

## Review Article

# Post-polypectomy bleeding after colonoscopy on uninterrupted aspirin/non steroidal antiinflammatory drugs: Systematic review and meta-analysis

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## ARTICLE INFO

## Article history:

Received 15 June 2017

Received in revised form

12 September 2017

Accepted 7 October 2017

Available online 18 October 2017

## Keywords:

Colonic polyp

Adverse event

Acetilsalicylic acid

Colonoscopy

Bleeding

Hemorrhage

Antiinflammatory non steroidal drugs

## ABSTRACT

**Background and aim:** The aim of this systematic review and meta-analysis was to assess the risk of post-polypectomy bleeding (PPB) in patients that underwent colorectal polypectomy and exposed to ASA/NSAIDs.

**Methods:** Relevant publications were identified in MEDLINE/EMBASE for the period 1950–2016. Studies with specified ASA/NSAIDs exposure and bleeding rate were included. Study quality was ascertained according to Newcastle–Ottawa Scale. Forest plot was based on fixed or random effect models in relation to the heterogeneity.

**Results:** 11 studies (4 prospective and 7 retrospective) including 9307 patients were included in the analyses. Overall, 344 patients (OR 1.8; 95% CI 1.2–2.7; p-value 0.001, I<sup>2</sup> 52%) experienced rectal bleeding after procedure. While the rate of immediate PPB on aspirin and/or NSAIDs was not increased (OR 1.1; CI 95% 0.6–2.1; d.f. = 1, p = 0.64, I<sup>2</sup> 0%), the risk of delayed PPB was augmented (OR 1.7; 95% CI 1.2–2.2; d.f. = 8, p = 0.127, I<sup>2</sup> 36%).

**Conclusions:** ASA/NSAIDs are not a risk factor for immediate PPB but the chance of delayed is increased.

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## 1. Introduction

Endoscopic resection of adenomas is the best treatment for prevention of colorectal cancer because it is safe and efficacious [1]. Nonetheless, the reported percentage of post-polypectomy bleeding (PPB) ranges from 0.07–1.7% [2–4]. Prior studies recognized some features related to PPB, as polyp size, position in the right colon, sessile morphology, number of polyps, comorbidities, endoscopist's experience and use of antiplatelet/anticoagulant drugs [4–12]. There are no high quality evidences for an association between antiplatelet drugs and PPB. European Society of Gastrointestinal Endoscopy (ESGE) guidelines [13] stated that polyps can be safely removed without interruption (moderate evidence) of aspirin (ASA) therapy (with the exception of large colonic mucosectomy  $\geq 2$  cm), but systematic evidence about this matter still

lacks and also for post-procedural indications. On the other hand, an increased percentage of patients take these drugs because of a risk of ischaemic events if treatment is interrupted. Most studies indicated that ASA is not a risk factor for PPB [5,9,10,12,14,15]. In a retrospective survey, Pan et al. [16] showed a significant association between PPB and ASA, but not with Non Steroidal Anti-Inflammatory Drugs (NSAIDs). Shiffman et al. [14] concluded that, although the use of ASA/NSAIDs increased the incidence of minor self-limited bleeding, major bleedings were not significant. Metz et al. [17] showed a significant relationship between PPB and ASA, but the study was conducted on large colonic lesions. In particular, the use of a low-dose ASA regimen as an anti-thrombotic measure has become increasingly common. In 2007, the Agency for Healthcare Research and Quality (AHRQ) reported that nearly 20% of adults received a daily ASA regimen in the United States, with this number increasing to nearly 50% in those aged 65 and older [18]. According to data from SPoC prospective multicentre trial [6] based on 5178 polypectomies in 2692 patients, 14.3% of the patients received ASA. ASA, commonly used at low dosage (75–160 mg daily), and NSAIDs decrease platelet aggregation by

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irreversibly inhibiting cyclooxygenase-1. As a result, the synthesis of thromboxane A2, a potent platelet-activating agent, is blocked [19,20].

### 1.1. Objective

The aim of this systematic review and meta-analysis was to assess the risk of PPB in patients that underwent colorectal polypectomy and exposed to ASA/NSAIDs.

## 2. Methods

### 2.1. Eligibility criteria

We included studies with any kind of design, reported as full-text or abstract. We included adults ( $\geq 18$  years old) who underwent colorectal polypectomy (cold polypectomy, snare polypectomy, endoscopic mucosal resection, endoscopic submucosal dissection). We excluded studies where only endoscopic submucosal dissection was performed. We included studies comparing patients exposed to ASA/NSAIDs with those not exposed to these drugs in the periendoscopic period. Exposure was defined as consuming one of these drugs (any dosage) before (at least three days) or/and after colorectal polypectomy. We excluded studies where exposure status was not clearly defined in the methods. Studies that comprehended aspirin in the generic term “antithrombotics” (where other drugs could be aggregated as thienopyridines) were also excluded.

#### 2.1.1. Outcomes

Immediate PPB was defined as passage of blood from the site of polypectomy during the procedure (or within 6 h). Delayed PPB was defined as hematochezia between 6 h and 14 days after polypectomy. Clinically significant (CS) PPB was defined by [21] the International Society on Thrombosis and Haemostasis (ISTH) definition (death, hemodynamic instability, drop of  $>2$  g/dl of haemoglobin, need to repeat endoscopy with or without intervention, or need for  $>2$  blood transfusion). Primary outcome was to evaluate the risk of PPB in patients exposed and not exposed to ASA/NSAIDs. Secondary outcomes evaluated, in patients exposed and not exposed to ASA/NSAIDs, the risk of immediate, delayed, clinically significant bleeding and for lesions  $\geq 2$  cm.

### 2.2. Information sources

We identified studies in English language in Medline (from 1950 to November 2016) and Embase (from 1974 to November 2016) databases. We searched all records using the search strategy in Appendix A–Supplementary material. We checked reference lists of all primary studies and review articles for additional references.

### 2.3. Study selection

Two review authors [FP, HB] independently screened the abstracts for inclusion of all the potential studies identified as a result of the search. Then, the same authors independently screened the full-text and identified studies for inclusion and recorded reasons for exclusion. Any disagreement was resolved through discussion or, if required, a third person [RLC] was consulted. Duplicates were identified and excluded. If there was any suspicion of cohort overlap between studies, only the most large study was included. The selection process was recorded in sufficient detail to complete a PRISMA flow diagram [22].

### 2.4. Data collection process

A database was used to collect the data of studies' characteristics and outcomes. One review author [FP] extracted the following data from included studies: publication year, setting (single/multicentre study), study design (prospective/retrospective), matching of cases with controls and adjusting factors, method to define and to find cases and controls. Characteristics from participants and lesions were: number, age, gender, ASA/NSAIDs dosage, intake of ASA/NSAIDs before and/or after polypectomy, characteristics of lesions (size, location, morphology), techniques of polypectomy, endoscopist's experience, prophylactic tools employed for prevention of bleeding, exclusion criteria, management of incomplete information. For every study it was reported the severity (minor/major) and time (immediate/delayed) of bleeding. It was reported if data about cases/controls were explicated in the text or were deduced from the reviewer. For Example, Choung et al. [9] reported the rates of not bleeding and bleeding events in patients exposed to ASA (262/3746 and 3/42 respectively), aspirin + clopidogrel (67/3746 and 1/67 respectively) and anti-coagulant (127/3746 and 4/67 respectively). The rate of events (bleeding) and the rate of no-event (not bleeding) were computed taking into account exposed cases (patients receiving ASA/NSAIDs with a bleeding event), not exposed cases (total of cases – cases exposed to ASA/NSAIDs – cases exposed to ASA and clopidogrel – cases exposed to anticoagulants), exposed controls (patients receiving ASA/NSAIDs without a bleeding event), not exposed controls (total of controls – controls exposed to ASA – controls exposed to aspirin and clopidogrel – controls exposed to anticoagulants). The process was checked from another reviewer [GG].

### 2.5. Risk of bias in individual studies

Two review authors (FP, HB) independently assessed the risk of bias for each study using the criteria outlined in the Newcastle-Ottawa Scale [23]. We resolved any disagreements by discussion or by involving another author (RLC). We graded each potential source of bias together with a justification for our judgement. We summarised the risk of bias judgements across different studies for each of the domains listed.

### 2.6. Dealing with missing data

We contacted investigators in order to obtain missing numerical outcome data if possible (e.g. when a study is identified as abstract only). When it was not possible and the missing data were thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis.

### 2.7. Statistical analysis

For each endpoint, we analysed data obtained from different studies to determine pooled Odds Ratio (OR) and the 95% Confidence Intervals (CIs). We used a fixed-effect Mantel–Haenszel model in order to obtain a preliminary summary estimate. Heterogeneity in meta-analysis refers to the variation in study outcomes between studies. Heterogeneity was explored by Cochran's  $Q$ , which is calculated as the weighted sum of squared differences between individual study effects and the pooled effect across studies. The  $I^2$  statistic describes the percentage of variation across studies that is due to heterogeneity rather than chance [24]. If heterogeneity was consistent (by  $p$ -value of  $Q < 0.1$  and by  $I^2$  degree  $> 50\%$ ), a random effect model was used. Sources of heterogeneity were explored using subgroup analyses and meta regression analyses (only if there were more than 10 trials and data

about main confounding factors were present in every study). The influence of each study was performed through a sensitivity analysis and results were discussed. In order to assess the publication bias, the Egger regression asymmetry test was performed [25]. The regression of the standardized effect estimates against precision to determine whether the intercept significantly deviates from zero. A  $p$  value  $< 0.10$  suggests a greater likelihood of publication bias. A funnel plot was also provided to visual asymmetry if we were able to pool more than 10 trials. If publication bias was present, the pooled odd ratio was recalculated by trim and fill method [26]. Analyses were performed with STATA version 13 (StataCorp LP, TX, USA).

### 3. Results

#### 3.1. Study selection

2371 and 323 records were identified through databases searching with EMBASE and PUBMED respectively. After removal of duplicates, 2427 studies were screened on basis of title and abstract. 135 full-text records were consequently examined for eligibility. Not eligible studies were excluded because of absence of data about ASA/NSAIDs, absence of data about bleeding or if there were reviews or commentary. Sixteen studies were finally included in the qualitative analysis (5,6,8–10,12,14–17,27–32). Because of lack of sufficient explanation in the methods about exposure to ASA/NSAIDs, five more studies [6,8,28–30] were excluded. For details, see PRISMA FlowDiagram (Supplementary Fig. 1). See Supplementary Table 1 for reasons of exclusion.

#### 3.2. Study characteristics

Eleven studies [5,9,10,12,14–17,27,31–32] were included in the quantitative analysis. Publication year ranged from 1994 to 2014. Most of the studies (9/11) were performed in a single centre and 4/11 studies were observational prospective trials (Table 1).

#### 3.3. Study participants

Data from 9720 patients were included in the meta-analysis. Median number of patients included in the studies was 464 (min–max, 120–3788). Mean age of patients included in the meta-analysis ranged from 59.1 to 72.1 years. Male sex was distributed in the studies from 54.0% to 97.7% of cases. In two studies, data about gender were not available. NSAIDs exposure was described in 4/11 studies and ASA dosage was described only in a study. Time of exposure to ASA/NSAIDs in the periendoscopic period was quite variable. Patients consumed ASA/NSAIDs before colonoscopy in 9/11 studies. After the polypectomy, ASA/NSAIDs consumption was not described in 5/11 studies and in the other cases drugs were not suspended. Delayed PPB was always evaluated (11/11 cases) and immediate cases of bleeding were evaluated in 4/11 studies. In the same way, CSPPB episodes were calculated in all studies and minor PPB in 3/11 studies. In 2/11 cases, participants' characteristics were adjusted for potential confounding factors (Tables 1 and 2).

#### 3.4. Characteristics of colorectal lesions and resection techniques of the included studies

Number of removed polyps ranged from 120 to 5981, but in most of the studies, even if more than one lesion was removed, only a polyp per patient was chosen for the statistical analysis. Description of lesion size was quite heterogeneous (mean  $\pm$  standard deviation, mean and ranges, minimum and maximum, percentage of lesions more than 10 or 20 mm). 2/11 studies considered only lesions

$\geq 20$  mm (specified in the study design) and the rest of the studies included polyps of any dimension in their sample. Morphology of lesions was described in 4/11 studies and in one of them only non-polypoid lesions were resected. Location of lesions, described in 5/11 cases, showed equal distribution among proximal and distal lesions. A variability among resection techniques was also present. In two studies only endoscopic mucosal resection were performed and in 5 studies lesions were removed only with cold snare, hot biopsy or hot snare polypectomy. Only in one study endoscopic submucosal dissection was performed but the number was not significant respect to the total of lesions (8/208). Employment of prophylactic devices for haemostasis (mainly metallic clip) was described in 2/11 cases (Table 3).

#### 3.5. Risk of bias within studies

All studies were included if ascertainment of exposure was described in the 'methods' section. A potential selection bias could be the lack of comparability of cases and controls. This meta-analysis included three studies that compared groups of patients that differed only for ASA/NSAIDs exposure or not. The rest of the studies examined groups of patients with and without bleeding events and role of various risk factors including ASA/NSAIDs.

Exposure time to ASA/NSAIDs could be a potential bias because there are differences between studies. Eleven studies [5,9,10,12,14–17,31–33] defined aspirin exposure prior to polypectomy with a variable time from 3 to 7 days. Sawhney et al., Manocha et al., Shiffman et al., and Pan et al., [5,10,14,16] did not interrupt ASA/NSAIDs neither before or after polypectomy. Exposure status after polypectomy was not assessed in 5/11 cases (Table 3).

All studies reported criteria for defining immediate and/or delayed PPB. Every study reported data about delayed PPB but only four studies [10,12,17,31] included cases of immediate bleeding. The description of the severity of PPB was more heterogeneous. CSPPB was defined in 5/11 studies [5,16,31,10,9] according to ISTH definition. Hui et al. [12] graded the PPB according to a modified classification proposed by Cotton and Williams for post-sphincterotomy bleeding [34]. The rest of the studies identified the bleeding as CS if patients required a second post-procedural colonoscopy [15,32] or evaluation at the emergency room [14,17,27] (Table 3).

The quality assessment of studies using the Newcastle–Ottawa scores was resumed in the Supplementary Table 2. The mean quality score was 5 (minimum 4, maximum 7).

#### 3.6. Synthesis of results

Data about bleeding events were available for all the studies. Because in 7 studies it has been reported data about bleeding events and association with other anti thrombotic/anticoagulant drugs, the total number of analysed patients (after removal of events and non-events related to these drugs) was 9287. In the pooled analysis, ASA/NSAIDs were positively associated with the risk of overall PPB (OR 1.6, 95%CI 1.3–2.1,  $p$ -value 0.001). Because of significant heterogeneity among these results ( $Q = 21.07$ , d.f. 10,  $I^2$  52%), a random model was applied. The random model with inverse of variance showed again a positive association between ASA/NSAIDs and overall PPB (OR 1.8, 95%CI 1.2–2.7,  $p$ -value 0.001). (Fig. 1). All studies reported data about ASA/NSAIDs and CSPPB, but three studies [10,12,14] reported also data about minor PPB. Taking into accounts only CSPPB in the analysis, the pooled results showed a positive associations with ASA/NSAIDs (OR 1.6, CI95% 1.2–2.2;  $Q = 17.67$ ,  $I^2$  51%; random pooled OR 1.8, 95%CI 1.1–2.8,  $p$ -value 0.002). (see Supplementary Fig. 2). Two [10,12] of four studies reporting cases of immediate PPB distinguished in the analysis the time of bleeding. The pooled results did not show an association with ASA/NSAIDs

**Table 1**

Main characteristics of the study populations in the included studies.

| Study          | Study design, setting | No. of patients | Age of patient (years)     | Male sex (%)    | ASA dosage (mg) | NSAIDs use | Suspension of ASA/NSAIDs before/after polypectomy |
|----------------|-----------------------|-----------------|----------------------------|-----------------|-----------------|------------|---------------------------------------------------|
| Burgess, [31]  | Multi, prosp          | 1172            | 67.8                       | NA              | NA              | No         | No/NA                                             |
| Manocha, [10]  | Single, retro         | 1174            | 65.5                       | 97.7            | NA              | No         | No/no                                             |
| Yousfi, [15]   | Multi, retro          | 162             | 72.0 <sup>a</sup>          | 61.7            | NA              | No         | No/NA                                             |
| Metz, [17]     | Single, prosp         | 288             | 68                         | NA              | NA              | No         | No/NA                                             |
| Pan, [16]      | Single, retro         | 493             | 72.1 ± 0.7                 | 57.2            | NA              | Yes        | No/no                                             |
|                |                       |                 | 62.2 ± 0.7 <sup>a</sup>    | 54.9            |                 |            |                                                   |
| Hui, [12]      | Single, retro         | 1657            | 68.7 ± 9.7                 | 54              | 100–365         | Yes        | No/NA                                             |
|                |                       |                 | 64.2 ± 13.0 <sup>a,b</sup> | 56 <sup>a</sup> |                 |            |                                                   |
| Sawhney, [5]   | Single, retro         | 173             | 64.3 ± 16.7                | 97.7            | NA              | No         | No/no                                             |
|                |                       |                 | 65.4 ± 10.5 <sup>a,b</sup> |                 |                 |            |                                                   |
| Shiffman, [14] | Single, prosp         | 464             | 59.1 (18–81) <sup>c</sup>  | 78.0            | NA              | Yes        | No/no                                             |
| Beppu, [32]    | Single, retro         | 208             | 59.5 ± 11.6                | 85.0            | NA              | No         | Yes/no                                            |
| Choung, [9]    | Single, retro         | 3788            | 58.6 ± 11.3                | 59.3            | NA              | No         | Yes/no                                            |
| Wu, [27]       | Single, prosp         | 120             | 66.1 ± 11.7                | 62              | NA              | Yes        | No/NA                                             |

Data expressed as mean ± standard deviation or median (\*) or mean and range (<sup>c</sup>). (NA) not assessed in the study.<sup>a</sup> Data expressed for cases and controls respectively.<sup>b</sup> Data expressed for bleeders and not bleeders respectively.**Table 2**

Characteristics of post-polypectomy bleeding and main confounders reported.

| Study         | Timing of bleeding | Gravity of bleeding | Matching Controlled confounders                                |
|---------------|--------------------|---------------------|----------------------------------------------------------------|
| Burgess [31]  | Immediate/delayed  | Major               | None<br>1, 3, 4, 5, 6, 7, 8, 9, 10                             |
| Manocha [10]  | Immediate/delayed  | Minor/major         | 1, 11, 12, 4, 5, 13<br>14                                      |
| Yousfi [15]   | Delayed            | Major               | None<br>1, 2, 4, 7, 14, 15                                     |
| Metz [17]     | Immediate/delayed  | Major               | None<br>1, 2, 3, 4, 5, 7, 15, 8, 9                             |
| Pan [16]      | Delayed            | Major               | 2, 13, 14, 7, 15<br>1                                          |
| Hui [12]      | Immediate/delayed  | Minor/major         | None<br>1, 2, 6, 7, 8, 13, 15                                  |
| Sawhney [5]   | Delayed            | Major               | None<br>1, 2, 4, 5, 6, 7, 9, 11, 12, 16, 17,                   |
| Shiffman [14] | Delayed            | Minor/major         | NA                                                             |
| Beppu [32]    | Delayed            | Major               | None<br>1, 2, 7, 8, 9, 11, 12, 15                              |
| Choung [9]    | Delayed            | Major               | None<br>1, 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 15, 18, 19, 20, 21 |
| Wu [27]       | Delayed            | Major               | None<br>1, 2, 4, 7, 8, 9, 10, 12, 14, 15, 16, 18, 19, 22, 23   |

(1) Age, (2) gender, (3) ASA grade, (4) cardio vascular disease, (5) lung disease, (6) renal failure, (7) lesion size, (8) lesion location, (9) lesion morphology, (10) histology, (11) hypertension, (12) diabete mellitus, (13) non steroidal antiinflammatory drugs, (14) number of polyps/patient, (15) polypectomy technique, (16) race, (17) INR, (18) smoking, (19) alcohol, (20) endoscopist experience, (21) liver failure, (22) body mass index, (23) bowel preparation.

(OR 1.1, CI95% 0.6–2.1;  $Q=0.48$ , d.f. = 1,  $p=0.64$ ,  $I^2$  0%). (Supplementary Fig. 3). There were 9/11 studies that reported data about ASA/NSAIDs and risk of only delayed PPB. The pooled effect (OR) of ASA/NSAIDs and delayed PPB was 1.7 (95%CI 1.2–2.2;  $Q=12.60$ , d.f. = 8,  $p=0.001$ ,  $I^2$  36%). (Supplementary Fig. 4). The last secondary outcome explored the risk of PPB in patients that consumed ASA/NSAIDs and removed large colorectal lesions. The pooled odd ratio was 2.6 (95%CI 1.3–5.1;  $Q=4.6$ , d.f. = 1,  $p=0.003$ ,  $I^2$  78%). The random pooled effect was 3.5 (95%CI 0.7–17.4), that means no risk associated (see Supplementary Fig. 5).

### 3.6.1. Adjunctive analysis

Meta regression was not performed because there was a large variability in the confounding factors considered and studies with adjusted covariates were less respect to the total of studies. In order to explain the heterogeneity among the studies, subgroup analysis were performed according to the secondary outcomes previously described. A sensitivity analysis that investigated the influence of each every individual study (including excluded studies) on the

overall meta-analysis summary estimate was performed. No individual study was suspected of excessive influence. (OR1.4, 95%CI 1.2–1.7) (Supplementary Fig. 6).

### 3.7. Risk of bias across studies

In order to evaluate the publication bias, a funnel plot was displayed (Supplementary Fig. 7). This scatter plot gives a measure of study size on the vertical axis against intervention or treatment effect on the horizontal axis. If there is bias, for example because smaller studies showing no statistically significant effects remain unpublished, then such publication bias will lead to an asymmetrical appearance of the funnel plot. The analogue visualization of the funnel plot did not show a clear asymmetry, so Egger test was performed. Egger test showed significant “small study effect” for overall PPB ( $p$ -value 0.06, 95%CI 0.2–7.1) but not for CSPPB ( $p$ -value 0.28, 95%CI 5.0–14.8), delayed PPB ( $p$ -value 0.22, 95%CI 4.3–15.7). The Egger test was not calculated for immediate PPB and PPB for lesions  $\geq 2$  cm because of the small number of studies. Trim and fill



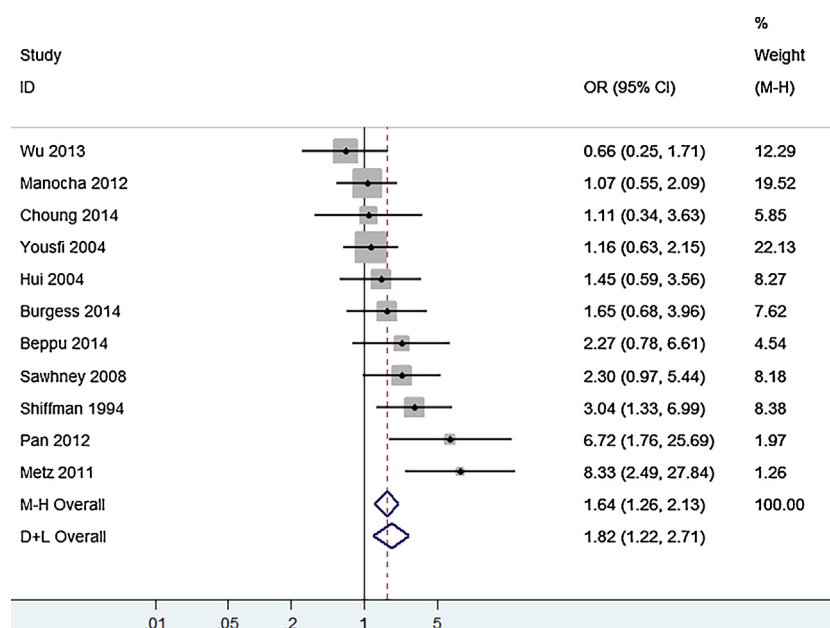
**Table 3**  
Main characteristics of the colorectal lesions and resection techniques in the included studies.

| Study         | No. of polyps | Lesion size                 | Morphology (%) |      |              | Location (%) |      | Resection techniques (%) |                     |                |     | Clip (%)         |
|---------------|---------------|-----------------------------|----------------|------|--------------|--------------|------|--------------------------|---------------------|----------------|-----|------------------|
|               |               |                             | Is             | Ip   | Non-polypoid | Prox         | Dist | Cold snare               | Hot snare           | EMR            | ESD |                  |
| Burgess [31]  | 1171          | 35.5 ± 15.3                 | 24.8           | 0    | 75.2         | 64.6         | 35.4 | 0                        | 0                   | 100            | 0   | NA               |
| Manocha [10]  | 3016          | 2–95 <sup>*</sup>           | NA             |      |              | NA           |      | 48.6                     | 68.5                | 0              | 0   | 1.8              |
|               |               |                             |                |      |              |              |      | 46.5 <sup>a</sup>        | 69.0 <sup>a</sup>   |                |     | 1.3 <sup>a</sup> |
| Yousfi [15]   | 440           | 9.2% >1 cm                  | NA             |      |              | NA           |      | 5                        | 85                  | 7              | 0   |                  |
|               |               |                             |                |      |              |              |      | 12 <sup>a</sup>          | 88 <sup>a</sup>     | 3 <sup>a</sup> |     |                  |
| Metz [17]     | 302           | 34.5                        | 0              | 0    | 100          | 72           | 28   | 0                        | 0                   | 100            | 0   | NA               |
|               |               | 30.6 <sup>a,b</sup>         |                |      |              |              |      |                          |                     |                |     |                  |
| Pan [16]      | 1502          | 9.6 ± 0.7                   | NA             |      |              | NA           |      | 24.1                     | 75.9                | 0              | 0   | NA               |
|               |               | 9.2 ± 0.5 <sup>a</sup>      |                |      |              |              |      | 25.9 <sup>a</sup>        | 74.1 <sup>a</sup>   |                |     |                  |
| Hui [12]      | 1657          | 10.0 ± 8.6                  | NA             |      |              | 50           | 50   | NA                       | 97.3                | NA             | NA  | NA               |
|               |               | 9.9 ± 18.7 <sup>a,b</sup>   |                |      |              |              |      |                          | 99.1 <sup>a,b</sup> |                |     |                  |
| Sawhney [5]   | NA            | 10.5 ± 7.1                  | NA             |      |              | NA           |      | NA                       |                     |                |     | NA               |
|               |               | 6.7 ± 5.5 <sup>a,b</sup>    |                |      |              |              |      |                          |                     |                |     |                  |
| Shiffman [14] | 464           | 10.8% >1 cm                 | NA             |      |              | NA           |      | 30                       | 70                  | 0              | 0   | NA               |
| Beppu [32]    | 208           | 100% >1 cm                  | NA             |      |              | NA           |      | 0                        | 29                  | 63             | 8   | NA               |
|               |               | 31% >2 cm                   |                |      |              |              |      |                          |                     |                |     |                  |
|               |               | 26% >20 mm                  |                |      |              |              |      |                          |                     |                |     |                  |
| Choung [9]    | 5981          | 6.3 ± 3.1                   | 59.6           | 31.6 | 8.7          | 52.0         | 47.4 | 25.5                     | 72.0                | 2.5            | 0   | 7.8              |
| Wu [27]       | 120           | 2.4 (0.3–13.0) <sup>*</sup> | 88.3           | 12.7 | 0            | 68.3         | 32.7 | NA                       |                     |                |     | NA               |

Data expressed as mean ± standard deviation or range (\*) or mean and range (°). (NA) not assessed in the study.

<sup>a</sup> Data expressed for cases and controls respectively.

<sup>b</sup> Data expressed for bleeders and not bleeders respectively.



**Fig. 1.** Forest plot of ASA/NSAID therapy and risk of post-polypectomy bleeding (PPB).

method adjusted the meta-analysis only for the subgroup of PPB with lesions  $\geq 2$  cm. Adding one missing study, the pooled OR was 1.6 [95%CI 1.0–2.2) with fixed model and 1.6 (95%CI 5.2–8.4) with random model.

#### 4. Discussion

ASA/NSAIDs and colon polypectomy are frequently associated in daily practice. High quality evidence are wanted in order to avoid potential hazardous complications as PPB or ischaemic events related to the intake or interruption of these drugs respectively. ESGE guidelines [13] suggest that low doses of ASA and NSAIDs may be continued safely in the periendoscopic period with moderate quality evidence.

This analysis showed that ASA/NSAIDs are risk factors for CS and delayed PPB but not for immediate PPB. Because most of the

studies included in this review examined the risk of CS delayed PPB, the analysis of these subgroups reflected the pooled effect for overall PPB. In order to explain heterogeneity ( $I^2 = 52\%$ ) of the overall PPB pooled effect, we tried to identify possible variables or characteristics moderating the results obtained. One of them is the variability due to sampling error (within-study variability) because every single study uses different samples. Instead, the between-studies variability is due to the influence of an indeterminate number of characteristics that vary among studies. Subgroup analysis showed that ASA is not a risk factor for immediate PPB but, even if heterogeneity was 0%, there are only two studies that explore this outcome. For the same reason it cannot be recommended that ASA is safe for large colorectal lesions because there are only two studies selective for lesions  $\geq 2$  cm and high degree of heterogeneity. Recently, a systematic review and meta-analysis was performed to determine the risk of (PPB) in patients

taking anti-platelet drugs [35]. According to us, there was a bias in the selection of the studies: there were four studies included [10,16,36,37] but one of them did not report the management in the periendoscopic period of ASA/NSAIDs [37] and another one did not distinguish among different kinds of antiplatelet agents [36]. The major limit of our meta-analysis is related to the heterogeneity (sample size, study design, intake before/after polypectomy, size of lesions) among studies considered. Many factors are involved in the risk of PPB. When ASA/NSAIDs are added to others possible risk factors as age, characteristics of the lesion (size, location, morphology), comorbidity etc, the risk of PPB increases. For example, in this meta-analysis two studies examined the risk of PPB for lesions  $\geq 2$  cm and the rest of the studies took into account any size of polyps. Lesions bigger in dimensions are more at risk of PPB respect to smaller lesions because they are more vascularized. In the “real world” a patient carries more than a risk factor. Bahin et al. [30] developed a risk score for CSPPB for large colorectal lesions. This score comprises four variables (lesion size, proximal colonic location, presence of a major comorbidity, and use of epinephrine in the injection solution). The probability of CSPPB in patients with a low-risk score was 2–3% compared with patients with a high-risk score at 16–18%. Before the polypectomy, the endoscopist should evaluate if the patient's risk of PPB could be increased by multiple factors. Nonetheless, the endoscopist should also consider the risk of ischaemic events related to the temporary cessation of these drugs. In patients on long-term low-dose ASA for secondary prevention, ASA interruption was associated with a three-fold increased risk of cardiovascular or cerebrovascular events, and 70% of these events occurred within 7–10 days after interruption [38]. Main limit of this meta-analysis is related to heterogeneity within studies. Subgroup analysis should be undertaken with caution because of confounding bias. To further improve upon the quality of the evidence presented, future studies should adhere to specific aspects of colorectal polypectomy in order to render the results between studies more comparable. Also, the implementation of bleeding risk score assessment would be useful in routine daily practice. In conclusion ASA/NSAIDs are not a risk factor for immediate PPB but the chance of delayed bleeding is increased.

## Guarantor of the article

Flavia Pigò.

## Specific author contributions

FP developed the study design, acquired the data, analysed the data and drafted the manuscript. AF and BC contributes to the search of the studies. HB and GG contributes to the acquisition of the data. HB and RLC contributed to the interpretation of the data. HB, GG, FA, BC, SV and RLC approved the final draft submitted.

## Financial support

None.

## Potential competing interests

None.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.dld.2017.10.005>

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