**Geographic Disparity in 10-Year Mortality After Coronary Artery Revascularization in the SYNTAXES Trial**

**Short title:** Regional difference in 10-year mortality in SYNTAXES trial

Shigetaka Kageyama, MD1,\* Patrick W. Serruys, MD, PhD1,2,\* Scot Garg, MD, PhD3, Kai Ninomiya, MD1, Shinichiro Masuda, MD1, Nozomi Kotoku, MD, PhD1, Antonio Colombo, MD4, Michael J. Mack, MD, PhD5, Adrian P. Banning, MD6, Marie-Claude Morice, MD7, Adam Witkowski, MD, PhD8, Nick Curzen, BM(Hons), PhD9, Francesco Burzotta, MD, PhD10, Stefan James, MD, PhD11, Robert-Jan van Geuns, MD, PhD12, Piroze M. Davierwala, MD13,14, David R Holmes Jr, MD15, David A Wood MD2,16, John William McEvoy,MB BCh MHS1,16, Yoshinobu Onuma, MD, PhD1, for the SYNTAX Extended Survival Investigators

\*Equally contributed to the writing of the manuscript, PWS vouched for the accuracy of the data

**Affiliations:**

1. Department of Cardiology, National University of Ireland, Galway (NUIG), Galway, Ireland

2. National Heart and Lung Institute, Imperial College London, London, UK.

3. Department of Cardiology, Royal Blackburn Hospital, Blackburn, United Kingdom.

4. Department of Biomedical Sciences, Humanitas University, Pieve Emanuele-Milan, Italy

-Humanitas Clinical and Research Center IRCCS, Rozzano-Milan, Italy

5. Department of Cardiothoracic Surgery, Baylor University Medical Center, Dallas, TX, USA

6. Department of Cardiology, John Radcliffe Hospital, Oxford University Hospitals, Oxford, UK.

7. Département of Cardiologie, Hôpital privé Jacques Cartier, Générale de Santé Massy, France

8. Department of Interventional Cardiology and Angiology, National Institute of Cardiology, Warsaw, Poland

9. Faculty of Medicine, University of Southampton, Southampton, & Cardiothoracic Unit, University Hospital Southampton NHS Trust, Southampton, UK.

10. Institute of Cardiology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy

11. Department of Medical Sciences, Uppsala University, Sweden.

12. Department of Cardiology, Radboud University Medical Centre, Nijmegen, the Netherlands

13. Department of Surgery, University of Toronto, Toronto, Canada

Division of Cardiovascular Surgery, Peter Munk Cardiac Centre, Toronto General Hospital, Canada

14. University Health Network, Toronto, Ontario, Canada

15. Department of Cardiovascular Diseases and Internal Medicine, Mayo Clinic, Rochester, MN, USA

16. National Institute of Prevention and Cardiovascular Health, National University of Ireland, Galway, Ireland.

**\*Corresponding author** Patrick W. Serruys, MD, PhD, FESC, FACC

Established Professor of Interventional Medicine and Innovation at the National University of Ireland, Galway (NUIG) and Senior Consultant of the Cardiovascular Research Centre for Advanced Imaging and Core Lab (CORRIB) Research Centre, Investigator of the Science Foundation of Ireland (SFI).

University Road, Galway, H91 TK33, Ireland.

Tel: +353 91 524411

E-mail: [patrick.serruys@nuigalway.ie](mailto:patrick.serruys@nuigalway.ie)

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**Abstract**

Aims: To investigate geographic disparity in long-term mortality following revascularization in patients with complex coronary artery disease (CAD).

Methods and results: The SYNTAXES trial randomized 1800 patients with three-vessel and/or left main CAD to percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) and assessed their survival at 10 years. Patients were stratified according to the region of recruitment: North America (N-A, n=245), Eastern Europe (E-E, n=189), Northern Europe (N-E, n=425), Southern Europe (S-E, n=263), and Western Europe (W-E, n=678), which also served as the reference group. Compared to W-E, patients were younger in E-E (62 vs 65 years, p<0.001), and less frequently male in N-A (65.3% vs 79.6%, p<0.001). Diabetes (16.0% vs 25.4%, p<0.001) and peripheral vascular disease (6.8% vs 10.9%, p=0.025) were less frequent in N-E than W-E. Ejection fraction was highest in W-E (62% vs 56%, p<0.001). Compared to W-E, the mean anatomic SYNTAX score was higher in S-E (29 vs 31, p=0.008) and lower in N-A (26, p<0.001). Crude ten-year mortality was similar in N-A (31.6%), and W-E (30.7%), and significantly lower in E-E (22.5%, p=0.041), N-E (21.9%, p=0.003) and S-E (22.0%, p=0.014). Compared to W-E, adjusted mortality in N-E (HR 0.85, p=0.019) and S-E (HR 0.72, p=0.043) remain significantly lower after adjustment for pre- and peri-procedural factors, but no significant interaction (Pinteraction=0.728) between region and modality of revascularization was seen.

Conclusion: In the era of globalization, knowledge, and understanding of geographic disparity are of paramount importance for the correct interpretation of global studies.

Keywords: geographic disparity, revascularization, complex coronary artery disease, ten-year mortality

**Introduction**

Cardiovascular disease (CVD) is the leading cause of death worldwide. According to the latest report from the World Health Organization (WHO), an estimated 17.9 million people died from CVD in 2019, representing 32% of all global deaths.1 Regional variation in morbidity and cardiovascular mortality exists, and this has been attributed to factors such as household income, medical insurance, provision and availability of healthcare services and medical equipment, density of doctors and hospitals, and other less well-identified factors such as diet and regional epigenetics.2 Notably, the individual preference of patients and healthcare professionals regarding the modality of coronary revascularization, and the availability and costs of percutaneous and surgical treatments, are also heterogeneous between countries.3 Previous studies show that patient characteristics and clinical patterns differ significantly between countries, impacting 5-year health care outcomes,4-6 with geographic variation also seen in the rate of atheroma progression and cardiac events.7

The SYNTAXES trial was an extended 10-year survival status follow-up of 1800 patients with de novo three-vessel disease (3VD) and/or left main (LM) coronary artery disease (CAD) who were originally randomized in the SYNTAX trial.8 The overall main result of the SYNTAXES trial showed no significant difference in all-cause death between percutaneous coronary intervention (PCI) using first-generation paclitaxel-eluting stents and coronary artery bypass grafting (CABG) at 10 years, however, CABG provided a significant survival benefit in patients with 3VD, but not in patients with LMCAD.

Regional differences in long-term outcomes after PCI with drug-eluting stents (DES) and/or CABG for complex CAD have not been fully elucidated, especially beyond 5 years.9,10 The aims of the present study are, therefore (i) to describe the regional differences in all-cause death at 10 years; (ii) to assess the interaction between treatment effect (PCI vs CABG) and region.

**Methods**

**Study design**

The design and the primary results of the SYNTAX study (NCT00114972) have been reported previously.11–13 Briefly, all-comer patients with de novo 3VD and/or left main CAD were enrolled and randomized to either CABG (n=897) or PCI (n=903) with the paclitaxel DES (TAXUS, Boston Scientific, Marlborough, MA, USA). The SYNTAX trial completed patient follow-up at 5 years.13 The SYNTAXES study (NCT03417050) was an investigator-driven investigation that extended follow-up and aimed to evaluate vital status at up to 10 years.11 The German Heart Research Foundation (GHF, Frankfurt am Main, Germany) funded the extended follow-up, which was performed under the local regulations of each participating center and complied with the declaration of Helsinki.

The current analysis is a sub-study of the SYNTAXES trial that examines the impact of geographic differences in all-cause death at 10 years in the United States of America (USA) and Europe divided into four regions according to the United Nations geoscheme14: Eastern-Europe-(E-E: Poland, Hungary, Czech), Northern-Europe (N-E: United Kingdom, Sweden, Norway, Latvia, Finland, and Denmark), Southern-Europe (S-E: Spain, Portugal, and Italy), and Western-Europe (W-E: Netherlands, Germany, France, Belgium, and Austria), and additionally subdivided into individual countries.

The 10-year mortality of each region was analysed with and without adjustment for baseline and procedural characteristics. In addition, the difference in post-procedural medication after 5 years is reported for the different geographic regions, but is not part of the adjustment, considering the limited collection of these data up to five years. We focused on optimal medical therapy (OMT) defined by a combination of 4 components as we previously published; antiplatelet therapy, angiotensin-converting enzyme inhibitor and/or angiotensin II receptor blocker, beta-blockers, and statins. The status of medications was tabulated at discharge from the index revascularization, and at 1, 3, and 5 years after revascularization.15

**Study endpoints**

The primary endpoint was all-cause death at 10 years. Vital status was confirmed by contact with medical care personnel, by electronic healthcare record review, or by municipal survival record. All data were recorded in the electrical case report form.

**Statistical analysis**

Categorical variables are expressed as numbers and percentages, and continuous variables as mean ± standard deviation, unless otherwise indicated. Patient characteristics were compared between the groups using unpaired t-tests or one-way analysis of variance for continuous variables and Fisher’s exact test or chi-square test for categorical variables. Time-to-event Kaplan–Meier estimates with the log-rank test were used to assessing 10-year mortality. As described earlier, the population was stratified into 5 groups according to the United Nation’s geoscheme.14 In the comparison of the 5 regions, W-E was selected as the reference because it had the largest population enrolled in the trial. Baseline characteristics were categorized according to thresholds derived from previous sub-studies in the SYNTAXES trial population.15-25 Predicted 10-year mortality was calculated in each region according to the SYNTAX score 2020.26,27

Multivariable analysis and adjustment of survival curves were performed based on the Cox regression analysis. Hazard ratio (HR) with a 95% confidence interval (CI) was assessed based on Cox proportional hazards regression modified by age, sex, medically treated diabetes, current smokers, peripheral vascular disease (PVD), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD, defined as creatinine clearance <60 mL/min), left ventricular ejection fraction (LVEF), disease type (LMCAD or 3VD), and anatomical SYNTAX score. Other baseline characteristics including comorbidities (e.g., hypertension, and dyslipidemia) and blood tests (e.g., hemoglobin, C reactive protein, and lipid profiles) are taken into consideration in the sub-analysis to determine the concordance to the main analysis.15-25 In addition to these factors, the impact of the geographic disparities with and without adjustment for procedural characteristics specific to each modality of revascularization was analyzed (supplement).

All statistical analyses were performed using R 4.1.1 (The R Foundation for Statistical Computing, Vienna, Austria) and SPSS ver.25 (IBM, IL, USA). All reported P-values were two-sided, and P<0.05 was considered statistically significant. Significant predictors of clinical events were presented with HR and 95% CI.

**Results**

**Baseline characteristics**

In the randomized cohort of the SYNTAX study, 1800 patients were recruited from 19 countries, in N-A (n=245), E-E (n=189), N-E (n=425), S-E (n=263), and W-E (n=678). A total of 5 patients did not participate in 10-year follow-up and these patients are censored at 5 years.

The median follow-up was 11.2 (interquartile range: 7.7, 12.1) years. Baseline characteristics stratified according to the five regions are shown in Table 1.

Table 1 describes the baseline characteristics of the different geographic regions. There exist many differences in baseline characteristics among the various regions; according to the analysis of variance, 3 baseline characteristics did not differ among the regions; previous PVD smoking habits (current smoker) and COPD.

**Regional differences in procedural characteristics of PCI and CABG**

Based on randomization, the allocation to treatment strategy was well balanced per country as well as per region, however, procedural characteristics in each allocated strategy differed among regions.

In the PCI arm, the anatomic SYNTAX score was lower than in W-E (24.9±11.4 vs 29.4±11.8, p<0.001), with a lower prevalence of total occlusions (13.8% vs 26.6%) and a shorter mean total stent length in N-A (69.0±45.0mm vs 87.0±46.6 mm, Table 2a).

In the CABG arm, compared to W-E, emergent/urgent procedures were more frequent in E-E (18.1% vs 5.5%), whilst off-pump procedures were more common in N-A (31.9% vs 13.2%). Bilateral internal mammary artery (IMA) use was most frequent in W-E (47.0% vs 15.2%) (Table 2b). Patients in N-A had higher rates of complete revascularization and longer operation times compared to those in W-E (72.1% vs 63.6%, 235±72min vs 209±64min, respectively). Compared to the entire European population, the N-A patients were more frequently revascularized with venous conduits (1.83±0.83/patient vs 1.29±0.80/patient, p<0.001).

**Post-procedural medication after revascularization**

Table 3 and Figure 1 show the rate of OMT prescriptions for each region at discharge, and at 1, 3, and 5 years following the index revascularization.

E-E achieved a higher rate of OMT than W-E throughout follow up: at discharge (59.8% vs 38.1%, p<0.001), at 1-year (68.4% vs 46.1%, p<0.001), at 3-years (67.6% vs 42.5%, p<0.001), and at 5-years (71.0% vs 43.0%, p<0.001). S-E had the lowest OMT rate at discharge and 1 year (29.7% vs 38.1%, p=0.021, and 35.8% vs 46.1%, p=0.007 vs W-E), whilst N-A had the lowest rate at 3 years (34.4% vs 43.0%, p=0.049 when compared to W-E).

Compared to the European population (n=1555), N-A has a significantly lower rate of OMT at 5 years (37.2% vs 47.4%, p=0.008). The highest rate of OMT was observed in E-E. In addition, in the N-A population, statin and beta-blocker prescriptions decreased gradually by 10.9% (absolute percentage) in the first 5 years of the follow-up while in S-E, the use of statin went up in absolute value by 12.4% (81.9%) at 5 years (Supplemental table 1 and figure 1).

In the PCI arm, the rate of statin prescription was significantly higher in N-E than in W-E at discharge, and at 1- and 5-year follow-up (95.3% vs 82.8%, p<0.001, 92.3% vs 85.8%, p=0.026, 91.0% vs 80.5%, p=0.001, respectively).

**10-year mortality after revascularization in 5 regions**

Compared to W-E, the rate of 10-year crude mortality was significantly lower in E-E (HR 0.89, 95%CI [0.79-0.995], p=0.041), N-E (HR 0.83, 95%CI [0.73-0.94], p=0.003) and S-E (HR 0.69, 95%CI [0.51-0.93], p=0.014) (Log-rank p<0.001, Figure 2A), whereas it was similar in N-A. When the differences in baseline and procedural characteristics were adjusted, compared to W-E mortality was still significantly lower in N-E (HR 0.85, 95%CI [0.74-0.97], p=0.019) and trended lower in S-E (HR 0.72 95%CI [0.52-0.99] p=0.043) (Figure 2B). The results were consistent when adjusted for all the baseline characteristics listed in table 1 and all the baseline values that differ among 5 geographic regions. (Supplemental figure 1).

In the PCI arm, N-E (HR 0.82, 95%CI [0.69-0.97], p= 0.020) and S-E (HR 0.58, 95%CI [0.38-0.88], p=0.011) had significantly lower 10-year mortality compared to W-E (Log-rank p=0.036), with similar trends following adjustment for confounding factors (N-E: HR 0.80, 95%CI [0.66-0.97], p=0.026 and S-E: HR 0.62, 95%CI [0.39-0.98], p=0.042, Figure 3A).

In CABG arm, there were no significant regional differences in unadjusted and adjusted survival (Log-rank p=0.112, Figure 3B).

**Treatment effects of PCI and CABG and geography**

Figure 4A shows the relation between 10-year mortality after PCI and CABG in each region. Whilst overall there was no significant difference in the risk of 10-year mortality following PCI or CABG, it was numerically higher with PCI compared to CABG in E-E, N-E, and W-E, whilst it was similar in N-A and S-E. A forest plot for the 5 regions is shown in Figure 4B, with no significant interaction seen between the 5 regions and revascularization mode (p=0.728). Hazard ratio of PCI against CABG in each country was presented in supplemental figure 2.

**Discussion**

The main findings of this study are:

1. Rates of crude 10-year mortality were significantly lower in E-E, N-E, and S-E compared to W-E and N-A.
2. The differences in 10-year mortality remained significantly lower with N-E and S-E even after adjustment for confounding factors, including the SYNTAX score 2020.
3. However, when comparing PCI to CABG in the five geographic regions, there were no statistically significant interactions between the geographic disparity and revascularization strategy.

At baseline, we observed significant geographical differences in most pre-procedural factors including age, comorbidities (e.g., CKD, medically treated diabetes, PVD, and COPD), ejection fraction, lesion complexity, and extent of CAD (anatomic SYNTAX score). These factors are all integrated into the SYNTAX score 2020, a comprehensive risk score predicting all-cause mortality at 10 years.27 Compared to W-E, the scores and predicted mortalities were similar in N-A and S-E and significantly lower in E-E and N-E, whereas the observed mortalities were significantly lower in N-E and S-E. Notably, anemia at baseline in N-A—a parameter not included in the SYNTAX score 2020—was twice as high as in W-E, which may have unfavorably impacted prognosis in N-A. Furthermore, rates of Black, Hispanic, and Alaskan natives, who are all high-risk races for cardiovascular events, especially in the US due to socio-economic reasons, were significantly higher in N-A than in W-E.

Patients enrolled in N-A had relatively less complex coronary anatomy, according to the anatomic SYNTAX Score, however, the region’s rate of LMCAD PCI, authorized as treatment in the context of an Investigational device exemption of the Food Drug Administration, was the highest, presumably because US guidelines at the time of recruitment into the SYNTAX trial did not recommend PCI as treatment of unprotected LMCAD28. Of note, a recent patient-based meta-analysis performed by the TIMI group of four randomized trials involving LMCAD has demonstrated equipoise in all-cause mortality between PCI and CABG, and may influence future guideline recommendations in Europe and USA.29

Overall in Europe, the prevalence of enrolled patients with 3VD and complex anatomy was higher and accounted for a more unfavourable prognosis after percutaneous revascularization. Along the same line, E-E did not hesitate to enrol emergent PCI cases that are well known for their poorer outcomes.

Several prominent observations can be made regarding procedural treatment. The large number of stents implanted and the longest total stent length documented in E-E might plausibly be explained by the enthusiasm of operators in E-E for the DES, a novel and expensive technology at the time of the trial (2005), but provided free of charge by the industrial sponsor.Fewer stents were implanted in the other geographic regions, and the total stent length was shortest in N-A.

Complete revascularization rate with CABG was more frequently achieved in N-A than in W-E. Despite all these disparities, it cannot be overlooked that there was no statistically significant interaction in the unadjusted or the adjusted populations between revascularization treatment strategy and geographic region.

Based on many clinical trials in secondary prevention, the European Society of Cardiology (ESC) frequently updates its guidelines on lipid-lowering therapy and antiplatelet therapy.30 Previously we have reported the favorable impact on ten-year mortality of OMT, at least documented for up to five years.15,31 However we did not adjust the Kaplan-Meier curves for pharmacological treatment, since this information was only available for up to five years, is a time-varying factor, and has already been reported at five years by our group.15 Nevertheless it has to be underscored that the rates and trends of prescribing OMT, documented over the first five years, are very heterogeneous among the five regions (Figure 1). In two regions, E-E and S-E, rates of prescriptions for OMT increased, with the highest level achieved at five years in E-E (71%). In two other regions, W-E and N-E, there was a more or less stable pattern of prescribing OMT in the range of 40 to 50%, whilst in N-A, rates of OMT fell by 6% between the index procedure and 5 years. Baum et al recently reported significant geographic variations in lipid-lowering therapy utilization, LDL-C levels, and percentages of patients meeting the ACC/AHA criteria for optimal lipid-lowering in a real-world population of patients with major atherosclerotic cardiovascular events in the United States.32 We assume that one of the reasons for the sharp increase in mortality after 5 years in N-A is related to low OMT rate and the high rate of venous conduits compared to the European population. In a previous report, we have demonstrated the importance of OMT on the late survival.15 We also reported the association between the use of multiple arterial grafts and good 10-year survival outcomes compared to a single arterial group mixed with venous conduits and PCI group.33 Venous conduit failure is known to accelerate 4-5 years after surgery.34

Crude ten-year mortality was significantly lower in E-E, N-E, and S-E than in W-E. Following adjustment for the pre- and peri-procedural factors, the difference in cumulative mortality remained significant for N-E and S-E versus W-E, but was no longer significant between E-E and W-E. Contemporary data from the European heart network show that death rates from both ischaemic heart disease and stroke are generally higher in Central and Eastern Europe compared to Northern, Southern, and Western Europe.35 It also implies that several pre- and peri-procedural factors—sometimes counteracting each other—are also influencing the regional differences in all-cause mortality after revascularization.

The significant differences in 10-year mortality among the 5 regions are essentially only observed in the PCI arm. It has been well established that the outcome from CABG is not affected by the extent and complexity of CAD, but is mainly influenced by the presence of concomitant comorbidities.10,29 Up to five years, all-cause mortality in the SYNTAXES trial is similar to the survival outcome of the EXCEL trial; however, after 5 years, at least in the PCI arm, the survival curves of N-E and S-E start to diverge from the three other regions.

In the case of S-E, secondary prevention may have played a predominant role. Hypertension and metabolic syndrome were not identified as prominent risk factors in the SYNTAX score 2020, nevertheless, they were significantly more frequent in W-E than in N-E and S-E. Lipid and CRP profiles were more favorable at baseline or were better controlled at follow-up in N-E and S-E than in W-E. In addition, statin prescription rates were consistently higher in N-E than W-E from inclusion to 5-year follow-up. These factors, known to favorably affect the outcome, were more prominent in N-E and S-E than in W-E.

Furthermore, many socio-economic factors were not recorded in the case report form of the SYNTAX trial that could have affected long-term mortality. Most cardiovascular diseases can be prevented by addressing behavioral risk factors such as tobacco use, unhealthy diet, physical inactivity, and harmful use of alcohol. For example, the Mediterranean diet is deemed to be beneficial not only in the primary prevention of CAD but is also associated with a reduced risk of no-reflow after ST-elevation myocardial infarction and is strongly advocated in the 2021 ESC guidelines of CVD prevention.30,36 That is another putative explanation put forward for the superior 10-year vital prognosis in E-E (Table 3, Figure 1).

Finally, practical implications of the study are the following; when we are conducting a global trial involving multiple countries in different regions of the globe, we always face the issue of large heterogeneity of the baseline characteristics, socio-economy of the region and genomic factors relate to the ethnicity population related to the trial (e.g. Japanese sensitivity to P2Y12 inhibitors37, decreased Lp-PLA2 activity in Korean population38, etc.), the technique of revascularization, and quality of the operators, as well as post-procedural medication, and lifestyle after intervention. The dilemma is whether we prefer to conduct a study in a very homogeneous region. In that way, we probably eliminate some of the global heterogeneity, but then the result can only be generalized to that region and vice versa. Thus, we should not only consider sub-analysis stratified by baseline, and procedure characteristics but we should also consider stratifying by the geographic region and detect at epidemiological level factors of bad prognosis that could be remedied by proactive measures. Since this report has the aspect of both interventional and epidemiological aspects, deep learning methods may be able to unravel other as yet unidentified factors related to 10-year mortality.39

The current study has several limitations. First, the present study on geographic disparities was not prespecified and is a post hoc analysis. The decision to use W-E as the reference was made as it had the largest sample size, but this decision could be criticized as being arbitrary. All reported findings should be considered exploratory and hypothesis-generating. Second, the SYNTAX trial was conducted between 2005 and 2007 with the predominant use of first-generation paclitaxel-eluting stents in PCI arm, which may limit the generalizability of our findings to current clinical practice. Third, differences in social and financial circumstances between regions undoubtedly directly and/or indirectly affected not only decision-making relating to treatment (e.g., stent implantation trends in E-E) but also secondary prevention, as well as comorbidity outside CVD. Fourth, the SYNTAXES study was performed to evaluate survival up to 10 years, and the endpoint was all-cause death only. However, the SYNTAXES study provides the first randomized trial that was meticulously collected and achieved a high follow-up rate of 93.8% for 10-year vital status (1689 of 1800 enrolled patients). Even though the overall sample size was sufficient and the 10-year follow-up rate was high enough for the primary purpose of the SYNTAXES trial, the subdivision of the global cohort into five regions resulted in small sample sizes for subgroup analysis. Finally, we mention missing data. Epidemiologically, it is ideal to input all the factors at the baseline to adjust survival curves among 5 regions. However, the more factors are involved, the more we lose patients after modification. Even if the methodology is appropriate, there is a risk of losing sight of overall trends if not enough patients are included. Although we presented the main results modified by SYNTAX score 2020-related factors, we also performed adjustments using all the presented baseline characteristics both in crude data and multiple imputations data and found that the results were consistent.

It is desirable in a world moving towards globalization that large patient-based meta-analyses with very long-term follow-up are generated to unravel the true factors that impact the vital prognosis of CAD after percutaneous or surgical revascularization.29

**Conclusions**

After revascularization of complex coronary artery disease, adjusted 10-year mortality in N-E and S-E was significantly lower than in W-E. In N-A and W-E mortality rates were similar, however, the causative factors differed significantly, emphasizing the difficulty in interpreting the average treatment effect on mortality. However, there was no significant interaction between the geographic disparity in pre- and peri-procedural characteristics and all-cause mortality observed after percutaneous or surgical revascularization. In the era of globalization, knowledge, and understanding of geographic disparity are of paramount importance for the correct interpretation of global studies.

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