Heart Surgery Forum 2024; 27(12): E1414–E1421
doi: 10.59958/hsf.8051

Article

Impact of Preoperative Platelet ADP/P2Y12 Receptor Antagonist Management in Patients Undergoing Elective Isolated Coronary Artery Bypass Grafting

Agustina Bayon[1], Laura Vogels-Schuerman[1], Gijs J. van Steenbergen[1], Jan Hartog[1], Joost F. ter Woorst[1], Mohamed A. Soliman-Hamad[1,*]

[1]Department of Cardiothoracic Surgery, Catharina Hospital, 5602 Eindhoven, The Netherlands
*Correspondence: mohammed.soliman@catharinaziekenhuis.nl (Mohamed A. Soliman-Hamad)

Submitted: 12 September 2024 Revised: 30 October 2024 Accepted: 5 November 2024 Published: 22 December 2024

Abstract

Background: Postoperative bleeding remains an important issue in patients undergoing coronary artery bypass grafting (CABG), being associated with blood product transfusions (BPT) and re-exploration. Since 2020, We have implemented a strict preoperative antithrombotic, specifically platelet ADP/P2Y12 receptor antagonist, management based on the results of a previous study of our institution. The objective of the present study was to assess its impact on clinical outcomes. **Methods**: Patients who underwent elective isolated CABG between 2017 and 2022 at the Catharina Hospital Eindhoven were included and divided into two groups, based on whether they were treated according to the modified antithrombotic management. The primary endpoints were perioperative BPT and re-exploration for bleeding. Secondary endpoints included length of hospital stay, in-hospital stroke, myocardial infarction (MI) and 30-day mortality. Propensity score matching was performed to compare outcomes of both cohorts. **Results**: A total of 1506 patients were included, of which 1064 belonged to the first historical cohort. The remaining 442 patients (second cohort) were treated according to the modified management. In the 439 matched pairs, the implementation of the strict protocol was associated with a reduced incidence of blood product transfusions (14.8% vs. 24.1%, $p = 0.001$) and a shorter length of hospital stay (5 [interquartile range (IQR) 4–6] days vs. 6 [IQR 5–7.5] days, $p < 0.001$), whereas the incidence of postoperative MI and stroke did not differ. Re-exploration for bleeding was less frequently observed in the second cohort (1.4% vs. 3.6%, $p = 0.052$). **Conclusions**: The implementation of the modified strict preoperative ADP/P2Y12 antagonist management resulted in decreased incidence of blood product transfusions, shorter hospital stay and a clinically relevant decreased rate of re-exploration for bleeding.

Keywords

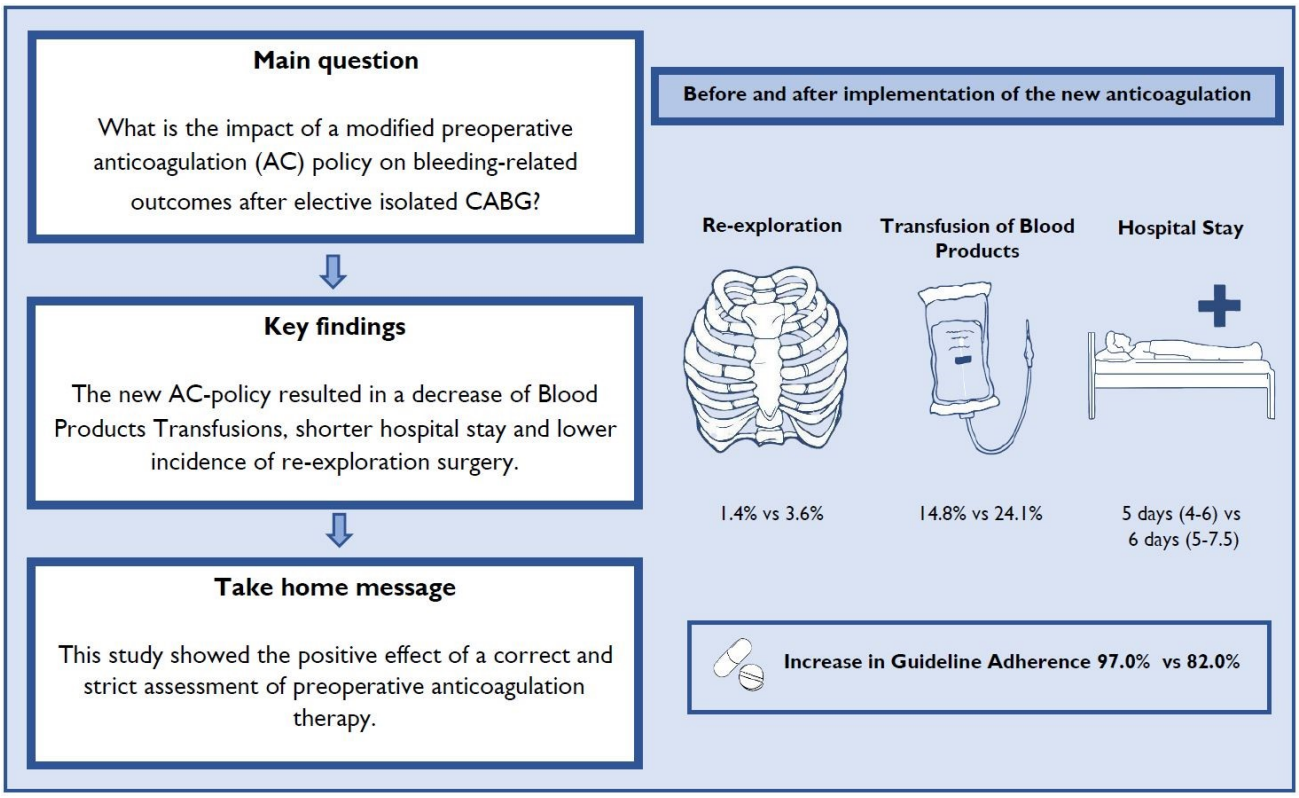
coronary artery bypass grafting; anticoagulation; blood transfusion; postoperative bleeding; re-exploration

Introduction

Despite a declining incidence of re-exploration surgery following coronary artery bypass grafting (CABG) and the gradual improvement in clinical outcomes, bleeding-related complications and blood products transfusion (BPT) continue to be significant concerns. Both are associated with a higher risk of infections, atrial fibrillation, respiratory complications, kidney injury, short- and long-term mortality and an increased length of hospital stay and healthcare costs [1–5].

Proper management of the patient's preoperative antithrombotic (AT) therapy is essential for preventing the bleeding-related outcomes. According to the current guidelines [6,7], all patients undergoing CABG should be treated with acetyl salicylic acid (ASA), which should be continued throughout the preoperative period [6,7]. This practice reduces the incidence of ischaemic events such as myocardial infarction (MI) and stroke and can lead to a decrease in mortality. Dual antiplatelet therapy (DAPT), which combines ASA with a P2Y12 inhibitor, is typically used for patients after a recent MI or percutaneous coronary intervention (PCI). However, for patients scheduled for elective CABG, the continuation of P2Y12 inhibitor, apart from ASA, is not recommended. The guidelines provide specific recommendations for the timely interruption of these therapies to minimize bleeding risks [2].

A previous retrospective analysis at our institution revealed that 40% of patients did not adhere to guideline recommendations for the timely cessation of preoperative antithrombotic therapy, particularly dual antiplatelet therapy (DAPT) [8]. Consequently, this non-adherence was associated with higher rates of re-exploration for bleeding and increased blood product transfusions. In response, our in-



Graphical Abstract

stitution enforced stricter preoperative antithrombotic management measures in 2020. This study assesses the impact of these measures on bleeding-related complications in patients undergoing elective isolated coronary artery bypass grafting (CABG).

Materials and Methods

Study Design and Population

This is an observational study conducted at the Department of Cardiothoracic Surgery of the Catharina Hospital Eindhoven, in the Netherlands. All patients undergoing elective, isolated CABG between January 2017 and December 2022 were eligible for inclusion. Exclusion criteria included minimally invasive revascularisation surgery, prior cardiac surgery, concomitant procedures—for example, surgical ablation—and non-elective surgery.

The studied population consisted of two cohorts. Cohort I included patients who underwent elective CABG prior to the implementation of the modified AT management (2017–2019), with data retrieved retrospectively from patient files. Cohort II included patients who underwent the procedure after the implementation (2020–2022), with collected data prospectively in a registry.

The study was approved by the local Medical Ethics Committee (W22.005) which waived the need for a patient informed consent.

Strict Preoperative Platelet ADP/P2Y12 Receptor Antagonist Management

Based on the findings of a previously published study conducted at our institution, we revised our approach to AT therapy management for patients undergoing elective CABG. Our modifications align with the guidelines set forth by the relevant scientific organizations in cardiology, cardiac surgery, and anesthesia. These changes are intended to assist clinicians in adhering to guideline-directed AT management [6,7] and to improve postoperative outcomes. The measures implemented are as follows (Fig. 1):

- An assessment of all patients accepted for CABG and receiving a P2Y12-inhibitor during screening at the preoperative outpatient clinic. In those patients having no absolute indication, such as recent PCI or recent (N)STEMI or acute coronary syndrome (ACS), the P2Y12-inhibitor is immediately stopped during the preoperative screening and the ASA is continued until the time of the operation. The most commonly used P2Y12 inhibiting agents in our population are clopidogrel and ticagrelor (n = 365; 24.2%). The usual practice of the referring cardiologists was to give clopidogrel 75 mg once a day and ticagrelor 90 mg twice a day.
- For patients with a non-cardiac indication for a P2Y12 inhibitor (medical history of stroke, peripheral vascular disease), the P2Y12 inhibitor is switched to dipyridamole until the date of the operation. According to our earlier investigation [8], preoperative use of dipyri-

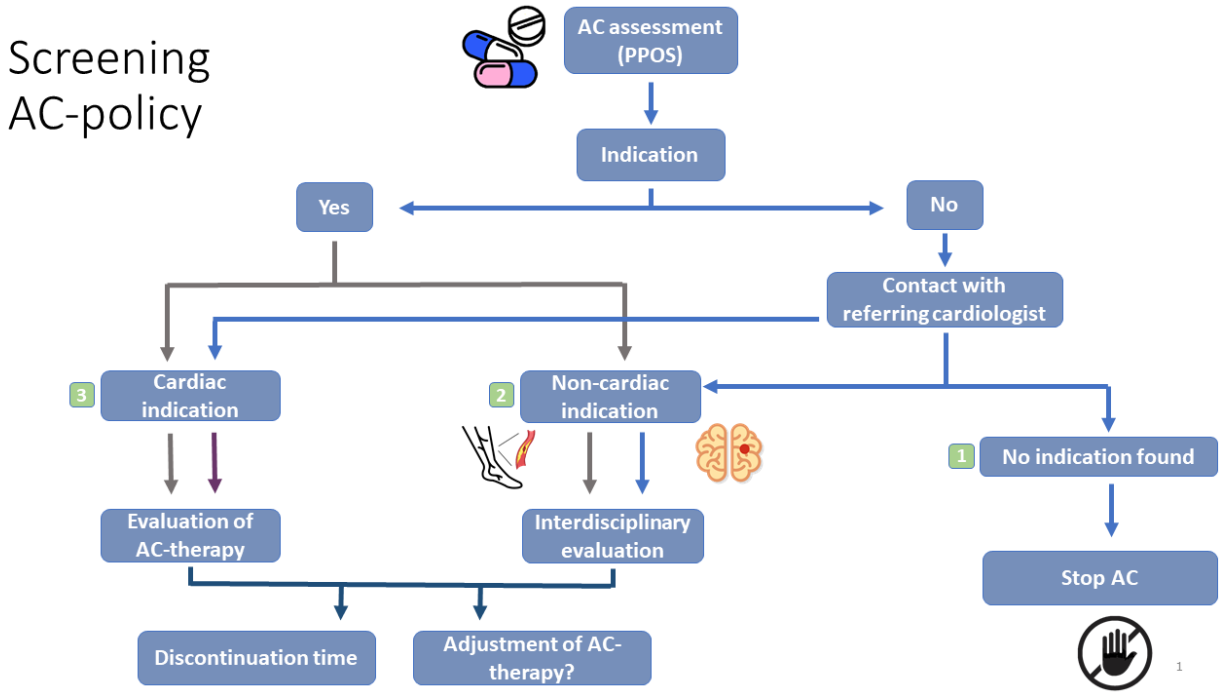


Fig. 1. Summary of refining the preoperative antithrombotic management. AC, anticoagulation; PPOS, Preoperative Policlinic Screening.

damole was not associated with postoperative bleeding complication. This decision is made after an interdisciplinary consultation takes place with an expert vascular surgeon or neurologist of our institution.

- Patients were instructed by their treating physician to discontinue their AT medication prior to surgery (5 days for clopidogrel and phenprocoumon, 3 days for acenocoumarol and ticagrelor, and 2 days for direct oral anticoagulants).
- All patients are called promptly before the date of the operation and are instructed to timely stop the AT therapy. Special attention was given to the timely cessation of the platelet ADP/P2Y12 receptor antagonist. Clopidogrel was stopped 5 days preoperatively and ticagrelor 3 days preoperatively. In all cases, ASA was always continued until the time of operation without need to bridge using other anti-platelet agents.
- Upon hospital admission the day before surgery, the discontinuation was verified. If platelet ADP/P2Y12 receptor antagonist was not stopped timely, the operation was postponed.
- Only patients with recent PCI or (N)STEMI less than three months preoperatively are allowed to continue DAPT until the time of the operation. These patients were recommended for off-pump CABG during the preoperative screening.

Study Endpoints

Primary endpoints of the study included re-exploration for bleeding and transfusions of blood products. Secondary endpoints included the length of hospital stay, in-hospital stroke, MI and 30-day mortality.

Definition of included variables are provided in the supplementary materials.

Statistical Analysis

A subdivision of patients was made according to the patient's type of AT-therapy, whether they belonged to the "ASA only" category or "Other AT than ASA only". For this subdivision of patients on other AT-regimens than ASA only, we compared the adherence to guidelines' recommendation between cohorts.

Normality of the continuous variables was analysed by verifying skewness and kurtosis, by visual inspection of histograms and was tested with the Shapiro–Wilk test. Continuous normal distributed data was presented as mean ± SD, and as median with interquartile range (IQR) for not normally distributed data. The students *t*-test or Mann Whitney U test were applied to compare groups accordingly. Categorical data was presented as absolute and relative frequencies and were compared using the Chi-square test, or the Fisher's exact test when the minimum expected cell-size assumption did not apply.

Missing values of patients' characteristics were limited (0.24%) and considered random. Missing data was

handled with multiple imputation. Propensity score matching analysis was performed on the main study cohorts to adjust for potential confounders, using nearest neighbour matching in a 1:1 ratio; without replacement and with the calliper distance was set at 0.1. Standardized mean difference was used to compare the difference in means in units of the pooled standard deviation. A value higher than 0.10 was considered an index of significant residual imbalance. The propensity score matching model was calculated using the following baseline characteristics as covariates: type of AT therapy (ASA-only vs. other AT-regimens), use of extracorporeal circulation (ECC), preoperative haemoglobin, age, sex, body mass index (BMI), renal impairment, chronic pulmonary disease, hypertension, left ventricular ejection fraction (LVEF) <30%, peripheral arterial disease (PAD), medical history of stroke, and diabetes. Logistic regression analysis was used to adjust for residual imbalance and to assess the effect size of treatment protocol impact on the primary and secondary outcomes.

A p-value < 0.05 was considered significant, all the analyses were performed using SPSS 26 (IBM Corp., Armonk, NY, USA) or R Statistical Software (v4.1.2; R Core Team 2021, Boston, MA, USA).

Results

This study included a total of 1506 patients who underwent isolated elective CABG of which 1064 patients were treated before implementation of the modified AT management (cohort I) and 442 patients thereafter (cohort II). Subdivisions within Cohorts I and II were made based on antithrombotic therapy types on the screening day, with Cohort I comprising 741 patients (69.6%) on ASA only and 323 patients (30.4%) on other AT therapies while Cohort II included 308 patients (69.7%) on ASA only and 134 patients (30.3%) on other AT therapies.

Cohort II had a higher percentage of male patients (88.2% vs. 83.7%, $p = 0.026$) and more often presented with diabetes mellitus (31.2% vs. 24.7%, $p = 0.009$) and hypertension (72.4% vs. 61.7%, $p < 0.001$) compared to patients in cohort I. Patients in cohort II were less frequently operated on using ECC (63.3% vs. 72.7%, $p < 0.001$) in comparison to patients in cohort I. ASA only was administered to 69.6% of cohort I and 69.7% of cohort II, demonstrating no significant difference between the two groups ($p = 0.99$). Within the subgroups of ASA only and other AT regimens, significant differences in peripheral arterial disease (PAD) and history of cerebrovascular accidents (CVA) were observed (Cohort I: PAD 14% vs. 18.9%, $p = 0.044$, CVA 3.8% vs. 14.9%, $p < 0.001$; Cohort II: PAD 6.2% vs. 26.1%, $p < 0.001$, CVA 1% vs. 12.7%, $p < 0.001$). As a result, EuroSCORE II was higher in patients with other AT regimens, measuring 1.24 [0.85–1.82] in Cohort I and 1.89 [1.32–2.90] in Cohort II, compared to those on ASA monotherapy with scores of 0.99 [0.71–1.51] in Cohort I and 0.92 [0.68–2.21] in Cohort II ($p < 0.001$ for both comparisons, **Supplementary Table 1**). Guideline adherence regarding timely preoperative discontinuation of AT was higher in cohort II compared to cohort I (97.0% vs. 82.0%,

Table 1. Baseline characteristics of both cohorts before matching.

	Cohort 1 (N = 1064)	Cohort 2 (N = 442)	p-value
Patient demographics, no (%)/median [IQR]			
Age, years	69 [62–73]	68 [61–75]	0.21
Sex, male	891 (83.7)	390 (88.2)	0.026
Clinical characteristics, no (%)/ median [IQR]			
BMI, kg/m^2	26.8 [24.7–30.4]	27.5 [24.9–30.8]	0.29
LVEF ≤30%	31 (2.9)	14 (3.2)	0.79
Diabetes Mellitus	263 (24.7)	138 (31.2)	0.009
Chronic pulmonary disease	90 (8.5)	39 (8.8)	0.82
Peripheral vascular disease	165 (15.5)	54 (12.2)	0.102
History of stroke	76 (7.1)	20 (4.5)	0.058
Hypertension	656 (61.7)	320 (72.4)	<0.001
eGFR ≤50 mL/min/1.73 m^2	109 (10.2)	45 (10.2)	0.97
Preoperative Hb, mmol/L	8.7 [8.1–9.2]	8.8 [8.1–9.4]	0.09
Procedural characteristics, no (%)/median [IQR]			
ASA only	741 (69.6)	308 (69.7)	0.99
EuroSCORE II	1.07 [0.75–1.62]	1.02 [0.76–1.65]	0.17
ECC use, n (%)	773 (72.7)	280 (63.3)	<0.001

ASA, acetylsalicylic acid; BMI, body mass index; ECC, extracorporeal circulation; eGFR, estimated glomerular filtration rate; EuroSCORE II, European System for Cardiac Operative Risk Evaluation; Hb, hemoglobin; IQR, interquartile range; LVEF, left ventricular ejection fraction.

$p < 0.001$). The other baseline characteristics showed no significant differences between the two cohorts (Table 1). Propensity score matching generated 439 pairs of patients with well-balanced covariates (**Supplementary Table 2**).

In the matched population, patients in Cohort II required fewer transfusions of any blood products (14.8% vs. 24.1%, $p = 0.001$, OR = 0.55 [0.39–0.77]). Significant differences were observed between the cohorts regarding the postoperative administration of red blood cells (RBC) (12.1% vs. 18.5%, $p = 0.011$, OR = 0.61 [0.42–0.88]) and platelets (PLT) (4.3% vs. 10.0%, $p = 0.002$, OR = 0.41 [0.24–0.71]). No difference was observed regarding the use of fresh frozen plasma (FFP) (4.3% vs. 5.9%, $p = 0.36$, OR = 0.72 [0.40–1.32]). The total length of hospital stay was significantly shorter in Cohort II (5 days [IQR 4–6] vs. 6 days [IQR 5–7.5], $p < 0.001$). Re-exploration for bleeding occurred less often in Cohort II, although this difference was not statistically significant (1.4% vs. 3.6%, $p = 0.052$, OR = 0.38 [0.15–0.96]). No differences were observed between the two cohorts with regard to postoperative stroke (0.9% vs. 0.7%, $p = 1.00$, OR = 1.29 [0.32–5.24]), postoperative myocardial infarction (MI) (0.9% vs. 1.6%, $p = 0.29$, OR = 1.00 [0.27–3.72]) or 30-day all-cause mortality (0.5% vs. 0.8%, $p = 0.52$, OR = 1.00 [0.17–5.80], Table 2).

Discussion

This study sought to evaluate the regular clinical practice of the preoperative assessment of patients undergoing elective isolated CABG with regard to anti-thrombotic management. After the results obtained in our previously published study [8], our department of cardiothoracic surgery strived for an improvement of postoperative outcomes by strictly adhering to the EACTS/EACTA guideline's recommendations on timely discontinuation of antithrombotic agents (other than ASA) prior to surgery.

The current study is an important example of implementing improvement measures based on analysis of own data. Despite earlier measures to minimize the incidence of postoperative re-exploration for bleeding in our department, we continued to search for other factors that could influence this outcome. We observed that an unexpected high percentage of patients accepted for elective CABG receive DAPT preoperatively. This was the main reason why we performed the first retrospective analysis [8] which confirmed this observation. In almost 40% of patients receiving preoperative DAPT, no absolute indication for the use of P2Y12 inhibitor was retrieved. Moreover, the majority of these patients did not timely stop the P2Y12 inhibitor preoperatively according the guidelines. In this particular group, the incidence of postoperative re-exploration for bleeding and blood transfusions was significantly higher compared to other CABG patients [8].

A correct clinical assessment, as well as an interdisciplinary approach, and the eventual adjustment of antithrombotic medication are recommended [9]. Multiple studies [10–14] have demonstrated that continuation of DAPT until cardiac surgery increases the risk of perioperative bleeding, transfusions and re-exploration and it is advised to discontinue the P2Y12 inhibitor whenever possible before elective cardiac surgery [2,7,15].

The implementation of the strict policy meant a thorough assessment of the patient's AT therapy and therefore, a tailored adjustment of these treatments according to the patient's profile and indication. These customized modifications of therapy were made interdisciplinary and aimed to avoid exposing the patient to the risks associated to the pe-

Table 2. Post-operative outcomes.

	Unmatched patients			Propensity matched patients			
	Cohort 1 (N = 1064)	Cohort 2 (N = 442)	*p*-value	Cohort 1 (N = 439)	Cohort 2 (N = 439)	*p*-value	OR (95% CI) *
Primary outcomes, no (%)							
Re-exploration for bleeding	32 (3.0)	8 (1.8)	0.19	16 (3.6)	6 (1.4)	0.052	0.38 (0.15–0.96)
Blood product use	270 (25.4)	65 (14.7)	<0.001	106 (24.1)	65 (14.8)	0.001	0.55 (0.39–0.77)
Secondary outcomes, no (%)/median [IQR]							
30-day all-cause mortality	8 (0.8)	2 (0.5)	0.52	2 (0.5)	2 (0.5)	1.00	1.00 (0.17–5.80)
Postoperative MI	17 (1.6)	4 (0.9)	0.29	4 (0.9)	4 (0.9)	1.00	1.00 (0.27–3.72)
Postoperative stroke	7 (0.7)	4 (0.9)	0.61	3 (0.7)	4 (0.9)	1.00	1.29 (0.32–5.24)
Length of hospital stay	6 [5–8]	5 [4–6]	<0.001	6 [5–8]	5 [4–6]	<0.001	0.32 (0.26–1.58)
Transfusion of RBC	218 (20.5)	53 (12.0)	<0.001	81 (18.5)	53 (12.1)	0.011	0.61 (0.42–0.88)
Transfusion of PLT	101 (9.5)	19 (4.3)	<0.001	44 (10.0)	19 (4.3)	0.002	0.41 (0.24–0.71)
Transfusion of FFP	65 (6.1)	19 (4.3)	0.16	26 (5.9)	19 (4.3)	0.36	0.72 (0.40–1.32)

FFP, fresh frozen plasma; IQR, interquartile range; PLT, platelets; MI, myocardial infarction; RBC, red blood cells.

*Effect size of undergoing CABG after implementation of the modified AT protocol on the outcomes.

rioperative use of antithrombotic agents. After refining our preoperative management, we observed a 97.0% adherence to guidelines' recommendations regarding the preoperative discontinuation other AC-therapy than ASA.

Postoperative bleeding is a relatively common complication after CABG with consequent adverse outcomes, including re-exploration surgery and blood product transfusion [16]. Re-exploration has been associated with an increased mortality rate, postoperative stroke, renal injury with need for dialysis, prolonged mechanical ventilation, and postoperative mechanical circulation support [17]. Likewise, transfusion of blood products has also been related to a higher incidence of complications, including infections, acute renal injury, post-cardiotomy syndrome and mortality [18–21]. Even the transfusion of 1 or 2 units of RBC has been associated with a substantial increase in morbidity, mortality and healthcare costs [7].

Blood product transfusion is a critical facet of the care of cardiac surgery patients and understanding the importance of blood-preservation and the techniques to prevent haemorrhage are key factors to a broader term: "Patient Blood Management", referred to the STS/SCA/AmSECT/SABM guidelines updated in 2021 [22]. The implementation of the strict AT policy in our institution reflects the results of correctly following the major principles of "Patient Blood Management" and intends to promote its practice. It is important to note that our transfusion protocol remained the same before and after refining the preoperative anti-thrombotic management. In general, we adopt a restrictive transfusion policy especially in CABG patients.

Although the findings of the current study are not surprizing, we tried to demonstrate that adherence to the guidelines is not self-evident. Logistic factors and personal attitude of surgeons and intensive care consultants can influence this adherence in the daily practice. This was one of the conclusions of our first study [8]. According to an earlier report in the Netherlands [4], there were major differences across various Dutch cardiothoracic centres regarding the perioperative management of antithrombotic therapy. Although surprising, the study of Janssen *et al*. [4] shows the discrepancy between the real-world practice and the guidelines, a fact that elaborates the importance of the current study.

The strict preoperative AT management shows the importance of own-data analysis and taking measures to improve outcomes as an example of real-world practice. In the last years, own-data analysis in our department has played a crucial role in the improvement of outcomes after cardiac surgery. The implementation of a restrictive transfusion of RBC (instead of liberal), has led to both a reduced probability, and number of transfusions of red blood cells, without increasing the risk of morbidity and mortality [23,24]. Similar practices, such as avoiding the direct availability of RBC at the operating theatre, have also shown to considerably decrease the incidence of RBC transfusions [25]; and other simple and low-cost strategies, such as the incorporation of intraoperative checklists [26], have demonstrated to be effective in reducing the incidence of re-exploration due to bleeding.

An interesting aspect of our findings was the observed rates of secondary outcomes such as in-hospital stroke and myocardial infarction. Despite the strict management of antithrombotic therapy and consequently the temporarily cessation thereof, the incidence of these postoperative complications remained remarkably low, which suggests that the timely discontinuation and management of P2Y12 inhibitors and other anticoagulants did not compromise cardiac or cerebrovascular safety. It is to be noted that, in both cohorts of the current study, ASA was always continued until the time of the operation. No other anti-platelet agent was used for bridging after preoperative cessation of clopidogrel and ticagrelor (5 and 3 days respectively). Earlier Dutch investigations [12,27] have shown that P2Y12 inhibitors could be safely discontinued before elective CABG. In these studies, ASA was always continued until the time of surgery without bridging with other ant-platelet agents. No increase in the postoperative thromboembolic complication was observed. In the most recent EACTS guidelines (2024), ASA should be continued until surgery and preoperative bridging should be considered only in urgent patients with high thromboembolic risk. In case of elective cardiac surgery, ASA should be continued and no bridging is recommended after discontinuation of P2Y12 receptor antagonists [28].

Furthermore, the low rate of myocardial infarction and stroke in the context of strict antithrombotic management calls for a preoperative detailed examination of patient-specific factors such as preoperative medication adherence, patient physiological profile, and intraoperative management strategies. It is noteworthy, however, that the study was not powered for thromboembolic outcomes as endpoints.

Limitations

Despite the data of the second cohort was prospectively collected, data of the first cohort was retrospectively obtained and this present study should be viewed in the context of the limitations of observational research.

Due to the small number of re-exploration surgeries, we could not reach a significant difference regarding the incidence of this complication between the two cohorts, or a possible correlation between this outcome and the implementation of the antithrombotic policy. However, the difference in the rate of re-exploration is clinically significant.

Conclusions

The implementation of the strict preoperative platelet ADP/P2Y12 receptor antagonist management was associated with decreased transfusions of blood products, shorter hospital stay, improved adherence to guidelines' recommendations and a clinically relevant decrease in re-exploration surgery.

Abbreviations

AT, anti-thrombotic; ASA, acetyl salicylic acid; BPT, blood products transfusions; CABG, coronary artery bypass grafting; CVA, cerebral vascular accident; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulants; ECC, extracorporeal circulation; eGFR, estimated glomerular filtration rate; FFP, fresh frozen plasma; MI, myocardial infarction; PCI, percutaneous coronary intervention; PDE, phosphodiesterase; PLTs, platelets/thrombocytes; RBC, red blood cells; TIA, transient ischemic attack; VKA, vitamin K antagonists.

Declaration of Generative AI and AI-assisted Technologies in the Writing Process

During the preparation of this work the author(s) used ChatGPT in order to improve readability and language. After using this service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

All the authors substantially contributed to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work. MASH contributed to the design of this work. MASH, AB and GJvS, contributed to the interpretation of data. AB, GJvS, LVS, and JH analyzed the data. AB and GJvS drafted the work. MASH and JFtW contributed by critically revising for important intellectual content. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

The study was carried out in accordance with the guidelines of the Declaration of Helsinki and approved by the local Medical Ethics Committee (W22.005) which waived the need for a patient informed consent.

Acknowledgment

We extend our gratitude to Dr. Saskia Houterman, epidemiologist at the Catharina Hospital in Eindhoven, for her support in supervising the statistical analyses of this study.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.59958/hsf.8051.

References

[1] Čanádyová J, Zmeko D, Mokráček A. Re-exploration for bleeding or tamponade after cardiac operation. Interactive Cardiovascular and Thoracic Surgery. 2012; 14: 704–707. https://doi.org/10.1093/icvts/ivs087.

[2] Raphael J, Mazer CD, Subramani S, Schroeder A, Abdalla M, Ferreira R, *et al*. Society of Cardiovascular Anesthesiologists Clinical Practice Improvement Advisory for Management of Perioperative Bleeding and Hemostasis in Cardiac Surgery Patients. Journal of Cardiothoracic and Vascular Anesthesia. 2019; 33: 2887–2899. https://doi.org/10.1053/j.jvca.2019.04.003.

[3] Newcomb AE, Dignan R, McElduff P, Pearse EJ, Bannon P. Bleeding After Cardiac Surgery Is Associated With an Increase in the Total Cost of the Hospital Stay. The Annals of Thoracic Surgery. 2020; 109: 1069–1078. https://doi.org/10.1016/j.athoracsur.2019.11.019.

[4] Janssen PWA, Claassens DMF, Willemsen LM, Bergmeijer TO, Klein P, Ten Berg JM. Perioperative management of antiplatelet treatment in patients undergoing isolated coronary artery bypass grafting in Dutch cardiothoracic centres. Netherlands Heart Journal: Monthly Journal of the Netherlands Society of Cardiology and the Netherlands Heart Foundation. 2017; 25: 482–489. https://doi.org/10.1007/s12471-017-1006-z.

[5] Gunertem E, Urcun S, Pala AA, Budak AB, Ercisli MA, Gunaydin S. Predictiveness of different preoperative risk assessments

for postoperative bleeding after coronary artery bypass grafting surgery. Perfusion. 2021; 36: 277–284. https://doi.org/10.1177/0267659120941327.

[6] Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, *et al*. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. European Heart Journal. 2018; 39: 213–260. https://doi.org/10.1093/eurheartj/ehx419.

[7] Pagano D, Milojevic M, Meesters MI, Benedetto U, Bolliger D, von Heymann C, *et al*. 2017 EACTS/EACTA Guidelines on patient blood management for adult cardiac surgery. European Journal of Cardio-thoracic Surgery: Official Journal of the European Association for Cardio-thoracic Surgery. 2018; 53: 79–111. https://doi.org/10.1093/ejcts/ezx325.

[8] van Steenbergen GJ, van Straten AHM, Kabak S, van Veghel D, Dekker L, Soliman-Hamad MA. Impact of preoperative antithrombotic therapy in patients undergoing elective isolated coronary artery bypass grafting. Interactive Cardiovascular and Thoracic Surgery. 2021; 33: 702–709. https://doi.org/10.1093/icvts/ivab176.

[9] Kietaibl S, Ahmed A, Afshari A, Albaladejo P, Aldecoa C, Barauskas G, *et al*. Management of severe peri-operative bleeding: Guidelines from the European Society of Anaesthesiology and Intensive Care: Second update 2022. European Journal of Anaesthesiology. 2023; 40: 226–304. https://doi.org/10.1097/EJA.0000000000001803.

[10] Pickard AS, Becker RC, Schumock GT, Frye CB. Clopidogrel-associated bleeding and related complications in patients undergoing coronary artery bypass grafting. Pharmacotherapy. 2008; 28: 376–392. https://doi.org/10.1592/phco.28.3.376.

[11] Hansson EC, Jidéus L, Åberg B, Bjursten H, Dreifaldt M, Holmgren A, *et al*. Coronary artery bypass grafting-related bleeding complications in patients treated with ticagrelor or clopidogrel: a nationwide study. European Heart Journal. 2016; 37: 189–197. https://doi.org/10.1093/eurheartj/ehv381.

[12] Tomšič A, Schotborgh MA, Manshanden JSJ, Li WWL, de Mol BAJM. Coronary artery bypass grafting-related bleeding complications in patients treated with dual antiplatelet treatment. European Journal of Cardio-thoracic Surgery: Official Journal of the European Association for Cardio-thoracic Surgery. 2016; 50: 849–856. https://doi.org/10.1093/ejcts/ezw149.

[13] Fox KAA, Mehta SR, Peters R, Zhao F, Lakkis N, Gersh BJ, *et al*. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) Trial. Circulation. 2004; 110: 1202–1208. https://doi.org/10.1161/01.CIR.0000140675.85342.1B.

[14] Held C, Asenblad N, Bassand JP, Becker RC, Cannon CP, Claeys MJ, *et al*. Ticagrelor versus clopidogrel in patients with acute coronary syndromes undergoing coronary artery bypass surgery: results from the PLATO (Platelet Inhibition and Patient Outcomes) trial. Journal of the American College of Cardiology. 2011; 57: 672–684. https://doi.org/10.1016/j.jacc.2010.10.029.

[15] Society of Thoracic Surgeons Blood Conservation Guideline Task Force, Ferraris VA, Brown JR, Despotis GJ, Hammon JW, Reece TB, *et al*. 2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. The Annals of Thoracic Surgery. 2011; 91: 944–982. https://doi.org/10.1016/j.athoracsur.2010.11.078.

[16] Lopes CT, Brunori EFR, Cavalcante AMRZ, Moorhead SA, Swanson E, Lopes JDL, *et al*. Factors associated with excessive bleeding after cardiac surgery: A prospective cohort study. Heart & Lung: the Journal of Critical Care. 2016; 45: 64–69.e2. https://doi.org/10.1016/j.hrtlng.2015.09.003.

[17] Fröjd V, Jeppsson A. Reexploration for Bleeding and Its Association With Mortality After Cardiac Surgery. The Annals of Thoracic Surgery. 2016; 102: 109–117. https://doi.org/10.1016/j.athoracsur.2016.01.006.

[18] Schwann TA, Habib JR, Khalifeh JM, Nauffal V, Bonnell M, Clancy C, *et al*. Effects of Blood Transfusion on Cause-Specific Late Mortality After Coronary Artery Bypass Grafting-Less Is More. The Annals of Thoracic Surgery. 2016; 102: 465–473. https://doi.org/10.1016/j.athoracsur.2016.05.023.

[19] Goel R, Patel EU, Cushing MM, Frank SM, Ness PM, Takemoto CM, *et al*. Association of Perioperative Red Blood Cell Transfusions With Venous Thromboembolism in a North American Registry. JAMA Surgery. 2018; 153: 826–833. https://doi.org/10.1001/jamasurg.2018.1565.

[20] Horvath KA, Acker MA, Chang H, Bagiella E, Smith PK, Iribarne A, *et al*. Blood transfusion and infection after cardiac surgery. The Annals of Thoracic Surgery. 2013; 95: 2194–2201. https://doi.org/10.1016/j.athoracsur.2012.11.078.

[21] Sanaiha Y, Hadaya J, Verma A, Shemin RJ, Madani M, Young N, *et al*. Morbidity and Mortality Associated With Blood Transfusions in Elective Adult Cardiac Surgery. Journal of Cardiothoracic and Vascular Anesthesia. 2023; 37: 1591–1598. https://doi.org/10.1053/j.jvca.2022.11.012.

[22] Tibi P, McClure RS, Huang J, Baker RA, Fitzgerald D, Mazer CD, *et al*. STS/SCA/AmSECT/SABM Update to the Clinical Practice Guidelines on Patient Blood Management. Journal of Cardiothoracic and Vascular Anesthesia. 2021; 35: 2569–2591. https://doi.org/10.1053/j.jvca.2021.03.011.

[23] Chen QH, Wang HL, Liu L, Shao J, Yu J, Zheng RQ. Effects of restrictive red blood cell transfusion on the prognoses of adult patients undergoing cardiac surgery: a meta-analysis of randomized controlled trials. Critical Care (London, England). 2018; 22: 142. https://doi.org/10.1186/s13054-018-2062-5.

[24] Haanschoten MC, van Straten AHM, Verstappen F, van de Kerkhof D, van Zundert AAJ, Soliman Hamad MA. Reducing the immediate availability of red blood cells in cardiac surgery, a single-centre experience. Netherlands Heart Journal: Monthly Journal of the Netherlands Society of Cardiology and the Netherlands Heart Foundation. 2015; 23: 28–32. https://doi.org/10.1007/s12471-014-0618-9.

[25] Shehata N, Mistry N, da Costa BR, Pereira TV, Whitlock R, Curley GF, *et al*. Restrictive compared with liberal red cell transfusion strategies in cardiac surgery: a meta-analysis. European Heart Journal. 2019; 40: 1081–1088. https://doi.org/10.1093/eurheartj/ehy435.

[26] van Boxtel AGM, van Veghel D, Soliman Hamad MA, Schulz DN, Stepaniak PS, van Straten AHM. Use of an intraoperative checklist to decrease the incidence of re-exploration for postoperative bleeding after cardiac surgery. Interactive Cardiovascular and Thoracic Surgery. 2017; 25: 555–558. https://doi.org/10.1093/icvts/ivx130.

[27] Firanescu CE, Martens EJ, Schönberger JPAM, Soliman Hamad MA, van Straten AHM. Postoperative blood loss in patients undergoing coronary artery bypass surgery after preoperative treatment with clopidogrel. A prospective randomised controlled study. European Journal of Cardio-thoracic Surgery: Official Journal of the European Association for Cardio-thoracic Surgery. 2009; 36: 856–862. https://doi.org/10.1016/j.ejcts.2009.05.032.

[28] Jeppsson A, Rocca B, Hansson EC, Gudbjartsson T, James S, Kaski JK, *et al*. 2024 EACTS Guidelines on perioperative medication in adult cardiac surgery. European Journal of Cardio-thoracic Surgery: Official Journal of the European Association for Cardio-thoracic Surgery. 2024; ezae355. https://doi.org/10.1093/ejcts/ezae355. (online ahead of print)