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

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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

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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 ≥90% of cases).

Comparison groups

For the primary aim, the intervention was defined as resuming aspirin following NVUGIB (separate data for aspirin subgroup, or ≥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

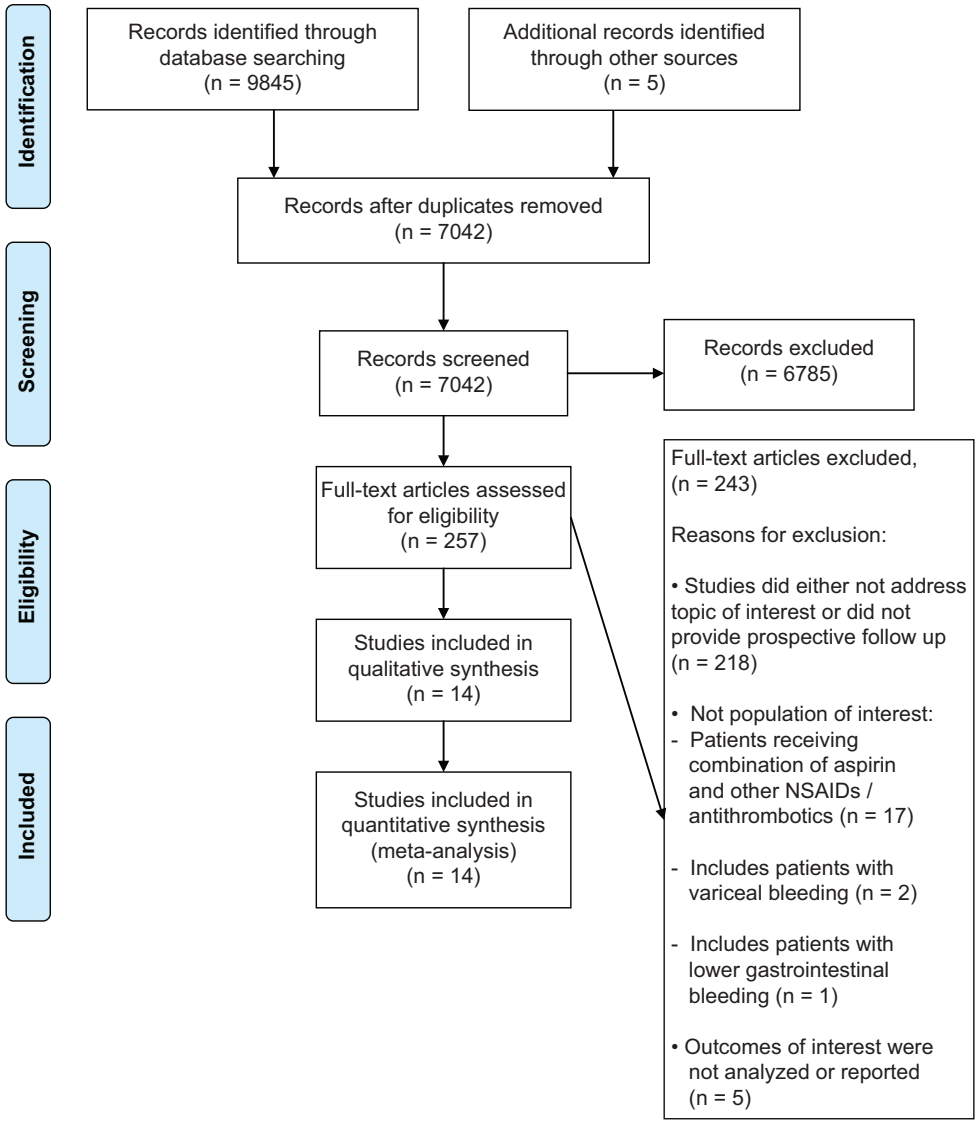

Figure 1 PRISMA 2009 flow diagram
NSAIDs, nonsteroidal anti-inflammatory drugs

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

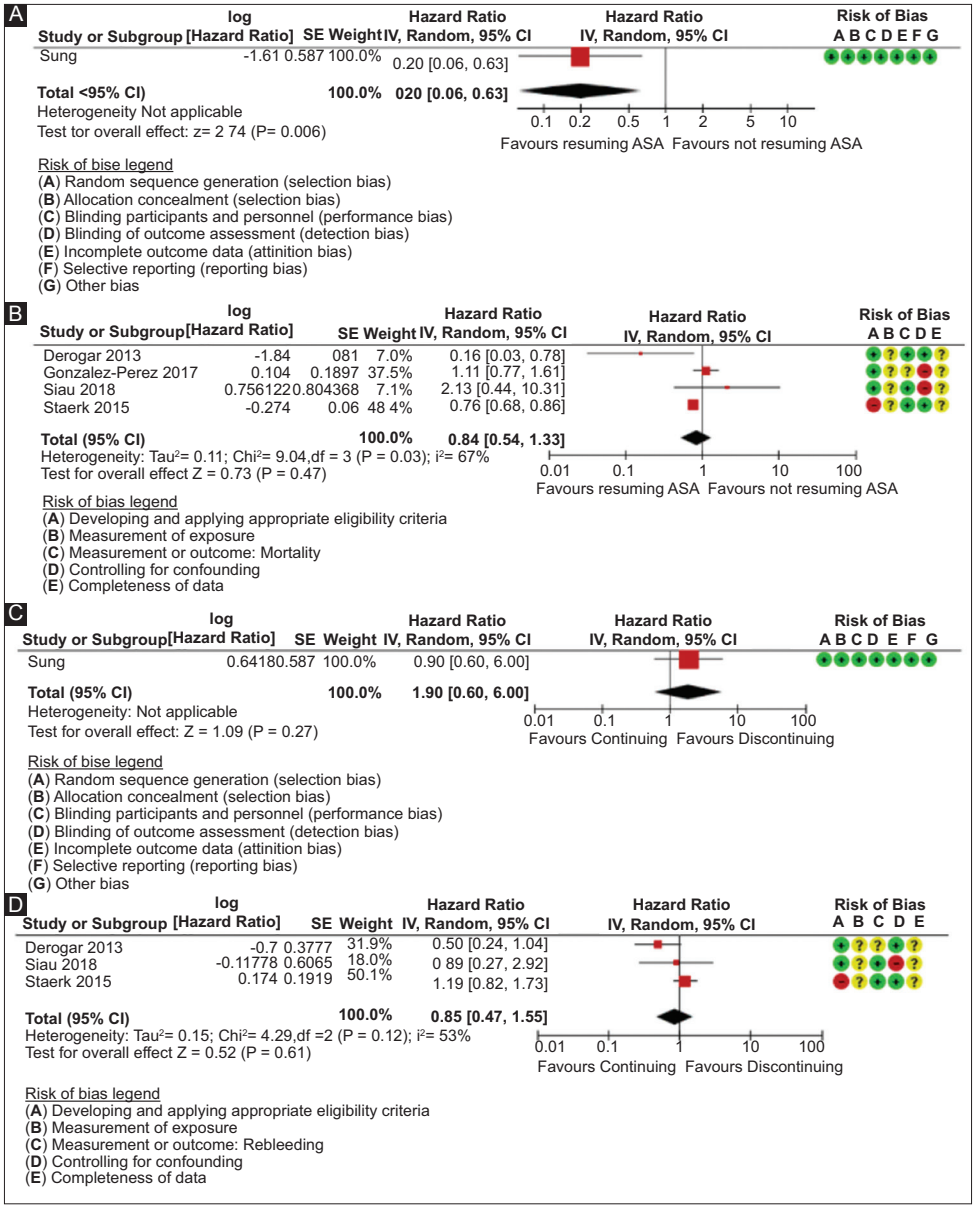

Figure 2 Effects of aspirin resumption on mortality in patients with non-variceal upper gastrointestinal bleeding (NVUGIB); (A) randomized controlled trial (RCT); (B) observational studies; and effects of aspirin resumption on re-bleeding in patients with NVUGIB; (C) RCT; (D) observational studies
CI,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

Certainty assessment							No of patients (%)		Effect		Certainty	Importance
No of studies	Study design	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 $I^2 = 67\%$ 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 $I^2 = 53\%$ e. Wide CI and very low number of events

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

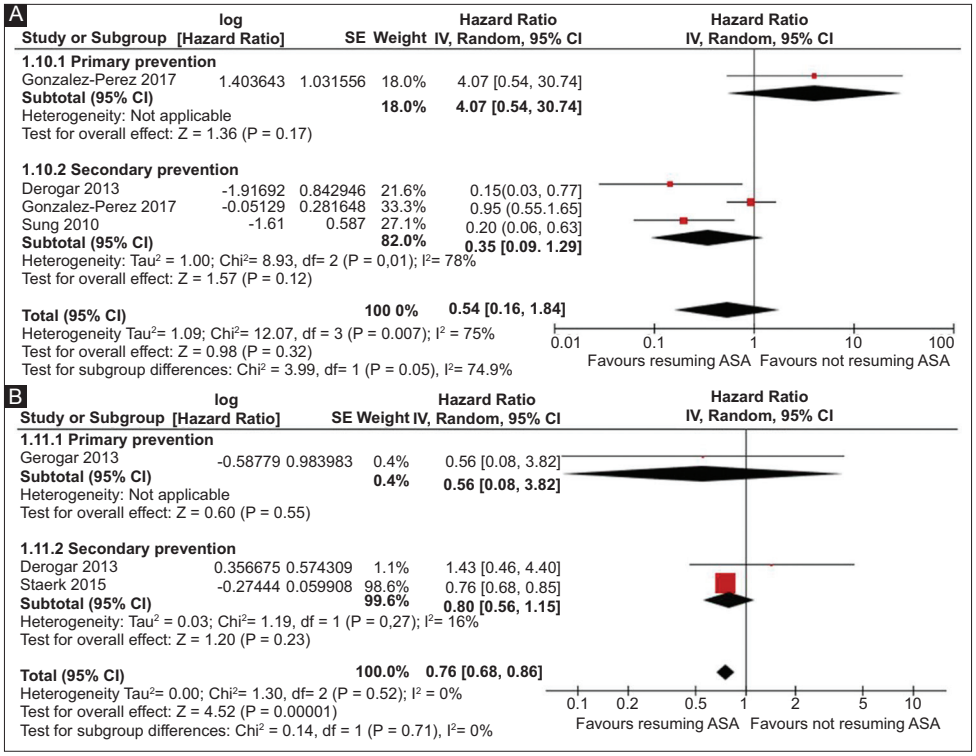

Figure 3 Effects of aspirin resumption on mortality in patients with non-variceal upper gastrointestinal bleeding (NVUGIB) stratified by whether it was used for primary or secondary prevention; (A) mortality within 6 months following NVUGIB; (B) mortality after more than 6 months following NVUGIB
CI, 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; I^2=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.

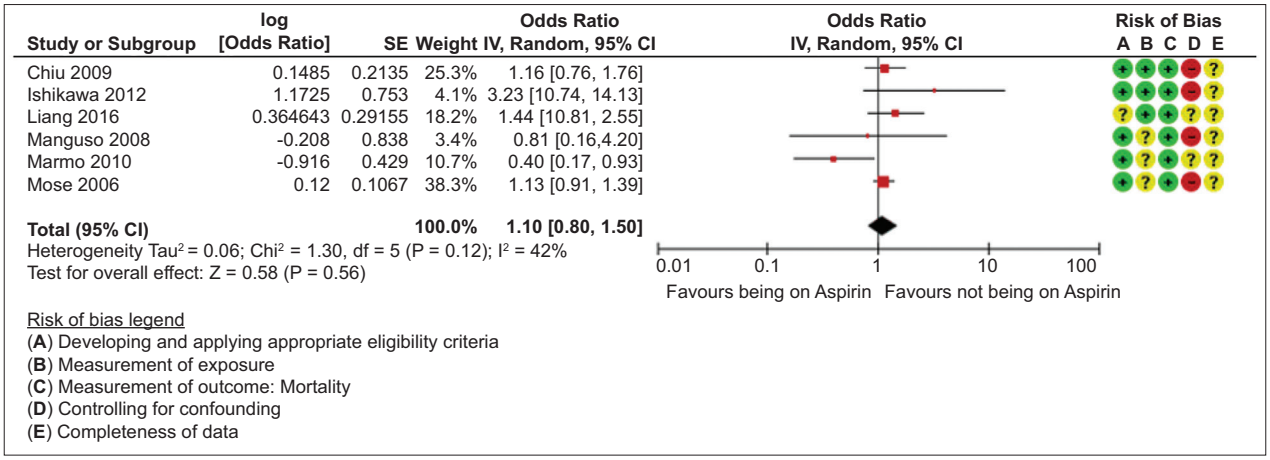

Figure 4 Effects of aspirin use prior to non-variceal upper gastrointestinal bleeding on mortality
CI, confidence interval

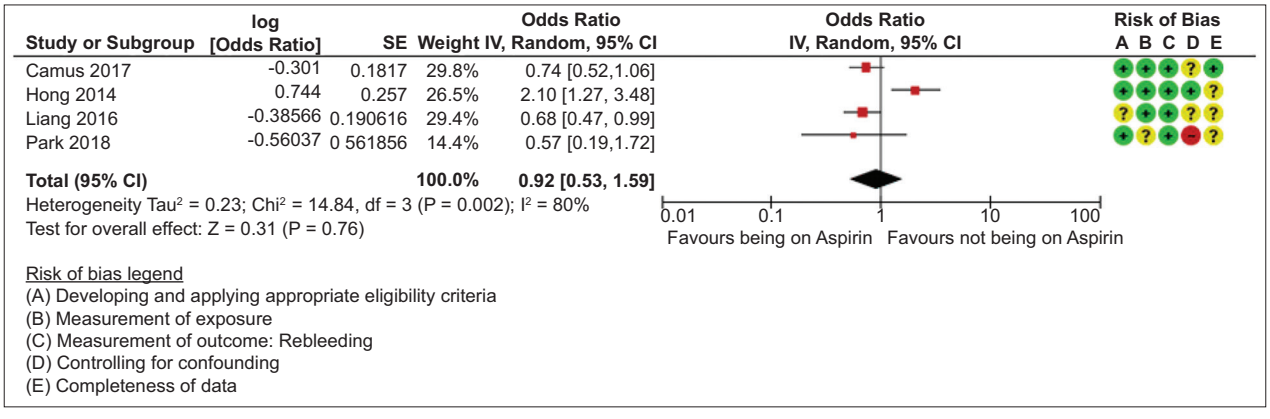

Figure 5 Effects of aspirin use prior to non-variceal upper gastrointestinal bleeding on re-bleeding
CI, confidence interval

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

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