

## SCIENTIFIC LETTER

## International comparison of mortality rates in patients with non-ST elevation acute coronary events

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Recently, authors of several studies on acute coronary syndromes have reported that study participants from eastern Europe and South America had poorer outcomes compared to their North American and western European counterparts.<sup>1–3</sup> Taking into consideration that all of these studies have in common a very small proportion of participants from regions outside the USA, Canada, or western Europe, this inference may have been based on insufficient data. We sought to compare the inter-regional mortality in the only study that included a comparable proportion of patients from different continents.

## METHODS

The TIMI (thrombolysis in myocardial infarction) 11B trial recruited 3910 patients in 200 centres in North and South America and Europe over a period of 19 months (Canada, USA, UK, Spain, France, Germany, The Netherlands, Argentina, Chile, and Uruguay). The design and overall results of the trial have been published.<sup>4</sup> Patients were allocated in a double blind manner to either intravenous unfractionated heparin or enoxaparin for at least three days, followed by partial dose of enoxaparin or placebo up to day 43 after inclusion. The present analysis was conducted in a “post hoc” manner to analyse all cause mortality. A central committee adjudicated events. Mortality rates were compared at 48 hours, during hospital stay, 43 days, six months, and one year by geographic region. We also compared mortality among regions for each stratum of the TIMI risk score, which is determined by the sum of the following variables: age, at least three risk factors for coronary artery disease, significant coronary stenosis, ST segment deviation, severe angina status, use of aspirin in the last seven days, and raised serum cardiac markers.<sup>5</sup> Logistic and Cox

proportional models were constructed and adjusted odds ratios for mortality were calculated holding constant the region of inclusion and the covariates from the TIMI risk score. The European cohort was used as the referent for the purposes of the adjusted comparisons. An  $\alpha$  level of 0.05 was pre-specified for all comparisons. Statistical calculations were done with the STATA software (College Station, Texas, USA). The institutional review board corresponding to each site approved the study protocol. All participants gave written informed consent.

## RESULTS

The study population consisted of 3910 participants. The European sites recruited 1787 patients (46%). North America contributed 1328 patients (34%) and Latin America 795 (20%). A total of 291 deaths occurred in a period of one year. Differences in baseline characteristics of clinical relevance included more patients with angina before a qualifying event in North and South America, and fewer patients with elevated serum markers on admission in Europe and North America than in South America. Prior aspirin users were more frequently observed in North America, probably related to a higher proportion of patients with a history of myocardial infarction or coronary interventions. On the other hand, the rate of non-ST segment elevation myocardial infarction as a final diagnosis was higher in the south of the American continent than in the north and in Europe.

Unadjusted in-hospital mortality rates by region did not differ significantly among Europe (2.6%), North America (2.0%) or South America (2.6%). Similarly, no significant differences were observed at 43 days (4.1% v 3.5% v 4.5% respectively), six months (6.3% in Europe, 5.7% North America, and 6.2% in South America), and one year (8.0% in Europe, 6.8% in North America, and 7.3% in South America). At no time point was there any significant difference in mortality rates between the groups. After adjusting for the TIMI risk score covariates, no significant differences in the OR for mortality were observed at any time point up to one year of follow up (table 1).

## DISCUSSION

As opposed to other inter-regional comparisons, we did not observe any significant difference in mortality between Latin America, Europe, and North America for patients suffering from acute non-ST elevation coronary events.

Prior reports have failed to consider important factors such as the relative proportion of patients from each region, the

Table 1 Adjusted odds ratios for mortality\*

	n (%)	OR	95% CI
In-hospital death			
North America	27 (2.0)	0.76	0.47 to 1.21
South America	21 (2.6)	1.07	0.65 to 1.74
Europe	47 (2.6)	1	†
Death at 43 days			
North America	47 (3.5)	0.91	0.61 to 1.35
South America	36 (4.5)	1.24	0.82 to 1.90
Europe	73 (4.1)	1	†
Death at 6 months			
North America	76 (5.7)	0.97	0.72 to 1.32
South America	49 (6.2)	1.10	0.78 to 1.54
Europe	112 (6.3)	1	†
Death at 1 year			
North America	90 (6.8)	0.90	0.68 to 1.19
South America	58 (7.3)	1.03	0.76 to 1.41
Europe	143 (8.0)	1	†

\*Adjusted for continent and the co-variables included in the TIMI risk score.

†Referent.

CI, confidence interval; OR, odds ratio.

**Abbreviations:** ESSENCE, efficacy and safety of subcutaneous enoxaparin in unstable angina and non-Q wave myocardial infarction; GRACE, global registry of acute coronary events; OASIS, organisation to assess strategies for ischaemic syndromes; PURSUIT, platelet glycoprotein IIb/IIIa in unstable angina: receptor suppression using Integrilin; TIMI, thrombolysis in myocardial infarction

number of sites involved in each country, and the overall risk profile of patients. The authors of a post-hoc analysis of the PURSUIT trial data compared mortality rates between the 585 patients from Latin America and the 4385 that participated in North America, and observed that the rate in the former region was higher than in the latter.<sup>1</sup> Of note, the 95% confidence intervals for the odds ratios reported for eastern Europe and Latin America were imprecise and included the null value. In a subanalysis from the ESSENCE trial, Fox and colleagues found a higher rate of combined major cardiac end points in Argentina and France.<sup>3</sup> Interestingly, in ESSENCE the same compounds as in TIMI 11B were tested, with a different administration regimen. Again, sample size considerations may have influenced the effect of chance, because France contributed 3% of the total sample and Argentina 8%. Further, roughly 80% of the 256 Argentine patients were included in a single tertiary centre to which individuals at highest risk are expected to be referred, thus limiting the external validity of the observation.

International registries are a helpful tool to complement the focused nature of clinical trials. No differences in mortality were observed between the USA and Brazil in the OASIS cohort of patients with non-ST elevation acute coronary events.<sup>6</sup> The GRACE registry is enrolling consecutive patients from representative clusters in several regions and will undoubtedly contribute to improve our knowledge about inter-regional differences.

We acknowledge that the post hoc nature of all of the published studies, including ours, poses limitations. Despite the relatively larger number and proportion of Latin American participants in our analysis, the study was underpowered to detect differences in mortality.

We need to withhold premature conclusions until we have the proper data to identify inter-regional variability in morbidity and mortality. The issue deserves attention, and future studies should contemplate its inclusion in the project design.

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