ORIGINAL CONTRIBUTION

Complications Arising From Perioperative Anticoagulant/Antiplatelet Therapy in Major Colorectal and Abdominal Wall Surgery

Rebecca Bei Jia Cui, B.Med.[1,2] • Kheng-Seong Ng, M.B.B.S.(HonsI.), Ph.D.[1,2]
Christopher J. Young, M.B.B.S., M.S., F.R.A.C.S.[1,2]

1 University of Sydney, NSW, Australia
2 Department of Colorectal Surgery, Royal Prince Alfred Hospital, Sydney, NSW, Australia

BACKGROUND: Postoperative hemorrhage and thromboembolism are recognized complications following colorectal and abdominal wall surgery, but accurate documentation of their incidence, trends, and outcomes is scant. This is relevant given the increasing number of surgical patients with cardiovascular comorbidity on anticoagulant/antiplatelet therapy.

OBJECTIVE: This study aims to characterize trends in the use of anticoagulant/antiplatelet therapy among patients undergoing major colorectal and abdominal wall surgery within the past decade, and to assess rates of, outcomes following, and risk factors for hemorrhagic and thromboembolic complications.

DESIGN AND SETTING: This is a retrospective cross-sectional study conducted at a single quaternary referral center.

PATIENTS: Patients who underwent major colorectal and abdominal wall surgery during three 12-month intervals (2005, 2010, and 2015) were included.

MAIN OUTCOME MEASURES: The primary outcomes measured was the rate of complications relating to postoperative hemorrhage or thromboembolism.

RESULTS: One thousand one hundred twenty-six patients underwent major colorectal and abdominal wall surgery (mean age, 61.4 years (SD 16.3); 575 (51.1%) male). Overall, 229 (21.7%) patients were on anticoagulant/antiplatelet agents; there was an increase in the proportion of patients on clopidogrel, dual antiplatelet therapy, and novel oral anticoagulants over the decade. One hundred seven (9.5%) cases were complicated by hemorrhage/thromboembolism. Aspirin (OR, 2.22; 95% CI, 1.38–3.57), warfarin/enoxaparin (OR, 3.10; 95% CI, 1.67–5.77), and dual antiplatelet therapy (OR, 2.99; 95% CI, 1.37–6.53) were most implicated with complications on univariate analysis. Patients with atrial fibrillation (adjusted OR 2.67; 95% CI, 1.47–4.85), ischemic heart disease (adjusted OR, 2.14; 95% CI, 1.04–4.40), and mechanical valves (adjusted OR, 7.40; 95% CI 1.11–49.29) were at increased risk of complications on multivariate analysis. The severity of these events was mainly limited to Clavien-Dindo 1 (n = 37) and 2 (n = 46) complications.

LIMITATIONS: This is a retrospective study with incomplete documentation of blood loss and operative time in the early study period.

CONCLUSIONS: One in ten patients incurs hemorrhagic/thromboembolic complications following colorectal and abdominal wall surgery. "High-risk" patients are identifiable, and individualized management of these patients concerning multidisciplinary discussion and critical-care monitoring may help improve outcomes. Prospective studies are required to formalize protocols in these "high-risk" patients. See **Video Abstract** at http://links.lww.com/DCR/A747.

KEY WORDS: Anticoagulation; Antiplatelet; Colorectal surgery; Complications; Hemorrhage; Thromboembolism.

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Correspondence: Christopher J. Young, M.B.B.S., M.S., F.R.A.C.S., RPAH Medical Centre, Suite 415, 100 Carillon Ave, Newtown NSW 2042, Australia. E-mail: cyoungnsw@aol.com. Twitter: @ChrisJFYoung.

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The decision surrounding perioperative cessation and resumption of anticoagulant/antiplatelet therapy involves balancing the competitive risks of hemorrhage and thromboembolism. This requires careful consideration of patient comorbidities and surgical factors to achieve a management plan that minimizes complications. This surgical quandary is becoming more relevant, because the use of anticoagulant/antiplatelet agents in the Western population has increased within the past 20 years.[1,2] This, combined with a protracted life expectancy within the surgical population,[3,4] has meant that surgeons are now operating on increasingly complex patients,[5,6] many of whom are on novel anticoagulant/antiplatelet regimes not encountered a decade or 2 ago. The complexity of this situation, and the recognition of the impact of hemorrhagic/thromboembolic complications following surgery,[7,8] has necessitated the development of generic guidelines that aim to optimize the perioperative care of complex patients.[9,10]

These guidelines are based on literature studying a heterogeneous group of patients arbitrarily categorized into "high" and "low" risk, but few studies have assessed the incidence, trends, outcomes, and risk factors for hemorrhagic/thromboembolic complications specifically for patients undergoing major colorectal surgery.[5,6] Although the incidence of thromboembolism following colorectal surgery has been documented to be 2% to 6%,[11,12] data on the incidence of bleeding complications is scant. Moreover, with increasing utilization of minimally invasive approaches[13,14] and the introduction of novel oral anticoagulants (NOACs),[1] there are more uncertainties regarding the burden and outcomes of these adverse events among colorectal patients.[11,12]

This study aimed to characterize trends in the use of anticoagulant/antiplatelet therapy among patients undergoing major colorectal and abdominal wall surgery within the past decade, as well as assess the rates of, outcomes following, and risk factors for hemorrhagic and thromboembolic complications in this group of patients.

MATERIALS AND METHODS

A retrospective cross-sectional study was performed of consecutive patients undergoing major colorectal and abdominal wall surgery during three 12-month intervals over a 10-year period (2005, 2010, and 2015) at Royal Prince Alfred Hospital, a large quaternary referral center in Sydney, Australia.

Study Population

Consecutive patients who underwent major colorectal and abdominal wall surgery during the included time periods were identified based on an a priori list of Medicare operation codes recorded in the operation reports. Major colorectal surgery was defined based on the typical case-mix of an Australian colorectal unit, and included any elective or emergency procedure requiring small- or large-bowel resection, adhesiolysis, and stoma formation/reversal. Abdominal wall repairs performed by colorectal surgeons were also included. Individual surgeries were then grouped into those of the 1) rectum: anterior resection, reversal of Hartmann procedure, abdominoperineal excision of rectum, and proctocolectomy; 2) colon: right hemicolectomy, total/subtotal colectomy, and Hartmann procedure; 3) small bowel: small-bowel resection and adhesiolysis; 4) abdominal wall: incisional hernia repair and creation/reversal of defunctioning ileostomy/colostomy; and 5) pelvic floor: abdominal rectopexy and perineal rectosigmoidectomy. Patients under 18 years of age were excluded, as were those who underwent pelvic exenteration or minor colorectal surgical procedures (eg, hemorrhoidectomy, pilonidal sinus surgery).

Data Collection and Clinicopathological Variables

A full review of patients' electronic and paper medical records was performed. Recorded patient demographics included: age at surgery, sex, year of surgery (2005, 2010, and 2015), operation type (open/laparoscopic), emergency/elective surgery, and indication for surgery (ie, principal diagnosis). Type(s) of anticoagulant/antiplatelet therapy and indication for such therapy were collected, along with details of continuation/cessation perioperatively, bridging anticoagulation, time to restarting therapeutic anticoagulation postoperatively, and medical (ie, cardiology/hematology) input regarding perioperative anticoagulant/antiplatelet management.

Outcome Measures

Primary outcome measures included rates of complications relating to hemorrhage/thromboembolism. These were identified using *International Classification of Diseases, 10th Revision* (ICD-10) codes recorded for the index or subsequent admissions, and included hemorrhage/hematoma (ICD T81.0), venous thromboembolism (pulmonary embolism or deep vein thrombosis) (ICD I26.9, ICD I80.2, ICD I82.8), acute coronary syndromes (ICD I21.3, ICD I21.4, ICD I25.11, ICD I24.2, ICDI 25.9), intracerebral hemorrhage (ICD I60.9, ICD I62.0), ischemic stroke (ICD I63.0), and limb ischemia (ICD I97.8). The severities of these complications were graded by using the Clavien-Dindo classification for surgical complications.[15]

Secondary outcome measures included 1) 30-day hospital readmission rates; 2) return to the operating room within 30 days; and 3) 30-day mortality rates.

Statistical Analysis

Descriptive statistics and univariate analyses using *t* test, Wilcoxon rank-sum test, and contingency analysis for parametric, nonparametric, and categorical data were used to

assess patient and clinical characteristics and the "crude" association with primary and secondary outcomes. Univariate logistic regression models assessed the association between explanatory variables and study outcomes. All variables associated with study outcomes ($p < 0.2$) were included in multivariable models to assess the association while considering potential confounding by patient and clinical risk factors. Biologically plausible interactive effects were also included and tested. All analyses were conducted using SPSS version 21 (SPSS Inc, Chicago, IL), and $p < 0.05$ was considered statistically significant. This study was approved by the Sydney Local Health District Ethics Committee.

RESULTS

Study Population

Over the study period, 1126 patients underwent major colorectal and abdominal wall surgery (mean age, 61.4 years (SD 16.3); 575 (51.1%) male). There was a relatively even distribution of surgeries performed between the 3 years (2005: n = 318; 2010: n = 409; and 2015: n = 399). These operations were performed on the abdominal wall (32.4%), rectum (28.3%), colon (25.8%), small bowel (10.2%), and pelvic floor (3.3%) (Table 1).

Clinicopathological Variables

There was an increasing number of laparoscopic cases performed over the study period (2005: 14.7%, 2010: 30.1%, and 2015: 34.3%; $p < 0.001$), with the proportion of emergency operations remaining stable (2005: 26.1%, 2010: 23.7%, and 2015: 27.3%). The majority of surgeries were performed for malignant tumors (42.4%), parastomal/incisional hernias (9.8%), and ischemic bowel/abdominal sepsis (9.3%) (Table 1).

Overall, 229 (21.7%) patients were on anticoagulant/antiplatelet therapy, most commonly aspirin (100 mg) (14.2%), warfarin (5.3%), and clopidogrel (3.3%). Over the decade of study, the proportion of patients on anticoagulant/antiplatelet therapy increased (2005: 17.0%, 2010: 23.3%, and 2015: 23.6%), but did not reach significance ($p = 0.083$). There was a significant increase in the proportion of patients on clopidogrel, dual antiplatelet therapy (DAPT), and NOACs ($p < 0.05$). The key indications for the use of these agents remained constant, with the exception of cardiac stents, which increased from 2.1% of patients in 2005 to 8.0% in 2015 ($p = 0.004$).

Of patients on anticoagulant/antiplatelet therapy, 46 (20.1%) continued their therapy throughout the perioperative period. Of those in whom therapy was withheld, it was for an average of 6.0 days (SD 7.5). The average time to restarting therapeutic anticoagulation postoperatively was also 6.0 days (SD 5.5). Bridging anticoagulation was administered to 17.5%, most commonly enoxaparin (9.6%). Of the 40 patients bridged, the overwhelming majority (n = 38; 95%) were bridged for anticoagulant, rather than antiplatelet, therapy. Cardiology or hematology advice regarding perioperative anticoagulation was sought in one-third (38.9%) of patients.

There were significant changes identified over the 10 years concerning the above parameters. There was an increase in time to recommencing therapeutic anticoagulation postoperatively, from 3.9 days (SD 3.0) in 2005, to 5.1 days (SD 4.6) in 2010, to 8.0 days (SD 6.4) in 2015 ($p < 0.001$). There was a decrease in bridging anticoagulation during the study period, from 22.9% of patients in 2005 to 13.2% of patients in 2015, which failed to reach significance ($p = 0.122$); and there was a significant decrease in the use of heparin as the bridging agent ($p < 0.001$) (Table 2).

Outcomes Measured

Overall, 107 (9.5%) patients had hemorrhagic/thromboembolic complications. Of these, the most common were hemorrhage/hematoma (n = 76; 6.7%) and deep vein thrombosis (DVT) (n = 18; 1.6%) (Table 3). Notably, the severity of events was mainly limited to Clavien-Dindo grade 1 (n = 37; 3.3%) and grade 2 (n = 46; 4.1%). Ten patients (0.9%) required readmission within 30 days for sequelae associated with these complications, 9 (0.8%) required return to the operating room, and there were 4 mortalities (0.4%).

Of the 76 patients with hemorrhage/hematoma, 45 (59.2%) required a blood product transfusion. Eighteen patients had DVT, of which 15 (83.3%) were during admission and 3 (16.7%) were following discharge. Of the 5 patients with pulmonary embolism (PE), 4 (80%) were during admission and 1 (20%) was following discharge. Of the 76 patients with hemorrhage/hematoma, 45 (59.2%) required a blood product transfusion. Of the 13 patients that experienced postoperative myocardial infarction, 3 had cardiac stents preoperatively. All 3 of these patients were on aspirin monotherapy, 2 of which had aspirin withheld preoperatively.

There was an increase in complications between 2005 (7.9%) and 2010 (12.7%), but this subsequently declined to 7.5% in 2015 (Table 3). Otherwise, there was no difference in 30-day readmission, return to the operating room, and mortality rates between 2005, 2010, and 2015.

Of the 13 patients that experienced postoperative myocardial infarction, 3 had cardiac stents preoperatively. All 3 of these patients were on aspirin monotherapy; 2 had their aspirin withheld preoperatively, and data are missing for the other patient.

Risk Factors for the Development of Hemorrhagic/Thromboembolic Complications: Univariate Analyses

On univariate analysis, men were at a higher risk of developing hemorrhagic/thromboembolic complications (OR, 1.55; 95% CI, 1.03–2.33), as were older patients (mean, 65.0 years (SD 17.6) vs 61.0 (SD 16.0), $p = 0.015$). Complications were significantly associated with the use of

Table 1. Demographics and clinicopathological variables

Variable	*2005 (n = 318)*	*2010 (n = 409)*	*2015 (n = 399)*	*p value*	*Total (n = 1126)*
Male, n (%)	148 (46.5)	216 (52.8)	211 (52.9)	0.163	575 (51.1)
Age, mean (SD)	62.1 (15.1)	61.6 (17.3)	60.7 (16.1)	0.513	61.4 (16.3)
Anticoagulant/antiplatelet therapy, n (%)	48 (17.0)	90 (23.3)	91 (23.6)		229 (21.7)
Aspirin	31 (11.0)	57 (14.7)	62 (16.0)	0.172	150 (14.2)
Warfarin	16 (5.7)	26 (6.7)	14 (3.6)	0.151	56 (5.3)
Clopidogrel	3 (1.1)	14 (3.6)	18 (4.7)	0.034	35 (3.3)
Enoxaparin	1 (0.4)	7 (1.8)	1 (0.3)	0.037	9 (0.9)
Novel oral anticoagulants (dabigatran, rivaroxaban, apixiban)	0 (0.0)	0 (0.0)	12 (3.1)	<0.001	12 (1.2)
Dual antiplatelet therapy	3 (1.1)	17 (4.4)	17 (4.4)	0.033	37 (3.3)
Any	48 (17.0)	90 (23.3)	91 (23.6)	0.083	229 (21.7)
Etiology, n (%)				0.32	
Malignancy	125 (43.9)	180 (44.1)	157 (39.5)		462 (42.4)
Benign tumor	22 (7.7)	29 (7.1)	22 (5.5)		73 (6.7)
IBD	30 (10.5)	43 (10.5)	35 (8.8)		108 (6.7)
Diverticular disease	18 (6.3)	29 (7.1)	34 (8.6)		81 (7.4)
Pelvic floor	12 (4.2)	14 (3.4)	18 (4.5)		44 (4.0)
Parastomal/incisional hernia	24 (8.4)	38 (9.3)	45 (11.3)		107 (9.8)
Bowel ischemia, abdominal sepsis	16 (5.6)	35 (8.6)	50 (12.6)		101 (9.3)
Bowel obstruction	27 (9.5)	26 (6.4)	29 (7.3)		82 (7.5)
Other	11 (3.9)	14 (1.3)	7 (1.8)		32 (2.9)
Surgery type, n (%)				0.07	
Anterior resection	62 (18.5)	87 (21.3)	81 (20.3)		230 (20.4)
Right hemicolectomy	52 (16.4)	77 (18.8)	62 (15.5)		191 (17)
Reversal of ileostomy/colostomy	41 (12.9)	61 (14.9)	51 (12.8)		153 (13.6)
Incisional hernia repair	28 (8.8)	38 (9.3)	41 (10.3)		107 (9.5)
Formation of a defunctioning stoma	20 (6.3)	41 (10.0)	44 (11.0)		105 (9.3)
Small-bowel resection with anastomosis	16 (5.0)	17 (4.2)	24 (6.0)		57 (5.1)
Adhesiolysis/exploratory laparotomy	26 (8.2)	9 (0.8)	16 (4.0)		51 (4.5)
Total/subtotal colectomy	21 (6.6)	23 (5.6)	23 (5.8)		67 (6.0)
Proctocolectomy	11 (3.5)	19 (4.6)	8 (2.0)		38 (3.4)
Hartmann procedure	12 (3.8)	7 (1.7)	13 (3.3)		32 (2.8)
Abdominoperineal resection	7 (2.2)	12 (2.9)	10 (2.5)		29 (2.6)
Abdominal rectopexy	8 (2.5)	8 (2.0)	11 (2.8)		27 (2.4)
Reversal of Hartmann	9 (2.8)	5 (1.2)	8 (2.0)		22 (2.0)
Perineal rectosigmoidectomy	5 (1.6)	2 (0.5)	3 (0.8)		10 (0.9)
Abdominal washout	0 (0.0)	3 (0.7)	4 (1.0)		7 (0.6)
Surgery location, n (%)				0.137	
Rectum	89 (28.0)	123 (30.1)	107 (26.8)		319 (28.3)
Colon	85 (26.7)	107 (26.2)	98 (24.6)		290 (25.8)
Small bowel	42 (13.2)	29 (7.1)	44 (11.0)		115 (10.2)
Abdominal wall	89 (28.0)	140 (34.2)	136 (34.1)		365 (32.4)
Pelvic floor	13 (4.1)	10 (2.4)	14 (3.5)		37 (3.3)
Laparoscopic/open, n (%)					
Laparoscopic	42 (14.7)	123 (30.1)	137 (34.3)	<0.001	302 (27.6)
Emergency/elective, n (%)					
Emergency	83 (26.1)	97 (23.7)	109 (27.3)	<0.001	289 (25.7)
Preoperative treatment, n (%)					
Radiotherapy	13 (4.6)	48 (11.7)	49 (13.2)	0.001	110 (10.3)
Chemotherapy	16 (5.7)	51 (12.9)	57 (15.3)	0.001	124 (11.8)
Indication for anticoagulation, n (%)					
Atrial fibrillation	9 (3.2)	44 (11.3)	33 (8.5)	0.001	86 (8.1)
Venous thromboembolism	13 (4.6)	25 (6.4)	30 (7.8)	0.262	68 (6.4)
Ischemic heart disease/myocardial infarction	27 (9.6)	39 (10.0)	54 (14.0)	0.124	120 (11.3)
Transient ischemic attack/cerebrovascular accident	14 (5.0)	18 (4.6)	15 (3.9)	0.777	47 (4.4)
Cardiac stent	6 (2.1)	20 (5.1)	31 (8.0)	0.004	57 (5.4)
Mechanical valve	2 (0.7)	2 (0.5)	2 (0.5)	0.933	6 (0.6)
Peripheral vascular disease	12 (4.3)	21 (5.4)	9 (2.3)	0.087	42 (4.0)
Comorbidities, n (%)					
Hypertension	119 (42.2)	166 (42.7)	156 (40.2)	0.765	441 (41.6)
Diabetes mellitus	38 (13.5)	46 (11.8)	69 (17.8)	0.051	153 (14.5)
Hypercholesterolemia	68 (21.4)	109 (28)	103 (26.5)	0.526	280 (26.4)
Liver disease	7 (2.5)	15 (3.9)	20 (5.2)	0.211	42 (4.0)
Renal disease	13 (4.6)	19 (4.9)	38 (9.8)	0.006	70 (6.6)

Table 2. Features of patients on anticoagulants/antiplatelets

Variable	*2005 (n = 48)*	*2010 (n = 90)*	*2015 (n = 91)*	*p value*	*Total (n = 229)*
Duration anticoagulant/antiplatelet agent withheld preoperatively					
Mean days (SD)	6.7 (6.0)	6.4 (9.8)	5.4 (5.3)	0.626	6.0 (7.5)
Not withheld, n (%)	7 (14.6)	21 (23.3)	18 (19.8)		46 (20.1)
Time before restarting therapeutic anticoagulation postoperatively					
Mean days (SD)	3.9 (3.0)	5.1 (4.6)	8.0 (6.4)	<0.001	6.0 (5.5)
Day 0, n (%)	0 (0)	3 (3.3)	1 (1.1)		4 (1.7)
Never restarted, n (%)	0 (0)	6 (6.7)	5 (5.5)		11 (4.8)
Bridging therapy, n (%)	11 (22.9)	17 (18.9)	12 (13.2)	0.122	40 (17.5)
Heparin	10 (20.8)	5 (5.6)	4 (4.4)	<0.001	19 (8.3)
Enoxaparin	2 (4.2)	11 (12.2)	9 (9.9)	0.461	22 (9.6)
Cardiology/hematology consult obtained, n (%)	19 (39.6)	40 (44.4)	30 (33.0)	0.285	89 (38.9)

any anticoagulant/antiplatelet agents (OR, 2.73; 95% CI, 1.79–4.15), in particular, aspirin (OR, 2.22; 95% CI, 1.38–3.57), warfarin/enoxaparin (OR, 3.10; 95% CI, 1.67–5.77), and DAPT (OR, 2.99; 95% CI, 1.37–6.53).

Complications were significantly associated with the indication for and site of surgery (Table 4). Complications were more commonly identified in patients undergoing surgery for diverticular disease (13.1% vs 6.9%) and bowel ischemia/sepsis (16.8% vs 7.6%), but were relatively rare in patients undergoing incisional hernia repair (1.9% vs 10.7%) or pelvic floor surgery (0.9% vs 4.5%) (Table 4). Complications were not associated with the type of surgery (ie, laparoscopic vs open), but there was a 2-fold increased risk seen in emergency compared with elective procedures (OR, 2.08; 95% CI, 1.37–3.13).

There was an increased risk of complications in patients with atrial fibrillation (AF) (OR, 3.38; 95% CI, 1.97–5.80) and ischemic heart disease (IHD) (OR, 3.28; 95% CI, 2.03–5.32), an increased risk in those with cardiac stents (OR, 4.77; 95% CI, 2.61–8.70), and an increased risk in those with mechanical heart valves (OR, 18.1; 95% CI, 3.28–100.01) (Table 4). There was also an increased risk of hemorrhagic/thromboembolic complications among patients who had anticoagulants/antiplatelet therapy withheld perioperatively (OR, 2.10; 95% CI, 1.30–3.38), with the most common complication being hemorrhage (n = 21; 12.7%), followed by myocardial infarction (MI) (n = 6; 3.6%); only 4 patients (2.4%) who had anticoagulant/antiplatelet therapy withheld experienced a transient ischemic attack/stroke.

Table 3. Outcomes of patients with hemorrhagic/thromboembolic complications

Outcomes	*2005 (n = 318)*	*2010 (n = 409)*	*2015 (n = 399)*	*p value*	*Total (n = 1126)*
Type of complication, n (%)					
Hemorrhage	19 (6.0)	37 (9.0)	20 (5.0)	0.051	76 (6.7)
Myocardial infarction	4 (1.3)	6 (1.5)	3 (0.8)	0.580	13 (1.2)
Deep vein thrombosis	2 (0.6)	8 (2.0)	8 (2.0)	0.316	18 (1.6)
During admission	1 (0.3)	6 (1.5)	8 (2.0)		15 (1.3)
Following discharge	1 (0.3)	2 (0.5)	0 (0)		3 (0.3)
Pulmonary embolism	0 (0)	2 (0.5)	3 (0.8)	0.352	5 (0.5)
During admission	0 (0)	2 (0.5)	2 (0.5)		4 (0.4)
Following discharge	0 (0)	0 (0)	1 (0.3)		1 (0.1)
Intracranial hemorrhage	0 (0)	0 (0)	0 (0)	-	0 (0)
Ischemic stroke/transient ischemic attack	2 (0.6)	4 (1.0)	1 (0.3)	0.403	7 (0.6)
Peripheral ischemia	0 (0)	0 (0)	1 (0.3)	0.425	1 (0.1)
Any hemorrhagic/thromboembolic complication	25 (7.9)	52 (12.7)	30 (7.5)	0.021	107 (9.5)
Severity of complication, n (%)					
Clavien-Dindo 1	4 (1.3)	23 (5.6)	10 (2.5)	0.004	37 (3.3)
Clavien-Dindo 2	13 (4.1)	19 (4.6)	14 (3.5)		46 (4.1)
Clavien-Dindo 3	4 (1.3)	2 (0.5)	3 (0.8)		9 (0.8)
Clavien-Dindo 4	2 (0.6)	8 (2.0)	1 (0.3)		11 (1.0)
Clavien-Dindo 5	0 (0)	0 (0)	2 (0.5)		2 (0.2)
30-day outcomes, n (%)					
30-day readmission	1 (0.3)	6 (1.5)	3 (0.8)	0.254	10 (0.9)
30-day return to operating room	2 (0.6)	5 (1.2)	2 (0.5)	0.467	9 (0.8)
30-day mortality	0 (0)	1 (0.2)	3 (0.8)	0.245	4 (0.4)

Table 4. Univariate analysis of clinicopathological features associated with outcomes

Variable	*Hemorrhagic/ thromboembolic complications (n = 107)*	*No hemorrhagic/ thromboembolic complications (n = 938)*	*p value*	*OR (95% CI)*
Sex, n (%)				
Male	65 (60.7)	469 (50.0)	0.035	1.55 (1.03–2.33)
Age, mean (SD)	65.0 (17.6)	61.0 (16.0)	0.015	
Anticoagulant/antiplatelet therapy, n (%)	43 (40.2)	184 (19.8)	<0.001	2.73 (1.79–4.15)
Aspirin	27 (25.2)	123 (13.2)	0.001	2.22 (1.38–3.57)
Warfarin/enoxaparin	15 (14.2)	47 (5.0)	<0.001	3.10 (1.67–5.77)
Clopidogrel	7 (6.6)	28 (3.0)	0.052	2.28 (0.97–5.36)
Novel oral anticoagulants	2 (1.9)	10 (1.1)	0.459	1.77 (0.38–8.19)
Dual antiplatelet therapy	9 (8.5)	28 (3.0)	0.004	2.99 (1.37–6.53)
Etiology, n (%)				
Malignancy	51 (47.7)	398 (42.5)	<0.001	
Benign	5 (4.7)	66 (7.0)		
IBD	10 (9.3)	94 (10.0)		
Diverticular	14 (13.1)	65 (6.9)		
Pelvic floor	1 (0.9)	42 (4.5)		
Parastomal/incisional hernia	2 (1.9)	100 (10.7)		
Bowel ischemia/sepsis	18 (16.8)	71 (7.6)		
Bowel obstruction	5 (4.7)	73 (7.8)		
Other	1 (0.9)	28 (3.0)		
Surgery location, n (%)				
Rectum	39 (36.4)	274 (29.2)	0.018	
Colon	34 (31.8)	232 (24.7)		
Small bowel	11 (10.3)	85 (9.1)		
Abdominal wall	23 (21.5)	311 (33.2)		
Pelvic floor	0 (0)	36 (3.8)		
Laparoscopic/open, n (%)				
Laparoscopic	34 (31.8)	260 (27.7)	0.38	0.82 (0.54–1.27)
Emergency/elective, n (%)				
Emergency	41 (38.3)	215 (22.9)	<0.001	2.08 (1.37–3.13)
Preoperative treatment, n (%)				
Radiotherapy	5 (4.7)	105 (11.5)	0.033	0.38 (0.15–0.96)
Chemotherapy	6 (5.7)	117 (12.9)	0.033	0.41 (0.18–0.96)
Indication for anticoagulation, n (%)				
Atrial fibrillation	21 (19.6)	63 (6.7)	<0.001	3.38 (1.97–5.80)
Venous thromboembolism	9 (8.4)	59 (6.3)	0.406	1.36 (0.66–2.83)
Ischemic heart disease/myocardial infarction	28 (26.2)	91 (9.7)	<0.001	3.28 (2.03–5.32)
Transient ischemic attack/cerebrovascular accident	8 (7.5)	39 (4.2)	0.119	1.85 (0.84–4.08)
Cardiac stent	18 (16.8)	38 (4.1)	<0.001	4.77 (2.61–8.70)
Mechanical valve	4 (3.7)	2 (0.2)	<0.001	18.10 (3.28–100.01)
Peripheral vascular disease	8 (7.5)	34 (3.6)	0.056	2.14 (0.96–4.75)
Comorbidities, n (%)				
Hypertension	49 (45.8)	386 (41.3)	0.375	1.20 (0.80–1.80)
Diabetes mellitus	18 (16.8)	133 (14.2)	0.47	1.22 (0.71–2.09)
Hypercholesterolemia	34 (31.8)	240 (25.7)	0.176	1.35 (0.87–2.08)
Liver disease	6 (5.6)	36 (3.9)	0.383	1.48 (0.61–3.60)
Renal disease	9 (8.4)	60 (6.4)	0.434	1.34 (0.64–2.78)
Cardiology/hematology consult, n (%)	21 (19.6)	68 (7.3)	0.038	2.14 (1.03–4.44)
Withheld preoperatively, n (%)	31 (35.2)	132 (14.1)	0.002	2.10 (1.30–3.39)
Bridging, n (%)	11 (10.3)	28 (3.0)	0.078	2.05 (0.91–4.61)
Time to restart anticoagulation, mean (SD)	8.9 (6.6)	5.5 (5.0)	0.01	
Duration withheld, mean (SD)	4.6 (5.9)	6.3 (7.8)	0.21	

Risk Factors for the Development of Hemorrhagic/ Thromboembolic Complications: Multivariate Analyses

Multivariate analysis of indications for anticoagulant/antiplatelet therapy revealed AF (adjusted OR (aOR), 2.67; 95% CI, 1.47–4.85), IHD (aOR, 2.14; 95% CI, 1.04–4.40), and mechanical valve (aOR, 7.40; 95% CI, 1.11–49.29) as significant factors (Table 5). Only aspirin (aOR, 2.20; 95% CI, 1.32–3.69) and warfarin/enoxaparin (aOR, 3.49; 95% CI, 1.86–6.55) use remained significant factors following multivariate analysis of anticoagulant/antiplatelet therapy (Table 6).

Table 5. Multivariate analysis: indications for antiplatelet/anticoagulant agents

	Hemorrhagic/thromboembolic complications (n = 107)	
Indication	*OR (95% CI)*	*p value*
Atrial fibrillation	2.67 (1.47–4.85)	0.001
Ischemic heart disease/myocardial infarction	2.14 (1.04–4.40)	0.038
Transient ischemic attack/cerebrovascular accident	1.22 (0.53–2.84)	0.640
Cardiac stents	2.27 (0.94–5.47)	0.068
Mechanical valve	7.40 (1.11–49.29)	0.039
Peripheral vascular disease	1.26 (0.52–3.07)	0.604
Hypercholesterolemia	0.71 (0.42–1.22)	0.213

DISCUSSION

In this study of patients undergoing major colorectal and abdominal wall surgery, 1 in 10 had hemorrhagic/thromboembolic complications postoperatively despite twice the number being on anticoagulant/antiplatelet therapy. Hemorrhagic complications were almost 3-fold more common than thromboembolic ones, but overall, the severity of these complications was favorable, being largely limited to Clavien-Dindo grades 1 and 2; only 4 mortalities were recorded. Between 2005 and 2015, there was an increasing use of clopidogrel, DAPT, and NOACs. This was not reflected in the change over time of hemorrhagic/thromboembolic complications, with these complications appearing to peak in 2010, suggesting greater awareness and efficacious management of these complications in the latter part of the study period. Patients who were older, male, and undergoing emergency surgery were more likely to have hemorrhagic/thromboembolic complications. As expected, patients on perioperative anticoagulant/antiplatelet therapy, were also at greater risk, with aspirin and warfarin, in particular, being implicated. At highest risk were patients with a cardiac history of AF, IHD, and mechanical heart valve replacement.

This study intentionally assessed the typical case-mix of an Australian colorectal unit, and included patients undergoing major emergency or elective surgery of the small or large bowel and subsequent operations incurred thereof (including those of the abdominal wall). Notably, our study population aligns well with those who underwent colorectal surgery in the United Kingdom National Health and Social Care Information Centre Database, with similar sex and age characteristics between the 2 groups, and with the majority of surgeries being performed for malignant tumors.[16] Our rate of emergency operating (25.7%) is also similar to other centers, which range from 16% to 30%.[16,17] The parallelism in clinical experiences between our unit and others likely extends to trends in perioperative anticoagulant/antiplatelet use. The increase in the proportion of patients on clopidogrel, DAPT, and NOACs during our study period is supported by unrelated studies in the United States, United Kingdom, and Denmark,[1,2,18] and our finding of increased antiplatelet use for coronary stents is remarkably consistent with contemporary literature.[19,20] Our experiences of complications relating to such therapy would likely apply to other units worldwide.

Table 6. Multivariate analysis: type of antiplatelet/anticoagulant agent

	Hemorrhagic/thromboembolic complications (n = 107)	
Agent	*OR (95% CI)*	*p value*
Aspirin	2.20 (1.32–3.69)	0.003
Clopidogrel	1.51 (0.61–3.74)	0.375
Warfarin/enoxaparin	3.49 (1.86–6.55)	0.000

Hemorrhagic complications outnumbered thromboembolic ones almost 3-fold. This finding has not been previously reported. In fact, rates of postoperative hemorrhage are scarcely documented following major colorectal surgery; however, our rate of 6.7% is consistent with that of a previous study limited to proctological surgery.[21] By contrast, rates of thromboembolic complications are more clearly documented in the published literature, and our relatively low rates of DVT (1.7%), PE (0.5%), and MI (1.2%) are consistent with those previously reported (DVT, 1.4%–1.8%; PE, 0.5%–0.8%[22,23]; and MI, 0.4%–1.5%[23,24]).

There appeared to be an increase in complication rates between 2005 and 2010, and a subsequent decrease by 2015. Changes over time are difficult to extrapolate with only 3 time points, but do pose the question whether improved understanding and preemptive management of complications led to lower rates in 2015. Indeed, development and ad hoc adoption of contemporary guidelines[25,26] during this period could help explain our improved outcomes. Furthermore, there was an increase in the time interval to resuming anticoagulant/antiplatelet therapy postsurgery; this observation could be interpreted as our unit's conscious effort to minimize hemorrhagic complications in the face of increased anticoagulant/antiplatelet use. Despite the delay in resuming therapy, there was no discernible increase in thromboembolic complications; this finding, combined with the observation that hemorrhagic complications outnumbered thromboembolic ones almost 3-fold, suggests it may be safe to err on delaying reanticoagulation, especially in high-risk patients. The latter part of our study period was also characterized by a decreased tendency to use bridging therapy, a pertinent finding in light of a previous study which found that patients undergoing elective colorectal surgery with preoperative AF had increased complications if they were bridged.[27]

This study importantly identified patients most at risk of hemorrhagic/thromboembolic complications. This is vitally important in identifying "high-risk" patients for whom an individualized management approach, involving accurate preoperative counseling and consent, may be considered. On univariate analysis, older age and male sex were associated with increased risk; whereas older age has previously been described as a risk factor for development of DVT/PE,[22,28] sex was not found to influence complication rates in 1 recent study.[29] Perioperative anticoagulant/antiplatelet therapy was significantly associated with complication rates, with aspirin and warfarin each implicated. This suggests that single-agent therapy, such as with aspirin, may not be as benign as commonly presumed. Surprisingly, there are relatively few studies that address this issue, and those that do, conflict; 1 study identified that patients on preoperative antiplatelet therapy had increased rates of blood transfusion,[30] another showed no difference in rates of blood loss/transfusion between those who continued a single antiplatelet compared with those who withheld it preoperatively.[31]

The indications for surgery and operation type were also significantly associated with outcomes. In our study, patients undergoing surgery for bowel ischemia were at increased risk, consistent with results from another study.[32] By contrast, patients undergoing surgery of the abdominal wall and pelvic floor had lower rates of hemorrhage/thromboembolism. This is despite some evidence that prolonged pelvic procedures have an associated increased risk of thromboembolism, likely explained by their lengthy dissection and lithotomy positioning; this, however, seems to apply most to surgery for malignancy and IBD, rather than surgery of the pelvic *floor*, as seen in our study.[33,34] Elective operations were associated with one-half the risk of complications compared with their emergency counterparts, likely because of the benefits afforded by time for preoperative planning and multidisciplinary discussion.[35,36] Notably, we did not identify a significant difference in complication rates following laparoscopic in comparison with open surgery; this conflicts with 1 previous study, which identified that patients undergoing laparoscopic surgery were at decreased risk, although that study was limited to warfarin and clopidogrel use only.[37]

There is little doubt regarding the role of cardiac comorbidities in determining surgical risk, explaining their importance in various surgical risk prediction models.[38,39] Few studies, however, specifically assess the importance of these comorbidities in colorectal patients.[8,40] Even existing guidelines by the American College of Cardiology,[41] American Heart Association,[26] American College of Chest Physicians,[25] and the British Society of Hematology[42] only group surgical procedures into high- and low-risk procedures, or risk assessed by operating surgeon, with virtually no information on specific colorectal procedures. Moreover, few risk prediction scores assess the influence of "non–heart failure" comorbidities (eg, cardiac arrhythmias) on surgical outcomes. Our study makes an important finding that AF, IHD, and mechanical heart valves are significant risk factors for the development of hemorrhagic/thromboembolic complications. The highest-risk cardiac comorbidity was mechanical heart valve replacement, with these patients being at an 8-fold increased risk, although a recent study demonstrated that strict adherence to guidelines might help reduce this risk.[43]

This study was limited by its retrospective design, and we were reliant on extant data routinely collected for clinical purposes but not necessarily targeted to this study. For example, we only assessed the impact of prescription anticoagulant/antiplatelet agents on perioperative complications, and were not able to establish data relating to over-the-counter medications (eg, dietary/herbal supplements), which have known effects on coagulation.[44] We would have liked to present accurate data on operative times and exact blood loss during surgery, but these were not always accurately recorded, especially early in the study period. Additionally, our complication rates may be underestimated if patients presented to a different center following discharge. Despite these limitations, we have included a large study population (>1000 patients), and our study is unique in specifically examining those undergoing major colorectal and abdominal wall surgery and systematically characterizing hemorrhagic/thromboembolic complications according to the Clavien-Dindo system.

Through this study, we have identified that the "burden" of anticoagulant/antiplatelet use in patients undergoing major colorectal and abdominal wall surgery increased between 2005 and 2015, especially concerning the use of clopidogrel, DAPT, and NOACs. Overall, patients on such therapy appear to be well-managed perioperatively, because only 1 in 10 incurs hemorrhagic/thromboembolic complications, despite double the number being on therapy. Nevertheless, there still exists scope for improvement, likely through the identification of "high-risk" groups to help guide perioperative decision making. Preemptive management, multidisciplinary discussion, and surgical monitoring in a critical care environment are likely indicated in older male patients, those undergoing emergency procedures for etiologies including ischemic bowel and diverticular disease, and those on warfarin or aspirin for AF, IHD, and mechanical heart valves. Our study suggests there is probably room for safe delay in recommencing anticoagulant/antiplatelet therapy if clinically indicated, but prospective studies are required to formalize protocols in the perioperative management of these "high-risk" patients undergoing major colorectal and abdominal wall surgery.

REFERENCES

1. Loo SY, Dell'Aniello S, Huiart L, Renoux C. Trends in the prescription of novel oral anticoagulants in UK primary care. *Br J Clin Pharmacol*. 2017;83:2096–2106.

2. Adelborg K, Grove EL, Sundbøll J, Laursen M, Schmidt M. Sixteen-year nationwide trends in antithrombotic drug use in Denmark and its correlation with landmark studies. *Heart*. 2016;102:1883–1889.
3. Jafari MD, Jafari F, Halabi WJ, et al. Colorectal cancer resections in the aging US population: a trend toward decreasing rates and improved outcomes. *JAMA Surg*. 2014;149:557–564.
4. Nitsche U, Späth C, Müller TC, et al. Colorectal cancer surgery remains effective with rising patient age. *Int J Colorectal Dis*. 2014;29:971–979.
5. van Leersum NJ, Janssen-Heijnen ML, Wouters MW, et al. Increasing prevalence of comorbidity in patients with colorectal cancer in the South of the Netherlands 1995-2010. *Int J Cancer*. 2013;132:2157–2163.
6. Nathan H, Segev DL, Mayo SC, et al. National trends in surgical procedures for hepatocellular carcinoma: 1998-2008. *Cancer*. 2012;118:1838–1844.
7. Borly L, Wille-Jørgensen P, Rasmussen MS. Systematic review of thromboprophylaxis in colorectal surgery – an update. *Colorectal Dis*. 2005;7:122–127.
8. Torn M, Rosendaal FR. Oral anticoagulation in surgical procedures: risks and recommendations. *Br J Haematol*. 2003;123:676–682.
9. Kraft CT, Bellile E, Baker SR, Kim JC, Moyer JS. Anticoagulant complications in facial plastic and reconstructive surgery. *JAMA Facial Plast Surg*. 2015;17:103–107.
10. Lip GY, Durrani OM, Roldan V, Lip PL, Marin F, Reuser TQ. Peri-operative management of ophthalmic patients taking antithrombotic therapy. *Int J Clin Pract*. 2011;65:361–371.
11. Moghadamyeghaneh Z, Hanna MH, Carmichael JC, Nguyen NT, Stamos MJ. A nationwide analysis of postoperative deep vein thrombosis and pulmonary embolism in colon and rectal surgery. *J Gastrointest Surg*. 2014;18:2169–2177.
12. Clouston HW, Shaker H, Duff S, Kirwan CC. PO-09 - Incidence of pre-operative and post-operative deep vein thrombosis in colorectal cancer surgery. Interim results of a prospective clinical study. *Thromb Res*. 2016;140(suppl 1):S179–S180.
13. Keller DS, Delaney CP, Hashemi L, Haas EM. A national evaluation of clinical and economic outcomes in open versus laparoscopic colorectal surgery. *Surg Endosc*. 2016;30:4220–4228.
14. Schwenk W, Haase O, Neudecker J, Müller JM. Short term benefits for laparoscopic colorectal resection. *Cochrane Database Syst Rev*. 2005;(3):CD003145.
15. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240:205–213.
16. Byrne BE, Mamidanna R, Vincent CA, Faiz OD. Outlier identification in colorectal surgery should separate elective and nonelective service components. *Dis Colon Rectum*. 2014;57:1098–1104.
17. Due SL, Wattchow DA, Sweeney JL, Milliken L, Luke CG. Colorectal cancer surgery 2000-2008: evaluation of a prospective database. *ANZ J Surg*. 2012;82:412–419.
18. Fohtung RB, Novak E, Rich MW. Effect of new oral anticoagulants on prescribing practices for atrial fibrillation in older adults. *J Am Geriatr Soc*. 2017;65:2405–2412.
19. Yeoh J, Yudi MB, Andrianopoulos N, et al; Melbourne Interventional Group. Evolution of Australian percutaneous coronary intervention (from the Melbourne Interventional Group [MIG] Registry). *Am J Cardiol*. 2017;120:47–54.
20. Bangalore S, Gupta N, Guo Y, Feit F. Trend in the use of drug eluting stents in the United States: insight from over 8.1 million coronary interventions. *Int J Cardiol*. 2014;175:108–119.
21. Pigot F, Juguet F, Bouchard D, Castinel A. Do we have to stop anticoagulant and platelet-inhibitor treatments during proctological surgery? *Colorectal Dis*. 2012;14:1516–1520.
22. Greaves SW, Holubar SD. Preoperative hospitalization is independently associated with increased risk for venous thromboembolism in patients undergoing colorectal surgery: a National Surgical Quality Improvement Program Database Study. *Dis Colon Rectum*. 2015;58:782–791.
23. Ricciardi R, Roberts PL, Read TE, Hall JF, Marcello PW, Schoetz DJ. Which adverse events are associated with mortality and prolonged length of stay following colorectal surgery? *J Gastrointest Surg*. 2013;17:1485–1493.
24. Moghadamyeghaneh Z, Mills SD, Carmichael JC, Pigazzi A, Stamos MJ. Risk factors of postoperative myocardial infarction after colorectal surgeries. *Am Surg*. 2015;81:358–364.
25. Douketis JD, Spyropoulos AC, Spencer FA, et al. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e326S–e350S.
26. Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;130:2215–2245.
27. Iqbal CW, Cima RR, Pemberton JH. Bleeding and thromboembolic outcomes for patients on oral anticoagulation undergoing elective colon and rectal abdominal operations. *J Gastrointest Surg*. 2011;15:2016–2022.
28. Nelson DW, Simianu VV, Bastawrous AL, et al; Colorectal Writing Group for Surgical Care and Outcomes Assessment Program–Comparative Effectiveness Research Translation Network (SCOAP-CERTAIN) Collaborative. Thromboembolic complications and prophylaxis patterns in colorectal surgery. *JAMA Surg*. 2015;150:712–720.
29. Manilich E, Vogel JD, Kiran RP, Church JM, Seyidova-Khoshknabi D, Remzi FH. Key factors associated with postoperative complications in patients undergoing colorectal surgery. *Dis Colon Rectum*. 2013;56:64–71.
30. Del Rio P, Sozzi F, Bertocchi E, et al. Evaluation of surgery risk factor associated to antithrombotic therapy in patients who underwent colorectal surgery. *Ann Ital Chir*. 2016;87:56–60.
31. Fujikawa T, Tanaka A, Abe T, et al. Does antiplatelet therapy affect outcomes of patients receiving abdominal laparoscopic surgery? Lessons from more than 1,000 laparoscopic operations in a single tertiary referral hospital. *J Am Coll Surg*. 2013;217:1044–1053.
32. Hernandez-Boussard TM, McDonald KM, Morrison DE, Rhoads KF. Risks of adverse events in colorectal patients: population-based study. *J Surg Res*. 2016;202:328–334.
33. Ramirez JI, Vassiliu P, Gonzalez-Ruiz C, et al. Sequential compression devices as prophylaxis for venous thromboembolism in high-risk colorectal surgery patients: reconsidering

American Society of Colorectal Surgeons parameters. *Am Surg.* 2003;69:941–945.
34. Bergqvist D. Venous thromboembolism: a review of risk and prevention in colorectal surgery patients. *Dis Colon Rectum.* 2006;49:1620–1628.
35. Sjo OH, Larsen S, Lunde OC, Nesbakken A. Short term outcome after emergency and elective surgery for colon cancer. *Colorectal Dis.* 2009;11:733–739.
36. Morris EJ, Taylor EF, Thomas JD, et al. Thirty-day postoperative mortality after colorectal cancer surgery in England. *Gut.* 2011;60:806–813.
37. Sulu B, Aytac E, Stocchi L, Vogel JD, Kiran RP. The minimally invasive approach is associated with reduced perioperative thromboembolic and bleeding complications for patients receiving preoperative chronic oral anticoagulant therapy who undergo colorectal surgery. *Surg Endosc.* 2013;27:1339–1345.
38. Prytherch DR, Whiteley MS, Higgins B, Weaver PC, Prout WG, Powell SJ. POSSUM and Portsmouth POSSUM for predicting mortality. Physiological and operative severity score for the enumeration of mortality and morbidity. *Br J Surg.* 1998;85:1217–1220.
39. Cohen ME, Liu Y, Ko CY, Hall BL. An examination of American College of Surgeons NSQIP Surgical Risk Calculator Accuracy. *J Am Coll Surg.* 2017;224:787–795.e1.
40. Long G, Suqin S, Li G, Weihong Y, Zhenhu W. Impact of atrial fibrillation on postoperative outcomes after total knee arthroplasty: a retrospective study. *J Orthop Sci.* 2016;21:652–657.
41. Doherty JU, Gluckman TJ, Hucker WJ, et al. 2017 ACC Expert consensus decision pathway for periprocedural management of anticoagulation in patients with nonvalvular atrial fibrillation: a report of the American College of Cardiology Clinical Expert Consensus Document Task Force. *J Am Coll Cardiol.* 2017;69:871–898.
42. Keeling D, Tait RC, Watson H; British Committee of Standards for Haematology. Peri-operative management of anticoagulation and antiplatelet therapy. *Br J Haematol.* 2016;175:602–613.
43. Biteker M, Tekkeşin Aİ, Can MM, Dayan A, Ilhan E, Türkmen FM. Outcome of noncardiac and nonvascular surgery in patients with mechanical heart valves. *Am J Cardiol.* 2012;110:562–567.
44. Wang CZ, Moss J, Yuan CS. Commonly used dietary supplements on coagulation function during surgery. *Medicines (Basel).* 2015;2:157–185.