# Look inside the management of colonic diverticular rebleeding: a systematic review

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***Abstract***

**Background:** Colonic diverticular bleeding is the most common cause of lower gastrointestinal bleeding in adults and carries a significant risk of recurrence. However, there are many uncertainties regarding the management of the prevention of diverticular rebleeding.

**Objectives:** To review the current evidence on the potential role of lifestyle, pharmacological and endoscopic treatments and to discuss the unmet needs in the prevention of colonic diverticular rebleeding.

**Design:** A systematic review.

**Data sources and methods:** Based on the identified Patients-Interventions-Comparators-Outcomes questions, a detailed and comprehensive literature search was conducted, from inception to 12 January 2024, without language restriction, according to the modified Preferred Reporting Items for Systematic review and Meta-Analyses reporting guidelines.

**Results:** We did not find any dietary or lifestyle interventions (fibre intake, smoking, physical activity, alcohol consumption, BMI) to prevent colonic diverticular rebleeding. We also did not find any interventional studies of specific pharmacological treatments (such as rifaximin, mesalazine or probiotics) to prevent diverticular rebleeding. Data comparing endoscopic and conservative approaches used during the index episode come from observational studies and show conflicting results. Finally, there is a paucity of data regarding the timing of resumption of antiplatelet and anticoagulant therapy after an episode of colonic diverticular bleeding, and this remains to be determined.

**Conclusion:** This review highlights the paucity of data on the possible role of lifestyle, pharmacological and endoscopic treatments in the prevention of colonic diverticular rebleeding and advocates future studies aimed at finding effective therapeutic strategies.

***Keywords:*** anticoagulant treatment, antiplatelet treatment, diverticular disease, endoscopic management

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## Introduction

Colonic diverticulosis is a common condition, particularly in developed countries, with high prevalence rates in Europe and the United States.[1] Most patients with diverticulosis remain asymptomatic throughout their lives. The two main diverticular complications, namely acute diverticulitis and diverticular bleeding, occur in 1%–5% of patients.[2,3]

Colonic diverticular bleeding (CDB), which represents the most common cause of lower gastrointestinal (GI) bleeding in adult patients, carries a significant risk of recurrence. Recurrence

rates for CDB vary widely, ranging from 3.8% to 15.1% and 6.9% to 25% at 1 and 5 years, respectively.[4–6]

Although most cases of diverticular bleeding resolve spontaneously (80%–90%), a small proportion progresses to haemorrhagic shock requiring intensive care.[2] The in-hospital mortality rate due to CDB ranges from 0.7% to 2.5%, with older age and multiple comorbidities being the strongest predictors of mortality.[7,8]

Patients with spontaneous bleeding resolution not undergoing urgent Gl evaluation (i.e. colonoscopy, contrast-enhanced angiography, interventional radiology) remain underdiagnosed and therefore the suspected diverticular source of bleeding is only presumed, additionally masking the real epidemiology of this condition.[9,10]

Mechanisms hypothesised to be involved in CDB are vascular disease and/or structural weakness leading to arterial rupture. Inflammation does not appear to play a role in CDB since acute diverticulitis is rarely complicated by bleeding and the risk factors associated with these two complications may be different. It can be assumed that an alteration in the function of the colonic muscle may also contribute to the pathogenesis of this complication.[11]

Although recurrent CDB is a common condition, only a few studies, mostly from Eastern countries, investigated risk factors for preventing recurrence.

This review aims to ascertain the current evidence regarding the potential role of lifestyle, pharmacological and endoscopic treatment and discuss the unmet needs regarding the prevention of colonic diverticular rebleeding.

## Materials and methods

An expert panel composed of six gastroenterologists with long-lasting experience in colonic diverticular disease was involved in identifying the most important open questions regarding the management of this condition. In a face-to-face meeting, chaired by a panel moderator experienced in facilitating group discussions and criteria development, the experts were asked to generate relevant clinical questions using the Patients-Interventions-Comparators-Outcomes (PICO) format. Based on the identified PICO questions, a detailed and comprehensive literature search was conducted, from inception to 12th January 2024, without language restriction, according to the modified Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) reporting guidelines.[12] The search strategy is reported in Supplemental Table 1. Following the search strategy, papers published in languages other than English were not considered. The references of the selected papers were also reviewed to identify additional papers of potential interest. The final list of references was evaluated by the panel experts, who were asked to check for any lack of relevant studies. Information on patient population, study design, interventions, control group and outcomes assessed was collected by two authors independently. Discordance regarding the pertinence of the study to address each PICO was resolved in a face-to-face meeting. We have not registered our review in PROSPERO; we plan to do so for future studies.

## Results

Three PICO questions were identified regarding the management of diverticular disease after a CDB episode (Table 1). The literature search initially identified 362 papers, of which 45 were considered relevant to address the PICO questions (Figure 1). When available, the results of meta-analyses were used as the primary source of information.

### *Role of dietary and lifestyle interventions in preventing colonic diverticula rebleeding*

The bibliographic search did not allow to identify any dietary or lifestyle intervention studies (dietary fibre intake, smoking, physical activity, alcohol consumption, body weight) to prevent diverticular rebleeding.

Several observational studies have investigated risk factors associated with diverticular rebleeding[13–27] (Table 2). In all, 11 of the 15 studies were conducted in Asian countries, with the majority coming from Japan. Of the remaining studies, two were from the USA, one from Portugal and one from France.

All the studies were retrospective, and most were small. They evaluated the risk of rebleeding after a variable time from the index episode (ranging

**Table 1.** PICO questions identified by the expert panel.

| Question | Population | Intervention | Control | Outcomes |
|---|---|---|---|---|
| Question #1 | Patients with a previous episode of diverticular bleeding | Dietary/lifestyle interventions:<br>1. High-fibre diet/fibre supplementation<br>2. Lifestyle intervention (smoking cessation, physical activity, alcohol consumption, weight management). | 1. Free diet<br>2. No lifestyle intervention | Recurrence of bleeding<br>Diverticulitis<br>Quality of life<br>Hospitalisations<br>Need for surgical intervention<br>Resource utilisation<br>Mortality |
| Question #2 | Patients with a previous episode of diverticular bleeding | Pharmacological treatment:<br>1. Rifaximin<br>2. Mesalazine<br>3. Probiotics<br>Endoscopic treatment adopted during the index episode | Placebo<br>Usual practice<br>Head-to-head comparison | Recurrence of bleeding<br>Diverticulitis<br>Quality of life<br>Hospitalisations<br>Need for surgical intervention<br>Resource utilisation<br>Mortality |
| Question #3 | Patients on antiplatelet/ anticoagulant treatment with an episode of diverticular bleeding | Resumption of antiplatelet/ anticoagulant treatment after the episode of diverticular bleeding | Different timing of resumption of antiplatelet/ anticoagulant treatment<br>Interruption of antiplatelet/ anticoagulant treatment | Recurrence of bleeding<br>thrombosis<br>Cardiovascular events<br>Need for surgery/ interventional radiology<br>Mortality |

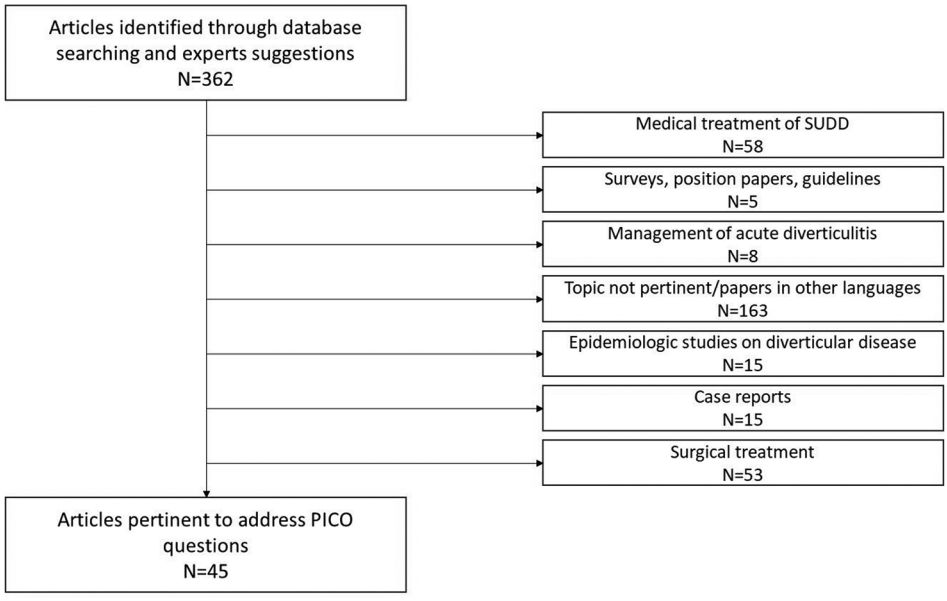


**Figure 1.** Study flow chart.

**Table 2.** Observational studies on risk factors associated with diverticular rebleeding.

| Author (year)[Ref.] | Study design | Number of patients | Risk factors evaluated | Independent predictors of rebleeding |
|---|---|---|---|---|
| Gonai (2022)[13] | Retrospective (re-bleeding within 1 month) | 370 | Age, sex, systolic blood pressure, hypertension, diabetes, CKD, neoplasms, SRH, haemostatic treatment, performance status, antithrombotic agents (ATs), number of ATs, continuation/discontinuation of ATs, NSAIDs, steroids. | ATs (yes vs no) (HR = 2.38; 95% CI 1.10–2.50; $p = 0.03$). Multiple ATs versus no ATs (HR = 3.88; 95% CI 1.49–10.0; $p = 0.007$). Continuation of ATs versus no ATs (HR = 3.30; 95% CI 1.23–8.63; $p = 0.02$). |
| Gonai (2021)[14] | Retrospective (re-bleeding within 1 year) | 324 | Age, sex, systolic blood pressure, hypertension, diabetes, CKD, neoplasms, haemostatic treatment, antithrombotic agents (ATs), number of ATs, continuation/discontinuation of ATs, NSAIDs, steroids. | ATs (HR = 3.89; 95% CI 1.53–10.74; $p = 0.004$ |
| Sato (2021)[15] | Retrospective, case–control (late re-bleeding: >30 days) | 519 | Age, sex, hypertension, diabetes, CKD, cardiovascular disease, cerebrovascular disease, respiratory disease, antithrombotic agents, NSAIDs, bilateral diverticula, bleeding source, type of SRH, CT extravasation, endoscopic haemostasis, shock index, blood transfusion | Chronic kidney disease (OR = 2.22; 95% CI 1.49–3.27; $p < 0.001$) NSAIDs (OR = 2.27; 95% CI 1.37–3.78; $p = 0.002$) Bilateral diverticula (OR = 1.98; 95% CI 1.361–2.895; $p < 0.001$). |
| Jalil (2018)[16] | Retrospective, case–control (re-bleeding within 2 years) | 93 cases and 152 controls | Age, sex, race, length of stay, hypertension, Hb at admission, BMI, diabetes, CKD, cardiovascular disease, cerebrovascular disease, obstructive sleep apnoea, gout, alcohol and tobacco consumption, antithrombotic agents, NSAIDs, proton pump inhibitors, ACEi/ARBs, beta-blockers, calcium channel blockers. | No statistically significant predictors of rebleeding were found in multivariate analysis. |
| Kitagawa (2019)[17] | Retrospective (re-bleeding within 90 days) | 144 | Age, sex, race, length of stay, Hb at admission, BMI, history of diverticular bleeding, blood transfusion, shock on admission, hypertension, diabetes, CKD, hyperlipidaemia, cardiovascular disease, cerebrovascular disease, antiplatelets, aspirin, anticoagulants, NSAIDs, steroids, SRH diverticula | Shock on admission (OR = 5.12; 95% CI, 1.17–22.43, $p = 0.030$) |
| Vajravelu (2018)[18] | Retrospective (re-bleeding >30 days) | 14,925 | Anticoagulants and PAIs, aspirin, NSAIDs, SSRIs, age, sex, race, comorbidities | Platelet aggregation inhibitors (OR = 1.47; 95% CI 1.15–1.88; $p < 0.05$). |
| Taki (2017)[19] | Case-control (re-bleeding at 1 year) | 100 cases and 200 controls | Age, gender, location of diverticulosis, BMI, hypertension, dyslipidaemia, diabetes mellitus, cerebrovascular disease, ischaemic heart disease, medication use (NSAIDs, COX-2 inhibitors, low-dose aspirin, non-aspirin antiplatelet drugs, anticoagulants, steroids, proton-pump inhibitors), dialysis, haemostasis, colonoscopy within 24 h. | Steroids (HR = 4.31; 95% CI 2.35–45.84; $p = 0.002$). |
| Lorenzo (2017)[20] | Retrospective (median FUP 3.9 years) | 365 | Age > 80 years, gender, anticoagulant or antiplatelet therapy prior to re-bleeding, Charlson comorbidity score >2, past history of bleeding. | No statistically significant predictors of rebleeding were found in multivariate analysis. |

*(Continued)*

**Table 2.** (Continued)

| Author (year)[Ref.] | Study design | Number of patients | Risk factors evaluated | Independent predictors of rebleeding |
|---|---|---|---|---|
| Joaquim (2017)[21] | Retrospective (re-bleeding at 1 year) | 74 | Age, gender, location of diverticula, severe bleeding at the index episode, treatment for the first episode, hypertension, hyperlipidaemia, diabetes, CKD, cardiovascular disease, peripheral vascular disease, arrhythmia, ischaemic heart disease, CHF, valvular heart disease, cerebrovascular disease, osteoarticular disease, chronic pulmonary disease, malignant neoplasia, Charlson-age comorbidity index, medication (NSAIDs, anticoagulant, antiaggregant). | No statistically significant predictors of rebleeding were found at multivariate analysis. |
| Nagata (2015)[22] | Prospective (re-bleeding at 1 year) | 41 | NSAIDs | NSAIDs discontinuation (HR = 0.06; 95% CI 0.01–0.31) |
| Watanabe (2014)[23] | Retrospective (median interval 11.5 months) | 151 | Age, sex, length of stay, treatment for the first episode, BMI, antiplatelets, aspirin, anticoagulants, NSAIDs, hypertension, ischaemic heart disease, cerebrovascular disease, diabetes, hyperlipidaemia, alcohol and tobacco consumption, systolic blood pressure, heart rate at admission, Hb, creatinine, blood transfusion, the position of haemorrhage. | Hypertension (OR = 6.72; 95% CI 2.33–23.5; $p < 0.001$)<br>Hyperlipidaemia (OR = 3.55; 95% CI 1.56–8.35; $p = 0.002$)<br>Heart rate at admission (OR = 1.03; 95% CI 1.01–1.06; $p = 0.01$)<br>Length of stay (OR = 1.19; 95% CI 1.05–1.35; $p = 0.005$). |
| Fujino (2013)[24] | Retrospective (re-bleeding within 1 month) | 90 | Age, gender, history of diverticular bleeding, hypertension, NSAIDs, antithrombotic agents, time from the start of bleeding to admission, signs of shock, Hb, active bleeding on the first colonoscopy, transfusion before first re-bleeding | Signs of shock on admission (OR = 5.23; 95% CI 1.84–14.90; $p = 0.0019$). |
| Niikura (2012)[25] | Retrospective (re-bleeding at a median interval of 1535 days). | 72 | NSAIDs, steroids, antithrombotic agents, hypertension, diabetes mellitus, hyperlipidaemia, cardio/cerebrovascular disease, chronic hepatic dysfunction, chronic renal failure, alcohol and tobacco consumption. | NSAIDs (HR = 2.57; 95% CI 0.89–7.46; $p = 0.08$); antiplatelet agents (HR = 2.39; 95% CI 1.01–5.67; $p = 0.05$); hypertension (HR = 4,16; 95% CI 1.22–14.2; $p = 0.02$) |
| Tanaka (2012)[26] | Retrospective (re-bleeding within 1 month and >1 month) | 111 | Age, sex, BMI, hypertension, diabetes mellitus, hyperlipidaemia, cardio/cerebrovascular disease, steroid, antiplatelets, NSAIDs, anticoagulants, antihypertensives, colonoscopic findings | Multivariate analysis not performed. At univariate analysis, patients with re-bleeding had higher BMI. Colonoscopic findings of actively bleeding or nonbleeding visible vessels in the responsible diverticula were more frequent in the group with re-bleeding. |
| Okamoto (2012)[27] | Retrospective (mean FUP 2.4 years) | 62 | Sex, age, hypertension, hyperlipidaemia, diabetes, cardio/cerebrovascular disease, anticoagulant drugs, NSAIDs, treatment using haemoclips | NSAIDs (HR = 6.3, 95%CI 1.7–20.7; $p = 0.007$) |

BMI, body mass index; CHF, chronic heart failure; CKD, chronic kidney disease; FUP, follow-up; NSAIDs, non-steroidal anti-inflammatory drugs; PAI, platelet aggregation inhibitors; SRH, stigmata of recent haemorrhage; SSRI, selective serotonin reuptake inhibitors.

from within a month to several years) and reported a considerable number of different risk factors. Some of these studies have evaluated the role of smoking and alcohol consumption,[16,23,25] but an independent role of these risk factors has not been demonstrated. The role of body mass index (BMI) has also been investigated in several studies,[16,17,19,23,26] but it has never been found to be an independent predictor of diverticular rebleeding in multivariate analysis. In one study,[26] patients with rebleeding had a higher BMI on univariate analysis, but no multivariate analysis was performed.

Therefore, based on observational data, there is currently no evidence to suggest that lifestyle or dietary factors are associated with the risk of diverticular bleeding recurrence.

### *Role of pharmacological management in the prevention of recurrent CDB*

The bibliographic search did not allow us to identify any pharmacological treatment intervention studies focusing on drugs commonly used in diverticular disease (rifaximin, mesalazine, probiotics) to prevent diverticular rebleeding.

### *Role of endoscopic management of the index episode in the prevention of recurrent CDB*

*Endoscopic treatment versus conservative approach.* To the best of our knowledge, there are no studies directly comparing endoscopic versus a conservative and the available data come from observational studies. In a small cohort study,[28] 17 and 10 patients with a definite source of bleeding were managed conservatively and endoscopically, respectively. Of the 17 patients treated conservatively, 9 had recurrent or persistent bleeding requiring additional transfusion. Three of these were managed with medical treatment that stopped the bleeding, while the remaining six patients had severe bleeding and required emergency hemicolectomy. None of the 10 patients treated endoscopically had recurrent bleeding or complications or required further red cell transfusions or surgery. No delayed re-bleeding was observed in either group.

Another observational study compared 88 patients who underwent endoscopic (i.e. injection and/or clipping) or conservative treatment.[29] In all, 16 (61.5%) of 26 endoscopically treated patients and 24 (38.7%) of 62 conservatively treated patients experienced CDB recurrence during a median follow-up of 42.7 months. Kaplan–Meier analysis showed that the recurrence rate was significantly higher ($p < 0.05$) in endoscopically treated cases compared to conservatively treated cases, with a mean time to recurrence of 55.3 months (95% CI 30.8–79.9) versus 99.9 months (95% CI 80.7–119.1). These observational studies have important methodological limitations, mainly related to the difficulty in assessing whether patients treated endoscopically and those treated conservatively had similar characteristics at baseline in terms of disease severity and risk factor distribution.

More recently, a large nationwide retrospective study of 5,823 patients with CDB undergoing colonoscopy in 49 Japanese hospitals compared three strategies: (1) find stigmata of recent haemorrhage (SRH) and treat endoscopically, (2) find SRH and treat conservatively and (3) treat conservatively without finding SRH (presumed CDB).[30] When conducting pairwise comparisons of outcomes in these groups, the propensity score matching technique was used to balance baseline characteristics between the compared groups. Both early and late recurrent bleeding rates were significantly lower in patients with proven CDB treated endoscopically compared to those with presumed CDB treated conservatively (<30 days, 19.6% vs 26.0% ($p < 0.001$); <365 days, 33.7% vs 41.6% ($p < 0.001$), respectively). In patients with established CDB, the rate of early recurrent bleeding was significantly lower in those treated endoscopically compared to those treated conservatively (17.4% vs 26.7%; $p = 0.038$ for a single hypothesis test). However, this difference was no longer significant after correction for multiple testing. The rate of late recurrent bleeding was also lower in the endoscopically treated group, but the difference was not statistically significant. Patients with established CDB treated endoscopically had significantly lower rates of early and late recurrent bleeding rates than patients with established CDB treated conservatively with active bleeding, non-active bleeding and in the right colon but not the left colon. Promising observations on the usefulness of endoscopic treatment in reducing late bleeding (within 30 days) could be hypotheses, in the light of the conclusions of the recent study by Aoki et al.[31] where the analysis is restricted to patients

with SRH; the authors found that in the presence of diverticular bleeding and HRS, endoscopic therapy does indeed reduce the risk of rebleeding by 40%.

*Endoscopic treatment: Clipping versus ligation.* The role of the endoscopic approach used for the index episode of CDB in reducing the risk of recurrence has been evaluated in several studies and summarised in a recent systematic review.[32] This review assessed the comparative effectiveness of endoscopic clipping versus band ligation for the prevention of CDB recurrence. In all, 16 studies met the eligibility criteria, with a total of 790 participants. Band ligation showed a significantly lower pooled prevalence of both early (within 30 days) and late (within 1 year) rebleeding compared with clipping (0.08 vs 0.19 (test for heterogeneity, $p = 0.012$), 0.09 vs 0.29 (test for heterogeneity, $p = 0.024$), respectively). There was no significant difference in the initial haemostasis between the two groups. The overall prevalence of patients requiring transcatheter arterial embolisation or surgery was significantly lower with band ligation than with clipping (0.01 vs 0.02; test for heterogeneity, $p = 0.031$). Two cases of colonic diverticulitis were reported after band ligation, but none after clipping.

*Endoscopic treatment: Direct versus indirect clipping.* Regarding the type of endoscopic approach, we found only one large Japanese observational study comparing direct and indirect clipping.[33] In direct clipping, the vessel was clamped directly, whereas in indirect clipping, the diverticular orifice was closed in a zipper-like fashion. The study included 1041 patients with CDB, of whom 360 underwent direct clipping and 681 underwent indirect clipping. Multivariate analysis adjusted for age, sex and important confounders (heart rate $\geq 100$ bpm, modified CCI $\geq 2$, extravasation on computed tomography, active bleeding, use of an endoscopic distal attachment cap and use a waterjet scope) showed that direct clipping was independently associated with a reduced risk of early rebleeding ($<30$ days; adjusted odds ratio (AOR) 0.592, $p = 0.002$), late rebleeding ($<1$ year; AOR 0.707, $p = 0.018$) and need for blood transfusion requirement (AOR 0.741, $p = 0.047$) compared to indirect clipping. There was no significant difference in initial haemostasis rates observed between the two groups. Propensity score matching showed a significant reduction in the early and late rebleeding rates with direct clipping compared to indirect clipping. Therefore, when comparing band ligation versus clipping or clipping versus conservative approach, the type of clipping (direct vs indirect) should be considered.

### *Resumption of antiplatelet and anticoagulant therapy after an episode of diverticular bleeding*

*Antiplatelet therapy.* No studies have evaluated when antiplatelet therapy (i.e. aspirin, thienopyridine, cilostazol, eicosapentaenoic acid, sarpogrelate hydrochloride, dipyridamole and prostaglandin E1 derivatives) should be resumed after an interruption in patients with CDB.

A retrospective, cohort study of 295 patients with lower GI bleeding (not limited to CDB) on aspirin showed that continuation of aspirin was associated with an almost three-fold increased risk of recurrent bleeding but also with a 1.6-fold reduced risk of major cardiovascular events and a more than three-fold reduced risk of death within 5 years, which underlies the net benefit of resuming aspirin after the bleeding event.[34]

*Anticoagulant therapy.* Only one study evaluated whether anticoagulant therapy should be restarted after a CDB episode.[18] In CDB patients treated for ischaemic stroke prophylaxis, there was no increased relative risk of recurrent CDB in those who continued any form of anticoagulant therapy compared with those who discontinued (HR 0.98, 95% CI 0.79–1.22). However, discontinuation of anticoagulation was associated with an increased relative risk of ischaemic stroke (HR 1.93, 95% CI 1.17–3.19).

Given the paucity of studies specifically focusing on CDB, we analysed the available data on GI bleeding (not limited to CDB) with appropriate caution to identify possible risk factors for diverticular rebleeding. Several cohort studies have evaluated the effect of resuming anticoagulant therapy after withdrawal due to acute GI bleeding (therefore not specific to diverticular bleeding) and have shown that prolonged interruption of anticoagulant therapy is associated with a risk of thromboembolism[35–37] and subsequent increased mortality at 3[36] and 12 months.[37]

A meta-analysis of three observational studies showed that restarting warfarin was associated with a significant reduction in thromboembolic

events (hazard ratio (HR) 0.68; 95% CI 0.52–0.88, $p < 0.004$, $I^2 = 82\%$).[38] There was no statistically significant increase in recurrent GI bleeding in patients who resumed warfarin compared to those who did not (HR 1.20; 95% CI 0.97–1.48, $p = 0.10$, $I^2 = 0\%$). Restarting warfarin was associated with a significant reduction in mortality (HR 0.76; 95% CI 0.66–0.88, $p < 0.001$, $I^2 = 87\%$).

A more recent meta-analysis of 10 observational studies included 2080 patients who resumed anticoagulation and 2296 patients who discontinued anticoagulation after a GI bleeding episode.[39] The anticoagulant used in seven studies was warfarin alone, and three studies included patients on DOACs. The duration of anticoagulation withdrawal after GI bleeding ranged from 4 days (IQR 2–9 days) to 50 days (IQR 21–78 days). Resumption of anticoagulation was associated with a significant increase in recurrent GI bleeding (OR 1.646; 95% CI 1.035–2.617, $p = 0.035$). However, a significant reduction in thromboembolic events was observed in patients who resumed anticoagulant therapy compared to those who did not (OR 0.340; 95% CI 0.178–0.652, $p = 0.001$, $I^2 = 62.7\%$). Resumption of anticoagulant therapy was also associated with a significant reduction in all-cause mortality (OR 0.499; 95% CI 0.419–0.595, $p < 0.0001$). Taken together, these data, deriving from observational studies not limited to CDB, suggest that resuming the anticoagulant therapy may increase the risk of GI bleeding but reduce the overall risk of thromboembolic events and mortality. However, selection bias may limit the interpretation of these results. Indeed, we cannot exclude the possibility that anticoagulation was less likely to be resumed in frail patients, who have a higher risk of thromboembolic events and mortality.

The above-mentioned meta-analysis by Tapaskar et al.[39] looked specifically at the timing of anticoagulation resumption, which was reported in five studies.[36,37,40–42] The median time to restart therapy ranged from 4 days[36] to 50 days.[37] Overall, these studies suggest that restarting anticoagulation between 2 and 6 weeks after the initial discharge or index bleeding episode may be optimal and warranted.[39] However, it has been argued that this suggestion should be considered with caution, as it is not based on the results of a meta-analysis, but on an unstructured review that was not subjected to formal statistical analysis.[43] In addition, most of the data came from patients treated with vitamin K antagonists (VKAs), with the exception of one study of direct oral anticoagulants (DOACs). Therefore, the faster onset of action of the DOAC must be taken into account and it may be necessary to delay the resumption times of the DOAC longer than the resumption times of warfarin. A larger prospective study of a DOAC or VKA comparing early and late resumption of oral anticoagulants after GI bleeding would be ideal to answer the optimal timing of resumption of oral anticoagulants.[43]

A longitudinal study[44] included 948 patients hospitalised for GI bleeding occurring during treatment with vitamin K antagonists ($n = 531$) or DOACs ($n = 417$). In a time-dependent analysis, anticoagulant treatment was associated with a higher risk of recurrent clinically relevant bleeding (HR 1.55; 95% CI 1.08–2.22), but a lower risk of thromboembolism (HR 0.34; 95% CI 0.21–0.55) and death (HR 0.50; 95% CI 0.36–0.68). Previous bleeding, index major bleeding and lower glomerular filtration rate were associated with a higher risk of recurrent bleeding. The incidence of recurrent bleeding increased after anticoagulation was resumed, regardless of the timing of the resumption. The study suggests that the risk of recurrent bleeding seems to be influenced by patient characteristics rather than the timing of anticoagulation resumption.

### *Effect of non-steroidal anti-inflammatory drugs and aspirin use in colonic diverticular rebleeding*

In view of the known adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin on the GI tract, we have also analysed the potential effect of these drugs on colonic diverticular rebleeding. As shown in Table 2, data from observational studies indicate that the only modifiable risk factor that may reduce the risk of CDB is the discontinuation of NSAIDs. Indeed, the use of NSAIDs is a strong independent risk factor for rebleeding in some studies,[15,22,25,27] although other studies have found no significant association between the use of NSAIDs and the risk of rebleeding.[13,14,16–19,21,23,24,26] A possible explanation for this conflicting result may be related to the frequency of use and dosage of NSAIDs.

In Table 3, the risk of diverticular rebleeding in relation to NSAIDs and aspirin dosage and

**Table 3.** Risk of diverticular rebleeding with respect to the NSAIDs/aspirin dosage and frequency use.

| Author (year) | Study design | Number of patients | Risk of CDB in NSAIDs high dosage/regular use | Risk of CDB in NSAIDs low dosage / occasional use | Risk of CDB in aspirin occasional use | Risk of CDB in aspirin chronic use (as antiplatelets) |
|---|---|---|---|---|---|---|
| Gonai (2022)[13] | Retrospective (re-bleeding within 1 month) | 370 | Not specified | Not specified | Not specified | Not specified |
| Gonai (2021)[14] | Retrospective (re-bleeding within 1 year) | 324 | Not specified | Not specified | Not specified | Not specified |
| Sato (2021)[15] | Retrospective, case–control (late re-bleeding: >30 days) | 519 | Not specified | Not specified | Not specified | Not specified |
| Jalil (2018)[16] | Retrospective, case–control (re-bleeding within 2 years) | 93 cases and 152 controls | Not specified | Not specified | Not specified | Not specified |
| Kitagawa (2019)[17] | Retrospective (re-bleeding within 90 days) | 144 | Not specified | Not specified | Not specified | Not specified |
| Vajravelu (2018)[18] | Retrospective (re-bleeding >30 days) | 14,925 | Not specified | Not specified | Not specified | Not specified |
| Taki (2017)[19] | Case–control (re-bleeding at 1 year) | 300 | Regular use HR = 0.87 (0.21–3.58) | Not specified | Not specified | Low-dose aspirin HR = 0.80 (0.27–2.39) |
| Lorenzo (2017)[20] | Retrospective (median FUP 3.9 years) | 365 | Not specified | Not specified | Not specified | Not specified |
| Joaquim (2017)[21] | Retrospective (re-bleeding at 1 year) | 74 | Not specified | Not specified | Not specified | Not specified |
| Nagata (2015)[22] | Prospective (re-bleeding at 1 year) | 41 | NSAIDs discontinuation HR = 0.06 (0.01–0.31) | Not assessed | Not assessed | Low-dose aspirin at discharge was not significant in multivariate analysis |
| Watanabe (2014)[23] | Retrospective (median interval 11.5 months) | 151 | Not specified | Not specified | Not specified | Not specified |
| Fujino (2013)[24] | Retrospective (re-bleeding within 1 month) | 90 | Not specified | Not specified | Not specified | Not specified |
| Niikura (2012)[25] | Retrospective (re-bleeding at a median interval of 1535 days). | 72 | Not specified | Not specified | Not specified | Not specified |
| Tanaka (2012)[26] | Retrospective (re-bleeding within 1 month and >1 month) | 111 | Not specified | Not specified | Not specified | Not specified |
| Okamoto (2012)[27] | Retrospective (mean FUP 2.4 years) | 62 | Not specified | Not specified | Not assessed | Not assessed |

frequency of use has been reported. Unfortunately, most studies do not report data on the duration and/or dosage of treatment.

## Discussion

It has been estimated that CDB is the most common cause of lower GI bleeding in adult

patients,[44–47] accounting for more than 40% of bleeding episodes.

In this review, we aimed to evaluate the current evidence on the prevention of colonic diverticular rebleeding, assessing the potential role of lifestyle, pharmacological and endoscopic treatments.

In assessing dietary and lifestyle risk factors (intake of dietary fibre, smoking, physical activity, alcohol consumption, BMI), we did not identify any interventions to prevent diverticular rebleeding. Several small, retrospective studies have investigated smoking, alcohol consumption and BMI as potential risk factors for CDB recurrence, without identifying them as independent predictors. Despite large prospective studies linking obesity with CDB[48] and alcohol consumption in general with GI bleeding (not limited to CDB),[49] there is, unfortunately, no evidence of their effect on CDB recurrence, so this remains an area for further research.

Unfortunately, the bibliographic search did not identify any specific pharmacological treatment (such as rifaximin, mesalazine or probiotics) able to prevent diverticular rebleeding. On the contrary, the role of the endoscopic approach used during an index episode of CDB in reducing the risk of recurrence has been evaluated in several studies.

Data comparing endoscopic and conservative approaches to CDB are from observational studies and show conflicting results. In particular, one cohort study showed that endoscopic management was associated with fewer recurrences, complications and need for surgery compared with conservative management.[28] On the other hand, another observational study showed that patients treated conservatively had fewer CDB recurrences during follow-up than those treated endoscopically.[29] Another large retrospective study showed that endoscopic management of confirmed CDB was more effective in reducing short- and long-term recurrences than conservative management of confirmed or presumed CDB.[30] A possible explanation for these conflicting results is the possible differences in the baseline characteristics of the patients, as all these studies are observational, which may have led to selection bias. Although a more recent study[31] also provides promising data on the role of endoscopic treatment, the generalisability of the data seems limited. First, HRS is much less common in Western countries than described in the Japanese population, as Western guidelines do not support early endoscopy (within 24 h); second, the benefit of endoscopic treatment is mainly for right colonic bleeding, which is clearly more common in Eastern than in Western populations. Further prospective randomised studies, also in Western countries, are needed to better determine whether endoscopic treatment is superior to observation management in preventing colonic diverticular rebleeding.

Regarding the endoscopic technique that should be used to prevent CDB recurrence, a recent review showed that band ligation had fewer cases of both early and late rebleeding compared with clipping, although there was no significant difference in the rate of initial haemostasis between the two methods.[27,32] Furthermore, in a large observational study comparing direct clipping and indirect clipping, direct clipping was independently associated with a lower risk of early and late rebleeding and the need for blood transfusion.[32,33] Therefore, when comparing endoscopic techniques for the management of CDB (band ligation vs clipping), the type of clipping (direct vs indirect) should also be considered.

The timing of resumption of antiplatelet and anticoagulant therapy remains to be determined. In fact, we found only one study that investigated this aspect in CDB. The only available study that investigated the resumption of anticoagulant therapy after its discontinuation in patients with CDB showed that there was no increased relative risk of CDB recurrence in those who resumed any of the anticoagulant therapies.[18]

Instead, most of the available data from observational studies focus on general acute GI bleeding. Evidence from studies not limited to CDB suggests that although resumption of anticoagulant therapy may increase the risk of GI bleeding, it may also reduce the risk of thromboembolic events and mortality. We have assumed that management approaches and findings from GI bleeding studies may be applicable to CDB, but this assumption has not been definitively proven. As a

result, clinicians must rely on indirect evidence when making decisions about both the management and timing of the resumption of antiplatelet or anticoagulant therapy in patients with CDB.

Finally, the only modifiable risk factor associated with a reduction in the risk of CDB is the discontinuation of NSAIDs. However, there are inconsistencies in the available data, probably due to differences in dosage and frequency of use. In fact, therapeutic regimens are often poorly characterised in these studies, contributing to the conflicting results. There is also a paucity of data on complications and mortality associated with discontinuing NSAIDs.

### *Limitation*

Factors limiting the generalisability of these data are that most of the evidence comes from Asia, making it difficult to apply the findings to Western countries, due to differences in population, but also to differences in the diverticular disease itself, including the different location of diverticula. Future research perspectives include the need for studies conducted in Western countries to understand whether the location of diverticula might affect the outcome of treatments, especially endoscopic ones. Another aspect to be studied in the future is to evaluate the timing of reintroduction of antiplatelet and anticoagulant therapies, which are widely used in the elderly population, where the prevalence of colonic diverticula is significant.

## Conclusion

In conclusion, this review highlights the paucity of data on the possible role of lifestyle, pharmacological and endoscopic treatments in the prevention of colonic diverticular rebleeding and advocates future studies aimed at finding effective therapeutic strategies.

## Declarations

### *Ethics approval and consent to participate*

Not applicable.

### *Consent for publication*

Not applicable.

### *Author contributions*

**Marilia Carabotti:** Conceptualisation; Data curation; Formal analysis; Writing – original draft; Writing – review & editing.

**Giovanni Marasco:** Conceptualisation; Data curation; Formal analysis; Writing – original draft; Writing – review & editing.

**Franco Radaelli:** Conceptualisation; Data curation; Formal analysis; Writing – original draft; Writing – review & editing.

**Giovanni Barbara:** Conceptualisation; Data curation; Formal analysis; Writing – original draft; Writing – review & editing.

**Rosario Cuomo:** Conceptualisation; Data curation; Formal analysis; Writing – original draft; Writing – review & editing.

**Bruno Annibale:** Conceptualisation; Data curation; Formal analysis; Writing – original draft; Writing – review & editing.

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### *Competing interests*

M.C. and F.R. none to declare. G.M. served as an advisory board member for AlfaSigma, EG Pharma, Monteresearch srl, Recordati and Cineca. Received lecture grants from Agave, AlfaSigma, Bromatech, Clorofilla, Echosens, Ferring, Mayoly Spindler, Menarini and Schwabe Pharma. G. B. has served as a speaker and consultant for Alfasigma/Alfa Wassermann, Allergan, CaDiGroup, Danone, Ironwood, Italchimici, Malesci, Menarini, Noos, Shire, Synergy, Sofar, Yakult and Zespri, and has received research funding from Alfasigma/Alfa Wassermann, Cadigroup, Falk Pharma, IMA, Italchimici, Lorenzatto, Parmalat Sofar, Yakult and Zespri. R.C. has served as a speaker and consultant for Alfasigma/Alfa Wassermann, Allergan, Malesci,

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**Supplemental material**
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