Outcomes of patients in clinical trials with ST-segment elevation myocardial infarction among countries with different gross national incomes

Andrés Orlandini1*, Rafael Díaz1, Daniel Wojdyla1, Karen Pieper2, Frans Van de Werf3, Christopher B. Granger2, Robert A. Harrington2, Eric Boersma4, Robert M. Califf2, Paul Armstrong5, Harvey White6, John Simes7, and Ernesto Paolasso1

1Estudios Clínicos Latino America (ECLA) Collaborative Group, Jujuy 1415, Rosario 2000, Argentina; 2Duke University Medical Center, Durham, NC, USA; 3Gasthuisberg University Hospital, Leuven, Belgium; 4Erasmus MC, Rotterdam, The Netherlands; 5University of Alberta, Edmonton, Alberta, Canada; and 6Green Lane Hospital, Auckland, New Zealand; and 7NHMRC Clinical Trials Centre, University of Sydney, Sydney, Australia

Received 7 February 2005; revised 22 November 2005; accepted 1 December 2005; online publish-ahead-of-print 12 January 2006

This paper was guest edited by Prof. Gianni Tognoni, Instituto Mario Negri, Department of Cardiology, Milano, Italy

Aims To evaluate whether there is an association between 30-day mortality in patients with ST-segment elevation myocardial infarction (STEMI) included in clinical trials and country gross national income (GNI).

Methods and results A retrospective analysis of the databases of five randomized trials including 50,310 patients with STEMI (COBALT 7169, GIK-2 2931, HERO-2 17,089, ASSENT-2 17,005, and ASSENT-3 6116 patients) from 53 countries was performed. Countries were divided into three groups according to their GNI based on the World Bank data: low (less than US$ 2900), medium (between US$ 2900 and 9000), and high GNI (more than US$ 9000 per capita). Baseline characteristics, in-hospital management variables, and 30-day outcomes were evaluated. A previously defined logistic regression model was used to adjust for differences in baseline characteristics and to predict mortality. The observed mortality was higher than the predicted mortality in the low (12.1 vs. 11.8%) and in the medium income groups (9.4 vs. 7.9%), whereas it was lower in the high income group (4.9 vs. 5.6%).

Conclusion An inverse relationship between mortality and GNI was observed in STEMI clinical trials. Most of the variability in mortality can be explained by differences in baseline characteristics; however, after adjustment, lower income countries have higher mortality than the expected.

Introduction

During the last two decades, large clinical trials have been established as the preferred method to evaluate clinical effects of treatments in cardiology. Initially, these studies were confined to North America, Western Europe, Australia, and New Zealand, but in the middle of the 1980s, they were expanded to include Latin America and Eastern Europe. This research globalization allows a comparison among different regions over the world.

Recent studies1–9 have suggested different outcomes in patients with acute coronary syndromes among these different regions. These differences seem to be most dramatic between industrialized and developing countries.10 Outcome variations could have been caused by differences in the disease itself, in baseline characteristics of the population, in treatments, in the use of invasive cardiac procedures, or in any other unmeasured variable, for instance, socioeconomic characteristics of the population.

Nevertheless, these differences have primarily been previously examined by combining countries into regions of the world. However, some regions may have too few patients for reliable sampling and regions have often been defined differently in different studies.1,2,7

Furthermore, evaluation of outcomes on an individual country basis3,5,6 may have inadequate sample sizes and there may be limitations related to the multiplicity of testing. Thus, if 20 countries are evaluated, one may have different outcomes reaching conventional statistical significance by chance alone. Moreover, relatively few trials with ST-segment elevation myocardial infarction (STEMI) have focused on this topic.11,12

Therefore, a retrospective analysis of the databases of five trials including 50,310 patients from 53 countries in five continents was performed with the aim of evaluating whether mortality in STEMI clinical trials is associated with country wealth assessed by gross national incomes (GNIs).

KEYWORDS
Regional differences; Outcomes; ST-elevation myocardial infarction; Clinical trials; Gross national income
Objectives
The primary objective of this analysis was to evaluate whether there is an association between 30-day mortality in patients with STEMI included in clinical trials and country GNI.

If the primary objective were verified, the secondary objective was to determine what appeared to explain the difference in outcome; specifically whether differences in baseline characteristics, reperfusion strategies, or the use of concomitant medications could explain any differences noted in the mortality rates across levels of GNI.

Methods
Population
In total, 50 310 patients with STEMI, enrolled within 6 (all trials other than GIK-2) to 12 h (GIK-2) from symptom onset in five large multicentre clinical trials, were included in this analysis. The enrolment date ranged from January 1995 to May 2002. The earliest trial was the Continuous Infusion vs. Double-Bolus Administration of Alteplase (COBALT) trial, which included 7169 patients. The Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) trial randomized 17 005 patients to receive an infusion of alteplase (t-PA) (up to 100 mg) or single-bolus injection of tenecteplase (TNK) (30–50 mg), according to the body weight. The 17 089 participants in the Hirulog Early Reperfusion/Occlusion (HERO-2) trial were randomly assigned to an intravenous bolus and 48 h infusion of either bivalirudin or unfractioned heparin, together with a standard dose of streptokinase. The Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT-3) trial included 6116 patients who were randomly assigned one of three regimes: full-dose tenecteplase and enoxaparin for a maximum of 7 days; half-dose tenecteplase with weight-adjusted low-dose unfractionated heparin and a 12 h infusion of abciximab; or full-dose tenecteplase with weight-adjusted unfractionated heparin for 48 h. In this analysis, the 2931 patients randomized until May 2002 in the ongoing GIK-2 Glucose–Insulin–Potassium Full Scale Trial comparing a high dose of glucose–insulin–potassium solution (GIK) vs. control were also included.

Variables
Patient’s data on baseline characteristics, prior history of coronary heart disease, known risk factors, and clinical presentation were available from each trial. Prior stroke and family history of cardiovascular disease were not used in the analysis, because they were collected in only two trials.

In-hospital medication data were available for anticoagulation (any type), beta-blockers, aspirin, and angiotensin-converting enzyme (ACE)-inhibitors (except HERO-2). In-hospital data for type of and time to fibrinolytic therapy and revascularization procedures performed by either percutaneous coronary intervention (PCI) or coronary artery by-pass graft (CABG) were also collected. The primary outcome in this analysis was 30-day all-cause mortality.

Country categorization
Patients recruited in 53 countries on five continents were included in this analysis. Countries were divided into three groups, according to their GNI per capita based on the World Bank data (Table 1).

Table 1 Country groups according to their GNI based on the World Bank Data

<table>
<thead>
<tr>
<th>Country Group</th>
<th>Low GNI</th>
<th>Medium GNI</th>
<th>High GNI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low GNI</td>
<td>1660</td>
<td>Argentina 7460</td>
<td>USA 34 100</td>
</tr>
<tr>
<td>Argentina 7460</td>
<td>6261</td>
<td>Poland 4190</td>
<td>2010</td>
</tr>
<tr>
<td>Georgia 630</td>
<td>1153</td>
<td>Brazil 3580</td>
<td>2010</td>
</tr>
<tr>
<td>Bulgaria 1520</td>
<td>867</td>
<td>Mexico 5070</td>
<td>The Netherlands 24 970</td>
</tr>
<tr>
<td>India 450</td>
<td>658</td>
<td>South Africa 3020</td>
<td>UK 24 430</td>
</tr>
<tr>
<td>Ukraine 700</td>
<td>512</td>
<td>Croatia 4620</td>
<td>Australia 20 240</td>
</tr>
<tr>
<td>Romania 1670</td>
<td>494</td>
<td>Venezuela 4310</td>
<td>Belgium 24 540</td>
</tr>
<tr>
<td>Columbia 2020</td>
<td>101</td>
<td>Hungary 4710</td>
<td>Germany 25 120</td>
</tr>
<tr>
<td>Dominican Republic 2130</td>
<td>101</td>
<td>Turkey 3100</td>
<td>Spain 15 080</td>
</tr>
<tr>
<td>Paraguay 1440</td>
<td>19</td>
<td>Czech Republic 5250</td>
<td>Spain 15 080</td>
</tr>
<tr>
<td>Philippines 1040</td>
<td>13</td>
<td>Chile 4590</td>
<td>Sweden 27 140</td>
</tr>
<tr>
<td>Thailand 2000</td>
<td>8</td>
<td>Latvia 2920</td>
<td>Canada 21 130</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slovakia 3700</td>
<td>Israel 16 710</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Malaysia 3380</td>
<td>Greece 11 960</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Estonia 3580</td>
<td>France 24 090</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Panama 3260</td>
<td>New Zealand 12 990</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lithuania 2930</td>
<td>United Arab Emirates 18 060</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Norway 34 530</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Kuwait 18 030</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Austria 25 220</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Portugal 11 120</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Denmark 32 280</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ireland 22 660</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Finland 25 130</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Switzerland 38 140</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hong Kong 25 920</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Singapore 24 740</td>
</tr>
<tr>
<td>Total 10 187</td>
<td></td>
<td>10 077</td>
<td>30 046</td>
</tr>
</tbody>
</table>
These groups were previously defined on the basis of the observation that there were significant gaps in GNI across the countries, leading to cut points.

The low-GNI group comprised 11 countries with a GNI of less than US$ 2900 per capita and included 10 187 patients, most of them from Eastern European countries. India and several Latin American countries were also included in this group. Countries in the medium group had a GNI between US$ 2900 and 9000 per capita. This group comprised 10 077 patients from 17 countries, approximately half of them from Argentina and Poland.

The 30 046 patients in the high-GNI class—more than US$ 9000—were randomized in industrialized countries including the USA, Canada, Western Europe, Australia, and New Zealand. Patients randomized in the United Arab Emirates, Kuwait, and Israel were also included in this group.

Statistical analysis

Baseline characteristics were compared among the three GNI groups. Mean values and standard deviations were used to describe the distributions for continuous variables; and frequencies and percentages for categorical variables. Differences among the groups were evaluated with Pearson’s χ² test for categorical variables and the analysis of variance test for continuous variables. Overall tests to detect differences among the three groups were performed. In-hospital medication, in-hospital procedures, and mortality rates were compared among the three groups.

The relationship between GNI and 30-day mortality was evaluated using GNI as a continuous measure. Therefore, a linear spline was applied to define the appropriate transformation of this factor relative to the outcome.19

A previously developed prediction model of 30-day mortality20 was used to adjust for patient differences in baseline factors among countries. This model included the following variables: age, height, weight, Killip class, systolic blood pressure and heart rate at admission, infarct location, previous myocardial infarction (MI), previous CABG, history of hypertension, smoking status, diabetes, type of thrombolytic used, and time to reperfusion. Continuous GNI was added to this model to evaluate the importance of this factor once differences in baseline characteristics are taken into account. Differences among studies were assessed including indicator variables for each study in the model. Overall statistical significance of the study effect was not reached (P > 0.05), indicating no statistical differences among studies concerning 30-day mortality. Therefore, further analyses did not include a study effect.

The actual rates of 30-day death are calculated for each of the three GNI groups. Predicted values are obtained for each patient by applying a logistic regression model of the variables found in the predictive model. These simply show the event rate we would expect to see, given the baseline risk sets of each of the three groups.

A logistic model that included both the predictive model variables and the continuous GNI as a linear spline is then applied. The coefficients from this model are used to obtain predicted values for every patient in the study (regardless of GNI group) as if he/she were in the low-GNI group. The median GNI for the countries in the low group is used to compute these predicted values. Likewise, predicted values are obtained for every patient as if he/she were in the medium group and then as if he/she were in the high-GNI group using the median GNI within each group. The predictions are averaged across all patients for each of these three sets. This gives the average expected adjusted probability of 30-day death for low, medium, and high GNI. By averaging across the baseline characteristics of all patients, systematic underlying differences among the three groups cannot be excluded.

All analyses were performed using SAS⁵ statistical software. P-values of 0.05 or less were considered statistically significant.2¹

Results

Baseline characteristics and previous history

The main baseline characteristics of the three GNI groups are summarized in Table 2. Several higher risk characteristics—including female gender, higher heart rate, more severe Killip class, anterior MI location, and prior MI—were more common in lower income and less common in higher income countries.

Fibrinolytic therapy

Differences in the type of fibrinolytic agent used were observed among the three groups (Table 3). Most trials with t-PA or TNK were performed in countries with a high GNI. In addition, the times elapsed from symptom onset to randomization and from randomization to fibrinolytic therapy were shorter as the GNI increased.

Concomitant medication

In accordance with a high incidence of heart failure, fewer patients were treated with beta-blockers and more with ACE-inhibitors in the low-GNI group (Table 3). It should be noted that administration of ACE-inhibitors was not recorded for patients in the HERO-2 trial, which contributed a large number of patients in the low-GNI class. Anticoagulation and antiplatelet treatments were equally used in the three groups.

Invasive procedures

A significant difference among groups was observed with the use of invasive procedures. Revascularization procedures in high-GNI countries were 15 times more frequent than in low-GNI countries and twice as frequent as in medium-GNI countries.

30-day outcomes

The primary outcome of this analysis was 30-day all-cause mortality. A large difference in the actual mortality rates is seen across the three groups (12.1, 9.4, and 4.9% from low to high GNI). All P-values for the differences among these three groups were less than 0.0001 (Figure 1). The mortality for patients in the medium group was 90% higher than for patients enrolled in the high-GNI countries (OR: 1.9; 95% CI: 1.7–2.1).

This inverse relationship between GNI and 30-day mortality rate is also observed as a continuous function of GNI (Figure 2), especially once GNI drops below US$ 10 000. This is where the countries of low and medium GNI are concentrated. The mortality rate is fairly constant above US$ 20 000, which included most of the high-GNI countries.

Multivariable logistic regression model

Five thousand eight hundred and twenty-two patients (11.6%) were not included in the multivariable logistic regression analysis because of missing values in at least one covariate or missing 30-day survival status.

The mortality rate for those patients included in the STEMI trials in low-GNI countries was more than twice the mortality of patients included in high-GNI countries (OR: 2.4; 95% CI: 2.3–2.6). This difference was diminished after...
adjusting for the baseline risk in each group. Nevertheless, the baseline factors were not different enough to explain the entire variation among these groups. Even after adjustment, the observed mortality was higher than expected in the low- and medium-GNI groups and lower than expected in the higher income group. When GNI is included as a continuous variable in the predictive model, the agreement between predicted and actual rates is somewhat improved.
especially in the medium groups (Table 4). Moreover, GNI was a significant factor after adjusting for the baseline risk set. Considering the model as a lineal spline with a cut-off of GNI of 18,000 dollars, the OR for GNI was 0.958 (95% CI: 0.948–0.967).

Discussion

The unadjusted analysis of 30-day mortality rate shows that in STEMI clinical trials, mortality was inversely correlated with GNI, an indicator of a country’s economic development.

Patients from countries with low GNI are substantially different from those with high GNI with respect to baseline characteristics and reperfusion management (different type of thrombolytic and increased time from the onset of symptoms to reperfusion). The predicted mortality rate according to the pre-defined models was different across the groups, implicating that patients from countries with lower GNI are at higher risk upon entry into clinical trials.

Whether this is a result of investigators including a higher risk subset of patients relative to those enrolled in higher income countries, or whether the general risk of the population in these countries varies, we cannot determine in this analysis. However, in an analysis performed by the HERO-2 investigators on patients, the significantly greater proportion of potentially eligible patients admitted at CCU with diagnosed STEMI were randomized from developing countries (Eastern Europe 54% and Russia 69%) rather than from developed countries (western countries 11%). This suggests that risk profile is largely determined by patient selection rather than purely by differences in the general acute MI populations.

In addition, the increase in time delay from the onset of symptoms to randomization as the GNI decreased may be explained by a delay in the pre-hospital process. The time spent from randomization to thrombolysis was also longer in the developing countries. Both these result in a delay in reperfusion, which would be expected to increase mortality. These two factors are modifiable, and effects to minimize the pre-hospital and the door-to-needle time, especially in poorer countries, are required.

Nevertheless, after adjustment for known predictors of mortality, including risk factors, haemodynamic status, fibrinolytic treatment, and time to treatment, mortality was still higher in lower income countries, although the relationship was attenuated.

This suggests that there are other factors beyond measurable differences in the patients themselves that can contribute to higher mortality in low income countries. These could relate to intermediate factors such as hospital volume, nutritional status, care facilities, or educational level of patients.

Probably, owing to the high incidence of heart failure in low-GNI countries, beta-blockers were less frequently used and ACE-inhibitors were more frequently used. Aspirin and anticoagulation were used with almost the same frequency in all groups. Consequently, the medications with proven

---

Table 4 30-day mortality rate according to the GNI class

<table>
<thead>
<tr>
<th>Model</th>
<th>GNI class</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td>Medium</td>
<td>High</td>
</tr>
<tr>
<td>Observed</td>
<td>12.05*</td>
<td>9.36*</td>
<td>4.94*</td>
</tr>
<tr>
<td>Predictive model alonea</td>
<td>11.78 (CI 11.51–12.05)</td>
<td>7.90 (CI 7.68–8.11)</td>
<td>5.56 (CI 5.47–5.65)</td>
</tr>
<tr>
<td>Predictive model + continuous GNIb</td>
<td>9.75 (CI 9.65–9.86)</td>
<td>8.92 (CI 8.82–9.03)</td>
<td>5.54 (CI 5.47–5.61)</td>
</tr>
</tbody>
</table>

*aAll P-values among the groups <0.0001.
bPreviously developed prediction model of 30-day mortality.
cContinuous GNI was added to the previous model to evaluate the importance of this factor once differences in baseline characteristics are taken into account.
beneficial effect—an indirect indicator of medical care quality—seem not to be related to the differences in mortality.

Finally, we observed a direct relationship between the GNI and the use of invasive diagnostic and revascularization procedures.

This relationship existed with respect to both previous and in-hospital procedures. We did not attempt to analyse the impact of invasive procedures because of multiple sources of confounding. Moreover, a 30-day endpoint is not a good one for evaluating the effects of revascularization, and particularly of surgical revascularization, where the survival benefit may not be reliably assessed until at least 1 year after the procedure. The known risk during the first days and weeks following procedures would suggest that the advantageous differential in observed vs. expected mortality in higher income countries may be even greater at later timepoints.

Limitations

This is a retrospective design analysis compiled from the database of five randomized STEMI clinical trials. Pooling data across the various studies require similar definitions of the variables employed. In all of the five trials, the variables used in the logistic retrospective model were collected and defined almost equally; however, we have 11% of missing values but not in the relevant ones (most of them in the height value).

The predicted model is based on the data taken from 15 countries, most of them high-GNI countries. The applicability of this model in low- and medium-GNI countries could over or underestimate the risk in these countries. Nevertheless, this model is widely accepted and the variables used are the most relevant risk markers. Moreover, these risk factors appear to confirm a similar relative risk ranking in different settings (similar models in GUSTO, TIMI, and GRACE).

Given 7 years time frame encompassed by the analysis, it is possible that some GNI changed among the different countries and that some countries might have even crossed over from one GNI stratum. Nevertheless, owing to the magnitude of the gaps among the three GNI groups, it is unlikely that a country changed during the period considered in the study.

In a retrospective analysis, we can only consider admission variables and not those that develop after admission, such as in-hospital invasive procedure rates, which can influence mortality.

Finally, in this study, we could not collect any data concerning participating hospital characteristics or the available process of care on-site, which may also explain differences in outcomes. Moreover, clinical trials were performed in teaching or tertiary hospitals which do not represent the reality of the whole country.

Conclusions

Early post-MI mortality increases as GNI decreases across countries participating in clinical trials. This higher mortality is partly related to the higher risk baseline characteristics, as well as longer delay in the reperfusion therapy in patients enrolled in trials from developing countries. Nevertheless, significant residual differences remain after all the adjustment that we could make. This different mortality rate does not appear to be related to major differences in the use of concomitant medications.

These findings suggest opportunity to improve worldwide care of acute MI by focusing on rapid delivery of effective reperfusion therapy, especially in developing countries.

Finally, in order to randomize large numbers of patients in trials with hard clinical endpoints, it is necessary to include a large number of countries. Including countries with low GNIs enables higher risk patients to be randomized and greater power to detect clinically important differences related to larger number of events. In addition to achieving efficiency and lower costs, multinational trials that include a wide variety of countries allow wider applicability of results to the global community rather than trials that simply focus on industrialized countries.

Acknowledgement

We are indebted to Ms Paola Pazcel for her assistance with manuscript preparation and to all the study investigators, coordinators, and patients who participated in the trials.

Conflict of interest: none declared.

References


