Supplementary Table 1 Evidence profile for the secondary aim

Certainty assessment							No of patients		Effect		Certainty	Importance
No of stu dies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	On aspirin prior to NVUGIB	Not on aspirin prior to NVUGIB	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality - observational studies												
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
Rebleeding - 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

Explanations a. I^2 = 42% b. 95%CI includes values consistent with potential harm and values consistent with potential benefit c. Unexplained heterogeneity I^2 = 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 stomac* or (upper adj2 gastro*) or gastri* or epigastr* 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-hemorhag* or re- hemorrhag* or haemorrhag* or haemorhag* 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 gastrorrha* 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 stomac*[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 epigastr*[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 haemorhag*[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 gastrorrha*[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 stomac* or gastri* or oesopha* or esopha* or duoden* or peptic* or nonvaric* or (non adj varic*)) adj2 (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*)).ti,ab,sh.
6. (melena* or melaena* or hematem* or haematem* or hematochez* or haematochez* or gastrorrha* or gastrorha* or NVGIB).ti,ab,sh.
7. exp hematemesis/
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 stomac* or (upper near/2 gastro*) or gastri* or epigastr* 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 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*: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 gastrorrha* 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 stomac* OR gastri* OR epigastr* OR oesopha* OR esopha* 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 gastrorrha* 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, Clincal 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

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]	• Parallel, randomized, double-blinded, placebo-controlled non-inferiority trial (RCT) • Follow up after 30 and 56 days from discharge	• 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	• 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: *Consultancies:* F.K.L. Chan (Pfizer, Otsuka). *Honoraria:* F.K.L. Chan (Pfizer, Takeda, AstraZeneca). *Grants pending:* F.K.L. Chan (Takeda). *Patents pending:* J.J.Y. Sung (Nycomed). *Other:* 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 sequence 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]	• Retrospective cohort study withprospective follow up	• 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%	• 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	• 47 patients had discontinuation of aspirin without any intention of resumption	• All-cause mortality • Re-bleeding: Had to be endoscopically verified • Follow-up period: 3 years	• Funding: "Omid Sadr–Azodi was supported by a postdoctoral scholarship from Olle Engkvist Byggmästare Foundation" • The authors disclosed no conflict of interest
Gonzalez-Perez 2017 [16]	• Retrospective cohort study withprospective follow up beginning 30 days after the bleeding episode	• 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%	• Patients divided into aspirin non-users, aspirin continuers, aspirin re-initiators, and aspirin discontinuers based on receiving aspirin prescription within some time periods	• Aspirin non-users	• All-cause mortality • Follow up time: Maximum of 5 years	• "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]	• Retrospective cohort study withprospective follow up beginning 90 days after the bleeding episode	• 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%	• 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	• 924 patients had non-resumption of ATs	• All-cause mortality • Re-bleeding • Follow-up time: Maximum of 5 years	• 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]	• Retrospective study with prospective follow up	• 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	• 18 patients had resumption of aspirin on discharge	• 32 patients had non-resumption of aspirin on discharge	• All-cause mortality • Re-bleeding • Maximum follow up: 1 year	• 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	• 0.1264 patients with severe PUB • 2 US tertiary centers • Mean age: 61 • Males: 74%	• 468 patients were on aspirin (not exclusively) • Aspirin dose: not mentioned • Reason for aspirin intake: not mentioned	• 796 not on aspirin Patients could have been receiving other ATs.	• In-hospital mortality • Re-bleeding • Follow-up time: 30 days
Chiu 2009 [14]	• Prospective study	• 3220 patients with PUB requiring endoscopic therapy • Single-center • Mean age: Not mentioned • Males: 67%	0.336 patients were on aspirin (Not clear if exclusive) • Aspirin dose: Not mentioned • Reason for aspirin intake: Not mentioned	• 2884 were not on aspirin	• In-hospital mortality
Hong 2014 [17]	• Prospective study	• 522 patients with PUB and successful hemostasis • Single-center • Mean age: 62 • Males: 75%	• 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	• 400 patients were not on ATs	• Re-bleeding • Follow-up time: 30 days
Ishikawa, 2012 [18]	• Prospective study	• 0.305 patients with severe PUB • Single-center • Mean age: 66 • Males: 76%	• 55 patients were on aspirin (Not exclusive) • Aspirin dose: 80-100 mg/d • Reason for aspirin use: Not mentioned	• 156 patients not taking aspirin nor NSAIDs	• All-cause in-patient mortality
Liang 2016 [19]	• Retrospective study with prospective follow up	• 1229 patients with PUB[1] and endoscopic hemostasis • Multi-center (Taiwan) • Mean age: 63 • 35% were males • 15% had CKD	• 116 patients were on aspirin (Not exclusive) • Aspirin dose: not mentioned • Reason for aspirin intake: not mentioned	• 1113 patients not on aspirin • Patients could have been receiving other ATs	• Mortality • Re-bleeding • Follow-up period: 10 years
Manguso 2008[21]	• Prospective study	• 142 patients with PUB FORREST 1 • Single-center • Mean age: 66 • Males: 69%	• 41 patients were on low-dose aspirin • Patients could have been taking other ATs • Reason for aspirin use: Not mentioned	• 101 not taking aspirin • Patients could have been taking other ATs	• In-hospital mortality • Re-bleeding (within 24 h of endoscopic hemostasis)
Marmo 2010 [22]	• Prospective study	• 1360 patients with NVUGIB • Multi-center • Mean Age: 68 • Males: 67%	• 248 patients were on aspirin (Not mentioned if exclusive) • Aspirin dose: mean of 100 mg/d • Reason for aspirin use: Not mentioned	• 1112 patients not taking aspirin	• All-cause mortality • Re-bleeding • Follow-up time: 30 days
Mose 2006 [23]	• Retrospective study with prospective follow up	• 7204 patients with a first episode of PUB • Multi-center • Median age: 71 • Males: 52%	• 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	• 5466 patients who never used aspirin (not even previous use)	• All-cause mortality • Follow-up time: 30-days
Park 2018 [24]	• Prospective RCT	• 319 patients with PUB and high-risk stigmata for re-bleeding • Multi-center (7 hospitals) • Mean age: 58 • Males: 76%	• 78 patients were on aspirin (not clear if exclusively) • Aspirin dose: not mentioned • Reason for aspirin use: Not mentioned	• 241 patients were not on aspirin • Patients could have been receiving other ATs	• 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