Effects of antithrombotic therapy on bleeding after endoscopic sphincterotomy: A systematic review and meta-analysis

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ABSTRACT

Background and study aims Bleeding is a common complication of following endoscopy sphincterotomy (EST), and antithrombotic therapy use during the procedure often increases risk of it. Although several guidelines have been released regarding the use of antithrombotic agents during EST, many issues about it remain controversial. We carried out a systematic review and meta-analysis to evaluate the effect of antithrombotic medication on the risk of EST bleeding.

Methods A structured literature search was carried out in Web of Science, EMBASE, PubMed, and Cochrane Library databases. RevMan 5.2 was used for meta-analysis to investigate the rate of post-EST bleeding.

Results Seven retrospective articles were included. Compared with patients who had never taken antithrombotic drugs, patients who discontinued antithrombotic drugs 1 day before the procedure had a significantly increased risk of post-EST bleeding (OR, 1.95; 95 %CI, 1.57–2.43), particularly for severe bleeding (OR, 1.83; 95 %CI, 1.44–2.34). In addition, compared with patients who discontinued antithrombotic therapy for at least 1 day, patients who continued taking antithrombotic drugs did have an increased risk of post-EST bleeding (OR, 0.70; 95 %CI, 0.40–1.23).

Conclusions The use of antithrombotic drugs may increase the bleeding rate of EST, but discontinuing therapy 1 day before endoscopy does not significantly reduce the bleeding rate.

Introduction

With the increasing aging of society, the number of patients with various cardiovascular diseases is growing and the use of antithrombotic drugs (antiplatelet agents and anticoagulants) has become increasingly widespread to reduce the occurrence of thromboembolic events. Meanwhile, antithrombotic drugs often place patients at greater risk of bleeding during medical treatment, especially when invasive surgery is performed. Reports from the surgical field indicate that patients using antithrombotic drugs are 2.3 times more likely to experience postoperative bleeding [1]. Such problems also exist in the field of digestive endoscopy. Among patients taking heparin, endoscopy-related gastrointestinal bleeding rates may be as high as 38 % [2, 3]. Therefore, whether and how to discontinue the use of antithrombotic drugs is a serious issue to be considered before endoscopic procedures.

Endoscopic retrograde cholangiopancreatography (ERCP) is regarded as a technique for diagnosis and treatment of biliopancreatic diseases using endoscopy, and it is primarily used in patients with acute biliary pancreatitis (ABP) and indicated in those who have evidence of cholangitis superimposed on ABP [4]. Those kinds of patients often have acute onset and critical condition, which requires quick and decisive treatment by endoscopists. There is a clear indication for emergency ERCP within 72 hours in patients with ABP and choledochal obstruc-

tion, and for ERCP within 24 hours in cases of cholangitis [5, 6]. Unlike with elective ERCP, when the procedure is emergent, it is not possible to adjust a patient's antithrombotic medication regimens or to stop antithrombotic therapy. Furthermore, during the ERCP process, endoscopic sphincterotomy (EST) is often an essential procedure, which greatly increases risk of bleeding [7–12].

The question of how to adjust anticoagulants to reduce the risk of EST bleeding during emergency ERCP has become a focus of attention among gastrointestinal endoscopists. Several societies, including the Asian Pacific Society for Digestive Endoscopy (APSDE), European Society of Gastrointestinal Guidelines Endoscopy (ESGE), and American Society of Gastrointestinal Endoscopy (ASGE), have published guidelines to assist endoscopists in managing perioperative antithrombotic drugs and making clinical decisions [13–15]. However, because the evidence is weak evidence, there is no widespread agreement about these clinical recommendations. Moreover, there is even controversy about some recommendations in the guidelines for management of antithrombotic drugs during EST. Therefore, we carried out a systematic review and meta-analysis to assess the effect of antithrombotic medication on risk of EST bleeding in this study.

Methods

Literature research

A structured search of the published literature was conducted on December 20, 2020 using EMBASE, PubMed, Web of Science, and Cochrane. The search query for PubMed was ("Platelet Aggregation Inhibitors"[Mesh] OR "Anticoagulants"[Mesh] OR antithrombotic OR "Aspirin"[Mesh] OR "Warfarin"[Mesh] OR "Clopidogrel"[Mesh]) AND ("Sphincterotomy, Endoscopic"[Mesh] OR "Cholangiopancreatography, Endoscopic Retrograde"[Mesh]) AND "Hemorrhage"[Mesh].

Selection criteria

The inclusion criteria for this review were: 1) patients receiving antithrombotic therapy who underwent EST; 2) a control group who were not taking antithrombotic therapy who underwent EST; 3) discontinuous use of antithrombotic agents defined as withdrawal of antithrombotic agents for more than 1 day prior to EST, continuation of antithrombotic agents were defined as continuous use of antithrombotic agents or withdrawal less than 1 day prior to EST, including use of heparin-based bridge therapy after interruption of oral anticoagulation; and 4) publication in English with searchable full text. Exclusion criteria were: 1) reports on research other than original studies (e.g., case reports, reviews, letters to the editor, and comments); 2) lack of a no control group; and 3) animal studies.

Data extraction

Two authors (Gang Huang, Yan-Bo Yu) independently scanned the title and abstract of these trials to find potentially eligible studies, with discrepancies resolved by the consensus of these two researchers. The following sets of data were recorded: 1) study characteristics, including author, title, country, year of publication, number of participants; 2) patient characteristics, including number of participants, average age, sex ratio; and 3) outcome assessment, including risk of post-EST hemorrhage (severe hemorrhage, early, and delayed).

Definition of outcomes

According to published criteria [16], post-EST bleeding was defined as either immediate bleeding, which did not stop spontaneously after the end of the procedure, or delayed bleeding confirmed endoscopically, which resulted in a drop of more than 2 g/dL of hemoglobin, hematemesis, or detection of melena. Severe bleeding was determined on the basis of the requirement for transfusion of 5 units or intervention (angiographic or surgical).

Quality assessment

The quality of trials was independently evaluated by two authors using the 9-star Newcastle-Ottawa Scale (NOS) [17]. Each trial is judged on eight items, which are categorized into three topics including selection of the study groups, comparability of the groups, and the outcome assessment. Stars are awarded for each quality item and the highest total score with this scale is 9. If a study score is greater than 5, it is considered to have high methodological quality.

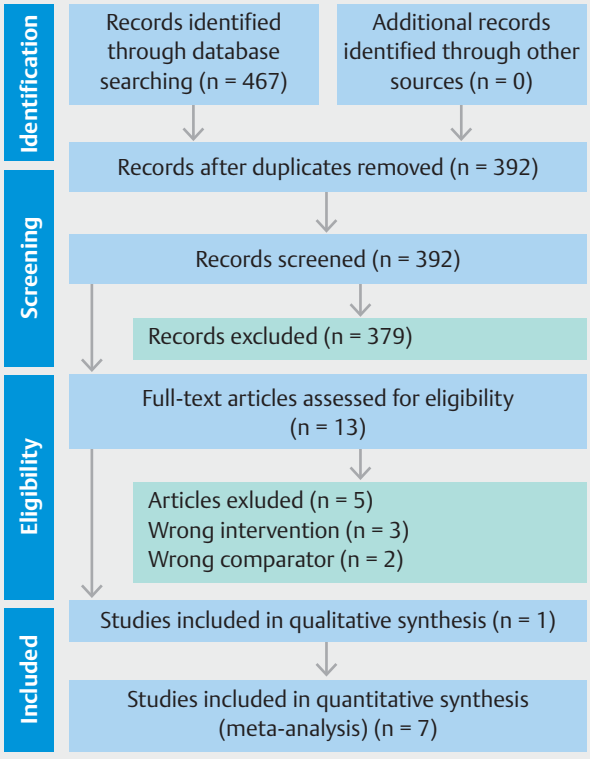
Statistical analysis

Statistical analysis was conducted using Review Manager Software 5.3 (RevMan 5.3) from the Cochrane Collaboration. The results were acquired by direct extraction or by indirect calculation and then the rate of post-EST bleeding was analyzed. Heterogeneity of the trials was assessed with the χ^2 test and I^2-statistic and significant heterogeneity was defined as $I^2 > 50\,\%$ and $P < 0.1$. The outcomes of dichotomous variables without evidence of heterogeneity were calculated using the fixed-effects model, otherwise using the random-effects model. We used a Forest plot for graphical display of the results. Sensitivity analyses were performed by changing analysis model, excluding individual trials, and recalculating the pooled odds ratio.

Results

Study characteristics

In total, 467 articles (75 duplicates) were obtained through the initial literature search using the previously described search strategy. A total of 379 articles were excluded after the screening process. Of these, 13 studies were assessed in full-text form. The remaining six articles were excluded for the following reasons: the results for comparator group of no antithrombotic therapy not provided in two articles; the population was not rigorously divided into discontinued or continued groups in three articles; and no key data provided in one article. Seven articles were finally considered eligible to be included in this meta-analysis, as shown in ▶ **Fig. 1** [18–24]. All of them were retrospective studies and separately conducted in China, Japan, South Korea, and Germany. The set of seven studies has an N of 59,430 patients, including 5,279 who discontinued taking antithrombotic agents prior to EST, 1251 who continued taking



▶ **Fig. 1** PRISMA flow diagram. From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6: e1000097. doi:10.1371/journal.pmed1000097

antithrombotic agents, and 52,900 who never took antithrombotic agents. The characteristics of the eligible included researches are presented in ▶ **Table 1**. The quality of the studies is shown in ▶ **Table 2**.

Discontinuation of antithrombotic group versus non-antithrombotic group

Five retrospective studies [19, 21–24] met the inclusion criteria, with 5,234 subjects who discontinued antithrombotic agents and 51,418 controls (▶ **Fig. 2**). Patients who discontinued antithrombotic drugs 1 day before the procedure had a significantly increased risk of post-EST bleeding (OR, 1.95; 95 %CI, 1.57–2.43), compared with those in the non-antithrombotic group (▶ **Fig. 2**). There was no significant heterogeneity among the study results ($I^2 = 44\%$; $P = 0.13$).

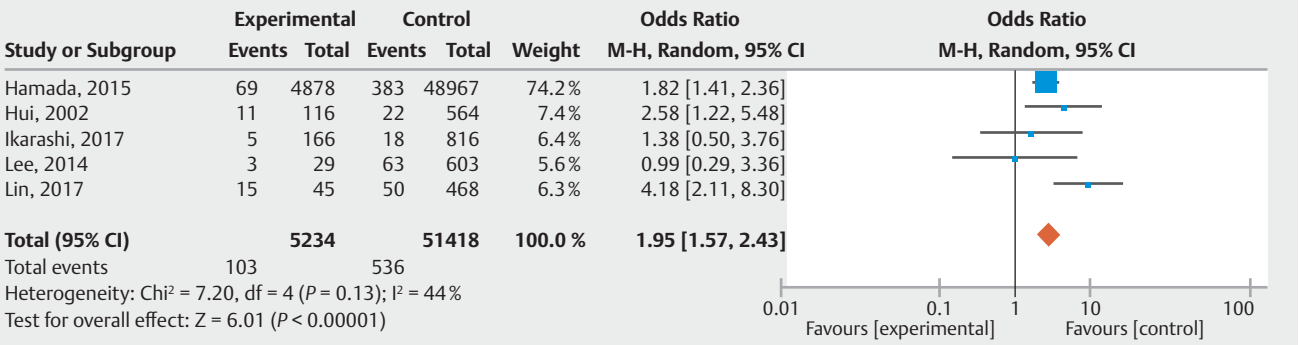
Although relatively rare, severe bleeding can be fatal when it occurs and usually requires red blood cell transfusion, endoscopic hemostasis, or even transcatheter arterial embolization [9, 25]. In four relevant studies [19, 22–24], patients who discontinued taking antithrombotic agents for at least 1 day had a significantly increased risk of severe bleeding (OR, 1.83; 95 % CI, 1.44–2.34) (▶ **Fig. 3**). There was no significant heterogeneity among the study results ($I^2 = 0\%$; $P = 0.50$).

We also investigated the effect of antiplatelet agents on the bleeding rate, and the results were inconclusive. In four relevant studies [21–24], we found that patients who discontinued taking antiplatelet agents for at least 1 day apparently had an increased risk of post-EST bleeding compared with those who never used antiplatelets (OR, 1.89; 95 %CI, 1.46–2.44) (▶ **Fig. 4**). Due to the significant heterogeneity among

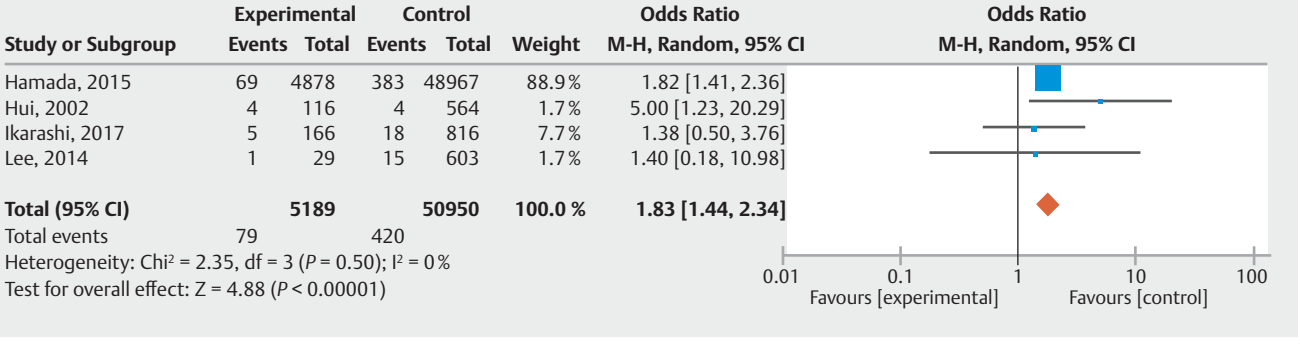
▶ **Table 1** Characteristics of eligible studies.

Author	Country	Method	Discontinued antithrombotics			Continued antithrombotics			No antithrombotics		
			Age, mean (years)	Sex (M/F)	Bleeding rate	Age, mean (years)	Sex (M/F)	Bleeding rate	Age, mean (years)	Sex (M/F)	Bleeding rate
Yamamiya et al 2019 [18]	Japan	Antithrombotic	65	34/11	0/45	78	21/10	0/31	NG	NG	NG
Ikarashi et al 2017 [19]	Japan	Antithrombotic	NG	NG	5/166	NG	NG	NG	NG	NG	18/816
Samie et al 2017 [20]	Germany	Antithrombotic	NG	NG	NG	NG	NG	20/316	70	617/865	54/1482
Lin et al 2017 [21]	China	Antithrombotic	NG	NG	15/45	NG	NG	NG	NG	NG	50/468
Hamada et al 2015 [22]	Japan	Antithrombotic	NG	NG	69/4878	NG	NG	4/648	NG	NG	383/48967
Lee et al 2014 [23]	Korea	Antiplatelet	74.9	19/10	3/29	72.3	82/50	13/132	60.8	329/272	63/603
Hui et al 2002 [24]	China	Aspirin	76.8	64/52	11/116	77.6	60/64	12/124	73.3	239/325	22/564

M/F, male/female; NG, not given.



▶ **Fig. 2** Forest plot of patients who discontinued antithrombotic agents for at least 1 day versus who never used antithrombotics. CI, confidence interval; M-H, Mantel-Haenszel.



▶ **Fig. 3** Forest plot of post-EST severe bleeding, comparing discontinuation of antithrombotic drugs for at least 1 day with never taking antithrombotic drugs. CI, confidence interval; M-H, Mantel-Haenszel.

▶ **Table 2** Quality of studies with NOS scores.

Studies	Selection	Comparability	Exposure	Stars
Yamamiya et al 2019 [18]	3	1	3	7
Ikarashi et al 2017 [19]	3	0	3	6
Samie et al 2017 [20]	3	1	3	7
Lin et al 2017 [21]	2	2	2	6
Hamada et al 2015 [22]	2	1	3	6
Lee et al 2014 [23]	3	1	3	7
Hui et al 2002 [24]	3	1	3	7

NOS, Newcastle-Ottawa Scale.

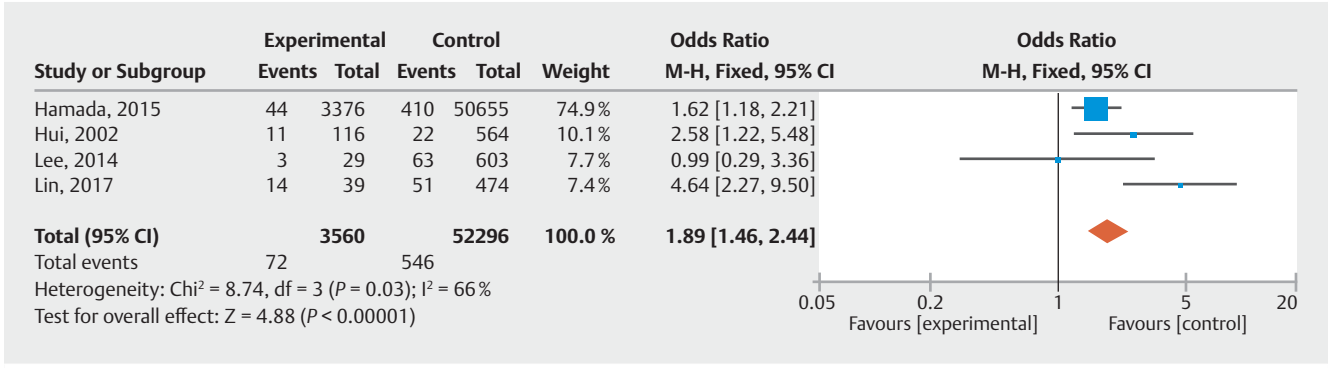
the study results ($I^2 = 66\%$; $P = 0.03$), the fixed-effects model was changed to a random-effects model in the sensitivity analysis, but the results did not change (OR, 2.20; 95%CI, 1.23–3.92) (▶ **Fig. 5**). In addition, the result was different if the cessation of antiplatelet drugs was set at 7 days. There was no significant difference in bleeding rate between the group who discontinued taking antiplatelet agents and those who never used antiplatelets in two relevant studies (OR, 1.89; 95%CI, 1.01–3.54) (▶ **Fig. 6**) [23, 24]. There was no significant heterogeneity among the study results ($I^2 = 42\%$; $P = 0.19$).

Continuation of antithrombotic group versus discontinuation of antithrombotic group

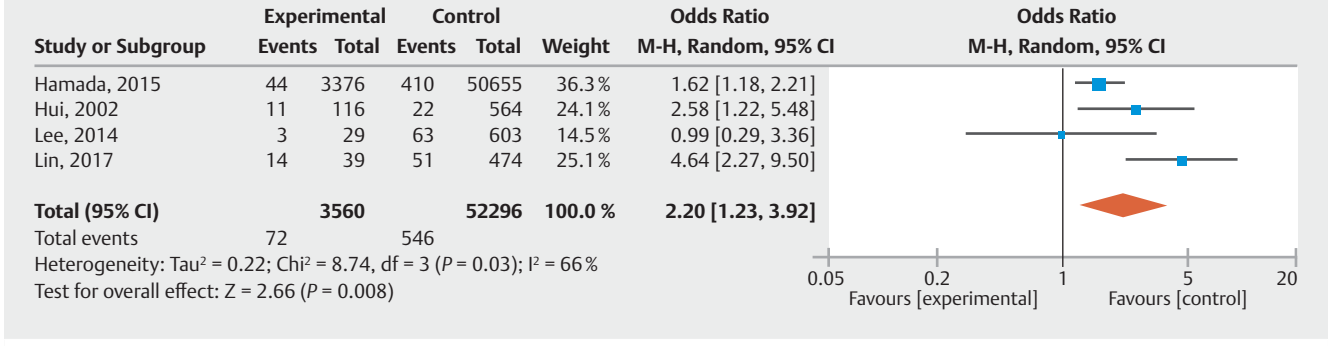
Four studies [18, 22–24] met the selection criteria in this group, with 935 subjects on continued antithrombotic agents and 5,068 controls who discontinued these agents (▶ **Fig. 7**). Patients who continued antithrombotic therapy did not have an increased risk of post-EST bleeding (OR, 0.70; 95%CI, 0.40–1.23), compared with patients who discontinued antithrombotic agents 1 day before the procedure (▶ **Fig. 7**). There was no significant heterogeneity among the trial results ($I^2 = 0\%$; $P = 0.41$).

In addition, three studies [22–24] reported post-EST severe bleeding in both the continuing and discontinuing groups (for at least 1 day). No significant difference was found between the two groups (OR, 0.50; 95%CI, 0.23–1.09) (▶ **Fig. 8**). There was no significant heterogeneity among the trial results ($I^2 = 0\%$; $P = 0.86$).

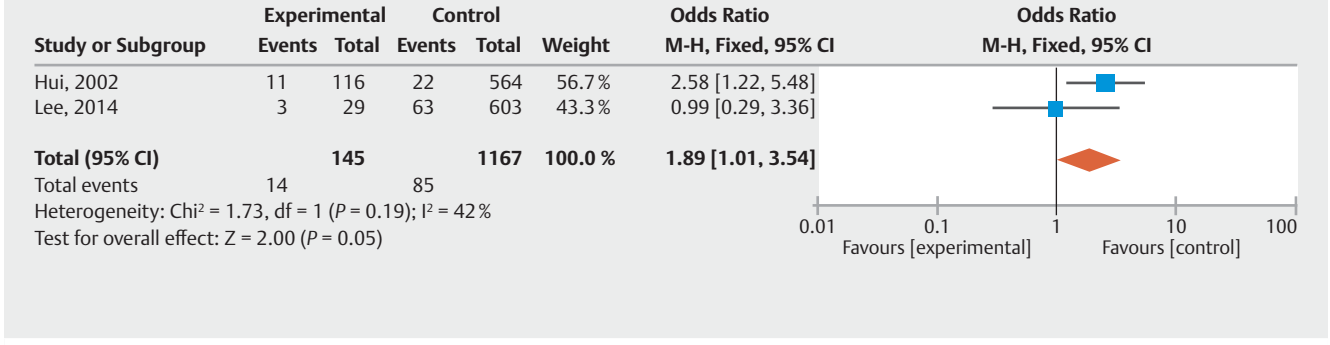
Three studies [22–24] evaluated the antiplatelet agents independently. No significant difference was found between those who discontinued antiplatelet therapy for at least 1 day and those who continued to use antiplatelet therapy (OR, 0.80; 95%CI, 0.44–1.44) (▶ **Fig. 9**). There was no significant



▶ **Fig. 4** Forest plot of patients who discontinued taking antiplatelet drugs for at least 1 day versus who never used antithrombotics. CI, confidence interval; M-H, Mantel-Haenszel.



▶ **Fig. 5** Forest plot of patients who discontinued taking antiplatelet drugs for at least 1 day versus who never used antithrombotics, when analysis model was changed. CI, confidence interval; M-H, Mantel-Haenszel.

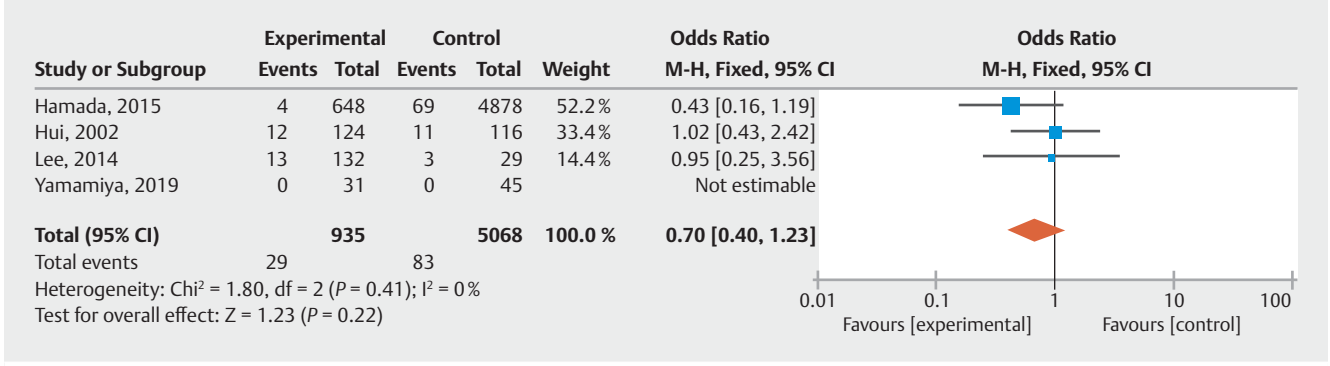


▶ **Fig. 6** Forest plot of patients who discontinued taking antiplatelet drugs for at least 7 days versus who never used antithrombotics, when analysis model was changed. CI, confidence interval; M-H, Mantel-Haenszel.

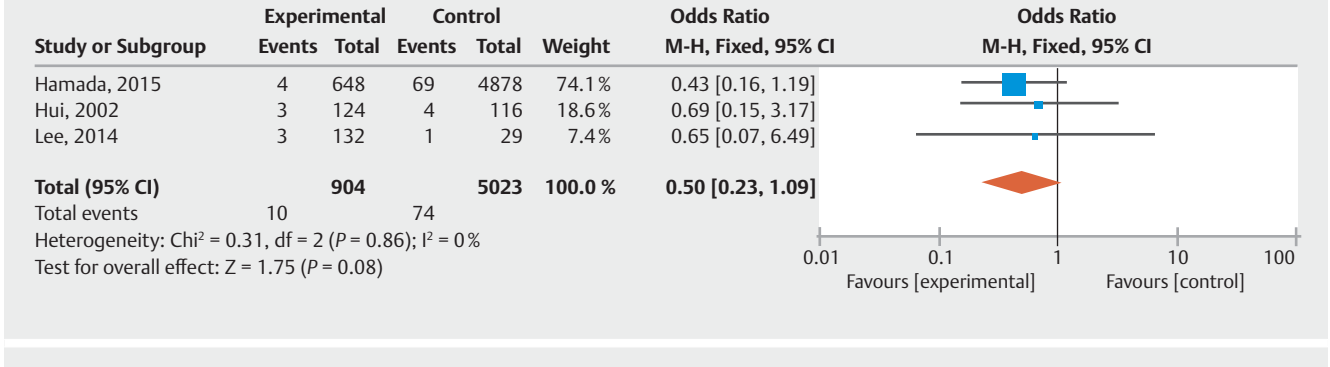
heterogeneity among the trial results ($I^2 = 0\%$; $P = 0.62$). If the withdrawal time from antiplatelet agents was set at 7 days, there were two studies [21, 24] involved and the meta-analysis results remain unchanged. Continued use of antiplatelet agents did not affect post-EST bleeding compared with discontinuation of agents. (OR, 1.00; 95%CI, 0.49–2.06) (▶ **Fig. 10**). There was no significant heterogeneity among the trial results ($I^2 = 0\%$; $P = 0.92$).

Discussion

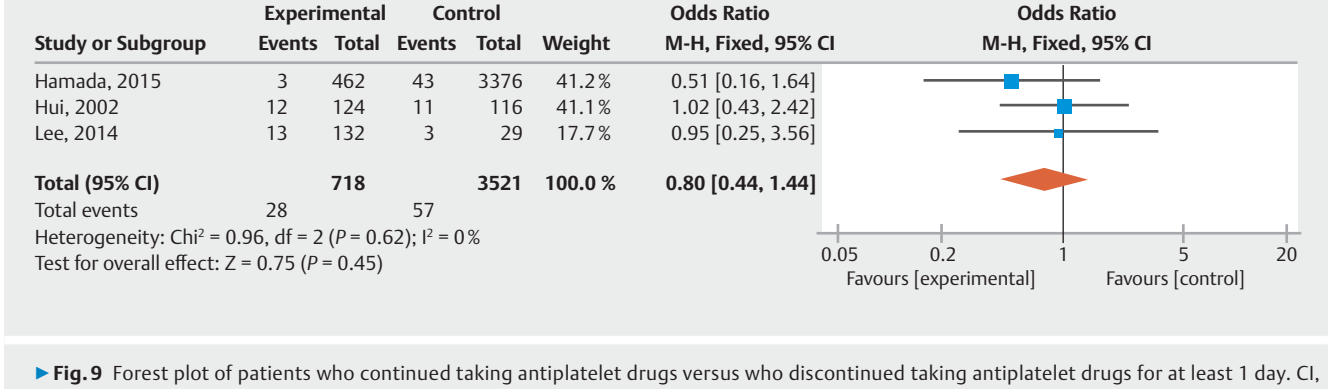
To date, three guidelines have been released to assist endoscopists in making decisions regarding antithrombotic therapy management during EST [13–15]. However, the quality of evidence guiding clinical decisions is poor and is often based on observational studies or expert consensus. Therefore, our study was designed to collect and sort the previous data and comprehensively evaluate the research results through the method of meta-analysis and provide a fuller theoretical basis for improv-



▶ **Fig. 7** Forest plot of patients who continued antithrombotic drugs versus who discontinued antithrombotic drugs for at least 1 day. CI, confidence interval; M-H, Mantel-Haenszel.



▶ **Fig. 8** Forest plot of post-EST severe bleeding, when comparing continuation of antithrombotic drugs with discontinuation antithrombotic drugs for at least 1 day. CI, confidence interval; M-H, Mantel-Haenszel.

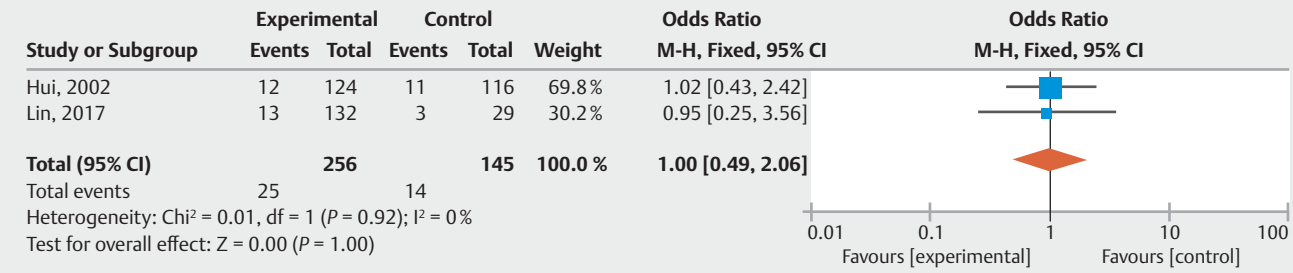


▶ **Fig. 9** Forest plot of patients who continued taking antiplatelet drugs versus who discontinued taking antiplatelet drugs for at least 1 day. CI, confidence interval; M-H, Mantel-Haenszel.

ing endoscopy management and better guiding clinical decision-making.

Most of the guidelines [13–15] recommend discontinuation of antithrombotic drugs before the procedure as a way of reducing the risk of bleeding. However, our meta-analysis showed that use of antithrombotic agents may increase risk of post-EST bleeding, especially severe bleeding, and that preoperative discontinuance has no effect on reducing hemorrhage in antithrombotic drug users. Here, we will discuss our findings on the effects of various antithrombotics on the bleeding rate post-EST.

Some studies have shown that aspirin (ASA) should not be discontinued prior to endoscopic procedures to prevent possible fatal thromboembolic complications [25–27]. Hui et al argued that ASA increased the risk of post-EST bleeding (P= 0.01), and discontinuation of ASA for 7 days prior to EST did not appear to decrease risk of EST bleeding (P=0.96) [24]. Meanwhile, some studies reported that there was no statistically significant increase in the rate of bleeding in patients who continued to use ASA [20, 28]. Based on these current studies, continuous use of ASA may be safe during EST. Due to the limited data, we were unable to perform the meta-analysis. Fur-



▶ **Fig. 10** Forest plot of patients who continued taking antiplatelet drugs versus who discontinued taking antiplatelet drugs for at least 7 days. CI, confidence interval; M-H, Mantel-Haenszel.

ther studies are required to determine the relationship between ASA and post-EST bleeding.

Clopidogrel, a thiophene pyridine drug, has been used more frequently as an antiplatelet agent in recent years. In patients treated with percutaneous coronary intervention, treatment with ASA is required for up to 12 months after stent placement [29]. Current guidelines recommend that ASA be continued and that thienopyridines be discontinued before EST [13–15]. However, there are no reliable data to support this recommendation. In addition, EST usually is performed as an emergency procedure, and the pharmacological action of thiophene pyridines may last up to 7 days [30–32]. This makes the clinical decision-making about digestive endoscopy challenging. A randomized, double-blind, single-center study showed that continued use of clopidogrel did not significantly increase bleeding in EST [28]. A few studies also have focused on the safety of continuing dual antiplatelet therapy. In a small series, we did not observe an increased rate of bleeding after EST in patients treated with dual antiplatelet therapy [33]. In another study, no bleeding was observed in the dual antiplatelet group with 18 patients [20]. Other studies also support the safety of continued dual antiplatelet therapy during EST [34, 35]. Due to limited research data, larger sample size studies are still needed to further determine whether P2Y12 receptor inhibitors including clopidogrel should be discontinued before EST.

Regarding the relationship between antiplatelet therapy and post-EST bleeding, some studies suggested that continuous use of antiplatelet agents did not affect the EST bleeding rate [28, 36–38]. However, these studies tended to have small sample sizes, and most of the antiplatelet drugs used in the study populations were ASA. Our meta-analysis found that patients who discontinued taking antiplatelet agents for at least 1 day apparently had an increased risk of post-EST bleeding compared with those who never used antiplatelets, while patients who discontinued taking antiplatelet agents for at least 7 days had no significant increase in risk of bleeding. The post-EST bleeding rate did not decrease in patients after 1 day or 7 days of antiplatelet agent withdrawal compared with the continuation group. Therefore, we would argue that antiplatelet agents can be used during EST. However, further research is warranted to determine the appropriate management of antiplatelet drugs, especially P2Y12 receptor inhibitors, in the periprocedural period for EST.

The main oral anticoagulants commonly used are traditional warfarin and novel oral anticoagulants (NOACs), which include dabigatran, rivaroxaban, and apixaban. Because of various advantages, such as shorter half-life, a rapid offset and onset of action, and low rates of cardiovascular or major bleeding events, the number of patients routinely taking NOACs is increasing [39–43]. A large nationwide database analysis in Japan showed that risk of gastrointestinal hemorrhage was significantly lower in the NOAC group than in the warfarin group (9.9% vs 12.0%; $P = 0.002$) [2].

Similarly, a recent study [44] showed that risk of post-EST bleeding with continuation of NOACs was significantly lower than that with continuation of warfarin (0 vs 16.6%; $P = 0.021$). These studies demonstrated the advantages of using NOACs in endoscopic procedures in reducing bleeding complications, but the relationship between anticoagulants and post-EST bleeding requires further investigation.

Bridging therapy is usually designed to protect patients from thromboembolism associated with discontinuation of oral anticoagulation while better controlling bleeding. Some studies have shown that for atrial fibrillation patients with low CHA2DS2-VASC scores, heparin bridging therapy for invasive surgery does not reduce the incidence of thromboembolic complications, but significantly increases the surgically related bleeding rate [45–47]. Consistent with this, the guidelines [13–15] only recommend heparin-based bridging therapy for patients at high risk of thrombosis. Recently, several studies have suggested that presence of bridge anticoagulation is a risk factor for post-EST bleeding among patients on warfarin [2, 19, 48, 49]. One study that recruited over 1000 patients demonstrated that bridging therapy with heparin significantly increased risk of post-EST bleeding (OR 3.76; 95%CI, 1.42–9.98; $P = 0.008$) by multivariate analysis [19]. In contrast, a large multicenter retrospective study [44] showed no difference in post-EST bleeding between continuation group of warfarin (16.6%, 2/12) and the heparin replacement group (8.0%, 6/75; $P = 0.37$), and that the group that continued on NOACs (0%, 0/31) had a lower bleeding rate than the heparin replacement group (12.9%, 4/31; $P = 0.016$).

Due to the lack of original data, our meta-analysis was not able to assess the impact on postoperative bleeding complications of continued warfarin or NOACs versus heparin transition therapy during the perioperative period of EST. Even so, based on current evidence, there are two possibilities for heparin replacement in patients at high risk of thromboembolic events. One is replacing warfarin with heparin in patients on continuous warfarin who require EST. The other, as is recommended in some recent guidelines, is continuation of NOACs without bridging therapy for high-risk endoscopic surgery, including EST [14, 15].

Few studies are available to guide optimal timing of resumption of anticoagulant drug for endoscopic procedures. In a retrospective cohort study [50], 96 people who stopped using anticoagulant drug before receiving EST were divided into three groups: very early (< 24 h), early (24–48 h), and late resumption (> 48 h) of anticoagulant after EST. The authors demonstrated that the rate of delayed bleeding was not significantly affected by different times of anticoagulant recovery (5 % vs. 9 % vs. 0, $P = 0.47$), and that risk of thromboembolic events was significantly higher in the group with late anticoagulation recovery (0 vs. 0 vs. 24 %, $P < 0.001$). Moreover, a prospective study also found that restarting anticoagulation within 1 week did not significantly increase risk of bleeding with a reduced risk of thromboembolic events [51]. Therefore, considering the serious consequences of thrombotic events, antithrombotic agents should be resumed as soon as possible after EST.

Our study has limitations that should be considered. First, the studies analyzed are all retrospective clinical studies and not randomized controlled trials. Second, the cut-off point for discontinuation of antithrombotic agents differed among the studies. Discontinuation of antithrombotic agents in three reports [18, 23, 24] was defined as over 7 days, while in two reports [20, 22], it was defined as more than 1 day, and in one report [19], it was not specified.

Conclusions

In conclusion, our meta-analysis suggests that use of antithrombotic drugs does increase the bleeding rate of EST and that discontinuation of the therapy 1 day before endoscopy does not significantly reduce the bleeding rate. The effect of antithrombotic drugs in patients undergoing EST should be further assessed with future higher-quality evidence.

Competing interests

The authors declare that they have no conflict of interest.

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A review protocol can be accessed (https://www.crd.york.ac.uk/prospero/) and the registration number is CRD42020220461.

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