**Name of Journal:** *World Journal of Meta-Analysis*

**Manuscript NO:** 59547

**Manuscript Type:** META-ANALYSIS

**Effects of antithrombotic agents on post-operative bleeding after endoscopic resection of gastrointestinal neoplasms and polyps: A systematic review and meta-analysis**

Xiang BJ *et al*. Antithrombotic agents and ER

Bing-Jie Xiang, Yu-Hong Huang, Min Jiang, Cong Dai

**Bing-Jie Xiang, Yu-Hong Huang, Min Jiang, Cong Dai,** Department of Gastroenterology, First Affiliated Hospital, China Medical University, Shenyang 110001, Liaoning Province, China

**Author contributions:** Xiang BJ had the original idea for the paper, formulated the protocol; Xiang BJ and Huang YH carried out the literature search, selection, validity assessment, data abstraction and data analysis; Xiang BJ and Dai C wrote the paper and incorporated the comments from other authors; and all authors reviewed and approved the final draft of the paper.

**Supported by** Liaoning Science and Technology Foundation, No. 20170541052.

**Corresponding author: Cong Dai, PhD, Assistant Professor,** Department of Gastroenterology, First Affiliated Hospital, China Medical University, No. 92 Beier Road, Heping District, Shenyang 110001, Liaoning Province, China. congdai2006@sohu.com

**Received:** September 17, 2020

**Revised:** October 7, 2020

**Accepted:** October 27, 2020

**Published online:**

**Abstract**

BACKGROUND

There are some studies investigating the relationship between antithrombotic medication and postoperative bleeding after endoscopic resection (ER) with controversial results.

AIM

To perform a meta-analysis evaluating the effects of antithrombotic therapy on postoperative bleeding after ER.

METHODS

A systematic search was conducted on PubMed, Web of Science, Cochrane Library. The Newcastle-Ottawa scale was used to evaluate the quality of studies. Stata 12.0 was used for statistical analysis. The odds ratio (OR) and 95%CI were calculated and heterogeneity was quantified using Cochran’s *Q* test and *I*2.

RESULTS

Total 66 studies were included in the meta-analysis. Pooled data suggested that antithrombotic therapy was significantly associated with postoperative bleeding (OR = 2.302, 95%CI: 2.057-2.577, *P* = 0.000) after ER. The risk of postoperative bleeding after endoscopic submucosal dissection, endoscopic mucosal resection and polypectomy in the antithrombotic group was higher than the non-antithrombotic group (OR = 2.439, 95%CI: 1.916-3.105; OR = 2.688, 95%CI: 1.098-6.582; OR = 2.112, 95%CI: 1.434-3.112).

CONCLUSION

The risk of postoperative bleeding after ER correlated with the types and management of antithrombotic agents by our meta-analysis.

**Key Words:** Endoscopic resection; Antithrombotic; Anticoagulants; Postoperative bleeding; Endoscopic mucosal resection; Endoscopic submucosal dissection

Xiang BJ, Huang YH, Jiang M, Dai C. Effects of antithrombotic agents on post-operative bleeding after endoscopic resection of gastrointestinal neoplasms and polyps: A systematic review and meta-analysis. *World J Meta-Anal* 2020; In press

**Core Tip:** In recent years, more and more people suffering from cardiovascular disease and/or cerebrovascular disease receive antithrombotic therapy which change patients’ coagulation status and may lead to high risk of postoperative bleeding after endoscopic resection (ER). The relationship between the postoperative bleeding after ER and antithrombotic agents is still uncertain. With this reason, a systematic review and meta-analysis was carried out to identify whether the use of antithrombotic drugs increases the risk of the postoperative bleeding after ER.

**INTRODUCTION**

Endoscopic resection (ER) is deemed as an effective method for gastrointestinal neoplasia and polyp. ER is an acceptable technique to enable *en bloc* resection of gastric adenomas, early oesophageal, gastric and colorectal cancer and incidence and its related mortality of colorectal cancer[1-3]. This includes polypectomy, endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). For example, patients with oesophageal neoplasia receiving ER can maintain the integrity of oesophageal structure and function, whereas the quality of life can be affected by oesophagectomy[4].

Although the therapeutic effect of ER has been greatly affirmed, Postoperative bleeding as a major complication is still a problem to be solved. Postoperative bleeding after ER is defined as bleeding within 30 d from a mucosal defect shown by massive melena, a decrease in blood hemoglobin level of more than 2 g/dL, or requirement of endoscopic hemostasis or transfusion[1,5,6]. A study has shown that the incidence rate of postoperative bleeding after esophageal or colorectal ESD ranged from 0.0% to 4.6%[7]. And the incidence rate of postoperative bleeding after ESD due to gastric neoplasm ranged from 1.8% to 15.6%[7]. A study that included 3788 cases of polypectomy by Choung found that postoperative bleeding occurred in 42 cases (1.1%)[8]. Another study with 30881 cases of polypectomy by Rutter also reported that the postoperative bleeding developed in 291 cases (0.94%)[9]. Preventive strategies such as acid secretion inhibitors and prophylactic clipping have been developed to reduce the postoperative bleeding risk after ER, but postoperative bleeding cannot be completely avoided. Some factors such as the size of polyp and a patient’s coagulation status have been reported to be associated with the risk of postoperative bleeding after ER.

In recent years, more and more people suffering from cardiovascular disease and/or cerebrovascular disease receive antithrombotic therapy which change patients’ coagulation status and may lead to high risk of postoperative bleeding after ER. The relationship between the postoperative bleeding after ER and antithrombotic agents is still uncertain. With this reason, a systematic review and meta-analysis was carried out to identify whether the use of antithrombotic drugs increases the risk of the postoperative bleeding after ER.

**MATERIALS AND METHODS**

We carried out a systematic review and meta-analysis of the hemorrhagic data of different antithrombotic users after ER from published studies. The review and analysis was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines[10].

***Search method***

We used PubMed, Web of Science and Cochrane Library to search for articles published in English from inception to February 2019. The search queries were: (1) ( ( (antithrombotic OR anticoagulant OR antiplatelet OR heparin OR warfarin OR aspirin)) AND (endoscopic submucosal dissection OR ESD)) AND (bleeding OR hemorrhage); (2) ( ( (antithrombotic OR anticoagulant OR antiplatelet OR heparin OR warfarin OR aspirin)) AND (EMR OR endoscopic mucosal resection)) AND (bleeding OR hemorrhage); (3) ( ( (antithrombotic OR anticoagulant OR antiplatelet OR heparin OR warfarin OR aspirin)) AND (endoscopic polypectomy)) AND (bleeding OR hemorrhage); and (4) ( ( (antithrombotic OR anticoagulant OR antiplatelet OR heparin OR warfarin OR aspirin)) AND (APC OR argon plasma coagulation)) AND (bleeding OR hemorrhage).

***Study selection***

The studies that met the following inclusion criteria were included: (1) Polypectomy, EMR, ESD, polypectomy incorporated argon plasma coagulation and the hot and cold snare; (2) Randomized controlled trials, retrospective studies or cohort studies were performed to investigate the risk of postoperative bleeding after ER in patients with gastrointestinal neoplasm receiving antithrombotic medication; (3) The incidence rate of postoperative bleeding can be extracted in the antithrombotic medication group and the non-antithrombotic medication group; and (4) Anticoagulants and antiplatelet drugs were incorporated in antithrombotic agents.

The studies were excluded if: (1) The postoperative bleeding rate or antithrombotic therapy information could not be extracted; (2) Antithrombotic drugs and NSAIDS were recorded together; (3) Endoscopic treatment such as biopsy, sphincterotomy or ampullectomy was carried out; (4) Reviews, case reports, guidelines, or animal studies were screened out; (5) The articles were not written in English; and (6) The full text could not be obtained.

***Methodological quality assessment***

The Newcastle-Ottawa scale was used to evaluate the quality of the included studies. And the Newcastle-Ottawa scale includes three aspects: selection, comparability, exposure (retrospective studies) or outcome (cohort studies)[11].

***Data extraction***

Two authors worked together to extract the basic information about the first author, publication year, country, research method (retrospective/cohort), ER method (ESD/EMR/polypectomy), number, age and gender. Moreover, the odds ratio (OR) and 95%CI of the postoperative bleeding rate were calculated in the antithrombotic group (continued/discontinued) and the non-antithrombotic group.

***Statistical analysis***

Statistical analysis was performed by Stata 12.0. The Cochran’s *Q* test and *I*2 (*P* < 0.10 was considered significant) were used to identify heterogeneity. The value *I*2 of 0-25% indicated insignificant heterogeneity; 26%-50%, low heterogeneity; 51%-75%, moderate heterogeneity; and greater than 75%, high heterogeneity[12]. If there was no significant heterogeneity, the OR and 95%CI were calculated in a fixed-effect model. Otherwise, a random-effect model was used. The funnel plot was used to assess publication bias.

**RESULTS**

***Assessment of the studies***

The initial literature yielded 1258 articles (454 articles from PubMed, 679 articles from Web of Science, 125 articles from Cochrane Library). After the exclusion of 929 articles due to duplicates and lack of relevance, 329 articles were retrieved for full text evaluation. 263 articles were excluded after reviewing the full text (Figure 1). Ultimately, 66 studies were included in the meta-analysis (Fifty-nine retrospective studies, seven prospective observational studies). The characteristics of included studies were described in the Table 1. The included studies were carried out from different countries (Fifty from Japan, six from Korean, five from USA, two from Italy, one from UK, one from Australia, one from Holland). The mean age was older than 60 years old in most studies.

***Effect analysis***

A total of 48691 cases after ER were enrolled, of which 8918 cases were receiving antithrombotic medication and 39773 cases were not taking any antithrombotic drugs[1,2,4,6,13-33]. The average postoperative bleeding rate in the antithrombotic group was 8.44%, while it was 5.28% in the non-antithrombotic group. With the random-effects model, the risk of postoperative bleeding in the antithrombotic group was higher than the non-antithrombotic group (OR = 2.421, 95%CI: 1.831-3.200, *P* = 0.000, *I*2 = 82.5%). In addition, a more homogeneous analysis (*I*2 = 36.0%) was carried out after six articles[3,5,29,34-36] were screened out in the sensitivity analysis and the results remained unchanged (OR = 2.302, 95%CI: 2.057-2.577, *P* = 0.000) (Figure 2). Besides this, the results were not changed when data from retrospective and prospective studies were separately analyzed.

A total of 27014 cases after ESD were enrolled in this meta-analysis (3624 cases were receiving antithrombotic medication and 23390 cases were not taking antithrombotic drugs[1,6,13-30,33,37-41]). The average postoperative bleeding rate after ESD in the antithrombotic group was 13.91%, while it was 7.77% in the non-antithrombotic group. With the random-effects model, the risk of postoperative bleeding after ESD in the antithrombotic group was higher than the non-antithrombotic group (OR = 2.439, 95%CI: 1.916-3.105, *P* = 0.000, *I*2 = 63.5%). Moreover, a more homogeneous analysis (*I*2 = 0.0%) was carried out after six articles[6,20,24,26,29,36] were screened out in the sensitivity analysis and the results remained unchanged (OR = 2.507, 95%CI: 2.185-2.875, *P* = 0.000, Figure 3). The risk of postoperative bleeding after gastric ESD in the antithrombotic group was higher than the non-antithrombotic group (OR = 2.295, 95%CI: 1.757-2.998, *P* = 0.000, *I*2 = 64.1%)[6,13-15,17,19,20,22-29,33]. Meanwhile, the risk of postoperative bleeding after colorectal ESD in the antithrombotic group was higher than the non-antithrombotic group (OR = 3.305, 95%CI: 1.561-6.998, *P* = 0.002, *I*2 = 65.0%)[1,15,18,21,36].

A total of 5514 cases after EMR were enrolled in this meta-analysis (1475 cases were receiving antithrombotic medication and 4039 cases were not taking any antithrombotic drugs[1,2,4,5,42]). The average postoperative bleeding rate after EMR in the antithrombotic group was 2.85%, while it was 1.29% in the non-antithrombotic group. With the random-effects model, the risk of postoperative bleeding after EMR in the antithrombotic group was higher than the non-antithrombotic group (OR = 2.688, 95%CI: 1.098-6.582, *P* = 0.030. *I*2 = 72.7%). Furthermore, a more homogeneous analysis (*I*2 = 5.3%) was carried out after one article[5] was screened out in the sensitivity analysis and the results remained unchanged (OR = 3.765, 95%CI: 2.380-5.954, *P* = 0.000, Figure 4). The risk of postoperative bleeding after colorectal EMR in the antithrombotic group was higher than the non-antithrombotic group (OR = 3.711, 95%CI: 2.332-5.904, *P* = 0.005, *I*2 = 32.9%). But the analysis on the risk of postoperative bleeding after gastric EMR could not be carried out due to insufficient data.

A total of 10709 cases of polypectomy were enrolled in this meta-analysis (2554 cases were receiving antithrombotic medication and 8155 cases were not taking any antithrombotic drugs[1,3,35,43-46]). The average postoperative bleeding rate in the antithrombotic group was 4.89%, while it was 1.69% in the non-antithrombotic group. With the random-effects model, there was no significant difference (OR = 2.338, 95%CI: 0.610-8.954, *P* = 0.215, *I*2 = 93.6%) in the postoperative bleeding rate between the two groups. Another more homogeneous analysis (*I*2 =44.4%) was carried out after two articles[3,35] were screened out in the sensitivity analysis and the results were found to have changed (OR = 2.112, 95%CI: 1.434-3.112, *P* = 0.006, Figure 5). The risk of postoperative bleeding after colorectal polypectomy in the antithrombotic group was higher than the non-antithrombotic group (OR = 2.921, 95%CI: 1.821-4.687, *P* = 0.000, *I*2 = 31.9%). Table 2 shows the number of cases with or without antithrombotic agents and hemorrhagic outcome.

***Quality assessment and publication bias***

The Newcastle-Ottawa scale was used to assess the quality of the included studies in this meta-analysis. Thirteen articles had 6 stars, twenty-three articles had 7 stars, twenty-eight articles had 8 stars, and the others had 9 stars (Table 3). At the same time, the funnel plot did not show any features associated with publication bias (Figure 6).

***Subgroup analyses***

Among the ESD group, we performed several subgroup analyses to independently evaluate the effects of different types of antithrombotic agents in postoperative bleeding: (1) In gastric ESD retrospective comparison studies of single antithrombotic user (No. bleeding/total = 43/524) *vs* non-antithrombotic agent user (No. bleeding/total = 112/2671)[15,17,27]: The risk of postoperative bleeding in single antithrombotic agent group was significantly higher than the non-antithrombotic agent group [OR = 2.061, 95%CI: 1.405-3.024, *P* = 0.000 (*I*2 = 0.0%)]; (2) In gastric ESD retrospective comparison studies of multiple antithrombotic user (No. bleeding/total = 33/179) *vs* non-antithrombotic agent user (No. bleeding/total = 150/3361)[15,17,27,41]: The risk of postoperative bleeding in multiple antithrombotic agents group was significantly higher than the non-antithrombotic agent group [OR = 4.985, 95%CI: 3.251-7.561, *P* = 0.000 (*I*2 = 40.6%)]; (3) In gastric ESD retrospective comparison studies of multiple antithrombotic (No. bleeding/total = 33/179) user *vs* single antithrombotic user (No. bleeding/total = 55/666)[15,17,27,41]: The risk of postoperative bleeding in multiple antithrombotic agents group was higher than the single antithrombotic agent group [OR = 2.492, 95%CI: 1.563-3.974, *P* = 0.000 (*I*2 = 43.9%)]; (4) In gastric ESD retrospective comparison studies of discontinued antithrombotic user *vs* (No. bleeding/total = 81/1074) non-antithrombotic agent user (No. bleeding/total = 216/3894)[14,25,27,47-49]: The risk of postoperative bleeding in discontinued antithrombotic agent group was slightly higher than the non-antithrombotic agent group [OR = 1.405, 95%CI: 1.069-1.848, *P* = 0.015 (*I*2 = 34.4%)]; (5) In gastric ESD retrospective comparison studies of continuous antithrombotic user (No. bleeding/total = 18/144) *vs* non-antithrombotic user (No. bleeding/total = 50/1081)[25,27,49]: The risk of postoperative bleeding in continuous antithrombotic agent group was higher than the non-antithrombotic agent group [OR = 2.886, 95%CI: 1.513-5.504, *P* = 0.001 (*I*2 = 0.0%)]; (6) In gastric ESD retrospective comparison studies of continuous antithrombotic user (No. bleeding/total = 18/144) *vs* discontinued antithrombotic user (No. bleeding/total = 55/660)[25,27,49]: There was no significant difference in the risk of postoperative bleeding between the two groups [OR = 1.615, 95%CI: 0.919-2.837, *P* = 0.096 (*I*2 = 32.9%)]; (7) In gastric ESD retrospective comparison studies of antiplatelet (APT) (No. bleeding/total = 100/891) user *vs* non-antithrombotic user (No. bleeding/total = 212/4620)[15,38,41,50,51]: The risk of postoperative bleeding in the APT agent group was higher than the non-antithrombotic agent group [OR = 2.545, 95%CI: 1.979-3.273, *P* = 0.000 (*I*2 = 38.8%)]. In colorectal ESD retrospective comparison studies of APT user (No. bleeding/total = 22/425) *vs* non-antithrombotic user (No. bleeding/total = 90/2914)[52-55]: The risk of postoperative bleeding in the APT agent group was higher than the non-antithrombotic agent group [OR = 1.821, 95%CI: 1.127-2.944, *P* = 0.014 (*I*2 = 25.8%)]; (8) In gastric ESD retrospective comparison studies of discontinued APT user (No. bleeding/total = 17/271) *vs* non-antithrombotic user (No. bleeding/total = 127/2450)[41,51,56]: There was no significant difference in the risk of postoperative bleeding risk between the two groups [OR = 1.218, 95%CI: 0.721-2.060, *P* = 0.461 (*I*2 = 0.0%)]. In colorectal ESD retrospective comparison studies of discontinued APT user (No. bleeding/total = 9/179) *vs* non-antithrombotic user (No. bleeding/total = 69/1787)[53,54,57]: There was no significant difference in the risk of postoperative bleeding between the two groups [OR = 1.494, 95%CI: 0.725-3.081, *P* = 0.277 (*I*2 = 0.0%)]; (9) In gastric ESD retrospective comparison studies of continuous APT user (No. bleeding/total = 43/350) *vs* non-antithrombotic user (No. bleeding/total = 141/2710)[25,41,51,56,58]: The risk of postoperative bleeding in continuous APT agent group was higher than the non-antithrombotic agent group [OR = 2.955, 95%CI: 2.026-4.310, *P* = 0.000 (*I*2 = 0.0%)]. In colorectal ESD retrospective comparison studies of continuous APT user (No. bleeding/total = 9/75) *vs* non-antithrombotic user (No. bleeding/total = 69/1787)[53,54,57]: The risk of postoperative bleeding risk in continuous APT agent group was higher than the non-antithrombotic agent group [OR = 3.409, 95%CI: 1.652-7.036, *P* = 0.001 (*I*2 = 43.9%)]; (10) In gastric ESD retrospective comparison studies of continuous APT user (No. bleeding/total = 44/299) *vs* discontinued APT user (No. bleeding/total = 20/297)[41,56,59,60]: The risk of postoperative bleeding in continuous APT agent group was higher than the discontinued APT agent group [OR = 2.004, 95%CI: 1.095-3.668, *P* = 0.024 (*I*2 = 0.0%)]. In colorectal ESD retrospective comparison studies of continuous APT user (No. bleeding/ total = 9/75) *vs* discontinued APT user (No. bleeding/total = 9/179)[53,54,57]: There was no significant difference in the risk of postoperative bleeding between the two groups [OR = 1.740, 95%CI: 0.616-4.910, *P* = 0.296 (*I*2 = 50.6%)]; (11) In gastric ESD retrospective comparison studies of multiple APT user (No. bleeding/total = 33/131) *vs* non-antithrombotic user (No. bleeding/total = 89/1815)[15,41,50,56]: The risk of postoperative bleeding in multiple APT agent group was higher than the non-antithrombotic agent group [OR = 6.437, 95%CI: 4.048-10.237, *P* = 0.000 (*I*2 = 7.3%)]; (12) In gastric ESD retrospective comparison studies of multiple APT user (No. bleeding/total = 48/185) *vs* single APT user (No. bleeding/total = 40/494)[15,41,50,56,60]: The risk of postoperative bleeding in multiple APT agent group was higher than the single APT agent group [OR = 3.606, 95%CI: 2.270-5.726, *P* = 0.000 (*I*2 = 39.4%)]; (13) In gastric ESD retrospective comparison studies of continuous single APT user (No. bleeding/total = 5/96) *vs* non-antithrombotic user (No. bleeding/total = 71/1262)[17,41,50,58]: There was no significant difference in the risk of postoperative bleeding between the two groups [OR = 1.427, 95%CI: 0.524-3.886, *P* = 0.486 (*I*2 = 0.0%)]; (14) In gastric ESD retrospective comparison studies of aspirin user (No. bleeding/total = 38/491) *vs* non-antithrombotic user (No. bleeding/total = 145/3396): The risk of postoperative bleeding in aspirin agent group was higher than the non-antithrombotic agent group [OR = 1.889, 95%CI: 1.293-2.759, *P* = 0.000 (*I*2 = 47.0%)]; (15) In gastric ESD retrospective comparison studies of continuous aspirin user (No. bleeding/total = 36/320) *vs* discontinued aspirin user (No. bleeding/total = 34/391): There was no significant difference in the postoperative bleeding risk between the two groups [OR = 1.430, 95%CI: 0.786-2.603, *P* = 0.241 (*I*2 = 0.0%)]; (16) In gastric ESD retrospective comparison studies of discontinued aspirin user (No. bleeding/total = 31/325) *vs* non-antithrombotic user (No. bleeding/total = 147/3047)[27,51,53,56]: The risk of postoperative bleeding in discontinued aspirin agent group was higher than the non-antithrombotic agent group [OR = 2.093, 95%CI: 1.349-3.246, *P* = 0.001 (*I*2 = 33.1%)]; (17) In gastric ESD retrospective compatison studies of thienopyridine derivatives user (No. bleeding/total = 0/41) *vs* non-antithrombotic user (No. bleeding/total = 123/2903)[14,15,38,50]: There was no significant difference in the risk of postoperative bleeding between the two groups [OR = 0.983, 95%CI: 0.234-4.132, *P* = 0.981 (*I*2 = 0.0%)]; (18) In gastric ESD retrospective comparison studies of aspirin user (No. bleeding/total = 39/440) *vs* thienopyridine derivatives user (No. bleeding/total = 78/2009)[14,15,38,50,60]: The risk of postoperative bleeding in the aspirin agent group was higher than the thienopyridine derivatives agent group [OR = 1.806, 95%CI: 1.062-3.037, *P* = 0.029 (*I*2 = 47.0%)]; (19) In gastric ESD comparison studies (two retrospective studies and one prospective study) of anticoagulant user (No. bleeding/total = 21/145) *vs* non-antithrombotic user (No. bleeding/total = 154/3788)[38,41,59]: The risk of postoperative bleeding [OR = 4.029, 95%CI: 2.442-6.646, *P* = 0.000 (*I*2 = 18.1%)] in the anticoagulant agent group was significantly higher than the non-antithrombotic agent group; (20) In gastric ESD comparison studies (three retrospective studies and one prospective study) of warfarin user (No. bleeding/total = 24/127) *vs* direct oral anticoagulants (DOAC) user (No. bleeding/total = 10/60)[38,47,59]: There was no significant difference in the risk of postoperative bleeding between the two groups [OR = 0.940, 95%CI: 0.407-2.171, *P* = 0.885 (*I*2 = 0.0%)]; (21) In gastrointestinal ESD retrospective comparison studies of anticoagulant user (No. bleeding/total = 13/89) *vs* APT user (No. bleeding/total = 49/501)[38,41,52]: There was no significant difference in the risk of postoperative bleeding between the two groups [OR = 1.677, 95%CI: 0.852-3.302, *P* = 0.135 (*I*2 = 64.1%)]; (22) In gastric ESD retrospective comparison studies of heparin replacement (HR) (No. bleeding/total = 25/128) user *vs* non-antithrombotic user (No. bleeding/total = 154/3681)[23,27,38,41]: The risk of postoperative bleeding [OR = 5.547, 95%CI: 3.457-8.900, *P* = 0.000 (*I*2 = 16.9%)] in HR agent group was significantly higher than the non-antithrombotic agent group; (23) In gastric ESD retrospective comparison studies of HR user (No. bleeding/total = 32/125) *vs* continuous antithrombotic user (No. bleeding/total = 10/101)[17,25,27,61]: The risk of postoperative bleeding in the HR agent group was significantly higher than the continuous antithrombotic agent group [OR = 2.859, 95%CI: 1.257-6.503, *P* = 0.012 (*I*2 = 0.0%)]; and (24) In gastric ESD retrospective comparison studies of HR user (No. bleeding/total = 29/120) *vs* continuous single APT user (No. bleeding/total = 7/83)[17,27,41]: The risk of postoperative bleeding in HR agent group was significantly higher than the continuous single APT agent group (OR = 2.988, 95%CI: 1.173-7.761, *P* = 0.000 (*I*2 = 3.1%)].

Among the EMR group, we performed several subgroup analyses to evaluate the effects of different types of antithrombotic agents on postoperative bleeding: (1) APT (No. bleeding/total = 13/605) user *vs* non-antithrombotic user (No. bleeding/total = 36/1445)[2,5,42]: OR = 1.744, 95%CI: 0.398-7.643, *P* = 0.461 (*I*2 = 78.8%). There were two retrospective studies and one prospective study in the subgroup analysis. There were two studies about colorectal EMR and one study about gastric EMR in the subgroup analysis; (2) Anticoagulant user (No. bleeding/total = 44/567) *vs* non-antithrombotic user (No. bleeding/total = 218/8131)[2,5,42]: There was no significant difference in the risk of postoperative bleeding risk between the two groups [OR = 1.409, 95%CI: 0.552-3.597, *P* = 0.474 (*I*2 = 0.0%)]. There were two retrospective studies and one prospective study in the subgroup analysis. There were two studies about colorectal EMR and one study about gastric EMR in the subgroup analysis; and (3) Anticoagulant user (No. bleeding/total = 5/147) *vs* APT user (No. bleeding/total = 13/605)[2,5,42]: There was no significant difference in the risk of postoperative bleeding between the two groups [OR = 0.768, 95%CI: 0.261-2.261, *P* = 0.631 (*I*2 = 0.0%)]. There were two retrospective studies and one prospective study in the subgroup analysis. There were two studies about colorectal EMR and one study about gastric EMR in the subgroup analysis.

Among the polypectomy group, we also performed several subgroup analyses to evaluate the effects of different types of antithrombotic agents on postoperative bleeding: (1) APT (No. bleeding/total = 56/994) user *vs* non-antithrombotic user (No. bleeding/total = 121/5983)[3,43,45]: OR = 1.766, 95%CI: 1.192-2.616, *P* = 0.005 (*I*2 = 73.9%) (retrospective studies). There were two studies about colorectal polypectomy and one study about gastric polypectomy in the subgroup analysis; (2) Anticoagulant user (No. bleeding/total = 16/128) *vs* APT user (No. bleeding/total = 33/1106)[45,62,63]: The risk of postoperative bleeding after colorectal polypectomy in the anticoagulant agent group was significantly higher than the APT agent group [OR = 3.132, 95%CI: 1.442-6.803, *P* = 0.004 (*I*2 = 9.0%)] (retrospective studies); and (3) Warfarin user (No. bleeding/total = 32/226) *vs* DOAC (No. bleeding/total = 13/98)[35,36,64]: There was no significant difference in the risk of postoperative bleeding between the two groups [OR = 1.126, 95%CI: 0.557-2.275, *P* = 0.741 (*I*2 = 0.0%)] (retrospective studies). There were two studies about colorectal polypectomy and one study about gastric polypectomy in the subgroup analysis.

A subgroup analysis was planned to assess the risk of postoperative bleeding according to the difference in the size of the lesion, dosage and cessation period of antithrombotic agent, but we failed to perform the analysis because of insufficient data.

***Thromboembolic event***

Thromboembolic event is defined as arterial thromboembolism. This includes stroke, transient ischemic attack and infarction perioperative period. These thromboembolic events in included studies were available in nineteen articles (one event in the heparin therapy group[17], five events in the antithrombotic group[5,27], three events in the HR group[35,47,64], one event in the discontinued anticoagulant therapy group[30], one event in the discontinued antithrombotic therapy group[32], two events in the withdrawal period of antiplatelet therapy group[2,51], one event in the anticoagulant therapy group[44], one event in the withdrawal period of anti-vitamin K antagonisis therapy group[65], four events in the low dose aspirin interrupted group[66]). No thromboembolic events occurred in seven studies[36,41,49,58,59,67].

**DISCUSSION**

Despite several practice guidelines about the cessation or continuation of antithrombotic drugs before ER made by the British Society of Gastroenterology[68], the European Society of Gastrointestinal Endoscopy[68], the American Society for Gastrointestinal Endoscopy[69] and the Japan Gastroenterological Endoscopy Society[70], the effect of antithrombotic drugs on the risk of postoperative bleeding was still controversial in some studies[4,6,13,14,16,19-22,24,26,27,31,37,48,57]. Our study found that antithrombotic agents confer a higher risk for postoperative bleeding after ESD and EMR. But the risk of postoperative bleeding after polypectomy was not significantly elevated in the patients with antithrombotic drugs from our study, which was in consistent with the results of a study by Matsumoto *et al*[46]. Nevertheless, there was significant heterogeneity in the analysis of antithrombotic group *vs* non-antithrombotic group. To explain the heterogeneity (*I*2 = 82.5%) of our meta-analysis, we got the following findings: (1) different methods were used to prevent postoperative bleeding; (2) different definitions on postoperative bleeding[2,19]; (3) different types and doses of antithrombotic agents; and (4) different follow-up time, ranging 24 h to 3 mo. In order to reduce the heterogeneity, we have done the subgroup analyses to assess the effect of different types of antithrombotic agents in the risk of postoperative bleeding.

Some studies found that APT did not correlate with the risk of postoperative bleeding[32,52]. At the same time, the risk of delayed postoperative bleeding after ESD was not increased in a single APT agent (continued or discontinued)[17]. In contrast, it has been demonstrated that APT (especially dual APT) increases the risk of postoperative bleeding[50]. A retrospective study by Singh *et al*[71] showed that clopidogrel alone was not an independent risk factor for postoperative bleeding, but a randomized trial by Chan *et al*[72] showed that continued clopidogrel use results in a higher risk of postoperative bleeding compared to the discontinued clopidigrel use group. Our study found that continued single APT agent use did not increase the risk of postoperative bleeding, but multiple APT agents increased the risk of postoperative bleeding after ER.

Some studies found that low dose aspirin and continued use of aspirin didn’t induce a higher risk of postoperative bleeding after polypectomy and gastric ESD[23,43,50]. However, Ninomiya *et al*[53] found that continued use of aspirin increased the risk of postoperative bleeding after colorectal ESD. A study by Metz *et al*[2] demonstrated that the use of aspirin within 7 d of the operation was an independent risk factor for postoperative bleeding after colonic EMR. In a meta-analysis by Shalman *et al*[73], the risk of immediate bleeding in patients with aspirin was not increased, but the risk of delayed bleeding in patients with aspirin or thienopyridine derivatives was increased. Our study found that the use of aspirin significantly increased the risk of postoperative bleeding, but thienopyridine derivatives did not increase the risk of postoperative bleeding after ER. Nevertheless, the guidelines recommend continuing aspirin and withdrawing thienopyridine derivatives in the endoscopic resection[68-70]. Therefore, more prospective or randomized controlled trials are needed to determine the effects of aspirin and thienopyridine on the risk of postoperative bleeding after ER.

 Several guidelines about gastroenterological endoscopy recommend that anticoagulant agent should be discontinued with HR[68-70]. APT plus HR (meaning that anticoagulants were substituted by heparin before polypectomy) were not correlated with postoperative bleeding, but anticoagulant or anticoagulant plus HR were risk factors for postoperative bleeding[32]. Besides, HR alone was related to postoperative bleeding in univariate analysis but was not in multivariate analysis[32]. And our study has reached the same conclusion. Cessation of antithrombotic therapy could result in thromboembolic events such as cerebral infarction and hemorrhagic shock. But the risk of the thromboembolic events in the included studies is relatively low.

There were several drawbacks in this meta-analysis. First of all, the results of our meta-analysis were derived from retrospective studies. Retrospective studies may underestimate the risk of postoperative bleeding. Further prospective studies are needed to confirm our results. Secondly, the surveillance periods of included studies were not exactly the same. Finally, different types and doses of antithrombotic agents were used in the included studies, which may lead to bias.

**CONCLUSION**

In conclusion, the risk of postoperative bleeding after ER (polypectomy, EMR and ESD) correlated with the types and management of the antithrombotic agents according to our meta-analysis. Interrupting or switching antithrombotic therapy might result in the increased risk of serious thromboembolic events. Therefore, it is important to comprehensively assess the risk of postoperative bleeding and thromboembolic events in the patients with antithrombotic drugs after ER.

**ARTICLE HIGHLIGHTS**

***Research background***

Endoscopic resection (ER) is deemed as an effective method for gastrointestinal neoplasia, polyp, gastric adenomas, early oesophageal, gastric and colorectal cancer. More and more people suffering from cardiovascular disease and/or cerebrovascular disease receive antithrombotic therapy which change patients’ coagulation status and may lead to high risk of postoperative bleeding after ER. The relationship between the postoperative bleeding after ER and antithrombotic agents is still uncertain.

***Research motivation***

This study explored the relationship between the postoperative bleeding after ER and antithrombotic agents.

***Research objectives***

The aim of this study is to identify whether the use of antithrombotic drugs increases the risk of the postoperative bleeding after ER by a systematic review and meta-analysis.

***Research methods***

A systematic search was conducted on PubMed, Web of Science, Cochrane library. The Newcastle-Ottawa scale was used to evaluate the quality of studies. Stata 12.0 was used for statistical analysis. The odds ratio and 95%CI were calculated and heterogeneity was quantified using Cochran’s *Q* test and *I*2.

***Research results***

Total 66 studies were included in the meta-analysis. Pooled data suggested that antithrombotic therapy was significantly associated with postoperative bleeding after ER. The risk of postoperative bleeding after endoscopic submucosal dissection, endoscopic mucosal resection and polypectomy in the antithrombotic group was higher than the non-antithrombotic group.

***Research conclusions***

The risk of postoperative bleeding after ER correlated with the types and management of antithrombotic agents by our meta-analysis.

***Research perspectives***

Our results can guide the use of antithrombotic drugs before ER and evaluate the risk of postoperative bleeding.

**REFERENCES**

1 **Shibuya T**, Nomura O, Kodani T, Murakami T, Fukushima H, Tajima Y, Matsumoto K, Ritsuno H, Ueyama H, Inami Y, Ishikawa D, Matsumoto K, Sakamoto N, Osada T, Nagahara A, Ogihara T, Watanabe S. Continuation of antithrombotic therapy may be associated with a high incidence of colonic post-polypectomy bleeding. *Dig Endosc* 2017; **29**: 314-321 [PMID: 27809364 DOI: 10.1111/den.12760]

2 **Metz AJ**, Bourke MJ, Moss A, Williams SJ, Swan MP, Byth K. Factors that predict bleeding following endoscopic mucosal resection of large colonic lesions. *Endoscopy* 2011; **43**: 506-511 [PMID: 21618150 DOI: 10.1055/s-0030-1256346]

3 **Pigò F**, Bertani H, Manno M, Mirante VG, Caruso A, Mangiafico S, Manta R, Rebecchi AM, Conigliaro RL. Colonic Postpolypectomy Bleeding Is Related to Polyp Size and Heparin Use. *Clin Endosc* 2017; **50**: 287-292 [PMID: 28183158 DOI: 10.5946/ce.2016.126]

4 **Al-Mammari S**, Owen R, Findlay J, Koutsoumpas A, Gillies R, Marshall R, Bailey AA, Maynard N, Sgromo B, Braden B. Endoscopic mucosal resection of early oesophageal neoplasia in patients requiring anticoagulation: is it safe? *Surg Endosc* 2016; **30**: 2390-2395 [PMID: 26307599 DOI: 10.1007/s00464-015-4489-y]

5 **Namasivayam V**, Prasad GA, Lutzke LS, Dunagan KT, Borkenhagen LS, Okoro NI, Tomizawa Y, Buttar NS, Michel WL, Wang KK. The risk of endoscopic mucosal resection in the setting of clopidogrel use. *ISRN Gastroenterol* 2014; **2014**: 494157 [PMID: 24944824 DOI: 10.1155/2014/494157]

6 **Mukai S**, Cho S, Kotachi T, Shimizu A, Matuura G, Nonaka M, Hamada T, Hirata K, Nakanishi T. Analysis of delayed bleeding after endoscopic submucosal dissection for gastric epithelial neoplasms. *Gastroenterol Res Pract* 2012; **2012**: 875323 [PMID: 22536221 DOI: 10.1155/2012/875323]

7 **Kataoka Y**, Tsuji Y, Sakaguchi Y, Minatsuki C, Asada-Hirayama I, Niimi K, Ono S, Kodashima S, Yamamichi N, Fujishiro M, Koike K. Bleeding after endoscopic submucosal dissection: Risk factors and preventive methods. *World J Gastroenterol* 2016; **22**: 5927-5935 [PMID: 27468187 DOI: 10.3748/wjg.v22.i26.5927]

8 **Choung BS**, Kim SH, Ahn DS, Kwon DH, Koh KH, Sohn JY, Park WS, Kim IH, Lee SO, Lee ST, Kim SW. Incidence and risk factors of delayed postpolypectomy bleeding: a retrospective cohort study. *J Clin Gastroenterol* 2014; **48**: 784-789 [PMID: 24231934 DOI: 10.1097/MCG.0000000000000027]

9 **Rutter MD**, Nickerson C, Rees CJ, Patnick J, Blanks RG. Risk factors for adverse events related to polypectomy in the English Bowel Cancer Screening Programme. *Endoscopy* 2014; **46**: 90-97 [PMID: 24477363 DOI: 10.1055/s-0033-1344987]

10 **Moher D**, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009; **151**: 264-269, W64 [PMID: 19622511 DOI: 10.7326/0003-4819-151-4-200908180-00135]

11 **Stang A**. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010; **25**: 603-605 [PMID: 20652370 DOI: 10.1007/s10654-010-9491-z]

12 **Higgins JP**, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557-560 [PMID: 12958120 DOI: 10.1136/bmj.327.7414.557]

13 **Goto O**, Fujishiro M, Kodashima S, Ono S, Niimi K, Hirano K, Yamamichi N, Koike K. A second-look endoscopy after endoscopic submucosal dissection for gastric epithelial neoplasm may be unnecessary: a retrospective analysis of postendoscopic submucosal dissection bleeding. *Gastrointest Endosc* 2010; **71**: 241-248 [PMID: 19922919 DOI: 10.1016/j.gie.2009.08.030]

14 **Ueki N**, Futagami S, Akimoto T, Maruki Y, Yamawaki H, Kodaka Y, Nagoya H, Shindo T, Kusunoki M, Kawagoe T, Gudis K, Miyake K, Iwakiri K. Effect of Antithrombotic Therapy and Long Endoscopic Submucosal Dissection Procedure Time on Early and Delayed Postoperative Bleeding. *Digestion* 2017; **96**: 21-28 [PMID: 28609771 DOI: 10.1159/000475924]

15 **Gotoda T**, Hori K, Iwamuro M, Kono Y, Miura K, Kanzaki H, Kawano S, Kawahara Y, Okada H. Evaluation of the bleeding risk with various antithrombotic therapies after gastric endoscopic submucosal dissection. *Endosc Int Open* 2017; **5**: E653-E662 [PMID: 28691050 DOI: 10.1055/s-0043-110050]

16 **Odagiri H**, Yasunaga H, Matsui H, Fushimi K, Iizuka T, Kaise M. Hospital volume and the occurrence of bleeding and perforation after colorectal endoscopic submucosal dissection: analysis of a national administrative database in Japan. *Dis Colon Rectum* 2015; **58**: 597-603 [PMID: 25944432 DOI: 10.1097/DCR.0000000000000335]

17 **Furuhata T**, Kaise M, Hoteya S, Iizuka T, Yamada A, Nomura K, Kuribayashi Y, Kikuchi D, Matsui A, Ogawa O, Yamashta S, Mitani T. Postoperative bleeding after gastric endoscopic submucosal dissection in patients receiving antithrombotic therapy. *Gastric Cancer* 2017; **20**: 207-214 [PMID: 26754296 DOI: 10.1007/s10120-015-0588-7]

18 **Suzuki S**, Chino A, Kishihara T, Uragami N, Tamegai Y, Suganuma T, Fujisaki J, Matsuura M, Itoi T, Gotoda T, Igarashi M, Moriyasu F. Risk factors for bleeding after endoscopic submucosal dissection of colorectal neoplasms. *World J Gastroenterol* 2014; **20**: 1839-1845 [PMID: 24587661 DOI: 10.3748/wjg.v20.i7.1839]

19 **Higashiyama M**, Oka S, Tanaka S, Sanomura Y, Imagawa H, Shishido T, Yoshida S, Chayama K. Risk factors for bleeding after endoscopic submucosal dissection of gastric epithelial neoplasm. *Dig Endosc* 2011; **23**: 290-295 [PMID: 21951088 DOI: 10.1111/j.1443-1661.2011.01151.x]

20 **Mannen K**, Tsunada S, Hara M, Yamaguchi K, Sakata Y, Fujise T, Noda T, Shimoda R, Sakata H, Ogata S, Iwakiri R, Fujimoto K. Risk factors for complications of endoscopic submucosal dissection in gastric tumors: analysis of 478 lesions. *J Gastroenterol* 2010; **45**: 30-36 [PMID: 19760133 DOI: 10.1007/s00535-009-0137-4]

21 **Terasaki M**, Tanaka S, Shigita K, Asayama N, Nishiyama S, Hayashi N, Nakadoi K, Oka S, Chayama K. Risk factors for delayed bleeding after endoscopic submucosal dissection for colorectal neoplasms. *Int J Colorectal Dis* 2014; **29**: 877-882 [PMID: 24825723 DOI: 10.1007/s00384-014-1901-3]

22 **Okada K**, Yamamoto Y, Kasuga A, Omae M, Kubota M, Hirasawa T, Ishiyama A, Chino A, Tsuchida T, Fujisaki J, Nakajima A, Hoshino E, Igarashi M. Risk factors for delayed bleeding after endoscopic submucosal dissection for gastric neoplasm. *Surg Endosc* 2011; **25**: 98-107 [PMID: 20549245 DOI: 10.1007/s00464-010-1137-4]

23 **Matsumura T**, Arai M, Maruoka D, Okimoto K, Minemura S, Ishigami H, Saito K, Nakagawa T, Katsuno T, Yokosuka O. Risk factors for early and delayed post-operative bleeding after endoscopic submucosal dissection of gastric neoplasms, including patients with continued use of antithrombotic agents. *BMC Gastroenterol* 2014; **14**: 172 [PMID: 25280756 DOI: 10.1186/1471-230X-14-172]

24 **Toyokawa T**, Inaba T, Omote S, Okamoto A, Miyasaka R, Watanabe K, Izumikawa K, Horii J, Fujita I, Ishikawa S, Morikawa T, Murakami T, Tomoda J. Risk factors for perforation and delayed bleeding associated with endoscopic submucosal dissection for early gastric neoplasms: analysis of 1123 lesions. *J Gastroenterol Hepatol* 2012; **27**: 907-912 [PMID: 22142449 DOI: 10.1111/j.1440-1746.2011.07039.x]

25 **Shindo Y**, Matsumoto S, Miyatani H, Yoshida Y, Mashima H. Risk factors for postoperative bleeding after gastric endoscopic submucosal dissection in patients under antithrombotics. *World J Gastrointest Endosc* 2016; **8**: 349-356 [PMID: 27076874 DOI: 10.4253/wjge.v8.i7.349]

26 **Takizawa K**, Oda I, Gotoda T, Yokoi C, Matsuda T, Saito Y, Saito D, Ono H. Routine coagulation of visible vessels may prevent delayed bleeding after endoscopic submucosal dissection--an analysis of risk factors. *Endoscopy* 2008; **40**: 179-183 [PMID: 18322872 DOI: 10.1055/s-2007-995530]

27 **Igarashi K**, Takizawa K, Kakushima N, Tanaka M, Kawata N, Yoshida M, Ito S, Imai K, Hotta K, Ishiwatari H, Matsubayashi H, Ono H. Should antithrombotic therapy be stopped in patients undergoing gastric endoscopic submucosal dissection? *Surg Endosc* 2017; **31**: 1746-1753 [PMID: 27530896 DOI: 10.1007/s00464-016-5167-4]

28 **Ono S**, Ishikawa M, Matsuda K, Tsuda M, Yamamoto K, Shimizu Y, Sakamoto N. Clinical impact of the perioperative management of oral anticoagulants in bleeding after colonic endoscopic mucosal resection. *BMC Gastroenterol* 2019; **19**: 206 [PMID: 31791254 DOI: 10.1186/s12876-019-1124-8]

29 **Takeuchi T**, Ota K, Harada S, Edogawa S, Kojima Y, Tokioka S, Umegaki E, Higuchi K. The postoperative bleeding rate and its risk factors in patients on antithrombotic therapy who undergo gastric endoscopic submucosal dissection. *BMC Gastroenterol* 2013; **13**: 136 [PMID: 24010587 DOI: 10.1186/1471-230X-13-136]

30 **Tokioka S**, Umegaki E, Murano M, Takeuchi N, Takeuchi T, Kawakami K, Yoda Y, Kojima Y, Higuchi K. Utility and problems of endoscopic submucosal dissection for early gastric cancer in elderly patients. *J Gastroenterol Hepatol* 2012; **27 Suppl 3**: 63-69 [PMID: 22486874 DOI: 10.1111/j.1440-1746.2012.07075.x]

31 **Amato A**, Radaelli F, Dinelli M, Crosta C, Cengia G, Beretta P, Devani M, Lochis D, Manes G, Fini L, Paggi S, Passoni GR, Repici A; SIED Lombardy group. Early and delayed complications of polypectomy in a community setting: The SPoC prospective multicentre trial. *Dig Liver Dis* 2016; **48**: 43-48 [PMID: 26493629 DOI: 10.1016/j.dld.2015.09.007]

32 **Kubo T**, Yamashita K, Onodera K, Iida T, Arimura Y, Nojima M, Nakase H. Heparin bridge therapy and post-polypectomy bleeding. *World J Gastroenterol* 2016; **22**: 10009-10014 [PMID: 28018108 DOI: 10.3748/wjg.v22.i45.10009]

33 **Yano T**, Tanabe S, Ishido K, Suzuki M, Kawanishi N, Yamane S, Watanabe A, Wada T, Azuma M, Katada C, Koizumi W. Different clinical characteristics associated with acute bleeding and delayed bleeding after endoscopic submucosal dissection in patients with early gastric cancer. *Surg Endosc* 2017; **31**: 4542-4550 [PMID: 28378078 DOI: 10.1007/s00464-017-5513-1]

34 **Ishigami H**, Arai M, Matsumura T, Maruoka D, Minemura S, Okimoto K, Kasamatsu S, Saito K, Nakagawa T, Katsuno T, Yokosuka O. Heparin-bridging therapy is associated with a high risk of post-polypectomy bleeding regardless of polyp size. *Dig Endosc* 2017; **29**: 65-72 [PMID: 27368065 DOI: 10.1111/den.12692]

35 **Yanagisawa N**, Nagata N, Watanabe K, Iida T, Hamada M, Kobayashi S, Shimbo T, Akiyama J, Uemura N. Post-polypectomy bleeding and thromboembolism risks associated with warfarin *vs* direct oral anticoagulants. *World J Gastroenterol* 2018; **24**: 1540-1549 [PMID: 29662292 DOI: 10.3748/wjg.v24.i14.1540]

36 **Yamashita K**, Oka S, Tanaka S, Boda K, Hirano D, Sumimoto K, Mizumoto T, Ninomiya Y, Tamaru Y, Shigita K, Hayashi N, Sanomura Y, Chayama K. Use of anticoagulants increases risk of bleeding after colorectal endoscopic submucosal dissection. *Endosc Int Open* 2018; **6**: E857-E864 [PMID: 29978006 DOI: 10.1055/a-0593-5788]

37 **Koh R**, Hirasawa K, Yahara S, Oka H, Sugimori K, Morimoto M, Numata K, Kokawa A, Sasaki T, Nozawa A, Taguri M, Morita S, Maeda S, Tanaka K. Antithrombotic drugs are risk factors for delayed postoperative bleeding after endoscopic submucosal dissection for gastric neoplasms. *Gastrointest Endosc* 2013; **78**: 476-483 [PMID: 23622974 DOI: 10.1016/j.gie.2013.03.008]

38 **Sato C**, Hirasawa K, Koh R, Ikeda R, Fukuchi T, Kobayashi R, Kaneko H, Makazu M, Maeda S. Postoperative bleeding in patients on antithrombotic therapy after gastric endoscopic submucosal dissection. *World J Gastroenterol* 2017; **23**: 5557-5566 [PMID: 28852315 DOI: 10.3748/wjg.v23.i30.5557]

39 **Azumi M**, Takeuchi M, Koseki Y, Kumagai M, Kobayashi Y, Takatsuna M, Yoshioka A, Yoshikawa S, Miura T, Terai S. The search, coagulation, and clipping (SCC) method prevents delayed bleeding after gastric endoscopic submucosal dissection. *Gastric Cancer* 2019; **22**: 567-575 [PMID: 30267178 DOI: 10.1007/s10120-018-0878-y]

40 **Izumikawa K**, Iwamuro M, Inaba T, Ishikawa S, Kuwaki K, Sakakihara I, Yamamoto K, Takahashi S, Tanaka S, Wato M, Okada H. Bleeding in patients who underwent scheduled second-look endoscopy 5 days after endoscopic submucosal dissection for gastric lesions. *BMC Gastroenterol* 2018; **18**: 46 [PMID: 29631560 DOI: 10.1186/s12876-018-0774-2]

41 **Kono Y**, Obayashi Y, Baba Y, Sakae H, Gotoda T, Miura K, Kanzaki H, Iwamuro M, Kawano S, Kawahara Y, Tanaka T, Okada H. Postoperative bleeding risk after gastric endoscopic submucosal dissection during antithrombotic drug therapy. *J Gastroenterol Hepatol* 2018; **33**: 453-460 [PMID: 28696019 DOI: 10.1111/jgh.13872]

42 **Bronsgeest K**, Huisman JF, Langers A, Boonstra JJ, Schenk BE, de Vos Tot Nederveen Cappel WH, Vasen HFA, Hardwick JCH. Safety of endoscopic mucosal resection (EMR) of large non-pedunculated colorectal adenomas in the elderly. *Int J Colorectal Dis* 2017; **32**: 1711-1717 [PMID: 28884225 DOI: 10.1007/s00384-017-2892-7]

43 **Yousfi M**, Gostout CJ, Baron TH, Hernandez JL, Keate R, Fleischer DE, Sorbi D. Postpolypectomy lower gastrointestinal bleeding: potential role of aspirin. *Am J Gastroenterol* 2004; **99**: 1785-1789 [PMID: 15330919 DOI: 10.1111/j.1572-0241.2004.30368.x]

44 **Witt DM**, Delate T, McCool KH, Dowd MB, Clark NP, Crowther MA, Garcia DA, Ageno W, Dentali F, Hylek EM, Rector WG; WARPED Consortium. Incidence and predictors of bleeding or thrombosis after polypectomy in patients receiving and not receiving anticoagulation therapy. *J Thromb Haemost* 2009; **7**: 1982-1989 [PMID: 19719825 DOI: 10.1111/j.1538-7836.2009.03598.x]

45 **Kishida Y**, Hotta K, Imai K, Ito S, Yoshida M, Kawata N, Tanaka M, Kakushima N, Takizawa K, Ishiwatari H, Matsubayashi H, Ono H. Risk Analysis of Colorectal Post-Polypectomy Bleeding Due to Antithrombotic Agent. *Digestion* 2019; **99**: 148-156 [PMID: 30179871 DOI: 10.1159/000490791]

46 **Matsumoto M**, Yoshii S, Shigesawa T, Dazai M, Onodera M, Kato M, Sakamoto N. Safety of Cold Polypectomy for Colorectal Polyps in Patients on Antithrombotic Medication. *Digestion* 2018; **97**: 76-81 [PMID: 29393134 DOI: 10.1159/000484219]

47 **Yoshio T**, Nishida T, Kawai N, Yuguchi K, Yamada T, Yabuta T, Komori M, Yamaguchi S, Kitamura S, Iijima H, Tsutsui S, Michida T, Mita E, Tsujii M, Takehara T. Gastric ESD under Heparin Replacement at High-Risk Patients of Thromboembolism Is Technically Feasible but Has a High Risk of Delayed Bleeding: Osaka University ESD Study Group. *Gastroenterol Res Pract* 2013; **2013**: 365830 [PMID: 23843783 DOI: 10.1155/2013/365830]

48 **Miyahara K**, Iwakiri R, Shimoda R, Sakata Y, Fujise T, Shiraishi R, Yamaguchi K, Watanabe A, Yamaguchi D, Higuchi T, Tominaga N, Ogata S, Tsuruoka N, Noda T, Hidaka H, Mannen K, Endo H, Yamanouchi K, Yamazato T, Sakata H, Fujimoto K. Perforation and postoperative bleeding of endoscopic submucosal dissection in gastric tumors: analysis of 1190 lesions in low- and high-volume centers in Saga, Japan. *Digestion* 2012; **86**: 273-280 [PMID: 22986899 DOI: 10.1159/000341422]

49 **So S**, Ahn JY, Kim N, Na HK, Jung KW, Lee JH, Kim DH, Choi KD, Song HJ, Lee GH, Jung HY. Comparison of the effects of antithrombotic therapy on delayed bleeding after gastric endoscopic resection: a propensity score-matched case-control study. *Gastrointest Endosc* 2019; **89**: 277-285.e2 [PMID: 30145315 DOI: 10.1016/j.gie.2018.08.028]

50 **Tounou S**, Morita Y, Hosono T. Continuous aspirin use does not increase post-endoscopic dissection bleeding risk for gastric neoplasms in patients on antiplatelet therapy. *Endosc Int Open* 2015; **3**: E31-E38 [PMID: 26134769 DOI: 10.1055/s-0034-1390764]

51 **Lim JH**, Kim SG, Kim JW, Choi YJ, Kwon J, Kim JY, Lee YB, Choi J, Im JP, Kim JS, Jung HC, Song IS. Do antiplatelets increase the risk of bleeding after endoscopic submucosal dissection of gastric neoplasms? *Gastrointest Endosc* 2012; **75**: 719-727 [PMID: 22317881 DOI: 10.1016/j.gie.2011.11.034]

52 **Yoshida N**, Naito Y, Murakami T, Hirose R, Ogiso K, Siah KT, Inada Y, Yagi N, Itoh Y. High incidence of postoperative hemorrhage in colorectal endoscopic submucosal dissection during anticoagulant therapy. *Int J Colorectal Dis* 2016; **31**: 1487-1488 [PMID: 26951182 DOI: 10.1007/s00384-016-2540-7]

53 **Ninomiya Y**, Oka S, Tanaka S, Nishiyama S, Tamaru Y, Asayama N, Shigita K, Hayashi N, Chayama K. Risk of bleeding after endoscopic submucosal dissection for colorectal tumors in patients with continued use of low-dose aspirin. *J Gastroenterol* 2015; **50**: 1041-1046 [PMID: 25682173 DOI: 10.1007/s00535-015-1053-4]

54 **Arimoto J**, Higurashi T, Chiba H, Misawa N, Yoshihara T, Kato T, Kanoshima K, Fuyuki A, Ohkubo H, Goto S, Ishikawa Y, Tachikawa J, Ashikari K, Nonaka T, Taguri M, Kuriyama H, Atsukawa K, Nakajima A. Continued Use of a Single Antiplatelet Agent Does Not Increase the Risk of Delayed Bleeding After Colorectal Endoscopic Submucosal Dissection. *Dig Dis Sci* 2018; **63**: 218-227 [PMID: 29177848 DOI: 10.1007/s10620-017-4843-0]

55 **Seo M**, Song EM, Cho JW, Lee YJ, Lee BI, Kim JS, Jeon SW, Jang HJ, Yang DH, Ye BD, Byeon JS. A risk-scoring model for the prediction of delayed bleeding after colorectal endoscopic submucosal dissection. *Gastrointest Endosc* 2019; **89**: 990-998.e2 [PMID: 30521794 DOI: 10.1016/j.gie.2018.11.029]

56 **Harada H**, Suehiro S, Murakami D, Nakahara R, Nagasaka T, Ujihara T, Sagami R, Katsuyama Y, Hayasaka K, Amano Y. Feasibility of gastric endoscopic submucosal dissection with continuous low-dose aspirin for patients receiving dual antiplatelet therapy. *World J Gastroenterol* 2019; **25**: 457-468 [PMID: 30700942 DOI: 10.3748/wjg.v25.i4.457]

57 **Cho SJ**, Choi IJ, Kim CG, Lee JY, Nam BH, Kwak MH, Kim HJ, Ryu KW, Lee JH, Kim YW. Aspirin use and bleeding risk after endoscopic submucosal dissection in patients with gastric neoplasms. *Endoscopy* 2012; **44**: 114-121 [PMID: 22271021 DOI: 10.1055/s-0031-1291459]

58 **Horikawa Y**, Mizutamari H, Mimori N, Kato Y, Sawaguchi M, Fushimi S, Sato S, Okubo S. Effect of Continued Administration of Low-dose Aspirin for Intraoperative Bleeding Control in Gastric Endoscopic Submucosal Dissection. *Digestion* 2019; **100**: 139-146 [PMID: 30513522 DOI: 10.1159/000494250]

59 **Sanomura Y**, Oka S, Tanaka S, Yorita N, Kuroki K, Kurihara M, Mizumoto T, Yoshifuku Y, Chayama K. Taking Warfarin with Heparin Replacement and Direct Oral Anticoagulant Is a Risk Factor for Bleeding after Endoscopic Submucosal Dissection for Early Gastric Cancer. *Digestion* 2018; **97**: 240-249 [PMID: 29421806 DOI: 10.1159/000485026]

60 **Oh S**, Kim SG, Kim J, Choi JM, Lim JH, Yang HJ, Park JY, Han SJ, Kim JL, Chung H, Jung HC. Continuous Use of Thienopyridine May Be as Safe as Low-Dose Aspirin in Endoscopic Resection of Gastric Tumors. *Gut Liver* 2018; **12**: 393-401 [PMID: 29429155 DOI: 10.5009/gnl17384]

61 **Harada H**, Suehiro S, Murakami D, Shimizu T, Nakahara R, Katsuyama Y, Miyama Y, Tounou S, Hayasaka K. Continuous use of low-dose warfarin for gastric endoscopic submucosal dissection: a prospective study. *Endosc Int Open* 2017; **5**: E348-E353 [PMID: 28484736 DOI: 10.1055/s-0043-105493]

62 **Sawhney MS**, Salfiti N, Nelson DB, Lederle FA, Bond JH. Risk factors for severe delayed postpolypectomy bleeding. *Endoscopy* 2008; **40**: 115-119 [PMID: 18253906 DOI: 10.1055/s-2007-966959]

63 **Park SK**, Seo JY, Lee MG, Yang HJ, Jung YS, Choi KY, Kim H, Kim HO, Jung KU, Chun HK, Park DI. Prospective analysis of delayed colorectal post-polypectomy bleeding. *Surg Endosc* 2018; **32**: 3282-3289 [PMID: 29344790 DOI: 10.1007/s00464-018-6048-9]

64 **Sakai T**, Nagami Y, Shiba M, Hayashi K, Kinoshita Y, Maruyama H, Kato K, Minamino H, Ominami M, Fukunaga S, Otani K, Hosomi S, Tanaka F, Taira K, Kamata N, Yamagami H, Tanigawa T, Watanabe T, Fujiwara Y. Heparin-bridging therapy is associated with post-colorectal polypectomy bleeding in patients whose oral anticoagulation therapy is interrupted. *Scand J Gastroenterol* 2018; **53**: 1304-1310 [PMID: 30345853 DOI: 10.1080/00365521.2018.1503325]

65 **Inoue T**, Iijima H, Yamada T, Okuyama Y, Takahashi K, Nishida T, Ishihara R, Akasaka T, Kobayashi I, Kuroshima T, Yasunaga Y, Yamamoto K, Nakahara M, Doi Y, Nakajima S, Mukai A, Masuda E, Yoshii S, Hayashi Y, Minamiguchi H, Sakata Y, Yamamoto K, Tsujii M, Takehara T. A prospective multicenter observational study evaluating the risk of periendoscopic events in patients using anticoagulants: the Osaka GIANT Study. *Endosc Int Open* 2019; **7**: E104-E114 [PMID: 30705940 DOI: 10.1055/a-0754-1997]

66 **Sanomura Y**, Oka S, Tanaka S, Numata N, Higashiyama M, Kanao H, Yoshida S, Ueno Y, Chayama K. Continued use of low-dose aspirin does not increase the risk of bleeding during or after endoscopic submucosal dissection for early gastric cancer. *Gastric Cancer* 2014; **17**: 489-496 [PMID: 24142107 DOI: 10.1007/s10120-013-0305-3]

67 **Fujita M**, Murao T, Osawa M, Hirai S, Fukushima S, Yo S, Nakato R, Ishii M, Matsumoto H, Tamaki T, Sakakibara T, Shiotani A. Colonic endoscopic mucosal resection in patients taking anticoagulants: Is heparin bridging therapy necessary? *J Dig Dis* 2018; **19**: 288-294 [PMID: 29687957 DOI: 10.1111/1751-2980.12598]

68 **Veitch AM**, Vanbiervliet G, Gershlick AH, Boustiere C, Baglin TP, Smith LA, Radaelli F, Knight E, Gralnek IM, Hassan C, Dumonceau JM. Endoscopy in patients on antiplatelet or anticoagulant therapy, including direct oral anticoagulants: British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE) guidelines. *Gut* 2016; **65**: 374-389 [PMID: 26873868 DOI: 10.1136/gutjnl-2015-311110]

69 **ASGE Standards of Practice Committee**, Acosta RD, Abraham NS, Chandrasekhara V, Chathadi KV, Early DS, Eloubeidi MA, Evans JA, Faulx AL, Fisher DA, Fonkalsrud L, Hwang JH, Khashab MA, Lightdale JR, Muthusamy VR, Pasha SF, Saltzman JR, Shaukat A, Shergill AK, Wang A, Cash BD, DeWitt JM. The management of antithrombotic agents for patients undergoing GI endoscopy. *Gastrointest Endosc* 2016; **83**: 3-16 [PMID: 26621548 DOI: 10.1016/j.gie.2015.09.035]

70 **Fujimoto K**, Fujishiro M, Kato M, Higuchi K, Iwakiri R, Sakamoto C, Uchiyama S, Kashiwagi A, Ogawa H, Murakami K, Mine T, Yoshino J, Kinoshita Y, Ichinose M, Matsui T; Japan Gastroenterological Endoscopy Society. Guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment. *Dig Endosc* 2014; **26**: 1-14 [PMID: 24215155 DOI: 10.1111/den.12183]

71 **Singh M**, Mehta N, Murthy UK, Kaul V, Arif A, Newman N. Postpolypectomy bleeding in patients undergoing colonoscopy on uninterrupted clopidogrel therapy. *Gastrointest Endosc* 2010; **71**: 998-1005 [PMID: 20226452 DOI: 10.1016/j.gie.2009.11.022]

72 **Chan FKL**, Kyaw MH, Hsiang JC, Suen BY, Kee KM, Tse YK, Ching JYL, Cheong PK, Ng D, Lam K, Lo A, Lee V, Ng SC. Risk of Postpolypectomy Bleeding With Uninterrupted Clopidogrel Therapy in an Industry-Independent, Double-Blind, Randomized Trial. *Gastroenterology* 2019; **156**: 918-925.e1 [PMID: 30518511 DOI: 10.1053/j.gastro.2018.10.036]

73 **Shalman D**, Gerson LB. Systematic review with meta-analysis: the risk of gastrointestinal haemorrhage post-polypectomy in patients receiving anti-platelet, anti-coagulant and/or thienopyridine medications. *Aliment Pharmacol Ther* 2015; **42**: 949-956 [PMID: 26290157 DOI: 10.1111/apt.13367]

**74 Beppu K**, Osada T, Sakamoto N, Shibuya T, Matsumoto K, Nagahara A, Terai T, Ogihara T, Watanabe S. Optimal timing for resuming antithrombotic agents and risk factors for delayed bleeding after endoscopic resection of colorectal tumors. *Gastroenterol Res Pract* 2014; **2014**: 825179 [PMID: 25548556 DOI: 10.1155/2014/825179]

75 **Lin D**, Soetikno RM, McQuaid K, Pham C, Doan G, Mou S, Shergill AK, Somsouk M, Rouse RV, Kaltenbach T. Risk factors for postpolypectomy bleeding in patients receiving anticoagulation or antiplatelet medications. *Gastrointest Endosc* 2018; **87**: 1106-1113 [PMID: 29208464 DOI: 10.1016/j.gie.2017.11.024]

**76 Kono Y**, Matsubara M, Toyokawa T, Takenaka R, Suzuki S, Nasu J, Yoshioka M, Nakagawa M, Mizuno M, Sakae H, Abe M, Gotoda T, Miura K, Kanzaki H, Iwamuro M, Hori K, Tsuzuki T, Kita M, Kawano S, Kawahara Y, Okada H. Multicenter Prospective Study on the Safety of Upper Gastrointestinal Endoscopic Procedures in Antithrombotic Drug Users. *Dig Dis Sci* 2017; **62**: 730-738 [PMID: 28050786 DOI: 10.1007/s10620-016-4437-2]

**77 Inoue T**, Nishida T, Maekawa A, Tsujii Y, Akasaka T, Kato M, Hayashi Y, Yamamoto S, Kondo J, Yamada T, Shinzaki S, Iijima H, Tsujii M, Takehara T. Clinical features of post-polypectomy bleeding associated with heparin bridge therapy. *Dig Endosc* 2014; **26**: 243-249 [PMID: 23730922 DOI: 10.1111/den.12123]

**78 Yoshio T**, Tomida H, Iwasaki R, Horiuchi Y, Omae M, Ishiyama A, Hirasawa T, Yamamoto Y, Tsuchida T, Fujisaki J, Yamada T, Mita E, Ninomiya T, Michitaka K, Igarashi M. Effect of direct oral anticoagulants on the risk of delayed bleeding after gastric endoscopic submucosal dissection. *Dig Endosc* 2017; **29**: 686-694 [PMID: 28295638 DOI: 10.1111/den.12859]

**Footnotes**

**Conflict-of-interest statement:** No conflict of interest.

**PRISMA 2009 Checklist statement:** The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Peer-review started:** September 18, 2020

**First decision:** September 29, 2020

**Article in press:**

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** China

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): E

**P-Reviewer:** Hosoe N, Komeda Y, Rege S **S-Editor:** Wang JL **L-Editor: P-Editor:**

**Figure Legends**



**Figure 1 A flow diagram of articles retrieved and inclusion progress through the stage of meta-analysis.**

****

**Figure 2 Forest plot of antithrombotic group *vs* non-antithrombotic group in endoscopic resection.**

****

**Figure 3 Forest plot of antithrombotic group *vs* non-antithrombotic group in endoscopic submucosal dissection.**

****

**Figure 4 Forest plot of antithrombotic group *vs* non-antithrombotic group in endoscopic mucosal resection.**

****

**Figure 5 Forest plot of antithrombotic group *vs* non-antithrombotic group in polypectomy.**

****

**Figure 6 Funnel plot of antithrombotic group *vs* non-antithrombotic group in endoscopic resection.**

**Table 1 Characteristics of included studies and participants**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Ref.  | Country | Research method | Location | Age (yr) | Gender male, %  |
| So *et al*[49], 2019 | South Korea | Retrospective study | Gastric lesion | 68.8/68.5 | 954, 79.7% |
| Kishida *et al*[45], 2019 | Japan | Retrospective study | Colorectal lesion | 64/68 | 55, 41.66% |
| Inoue *et al*[65], 2019 | Japan | Prospective observationalstudy | Gastrointestinal lesion | 67.4 ± 8.3 | 201, 58.6% |
| Harada *et al*[56], 2019 | Japan | Retrospective study | Gastric lesion | 72.3 ± 8.82 | 414, 69.3% |
| Arimoto *et al*[54], 2018 | Japan | Retrospective study | Colorectal lesion | 68.5 | 492, 58.3% |
| Azumi *et al*[39], 2018 | Japan | Retrospective study | Gastric lesion | 73 (41-94) | 284, 64.8% |
| Fujita *et al*[67], 2018 | Japan | Retrospective study | Colorectal lesion | 72.2 ± 7.4/72.9 ± 8.3 | 63, 73.8% |
| Horikawa *et al*[58], 2018 | Japan | Retrospective study | Gastric lesion | 78 (56-89) | 77, 77% |
| Izumikawa *et al*[40], 2018 | Japan | Retrospective study | Gastric lesion | - | 255, 75.25% |
| Kono *et al*[41], 2018 | Japan | Retrospective study | Gastric lesion | 72 (66-78) | 652, 74.77% |
| Oh *et al*[60], 2018 | South Korea | Retrospective study | Gastric lesion | 70 (49-85) | 173, 80.47% |
| Park *et al*[63], 2018 | South Korea | Prospective observationalstudy | Colorectal lesion | 55.8 ± 11.9/52.4 ± 12.3 | 2661, 68.46% |
| Sanomura *et al*[59], 2018 | Japan | Retrospective study | Gastric lesion | 69.8 ± 9.2 | 719, 70% |
| Seo *et al*[55], 2018 | South Korea | Retrospective study | Colorectal lesion | 63 (55-69.5) | 723, 60.8% |
| Sakai *et al*[64], 2018 | Japan | Retrospective study | Colorectal lesion n | 72.6 ± 7.2/69.1 ± 10.9 | 669, 66.63% |
| Yamashita *et al*[36], 2018 | Japan | Retrospective study | Colorectal lesion | 66.6 ± 10.6 | 373, 57.4% |
| Yanagisawa *et al*[35], 2018 | Japan | Retrospective study | Gastrointestinal lesion | - | 314, 72.02% |
| Matsumoto *et al*[46], 2018 | Japan | Retrospective study | Colorectal lesion | 70/65 | 551, 65.44% |
| Harada *et al*[61], 2017 | Japan | Prospective observational study | Gastric lesion | 76.8 ± 6.0/72.7 ± 7.9 | 40, 88.88% |
| Yano *et al*[33], 2017 | Japan | Retrospective study | Gastric lesion | 72 (33-94) | 1319, 74.65% |
| Ueki *et al*[14], 2017 | Japan | Retrospective cohort study | Gastric lesion | 71.2 ± 8.4 | 264, 72.5% |
| Yoshio *et al*[78], 2017 | Japan | Retrospective study | Gastric lesion | 75/76 | 90, 90.91% |
| Gotoda *et al*[15], 2017 | Japan | Retrospective study | Gastric lesion | 75, 68.8-81.0 | 410, 77.5% |
| Furuhata *et al*[17], 2017 | Japan | Retrospective study | Gastric lesion | 69 | 1377, 77.3% |
| Shibuya *et al*[1], 2017 | Japan | Retrospective study | Colonic lesion | - | Unclear |
| Bronsgeest *et al*[42], 2017 | Holland | Retrospective study | Colorectal lesion | 67.4 ± 8.3 | 201, 58.6% |
| Ishigami *et al*[34], 2017 | Japan | Retrospective study | Lower gastrointestinal lesion | 64.9 ± 11.1 | 526, 68% |
| Pigò *et al*[3], 2017 | Italy | Retrospective study | Colorectal lesion | 65.4 | 385, 63.2% |
| Kono *et al*[76], 2017 | Japan | Prospective observationalstudy | Upper gastrointestinal lesion | 74 ± 8.3 | 44, 89.8% |
| Lin *et al*[75], 2017 | United States | Retrospective study | Colorectal lesion | - | Unclear |
| Sato *et al*[38], 2017 | Japan | Retrospective study | Gastric lesion | 71.1 | 1786, 75.1% |
| Igarashi *et al*[27], 2017 | Japan | Retrospective study | Gastric lesion | 72.4 | 758, 77.7% |
| Amato *et al*[31], 2016 | Italy | Prospective observational study | Gastrointestinal lesion | 59 ± 12.1 | 54.3% |
| Kubo *et al*[32], 2016 | Japan | Retrospective study | Gastrointestinal lesion | 63.9 | 467,59.3% |
| Shindo *et al*[25], 2016 | Japan | Retrospective study | Gastric lesion | 71 ± 8, 32-87 | 190, 72.5% |
| Yoshida *et al*[52], 2016 | Japan | Retrospective study | Colorectal lesion | 68.2 ± 10.3 | Unclear |
| Ninomiya *et al*[53], 2015 | Japan | Retrospective study | Colorectal lesion | 67 ± 11.1 | 410, 70.4% |
| Al-Mammari *et al*[4], 2015 | United Kingdom | Prospective observational study | Oesophageal lesion | 71, 65-78 | 85, 72.6% |
| Odagiri *et al*[16], 2015 | Japan | Retrospective cohort study | Colorectal lesion | - | 4495, 59.4% |
| Namasivayam *et al*[5], 2014 | United States | Retrospective study | Gastrointestinal lesion | 69 | Unclear |
| Terasaki *et al*[21], 2014 | Japan | Retrospective study | Colorectal lesion | 66.9 ± 11.2 | 233, 64.2% |
| Tounou *et al*[50], 2014 | Japan | Retrospective study | Gastric lesion | 71.8, 36-92 | 257, 73.4% |
| Suzuki *et al*[18], 2014 | Japan | Retrospective study | Colorectal lesion | 65.5, 29-86 | 183, 57.7% |
| Matsumura *et al*[23], 2014 | Japan | Retrospective study | Gastric lesion | 72.1 ± 8.6 | 302, 71.1% |
| Beppu *et al*[74], 2014 | Japan | Retrospective study | Colorectal lesion | 59.5 ± 11.6 | 176, 84.6% |
| Inoue *et al*[77], 2014 | Japan | Retrospective study | Colorectal lesion | 69.2 | 95, 81.2% |
| Sanomura *et al*[66], 2014 | Japan | Retrospective study | Gastric lesion | 73.7 ± 8.9 | 64, 82.1% |
| Yoshio *et al*[47], 2013 | Japan | Retrospective study | Gastric lesion | 70 | 951, 76.1% |
| Takeuchi *et al*[29], 2013 | Japan | Retrospective study | Gastric lesion | 5.2 | 477, 57.2% |
| Koh *et al*[37], 2013 | Japan | Retrospective study | Gastric lesion | 70.3 ± 8.6 | 817, 74% |
| Mukai *et al*[6], 2012 | Japan | Retrospective study | Gastric lesion | 72.4 ± 8.8 | 116, 72% |
| Lim *et al*[51], 2012 | South Korea | Retrospective study | Gastric lesion | 62.6 | 1143, 71.8% |
| Miyahara *et al*[48], 2012 | Japan | Retrospective study | Gastric lesion | 71.7 ± 8.9, 36-92 | 763, 70.5% |
| Cho *et al*[57], 2012 | South Korea | Retrospective study | Colorectal lesion | 62.2 | 385, 74.9% |
| Toyokawa T *et al*[24], 2011 | Japan | Retrospective study | Gastric lesion | 26-95 | 811, 72.2% |
| Higashiyama *et al*[19], 2011 | Japan | Retrospective study | Gastric lesion | 69, 29-91 | 702, 76% |
| Metz *et al*[2], 2011 | Australia | Prospective observational study | Colonic lesion | 68, 26-93 | unclear |
| Tokioka *et al*[30], 2011 | Japan | Retrospective study | Gastric lesion | 69.4 | 378, 73.4% |
| Okada K *et al*[22], 2011 | Japan | Retrospective study | Gastric lesion | 68.4, 33-94 | 425, 73% |
| Mannen *et al*[20], 2010 | Japan | Retrospective study | Gastric lesion | 71.6 ± 8.6, 36-91 | 323, 74.1% |
| Goto *et al*[13], 2010 | Japan | Retrospective study | Gastric lesion | 68.3 | 347, 76.4% |
| Witt *et al*[44], 2009 | United States | Retrospective cohort study | Colorectal lesion | 69.6 | 691, 56.4% |
| Ono *et al*[28], 2019 | Japan | Retrospective study | Gastric lesion | 67 | Unclear |
| Takizawa *et al*[26], 2008 | Japan | Retrospective study | Gastric lesion | 66 ± 10, 29-93 | 779, 80.5% |
| Sawhney *et al*[62], 2007 | United States | Retrospective study | Colorectal lesion | 65.1 | 169, 97.7% |
| Yousfi *et al*[43], 2004 | United States | Retrospective study | Gastrointestinal lesion | 70.5, 45-91 | 100, 61.7% |

**Table 2 Number of cases with or without antithrombotic agents and hemorrhagic outcome**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Ref.** | **Resection****method** | **Total** | **Drug** | **Post-bleeding** | **No bleeding** |
| So *et al*[48], 2019 | ER | 1197 | Antithrombotic agent (+/-) | 40/50 | 359/748 |
| Continued antithrombotic agent (+/-) | 11/7 | 69/138 |
| Discontinued antithrombotic agent (+/-) | 29/43 | 330/657 |
| HR (+) | 5 | 9 |
| Kishida *et al*[45],2019 | Polypectomy | 6382 | Antithrombotic agent (+/-) | 15/40 | 986/5341 |
| Single APT (+) | 4 | 683 |
| Single anticoagulants (+) | 2 | 85 |
| Multiple APT (+) | 3 | 163 |
| Multiple antithrombotic agents (+) | 2 | 39 |
| Single antithrombotic agent (+) | 13 | 947 |
| HR (+) | 4 | 16 |
| Inoue *et al*[65], 2019 | EMR | 102 | VKA (+) | 12 | 73 |
| Discontinued VKA (+) | 0 | 4 |
| Continued VKA (+) | 0 | 2 |
| HR (+) | 15 | 98 |
| DOAC (+) | 3 | 14 |
| Discontinued DOAC (+) | 0 | 3 |
| Inoue *et al*[65], 2019 | ESD | 54 | VKA (+) | 14 | 31 |
| Discontinued VKA (+) | 1 | 2 |
| Continued VKA (+) | 0 | 1 |
| HR (+) | 13 | 31 |
| DOAC (+) | 2 | 7 |
| Discontinued DOAC (+) | 2 | 4 |
| Harada *et al*[56], 2019 | ESD | 597 | Antithrombotic agent (-) | 21 | 422 |
| Single-LDA (+) | 10 | 85 |
| DAPT (+) | 10 | 49 |
| Continued LDA (+) | 15 | 80 |
| Discontinued APT (+) | 5 | 54 |
| Arimoto *et al*[54], 2018 | ESD | 919 | Antithrombotic agent (-) | 26 | 757 |
| APT (+) | 5 | 131 |
| Discontinued APT (+) | 5 | 105 |
| Continued APT (+) | 0 | 26 |
| Azumi *et al*[39], 2018 | ESD | 438 | Antithrombotic agent (+/-) | 6/15 | 72/345 |
| Fujita *et al*[67], 2018 | EMR | 84 | Discontinued anticoagulants (+) | 1 | 42 |
| HR (+) | 4 | 37 |
| Horikawa *et al*[58], 2018 | ESD | 100 | Antithrombotic agent (-) | 1 | 49 |
| Continued LDA | 1 | 49 |
| Izumikawa *et al*[40], 2018 | ESD | 273 | Antithrombotic agent (+/-) | 15/11 | 66/207 |
| Kono *et al*[41], 2018 | ESD | 872 | Antithrombotic agent (+/-) | 23/38 | 159/652 |
| Single antithrombotic agent | 12 | 130 |
| Multiple antithrombotic agents (+) | 11 | 29 |
| Discontinued antithrombotic agent (+) | 8 | 120 |
| Discontinued |  |  |
| Single APT (+) | 3 | 88 |
| Multiple APT (+) | 3 | 16 |
| Single anticoagulants (+) | 1 | 13 |
| Continued |  |  |
| Single APT (+) | 1 | 16 |
| Multiple APT (+) | 4 | 2 |
| Single anticoagulants (+) | 7 | 13 |
| HR (+) | 10 | 21 |
| Oh *et al*[60], 2018 | ESD | 215 | Single APT (+) | 14 | 147 |
| Multiple APT (+) | 15 | 39 |
| LDA (+) | 12 | 82 |
| Thienopyridine (+) | 2 | 54 |
| Continued APT (+) | 23 | 130 |
| Discontinued APT (+) | 6 | 56 |
| Park *et al*[63], 2018 | Polypectomy | 3887 | APT (+) | 12 | 339 |
| Anticoagulants (+) | 0 | 15 |
| Sanomura *et al*[58], 2018 | ESD | 1243 | Antithrombotic agent (-) | 40 | 1127 |
| Anticoagulants (+) | 11 | 65 |
| Warfarin (+) | 5 | 32 |
| DOAC (+) | 4 | 14 |
| Seo *et al*[55], 2018 | ESD | 1189 | Antithrombotic agent (-) | 26 | 945 |
| APT (+) | 7 | 175 |
| Aspirin (+) | 2 | 139 |
| Warfarin (+) | 0 | 10 |
| DOAC (+) | 1 | 2 |
| Single antithrombotic agent (+) | 10 | 326 |
| Multiple antithrombotic agents (+) | 0 | 23 |
| Discontinued antithrombotic agent (+) | 7 | 206 |
| Continued antithrombotic agent (+) | 0 | 5 |
| Sakai *et al*[64], 2018 | Polypectomy | 1004 | Discontinued anticoagulants (+) | 12 | 0 |
| HR (+) | 8 | 70 |
| Warfarin (+) | 7 | 55 |
| DOAC (+) | 1 | 15 |
| Yamashita *et al*[36], 2018 | ESD | 650 | Antithrombotic agent (+/-) | 7/18 | 21/652 |
| Warfarin (+) | 5 | 14 |
| DOAC | 2 | 7 |
| Yanagisawa *et al*[35], 2018 | Polypectomy | 436 | Antithrombotic agent (+/-) | 30/2 | 188/216 |
| Discontinued anticoagulants (+) | 0 | 23 |
| Continued anticoagulants (+) | 10 | 83 |
| HR (+) | 20 | 82 |
| Continued warfarin (+) | 2 | 41 |
| Continued DOAC (+) | 8 | 42 |
| Warfarin (+) | 20 | 125 |
| DOAC (+) | 10 | 63 |
| Matsumoto *et al*[46], 2018 | Polypectomy | 1003 | Antithrombotic agent (+/-) | 2/2 | 184/815 |
| Harada *et al*[61], 2017 | ESD | 45 | Continued warfarin (+) | 2 | 20 |
| HR | 5 | 18 |
| Yano *et al*[33], 2017 | ESD | 144 | Antithrombotic agent (+/-) | 47/103 | 287/1330 |
| Ueki *et al*[14], 2017 | ESD | 364 | Antithrombotic agent (+/-) | 7/17 | 67/273 |
| Discontinued antithrombotic agent (-) | 7 | 67 |
| Discontinued single APT (+) | 4 | 57 |
| Discontinued single anticoagulants (+/-) | 2 | 4 |
| Aspirin (+) | 4 | 43 |
| Thienopyrindine (+) | 0 | 7 |
| Yoshio *et al*[78], 2017 | ESD | 97 | Warfarin (+) | 18 | 55 |
| DOAC | 5 | 19 |
| Gotoda *et al*[15], 2017 | ESD | 529 | Antithrombotic agent (+/-) | 12/14 | 96/407 |
| APT (+) | 8 | 80 |
| Single antithrombotic agent (+) | 6 | 80 |
| Multiple antithrombotic agents (+) | 7 | 17 |
| Single APT (+) | 3 | 69 |
| Multiple APT (+) | 5 | 11 |
| Warfarin (+) | 3 | 11 |
| Aspirin (+) | 2 | 33 |
| Thienopyridine (+) | 0 | 10 |
| Furuhata *et al*[17], 2017 | ESD | 1781 | Antithrombotic agent (+/-) | 33/68 | 220/1460 |
| Single antithrombotic agent (+) | 11 | 139 |
| Multiple antithrombotic agents (+) | 6 | 30 |
| Continued single APT (+) | 1 | 14 |
| HR (+) | 15 | 37 |
| Shibuya *et al*[1], 2017 | ESD | 259 | Antithrombotic agent (+/-) | 4/6 | 32/217 |
| Shibuya *et al*[1], 2017 | EMR | 3018 | Antithrombotic agent (+/-) | 16/15 | 510/2477 |
| Shibuya *et al*[1], 2017 | Polypectomy | 892 | Antithrombotic agent (+/-) | 3/5 | 163/721 |
| Bronsgeest *et al*[42], 2017 | EMR |  | Antithrombotic agent (+/-) | 13/15 | 107/277 |
| APT (+) | 4 | 53 |
| Anticoagulants (+) | 4 | 43 |
| Ishigami *et al*[34], 2017 | ER | 773 | Antithrombotic agent (+/-) | 10/14 | 35/714 |
| HR (+) | 10 | 35 |
| Pigò *et al*[3], 2017 | Polypectomy | 609 | Antithrombotic agent (+/-) | 38/32 | 72/467 |
| Single APT | 14 | 57 |
| Multiple APT | 3 | 8 |
| HR (+) | 21 | 7 |
| Aspirin (+) | 10 | 32 |
| Thienopyridine | 4 | 25 |
| Kono *et al*[76], 2017 | ESD/EMR | 49 | Single antithrombotic agent (+) | 4 | 24 |
| Multiple antithrombotic agents (+) | 7 | 14 |
| Discontinued antithrombotic agent (+) | 5 | 20 |
| Continued antithrombotic agent (+) | 6 | 18 |
| HR (+) | 4 | 12 |
| Lin *et al*[75], 2017 | Polypectomy | 4923 | Aspirin (+) | 36 | 3897 |
| Thienopyridine (+) | 5 | 590 |
| Sato *et al*[38], 2017 | ESD | 2378 | Antithrombotic agent (+/-) | 46/76 | 401/1855 |
| APT (+) | 35 | 270 |
| Anticoagulants (+) | 2 | 33 |
| HR (+) | 6 | 33 |
| Aspirin (+) | 12 | 199 |
| Thienopyridine (+) | 0 | 19 |
| Warfarin (+) | 1 | 16 |
| DOAC (+) | 1 | 17 |
| Igarashi *et al*[27], 2017 | ESD | 976 | Antithrombotic agent (+/-) | 35/30 | 332/692 |
| Discontinued antithrombotic agent (+) | 26 | 250 |
| Continued antithrombotic agent (+) | 5 | 49 |
| HR | 4 | 33 |
| Multiple antithrombotic agents (+)  | 9 | 70 |
| Single antithrombotic agent (+) | 26 | 262 |
| Continued aspirin (+) | 4 | 29 |
| Discontinue aspirin (+) | 19 | 152 |
| Continued thienopyridine (+) | 1 | 17 |
| Discontinued thienopyridine (+) | 9 | 63 |
| Continued anticoagulants (+) | 1 | 11 |
| Discontinued anticoagulants (+) | 3 | 27 |
| Amato *et al*[31], 2016 | ER | 2692 | Antithrombotic agent (+/-) | 16/16 | 595/2069 |
| APT (+) | 11 | 461 |
| Anticoagulants (+) | 5 | 134 |
| Kubo *et al*[32], 2016 | ER | 788 | Antithrombotic agent (+/-) | 16/13 | 194/565 |
| APT (+) | 8 | 146 |
| Anticoagulants (+) | 11 | 72 |
| HR (+) | 10 | 63 |
| Shindo *et al*[25], 2016 | ESD | 262 | Antithrombotic agent (+/-) | 10/13 | 38/201 |
| Discontinued antithrombotic agent (+) | 0 | 25 |
| Continued APT (+) | 2 | 8 |
| HR (+) | 8 | 5 |
| Yoshida *et al*[52], 2016 | ESD | 678 | Antithrombotic agent (-) | 10 | 585 |
| APT (+) | 3 | 60 |
| Anticoagulants (+) | 3 | 17 |
| Ninomiya *et al*[53], 2015 | ESD | 609 | Antithrombotic agent (-) | 28 | 537 |
| Discontinued APT (+) | 2 | 11 |
| Continued APT (+) | 5 | 26 |
| Al-Mammari *et al*[4], 2015 | EMR | 117 | Antithrombotic agent (+/-) | 1/1 | 14/101 |
| Odagiri *et al*[16], 2015 | ESD | 7567 | Antithrombotic agent (+/-) | 49/282 | 440/6796 |
| Namasivayam *et al*[5],2014 | EMR | 1712 | Antithrombotic agent (+/-) | 4/10 | 772/912 |
| APT (+) | 3 | 521 |
| Anticoagulants (+) | 0 | 89 |
| Single antithrombotic agent (+) | 1 | 617 |
| Multiple antithrombotic agents (+) | 3 | 111 |
| Thienopyridine (+/-) | 0/10 | 17/912 |
| Terasaki *et al*[21], 2014 | ESD | 363 | Antithrombotic agent (+/-) | 4/20 | 36/303 |
| Tounou *et al*[50], 2014 | ESD | 350 | Antithrombotic agent (-) | 16 | 245 |
| Discontinued single APT (+) | 7 | 37 |
| Continued single APT (+) | 2 | 12 |
| Dual APT (+) | 11 | 20 |
| Aspirin (+) | 9 | 44 |
| Thienopyridine (+) | 0 | 5 |
| Suzuki *et al*[18], 2014 | ESD | 317 | Antithrombotic agent (+/-) | 1/13 | 27/276 |
| HR | 0 | 6 |
| Matsumura *et al*[23], 2014 | ESD | 425 | Antithrombotic agent (+/-) | 10/10 | 77/328 |
| Discontinued antithrombotic agent (+) | 2 | 39 |
| Continued antithrombotic agent (+),HR (-) | 3 | 22 |
| HR (+) | 5 | 16 |
| Beppu *et al*[74], 2014 | ER | 208 | APT (+) | 9 | 18 |
| Anticoagulants (+) | 12 | 9 |
| Aspirin (+) | 6 | 11 |
| Thienopyridine (+) | 3 | 7 |
| Inoue *et al*[77], 2014 | Polypectomy | 117 | Discontinued antithrombotic agent (+) | 1 | 71 |
| HR (+) | 9 | 36 |
| Sanomura *et al*[66], 2014 | ESD | 78 | Continued LDA (+)  | 1 | 27 |
| Discontinued LDA (+) | 3 | 63 |
| Yoshio *et al*[47], 2013 | ESD | 1250 | Antithrombotic agent (-) | 45 | 972 |
| Discontinued antithrombotic agent (-) | 12 | 197 |
| HR (+) | 9 | 15 |
| Takeuchi *et al*[29], 2013 | ESD | 833 | Antithrombotic agent (+/-) | 21/15 | 69/728 |
| Koh *et al*[37], 2013 | ESD | 1166 | Antithrombotic agent (+/-) | 17/45 | 158/946 |
| Mukai *et al*[6], 2012  | ESD | 161 | Antithrombotic agent (+/-) | 4/17 | 29/111 |
| Lim *et al*[51], 2012 | ESD | 1591 | Antithrombotic agent (-) | 68 | 1249 |
| Discontinued APT (+) | 6 | 96 |
| Continued APT (+) | 20 | 152 |
| Miyahara *et al*[48], 2012 | ESD | 1082 | Antithrombotic agent (-) | 68 | 883 |
| Discontinued antithrombotic agent (+) | 7 | 124 |
| Cho *et al*[57], 2012 | ESD | 514 | Antithrombotic agent (-) | 15 | 424 |
| Discontinued APT (+) | 2 | 54 |
| Continued APT (+) | 4 | 15 |
| Toyokawa *et al*[24], 2011 | ESD | 1123 | Antithrombotic agent (+/-) | 8/48 | 175/892 |
| Higashiyama *et al*[19], 2011 | ESD | 924 | Antithrombotic agent (+/-) | 123/773 | 3/25 |
| Metz *et al*[2], 2011 | EMR | 269 | Antithrombotic agent (+/-) | 8/11 | 30/220 |
| APT (+) | 6 | 18 |
| Anticoagulants (+) | 1 | 10 |
| HR (+) | 1 | 2 |
| Aspirin (+) | 5 | 12 |
| Thienopyridine (+) | 1 | 6 |
| Tokioka *et al*[30], 2011 | ESD | 515 | Antithrombotic agent (+/-) | 3/23 | 37/452 |
| Okada *et al*[22], 2011 | ESD | 582 | Antithrombotic agent (+/-) | 4/24 | 70/484 |
| Mannen *et al*[20], 2010 | ESD | 436 | Antithrombotic agent (+/-) | 1/38 | 32/365 |
| Goto *et al*[13],2010 | ESD | 454 | Antithrombotic agent (+/-) | 5/21 | 52/376 |
| Witt *et al*[44], 2009 | Polypectomy | 1225 | Antithrombotic agent (+/-) | 11/2 | 414/798 |
| Ono *et al*[28], 2019 | ESD | 444 | Antithrombotic agent (+/-) | 6/20 | 50/368 |
| Takizawa *et al*[26], 2008 | ESD | 968 | Antithrombotic agent (+/-) | 3/60 | 74/831 |
| Sawhney *et al*[62], 2007 | Polypectomy | 173 | APT (+) | 17 | 51 |
| Anticoagulants (+) | 14 | 12 |
| Yousfi *et al*[43], 2004 | Polypectomy | 162 | Antithrombotic agent (+/-) | 32/49 | 27/54 |
| APT (+) | 32 | 27 |

ER: Endoscopic resection; ESD: Endoscopic submucosal dissection; EMR: Endoscopic mucosal resection; APT: Antiplatelet; LDA: Low dose of aspirin; HR: Heparin replacement; DOAC: Direct oral anticoagulant; Thienopyridine: Thienopyridine derivatives.

**Table 3 The quality assessment of included studies**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Ref.** | **Selection** | **Comparability** | **Outcome/exposure** | **Stars** |
| **1** | **2** | **3** | **4** | **1** | **2** | **3** |
| So *et al*[49], 2019 | \* | \* | \* | \* | \* | \* | \* | \* | \* | 9 |
| Kishida *et al*[45], 2019 | \* | \* |  |  | \* |  | \* | \* | \* | 6 |
| Inoue *et al*[65], 2019 | \* | \* | \* |  | \* | \* | \* | \* | \* | 8 |
| Harada *et al*[56], 2019 | \* | \* |  | \* | \* | \* | \* | \* | \* | 8 |
| Arimoto *et al*[54], 2018 | \* | \* | \* | \* | \* |  | \* | \* | \* | 8 |
| Azumi *et al*[39], 2018 | \* | \* |  | \* | \* | \* | \* | \* | \* | 8 |
| Fujita *et al*[67], 2018 | \* | \* |  | \* | \* | \* | \* | \* | \* | 8 |
| Horikawa *et al*[58], 2018 | \* | \* |  | \* | \* | \* | \* | \* | \* | 8 |
| Izumikawa *et al*[40], 2018 | \* | \* |  |  | \* |  | \* | \* | \* | 6 |
| Kono *et al*[41], 2018 | \* | \* |  | \* | \* |  | \* | \* | \* | 7 |
| Oh *et al*[60], 2018 | \* | \* |  | \* |  |  | \* | \* | \* | 6 |
| Park *et al*[63], 2018 | \* | \* | \* |  | \* | \* | \* | \* | \* | 8 |
| Sanomura *et al*[59], 2018 | \* | \* |  | \* | \* |  | \* | \* | \* | 7 |
| Seo *et al*[55], 2018 | \* | \* | \* | \* | \* |  | \* | \* | \* | 8 |
| Sakai *et al*[64], 2018 | \* | \* |  | \* | \* |  | \* | \* | \* | 7 |
| Yamashita *et al*[36], 2018 | \* | \* |  | \* | \* |  | \* | \* | \* | 7 |
| Yanagisawa *et al*[35], 2018 | \* | \* |  | \* | \* | \* | \* | \* | \* | 8 |
| Matsumoto *et al*[46], 2018 | \* | \* |  | \* |  |  | \* | \* | \* | 6 |
| Harada *et al*[61], 2017 | \* | \* |  | \* | \* |  | \* | \* | \* | 7 |
| Yano *et al*[33], 2017 | \* | \* |  | \* | \* |  | \* | \* | \* | 7 |
| Ueki *et al*[14], 2017 | \* | \* |  | \* | \* |  | \* | \* | \* | 7 |
| Yoshio *et al*[78], 2017 | \* | \* | \* | \* | \* |  | \* | \* | \* | 8 |
| Gotoda *et al*[15], 2017 | \* | \* |  | \* | \* |  | \* | \* |  | 6 |
| Furuhata *et al*[17], 2017 | \* | \* |  | \* | \* | \* | \* | \* | \* | 8 |
| Shibuya *et al*[1], 2017 | \* | \* |  | \* | \* | \* | \* | \* | \* | 8 |
| Bronsgeest *et al*[42], 2017 | \* | \* | \* | \* | \* |  | \* | \* | \* | 8 |
| Ishigami *et al*[34], 2017 | \* | \* |  | \* | \* |  | \* | \* | \* | 7 |
| Pigò *et al*[3], 2017 | \* | \* |  | \* | \* |  | \* | \* | \* | 7 |
| Kono *et al*[76], 2017 | \* | \* | \* | \* | \* |  | \* | \* | \* | 8 |
| Lin *et al*[75], 2017 | \* | \* |  | \* | \* |  | \* | \* | \* | 7 |
| Sato *et al*[38], 2017 | \* | \* |  | \* | \* | \* | \* | \* | \* | 8 |
| Igarashi *et al*[27], 2017 | \* | \* |  | \* | \* | \* | \* | \* |  | 7 |
| Amato *et al*[31], 2016 | \* | \* | \* |  | \* |  | \* | \* | \* | 7 |
| Kubo *et al*[32], 2016 | \* | \* | \* | \* | \* |  | \* | \* |  | 7 |
| Shindo *et al*[25], 2016 | \* | \* |  | \* | \* |  | \* | \* |  | 6 |
| Yoshida *et al*[52], 2016 | \* | \* |  | \* | \* |  | \* | \* |  | 6 |
| Ninomiya *et al*[53], 2015 | \* | \* |  | \* | \* |  | \* | \* |  | 6 |
| Al-Mammari *et al*[4], 2015 | \* | \* | \* |  | \* |  | \* | \* | \* | 7 |
| Odagiri *et al*[16], 2015 | \* | \* | \* | \* | \* |  | \* | \* |  | 7 |
| Namasivayam *et al*[5], 2014 | \* | \* |  | \* | \* |  | \* | \* |  | 6 |
| Terasaki *et al*[21], 2014 | \* | \* |  | \* | \* | \* | \* | \* |  | 7 |
| Tounou *et al*[50], 2014 | \* | \* |  | \* | \* |  | \* | \* | \* | 7 |
| Suzuki *et al*[18], 2014 | \* | \* |  | \* | \* |  | \* | \* | \* | 7 |
| Matsumura *et al*[23], 2014 | \* | \* |  |  | \* | \* | \* | \* |  | 6 |
| Beppu *et al*[74], 2014 | \* | \* |  | \* | \* | \* | \* | \* | \* | 8 |
| Inoue *et al*[77], 2014 | \* | \* |  | \* | \* | \* | \* | \* | \* | 8 |
| Sanomura *et al*[66], 2014 | \* | \* |  | \* | \* | \* | \* | \* | \* | 8 |
| Yoshio *et al*[47], 2013 | \* | \* | \* | \* | \* |  | \* | \* |  | 7 |
| Takeuchi *et al*[29], 2013 | \* | \* |  | \* | \* | \* | \* | \* | \* | 8 |
| Koh *et al*[37], 2013 | \* | \* |  | \* | \* | \* | \* | \* | \* | 8 |
| Mukai *et al*[6], 2012 | \* | \* |  | \* | \* |  | \* | \* |  | 6 |
| Lim *et al*[51], 2012 | \* | \* |  | \* | \* | \* | \* | \* | \* | 8 |
| Miyahara *et al*[48], 2012 | \* | \* | \* | \* | \* | \* | \* | \* |  | 8 |
| Cho *et al*[57], 2012 | \* | \* |  | \* | \* | \* | \* | \* | \* | 8 |
| Toyokawa T *et al*[24], 2011 | \* | \* | \* | \* | \* |  | \* | \* |  | 7 |
| Higashiyama *et al*[19], 2011 | \* | \* |  | \* | \* |  | \* | \* | \* | 7 |
| Metz *et al*[2], 2011 | \* | \* | \* |  | \* | \* | \* | \* | \* | 8 |
| Tokioka *et al*[30], 2011 | \* | \* |  | \* | \* | \* | \* | \* | \* | 8 |
| Okada K *et al*[22], 2011 | \* | \* |  | \* | \* |  | \* | \* |  | 6 |
| Mannen *et al*[20], 2010 | \* | \* |  | \* | \* |  | \* | \* |  | 6 |
| Goto *et al*[13], 2010 | \* | \* |  | \* | \* | \* | \* | \* | \* | 8 |
| Witt *et al*[44], 2009 | \* | \* |  | \* | \* |  | \* | \* | \* | 7 |
| Ono *et al*[28], 2019 | \* | \* |  | \* | \* | \* | \* | \* |  | 7 |
| Takizawa *et al*[26], 2008 | \* | \* |  | \* | \* | \* | \* | \* | \* | 8 |
| Sawhney *et al*[62], 2007 | \* | \* |  | \* | \* | \* | \* | \* | \* | 8 |
| Yousfi *et al*[43], 2004 | \* | \* | \* | \* | \* | \* | \* | \* | \* | 9 |