SUPPLEMENT 1 SEARCH METHODOLOGY, SEARCH STRATEGY, AND CORRESPONDING AUTHOR OUTREACH FOR ELIGIBILITY VERIFICATION

Search Methodology

Database Searching. A comprehensive search strategy was developed and modified for the various databases searched with the assistance of a health research librarian. The search was initially run in all databases on July 3, 2019, and updated on April 7, 2021 by fully rerunning the search in each database from inception through April 7, 2021. No peer review of the search strategy was performed, and no published search filters were used. The full search strategy for each database is available in Supplementary Table 1.

Deduplication of Results. Duplicates were removed automatically during import into Covidence. Covidence identifies duplicate references based on title, year, and volume, all of which must match exactly to remove the duplicate record from the screening list.

Citation Tracking. Following screening of all articles identified through database searching and outreach to topic experts in the field, citation tracking for all articles included for data extraction was performed on April 16, 2021, using the Web of Science Core Collection. Article titles were searched in Web of Science, and all references cited and citing articles were exported from the Web of Science Core Collection and imported into Covidence, where they underwent deduplication and title and abstract screening. A total of 527 articles were identified through citation tracking of included articles, of which 355 underwent title and abstract screening.

Contact of Field Experts and Study Authors. In March 2021, the lead author (JEK) contacted three topic experts in the field to inquire about other potentially relevant articles for inclusion that may not have been captured by the search. No new studies that were not retrieved by the database search strategy were identified for inclusion through contact of topic experts.

Additionally, authors for 5 studies identified through database searching were contacted by a study representative (DH) for additional information regarding their research throughout the course of the review. Three authors were contacted to verify whether their studies met prespecified eligibility criteria and were able to be included for qualitative synthesis. One author was contacted to determine whether the results of a subanalysis of participants randomized to receive a proton pump inhibitor in their randomized controlled trial had been published as of the date of contact. A final author was contacted to determine whether there was overlap between study cohorts in 2 separate articles published on this topic. Details related to author contacts are included in Supplementary Table 2.

Supplementary Table 1 Database Specific Search Strategies

Database	Search Input
Pubmed	("anticoagulants"[mh] OR anticoagula*[tw] OR "antivitamin k"[tw] OR "vitamin k antagonist"[tw] OR "warfarin"[mh] OR warfarin[tw] OR coumadin [tw] OR jantoven[tw] OR "non vitamin k oral anticoagulants"[tw] OR "non vitamin k antagonist oral anticoagulant"[tw] OR "doac"[tw] OR "noac"[tw] OR "dabigatran"[mh] OR dabigatran[tw] OR pradaxa[tw] OR apixaban[tw] OR eliquis[tw] OR "rivaroxaban"[mh] OR rivaroxaban[tw] OR xarelto[tw] OR edoxaban[tw] OR savaysa[tw] OR lixiana[tw]) AND (gastroprotect*[tw] OR "proton pump inhibitors"[mh] OR "proton pump inhibitors"[tw] OR "proton pump inhibitor"[tw] OR "proton pumps"[mh] OR "proton pumps"[tw] OR "omeprazole"[mh] OR omeprazole[tw] OR prilosec[tw] OR "esomeprazole" [mh] OR esomeprazole[tw] OR nexium[tw] OR "lansoprazole"[mh] OR lansoprazole[tw] OR prevacid[tw] OR "rabeprazole"[mh] OR rabeprazole[tw] OR aciphex[tw] OR "pantoprazole"[mh] OR pantoprazole[tw] OR protonix[tw] OR "dexlansoprazole"[mh] OR dexlansoprazole[tw] OR dexilant[tw] OR zegerid [tw] OR "histamine h2 antagonists"[mh] OR "histamine h2 antagonists"[tw] OR "h2 blocker"[tw] OR "famotidine"[mh] OR famotidine[tw] OR pepcid[tw] OR "cimetidine"[mh] OR cimetidine[tw] OR tagamet[tw] OR "ranitidine"[mh] OR ranitidine[tw] OR zantac[tw] OR "nizatidine"[mh] OR nizatidine[tw] OR axid[tw] OR "acid suppressant"[tw] OR "acid suppressor"[tw] OR "acid suppressing"[tw] OR "antacid"[tw]) AND ("gastrointestinal hemorrhage"[mh] OR "gastrointestinal hemorrhage"[tw] OR "gastrointestinal haemorrhage"[tw] OR "gastrointestinal bleeding"[tw] OR "upper gastrointestinal bleeding"[tw] OR ugib[tw] OR "ulcer bleeding"[tw] OR "upper gastrointestinal tract/drug effects"[mh] OR "peptic ulcer"[mh] OR "peptic ulcer bleeding"[tw] OR "gi bleeding"[tw] OR melena[tw] OR melaena[tw] OR "duodenal bleeding"[tw] OR "small intestine hemorrhage"[tw] OR "small intestine haemorrhage"[tw] OR "stomach hemorrhage"[tw] OR "stomach haemorrhage"[tw] OR "hematemesis"[mh] OR "hematemesis"[tw] OR "haematemesis"[tw] OR "intestinal hemorrhage"[tw] OR "intestinal bleeding"[tw])
EMBASE	('anticoagulant agent'/de OR 'antivitamin k'/exp OR 'antivitamin k':ti,ab OR 'vitamin k antagonist':ti,ab OR 'warfarin'/exp OR warfarin:ti,ab OR coumadin: ti,ab OR jantoven:ti,ab OR 'non vitamin k oral anticoagulant':ti,ab OR 'non vitamin k antagonist oral anticoagulant':ti,ab OR 'doac':ti,ab OR 'noac':ti,ab OR 'dabigatran'/exp OR dabigatran:ti,ab OR 'dabigatran etexilate'/exp OR 'dabigatran etexilate':ti,ab OR pradaxa:ti,ab OR 'apixaban'/exp OR apixaban:ti, ab OR eliquis:ti,ab OR 'rivaroxaban'/exp OR rivaroxaban:ti,ab OR xarelto:ti,ab OR 'edoxaban'/exp OR edoxaban:ti,ab OR savaysa:ti,ab OR lixiana:ti,ab) AND (gastroprotect*:ti,ab OR 'proton pump inhibitor'/exp OR 'proton pump inhibitor':ti,ab OR 'proton pump inhibitors':ti,ab OR 'omeprazole'/exp OR omeprazole:ti,ab OR prilosec:ti,ab OR 'esomeprazole'/exp OR esomeprazole:ti,ab OR nexium:ti,ab OR 'lansoprazole'/exp OR lansoprazole:ti,ab OR prevacid:ti,ab OR 'rabeprazole'/exp OR rabeprazole:ti,ab OR aciphex:ti,ab OR 'pantoprazole'/exp OR pantoprazole:ti,ab OR protonix:ti,ab OR 'dexlansoprazole'/exp OR dexlansoprazole:ti,ab OR dexilant:ti,ab OR 'bicarbonate plus omeprazole'/exp OR 'bicarbonate plus omeprazole':ti,ab OR zegerid:ti,ab OR 'histamine h2 receptor antagonist'/exp OR 'histamine h2 receptor antagonist':ti,ab OR 'h2 blocker':ti, ab OR 'famotidine'/exp OR famotidine:ti,ab OR pepcid:ti,ab OR 'cimetidine'/ exp OR cimetidine:ti,ab OR tagamet:ti,ab OR 'ranitidine'/exp OR ranitidine:ti, ab OR zantac:ti,ab OR 'nizatidine'/exp OR nizatidine:ti,ab OR axid:ti,ab OR 'acid suppress*':ti,ab OR 'antacid agent'/mj) AND ('gastrointestinal hemorrhage'/mj OR 'gastrointestinal hemorrhage':ti,ab OR 'gastrointestinal haemorrhage':ti,ab OR 'upper gastrointestinal bleeding'/exp OR 'upper gastrointestinal bleeding':ti,ab OR 'ulcer bleeding'/exp OR 'ulcer bleeding':ti, ab OR 'peptic ulcer bleeding'/exp OR 'peptic ulcer bleeding':ti,ab OR 'gi bleeding':ti,ab OR 'melena'/exp OR melena:ti,ab OR melaena:ti,ab OR 'duodenum bleeding'/exp OR 'duodenum bleeding':ti,ab OR 'intestinal

Supplementary Table 1 (*Continued*)

Database	Search Input
	bleeding'/exp OR 'intestinal bleeding':ti,ab OR 'small intestine hemorrhage'/exp OR 'small intestine hemorrhage':ti,ab OR 'small intestine haemorrhage':ti,ab OR 'stomach hemorrhage'/exp OR 'stomach hemorrhage':ti,ab OR 'stomach haemorrhage':ti,ab OR 'intestinal hemorrhage':ti,ab OR 'hematemesis'/exp OR 'haematemesis':ti,ab)
Cochrane Library	(anticoagulant OR "antivitamin k" OR "vitamin k antagonist" OR "non vitamin k antagonist oral anticoagulant" OR "non vitamin k oral anticoagulant" OR doac OR noac) AND ("proton pump inhibitors" OR "proton pump inhibitor" OR ppi OR "h2 blocker" OR "histamine h2 antagonist" OR gastroprotect*) AND ("gastrointestinal hemorrhage" OR "upper gastrointestinal bleeding" OR "gastrointestinal bleeding" OR "ulcer bleeding" OR "gastrointestinal haemorrhage")
Scopus	TITLE-ABS-KEY (({anticoagulant agent} OR anticoagula* OR {antivitamin k} OR {vitamin k antagonist} OR warfarin OR coumadin OR jantoven OR {non vitamin k antagonist oral anticoagulant} OR {non vitamin k oral anticoagulant} OR doac OR noac OR dabigatran OR pradaxa OR apixaban OR eliquis OR rivaroxaban OR xarelto OR edoxaban OR savaysa OR lixiana) AND (gastroprotect* OR {proton pump inhibitor} OR {proton pump inhibitors} OR {proton pump} OR omeprazole OR prilosec OR esomeprazole OR nexium OR lansoprazole OR prevacid OR rabeprazole OR aciphex OR pantoprazole OR protonix OR dexlansoprazole OR dexilant OR zegerid OR {histamine h2 antagonists} OR {h2 blocker} OR famotidine OR pepcid OR cimetidine OR tagamet OR ranitidine OR zantac OR nizatidine OR axid OR {acid suppress*} OR antacid) AND ({gastrointestinal hemorrhage} OR {gastrointestinal bleeding} OR {upper gastrointestinal bleeding} OR {peptic ulcer bleeding} OR {ulcer bleeding} OR {gastrointestinal tract bleeding} OR {gi bleeding} OR {ugib} OR {gastrointestinal haemorrhage} OR {duodenum bleeding} OR {intestinal bleeding} OR melena OR melaena OR {stomach hemorrhage} OR {stomach haemorrhage} OR {small intestine hemorrhage} OR {small intestine haemorrhage} OR {intestinal hemorrhage} OR hematemesis OR haematemesis))
Web of Science	ALL= (("anticoagulant agent" OR anticoagula* OR "antivitamin k" OR "vitamin k antagonist" OR warfarin OR coumadin OR jantoven OR "non vitamin k antagonist oral anticoagulant" OR "non vitamin k oral anticoagulant" OR doac OR noac OR dabigatran OR pradaxa OR apixaban OR eliquis OR rivaroxaban OR xarelto OR edoxaban OR savaysa OR lixiana)AND (gastroprotect* OR "proton pump inhibitor" OR "proton pump inhibitors" OR "proton pump" OR omeprazole OR Prilosec OR esomeprazole OR Nexium OR lansoprazole OR prevacid OR rabeprazole OR aciphex OR pantoprazole OR protonix OR dexlansoprazole OR dexilant OR zegerid OR "histamine h2 antagonists" OR famotidine OR Pepcid OR cimetidine OR tagamet OR ranitidine OR zantac OR nizatidine OR axid OR "acid suppress*" OR antacid)AND ("gastrointestinal hemorrhage" OR "gastrointestinal bleeding" OR "upper gastrointestinal bleeding" OR "gastrointestinal tract bleeding" OR "gi bleeding" OR "peptic ulcer bleeding" OR "ulcer bleeding" OR "gastrointestinal haemorrhage" OR "gi bleeding" OR "ugib" OR "duodenum bleeding" OR "intestinal bleeding" OR melena OR melaena OR "stomach hemorrhage" OR "stomach haemorrhage" OR "small intestine hemorrhage" OR "small intestine haemorrhage" OR "intestinal hemorrhage" OR hematemesis OR haematemesis))
ClinicalTrials.gov	(anticoagulants OR "antivitamin K" OR "vitamin k antagonists" OR "non vitamin k oral anticoagulant" OR doac OR noac) AND ("proton pump inhibitors" OR "proton pump inhibitor" OR "histamine h2 antagonists" OR "h2 blocker" OR gastroprotect* OR antacid)

Supplementary Table 2 Corresponding Author Outreach for Eligibility Verification

Title	Corresponding Author	Date of Contact	Reason for Contact	Response	Date of Response
Dabigatran in patients with myocardial injury after noncardiac surgery (MANAGE): an international, randomised, placebo-controlled trial (2018)	PJ Devereaux Pj.devereaux@phri.ca	1/22/2020	Article states that results from the PPI randomization arm of the trial would be published elsewhere. The reviewers were unable to find these results published elsewhere and contacted the author to inquire whether they had yet been published.	Author responded that the paper had been delayed due to competing responsibilities and was recently finalized and about to submitted for publication.	1/23/2020
Association of Proton Pump Inhibitors with Reduced Risk of Warfarin-Related Serious Upper Gastrointestinal Bleeding (2016) and *Association of Oral Anticoagulants and Proton-Pump-Inhibitor Co-Therapy with Hospitalization for Upper Gastrointestinal Bleeding* (2018)	Wayne Ray Wayne.ray@vanderbilt.edu	3/24/2020	Reviewers were unsure whether there was overlap between the study cohorts included in each publication, specifically between the US Medicare beneficiary file data used for analysis in the 2018 study and the longitudinal 5% National Medicare sample used for the 2016 study, with potential overlap for the 2011-2013 data. Author was contacted to determine whether cohort overlap exists.	Author responded and clarified that cohort overlap does exist for the warfarin patients and stated that approximately 5% of warfarin treated patients included from 2011-2013 in the 2018 study were also included in the Medicare cohort in the 2016 study.	3/25/2020
Prevention of Dabigatran-Related Gastrointestinal Bleeding with Gastroprotective Agents: a Population-Based Study (2015)	Ian CK Wong wongick@hku.hk	4/8/2020	In the referenced study, the authors stated that a subcategory analysis of upper versus nonupper GI bleeding was performed and found that gastroprotective agents significantly reduce upper but not nonupper GI bleeding risk. The author was contacted to inquire about availability of data (ie, tables, statistical output) from any subcategory analyses that split gastroprotective agents into PPI and H2RAs.	Author responded that they did not conduct any analyses looking at PPIs and H2RAs separately, and all analyses were performed with gastroprotective agents grouped together.	4/8/2020 6/8/2020

Supplementary Table 2 (*Continued*)

Title	Corresponding Author	Date of Contact	Reason for Contact	Response	Date of Response
Difference Between the Upper and the Lower Gastrointestinal Bleeding in Patients Taking Nonvitamin K Oral Anticoagulants (2018)	Takatsugu Yamamoto ymmt@med.teikyo-u.ac.jp	4/8/2020, 5/5/2020	No age restrictions were explicitly stated in the publication and reviewers were also curious whether any additional variables were included for the analysis in Table 5 of the publication.	The author responded and clarified that no participants younger than age 18 were included in the study cohort and the analysis presented in Table 5 included all factors except HAS-BLED and CHADS as variables, with only PPI use and history of ulcers showing significance.	
Proton Pump Inhibitor Co-Therapy in Patients with Atrial Fibrillation Treated with Oral Anticoagulants and a Prior History of Upper Gastrointestinal Tract Bleeding (2021)	Eue-Keun Choi Choiek17@snu.ac.kr	4/15/2021, 7/19/2021	Author was initially contacted to determine whether all patients included in the study cohort were older age 18. Author was contacted again in July 2021 to request additional data on outcomes for upper GI bleeding for all oral anticoagulants from the sensitivity analysis reported in the supplemental materials.	Author responded and clarified that the study cohort only included adults older than 20 years. Author responded to clarify that results related to upper GI bleeding outcomes for all oral anticoagulants were unavailable.	4/15/2021, 7/20/2021
Risk of Upper and Lower Gastrointestinal Bleeding in Patients Taking NSAIDs, Antiplatelet Drugs, or Anticoagulants (2015)	Angel Lanas	7/21/2021	Author was contacted to request additional data related to that presented in supplementary Table 3 of the initial publication comparing patients using anticoagulants with PPI co-therapy to those without PPI co-therapy.	Author responded and supplied requested data.	Initial response received on7/22/2021, data shared with review team on 8/30/2021

GI = gastrointestinal; H2RA = histamine-2 receptor antagonist; PPI = proton pump inhibitor.

SUPPLEMENT 2 PRISMA 2020 CHECKLIST

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Line 3
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Line 62-84
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Line 95-115
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Line 127-128
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Line 128-140
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Line 122-126
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplement 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Line 141-145
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Line 148-152
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Prospero protocol, Table 1, Table 2
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Line 147-149
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Line 149-152
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Table 3, Figure 2
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Line 248-255
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Line 161-174
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Line 161-174
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Line 161-174
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Line 171-174
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Line 171-174
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA

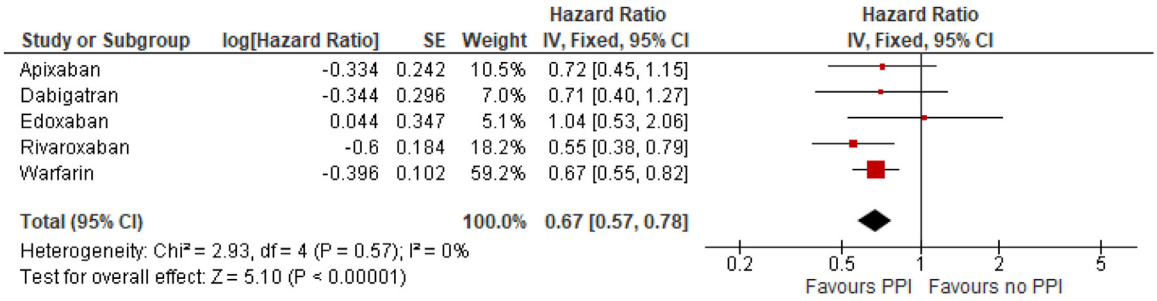
(*Continued*)

Section and Topic	Item #	Checklist item	Location where item is reported
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	NA
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table 1
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Table 1
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Table 3, Figure 2
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Line 73-75, line 248-255
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Line 253-255
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Line 258-289
	23b	Discuss any limitations of the evidence included in the review.	Line 290-297
	23c	Discuss any limitations of the review processes used.	Line 290-297
	23d	Discuss implications of the results for practice, policy, and future research.	Line 298-310
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Line 36-37, Line 119
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Line 119
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Line 23-24
Competing interests	26	Declare any competing interests of review authors.	Line 26-31
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Line 174

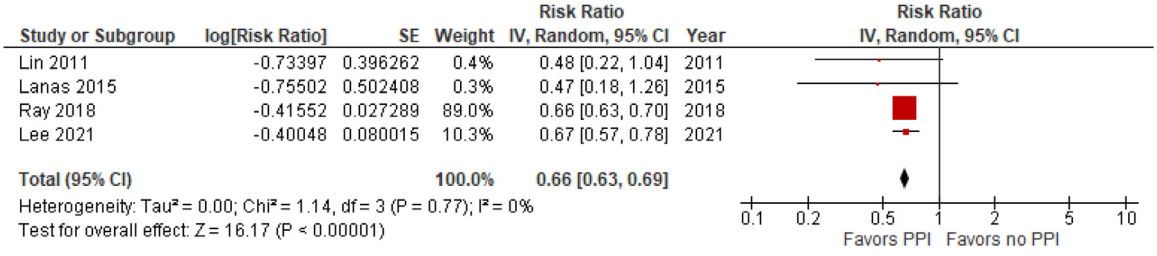
From: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

SUPPLEMENT 3 FOREST PLOT FOR EFFECT OF PPIS ON UPPER GASTROINTESTINAL BLEEDING FOR PATIENTS USING WARFARIN AND DOACS IN LEE ET AL, 2021



SUPPLEMENT 4 SENSITIVITY ANALYSIS OF THE ASSOCIATION BETWEEN PPI USE AND RISK OF UPPER GASTROINTESTINAL BLEEDING EXCLUDING THE TRIAL BY MOAYYEDI ET AL[18]



The study by Maruyama et al[25] was not included because the confidence interval could not be estimated. The study by Ray et al[24] from 2016 was not included because its study sample overlapped with Ray et al[23] from 2018.