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Protective effect of proton pump inhibitor against gastrointestinal bleeding in patients receiving oral anticoagulants: A systematic review and meta-analysis

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Abstract

Aim: The evidence of a protective effect of proton pump inhibitor (PPI) in oral anticoagulant (OAC) treated patients against gastrointestinal bleeding (GIB) is still lacking. We conducted a meta-analysis to estimate the risk of GIB in patients with OAC and PPI co-therapy.

Methods: A systematic search of PubMed, EMBASE, Cochrane, and Scopus databases was performed for studies reporting GIB risk in OAC and PPI co-therapy. Primary outcomes were total GIB and major GIB events. Pooled estimates of GIB risk were calculated by a random-effect meta-analysis and reported as odds ratios (OR) and 95% confidence interval (CI).

Results: A total of 10 studies and 1,970,931 patients were included. OAC and PPI co-therapy were associated with a lower odds of total and major GIB; OR (95% CI) was 0.67 (0.62-0.74) for total and 0.68 (0.63-0.75) for major GIB, respectively. No differences in the GIB of PPI co-therapy were observed between Asians and non-Asians (*p*-for-difference, total GIB=0.70, major GIB=0.75, respectively). For all kinds of OAC except for edoxaban, PPI cotreatment was related to a lower odds of GIB by 24–44%. The protective effect of PPI on total GIB was more significant in concurrent antiplatelets or non-steroidal anti-inflammatory drug users and those with high bleeding risks: patients with previous GIB history, HAS-BLED ≥3, or underlying gastrointestinal diseases.

Conclusion: In patients who receive OAC, PPI co-therapy is associated with a lower total and major GIB irrespective of ethnic group and OAC type, except for edoxaban. PPI co-therapy can be considered particularly in high GIB risk patients.

Keywords: gastrointestinal bleeding, oral anticoagulant, proton pump inhibitor

Introduction

Oral anticoagulants (OACs) are widely used to prevent or treat arterial/venous thromboembolism in high-risk patients such as those with atrial fibrillation (AF), venous thromboembolism (VTE), or other cardiovascular diseases (CVDs).[1, 2] The use of OAC is on the rise as the population ages, increasing the prevalence of CVD.[3-6] Until the availability of direct oral anticoagulants (DOACs), warfarin was the only option available to clinicians, but there are several concerns about bleeding side effects, including intracranial hemorrhage, potential interactions with various drugs and foods, and challenges in achieving optimal anticoagulation control. DOACs show superior safety, especially in terms of the risk of intracranial hemorrhage, and have shown comparable efficacy to warfarin in pivotal randomized clinical trials (RCTs).[7] In this regard, the prescription of DOACs has increased rapidly, and together with warfarin, all OACs are essential drugs to prevent thromboembolic events. [8-10]

Bleeding complications are unavoidable adverse events of anticoagulation therapy. Not only do they result in significant morbidity, but they also inevitably lead to the temporary termination of anticoagulant treatment, increasing the risk of thromboembolism during this time.[11-13] In particular, gastrointestinal bleeding (GIB) accounts for 40% of major anticoagulant-related hemorrhagic events, and DOACs are associated with a higher risk of major GIB than that of warfarin.[7, 14] Considering DOAC is mostly selected as a primary OAC except for preferential cases of warfarin with clinical indications, further efforts to reduce GIB following anticoagulant administration are essential to enhance the effectiveness and safety of anticoagulant therapy.

Proton-pump inhibitors (PPIs) are important medications for the prevention and treatment of upper GIB and several digestive disorders, such as ulcers and reflux esophagitis.[15, 16] When long-term treatment of non-steroidal anti-inflammatory drugs (NSAIDs) or antiplatelet (APT) drugs that increase the risk of GIB is required, the clinical benefit of PPI utilization for primary prevention is well-documented.[17, 18] In the case of anticoagulants, which are also linked to an elevated risk of GIB, a recent meta-analysis concluded that concurrent use of warfarin and PPI is associated with a lower risk of upper GIB by 44%.[19] However, the meta-analysis included a relatively small number of case-control or cohort studies, and data on various types of DOAC were limited. Following the publication of the meta-analysis,[19] an RCT and several nationwide observational studies evaluated whether PPI co-therapy is associated with a decreased risk of GIB or GI events.[20-23]

Therefore, we conducted a systematic review and meta-analysis to update the data on the investigation of the protective effect of PPI against GIB in patients with OAC, taking into account the numerous DOACs widely used nowadays.

Methods

This systematic review and meta-analysis were performed according to the Meta-analyses of Observational Studies in Epidemiology (MOOSE) (**Supplementary Table 1**) [24] and Preferred Reporting Items for Systematic review and Meta-Analysis protocols (PRISMA-P) (**Supplementary Table 2**) [25, 26] guidelines and recommendations. The study protocol was registered in the international prospective register of systematic reviews (PROSPERO, CRD 42022306876).

Searching strategy

A comprehensive literature search was performed on PubMed, EMBASE, the Cochrane Database of Systematic Reviews, and Scopus database from inception to December 2021. Relevant keywords—GIB, PPI, and OAC—in the titles and abstracts were used to retrieve all eligible articles. The complete search strategy is described in **Supplementary Table 3** and was applied on 3 January 2022.

Selection criteria

The included studies met the following criteria: (1) observational or RCT; (2) study subjects (entire or subgroup) who were prescribed OAC; (3) comparing concurrent PPI users to non-users; (4) reporting GIB risk as an adjusted estimate; and (5) published in English and available as full text. We excluded (1) studies evaluating the use of gastro-protective agents other than PPI, such as histamine-2 receptor antagonist (H2RA); (2) studies only providing unadjusted risk estimates to minimize the risk of bias introduced by confounding factors; and (3) unpublished studies or conference abstracts. All the records selected systematically and sequentially after the screening phase were independently evaluated for eligibility, followed by full-text reviews by two reviewers (HJA and SRL). Any disagreements were resolved by discussion with a third author (TMR).

Outcomes definition

The primary outcome was the incidence of total GIB, defined as per the included studies. We also investigated the risk of major GIB according to PPI use, incorporating studies providing outcomes that could be interpreted as major GIB: the occurrence of GIB (1) requiring hospitalization; (2) meeting the criteria of the International Society on Thrombosis and Haemostasis (ISTH) major bleeding;[27] and (3) when the investigators specified major events

according to their study definition.

Data extraction, quality assessment, and the certainty of the evidence

Two reviewers (HJA and SRL) independently extracted data from the included studies and assessed the risk of bias. The study population, baseline characteristics of the cohort (age, indications of prescribed OAC, nationality), details of individual OAC and PPI, the definition of outcomes used in each study, and adjusted estimates of outcome risk were collected. We only included adjusted values of patients prescribed OAC with or without PPI, which is provided as a total or subgroup of each study population.

For observational studies, the Newcastle-Ottawa Scale (NOS) [28] which is composed of three domains (patient selection, study group comparability, and outcome) with a maximum of nine points and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach [29] was used to evaluate the methodological quality and certainty of evidence. The included RCT was assessed using the Cochrane Collaboration's tool.[30] All observational studies were of high methodological quality with a NOS score of ≥ 8 points and certainty of evidence with low to moderate. Cochrane Collaboration's tool evaluated a low risk of bias for one included RCT (**Supplementary Figure 1 and Supplementary Table 4**).

Statistics

Pooled estimates of the included studies were evaluated using the DerSimonian–Laird random-effects method and reported as ORs and 95% CI. Statistical heterogeneity was assessed using Cochran's Q test. We measured the inconsistency index (I^2) to determine heterogeneity: low heterogeneity for $I^2 < 25\%$, moderate heterogeneity for $25\% < I^2 < 75\%$, and high heterogeneity for $I^2 > 75$.[31] Statistical significance was set at P value < 0.05. To evaluate the impact of the included studies on the pooled estimate of the primary outcomes, sensitivity analyses were

performed using a 'leave-one-out' method, in which individual studies were removed one at a time. Also, we evaluated the robustness of the results by performing another sensitivity analyses applying fixed-effects models.

Subgroup analyses were performed for the total GIB and major GIB according to the origin of GIB (upper GIB and others), ethnic group (Asian vs. non-Asian), specific OAC prescribed (warfarin, dabigatran, apixaban, rivaroxaban, and edoxaban), and risk of GIB (low vs. high). The high-GIB risk group was classified in two ways: a group with concurrent use of APT or non-steroidal anti-inflammatory drugs (NSAIDs)[20, 21, 32] or a group of subjects suggested to have high GI bleeding risk factors (previous GI bleeding history,[20, 33] HAS-BLED score ≥ 3,[21] investigator defined GI bleeding risk score ≥ 2,[23] and history of GI bleeding risk factors such as peptic ulcer, gastritis, abdominal pain, blood in stool/GI bleeding, or anemia[32]). Statistical differences in pooled estimates between subgroups were evaluated using meta-regression analyses.

Publication bias in studies reporting GIB was evaluated through visual inspection of funnel plots and statistical assessment using the Egger's test. Statistical analyses and graphical visualizations were performed using Stata (version 17; StataCorp LLC, College Station, TX, USA). *Identification and characteristics of included studies*

The flow of literature search and study selection is summarized in **Figure 1**. After the removal of duplicates, screening, and assessment of eligibility, a total of 1,394 research were retrieved (227 from PubMed, 626 from EMBASE, 157 from Cochrane, and 384 from Scopus). During the full-text review, ten studies were excluded, and the reasons for exclusion are described in **Supplementary Table 5**. The studies were excluded for inappropriate study design (patients, control, intervention, and outcome), which is not suitable for our theme, or unavailable adjusted

risk estimates, thereby containing a high probability of confounding bias. Finally, ten studies (nine observational studies and one RCT) were included in the analyses. Detailed characteristics of the included studies are summarized in **Table 1**. The major indications for OAC were AF, deep vein thrombosis, or other CVDs. Three studies were conducted in Asia, four in Europe, two in North America, and one in various geographical regions. Most studies defined the total GIB or major GIB by either International Classification of Diseases (ICD) codes and inpatient/outpatient utilization records or by incorporating clinical information of symptoms, laboratory data, endoscopic evaluation, and laboratory data.

Gastrointestinal bleeding in OAC and PPI co-therapy

Among the ten studies with 1,970,931 patients who received OAC, PPI co-therapy was associated with a lower odds of total GIB; the OR (95% CI) was 0.67 (0.62–0.74), with no heterogeneity among the included studies (**Figure 2A**). Similarly, OAC and PPI co-therapy was also associated with a lower odds of major GIB (OR, 0.68; 95% CI, 0.63–0.75). Heterogeneity was not observed (**Figure 2B**). On sensitivity analyses performed using the 'leave-one-out' method, we found no evidence of the significant influence of single studies on the pooled estimates (**Supplementary Figure 2**). Another sensitivity analysis applying fixed-effects model validated the consistent protective effect of OAC-PPI co-therapy in GIB with almost the same estimated ORs (**Supplementary Figure 3**).Visual inspection of the funnel plots and Egger's test revealed no apparent publication bias for total GIB and major GIB (Egger's test, $p = 0.931$ for total GIB and 0.224 for major GIB; **Supplementary Figure 4**).

Subgroup analyses

In subgroup analyses based on the origin of GIB, we observed that OAC and PPI co-therapy was associated with a lower odds of upper GIB, with no heterogeneity (OR, 0.67; 95% CI,

0.64–0.70; I^2 = 0.0%), whereas the risk of GIB originating from other sites, predominantly lower GIB, was not relevant to the concurrent use of PPI (OR, 1.10; 95% CI, 1.06–1.13; I^2 = 0.0%) (**Figure 3**). In the case of upper GIB, OAC and PPI co-therapy was also associated with a lower odds of major upper GIB (OR, 0.69; 95% CI, 0.63–0.75; I^2 = 0.0%) (**Supplementary Figure 5).**

In the stratified analyses by ethnic group, OAC and PPI co-therapy was related to both lower total and major GIB, irrespective of the geographic region where the study population was included; with *p*-for-difference of the total GIB of 0.695 and of the major GIB of 0.748 (**Figure 4A**). A separate analysis based on the OAC classification is summarized in **Figure 4B**. Overall, the concurrent use of OAC and PPI was associated with 24% to 44% lower odds for total and major GIB in patients with all kinds of OAC, except for edoxaban; dabigatran was observed to have the lowest pooled estimate for the total GIB (OR, 0.56; 95% CI, 0.45–0.69; I^2 = 23.8%), and rivaroxaban exhibited the lowest decreased odds for both the total GIB (OR 0.76, 95% CI 0.62–0.91) and major GIB (OR, 0.76; 95% CI, 0.62–0.92) in each of the four investigated studies. Furthermore, the subgroup analysis according to the presence of combined medications or risk factors of GIB confirmed that the lower odds of total GIB in the PPI co-therapy group were more accentuated in patients with any concurrent use of APT or NSAID and any indicators of high GI bleeding risk factors than in the others; OR (95% CI) was 0.62 (0.52–0.73) in the concurrent use of APT or NSAID vs. 0.77 (0.69–0.86) in the others, *p*-for-difference = 0.101 and 0.93 (0.79–1.09) in the low GI bleeding risk vs. 0.65 (0.61–0.70) in the high GI bleeding risk group, *p*-for-difference = 0.006 (**Figure 4C**).

Discussion

In this systematic review and meta-analysis, our principal findings were as follows: (1) OAC with PPI co-therapy was associated with a lower odds of total GIB by 33% and major GIB by 32% compared to that of OAC without PPI co-therapy; (2) the protective effect of PPI co-therapy was mainly driven by the lower odds in the upper GIB; (3) the primary findings were consistent, regardless of ethnicity and individual DOAC, except for edoxaban; and (4) the benefit of PPI co-therapy was more accentuated in patients with any concurrent use of APT or NSAID and those at high risk of GIB.

GIB is a common source of major bleeding in anticoagulated patients [14]. Even among patients taking a very low dose of DOAC (edoxaban, 15 mg once daily), the risk of major GIB is almost three-fold higher than those not anticoagulated.[34] Although DOACs showed a lower absolute risk of intracranial hemorrhage than warfarin, the risk of GIB was comparable to or even higher, depending on the particular type and dose of DOAC as compared to that of warfarin.[35-38] Given that GIB can lead to serious clinical consequences, including an increased risk of thromboembolism due to discontinuation of OAC and poor quality of life, it is essential to consider optimal GIB prevention strategies even in the DOAC era.[11-13, 39]

Despite the necessity, limited research has systematically approached the lower risk of GIB or GI events according to co-therapy with PPI and OAC. Only one RCT regarding the protective effect of PPI in patients with OAC was conducted; the COMPASS trial reported the combined administration of low-dose rivaroxaban (rivaroxaban, 2.5 mg twice daily with aspirin; or rivaroxaban, 5 mg twice daily alone) and pantoprazole significantly reduced upper gastrointestinal clinical events.[22] Although the study was a well-designed RCT and included a large number of patients, it is difficult to apply the results to all patients taking OACs, as it

only administered a very low dose of DOAC compared to the conventional dose used for the treatment or prevention of thromboembolism.[36]

Moreover, evidence for whether the combined administration of PPI is superior in the occurrence of upper GIB is still limited to a specific subtype of OAC (especially warfarin) or a subpopulation of OAC users who take another medication that can increase the GIB risk. A recent study systematically reviewing drug-drug interactions with warfarin reported a protective effect of PPI against warfarin-related GIB (OR 0.69).[40] The protective effect of PPI on the risk of composite upper gastrointestinal clinical events was well documented for patients with dual APT, through a large-scale RCT.[41] However, antiplatelet agents and OACs have different mechanisms for increasing the risk of GIB, making it challenging to extend the protective effect of concurrent APT-PPI use against GIB in patients taking OAC.[17, 18, 40, 42] Meanwhile, nationwide claims data-based research reflecting real-world DOAC utilization after its introduction reported that the clinical benefit of combined PPI administration could reduce GIB (mainly upper GIB) by 30%–60%.[21, 23, 32, 33, 43-47] In our study, observational studies and an RCT incorporating currently available all kinds of OAC were included in the analyses. We concluded concurrent use of OAC (warfarin or DOAC) and PPI is associated with a 0.67-fold lower odds of total GIB, which is a comparable estimate with the previous report for that of warfarin (OR 0.69).[40]

For the risk of GIB with DOAC compared to that with warfarin, there was a significant interaction between Asian and non-Asian patients.[48, 49] Among non-Asians, DOACs have been reported to have a higher risk of GIB than warfarin, but Asians show the opposite tendency.[49] In this analysis, the protective effect of PPI co-therapy against GIB was consistent, regardless of ethnicity. Although the relative risk for GIB was lower with DOAC than with warfarin among Asians, Asians appear to be more sensitive in relation to major

bleeding risk,[50] partly related to DOAC concentrations.[51] Considering that GIB risk is also correlated with plasma concentration of DOAC,[52] PPI co-therapy might be especially beneficial in Asian patients at high risk of bleeding. Indeed, one of the studies included in our analysis was the largest number of Asian participants that evaluated the preventive effect of PPI against GIB among patients with a history of upper GIB before OAC initiation, who could be classified as a high GIB risk group.[20]

In the subgroup analyses according to the type of OAC, PPI co-therapy was associated with a lower GIB, except for edoxaban. Looking into the detailed results of the individual studies, there is conflicting evidence on a specific OAC type and the benefit of PPI co-therapy, especially for DOACs.[21, 23, 43] Although there is no direct comparison between DOACs, the intrinsic risk of GIB varies among different DOACs, which may influence the relative benefit of PPI co-therapy with different DOACs.[53-55] We hypothesized that a specific OAC with a higher inherent risk of GIB would benefit more from PPI cotreatment. Furthermore, the varying bleeding risk profile of participants, the dose of DOAC in each study, and different cumulative data of individual DOAC utilization in the real world could result in a distinctive GIB risk according to PPI use.

In recent position papers and guidelines, patients receiving dual APT with OAC (so-called triple therapy) were recommended preemptive PPI therapy.[56-58] However, there is no confirmative recommendation for PPI co-therapy in patients receiving a single APT with OAC.[59, 60] Given the more accentuated protective effect of PPI co-therapy among patients receiving concurrent APT or NSAID with OAC, a sub-population might benefit more from PPI co-therapy against GIB. Nonetheless, further studies are required to determine the specific indications for preemptive PPI co-therapy in patients taking OAC.

Several clinical points need to be addressed for careful administration of OAC and PPI: a possible OAC-PPI drug-drug interaction and long-term safety issues related to PPI use. PPI may alter cytochrome P450 activity which mediates the metabolism of direct factor Xa inhibitors.[61-63] Some observational studies reported that there was no significant differences in trough/peak anti-Xa activity (i.e., rivaroxaban and apixaban) according to the PPI status [64, 65]. However, analysis of dabigatran-treated patients found that PPI recipients had significantly lower dabigatran trough and peak levels [66, 67]. Whether PPI affects on-treatment levels of anti-Xa activity remains unanswered due to limitations such as a small number of patient samples with a non-randomized study design and varying doses of factor Xa inhibitors [64]. Given potential pharmacologic interactions between OAC and PPI, the concurrent use might call for caution, especially in patients with high thromboembolic risks. Another concerns that should be taken into account are PPI-associated adverse effects, such as acute kidney injury [68] that could alter the concentration of OAC, an increased risk of GI infections [69, 70], and mortality [71, 72]. Therefore, clinicians should arouse vigilance of (long-term) PPI use with appropriate patient selection.

Limitations

Our results should be interpreted with caution for the following limitations. First, only one RCT [22] was included in the analyses, directing DOAC users with less common indications (stable CVD and peripheral artery disease) with unconventional doses. Instead, we selected observational studies with high methodological quality, acceptable certainty of the evidence, and adjusted relative risks. Second, limited data were available regarding the individual choice and dose of PPI and DOAC, which might introduce bias in the overall rate of GI events. Third,

the duration of and adherence to PPI could not be fully assessed. Fourth, the definition of high GIB risk in our study is arbitrary, although we classified GIB risk as low or high based on explanations of individual studies. Fifth, the non-significant protective effect of PPI on patients taking edoxaban could be related to the limited number of studies. Sixth, most of the data were collected from administrative and electronic medical records of observational studies, selection and information bias would be introduced with possible unmeasured confounders. Also, patients could be misclassified due to various treatment indications of OAC, PPI, and over-the-counter prescriptions. Lastly, some publications would be missed due to the limited number of primary database included. Given these limitations, further RCTs are required to identify and consolidate the preventive effect of PPI against GIB in patients receiving the conventional dose of OAC treatment for major indications.

Conclusion

The PPI co-therapy in patients who receive OAC is associated with a lower total GIB and major GIB. The protective effect of PPI was mainly related to upper GIB and was consistent among different ethnic groups and individual OAC types, with the exception of edoxaban. PPI co-therapy could be considered, especially in patients on concomitant APT and NSAID use or in patients with high GIB risk factors such as previous GIB history, HAS-BLED score ≥ 3, and underlying gastrointestinal diseases.

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Disclosure

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None

Author contributions

Conception and design: HJA, SRL, and EKC. Acquisition of data: HJA. Analysis and interpretation of data: HJA and TMR. Writing-original draft: HJA and SRL. Writing-review &

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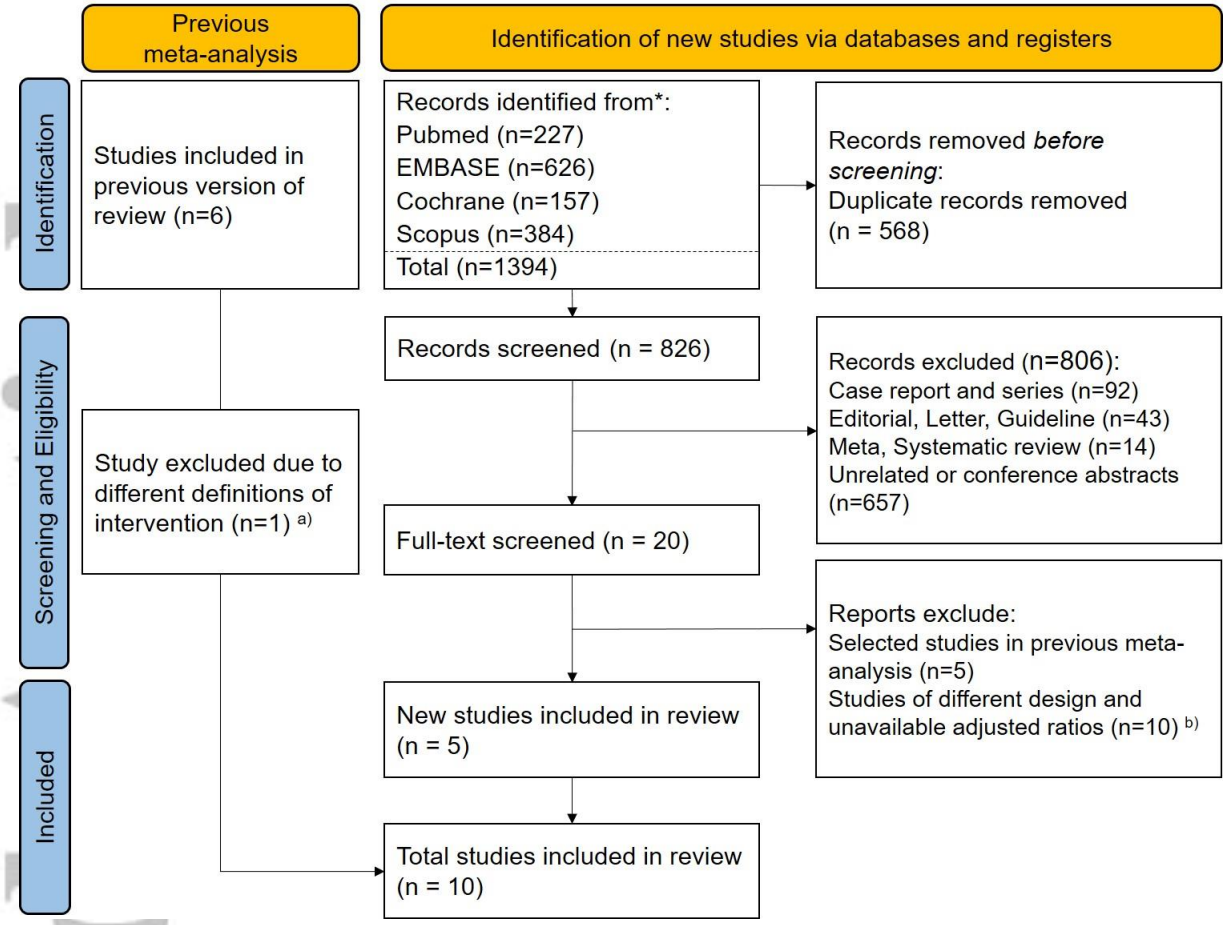

Figure 1. PRISMA flow-chart of the study

a) The study did not distinguish the individual gastroprotective agents, PPI and H2RA, to evaluate the association with gastrointestinal bleeding in OAC treated patients.

b) Details of excluded studies are described in Supplementary Table 2.

Abbreviations: PPI, proton-pump inhibitor; H2RA, histamine-2 receptor antagonist; OAC, oral anticoagulant

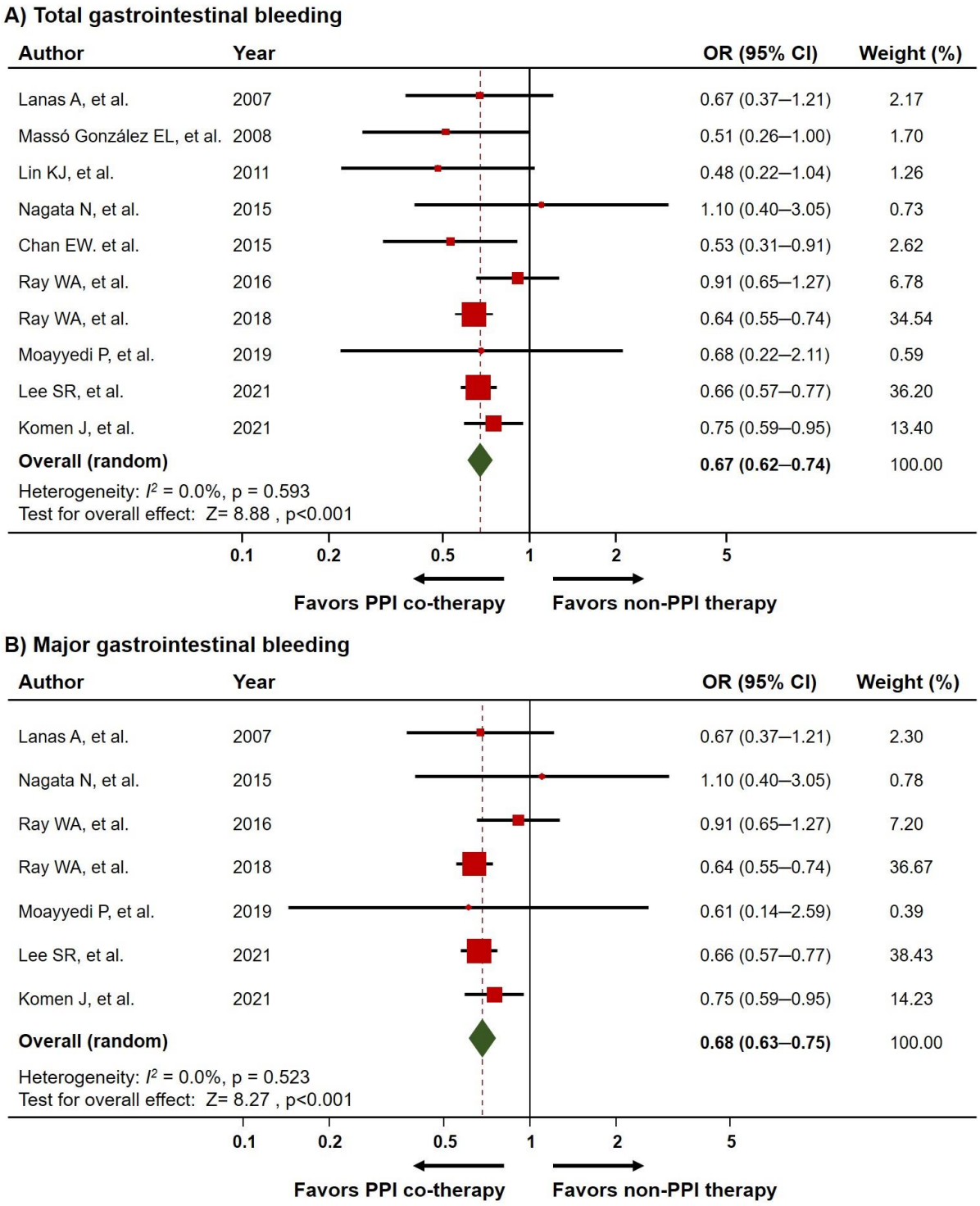

Figure 2. Proton pump inhibitor co-therapy in patients receiving oral anticoagulants and the risk of (A) total gastrointestinal bleeding and (B) major gastrointestinal bleeding

Abbreviations: OR, odds ratio; CI, confidence interval; PPI, proton pump inhibitor

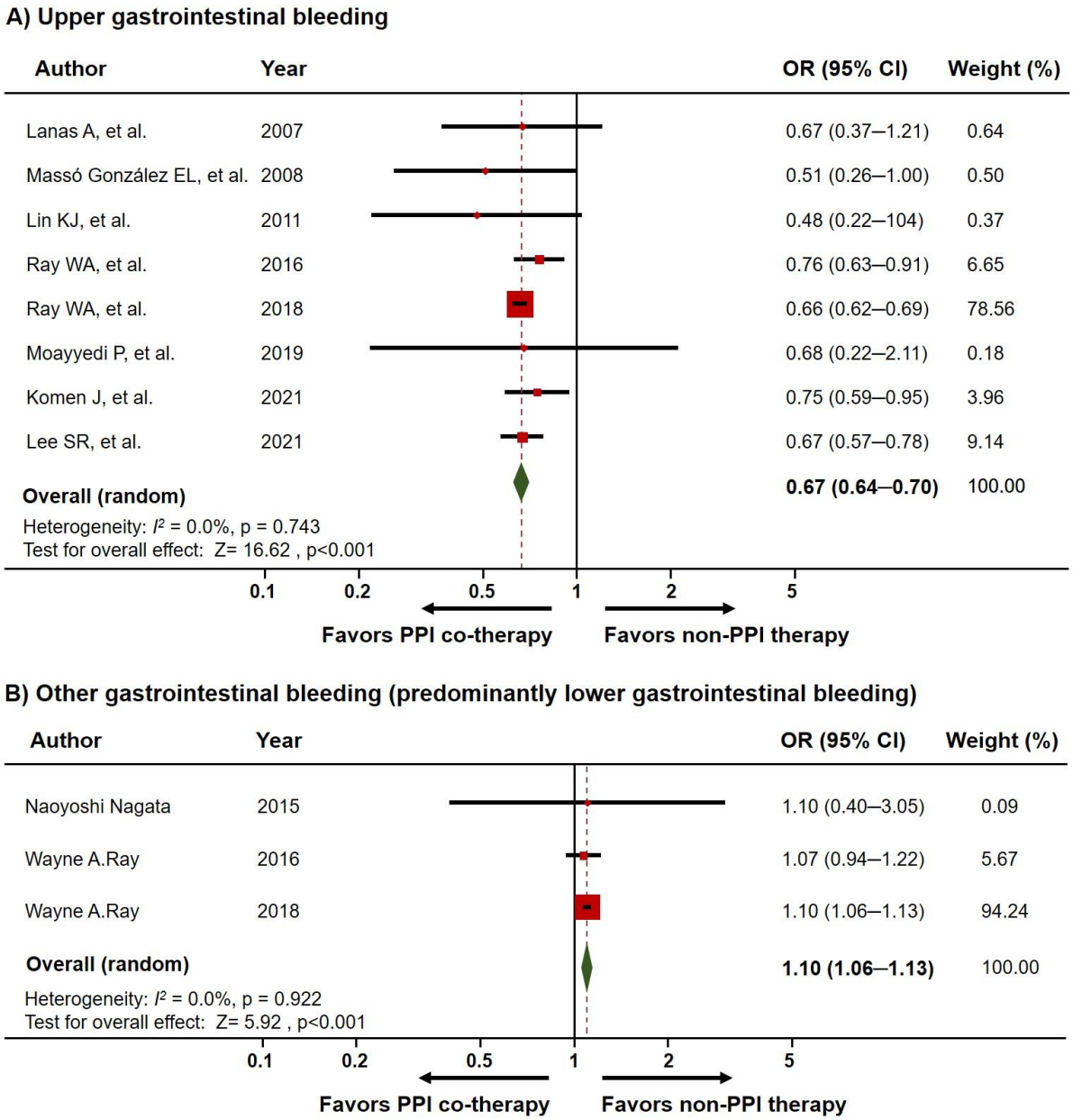

Figure 3. Proton pump inhibitor co-therapy in patients receiving oral anticoagulants and the risk of (A) upper gastrointestinal bleeding and (B) other gastrointestinal bleeding (predominantly lower gastrointestinal bleeding)

Abbreviations: OR, odds ratio; CI, confidence interval; PPI, proton pump inhibitor

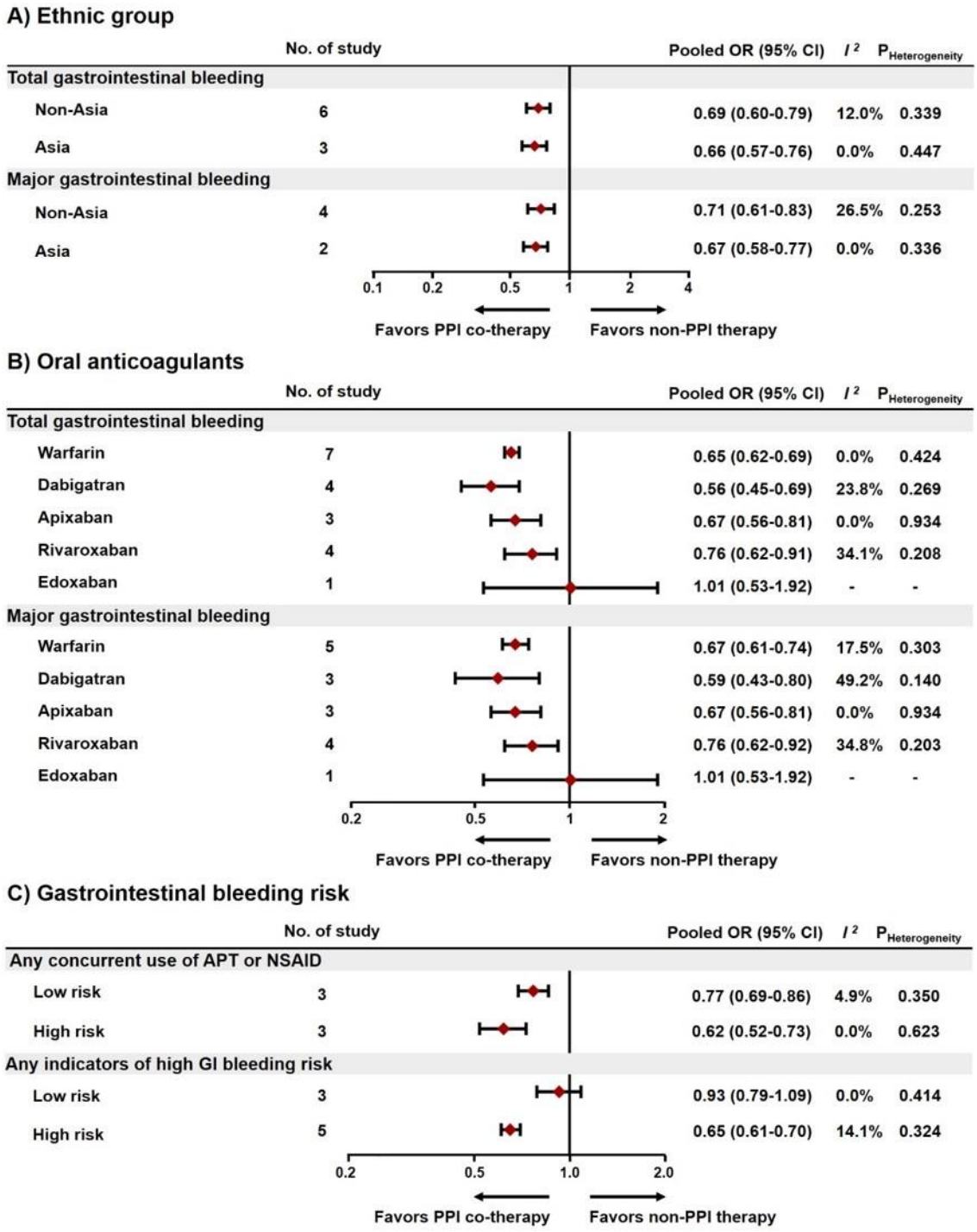

Figure 4. Proton pump inhibitor co-therapy in patients receiving oral anticoagulants and the risk of gastrointestinal bleeding according to (A) ethnic group, (B) individual oral anticoagulants, and (C) gastrointestinal bleeding risk

Abbreviations: OR, odds ratio; CI, confidence interval; PPI, proton pump inhibitor

* (C) summarizes the pooled estimates of the total gastrointestinal bleeding.

Table 1. List of studies included in the meta-analysis

Abbreviations: PPI, proton pump inhibitor; Yr, year; AF, atrial fibrillation; N/S, not specified; OAC, oral anticoagulant; GIB, gastrointestinal bleeding; UGIB, upper gastrointestinal bleeding; IQR, interquartile range; NOAC, non-vitamin K antagonist oral anticoagulant; PY, person-year; d, days; CVD, cardiovascular disease; PAD, peripheral artery disease; UGIE, upper gastrointestinal event; UGIS, upper gastrointestinal symptom; DVT, deep vein thrombosis; LGIB, lower gastrointestinal bleeding.

a) We included individuals who were prescribed OAC in the total or subgroup of each study population.

b) The outcome was also classified into MGIB in subgroup analyses.

c) Only the UGIB outcome of "Rivaroxaban 5 mg group" was included in the analyses. Subportions of UGIB were further categorized as MGIB.

Study	Year	Study type	Anticoagulants	Indication of anticoagulants	PPI	Patients	Primary Outcome	Patient number [a]	Age (Mean±SD, year)	Follow-up (year)	Nationality
Lee SR, et al. [20]	2021	Retrospective	Warfarin Rivaroxaban Dabigatran Apixaban Edoxaban	AF	N/S	OAC-naïve patients with AF and a history of upper GIB before initiating OAC treatment (2010-2018)	Major GIB [b] Major UGIB	42,048	PPI group: 71.8 ± 9.6 Non-PPI group: 71.5 ± 10.6	0.6 (IQR 0.2–1.7)	Republic of Korea
Komen J, et al. [21]	2021	Retrospective	Rivaroxaban Dabigatran Apixaban Edoxaban	AF	(Mostly) Omeprazole Pantoprazole	All patients dispensed a NOAC with a known history of AF (2011-2018)	UGIB as a registration of such a bleed in secondary inpatient care (Severe UGIB) [b]	35,031	PPI group: 75.3 ± 10.4 Non-PPI group: 74.3 ± 11.1		Sweden
				AF				110,225	PPI group: 75.8 ± 10.2 Non-PPI group: 74.5 ± 11.1	272570 PYs	Denmark
				AF				19,034	PPI group: 73.3 ± 10.1 Non-PPI group: 71.0 ± 11.0		Germany

Moayyedi P, et al. [22]	2019	Randomized trial	Rivaroxaban	Stable CVD, PAD	Pantoprazole	Patients with stable atherosclerotic vascular disease between 2013 and 2016	UGIE (composite of UGIB and UGIS) UGIB [c)] UGIS	17,598	Total: 67.6	3.0 ± 0.8	International
Ray WA, et al. [23]	2018	Retrospective	Warfarin Rivaroxaban Dabigatran Apixaban	Mostly AF	N/S	Patients ≥ 30 yr initiating OAC (2011-2015)	Hospitalizations for UGIB [b)]	1,643,123	Total: 76.4 ± 2.4	754389 PYs	United States
Ray WA, et al. [32]	2016	Retrospective	Warfarin	AF, DVT, Other CVD	Dexlansoprazole Esomeprazole Lansoprazole Omeprazole Pantoprazole Rabeprazole	Patients ≥ 30 yr whose first prescription for warfarin was filled during 1996-2013	Hospitalizations for UGIB potentially preventable by PPIs and for bleeding at other sites. [b)]	97,430	PPI group: 68.2 Non-PPI group: 67.7	75720 PYs	United States
Nagata N, et al. [44]	2015	Prospective	Warfarin	N/S	Omeprazole Esomeprazole Lansoprazole Rabeprazole	Patients ≥ 18 years old with outpatient onset of acute, continuous, or frequent LGIB and emergent hospitalization who underwent colonoscopy between 2010 and 2014	LGIB defined as bleeding from a source distal to the ileocecal valve found on endoscopy [b)]	235	N/S	N/S	Japan
Chan EW. et al. [45]	2015	Retrospective	Dabigatran	N/S	N/S	All patients who were newly prescribed dabigatran (2010-2013)	GIB	5,041	Total: 72.0 ± 10.9	215 ± 255 d	Hong Kong

Lin KJ, et al. [46]	2011	Retrospective	Warfarin	N/S	N/S	Patients of 40 – 84 yr (2000-2007) and who were enrolled permanently with a primary care practitioners	UGIB	749	N/S	N/S	United Kingdom
Massó González EL, et al. [33]	2008	Retrospective	Warfarin	N/S	N/S	Patients of 40–84 yrs with a diagnosis of UGIB (2000-2005)	Recurrence of UGIB	33	N/S	3.0	United Kingdom
Lanas A, et al. [47]	2007	Retrospective	Warfarin	N/S	N/S	Patients 20–85 yr	Hospitalization due to UGIB [b)]	384	N/S	N/S	Spain