Relation between baseline risk and treatment decisions in non-ST elevation acute coronary syndromes: an examination of international practice patterns

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Objectives: To examine the interaction between ST segment depression on the baseline ECG and subsequent in-hospital revascularisation on six month mortality among patients with non-ST elevation acute coronary syndromes. To examine whether ST segment depression influenced clinical decision making and whether there was international variation in the use of cardiac procedures across ST segment depression categories.

Methods: 11 453 patients enrolled in GUSTO-IIB (global use of strategies to open occluded coronary arteries), PARAGON (platelet IIb/IIIa antagonism for the reduction of acute coronary syndrome events in a global organisation network) -A, and PARAGON-B were studied. Patients were categorised as having no ST segment depression, 1 mm ST segment depression in two contiguous leads, and ST segment depression ≥ 2 mm in two contiguous leads. International practice across four geographic regions was examined: USA, Canada, Europe, and Australia/New Zealand.

Results: Revascularisation appeared to have no impact on survival among patients with no ST segment depression; however, revascularisation was associated with a significant survival benefit among patients with ST segment depression ≥ 1 mm. There was an inverse relation between the extent of ST segment depression and the use of angiography as well as angioplasty (p < 0.01). However, patients with ST segment depression ≥ 2 mm were more likely to undergo bypass surgery. The only significant trend of increasing use of revascularisation procedures with increasing ST segment depression was observed in the USA.

Conclusions: International practice patterns in procedure use appear to be insensitive to the extent of ST segment depression. Major opportunities for more efficient delivery of care exist in all regions.
patients enrolled during 1998 in the PARAGON-B troponin substudy. The 1160 patients enrolled in the PARAGON-B troponin substudy, whose ECGs were evaluated by a central core laboratory, constituted a prospectively selected random sample of the overall 5225 patients enrolled in the PARAGON-B trial. Of the total 11 453 patients, baseline ECG data were available for 10 369 (91%). Patients (n = 1521) with factors potentially confounding ECG interpretation—that is, left bundle branch block, right bundle branch block, interventricular conduction delay, left ventricular hypertrophy, ventricular rhythm, or ventricular pacing—were excluded from this study.

**ECG parameters**

ECGs were evaluated at central core laboratories at Duke University, the Canadian Heart Research Centre, and the University of Alberta. Baseline ECGs were recorded in 12 lead format at a paper speed of 25 mm/s. ST segment depression was judged to be present if the J point was depressed by 1 mm or more and was followed by a horizontal or downward sloping ST segment for at least 0.08 seconds in all leads except aVR. ST segment depression was measured and rounded off to the nearest 1 mm. For our analysis, patients were categorised into three mutually exclusive groups: no ST depression, 1 mm ST depression, or ≥ 2 mm ST depression. For limb leads, a minimum of two leads in orderly arrangement (aVL and I, II and aVF, or aVF and III) each having 1 or 2 mm ST depression was required for qualifying as 1 or 2 mm ST depression, respectively. For precordial leads, a minimum of two contiguous leads (V1 and V2, V2 and V3, V3 and V4, and so on) each having 1 or 2 mm ST depression was required for qualifying as 1 or 2 mm ST depression, respectively.

**International practice patterns**

To examine variations in international practice patterns, patients were grouped according to country of enrolment. Four regions were identified: USA (2143); Canada (1023); Europe (4438); and Australia/New Zealand (1013). Owing to the diverse geographic distribution of the remaining 231 patients (Argentina (159), Israel (76), South Africa (46), and Brazil (4)), they were excluded from the analysis. In PARAGON-B, the protocol did not specify guidelines regarding the use of cardiac procedures and all procedures were performed according to local standards of practice.

Revascularisation procedures were recorded for all patients if they were done within the index hospitalisation. Thirty day rates of revascularisation reported by patients were also collected in all three trials. Index hospital rates of use of diagnostic procedures (stress tests and angiography) and revascularisation procedures (PCI and CABG) across ST segment depression category, overall and within each region, were compared. The rates of revascularisation procedure use for patients who underwent angiography were also examined.

**Statistical analyses**

χ² tests (for categorical variables) and the non-parametric Kruskal-Wallis tests (for continuous variables) were used to compare characteristics across groups of patients. Angiography and revascularisation procedure rates across ST segment depression categories were compared by χ² tests for trends. Kaplan-Meier analysis was used to study the association between revascularisation and six month mortality across ST segment depression categories. To reduce selection bias associated with treating patients who did not survive long enough to undergo revascularisation as non-revascularised patients, we performed a landmark analysis. In this analysis, which effectively removes the bias as a result of early hazard, only those patients who had survived to six days (that is, who had the opportunity to undergo

### Table 1 Baseline characteristics by extent of ST segment depression

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>None [n = 4160]</th>
<th>1 mm [n = 3098]</th>
<th>≥2 mm [n = 1590]</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63 (53, 71)</td>
<td>66 (57, 73)</td>
<td>68 (60, 75)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Women (n)</td>
<td>33.5%</td>
<td>37.3%</td>
<td>31.4%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>71 (61, 81)</td>
<td>75 (65, 85)</td>
<td>80 (70, 94)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>135 (120, 150)</td>
<td>140 (122, 155)</td>
<td>140 (120, 155)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>80 (70, 89)</td>
<td>80 (70, 90)</td>
<td>80 (70, 90)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypertension</td>
<td>45.6%</td>
<td>48.9%</td>
<td>50.3%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diabetes</td>
<td>17.3%</td>
<td>19.2%</td>
<td>19.8%</td>
<td>0.03</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>42.1%</td>
<td>38.8%</td>
<td>36.7%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>41.7%</td>
<td>43.0%</td>
<td>41.9%</td>
<td>0.51</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>5.0%</td>
<td>7.4%</td>
<td>8.4%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Previous angina</td>
<td>74.8%</td>
<td>73.7%</td>
<td>74.0%</td>
<td>0.55</td>
</tr>
<tr>
<td>Previous MI</td>
<td>31.1%</td>
<td>29.3%</td>
<td>34.8%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>12.4%</td>
<td>9.5%</td>
<td>6.8%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>11.2%</td>
<td>11.7%</td>
<td>8.4%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>COPD</td>
<td>2.8%</td>
<td>2.6%</td>
<td>3.6%</td>
<td>0.12</td>
</tr>
<tr>
<td>PVD</td>
<td>6.2%</td>
<td>8.4%</td>
<td>11.3%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Enrolment MI</td>
<td>35.2%</td>
<td>43.0%</td>
<td>58.9%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Regions</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>USA</td>
<td>58.8%</td>
<td>26.6%</td>
<td>14.6%</td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>55.5%</td>
<td>28.0%</td>
<td>16.5%</td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>40.6%</td>
<td>38.7%</td>
<td>20.7%</td>
<td></td>
</tr>
<tr>
<td>Australia/NZ</td>
<td>42.6%</td>
<td>42.1%</td>
<td>15.3%</td>
<td></td>
</tr>
</tbody>
</table>

Continuous variables presented as median (25th, 75th centile).
BP, blood pressure; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; NZ, New Zealand; PCI, percutaneous transluminal coronary angioplasty; PVD, peripheral vascular disease.
revascularisation) were included. The six day cut off was chosen because the median time to revascularisation in the cohort was six days (interquartile range 3–10 days). Survival curves were compared by the log rank test statistic. We used Cox regression analysis to examine the association between baseline variables and six month mortality. Given that revascularisation is not a baseline variable, it was included as a time dependent covariate, and the interaction between revascularisation status and the presence of ST segment depression > 1 mm was examined.15

RESULTS

Patient population

Of the total 11 453 study patients, ECG data were available for 10 369 (91%). Patients with missing ECG data were less likely to have a myocardial infarction on presentation and had lower frequency of prior revascularisation procedures. There were no other significant differences in baseline characteristics between the two groups. After exclusion of 1521 patients with ECG confounders, the final study sample comprised 8848 patients. The distribution of these patients across ST segment depression categories was as follows: 4160 (47%) had no ST segment depression; 3098 (35%) had ST segment depression of 1 mm; and 1590 (18%) had ST segment depression > 2 mm.

Table 1 provides baseline and clinical characteristics of study patients according to ST segment depression status. Patients with ST segment depression > 2 mm were older, more likely to be men, and less likely to have undergone a previous PCI or CABG. The frequency of risk factors including hypertension and diabetes was higher in these patients and they more often had congestive heart failure, previous myocardial infarction, and peripheral vascular disease. In addition, the likelihood of presenting with myocardial infarction as the index event increased with the extent of ST segment depression (35% among patients with no ST segment depression, 43% among patients with ST segment depression of 1 mm, and 59% among patients with ST segment depression > 2 mm; p < 0.01). In keeping with the higher risk profile, six month mortality was significantly higher among patients with ST segment depression > 2 mm compared to those with no ST segment depression (0.35 vs. 0.22; HR 1.59, 95% CI 1.28 to 2.00, p < 0.01).

Table 2 Variables associated with a higher mortality hazard at six months based on Cox regression analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>( z^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.06</td>
<td>1.05 to 1.07</td>
<td>128.6</td>
</tr>
<tr>
<td>ST segment depression &gt; 1 mm</td>
<td>1.96</td>
<td>1.59 to 2.41</td>
<td>39.1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.74</td>
<td>1.43 to 2.12</td>
<td>31.0</td>
</tr>
<tr>
<td>MI on enrolment</td>
<td>1.57</td>
<td>1.31 to 1.89</td>
<td>23.4</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1.84</td>
<td>1.45 to 2.33</td>
<td>24.8</td>
</tr>
<tr>
<td>COPD</td>
<td>1.96</td>
<td>1.40 to 2.76</td>
<td>15.3</td>
</tr>
<tr>
<td>PVD</td>
<td>1.29</td>
<td>1.25 to 2.03</td>
<td>14.0</td>
</tr>
<tr>
<td>Previous MI</td>
<td>1.43</td>
<td>1.18 to 1.74</td>
<td>13.7</td>
</tr>
<tr>
<td>Previous angina</td>
<td>1.52</td>
<td>1.17 to 1.97</td>
<td>9.6</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>0.85</td>
<td>0.70 to 1.02</td>
<td>2.9</td>
</tr>
<tr>
<td>CI, confidence interval; HR, hazard ratio.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio.

Figure 1 Use of angiography and revascularisation procedures across ST segment depression (ST ↓) categories (left) overall and (right) among patients who underwent angiography. CABG, coronary artery bypass graft surgery; PCI, percutaneous coronary intervention. *χ² test for trend significant at p < 0.05.

Figure 2 Unadjusted six month survival by ST segment category and revascularisation status. To reduce selection bias associated with treating patients who did not survive long enough to undergo revascularisation as non-revascularised patients, this analysis was restricted to patients who had survived to six days after admission.
The key finding of our study was the paradoxical absence of a relation between the extent of baseline ST segment depression and the use of an invasive diagnostic and management strategy for patients with ACS. In fact, an invasive strategy was selected least often for those at highest risk for adverse outcomes. The potential consequences of this are twofold. However, the interaction between revascularisation and the presence of ST segment depression ≥ 1 mm was significant (hazard ratio 0.62, 95% CI 0.38 to 1.0) suggesting that revascularisation was beneficial for patients with ST segment depression of ≥ 1 mm, after adjustment for baseline variables.

**International practice patterns**

Of the 8848 patients enrolled in the study, 2143 (24%) were enrolled in the USA, 1023 (12%) in Canada, 4438 (50%) in Europe, 1013 (11%) in Australia/New Zealand, and 231 (3%) in other countries that were excluded from the analysis. Table 1 shows the distribution of ST segment depression across region of enrolment. Compared with the other regions, European countries enrolled a significantly higher number of patients with ST segment depression ≥ 2 mm (15% in the USA, 17% in Canada, 21% in Europe, and 15% in Australia/New Zealand, p < 0.01).

The use of stress tests was higher in Canada and Europe, whereas the rates of angiography use were significantly higher in the USA than in the other regions (fig 3). There were no significant differences in the use of angiography across ST segment depression categories. Figure 4 presents region specific procedure rates across ST segment depression categories. In general, use of PCI decreased with extent of ST segment depression (fig 4, panel B) in both the USA and Europe. The highest correlation between ST segment depression and CABG use was in the USA with rates of 17% in patients with no ST segment depression, 24% in patients with 1 mm ST segment depression, and 33% in patients with ST segment depression ≥ 2 mm (p value for trend < 0.01). When we examined the combined revascularisation rates (for PCI or CABG), the only significant trends in procedure use across ST segment depression categories was observed in the USA (fig 4, panel C). The patterns across ST segment depression categories remained consistent when revascularisation rates were calculated for only those patients who had undergone coronary angiography.
subanalyses of the FRISC-II study.16 17 In the FRISC-II ECG laboratory ECG evaluations, are consistent with the results of based on the largest database of patients with ACS with core tion and mortality across ST segment depression categories, Our findings of the association between early revascularisa-

Prior studies
Our findings of the association between early revascularisation and mortality across ST segment depression categories, based on the largest database of patients with ACS with core laboratory ECG evaluations, are consistent with the results of subanalyses of the FRISC-II study. In the FRISC-II ECG

International practice patterns
Assessing performance and providing feedback have been described as integral components of improving quality of health care delivery.18 Our examination of international practice patterns between 1995 and 1998 is an excellent benchmark against which to measure the impact of recent American College of Cardiology/American Heart Association guidelines and European Society of Cardiology guidelines, which offer a class 1A recommendation for the use of early invasive treatment for patients with ACS presenting with new or presumably new ST segment deviations.19 20 Our study has several findings that are relevant to clinical practitioners as well as policymakers. Firstly, a higher percentage of patients with ST segment depression was enrolled in Europe (59%) than in North America (41% in the USA and 44% in Canada; table 1). This may contribute to the increased mortality documented in European countries in previous studies.21 22 Secondly, as documented previously, the USA had the highest rates of angiography among the regions (fig 3). A consequence of such an aggressive management strategy was the identification of the highest percentage of candidates for CABG not only among patients with ST segment depression ≥ 2 mm (33% compared with 14% in Canada, 15% in Europe, and 11% in Australia/New Zealand) but also among patients with no ST segment depression (17% compared with 8% in Canada, 9% in Europe, and 8% in Australia/New Zealand). This may, in part, explain the observed benefit from an early invasive risk stratification strategy compared with a conservative strategy in clinical trials. Thirdly, and most important, major opportunities remain to improve clinical decision making with respect to the use of revascularisation in all regions but especially in Canada and Europe. In these regions, there were no significant differences in revascularisation rates across ST segment depression categories, and only a third of the patients most likely to benefit from revascularisation received it. In the USA, although revascularisation rates appear more sensitive to the extent of ST segment depression, of the 59% of patients without ST segment depression for whom revascularisation appears to offer no benefit, 81% underwent angiography and 49% underwent PCI or CABG. Channelling of these resources towards more high risk patients should result in more cost effective and efficient delivery of care.

Some limitations of our study should be noted. Owing to the observational nature of the study design and the fact that revascularisation was a post-randomisation event, the association between revascularisation and outcomes must be considered hypothesis generating. Secondly, our study examined practice patterns within the context of clinical trials, which may not be entirely representative of overall practice. However, to the extent that practice patterns among clinicians participating in clinical trials are likely to be more evidence based, even more opportunities to improve practice probably exist at a population level. Thirdly, protocols for GUSTO-IIB and PARAGON-A discouraged the use of early revascularisation unless necessitated by the presence of recurrent ischaemia. Although this may be a factor, it is

Figure 4 Use of revascularisation procedures by ST segment depression categories and geographic region: (A) PCI; (B) CABG; (C) either PCI or CABG.
unlikely to explain the large differences in practice patterns across ST segment categories in the four regions. This is substantiated by the similarity of patterns in PARAGON-B in which revascularisation decisions were left entirely to the practitioner’s discretion. Fourthly, our study did not capture procedure rates beyond 30 days. To the extent that time to revascularisation, especially for CABG, is longer in Europe, our rates may underestimate the overall revascularisation rates in this region. Lastly, several countries were grouped together in the European region and the contributions of patients to the three trials differed significantly for many of the countries. The heterogeneity of countries within these regions is not accounted for in these analyses.

Conclusions
We found in data from three large international ACS trials with core laboratory ECG evaluations that revascularisation had no apparent impact on outcomes among patients with no ST segment depression but was associated with significantly lower mortality rates among patients with $\geq 1$ mm ST segment depression. International practice patterns with respect to diagnostic and revascularisation procedures appear to be insensitive to the extent of ST segment depression on the baseline ECG. Major opportunities for more efficient delivery of care exist in all regions.

ACKNOWLEDGEMENTS
The GUSTO-IIB trial was supported in part by Guidant Corporation, Redwood City, California and by Ciba-Geigy, Summit, New Jersey. The PARAGON-A trial was supported by F Hoffmann-La Roche Ltd, Basel, Switzerland. The PARAGON-B trial was supported by F Hoffmann-La Roche Ltd, Basel, Switzerland; Roche Diagnostics Corporation, Indianapolis, Indiana, USA; and Roche Diagnostics GmbH, Mannheim, Germany.

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*Also Duke University, Durham, North Carolina, USA

APPENDIX
List of countries (number of patients enrolled in all three trials)
USA (2143); Canada (1023); Europe (4438): Belgium (665); France (585); Germany (176); Italy (1003); Netherlands (755); Spain (670); Sweden (188);United Kingdom (179); Switzerland (68); Poland (451); Portugal (28); Iceland (67); Finland (182); Denmark (54); Hungary (145); Australia/New Zealand (1013): Australia (855); New Zealand (158); Other (231): Argentina (159); Brazil (4); Israel (76); South Africa (46).

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*Heart* 2005 91: 876-881
doi: 10.1136/hrt.2004.042887

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