

# Aspirin Plus Clopidogrel and Risk of Infection After Coronary Artery Bypass Surgery

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**Background:** The risks associated with the use of the combination of aspirin and clopidogrel before surgery are incompletely understood. Pharmacologic suppression of platelet function may increase the risk of postoperative infection by inhibiting hemostasis, immunity, or both.

**Methods:** We performed a retrospective cohort study of 1677 patients undergoing coronary artery bypass surgery to determine the relationship of the preoperative use of aspirin plus clopidogrel vs aspirin alone to the 30-day incidence of postoperative surgical site infection and bacteremia.

**Results:** The cumulative incidence of infection at 30 days was 23.1% and 16.1% in patients who were receiving dual antiplatelet therapy and aspirin monotherapy, respectively (unadjusted hazard ratio [HR], 1.51; 95% confidence interval [CI], 1.09-2.08). The risk of infection remained higher among patients who were receiving dual antiplatelet therapy after adjustment for demographic, socioeconomic, preoperative, and intraoperative risk factors (HR, 1.42; 95% CI, 1.01-2.00) and propensity score

(HR, 1.43; 95% CI, 1.01-2.01]). Transfusion rates were also higher among patients who were receiving dual antiplatelet therapy than among patients who were receiving aspirin monotherapy (68.4% vs 60.4%,  $P = .04$ ), but transfusion played a modest role in mediating the risk of infection (adjusted HR, 1.37; 95% CI, 0.96-1.93]). Mortality rates at 30 days were 5.2% and 3.1% in patients who were receiving dual antiplatelet and aspirin monotherapy, respectively (adjusted HR, 1.44; 95% CI, 0.70-2.99]).

**Conclusions:** Preoperative use of aspirin plus clopidogrel is associated with an increased risk of infection after coronary artery bypass surgery. These findings merit additional work to clarify the risks and benefits of uninterrupted dual antiplatelet therapy in surgical patients and the impact of platelet inhibition on infectious outcomes in populations that are at heightened infectious risk.

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**D**UAL ANTIPLATELET THERAPY with aspirin and clopidogrel reduces the incidence of adverse cardiovascular events in patients with acute coronary syndromes<sup>1-3</sup> and after percutaneous coronary intervention (PCI).<sup>4-6</sup> The combination of aspirin, which is an inhibitor of thromboxane-dependent platelet activation,<sup>7</sup> and clopidogrel, which is an inhibitor of adenosine diphosphate-dependent platelet activation,<sup>8</sup> reduces coronary occlusive events compared with aspirin alone. Considerable concern has been raised that early withdrawal of clopidogrel treatment may precipitate myocardial infarction (MI) and death.<sup>9,10</sup> Recently published expert guidelines advise continuation of dual antiplatelet therapy for at least 12 months after drug-eluting coronary stent deployment and deferral of elective surgery for 1 year.<sup>11,12</sup>

Unfortunately, a prolonged delay of surgery is not always possible or desirable in all patients who require dual antiplatelet therapy, eg, in patients with recent acute coronary syndromes who require coronary artery bypass (CAB) grafting or in patients with recent PCI who require surgery for cancer.

Although the antithrombotic benefits of dual antiplatelet therapy in nonsurgical patients are clear, the risks of uninterrupted preoperative therapy in surgical patients are incompletely understood. An increase in bleeding complications is well recognized with the combination of aspirin and clopidogrel compared with aspirin alone in both medical<sup>1</sup> and surgical<sup>13,14</sup> patients. Excess bleeding in surgical patients could increase the risk of infection by increasing the need for blood transfusion<sup>15,16</sup> or surgical reexploration.<sup>17</sup> Also, laboratory studies have suggested that

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platelets play a direct role in innate<sup>18,19</sup> and adaptive<sup>20</sup> immunity. Platelets assist in the recruitment of leukocytes to sites of vascular injury, release cytokines that can amplify the immune response, stimulate antibody formation from lymphocytes, and release bactericidal agents. However, the clinical impact of platelet function inhibition on host defense from infection is unknown and is of particular importance to surgical patients, who face heightened infectious risk.

The purpose of this study was to examine the association of dual antiplatelet therapy with infectious complications in patients undergoing CAB surgery. We hypothesized that combined therapy with aspirin and clopidogrel would increase their risk of postoperative infection. Because operative transfusion is associated with infection and mortality in cardiac surgery patients,<sup>15,16</sup> we specifically sought to determine whether a potential association between dual antiplatelet therapy and infection is mediated by an increased risk of transfusion in patients who are receiving clopidogrel therapy.

## METHODS

### STUDY SUBJECTS AND DESIGN

We performed a retrospective cohort study of patients undergoing CAB surgery at Johns Hopkins Hospital (JHH), Baltimore, Maryland, from January 1, 2000, through June 30, 2003. Patients were eligible for inclusion if they were 21 years or older, underwent single-vessel or multivessel CAB (with or without concurrent valve surgery), and were treated with aspirin within 5 days of surgery (N=1732). Inclusion was restricted to patients taking aspirin because previous studies demonstrated improved survival after CAB surgery in patients who were treated with aspirin 5 days or less before surgery compared with patients who were not taking aspirin.<sup>21</sup> Fifty-five patients (3.2%) were excluded because of missing data. Perioperative antibiotic prophylaxis was standardized, consisting of cefazolin (2 g) before surgical incision, with redosing every 2 hours during surgery and every 8 hours after surgery ( $\times 2$  doses). For patients who were allergic to penicillin, prophylaxis consisted of vancomycin (1 g) before surgical incision, with redosing at the end of cardiopulmonary bypass and 1 additional dose 12 hours after surgery. This study was approved by the Johns Hopkins institutional review board, which granted a waiver of written informed consent.

### DATA COLLECTION

The JHH cardiac surgical service participates in the Society of Thoracic Surgeons national database for reporting cardiac surgery outcomes and maintains a local database that includes the Society of Thoracic Surgeons and locally defined data variables. Data are prospectively collected and entered into this database by cardiac surgery personnel for all cardiac surgical procedures. The local cardiac surgery database was used to obtain information on age; race; sex; body mass index; current smoking status; presence of comorbidities (diabetes, cerebrovascular disease, peripheral artery disease, MI, angina, congestive heart failure, hypertension, chronic lung disease, and renal failure); New York Heart Association class; previous CAB surgery; previous PCI; preoperative use of medications (statins,  $\beta$ -blockers, and angiotensin-converting enzyme inhibitors); duration of preoperative hospital stay; type of surgical procedure; duration of surgery; whether the procedure was elective or emer-

gent; use of the internal mammary artery for bypass grafting; intraoperative transfusion of allogeneic blood products (red blood cells, platelets, and fresh-frozen plasma); and 30-day outcome data (outpatient surgical site infection and mortality).

The JHH Department of Hospital Epidemiology and Infection Control uses definitions for infectious outcomes based on the Centers for Disease Control and Prevention, National Nosocomial Infections Surveillance system (now called the National Healthcare Safety Network [<http://www.cdc.gov/ncidod/dhqp/pdf/nnis/NosInfDefinitions.pdf>]). Infection control personnel prospectively evaluate all patients who undergo CAB surgery and identify cases that meet the definition of surgical site infection and primary blood stream infection. Once classified, the cases are entered into an Access database (Microsoft Corp, Redwood, Washington) that includes microbiological data. This database was used to identify surgical site infections and bacteremias that occurred during inpatient hospitalization at JHH. Additional cases of bacteremia were identified from examination of microbiological data contained within the electronic patient record.

Medical records were reviewed to abstract information on the American Society of Anesthesiologists classification, chest tube drainage in the first 24 hours after surgery, marital status, insurance status, and preoperative exposure to aspirin and clopidogrel. The patients were classified as exposed to antiplatelet therapy when the use of aspirin or aspirin plus clopidogrel was documented in the medical record and the last dose of antiplatelet therapy was documented as occurring 5 days or less before surgery. Chart review was also used to retrieve any data elements that were missing from the cardiac surgery database.

### STUDY OUTCOMES

The primary study outcome was 30-day incidence of surgical site infection and bacteremia. Surgical site infection (superficial or deep) involving either the sternal or saphenous vein harvest site was defined according to the Centers for Disease Control and Prevention surveillance criteria.<sup>22</sup> Bacteremia was defined as 1 or more blood cultures positive for pathogenic organisms or 2 or more blood cultures positive for the same skin organism obtained on separate occasions.<sup>22</sup> Infectious outcomes for hospitalized patients were obtained from the infection control database and from blood culture data in the electronic medical record. Infectious outcomes for outpatients were obtained from the cardiac surgery database. Secondary outcomes were 30-day mortality rate, site-specific incidence rates for infectious outcomes, and the composite rate for infectious complications and mortality. Thirty-day outcome measures included both the inpatient and the outpatient phases of care.

### STATISTICAL ANALYSIS

Means, standard deviations (SDs), and percentages were used to summarize continuous and dichotomous variables, as appropriate. The association of demographic, preoperative, and operative variables with clopidogrel use and with infection was evaluated with *t* tests,  $\chi^2$  tests, and Fisher exact tests, as appropriate. Hazard ratios (HRs) and 95% confidence intervals (CIs) for postoperative infection and mortality were estimated using Cox proportional hazards models unadjusted and adjusted for demographic, socioeconomic, preoperative, and operative subject characteristics. For the 30-day infectious outcome, patients were considered to enter the study on their operative day and were followed up for the occurrence of infection, death, or through 30 days after surgery, whichever occurred first. A propensity score for dual treatment with aspirin and clopidogrel was created for each subject using a logistic

**Table 1. Characteristics of the Study Population by Preoperative Antiplatelet Therapy Use**

Variable	Aspirin Plus Clopidogrel <sup>a</sup> (n=194)	Aspirin Monotherapy <sup>a</sup> (n=1483)	P Value
Demographic and socioeconomic characteristics			
Age, mean (SD), y	63.4 (11.5)	65.6 (10.9)	.01
Sex, % female	25.8	27.4	.64
Race, % white	84.5	80.0	.13
Married, %	66.5	62.3	.25
Health insurance			.24
None	7.7	4.6	
Medicaid	0.5	2.6	
Medicare	40.7	44.3	
Commercial	51.1	48.5	
Preoperative risk factors			
Diabetes	29.9	32.5	.47
Hypertension	77.3	72.2	.13
Current smoker	25.8	23.8	.55
BMI, mean (SD)	28.7 (6.6)	28.4 (6.7)	.57
Cerebrovascular disease	19.6	10.2	<.001
Peripheral artery disease	19.6	16.6	.29
Previous MI	70.6	55.4	<.001
Unstable angina	57.2	50.4	.08
NYHA class, % class III-IV	88.1	81.3	.02
CHF	9.8	14.5	.08
Chronic lung disease	3.6	1.8	.09
Renal failure	5.7	5.1	.73
Previous CAB	11.3	4.8	<.001
Previous PCI	41.2	18.3	<.001
Statin therapy	82.5	70.4	<.001
β-Blocker therapy	71.1	62.0	.01
ACE inhibitor therapy	43.3	32.7	.003
Preoperative hospital stay, mean (SD), d	2.4 (2.8)	2.3 (2.9)	.73
ASA class, % class ≥4	86.1	80.6	.07
Operative risk factors			
Valve procedure	5.7	7.5	.46
Duration of surgery, mean (SD), h	4.7 (1.6)	4.5 (1.4)	.08
Emergency procedures	4.6	5.2	.86
Internal mammary grafting	80.9	89.8	<.001

Abbreviations: ACE, angiotensin-converting enzyme; ASA, American Society of Anesthesiologists; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CAB, coronary artery bypass; CHF, congestive heart failure; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

<sup>a</sup>Values are expressed as percentages unless otherwise indicated.

regression model that included all demographic, socioeconomic, preoperative, and operative patient characteristics ( $c=0.76$ ). Quintiles of the propensity score were introduced in the model as indicator variables to adjust for confounding in multivariable models.

The role of transfusion, blood loss, and reoperation as mediators of the association between dual antiplatelet therapy and 30-day infectious outcome was determined by including these variables in fully adjusted Cox proportional hazard models. Heterogeneity of the association between dual antiplatelet therapy and outcome was explored in subgroups defined by the presence or absence of specific comorbidities (eg, diabetes, MI, or previous CAB). Statistical analyses were performed using R, version 2.6.2 ([www.r-project.org](http://www.r-project.org)).

## RESULTS

The study sample comprised 1677 patients (mean [SD] age, 65.3 [11.0] years); 72.8% were male and 80.5% were white. One hundred ninety-four subjects (11.6%) were treated with a combination of aspirin and clopidogrel 5 days or less before surgery (**Table 1**). Compared with patients who were

receiving aspirin monotherapy, patients who were receiving dual antiplatelet therapy were more likely to have a history of cerebrovascular disease, MI, or coronary revascularization (CAB or PCI); to have a New York Heart Association functional status of III or IV; and to use statins, β-blockers, or angiotensin-converting enzyme inhibitors before surgery. Patients who were receiving dual therapy were also younger and less likely to receive an internal mammary artery graft (Table 1).

Two hundred seventy-eight patients developed a surgical site infection or bacteremia in the 30 days after surgery (30-day cumulative incidence, 16.9%): 116 had isolated sternal surgical site infection (41.7% of those with infection); 93 (33.4%) had a surgical site infection isolated to the saphenous vein harvest site; 54 (19.4%) had bacteremia; and 15 (5.4%) had surgical site infections at both sternal and saphenous vein harvest sites. Among the patients who developed an infection, the mean (SD) time from surgery to infection was 11.9 (7.3) days. Patients with infection were older, were more likely to be female, and differed by insurance status. They had a higher

**Table 2. Characteristics of the Study Population by Postoperative Infection Status**

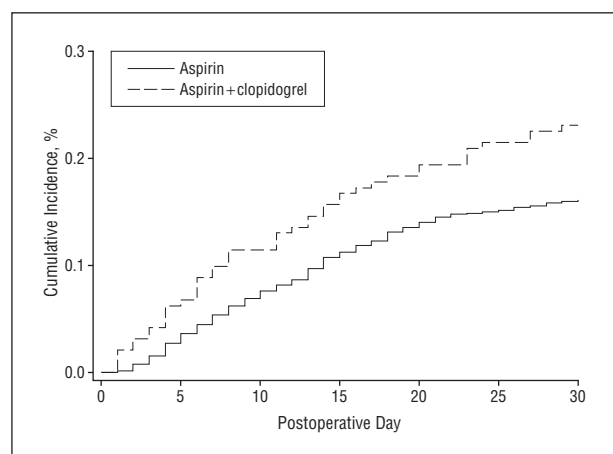
Variable	Infection Present <sup>a</sup> (n=278)	Infection Absent <sup>a</sup> (n=1399)	P Value
Demographic and socioeconomic characteristics			
Age, mean (SD), y	66.9 (10.5)	65.0 (11.1)	.008
Sex, % female	34.2	25.8	.004
Race, % white	79.9	80.6	.77
Married	63.0	62.7	.93
Health insurance			.006
None	3.2	5.3	
Medicaid	3.2	2.2	
Medicare	52.9	42.1	
Commercial	40.7	50.4	
Preoperative risk factors			
Diabetes	41.0	30.5	<.001
Hypertension	74.5	72.5	.50
Current smoker	22.3	24.4	.46
BMI, mean (SD)	30.3 (10.9)	28.1 (5.3)	<.001
Cerebrovascular disease	17.6	10.0	<.001
Peripheral artery disease	21.6	16.0	.02
Previous myocardial infarction	60.1	56.6	.29
Unstable angina	54.7	50.5	.21
NYHA class, % class III-IV	83.8	81.7	.40
CHF	19.8	12.8	.002
Chronic lung disease	2.9	1.8	.24
Renal failure	7.9	4.6	.02
Previous coronary artery bypass	8.6	4.9	.01
Previous percutaneous coronary intervention	22.7	20.6	.44
Statin therapy	72.7	71.6	.73
β-Blocker therapy	66.9	62.3	.14
ACE inhibitor therapy	35.6	33.6	.52
Preoperative hospital stay, mean (SD), d	2.9 (3.7)	2.2 (2.6)	.007
ASA class, mean (SD), % class ≥4	83.1	80.9	.40
Operative risk factors			
Valve procedure	8.6	7.0	.34
Duration of surgery, mean (SD), h	4.9 (1.4)	4.5 (1.4)	<.001
Emergency procedures	7.9	4.6	.02
Internal mammary grafting	83.1	89.9	.002

Abbreviations: ACE, angiotensin-converting enzyme; ASA, American Society of Anesthesiologists; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CHF, congestive heart failure; NYHA, New York Heart Association.

<sup>a</sup>Values are expressed as percentages unless otherwise indicated.

body mass index and were more likely to have a history of diabetes, cerebrovascular disease, congestive heart failure, peripheral artery disease, renal failure, and CAB surgery (**Table 2**). Patients with infection had longer preoperative hospital stays, underwent longer surgical procedures, were more likely to undergo an emergency procedure, and were less likely to receive an internal mammary graft (Table 2).

The cumulative incidence of infection at 30 days was 23.1% for the group treated with dual antiplatelet therapy before surgery and 16.1% for the group treated with aspirin monotherapy (unadjusted HR, 1.51; 95% CI, 1.09-2.08). The difference between groups in the rates of postoperative infection occurred early and persisted throughout the 30-day study interval (**Figure 1**). The association between clopidogrel use and postoperative infection persisted after sequential adjustments for demographic and socioeconomic characteristics (HR, 1.59; 95% CI, 1.15-2.19), for preoperative risk factors (HR, 1.43; 95% CI, 1.02-2.02), and for operative risk factors (HR, 1.42; 95% CI, 1.01-2.00) or after adjustment for propensity score (HR, 1.43; 95% CI, 1.01-2.01).



**Figure 1.** Cumulative incidence of postoperative surgical site infection or bacteremia by preoperative antiplatelet therapy use.

A greater proportion of patients who were treated with dual antiplatelet therapy received transfusions, and those who were treated with dual therapy received, on aver-

**Table 3. Transfusion and Bleeding Outcomes by Preoperative Antiplatelet Therapy Use**

Variable	Aspirin Plus Clopidogrel (n=194)	Aspirin Monotherapy (n=1483)	P Value
Intraoperative blood transfusion			
Any allogeneic blood product, %	68.0	60.4	.04
Red blood cells, mean (SD), U	2.9 (3.7)	2.0 (2.6)	.002
Fresh-frozen plasma, mean (SD), U	0.9 (2.3)	0.6 (1.7)	.10
Platelets, mean (SD), packs <sup>a</sup>	0.5 (0.7)	0.3 (0.6)	.002
Blood loss and reoperation for bleeding			
24-Hour chest tube drainage, <sup>b</sup> mean (SD), mL	700 (517)	553 (367)	<.001
Reoperation for bleeding, %	2.6	1.0	.06

<sup>a</sup>One pack of platelets equals 4 to 6 single donor units.

<sup>b</sup>Based on 1608 patients with available data.

age, a greater number of units of red blood cells and platelets (**Table 3**). The average chest tube drainage was also greater among patients who were receiving dual antiplatelet therapy, and there was a trend toward a higher rate of reoperation for bleeding in the group of patients who were receiving dual antiplatelet therapy. Inclusion of transfusion status (HR, 1.39; 95% CI, 0.99-1.96) or the number of units (red blood cells, fresh-frozen plasma, and platelets) transfused (HR, 1.37; 95% CI, 0.96-1.93) in fully adjusted Cox proportional hazards models had a limited effect on the HRs for infection associated with dual antiplatelet therapy. Similar results were observed when chest tube drainage and reoperation were included in the hazards models.

Cumulative incidence rates for each of the individual infectious outcomes were higher at 30 days among the patients who were treated with the combination of aspirin and clopidogrel compared with aspirin alone (**Table 4**). Cumulative mortality rates at 30 days were also higher with dual antiplatelet therapy than with aspirin alone (5.2 vs 3.1%, respectively; propensity score-adjusted HR, 1.44; 95% CI, 0.70-2.99); however, these differences were not significant ( $P = .32$ ). Dual antiplatelet therapy was associated with a worse outcome in most of the comorbidity subgroups examined (**Figure 2**).

#### COMMENT

This is the first study (to our knowledge) to demonstrate that preoperative use of dual antiplatelet therapy with aspirin and clopidogrel is associated with an increased risk of infection after CAB surgery. Increased risk was not explained by a variety of demographic, socioeconomic, preoperative, or intraoperative factors and was consistent across the subgroups examined. Preoperative use of dual antiplatelet therapy was also associated with increased postoperative bleeding and transfusion, but the impact of bleeding and transfusion was limited in mediating the relationship between dual antiplatelet therapy and increased risk of infection. Also, dual antiplatelet therapy was associated with increased postoperative mortality, although this association did not reach statistical significance ( $P = .32$ ).

Surgical site infections are common and serious complications of surgical procedures and are associated with increased mortality and excess health care expen-

ditures.<sup>23,24</sup> In an effort to reduce these complications, the Centers for Medicare & Medicaid Services has initiated a program to reduce payments for CAB procedures that are complicated by sternal surgical site infection, which is considered an avoidable complication. The 30-day cumulative incidence for sternal surgical site infection and saphenous vein graft surgical site infection in our population was 8.4% and 7.0%, respectively, which is in accordance with previous studies using active inpatient and postdischarge infection surveillance.<sup>25-28</sup> Similarly, the 30-day overall mortality rate (3.3%) in our study was in line with previous reports on CAB surgery.<sup>29</sup>

Many risk factors for postoperative infection and mortality have previously been identified,<sup>25,29,30</sup> and a recent report suggests that the increase in the rate of sternal surgical site infection over time is related to an increased prevalence of these morbidity risk factors in the CAB population.<sup>31</sup> These morbidity risk factors (eg, diabetes, obesity, and cerebrovascular disease) were common in our cohort; however, the increase in the risk of infection with dual antiplatelet therapy that we observed was independent of these previously identified factors. Therefore, our findings indicate that the preoperative use of aspirin plus clopidogrel is a novel risk factor for postoperative infection.

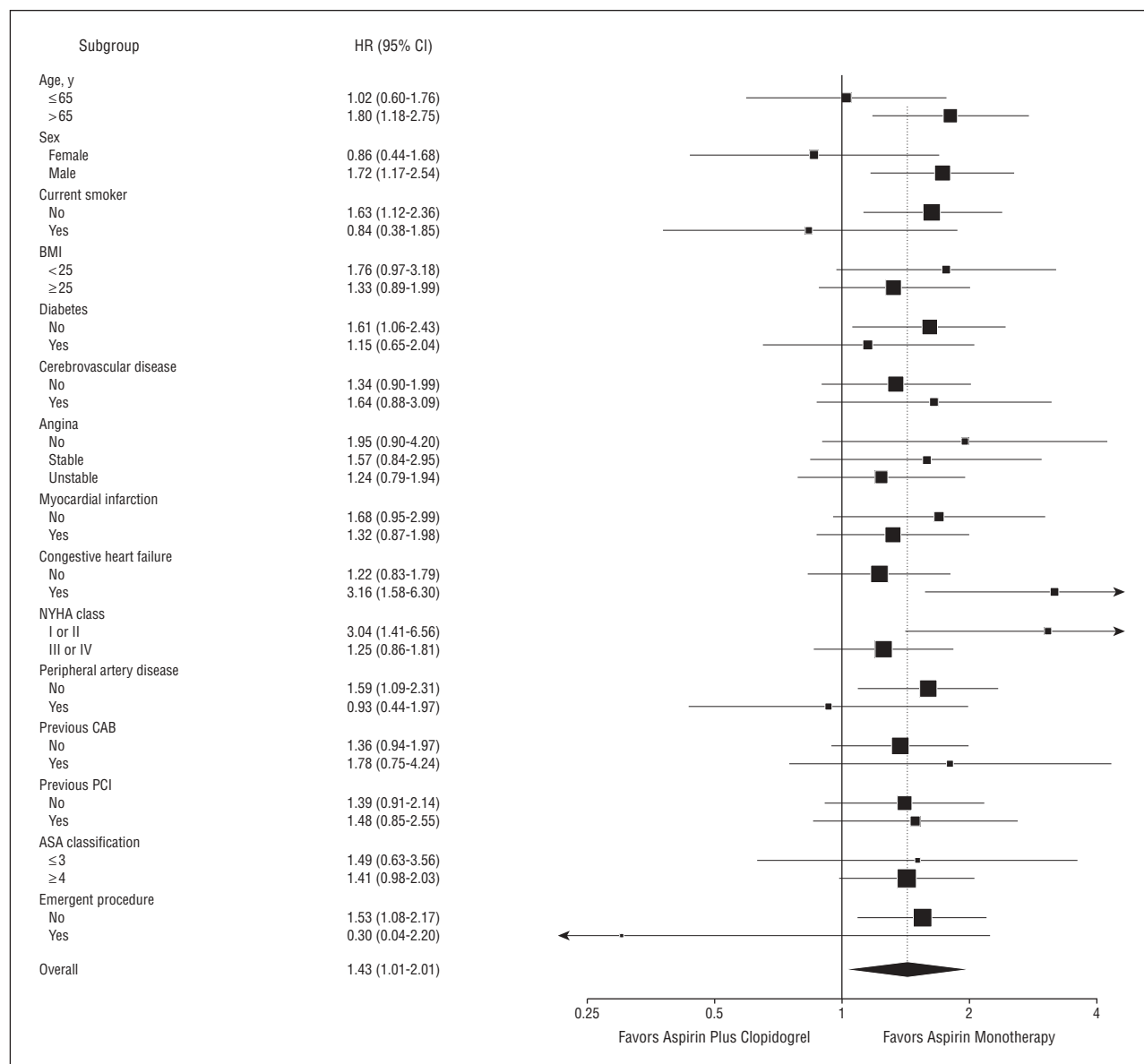
We found no evidence of heterogeneity among individual infectious outcomes, which were higher for sternal surgical site infection, saphenous vein surgical site infection, and bacteremia in the patients who were treated with dual antiplatelet therapy. We also found little evidence of heterogeneity in the relationship between dual antiplatelet therapy and infection in comorbidity subgroups. Of particular interest was the evidence of excess infectious risk with dual therapy for subgroups with and without previous MI, cerebrovascular disease, previous CAB, and previous PCI, suggesting that the severity of atherosclerosis or previous revascularization did not alter the relationship between dual antiplatelet therapy and risk of infection. Importantly, we saw no evidence of a perioperative mortality benefit with dual antiplatelet therapy, a finding that does not agree with previous reports on preoperative use of aspirin alone.<sup>21</sup> Indeed, we observed a trend toward higher 30-day mortality rates in patients who received dual antiplatelet therapy, although this association was not significant in adjusted analysis ( $P = .32$ ).

**Table 4. Thirty-Day Cumulative Incidences and Hazard Ratios (HRs) for Specific Infectious Outcomes and Mortality by Preoperative Antiplatelet Therapy Use**

Outcome	Aspirin Plus Clopidogrel (n=194)		Aspirin Monotherapy (n=1483)		HR (95% CI)	
	No. of Events	Cumulative Incidence, %	No. of Events	Cumulative Incidence, %	Crude	Adjusted
Surgical site infection and bacteremia	44	23.1	234	16.1	1.51 (1.09-2.08)	1.42 <sup>a</sup> (1.01-2.00)
Surgical site infection and bacteremia	44	23.1	234	16.1	1.51 (1.09-2.08)	1.43 <sup>b</sup> (1.01-2.01)
Sternal surgical site infection	21	11.9	110	8.0	1.54 (0.96-2.45)	1.52 <sup>b</sup> (0.93-2.49)
Saphenous vein harvest site infection	14	8.3	94	6.9	1.20 (0.68-2.10)	1.12 <sup>b</sup> (0.62-2.02)
Bacteremia	10	5.3	44	3.1	1.80 (0.90-3.57)	1.68 <sup>b</sup> (0.81-3.47)
Mortality	10	5.2	46	3.1	1.67 (0.84-3.31)	1.44 <sup>b</sup> (0.70-2.99)
Any infection or mortality	50	25.9	271	18.3	1.48 (1.09-2.00)	1.38 <sup>b</sup> (1.00-1.90)

<sup>a</sup>Multivariable adjusted model including all demographic, socioeconomic, preoperative, and intraoperative risk factors.

<sup>b</sup>Propensity score-adjusted model.



**Figure 2.** Propensity score-adjusted hazard ratios (HRs) for postoperative surgical site infection or bacteremia comparing aspirin plus clopidogrel with aspirin monotherapy by clinically relevant subgroups. ASA indicates American Society of Anesthesiologists; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CAB, coronary artery bypass; CI, confidence interval; NYHA, New York Heart Association; and PCI, percutaneous coronary intervention.

The relationship between preoperative use of dual antiplatelet therapy and increased risk of infection may be explained by several mechanisms involving inhibition of platelet-dependent hemostasis. The combination of aspirin and clopidogrel is reported to increase the risk of perioperative bleeding, reoperation, and transfusion in CAB surgery compared with aspirin monotherapy.<sup>13,14</sup> Greater blood loss and the need for reoperation are associated with increased postoperative infection,<sup>17</sup> possibly by extending the duration of patient exposure to infecting pathogens. Greater blood accumulation within a surgical wound may also promote local pathogen growth. Transfusion is well recognized to be associated with an increased risk of postoperative infection,<sup>16</sup> potentially by inducing immune tolerance.<sup>32</sup> Similar to previous studies, we found greater blood loss and transfusion in patients who were treated with aspirin and clopidogrel before surgery compared with aspirin alone as well as a trend toward more reoperations. Adjustment of infection risk models for blood loss, reoperation, and transfusion had a limited impact on the relationship between dual antiplatelet therapy and infection; ie, HRs were reduced from 1.42 (95% CI, 1.01-2.00) to 1.37 (95% CI, 0.96-1.93). These data suggest that excess bleeding, reoperation, and transfusion may mediate, in part, the association between dual antiplatelet therapy and infection; however, these hemostasis-related variables do not appear to fully account for the relationship between dual antiplatelet therapy and infection.

In addition to their well-known function in primary hemostasis, platelets also participate in innate and adaptive immunity through a variety of mechanisms that depend on platelet activation. Activated platelets accumulate at sites of vascular injury and express P-selectin,<sup>33</sup> which serves as a receptor for recruitment of neutrophils and monocytes via engagement of P-selectin glycoprotein ligand 1.<sup>34,35</sup> The interaction of P-selectin on activated platelets with leukocyte P-selectin glycoprotein ligand 1 in turn stimulates neutrophils and monocytes to release proteolytic granules<sup>36,37</sup> and cytokines<sup>38,39</sup> that augment the immune response. Activated platelets can also release proteins that are directly bactericidal<sup>40</sup> and can synthesize and release cytokines that enhance the antimicrobial functions of leukocytes.<sup>41</sup> By inhibiting platelet activation, all antiplatelet agents have the theoretical potential to diminish these activation-dependent platelet immune functions. Our data are the first (to our knowledge) to suggest that pharmacologic suppression of platelet function is associated with clinical infection in a human population. Additional work is needed to confirm these observations and to determine the impact of antiplatelet therapy on host immunity in the clinical setting.

Our study has several limitations. First, although we controlled for a large number of potential confounders and found consistent results in subgroup analyses, we cannot rule out the possibility that residual confounding contributed to the observed relationship between dual antiplatelet therapy and increased risk of infectious outcome. Therefore, the results of this study require confirmation in future studies. Second, we are unable to determine whether the relationship between dual antiplatelet therapy and infectious outcome is specific to the com-

bination of aspirin and clopidogrel, which causes a combination of COX-1<sup>7</sup> and P2Y12 receptor blockade<sup>8</sup> or whether it is a more generalizable consequence of intense inhibition of platelet function. Similarly, this study was not designed to evaluate the contributions to infectious outcome that are separately attributable to the use of aspirin and clopidogrel, which individually cause less intense platelet suppression than the combination of the two. However, the clinical relevance of a more detailed analysis of the relationship between aspirin monotherapy and infection is uncertain given that previous work has demonstrated improved survival in surgical patients who were treated with aspirin alone compared with patients who were not taking aspirin.<sup>21</sup> Third, very few patients in our cohort were documented to have discontinued chronic clopidogrel therapy more than 5 days before surgery, which prevented evaluation of the relationship between a protracted period of clopidogrel withdrawal and infectious outcome. However, the 5-day discontinuation period that we evaluated is in accord with the pharmacodynamics of clopidogrel, whose antiplatelet effect is not detectable approximately 1 week after discontinuation,<sup>42</sup> and is consistent with the discontinuation period evaluated for aspirin monotherapy in other studies of CAB surgery.<sup>21</sup>

In summary, we found an increase in the incidence of surgical site infection and bacteremia after CAB surgery in patients who were treated preoperatively with a combination of aspirin and clopidogrel compared with patients who were receiving aspirin monotherapy. Current guidelines recommend discontinuation of clopidogrel treatment 5 days or more before CAB surgery in patients with ST elevation MI.<sup>43</sup> However, recent studies also demonstrate excess risk of MI and death if clopidogrel is withdrawn from patients who have undergone drug-eluting stent placement<sup>9</sup> or experienced a recent acute coronary syndrome.<sup>10</sup> Other recently published guidelines advise a prolonged and uninterrupted course of dual antiplatelet therapy after drug-eluting stent deployment, including a warning against discontinuation of clopidogrel therapy and deferral of surgery until a prolonged antiplatelet course can be completed.<sup>11,12</sup> The absence of randomized controlled trials that assess the risks and benefits of a short-term withdrawal of dual antiplatelet therapy in surgical patients has created considerable uncertainty regarding the appropriate management of antiplatelet therapy in the perioperative period. This problem is likely to worsen given the increasing number of patients undergoing PCI and the longer durations recommended for dual antiplatelet therapy. Our study suggests that there may be significant infectious risks due to uninterrupted preoperative use of dual antiplatelet therapy in CAB surgery and potentially in other patient populations that are at high risk for infection. Additional studies are needed to clarify the risks and benefits of uninterrupted dual antiplatelet therapy in surgical patients and other populations that are at heightened infectious risk.

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**Author Contributions:** Dr Faraday had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Blasco-Colmenares, Perl, Baumgartner, and Faraday. *Acquisition of data:* Blasco-Colmenares, Perl, Guallar, Conte, Alejo, Pastor-Barriuso, Sharett, and Faraday. *Drafting of the manuscript:* Blasco-Colmenares, Guallar, and Faraday. *Critical revision of the manuscript for important intellectual content:* Blasco-Colmenares, Perl, Guallar, Baumgartner, Conte, Alejo, Pastor-Barriuso, Sharett, and Faraday. *Statistical analysis:* Blasco-Colmenares, Guallar, and Pastor-Barriuso. *Obtained funding:* Faraday. *Administrative, technical, and material support:* Blasco-Colmenares, Perl, and Faraday. *Study supervision:* Baumgartner, Conte, Sharett, and Faraday. **Financial Disclosure:** Dr Faraday has received research funding from NovoNordisk (within the past 5 years) and has a patent pending on novel antithrombotic agents and their methods of use.

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