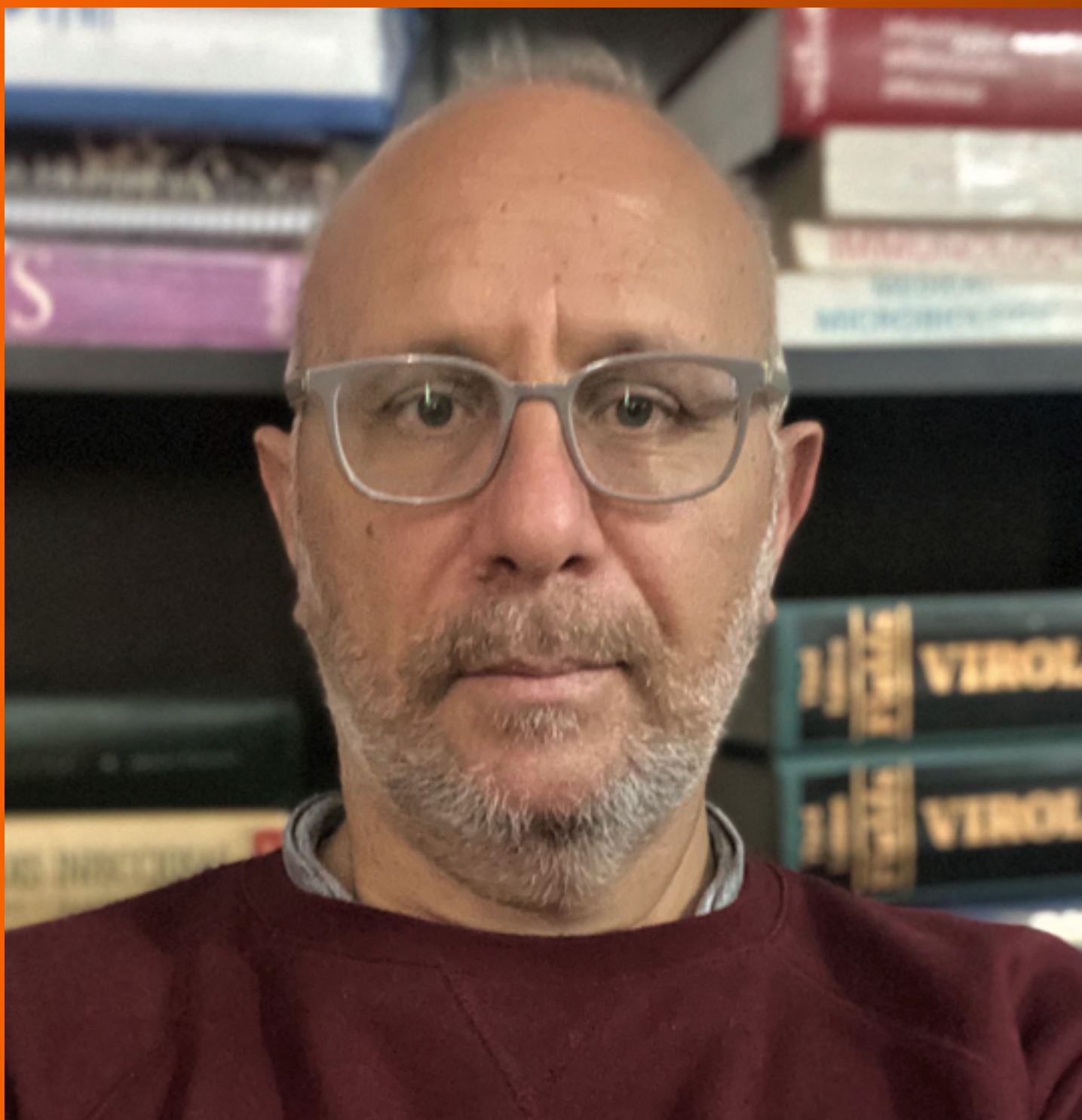


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# Safety of liver resection in patients receiving antithrombotic therapy: A systematic review of the literature

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## Abstract

### BACKGROUND

Little is unknown about the effect of chronic antithrombotic therapy (ATT) on bleeding complication during or after hepatectomy. In addition, the safety and effectiveness of chemical prevention for venous thromboembolism (VTE) is still controversial.

### AIM

To clarify the effect of ATT on thromboembolism and bleeding after liver resection.

### METHODS

Articles published between 2011 and 2020 were searched from Google Scholar and PubMed, and after careful reviewing of all studies, studies concerning ATT and liver resection were included. Data such as study design, type of surgery, type of antithrombotic agents, and surgical outcome were extracted from the studies.

### RESULTS

Sixteen published articles, including a total of 8300 patients who underwent hepatectomy, were eligible for inclusion in the current review. All studies regarding patients undergoing chronic ATT showed that hepatectomy can be performed safely, and three studies have also shown the safety and efficacy of preoperative continuation of aspirin. Regarding chemical prevention for VTE, some studies have shown a potentially high risk of bleeding complications in patients undergoing chemical thromboprophylaxis; however, its efficacy against VTE has not been shown statistically, especially among Asian patients.

### CONCLUSION

Hepatectomy in patients with chronic ATT can be performed safely without increasing the incidence of bleeding complications, but the safety and effectiveness of chemical thromboprophylaxis against VTE during liver resection is still

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controversial, especially in the Asian population. Establishing a clear protocol or guideline requires further research using reliable studies with good design.

**Key Words:** Liver resection; Bleeding complication; Antithrombotic therapy; Thromboembolic complication; Thromboprophylaxis

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**Core Tip:** A total of 16 published articles on antithrombotic therapy and hepatectomy have been reviewed systematically. The articles showed that the risk of thromboembolic and/or bleeding events in patients with continued preoperative aspirin was not different from those in patients with no antithrombotic or interrupted antiplatelet drugs, although pharmacological prophylaxis of venous thromboembolism is still controversial, especially when performing hepatectomy in Asian patient populations.

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## INTRODUCTION

Heart disease, cerebrovascular disease, and cancer are the three leading causes of death in the world. With the aging of society in recent years, patients with cerebrovascular and/or cardiovascular diseases are increasingly required to undergo non-cardiac surgery. Most of these patients receive antithrombotic therapy (ATT) in order to prevent thromboembolic events. The perioperative period in patients undergoing ATT is at high risk for both thromboembolism and bleeding, which can be very cumbersome for surgeons[1-3].

ATT is classified into two types of drugs: Antiplatelet drugs and anticoagulants. Antiplatelet drugs are frequently used for prevention of cerebrovascular or cardiovascular diseases, and can prevent thromboembolism by reduction of platelet aggregation. Antiplatelet agents include thienopyridine (e.g., clopidogrel, prasugrel, or ticlopidine), aspirin, and type III phosphodiesterase inhibitor (e.g., cilostazol)[4]. Anticoagulants, on the other hand, prevent coagulation of blood by suppressing the coagulation cascade. They are usually used for deep vein thrombosis, atrial fibrillation, acute coronary syndrome, and cardiac endoprostheses. Anticoagulants are also used for perioperative thromboprophylaxis of venous thromboembolism (VTE). Oral anticoagulants include warfarin, factor Xa inhibitors (e.g., apixaban, rivaroxaban, edoxaban), and direct thrombin inhibitors (e.g., dabigatran)[4,5]. The latter two types are called direct-acting oral anticoagulants (DOACs) or non-vitamin K antagonist oral anticoagulants (NOACs), and now increasingly used. Table 1 summarizes the type and the duration of action of each antithrombotic agent.

Minimizing intraoperative and postoperative bleeding complication is an important challenges in liver resection, and several technical improvement has been demonstrated, such as Pringle maneuver or sustained low central venous pressure (CVP)[6-8]. However, sustained low CVP during hepatectomy may increase the risk of thrombosis in ATT-received patients. Rigorous perioperative management of antithrombotics and strict hemostasis are requisite to prevent both thromboembolic and bleeding events. To date, there has been no consensus on the safety of hepatectomy and proper perioperative management of antithrombotics in patients undergoing ATT, and the optimal thrombotic prophylaxis for VTE remains unknown.

The aim of the current review is to clarify the effect of ATT on thromboembolic and bleeding complications in liver resection.

**Table 1** Types, specific agents, and acting duration of commonly used antithrombotic drugs

Class of agents	Type	Specific agents	Duration of action
Antiplatelets	Thienopyridines	Clopidogrel (Plavix), ticlopidine (Panardine), prasugrel (Effient), ticagrelor (Brilinta)	5-7 d <sup>1</sup>
	Type III PDE inhibitor	Cilostazol (Pretal)	2 d
	Acetylsalicylic acid	Aspirin	7-10 d
	Other NSAIDs	Ibuprofen (Brufen, Advil), loxoprofen (Loxonin), diclofenac (Voltaren) <i>etc.</i>	Varies
Anticoagulants	Heparin (unfractionated)	Heparin	1-2 h
	Heparin (LMWH)	Dalteparin (Fragmin iv), enoxaparin (Clexane, s.c.), nadroparin (s.c.)	6-12 h <sup>2</sup>
	Vitamin K antagonist	Warfarin (Coumadin)	5 d
	Factor Xa inhibitor (s.c.)	Fondaparinux (Arixtra)	1-1.5 d
	DOACs		
	Direct thrombin inhibitor	Dabigatran (Pradaxa)	1-2 d
	Factor Xa inhibitors	Rivaroxaban (Xarelto), apixaban (Eliquis), edoxaban (Lixiana)	1-2 d

<sup>1</sup>In ticlopidine, duration of action is 10-14 d.

<sup>2</sup>In dalteparin, duration of action is 2-4 h. PDE: Phosphodiesterase; NSAID: Non-steroidal anti-inflammatory drug; DOAC: Direct-acting oral anticoagulant.

## MATERIALS AND METHODS

Papers published between 2011 and 2020, which were written in English, were collected from Google Scholar and PubMed. The following key words were adopted for searching: “liver resection or hepatectomy” AND “antithrombotic therapy, aspirin, clopidogrel, antiplatelet therapy, anticoagulation, warfarin, DOAC, or NOAC” AND “bleeding or hemorrhage”. Only articles which were published in the peer review journal were included in the current review. Eligible study types include prospective cohort studies, retrospective cohort studies, randomized clinical trials, or case-control studies, but case reports, reviews, or guidelines were not included.

Duplicate articles were first removed, and then articles were excluded systematically by reviewing each study carefully. Eligible articles were finally determined after the quality of each study was evaluated according to the study design. Complete data, including study design, sample size, publication year, type of surgery, type of antithrombotics, and surgical outcome, were extracted from the studies. Bleeding events included two categories; postoperative bleeding complications (BC) and increased surgical blood loss (SBL).

## RESULTS

### Study characteristics

Collection and screening of research were performed from December 2020 to January 2021 (Figure 1). The current review included a total of 16 published articles, with 8300 patients undergoing hepatectomy. There were no randomized clinical trials, but only case-control studies or cohort studies. Ten of the 16 studies were observational cohort studies, and only one was prospective studies; 6 studies were on the management of patients with chronic ATT[9-14] (Table 2) and 10 studies were on the pharmacological prevention for VTE (Table 3)[15-24]. Among studies regarding the management of chronic ATT, two studies were investigated using the propensity score matching method[9,12]. Nine of the 10 articles on pharmacological prophylaxis for VTE were observational studies; one was multicenter prospective and 8 were retrospective cohort studies.

Of the 6 studies on the management of patients receiving chronic ATT, three focused on the safety of continued perioperative aspirin during hepatectomy[9,12,13]. In 10 studies on pharmacological prevention for VTE, patients were primarily controlled by low-molecular-weight heparin during the perioperative period.

**Table 2** Reported data concerning bleeding complications of liver resection in patients with antithrombotic therapy

Ref.	Year, type	Surgery type	Drug use and exposure	Bleeding events	TE, mortality
Naito <i>et al</i> [9]	2020, PSM	Liver resection ( <i>n</i> = 425)	Patients with continued ASA ( <i>n</i> = 63); Patients not on continued APT (control, <i>n</i> = 362); Post-PSM: 63 <i>vs</i> 63 matched cases	BC 4.8% in continued ASA <i>vs</i> 4.8% in control ( <i>P</i> = 1.00); SBL was identical ( <i>P</i> = 0.54)	TE 1.6% in continued ASA <i>vs</i> 4.8% in control ( <i>P</i> = 0.62); Mortality 1.6% <i>vs</i> 1.6% ( <i>P</i> = 1.00)
Fujikawa <i>et al</i> [10]	2017, RCS	Liver resection ( <i>n</i> = 258) including 77 laparoscopic liver resection	Patients with ATT ( <i>n</i> = 100); Patients without ATT (control; <i>n</i> = 158)	BC 3.0% in ATT <i>vs</i> 3.8% in control ( <i>P</i> > 0.05); No BC in laparoscopic surgery; SBL was identical	TE 1.0% <i>vs</i> 1.3% ( <i>P</i> > 0.05); No TE in laparoscopic surgery; Mortality 1.0% <i>vs</i> 0% ( <i>P</i> = 0.350)
Ishida <i>et al</i> [11]	2017, CCS	HBP surgery ( <i>n</i> = 886) including 520 liver resection	Patients with ACT ( <i>n</i> = 39); Patients with APT ( <i>n</i> = 77); Patients without ATT (control, <i>n</i> = 770)	BC 0.0% in ACT <i>vs</i> 1.3% in APT <i>vs</i> 3.4% in control ( <i>P</i> = 0.32); SBL was identical ( <i>P</i> = 0.99)	TE 0% <i>vs</i> 1.3% <i>vs</i> 0.8% ( <i>P</i> = 0.75); Mortality 0% <i>vs</i> 0% <i>vs</i> 1.2% ( <i>P</i> = 0.50)
Gelli <i>et al</i> [12]	2018, PSM	Liver resection ( <i>n</i> = 1803)	Patients with continued ASA ( <i>n</i> = 118); Patients not on continued APT (control, <i>n</i> = 1685); Post-PSM: 108 <i>vs</i> 108 matched cases	Overall BC 10.2% in continued ASA <i>vs</i> 12.0% in control ( <i>P</i> > 0.05); Major BC 6.5% <i>vs</i> 5.6% ( <i>P</i> > 0.05)	Mortality 5.6% <i>vs</i> 4.6% ( <i>P</i> > 0.05)
Monden <i>et al</i> [13]	2017, CCS	Liver resection ( <i>n</i> = 378)	Patients with continued ASA ( <i>n</i> = 31); Patients not on continued APT (control, <i>n</i> = 347)	Major BC 0% in continued ASA <i>vs</i> 0.3% in control ( <i>P</i> > 0.05); SBL 450 mL <i>vs</i> 360 mL ( <i>P</i> = 0.735)	TE 3.2% <i>vs</i> 0% ( <i>P</i> > 0.05); Mortality 3.2% <i>vs</i> 0.9% ( <i>P</i> = 0.291)
Fujikawa <i>et al</i> [14]	2019, CCS	HBP surgery ( <i>n</i> = 105) including 37 liver resection	Patients with DOAC ( <i>n</i> = 35); Patients with WF (control, <i>n</i> = 80)	BC 2.9% in DOAC <i>vs</i> 0% in WF ( <i>P</i> = 0.304); SBL was identical ( <i>P</i> = 0.782)	No TE event in both groups; No mortality in both groups

RCS: Retrospective cohort study; mRCS: Multicenter retrospective cohort study; CCS: Case-control study; PSM: Case-control study with propensity-score matching; ATT: Antithrombotic therapy; APT: Antiplatelet therapy; ACT: Anticoagulation therapy; ASA: Aspirin; LAP: Laparoscopic; SBL: Surgical blood loss; BC: Postoperative bleeding complication; TE: Thromboembolism.

### Safety of liver resection in patients receiving chronic ATT

In all 6 studies regarding the management of ATT-received patients, the authors generally demonstrated the safety of hepatectomy even in patients with chronic ATT. Among patients undergoing chronic ATT, the rates of major and overall BCs were 0%-6.5% and 1.3%-10.2%, retrospectively; the incidence of postoperative thromboembolic complication was 0%-3.2%. In all included studies, the rates of bleeding and thromboembolic complications between ATT-received patients and those without ATT were not significantly different (Table 2).

The safety of continued perioperative aspirin during hepatectomy was focused on in 3 case-control studies, including 2 studies using the propensity score matching method[9,12,13]. All three studies have shown that continued preoperative aspirin is not associated with increased intraoperative and postoperative bleeding events in patients with chronic antiplatelet therapy during or after hepatectomy. These studies suggested that continued preoperative aspirin in patients with chronic antiplatelet therapy is safe and should be considered preferable even when performing hepatectomy.

### Safety of chemical thromboprophylaxis for VTE

In 10 articles regarding pharmacological prevention for VTE, 9 were observational cohort studies, including 8 retrospective and 1 prospective studies. The included studies generally showed potentially elevated risks of BC in patients receiving pharmacological thromboprophylaxis; the rates of overall and major BCs in the group receiving pharmacological thromboprophylaxis were 5.2%-26.6% and 1.6%-10.9%, respectively. Concerning the efficacy of thromboprophylaxis, 3 studies showed that the occurrence of VTE in patients receiving pharmacological thromboprophylaxis was significantly lower compared to the control group[15,20,24], but the other 7 studies, including 2 studies from Japan[18,19] did not demonstrate its effectiveness due to the small sample size (Table 3).

Analysis of these studies have demonstrated a potentially high risk of postoperative bleeding in patients undergoing pharmacological prevention for VTE, but the efficacy of pharmacological thromboprophylaxis after hepatectomy has not been shown, especially in Asian patient population.

**Table 3 Reported data concerning the safety of thromboprophylaxis for venous thromboembolism during liver resection**

Ref.	Year, type	Surgery type	Drug use and exposure	Bleeding events	TE, mortality
Ainoa <i>et al</i> [15]	2020, RCS	Liver resection ( <i>n</i> = 512)	Patients with preop TP ( <i>n</i> = 253); Patients with postop TP (control, <i>n</i> = 259)	BC 15.0% in preop TP <i>vs</i> 13.9% in control ( <i>P</i> > 0.05)	VTE 1.2% <i>vs</i> 9.7% ( <i>P</i> < 0.0001); PE 1.2% <i>vs</i> 9.3% ( <i>P</i> < 0.0001)
Ejaz <i>et al</i> [16]	2014, RCS	Liver resection ( <i>n</i> = 599)	Patients with TP ( <i>n</i> = 454); Patients without TP (control, <i>n</i> = 145)	Not mentioned	VTE 5.1% in TP <i>vs</i> 3.4% in control ( <i>P</i> = 0.42)
Nathan <i>et al</i> [17]	2014, RCS	Liver resection ( <i>n</i> = 2147)	Patients with early TP ( <i>n</i> = 1295); Patients with late or no TP (control, <i>n</i> = 852)	Major BC 1.7% in early TP <i>vs</i> 1.6% in control ( <i>P</i> > 0.05)	VTE 2.1% <i>vs</i> 3.3% ( <i>P</i> > 0.05); Overall mortality 1.9%
Eguchi <i>et al</i> [18]	2020, mPCS	Major HBP surgery ( <i>n</i> = 133) including 74 liver resection	Patients with TP [LMWH (enoxaparin), <i>n</i> = 133, single arm]	Major BC 2.3%; Minor BC 5.2%	No PE event in whole cohort
Hayashi <i>et al</i> [19]	2014, RCS	Major HBP surgery ( <i>n</i> = 349) including 138 liver resection	Patients with TP ( <i>n</i> = 207); Patients without TP (control, <i>n</i> = 142)	BC 26.6% in TP <i>vs</i> 8.5% in control ( <i>P</i> < 0.05); Rate of major BC is identical	VTE 2.9% <i>vs</i> 7.7% ( <i>P</i> > 0.05)
Wang <i>et al</i> [20]	2018, CCS	Liver resection ( <i>n</i> = 233)	Patients with TP (LMWH, <i>n</i> = 117); Patients without TP (control, <i>n</i> = 116)	Not mentioned	VTE 0.85% in TP <i>vs</i> 13.8% ( <i>P</i> < 0.05)
Kim <i>et al</i> [21]	2017, RCS	Liver resection ( <i>n</i> = 124)	Patients with extended TP [LMWH (enoxaparin), <i>n</i> = 124, single arm]	BC 1.6% in extended TP	No VTE in whole cohort
Doughtie <i>et al</i> [22]	2014, RCS	Major HBP surgery ( <i>n</i> = 223) including 110 liver resection	Patients with preop TP (LMWH, <i>n</i> = 93); Patients without preop TP (control, <i>n</i> = 130)	Major BC 10.9% in preop TP <i>vs</i> 3.1% in control ( <i>P</i> = 0.026); SBL was identical	VTE 1.1% <i>vs</i> 6.1% ( <i>P</i> = 0.05)
Melloul <i>et al</i> [23]	2012, RCS	Liver resection ( <i>n</i> = 410)	Patients with TP ( <i>n</i> = 410, single arm)	Not mentioned	PE 6% (24/410) in TP
Reddy <i>et al</i> [24]	2011, RCS	Major liver resection ( <i>n</i> = 419)	Patients with TP ( <i>n</i> = 275); Patients without TP (control, <i>n</i> = 144)	RBC transfusion rate 35.0% in TP <i>vs</i> 30.6% in control ( <i>P</i> = 0.36)	CR-VTE 2.2% in TP <i>vs</i> 6.3% in control ( <i>P</i> = 0.03); PE 2.2% <i>vs</i> 4.2% ( <i>P</i> = 0.35)

mRCT: Multicenter randomized controlled trial; RCS: Retrospective cohort study; mRCS: multicenter retrospective cohort study; LMWH: Low-molecular-weight heparin; TP: Thromboprophylaxis; LAP: Laparoscopic; CR: Clinically relevant; BC: Postoperative bleeding complication; VTE: Venous thromboembolism; PE: Pulmonary embolism; AOR: Adjusted odds ratio.

## DISCUSSION

As far as we know, the current study is the first systematic review to investigate the effect of ATT on thromboembolic and bleeding complications in hepatectomy. The current study reviewed 16 published articles with special reference to ATT, in which a total of 8300 patients receiving hepatectomy were included. Concerning the effects of chronic ATT administration on bleeding events, most of the studies showed that hepatectomy can be performed safely in patients receiving chronic ATT, even if they continue to have aspirin preoperatively. Regarding pharmacological prevention for VTE, some studies have reported that patients undergoing pharmacological prophylaxis may be at increased risk of bleeding, but their efficacy against VTE has not been proven especially in the population of Asian patients.

Minimizing intraoperative and postoperative bleeding complication is one of the most important tasks in hepatectomy, and several technical improvement has been demonstrated, such as Pringle's procedure, the liver hanging maneuver, or the two-surgeon technique[25-27]. Pringle's procedure is generally used during transection of the liver parenchyma in order to control hepatic inflow; sustained low CVP is usually employed in order to control backflow bleeding from the hepatic vein[8]. However, sustained low CVP may expose the ATT-received patients to the increased risks of stroke or myocardial infarction. Rigorous perioperative management of antithrombotic agents and strict procedures of hemostasis are requisite in order to prevent both thromboembolic and bleeding complications.

Regarding the management of chronically ATT-received patients, guidelines regarding ATT management during non-cardiac surgery were recently updated and demonstrated that the prevention of thromboembolism is more significant than prophylaxis of bleeding, since it might cause severe sequelae or death[5,28-31]. To date, there are little consensus or evidence on the safety of hepatectomy and proper



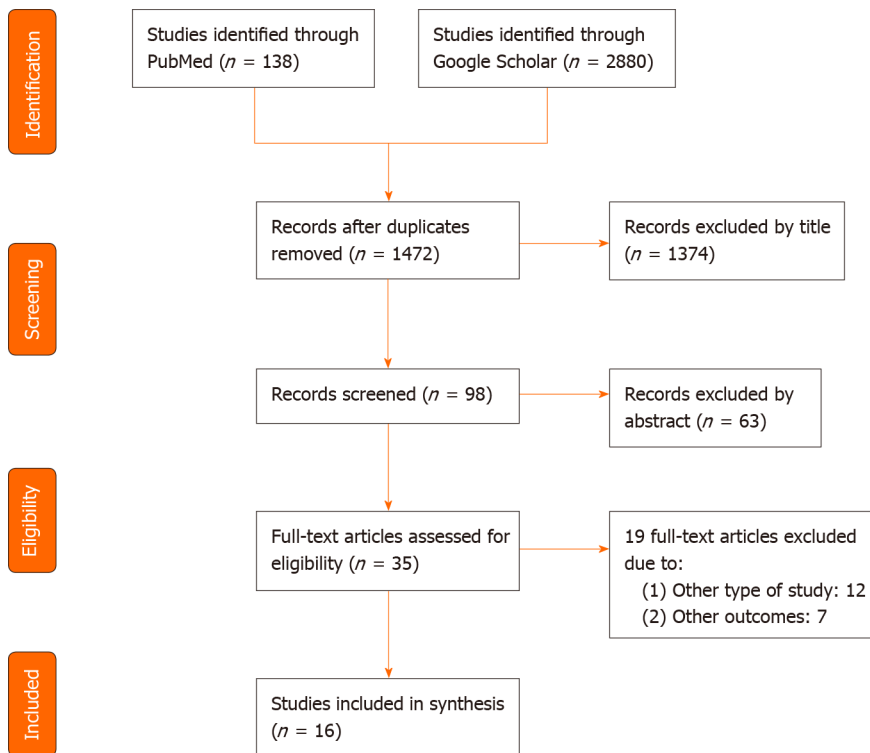


Figure 1 PRISMA flow diagram demonstrating articles selection process.

perioperative ATT management in ATT-received patients, and the optimal prevention for VTE also remains unknown.

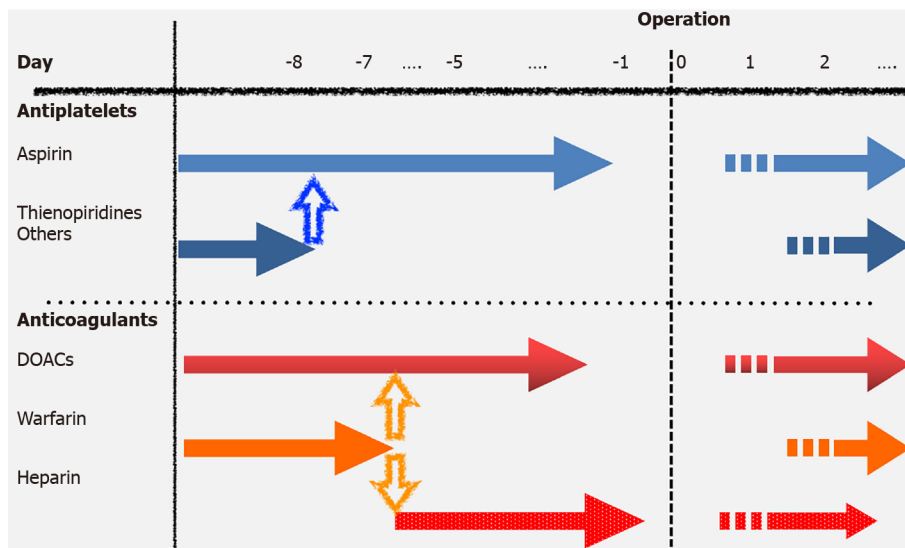
Our hospital is a high-volume institution for referrals to patients with digestive cancer who are receiving ATT. Accordingly, we presently use a centralized management protocol in ATT-received patients undergoing digestive surgery including hepatectomy (Figure 2)[32], which was established and have been updated with reference to several guidelines and recently reported studies regarding perioperative ATT management for non-cardiac surgeries or endoscopic procedures[5,6,28-30]. The management consists of 3 ways according to ATT types; antiplatelets, warfarin, and DOACs. In patients with the risk of thromboembolism, preoperative aspirin monotherapy is sustained in antiplatelet-received patients, and warfarin is substituted by DOAC bridging (preferred) or heparin bridging. Regarding patients with DOACs, short-period discontinuation of DOACs (usually 1-2 d) is recommended and heparin bridging is usually not required, but heparin bridging might be considered if the thromboembolic risk is very high. Postoperatively, every antithrombotic drug is reinstituted as soon as possible.

Concerning the management of patients with antiplatelet drugs, some studies such as POISE-2 study have suggested that a slight increase in bleeding risk was observed in patients with continued antiplatelets during non-cardiac surgery[33,34], but most of other studies demonstrated that the bleeding events were not significantly increased [35,36]. Moreover, one large-scale retrospective cohort study was recently showed that the continued preoperative aspirin significantly reduced the rate of postoperative thromboembolism but was not associated with the occurrence of bleeding events[37]. In the current review, three studies showed that continued preoperative aspirin is not related to excessive SBL or increased occurrence of BC in patients with chronic antiplatelet therapy during or after hepatectomy[9,12,13]. Although the favorable management of antiplatelet-received patients during hepatectomy is still controversial, continued preoperative aspirin is one of the preferred options and should be considered.

In the clinical setting, when neurosurgeons or cardiologists judge the risk of thromboembolism as high, antiplatelet-recipient patients are sometimes managed by heparin bridging during perioperative discontinuation of antiplatelet drugs. This situation is probably because some cardiologists and surgeons are unaware of the preferred option of continued aspirin monotherapy for the perioperative management. The mechanism of heparin is different from that of antiplatelets, and heparin bridging is presently reported to be a significant risk factor for postoperative bleeding events



Kokura Protocol (Ver 2.1)



**Figure 2 Recommended perioperative management protocol for patients undergoing antithrombotic therapy in case of hepatobiliary-pancreatic and gastrointestinal surgery.** The management generally consists of 3 ways according to types of antithrombotic therapy; antiplatelet therapy, warfarin, and direct-acting oral anticoagulant (DOACs). In patients with thromboembolic risks, aspirin monotherapy is continued in patients receiving antiplatelet therapy, and warfarin is substituted by DOAC bridging (preferred) or heparin bridging. In case of DOAC, short-period discontinuation of DOACs (usually 1-2 d) without heparin bridging is generally recommended (with some modification needed if decreased renal function exists). Postoperatively, every antithrombotic agent is reinstituted as soon as possible (POD1-2). DOAC: Direct-acting oral anticoagulant.

[38,39]. Therefore, heparin bridging during antiplatelet discontinuation is not recommended and should not be used.

Concerning DOACs, only one report was included in the present review[14]. This study showed that perioperative short-period discontinuation of DOACs without heparin bridging was safe even for patients who undergo digestive surgery including hepatectomy, but patients who were managed by heparin bridging during DOAC discontinuation was at high risk of postoperative bleeding. Presently, DOACs are increasingly used for the prophylaxis of venous or arterial thromboembolic events. They are fast-acting drugs with their anticoagulant effect fading within 48 h after their withdrawal[28]. One large-scale multicenter prospective cohort study (the PAUSE study) was recently published, which examined outcomes in 3007 adult patients with atrial fibrillation who underwent DOAC therapy and received an elective non-cardiac procedure or surgery[40]. DOAC therapy was interrupted 1-2 d prior and reinstituted 1-2 d after the procedure or surgery. The occurrence of major bleeding 30 d after the procedure or surgery was 0.90%-1.85%, and arterial thromboembolic complication was occurred at the rate of 0.16%-0.60%. The study recommended that a centralized perioperative management of DOACs without heparin bridging can be performed safely for patients with atrial fibrillation. Although the PAUSE study included only a limited number of patients undergoing major gastroenterological surgery, the study included in the present review also suggested that the perioperative short-period cessation of DOACs without heparin bridging is the preferred management even for patients who receive major gastroenterological surgery including hepatectomy[14,37].

Regarding chemical prevention for VTE in hepatectomy, most of the studies included in the present review have demonstrated a potential risk of postoperative bleeding events in patients receiving pharmacological thromboprophylaxis, although its efficacy against VTE has not been shown, particularly in Asian patient population. VTE is fatal when it occurs during the perioperative period, and its prevention is of paramount importance. Although some guidelines in Western countries recommend pharmacological prevention for VTE during non-cardiac surgery[41-43], it is reported that there are racial differences in the rate of VTE between Western people and Asians [44]. In addition, in one systematic review regarding pharmacological prevention for VTE in Asian surgical patients[45], the risk of perioperative VTE in Asian patients is reported to be low even in the context of high risk for thromboembolism. The two large-scale cohort studies from Japan were recently showed that the incidence of clinically relevant VTE during or after major digestive surgery was 0-0.3%[37,46]. Currently, the safety and efficacy of pharmacological prevention with anticoagulation

drugs for VTE during hepatectomy is still controversial, particularly in Asian patient population. It is important to build evidence in order to classify risks individually according to each race is essential.

### **Summary and recommendations for future studies**

Presently, the numbers of studies regarding the management of ATT during hepatectomy is limited. This patient population is expanding further, as the population ages and the prevalence of cardiovascular disease increases. Using reliable studies with good design, the definite guideline should be determined. Currently, one promising prospective multicenter cohort study was registered in the University Hospital Medical Information Network Clinical Trials Registry and is ongoing [“Study on the safety and feasibility of gastroenterological surgery in patients undergoing antithrombotic therapy (GSATT Study)”, UMIN000038280]. In the future, the safety of ATT management during liver resection will be demonstrated by well-designed analyses like this study.

## **CONCLUSION**

Hepatectomy in patients with chronic ATT can be performed safely without increase in the rates of bleeding complications, although the efficacy and safety of pharmacological prevention for VTE during hepatectomy remains controversial. Further investigation using reliable studies with good design must be required to establish definite protocol or guidelines.

## **ARTICLE HIGHLIGHTS**

### **Research background**

Little is unknown about the effect of chronic antithrombotic therapy (ATT) on bleeding complication during or after hepatectomy. In addition, the safety and effectiveness of chemical prevention for venous thromboembolism (VTE) remain controversial.

### **Research motivation**

The goal of the present review was to clarify the effect of ATT on bleeding complications or increased surgical blood loss in hepatectomy.

### **Research objectives**

The objective of the current systematic review was to investigate the effect of ATT on thromboembolism and bleeding in hepatectomy.

### **Research methods**

Articles published between 2011 and 2020 were searched from Google Scholar and PubMed, and after careful reviewing of all studies, studies concerning ATT and hepatectomy were included. Data such as study design, type of surgery, type of antithrombotic agents, and surgical outcome were extracted from the studies.

### **Research results**

Sixteen published articles, including a total of 8300 patients who underwent hepatectomy, were eligible for inclusion in the current review. All studies regarding patients undergoing chronic ATT showed that hepatectomy can be performed safely, and three studies have also shown the safety and efficacy of preoperative continuation of aspirin. Regarding chemical prevention for VTE, some studies have shown a potentially high risk of bleeding complications in patients undergoing chemical thromboprophylaxis; however, its efficacy against VTE has not been shown statistically, especially among Asian patients.

### **Research conclusions**

Liver resection in chronically ATT-received patients can be performed safely without increase in the rate of bleeding complications, although the safety and efficacy of chemical thromboprophylaxis for VTE during liver resection is still controversial especially in Asian population.

**Research perspectives**

Further investigation using reliable studies with good design must be requisite to establish definite protocol or guidelines.

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