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Preoperative Aspirin Use and Its Effect on Adverse Events in Patients Undergoing Cardiac Operations

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Background. **Preoperative aspirin use within 5 days of cardiac operations is controversial. Aspirin could reduce cardiovascular complications and yet might increase risk of bleeding. Recent reports showed conflicting results, and whether aspirin has variable effects for different cardiac surgical procedures is unclear.**

Methods. **A single-center retrospective cohort analysis was performed. After propensity score matching (PSM) for identified confounders, the relationship between preoperative aspirin use and 30-day all-cause mortality, postoperative renal failure, major adverse cardiocerebral events (MACE), blood transfusion, reoperation for bleeding, and postoperative infection were estimated with separate logistic regression models.**

Results. **Preoperative aspirin therapy was associated with a 49% ($p = 0.04$) increased risk of reoperation for bleeding among 868 matched pairs of patients undergoing valve operations. Among 725 matched patients undergoing coronary artery bypass grafting (CABG), preoperative aspirin therapy was not associated with a statistically significant higher risk of reoperation for bleeding. However, preoperative aspirin use, compared with nonuse, was not associated with risks of MACE, 30-day mortality, postoperative renal failure, blood transfusion, or postoperative infection in the entire cohort, in patients undergoing valve operations only, and in patients undergoing CABG only after PSM.**

Conclusions. **Preoperative aspirin use in all patients undergoing cardiac operations was not associated with risks of major cardiac, cerebral, or renal complications and infections and death; however, the risk of reoperation for bleeding was elevated among preoperative aspirin users compared with nonusers in a subpopulation of patients undergoing valve operations only.**

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Aspirin has been widely used in nonsurgical settings to reduce mortality, myocardial infarction, and stroke for patients with cardiovascular diseases [1, 2]. To balance the risk of thrombosis during the hypercoagulopathic perioperative period and the risk of bleeding from aspirin use, surgeons and anesthesiologists look for guidance to decide when they should discontinue aspirin and safely restart aspirin in the perioperative period.

In cardiac surgical settings, this issue is even more complex because all patients have cardiovascular disease and could be protected by aspirin. In the postoperative period, early aspirin therapy has been consistently reported to improve clinical outcomes for patients undergoing coronary artery bypass grafting (CABG), including better graft patency [3–6] and a reduced risk of death and ischemic complications [7]. However, whether aspirin should be used in the preoperative period remains controversial [8–13]. Several studies showed lower mortality [8, 9] in patients undergoing CABG, whereas others found a similar mortality rate and higher transfusion requirement [10, 14–17]. Decisions about preoperative aspirin therapy in patients undergoing CABG are made widely on the basis of individual and institutional experiences [11–13]. Actually, the American Heart Association, American College of Cardiology [18], The Society of Thoracic Surgeons (STS) [19], and the European Association for Cardio-Thoracic Surgery [20] even make different recommendations about when preoperative aspirin therapy should be terminated, ranging between 2 and 10 days before elective cardiac operations.

For valve operations, the risk and benefit of aspirin is even less clear, and there is only 1 report evaluating combined CABG and valve operations that found that aspirin was associated with similar adverse events

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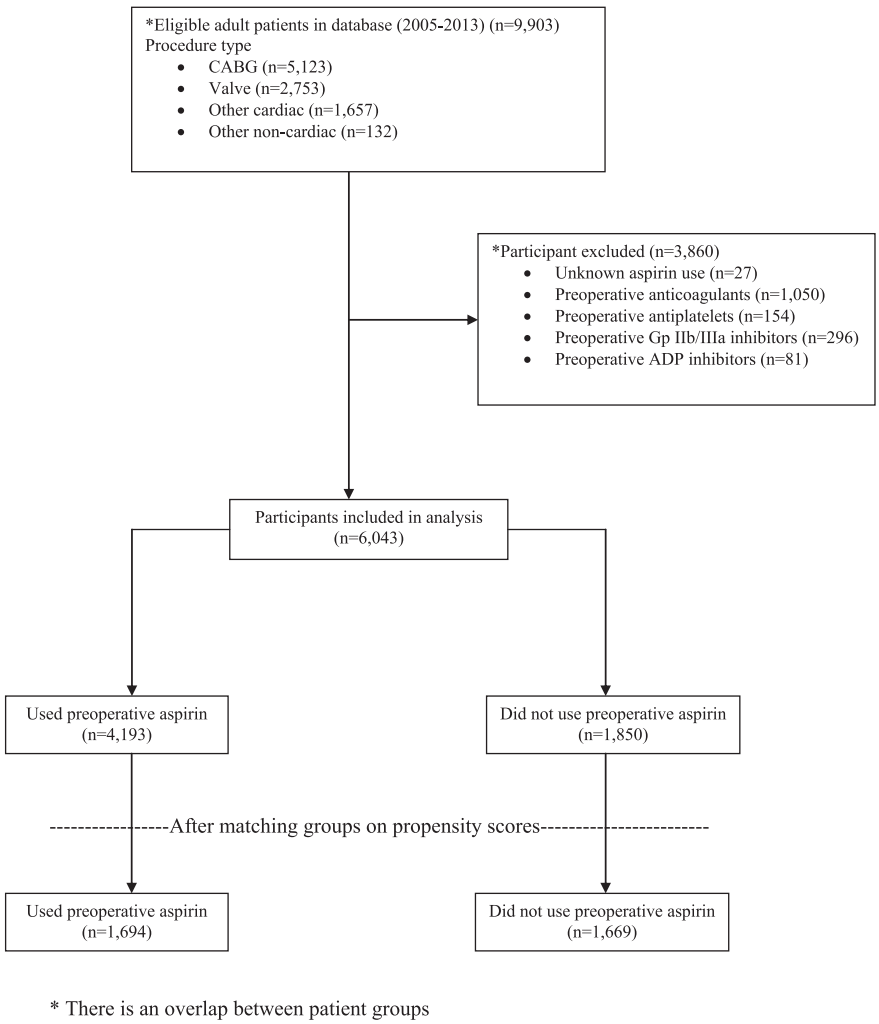

Fig 1. Study sample selection. (ADP = adenosine diphosphate; CABG = coronary artery bypass grafting.)

and more blood transfusions in CABG and valve operations [21]. Cao and associates [11, 12] assessed a cohort consisting of all cardiac procedures and found that aspirin was associated with a lower cumulative incidence of major adverse cardiocerebral events (MACE), renal failure, intensive care unit stay, and 30-day mortality [11, 12].

Our goal was to separately evaluate the effects of aspirin for patients undergoing CABG only and patients undergoing valve operations only. In addition, we evaluated the overall effects of aspirin in all cardiac procedures to reflect current real-life clinical practice. To elucidate possible mechanisms for aspirin effects, we further analyzed and compared the coagulation status between aspirin and nonaspirin groups.

Material and Methods

Data Collection

Institutional review board approval was obtained before conduct of the study and individual consent was waived. A retrospective cohort analysis of 9,903 consecutive patients undergoing cardiac operations at Jewish Hospital, Louisville, Kentucky from January 2005 to May 2013 was performed. Patient data were collected and organized to follow the template of the STS national database, including demographics, patient history, medical record information, preoperative risk factors, preoperative medications, intraoperative data, postoperative cardiocerebral events, renal failure, and 30-day all-cause mortality. Preoperative use of aspirin in this analysis was defined as a patient's use of aspirin within the 5 days preceding the surgical procedure. Fig 1 shows our study sample selection.

Definition of Major Outcomes and Other Covariates

Major outcomes of this study are 30-day all-cause mortality, requirement for postoperative renal failure/dialysis, reoperation for bleeding, blood transfusion (packed red cells, fresh frozen plasma, cryoprecipitate, or platelets), postoperative infection, and a composite outcome—major adverse cardiocerebral events (MACE). The latter included permanent or transient stroke, coma, perioperative myocardial infarction, heart block, and cardiac arrest according to the STS national criteria.

For coagulation studies, preoperative platelet count on the day of the operation, platelet aggregation test, activated partial thromboplastin time (APTT), and international normalized ratio (INR) were identified by combining 2005 laboratory data from the Jewish Hospital and the STS database. The mean and standard deviation of those factors were used.

Statistical Analysis

Standardized difference scores were estimated to compare baseline covariates between users and nonusers of preoperative aspirin. Most of these variables were not balanced between preoperative aspirin use and nonuse. A 1:1 propensity score matching (PSM) of preoperative aspirin users and nonusers minimized this potential selection bias. The propensity scores were estimated with a multivariable logistic regression models. Standardized differences for all baseline covariates were less than 10 in the matched sample, which suggests a balance of covariates between the aspirin and nonaspirin therapy groups [22]. The final PSM sample consisted of 1,669 identical pairs of preoperative aspirin users and nonusers for all cardiac procedures analyzed. Additionally, 725 pairs of patients who underwent CABG only and 868 pairs of patients who underwent valve operations only were matched with propensity scores for comparison.

Separate logistic regression models were used to estimate the associations (odds ratio [OR]) between preoperative aspirin therapy and each major outcome after cardiac procedures using both unmatched and PSM samples. Each of the models fitted to the unmatched data was adjusted with the logit of the propensity scores (quintiles) to control for preoperation confounders. The greedy matching algorithm was implemented for matching aspirin users and nonusers. This macro comes with prespecified parameters and has been extensively applied for matching cases and controls. We performed covariate adjustment by using the quintiles of propensity scores to estimate adjusted ORs for the association between preoperative aspirin therapy and postsurgical outcomes.

We reported unadjusted ORs from models fitted to the PSM sample because further propensity score adjustment did not alter the ORs. For prespecified subgroup analysis, similar statistical methods were applied to evaluate the associations between preoperative aspirin therapy and cardiac surgical outcomes in patient samples stratified by type of cardiac procedure. Separate PSM analysis was performed to create matched patient samples for patients undergoing CABG only and patients undergoing valve procedures only. All reported p values were 2-sided, and p values less than 0.05 were considered statistically significant. All statistical analyses were completed with SAS, version 9.3 (SAS Institute, Cary, NC) statistical software.

Results

Demographic Analysis

Of 9,903 patients in the database, 6,043 (61.0%) met the inclusion criteria and 4,193 (69.4%) patients received preoperative aspirin within 5 days before the surgical procedure compared with 1,850 (30.6%) patients who did not (Fig 1). The preoperative aspirin therapy group tended to be older male patients who had a higher body mass index and smoked more often and had more family history of coronary artery disease, diabetes, hypertension, peripheral vascular disease, cerebrovascular disease, chronic lung disease, and myocardial infarction (Table 1). Interestingly, there was a significantly lower prevalence of renal insufficiency and congestive heart failure in the preoperative aspirin group.

In the unmatched sample, preoperative aspirin therapy was not associated with risk of MACE, postoperative renal failure, 30-day mortality, and reoperation for bleeding or postoperative infection after adjusting for all potential confounders listed in Table 1. Nonetheless, preoperative aspirin use was associated with statistically significant 32% ($p = 0.03$) and 12% reductions ($p = 0.03$) in postoperative permanent stroke and blood transfusions in all patients undergoing cardiac procedures.

Aspirin for All Patients Undergoing Cardiac Operations

Preoperative aspirin use, compared with nonuse, was not associated with MACE (OR, 1.01; 95% confidence interval [CI], 0.79–1.28; $p = 0.96$). When stratified by various cardiac outcomes that constituted the definition of MACE, preoperative aspirin therapy was associated with a 34% lower risk of permanent stroke but a 41%, 10%, and 18% elevated risk of transient ischemic attack, heart block, and cardiac arrest, respectively (Table 2). These associations were not statistically significant.

Regarding other major clinical outcomes after cardiac operations, preoperative aspirin use was associated with a nonstatistically significant 11% lower risk of 30-day mortality, a 10% lower risk of postoperative renal failure, and an 8% lower risk of blood product use. Conversely, the risk of reoperation for bleeding and postoperative infection was elevated by 19% and 7%, respectively (Table 2).

Aspirin Use in Patients Undergoing CABG Only

In our prespecified subgroup analysis, surgical procedure–specific stratified associations were estimated (Table 3). Among patients undergoing CABG only, preoperative aspirin use was associated with an elevated risk of MACE (OR, 1.10), reoperation for bleeding (OR, 1.05), and 30-day mortality (OR, 1.24); however, preoperative aspirin use was associated with lower risks of postoperative renal failure (OR, 0.91), blood transfusion (OR, 0.94), and infection (OR, 0.72). None of these associations was statistically significant.

Aspirin Use in Patients Undergoing Valve Operations Only

Among patients undergoing valve operations only, preoperative aspirin therapy was associated with a statistically significant 49% (OR, 1.49; 95% CI, 1.02–2.17; $p = 0.04$) elevated risk of reoperation for bleeding. Even though preoperative aspirin therapy also elevated the risk of MACE and decreased the risk of postoperative renal

failure, blood transfusion, and infection, these associations were not statistically significant (Table 4).

Preoperative Coagulation Status

Analysis of preoperative platelet count, platelet aggregation test, APTT, and INR on the day of operation for patients undergoing CABG in 2005 demonstrated similar mean and standard deviation between the aspirin group and the nonaspirin group. Especially for platelet counts and aggregation, the aspirin group results were 243.76 $\times$ $10^3/\mu L$ with aggregation of 71%, and the nonaspirin group was 246.94 $\times$ $10^3/\mu L$ with aggregation of 72.64% (Table 4).

Comment

Effects of preoperative aspirin on clinical outcomes during cardiac operations are predominantly retrospective, have had similar but variable results, and generally reflect only those patients undergoing CABG. In our entire cardiac procedure cohort study, there was no significant association between aspirin use and MACE, 30-day mortality, postoperative renal failure, reoperation for bleeding, and blood transfusion. Blood transfusion carries significant negative effects on clinical outcomes, including risk of infection [23]. If aspirin affects blood product use, aspirin might also affect postoperative risk of infection. However, we found that aspirin use was not associated with blood transfusion or postoperative infection.

Because different cardiac procedures carry nonsimilar clinical risks, and the influence of aspirin might be disparate, it is important to analyze aspirin use in individual cardiac procedures. Most aspirin studies have focused on patients undergoing CABG because of the known protective actions of aspirin in coronary artery disease. Several retrospective studies demonstrated clinical outcome superiority of preoperative aspirin use in patients undergoing CABG [8, 9, 24]. In contrast, there is research supporting discontinuation of aspirin before cardiac operations [10]. In our study, we found that in

Table 1. Demographic and Clinical Characteristics Between Aspirin and Nonaspirin Groups

	Preoperative Use of Aspirin Within 5 Days Before Operation			
	Before Propensity Score Matching, %		After Propensity Score Matching, %	
Patient Characteristics	No (n = 1,850)	Yes (n = 4,193)	No (n = 1,669)	Yes (n = 1,694)
Age (y)				
<60	45.9	36.0	42.8	42.1
60–75	39.7	45.4	41.6	43.6
≥75	14.3	18.6	15.6	14.3
Male sex	59.7	67.1	60.5	61.9
BMI (kg/m^2)				
<25.0	27.7	21.7	27.2	24.0
25.0–29.9	32.4	35.9	31.9	34.7
≥30.0	39.9	42.4	40.9	41.3
White race	85.1	88.7	86.2	85.1
Current smoker	18.8	23.5	19	20.0
Family history of CAD	31.2	41.2	32.8	33.9
History of diabetes	26.4	36.2	28	29.5
History of hypertension	75.7	86.5	78.8	79.1
Peripheral vascular disease	12.3	18.2	12.8	13.2
Cerebrovascular disease	13.1	17.1	13.3	13.3
History of chronic lung disease	26.7	30.9	27.6	28.7
History of congestive heart failure	57.2	52.0	56.9	58.3
Myocardial infarction	5.5	10.7	6.0	6.5
Taking ACEI/ARB	29.0	38.2	31.3	31.6
Taking β-blockers	58.8	77.3	62.6	61.9
Previous cardiovascular intervention	27.2	35.5	26.2	27.4
Preoperative status				
Elective	72.5	65.6	72.9	72.4
Urgent	21.6	32.3	22.8	23.7
Emergent/salvage	5.8	2.1	4.3	3.8
Renal insufficiency	8.1	6.0	7.6	8.6
Perfusion time (min), mean (SD)	105.7 (54.0)	97.5 (44.8)	103.0 (51.0)	102.1 (50.0)
Cross-clamp time (min), mean (SD)	77.4 (37.2)	70.8 (32.5)	75.3 (34.2)	75.2 (36.3)

ACEI = angiotensin conversion enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; CAD = coronary artery disease; SD = standard deviation.

Table 2. Association Between Preoperative Aspirin Use and Major Clinical Outcomes After Cardiac Operations in a Sample of Propensity Score–Matched Patients

	No Preoperative Aspirin (n = 1,669)		Preoperative Aspirin (n = 1,694)			95% CI		
Outcome	N	%	N	%	Odds Ratio	LCI	UCI	*p* Value
MACE	137	9	135	8.9	1.01	0.79	1.28	0.96
Permanent stroke	47	3.1	37	2.4	0.66	0.43	1.00	0.05
TIA	15	1	21	1.4	1.41	0.71	2.81	0.32
Heart block	48	3.1	48	3.1	1.10	0.73	1.64	0.66
Cardiac arrest	35	2.3	37	2.4	1.18	0.76	1.83	0.47
Postoperative renal failure	171	11.2	136	8.9	0.90	0.73	1.12	0.36
30-day mortality	57	3.7	44	2.9	0.89	0.62	1.28	0.52
Reoperation for bleeding	73	4.8	83	5.4	1.19	0.87	1.62	0.28
Blood transfusion (yes/no)	742	48.7	704	46.2	0.92	0.81	1.06	0.25
Postoperative infection	50	3	54	3.2	1.07	0.72	1.58	0.75

CI = confidence interval; LCI = lower confidence interval; MACE = major adverse cardiocerebral events; TIA = transient ischemic attack; UCI = upper confidence interval.

patients undergoing CABG only, preoperative aspirin use was not associated with risks of MACE, postoperative renal failure, 30-day mortality, reoperation for bleeding, blood transfusion, or postoperative infection. Our study is a single-center retrospective study, which allowed for better control of institutional practice variation. Because there was no adverse event associated with preoperative aspirin use, this information might help clinicians to continue aspirin preoperatively and postoperatively without interruption. In addition, patients undergoing CABG frequently have peripheral vascular diseases and a history of ischemic stroke; continuing aspirin preoperatively might benefit these patients for the indicated diseases. Given the disparate studies showing variable benefit from preoperative aspirin use, and given the relatively safe outcomes associated with preoperative aspirin in our study, the benefit of aspirin on outcomes, if any, is likely to be small, and aspirin is relatively safe in patients undergoing CABG.

There was only 1 study in PubMed reporting on patients undergoing combined CABG and valve operations. There were no differences in outcome except that more patients who used aspirin preoperatively (within 5 days of the surgical procedure) received transfusions [21]. Patients undergoing only valve operations might have increased bleeding from multiple factors, such as longer suture lines, subclinical von Willebrand deficiency, and platelet dysfunction. To make a fair comparison, we performed PSM between aspirin and nonaspirin groups in patients undergoing valve operations only to eliminate

Table 3. Association Between Preoperative Aspirin Use and Major Clinical Outcomes After Cardiac Operations by Type of Surgical Procedure in a Sample of Propensity Score–Matched Patients

	No Preoperative Aspirin		Preoperative Aspirin			95% CI		
Outcome	N	%	N	%	Odds Ratio	LCI	UCI	*p* Value
CABG only	725	49.9	728	50.1	. . .	. . .	. . .	. . .
MACE	43	5.9	47	6.5	1.10	0.71	1.68	0.68
Postoperative renal failure	82	11.3	76	10.4	0.91	0.66	1.27	0.59
30-day mortality	17	2.3	21	2.9	1.24	0.65	2.37	0.52
Reoperation for bleeding	18	2.5	19	2.6	1.05	0.55	2.02	0.88
Blood transfusion (yes/no)	312	43	303	41.6	0.94	0.77	1.16	0.59
Postoperative infection	22	3	16	2.2	0.72	0.37	1.38	0.32
Valve operation only	872	50.1	868	49.9	. . .	. . .	. . .	. . .
MACE	105	11.8	117	13	1.11	0.84	1.48	0.45
Postoperative renal failure	102	11.5	101	11.2	0.97	0.73	1.31	0.86
30-day mortality	40	4.5	41	4.6	1.01	0.65	1.58	0.96
Reoperation for bleeding	49	5.5	72	8	1.49	1.02	2.17	0.04
Blood transfusion (yes/no)	504	56.8	549	61.1	0.94	0.77	1.16	0.59
Postoperative infection	31	3.5	37	4.1	0.72	0.37	1.38	0.32

CABG = coronary artery bypass grafting; CI = confidence interval; LCI = lower confidence interval; MACE = major adverse cardiocerebral events; UCI = upper confidence interval.

Table 4. Mean Distribution of Anticoagulation Factors Between Preoperative Aspirin Users and Nonusers Among Matched Patients Undergoing CABG in 2005

	Unmatched				Matched			
	No Preoperative Aspirin (n = 227)		Preoperative Aspirin (n = 544)		No Preoperative Aspirin (n = 199)		Preoperative Aspirin (n = 201)	
Anticoagulation Factors	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Platelet aggregation	73.24	24.0	71.90	24.3	72.64	25.4	71.00	23.7
APTT	31.35	14.3	30.28	13.4	31.04	12.8	31.21	14.7
INR	1.08	0.2	1.07	0.3	1.07	0.2	1.08	0.3
Platelet number	245.46	80.4	247.62	76.8	246.94	79.7	243.76	71.4

APTT = activated partial thromboplastin time; CABG = coronary artery bypass grafting; INR = international normalized ratio; SD = standard deviation.

these confounding factors. After PSM, we still found that preoperative aspirin use was associated with a 49% increased risk of reoperation for bleeding among our 1,740 patients undergoing valve operations only. Nonetheless, the risk of MACE, 30-day mortality, postoperative renal failure, blood transfusion, and postoperative infection were not statistically significant. Patients undergoing valve operations only might take aspirin for various reasons, such as pain control, mild coronary artery disease, peripheral vascular disease, previous coronary artery stenting, or stroke. Physicians need to make a weighted decision about whether to discontinue aspirin in patients undergoing valve operations only. Despite the findings that aspirin use was not associated with other adverse events except reoperation for bleeding, the previously mentioned comorbidities should guide physicians to balance aspirin's risks and benefits in patients undergoing valve operations only.

To address whether bleeding risks associated with aspirin are greatest in high-risk patients, we analyzed the coagulation studies of our 2005 cohort. Platelet counts and function (platelet aggregation tests), APTT, and INR analysis showed similar results between the aspirin group and the nonaspirin group, and all were within normal limits. Commensurate coagulation status suggested that the increased risk of reoperation for bleeding might not be related to other preoperative bleeding risks.

Because there was no significant difference in the whole cohort regarding reoperation for bleeding, patients undergoing other cardiac procedures might benefit even more without increasing risks of reoperation for bleeding from aspirin (excluding patients undergoing CABG only and patients undergoing valve operations only). Further studies in cardiac procedure–specific populations should be performed to identify which surgical procedures might benefit the most from preoperative aspirin use. Additionally, it is possible that aspirin interacts with other antiplatelet or anticoagulant drugs in a synergistic manner, causing either improved outcomes or increased bleeding. We are in the process of collecting preoperative platelet count, function (aggregation test), APTT, and INR determined on the day of operation in all cohort patients, including patients who received other anticoagulants. The use of other anticoagulants would be reflected by those test results. A correlation analysis would then be performed between those factors and outcome variables to identify the possible associations.

Platelet response to aspirin and other antiplatelet drugs is variable, and recovery of platelet function after stopping the medication is likewise inconsistent. Actually, Kempfer and coworkers [25] reported a 28.8% aspirin resistance in patients before CABG. One way to address the true influence of aspirin is to study the exact timing of preoperative aspirin stoppage. Unfortunately, this information is not reported on patient medical records. Although we could not perform a formal logistic regression analysis because of limited study numbers, our platelet count and function test analysis in our 2005 cohort demonstrated that the effects of aspirin on platelet number and function appear to be small and insignificant.

There are several limitations in this study. First, there are potential biases from uncontrollable confounding factors, including comorbidities, medication use, and physician selection bias. These potential biases were minimized in our study through PSM methods. However, exposure biases might still be present as a result of the noninclusion of unmeasured and unknown confounders in our PSM analysis. Second, postoperative use of aspirin might also affect the outcome in cardiac operations [26]. However, these data are not available in our database, and it is our standard order that aspirin be routinely started after cardiac operations. The influence of postoperative aspirin use on clinical outcomes should reasonably be expected to be evenly distributed in both groups. Third, aspirin dosage and the exact timing of last aspirin administration were not accessible in our database. Both of these factors might affect clinical outcomes significantly. We found that platelet counts and function analysis were similar between the aspirin and nonaspirin groups. However, lack of antithrombotic efficiency should not be the only reason for discontinuing aspirin preoperatively, because aspirin possesses antiinflammatory and other important properties.

In conclusion, preoperative aspirin use was associated with an elevated risk of reoperation for bleeding compared with nonuse of aspirin in patients undergoing valve operations only. Aspirin was not associated with

MACE, 30-day mortality, postoperative renal failure, postoperative infection, and reoperation for bleeding in all cardiac procedures or patients undergoing CABG only. Further studies, including randomized and large prospective studies, are needed to elucidate potential roles of preoperative aspirin therapy in individual patients undergoing cardiac procedures.

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INVITED COMMENTARY

The current study is a single-institution retrospective analysis of 5,385 patients, of whom 3,871 (72.2%) patients received preoperative aspirin while 1,711 (27.8%) did not [1]. The authors studied the entire cohort and subdivided the group into coronary artery bypass graft (CABG)-only and valve-only patients to understand further what effect preoperative aspirin use might have on adverse events (eg, bleeding, mortality, renal failure, cerebrovascular

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