SYSTEMATIC REVIEW AND META-ANALYSIS

DOI: http://dx.doi.org/10.15403/jgld-4607

The Risk of Postpolypectomy Bleeding in Patients Receiving Direct Oral Anticoagulants compared to Warfarin or Nonanticoagulation: A Systematic Review with Meta-Analysis

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Received: 06.09.2022
Accepted: 30.11.2022

ABSTRACT

Aim: The aim of our systematic review and meta-analysis was to assess the risk of postpolypectomy bleeding (PPB) in patients exposed to direct oral anticoagulants (DOACs).

Methods: A systematic search was conducted by searching the PubMed, Embase, and Cochrane Library databases using the following search terms: "(nonvitamin K antagonist oral anticoagulants or NOAC or apixaban or dabigatran or rivaroxaban or edoxaban or DOAC or direct oral anticoagulants) and polypectomy". Studies evaluating the association between DOACs and PPB were identified.

Results: The bibliographical search yielded 103 studies. Twelve studies involving 621,279 participants were ultimately included (11 cohort studies, of which 10 were retrospective, and a randomized controlled trial.). Pooled estimates revealed a higher risk of PPB among patients using DOACs than among those without anticoagulation (odds ratio [OR]: 6.170, 95% confidence interval [CI]: 3.079 to 12.363). The same result occurred when DOACs were stopped 24 hours before polypectomy (OR: 8.66, 95% CI: 4.588 to 16.348). No significant difference was noted between overall DOACs and warfarin (OR 0.826, 95% CI 0.583 to 1.172), while for subgroups, dabigatran showed a lower PPB rate than warfarin (OR: 0.582, 95% CI: 0.340 to 0.994).

Conclusions: DOACs can significantly raise the risk of PPB, even with 24-hour withdrawal before polypectomy. In addition, a lower risk of PPB was detected for dabigatran than for warfarin.

Key words: direct oral anticoagulant – warfarin – post polypectomy bleeding – gastrointestinal hemorrhage.

Abbreviations: AF: atrial fibrillation; CI: confidence intervals; CMA: comprehensive meta-analysis; DOAC: direct oral anticoagulants; EMR: endoscopic mucosal resection; ESD: endoscopic submucosal dissection; ESGE: European Society of Gastrointestinal Endoscopy; GI: gastrointestinal; INR: international normalized ratio; JGES: Japan Gastroenterological Endoscopy Society; NOAC: nonvitamin K antagonist oral anticoagulants; NOS: Newcastle - Ottawa Scale; OR: odds ratio; PPB: postpolypectomy bleeding; RCT: randomized controlled trial; ROB: risk of bias.

INTRODUCTION

Direct oral anticoagulants (DOACs), also known as nonvitamin K antagonist oral anticoagulants (NOACs), including oral factor Xa inhibitors, including rivaroxaban, apixaban and edoxaban, and oral direct thrombin inhibitors, such as dabigatran, have been increasingly used in the treatment of atrial fibrillation (AF) [1, 2]. As first-line drugs, DOACs have many advantages over traditional vitamin K antagonists (warfarin), such as higher persistence, efficacy, safety and convenience [3]. However, some studies found that DOACs were paradoxically related to an increase in gastrointestinal bleeding, which made invasive procedures in the digestive tract challenging [4, 5].

Gastrointestinal endoscopy is now widely used both to detect and remove precancerous polyps, especially in elderly patients. Nevertheless, postpolypectomy bleeding (PPB) is considered one of the highest risks for endoscopic resection of polyps [6]. Since the susceptible populations of gastrointestinal polyps and AF were partly similar, it was unclear whether there was an association between DOACs and PPB [7]. According to the guidelines from the European Society of Gastrointestinal Endoscopy (ESGE), DOACs should be withdrawn at least 48 hours before high-risk procedures such as endoscopic polypectomy based on low-level evidence [8]. However, one recent study revealed that there was no statistically significant

difference in the PPB rate in patients treated with DOACs compared with those not receiving antithrombotic agents [9]. It remains unclear whether DOACs could raise the risk of PPB. In addition, DOACs were not always discontinued in accordance with ESGE guidelines before endoscopic polypectomy [10-12]. Therefore, based on these contradictory results, we carried out this systematic review and meta-analysis to assess the risk of PPB in patients receiving DOACs treatment and to further provide high-level evidence-based medical proof for the application of DOACs in polypectomy.

METHODS

This protocol has been registered in the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY), with registration number (INPLASY2022100124).

Relevant studies were identified by searching PubMed (until December 2021), EMBASE (until December 2021), and the Cochrane Central Register of Controlled trials (Issue 12 of 12, until December 2021). The search terms used for all databases included the following: (nonvitamin K antagonist oral anticoagulants or NOAC or apixaban or dabigatran or rivaroxaban or edoxaban or DOAC or direct oral anticoagulants) and polypectomy. The search terms were slightly modified in different databases.

Two reviewers performed retrieval independently. The inclusion criteria were as follows: (1) patients: those who received endoscopic polypectomy (cold snare polypectomy or hot snare polypectomy) of the esophagus, stomach, colon, or rectum; (2) intervention: DOACs received before the endoscopic polypectomy; (3) comparator: patients received warfarin or nonanticoagulation before the endoscopic polypectomy; and (4) outcome: PPB after endoscopic polypectomy.

The exclusion criteria were as follows: (1) articles not reporting the prevalence of PPB; (2) information on PPB prevalence and sample size not available; (3) articles that included less than two branches of treatment consisting of DOACs; and (4) articles that were comments, reviews, letters, or case reports.

Postpolypectomy bleeding was defined as any bleeding occurring within 30 days of the completion of the procedure, including hematemesis, melena, spots of bleeding observed endoscopically, a fall in hemoglobin level of > 2 g/dL, or an event when emergency endoscopy with endoscopic hemostasis or transfusion of two or more units of red cells was needed. The PPB included immediate and delayed bleeding, while intraoperative bleeding was not included.

Two independent investigators extracted the data using standardized data extraction forms. Any discrepancies were resolved by consensus. The data collected included the year of publication, study design, number of patients in each treatment arm, prevalence of PPB, and endoscopic procedures.

Two reviewers assessed the quality of each cohort study independently using a 9-point Newcastle–Ottawa Scale (NOS). The scores were counted according to three aspects: selection of study subjects, comparability of groups, and assessment of outcome. The RCT was assessed by two reviewers independently using the Cochrane Risk of Bias (ROB) tool 2.0, according to five aspects of bias: bias for randomization, bias for deviations from intended interventions, bias for missing outcome data, bias for outcome measurement and bias for selective reporting of results. Discrepancies between the reviewers were resolved by consulting a third reviewer for adjudication.

The data analysis was performed using Comprehensive Meta-Analysis software, Version 2 (Biosta, Inc. USA).

For each study, we calculated the odds ratio (OR) for the primary measurement. The ORs are presented with 95% confidence intervals (CIs). The proportion of individuals with PPB in each study was combined to achieve a pooled prevalence of PPB. Moreover, pooled ORs were calculated to evaluate the prevalence of PPB among each treatment arm. All results are presented with 95% CIs.

The degree of heterogeneity of the studies was evaluated using the $\chi 2$ test (with a value less than 0.1 considered significant) and the I^2 test (25, 50, and 75% representing low, moderate, and high heterogeneity, respectively). To reduce the error caused by differences between studies, we conservatively used the random effect model to combine the effect sizes in these groups. To explore the different PPB risks between different DOAC regimens and warfarin, we conducted several subgroup analyses. Regarding the difference in polyp regions, we simply classified them as upper and lower gastrointestinal (GI) tract, and subgroup analyses were also performed in these groups. Since Japanese studies formed a large part of our included studies and because different dosages of warfarin have been suggested by Japanese guidelines, we deemed it necessary to conduct subgroup analyses of Japanese and non-Japanese studies to reduce bias. Regrettably, there was not sufficient information on the size of polyps for us to perform a subgroup analysis. To assess the stability of the results, a sensitivity analysis was also performed by excluding every single study. Publication bias was assessed by Egger's test and funnel plots.

RESULTS

Selection of Studies

A total of 103 studies were identified, and 35 duplicate studies were excluded. Forty-two studies were removed according to titles and abstracts, leaving 25 records to be examined. After reviewing the full-text articles, 6 studies of ineligible regimens and 7 studies with insufficient data were excluded. Ultimately, 12 studies were included (Fig. 1 and Table I) [9-20]. None of these studies reported receiving industry funding.

The sample size of these studies ranged between 55 and 605,044. Of the 12 studies, 10 studies were retrospective cohort studies [9, 11-18, 20], one was a prospective cohort study [10], and one was a randomized controlled trial (RCT) [19]. Three studies were conducted in China [14, 16, 18], two were conducted in the USA [9, 10], and the others were conducted in Japan [11-13, 15, 17, 19, 20]. Six studies investigated the prevalence of PPB among patients receiving DOACs and those without anticoagulation [9-12, 16, 18]. Furthermore, four studies mentioned the withdrawal timing of DOACs [10, 11, 12, 18]. Regarding the types of DOACs, six studies included dabigatran, rivaroxaban, apixaban, and edoxaban [11-14, 17,

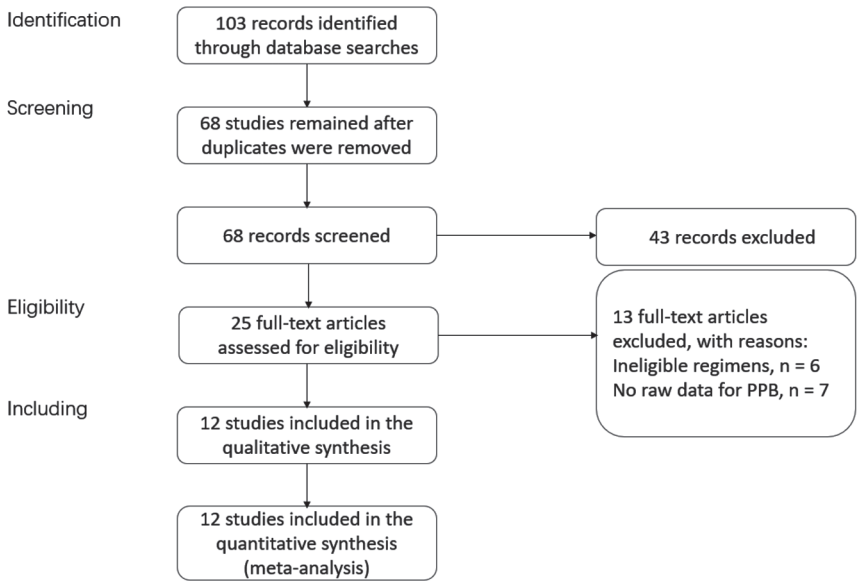


Fig. 1. Diagram of the study selection process.

20]. Warfarin was examined in all of the studies except one [9-17, 19, 20]. Table II presents the outcomes of PPB of the included studies.

Quality of Studies

The methodological quality of the included cohort studies was assessed using the NOS, and the scores varied from 5 to 8. The average score was 7.27. The only RCT was assessed using the Cochrane ROB tool 2.0 on its own, and the outcome showed a low risk of bias. Most of the cases, except one study in which patients who received cold snare polypectomy were included only, were highly represented. The exposure of all the participants was ascertained by surgical records. The follow-up of PPB was not defined or was too short in three studies (Supplementary file, Table I).

DOAC vs. Nonanticoagulation

Moderate heterogeneity was observed among these studies [9,10,11,12,16,18], and a random effects model was used (p=0.018; I^2=63.43%). The risk of PPB in the group with DOACs was higher than that in the group without anticoagulants. The summary OR was 6.170 (95%CI: 3.079-12.363). The results were stable regardless of which study was excluded according to sensitivity analysis (Fig. 2).

Dabigatran vs. Nonanticoagulation

Only two studies evaluated the risks of PPB with dabigatran treatment compared to those with nonanticoagulation [11, 12]. The risk of PPB in the group receiving dabigatran was higher than that in the group without anticoagulants in both studies.

Rivaroxaban vs Nonanticoagulation

Only two studies evaluated the risks of PPB with rivaroxaban treatment compared to that with nonanticoagulation [11, 12]. The risk of PPB in the group receiving rivaroxaban was higher than that in the group without anticoagulants in both studies.

Apixaban vs. Nonanticoagulation

Only two studies evaluated the risks of PPB with apixaban treatment compared to that with nonanticoagulation [11, 12].

Table I. The characteristics of included studies

Author, reference	Year	Country	Design type	Single/Multi center	Location
Lau et al. [14]	2022	China	Retrospective	Multicenter	Lower GI
Harada et al. [12]	2021	Japan	Retrospective	Multicenter	Lower GI
Kubo et al. [13]	2021	Japan	Retrospective	Multicenter	Upper/Lower GI
Song et al. [10]	2021	USA	Prospective	Single center	Lower GI
Yan et al. [16]	2021	China	Retrospective	Single center	Lower GI
Takeuchi et al. [19]	2019	Japan	RCT	Multicenter	Lower GI
Tomida et al. [20]	2019	Japan	Retrospective	Multicenter	Lower GI
Yu et al. [9]	2019	USA	Retrospective	Multicenter	Lower GI
Nagata et al. [15]	2018	Japan	Retrospective	Multicenter	Upper/Lower GI
Yanagisawa et al. [11]	2018	Japan	Retrospective	Single center	Lower GI
Lam et al. [18]	2017	China	Retrospective	Multicenter	Lower GI
Horiuchi et al. [17]	2016	Japan	Retrospective	Single center	Lower GI

GI: gastrointestinal.

Table II. The outcomes of PPB for all eligible studies

Study	DOACs		Warfarin		Non-anticoagulation	
	PPB, n	Total, n	PPB, n	Total, n	PPB, n	Total, n
Lau et al. [14]	38	1,665	116	2,222		
Harada et al. [12]	24	249	10	138	63	5,062
Kubo et al. [13]	37	389	53	383		
Song et al. [10]	5	13	1	5	2	81
Yan et al. [16]	1	26	4	31	21	1,785
Takeuchi et al. [19]	11	113	3	55		
Tomida et al. [20]	10	143	2	122		
Yu et al. [9]	10	1,590	43	3,471	1,430	599,983
Nagata et al. [15]	232	1,403	283	1,435		
Yanagisawa et al. [11]	10	73	20	145	2	218
Lam et al. [18]	7	106			6	318
Horiuchi et al. [17]	2	16	0	39		

PPB: postpolypectomy bleeding; DOAC: DOAC: direct oral anticoagulants.

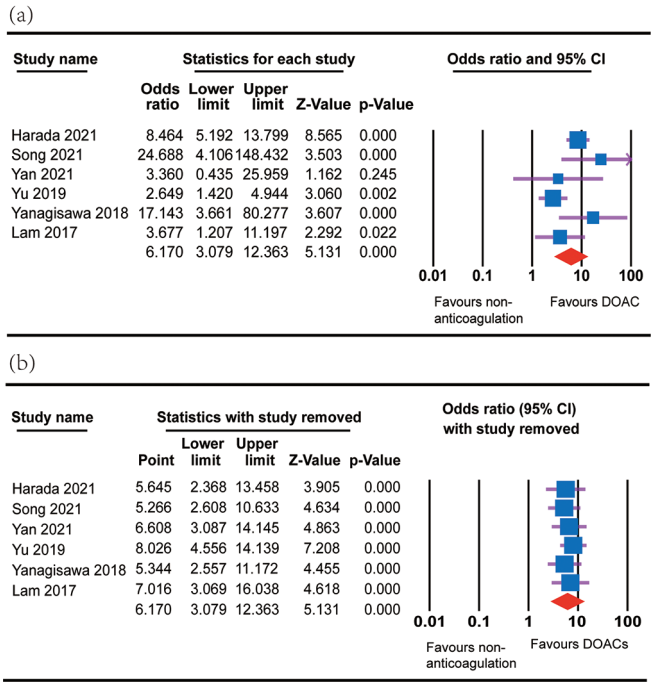


Fig. 2. Forest plot comparing the overall risk of PPB between the DOAC group and the nonanticoagulation group. (a) Comparison between the DOAC group and the nonanticoagulation group on PPB risk. (b) Sensitivity analysis.

The risk of PPB in the group receiving apixaban was higher than that in the group without anticoagulants in both studies.

Edoxaban vs. Nonanticoagulation

Only one study evaluated the risks of PPB with edoxaban treatment compared to that with nonanticoagulation [12]. The risk of PPB in the group receiving edoxaban was higher than that in the group without anticoagulants.

DOACs Stopped 24 Hours Ahead vs. Nonanticoagulation

Four studies evaluated the risk of PPB with 24-hour withdrawal of DOACs compared to that with nonanticoagulation [10-12, 18]. Low heterogeneity was observed among these studies, and a random effects model was used (p=0.229; I^2=30.6%). The risk of PPB in the group undergoing a 24-hour withdrawal of DOACs ahead of polypectomy was higher than that in the group not receiving any anticoagulants. The summary OR was 8.66 (95%CI: 4.588-16.348) (Fig. 3).

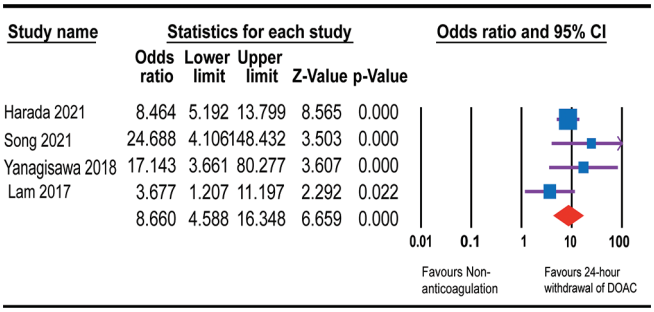


Fig. 3. Forest plot comparing the overall risk of PPB between the group undergoing a 24-hour withdrawal of DOACs ahead of polypectomy and the nonanticoagulation group.

DOACs vs. Warfarin

Moderate heterogeneity was observed among these studies [9-17, 19, 20], and a random effects model was used (p=0.004; I^2=61.68%). No significant difference was found between the DOAC and warfarin groups regarding the risk of PPB. The summary OR was 0.826 (95%CI: 0.583-1.172). The results were stable regardless of which study was excluded according to the sensitivity analysis (Fig. 4). The exclusion of the RCT did not influence the results (Supplementary file, Fig.S2) [19].

Dabigatran vs. Warfarin

Six studies evaluated the risk of PPB with dabigatran treatment compared to that with warfarin treatment [11-14, 17, 20]. Low heterogeneity was observed among these studies, and a random effects model was used (p=0.33; I^2=13.17%). The risk of PPB in the group receiving dabigatran was lower than

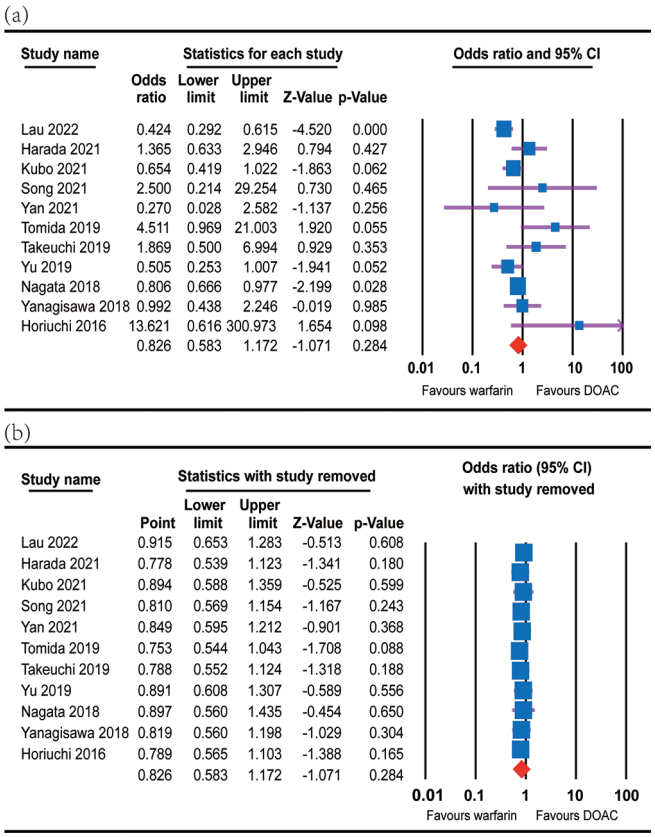


Fig. 4. Forest plot comparing the overall risk of PPB between the DOAC group and the warfarin groups. (a) Comparison between the DOAC group and the warfarin group on PPB risk. (b) Sensitivity analysis.

that in the group treated with warfarin. The summary OR was 0.582 (95% CI: 0.340-0.994) (Fig. 5a).

Rivaroxaban vs. Warfarin

Five studies evaluated the risk of PPB with rivaroxaban treatment compared to that with warfarin treatment [11-14, 20]. Moderate heterogeneity was observed among these studies, and a random effects model was used (p=0.008; I^2=71.09%). No significant difference was found between the rivaroxaban and warfarin groups regarding the risk of PPB. The summary OR was 1.018 (95%CI: 0.491-2.109) (Fig. 5b).

Apixaban vs. Warfarin

Six studies evaluated the risk of PPB with apixaban treatment compared to that with warfarin treatment [11-14, 17, 20]. Moderate heterogeneity was observed among these studies, and a random effects model was used (p=0.003; I^2=72.32%). No significant difference was found between the apixaban and warfarin groups regarding the risk of PPB. The summary OR was 1.125 (95% CI: 0.468-2.706) (Fig. 5c).

Edoxaban vs. Warfarin

Three studies evaluated the risk of PPB with edoxaban treatment compared to that with warfarin treatment [12, 13, 20]. Moderate heterogeneity was observed among these studies, and a random effects model was used (p=0.177; I^2=42.26%). No significant difference was found between the edoxaban and

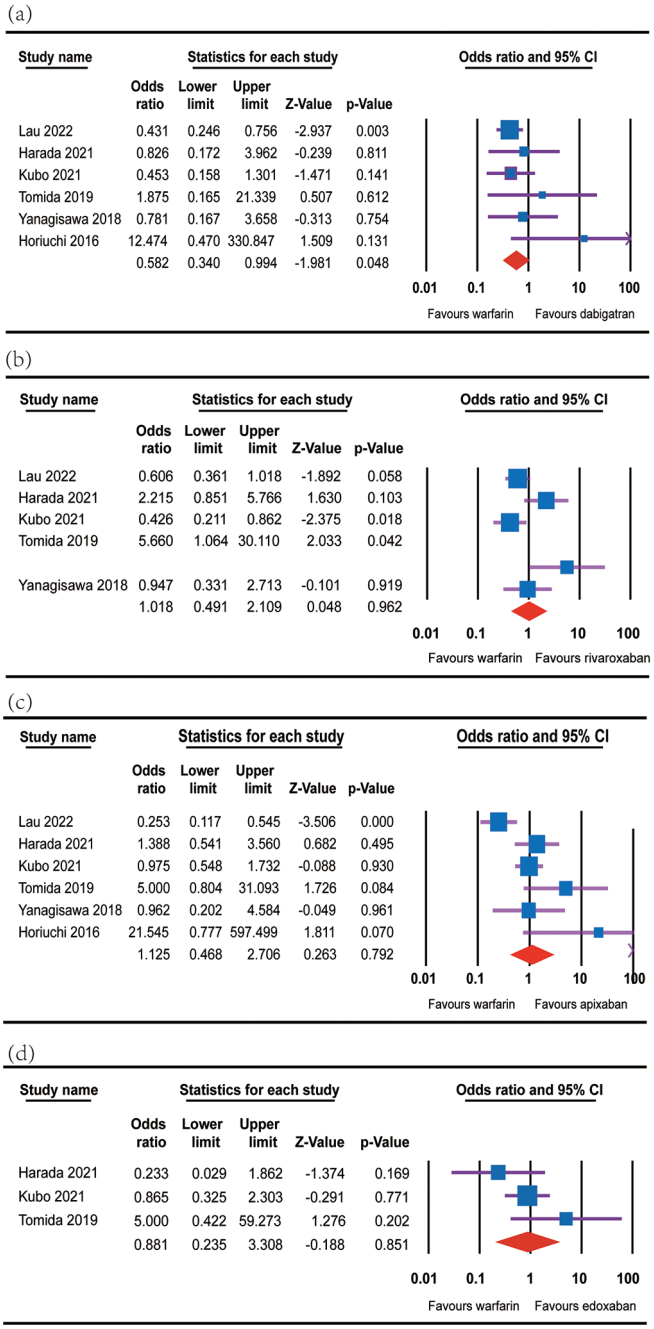


Fig. 5. Forest plot comparing the overall risk of PPB between the DOAC group and the warfarin group. (a) Comparison between the dabigatran group and the warfarin group on PPB risk. (b) Comparison between the rivaroxaban group and the warfarin group on PPB risk. (c) Comparison between the apixaban group and the warfarin group on PPB risk. (d) Comparison between the edoxaban group and the warfarin group on PPB risk.

warfarin groups regarding the risk of PPB. The summary OR was 0.881 (95%CI: 0.235-3.308) (Fig. 5d).

DOAC vs. Nonanticoagulation in Japanese Studies

Only two studies evaluated the risks of PPB with DOAC treatment compared to warfarin in patients among Japanese studies [11, 12]. The risk of PPB in the group receiving DOACs was higher than that in the group without anticoagulants in both studies.

DOAC vs. Nonanticoagulation in Non-Japanese Studies

Low heterogeneity was observed among the four studies [9, 10, 16, 18], and a random effects model was used (p=0.150; I^2=43.65%). Among non-Japanese studies, the risk of PPB in the group with DOACs was higher than that in the group without anticoagulants. The summary OR was 4.220 (95% CI: 1.861-9.571) (Fig. 6). The results were stable regardless of which study was excluded according to sensitivity analysis.

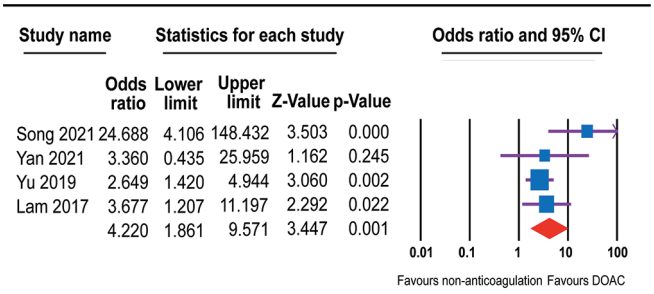
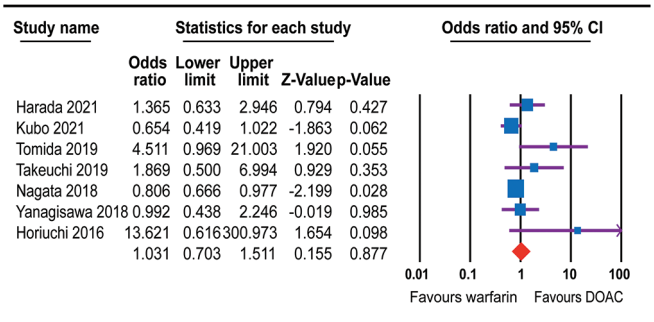


Fig. 6. Forest plot comparing the overall risk of PPB between the DOAC group and the nonanticoagulation group among non-Japanese studies.

DOAC vs. Warfarin in Japanese Studies

Moderate heterogeneity was observed among the six studies [11-13, 15, 17, 19, 20], and a random effects model was used (p=0.058; I^2=50.72%). No significant difference was found between the DOAC and warfarin groups among Japanese studies regarding the risk of PPB. The summary OR was 1.031 (95%CI: 0.703-1.511) (Fig. 7a). The results were stable even though the RCT was excluded according to the sensitivity analysis (Supplementary file, Fig. S3) [19].

(a)



(b)

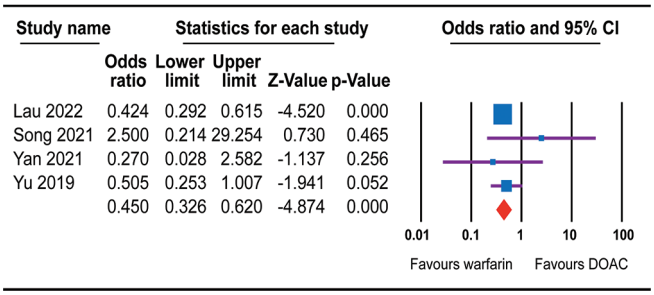


Fig. 7. Forest plot comparing the overall risk of PPB between the DOAC group and the warfarin group. (a) Comparison among Japanese studies. (b) Comparison among non-Japanese studies.

DOAC vs. Warfarin in Non-Japanese Studies

Low heterogeneity was observed among the four studies [9, 10, 14, 16], and a random effects model was used (p=0.519; I^2=0%). Among non-Japanese studies, the risk of PPB in the group receiving DOACs was lower than that in the group treated with warfarin. The summary OR was 0.450 (95% CI: 0.326 to 0.620) (Fig. 7b). The results were stable regardless of which study was excluded according to the sensitivity analysis.

DOAC vs. Warfarin in the Upper GI Tract

Only one study evaluated the risks of PPB with DOAC treatment compared to warfarin in patients receiving a polypectomy of the upper GI tract [15]. The risk of PPB in the group receiving DOACs was lower than that in the group with warfarin.

DOAC vs. Warfarin in the Lower GI Tract

Moderate heterogeneity was observed among these studies [9-17, 19, 20], and a random effects model was used (p=0.003; I^2=63%). No significant difference was found between the DOAC and warfarin groups regarding the risk of PPB. The summary OR was 0.859 (95% CI: 0.590-1.250) (Fig. 8). Sensitivity analysis revealed that the results were stable even the RCT was excluded (Supplementary file, Figure S4) [19].

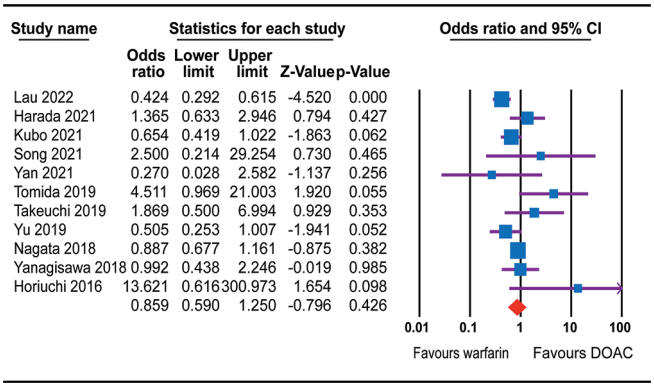


Fig. 8. Forest plot comparing the overall risk of PPB between the DOAC group and the warfarin group in the lower GI.

Publication Bias

No significant publication bias was identified by the funnel plot. Egger's regression test (p=0.26) and Begg's test (p= 0.16) also did not show significant bias (Fig. 9).

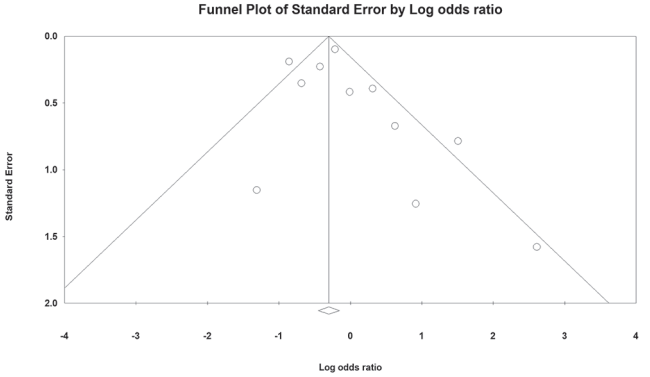


Fig. 9. Funnel plot for publication bias of included studies.

DISCUSSION

This is the first meta-analysis which examines the prevalence of PPB occurrence rates comparing DOACs with nonanticoagulation. The results of this meta-analysis showed that the incidence of PPB was much higher in the DOAC group than in the nonanticoagulation group (OR=6.170, 95%CI: 3.079-12.363), which indicated that DOACs were independent risk factors for PPB.

For subgroups, our study explored the correlation between the withdrawal timing of DOACs and the risk of PPB. As the latest ESEG guideline suggested, DOACs should be stopped at least 48 hours before high-risk endoscopic procedures, including polypectomy [8]. Moreover, more substantial and solid evidence is required for confirmation. However, the JGES guideline in 2014 posted a different suggestion, namely, that DOACs should be stopped 24-48 hours before the procedures [21]. We found that the PPB rate was obviously higher in the 24-hour withdrawal group (OR=8.66, 95%CI: 4.588-16.348) than in the nonanticoagulation group. This result provided strong evidence for ESGE guidelines that DOACs should be stopped 48 hours ahead of polypectomy to prevent a hemorrhage.

Rivaroxaban, apixaban, dabigatran and edoxaban were the most commonly and extensively used DOACs. The results of the subgroup analysis showed that the abovementioned DOACs were all risk factors for PPB. Rivaroxaban, apixaban, and edoxaban inhibit the extrinsic and intrinsic pathways of blood coagulation by inhibiting factor Xa directly. Dabigatran acts as an oral direct thrombin inhibitor for free and fibrin-bound thrombin, and the safety of these drugs is of great concern. According to the ESEG guidelines, several studies have shown that dabigatran is associated with an increased risk of GI bleeding [22, 24]. The mechanism of the high bleeding risk was proposed to be the low pH of the GI tract caused by the tartaric acid core contained in the dabigatran particles [22, 23]. Interestingly, our results also showed that dabigatran was superior to warfarin in terms of PPB (OR=0.582, 95%CI: 0.34-0.994), which may be attributed to several reasons. First, our study focused on PPB, especially in the lower GI, while previous studies simply analyzed GI bleeding without limitations on the procedures or segments of GI. Second, a lower GI is not affected to a large extent by gastric acid. This result indicated that dabigatran might be a better choice in polypectomy.

In addition, our meta-analysis compared DOACs with warfarin. No significant difference between DOACs and warfarin was detected regarding the risk of PPB (OR=0.826, 95%CI: 0.583-1.172). However, a recent meta-analysis comparing DOACs with warfarin reported a decrease in post-procedural bleeding risk using DOACs instead of warfarin, following endoscopic resection [25]. This opposite result may be due to the different endoscopic procedures incorporated. Since Zhu et al. [25] focused on endoscopic resection, including cold polypectomy, hot polypectomy, endoscopic submucosal dissection (ESD), and endoscopic mucosal resection (EMR), we only focused on polypectomy. Furthermore, 27 of 30 studies included in their meta-analysis came from Japan, suggesting a probable existence of geographical bias. With a more precise scope of study and less bias, our study has a greater clinical significance for polypectomy in anticoagulant users.

Since most of the studies that focused on the relationship between DOACs and PPB came from Japan, we performed a subgroup analysis according to the country of origin of the studies. The results suggested that compared with warfarin, DOACs had a decreased PPB risk among non-Japanese studies, while in Japanese studies, no significant difference was found between DOACs and warfarin regarding PPB risk. The different outcomes between Japan and other regions may be due to the different doses of warfarin according to different guidelines. Japanese patients usually receive a small dose of warfarin to achieve a target international normalized ratio (INR) of 1.6 to 2.6 [26], while in other countries, the target INR is defined as 2.0 to 3.0 [27, 28], which may be due to the increased risk of bleeding in the Asian population compared to Caucasians under warfarin treatment according to recent research [29]. With a smaller dose of warfarin, those patients who received warfarin as anticoagulants in Japanese studies would probably have less PPB risks than those in other regions. Ethnic differences should also be taken into consideration. Our outcome is different from Zhu et al. [25] work, which included 27 of 30 studies in their meta-analysis from Japan [25]. These different outcomes between our Japanese-study subgroup and their works are mainly due to the different internalized studies, especially Harada et al. [12] work, which was published recently and with a high preponderance in our analysis. In this study, a higher PPB risk was detected in the DOACs group than in the warfarin group (DOACs: 9.2%, warfarin: 7.2%, p= 0.572]). More research from other regions should be included in the future to increase the applicability of the results.

As they are the second highest level of evidence, RCTs are more valid than cohort studies. However, due to the ethical dilemmas, few RCTs have examined the relationship between anticoagulants and PPB. Our search strategy only identified one RCT that examined the risk of PPB in DOACs or warfarin users. In this trial, the PPB rate of DOAC users showed no statistical difference compared with those using warfarin (DOACs: 9.7%, warfarin: 5.5%; p=0.519), which was consistent with our pooled results.

There were also several potential limitations of our meta-analysis. First, the number of studies examining DOACs for PPB was limited. Therefore, further studies are warranted. Second, significant heterogeneity was found when the data were pooled. The reason may be different characteristics among studies. The random-effect model was used to provide a more conservative result. Third, incomplete reporting of detailed data such as localization of resected polyps was found in some included studies. Although the polyps were localized in the upper or lower GI, the specific localization was not counted in most of the studies, which may lead to potential bias. Additionally, most included studies were cohort studies. We could only describe the association between DOACs and PPB. More RCT studies are required to detect causal relationships.

CONCLUSIONS

Direct oral anticoagulants were independent risk factors for PPB, even with 24-hour withdrawal before polypectomy. In addition, the superiority of dabigatran over warfarin for use in polypectomy was identified.

Conflicts of interest: None to declare.

Authors' contribution: H.-Z.Y. and B.W. designed the study. H.-Z.Y. and J.-J.G. collected the data. B.W. analyzed the data. H.-Z.Y. and J.-J.G. interpreted the results. H.-Z.Y. drafted the manuscript. B.W., J.-J.G., H.Z., Z.-W.L. and H.-W.X. critically revised the manuscript. All authors approved the final version to be published, and agree to be accountable for all aspects of the work.

Supplementary material: To access the supplementary material visit the online version of the *J Gastrointestin Liver Dis* at http://dx.doi.org/10.15403/jgld-4607.

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