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Original Article

Impact of Clopidogrel Stop Interval on Major Adverse Bleeding Events in Cardiac Surgery

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ABSTRACT

Background: Major societal guidelines recommend a 5-day stop interval before cardiac surgery for patients with acute coronary syndrome receiving clopidogrel. Yet, many such patients present with high acuity, generating surgeon inclination toward use of shorter stop intervals. Thus, this study aimed to determine the impact of the duration and timing of the interval of clopidogrel cessation on adverse bleeding events.

Methods: Patients who underwent cardiac surgery between 2009 and 2016 at a tertiary-care centre were included in this retrospective cohort study. Multivariable logistic regression models adjusted for clopidogrel stop interval, age, urgency of procedure, and procedure type were used to quantify the effect of clinically relevant baseline demographic characteristics on incidence of massive transfusion as well as hemorrhagic complication outcomes.

RÉSUMÉ

Introduction : Les grandes lignes directrices sociétales recommandent une interruption de cinq jours avant l'intervention chirurgicale du cœur des patients atteints d'un syndrome coronarien aigu qui prennent du clopidogrel. Toutefois, comme il s'agit pour plusieurs d'entre eux de patients de haute acuité, le chirurgien penche vers l'utilisation d'une interruption plus courte. Par conséquent, la présente étude avait pour objectif de déterminer les conséquences de la durée et du moment de la cessation du clopidogrel sur les événements hémorragiques indésirables.

Méthodes : La présente étude de cohorte rétrospective portait sur les patients qui avaient subi une intervention chirurgicale au cœur entre 2009 et 2016 dans un centre de soins tertiaires. Nous avons utilisé les modèles multivariés de régression logistique ajustés à l'interruption du clopidogrel, à l'âge, à l'urgence de l'intervention chirurgicale et au type

P2Y12 inhibitors are the standard of care for patients presenting with acute coronary syndrome (ACS), as these inhibitors reduce major adverse cardiovascular events.[1-3] However, many ACS patients require in-hospital coronary artery bypass graft (CABG) surgery; in this context, these agents increase the risk of bleeding, re-exploration, and higher transfusion rates, with adverse perioperative outcomes, including mortality and prolonged ventilation.[4-14]

Clinical practice guidelines recommend a 5-day waiting period preoperatively before CABG surgery, to reduce these risks.[15-18] Atlhough the European Society of Cardiology (ESC) firmly recommends a 5-day stop interval, the Canadian Cardiovascular Society (CCS)/Canadian Association of Interventional Cardiology (CAIC) and American Heart Association (AHA)/American College of Cardiology (ACC) weakly recommend a shorter stop interval for those requiring urgent surgical care.[15,16,18] We and others have published observational studies indicating that a shorter washout period is reasonable, with some evidence that bleeding outcomes for patients with 3-day stop intervals are comparable to those with 5-day stop intervals.[6,9,12,19] Moreover, adherence to a 5-day stop interval is uncommon in clinical practice, especially in the context of a recent ACS event, owing to patient acuity as

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See page 18 for disclosure information.

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Results: A total of 5748 patients underwent cardiac surgery. In this cohort, 1743 patients (30.3%) received clopidogrel preoperatively, and 884 (50.7%) of these patients discontinued clopidogrel 5 days before presenting to the operating room. The administration of clopidogrel 1-2 days before surgery (odds ratio 1.97; 95% confidence interval: 1.18 to 3.29) was an independent predictor for massive transfusions and hemorrhagic complications (odds ratio 1.85; 95% confidence interval: 1.01 to 3.37). The 3-4 day group did not have an increased risk of major bleeding complications. The risk for both massive transfusions and hemorrhagic complications also increased with the urgency and complexity of surgery.

Conclusion: A clopidogrel stop interval of 3-4 days preoperatively was not associated with an increased risk for major bleeding complications.

Résultats : Un total de 5 748 patients ont subi une intervention chirurgicale au cœur. Dans cette cohorte, parmi les 1 743 patients (30,3 %) qui avaient reçu du clopidogrel avant l'opération, 884 (50,7 %) avaient cessé le clopidogrel cinq jours avant leur admission à la salle d'opération. L'administration du clopidogrel un à deux jours avant l'intervention chirurgicale (ratio d'incidence approché 1,97; intervalle de confiance [IC] à 95 % : de 1,18 à 3,29) était un prédicteur indépendant des transfusions massives et des complications hémorragiques (ratio d'incidence approché 1,85; [IC] à 95 % : de 1,01 à 3,37). Le groupe de l'interruption de trois à quatre jours n'a pas montré de risque accru de complications hémorragiques graves. Le risque de transfusions massives et de complications hémorragiques a aussi contribué à l'augmentation de l'urgence et de la complexité de l'intervention chirurgicale.

Conclusion : Une interruption du clopidogrel de trois à quatre jours avant l'opération n'a pas été associée à un risque accru de complications hémorragiques graves.

well as bed-occupancy pressures.[6,20,21] Taken together, these findings reflect uncertainty about the necessity of a 5-day stop interval, a duration that may impede timely revascularization.

Thus, this study aimed to determine the impact of the length of the interval for cessation of clopidogrel on adverse bleeding events, need for massive transfusion, mortality, and major adverse cardiovascular events.

Methods and Materials

Patient population

The study population included patients who underwent cardiac surgical procedures between April 2009 and April 2016 at the Queen Elizabeth II Health Sciences Centre (QEII HSC) in Halifax, Nova Scotia, Canada. The QEII HSC is the sole provider of cardiac surgical care for Nova Scotia. Procedure types included isolated CABG, isolated valve repair or replacement, or combined CABG and single-valve procedures. Patients were excluded if they underwent transplantation, multiple-valve procedures, transcatheter aortic valve replacement, or treatment with ticagrelor, and if they had a history of trauma. Elective, urgent (defined as the need for intervention within 24 hours), and emergent procedures were also included. Cardiac surgery was performed with cardiopulmonary bypass, and anticoagulation was achieved using intravenous heparin given at a dose of 400 IU/kg, with a target activated clotting time $>$ 450 seconds. Antifibrinolytic agents were used routinely and consisted mainly of tranexamic acid. Intermittent cold-blood cardioplegia was delivered in an antegrade or retrograde fashion, based on surgeon preference. Protamine sulfate was given for reversal of heparin effects in all patients.

Data source

Data were obtained from the Maritime Heart Centre Cardiac Surgery Registry. This registry is a detailed, prospectively collected clinical database containing perioperative data on all cardiac surgery cases performed from March 1995 to present at the QEII HSC. We have previously published a similar report utilizing the same data source.[12] The QEII HSC is the only cardiac surgical centre for the province of Nova Scotia, serving a base population of nearly one million. Moreover, by linking our observational data with a laboratory information system that is run by the Department of Pathology and Laboratory Medicine at the QEII HSC, comprehensive perioperative information on the timing, amount, type, and number of products transfused for each patient was obtained.

Primary outcome

The primary end point was the development of adverse bleeding events, including massive transfusions and hemorrhagic complications. Massive transfusion was defined as any transfusion of $>$ 4 units of packed red blood cells (PRBCs) either intraoperatively or within the first 48 hours postoperatively. Previous literature defines massive transfusion as the use of $\geq$ 4 units of PRBCs.[22,23] Hemorrhagic complications were defined as either cardiac tamponade, as established by bedside echocardiography, or re-exploration for bleeding.

Secondary outcomes

Secondary outcomes included the need for transfusion of any blood products intraoperatively or within the first 48 hours postoperatively. Transfusion parameters, including number of units, and type and timing of transfusion, were reported. Major adverse clinical events of interest included mortality, prolonged mechanical ventilation beyond 24 hours, and deep sternal wound infection.

Variable selection and analysis

Other preoperative clinical characteristics of interest included age, sex, aspirin use, clopidogrel stop intervals, hemoglobin, body mass index, urgency, serum creatinine level,

dialysis status, chronic obstructive pulmonary disease, diabetes status, peripheral and/or cerebral vascular disease, and ejection fraction. Individual procedure types were categorized as isolated CABG, isolated aortic or mitral valve replacement or repair, or combined coronary artery bypass with single valve replacement.

Statistical analysis

Baseline demographic information and pretreatment clinical measures were summarized using descriptive statistics. Categorical data were presented as frequencies and percentages. Continuous data were presented as mean ± standard deviation. Comparisons across categories of the timing of clopidogrel discontinuation were made using the χ^2 test and analysis of variance, as appropriate. Outcome data were summarized as frequencies with percentages and compared across timing categories and transfusion status using Fisher's exact tests. Transfusion outcomes were also summarized across categories of the timing of clopidogrel stop intervals, including $<$ 24 hours, 1-2 days, 2-3 days, 3-4 days, 4-5 days, and $>$ 5 days.

Multivariable logistic regression analysis was used to quantify the relationship between clinically relevant baseline demographic characteristics and massive transfusion as well as hemorrhagic complication outcomes. Patient characteristics in the adjusted model identified a priori include the following: clopidogrel stop interval, acetylsalicylic acid status, age at time of surgery, sex, preoperative hemoglobin level, body mass index, urgency of procedure, kidney function, ejection fraction, procedure type, platelet count, and status of diabetes, peripheral vascular diseases, cerebrovascular disease, and chronic obstructive pulmonary disease. All statistical analysis was performed using SAS software, version 9.4 (SAS Institute, Cary, NC).

Ethics

This study was conducted with the full approval of the institutional (Nova Scotia Health Authority) research ethics board (file no. 1023270). The requirement to obtain informed consent was waived under Section 2.1c of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans. All personal identifiers were stripped prior to data analysis, to ensure patient anonymity and confidentiality. The research reported in this paper adhered to the **St**rengthening the **R**eporting of **Ob**servational Studies in **E**pidemiology (STROBE) guidelines.

Results

Study population and descriptive analysis

A total of 5748 patients were included in our study. The mean age was 68 years (standard deviation 10.2), and 1423 patients (24.8%) were female. A total of 1743 patients (30.3%) received clopidogrel preoperatively. Among these, 884 (50.7%) had discontinued clopidogrel 5 days preprocedurally (Table 1). Overall, 3910 patients (68.0%) underwent CABG surgery, 681 (11.8%) underwent isolated valve repair or replacement, and 1157 (20.1%) underwent combined CABG and valve surgery. Among the patients who discontinued clopidogrel before surgery, 54 patients (0.9%) stopped within 24 hours, 211 (3.7%) stopped 1-2 days before surgery, 199 (3.5%) stopped 2-3 days before surgery, 191 (3.3%) stopped 3-4 days before surgery, 229 (4.0%) stopped 4-5 days before surgery, and 859 (14.9%) discontinued clopidogrel $>$ 5 days before surgery. As demonstrated in Table 1, patients who discontinued clopidogrel 1-2 days preoperatively were more likely to be emergent or urgent cases and have a hemoglobin level $<$ 130g/L. Those receiving clopidogrel $<$ 24 hours and 1-2 days before surgery were more likely to have a high serum creatinine level, renal failure, and a low ejection fraction, and they were more likely to receive preoperative hemoglobin and platelets. Patients in these 2 groups were also more often referred for emergent or urgent care (Table 1). Patients who received clopidogrel 3-4 days before surgery were more likely to be elective cases with higher preoperative hemoglobin levels, and they demonstrated less need for preoperative platelets. Those not prescribed clopidogrel were more likely to receive combination CABG and valve surgery.

Unadjusted intraoperative and postoperative outcomes

In the study population, 159 patients (9.1%) received a massive transfusion, and 95 patients (5.5%) experienced hemorrhagic complications (Table 2). Among those discontinuing clopidogrel within 24 hours before surgery or 1-2 days before surgery, 12 patients (22.2%) and 36 patients (17.1%) received a massive transfusion, and 3 patients (5.6%) and 21 patients (10%) patients experienced hemorrhagic complications, respectively. The rates of mortality, prolonged ventilation, sepsis, pneumonia, and bleeding were significantly higher among those who received clopidogrel either within 24 hours or 1-2 days preoperatively. Similarly, these postoperative outcomes were more common among those who received any transfusion(s), compared with those who were not transfused (Table 3).

Intraoperative and postoperative transfusions

Of all transfusion products, patients received a greater number of units of PRBCs, compared with the units of platelets and fresh-frozen plasma (FFP; Table 4). Patients receiving clopidogrel within 24 hours of surgery received the most units of transfusion products, including PRBCs (mean: 2.2 ± 4.0 units), platelets (mean: 0.5 ± 1.2 units), and FFP (mean: 0.6 ± 1.2 units). Comparably, patients dosed with clopidogrel 1-2 days before surgery were more commonly transfused with PRBCs (mean: 1.9 ± 3.7 units), platelets (mean: 0.4 ± 0.9 units), and FFP (mean: 0.5 ± 1.7 units). Those dosed with clopidogrel 1-2 days before surgery received more than twice the number of units of PRBCs, platelets, and FFP, compared with those not receiving clopidogrel, and they also had a higher transfusion rate overall. The cessation of clopidogrel 2-3 days before surgery achieved a rate of transfusion of 31.2%, similar to the percentage for those who stopped clopidogrel 4-5 days preoperatively. The average number of units of PRBCs, platelets, and FFP transfused was greater during surgery than postoperatively, across all groups.

Independent predictors of bleeding

The administration of clopidogrel 1-2 days before surgery (odds ratio [OR] 1.97; 95% confidence interval [CI]: 1.18 to

Table 1. Baseline characteristics of patients and timing of clopidogrel discontinuation prior to surgery

	Timing of clopidogrel discontinuation prior to surgery, d							
Variable	< 24 h (n = 54)	1–2 (n = 211)	2–3 (n = 199)	3–4 (n = 191)	4–5 (n = 229)	≥ 5 (n = 859)	No clopidogrel (n = 4005)	*P*
Female	15 (27.8)	56 (26.5)	44 (22.1)	49 (25.7)	53 (23.1)	206 (24)	1000 (25)	0.9044
Age, y, mean (SD)	66.4 (9.6)	67.4 (9.6)	67.1 (10.3)	65.9 (10.3)	65.2 (10.3)	66.6 (10.1)	67 (10.3)	0.1217
Age, y								
< 60	13 (24.1)	44 (20.9)	45 (22.6)	56 (29.3)	68 (29.7)	202 (23.5)	894 (22.3)	0.3611
60–69	20 (37)	85 (40.3)	71 (35.7)	59 (30.9)	81 (35.4)	302 (35.2)	1411 (35.2)	
70–79	16 (29.6)	57 (27)	63 (31.7)	59 (30.9)	66 (28.8)	271 (31.6)	1269 (31.7)	
> 80	5 (9.3)	25 (11.9)	20 (10.1)	17 (8.9)	14 (6.1)	84 (9.8)	431 (10.8)	
SCr, μmol/L,								
< 110	33 (63.5)	141 (66.8)	146 (73.4)	145 (75.9)	172 (75.1)	587 (68.5)	3012 (75.4)	0.0008
110–177	14 (26.9)	48 (22.8)	42 (21.1)	41 (21.5)	44 (19.2)	209 (24.4)	798 (20.0)	
> 177	5 (9.6)	16 (7.6)	7 (3.5)	4 (2.1)	9 (3.9)	43 (5.0)	131 (3.3)	
Preoperative dialysis	0 (0.0)	6 (2.8)	4 (2.0)	1 (0.5)	4 (1.8)	18 (2.1)	55 (1.4)	
Diabetes	21 (38.9)	86 (40.8)	83 (41.7)	79 (41.4)	111 (48.5)	407 (47.4)	1436 (35.9)	< 0.0001
BMI, m/kg^2, mean (SD)	30.1 (6.2)	29 (5.2)	29.4 (6.3)	29.7 (5.3)	29.8 (6.2)	29.8 (5.8)	29.9 (6.1)	0.3921
Renal failure	5 (9.3)	22 (10.4)	10 (5.0)	5 (2.6)	13 (5.7)	57 (6.6)	184 (4.6)	0.0008
EF < 40%	13 (24.1)	39 (18.8)	24 (12.2)	26 (13.6)	18 (7.9)	116 (13.6)	476 (12)	0.0019
CVD	10 (18.5)	28 (13.3)	28 (14.1)	35 (18.3)	37 (16.2)	175 (20.4)	382 (9.5)	< 0.0001
PVD	6 (11.1)	35 (16.6)	48 (24.1)	33 (17.3)	36 (15.7)	183 (21.3)	451 (11.3)	< 0.0001
COPD	6 (11.1)	30 (14.2)	24 (12.1)	21 (11)	36 (15.7)	139 (16.2)	471 (11.8)	0.0158
Urgency								
Elective	4 (7.4)	31 (14.7)	19 (9.6)	38 (19.9)	79 (34.5)	217 (25.3)	2018 (50.4)	< 0.0001
Emergent	20 (37)	11 (5.2)	3 (1.5)	1 (0.5)	2 (0.9)	1 (0.1)	75 (1.9)	
In-house	11 (20.4)	115 (54.5)	159 (79.9)	145 (75.9)	145 (63.3)	634 (73.8)	1792 (44.8)	
Urgent	19 (35.2)	54 (25.6)	18 (9.1)	7 (3.7)	3 (1.3)	7 (0.8)	119 (3)	
Procedure								
CABG	46 (85.2)	187 (88.6)	187 (94)	180 (94.2)	214 (93.5)	728 (84.8)	2368 (59.1)	< 0.0001
Valve	5 (9.3)	17 (8.1)	8 (4)	5 (2.6)	10 (4.4)	80 (9.3)	556 (13.9)	
Combined	3 (5.6)	7 (3.3)	4 (2)	6 (3.1)	5 (2.2)	51 (5.9)	1081 (27)	
Preoperative Hb, g/L, mean (SD)	124.1 (35.2)	124.1 (21.1)	128.4 (20.6)	130.7 (21.3)	131.6 (19.8)	128.7 (18.8)	132.2 (19.6)	< 0.0001
Preoperative platelets, × 10^9/L, mean (SD)	214.3 (59.7)	221.6 (85.4)	220.6 (72.1)	217.5 (66.0)	223.7 (69.6)	229.6 (89.3)	205.5 (75.7)	< 0.0001

Values are n (%), unless otherwise indicated.

BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; EF, ejection fraction; Hb, hemoglobin; PVD , peripheral vascular disease; SCr, serum creatinine; SD, standard deviation.

3.29; $P = 0.01$) was an independent predictor for massive transfusion in multivariable logistic regression analysis (Fig. 1). Other independent risk factors for massive transfusion included a low preoperative hemoglobin level, greater urgency of surgery, decreased renal function, a low ejection fraction, greater complexity of surgery, and peripheral vascular disease.

Clopidogrel administration 1-2 days before surgery (OR 1.85; 95% CI: 1.01 to 3.37; $P = 0.046$) was an independent predictor of hemorrhagic complications, defined as cardiac tamponade or re-exploration for bleeding (Fig. 1). The risk for hemorrhagic complications also increased with the use of aspirin, female gender, greater urgency of surgery, decreased renal function, and greater complexity of surgery. Beyond 3 days of clopidogrel administration, no increased risk of massive transfusion nor hemorrhagic complications were demonstrated.

Patients receiving clopidogrel were at an increased risk for receiving any transfusions at 1-2 days (OR 1.98; 95% CI: 1.37 to 2.86; $P = 0.0003$) and 4-5 days (OR 1.75; 95% CI 1.22 to 2.50; $P = 0.0023$).

Discussion

This study assessed the relationship between a clopidogrel stop interval and major bleeding risk among 5748 patients receiving isolated CABG surgery, isolated valve repair or replacement, or combined CABG and valve procedures. We demonstrate that patients receiving clopidogrel 1-2 days before surgery experienced significantly more massive transfusions (transfusion of > 4 units of PRBCs) and hemorrhagic complications, defined as cardiac tamponade and re-exploration for bleeding. Multivariate analysis revealed that, after controlling for other relevant risk factors, patients dosed with clopidogrel 1-2 days before surgery were at a roughly 2-fold increased risk for both massive transfusions and hemorrhagic complications.

Clopidogrel stop interval and bleeding outcomes

The American College of Cardiology and the American Heart Association recommend that clopidogrel be stopped for 5 days before elective CABG surgery and for at least 24 hours before urgent CABG surgery.[24] This recommendation stems from 3 studies, including the Study of **Plat**elet Inhibition and Patient **O**utcomes (PLATO) trial, which noted that among a subgroup of 627 patients, the drop in hemoglobin decreased in those receiving clopidogrel > 5 days before surgery.[25] Correspondingly, Berger et al. found that among 596 patients, those receiving clopidogrel within 5 days showed an increased risk for major bleeding and reoperation for bleeding complications.[7] The guidelines also cite Hongo and

Table 2. Unadjusted outcomes and timing of clopidogrel discontinuation prior to surgery

Variable	Timing of clopidogrel discontinuation prior to surgery, d							
	< 24 h	1–2	2–3	3–4	4–5	> 5	No clopidogrel	*P*
Hemorrhagic complications	3 (5.6)	21 (10)	16 (8)	10 (5.2)	7 (3.1)	38 (4.4)	151 (3.8)	0.0001
Massive transfusion	12 (22.2)	36 (17.1)	21 (10.6)	9 (4.7)	16 (7)	65 (7.6)	250 (6.2)	< 0.0001
Mortality	5 (9.3)	19 (9)	11 (5.5)	6 (3.1)	9 (3.9)	23 (2.7)	82 (2.1)	< 0.0001
Prolonged ventilation	30 (55.6)	73 (34.6)	36 (18.1)	27 (14.1)	43 (18.8)	134 (15.6)	588 (14.7)	<0 .0001
Sepsis	3 (5.6)	10 (4.7)	5 (2.5)	1 (0.5)	5 (2.2)	17 (2)	49 (1.2)	0.0002
Pneumonia	10 (18.5)	27 (12.8)	15 (7.5)	8 (4.2)	14 (6.1)	51 (5.9)	255 (6.4)	< 0.0001
Bleeding	8 (14.8)	24 (11.4)	20 (10.1)	13 (6.8)	13 (5.7)	61 (7.1)	234 (5.8)	0.0011
Sternal wound infection	1 (1.9)	3 (1.4)	2 (1)	0 (0)	3 (1.3)	7 (0.8)	37 (0.9)	0.7617

Values are n (%), unless otherwise indicated.

colleagues, who reported a nonsignificant trend toward lower incidence of hospital discharge among 224 patients receiving clopidogrel within 5 days of surgical care.[26] Additionally, the **A**cute **C**atheterization and **U**rgent **I**ntervention **T**riage Strate**gy** (ACUITY) trial found that a small subset of patients dosed with clopidogrel within 5 days of CABG surgery experienced increased transfusion rates postoperatively,[27] and the **C**lopidogrel in **U**nstable Angina to Prevent **R**ecurrent Ischemic **E**vents (CURE) trial reported a trend toward an increased risk for major bleeding in patients receiving clopidogrel within 5 days before CABG surgery.[1] However, the study failed to show a significant difference in patients receiving clopidogrel within 5 days preoperatively for rates of major bleeding, life-threatening bleeding, or reoperation.

The recommendation of a 5-day stop interval results in case delays, potentially for this entire time period, to avoid outcomes associated with major bleeding.[12] Many patients present classically with urgent/emergent surgical indications, such as tight left main disease, acute ischemia with myocardial dysfunction, or severe aortic stenosis with hemodynamic compromise.[12] Thus, it is not safe or feasible to discontinue clopidogrel for at least 5 days preoperatively, particularly when patients present urgently for surgical intervention.[12] In our study, of those patients receiving clopidogrel, half presented to the operating room after discontinuing clopidogrel for 5 days before surgery. The percentage is even higher in the reported literature, with up to 87% of ACS patients receiving surgical care within this timeframe.[12,20] Patient acuity, as well as bed-occupancy pressures, impacts the decision to minimize the duration of delay for safe surgery.[6] These factors contribute to the impetus to determine a shorter stop interval for clopidogrel before surgery, while maintaining patient safety.

The multivariate model indicated that patients receiving clopidogrel 1-2 days before surgery were at nearly a 2-fold increased risk for massive transfusions and hemorrhagic complications. Similarly, Ascione and colleagues found that clopidogrel administration within 48 hours of surgery produced higher rates of transfusion and adverse outcomes.[28] The risk for both massive transfusion and hemorrhagic complications was also independently increased by increased urgency and complexity of surgery, as we previously noted in a smaller study.[12] Our findings suggest that transfusion rates increase as the preoperative clopidogrel stop interval is shortened. However, this increased risk for massive transfusions is less pronounced from 3-4 days of clopidogrel discontinuation and upward. The multivariate model revealed no increased risk for either massive transfusions or hemorrhagic complications in the group with a preoperative 3-4-day stop interval. Similarly, one study of 7048 patients undergoing CABG surgery found that a preoperative clopidogrel stop interval of 3 days produced rates of re-exploration for major bleeding comparable to those obtained with a 5-day clopidogrel stop interval.[6] Further, Firanescu and colleagues found that the level of blood loss and use of blood products among patients stopping clopidogrel 3 days preoperatively were comparable to that among those discontinuing clopidogrel 5 days before surgery.[9] Although we did not demonstrate a statistically significant increase in major bleeding at 2-3 days, the OR was very close to unity for hemorrhagic complications (OR 1.81; 95% CI: 0.98-3.36). This result suggests that bleeding complications remain a concern at this time interval and should factor into management decisions.

Table 3. Unadjusted outcomes and transfusion status

Variable	Transfusion (n = 1612)	No transfusion (n = 4136)	*P*
Hemorrhagic complications (tamponade/redo sternotomy)	188 (11.7)	58 (1.4)	< 0.0001
Massive transfusion	409 (25.4)	0 (0)	< 0.0001
Mortality	100 (6.2)	55 (1.3)	< 0.0001
Prolonged ventilation	568 (35.2)	363 (8.8)	< 0.0001
Sepsis	69 (4.3)	21 (0.5)	< 0.0001
Pneumonia	231 (14.3)	149 (3.6)	< 0.0001
Bleeding	254 (15.8)	119 (2.9)	< 0.0001
Sternal wound infections	34 (2.1)	19 (0.5)	< 0.0001

Values are n (%), unless otherwise indicated. Massive transfusion is defined as $\geq$ 4 units transfused perioperatively.

Table 4. Transfusions and timing of clopidogrel discontinuation prior to surgery

	Timing of clopidogrel discontinuation prior to surgery, d						
	< 24 h	1–2	2–3	3–4	4–5	> 5	No clopidogrel
Any transfusion, n (%)	27 (50)	102 (48.3)	62 (31.2)	46 (24.1)	76 (33.2)	243 (28.3)	1056 (26.4)
PRBCs							
Total units	2.2 (4)	1.9 (3.7)	1.1 (2.7)	0.6 (1.6)	0.9 (2.1)	0.8 (2.1)	0.8 (2.1)
During surgery	1.3 (2.5)	1.3 (2.6)	0.6 (1.6)	0.4 (1.2)	0.5 (1.3)	0.5 (1.5)	0.4 (1.3)
Postoperative	0.9 (2.2)	0.6 (1.8)	0.5 (2)	0.2 (0.7)	0.4 (1.4)	0.3 (1.2)	0.3 (1.4)
Amount transfused	644 (1152.1)	541.6 (1067.4)	315.1 (784.5)	164.5 (448.2)	251.7 (621.1)	240.3 (616.3)	219 (593)
Platelets							
Total units	0.5 (1.2)	0.4 (0.9)	0.1 (0.5)	0.1 (0.5)	0.2 (0.7)	0.1 (0.5)	0.1 (0.5)
During surgery	0.5 (1.1)	0.3 (0.9)	0.1 (0.5)	0.1 (0.5)	0.1 (0.6)	0.1 (0.5)	0.1 (0.5)
Postoperative	0 (0.3)	0 (0.2)	0 (0)	0 (0)	0 (0.4)	0 (0)	0 (0.2)
Amount transfused	167.4 (390.6)	114.6 (280.6)	36 (145.2)	44.6 (153.4)	50.1 (227.9)	39.1 (151.7)	40.8 (169.3)
FFP							
Total units	0.6 (1.6)	0.5 (1.7)	0.1 (0.7)	0.1 (0.4)	0.2 (0.9)	0.2 (0.7)	0.2 (0.8)
During surgery	0.6 (1.6)	0.5 (1.5)	0.1 (0.7)	0.1 (0.4)	0.1 (0.7)	0.1 (0.7)	0.1 (0.6)
Postoperative	0 (0)	0 (0.3)	0 (0.1)	0 (0)	0.1 (0.7)	0 (0.2)	0 (0.5)
Amount transfused	281.8 (729.5)	225 (790.3)	53 (334.7)	49.4 (213.3)	73.2 (453.8)	75.6 (333.9)	78 (384.5)

Values are mean (standard deviation), unless otherwise indicated.
FFP, fresh-frozen plasma: PRBCs, packed red blood cells.

Mortality, prolonged ventilation, transfusions

Seese et al. recently reported that clopidogrel use before CABG surgery increased the rate of prolonged ventilation.[6] In our study, both groups that received clopidogrel within either 24 hours or 1-2 days of surgery demonstrated an increased rate of transfusions, prolonged ventilation, and greater mortality, compared with all other subgroups. Similarly, we have previously reported that clopidogrel administration within either 24 hours or 2 days of surgery increased the rate of transfusions, prolonged ventilation, and mortality, providing further support for postponing surgery for at least 3 days between clopidogrel dosage and surgical intervention.[12] Our study further suggests that an increased number of units are transfused intraoperatively, rather than postoperatively, among patients dosed with clopidogrel within 1-2 days of surgery, the first report of such a finding to our knowledge. However, after multivariable analysis, patients were at an increased risk for receiving any transfusion when administered clopidogrel either 1-2 days or 4-5 days preoperatively. Interestingly, patients who had a 4-5 day preoperative stop interval were neither more acute nor more complex in terms of surgery performed. Similarly, patients in this 4-5–day group were not more comorbid, nor older, and they did not have a lower mean hemoglobin level or platelet count. Thus, we are at a

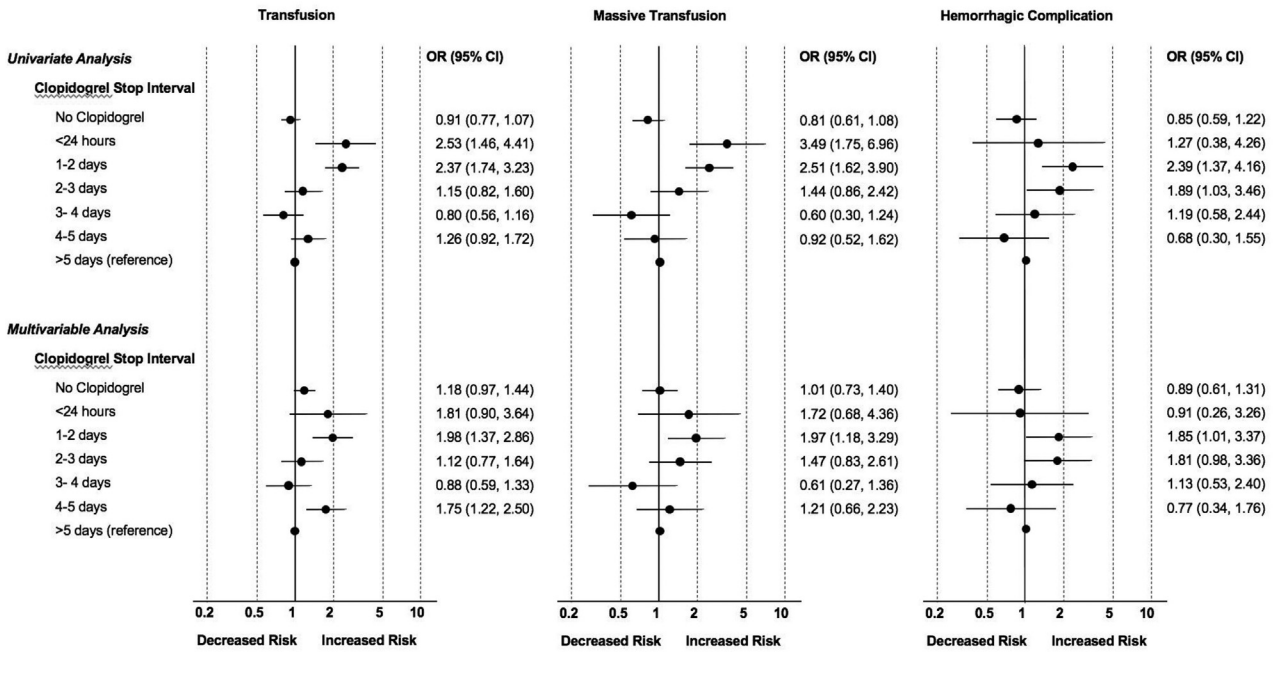

Figure 1. Multivariable predictors of massive transfusion and hemorrhagic complications post–cardiac surgery include the use of clopidogrel 1-2 days before surgery. CI, confidence interval; OR, odds ratio.

loss to explain the increased transfusion rates during this timeframe.

Limitations

We acknowledge that this study has limitations, including its susceptibility to confounding factors secondary to its retrospective approach. Furthermore, information about ACS presentation type was lacking. Although we did control for urgency of surgery, confounding by indication may have resulted in sicker patients receiving surgery earlier, which may correlate with bleeding complications and mortality, and this remains a limitation of this study. Additionally, statistical power was limited in the subgroup of patients receiving clopidogrel within 24 hours of cardiac surgery, although previous literature suggests that outcomes for major bleeding are likely similarly increased during this timeframe.[9,12,25,29] The impact on bleeding outcomes of variability among surgeons and their approach to the timing of cardiac surgery among patients receiving clopidogrel was not captured in this study. Our centre performs very few off-pump CABG procedures; thus, the safety of clopidogrel stop intervals in patients revascularized with this surgical modality was not addressed. Additionally, despite the large sample size, these patients were treated at a single institution, which may affect the generalizability of these findings. The increased risk for any transfusion based on a clopidogrel stop interval of 4-5 days remains unexplained in our cohort. Information about the use of anticoagulants was not available in this study, nor were the rates of postoperative myocardial infarction and cerebrovascular accidents. Although neither are used routinely at our centre, as their use increases, the optimal stop interval for ticagrelor and prasugrel remains an area for future study.

Conclusions

The administration of clopidogrel 1-2 days before surgery increases the risk for major bleeding outcomes, prolonged ventilation, and mortality, and should be avoided. Administration of clopidogrel 3-4 days before surgery was not associated with an increased risk for major transfusions or hemorrhagic complications, and this stop interval allows for more timely surgical intervention than the 5-day stop interval recommended by current guidelines.

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Disclosures

The authors have no conflicts of interest to disclose.

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