Management Patterns in Relation to Risk Stratification Among Patients With Non–ST Elevation Acute Coronary Syndromes

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Background: Randomized clinical trials have established the efficacy of an early invasive management strategy for high-risk non–ST elevation acute coronary syndromes (ACSs). We examined the use of in-hospital cardiac catheterization and medications in relation to risk across the broad spectrum of non–ST elevation ACSs.

Methods: We evaluated 4414 patients with non–ST elevation ACSs in the prospective, multicenter, Canadian ACS 1 (September 1, 1999–June 30, 2001) and ACS 2 (October 1, 2002–December 31, 2003) Registries. Patients were stratified into low-, intermediate-, and high-risk groups based on tertiles of the calculated Global Registry of Acute Coronary Events risk score (a validated predictor of in-hospital mortality).

Results: Although in-hospital mortality rates were similar, the in-hospital use of cardiac catheterization increased significantly over time (38.8% in the ACS 1 Registry vs 63.5% in the ACS 2 Registry; P<.001). The rates of cardiac catheterization in the low-, intermediate-, and high-risk groups were 48.0%, 41.1%, and 27.3% in the ACS 1 Registry, and 73.8%, 66.9%, and 49.7% in the ACS 2 Registry, respectively (P<.001 for trend for both). After adjusting for other confounders, intermediate-risk (adjusted odds ratio, 0.75; 95% confidence interval, 0.63-0.90; P<.001) and high-risk (adjusted odds ratio, 0.35; 95% confidence interval, 0.28-0.45; P<.001) patients remained less likely to undergo cardiac catheterization compared with low-risk patients. Furthermore, there existed a similar inverse relationship between risk and the use of in-hospital revascularization and medications.

Conclusions: Despite temporal increases in the use of cardiac catheterization and revascularization in the management of non–ST elevation ACSs, evidence-based invasive and pharmacological therapies remain paradoxically targeted toward low-risk patients. Strategies to eliminate this treatment-risk paradox must be implemented to fully realize the benefits and optimize the cost-effectiveness of invasive management.

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Group Information: A list of the Canadian Acute Coronary Syndromes 1 and 2 Registry Investigators appears on page 1014.

Based on evidence from randomized clinical trials,1-3 the American College of Cardiology/American Heart Association guidelines recommend an early invasive strategy in the management of high-risk non–ST elevation (NSTE) acute coronary syndromes (ACSs).4 Despite regional variations, there has been a tremendous increase in the use of invasive cardiac procedures in developed countries during the past decade.5,6 Previous studies7-15 have demonstrated that factors other than individual patient characteristics, such as physician specialty and availability of on-site cardiac catheterization facilities, may also be important determinants of invasive vs conservative medical treatment. Yet, indiscriminate use of invasive procedures may have an unfavorable effect on the treatment risk-benefit ratio for the individual patient and on the overall cost-effectiveness for society.5,16,17 Although selection bias is possible, several observational studies11-13,18 have reported a lack of association between higher rates of cardiac catheterization and improved clinical outcomes, suggesting that the benefits demonstrated in clinical trials have not been translated into “real-life” practice.

For editorial comment see page 987
SUDY DESIGN AND POPULATION
The objectives and study design of the Canadian ACS Registry have been published. In brief, patients were eligible if the following was true: (1) they were 18 years or older on presentation, (2) they were admitted to the hospital with a suspected ACS (defined by symptoms consistent with acute cardiac ischemia within 24 hours of onset), and (3) the qualifying ACS was not accompanied by a serious concurrent illness, such as trauma. To reduce patient selection bias, there were no other specific exclusion criteria, and consecutive patient recruitment was encouraged at all participating hospitals. At each site, the designated physician or study coordinator recorded data on standardized case report forms, which were then centrally scanned into an electronic database (Teleform, version 7.0; Cardiff, San Diego, Calif) at the Canadian Heart Research Centre. Data checks were performed centrally, and queries were sent to sites for data correction. The study received approval by the local hospital research ethics board, and all patients who were followed up after discharge provided informed consent.

Between September 1, 1999, and June 30, 2001, 5312 patients from 51 hospitals were recruited into the Canadian ACS 1 Registry. Of these patients, 4627 (87.1% of all patients enrolled) had a final ACS diagnosis according to the treating physician. The present study focuses on the 3293 patients with NSTE ACSs who did not have an ST segment elevation of 0.1 mV or greater in 2 or more contiguous leads on their admission electrocardiograms. The ACS 2 Registry included only patients with suspected NSTE ACS. Between October 1, 2002, and December 31, 2003, 2359 patients were enrolled from 36 participating hospitals, and 1956 (82.9%) had a final ACS diagnosis. Thus, 5251 patients with NSTE ACS were recruited in the Canadian ACS 1 and ACS 2 Registries. In this analysis, we excluded patients who were enrolled after being transferred from another acute care institution (397 [7.6%]). There-
short was 116 (94-141); the median (interquartile range) GRACE risk scores in the ACS 1 and ACS 2 Registries were 114 (93-140) and 118 (97-145), respectively (P < .001).

The all-cause mortality during hospitalization was 1.8% overall and did not differ significantly between the ACS 1 and ACS 2 Registries (1.8% vs 1.8%; P = .86). The composite end point of death or myocardial (re)infarction occurred in 5.0% and 5.8% of patients in the ACS 1 and ACS 2 Registries, respectively (P = .27). The GRACE risk score demonstrated good discrimination for in-hospital death, with a C statistic of 0.82 (95% CI, 0.77-0.86; P < .001). The GRACE risk score also predicted the composite end point of death or myocardial (re)infarction during the index admission (C statistic, 0.64; 95% CI, 0.61-0.68; P < .001).

Overall, 47.5% of patients underwent cardiac catheterization during the index hospitalization. There was a significant increase in the use of cardiac catheterization over time: the rates were 38.8% and 63.5% in the ACS 1 and ACS 2 Registries, respectively (P < .001). Overall, men underwent catheterization more frequently than women (50.8% vs 41.1%; P < .001). Patients treated by an attending cardiologist were more likely to be managed by an invasive strategy (59.8% vs 29.8%; P < .001). There was a positive association between on-site availability and the use of a cardiac catheterization laboratory in patient management (71.6% vs 38.9%; P < .001). These differences in the use of cardiac catheterization were observed in both registries.

The rates of cardiac catheterization by tertiles of GRACE risk score in the ACS 1 and ACS 2 Registries are illustrated in Figure 1. The calculated GRACE risk score was significantly lower among patients who underwent ACS 1

| Table 1. Baseline Characteristics of the Study Population* |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Characteristic   | ACS 1 Registry  | ACS 2 Registry  | ACS 1 Registry  | ACS 2 Registry  | ACS 1 Registry  | ACS 2 Registry  | ACS 1 Registry  | ACS 2 Registry  |
|                  | Low Risk (n = 2834) | Intermediate Risk (n = 2834) | High Risk (n = 2834) | Overall (n = 2834) | Low Risk (n = 2834) | Intermediate Risk (n = 2834) | High Risk (n = 2834) | Overall (n = 2834) |
| Age, y†         | 68 (59-79) | 70 (60-81) | 84 (70-103) | 73 (62-87) | 74 (63-85) | 73 (64-85) | 86 (70-101) | 76 (65-90) |
| Systolic blood pressure, mm Hg† | 155 (139-177) | 150 (133-169) | 139 (120-158) | 148 (130-169) | 154 (140-177) | 146 (130-168) | 143 (120-161) | 148 (130-168) |
| Killip class    | I 98.1 89.8 59.4 82.5 98.3 91.9 61.6 84.0 |
|                | II 1.9 10.0 30.5 14.1 1.7 7.6 25.8 11.6 |
|                | III/IV 0 0.2 10.1 3.4 0 0.6 12.6 4.4 |
|                | Cardiac arrest 0 0.1 2.2 0.8 0 0.6 1.1 0.6 |
|                | ST depression 3.5 13.9 38.5 18.6 4.9 16.1 45.2 22.0 |
|                | Abnormal 25.7 37.3 53.9 38.9 39.8 56.5 70.0 55.4 |
| Serum creatinine level, mg/dL† | 0.96 (0.84-1.10) | 1.01 (0.88-1.20) | 1.17 (0.95-1.47) | 1.03 (0.88-1.23) | 0.97 (0.89-1.11) | 1.03 (0.88-1.20) | 1.17 (0.96-1.50) | 1.04 (0.89-1.24) |

Abbreviations: ACS, Acute Coronary Syndrome; bpm, beats per minute; CABG, coronary artery bypass grafting; HF, heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

SI conversion factor: To convert creatinine to micromoles per liter, multiply by 88.4.

*Data are given as percentage of each group unless otherwise indicated.
†Data are given as median (25th-75th percentile).

Figure 1. In-hospital cardiac catheterization rates by tertiles of Global Registry of Acute Coronary Events risk score in the Acute Coronary Syndrome (ACS) 1 (n = 2834) and ACS 2 (n = 1580) Registries, P < .001 for trend (low- vs intermediate- vs high-risk groups) in both ACS 1 and 2 Registries.

P < .001. These differences in the use of cardiac catheterization were observed in both registries.

The rates of cardiac catheterization by tertiles of GRACE risk score in the ACS 1 and ACS 2 Registries are illustrated in Figure 1. The calculated GRACE risk score was significantly lower among patients who underwent
cardiac catheterization compared with those who did not (P < .001). Despite an overall increase in the rate of cardiac catheterization, the pattern of less frequent use among higher-risk patients persisted in the ACS 2 Registry (P < .001 for trend for both). Table 2 shows the relationship between medication use and risk in the overall study population.

In multivariable analysis, higher GRACE risk scores remained an independent negative predictor of cardiac catheterization during the index hospitalization (Table 3). The model C statistic and Hosmer-Lemeshow P value were 0.75 and 0.28, indicating good discrimination and adequate fit, respectively. The inverse relationship between GRACE risk groups and use of cardiac catheterization was similar irrespective of sex, physician specialty, the availability of an on-site cardiac catheterization laboratory, and time of recruitment (P values are not significant for the interaction). Analysis using imputed GRACE risk scores for patients with missing data yielded similar results. Moreover, the exclusion of late cardiac catheterizations (>10 days after admission), elderly patients (>75 years), patients with early (within 2 days of admission) or in-hospital death, and renal dysfunction (serum creatinine level, >2 mg/dL) did not modify the results. When age was entered into the model, the GRACE risk score maintained an independent negative association with the use of cardiac catheterization.

Cardiac catheterization was performed at a median (interquartile range) of 4 (2-7), 4 (3-7), and 5 (3-7) days after admission in the low-, intermediate-, and high-risk groups, respectively (P=.06). There was no significant correlation between the time to cardiac catheterization and GRACE risk score analyzed as a continuous variable. Cox proportional hazards regression analysis confirmed that the rates of cardiac catheterization were significantly lower among high-risk (adjusted hazard ratio, 0.82; 95% CI, 0.77-0.86; P < .001) and intermediate-risk (adjusted hazard ratio, 0.82; 95% CI, 0.77-0.86; P < .001) patients compared with the low-risk group.

Overall, 19.9% and 6.0% of patients underwent in-hospital PCI and CABG, respectively. Compared with their counterparts in the ACS 1 Registry, ACS 2 Registry patients were more frequently treated with PCI (13.7% vs 30.9%) and CABG (4.1% vs 9.4%) (P < .001 for both). Figure 2 and Figure 3 show the rates of PCI and CABG, respectively, according to tertiles of GRACE risk score. The overall rates

Table 2. Medication Use in Relation to GRACE Risk Score*

<table>
<thead>
<tr>
<th>Type of Medication</th>
<th>Low-Risk Group (n = 1477)</th>
<th>Intermediate-Risk Group (n = 1471)</th>
<th>High-Risk Group (n = 1465)</th>
<th>P Value for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within the first 24 h of admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>94.6</td>
<td>92.2</td>
<td>89.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Clopidogrel or ticlopidine</td>
<td>26.3</td>
<td>25.9</td>
<td>22.8</td>
<td>.03</td>
</tr>
<tr>
<td>Heparin</td>
<td>94.7</td>
<td>90.6</td>
<td>87.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIa inhibitor</td>
<td>7.4</td>
<td>8.2</td>
<td>6.1</td>
<td>.19</td>
</tr>
<tr>
<td>Discharge use†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>90.4</td>
<td>87.9</td>
<td>83.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Clopidogrel or ticlopidine</td>
<td>37.8</td>
<td>36.4</td>
<td>28.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Oral anticoagulant</td>
<td>3.4</td>
<td>6.9</td>
<td>13.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>82.5</td>
<td>80.1</td>
<td>71.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>53.6</td>
<td>57.1</td>
<td>61.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Lipid-modifying agents</td>
<td>71.1</td>
<td>68.1</td>
<td>53.1</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; GRACE, Global Registry of Acute Coronary Events; NA, data not applicable; OR, odds ratio.

*Data are given as percentage of each group.
†Among hospital survivors.
of revascularization (by either PCI or CABG) were significantly lower among high-risk patients (P<.001 for trend).

Among the 2096 patients who underwent cardiac catheterization, the rates of revascularization (PCI or CABG) were similar across the risk groups. However, higher-risk patients were less likely to be revascularized by PCI (P = .005 for trend) and more frequently underwent CABG (P = .002 for trend) in the ACS 2 Registry.

Follow-up data were available for 3894 survivors at 1 year. There was a persistent inverse relationship between GRACE risk score and the use of cardiac catheterization and PCI (P<.001 for trend for both) after the index hospitalization. There was no significant difference in the rates of postdischarge CABG among the 3 risk groups (P = .51 for trend).

The principal finding of this observational study is that despite substantial temporal increases in cardiac catheterization and revascularization, evidence-based invasive and pharmacological therapies remained paradoxically targeted toward lower-risk patients with NSTE ACSs. This treatment-risk mismatch was independent of other factors, such as physician specialty and the on-site availability of cardiac catheterization facilities. These findings suggest that use of resources and delivery of care for NSTE ACSs may be suboptimal.

The past decade has witnessed a considerable increase in the use of invasive cardiac procedures in the developed world. Although evidence from randomized clinical trials supports an early invasive strategy in the management of high-risk NSTE ACSs, several studies have raised concerns regarding its generalizability by demonstrating that higher rates of cardiac catheterization are often not associated with better outcomes. This discrepancy between treatment efficacy and effectiveness may arise when selectively beneficial, but potentially harmful, treatment is inappropriately directed to patients who are least likely to benefit. Consistent with previous studies, our results confirm that patient sex, physician specialty, and the availability of cardiac catheterization facilities on site may influence treatment decisions. However, even after controlling for these confounding factors, there exists a strong inverse relationship between baseline risk and treatment intensity.

The phenomenon of treatment-risk discordance we observed is not unique and has been documented in patients hospitalized for heart failure and in ambulatory patients with cardiovascular diseases. Guidelines recommend an early invasive strategy for high-risk patients, while conservative medical therapy is acceptable in the absence of adverse prognosticators. Although data from large administrative databases suggest that high-risk patients are less likely to undergo cardiac catheterization, such risk assessment included noncardiovascular comorbidities that might be particularly prevalent in these elderly cohorts. Because invasive treatment would not be expected to improve poor outcome due to serious comorbidities, it is unclear whether such decisions to withhold aggressive therapies were clinically appropriate. In contrast, randomized clinical trials have unequivocally shown that specific high-risk features, such as ST depression or elevated biomarker level, are associated with greater treatment benefits of an early invasive strategy. Recently, Roe and colleagues reported that patients with normal troponin levels underwent invasive procedures more frequently than those with mild troponin elevations, who had a worse outcome. However, care pattern in relation to comprehensive risk stratification, as recommended in contemporary practice guidelines, has not been well defined.

The GRACE risk score was derived from a large multinational registry of unselected patients with ACS and was specifically designed for risk stratification in routine clinical practice. It integrates hemodynamic variables, electrocardiographic findings, and biomarker results into overall risk assessment. The GRACE risk score has been externally validated in other patient cohorts. Furthermore, revascularization was independently associated with better long-term outcome only among high-risk patients stratified by GRACE risk score. Therefore, in addition to predicting outcome, the GRACE risk score may guide initial patient management. However, the present study demonstrates that higher-risk patients stratified by GRACE risk score were in fact less likely to undergo invasive procedures and receive proved medical therapies. Furthermore, this observation was not confounded by advanced age, a surrogate marker of comorbidities, or renal dysfunction, which may be perceived as relative contraindications to invasive management. The sensitivity analyses further confirmed the robustness of our results. Finally, the similar timing of cardiac catheterization irrespective of the patient risk profile indicates the lack of an effective triage system that ensures prompt treatment for the highest-risk patient. Although diagnostic cardiac catheterization per se would not improve patient outcome, it represents a critical point in the management of patients who are potential candidates for revascularization. Our data show that the overall lower rates of revascularization among high-risk patients were largely explained by the less frequent use of cardiac catheterization. Conversely, among patients who underwent cardiac catheterization in the ACS 2 Regis-
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try, higher GRACE risk scores may portend more extensive coronary artery disease or impaired left ventricular function, which may explain the preferential use of CABG for revascularization in this high-risk group.

A variety of reasons may account for the dissociation of risk and treatment propensity in the management of NSTE ACSs. Physicians may fail to recognize high-risk clinical features or to properly integrate them into over-
all risk stratification. Underestimation of risk could then lead to inappropriately conservative management. Some physicians may be skeptical of the applicability of clinical trial evidence to individual patients, especially those at high risk. Alternatively, physicians may not appreciate the greater absolute benefits that may outweigh the risk of treatment in these high-risk patients. Furthermore, under increasing scrutiny of operator performance, physicians may be reluctant to recommend or perform invasive procedures for patients at increased risk of treatment complications, despite an overall favorable benefit-risk ratio.23,24 Finally, “therapeutic nihilism”—misguided beliefs that treatment is ineffective in patients with poor outcome and is, therefore, not indicated—may result in undertreatment. Nevertheless, the treatment-risk paradox observed is probably multifactorial and future research should elucidate the precise mechanisms.

Several limitations of this study merit discussion. Consecutive patient enrollment was encouraged at all sites but could not be ascertained. Indeed, the relatively low in-hospital mortality rate implies that patients with early deaths were excluded. Although this may have introduced an unmeasurable selection bias, our findings should remain generalizable to survivors for whom risk stratification and early invasive management are applicable. While the GRACE risk score is an objective and validated tool for early risk stratification, it cannot replace clinical judgment in the management of individual patients. For example, revascularization may be indicated to improve functional status and quality of life even for low-risk patients. However, the patient’s course of hospitalization or hidden biases were unlikely to completely abrogate the substantial treatment-risk paradox we observed. In the ACS 2 Registry, patient preference was not a major reason for conservative management in the high-risk group (data not shown). Finally, we did not collect detailed information on absolute and relative contraindications to medications in the ACS 1 Registry.

In conclusion, we found a persistent, independent, and strong inverse relationship between baseline risk and likelihood of invasive management across the broad spectrum of NSTE ACSs, despite an overall proliferation in the use of the invasive cardiac procedures during the past few years. These findings underscore a significant opportunity to improve the care process for patients with NSTE ACSs. Quality improvement strategies should focus on eradicating the treatment-risk paradox so that treatment efficacy demonstrated in clinical trials can be better translated into tangible clinical benefits in the “real world.”

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