Resuming aspirin in patients with non-variceal upper gastrointestinal bleeding: a systematic review and meta-analysis

Jana G. Hashash^{a*}, Roni Aoun^{a*}, Nadim El-Majzoub^b, Assem Khamis^c, Don Rockey^d, Elie A. Akl^c, Kassem Barada^a

*Indicates shared first authorship

American University of Beirut, Riad El Solh, Beirut, Lebanon; Medical University of South Carolina, USA

Abstract

Background Our primary and secondary aims were to analyze the evidence surrounding mortality and re-bleeding risks in patients on aspirin with non-variceal upper gastrointestinal bleeding (NVUGIB) as a function of whether or not aspirin was resumed after the bleeding episode, and to determine whether aspirin intake upon admission affected the outcomes.

Methods A search for randomized controlled trials (RCTs) and prospective observational studies was performed. Data extraction and risk of bias assessment were done. Generic inverse variance and random-effects model were employed. Heterogeneity across studies was assessed using the I^2 test. Certainty of evidence was assessed using the GRADE approach for each comparison and outcome, and an evidence profile was created.

Results Evidence from 1 RCT and 4 observational studies suggests that early aspirin resumption reduced mortality (hazard ratio [HR] 0.20, 95% confidence interval [CI] 0.06-0.63) while increasing re-bleeding risk (HR 1.90, 95%CI 0.60-6.00); moderate certainty of evidence. The observational evidence was inconsistent for both mortality (HR 0.84, 95%CI 0.54-1.33) and re-bleeding (HR 0.85, 95%CI 0.47-1.55); very low certainty of evidence. Nine observational studies addressed our secondary aim: 6 provided inconsistent results regarding mortality (pooled odds ratio [OR] 1.1, 95%CI 0.80-1.50) and 4 provided inconsistent results regarding re-bleeding risk (pooled OR 0.92, 95%CI 0.53-1.59); very low certainty of evidence for both outcomes.

Conclusion Evidence supporting a protective effect of aspirin resumption soon after NVUGIB is of low-to-moderate certainty, and is not informative as to the optimal timing of aspirin resumption.

Keywords Aspirin, mortality, re-bleeding, non-variceal upper gastrointestinal bleeding

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Introduction

Aspirin use increases the risk of gastrointestinal bleeding (GIB) [1-3], but the effects of its use on patients' clinical outcomes

are uncertain. Many societies have issued recommendations regarding aspirin resumption in patients who develop GIB whilst on this drug. Some recommend that in patients using aspirin who develop non-variceal upper GIB (NVUGIB), aspirin resumption should be assessed [4]. Others recommend that aspirin should be discontinued in the majority of patients who are taking it for primary cardiovascular prevention, given the minimal cardiovascular benefit [4-7], while patients with cardiovascular disease (CVD) should resume it soon after the bleeding stops [4,7], because failure to do so may increase mortality risk [4,8]. One randomized controlled trial (RCT) showed that patients with CVD who resumed low-dose aspirin after achieving endoscopic hemostasis for NVUGIB had potentially reduced mortality rates up to 2 months from the bleeding event, but may have an increased risk of re-bleeding [8].

No studies have identified the safest timing for resuming aspirin. The Asia-Pacific working group recommended that "among patients with high cardio-thrombotic risk receiving antiplatelet agents, these agents should be resumed as soon as hemostasis can be established" [9]. They recommend resumption

^aDivision of Gastroenterology, American University of Beirut, Riad El Solh, Beirut, Lebanon (Jana G. Hashash, Roni Aoun, Kassem Barada);

^bAmerican University of Beirut, Riad El Solh, Beirut, Lebanon (Nadim El-Majzoub); ^cClinical Research Institute, American University of Beirut, Riad El Solh, Beirut, Lebanon (Assem Khamis, Elie A. Akl);

^dDivision of Gastroenterology, Medical University of South Carolina, USA (Don Rockey)

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Correspondence to: Kassem Barada, MD, Professor of Medicine, Division of Gastroenterology, American University of Beirut, Riad El Solh, 110236 Beirut, Lebanon, e-mail: kb02@aub.edu.lb

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of antiplatelet agents on day 1 if endoscopy shows a clean based ulcer, and waiting 72 h in patients who receive endoscopic therapy for control of NVUGIB [9]. European guidelines recommend holding aspirin until day 3 after endoscopic control of high-risk lesions [10]. Furthermore, American guidelines conditionally recommend the resumption of aspirin in patients with CVD, stating that “aspirin should be resumed as soon as possible after bleeding ceases in most patients: ideally within 1-3 days and certainly within 7 days” [4], or holding a discussion with the patient’s cardiologist if a patient with NVUGIB is receiving antiplatelet therapy [11]. Finally, a joint consensus statement from Cardiology and Gastroenterology organizations recommends resuming antiplatelet therapy 3-7 days after bleeding cessation in patients with CVD [6].

A major limitation of the current guidelines is that they are based on a limited number of studies involving a small number of patients who experienced a small number of events. In addition, there was substantial variability in the duration of follow up, timing of aspirin resumption, and the time point from which events were included in the analyses. Finally, some studies included only patients with severe bleeding who required endoscopic therapy, while others included all-comers with NVUGIB.

The primary aim of our study was to synthesize the evidence for all-cause mortality and re-bleeding with resuming vs. not resuming aspirin amongst patients admitted with NVUGIB. A secondary aim was to determine whether being on aspirin at the time of admission for NVUGIB is associated with better or worse outcomes compared to not being on aspirin.

Materials and methods

We designed and conducted this systematic review following the Cochrane methodology [12] and we report it following the PRISMA guidelines as demonstrated on the PRISMA checklist (Appendix 1). We registered the protocol in the International Prospective Register of Systematic Reviews (PROSPERO), with registration number: CRD42016037461 (Fig. 1).

Eligibility criteria

Study design

RCTs, prospective studies, and retrospective studies with prospective follow up were included. Full texts and abstracts in any language were included. For the secondary aim, only full-text articles written in languages familiar to reviewers (English or French) were included. There was no language restriction for articles addressing the primary aim.

Participants

Patients admitted with NVUGIB (study reported separate data for an NVUGIB subgroup, or NVUGIB patients accounted for $\geq 90\%$ of cases).

Comparison groups

For the primary aim, the intervention was defined as resuming aspirin following NVUGIB (separate data for aspirin subgroup, or $\geq 80\%$ of patients were on aspirin). The control group was defined as not resuming aspirin. For the secondary aim, exposure was defined as having been on aspirin prior to NVUGIB, while the non-exposed group was defined as not having been on it.

Outcomes

The primary outcome was all-cause mortality, while the secondary outcome was re-bleeding. We accepted the authors’ definition of re-bleeding.

Search methods for identification of studies

We searched MEDLINE Ovid (January 1946-September 2018), PubMed, EMBASE Ovid (January 1974-September 2018), Cochrane database of systematic reviews and Web of Science. Appendix 2 lists our search strategies. We also searched OpenGrey, MedNar, Proquest Dissertation and Theses open; and clinical trials registries: Clinicaltrials.gov, International Standard Randomized Controlled Trial Number, Register EU Clinical Trials Register, International Clinical Trial Registry Platform. We screened the reference lists of included studies and other relevant publications. We used no language restrictions.

Study selection

Two teams of 2 reviewers each (RA and JGH, and NEM and KB) selected studies for inclusion in duplicate and independently (titles and abstract screening followed by full text screening). Reviewers compared the results of full text screening and resolved discrepancies by discussion, or with the help of a third reviewer. We used a standardized full text screening form and all reviewers participated in calibration exercises.

Data collection

The 2 teams abstracted data from eligible studies in duplicate and independently and resolved disagreements by discussion, or with the help of a third reviewer. A standardized pilot tested form was used and reviewers participated in calibration exercises.

For the primary aim, we documented clinical characteristics, definition of NVUGIB, indication for aspirin use (primary or secondary prevention), use of other anticoagulants or antiplatelet agents, as well as relevant statistical data. Data regarding aspirin resumption, including its timing after

Figure 1 PRISMA 2009 flow diagram
NSAIDs, nonsteroidal anti-inflammatory drugs

NVUGIB, dose, and use of concomitant anticoagulants or antiplatelets, was also gathered. The follow-up period for each outcome, including all-cause mortality and cause-specific mortality, was recorded. When available, a definition for re-bleeding was recorded.

Assessment of risk of bias (RoB)

The RoB of RCTs was assessed using the Cochrane tool in duplicate and independently, and disagreements were resolved by discussion. For observational studies, methodological criteria included the development and application of appropriate eligibility criteria, measurement of exposure, measurement of outcome, controlling for confounders, and completeness of data as proposed by the GRADE working group [13].

Data synthesis

We extracted the hazard ratio (HR) effect estimates for mortality and re-bleeding when reported by the study. HR is a relative measure of an effect of an intervention on an outcome of interest over time and does not inform about the absolute risk. An HR of 1 means a lack of association, while an HR greater than 1 suggests an increased risk and an HR less than 1 suggests a smaller risk. In our manuscript, an HR greater than 1 suggested an increased risk of mortality or re-bleeding. Otherwise, we calculated the relative risk (RR) using the number of events. The log of the effect estimates (HR and RR) was pooled using a generic inverse variance method and a random-effects model in Review Manager 5. Heterogeneity across studies was assessed using the I^2 test and considered substantial if I^2 was >50%. Inverted funnel plots were created to check for possible publication bias. Certainty of evidence at the outcome level was assessed using the GRADE approach

for each comparison and outcome, and an evidence profile summarizing that assessment was created.

Subgroup analysis

We determined whether the relative effect of aspirin resumption on mortality was modified by whether aspirin was used for primary or secondary prevention, and by whether follow up was for more or less than 6 months from NVUGIB admission.

Results

Selection process

The initial bibliographic search identified 9845 citations. Fig. 1 shows the PRISMA flow diagram and details of the study selection. We identified 14 eligible studies: 13 observational [14-26] and 1 RCT [8]. Four observational studies [16,17,21,26] and the single RCT [8] addressed our primary aim. Nine observational studies addressed our secondary aim [14,15,18-20,22-25].

Primary aim: resuming vs. not resuming aspirin

Appendix 3 provides detailed information regarding the characteristics of the included studies and the RoB assessment.

Characteristics of studies

Five studies addressed our primary aim, 4 retrospective with prospective follow up [16,17,21,26], and 1 RCT [8]. Three were conducted in single centers [8,16,26], while 2 were multi-center [17,21]. Observational studies provided a prospective follow up for 2953 patients on aspirin prior to admission, while the RCT provided follow up for 156 patients. Two studies [8,16] exclusively included patients with peptic ulcer bleeding (PUB), while one [21] exclusively included patients with non-valvular atrial fibrillation. Timing of aspirin resumption varied from 24 h following endoscopic intervention to up to 60 days following the bleeding episode. Timing was not specified in 1 study [21].

Follow-up time varied from 8 weeks to 5 years. All 5 studies addressed mortality. All except for Gonzalez-Perez *et al* addressed re-bleeding rates [17]. Re-bleeding required endoscopic verification in 2 studies [8,16].

RoB assessment for observational studies

RoB for development and application of appropriate eligibility criteria was considered low for all studies except one [21], where patients could have been taking antithrombotics other than aspirin. In all 4 observational

studies [16,17,21,26], the assessment of aspirin use was based solely on trusted medical databases. We considered the RoB for measurement of exposure to be unclear for all studies, as patients could have been prescribed aspirin and not taken it. Aspirin is available over the counter, and could have been taken without prescription.

RoB for assessment of outcomes was considered low for all studies addressing mortality except for one [17], and for all those addressing re-bleeding except for one [16], where it was not clear how these outcomes were assessed. Controlling for important confounders was established in 2 studies [16,21] and RoB was deemed high in the other two [17,26]. There was no mention of missing data in any of the 4 studies. RoB for data completeness was therefore considered unclear.

RoB assessment for the RCT

There was a low risk for potential bias in the RCT (Appendix 3) [8].

Effects of aspirin resumption on mortality

In the RCT [8], HR for mortality in patients who resumed aspirin compared to those who did not was 0.20 (95%CI 0.06-0.63; Fig. 2A), with moderate certainty of evidence, rated down due to imprecision (Table 1).

A meta-analysis of 4 observational studies [16,17,21,26] for mortality generated a pooled HR of 0.84 (95%CI 0.54-1.33; $I^2=67\%$) in patients who resumed aspirin after NVUGIB compared to those who did not (Fig. 2B), with very low certainty of evidence due to inconsistency and imprecision (Table 1).

A meta-analysis of 4 observational studies [16,17,21,26] and the RCT [8] combined for mortality in patients who resumed aspirin compared to those who did not generated a pooled HR of 0.69 (95%CI 0.42-1.15; $I^2=72\%$), with very low certainty of evidence, rated down due to the RoB in observational studies as well as imprecision and inconsistency (Table 1).

A subgroup analysis was performed to determine whether the relative effect of aspirin resumption on mortality might be modified by whether patients were taking aspirin for primary or secondary prevention. When considering studies with less than 6 months of follow up after resumption of aspirin, a meta-analysis of 3 studies [8,16,17] where aspirin was used for secondary prevention revealed a pooled HR of 0.35 (95%CI 0.09-1.29; $I^2=78\%$) for mortality in patients who resumed aspirin compared to those who did not (Fig. 3A). Certainty of evidence was judged very low. On the other hand, one observational study [17] where aspirin was used for primary prevention found a HR of 4.07 (95%CI 0.54-30.74) for mortality in patients who resumed aspirin compared to those who discontinued it (Fig. 3A). Certainty of evidence was deemed very low. The P-value of the test for the subgroup effect was 0.05.

In studies where follow up was for more than 6 months after aspirin resumption, a meta-analysis of 2 studies [16,21] where aspirin was used for secondary prevention found a pooled HR of 0.80 (95%CI 0.56-1.15; $I^2=16\%$) for mortality in patients

Figure 2 Effects of aspirin resumption on mortality in patients with non-variceal upper gastrointestinal bleeding (NVUGIB); (A) randomized controlled trial (RCT); (B) observational studies; and effects of aspirin resumption on re-bleeding in patients with NVUGIB; (C) RCT; (D) observational studies
CI, confidence interval

who resumed aspirin compared to those who discontinued it (Fig. 3B). However, one observational study [16] where aspirin was used for primary prevention found an HR of 0.56 (95%CI 0.08-3.82) for mortality in patients who resumed aspirin compared to those who discontinued it (Fig. 3B). Certainty of evidence was very low. The P-value of the test for the subgroup effect was 0.71.

Effects of aspirin resumption on re-bleeding

The RCT [8] did not exclude an increase in the risk of re-bleeding in patients who resumed aspirin compared to those

who did not (Fig. 2C), with moderate certainty of evidence, rated down due to very serious imprecision (Table 1).

A meta-analysis of 3 observational studies [16,21,26] generated a pooled HR for re-bleeding in patients who resumed aspirin compared to those who discontinued it of 0.85 (95%CI 0.47-1.55; $I^2 = 53\%$; Fig. 2D), with very low certainty of evidence, rated down due to imprecision and inconsistency (Table 1).

A meta-analysis of 3 observational studies and the RCT [8,16,21,26] combined found a pooled HR for the effect of aspirin resumption on re-bleeding of 0.97 (95%CI 0.58-1.64; $I^2 = 45\%$), with very low certainty of evidence, rated down due to imprecision.

Table 1 Evidence profile for the primary aim

No of studies	Study design	Certainty assessment					No of patients (%)		Effect		Certainty	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resuming aspirin	Not resuming aspirin	Relative (95%CI)	Absolute (95%CI)		
All-cause mortality - observational studies												
4	Observational studies	Serious	Serious ^a	Not serious	Serious ^b	None	N/A*	N/A*	HR 0.84 (0.54 to 1.33)	14 fewer per 1000 (from 40 fewer to 28 more)	⊕○○○ VERY LOW	CRITICAL
All-cause mortality - RCT												
1	Randomized trials	Not serious	Not serious	Not serious	Very serious ^c	None	1/78 (1.3%)	7/78 (9.0%)	HR 0.20 (0.06 to 0.63)	71 fewer per 1000 (from 84 fewer to 32 fewer)	⊕⊕⊕○ MODERATE	CRITICAL
Rebleeding - observational studies												
3	Observational studies	Serious	Serious ^d	Not serious	Serious ^e	None		5.1%	HR 0.85 (0.47 to 1.55)	7 fewer per 1000 (from 27 fewer to 27 more)	⊕○○○ VERY LOW	IMPORTANT
Rebleeding - RCT												
1	Randomized trials	Not serious	Not serious	Not serious	Very serious ^e	None	8/78 (10.3%)	4/78 (5.1%)	HR 1.9 (0.6 to 6.0)	44 more per 1000 (from 20 fewer to 220 more)	⊕⊕⊕○ LOW	IMPORTANT

*Raw numbers not available for two studies

Explanations a. Unexplained heterogeneity I² = 67% b. 95%CI is consistent with potential harm (16 more per 1000) and potential benefit (33 fewer per 1000) c. Very low number of events d. Unexplained heterogeneity I² = 53% e. Wide CI and very low number of events.

C, confidence interval; HR, hazard ratio; RCT, randomized controlled trial

Figure 3 Effects of aspirin resumption on mortality in patients with non-variceal upper gastrointestinal bleeding (NVUGIB) stratified by whether it was used for primary or secondary prevention; (A) mortality within 6 months following NVUGIB; (B) mortality after more than 6 months following NVUGIB

CI, confidence interval

Secondary aim: being on aspirin vs. not being on aspirin at time of admission for NVUGIB

Appendix 3 provides detailed information regarding the characteristics of included studies as well as the RoB assessment.

Characteristics of included studies

Nine studies addressed our secondary question [14,15,18-20,22-25]. Among those, 1 was an RCT [25], 6 were prospective observational studies [14,15,18,19,22,23], and 2 were retrospective with prospective follow up [20,24]. These studies provided follow up for 14,762 patients. All studies but one included only patients with PUB [23].

Whether aspirin was used for primary vs. secondary prevention was not mentioned in any of the studies. Follow-up time varied from “in-hospital” to up to 10 years. Data regarding mortality was available from 7 studies [14,15,19,20,22-24], while data regarding re-bleeding was available from 6 studies [14,18,20,22,23,25].

RoB assessment

RoB for development and application of appropriate eligibility criteria was considered low for all studies, except for Liang 2016, where no specific diagnostic criteria for re-bleeding were mentioned [20].

RoB for measurement of exposure was considered low for 5 studies [14,15,18-20], as data regarding aspirin use

prior to NVUGIB were retrieved from trusted resources. In 4 studies [22-25], it was unclear how data regarding aspirin intake were retrieved. RoB for measurement of mortality and re-bleeding for all 9 studies was low [14,15,18-20,22-25].

Controlling for confounders was not established in 5 studies [15,19,22,24,25] and hence their RoB was deemed high. In 3 studies [14,20,23], it was unclear whether patients were taking other antithrombotics, thus the RoB was considered to be unclear. Controlling for all confounders was well established in one study [18]. There was no mention of missing data in any of the studies (unclear risk) except for Camus *et al*, where the risk was low [14].

Association of aspirin use prior to NVUGIB with mortality

A meta-analysis of 6 studies [15,19,20,22-24] generated a pooled odds ratio (OR) of 1.1 (95%CI 0.80-1.5; $P=42\%$) for mortality in patients who were on aspirin prior to NVUGIB compared to those who were not (Fig. 4), with very low certainty of evidence due to imprecision.

Effect of aspirin use prior to NVUGIB on re-bleeding

A meta-analysis of 4 observational studies [14,18,20,25] generated a pooled OR of 0.92 (95%CI 0.53-1.59; $I^2=80\%$) for re-bleeding in patients who were on aspirin prior to NVUGIB

compared to those who were not (Fig. 5), with very low certainty of evidence due to imprecision and heterogeneity (Supplementary Table 1).

Discussion

This is the first systematic review to examine the effect of aspirin resumption on mortality and re-bleeding and evaluate the association between being on aspirin and clinical outcomes in patients with NVUGIB. We found that starting aspirin after NVUGIB may be associated with lower mortality, although the evidence supporting this conclusion is weak [8,16,17,21,26]. No study compared different timings of aspirin resumption. We observed variability in the indications for aspirin use, duration of follow up, and time point from which follow up began (Appendix 3). Furthermore, an increased risk of re-bleeding cannot be excluded with early aspirin resumption. Re-bleeding is common after initial NVUGIB [27] and is a predictor of mortality. Most re-bleeding episodes occur within a month of the initial event [8] and the risk continues to increase with time [21]. Evidence

concerning the effects of resuming aspirin on re-bleeding is less conclusive than that concerning mortality, because of the small number of patients and re-bleeding events [8,16]. Drawing firm conclusions about the benefits of early aspirin resumption is complicated by observations that this is associated with reduced mortality not only from thrombotic events, but also from non-cardiovascular causes [8]. Additionally, many patients on aspirin are also taking other antithrombotics and it is difficult to ascertain the outcomes related to aspirin alone. In the secondary aim, we evaluated the effect of being on aspirin on mortality and re-bleeding, as there were prospective and retrospective studies suggesting that it confers a protective effect [23,28]. This might inform risk stratification and prognostication in patients with NVUGIB. We were unable to confirm a decrease or increase in the odds of mortality or re-bleeding in patients on aspirin [14,15,18–20,22–25]. There was considerable clinical heterogeneity among studies. Moreover, it was unclear whether patients on aspirin were on other antithrombotics. Finally, the duration of follow up was 30 days in most, but not in all studies. Our results are therefore based on a small number of studies that are clinically heterogeneous and hence the evidence is of very low certainty.

Figure 4 Effects of aspirin use prior to non-variceal upper gastrointestinal bleeding on mortality
 CI, confidence interval

Figure 5 Effects of aspirin use prior to non-variceal upper gastrointestinal bleeding on re-bleeding
 CI, confidence interval

Limitations of this meta-analysis include limitations in the methodology and the data analyzed, due to the poor quality of the majority of studies and the high levels of clinical and statistical heterogeneity. In that regard, current guidelines are based on limited data and/or expert opinion.

For patients taking aspirin for primary prophylaxis, our meta-analysis lends support to guidelines recommending stopping it after NVUGIB, although the evidence for that is weak. For patients taking aspirin for secondary prophylaxis, this review lends some support to resuming it once hemostasis is established, as this may be associated with reduced mortality, but may increase the risk of re-bleeding. Evidence supporting this recommendation is weak to moderate. Most thrombotic events start to occur about 8 days after aspirin is discontinued, and re-bleeding events occur within the first 5 days in those who resume it [29]. An RCT is needed comparing resumption of aspirin vs. interruption of aspirin for 1 week in patients who require aspirin for secondary prevention. This RCT would compare the risk of re-bleeding in a homogeneous group of patients with high-risk stigmata who resume aspirin vs. those who do not. Time-dependent events would be expected to provide evidence on the best timing for aspirin resumption. Many questions remain unanswered. Whether aspirin should be discontinued at all in NVUGIB patients who are taking it for secondary prevention is unclear. Additionally, the exact timing for aspirin resumption remains unknown, and it remains challenging to balance the risks of thromboembolic events and re-bleeding.

Summary Box

What is already known:

- Aspirin use increases the risk of gastrointestinal bleeding, but its effects on patients' clinical outcomes are uncertain
- After non-variceal upper gastrointestinal bleeding, aspirin should not be resumed in patients taking it for primary prevention
- After non-variceal upper gastrointestinal bleeding, aspirin should be resumed in patients taking it for secondary prevention

What the new findings are:

- Evidence supporting a protective effect of aspirin resumption soon after non-variceal upper gastrointestinal bleeding is of low-to-moderate certainty
- The available evidence is not informative as to the optimal timing of aspirin resumption

References

1. Malfertheiner P, Chan FK, McColl KE. Peptic ulcer disease. *Lancet* 2009;**374**:1449-1461.

2. Feinstein LB, Holman RC, Yorita Christensen KL, Steiner CA, Swerdlow DL. Trends in hospitalizations for peptic ulcer disease, United States, 1998-2005. *Emerg Infect Dis* 2010;**16**:1410-1418.
3. Hernández-Díaz S, García Rodríguez LA. Cardioprotective aspirin users and their excess risk of upper gastrointestinal complications. *BMC Med* 2006;**4**:22.
4. Laine L, Jensen DM. Management of patients with ulcer bleeding. *Am J Gastroenterol* 2012;**107**:345-360.
5. Baigent C, Blackwell L, Collins R, et al; Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009;**373**:1849-1860.
6. Abraham NS, Hlatky MA, Antman EM, et al; ACCF/ACG/AHA. ACCF/ACG/AHA 2010 expert consensus document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use. *Am J Gastroenterol* 2010;**105**:2533-2549.
7. Oakland K, Chadwick G, East JE, et al. Diagnosis and management of acute lower gastrointestinal bleeding: guidelines from the British Society of Gastroenterology. *Gut* 2019;**68**:776-789.
8. Sung JJ, Lau JY, Ching JY, et al. Continuation of low-dose aspirin therapy in peptic ulcer bleeding: a randomized trial. *Ann Intern Med* 2010;**152**:1-9.
9. Sung JJ, Chiu PW, Chan FKL, et al. Asia-Pacific working group consensus on non-variceal upper gastrointestinal bleeding: an update 2018. *Gut* 2018;**67**:1757-1768.
10. Gralnek IM, Dumonceau JM, Kuipers EJ, et al. Diagnosis and management of nonvariceal upper gastrointestinal hemorrhage: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2015;**47**:a1-a46.
11. Acosta RD, Abraham NS, Chandrasekhara V, et al; ASGE Standards of Practice Committee. The management of antithrombotic agents for patients undergoing GI endoscopy. *Gastrointest Endosc* 2016;**83**:3-16.
12. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from: <http://handbook.cochrane.org> [Accessed 22 February 2021].
13. Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias). *J Clin Epidemiol* 2011;**64**:407-415.
14. Camus M, Jensen DM, Kovacs TO, Jensen ME, Markovic D, Gornbein J. Independent risk factors of 30-day outcomes in 1264 patients with peptic ulcer bleeding in the USA: large ulcers do worse. *Aliment Pharmacol Ther* 2016;**43**:1080-1089.
15. Chiu PW, Ng EK, Cheung FK, et al. Predicting mortality in patients with bleeding peptic ulcers after therapeutic endoscopy. *Clin Gastroenterol Hepatol* 2009;**7**:311-316.
16. Derogar M, Sandblom G, Lundell L, et al. Discontinuation of low-dose aspirin therapy after peptic ulcer bleeding increases risk of death and acute cardiovascular events. *Clin Gastroenterol Hepatol* 2013;**11**:38-42.
17. González-Pérez A, Sáez ME, Johansson S, Nagy P, García Rodríguez LA. Mortality in patients who discontinue low-dose acetylsalicylic acid therapy after upper gastrointestinal bleeding. *Pharmacoepidemiol Drug Saf* 2017;**26**:215-222.
18. Hong MJ, Lee SY, Kim JH, et al. Rebleeding after initial endoscopic hemostasis in peptic ulcer disease. *J Korean Med Sci* 2014;**29**:1411-1415.
19. Ishikawa S, Inaba T, Mizuno M, et al. Characteristics of serious complicated gastroduodenal ulcers in Japan. *Hepatogastroenterology* 2012;**59**:147-154.
20. Liang CM, Hsu CN, Tai WC, et al. Risk factors influencing the outcome of peptic ulcer bleeding in chronic kidney disease after

- initial endoscopic hemostasis. A nationwide cohort study. *Medicine (Baltimore)* 2016;**95**:e4795.
21. Staerk L, Lip GY, Olesen JB, et al. Stroke and recurrent haemorrhage associated with antithrombotic treatment after gastrointestinal bleeding in patients with atrial fibrillation: nationwide cohort study. *BMJ* 2015;**351**:h5876.
22. Manguso F, Riccio E, Bennato R, et al. In-hospital mortality in non-variceal upper gastrointestinal bleeding Forrest 1 patients. *Scand J Gastroenterol* 2008;**43**:1432-1441.
23. Marmo R, Koch M, Cipolletta L, et al; Italian registry on upper gastrointestinal bleeding (Progetto Nazionale Emorragie Digestive—PNED 2). Predicting mortality in non-variceal upper gastrointestinal bleeders: validation of the Italian PNED Score and prospective comparison with the Rockall Score. *Am J Gastroenterol* 2010;**105**:1284-1291.
24. Mose H, Larsen M, Riis A, et al. Thirty-day mortality after peptic ulcer bleeding in hospitalized patients receiving low-dose aspirin at time of admission. *Am J Geriatr Pharmacother* 2006;**4**:244-250.
25. Park SJ, Park H, Lee YC, et al. Effect of scheduled second-look endoscopy on peptic ulcer bleeding: a prospective randomized multicenter trial. *Gastrointest Endosc* 2018;**87**:457-465.
26. Siau K, Hannah JL, Hodson J, Widlak M, Bhala N, Iqbal TH. Stopping antithrombotic therapy after acute upper gastrointestinal bleeding is associated with reduced survival. *Postgrad Med J* 2018;**94**:137-142.
27. Wong GL, Wong VW, Chan Y, et al. High incidence of mortality and recurrent bleeding in patients with Helicobacter pylori-negative idiopathic bleeding ulcers. *Gastroenterology* 2009;**137**:525-531.
28. Wehbeh A, Tamim HM, Abu Daya H, et al. Aspirin has a protective effect against adverse outcomes in patients with nonvariceal upper gastrointestinal bleeding. *Dig Dis Sci* 2015;**60**:2077-2087.
29. Lanis A, Dumonceau JM, Hunt RH, et al. Non-variceal upper gastrointestinal bleeding. *Nat Rev Dis Primers* 2018;**4**:18020.

Supplementary material

Supplementary Table 1 Evidence profile for the secondary aim

No of studies	Certainty assessment					No of patients		Effect		Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	On aspirin prior to NVUGIB	Not on aspirin prior to NVUGIB	Relative (95% CI)		
6	Observational studies	Not serious	Not Serious ^a	Not serious	Serious ^b	None	1,825	10,832	OR 1.1 (0.80 to 1.5)	⊕○○○ VERY LOW	CRITICAL
All-cause mortality - observational studies											
4	Observational studies	Not serious	Serious ^c	Not serious	Serious ^b	None	784	2,550	OR 0.92 (0.53 to 1.59)	⊕○○○ VERY LOW	IMPORTANT
Rebleeding - observational studies											

Explanations a. I² = 42% b. 95%CI includes values consistent with potential harm and values consistent with potential benefit c. Unexplained heterogeneity I² = 80%
CI, confidence interval; OR, odds ratio

Appendix 1 PRISMA 2009 checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	7-8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	7-8
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	8-9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	8-9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made	8-9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including Specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means)	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis	9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies)	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	10

Appendix 1 (Continued)

Section/topic	#	Checklist item	Reported on page #
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations	10-11, 14
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12)	11-12, 14-15
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot	11-12, 14-15
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	12-14, 15
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15)	11-12, 14-15
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16])	12-13
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers)	16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias)	17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review	2

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009;6:e1000097

Appendix 2 Search strategy

Search strategy for Medline (Via Ovid)

1. exp Aspirin/ (39695)
2. (Aspirin* or dispril or polopiryna or zorprin or (acetylsalicylic adj acid) or polopirin or colfarit or aloxiprimum or micristin or easprin or magnecyl or solprin or ecotrin or (2- acetyloxy benzoic adj acid) or endosprin or acylpyrin or solupsan or acetysal*).ti,ab,sh.
3. 1 or 2
4. exp Upper Gastrointestinal Tract/
5. (((upper adj2 (gi or alimentar* or digestiv* or intestin* or enteral* or enteric*)) or ugi or stomach* or (upper adj2 gastro*) or gastri* or epigastri* or oesopha* or esopha* or duoden* or peptic* or antrum* or antral* or pylor* or nonvaric* or (non adj varic*))).ti,ab,sh.
6. 4 or 5
7. exp Hemorrhage/
8. (hemorrhag* or hemorhag* or rehemorhag* or rehemorrhag* or re-hemorrhag* or re- hemorrhag* or haemorrhag* or haemorrhag* or rehaemorrhag* or re-haemorrhag* or rehaemorhag* or bleed* or re-bleed* or rebleed*).ti,ab,sh.
9. 7 or 8
10. 6 and 9
11. (melena* or melaena* or hematem* or haematem* or coffee or hematochez* or haematochez* or gastrorrh* or gastrorha* or (Mallory adj Weis*) or Dieulafo* or NVGIB or NVUGIB).ti,ab,sh.
12. exp Peptic Ulcer Hemorrhage/ or exp Mallory-Weiss Syndrome/
13. exp Gastrointestinal Hemorrhage/
14. 13 and (4 or 5)
15. 10 or 11 or 12 or 14
16. 3 and 15
17. 16 not (animals/ not (animals/ and humans/))

Search strategy for PubMed

1. Aspirin
2. Aspirin*[tw] OR dispril[tw] OR polopiryna[tw] OR zorprin[tw] OR acetylsalicylic acid*[tw] OR polopirin[tw] OR colfarit[tw] OR aloxiprimum[tw] OR micristin[tw] OR easprin[tw] OR magnecyl[tw] OR solprin[tw] OR ecotrin[tw] OR 2-acetyloxy benzoic acid*[tw] OR endosprin[tw] OR acylpyrin[tw] OR solupsan[tw] OR acetysal*[tw] OR acetylsalicylate*[tw]
3. #1 OR #2
4. Upper Gastrointestinal Tract
5. upper gi*[tw] OR ugi[tw] OR upper digestiv*[tw] OR upper alimentar*[tw] OR stomach*[tw] OR gastri*[tw] OR upper gastroi*[tw] OR upper gastro-i*[tw] OR gastrod*[tw] OR gastro-d*[tw] OR upper gastroe*[tw] OR upper gastro-e*[tw] OR epigastri*[tw] OR oesopha*[tw] OR esopha*[tw] OR duoden*[tw] OR upper intestin*[tw] OR upper enteral*[tw] OR upper enteric*[tw] OR peptic*[tw] OR antrum*[tw] OR antral*[tw] OR pylor*[tw] OR nonvaric*[tw] OR non-varic*[tw]
6. #4 OR #5
7. Hemorrhage
8. hemorrhag*[tw] OR hemorhag*[tw] OR haemorrhag*[tw] OR haemorrhag*[tw] OR rehemorrhag*[tw] OR re-hemorrhag*[tw] OR rehaemorrhag*[tw] OR re- haemorrhag*[tw] OR bleed*[tw] OR rebleed*[tw] OR re-bleed*[tw]
9. #7 OR #8
10. #6 AND #9
11. melena*[tw] OR melaena*[tw] OR hematem*[tw] OR haematem*[tw] OR coffee[tw] OR hematochez*[tw] OR haematochez*[tw] OR gastrorrh*[tw] OR gastrorha*[tw]

OR Mallory weis*[tw] OR Dieulafo*[tw] OR NVGIB[tw] OR NVUGIB[tw]

12. Peptic Ulcer Hemorrhage OR Mallory-Weiss Syndrome
13. Gastrointestinal Hemorrhage
14. #13 AND (#4 OR #5)
15. #10 OR #11 OR #12 OR #14
16. #3 AND #15
17. #16 NOT ("animals"[MESH] NOT ("animals"[MESH] AND "humans"[MESH]))

Search strategy for Embase (Ovid)

1. exp acetylsalicylic acid/
2. (aspirin* or (acetylsalicylic adj acid) or acetylsalicylate* or dispril or aloxiprimum or easprin or solprin or polopirin or polopiryna or zorprin or colfarit or micristin or magnecyl or ecotrin or acetyloxybenz* or endosprin or acylpyrin or solupsan or acetysal).ti,ab,sh.
3. 1 or 2
4. exp upper gastrointestinal tract/
5. (((upper adj (gi or gastro*)) or ugi or stomach* or gastri* or oesopha* or esopha* or duoden* or peptic* or nonvaric* or (non adj varic*)) adj2 (hemorrhag* or hemorhag* or rehemorrhag* or rehemorrhag* or re-hemorrhag* or re-hemorrhag* or haemorrhag* or haemorrhag* or rehaemorrhag* or re-haemorrhag* or rehaemorhag* or bleed* or re- bleed* or rebleed*).ti,ab,sh.
6. (melena* or melaena* or hematem* or haematem* or hematochez* or haematochez* or gastrorrh* or gastrorha* or NVGIB).ti,ab,sh.
7. exp hematemesi/
8. exp Peptic Ulcer Hemorrhage/
9. gastrointestinal hemorrhage/ or intestinal bleeding/ or small intestine hemorrhage/
10. exp duodenum bleeding/ or exp melena/ or exp peptic ulcer bleeding/ or exp stomach hemorrhage/ or exp upper gastrointestinal bleeding/
11. 9 and (4 or upper.mp.) [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
12. 5 or 6 or 7 or 8 or 10 or 11
13. 3 and 12
14. 13 not ((exp animal/ or nonhuman/) not exp human/)

Search strategy for Cochrane Database of Systematic Reviews

1. MeSH descriptor: [Aspirin] explode all trees
2. Aspirin* or dispril or polopiryna or zorprin or (acetylsalicylic next acid) or polopirin or colfarit or aloxiprimum or micristin or easprin or magnecyl or solprin or ecotrin or (2- acetyloxy benzoic next acid) or endosprin or acylpyrin or solupsan or acetysal:ti,ab,kw
3. #1 or #2
4. MeSH descriptor: [Upper Gastrointestinal Tract] explode all trees
5. (((upper near/2 (gi or alimentar* or digestiv* or intestin* or enteral* or enteric*)) or ugi or stomach* or (upper near/2 gastro*) or gastri* or epigastri* or oesopha* or esopha* or duoden* or peptic* or antrum* or antral* or pylor* or nonvaric* or (non next varic*)):ti,ab,kw
6. #4 or #5
7. MeSH descriptor: [Hemorrhage] explode all trees
8. hemorrhag* or hemorhag* or rehemorrhag* or rehemorrhag* or re-hemorrhag* or (re- hemorrhag*) or haemorrhag* or haemorrhag* or rehaemorrhag* or re-haemorrhag* or rehaemorhag* or bleed* or (re-bleed*) or rebleed*:ti,ab,kw

9. #7 or #8
10. #6 and #9
11. melena* or melaena* or hematem* or haematem* or coffee or hematochez* or haematochez* or gastrorrh* or gastrorha* or (mallory next weis*) or Dieulafo* or NVGIB or NVUGIB:ti,ab,kw
12. MeSH descriptor: [Gastrointestinal Hemorrhage] explode all trees
13. MeSH descriptor: [Mallory-Weiss Syndrome] explode all trees
14. #12 and #6
15. #10 or #11 or #13 or #14
16. #3 and #15

Search strategy for Web of Science

1. (((((Aspirin* OR dispril OR polopiryna OR zorprin OR polopirin OR colfarit OR aloxiprimum OR micristin OR easprin OR magnecyl OR solprin OR ecotrin OR endosprin OR acylpyrin OR solupsan OR acetysal*))))))
2. ((acetylsalicylic NEAR/1 acid))
3. ((“2-acetyloxy benzoic” NEAR/1 acid))
4. #3 OR #2 OR #1
5. ((((((“Upper Gastrointestinal Tract” OR ugi OR stomach* OR gastri* OR epigastri* OR oesoph* OR esoph* OR duoden* OR peptic* OR antrum* OR antral* OR pylor* OR nonvaric*))))))
6. ((upper NEAR/1 (gi OR alimentar* OR digestiv* OR intestin* OR enteral* OR enteric*)))
7. ((upper NEAR/2 gastro*))
8. ((non NEAR/1 varic*))
9. #8 OR #7 OR #6 OR #5

10. ((((((hemorrhag* OR hemorhag* OR rehemorhag* OR rehemorrhag* OR re-hemorhag* OR re-hemorrhag* OR haemorrhag* OR haemorhag* OR rehaemorrhag* OR re-haemorrhag* OR rehaemorhag* OR bleed* OR re-bleed* OR rebleed*))))))
11. #10 AND #9
12. (((((melena* OR melaena* OR hematem* OR haematem* OR coffee OR hematochez* OR haematochez* OR gastrorrh* OR gastrorha*) OR Dieulafo* OR NVGIB OR NVUGIB))))
13. (Mallory NEAR/1 Weis*)
14. #13 OR #12
15. #14 OR #11
16. #15 AND #4

Search strategy for ProQuest, OpenGrey, Mednar, Clinical Trials, ISRCTN, EU-CTR

(aspirin OR acetylsalicylates OR acetylsalicylic) AND (((upper gastrointestinal OR stomach OR esophageal OR duodenal OR peptic OR nonvariceal) AND (bleeding OR bleed OR rebleed OR hemorrhage OR rehemorrhage)) OR (melena OR hematemesis OR hematochezia OR NVGIB OR NVUGIB))

Search strategy for ICTRP

Aspirin AND Bleeding

Appendix 3 Characteristics of included studies and risk of bias assessment

Table 1 (A) Characteristics of included randomized controlled trials that addressed the primary aim

Author, year [Ref]	Study Design	Participants	Intervention	Control	Outcomes assessed	Funding and conflicts of interest
Sung 2010 [8]	<ul style="list-style-type: none"> Parallel, randomized, double-blinded, placebo-controlled non-inferiority trial (RCT) Follow up after 30 and 56 days from discharge 	<ul style="list-style-type: none"> 156 patients with PUB and high-risk stigmata for re-bleeding Low-dose aspirin prior to admission (≤ 325 mg/d) Reason for aspirin intake: secondary prophylaxis Single-center Mean age: 74 Males: 62% 	Re-introduction of aspirin 80 mg daily at 24 h after endoscopy	Introduction of placebo at 24 h after endoscopy	<ul style="list-style-type: none"> All-cause mortality Re-bleeding within 30 days of endoscopic treatment (One clinical feature+one confirming endoscopic evidence) Follow-up time: 8 weeks 	No external funding “Grant Support By an independent educational grant from the Institute of Digestive Disease, Chinese University of Hong Kong, Altana Pharma, Hong Kong, provided pantoprazole. Potential conflicts of interest: <i>Consultancies:</i> F.K.L. Chan (Pfizer, Otsuka), AstraZeneca). <i>Grants pending:</i> F.K.L. Chan (Takeda). <i>Patents pending:</i> J.Y. Sung (Nycomed). <i>Other:</i> F.K.L. Chan (chairman of the steering committee for Condor)”

PUB, peptic ulcer bleeding; RCT, randomized controlled trial

Table 1 (B) Risk of bias in included randomized controlled trials that addressed the primary aim

Author, year [Ref]	Random generation	Allocation concealment	Blinding	Completeness of data	Selective outcome reporting	Other bias
Sung 2010 [8]	Low risk Computer-generated list of random numbers. Number blocks were not used	Low risk “Consecutively numbered, identically designed treatment packs that contained sealed bottles of study drugs (aspirin or identical matching placebo tablets)”	Low risk for patients, physicians and outcome assessors “During hospitalization, a designated team of physicians and surgeons who were unaware of treatment assignment managed all study participants” “We included only events confirmed by an independent, blinded adjudication committee in the analysis”	Low risk All patients completed follow up	Low risk Authors reported all measured outcomes	Low risk

PUB, peptic ulcer bleeding; OTC, over the counter; ATs, antithrombotics; NVUGIB, non-variceal UGIB

Table 2 (A) Characteristics of included observational studies that addressed the primary aim

Author, year [Ref]	Study Design	Participants, setting	Exposure	Control	Outcomes	Notes
Derogar 2013 [15]	<ul style="list-style-type: none"> Retrospective cohort study with prospective follow up 	<ul style="list-style-type: none"> 118 patients with PUB receiving aspirin prior to admission Low-dose aspirin (75 mg or 160 mg/d) Reason for aspirin use: Not mentioned Single-center Median age: 78 Males: 60% 	<ul style="list-style-type: none"> 71 patients who resumed aspirin after temporary discontinuation 41% of patients resumed aspirin at discharge while 20% restarted aspirin after a median of 1 week 	<ul style="list-style-type: none"> 47 patients had discontinuation of aspirin without any intention of resumption 	<ul style="list-style-type: none"> All-cause mortality Re-bleeding: Had to be endoscopically verified Follow-up period: 3 years 	<ul style="list-style-type: none"> Funding: "Omid Sadr-Azodi was supported by a postdoctoral scholarship from Olle Engkvist Byggnästars Foundation" The authors disclosed no conflict of interest
Gonzalez-Perez 2017 [16]	<ul style="list-style-type: none"> Retrospective cohort study with prospective follow up beginning 30 days after the bleeding episode 	<ul style="list-style-type: none"> 0.547 patients with UGIB receiving aspirin prior to admission Aspirin dose: 75-300 mg/d 23% of patients used aspirin as primary prophylaxis while 77% used aspirin as secondary prophylaxis Multi-center Mean age: Not mentioned Males: 62% 	<ul style="list-style-type: none"> Patients divided into aspirin non-users, aspirin continuers, aspirin re-initiators, and aspirin discontinuers based on receiving aspirin prescription within some time periods 	<ul style="list-style-type: none"> Aspirin non-users 	<ul style="list-style-type: none"> All-cause mortality Follow up time: Maximum of 5 years 	<ul style="list-style-type: none"> "Multiple authors are on advisory boards of drug companies" Patients with cirrhosis were excluded from the study. Population was considered as "patients with NVUGIB"
Staerk 2015 [20]	<ul style="list-style-type: none"> Retrospective cohort study with prospective follow up beginning 90 days after the bleeding episode 	<ul style="list-style-type: none"> 0.3409 patients with non-valvular atrial fibrillation admitted for GI bleeding Receiving single or combined ATs Aspirin dose: Not mentioned Reason for aspirin use: Secondary prophylaxis Multi-center Mean age: 78 Males: 55% 	<ul style="list-style-type: none"> 1314 patients had resumption of single antiplatelet agent after NVUGIB Among those, 92% had resumption of aspirin (1212 patients) Timing of resumption of aspirin was not specified 	<ul style="list-style-type: none"> 924 patients had non-resumption of ATs 	<ul style="list-style-type: none"> All-cause mortality Re-bleeding Follow-up time: Maximum of 5 years 	<ul style="list-style-type: none"> No data regarding proportion of patients with variceal UGIB, although only 1.4% of patients had baseline liver failure. Population was considered as "NVUGIB" 92% of patients in ATs group were on aspirin; Group was considered as "Aspirin group"
Siau 2018 [25]	<ul style="list-style-type: none"> Retrospective study with prospective follow up 	<ul style="list-style-type: none"> 50 patients on aspirin monotherapy prior to admission for UGIB Aspirin dose: Not mentioned 84% used ATs as secondary prophylaxis Single-center Median age: 76 65% were males 	<ul style="list-style-type: none"> 18 patients had resumption of aspirin on discharge 	<ul style="list-style-type: none"> 32 patients had non-resumption of aspirin on discharge 	<ul style="list-style-type: none"> All-cause mortality Re-bleeding Maximum follow up: 1 year 	<ul style="list-style-type: none"> Patients whose ATs were downgraded were considered having "Discontinuation" Patients switched to other ATs were considered having "Continuation" Patients who died in hospital or did not have endoscopy were excluded

PUB, peptic ulcer bleeding; UGIB, upper gastrointestinal bleeding; ATs, antithrombotics; NVUGIB, non-variceal UGIB

Table 2 (B) Risk of bias in included observational studies that addressed the primary aim

Author, year [Ref]	Developing and applying appropriate eligibility criteria	Measurement of exposure	Measurement of outcome	Controlling for confounding	Completeness of data
Derogar 2013 [15]	Low risk Patients with PUB were retrieved from a hospital- administrative database at a local hospital in Stockholm, Sweden	Unclear risk Based on manual review of electronic medical records. Patients were not contacted and therefore actual restart of aspirin cannot be confirmed. Also, aspirin is available OTC and could have been taken without documentation	Low risk for mortality Information on death was retrieved from a trusted national registry Unclear risk for re-bleeding It was not clear how patients with re-bleeding were identified (was the same registry used?)	Low risk Controlling for important confounders was established	Unclear risk No mention of missing data
Gonzalez-Perez 2017 [16]	Low risk Based on a well characterized UK database containing computerized data on a large number of patients	Unclear risk Based on review of medical records showing prescription of aspirin Patients were not contacted and therefore actual restart of aspirin cannot be confirmed. Also, aspirin is available OTC and could have been taken without documentation	For mortality: unclear risk It is not clear how mortality was assessed	High risk Some patients were assigned to different groups: Data from the same patient but from different points in time have been assigned to 2 groups of interest, depending on whether patients had started/ stopped/re-initiated aspirin. This probably could have introduced confounding, given that taking/not taking aspirin is associated with different outcomes.	Unclear risk No mention of missing data
Staerk 2015 [20]	High risk Patients could have been taking other ATs prior to admission for NVUGIB	Unclear risk Information about exposure to aspirin gathered from a national prescription registry Patients were not contacted and therefore actual restart of aspirin cannot be confirmed. Also, aspirin is OTC and could have been taken without documentation	Low risk for mortality and re-bleeding Data for mortality and re-bleeding gathered from a trusted national database	Low risk Controlling for important confounders was established	Unclear risk It was not reported whether there are missing data
Siau 2018 [25]	Low risk Criteria were well defined and applied	Unclear risk Based on manual review of electronic medical records. Patients were not contacted and therefore actual restart of aspirin cannot be confirmed. Also, aspirin is available OTC and could have been taken without documentation	Low risk for mortality and re-bleeding Information was retrieved from a trusted national registry	High risk Controlling for comorbidities, for severity of bleeding as well as blood transfusions was not done	Unclear risk No reports of missing data

PUB, peptic ulcer bleeding; OTC, over the counter; ATs, antithrombotics; NVUGIB, non-variceal UGIB

Table 3 (A) Characteristics of included observational studies that addressed the secondary aim

Author, year [Ref]	Study Design	Participants, setting	Exposure	Control	Outcomes
Camus 2016 [13]	• Prospective study	<ul style="list-style-type: none"> • 0.1264 patients with severe PUB • 2 US tertiary centers • Mean age: 61 • Males: 74% 	<ul style="list-style-type: none"> • 468 patients were on aspirin (not exclusively) • Aspirin dose: not mentioned • Reason for aspirin intake: not mentioned 	<ul style="list-style-type: none"> • 796 not on aspirin • Patients could have been receiving other ATs. 	<ul style="list-style-type: none"> • In-hospital mortality • Re-bleeding • Follow-up time: 30 days
Chiu 2009 [14]	• Prospective study	<ul style="list-style-type: none"> • 3220 patients with PUB requiring endoscopic therapy • Single-center • Mean age: Not mentioned • Males: 67% 	<ul style="list-style-type: none"> • 0.336 patients were on aspirin (Not clear if exclusive) • Aspirin dose: Not mentioned • Reason for aspirin intake: Not mentioned 	<ul style="list-style-type: none"> • 2884 were not on aspirin 	<ul style="list-style-type: none"> • In-hospital mortality
Hong 2014 [17]	• Prospective study	<ul style="list-style-type: none"> • 522 patients with PUB and successful hemostasis • Single-center • Mean age: 62 • Males: 75% 	<ul style="list-style-type: none"> • 122 patients were on ATs • 0.96.7% were on aspirin (10% on both aspirin and clopidogrel) • Aspirin dose: 100 mg/d • Reason for aspirin intake: Not mentioned 	<ul style="list-style-type: none"> • 400 patients were not on ATs 	<ul style="list-style-type: none"> • Re-bleeding • Follow-up time: 30 days
Ishikawa, 2012 [18]	• Prospective study	<ul style="list-style-type: none"> • 0.305 patients with severe PUB • Single-center • Mean age: 66 • Males: 76% 	<ul style="list-style-type: none"> • 55 patients were on aspirin (Not exclusive) • Aspirin dose: 80-100 mg/d • Reason for aspirin use: Not mentioned 	<ul style="list-style-type: none"> • 156 patients not taking aspirin nor NSAIDs 	<ul style="list-style-type: none"> • All-cause in-patient mortality
Liang 2016 [19]	• Retrospective study with prospective follow up	<ul style="list-style-type: none"> • 1229 patients with PUB¹ and endoscopic hemostasis • Multi-center (Taiwan) • Mean age: 63 • 35% were males • 15% had CKD 	<ul style="list-style-type: none"> • 116 patients were on aspirin (Not exclusive) • Aspirin dose: not mentioned • Reason for aspirin intake: not mentioned 	<ul style="list-style-type: none"> • 1113 patients not on aspirin • Patients could have been receiving other ATs 	<ul style="list-style-type: none"> • Mortality • Re-bleeding • Follow-up period: 10 years
Manguso 2008[21]	• Prospective study	<ul style="list-style-type: none"> • 142 patients with PUB FORREST 1 • Single-center • Mean age: 66 • Males: 69% 	<ul style="list-style-type: none"> • 41 patients were on low-dose aspirin • Patients could have been taking other ATs • Reason for aspirin use: Not mentioned 	<ul style="list-style-type: none"> • 101 not taking aspirin • Patients could have been taking other ATs 	<ul style="list-style-type: none"> • In-hospital mortality • Re-bleeding (within 24 h of endoscopic hemostasis)
Marmo 2010 [22]	• Prospective study	<ul style="list-style-type: none"> • 1360 patients with NVUGIB • Multi-center • Mean Age: 68 • Males: 67% 	<ul style="list-style-type: none"> • 248 patients were on aspirin (Not mentioned if exclusive) • Aspirin dose: mean of 100 mg/d • Reason for aspirin use: Not mentioned 	<ul style="list-style-type: none"> • 1112 patients not taking aspirin 	<ul style="list-style-type: none"> • All-cause mortality • Re-bleeding • Follow-up time: 30 days
Mose 2006 [23]	• Retrospective study with prospective follow up	<ul style="list-style-type: none"> • 7204 patients with a first episode of PUB • Multi-center • Median age: 71 • Males: 52% 	<ul style="list-style-type: none"> • 1029 patients with current use of low-dose aspirin (at least 1 filled prescription within 100 days prior to bleeding episode; not exclusive) • Aspirin dose: 75-150 mg/d • Reason for aspirin use: not mentioned 	<ul style="list-style-type: none"> • 5466 patients who never used aspirin (not even previous use) 	<ul style="list-style-type: none"> • All-cause mortality • Follow-up time: 30-days
Park 2018 [24]	• Prospective RCT	<ul style="list-style-type: none"> • 319 patients with PUB and high-risk stigmata for re-bleeding • Multi-center (7 hospitals) • Mean age: 58 • Males: 76% 	<ul style="list-style-type: none"> • 78 patients were on aspirin (not clear if exclusively) • Aspirin dose: not mentioned • Reason for aspirin use: Not mentioned 	<ul style="list-style-type: none"> • 241 patients were not on aspirin • Patients could have been receiving other ATs 	<ul style="list-style-type: none"> • Re-bleeding • Follow-up time: 30 days

PUB, peptic ulcer bleeding; ATs, antithrombotics; CKD, chronic kidney disease; RCT, randomized controlled trial; NSAIDs, nonsteroidal anti-inflammatory drugs

Table 3 (B) Risk of bias in included observational studies that addressed the secondary aim

Author, year [Ref]	Developing and applying appropriate eligibility criteria	Measurement of exposure	Measurement of outcome	Controlling for confounding	Completeness of data
Camus 2016 [13]	Low risk Criteria were well defined and applied.	Low risk The authors reviewed the database. Research coordinator followed up to 1 month	Low risk Mortality and re-bleeding documented in database and by interview by a coordinator	Unclear risk Controlling for confounders was established. Patients in both groups could have been receiving other ATs.	Low risk Missing data for aspirin exposure: 0.4%
Chiu 2009 [14]	Low risk Criteria were well defined and applied	Low risk Not mentioned by authors. Reliable electronic records in Hong Kong	Low risk for mortality Only in-hospital mortality was evaluated	High risk Controlling for confounders was not established comparing aspirin users to non-users.	Unclear risk No report of missing data
Hong 2014 [17]	Low risk Criteria were well defined and applied	Low risk Medical records were checked prospectively	Low risk for re-bleeding Patients were followed up for more than 30 days after hemostasis.	Low risk Controlling for important confounders was established.	Unclear risk No report of missing data
Ishikawa 2012 [18]	Low risk Criteria were well defined and applied	Low risk Information retrieved from electronic medical records, medication information documents and phone calls to other hospitals.	Low risk for mortality In-hospital mortality was evaluated	High risk There are significant differences in age and use of ACs among aspirin and non-aspirin groups	Unclear risk No report of missing data
Liang 2016 [19]	Unclear risk No specific diagnostic criteria for re-bleeding were mentioned	Low risk Information was retrieved from drug prescription database	Low risk for mortality and re-bleeding Patients' outcomes were retrieved from national database	Unclear risk Controlling for confounders was established Patients in both groups could have been receiving other ATs.	Unclear risk No reports of missing data
Manguso 2008 [21]	Low risk Criteria were well defined and applied.	Unclear risk There is no information on how the data regarding medications was obtained.	Low risk for in-hospital mortality Low risk for re-bleeding (Inpatient follow up)	High risk There was no mention of controlling for confounders.	Unclear risk No report of missing data
Marmo 2010[22]	Low risk Criteria were well defined and applied.	Unclear risk There is no information on how the data regarding were was obtained.	Low risk for mortality and re-bleeding Clinical outcomes were tracked during hospital stay, after discharge to other health care facility, and after home discharge	Unclear risk Controlling for confounders was established. Patients in both groups could have been receiving other ATs.	Unclear risk No report of missing data
Mose 2006 [23]	Low risk Criteria were well defined and applied.	Unclear risk Aspirin intake relied solely on filled prescriptions. Patients were not contacted to confirm whether they took aspirin or not.	Low risk Accurate linkage between the used registries was performed.	High risk Adjustment for other PUD-associated drugs was not performed.	Unclear risk No reports of missing data
Park 2018 [24]	Low risk Criteria were well defined and applied.	Unclear risk There is no information on how the data regarding medications was obtained.	Low risk for re-bleeding Patients were followed-up for 30 days after endoscopic therapy.	High risk Only univariate analysis was conducted. Adjustment for other PUD associated drugs was not performed.	Unclear risk No reports of missing data

ATs, antithrombotics; ACs, anti-coagulants; PUD, peptic ulcer disease