Different antithrombotic strategies after coronary artery bypass grafting to prevent adverse events

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Abstract

Background

To evaluate the relationship between different postoperative antithrombotic strategies and in-hospital adverse events in patients undergoing isolated coronary artery bypass grafting surgery.

Methods

Data were extracted from the Medical Information Mart for Intensive Care III database. Patients undergoing isolated coronary artery bypass grafting surgery due to coronary artery disease were divided into the ASA (aspirin only) or DAPT (aspirin plus clopidogrel) group according to the antiplatelet strategy. Patients were also stratified into subgroups based on the type of anticoagulation. The risk of bleeding and adverse events was investigated and compared between groups.

Results

A total of 3274 patients were included in this study, with 2385 in the ASA group and 889 in the DAPT group. No significant difference was seen in the risk of major bleeding between the two groups according to the PLATO, TIMI or GUSTO criteria. There was no difference in the postoperative mortality. In subgroup analysis, patients given anticoagulant therapy had an increased incidence of bleeding-related events. Multivariable analysis revealed that postoperative anticoagulant therapy and the early use of heparin, but not dual antiplatelet therapy, were independent predictors of bleeding-related events.

Conclusions

Postoperative dual antiplatelet therapy was not associated with an increased occurrence of bleeding-related events in patients undergoing isolated coronary artery bypass grafting surgery and appears to be a safe antiplatelet therapy. The addition of anticoagulants to antiplatelet therapy increased the risk of bleeding and should be considered cautiously in clinical practice.

Background

Coronary artery bypass grafting surgery (CABG) is a major revascularization approach for patients with coronary artery disease (CAD) and is widely used across the world. According to the current guidelines, CABG is recommended for stable CAD with proximal left anterior descending stenosis, left main stenosis and three-vessel disease, especially when the patient has a high SYNTAX score or diabetes mellitus[1]. CABG is performed to relieve the symptoms of myocardial ischemia and improve the prognosis. Perioperative management is critical to reduce the main adverse cardiovascular and cerebrovascular events and complications after surgery.

Antithrombotic treatment plays an important role in reducing adverse cardiovascular events and is mandatory in CAD patients undergoing myocardial revascularization[2]. Antiplatelet therapy is recommended early after operation for patients with low bleeding risk[2] due to its prevention of early graft failure as well as its reduction of adverse events and death after CABG in some studies[3–5]. Early use of dual antiplatelet drugs is also reasonable for patients with a high risk of ischemia and thrombosis, but the risk of bleeding should be taken into consideration[2]. In addition, heparin for anticoagulation is administered in some centers at an early stage after CABG for the prevention of ischemic events[6]. For patients still on a ventilator in the cardiac surgery recovery unit, heparin is used as a bridging therapy to antiplatelet

drugs. However, the current guidelines make no recommendation on the early use of heparin after CABG. Whether it is safe and effective to prevent early adverse events is still unknown.

Methods

Database introduction

The Multiparameter Intelligent Monitoring in Intensive Care III (MIMIC III, V1.4) database is maintained by the Laboratory for Computational Physiology at the Massachusetts Institute of Technology. It contains information on more than 40000 patients in the ICU at Beth Israel Deaconess Medical Center from 2001 to 2012. The database is accessible to researchers who have completed “protecting human subjects” training. The institutional review boards of the Massachusetts Institute of Technology (Cambridge, MA) and Beth Israel Deaconess Medical Center (Boston, MA) approved the establishment of the database. Thus, consent was obtained for this study. Data presented in this study were extracted by author Zhang, who completed the online training course of the National Institutes of Health (certification number: 35943280). Data extraction was performed using PostgreSQL tools V.1.12.3.

Study population

Patients undergoing isolated CABG due to CAD were selected from the database. Perioperative administration of antithrombotic therapy was extracted, including the types of drugs and the duration of usage. The following information was also extracted: age; sex; weight; smoking history; comorbidity; history of percutaneous coronary intervention (PCI); history of CABG; type of operation; preoperative level of creatinine and platelet count; perioperative level of hemoglobin; postoperative mortality within 30 days; postoperative myocardial infarction (MI), stroke and bleeding; postoperative transfusion of packed red blood cells (PRBCs), fresh frozen plasma (FFP) and platelets; and postoperative mediastinal chest tube drainage (MCTD). Duplicated records and records with missing information on antithrombotic therapy were excluded.

Study (sub)groups

Patients were divided into subgroups based on the type of postoperative antithrombotic therapy. The main study groups were defined as follows:

(1) ASA group (single anti-platelet therapy with aspirin postoperatively).

(1a) ASA non-anticoagulation subgroup (aspirin without anticoagulative therapy postoperatively).

(1b) ASA anticoagulation subgroup (aspirin + anticoagulative therapy postoperatively).

(2) DAPT group (dual anti-platelet therapy of aspirin + clopidogrel postoperatively).

(2a) DAPT non-anticoagulation subgroup (aspirin + clopidogrel without anticoagulative therapy postoperatively).

(2b) DAPT anticoagulation subgroup (aspirin + clopidogrel + anticoagulative therapy postoperatively).

Anticoagulative therapy included heparin, low-molecular-weight heparin (LMWH), and warfarin alone and their combinations. Patients were also grouped by the early use of heparin postoperatively (within 48 h after surgery) or not.

Definitions and outcomes

The primary endpoint was postoperative bleeding events according to the PLATO, TIMI and GUSTO criteria. In the PLATO criteria[7], major life-threatening bleeding was defined as fatal bleeding, intracranial bleeding, intrapericardial bleeding with cardiac tamponade, hypovolemic shock or severe hypotension due to bleeding requiring pressors or surgery, a fall in hemoglobin of 50 g/L (3.1 mmol/L) or greater, or the need for transfusion of at least 4 units of red blood cells. Other major bleeding was defined as significantly disabling bleeding (such as intraocular bleeding with permanent vision loss), a drop in hemoglobin of at least 30 g/L (1.9 mmol/L) but < 50 g/L (3.1 mmol/L) or requiring transfusion of 2 to 3 units of red blood cells. The TIMI criterion for major bleeding was either intracranial hemorrhage or bleeding associated with a decrease in hemoglobin concentration of more than 50 g/L[8]. Severe bleeding in the GUSTO guideline was defined as fatal intracranial intrapericardial bleeding with cardiac tamponade, or the development of hypovolemic shock or severe hypotension due to bleeding requiring pressor support or surgery[9]. Secondary endpoints included postoperative mortality within 30 days, postoperative MI, postoperative stroke, and the composite of mortality, MI and stroke. Postoperative MI was defined in accordance with the fourth universal definition of myocardial infarction[10]. Other secondary endpoints included PRBCs, FFP (fresh frozen plasma) or platelet transfusion, and MCTD (mediastinal chest tube drainage) > 1 L within 12 h postoperatively.

Statistical analysis

Continuous variables are presented in the tables as the mean with SD or median with interquartile ranges. Student's t-test or the Mann-Whitney U-test was used as appropriate. Categorical variables are presented as percentages and were compared using the χ^2 test or Fisher's exact test. Multivariable binary logistic regression analysis with an enter selection method was performed to determine variables predictive of bleeding-related events and postoperative adverse events. Goodness of fit was assessed for all logistic regression models. A *P*-value of < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS Statistics 25 (IBM Corp., Armonk, NY, USA).

Results

Population and baseline characteristics

The MIMIC III database contains records of 9243 patients undergoing isolated CABG due to CAD, of whom 5969 were excluded because of duplicated or missing records. In the end, 3274 patients were included in this study. Of these, 72.8% (n = 2385) were treated with ASA alone postoperatively, and the rest (n = 889) were treated with ASA and clopidogrel. Moreover, 33.3% of the patients also accepted coagulative therapy after the surgery in both the ASA (n = 794) and DAPT (n = 296) groups.

The baseline characteristics of patients in the ASA and DAPT groups are presented in Table 1. The two groups were balanced regarding most comorbidities, preoperative ASA and heparin use, and postoperative coagulative therapy. The DAPT group had a higher proportion of patients with peripheral artery disease, previous PCI or previous CABG history. Additionally, lower preoperative hemoglobin values and higher preoperative platelet counts were seen in the DAPT group.

Table 1
the baseline characteristics of patients in the ASA and DAPT groups

	ASA group (n = 2385)	DAPT group (n = 889)	p-value
Age (years)	67.3 (59.7–74.7)	66.5 (58.5–74.0)	0.044
Male	1877 (78.7)	661 (74.4)	0.008
Weight (kg)	87.8 (77.5–97.0)	87.6 (76.8–96.6)	0.437
Smoke	246 (10.3)	87 (9.8)	0.657
Hypertension	1650 (69.2)	604 (67.9)	0.495
DM	963 (40.4)	366 (41.2)	0.681
Dyslipidemia	1618 (67.8)	574 (64.6)	0.077
Peripheral artery disease	96 (4.0)	81 (9.1)	< .001
Cerebrovascular accident	60 (2.5)	30 (3.4)	0.181
COPD	32 (1.3)	21 (2.4)	0.040
Renal dysfunction	242 (10.1)	101 (11.4)	0.313
Dialysis	13 (0.5)	2 (0.2)	0.381
Previous PCI	220 (9.2)	162 (18.2)	< .001
Redo CABG	28 (1.2)	29 (3.3)	< .001
Emergent operation	93 (3.9)	23 (2.6)	0.071
Preoperative laboratory values			
Hb	11.2 (10.1–12.5)	10.9 (9.9–12.2)	0.001
Creatinine	0.9 (0.8–1.1)	0.9 (0.8–1.1)	0.939
Platelet count	183.3 (150.6-222.4)	191.5 (155.6-235.6)	< .001
Preoperative ASA	2334 (97.9)	872 (98.1)	0.687
Preoperative heparin use	1098 (46.0)	402 (45.2)	0.676
Postoperative early use of heparin	251 (10.5)	91 (10.2)	0.811
Postoperative coagulation	794 (33.3)	296 (33.3)	0.998
DM: diabetes mellitus			
COPD: chronic obstructive pulmonary disease			
PCI: percutaneous coronary intervention			
CABG: coronary artery bypass grafting			
Hb: hemoglobin			
ASA: aspirin			

Primary and secondary outcomes in the ASA and DAPT groups

Differences in the rates of bleeding events in the ASA and DAPT groups are presented in Table 2. Overall, according to the PLATO definitions, major life-threatening bleeding occurred in 15.5% versus 12.9% (p = 0.069) of the patients in the ASA and DAPT groups, respectively. Correspondingly, other major bleeding occurred in 28.8% versus 28.1% (p = 0.7). Bleeding according to the TIMI major criteria occurred in 5.8% versus 5.5% (p = 0.7654) and TIMI minor criteria in 25.0% versus 25.9% (p = 0.623), in the ASA and DAPT groups, respectively. Similarly, the GUSTO severe bleeding rates were 0.9% and 1.5% (p = 0.144). There was no difference in the bleeding-related hemoglobin decrease or reoperation rate between the two groups. Intracranial bleeding was uncommon in both groups. MCTD of > 1 L in the first postoperative hours was more frequent in the DAPT group (4.7% vs 3.1%, p = 0.026). Patients in the DPAT group had a higher rate of platelet transfusion, but a lower rate of PRBC transfusion.

Table 2
the rates of bleeding events in the ASA and DAPT groups

	ASA group (n = 2385)	DAPT group (n = 889)	p-value
PLATO major bleeding	1007 (42.2)	346 (38.9)	0.088
PLATO major life-threatening bleeding	369 (15.5)	115 (12.9)	0.069
PLATO other major bleeding	687 (28.8)	250 (28.1)	0.700
TIMI major bleeding	138 (5.8)	49 (5.5)	0.764
TIMI minor bleeding	597 (25.0)	230 (25.9)	0.623
GUSTO severe bleeding	21 (0.9)	13 (1.5)	0.144
Intracranial bleeding	1 (0.0)	3 (0.3)	0.064
Reoperation due to bleeding	20 (0.8)	10 (1.1)	0.445
Bleed resulting in Hb decrease > 50g/L	138 (5.8)	49 (5.5)	0.764
Bleed resulting in Hb decrease > 30g/L	717 (30.1)	267 (30.0)	0.987
Transfusion PRBC > 4 U	210 (8.8)	59 (6.6)	0.044
Transfusion PRBC > 2 U	271 (11.4)	71 (8.0)	0.005
PRBC transfusion	356 (14.9)	92 (10.3)	0.001
FFP transfusion	200 (8.4)	84 (9.4)	0.336
Platelet transfusion	130 (5.5)	77 (8.7)	0.001
MCTD > 1 L within 12 h	74 (3.1)	42 (4.7)	0.026
Hb: hemoglobin			
PRBC: packed red blood cells			
FFP: fresh frozen plasma			
MCTD: mediastinal chest tube drainage			

The postoperative mortality at 30 days with ASA versus DAPT was 1.4% versus 1.8% (p = 0.437) (Table 3). The rate of postoperative MI was higher in the DAPT group (1.3% versus 0.2%, p < 0.001). A similar result was seen with the occurrence of postoperative stroke (DAPT 2.2% versus ASA 1.3%, p = 0.04). The difference in the rate of postoperative

MI and stroke drove an increase in the composite endpoint from 2.7% for the ASA group, to 4.0% for the DAPT group (p = 0.043).

Table 3
the secondary endpoints in the ASA and DAPT groups

	ASA group (n = 2385)	DAPT group (n = 889)	p-value
Postoperative mortality in 30 d	34 (1.4)	16 (1.8)	0.437
Postoperative MI	5 (0.2)	12 (1.3)	< .001
Stroke	30 (1.3)	20 (2.2)	0.040
Composite end point	64 (2.7)	36 (4.0)	0.043
MI: myocardial infarction			

Subgroup analysis

In the ASA group, 1591 were treated without anticoagulative therapy (subgroup 1), while 794 were treated with either heparin, LMWH, warfarin or a combination thereof (subgroup 3). Similarly, 593 patients in the DAPT group did not have any anticoagulative therapy (subgroup 2), while 296 received DAPT plus anticoagulative medication (subgroup 4). Significant increases were seen in the rates of PLATO major life-threatening bleeding, TIMI major bleeding and GUSTO severe bleeding in patients treated with ASA and anticoagulative therapy (subgroup 3) compared with non-anticoagulative ASA treatment (subgroup 1) (Table 4). Patients in subgroup 3 also had higher rates of reoperation, hemoglobin decrease, PRBC transfusion, and platelet transfusion due to bleeding than subgroup 1. Similarly, patients in subgroup 4 showed higher rates of PLATO major bleeding, TIMI minor bleeding, hemoglobin decrease, PRBC and platelet transfusion due to bleeding than subgroup 2. In addition, a minority of the patients in this study were given heparin within 48 postoperative hours (n = 342, 10.4%), who had significantly higher rates of PLATO major bleeding, TIMI major and minor bleeding, bleeding-related hemoglobin decrease and PRBC transfusion (Table 5).

Table 4
the rates of bleeding events in the subgroups

	Subgroup 1: ASA (n = 1591)	Subgroup 2: DAPT (n = 593)	Subgroup 3: ASA-anticoag (n = 794)	Subgroup 4: DAPT-anticoag (n = 296)	p-value 1 vs. 2	p-value 3 vs. 4	p-value 1 vs. 3	p-value 2 vs. 4
PLATO major bleeding	599 (37.6)	208 (35.1)	408 (51.4)	138 (46.6)	0.268	0.162	< .001	0.001
PLATO major life-threatening bleeding	177 (11.1)	67 (11.3)	192 (24.2)	48 (16.2)	0.909	0.005	< .001	0.039
PLATO other major bleeding	447 (28.1)	149 (25.1)	240 (30.2)	101 (34.1)	0.166	0.217	0.279	0.005
TIMI major bleeding	76 (4.8)	32 (5.4)	62 (7.8)	17 (5.7)	0.553	0.242	0.003	0.831
TIMI minor bleeding	394 (24.8)	138 (23.3)	203 (25.6)	92 (31.1)	0.470	0.068	0.670	0.012
GUSTO severe bleeding	8 (0.5)	7 (1.2)	13 (1.6)	6 (2.0)	0.139	0.662	0.005	0.376
Intracranial bleeding	0 (0.0)	1 (0.2)	1 (0.1)	2 (0.7)	0.272	0.181	0.333	0.259
Reoperation due to bleeding	8 (0.5)	6 (1.0)	12 (1.5)	4 (1.4)	0.226	0.845	0.011	0.738
Bleed resulting in Hb decrease > 50g/L	76 (4.8)	32 (5.4)	62 (7.8)	17 (5.7)	0.553	0.242	0.003	0.831
Bleed resulting in Hb decrease > 30g/L	457 (28.7)	165 (27.8)	260 (32.7)	102 (34.5)	0.679	0.593	0.044	0.042
Transfusion PRBC > 4 U	81 (5.1)	32 (5.4)	129 (16.2)	27 (9.1)	0.775	0.003	< .001	0.035
Transfusion PRBC > 2 U	123 (7.7)	38 (6.4)	148 (18.6)	33 (11.1)	0.293	0.003	< .001	0.014
PRBC transfusion	173 (10.9)	47 (7.9)	183 (23.0)	45 (15.2)	0.042	0.005	< .001	0.001
FFP transfusion	112 (7.0)	49 (8.3)	88 (11.1)	35 (11.8)	0.330	0.731	0.001	0.087

ASA: aspirin

DAPT: dual antiplatelet therapy

Hb: hemoglobin

PRBC: packed red blood cells

FFP: fresh frozen plasma

MCTD: mediastinal chest tube drainage

	Subgroup 1: ASA (n = 1591)	Subgroup 2: DAPT (n = 593)	Subgroup 3: ASA-anticoag (n = 794)	Subgroup 4: DAPT-anticoag (n = 296)	p-value 1 vs. 2	p-value 3 vs. 4	p-value 1 vs. 3	p-value 2 vs. 4
Platelet transfusion	82 (5.2)	42 (7.1)	48 (6.0)	35 (11.8)	0.083	0.001	0.366	0.018
MCTD > 1 L within 12 h	46 (2.9)	25 (4.2)	28 (3.5)	17 (5.7)	0.121	0.102	0.399	0.312

ASA: aspirin

DAPT: dual antiplatelet therapy

Hb: hemoglobin

PRBC: packed red blood cells

FFP: fresh frozen plasma

MCTD: mediastinal chest tube drainage

Table 5
early use of heparin and the rates of bleeding events

	Heparin not early used (n = 2932)	Heparin early used (n = 342)	p-value
PLATO major bleeding	1155 (39.4)	198 (57.9)	< .001
PLATO major life-threatening bleeding	397 (13.5)	87 (25.4)	< .001
PLATO other major bleeding	806 (27.5)	131 (38.3)	< .001
TIMI major bleeding	146 (5.0)	41 (12.0)	< .001
TIMI minor bleeding	712 (24.3)	115 (33.6)	< .001
GUSTO severe bleeding	30 (1.0)	4 (1.2)	0.776
Intracranial bleeding	3 (0.1)	1 (0.3)	0.357
Reoperation due to bleeding	27 (0.9)	3 (0.9)	0.936
Bleed resulting in Hb decrease > 50g/L	146 (5.0)	41 (12.0)	< .001
Bleed resulting in Hb decrease > 30g/L	830 (28.3)	154 (45.0)	< .001
Transfusion PRBC > 4 U	220 (7.5)	49 (14.3)	< .001
Transfusion PRBC > 2 U	289 (9.9)	53 (15.5)	0.001
PRBC transfusion	378 (12.9)	70 (20.5)	< .001
FFP transfusion	250 (8.5)	34 (9.9)	0.379
Platelet transfusion	189 (6.4)	18 (5.3)	0.395
MCTD > 1 L within 12 h	105 (3.6)	11 (3.2)	0.730
Hb: hemoglobin			
PRBC: packed red blood cells			
FFP: fresh frozen plasma			
MCTD: mediastinal chest tube drainage			

Multivariable analysis of bleeding-related events and postoperative adverse events

Logistic regression was performed to ascertain antithrombotic strategies predictive of bleeding-related events and postoperative adverse events (Table 6). Neither preoperative use of ASA nor postoperative use of DAPT was a predictive factor for major or severe bleeding according to PLATO, TIMI or GUSTO. In contrast, postoperative anticoagulant therapy independently predicted PLATO major bleeding (OR: 1.49; 95% CI: 1.26–1.76; $p < 0.001$), GUSTO severe bleeding (OR: 2.98; 95% CI: 1.44–6.15; $p = 0.003$), and bleeding-related reoperation (OR: 2.80; 95% CI: 1.30–6.03; $p = 0.008$). Similarly, postoperative use of heparin within 48 hours was a predictive factor for PLATO major bleeding (OR: 1.61; 95% CI: 1.24–2.09; $p < 0.001$) and TIMI major bleeding (OR: 2.53; 95% CI: 1.59–4.03; $p < 0.001$).

Table 6
multivariable analysis of bleeding-related events

	PLATO major		TIMI major		GUSTO severe		drainage > 1000mL/12h		Reoperation	
	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value
Pre. ASA	1.16 (0.70–1.91)	0.573	0.79 (0.35–1.81)	0.575	0.76 (0.10-6.00)	0.791	0.59 (0.18–2.01)	0.402	0.52 (0.06–4.29)	0.547
Pre. DAPT	1.34 (1.09–1.65)	0.006	0.84 (0.53–1.34)	0.469	1.43 (0.59–3.50)	0.429	1.98 (1.22–3.23)	0.006	2.12 (0.82–5.47)	0.120
Post. DAPT	0.78 (0.65–0.92)	0.004	1.00 (0.70–1.44)	0.999	1.48 (0.69–3.21)	0.318	1.21 (0.78–1.89)	0.390	0.99 (0.41–2.38)	0.986
Post. Anticoagulant therapy	1.49 (1.26–1.76)	< .001	1.01 (0.69–1.48)	0.945	2.98 (1.44–6.15)	0.003	1.46 (0.96–2.23)	0.078	2.80 (1.30–6.03)	0.008
Post. heparin early use	1.61 (1.24–2.09)	< .001	2.53 (1.59–4.03)	< .001	0.60 (0.19–1.88)	0.378	0.76 (0.37–1.55)	0.456	0.55 (0.15–2.02)	0.367
Redo CABG	1.54 (0.90–2.62)	0.114	2.43 (1.07–5.52)	0.034	1.37 (0.18–10.37)	0.762	0.85 (0.20–3.55)	0.820	1.63 (0.21–12.40)	0.637
Previous PCI	1.17 (0.94–1.46)	0.160	0.71 (0.42–1.21)	0.208	0.91 (0.31–2.62)	0.857	0.94 (0.53–1.67)	0.833	1.09 (0.37–3.20)	0.871
OR: odds ratio										
ASA: aspirin										
DAPT: dual antiplatelet therapy										
CABG: coronary artery bypass grafting										
PCI: percutaneous coronary intervention										

Postoperative DAPT was associated with higher risk of MI (OR: 8.35; 95% CI: 2.83–24.65; p < 0.001) and stroke (OR: 2.29; 95% CI: 1.26–4.18; p = 0.007); but was not a predictive factor of increased mortality within 30 days (OR: 0.98; 95% CI: 0.50–1.90; p = 0.943). Moreover, postoperative use of heparin within 48 hours was significantly associated with increased mortality within 30 days, a higher risk of stroke, and the occurrence of the composite endpoint (Table 7).

Table 7
multivariable analysis of postoperative adverse events

	Composite end point		30 d mortality		MI		Stroke	
	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value
Pre. ASA	0.61 (0.23–1.60)	0.313	1.70 (0.22–12.92)	0.611	0.24 (0.05–1.21)	0.083	0.48 (0.14–1.64)	0.242
Pre. DAPT	0;.86 (0.48–1.54)	0.612	2.19 (1.10–4.39)	0.026	0.58 (0.16–2.14)	0.409	0.43 (0.16–1.15)	0.093
Post. DAPT	1.64 (1.05–2.57)	0.031	0.98 (0.50–1.90)	0.943	8.35 (2.83–24.65)	< .001	2.29 (1.26–4.18)	0.007
Post. Anticoagulant therapy	2.83 (1.80–4.45)	< .001	2.96 (1.53–5.73)	0.001	2.83 (0.91–8.88)	0.074	3.55 (1.92–6.57)	< .001
Post. heparin early use	1.25 (0.72–2.16)	0.432	1.81 (0.88–3.71)	0.105	1.61 (0.47–5.50)	0.446	0.71 (0.31–1.62)	0.411
Redo CABG	1.43 (0.43–4.78)	0.559	2.38 (0.55–10.31)	0.245	0.88 (0.21–3.16)	0.745	0.80 (0.11–6.01)	0.824
Previous PCI	0.70 (0.35–1.41)	0.318	0.61 (0.22–1.72)	0.348	0.37 (0.05–2.84)	0.340	0.61 (0.22–1.72)	0.347
OR: odds ratio								
ASA: aspirin								
DAPT: dual antiplatelet therapy								
CABG: coronary artery bypass grafting								
PCI: percutaneous coronary intervention								

Discussion

Antiplatelet therapy is a major strategy to prevent post-CABG failure and adverse events. While aspirin therapy after CABG has been proven to be a safe approach to improve vein graft patency and reduce adverse events[11–13], there have been no dedicated large-scale studies in the CABG population to support postoperative dual antiplatelet therapy. Continuation of DAPT before the surgery increases the risk of excessive perioperative bleeding, transfusions, and re-exploration for bleeding[7,14,15], which suggests the likelihood of a high risk of bleeding in postoperative DAPT patients. In a meta-analysis of 20315 patients, DAPT (as compared to single antiplatelet therapy) was associated with reduced

cardiovascular mortality in observational studies, but not in randomized trials or in patients with stable ischemic heart disease. Additionally, DAPT was correlated with an increased risk for major bleeding in that study[16]. Another meta-analysis showed increased vein graft patency with DAPT, but increased postoperative bleeding was also noted[17]. Current guidelines recommend postoperative DAPT based upon the stability of coronary artery disease prior to CABG[2,18].

Our study demonstrated that patients who had postoperative DAPT were not at a higher risk for bleeding-related complications than patients who had ASA only. The incidence of major or severe bleeding was balanced between the DAPT and ASA groups, according to the PLATO, TIMI and GUSTO standards. However, platelet transfusion and MCTD of > 1 L within 12 postoperative hours were more often seen in the DAPT group. The multivariable analysis also suggested that postoperative DAPT was not an independent predictor for severe bleeding.

In our study, postoperative DAPT was not associated with a higher rate of perioperative mortality in either univariable or multivariable analysis but was associated with a trend toward an increased risk of postoperative MI and stroke. Since we were unable to know the reason DAPT or ASA was chosen for each patient in the MIMIC database, a possible explanation for these findings is that some patients were given DAPT to treat the onset of postoperative MI or stroke. Additionally, patients in the DAPT group showed a higher percentage of peripheral artery disease and previous PCI, possibly indicating a worse status of the artery, which was a reasonable explanation for both the use of DAPT and the higher risks of postoperative MI and stroke. Ticagrelor was regarded as a reasonable substitute for clopidogrel due to its lower risk of CABG-related bleeding in the PLATO trial[7], but it was not evaluated in this study.

Patients undergoing CABG may have an indication for anticoagulants due to various conditions, such as atrial fibrillation, mechanical heart valves, or venous thromboembolism. In some centers, anticoagulants are also used for the prevention of cardiovascular events and bridging therapy to antiplatelet drugs[6]. The addition of ASA or DAPT to anticoagulant therapy, however, results in at least a two- to threefold increase in bleeding complications[19,20]. Our study demonstrated that the addition of anticoagulants to either ASA or DAPT increased the risk of bleeding, including the early use of heparin. However, we were unable to explore the reason anticoagulant therapy was given to specific patients. Moreover, different types of anticoagulants were not distinguished, though 40.1% of the patients accepting anticoagulant therapy were treated with heparin only, 27.9% with warfarin only, and 32.0% with the combination.

Several limitations can be seen in this study. First, the retrospective and observational nature of this study leads to the presence of possible confounding variables that cannot be ruled out completely. Additionally, limited information can be extracted from the database, which could have led to a mismatch of variables and results. We reasoned that the use of DAPT is unlikely to lead to an increased risk of MI and stroke, and actual clinical decision-making reflects real practice and most likely would not contradict any randomized controlled trial results. Furthermore, different types of anticoagulants were not separated, as mentioned above, and the percentage of patients with early use of heparin was low. The durations of different antithrombotic therapies were also not covered in this study.

Conclusions

We demonstrated that postoperative DAPT was not associated with an increased occurrence of bleeding-related events in patients undergoing isolated CABG and appears to be a safe antiplatelet therapy. In contrast, the addition of anticoagulants to antiplatelet therapy increased the risk of bleeding and should be considered cautiously in clinical practice.

Abbreviations

ASA
aspirin
CABG
coronary artery bypass grafting
CAD
coronary artery disease
DAPT
dual anti-platelet therapy
FFP
fresh frozen plasma
MCTD
mediastinal chest tube drainage
MI
myocardial infarction
PCI
percutaneous coronary intervention
PRBCs
packed red blood cells.

Declarations

Ethics approval and consent to participate

The establishment of this database was approved by the Massachusetts Institute of Technology (Cambridge, MA) and Beth Israel Deaconess Medical Center (Boston, MA) and consent was obtained for the original data collection. Therefore, the ethical approval statement and the need for informed consent were waived for this manuscript.

Consent for publication

Not applicable.

Availability of data and materials

The essential data are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

CY contributed to the concepts and design of this study; ZLX and YW contributed to data extraction and selection from the database; LB and LG contributed to the data analysis; ZLX wrote the manuscript; CSL contributed to the revision of the text. All authors reviewed and approved the final manuscript.

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