

Long-Term Mortality of Patients With Acute Myocardial Infarction in the United States and Canada

Comparison of Patients Enrolled in Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO)-I

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Background—In a previous substudy of the GUSTO-I trial, we observed better functional and quality-of-life outcomes among patients in the United States (US patients) compared with patients in Canada. Rates of invasive therapy were significantly higher in the United States and were associated with a small mortality benefit (0.4%, adjusted $P=0.02$). We sought to determine whether Canadian-US differences in practice patterns in GUSTO-I had an impact on 5-year mortality.

Methods and Results—Mortality data for 23 105 US and 2898 Canadian patients enrolled in GUSTO-I were obtained from national mortality databases. Median follow-up was 5.46 years in the US and 5.33 years in the Canadian cohort. Five-year mortality rate was 19.6% among US and 21.4% among Canadian patients ($P=0.02$). After baseline adjustment, enrollment in Canada was associated with a higher hazard of death (1.17; 95% confidence interval, 1.07 to 1.28, $P=0.001$). Revascularization rates during the index hospitalization in the United States were almost 3 times those in Canada: 30.5% versus 11.4% for angioplasty and 13.1% versus 4.0% for bypass surgery ($P<0.01$ for both). After accounting for revascularization status as a time-dependent covariate, country was no longer a significant predictor of long-term mortality. These results were confirmed in a propensity-matched analysis.

Conclusions—Our results suggest, for the first time, that the more conservative pattern of care with regard to early revascularization in Canada for ST-segment elevation acute myocardial infarction may have a detrimental effect on long-term survival. Our results have important policy implications for cardiac care in countries and healthcare systems wherein use of invasive procedures is similarly conservative. (*Circulation*. 2004;110:1754-1760.)

Key Words: myocardial infarction ■ mortality ■ revascularization

Differences between Canada and the United States in the management of patients after acute myocardial infarction are well documented in the current literature. In a previously reported substudy of the landmark Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO-I) trial,¹ we compared 1-year functional status and mortality among a random sample of United States (US) and Canadian patients enrolled in the trial.² We hypothesized that the better functional status and quality of life among US patients compared with Canadian patients was attributable, in part, to differences in early revascularization strategies between the 2 countries. Other studies have provided data to support this hypothesis.³⁻⁵ Rates of cardiac catheterization, coronary angioplasty, and coronary bypass surgery are 2 to 3 times higher in US patients than in their Canadian counter-

parts.^{3,6,7} These dramatic differences in procedure rates have persisted during the past decade and highlight the disparity in the availability of onsite facilities in the 2 countries.

However, the obvious differences in practice patterns do not appear to have a significant impact on mortality rates. The 0.4% higher mortality rate, at 1 year, among Canadian patients found in the GUSTO-I study, though statistically significant after baseline adjustment, was not considered large enough to justify any policy recommendations about the use of revascularization services in either country. One year, however, may be an inadequate time to assess the impact of differences in early revascularization strategies on mortality. Mortality associated with revascularization, especially coronary bypass surgery, is characterized by an increased early risk followed by a 3- to 5-year period of declining mortality

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as the benefits of the procedures manifest themselves relative to medical therapy alone.⁸ Accordingly, we examined the effects of differences in practice patterns between Canada and the United States in the treatment of GUSTO-I patients on 5-year mortality.

Methods

As previously described, 41 021 patients with ST-segment-elevation acute myocardial infarction (STEMI) eligible for thrombolytic therapy were enrolled in the GUSTO-I study between December 1990 and February 1993.¹ Patients were randomly allocated to 1 of 4 treatment strategies: streptokinase with subcutaneous heparin, streptokinase with intravenous heparin, accelerated alteplase (tPA) with intravenous heparin, or a combination of tPA and streptokinase with intravenous heparin. The primary end point was death from any cause at 30 days; 1-year mortality was a secondary end point of the study.⁹ The present study population consisted of 23 105 GUSTO-I patients enrolled at US sites and 2898 patients enrolled in Canada.

Follow-Up Data

Detailed patient demographic information, including the address and telephone number of the patient and a contact, was collected on enrollment into GUSTO-I and updated at 1 year. For US patients, these data were submitted to the National Death Index (NDI), and each patient's vital status as of December 31, 1997, was obtained. The NDI is a database compiled by the National Center for Health Statistics of all deaths in the United States since 1979. Patient data submitted to the NDI were social security number, name, birth date, sex, race, marital status, and last known state of residence. All matches designated as true matches by the NDI were accepted as deaths for this analysis. In cases in which the probability of a match was high but not high enough to be considered a true match (eg, the patient matched on date of birth and/or social security number but did not match exactly on the name), the Social Security Index derived from the US Social Security Administration Death Master File was queried.

Mortality status as of December 31, 1997, for Canadian patients enrolled in GUSTO-I was obtained from the Canadian Mortality Database (CMDB). Records were linked from the patient's surname, given name, date of birth, and sex. Given that no unique patient identifier, eg, social insurance number, exists for these patients, an established method of probabilistic linkage was used.¹⁰ Each Canadian patient record in GUSTO-I was compared with each record in the CMDB. Each link was assigned a relative probability of being a definite link. This probability was compared with 2 predefined thresholds. If the probability was higher than the upper threshold, the link was considered to be true; if the probability fell between the 2 thresholds, it was considered a possible link, and these were examined in more detail to achieve manual resolution.

The validity of the linking process and the completeness of the CMDB and the NDI have been previously documented. The NDI may be considered a "gold standard" for mortality ascertainment and has repeatedly demonstrated high sensitivity and specificity rates.¹¹ For example, in a study of 500 deceased and 3487 veterans known to be alive, the NDI merge by social security number accurately identified 97% of the deaths (sensitivity rate). The corresponding specificity rate, ie, the percentage of living patients not identified as dead, was 99%.¹² Similarly, in a blinded merge of 757 known deaths and 1000 alive patients with the CMDB, 93.1% of all deaths and 97.6% of deaths within Canada were identified. The specificity rate for the merge was 99.5%.¹³

Statistical Analysis

For the study, all 4 treatment arms in GUSTO-I were combined, and US and Canadian patients were then compared. Baseline characteristics of patients were summarized as medians with 25th and 75th percentiles for continuous variables, and the Mann-Whitney *U* test was used for comparisons between groups. For categorical variables, the data were summarized in percentages, and Fisher's exact tests or

χ^2 tests were used to assess group differences. Unadjusted Kaplan-Meier survival curves were calculated for each of the 2 countries and compared by the log-rank statistic.

Univariate analysis was performed to assess the relation between baseline variables (presented in Table 1) and 5-year mortality. A multivariable Cox model was developed through backward, stepwise variable selection procedures to assess the joint effects of baseline and hospital variables on mortality.¹⁴ Hospital variables included a volume indicator (obtained by categorizing hospitals in quartiles based on the number of patients enrolled in the trial) and a variable indicating whether the hospital had onsite cardiac catheterization facilities. The impact of revascularization during the index hospitalization on long-term mortality was assessed by adding it to the aforementioned Cox regression model. Given that revascularization is not a baseline variable, it was included as a time-dependent covariate.¹⁵

Comparisons of care and outcomes across different healthcare systems are of necessity nonrandomized and observational. To adjust for confounding, we conducted a propensity-matched analysis, which attempts to simulate a randomized, controlled trial by matching patients in both cohorts on all observed characteristics.¹⁶ We conducted the propensity analyses in a sequential fashion. First, we developed a logistic regression model to measure the propensity of belonging to the Canadian cohort based on baseline demographic and clinical patient characteristics. The c index for the model was 0.66 (95% confidence interval [CI], 0.65 to 0.67). We used the propensity score generated by this model to create a 1-to-1 matched cohort of Canadian and US patients. A total of 1661 patients (57%) were matched at the 5-decimal level of the propensity score, 1056 (36%) were matched at the 4-decimal, 154 (5%) at the 3-decimal, 24 (0.1%) at the 2-decimal, and 1 at the 1-decimal level. Baseline characteristics of Canadian and US patients in this propensity-matched cohort were compared by Mann-Whitney *U* tests and χ^2 tests. Cox regression analyses were used to compare US and Canadian mortality rates in the matched cohort.

Next, we recalculated the propensity for belonging to the Canadian cohort after including revascularization status during the index hospitalization in the logistic regression model. Addition of this variable increased the c index of the model to 0.72 (95% CI, 0.71 to 0.73). We once again matched US and Canadian patients based on propensity scores derived from this model. Of 2898 matches, 45% matched at the 5-decimal level, 45% at 4-decimal, 9% at 3-decimal, 1% at 2-decimal, and 0.2% at 1-decimal level.

Results

Mortality status as of December 31, 1997, was known for 23 080 (99.9%) of the US patients and for 2862 (99.8%) of the Canadian patients enrolled in GUSTO-I. The median length of follow-up in the US cohort was 5.46 years (interquartile range, 4.99 to 5.94) and 5.33 years (interquartile range, 4.96 to 5.74) in the Canadian cohort.

As shown in Table 1, the US cohort had more women and higher rates of hypertension, diabetes, and prior revascularization (angioplasty and bypass surgery). In addition to higher rates of previous angina and anterior infarctions, time from symptom onset to treatment was significantly longer among Canadian patients. There was no difference in the percentage of patients assigned to the 4 treatment groups between the 2 countries.

Rates of cardiac catheterization and revascularization during the index hospitalization among US patients were more than twice those among Canadian patients (Figure 1, left). Cardiac catheterization rate was 72.6% in the US cohort compared with 31.2% in the Canadian cohort ($P < 0.01$). Similarly, angioplasty and bypass surgery rates were 30.5% and 13.1% among US patients and 11.4% and 4.0% among

TABLE 1. Baseline Characteristics of US and Canadian Patients Enrolled in GUSTO-I

Description	US (n=23 105)	Canada (n=2898)	P
Age, y	61 (52, 70)	61 (52, 70)	0.60
Female, %	27.2	23.8	<0.01
Height, cm	173 (165, 180)	170 (165, 177)	<0.01
Weight, kg	80 (70, 91)	77 (68, 86)	<0.01
Systolic blood pressure, mm Hg	126 (110, 142)	130 (113, 145)	<0.01
Heart rate, bpm	74 (63, 86)	72 (61, 84)	<0.01
Hypertension, %	42.7	33.2	<0.01
Diabetes, %	16.6	14.4	<0.01
Current smoker, %	42.7	42.4	0.78
Hypercholesterolemia, %	36.7	27.6	<0.01
Family history of CAD, %	46.0	44.2	0.07
Previous MI, %	17.2	16.9	0.64
Previous angina, %	35.0	37.9	<0.01
Cerebrovascular disease, %	2.3	2.1	0.55
Prior CABG, %	5.7	3.9	<0.01
Prior PTCA, %	5.7	2.5	<0.01
Killip class ≥ 2 , %	13.0	13.5	0.46
Infarct location, %			0.03
Anterior	37.3	39.7	
Inferior	59.6	57.1	
Other	3.1	3.2	
Time to treatment, h	2.7 (1.9, 3.9)	3.0 (2.2, 4.2)	<0.01
Treatment assignment, %			0.30
Accelerated alteplase (tPA)+IV heparin	25.6	24.7	
Streptokinase+SC heparin	23.2	24.8	
Streptokinase+IV heparin	25.7	25.2	
Combination tPA+streptokinase+IV heparin	25.5	25.3	

CAD indicates coronary artery disease; MI, myocardial infarction; CABG, coronary bypass artery graft surgery; PTCA, percutaneous transluminal coronary angioplasty; SC, subcutaneous; and IV, intravenous. Continuous variables are presented as median (interquartile range).

Canadian patients, respectively ($P<0.01$). These significant differences in procedure rates between the 2 countries persisted to 1 year, as evidenced by the revascularization rates reported in the US-Canada Economic and Quality of Life substudy of GUSTO-I (Figure 1, right).² This prospectively designed substudy included a random selection of 2600 US and 400 Canadian patients. At 1 year, the rates of cardiac catheterization were 78.8% among US patients and 42.0% among Canadian patients ($P<0.01$); angioplasty rates were 36.5% in the United States and 16.5% in Canada ($P<0.01$); and bypass surgery rates were 19.5% in the United States and 9.3% in Canada ($P<0.01$).

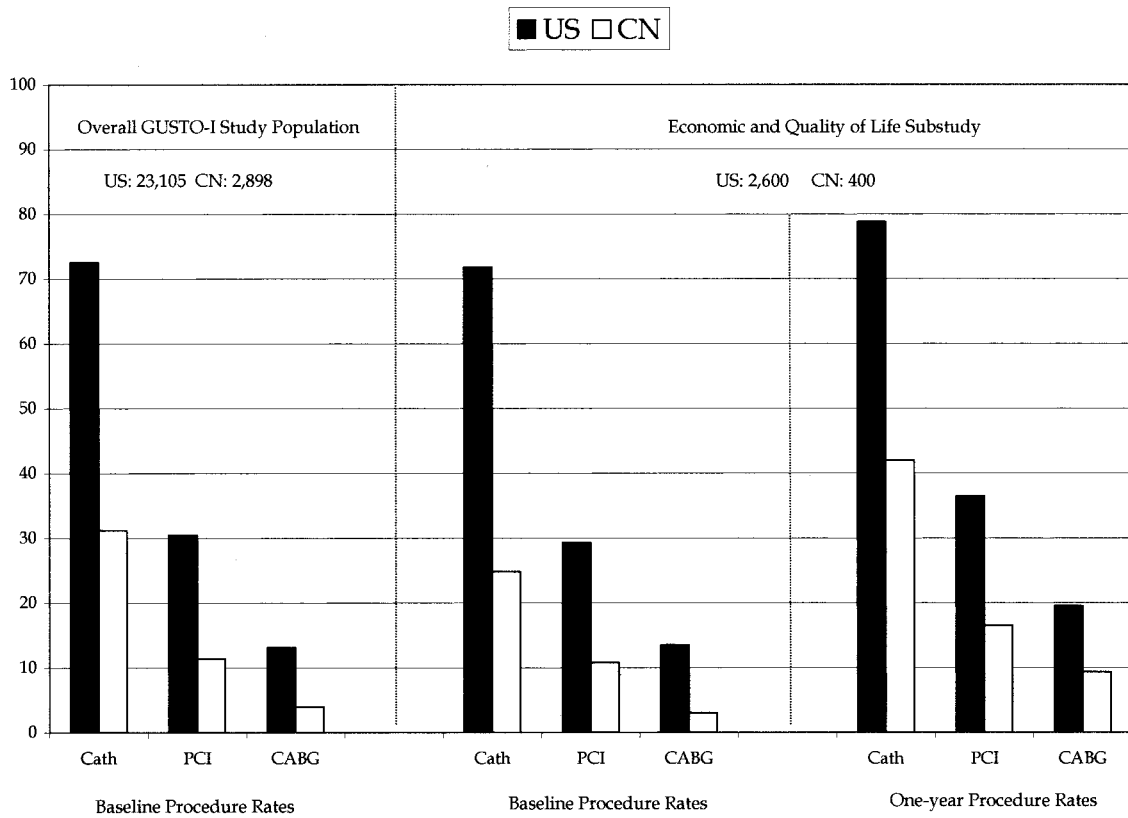
Unadjusted long-term mortality in the US and Canadian cohort is presented in Figure 2. The 5-year mortality rate among US patients was 19.6% and was 21.4% among Canadian patients ($P=0.02$). After adjusting for differences in baseline characteristics, enrollment in Canada continued to be associated with a higher hazard of death (hazard ratio [HR], 1.17; 95% CI, 1.07 to 1.28; $P=0.001$).

Other significant predictors of 5-year mortality included age, higher Killip class, higher heart rate, previous myocardial infarction, diabetes, and previous bypass surgery (Table 2). Hospital volume and admission to sites with onsite facilities were not significantly associated with 5-year mortality.

Differences in rates of revascularization during index hospitalization between Canada and the United States appeared to account for the intercountry difference in mortality. On inclusion of revascularization as a time-dependent covariate into the baseline Cox regression model, revascularization status was associated with a significantly lower 5-year mortality rate (HR, 0.72; 95% CI, 0.68 to 0.77; $P<0.01$), and country of enrollment was no longer a significant predictor (HR, 1.07; 95% CI, 0.98, 1.17; $P=0.14$).

Propensity-Matched Analysis

A total of 2897 Canadian and US patients were matched on propensity scores generated from the patients' baseline de-



All inter-country differences statistically significant at $p < 0.05$

Figure 1. Cardiovascular procedure rates during index hospitalization and at 1-year (based on EQOL substudy) in US and Canadian (CN) patients. Cath indicates catheterization; PCI, percutaneous coronary intervention; and CABG, coronary artery bypass graft. Other abbreviations are as defined in text.

mographic and clinical variables. There were no significant baseline differences among US and Canadian patients in this matched cohort (Table 3). In this propensity-matched cohort, enrollment in Canada was associated with a higher HR before and after adjustment (Table 4), suggesting that differences in patients' characteristics at baseline did not explain the difference in 5-year mortality between the 2 countries. On adjusting for revascularization status in calculating the propensity scores, the intercountry difference in mortality was no longer

significant (21.4% in Canada and 21.1% in the United States, $P = 0.55$).

Discussion

This study is the first to show that differing patterns of care for STEMI patients are associated with significant differences in long-term mortality. At 5 years, Canadian patients enrolled in GUSTO-I had a significantly higher mortality rate (21.4%) compared with their US counterparts (19.6%, $P = 0.02$). After adjusting for differences in baseline characteristics, country of enrollment remained a significant predictor, and an examination of the survival curves (Figure 2) suggests that the curves are diverging over time.

There were significant differences in revascularization rates in the 2 countries during the index hospitalization, and data previously collected as part of the Economic and Quality of Life substudy (GUSTO-I EQOL substudy) demonstrated that Canadian revascularization rates at 1 year were still almost 50% lower than in the United States (Figure 1).² In a multivariable regression analysis of mortality, the prognostic importance of country of enrollment was statistically "explained" by the differential use of revascularization during the index hospitalization.

These results were confirmed in a propensity-matched analysis of Canadian and US patients. Differences in baseline demographic and clinical variables did not explain the higher

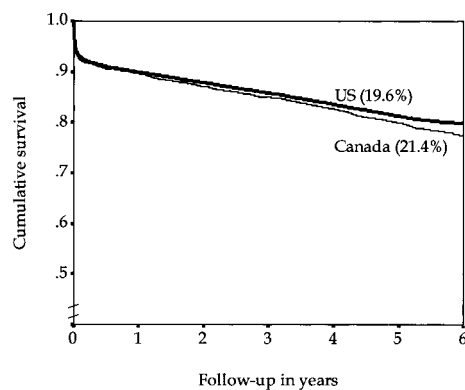


Figure 2. Long-term survival among GUSTO-I patients enrolled in United States and Canada. Country-specific mortality rate in parentheses. Abbreviations are as defined in text.

TABLE 2. Multivariable Associations Between Baseline Variables and Long-Term Mortality Based on Cox Proportional-Hazard Model

Variable	HR	Lower 95% CI	Upper 95% CI	χ^2
Age (10 y)	1.84	1.78	1.90	1383.0
Killip class*				284.0
2	1.61	1.49	1.73	
3	2.12	1.79	2.51	
4	3.36	2.67	4.22	
Heart rate (10 beats)	1.14	1.12	1.15	273.6
Previous MI	1.58	1.47	1.70	154.2
Diabetes	1.44	1.35	1.55	107.0
Previous CABG	1.63	1.47	1.81	86.5
Anterior MI	1.27	1.20	1.35	64.3
Current smoker	1.30	1.21	1.39	57.1
Systolic blood pressure (10 mm Hg)	0.96	0.95	0.97	46.6
Hypertension	1.23	1.16	1.31	45.9
Hypercholesterolemia	0.86	0.80	0.91	21.9
Time to treatment (10 min)	1.36	1.19	1.54	21.6
Previous CVD	1.38	1.20	1.58	20.4
Body mass index†	0.99	0.98	0.99	13.8
Canada	1.17	1.07	1.28	11.8
Family history of CAD	0.90	0.85	0.96	10.8
Previous angina	1.08	1.02	1.16	6.5
Previous PTCA	0.89	0.79	1.02	2.9

MI indicates myocardial infarction; CABG, coronary bypass artery graft surgery; CVD, cerebrovascular disease; CAD, coronary artery disease; and PTCA, percutaneous transluminal coronary angioplasty.

*Comparison group is patients in Killip class 1.

†There was significant interaction between age and body mass index (BMI) ($P<0.01$): Patients with low BMI (<20) were significantly older compared with patients with higher BMI.

mortality rate in the Canadian cohort. However, once revascularization status during the index hospitalization was incorporated into the propensity analysis, there was no significant difference in mortality rates in the 2 countries.

Although the United States and Canada share a common border, these 2 countries differ substantially in how they organize, deliver, and pay for health care. In Canada's regionalized system of care, availability of cardiac catheterization and revascularization services is restricted to selected tertiary care centers. It is therefore not surprising that Canada uses substantially fewer invasive cardiac procedures compared with the United States. In contrast, evidence-based medication use has been shown to be consistently higher in Canada compared with the United States.^{17,18} In the present study, a higher percentage of Canadian patients were discharged on β -blocker therapy (62.3%) compared with US patients (52.9%, $P<0.01$).

The results of our study have important implications for current and future treatment of STEMI patients. In light of the evidence from recent clinical trials and systematic reviews suggesting a mortality benefit, there has been a call for increasing use of early percutaneous coronary interventions in lieu of fibrinolytic therapies in STEMI patients.^{19,20} The effectiveness of this shift in treatment at a population level, given issues about geographic access and time to treatment,

has not been established. In countries such as Canada, with limited availability of revascularization facilities, substantial reorganization and investment in healthcare infrastructure will be required to improve efficiency of the referral process and transfer and triage of patients.

An international comparison of the type presented in this article is, of necessity, a nonrandomized study. The availability of detailed baseline clinical data allowed us to examine the independent relation between country of enrollment and long-term outcomes after controlling for a multitude of clinical factors. We have also undertaken a propensity-matched analysis to adjust for confounding. Although no observational comparison of this nature can definitively prove a causal relationship, our findings are strongly suggestive of a survival advantage for the US cohort based on more aggressive revascularization.

A key question, therefore, is whether the results are generalizable. There is evidence to suggest that Canadian patients enrolled in trials are younger, more often male, have less comorbid disease, and are more likely to undergo revascularization compared with those not enrolled in trials.²¹ In contrast, comparison of patients enrolled in the TIMI-9 trial with those in the TIMI-9 registry (both of which consisted predominantly of US patients) showed lower rates of cardiac catheterization and of angioplasty among trial

TABLE 3. Selected Baseline Characteristics of US and Canadian Patients in Propensity-Matched Analysis

Description	US (n=2897)	Canada (n=2897)	P
Age, y	61 (51, 70)	61 (52, 70)	0.86
Female, %	23.6	23.8	0.88
Systolic blood pressure, mm Hg	130 (114, 145)	130 (113, 145)	0.96
Heart rate, bpm	72 (62, 84)	72 (61, 84)	0.76
Hypertension, %	32.8	33.2	0.76
Diabetes, %	15.2	14.4	0.39
Current smoker, %	43.9	42.5	0.29
Hypercholesterolemia, %	28.4	27.6	0.50
Family history of CAD, %	44.9	44.2	0.62
Previous MI, %	16.7	16.8	0.94
Previous angina, %	37.1	37.9	0.59
Prior CABG, %	3.2	3.9	0.18
Prior PTCA, %	2.3	2.5	0.61
Killip class ≥ 2 , %	13.5	13.5	0.94
Anterior MI, %	40.6	39.7	0.81

CAD indicates coronary artery disease; MI, myocardial infarction; CABG, coronary bypass artery graft surgery; and PTCA, percutaneous transluminal coronary angioplasty. Continuous variables are presented as median (interquartile range).

patients.²² Based on these findings and the fact that Canadian revascularization patterns are more conservative than those in New York or the New England region, which are at the low end of regional revascularization rates within the United States, one might surmise that population-wide comparisons would demonstrate an even larger difference in intercountry revascularization rates and consequently, long-term survival.²³ The hypothesis of larger differences in revascularization rates is supported by a population-based comparison by Tu et al⁶ of elderly postmyocardial infarction US and Canadian patients in Ontario (21.8% of US compared with 2.8% of Canadian patients underwent revascularization within 30 days; relative rate, 7.9; 95% CI, 7.0 to 8.9); however, the study showed no survival advantage, with 1-year mortality rates of 34.3% among US and of 34.4% among Canadian patients.⁶ Because the present study showed only a very small survival advantage for the United States at 1 year, which increased over time, comparisons restricted to shorter

follow-up periods must be regarded as incomplete. Nonetheless, healthcare systems are complex and continually evolving, and our study provides a snapshot of a specific segment that needs to be supplemented by additional comparisons.

Among the 2600 US and 400 Canadian patients enrolled in the US-Canada EQOL substudy of GUSTO-I, Canadian patients reported lower education and income levels compared with US patients.² Canadian patients also had significantly fewer clinic visits with a cardiologist and lower rates of referral to cardiac rehabilitation within 30 days of the index event (14.9% in the United States and 2.8% in Canada, $P<0.01$).² In a backward multivariable Cox regression analysis restricted to patients in the EQOL study, lower income and increasing number of visits to cardiologists were associated with a higher risk of long-term mortality. However, even after adjusting for socioeconomic factors and differences in postdischarge management of patients, enrollment in Canada was associated with a trend toward higher mortality (HR, 1.45; 95% CI, 0.99 to 2.12; $P=0.06$). Unavailability of these data for the entire study cohort and other data such as the specialty of the treating physician remains a limitation of our study.

Our results are dependent on the completeness and accuracy of national death registries in Canada and the United States. Our ability to link with the national death registries was greatly facilitated by the availability of detailed patient identification data in GUSTO-I. Previous studies examining the validity of the NDI (US) and CMDB (Canadian) databases have reported sensitivity rates of 97% (NDI) and 93.1% (CMDB) and specificity rates of 99% (NDI) and 99.5% (CMDB).^{11–13} Based on these rates, even in the best-case scenario (ie, assuming 0.5% of the reported deaths in Canada were false and 3% of patients who were not noted to be dead

TABLE 4. Cox Proportional-Hazard Analyses of Country of Enrollment (Canada vs US) and 5-Year Mortality Among Propensity-Matched Patients (n=5794)

Model	HR (95% CI)	P
Unadjusted	1.13 (1.0–1.27)	0.047
Adjusted for propensity	1.13 (1.0–1.27)	0.047
Adjusted for propensity and baseline variables*	1.19 (1.05–1.34)	0.005

*Baseline variables included age, sex, height, weight, systolic blood pressure, heart rate, hypertension, diabetes, smoking, hypercholesterolemia, family history of coronary artery disease, previous myocardial infarction, previous angina, cerebrovascular disease, prior percutaneous transluminal coronary angioplasty, prior coronary artery bypass graft surgery, Killip class, anterior myocardial infarction location, time to treatment, and treatment assignment.

in the United States were actually dead), the difference in crude mortality rate still favors the United States by 1% ($P=0.20$). Baseline-adjusted mortality difference is likely to be even larger. By contrast, in the worst-case scenario (ie, assuming 6.9% of the Canadian patients currently presumed alive were actually dead and 1% of the US deaths were false), the intercountry mortality difference would be 4.2% higher in the Canadian cohort ($P<0.01$).

Conclusions

Our results suggest, for the first time, that the conservative pattern of care in Canada may be associated with a detrimental effect on long-term survival. Canadian rates of revascularization after myocardial infarction are, if anything, higher than those in Britain and most of continental Europe. For hundreds of thousands of patients who suffer an acute myocardial infarction in developing nations, revascularization is inaccessible. The results of our study may therefore have important policy implications for the delivery of cardiac care services worldwide.

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