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Platelet Counts And Postoperative Stroke After Coronary Artery Bypass Grafting Surgery

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Abstract

Background—Declining platelet counts may reveal platelet activation and aggregation in a postoperative prothrombotic state. Therefore, we hypothesized that nadir platelet counts after on-pump coronary artery bypass grafting (CABG) surgery are associated with stroke.

Methods—We evaluated 6,130 adult CABG surgery patients. Postoperative platelet counts were evaluated as continuous and categorical (mild vs. moderate to severe) predictors of stroke. Extended Cox proportional hazard regression analysis with a time-varying covariate for daily minimum postoperative platelet count assessed the association of day-to-day variations in postoperative platelet count with time to stroke. Competing risks proportional hazard regression models examined associations between day-to-day variations in postoperative platelet counts with timing of stroke (early: 0–1 days; delayed: ≥2 days).

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Results—Median [interquartile range] postoperative nadir platelet counts were 123.0 [98.0, 155.0] × 10^9/L. The incidences of postoperative stroke were 1.09%, 1.50%, and 3.02% for platelet counts, >150×10^9/L, 100–150×10^9/L, and <100×10^9/L, respectively. The risk for stroke increased by 12% on a given postoperative day for every 30 × 10^9/L decrease in platelet counts (adjusted hazard ratio [HR], 1.12; 95% confidence interval [CI], 1.01–1.24; *P*=0.0255). On a given day, patients with moderate to severe thrombocytopenia were twice as likely to develop stroke (adjusted HR, 1.99; 95% CI, 1.18–3.34; *P*=0.0093) as patients with nadir platelet counts >150×10^9/L. Importantly, such thrombocytopenia, defined as a time-varying covariate, was significantly associated with delayed (≥2days after surgery; adjusted HR, 2.87; 95% CI, 1.49–5.55; *P*=0.0016), but not early postoperative stroke.

Conclusion—Our findings suggest an independent association between moderate to severe postoperative thrombocytopenia and postoperative stroke, and timing of stroke after CABG surgery.

INTRODUCTION

Postoperative stroke remains a relatively common and often debilitating complication after cardiac surgery, affecting approximately 2% of patients, and carrying a 5-fold higher risk for postoperative mortality.(1) Despite important advances in patient care, surgical strategies, and cardiopulmonary bypass (CPB) equipment, this incidence of stroke has not changed significantly over the past 2 decades.(2) Thus, as increasing numbers of older patients with more comorbidities are undergoing cardiac surgery, and as more patients are surviving surgery, the prediction, management, and prevention of stroke after CABG surgery are healthcare priorities of increasing concern.

The etiology of stroke after on-pump CABG surgery is complex and multifactorial,(3,4) with important differences between early (0–1 days) and delayed (≥ 2 days) strokes. Most early strokes purportedly arise from particulate and gaseous embolism during surgery,(5) and/or are precipitated by intraoperative hemodynamic perturbations.(6) In contrast, a crucial factor in the development of delayed strokes is likely the prothrombotic postoperative state(7) promoted by significant and protracted humoral and cellular inflammatory responses,(8) and platelet activation(9,10) during and after cardiac surgery.

The role of platelets has come under significant scrutiny in various disease processes as they are increasingly recognized as important and ubiquitously present regulators of tissue inflammation.(11) We recently reported that, similar to observations in critically ill patients(12), postoperative thrombocytopenia, defined as the lowest in-hospital values, is associated with acute kidney injury (AKI) and increased risk for mortality after CABG surgery.(13) The cause of the postoperative decline in platelet counts and importantly, the connection between thrombocytopenia and the development of adverse outcomes, remain unknown. Because platelet counts frequently drop to a nadir after cardiac surgery,(13) the observed thrombocytopenia is likely the result of platelet activation and consumption in a setting of systemic hypercoagulability. We therefore hypothesized that thrombocytopenia after on-pump CABG surgery is associated with postoperative stroke.

METHODS

Study Population

After approval by the Institutional Review Board for Clinical Investigations at Duke University Medical Center (Durham, NC, USA), we conducted this retrospective observational study on patients over 18 years old who underwent isolated urgent or elective CABG surgery with CPB at the Duke University Medical Center from January 1, 2001 through July 18, 2015. For patients who had more than one cardiac surgery during that period, only data from the first surgery were evaluated. Of the original 6,921 patients, 6,131 had complete data for preoperative and postoperative platelet counts, and met criteria for inclusion in the present study. Of the 6,131 patients analyzed and reported in this study, 4,217 have been analyzed as part of a separate publication.(13)

Data Collection

A standard set of perioperative data were collected from Duke University Medical Center databases including the Duke Perioperative Electronic Database (Innovian® Anesthesia; Draeger Medical Inc, USA), Cardiac Surgery Quality Assurance Database, Duke Databank for Cardiovascular Diseases, and from Duke MAESTRO CARE (Medical Application Environments Supporting Transformation of Research and Operations: http://www.dukehealth.org/maestrocare), Duke Medicine's platform-based electronic health record (Copyright 2016 by Epic Systems Corporation, Verona, WI, USA; http://www.epic.com).

Clinical Risk Factors

The clinical risk factors for postoperative stroke included patient characteristics, preoperative and intraoperative cardiovascular medication use including prothrombin complex and recombinant factor VII, components of the European System for Cardiac Operative Risk Evaluation score (EuroSCORE),(14) CPB and aortic cross-clamp times, insertion of intraaortic balloon pump (IABP), intraoperative and postoperative blood transfusions, and hemoglobin and platelet counts. According to institutional practice, preoperative antiplatelet therapy with aspirin was maintained until the day before surgery; clopidogrel was discontinued 7 days or longer before surgery; and warfarin was discontinued 4 days before surgery and "bridged" with IV heparin infusion.(13)

Per institutional protocol, platelet counts were also measured preoperatively in the Duke Clinical Pathology Laboratory and for the first 10 days postoperatively or until discharge, whichever came first, as described previously.(13) We analyzed both the association of daily minimum postoperative platelet values, and that of lowest minimum (nadir) platelet counts with our stroke outcome. For the analysis of association of nadir platelet values we conditionally defined nadir platelets relative to stroke outcomes. When stroke preceded the postoperative nadir platelet counts, we used lowest pre-stroke platelets value as a predictor of postoperative stroke. These values were subsequently used as a *continuous predictor* of postoperative stroke. Further, based on laboratory definitions of thrombocytopenia, postoperative platelet values were used as a categorical predictor (mild thrombocytopenia [100–150 × 10^9/L], and moderate to severe thrombocytopenia [<100 × 10^9/L]) and as a

threshold for clinical characterization of patients with different grades of postoperative thrombocytopenia.

Similarly, serum hemoglobin concentrations were measured per institutional protocol, preoperatively and for the first 10 days postoperatively or until discharge, whichever came first. Daily and minimum serum hemoglobin concentrations were defined as the lowest in-hospital values measured during the first 10 postoperative days or to day of hospital discharge and were considered as adjustment variables in our analyses of postoperative stroke.

Classification of Outcome

Postoperative stroke was chosen as the outcome, and was ascertained and categorized in a manner similar to the study by Hogue et al.(4) In brief, postoperative stroke was defined as any new permanent global or focal neurologic deficit that could not be attributed to preexisting neurologic and/or non-neurologic pathophysiologic abnormalities. Reversible cerebral ischemic events, such as a transient ischemic attack, were not included in the current study because the residual effect of perioperative medications could hinder their detection. Per Duke institutional protocol, all patients undergoing cardiac surgery were screened daily during the postoperative period to identify patients with postoperative stroke. When a new postoperative neurologic deficit was detected, a stroke code was initiated. A subsequent diagnosis of stroke was established by the attending neurologist, and was substantiated in most patients by neuroimaging, eg, CT or MRI head scan. In the current study, the patients' electronic health records were screened for International Classification of Disease-9th Revision (ICD-9; http://www.cdc.gov/nchs/icd/icd9cm.htm) codes for cerebrovascular accident, eg, ischemic (434.91), embolic (434.11), hemorrhagic (430, 431, 432.0–432.9), thrombotic (434.01), and postoperative cerebrovascular accident (997.02). In parallel, electronic imaging records, as part of the electronic health records of all patients, were screened for the CPT billing codes for a CT scan of the head (70450 [CT scan of the head without contrast], 70460 [CT scan of the head with contrast], and 70470 [CT scan without contrast followed by a CT procedure with contrast]), and for an MRI scan of the brain (70551 [MRI Brain without contrast], 70552 [MRI Brain with contrast], and 70553 [MRI Brain without contrast followed by an MRI procedure with contrast]). CT and MRI scans with a date stamp within 30 days of CABG surgery, were selected and reviewed for a diagnosis of acute postoperative stroke. All stroke diagnoses and imaging reports were then reviewed by 3 investigators (AEM, JAK, MDK), and the diagnoses and timing of strokes were ascertained in relation to the date of surgery. New neurologic deficits identified before the end of postoperative day (POD) 1 were classified as early strokes, and neurologic deficits that occurred between POD 2 and 30 inclusively, were classified as delayed strokes.

STATISTICS

Summary statistics are presented as median (interquartile range) for continuous variables, or as group frequencies and percentages for categorical variables by categories of postoperative thrombocytopenia that were defined using the lowest in-hospital value or the lowest platelet

value prior to stroke. Kruskal-Wallis or chi-square tests were used for descriptive group comparisons as appropriate.

Univariable and multivariable Cox proportional hazard regression models were applied to evaluate the unadjusted and adjusted prognostic importance of postoperative platelet counts and risk for postoperative stroke. Given the day-to-day variations in postoperative platelet counts and serum hemoglobin concentrations in our study we used extended Cox regression analysis with time-varying covariates and hazard ratios to model the effects of day-to-day variations in postoperative platelet counts and serum hemoglobin concentrations on the risk for postoperative stroke.(15–17) We defined the time-varying platelet counts variable (both categorical and continuous) in our proportional hazards models based on the most recent daily minimum platelet counts relative to the time being evaluated. For all time points after discharge or POD 10, whichever came first, time-varying platelet counts model term were based on the last recorded daily minimum value. The resulting hazard ratio estimates for effect of postoperative platelet counts in these models should be interpreted as comparisons of the hazard for two patients with different postoperative platelet counts on the same day after surgery. Univariable associations with $P < 0.10$ were evaluated using a forward stepwise technique to derive the final multivariable Cox proportional hazard regression model containing variables with $P < 0.05$. Continuous variables (ie, age, serum creatinine, hemoglobin and platelet counts, and duration of CPB time) were evaluated for nonlinearity, and transformations were performed if warranted. Of note, including time-dependent covariates for postoperative platelet counts and serum hemoglobin concentrations precluded us from the evaluation of the discriminatory ability and calibration of the final multivariable Cox regression models.

In a subsequent analysis, we investigated the association between daily postoperative platelet counts and timing of stroke using the Fine-Gray method of proportional hazard models for the subdistribution of early and delayed strokes.(18) Under the Fine-Gray method, the subdistribution hazard for a given subevent is defined as the hazard for a patient who either suffers the subevent or not, and expands the risk set at a given time to include both those who have experienced a different subevent and those who are currently event free. This analysis method allows us to estimate the effect of daily postoperative platelet counts on the absolute risk of early and delayed stroke, and to estimate the cumulative impact of daily postoperative platelet counts on patient stroke prognosis.(19) We built multivariable models separately for each subevent using forward stepwise technique to derive final multivariable proportional hazards models containing variables with $P < 0.05$ for early and delayed stroke events. As in the main analysis, we used a time-varying effect for day-to-day variations in postoperative platelet counts (both categorical and continuous).

A sensitivity analysis was also performed to determine whether exclusion of patients with heparin-induced thrombocytopenia (HIT) affected the observed association between thrombocytopenia and stroke. The presence of HIT was ascertained by reviewing the patients' electronic health records for the diagnosis of HIT, and by searching laboratory records for enzyme-linked immunosorbent assays that were positive for human platelet factor 4/heparin complex antibodies. Hazard ratios (HRs) and odds ratios (ORs) with

corresponding 95% confidence limits are reported. SAS Version 9.4 (SAS Institute Inc, USA) was used for all statistical analyses.

RESULTS

The overall median [interquartile range] for postoperative nadir platelet counts was 123.0 [98.0, 155.0] × 10^9/L. The 6,130 patients studied were separated into 3 groups according to postoperative nadir platelet counts: (1) no thrombocytopenia (>150 × 10^9/L; 27%, n = 1,750); (2) mild thrombocytopenia (100–150 × 10^9/L; 44.4%, n = 2,726); and (3) moderate to severe thrombocytopenia (<100 × 10^9/L; 28.6%, n = 1,654). Demographic and clinical characteristics of the 3 groups according to postoperative nadir platelet counts are compared in Table 1. Several significant differences between the groups were found including age, race, female sex, medical history, comorbidities, preoperative and intraoperative medication use, and intraoperative characteristics. Of note, none of the patients who developed stroke had received prothrombin complex or recombinant factor VII.

Postoperative Stroke

The overall incidence of postoperative stroke was 1.8% (n = 110) within 30 days after surgery. In 101 patients (91%), the diagnosis of postoperative stroke was substantiated by neuroimaging such as a CT or MRI head scan; and in 9 patients (9%), the stroke diagnosis was established by the attending neurologist. Most of these strokes were ischemic (90%). Of the remainder, 4.5% were hemorrhagic, and 5.5% were embolic strokes. In cohorts with no thrombocytopenia, mild thrombocytopenia, and moderate to severe thrombocytopenia, the incidence of stroke was 1.09% (n = 19), 1.50% (n = 41), and 3.02% (n = 50), respectively.

Univariable predictors of postoperative stroke are shown in Table 2. Several preoperative and intraoperative variables were significantly associated with an increased risk for postoperative stroke (Table 2). Daily postoperative platelet counts as a time-varying covariate, defined as mild thrombocytopenia 100 – 150 × 10^9/L (unadjusted HR, 1.64; 95% CI, 1.02–2.62; P = 0.0406), moderate to severe thrombocytopenia <100 × 10^9/L (unadjusted HR, 2.77; 95% CI, 1.66–4.61; P < 0.0001), or as a continuous variable for every 30 × 10^9/L daily decrease (univariable HR, 1.19; 95% CI, 1.07–1.32; P = 0.001), were significantly associated with postoperative stroke. According to our multivariable analysis, age, history of peripheral vascular disease (PVD), intraoperative insertion of IABP, and packed red blood cell transfusion were independent risk factors for postoperative stroke, whereas preoperative statin use was associated with a reduced risk for postoperative stroke (Table 2). After adjusting for differences in baseline and clinical characteristics, categorical postoperative thrombocytopenia showed a strong association with postoperative stroke (Table 2). Multivariable analysis that incorporated postoperative platelet count as a time-varying continuous variable showed that, on a given postoperative day for every 30 × 10^9/L decrease in platelet counts, the risk for postoperative stroke increased by 12% (adjusted HR, 1.12; 95% CI, 1.01–1.24; P = 0.0255).

Early and delayed stroke

To study the impact of nadir platelet counts on timing of stroke after CABG surgery, patients were divided into 2 groups: early stroke (POD 0–1; n = 35) and delayed stroke (POD 2–30; n = 75). We then performed a stepwise multivariable competing risks proportional hazards model analysis following the Fine-Gray method to test for an association between severity of postoperative thrombocytopenia defined as a time-varying effect and timing of stroke. The results indicated that when postoperative platelet counts are defined as a time-varying covariate, moderate to severe thrombocytopenia was significantly associated with delayed, but not early postoperative stroke (Table 3). Similarly, when postoperative platelet counts were defined as a time-varying continuous predictor, for every 30×10^9/L decrease in platelet counts the risk for delayed postoperative stroke was significantly elevated (subdistribution adjusted HR, 1.18; 95% CI, 1.04–1.35; $P = 0.0109$).

Sensitivity Analysis

Of the 6,130 subjects studied, 0.38% (n = 23) developed and received treatment for postoperative HIT. To determine whether the association between postoperative thrombocytopenia and postoperative stroke persisted, we repeated the analysis excluding patients with HIT. Both associations between daily moderate to severe postoperative thrombocytopenia (adjusted HR, 2.02; 95% CI, 1.20–3.39; $P = 0.01$) and daily platelet counts as a continuous variable (adjusted HR for every 30×10^9/L decrease in platelet counts, 1.13; 95% CI, 1.02–1.25; $P = 0.02$) remained statistically significant. The association of delayed stroke with time-varying moderate to severe postoperative thrombocytopenia (adjusted subdistribution HR 2.93; 95% CI 1.52–5.68; $P = 0.001$) and time-varying postoperative platelet counts as a continuous variable (adjusted subdistribution HR 1.19; 95% CI 1.05–1.36; $P = 0.009$) also remained statistically significant.

DISCUSSION

In this single-center study of 6,130 patients undergoing on-pump CABG surgery, we identified that moderate to severe postoperative thrombocytopenia was an independent risk factor for the development of postoperative stroke. Importantly, analysis of the subdistribution hazards for early stroke (0–1 days post surgery) and delayed stroke (≥ 2 days post surgery) demonstrated relation of thrombocytopenia with delayed but not with early stroke. Perioperative stroke signifies a dramatic setback for patients undergoing CABG surgery, not only for its neurological implications. Indeed, similar to previous reports,(1) patients who developed postoperative stroke in our study were at a significantly higher rate of 30-day mortality compared to patients without postoperative stroke (16.4% versus 1.2%, $P < 0.0001$). These numbers bear striking witness on the importance to identify modifiable predictors influencing postoperative stroke after CABG surgery.

Currently, the main clinical focus regarding platelets in cardiac surgery is centered on bleeding complications secondary to both quantitative and qualitative platelet defects. However, complications associated with *increased* platelet thrombogenicity have gained additional attention.(20–23) Most prominently, Mangano et al(20) found that early initiation of aspirin therapy after CABG surgery is associated with a reduction in stroke, myocardial

infarction, renal failure, bowel infarction, and overall mortality. Aspirin appears safe in terms of bleeding risk,(24) but its efficacy to improve outcomes as a single agent may be limited by its relatively weak antiplatelet effect, as well as acquired perioperative aspirin resistance.(22) In addition, the timing of aspirin initiation immediately after CABG surgery varies considerably within the same institution and among institutions, which may explain inconsistent results with aspirin use as a single preventive therapy.(24) Platelet inhibition with clopidogrel has also been shown to reduce ischemic complications in patients undergoing CABG surgery, but concerns of higher risk for perioperative bleeding complications has led to the common practice of preoperative discontinuation of clopidogrel therapy.(25) Hence, the best strategy for perioperative antiplatelet therapy remains uncertain. Antiplatelet medications such as the novel P2Y12 and protease-activated receptor 1 (PAR1) inhibitors, may offer a better bleeding risk profile while protecting against postoperative cardiovascular complications including stroke.(26,27) For instance, addition of ticagrelor, a novel P2Y12 inhibitor, as compared to aspirin alone has recently been shown to reduce the risk for graft occlusion following CABG surgery.(27) A recent observational study demonstrated that vorapaxar, a novel PAR1 inhibitor, was associated with a reduced risk for composite outcomes of death, myocardial infarction, stroke, rehospitalization due to recurrent ischemia, and urgent revascularization, as compared to placebo after CABG surgery.(26) Neither ticagrelor or vorapaxar administration were associated with an increased risk for major bleeding complications.

Thrombocytopenia and platelet activation

We have recently demonstrated that low postoperative platelet counts are associated with an increased risk for AKI and death after CABG surgery,(13) which is similar to observations in critically ill patients(28) and in patients after transaortic valve replacement.(29) The mechanism for developing thrombocytopenia in these patients remains unclear, but the association of postoperative platelet counts with stroke after CABG surgery suggests that the reduction in platelet numbers likely occurs in a context of increased platelet reactivity. This notion is supported by the fact that in a non-cardiac surgical context, low platelet counts are predictive of deep vein thrombosis,(30,31) and that a drop in platelet numbers is a risk factor for recurrence of pulmonary embolism,(32) re-infarction after ST-elevation MI,(33) and severity of stroke.(34) In addition, a study in patients with acute coronary syndrome demonstrated that low platelet counts are associated with an increased risk for recurrent infarction, stroke, and death in drug-associated (ie, heparin, glycoprotein inhibitors) as well as drug-independent thrombocytopenia.(35)

Early and delayed stroke

We observed nadir platelet counts on POD 2, which coincides with the increased spontaneous and stimulant-evoked platelet reactivity reported for the first week after CABG surgery.(36) Interestingly, our data on day-to-day variations of postoperative platelet counts also tightly correlated with the timing of stroke in our study, and in the study by Tarakji et al who found that stroke risk peaked approximately 40 hours after CABG surgery, stayed significantly elevated until day 5 after surgery, and then on POD 6, stabilized at the steady background state reflective of the general risk factors in this population.(37) Indeed, a number of studies support our finding that most of the postoperative strokes were delayed

(68%; n = 75).(4,37,38) The definition of early vs delayed stroke varies slightly in the above studies, yet this distinction may highlight important differences in postoperative stroke mechanisms. Several reports suggest that cardioembolic events (39) and ischemic events resulting from intraoperative hypotension, cause most early strokes.(40) In contrast, underpinnings of delayed strokes may be significantly influenced by activation of systemic inflammation and hypercoagulability.(37) Of note, off-pump CABG is associated with a small reduction in stroke events compared to on-pump CABG; however, this difference was notable for early stroke only, which is consistent with reduced manipulation of the aorta.(41) Interestingly, as part of our ongoing study, we recently reported a similar pattern of perioperative nadir platelet counts in on-pump *versus* off-pump CABG raising the question about the role of platelets in postoperative stroke in off-pump CABG surgery.(42)

Our finding that moderate to severe thrombocytopenia was associated with delayed but not early stroke, is intriguing, and supports the hypothesis that a postoperative prothrombotic state with associated platelet activation is an important factor in delayed stroke. Defining the mechanisms that drive these events will be crucial to the development of improved strategies to prevent postoperative stroke.

Risk factors for stroke

We confirmed the value of many previously described risk factors for predicting postoperative stroke and timing of stroke after CABG surgery.(1,4,43,44) In particular, advanced age, peripheral vascular disease, absence of preoperative statin use, intraoperative insertion of IABP, and administration of packed red blood cell transfusions were consistently significant predictors of postoperative stroke in our risk-adjusted analysis. Further, when we studied the predictors of timing of postoperative stroke, we found that prior cerebrovascular accident was a predictor of early postoperative stroke, whereas advanced age and intraoperative insertion of IABP were associated with delayed postoperative stroke. Importantly, we found that most of these risk factors were also associated with postoperative thrombocytopenia.

Advanced age, prior cerebrovascular accident, and peripheral vascular disease have previously been found to increase the risk for postoperative stroke. Patients with these risk factors often have widespread systemic vascular and cerebrovascular disease resulting in impaired cerebral blood flow and increased susceptibility to atheroembolism and thromboembolism in the perioperative period.(1,4,43) Because platelets play a central role in the pathophysiology of most vascular diseases and their associated ischemic complications, perioperative management of high-risk patients should include an evaluation of the benefits of dual antiplatelet therapy(27,45) or novel monotherapy, the latter of which may offer a better bleeding risk profile in the post CABG surgery setting.(26)

Our finding that statin use was associated with a lower risk for postoperative stroke, highlights the importance of adhering to current guidelines on initiation and maintenance of statin use for primary and secondary prevention of cardiovascular events in patients with ischemic heart disease.(45) In addition to their well known favorable effect on lipid profile, statins affect platelet activation and aggregation, endothelial cell function, and proliferation and migration of vascular smooth muscle cells.(45,46) All of these so-called pleiotropic

properties of statins may substantially attenuate postoperative platelet activation and aggregation, and stabilize unstable atherosclerotic plaques, thereby reducing the risk for postoperative cardiovascular complications including stroke.

The use of IABP has been linked to platelet activation and increased microthrombi generation due to mechanical stress during the IABP cycle and prolonged exposure of blood components to the synthetic surface of the polyurethane balloon.(47) Thus, our finding that the use of IABP is associated with both low platelet counts and an increased risk for postoperative stroke, calls into question the appropriateness of using heparin alone for anticoagulation in these patients, and suggests the need for a personalized and more comprehensive anticoagulation strategy, such as using heparin in combination of a GP IIb/IIIa inhibitor, or a GP IIb/IIIa inhibitor alone.(48)

Furthermore, our results support previous findings that link transfusion of packed red blood cells to increased risk for postoperative stroke in cardiac surgery.(44,49) As in these studies, our data cannot provide evidence of the causative effect of blood transfusion and thus the increased risk for stroke may stem from the effects of preceding anemia as well as from specific abnormalities introduced by the transfusion itself.(50) It is noteworthy, that transfused blood may trigger prothrombotic and inflammatory responses but also may have limited oxygen-carrying capabilities, especially if stored over longer periods.(51) However, irrespective of such considerations, evidence such as ours further highlights the importance of ongoing efforts to avoid excessive hemodilution and to establish clear blood transfusion guidelines for patients undergoing CABG surgery.

Limitations

Our study has several limitations due to its retrospective design. Information on clinical risk factors for postoperative stroke was not prospectively collected. Instead, potentially relevant risk factors, medication use, and laboratory values, were retrieved from electronic health records, electronic intraoperative charts, physician documentation, and neuroimaging reports. Therefore, effects and the magnitude of effects of certain risk factors, medication use, and laboratory data may have been biased. However, the magnitude of their predictive values was similar to published findings from other studies.(4,43)

All patients were screened routinely during the postoperative period for evidence of postoperative stroke. While detailed preoperative baseline neurologic and neurocognitive assessments of these patients were not performed, the diagnosis of postoperative stroke was substantiated by neuroimaging, such as a CT or MRI head scan, in 91% of affected patients.

It has been suggested that intraoperative epiaortic ultrasound may reduce cerebral emboli during CABG surgery by reducing aortic manipulation in atheroma rich sites.(52) However, such intervention would predominantly affected early postoperative stroke occurrence and not the more common delayed stroke as observed in several other reports including ours.(4,53)

This study was performed at a single tertiary center and therefore, our findings may not be fully applicable to other institutions with different perioperative practices and levels of

experience. However, our reported incidences of postoperative stroke and risk factors were similar to other studies.(1,4)

In our study, we did not have a specific recorded time on perioperative blood product administration, and thus, we could not accommodate perioperative blood product administration in our extended Cox regression analysis as a time-dependent variable to model its potential effect on postoperative stroke. Consequently, its effect on postoperative stroke may have been biased. Nevertheless, perioperative blood product administration in CABG surgery most frequently occurs intraoperatively through day 2 after surgery; hence, the potential for observing a bias estimate of perioperative blood product administration on postoperative stroke is likely minimal.

Finally, no protocols were used to guide perioperative management of transfusion and anticoagulation therapies. Routine postoperative testing for HIT was left to the discretion of the intensive care unit team. Antiplatelet factor 4 antibodies are common after cardiac surgery with CPB, but only 3% of these patients develop HIT based on thrombotic sequel or serotonin-release assay.(54) As indicated by previous studies,(13,55) early-onset and persisting thrombocytopenia in cardiac surgery patients is seldom caused by HIT. Nevertheless, our sensitivity analysis indicated that after excluding patients with HIT, the association between postoperative thrombocytopenia and stroke persisted.

In summary, our findings suggest an independent association between moderate to severe postoperative thrombocytopenia and the development of postoperative stroke, and timing of stroke after CABG surgery. Our findings highlight the need for further studies to define mechanisms of perioperative platelet activation and its influence on adverse outcomes.

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Table 1

Demographic and clinical characteristics of the study population, N = 6,130

Characteristics	Normal Platelet Count, >150×10^9/L (n = 1,750)	Mild Thrombocytopenia, 100–150×10^9/L (n = 2,726)	Moderate/Severe Thrombocytopenia, <100×10^9/L (n = 1,654)	*P* value
Demographics				
Age categories, years				< 0.0001
<55	517 (29.5)	496 (18.2)	212 (12.8)	
55–64	593 (33.9)	862 (31.6)	464 (28.1)	
65–74	465 (26.6)	922 (33.8)	578 (35.0)	
75–84	165 (9.4)	410 (15.0)	360 (21.8)	
>84	10 (0.6)	36 (1.3)	40 (2.4)	
Race				0.0223
White	1280 (73.1)	2111 (77.4)	1258 (76.0)	
African American	364 (20.8)	469 (17.2)	298 (18.0)	
Other	106 (6.1)	146 (5.4)	98 (5.9)	
Female sex	496 (28.3)	670 (24.6)	527 (31.9)	< 0.0001
Medical history *				
EuroSCORE-related variables				
Chronic obstructive pulmonary disease	268 (15.3)	424 (15.6)	254 (15.4)	0.9720
Peripheral vascular disease	268 (15.3)	482 (17.7)	319 (19.3)	0.0086
Cerebrovascular accident	151 (8.6)	261 (9.6)	177 (10.7)	0.1217
Previous cardiac surgery	14 (0.8)	40 (1.5)	38 (2.3)	0.0016
Serum creatinine > 2 mg/dL	80 (4.6)	163 (6.0)	126 (7.6)	0.0009
Critical preoperative state	23 (1.3)	36 (1.3)	39 (2.4)	0.0158
Unstable angina pectoris	311 (17.8)	487 (17.9)	288 (17.4)	0.978
Left ventricular function				< 0.0001
Normal	915 (52.3)	1,375 (50.4)	711 (43.0)	
Moderate dysfunction	693 (39.6)	1,099 (40.3)	675 (40.8)	
Severe dysfunction	142 (8.1)	252 (9.2)	268 (16.2)	
Recent myocardial infarction	588 (33.6)	713 (26.2)	464 (28.1)	< 0.0001
	52 (3.0)	82 (3.0)	59 (3.6)	0.5203

Characteristics	Normal Platelet Count, >150×10^9/L (n = 1,750)	Mild Thrombocytopenia, 100–150×10^9/L (n = 2,726)	Moderate/Severe Thrombocytopenia, <100×10^9/L (n = 1,654)	*P* value
Pulmonary hypertension	737 (42.1)	983 (36.1)	633 (38.3)	0.0003
Diabetes mellitus				
Laboratory tests results				
Preoperative:				
Platelet count, 10^9/L	266.0 [230.0, 315.0]	208.0 [179.0, 243.0]	176 [147.0, 212.0]	< 0.0001
Creatinine, mg/dL	1.0 [0.9, 1.2]	1.1 [0.9, 1.3]	1.1 [0.9, 1.4]	< 0.0001
Hemoglobin, g/dL	12.9 [11.6, 14.2]	13.3 [11.9, 14.5]	13.0 [11.6, 14.3]	< 0.0001
Postoperative				
†Nadir platelet count, 10^9/L	177.0 [161.0, 201.0]	123.0 [111.0, 135.0]	82.0 [69.0, 92.0]	< 0.0001
Maximum creatinine, mg/dL	1.2 [1.0, 1.5]	1.2 [1.0, 1.6]	1.4 [1.1, 1.9]	< 0.0001
†Nadir hemoglobin, g/dL	8.9 [8.1, 9.7]	8.8 [8.1, 9.6]	8.7 [8.0, 9.4]	< 0.0001
Preoperative medications **				
Acetylsalicylic acid	1124 (64.9)	1768 (64.9)	1067 (64.5)	0.9382
Alpha-receptor blockers	75 (4.3)	142 (5.2)	96 (5.8)	0.1246
Angiotensin converting enzyme inhibitors	680 (39.0)	1036 (38.6)	616 (37.7)	0.6275
Angiotensin II receptor antagonist	153 (8.8)	230 (8.5)	138 (8.4)	0.9038
Beta-receptor blockers	1027 (59.3)	1590 (58.9)	971 (59.1)	0.9274
Calcium-channel blockers	341 (19.7)	499 (18.5)	293 (17.9)	0.3905
Clopidogrel	228 (13.2)	332 (12.3)	199 (12.2)	0.6123
Diuretics	473 (27.3)	663 (24.6)	486 (29.7)	0.0008
Nitrates	678 (39.2)	997 (36.9)	609 (37.3)	0.2955
Statins	961 (55.5)	1463 (54.2)	873 (53.4)	0.4518
Warfarin	32 (1.9)	79 (2.9)	71 (4.3)	0.0001
Intraoperative characteristics				
Year of surgery				< 0.0001
2001	155 (8.9)	349 (12.8)	240 (15.0)	
2002	159 (9.1)	313 (11.5)	210 (12.7)	
2003	130 (7.4)	251 (9.2)	141 (8.5)	
2004	135 (7.7)	178 (6.5)	99 (6.0)	

Characteristics	Normal Platelet Count, >150×10^9/L (n = 1,750)	Mild Thrombocytopenia, 100–150×10^9/L (n = 2,726)	Moderate/Severe Thrombocytopenia, <100×10^9/L (n = 1,654)	*P* value
2005	119 (6.8)	166 (6.1)	116 (7.0)	
2006	115 (6.6)	158 (5.8)	118 (7.1)	
2007	113 (6.4)	162 (5.9)	88 (5.3)	
2008	99 (5.7)	156 (5.7)	91 (5.5)	
2009	113 (6.5)	177 (6.5)	91 (5.5)	
2010	123 (7.0)	148 (5.4)	93 (5.6)	
2011	86 (4.9)	136 (5.0)	73 (4.4)	
2012	85 (4.8)	141 (5.2)	63 (3.8)	
2013	96 (5.5)	142 (5.2	82 (5.0)	
2014	133 (7.6)	155 (5.7)	84 (5.1)	
2015	89 (5.1)	94 (3.5)	57 (3.5)	
Duration of cardiopulmonary bypass, minutes	111.0 [91.0, 136.0]	121.0 [98.0148.0]	133.0 [106.0, 167.0]	< 0.0001
Duration of aortic cross clamp, minutes	64.0 [49.0, 83.0]	70.0 [52.0, 88.0]	75.0 [56.0, 95.0]	< 0.0001
Intraoperative insertion of intra-aortic balloon pump	88 (5.0)	180 (6.6)	248 (15.0)	< 0.0001
Intraoperative medications				
Aminocaproic acid	1256 (71.8)	1,959 (71.9)	1,143 (69.1)	0.1131
Aprotinin	182 (10.4)	322 (11.8)	250 (15.1)	0.0001
Epinephrine	532 (30.4)	907 (33.3)	750 (45.3)	< 0.0001
Norepinephrine	68 (3.9)	139 (5.1)	152 (9.2)	< 0.0001
Vasopressin	459 (26.2)	720 (26.4)	458 (27.7)	0.5647
Nitroprusside	484 (27.7)	788 (28.9)	490 (29.6)	0.4335
Nitroglycerin	890 (50.9)	1,546 (56.7)	935 (56.5)	0.0002
Esmolol	43 (2.5)	63 (2.3)	47 (2.8)	0.5473
Metoprolol	1067 (61.0)	1,698 (62.3)	949 (57.4)	0.0051
Tranexamic acid	251 (14.3)	294 (10.8)	176 (10.6)	0.0004
Perioperative blood product use within 2 days				
Red blood cells, mL	778 (44.5)	1,567 (57.5)	1,240 (75.0)	< 0.0001
Fresh frozen plasma, mL	193 (11.0)	573 (21.0)	576 (34.8)	< 0.0001
Platelets, mL	289 (16.5)	755 (27.7)	751 (45.4)	< 0.0001
Cryoprecipitate, mL	27 (1.5)	100 (3.7)	127 (7.7)	< 0.0001

Values are expressed as mean + standard deviation, median [interquartile range], or n (%).

*The definitions of these risk factors were based on the definitions used by the European System for Cardiac Operative Risk Evaluation (EuroSCORE) scoring system.[19]

†Postoperative nadir platelet counts and hemoglobin concentrations were defined as the lowest in-hospital values. In patients who experienced postoperative stroke, the lowest platelet value and hemoglobin value prior to stroke were used.

**Due to missing data (1.03%), preoperative medication use was computed for n = 1,731 patients with normal platelets, for n = 2,701 patient with mild thrombocytopenia, and for n = 1,635 patients with moderate/severe thrombocytopenia.

Table 2

Univariable and multivariable predictors of postoperative stroke

Predictors	Univariable		Multivariable*	
	Hazard Ratio (95% Confidence Interval)	*P* value	Hazard Ratio (95% Confidence Interval)	*P* value
Demographics				
Age at surgery, per 5-year increase	1.24 (1.13 – 1.36)	< 0.0001	1.18 (1.08 – 1.30)	0.0006
Race				
White	1.0			
African American	1.00 (0.62 – 1.62)	0.9846		
Other	0.46 (0.15 – 1.46)	0.1893		
Female sex	1.63 (1.11 – 2.39)	0.0132		
Clinical risk factors				
Chronic obstructive pulmonary disease	1.37 (0.86 – 2.19)	0.1828		
Peripheral vascular disease	1.79 (1.17 – 2.72)	0.0067	1.66 (1.09 – 2.52)	0.0193
Cerebrovascular accident	1.98 (1.21 – 3.24)	0.0069		
Previous cardiac surgery	1.22 (0.30 – 4.95)	0.7786		
Preoperative serum creatinine > 2 mg/dL	0.90 (0.40 – 2.05)	0.8068		
Critical preoperative state	2.95 (1.20 – 7.24)	0.0180		
Unstable angina pectoris	1.10 (0.68 – 1.76)	0.7030		
Left ventricular function				
Normal	1.0			
Moderate dysfunction	1.58 (1.05 – 2.37)	0.0283		
Severe dysfunction	1.78 (1.00 – 3.16)	0.0513		
Recent myocardial infarction	0.76 (0.49 – 1.19)	0.2312		
Pulmonary hypertension	0.57 (0.14 – 2.30)	0.4267		
Diabetes mellitus	0.88 (0.60 – 1.30)	0.5244		
Laboratory tests				
Preoperative:				
Platelet count, per 30×10^9/L decrease	1.08 (0.98 – 1.16)	0.1124		
Hemoglobin, per 1 g/dL decrease	1.02 (0.93 – 1.12)	0.6699		
Postoperative:				

Predictors	Univariable		Multivariable*	
	Hazard Ratio (95% Confidence Interval)	*P* value	Hazard Ratio (95% Confidence Interval)	*P* value
Daily hemoglobin, per 1 g/dL decrease	1.03 (0.89 – 1.19)	0.6826		
Daily platelet count				
Normal, >150×10^9/L	1.0		1.0	
Mild thrombocytopenia, 100–150×10^9/L	1.64 (1.02 – 2.62)	0.0406	1.40 (0.87 – 2.24)	0.1661
Moderate/severe thrombocytopenia, <100×10^9/L	2.77 (1.66 – 4.61)	< 0.0001	1.99 (1.18 – 3.34)	0.0093
Preoperative medications				
Acetylsalicylic acid	1.10 (0.74 – 1.63)	0.6547		
Alpha-receptor blockers	0.34 (0.08 – 1.37)	0.1286		
Angiotensin converting enzyme inhibitors	0.81 (0.55 – 1.20)	0.2986		
Angiotensin II receptor antagonist	0.95 (0.48 – 1.87)	0.8779		
Beta-receptor blockers	0.96 (0.66 – 1.40)	0.8363		
Clopidogrel	1.19 (0.70 – 2.02)	0.5167		
Diuretics	0.85 (0.55 – 1.32)	0.4634		
Nitrates	0.95 (0.64 – 1.40)	0.7806		
Statins	0.67 (0.46 – 0.98)	0.0384	0.69 (0.47 – 1.00)	0.0492
Warfarin	0.59 (0.15 – 2.41)	0.4658		
Intraoperative characteristics				
Year of surgery, per year increase	0.97 (0.92 – 1.01)	0.1096		
Duration of cardiopulmonary bypass, per 30-minute increase	1.10 (0.99 – 1.23)	0.0880		
Duration of aortic cross clamp, per 30-minute increase	1.03 (0.86 – 1.23)	0.7388		
Intraoperative insertion of intra-aortic balloon pump	2.14 (1.29 – 3.55)	0.0031	2.10 (1.26 – 3.51)	0.0043
Intraoperative medications				
Aminocaproic acid	0.91 (0.60 – 1.36)	0.6342		
Aprotinin	2.00 (1.27 – 3.15)	0.0026		
Epinephrine	1.40 (0.96 – 2.04)	0.0794		
Norepinephrine	1.61 (0.84 – 3.09)	0.1488		
Vasopressin	0.98 (0.64 – 1.50)	0.9406		
Esmolol	0.72 (0.18 – 2.92)	0.6482		
Metoprolol	0.97 (0.67 – 1.43)	0.8952		

Predictors	Univariable		Multivariable*	
	Hazard Ratio (95% Confidence Interval)	*P* value	Hazard Ratio (95% Confidence Interval)	*P* value
Tranexamic acid	0.51 (0.24 – 1.09)	0.0835		
Perioperative blood product use within 2 days				
Red blood cells	2.20 (1.42 – 3.39)	0.0004	1.62 (1.04 – 2.54)	0.0338
Fresh Frozen Plasma	1.60 (1.07 – 2.40)	0.0220		
Platelets	1.81 (1.24 – 2.64)	0.0220		
Cryoprecipitate	1.11 (0.45 – 2.72)	0.8226		

*The final multivariable Cox regression analysis was based on n = 6,067 due to missing information (n = 63) on preoperative medication use. Predictors of preoperative calcium-channel blocker use, and intraoperative nitroprusside and nitroglycerine use failed the proportional hazards assumption and could not be assessed via Cox regression analysis. The test of difference in survival function was performed via Wilcoxon test of the Kaplan-Meier estimate between strata, and indicated that the probability of remaining stroke free in patients with preoperative calcium-channel blocker use ($P = 0.1918$), and intraoperative nitroprusside ($P = 0.1071$) and nitroglycerine ($P = 0.2739$) use were not statistically not different compared to patients who did not receive these medications. The variables with $P < 0.05$ in the final multivariable model were selected by means of a forward stepwise technique.

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Table 3

Multivariable predictors of timing of stroke

Predictors	Model for Early Stroke		Model for Delayed Stroke	
	Subdistribution Hazard Ratio (95% Confidence Interval)	*P* value	Subdistribution Hazard Ratio (95% Confidence Interval)	*P* value
Age at surgery, per 5-year increase			1.22 (1.08 – 1.37)	0.0009
Female sex			1.74 (1.09 – 2.76)	0.0192
Previous cerebrovascular accident	2.74 (1.25 – 6.04)	0.0122		
Intraoperative nitroprusside administration	2.94 (1.51 – 5.71)	0.0015		
Intraortic balloon pump insertion			2.90 (1.65 – 5.11)	0.0002
Postoperative daily platelet count				
Normal, >150×10^9/L	1.0		1.0	
Mild thrombocytopenia, 100–150×10^9/L	1.17 (0.55–2.48)	0.6765	1.75 (0.95 – 3.22)	0.0736
Moderate/severe thrombocytopenia, <100×10^9/L	1.23 (0.51–2.99)	0.6497	2.87 (1.49 – 5.55)	0.0002

* The final multivariable Cox regression analysis was based on n = 6,067 due to missing information (n = 63) on preoperative medication use. While in the primary stroke outcome model intraoperative nitroprusside use failed the proportional hazards assumption, for the early stroke subevent analysis there was no evidence of a non-proportional hazard (test for time effect in model p=0.46), and thus, intraoperative nitroprusside use was included as predictor of this analysis.

Early strokes (n = 35), delayed strokes (n = 75).