Adjuvant vancomycin for antibiotic prophylaxis and risk of *Clostridium difficile* infection after coronary artery bypass graft surgery

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Objective: The incidence of hospital-acquired *Clostridium difficile* infection (CDI) has increased rapidly over the past decade; patients undergoing major surgery, including coronary artery bypass grafting (CABG), are at particular risk. Intravenous vancomycin exposure has been identified as an independent risk factor for CDI, but this is controversial. It is not known whether vancomycin administered for surgical site infection prophylaxis increases the risk of CDI.

Methods: Using data from the Premier Perspective Comparative Database, we assembled a cohort of 69,807 patients undergoing CABG surgery between 2004 and 2010 who received either a cephalosporin alone (65.1%) or a cephalosporin plus vancomycin (34.9%) on the day of surgery. Patients were observed for CDI until discharge from the index hospitalization. In these groups, we evaluated the comparative rate of postoperative CDI with Cox models; confounding was addressed using propensity scores.

Results: In all, 77 (0.32%) of the 24,393 patients receiving a cephalosporin plus vancomycin and 179 (0.39%) of the 45,414 patients receiving a cephalosporin alone had postoperative CDI (unadjusted hazard ratio [HR], 0.73; 95% confidence interval [CI], 0.56-0.95). After adjusting for confounding variables with either propensity score matching or stratification, there was no meaningful association between adjuvant vancomycin exposure and postoperative CDI (HR, 0.85; 95% CI, 0.61-1.19; and HR, 0.85; 95% CI, 0.63-1.15, respectively). Results of multiple sensitivity analyses were similar to the main findings.

Conclusions: After adjustment for patient and surgical characteristics, a short course of prophylactic vancomycin was not associated with an increased risk of CDI among patients undergoing CABG surgery. (J Thorac Cardiovasc Surg 2013;146:472-8)

Clostridium difficile infection (CDI) occurs commonly among hospitalized patients and has more than doubled in frequency during the past decade.[1] Patients undergoing major surgery, including cardiac surgery, are at particular risk.[2,3] For these patients, CDI lengthens hospitalization,[2] increases the amount of time patients spend in the intensive care unit,[2] prolongs mechanical ventilation,[2] can cause the need for readmission,[4] and increases mortality.[3] Therefore, identifying risk factors for the development of CDI and developing strategies to decrease its occurrence in the postoperative period are urgently needed.

Antibiotic exposure is the single most important risk factor for the development of CDI.[5,6] Antibiotics alter the native colonic flora, which allows *C difficile* to proliferate.[7] Studies have demonstrated an association between short courses of perioperative antibiotic use and the risk of CDI.[8] Indeed, *C difficile* can proliferate after just a single dose of antibiotics for prophylaxis in surgery.[9] In contrast, the prophylactic administration of antibiotics has demonstrated benefit in the prevention of surgical site infection (SSI) after cardiac and other surgical procedures. On the basis of evidence from randomized controlled clinical trials, The Society of Thoracic Surgeons guidelines recommend prophylaxis with a beta-lactam antibiotic for this

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Abbreviations and Acronyms
CABG = coronary artery bypass grafting
CDI = *Clostridium difficile* infection
CI = confidence interval
HR = hazard ratio
SSI = surgical site infection

purpose, including a cephalosporin among nonallergic patients, with the addition of vancomycin among those with known or presumed staphylococcal colonization, those from institutions with a high incidence of methicillin-resistant staphylococcal infections, those ''susceptible'' to colonization, or those receiving a prosthetic valve.[10]

There is concern that excessive use of vancomycin for SSI may lead to an increase in antibiotic resistance in *Staphylococcus* and *Enterococcus* organisms,[11,12] which has led to calls to curb its routine use for prophylaxis.[13] An addition potential concern is that vancomycin exposure may increase the risk for CDI. Exposure to intravenous vancomycin has recently been identified as an independent risk factor for the development of CDI in several studies of hospitalized patients,[14-16] but this remains controversial. Currently, there are limited data on whether adjuvant vancomycin used for SSI prophylaxis increases risk for CDI. We therefore sought to define the comparative risk of CDI associated with the adjunctive use of vancomycin as a prophylactic antibiotic versus use of a cephalosporin alone among patients undergoing coronary artery bypass grafting (CABG).

METHODS

Data Source

The study cohort was derived from the Premier Perspective Comparative Database. The database includes approximately one sixth of all hospitalizations in the United States. The database contains information about daily charges for all medications, procedures, and diagnostic tests conducted during each hospitalization, as well as patient demographic and hospital characteristics, discharge diagnoses, and discharge status (including death). Data are routinely audited, verified, and validated. Premier data have been extensively used to study medication use and health outcomes in the perioperative period.[17-19] The use of this data set for research was approved by the Institutional Review Board of the Brigham and Women's Hospital, Boston, Mass, and a Data Use Agreement was in place.

Cohort

We considered all patients who, during the course of a hospital stay, underwent a CABG (identified by procedure code 36.1, or any subcode thereof, from the *International Classification of Diseases, ninth revision*) between January 1, 2004, and December 31, 2010. Because the database does not record comorbidities or other information about patients at the time of their admission, we excluded patients who underwent CABG on the day of hospital admission, to allow time for accrual of information about patients' preoperative health status that might affect the choice of prophylactic antibiotic. We also excluded patients who were exposed to any systemic antibiotic from day 1 to the day before CABG to isolate the effect of the prophylactic antibiotics administered on the day of surgery. We further limited our analysis to those patients that received either a cephalosporin alone or a cephalosporin plus vancomycin, inasmuch as these are the most common prophylactic antibiotic regimens administered on the day of surgery in the United States and the ones that are in keeping with current guidelines for patients without a beta-lactam allergy.[10] Finally, we excluded those patients who died, were discharged, or had CDI develop in the first 2 postoperative days, inasmuch as 2 days is the minimum plausible induction time for CDI related to antibiotic exposure on the day of surgery.[14]

Classification of Drug Exposure and Study Outcome

Cephalosporin exposure was defined as charges on the day of surgery for 1 of the following intravenous medications: cefazolin, ceftriaxone, cefuroxime, cefadroxil, cefamandole, cefepime, cefonicid, cefoperazone, cefotaxime, cefotetan, ceftazidime, ceftizoxime, cephalothin, cephapirin, or cephradine. Vancomycin exposure was defined on the basis of charges on the day of surgery for intravenous vancomycin.

The main study outcome was CDI 48 hours or more postoperatively.[14] Our outcome was defined by the presence of all 3 of the following criteria: (1) a discharge diagnosis code of CDI (ICD 9 CM 008.45), (2) a charge code indicating that a stool study for *C difficile* toxin has been performed, and (3) a charge code indicating that appropriate CDI therapy (oral or intravenous metronidazole or oral vancomycin) had been initiated at least 2 hospital days after surgery. The time of the outcome event was defined by the third criterion, the date therapy was initiated.

Patient and Hospital-Level Covariates

We identified 5 groups of potential confounders: patient demographics, chronic comorbid conditions, markers of coexisting disease/disease severity, characteristics of the surgical procedure, and hospital characteristics. Demographics included age on admission, gender, marital status (classified as married, single, or other), race (classified as white, black, or other), and season and year of admission. The presence of chronic comorbid conditions was identified by discharge diagnoses including liver disease, malignancy, prior endocarditis, peripheral vascular disease, hemostatic disorder, carotid artery stenosis, prior stroke, and prior myocardial infarction.[20] The Romano modification[21] of the Charlson comorbidity index, a score indicating patients' severity of comorbid conditions, was also calculated for each patient.

Coexisting conditions and/or markers of disease severity were evaluated with drug use and procedures before the day of surgery and included diabetes mellitus, chronic obstructive pulmonary disease, end-stage renal disease, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, aldosterone agonists, beta-blockers, calcium channel blockers, loop diuretics, thiazide diuretics, aspirin, clopidogrel, dipyridamole, statins, fibrates, digoxin, antiarrhythmic medications (amiodarone, dronedarone, sotatol, procainamide, propafenone), proton pump inhibitor, H2 blocker, or sucralfate. We also assessed for preoperative charges for telemetry, echocardiogram, oxygen use, and intensive care use.

Surgical characteristics included type of admission (urgent/emergency vs elective), number of grafts, whether the patient received a thoracic artery graft, and whether the patient received an aortic, mitral, or tricuspid valve repair or replacement concurrently with their CABG.

Hospital characteristics were also assessed. Hospitals affiliated with medical schools accredited by the Association of American Medical Colleges Liaison Committee on Medical Education were classified as teaching hospitals and nonteaching hospitals otherwise. Geographic region of the hospital was classified as Midwest, Northeast, South, or West. Location was defined as urban or rural. The annualized volume of CABG patients treated by each hospital was estimated by dividing the total number of CABG patients for each hospital during the study time period by the number of years that each hospital performed 1 or more CABG operations. Hospitals were ranked in order of annualized volume and were then categorized into high-, medium- and low-volume hospital tertiles.[22]

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Statistical Analysis

In all analyses, follow-up began 2 hospital days after the CABG procedure. Patients were censored at the first of the outcome of interest, the time of death, or the time of hospital discharge. To adjust for potentially important baseline differences in those patients who received adjuvant vancomycin and those who did not, we conducted 2 separate analyses using propensity scores. For both analyses, a propensity score was estimated using a logistic regression model in which use of vancomycin as an adjuvant was the dependent variable and predicted based on all the covariates noted above without further selection.

For the first analysis, patients exposed to cephalosporin plus vancomycin were matched on propensity score to those exposed to cephalosporins alone in a fixed 1:1 ratio using a nearest neighbor algorithm with a caliper of .05 difference in propensity score.[23] This resulted in a matched cohort of 40,152 patients. Cox regression modeling was then performed in the matched cohort to calculate hazard ratio (HR) and 95% confidence interval (CI) for postoperative CDI associated with vancomycin exposure. In the second score analysis, all subjects with a propensity score value that corresponded to the 2.5 percentile or lower of propensity score distribution in the cephalosporin plus vancomycin group and the 97.5 percentile or higher of the propensity score distribution in the cephalosporin only group were identified and excluded from further analysis. This approach of trimming patients from the tails of the propensity score has been shown to further decrease residual confounding.[24] Propensity score deciles were then created in the remaining cohort (n = 62,221). A multivariable Cox model was then fit including deciles of propensity score as covariates, and HR and 95% CI for CDI associated with vancomycin exposure were determined.

Sensitivity Analyses

We repeated our analysis in the subgroup of patients (n = 58,320) exposed to the most commonly used cephalosporin, cefazolin (ie, cefazolin plus vancomycin vs cefazolin alone). We also repeated our analyses defining the onset of CDI based on time that the stool study was performed (as opposed to the time that appropriate antibiotics were initiated). Finally, we repeated our analyses defining CDI based on the presence of a diagnosis code for CDI and initiation of appropriate therapy (without the requirement for a charge code for a stool study). All analyses were performed using SAS version 9.2 (SAS Institute, Inc, Cary, NC).

RESULTS

Cohort Characteristics

Our cohort consisted of 69,807 patients who underwent CABG between 2004 and 2010, of whom 24,393 (34.9%) received adjuvant vancomycin and the remainder received a cephalosporin alone (Figure 1). CDI developed in 256 patients overall. Postoperative CDI was associated with increased risk of adverse outcome; 9.9% of patients with postoperative CDI died versus 1.7% of those that did not have CDI. Length of stay was also substantially longer in those who had CDI compared with those who did not (median length of stay [interquartile range] 22 days [range, 14-35 days] vs 9 [range, 8-13 days]). The proportion of patients who received adjuvant vancomycin increased substantially during the study period from 30.4% in 2004 to 42.7% in 2010 (Figure 2).

Baseline Characteristics

There were notable differences in the baseline characteristics of the 2 exposure groups (Table 1). Significant regional differences in the use of vancomycin existed, with higher incidence of use in the South and lower incidence in the Northeast. Teaching and urban hospitals also used vancomycin more commonly than did nonteaching and rural hospitals. A larger fraction of patients exposed to vancomycin were female and African American. Vancomycin-exposed patients had a higher rate of preoperative intensive care unit admission and were more often administered supplemental oxygen, beta-blockers, antiarrhythmics, and acid-suppression therapy. They also had slightly higher rates of comorbidity including chronic obstructive pulmonary disease, diabetes, prior myocardial infarction and

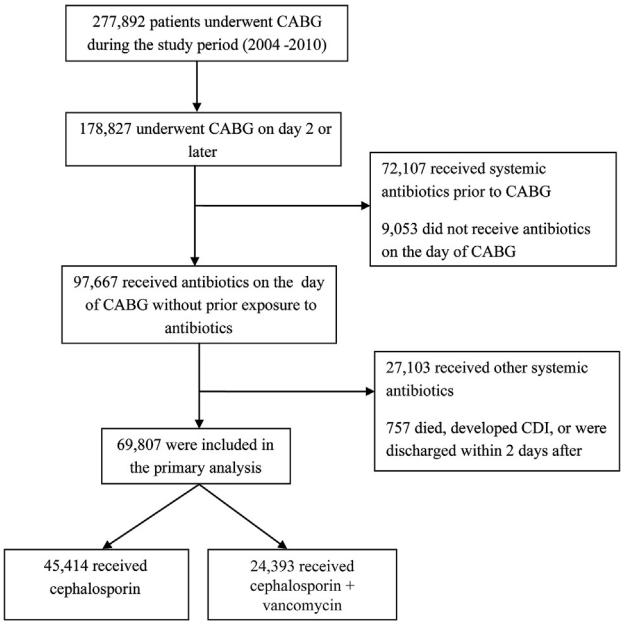

FIGURE 1. Patient flow chart. *CABG,* Coronary artery bypass graft; *CDI, Clostridium difficile* infection.

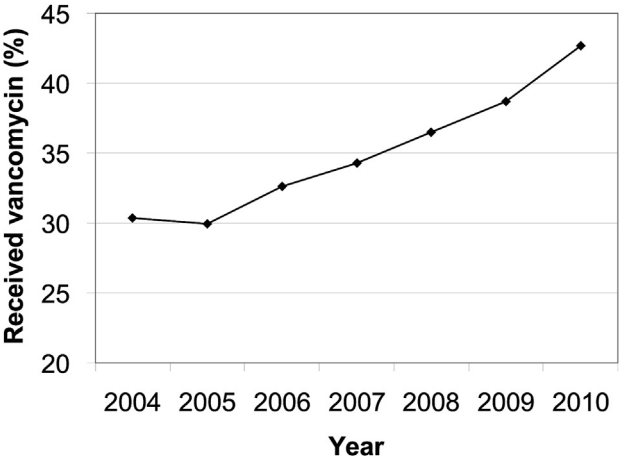

FIGURE 2. Proportion of cephalosporin-exposed patients undergoing coronary artery bypass grafting who received adjuvant vancomycin, by year.

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TABLE 1. Baseline characteristics of study population before and after PS matching

Characteristics	Before PS matching			After PS matching		
	Cephalosporins (N = 45,414)	Cephalosporins + vancomycin (N = 24,393)	Difference between cephalosporin and cephalosporins + vancomycin	Cephalosporin (N = 20,076)	Cephalosporin + vancomycin (N = 20,076)	Difference between cephalosporin and cephalosporins + vancomycin
Age (y, mean ± SD)	65.75 (11.07)	64.92 (11.12)	−0.05	65.24 (11.07)	65.13 (11.08)	−0.01
Male sex	33,858 (74.6%)	17,615 (72.2%)	2.4%	14,699 (73.2%)	14,673 (73.1%)	0.1%
Marital status						
Married	27,388 (60.3%)	15,179 (62.2%)	−1.9%	12,325 (61.4%)	12,476 (62.1%)	−0.7%
Single	13,844 (30.5%)	7756 (31.8%)	−1.3%	6137 (30.6%)	6225 (31.0%)	−0.4%
Other	4182 (9.2%)	1458 (6.0%)	3.2%	1614 (8.0%)	1375 (6.8%)	1.2%
Race/ethnicity						
White	32,777 (72.2%)	17,902 (73.4%)	−1.2%	14,482 (72.1%)	14,665 (73.0%)	−0.9%
African American	2642 (5.8%)	2253 (9.2%)	−3.4%	1506 (7.5%)	1501 (7.5%)	0%
Other	9995 (22.0%)	4238 (17.4%)	4.6%	4088 (20.4%)	3910 (19.5%)	0.9%
Index CABG						
Emergency admission	31,141 (68.6%)	16,069 (65.9%)	2.7%	13,351 (66.5%)	13,244 (66.0%)	0.5%
Thoracic graft	39,702 (87.4%)	20,856 (85.5%)	1.9%	17,387 (86.6%)	17,381 (86.6%)	0%
No. of grafts (mean ± SD)	3.22 (1.09)	3.28 (1.08)	0.01	3.25 (1.08)	3.26 (1.09)	−0.01
Repair/replacement of a valve						
Mitral valve	1426 (3.1%)	831 (3.4%)	−0.3%	661 (3.3%)	655 (3.3%)	0%
Aortic valve	3210 (7.1%)	1619 (6.6%)	0.5%	1328 (6.6%)	1311 (6.5%)	0.1%
Tricuspid valve	66 (0.1%)	60 (0.2%)	−0.1%	38 (0.2%)	36 (0.2%)	0%
Percutaneous coronary intervention	1809 (4.0%)	1131 (4.6%)	−0.6%	917 (4.6%)	881 (4.4%)	0.2%
Previous CABG surgery	810 (1.8%)	502 (2.1%)	−0.3%	389 (1.9%)	384 (1.9%)	0%
Preoperative LOS (d, mean ± SD)	2.79 (2.17)	3.04 (2.25)	−0.08	2.91 (2.20)	2.88 (2.16)	0.04
Comorbidities						
COPD/asthma*	4611 (10.2%)	2787 (11.4%)	−1.2%	2189 (10.9%)	2098 (10.5%)	0.4%
Diabetes mellitus†	13,042 (28.7%)	7318 (30.0%)	−1.3%	5846 (29.1%)	5790 (28.8%)	0.3%
End-stage renal disease‡	1045 (2.3%)	624 (2.6%)	−0.3%	483 (2.4%)	469 (2.3%)	0.1%
Chronic liver disease	602 (1.3%)	367 (1.5%)	−0.2%	302 (1.5%)	296 (1.5%)	0%
Cancer	4146 (9.1%)	2258 (9.3%)	−0.2%	1837 (9.2%)	1824 (9.1%)	0.1%
Endocarditis	33 (0.1%)	29 (0.1%)	0%	19 (0.1%)	17 (0.1%)	0%
PVD	4006 (8.8%)	2482 (10.2%)	−1.4%	1920 (9.6%)	1910 (9.5%)	0.1%
Hemostatic disorder	197 (0.4%)	139 (0.6%)	−0.2%	110 (0.5%)	100 (0.5%)	0%
Prior MI	6390 (14.1%)	3701 (15.2%)	−1.1%	2945 (14.7%)	2972 (14.8%)	−0.1%
Prior stroke	1769 (3.9%)	1181 (4.8%)	−0.9%	846 (4.2%)	875 (4.4%)	−0.2%
Carotid artery stenosis	2158 (4.8%)	1697 (7.0%)	−2.2%	1182 (5.9%)	1154 (5.7%)	0.2%
Charlson score	1.72 (1.49)	1.88 (1.55)	−0.06	1.82 (1.54)	1.80 (1.52)	0.02
Inpatient use of drugs or services before CABG						
Telemetry	15,192 (33.5%)	8349 (34.2%)	−0.7%	6658 (33.2%)	6818 (34.0%)	−0.8%
Echocardiogram	13,731 (30.2%)	8781 (36.0%)	−5.8%	6770 (33.7%)	6568 (32.7%)	1%
Oxygen use	14,337 (31.6%)	9429 (38.7%)	−7.1%	7360 (36.7%)	7444 (37.1%)	−0.4%
ICU	22,075 (48.6%)	12,985 (53.2%)	−4.6%	10,797 (53.8%)	10,527 (52.4%)	1.4%
ACE inhibitor	16,775 (36.9%)	9437 (38.7%)	−1.8%	7520 (37.5%)	7596 (37.8%)	−0.3%
Angiotensin receptor blocker	4408 (9.7%)	2488 (10.2%)	−0.5%	2006 (10.0%)	1989 (9.9%)	0.1%
Dipyridamole	690 (1.5%)	186 (0.8%)	0.7%	179 (0.9%)	181 (0.9%)	0%
Aldosterone agonist	983 (2.2%)	602 (2.5%)	−0.3%	448 (2.2%)	460 (2.3%)	−0.1%
Aspirin	27,024 (59.5%)	13,976 (57.3%)	2.2%	11,757 (58.6%)	11,851 (59.0%)	−0.4%
Beta-blocker	33,325 (73.4%)	18,605 (76.3%)	−2.9%	15,012 (74.8%)	15,030 (74.9%)	−0.1%
Calcium channel blocker	8562 (18.9%)	4959 (20.3%)	−1.4%	3941 (19.6%)	3909 (19.5%)	0.1%
Clopidogrel	6568 (14.5%)	3266 (13.4%)	1.1%	2756 (13.7%)	2756 (13.7%)	0%
Digoxin	1823 (4.0%)	903 (3.7%)	0.3%	766 (3.8%)	734 (3.7%)	0.1%

(Continued)

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TABLE 1. Continued

Characteristics	Before PS matching: Cephalosporins (N = 45,414)	Before PS matching: Cephalosporins + vancomycin (N = 24,393)	Before PS matching: Difference between cephalosporin and cephalosporins + vancomycin	After PS matching: Cephalosporin (N = 20,076)	After PS matching: Cephalosporin + vancomycin (N = 20,076)	After PS matching: Difference between cephalosporin and cephalosporins + vancomycin
Fibrate	1643 (3.6%)	983 (4.0%)	−0.4%	789 (3.9%)	800 (4.0%)	−0.1%
Loop diuretic	7281 (16.0%)	4235 (17.4%)	−1.4%	3310 (16.5%)	3324 (16.6%)	−0.1%
Thiazide diuretic	4218 (9.3%)	2537 (10.4%)	−1.1%	1981 (9.9%)	1998 (10.0%)	−0.1%
Statin	29,716 (65.4%)	15,836 (64.9%)	0.5%	12,883 (64.2%)	12,959 (64.5%)	−0.3%
Antiarrhythmic medication	3759 (8.3%)	3558 (14.6%)	−6.3%	2397 (11.9%)	2260 (11.3%)	0.6%
Proton-pump inhibitor	14,438 (31.8%)	8840 (36.2%)	−4.4%	6749 (33.6%)	6638 (33.1%)	0.5%
H2 blocker	6402 (14.1%)	4693 (19.2%)	−5.1%	3451 (17.2%)	3511 (17.5%)	−0.3%
Sucralfate	220 (0.5%)	100 (0.4%)	0.1%	86 (0.4%)	85 (0.4%)	0%
Hospital characteristics						
Teaching hospital	25,551 (56.3%)	14,907 (61.1%)	−4.8%	11,429 (56.9%)	11,353 (56.6%)	0.3%
Urban hospital	41,072 (90.4%)	23,076 (94.6%)	−4.2%	18,787 (93.6%)	18,759 (93.4%)	0.2%
High volume center	33,239 (73.2%)	17,099 (70.1%)	3.1%	13,721 (68.3%)	13,851 (69.0%)	−0.7%
Region						
Midwest	7221 (15.9%)	3756 (15.4%)	0.5%	3457 (17.2%)	3661 (18.2%)	−1%
Northeast	12,152 (26.8%)	1726 (7.1%)	19.7%	2000 (10.0%)	1726 (8.6%)	1.4%
South	16,459 (36.2%)	15,132 (62.0%)	−25.8%	11,127 (55.4%)	10,944 (54.5%)	0.9%
West	9582 (21.1%)	3779 (15.5%)	5.6%	3492 (17.4%)	3745 (18.7%)	−1.3%

PS, Propensity score; *SD,* standard deviation; *CABG,* coronary artery bypass graft; *LOS,* length of stay; *COPD,* chronic obstructive pulmonary disease; *PVD,* peripheral vascular disease; *MI,* myocardial infarction; *ICU,* intensive care unit; *ACE,* angiotensin-converting enzyme. *Based on preoperative beta-agonist, inhaled steroids, leukotriene inhibitors, ipratropium, or theophylline exposure. †Based on preoperative insulin or oral hypoglycemic exposure. ‡Based on preoperative dialysis, erythropoietin, or darbepoetin.

stroke, peripheral vascular disease, and carotid artery stenosis. They were, however, on average slightly younger than those exposed to cephalosporins alone. These imbalances were no longer present in the propensity score–matched cohort with a difference in proportions between the exposure groups of less than 2% for all covariates (Table 1). Duration of perioperative administration was similar between the 2 groups, suggesting that this is not an important confounder in our analysis; antibiotics were continued for 3 or more days in 18.5% of the cephalosporin-only group and 16.3% of the cephalosporin with vancomycin group.

Association of Vancomycin Exposure With *C difficile* Infection

Overall, 179 (0.39%) patients in the cephalosporin group and 77 (0.32%) patients in the cephalosporin plus vancomycin group had CDI. Vancomycin-treated patients had an unadjusted HR for CDI of 0.73 (95% CI, 0.56-0.95) (Table 2). After adjustment with propensity score matching or stratification, there was no meaningful association between adjuvant vancomycin exposure and CDI (HR, 0.85; 95% CI, 0.61-1.19; and HR, 0.85; 95% CI, 0.63-1.15, respectively).

Sensitivity Analyses

When we restricted our analyses to the patients exposed to cefazolin, the most commonly used cephalosporin in our cohort, the results were similar to those in the full cohort (Table 3).

Likewise, results were very similar when we defined onset of CDI based on the time that the stool study was performed (in propensity-matched analysis, HR, 0.88; 95% CI, 0.63-1.23) and when we defined CDI based on the presence of a diagnosis code for CDI and charge codes for appropriate antibiotic therapy, without the requirement for a charge code for a stool study (in propensity-matched analysis, HR, 0.86; 95% CI, 0.61-1.20).

DISCUSSION

In this large, nationally representative, hospital-based cohort study of 69,807 patients who underwent CABG between 2004 and 2010, we did not observe an increase in risk for CDI from the adjuvant use of vancomycin for SSI prophylaxis compared with cephalosporin use alone. These data suggest that concern about increased risk of CDI should not factor into clinicians' decision making regarding whether to administer vancomycin as an adjuvant to cephalosporins in this setting, especially given vancomycin's potential benefits for appropriately selected patients.

The lack of association between vancomycin exposure and CDI in our study contrasts with the findings of other studies identifying vancomycin exposure as an independent risk factor for CDI.[14-16,25] These studies evaluated patients hospitalized for a broad range of indications where vancomycin was likely used for therapeutic indications[14-16] and where vancomycin may have actually reflected illness severity, which itself is a risk factor for the

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TABLE 2. Hazard ratios of developing *C difficile* in patients treated with cephalosporin + vancomycin as compared with patients treated with cephalosporins only

	No. of patients	No. of events		HR (95% CI)
		Cephalosporin	*Cephalosporin + vancomycin*	
Unadjusted	69,807	179	77	0.73 (0.56-0.95)
Adjusted				
Age, sex, race, and calendar year	69,807	179	77	0.75 (0.57-0.98)
PS matching	40,152	73	64	0.85 (0.61-1.19)
PS stratification*	62,221	164	66	0.85 (0.63-1.15)

HR, Hazard ratio; *CI,* confidence interval; *PS,* propensity score. *All patients with a PS ≤ the value that corresponds to 2.5 percentile of the PS distribution in the cephalosporin plus vancomycin group and ≥ the PS value that corresponds to 97.5 percentile of the PS distribution in the cephalosporin group were excluded from this analysis (see text for more details).

development of CDI. In contrast, we evaluated the use of vancomycin as a prophylactic regimen in a cohort in which more than 80% of patients treated received this therapy for 2 days or less. Because duration of antibiotic exposure is strongly correlated with the risk of CDI,[16] it may be that the short course of exposure to vancomycin accounts for the lack of increased risk observed in our study. Nevertheless, given the sheer prevalence of vancomycin use (45% of patients at the end of the study cohort), it is reassuring that this treatment strategy does not appear to expose patients to excess risk.

During the study period from 2004 to 2010, we documented a nearly 50% increase in the administration of adjuvant vancomycin. Although our study did not document increased risk for CDI associated with its use, other concerns about the widespread use of vancomycin including selection of vancomycin-resistant *Enterococcus* and *Staphylococcus,* outcomes that we were unable to assess with our data, persist.[11,12] Our analysis does indicate highly heterogeneous use among regions and hospital types, suggesting the need for better definition of the patient groups most likely to benefit from the adjuvant use of this therapy in preventing endocarditis and deep mediastinal wound infections.[26,27]

Our study should be interpreted in the context of the limitations inherent in its design. Although the Premier Database contains highly granular data on the use of medications, laboratory test, and procedures, the information is collected for billing purposes and lacks certain clinical information such as the indication for the administration of adjuvant vancomycin. While we used rigorous statistical methodology, in the form of propensity scores, to adjust for baseline differences between those who did and did not receive adjuvant vancomycin, there may be unmeasured or unknown confounders that biased our results. We also did not have direct microbiologic data to confirm the diagnosis of CDI; previous data suggest a high sensitivity and specificity for diagnosis codes indicating CDI.[28-30] However, to increase the positive predictive value of our outcome definition, we required a charge code indicating stool study for *C difficile* toxin and a charge code indicating appropriate CDI therapy.[29,30] We only capture cases of CDI that occur during the index hospitalization. Although elevation in CDI risk persists for approximately 3 months after antibiotic exposure, the greatest risk is in the weeks immediately after antibiotic exposure.[31] Because of the extended postoperative hospital stay after CABG, we likely capture a large fraction of postoperative CDI cases. While, after accounting for relevant confounders, our study cannot preclude as much as a 19% increase in the risk of CDI associated with adjuvant vancomycin, it is unlikely that a better powered study could be performed with available data sources. The Premier Database is the largest of its kind, capturing detailed information on approximately one sixth of all hospitalizations in the United States. Thus, while the present study cannot definitely rule out a small increase in risk of CDI associated with adjuvant vancomycin, it provides high-quality evidence to guide clinicians with respect

TABLE 3. Hazard ratios of developing *C difficile* in patients treated with cefazolin + vancomycin as compared with patients treated with cefazolin only

	No. of patients	No. of events		HR (95% CI)
		Cefazolin	*Cefazolin + vancomycin*	
Unadjusted	58,320	162	59	0.74 (0.55-1.00)
Adjusted				
Age, sex, race, and calendar year	58,320	162	59	0.75 (0.56-1.01)
PS matching	32,278	65	55	0.83 (0.58-1.18)
PS stratification*	50,442	142	52	0.80 (0.57-1.10)

HR, Hazard ratio; *CI,* confidence interval; *PS,* propensity score. *All patients with a PS ≤ the value that corresponds to 2.5 percentile of the PS distribution in the cefazolin plus vancomycin group and ≥ the PS value that corresponds to 97.5 percentile of the PS distribution in the cefazolin group were excluded from this analysis (see text for more details).

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to this risk. Finally, to establish baseline demographic characteristics and comorbidities that might influence the decision to administer adjuvant vancomycin, we restricted our analysis to patients admitted at least 1 day before surgery. To isolate the effect of antibiotics administered on the day of surgery, we further excluded patients given antibiotics earlier in the admission. Although this excludes a substantial fraction of CABG patients, it is important in identifying potential confounders and thus ensuring the validity of our findings. It is also likely that the findings from our analysis would not be applicable to all CABG patients. We also do not analyze patients who received alternate antibiotic regimens, inasmuch as the small group sizes preclude meaningful analysis.

In conclusion, our analysis suggests that administration of adjuvant vancomycin for SSI prophylaxis does not increase the risk of CDI. The decision about whether to administer vancomycin should be made on the basis of other considerations. Given our finding that nearly half of all CABG patients received vancomycin in the most recent year of our study, and the substantial heterogeneity in practice with respect to its use, further research should focus on defining the risks and benefits of its administration.

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