

Coronary artery bypass graft surgery—care globalization: The impact of national care on fatal and nonfatal outcome

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Objective: In an international, prospective, observational study, we contrasted adverse vascular outcomes among four countries and then assessed practice pattern differences that may have contributed to these outcomes.

Methods: A total of 5065 patients undergoing coronary artery bypass graft surgery were analyzed at 70 international medical centers, and from this pool, 3180 patients from the 4 highest enrolling countries were selected. Fatal and nonfatal postoperative ischemic complications related to the heart, brain, kidney, and gastrointestinal tract were assessed by blinded investigators.

Results: In-hospital mortality was 1.5% (9/619) in the United Kingdom, 2.0% (9/444) in Canada, 2.7% (34/1283) in the United States, and 3.8% (32/834) in Germany ($P = .03$). The rates of the composite outcome (morbidity and mortality) were 12% in the United Kingdom, 16% in Canada, 18% in the United States, and 24% in Germany ($P < .001$). After adjustment for difference in case-mix (using the European System for Cardiac Operative Risk Evaluation) and practice, country was not an independent predictor for mortality. However, there was an independent effect of country on composite outcome. The practices that were associated with adverse outcomes were the intraoperative use of aprotinin, intraoperative transfusion of fresh-frozen plasma or platelets, lack of use of early postoperative aspirin, and use of postoperative heparin.

Conclusions: Significant between-country differences in perioperative outcome exist and appear to be related to hematologic practices, including administration of antifibrinolytics, fresh-frozen plasma, platelets, heparin, and aspirin. Understanding the mechanisms for these observations and selection of practices associated with improved outcomes may result in significant patient benefit.

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Coronary artery bypass graft (CABG) surgery was introduced approximately 50 years ago and is now performed in 1 million patients at a cost exceeding \$20 billion annually. As a technically complex procedure that is performed in high-risk patients, it has been scrutinized closely, resulting in substantial standardization of surgical, anesthetic, and postoperative care.¹⁻⁵ Consequently, one would expect that case-mix adjusted cardiovascular mortality and morbidity would be similar among high-volume centers, despite national differences in health care systems and reimbursement practices.⁶⁻⁸ However, there are few, if any, comprehensive, international data sets that allow comparison of the effects of country-specific, system-associated factors, such as length of stay, time from diagnosis to surgery, and variations in the pharmacologic management of hemostasis on morbidity and mortality, although these factors vary markedly depending on where CABG surgery is performed.⁸⁻¹³

Abbreviations and Acronyms

CABG	= coronary artery bypass graft
EuroSCORE	= European System for Cardiac Operative Risk Evaluation

The primary aim of this analysis was to determine and contrast the adverse vascular outcomes that occurred after CABG surgery among 4 countries; our hypothesis was that vascular outcomes differed among countries. Our secondary hypothesis was that practice pattern differences existed and accounted for between-country differences in outcome. The target population was patients undergoing elective CABG surgery (primary or repeat) or combined CABG-valve surgery (replacement or repair) among institutions of 4 countries, the United States, Canada, the United Kingdom, and Germany. Patients were randomly sampled by center, and a comprehensive set of individual perioperative data were collected, to allow definition of practice by center and by country.

Materials and Methods

Enrollment in the Multicenter Study of Perioperative Ischemia Research Group EPI II Study began in November 1996, and the in-hospital phase ended in June 2000. A total of 5436 patients scheduled for CABG surgery were enrolled in 72 medical institutions among 17 countries (4 continents). Details of the EPI II study have been described.¹⁴ Specifically, at each institution, after institutional review board approval, 100 patients were to be enrolled prospectively according to a systematic sampling scheme. To be eligible for enrollment, the patient had to be scheduled to undergo CABG using cardiopulmonary bypass, had to complete the preoperative interview, had to be at least 18 years old, could not be enrolled in another study or clinical trial, and had to give written informed consent.

Clinical Care

Clinical decisions were not controlled by the study protocol, and all patients qualifying for enrollment within the prespecified enrollment period were entered. Of the 5436 patients enrolled, 371 were excluded from the analysis for the following reasons: withdrawal from the study (32 patients), death before surgery (2 patients), cancellation or rescheduling of the surgery (97 patients), change in procedure (132 patients), incomplete data (97 patients), or inadvertent enrollment in another study (11 patients).

Study Data

For our comparison, we chose the 4 highest enrolling countries to obtain the largest and most homogeneous samples of patients undergoing elective CABG surgery. All surgery in these countries was performed at university or university-affiliated teaching hospitals. The distribution of the patients was as follows: United States (29 centers; $n = 1283$); Germany (9 centers; $n = 834$); United Kingdom (7 centers; $n = 619$); and Canada (8 centers; $n = 444$).

For each enrolled patient, more than 7500 fields of data were collected, including demographic, historical, clinical, laboratory,

electrocardiographic, special testing, resource use, and adverse outcome data. Independent investigators coded all medications received throughout hospitalization from admission to discharge or until death. All data fields for each patient were examined centrally for completeness and accuracy, with all changes documented before formal in-hospital database closure on October 15, 2001.

Measurement of Outcomes

All outcomes were prespecified by protocol and diagnosed by independent and blinded investigators. Fatal and nonfatal outcomes were classified as cardiac (myocardial infarction, heart failure), cerebral (stroke, encephalopathy), renal (dysfunction, failure), gastrointestinal (ischemia, infarction), or other adverse event complications.¹⁴ The diagnosis of myocardial infarction required¹⁵ the development of new Q waves (as defined by Minnesota Code 1-1-1 up to 1-2-7), new persistent ST-segment or T-wave changes (Minnesota Code 9-2, 4-1, 4-2, 5-1, or 5-2) associated with an elevation of creatine kinase-myocardial band isoenzyme values, or autopsy evidence of acute myocardial infarction. The diagnosis of heart failure required the use of a ventricular assist device, the use of continuous inotropic support for at least 24 hours, or autopsy verification of heart failure. Cerebral outcomes were classified¹⁶ as clinically diagnosed stroke or encephalopathy, or computed tomography, magnetic resonance imaging, or autopsy evidence of a focal or global lesion. Renal dysfunction was defined¹⁷ as a serum creatinine level of 2.00 mg/dL or greater accompanied by a 0.7 mg/dL or greater increase over baseline; renal failure was defined as dysfunction requiring dialysis or autopsy verification of renal failure. Gastrointestinal ischemia¹⁸ was defined as abdominal pain likely associated with bowel ischemia; gastrointestinal infarction was defined by bowel resection or evidence of intestinal infarction on autopsy. In addition, we defined a composite outcome consisting of mortality and/or any of the morbidities: myocardial infarction, congestive heart failure, stroke, encephalopathy, renal dysfunction, renal failure, and gastrointestinal ischemia/infarction.

Statistical Analysis

The prevalence of clinical characteristics and the incidence of individual adverse events comprising the composite outcome (death, myocardial infarction, congestive heart failure, stroke, encephalopathy, renal dysfunction, renal failure, or gastrointestinal ischemia/infarction) among the 4 countries were compared using the chi-square test. Continuous variables (eg, time to surgery and length of hospital stay) were compared using nonparametric tests.

The European System for Cardiac Operative Risk Evaluation (EuroSCORE)¹⁹ (one of the most common risk stratification systems for cardiac surgical patients) and other potential risk factors for adverse outcomes were investigated first using univariate logistic regression analysis. All risk factors statistically significant at P less than .20 in univariate analysis were then entered into a multivariate logistic regression model. Stepwise logistic regression was performed, with variables retained that were significant at a 2-tailed nominal P value of less than .05. To investigate the differences among countries, adjusting for their differences in risk profile, separate risk models were developed for mortality, morbidity, early morbidity (within 48 hours postsurgery), and late morbidity (after 48 hours postsurgery). All statistical analyses

TABLE 1. Baseline demographic and medical characteristics of the 3180 study patients

Characteristic	United Kingdom (n = 619)	Canada (n = 444)	United States (n = 1283)	Germany (n = 834)	P value
Demographic and clinical variables					
Age (y)					
Mean \pm SD	62 \pm 9.0	64 \pm 9.9	64 \pm 9.9	64 \pm 9.0	
Median	63.9*	66.1	65.2	64.3	<.001
Patients aged > 70 y, n (%)	141 (22.8)*	147 (33.1)	415 (32.4)	262 (31.4)	<.001
Weight (kg)					
Mean \pm SD	81.4 \pm 13.5	82.0 \pm 15	84.9 \pm 17.7	79.9 \pm 12.0	
Median	80.1	80.55	83.0	79.5	<.001
Body mass index > 30 kg/m ² , n (%)	165 (26.8)	151 (34.0)	569 (44.5)*	179 (21.6)	<.001
Female sex, n (%)	104 (16.8)	88 (19.8)	239 (18.6)	170 (20.4)	.350
African American or American Indian or Hispanic ethnic group, n (%)	1 (0.2)	11 (2.5)*	183 (14.3)*	0 (0.0)	<.001
Medical history					
Diabetes, n (%)	104 (16.8)*	138 (31.2)	478 (37.3)	228 (27.4)	<.001
History of smoking,† n (%)	494 (80.1)*	310 (69.8)	922 (72.1)	594 (71.3)	<.001
Current smoking, n (%)	49 (7.9)	51 (11.5)	201 (15.7)*	89 (10.7)	<.001
Unstable angina, n (%)	265 (43.9)	259 (60.5)*	787 (68.1)*	364 (49.8)	<.001
MI, n (%)	357 (58.0)	270 (60.8)	625 (49.2)*	428 (51.9)	<.001
CHF, n (%)	270 (43.7)	71 (16.0)*	348 (27.4)	286 (34.7)	<.001
PTCA, n (%)	44 (7.1)*	91 (20.5)	263 (20.6)	147 (17.7)	<.001
CABG, n (%)	23 (3.7)	31 (7.0)	122 (9.5)*	34 (4.1)	<.001
Preoperative diagnostic test results					
Ejection fraction < 44%, n (%)	107 (20.5)	77 (19.9)	304 (27.6)*	123 (15.9)	<.001
Coronary disease location					
Left main, n (%)	162 (26.6)*	166 (37.8)	555 (44.5)	300 (36.3)	<.001
Left anterior descending, n (%)	593 (96.3)	426 (96.2)	1229 (97.3)	800 (96.0)	.362
Circumflex, n (%)	559 (90.9)	386 (87.1)	1130 (90.3)	757 (90.8)	.151
Right, n (%)	570 (92.5)	398 (90.5)	1158 (92.1)	756 (90.8)	.446
Medications at admission, n (%)					
ACE inhibitors	161 (26.0)*	162 (36.5)	494 (38.5)	448 (53.7)	<.001
Beta-blockers	412 (66.6)	337 (75.9)*	793 (61.8)	550 (65.9)	<.001
Calcium channel blockers	352 (56.9)*	186 (41.9)*	326 (25.4)	205 (24.6)	<.001
Platelet inhibitors	211 (34.1)*	296 (66.7)	892 (69.5)	278 (33.3)*	<.001

ACE, Angiotensin-converting enzyme; CABG, coronary artery bypass graft; CHF, congestive heart failure; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angiography; SD, standard deviation. *Country with statistically different prevalence ($P < .01$ with Bonferroni adjustment) in characteristic, by pairwise comparisons. †Smoking is regular smoking of cigarettes, cigars, or pipe.

were performed with SAS Version 8.12 software (SAS Institute, Cary, NC).

The Ischemia Research and Education Foundation provided all funding for execution of the study, collection of the data, and analysis and publication of the findings.

Results

Patients typically had chronic and acute manifestations of vascular disease (Table 1). U.S. patients had the highest prevalence of body mass index greater than 30 kg/m², diabetes, unstable angina, prior CABG, left main coronary artery disease, ejection fraction less than 44%, and non-caucasian ethnicity. U.K. patients had a higher prevalence of heart failure and acute smoking cessation but were the youngest and least likely to have diabetes, unstable angina,

left main coronary artery disease, and previous coronary intervention. Angiotensin-converting enzyme inhibitors were used most commonly in Germany and the United States, calcium channel blockers were used most commonly in the United Kingdom and Canada, and antiplatelet medications were used most commonly in the United States and Canada. On the basis of the EuroSCORE, the United Kingdom had the highest proportion of patients in the low-risk group, whereas the United States cohort had the highest proportion in the high-risk group (Figure 1). The differences among countries in the overall distribution of the EuroSCORE were significant ($P < .001$). In addition, the process of care factors (Table 2) varied considerably among countries.

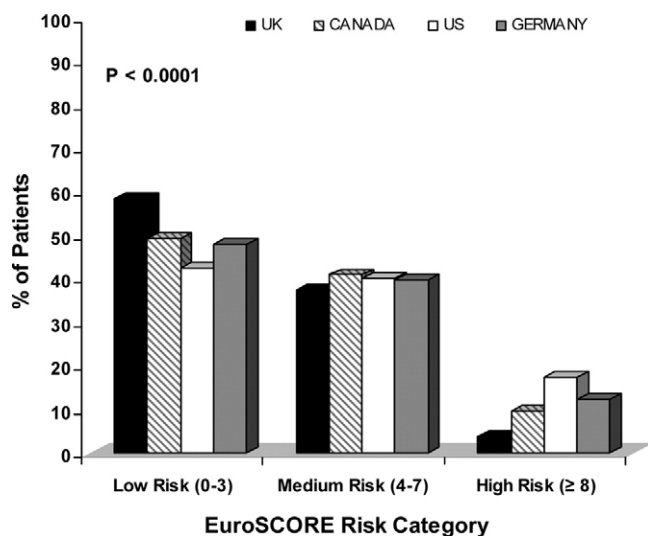


Figure 1. Comparison of EuroSCORE among 4 study countries. The distribution of the EuroSCORE (in low, medium, and high-risk groups) among 4 countries: United Kingdom, Canada, United States, and Germany. Data given in percentages. EuroSCORE, European System for Cardiac Operative Risk Evaluation.

Between-country Differences in Outcome

For mortality, unadjusted rates differed among countries (Table 3), but these differences did not survive multivariate logistic regression. For morbidity, we found significant differences among countries in cardiac, cerebral, and renal morbidity—but not gastrointestinal morbidity—as well as in overall composite outcome (Table 4). Multivariate logistic regression further demonstrated that the between-country differences in individual organ morbidities and composite morbidity remained significant.

Multivariate Analysis of Composite Outcome (Within and After 48 Hours After Surgery)

None of the individual admission/preoperative risk factors explained the inter-country differences in the risk of the composite outcome. Among intraoperative factors, administration of platelets (odds ratio = 1.6, 95% confidence interval: 1.0-2.3, $P = .03$) and fresh-frozen plasma (odds ratio = 1.5, confidence interval: 1.0-2.2, $P = .03$) were independently associated with the risk of the composite outcome, but neither of these eliminated the independent effect of country on composite outcome (Table 4). None of the process of care factors (Table 2) were independently associated with the composite outcome.

Early Outcomes (Within 48 Hours)

There were 338 patients with adverse events within 48 hours after surgery. After adjustment for significant confounders (admission, preoperative, and intraoperative fac-

tors, including the EuroSCORE), country no longer had an independent effect on the risk of the composite outcome within 48 hours. Reversible risk factors for early composite outcome were the use of aprotinin and transfusion of fresh-frozen plasma (Table 5, Figure 2).

Aprotinin use was most prevalent in Germany (69%), compared with 23% in the United Kingdom, 20% in the United States, and only 6% in Canada. The risk of the composite outcome (within 48 hours of surgery) was 13.5% in those treated with aprotinin versus 9.3% ($P < .001$) for those who did not receive aprotinin. The administration of fresh-frozen plasma during surgery was most prevalent in Germany (11%), followed by the United States (8%), the United Kingdom (2%), and Canada (1%). Use of fresh-frozen plasma was associated with more than a doubling of the risk of the composite outcome in this period (24.9% vs 9.6%, $P < .001$). None of the process of care factors was independently associated with the early composite outcome. Platelets were used during surgery most frequently in the United States (12%), followed by Germany (4%), the United Kingdom (1.5%), and Canada (0.75%), but the administration of platelets during surgery was not associated with the risk of early adverse outcomes.

Late Outcomes (After 48 Hours)

Patients with early composite outcomes were excluded in analyses of the factors associated with the risk of late composite outcome. Early postoperative use (within 48 hours) of aspirin was associated with a reduced risk of late outcomes, whereas use of intravenous heparin increased the risk (Table 6). The use of aspirin was most prevalent in Canada (83%), followed by the United Kingdom (70%), the United States (67%), and Germany (42%) (Figure 3). The administration of heparin was most prevalent in Germany (75%), followed by Canada (40%), the United Kingdom (17%), and the United States (15%).

Resource Use

Time on the waiting list for surgery differed significantly among countries, with the United Kingdom showing the longest time on the wait list (207 days), followed by Canada (37 days), Germany (21 days), and the United States (6 days) (Table 2). These findings were consistent across EuroSCORE risk groups. For all countries, higher risk groups (vs lower risk groups) were associated with shorter wait time. However, time on the wait list did not account for EuroSCORE differences.

There were significant inter-country differences in all intraoperative and postoperative time-related factors (Table 2). The United Kingdom had the shortest median bypass and crossclamp times (71 minutes and 38 minutes, respectively) in contrast with the United States (104 minutes and 69 minutes, respectively) and Germany (98 minutes and 58 minutes, respectively). After correction for the

TABLE 2. Resource use and timelines

Resource use	United Kingdom (n = 619)	Canada (n = 444)	United States (n = 1283)	Germany (n = 834)	P value
Timelines (median)					
Time on wait list (d) overall	206.5	37.0	6.0	21.0	<.001
EuroSCORE 0-3 (low risk)	221	37	7	23	<.001
EuroSCORE 4-7 (medium risk)	196	46	6	19	<.001
EuroSCORE \geq 8 (high risk)	74	36	3	18	<.001
Time preoperatively (h)	22.5	23.9	25.8	95.6	<.001
Time of anesthesia (min)	219.0	226.0	314.0	293.0	<.001
Time in OR (min)	170.0	170.0	246.0	213.0	<.001
Time on CPB (min)	71.0	72.5	104.0	98.0	<.001
Time of crossclamp (min)	38.0	44.0	69.0	58.0	<.001
Time ICU stay (h)	21.3	26.5	32.5	39.8	<.001
Time ICU discharge to hospital discharge (d)	5.0	4.0	4.0	8.0	<.001
Intraoperative blood products transfusion					
Transfusion of platelets in OR, n (%)	9 (1.5)*	3 (0.7)*	151 (11.8)	33 (4.0)	<.001
Number of units, mean (SD); median	1.1 (0.6); 1	6.3 (1.5); 6	6.9 (5.9); 6	4.6 (2.4); 5	
Transfusion of RBC in OR, n (%)	119 (19.2)	71 (16.0)	515 (40.2)*	397 (47.6)*	<.001
No. of units, mean (SD); median	1.6 (0.8); 1	1.8 (1.3); 2	2.5 (1.7); 2	2.8 (2.3); 2	
Transfusion fresh-frozen plasma in OR, n (%)	15 (2.4)*	6 (1.4)*	108 (8.4)	88 (10.6)	<.001
No. of units, mean (SD); median	1.9 (0.3); 2	3.0 (1.1); 3	3.3 (3.0); 2	3.3 (1.6); 3	
Blood loss within 24 h postsurgery (mL), mean (SD); median	765 (598); 630	697 (524); 600*	782 (621); 640	823 (677); 680	<.001
Aprotinin used in OR, n (%)	143 (23.1)	25 (5.7)*	250 (19.5)	578 (69.3)†	<.001
Return to OR, n (%)	30 (4.9)	23 (5.2)	69 (5.4)	68 (8.2)	.021
Medication within 48 h postsurgery, n (%)					
Aspirin	435 (70.3)	369 (83.1)	863 (67.3)	346 (41.5)*	<.001
Heparin	106 (17.1)	179 (40.3)	198 (15.4)	622 (74.6)*	<.001

CPB, Cardiopulmonary bypass; ICU, intensive care unit; EuroSCORE, European System for Cardiac Operative Risk Evaluation; OR, operating room; RBC, red blood cell; SD, standard deviation. All data are given as median. Time preoperatively (h) denotes hours from admission to hospital to operating room admission. *Country with statistically different prevalence ($P < .01$ with Bonferroni adjustment) in characteristic, by pairwise comparisons. †Country with statistically different prevalence in characteristic (* vs † are also statistically different).

number of bypass grafts, these times remained longer in the United States and Germany than in the United Kingdom or Canada.

Discussion

We compared serious adverse vascular outcomes among 4 countries and attempted to associate the practice patterns of each of those countries with those outcomes. Among the United States, German, United Kingdom, and Canadian centers, we found significant differences in outcomes and processes of care, most notably approaches to hemostasis. Practices that were associated with adverse outcomes included the intraoperative use of aprotinin and transfusion of fresh-frozen plasma or platelets, and the use of heparin or lack of administration of aspirin during the early postoperative period. Understanding the mechanisms for these observations and the selection of practices associated with improved outcomes may result in significant patient benefit.

Transfusion practices for red blood cells and blood products have been reported to vary widely between institutions and countries,²⁰⁻²² ranging from 0% to 97% for fresh-frozen

plasma. Prophylactic plasma administration has not been shown to reduce red cell transfusion,²³⁻²⁹ and recent studies have reported an independent risk of stroke and death after platelet or plasma transfusions.^{20,30} The association between blood product transfusion, aprotinin use, or aspirin administration and adverse outcome in our study suggests that the complex interaction of factors affecting blood coagulation and hemostasis may play an important role in clinical outcome.

We found that the use of aprotinin and fresh-frozen plasma was more prevalent among German centers, despite relatively little difference in blood loss compared with the other 3 countries studied. It is possible that frozen plasma administration, in combination with aprotinin, may have conferred additional risk. Although the large majority of randomized studies comparing aprotinin with placebo or other antifibrinolytic agents have not suggested additional risk with aprotinin, 6 recent investigations reported that the use of aprotinin is associated with increased adverse outcomes.³¹⁻³⁶ Therefore, our findings raise questions regarding the optimal hematologic management of patients who

TABLE 3. Between-country differences in outcome

Outcome variable, n (%)	United Kingdom (n = 619)	Canada (n = 444)	United States (n = 1283)	Germany (n = 834)	P value
In-hospital mortality (overall)	9 (1.5)‡	9 (2.0)	34 (2.7)	32 (3.8)	.034
EuroSCORE 0-3 (low risk)	2/363 (0.6)	0/219	3/547 (0.6)	4/400 (1.0)	.539
EuroSCORE 4-7 (medium risk)	3/232 (1.3)	5/182 (2.8)	11/514 (2.1)	12/332 (3.6)	.328
EuroSCORE ≥ 8 (high risk)	4/24 (16.7)	4/43 (9.3)	20/222 (9.0)	16/102 (15.7)	.245
Nonfatal morbidity	68 (11.0)‡	60 (13.5)	196 (15.3)	167 (20.0)	<.001
Morbidity and/or mortality*	77 (12.4)‡	69 (15.5)	231 (18.0)	199 (23.9)	<.001
Postoperative cardiac morbidity					
MI	42 (6.8)	14 (3.2)†	86 (6.7)	93 (11.2)	<.001
CHF	21 (3.4)†	43 (9.7)	96 (7.5)	88 (10.6)	<.001
Postoperative cerebral morbidity					
Encephalopathy	1 (0.2)†	5 (1.1)	16 (1.2)	24 (2.9)	<.001
Stroke	11 (1.8)	10 (2.3)	25 (2.0)	17 (2.0)	.956
Postoperative renal morbidity					
Renal failure	4 (0.6)	4 (0.9)	21 (1.6)	39 (4.7)†	<.001
Renal dysfunction	12 (1.9)†	10 (2.3)†	49 (3.8)	36 (4.3)	.034
Postoperative gastrointestinal morbidity					
GI ischemia/infarction	4 (0.6)	0 (0.0)	3 (0.2)	4 (0.5)	.257

CHF, Congestive heart failure; EuroSCORE, European System for Cardiac Operative Risk Evaluation; GI, gastrointestinal; MI, myocardial infarction. *Composite outcome. †Country with statistically different incidence ($P < .01$ with Bonferroni adjustment) in outcome, by pairwise comparisons. ‡Statistically different incidence ($P < .01$ with Bonferroni adjustment) in outcome only comparing United Kingdom and Germany. After adjustment for confounders, country no longer had an independent effect on the risk of the composite outcome within 48 hours.

undergo CABG in general and the coincident use of aprotinin with frozen plasma, platelets, or other prothrombotic agents.

Geographic variability has been reported to exist for cost, length of stay, volume, and access to and adverse events after CABG surgery,^{35,37,38} although no previous studies

have prospectively evaluated the processes of care and outcomes in the range of countries examined in this investigation. Peterson and colleagues³⁹ found that the hospital at which CABG surgery was performed was the strongest predictor of prolonged stay, although there was also limited correlation between mortality and other outcomes.

TABLE 4. Multivariate analysis for composite outcome: Admission, preoperative, and intraoperative risk factors

Variable	Incidence of composite outcome in subgroup No./total (%)	Adjusted OR (95% CI)	P value
By country			
Germany vs United Kingdom	199/834 (23.9)	1.92 (1.42-2.60)	<.001
United States vs United Kingdom	231/1283 (18.0)	1.09 (0.81-1.46)	.585
Canada vs United Kingdom	69/444 (15.5)	1.21 (0.84-1.74)	.306
United Kingdom (reference group)	77/619 (12.4)	1.00	
By patient			
EuroSCORE risk group			
Low risk (0-3)	193/1529 (12.6)	1.55 (1.34-1.79)	<.001
Medium risk (4-7)	241/1260 (19.1)		
High risk (≥8)	142/391 (36.3)		
Warfarin/Coumadin use within 1 wk before revascularization	60/198 (30.3)	1.73 (1.23-2.43)	.002
Heart failure at admission	175/633 (27.7)	1.60 (1.28-2.01)	<.001
Renal disease history	145/511 (28.4)	1.30 (1.00-1.69)	.047
Creatinine > 1.3 mg/dL on admission	131/454 (28.9)	1.54 (1.17-2.02)	.002
By practice			
Transfusion of fresh-frozen plasma, intraoperative	79/217 (36.4)	1.52 (1.03-2.25)	.034
Transfusion of platelets, intraoperative	66/196 (33.7)	1.56 (1.03-2.37)	.035

CI, Confidence interval; OR, odds ratio; EuroSCORE, European System for Cardiac Operative Risk Evaluation. (Country included as categorical variable, United Kingdom = reference group.)

TABLE 5. Multivariate analysis for composite outcome within 48 hours postsurgery: Admission, preoperative, and intraoperative risk factors

Variable	Incidence of early composite outcome in subgroup, No./total (%)	OR (95% CI)	P value
By patient			
EuroSCORE risk group			
Low risk (0-3)	114/1529 (7.5)	1.566 (1.32-1.84)	<.001
Medium risk (4-7)	132/1260 (10.5)		
High risk (≥ 8)	92/391 (23.5)		
Prior hospitalization for CHF	58/254 (22.8)	1.72 (1.22-2.42)	.002
Creatinine > 1.3 mg/dL on admission	81/454 (17.8)	1.53 (1.15-2.05)	.004
By practice			
Preoperative ACE inhibitors	173/1210 (14.3)	1.38 (1.09-1.76)	.008
Preoperative hypoglycemics	95/628 (15.1)	1.37 (1.04-1.79)	.023
Aprotinin use intraoperatively	135/996 (13.6)	1.36 (1.07-1.73)	.013
Transfusion of fresh-frozen plasma intraoperatively	54/217 (24.9)	2.03 (1.43-2.90)	<.001

ACE, Angiotensin-converting enzyme; CHF, congestive heart failure; CI, confidence interval; OR, odds ratio; EuroSCORE, European System for Cardiac Operative Risk Evaluation.

The waiting list time may impact outcome in that a country with a longer list time (eg, the United Kingdom) may effectively exclude sicker patients. On the other hand, longer wait times also have been shown to result in clinical deterioration, which could then predispose to worse outcomes in those patients waiting longer.⁴⁰ However, we found no substantial differences among the countries regarding acute or chronic disease severity at the time of

surgery, suggesting that if wait time did play a role, its effects may have been mitigated.

This study has some limitations. The patient selection procedures may not be representative of the countries studied, although the average volume of cardiac cases in centers that participated in EPI-II exceeded 1200 patients per year. We chose the EuroSCORE for risk adjustment because it is an established index using data from European patients.

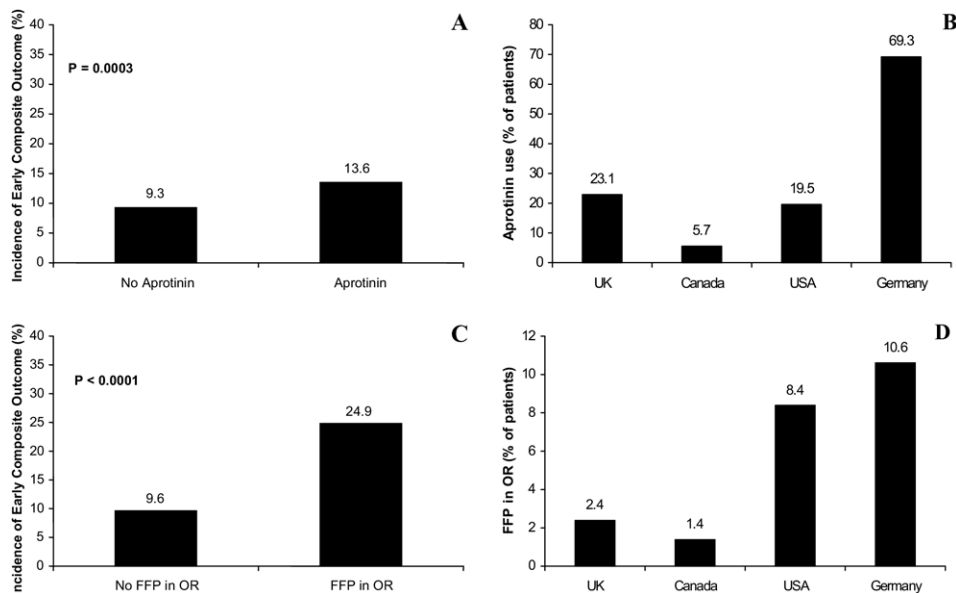


Figure 2. Factors explaining country differences in early composite outcome within 48 hours postsurgery. Incidence of composite outcome within 48 hours postsurgery by use of aprotinin (A and B) and fresh-frozen plasma transfusion (C and D). Use of risk factors within each study country: United Kingdom, Canada, United States, and Germany. Data given in percentages. FFP, Fresh-frozen plasma; OR, operating room.

TABLE 6. Multivariate analysis for composite outcome 48 hours postsurgery: Admission, preoperative, intraoperative, and postoperative (within 48 hours) risk factors

Variable	Incidence of late composite outcome in subgroup, No./total (%)	OR (95% CI)	P value
By patient			
EuroSCORE risk group			
Low risk (0-3)	79/1415 (5.6)	1.54 (1.25-1.88)	<.001
Medium risk (4-7)	109/1128 (9.7)		
High risk (≥8)	50/299 (16.7)		
Heart failure on admission	69/527 (13.1)	1.60 (1.16-2.21)	.004
By practice			
Aspirin use within 48 h postsurgery	114/1853 (6.2)	0.56 (0.42-0.73)	<.001
Heparin use within 48 h postsurgery	102/975 (10.5)	1.51 (1.14-2.00)	.004
Transfusion of fresh-frozen plasma intraoperatively or within 24 h postsurgery	71/467 (16.4)	1.95 (1.42-2.67)	<.001

CI, Confidence interval; OR, odds ratio; EuroSCORE, European System for Cardiac Operative Risk Evaluation.

Although some studies have suggested that the EuroSCORE can accurately predict short and long-term outcomes in North American patients, it is possible that it is less accurate in our non-European cohort. There may have been changes in the frequency of CABG surgery or the use of alternative techniques since completion of study enrollment, but the lack of major changes in the management of patients undergoing CABG with cardiopulmonary bypass makes our data current and applicable to this population. Finally, despite prospective data collection, it is possible that unmeasured

confounders may exist that could have affected either the risk adjustment or the strength of the outcome associations.

Conclusions

We found significant between-country differences in adverse vascular outcomes, as well as processes of care, in patients who underwent CABG surgery. In particular, the use of blood products, antifibrinolytics, and antithrombotic agents differed significantly and appeared to be significantly associated with the differences in outcome. Clearly, causal-

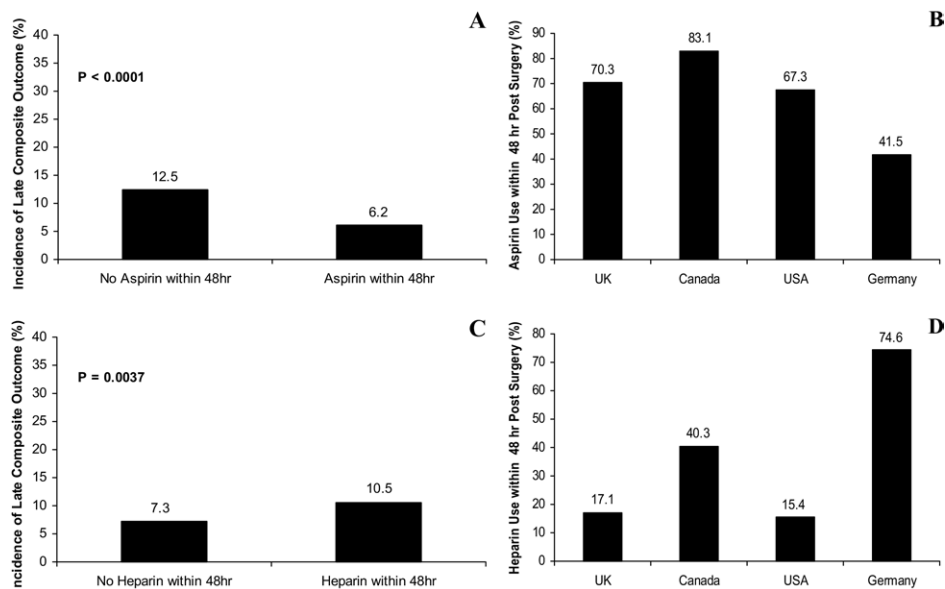


Figure 3. Factors explaining country differences in late composite outcome 48 hours postsurgery. Incidence of composite outcome 48 hours postsurgery by early use (within 48 hours postsurgery) of aspirin (A and B) and heparin (C and D). Use of risk factors within each study country: United Kingdom, Canada, United States, and Germany. Data given in percentages.

ity cannot be invoked; however, among those countries that more commonly used early aspirin therapy and avoided blood product transfusion and use of aprotinin, outcomes were improved. Therefore, we surmise that hematologic practice plays a critical role in determining the frequency of adverse outcomes after CABG surgery.

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Appendix

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