MORTALITY

Geographical Variations in Post Myocardial Infarction Mortality and Their Impact on Risk Selection

Abdelouahed Naslafkih, MD, MSc; Nandini Dendukuri, PhD; James M. Brophy, MD, PhD, FACC; François Sestier, MD, PhD, FACC

Objectives.—The objective is to assess the impact of geographical variations in mortality on risk selection in patients after acute myocardial infarction.

Method.—Mortality analysis is used with an actuarial methodology applied to follow-up studies based on data from randomized clinical trial and observational cohort studies of acute myocardial infarction patients from different geographic areas. Observed mortality was calculated as geometric average annual rate (\(\bar{q}\)) and compared to the expected geometric average annual mortality (\(q'\)) mortality calculated from different life tables. This comparison was expressed as mortality ratios (MR). Values of \(\bar{q}\) and MR were averaged within each country grouping. Variance, standard deviation, and variation coefficient (CV) were calculated.

Results.—Geometric average annual mortality rates varied by country. The lowest rate (2.7%) was observed in Japan, and the highest rates (7.5%) were seen in studies from the United Kingdom and Northern Europe (Denmark, Sweden, Finland). The average annual mortality rate was 4.9%. Mortality ratios averaged within countries vary from 182% to 212%, with an overall average value of 198%. Coefficient of variation (CV) was 36% for geometric average annual mortality rates and 6% for mortality ratios.

Conclusion.—Although annual mortality rates from all causes vary greatly between countries, mortality ratios do not vary and remain relatively constant. This highlights the interest of risk assessment using mortality analysis methodology, which makes the geographic variation in post-myocardial infarction mortality disappear.

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INTRODUCTION

Variation in mortality between countries is well documented.\(^1\) Cardiovascular disease and coronary heart disease greatly influence mortality in certain geographical regions of the world. In Europe where coronary heart disease remains the leading cause of mortality, cardiovascular mortality is higher in Northern Europe than in Southern Europe. This led the European Society of Cardiology...
to develop different risk assessment tables for Northern and Southern Europe. In western countries, coronary heart disease remains the leading cause of mortality.

The globalization of the insurance industry requires underwriting of lives in countries where cardiovascular mortality is very different. The example of different tables for Europeans by region for assessment of cardiovascular event risk should make us question the application of risk assessment tools in a different country than where the model was developed.

The present analysis was based on data from follow-up studies conducted during the last decade of acute myocardial infarction survivors in countries with different mortality patterns. We compared the observed mortality in those studies to the expected mortality of each country by calculating mortality ratios (MR). This assesses the geographic variations in mortality and permits more adequate risk assessment.

Because early mortality is very high following myocardial infarction, it is traditional to exclude early deaths (within 1 month) from the long-term follow-up experience. Therefore, we limited our analysis to patients who survived the in-hospital phase or the first 28 days.

**SELECTION OF STUDIES**

For identification of the relevant literature, a systematic search strategy was conducted, and explicit inclusion/exclusion criteria were defined *a priori.*

The intent of this analysis was to include all studies published in the English language following these inclusion criteria: published between 1992–2003, based on data from registries or randomized controlled trials, follow-up period ≥2 years, and ≥100 all-cause deaths (excluding early mortality during the first 30 days). Multicenter randomized clinical trials (RCT) involving several countries were excluded from our analysis if they did not report mortality by country.

A MEDLINE search for published articles in English, restricted to human studies, from January 1992 to June 2003 was performed using the terms “acute myocardial infarction and mortality.” Limiting the search to randomized clinical trials, out of 693 publications screened, we selected 14 randomized clinical trials that fulfilled our criteria. The bibliographies of these 14 were hand searched, and 6 other studies were found. A total of 20 randomized clinical trials fulfilled our inclusion criteria.

Using terms “acute myocardial infarction and mortality, not RCT,” we hand searched 4932 references and found 37 registry, population-based and consecutive-patient series studies meeting our inclusion criteria.

The selected articles were classified into 8 geographic regions: United States and Canada, Southern Europe (Italy, France, Spain), Central Europe (Germany, Poland, Netherlands), Northern Europe (Denmark, Sweden, Finland), United Kingdom, Israel, Australia and New Zealand, and Japan.

**MORTALITY ANALYSIS**

**Observed Mortality**

The reported mortality in each study was expressed as geometric average annual rate ( ), based on straightforward mortality analysis methodology.

**Expected Mortality**

Expected mortality for registry or unselected consecutive patient series studies was extracted from the appropriate population life tables for the corresponding country(s) included in each study. Most of those tables are available at the Human Mortality Database (http://www.mortality.org). Those tables provide expected mortality data for the general population. Place of residence is usually the only selection criterion, and all lives, standard, substandard, and uninsurable are included.

Expected mortality for randomized clinical trials was extracted from the US Society of
Actuaries (SOA) 1990–1995 life tables for studies conducted in the United States\textsuperscript{12–18} and from Canadian Institute of Actuaries (CIA) 1986–1992 tables, for randomized clinical trials conducted in Canada and other countries.\textsuperscript{25, 27, 28, 32, 33, 38, 43, 49, 53, 54, 60} These tables are available at the Web site of the Society of Actuaries (http://www.soa.org). Mortality rates from these tables were used to build tables for expected cumulative survival rate by age and duration of follow-up (published previously in \textit{J Insur Med}).\textsuperscript{61}

We found some other actuarial tables and compared the results with these. For the United Kingdom (Institute of Actuaries 1980 Assured Male/Female, Ultimate Tables) when comparing observed mortality in the AIREX study\textsuperscript{49} to the expected mortality from this table, MR was 280\% vs 282\% when calculated with expected mortality from the CIA 1986–92 table. This table seems old to be used for this analysis.

Using expected mortality based on the Japanese Experience Table 1996 (Institute of Actuaries of Japan), the MR was similar (MR = 162\%) to our calculated (MR = 161\%) using CIA 1986–92 tables for the RCT performed in Japan.\textsuperscript{60}

For Australia, comparing the observed mortality in LIPID study\textsuperscript{54} to the expected mortality extracted from the Australian actuarial tables (Institute of Actuaries 90–92, graduated \(q_x\) for male and female, duration 5 and over), we obtained an MR of 168\% vs 153\% when using the CIA 1986–92 table. We did not find any pertinent actuarial table for the other European countries or Israel.

In conclusion, we decided to use the CIA 1986–92 table as a reference for expected mortality in studies from countries outside North America, as only 3 country-specific actuarial life tables were available, and when used they did not significantly change the calculated MR.

One example of a step-by-step calculation is summarized in the Appendix.

**COMPARATIVE MORTALITY**

Calculations are performed to determine mortality ratio (MR), calculated as: \(\text{MR} = 100 \times \left[\frac{\bar{q}}{\bar{q}'}\right]\), which is the ratio of the observed vs the expected geometric average annual mortality rates \(\times 100\).

An MR of 100\% is standard (normal mortality). Values more than standard correspond to an excess mortality in the study group according to the reference population chosen.

**STATISTICAL ANALYSIS**

We calculated the mean observed geometric average annual mortality rates and the calculated mortality ratios across studies grouped by country or region. The mean values in each country or country group were averaged. The variance and standard deviation were calculated on the basis of these without any adjustment. We assessed the dispersion around the mean values by calculating the coefficient of variation for \(\bar{q}\) and MR.

**RESULTS**

Table 1 presents a summary of demographic characteristics, observed mortality, and comparative mortality of the selected studies. Observed mortality is expressed as a geometric average annual mortality rate. Comparative mortality is expressed as a mortality ratio of observed-to-expected mortality based on population life tables for the appropriate country(s) for observational studies and to the CIA 1986–1992 tables for randomized clinical trials (RCTs).

Geometric average annual mortality rate following a myocardial infarction varies considerably between countries, which ranged from 0.027 to 0.075 (mean = 0.049). The highest rate (0.075) was observed in United Kingdom and the lowest (0.027) in Japan.

Mortality ratios, averaged among studies within each geographical group vary much less, ranging from 182\% in Japan and Southern Europe to 212\% in the United Kingdom (mean = 198\%).

When using MR, the coefficient of variation among countries is smaller (6\%) than when using the average annual mortality rate (coefficient of variation = 36\%). Results are summarized in Table 2.
The Figure shows that $\bar{q}$ varies between countries. Nevertheless, when mortality is normalized for the expected mortality, such geographical differences disappear.

DISCUSSION

Mortality is affected by demographic characteristics, lifestyle, medication and many other factors. Some of these characteristics vary according to the geographic and ethnic background, and these may also change over years. The excess mortality risk could be quantified by calculating MRs, which compare the observed mortality in the medical literature of a specific medical condition to the expected mortality in a reference group. Data for the reference group is not reported in the majority of published articles, and expected mortality should be extracted from different mortality tables.

Study design (randomized clinical trials vs observational studies including registries of consecutive patients and population studies) was found to be an important variable influencing reported mortality. Patients in RCTs are highly selected.\(^{62}\) Several major causes of mortality are exclusion criteria for these studies, leading to a lower reported mortality than in studies from registries or cohorts of unselected patients. In a Bayesian analysis of our data (not shown), mortality was about 30% better in RCTs than in registries.

Insurance industry mortality is 20% to 25% better than population mortality. The expected mortality from insurance industry tables is lower than population mortality tables.\(^{63}\) Singer summarized survival selection bias in insurance applicants.\(^{64}\) In adults, the first-year select rate is about 25% to 35% of the population rate (1965–70 select table vs 1969–71 life table). The difference decreases with policy duration, but even ultimate insurance rates more than 15 years after policy issue remain lower than the corresponding population rate at the same attained age. This is the reason why actuarial life tables are used for underwriting life insurance, and MRs are significantly higher when using actuarial life tables for registries or cohorts. There is a similarity in improved survival in RCTs and insurance industry life tables. Therefore, using an insured population for comparative purposes\(^{65}\) when data came from RCTs is appropriate.

Enrollees in registries and observational studies are usually unselected consecutive patients and could be considered as a sample of the general population differing only by their medical condition. Observed mortality in this design could be adequately compared to the population mortality tables covering the same geographical area and the same period.\(^{66}\) This is because the place of residence is usually the only selection criterion used in the construction of these tables.

Other variables such as risk factors, treatment regimen and revascularization rates should be taken into consideration. A majority of studies did not report all variables, and imputations had to be done as carefully as possible. Another limitation of our analysis is that country demographics and treatment variables were known only at the aggregate level.

It is possible that the inclusion of other unidentified studies might alter our conclusions.
Table 1. Demographic Characteristics of Selected Studies, Mortality and Comparative Mortality According to Life Tables Selected as Described in Methods. **Legend:** RA = Randomized Clinical Trial; RE = Registry, Observational Study; No. = Number of Patients Surviving Early Mortality; FU = Follow-up (years); Age = Mean Age (years); Men = % of Men; d = Number of Deaths; q̅ = Geometric Average Annual Mortality Rate; MR% = Mortality Ratio (%)

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Design</th>
<th>No.</th>
<th>Age</th>
<th>Men</th>
<th>FU</th>
<th>d</th>
<th>q̅</th>
<th>MR%</th>
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<td>375</td>
<td>0.0658</td>
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<tr>
<td>Alter et al</td>
<td>RE</td>
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<td>66</td>
<td>65</td>
<td>5</td>
<td>6559</td>
<td>0.0688</td>
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<tr>
<td>Rodrigues et al</td>
<td>RE</td>
<td>67,651</td>
<td>65</td>
<td>65</td>
<td>3</td>
<td>13,682</td>
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<td>Kavanagh et al</td>
<td>RE</td>
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<td>Lesperance et al</td>
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<td>5</td>
<td>155</td>
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<tr>
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<td>GISSI</td>
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<td>84</td>
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<td><strong>Germany, Poland and Netherlands</strong></td>
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<td>Koenig et al</td>
<td>RE</td>
<td>1197</td>
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<td>Lowel et al</td>
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<td>Maas et al</td>
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<tr>
<td>van Domburg et al</td>
<td>RA</td>
<td>3395</td>
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<tr>
<td>TRACE-Registry</td>
<td>RE</td>
<td>6676</td>
<td>67</td>
<td>69</td>
<td>7</td>
<td>3177</td>
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<td>69</td>
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<td>3</td>
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<tr>
<td>Engstrom et al</td>
<td>RE</td>
<td>8544</td>
<td>70</td>
<td>59</td>
<td>3</td>
<td>2510</td>
<td>0.1094</td>
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<tr>
<td>Herlitz et al</td>
<td>RE</td>
<td>723</td>
<td>71</td>
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<td>Huikuri et al</td>
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<td>101</td>
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<tr>
<td>Hurlen et al</td>
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<td>3630</td>
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<td>77</td>
<td>4</td>
<td>283</td>
<td>0.0201</td>
<td>170</td>
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</table>
Furthermore, we did not process individual level data from different studies. Our data confirm that randomized trials generally recruit younger and less ill patients.

When comparing the mortality experience in the medical literature using an expected mortality, we should correct for the study design by comparing RCTs to actuarial tables and observational studies to population life tables. Our analysis suggests that MRs of patients surviving the early post-myocardial infarction phase is independent of geographic area, taking into account both age and study design.

However, some limitations should be noted. Comparing observed mortality in randomized clinical trials to expected mortality from population life tables may introduce a bias. Patients in the majority of RCTs are highly selected, because of the inclusion/exclusion criteria adopted in this study design. We compared mortality from RCTs to tables with a better survival than in population life tables, the actuarial life tables used in the in-

### Table 2. Geometric Average Annual Mortality Rates ($\bar{q}$) and Mortality Ratios Averaged Within Country Grouping

<table>
<thead>
<tr>
<th>Country Grouping</th>
<th>Geometric Average Annual Mortality Rate ($\bar{q}$)</th>
<th>Mortality Ratio (%)</th>
</tr>
</thead>
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<tr>
<td>1–United States, Canada$^{[4-24]}$</td>
<td>0.05683</td>
<td>206</td>
</tr>
<tr>
<td>2–Italy, France, Spain$^{[5-29]}$</td>
<td>0.0357</td>
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<tr>
<td>3–Germany, Poland, Netherlands$^{[30-34]}$</td>
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<td>4–Denmark, Sweden, Finlande, Norway</td>
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<td>202</td>
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<tr>
<td>5–United Kingdom$^{[44-49]}$</td>
<td>0.07506</td>
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</tr>
<tr>
<td>6–Israel$^{[50-53]}$</td>
<td>0.04102</td>
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<td>7–Australia, New Zealand$^{[54-56]}$</td>
<td>0.0404</td>
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<td>8–Japan$^{[57-60]}$</td>
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<tr>
<td>Mean</td>
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<tr>
<td>Variance ($\sigma^2$)</td>
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<td>Standard deviation ($\sigma$)</td>
<td>0.0179</td>
<td>12</td>
</tr>
<tr>
<td>Coefficient of variation (CV)</td>
<td>36%</td>
<td>6%</td>
</tr>
</tbody>
</table>
surance industry. SOA 1990–95 tables were used for RCTs from the United States, and CIA 1986–92 tables were used for those from Canada. However, actuarial life tables were not available for most of the other countries, and CIA 1986–92 tables were used as the standard of comparison for RCTs performed outside North America. Using US SOA 1990–95 instead of CIA 1986–92 did not significantly change the MRs. For underwriting life insurance, using these actuarial life tables will correct for the improved survival of the applicant.

**CONCLUSION**

Long-term mortality risk post-myocardial infarction is about twice the expected mortality using our method of accounting for study design, averaged across the countries included in our literature survey.

We conclude that applying mortality analysis methodology could adequately assess the magnitude of mortality risk. Using the appropriate life tables corrects for geographical variation in mortality reported in the published clinical medicine literature.

**APPENDIX**

The methodology normally used for mortality analysis was adopted in our analysis. This methodology compares the observed mortality reported in each study to the expected mortality given by different life tables.

**Observed Mortality**

Observed mortality was expressed as the geometric average annual mortality rate (\( \bar{q} \)) calculated as \( 1 - P^{1/\Delta t} \) (\( P \) is the cumulative survival rate, and \( \Delta t \) is the length of follow-up in years). The majority of our selected studies provide mortality data as number of deaths during the follow-up, from which we calculate the cumulative mortality rate (\( Q \)); \( P \) is calculated as its complement (\( P = 1 - Q \)), and geometric average annual mortality rate is derived as mentioned above.

As an example, the CHAMP study\(^{12} \) was a randomized open label study comparing combined warfarin and aspirin to aspirin alone in survivors of acute myocardial infarction, from the US Department of Veterans Affairs cooperative studies program. Of 20,036 patients with acute myocardial infarction screened, 5059 patients were entered in the study (between October 20, 1992 and December 31, 1997). The study ended after 6 years. At that time, 882 deaths were reported.

Dividing the number of deaths (\( d \)) during the follow-up by the number of living entrants (\( \ell \)) gives us the cumulative mortality rate \( (Q = d / \ell = 882 / 5059 = 0.1743) \). We calculate the cumulative survival rate (\( P \)) as the complement of the cumulative mortality rate (\( Q \)), ie, \( P = 1 - Q = 1 - 0.1743 = 0.8257 \).

The observed geometric average annual mortality rate is derived from \( P \) as: \( \bar{q} = 1 - P^{1/\Delta t}, \Delta t \) being the duration of follow-up of 6 years: \( \bar{q} = 1 - (0.8257)^{1/6} = 0.0314 \).

**Expected Mortality**

Expected mortality for patients enrolled in this randomized clinical trial was derived from tables based on mortality rates extracted from the US-SOA 1990–95 life table, and expressed as cumulative survival rates by age and duration of follow-up.\(^{61} \) In this study, the median age of patients was 62, expected cumulative survival rate for age 62 years followed for 6 years was: 0.8949 for men and 0.9358 for women. Ninety-eight percent of patients were men, and 2% were women. Therefore, the expected cumulative survival for the entire group is: \( P' = (0.8949 \times 98\%) + (0.9363 \times 2\%) = 0.8957 \).

Expected geometric average annual mortality rate is derived from the expected cumulative survival rate for the group as calculated for observed mortality, ie, \( \bar{q}' = 1 - (P')^{1/\Delta t} \bar{q}' = 1 - (0.8957)^{1/6} = 0.0181 \).

**Mortality Ratio (MR%)**

Mortality ratio (MR%) was calculated as 100 \( (\bar{q}/\bar{q}') \) MR = 100 \( (0.0314 / 0.0181) = 173\% \).
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