Open Access Library Journal, 2014, 1, 1-10
Published Online June 2014 in OALib. http://www.oalib.com/journal
http://dx.doi.org/10.4236/oalib.1100474

OALib

Digestive Surgery in Patients Treated with Antiplatelet Agents: How Risky?

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Received 10 April 2014; revised 17 May 2014; accepted 26 May 2014

Abstract

Purpose: To assess the risks of digestive surgery in patients under antiplatelet therapy. Increasing numbers of patients requiring a surgical digestive procedure are on APT. Several studies have shown that APT interruption during the perioperative period increased thrombotic risks, while in the case of maintaining APT, hemorrhagic complications were not increased. Methods: We included prospectively all patients under APT who were operated on from September 1, 2010 to October 31, 2011. Two groups were defined: patients who interrupted APT and those who maintained APT. Three surgical categories were distinguished, with Group I involving parietal surgery, Group II common abdominal surgery, and Group III complex abdominal surgery. The primary endpoints were hemorrhagic and thrombotic risks. Results: Among the 2047 patients undergoing digestive surgery, 130 (6.5%) were on APT, with 32 in Group APT− and 98 in Group APT+. In the overall series, patients taking APT did not receive significantly more transfusions. APT was significantly associated with a higher rate of bleeding complications and transfusion requirement in patients undergoing complex and major abdominal surgery (0% vs. 28%, $p = 0.03$). In Group APT−, only one patient out of 32 (3.1%) suffered from a thrombotic event involving a myocardial infarction. Conclusions: This study suggests stopping APT at least 5 - 7 days in patients undergoing complex and major abdominal surgery. In this other case, APT may be maintained without an increased risk of hemorrhage.

Keywords

Antiplatelet, Digestive Surgery, Hemorraghe, Thrombosis

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How to cite this paper: Menahem, B., Plard, L., Fiant, A.L., Dugue, A., Milliez, P., Alves, A. and Chiche, L. (2014) Digestive Surgery in Patients Treated with Antiplatelet Agents: How Risky? *Open Access Library Journal*, **1**: e474.
http://dx.doi.org/10.4236/oalib.1100474

1. Introduction

Increasing numbers of patients requiring elective surgery are on antiplatelet therapy (APT) either for vascular reasons (history of occlusive arterial disease of the lower limbs, transient ischemic attack, cerebrovascular accident) or for coronary disease with or without stents.

Several retrospective studies as well as a prospective randomized trial [1] have shown that the interruption of APT was associated with an increased risk of thrombosis. Moreover, APT maintenance was not associated with a significantly higher hemorrhagic risk. In addition, there are clear recommendations concerning patients with coronary stents and the management of APT in those patients likely to be operated on [2] [3].

Particularly in terms of hemorrhagic risks, no study to date has examined APT in the setting of digestive surgery alone. Furthermore, although the approach to APT in the case of stents is consensual, the perioperative management of diseases with different etiology appears to be less well codified.

Therefore, we conducted a prospective observational study in order to determine the risks of APT in patients requiring elective digestive surgery.

2. Materials and Methods

Among all patients operated on electively in the department of digestive surgery between September 1, 2010 and October 31, 2011, our study included prospectively only those receiving antiplatelet drugs (aspirin, clopidogrel, or aspirin-clopidogrel combination). Patients on treatment with anticoagulants exclusively or in combination with antiplatelet agents were excluded from the study. Two groups were subsequently defined: patients who interrupted APT (Group APT−) and those who maintained ATP (Group APT+).

All patients underwent a preoperative anesthesia consultation during which the following data pertaining to patient history, particularly cardiovascular history, was collected: type of stent and date of intervention, where applicable; American Society of Anesthesiologists (ASA) score; type of antiplatelet drugs; decision whether to interrupt APT or not; time required in the case of preoperative APT interruption. The intensive care anesthetist determined the approach to APT in line with the recommendations and in consultation with the surgeon. We considered APT to be interrupted preoperatively when the time between the interruption and surgery was at least 3 days.

Patient data relating to the type of surgical intervention and approach (laparotomy, laparoscopy) as well as to the pathology (cancerous, benign, or inflammatory) was collected. Patients were then classified into three surgical categories. Group I comprised patients undergoing parietal (hernia surgery and incisional hernia repair) and proctological surgery; Group II included patients undergoing common intra-abdominal surgery (cholecystectomy, biliary tract surgery, right or left colectomy, sleeve gastrectomy, surgery of static disorders, small bowel resection, and endocrine surgery); finally, Group III comprised patients undergoing major intra-abdominal surgery (esophagus and stomach surgery, liver and pancreatic surgery, proctectomy, subtotal colectomy, gastric bypass, and complex bile duct surgery).

Regarding per- and post-operative data, the major criteria studied were related to hemorrhagic and thrombotic risks, namely, the amount of blood loss during the intervention, need for a transfusion of labile blood products (red blood cells, fresh frozen plasma, or platelets), and preoperative (Day [D]-1) and postoperative (D1) platelet levels. For transfusions, the level of hemoglobin was set at 10 g/dL in patients with high cardiovascular risk. As to postoperative data, we recorded postoperative blood loss, the aspect and duration of post-operative drainage, need for a transfusion of labile blood products, and finally, the development of thrombosis within 1 month following the intervention. Patients systematically underwent a postoperative consultation, involving an interview, clinical examination, and complementary investigations in the case of potential thrombotic complications.

Finally, the following secondary criteria were recorded: duration of operation, duration of hospitalization, and postoperative complications according to the Clavien-Dindo classification.

The times to APT resumption and to initiating anticoagulant therapy at a preventive dose were also recorded.

3. Statistical Analysis

Variables were expressed as mean ± standard deviation, median [interquartile range], or number of patients (percentage) according to the type. Data at inclusion as well as per- and post-surgical data was compared between the two groups (APT interruption or maintenance) using Chi-squared or Fisher's exact test for qualitative

variables, and Student's t or Manny-Whitney test for quantitative variables. Statistical analyses and figures were generated using the R software, version 2.13.1.

4. Results

In the period studied, 2047 patients were electively operated on in our department of digestive surgery. Among them, 130 patients were taking at least one APT. The main characteristics of the patient population are given in **Table 1**. The cohort comprised 46 women and 84 men, with a mean age of 67.5 years. The majority of patients (n = 125) were classified as ASA 2-3. As to the types of APT, 84 patients received aspirin preoperatively, 31 clopidogrel, 13 an aspirin-clopidogrel combination, and two prasugrel. For 30 patients, clopidogrel or prasugrel was replaced by aspirin. The main indications for APT were due to a cardiac etiology without stents in 56 patients (primary prevention, angina, persistent ductus arteriosus, heart transplant, and myocardial infarction without angioplasty and stent), the presence of stents in 32 patients, peripheral vascular disease in 22, and neurological causes in 10.

As to surgical interventions, 86 patients were operated on for a benign pathology and 44 for cancer. There were 35 patients in surgical Group I, 53 in Group II, and 42 in Group III. In terms of the maintenance or interruption of APT, Group APT+ comprised 98 patients who continued APT with 75mg aspirin, including those where clopidogrel or prasugrel was replaced by aspirin, while Group APT− comprised 32 patients who interrupted APT.

4.1. Preoperative Data for Groups APT− and APT+

The two groups were similar, particularly in terms of gender, age, ASA stage, pathology, surgical grade, and surgical approach (p = 012, 0.24, 0.13, 0.094, 0.64, 0.089, and 0.059, respectively), although there was a trend towards a higher rate of the laparotomy approaches in patients maintaining APT (**Table 1**).

Table 1. Patient characteristics for the series.

	Group APT− n = 32 (%)	Group APT+ n = 98 (%)	p-value
Gender	Female 15/Male 17	Female 31/Male 67	0.12
Age	65 [58.75 - 73.25]	67.5 [62 - 76.75]	0.24
ASA score			
1	1 (3.1)	0 (0)	
2	20 (62.5)	48 (49)	0.13
3	11 (34.4)	46 (46.9)	
4	0 (0)	4 (4.1)	
APT			
Aspirin	17 (53.1)	67 (68.4)	
Aspirin + clopidogrel	2 (6.3)	11 (11.2)	0.094
Clopidogrel	13 (40.6)	18 (18.4)	
Prasugrel	0 (0)	2 (2)	
Pathology			
Benign	23 (71.9)	62 (63.3)	0.64
Cancer	9 (28.1)	35 (35.7)	
Inflammatory	0 (0)	1 (1)	
Surgical grade			
I	5 (15.6)	30 (30.6)	0.089
II	12 (37.5)	41 (41.8)	
III	15 (46.9)	27 (27.6)	
Surgical procedure			
Cervicotomy	0 (0)	3 (3)	
Coelioscopy	12 (37.5)	27 (27.6)	0.059
Laparotomy	18 (56.3)	68 (69.4)	
Proctology	2 (6.2)	0 (0)	

APT: antiplatelet therapy; ASA: American Society of Anesthesiologists.

4.2. Per- and Postoperative Data

4.2.1. Main Criteria: Hemorrhage and Thrombosis

Data from the per-operative period is provided in **Table 2**. In the overall series, patients operated on while continuing APT did not require significantly more transfusions and they did not suffer more blood loss. A summary of the hemorrhagic complications is given in **Table 3**. Nevertheless, the only patients receiving transfusions in the peroperative period were under APT. Particularly in terms of Group III patients who underwent major surgery, the patients under APT experienced more hemorrhagic complications and received significantly more transfusions ($p = 0.03$) (**Table 4**). Moreover, in the entire patient cohort, postoperative platelet levels were significantly higher in patients operated on under APT ($p = 0.048$).

Postoperative data for the two groups is summarized in **Table 5**. Patients who maintained APT did not undergo significantly more drainage procedures than those who interrupted APT ($p = 0.54$). The aspect of the drainage fluid was identical in the both groups at the three sampling dates, ($p = 1.0$, 0.87, and 0.22 for D1, D3, and D7, respectively) (**Table 5**). Examining the duration of drainages, the curves were found to be superimposable in the two groups ($p = 0.5$) (**Figure 1**).

In the group interrupting APT, only one patient experienced a thrombotic episode, notably myocardial infarction. The duration of hospitalization was identical in both groups ($p = 0.43$).

4.2.2. Other Study Criteria

The duration of surgery was comparable in the two groups ($p = 0.38$).

There were not significantly more Clavien Grade > IIIa complications in Group APT+ compared with Group APT− ($p = 0.72$). A total of 23 events were recorded, with 18 in patients maintaining APT (Group APT+) versus five in those interrupting APT (Group APT−). In addition, the rates for revision surgery and intensive care stays were not significantly higher in either of the two groups.

Nonetheless, in our patient cohort, three deaths were reported, all of which affected patients from Group APT+. One patient presented major cardiac failure, another acute respiratory distress with aspiration pneumonia, while the third presented symptomatic evisceration on postoperative peritonitis secondary to a fistula due to perianastomotic hematoma. The main characteristics of the deceased patients are given in **Table 6**.

Table 2. Per-operative data.

	Group APT− $n = 32$ (%)	Group APT+ $n = 98$ (%)	p-value
Duration of intervention (min)	120 [60 - 150]	85 [60 - 147.5]	0.38
Transfusion			
No	32 (100)	93 (94.9)	0.33
Yes	0 (0)	5 (5.1)	
Volume of blood loss (mL)			
Mean	169	129	0.93
Median (5 - 95ème percentile)	0 [0 - 350]	0 [0 - 150]	
Maximum	1300	1300	
Number of red blood cell packs transfused	0	10 in 5 patients	0.19
Preoperative platelet count	187,000 [167,000 - 203,000]	200,000 [178,000 - 221,500]	0.096
Postoperative platelet count	197,000 [180,000 - 215,000]	212,000 [187,500 - 231,500]	0.048

Table 3. Hemorrhagic complications.

	Group APT−	Group APT+	p-value
Type of complications			
Parietal wall hematoma	1	3	
Perinastomotic hematoma	0	3	0.50
Collection hepatectomy slice	1	0	
Hemobilia	0	1	

Table 4. Pre- and postoperative data for Group III patients.

	Group APT− (17)	Group APT+ (25)	p-value
Age			
ASA score			
1	1	0	
2	8	12	0.22
3	8	9	
4	0	4	
APT			
Aspirin	12	10	
Aspirin + clopidogrel	4	9	0.31
Clopidogrel	1	4	
Prasugrel	0	2	
Reason for APT			
Stent	0	10	
Cardiac without stent	13	11	0.0070
Neurological	2	2	
Vascular	2	2	
Perioperative transfusion			
Yes	0	5	0.070
No	17	20	
Perioperative red blood cell packs			
Yes	0	10	0.0026
No	17	15	
Postoperative transfusion			
Yes	0	7	0.030
No	17	18	
Postoperative red blood cell packs			
Yes	0	11	0.0012
No	17	14	
Drainage			
Yes	17	23	0.51
No	0	2	
Clavien classification			
I	7	12	
II	5	5	
IIIa	2	4	0.94
IIIb	1	2	
Iva	2	2	
IVb	0	0	
V	0	0	

APT: antiplatelet therapy; ASA: American Society of Anesthesiologists.

When the characteristics of patients presenting a postoperative event (Clavien IIIa) were compared with those who did not, the presence of cancer was found to be a significant factor ($p < 0.00011$), whereas APT was not (**Table 7**).

When considering the rate of events in terms of the three predefined surgical groups, we observed that surgical category did not play a statistically significant role (**Figure 2**), and nor did ASA classification. It should be noted; however, that complications were observed in all ASA Grade 4 patients (**Figure 3**).

5. Discussion

Over the last few years, there has been a significant improvement in the management of cardiovascular diseases,

Table 5. Postoperative data.

	Group 1 n = 32 (%)	Group 2 n = 98 (%)	P-value
Drainage			
No	14 (43.75)	49 (50)	0.54
Yes	18 (56.25)	49 (50)	
Appearance of drainage			
Day 1: Hematic	16(88.9)	41 (91.1)	
Serous	2(11.1)	4 (8.9)	1
Day 3: Hematic	9 (50)	23 (52.3)	
Serous	9 (50)	21 (47.7)	0.87
Day 7: Hematic	0 (0)	4 (25)	
Foul	1(14.3)	0 (0)	0.22
Serous	6 (85.7)	12 (75)	
Duration of drainage(days)	6 [5-7.75]	6 [5 - 7]	0.33
Intensive care stay			
No	30 (93.75)	91 (93.5)	1
Yes	2 (6.25)	7 (6.5)	
Duration of intensive care stay (days)	21 [14-28]	10 [7.75 - 12.25]	0.74
Volume of blood loss (mL)			
Mean	9.3	31.6	0.68
Median (5-95ème percentile)	0 [0 - 0]	0 [0 - 0]	
Maximum	200	900	
Number of red blood cell packs transfused			
Mean	0.05	0.16	0.42
Median (5 - 95ème percentile)	1	8	
Maximum	2	15	
Clavien classification			
I	20 (62.5)	69 (70.4)	
II	7 (21.9)	11 (11.2)	
IIIa	2 (6.3)	10 (10.2)	0.47
IIIb	1 (3.1)	2 (2)	
IVa	2 (6.3)	3 (3.1)	
V	0 (0)	3 (3.1)	
Number of events (>IIIa)			
No	27 (84.4)	80 (81.7)	0.72
Yes	5 (15.6)	18 (18.3)	
Duration of hospitalization	7 [4 - 11]	6 [4 - 10]	0.43
Revision surgery			
No	32 (100)	93 (94.9)	
Yes	0 (0)	5(5.1)	
Postoperative thrombosis			
No	31 (96.9)	94 (100)	
Yes	1 (3.1)	0 (0)	

especially coronary disease with the rise of interventional treatments (coronary stents and associated APT). Today, it is no longer rare to operate on a patient with a more or less severe cardiac history in whom APT was initiated.

In our series, 6.5% of the operated population was under APT, which is in line with the 5% rate reported in the literature [4].

Hemorrhagic risk is a major preoccupation of the digestive surgeon, particularly in difficult surgical procedures (*i.e.*, hepatectomy, pancreatectomy, esophagectomy, or proctectomy). The use of antiplatelet agents reinforces this concern, often leading to the interruption of APT. However, this interruption exposes the patient to an

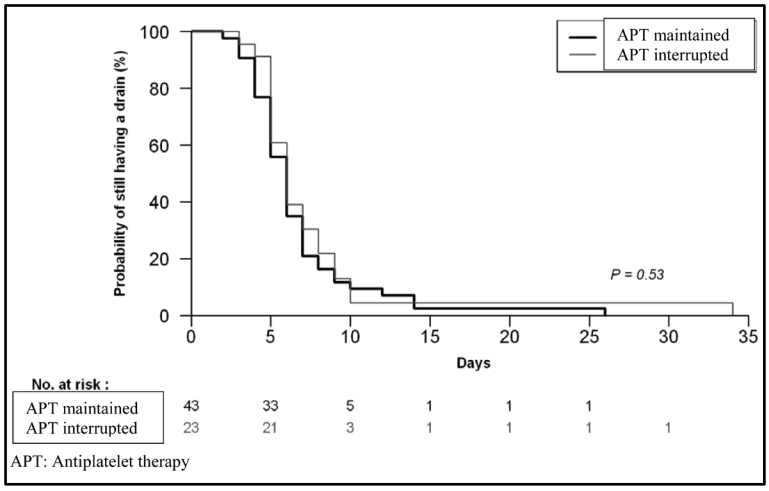

Figure 1. Duration of surgical drainage in the two groups.

Table 6. Postoperative data.

Patient	Age	ASA score	Stent	Pathology	Intervention type (surgical category)	Perioperative transfusion	Drainage	Cause of death	Revision surgery
No 1	46	4	no	Cancer	Surrenalectomy (II)	No	Yes	Cardiac failure	No
No 2	79	3	no	Cancer	Left colectomy (II)	No	Yes	Acute respiratory distress with aspiration pneumonia	No
No 3	74	3	yes	Benign	Left colectomy (II)	No	Yes	Postoperative fistula secondary to perianastomotic hematoma (septic shock)	Yes

Table 7. Factors favoring the occurrence of postoperative events (Clavien ≥ IIIa).

	Clavien < IIIa n = 101 (%)	Clavien ≥ IIIa n = 23 (%)	P value
Age (years)	67.9	65.2	0.30
Antiplatelet type			
Aspirin	68 (63.6)	16 (69.6)	
Aspirin + clopidogrel	12 (11.2)	1 (4.3)	0.43
Clopidogrel	1 (0.9)	1 (4.3)	
Prasugrel	26 (24.3)	5 (21.8)	
Pathology			
Cancer	29 (27.1)	15 (65.2)	0.00011
Benign	78 (72.9)	7 (30.4)	
Inflammatory	0 (0)	1 (4.4)	
History			
Cardiac	55 (51.4)	12 (52.2)	
Neurological	10 (9.4)	1 (4.4)	0.58
Stent	23 (21.5)	7 (30.4)	
Vascular	20 (18.7)	3 (13)	

equally dangerous thrombotic risk, which is further increased in the postoperative setting by a more or less marked inflammatory reaction. This theoretical data is supported by the literature [5]-[10]. The study of Collet *et al.* [11] revealed the risk of acute coronary syndrome from interrupting APT prior to surgery. Other cohort studies observed various thrombotic events (stroke, acute ischemia of the limbs, etc.) that were associated with stopping APT [12]-[16]. A randomized trial investigated the impact of the perioperative management of APT,

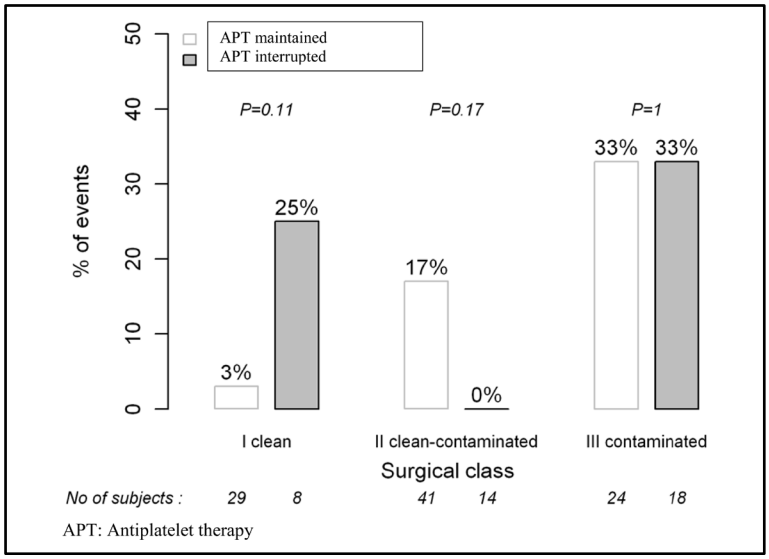

Figure 2. Number of events in relation to surgical grade.

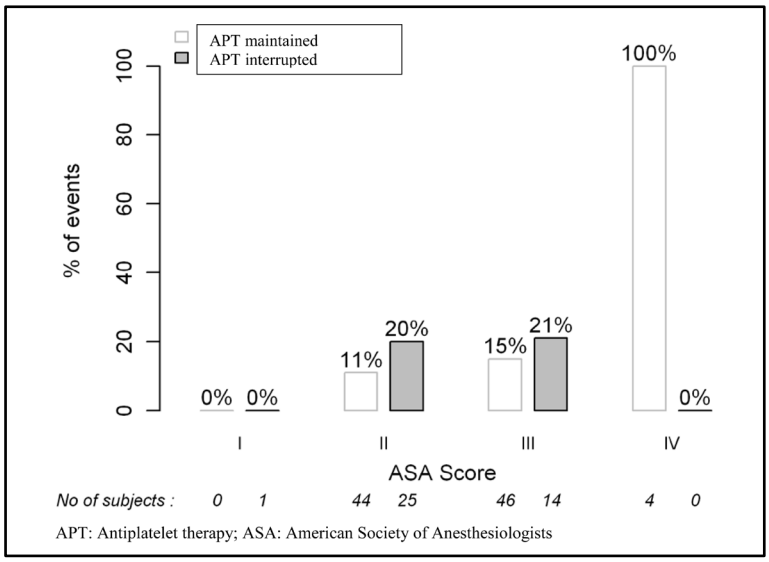

Figure 3. Number of events in relation to American Society of Anesthesiologists' score.

showing a reduction in thrombotic cardiovascular events in the group receiving aspiring. In contrast, no significant differences were found for perioperative hemorrhagic events [17]. In terms of patients with stents, a study published in 2000 reported on a cohort of patients undergoing emergency surgery in the weeks following the positioning of a bare-metal stent. In these patients, the postoperative mortality rate was close to 20% due to hemorrhagic or thrombotic events [18].

To date, few studies have evaluated the surgical risk of hemorrhage associated with the perioperative use of APT, particularly in the setting of digestive surgery. Burger *et al.* conducted a meta-analysis of 41 studies comprising 49,950 patients, with 14,981 taking aspirin. The frequency of hemorrhagic complications was found to vary from 0% (cataract) to 75% (prostate biopsy) depending on the procedure performed [19].

Our series, which was the first to study digestive surgery specifically, confirmed the absence of increased risk in terms of per- or postoperative hemorrhages for patients undergoing surgery while being treated with anti-platelet agents. Although, patients on anti-platelet therapy undergoing complex and major abdominal surgery (Group III) have a significantly higher rate of bleeding complications and transfusion requirement, a multifac-

torial analysis of the entire series revealed that the use of antiplatelet agents was not significantly associated with an increase in morbi-mortality. Only cancer played a significant role.

In our series, the decision was taken to interrupt APT in 25% of all patients prior to surgery at the cost of one successfully treated thrombosis case, whereas in the group where APT was maintained, no thrombotic events were recorded. The absence of increased morbidity in association with the continuation of antiplatelet agents supports the recommendation of not stopping APT whatever the pathology.

Finally, in a certain number of patients, clopidogrel or prasugrel treatment was replaced by aspirin, which was not related to any adverse event, which would further validate such an approach.

The mortality rate was three out of 130 patients (2.3%), which was rather low given that 42 of these patients (32.3%) underwent major surgery and that the overall patient population exhibited considerable cardiovascular risk factors (61 patients or 46.9% with an ASA score > 2).

Limitations of the current study include not only the limited number of patients but also the absence of a true control group. Although the power is limited, there is no significant difference between two groups, according to age, sex, operation, and study period. To our knowledge, the only randomized study, conducted for all types of surgery, had to be prematurely stopped due to the insufficient patient inclusions (1).

To conclude, the use of APT was not associated with increased morbi-mortality in the setting of elective digestive surgery, which ranged from simple to more complex procedures. Maintaining APT in coronary patients prevented thrombotic risks without increasing risk of hemorrhage, expect perhaps in the case of major interventions, which resulted in higher transfusion rates without corresponding increases in morbi-mortality rates. We suggest stopping anti-platelet therapy at least 5 - 7 days in this cohort of patients undergoing major or complex surgery.

It is therefore possible, even desirable, to maintain APT in patients requiring this treatment for any reason and for any procedure in digestive surgery.

Conflict of Interest Statement

Menahem B and other co-authors have no conflict of interest.

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