocardial revascularization procedures in the treatment of coronary artery disease. Eur J Cardiothorac Surg 2017;52:454–5.

Geographical differences in the ratio of percutaneous and surgical myocardial revascularization procedures in the treatment of coronary artery disease

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Keywords: Coronary artery bypass grafting • Coronary artery disease • Myocardial revascularization • Percutaneous coronary intervention • Practice • SYNTAX trial

Myocardial revascularization by means of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) constitutes the standard of care for patients with symptomatic coronary artery disease [1]. To date, despite a large number of trials comparing the 2 revascularization techniques across different anatomic and clinical settings, the effect of geographical variations on the treatment effect of PCI versus CABG has been left largely unexplored. In the field of cardiovascular medicine, several examples already demonstrate the importance of regional variation on the effect size of a given treatment. In the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial, spironolactone compared with placebo failed to reduce the primary composite end-point of cardiovascular death, hospitalization for heart failure or resuscitated cardiac arrest among 3455 patients with preserved heart failure [2]. Subgroup comparisons for the primary end-point revealed that spironolactone was associated with a significant 18% relative risk reduction among patients enrolled in the Americas (USA, Canada, Brazil and Argentina) but manifested a non-significant harmful effect among those recruited in the Eastern Europe (Russia and Georgia) [2]. It was not until very recently that the question of a true geographic difference in the TOPCAT trial lingered on [3], when further analysis of the trial showed that serum concentrations of canrenone, an active metabolite of spironolactone, were undetectable in a greater proportion of patients recruited in Russia compared with those included in the USA and Canada (30% vs 3%, respectively, $P < 0.001$) [4]. In addition to important concerns about the study conduct at some sites, this example illustrates to which extent regional variations are able to affect the overall results of a trial.

In this issue of the journal, Milojevic *et al.* [5] explored regional variations in the Synergy Between PCI With TAXUS and Cardiac Surgery (SYNTAX) trial, a landmark study that randomly assigned a total of 1800 patients with left main and/or multivessel coronary artery disease to either PCI or CABG. By stratifying the trial population in 8 groups, 7 corresponding to each country that recruited at least 80 patients (USA, UK, Italy, Germany, France, Netherlands, Belgium and Hungary) and 1 group representing all remaining countries, the authors analysed baseline characteristics, interventional features, medication prescription patterns and, most importantly, the treatment effect of randomly assigned treatment interventions throughout 5 years follow-up.

In terms of baseline and procedural characteristics, several differences between groups emerged with the greatest source of variation affecting the number of implanted stents, total stent length for PCI and the use of off-pump surgery and arterial revascularization for CABG. Antithrombotic therapy at discharge was similar among patients allocated to PCI, while oral anticoagulant therapy was preferred over antiplatelet therapy among patients undergoing CABG in the Netherlands and Germany. For the primary end-point, a composite of all-cause death, myocardial infarction, stroke or repeat revascularization, the treatment effect of PCI versus CABG substantially varied across countries, with the lowest hazard ratio (HR) in France [HR 0.79, 95% confidence intervals (CI) 0.48–1.28] and the highest in Hungary (HR 4.63, 95% CI 1.63–11.40). A similar variation was observed for the composite of all-cause death, myocardial infarction or stroke, with the largest differential treatment effect between PCI and CABG observed in France (HR 0.69, 95% CI 0.35–1.36) and Hungary (HR 3.32, 95% CI 0.70–15.63), respectively. Similarly, the risk of revascularization associated with PCI compared with CABG was lowest in France (HR 0.97, 95% CI 0.52–1.82) and highest in Hungary (HR 3.72, 95% CI 1.39–9.96).

How should we interpret the reported regional differences in the SYNTAX trial? There are several considerations that guide us to distinguish facts from fiction in the variation of the treatment

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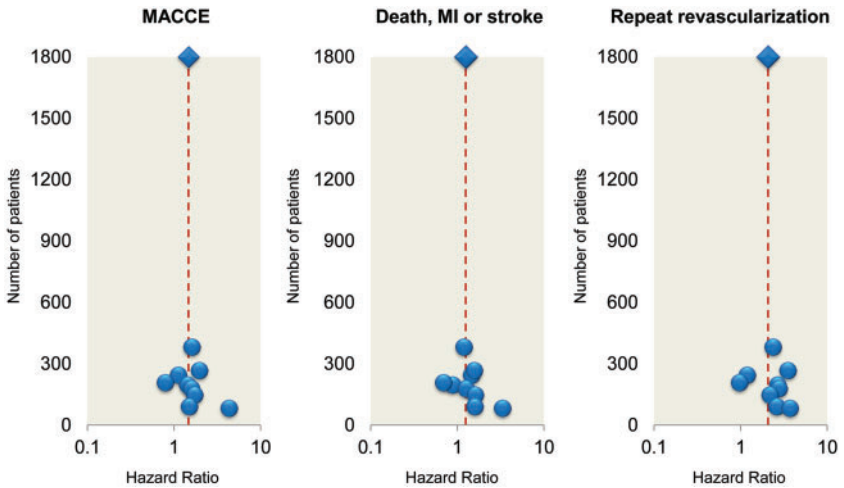

Figure 1: Regional variation in the Synergy Between PCI With TAXUS and Cardiac Surgery trial. Country-level hazard ratios are plotted against the number of participants included in each subgroup. Circles represent country-level hazard ratios. Diamonds represent study-level hazard ratio for all participants ($n = 1800$). MACCE: major adverse cardiovascular and cerebrovascular event; MI: myocardial infarction.

effect between PCI and CABG across various countries. The first information can be derived from a statistical test of heterogeneity, which, e.g. can be calculated by pooling the country-level HRs including 95% CI in a fixed-effect meta-analysis. Noteworthy, there was no evidence of significant heterogeneity for the primary endpoint ($P_{het} = 0.074$) as well as for the composite of death, myocardial infarction or stroke ($P_{het} = 0.51$) and repeat revascularization ($P_{het} = 0.071$). However, this test is usually limited by a low statistical power as occurred, e.g. in the case of the TOPCAT trial ($P_{het} = 0.11$). Second, visual inspection of risk estimates in a forest plot, as the authors did, provides ancillary information to the statistical test for heterogeneity by showing the extent of overlapping CIs across countries. In the SYNTAX trial, 95% CIs broadly overlapped for the composite of death, myocardial infarction or stroke as well as for repeat revascularization but not for the primary endpoint. Third, the distribution of the event rates across countries is a useful measure to understand the patient's risk profile as well as a possible under-detection of adverse events. For instance, while the rate of repeat revascularization in patients undergoing CABG was similar between countries, it was excessively high among patients undergoing PCI in Hungary (44.9%) compared with other countries (from 20.3% to 32.4%). This may be explained at least in part by the fact that, in Hungary, PCI was on average carried out with a large number of stents (mean 6), resulting in very long stented segments (mean 124 mm). Fourth, it is worth considering the effect size of the randomized treatment in relation to the number of patients included in each country (Fig. 1). As one would expect, the variation around the overall risk estimate was more pronounced for countries that included a lower number of patients and the pattern of a larger variation in results among small subgroups has been observed in other trials [6].

Collectively, these considerations allow us to conclude that the treatment effect of PCI versus CABG, particularly for the more prognostically relevant end-point of death, myocardial infarction or stroke, was consistent across countries that participated in the SYNTAX trial, despite substantial differences in baseline, angiographic and interventional features between various geographies. It is important for future trials to prespecify how regional variation will be explored prospectively, how different regions will be pooled and the degree of geographical variation, if any, to be expected.

Conflict of interest: Raffaele Piccolo received a research grant from the Veronesi Foundation. Stephan Windecker has received research grants to the institution from Abbott, Biotronik, Boston Scientific, Biosensors, Medtronic, Edwards and St Jude.

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