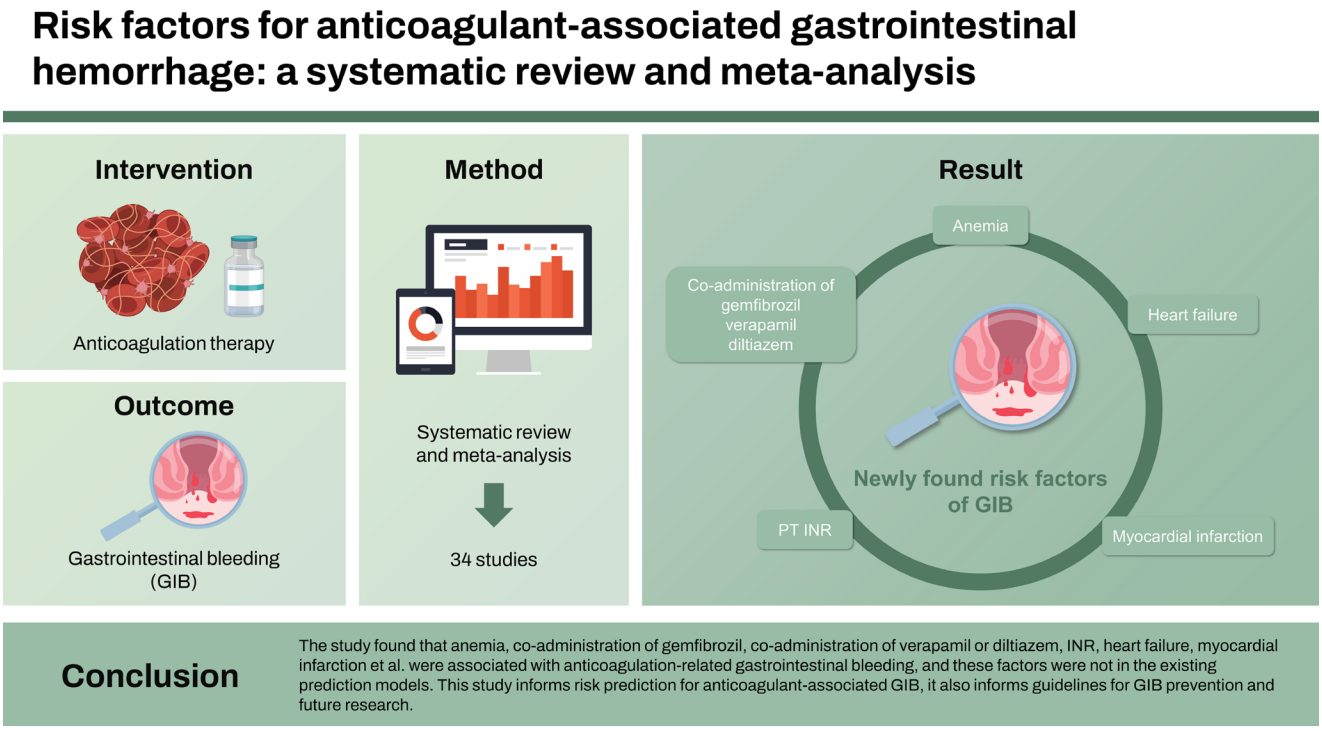
ORIGINAL ARTICLE

Korean J Intern Med 2024;39:77-85
https://doi.org/10.3904/kjim.2023.098

Risk factors for anticoagulant-associated gastrointestinal hemorrhage: a systematic review and meta-analysis

Fuxin Ma, Shuyi Wu, Shiqi Li, Zhiwei Zeng, and Jinhua Zhang

Department of Pharmacy, Fujian Maternity and Child Health Hospital College of Clinical Medicine for Obstetrics & Gynecology and Pediatrics, Fujian Medical University, Fuzhou, China



Background/Aims: There may be many predictors of anticoagulation-related gastrointestinal bleeding (GIB), but until now, systematic reviews and assessments of the certainty of the evidence have not been published. We conducted a systematic review to identify all risk factors for anticoagulant-associated GIB to inform risk prediction in the management of anticoagulation-related GIB.

Methods: A systematic review and meta-analysis were conducted to search PubMed, EMBASE, Web of Science, and Cochrane Library databases (from inception through January 21, 2022) using the following search terms: anticoagulants, heparin, warfarin, dabigatran, rivaroxaban, apixaban, DOACs, gastrointestinal hemorrhage, risk factors. According to inclusion and exclusion criteria, studies of risk factors for anticoagulation-related GIB were identified. Risk factors for anticoagulant-associated GIB were used as the outcome index of this review.

pISSN 1226-3303
eISSN 2005-6648
http://www.kjim.org

Results: We included 34 studies in our analysis. For anticoagulant-associated GIB, moderate-certainty evidence showed a probable association with older age, kidney disease, concomitant use of aspirin, concomitant use of the antiplatelet agent, heart failure, myocardial infarction, hematochezia, renal failure, coronary artery disease, helicobacter pylori infection, social risk factors, alcohol use, smoking, anemia, history of sleep apnea, chronic obstructive pulmonary disease, international normalized ratio (INR), obesity et al. Some of these factors are not included in current GIB risk prediction models. such as anemia, co-administration of gemfibrozil, co-administration of verapamil or diltiazem, INR, heart failure, myocardial infarction, etc.

Conclusions: The study found that anemia, co-administration of gemfibrozil, co-administration of verapamil or diltiazem, INR, heart failure, myocardial infarction et al. were associated with anticoagulation-related GIB, and these factors were not in the existing prediction models. This study informs risk prediction for anticoagulant-associated GIB, it also informs guidelines for GIB prevention and future research.

Keywords: Gastrointestinal hemorrhage; Risk factor; Predict; Meta-analysis

INTRODUCTION

Anticoagulants including heparin, low molecular heparin, fondaparinux, warfarin and novel oral anticoagulants (NOACs) are effective against acute or chronic thromboembolic complications [1-3]. Anticoagulants increase the risk of bleeding while exerting their antithrombotic effect. The annual rate of major bleeding in patients taking warfarin is reported to be as high as 8%, with gastrointestinal bleeding (GIB) being the most common [4]. The incidence of GIB during antithrombotic therapy with vitamin K antagonists (VKAs) ranges from 1.5% to 4.5% [5,6] and may result in a 10–15% short-term mortality rate [7-9]. And with millions of patients currently receiving anticoagulation therapy worldwide, it is necessary to accurately predict the risk of GIB associated with anticoagulants.

The risk assessment models (RAMs) for anticoagulation-related GIB consists of a combination of multiple predictors. Risk for specific endpoints can be obtained based on relevant predictors, thus providing recommendations for patient stratification [10].

Although these models can prevent GIB to some extent, most were developed using existing data rather than based on a systematic review of all potential risk factors [11]. The risk factors included in existing models are not comprehensive and may reduce the predictive power of the model. Therefore, this review conducts a systematic review and meta-analysis of risk factors for GIB that may inform anticoagulation therapy, future guideline recommendations, and the development of RAMs.

METHODS

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [12]. The protocol for this systematic review was prospectively registered with PROSPERO (CRD 42022340867).

Patient and public involvement

No patient involved.

Search strategy

Data were reviewed from four databases: PubMed, EMBASE, Web of Science, and the Cochrane Library. Studies in English published before January 21, 2022 were included. To ensure a comprehensive literature search, we also identified additional studies by searching the reference list of the literature.

Supplementary Material 1 provides detailed descriptions of the search strategy.

Study selection

Studies that met the following criteria were included: Use of anticoagulants (e.g., heparin, VKAs, NOACs); Comparison between the GIB group and the non-GIB group; The outcome index was risk factors or predictors.

Studies that met the following criteria were excluded: Patients with GIB treated with non-anticoagulant medications; Incomplete data (including data related to risk factors not obtained, a study in design or recruitment phase, permission

https://doi.org/10.3904/kjim.2023.098

to use data not obtained, the corresponding author contacted but not responded to).

Data extraction

For all identified studies, RAMs, and prognostic factor studies, the data extracted included the name of the first author, year of publication, time frame, population, and their demographics (e.g., sample size, number of centers, age, and sex), study design (e.g., cohort or case-control), outcomes and measures of association (e.g., odds ratio [OR] or risk ratio [RR] or hazard ratio [HR], 95% confidence interval [CI] and *p* value). GIB was defined as a reduction in the Hb level ≥ 2 g/dL, or transfusion of at least 2 units of blood.

Quality assessment

Risk of bias assessment

We assessed the risk of bias in the included studies by using the Prediction model Risk Of Bias Assessment Tool (PROBAST) for RAM studies and the Quality in Prognosis Studies (QUIPS) tool for prognostic factor studies [13-15].

Certainty of evidence assessment

We performed an assessment of the certainty of the evidence for each of the prognostic factors per outcome based on the GRADE approach. The approach considers the following domains: risk of bias, indirectness, inconsistency, imprecision, and publication bias. We developed evidence profiles and rated the overall certainty of evidence as high, moderate, and low or very low, depending on the grading of the individual domains [16].

Statistical analysis

We standardized each risk factor by log transformation and unifying the direction of the predictors. In studies that reported the measure of association as a HR or RR, we converted them to OR using the baseline risk reported in the studies [17,18]. We used the Review Manager 5.3 software for meta-analysis. The statistical indicators were OR and 95% CI. The chi-square test (χ^2) was used to test the heterogeneity of results. If $p \geq 0.1$ and $I^2 \leq 50\%$, the fixed-effect model was used for meta-analysis. The random-effect model was used when $p < 0.1$ and $I^2 > 50\%$.

RESULTS

The characteristics of included studies

Our search identified 13,042 citations, of which we included 114 studies for full-text assessment. Finally, 34 articles fulfilled the inclusion criteria and were included in this study. Figure 1 is a PRISMA flowchart. Supplementary Table 1 describes the characteristics of the included studies reporting on the outcomes of GIB. Thirty-three studies were risk factor studies [19-50,51]. One study was a prediction model development study [52]. Twnety-seven studies were cohorts [19-21,23-25,27-29,31,34,36-49,51,52]: 1 of which was prospective cohort [40], 26 of which were retrospective cohorts [19-21,23-25,27-29,31,34,36-39,41-49,51,52]. Two studies were case-control studies [26,32], 5 were randomized controlled trials (RCTs) [22,30,33,35,50]. Among the 34 studies, the populations of 23 studies were only stroke patients [19-22,25,27-37,39-41,43,44,47,50], the composition of the population indications in the remaining 11 studies included atrial fibrillation, venous thromboembolism, pulmonary embolism, deep vein embolism, and stroke [23,24,26,38,42,45,46,48,49]. Most patients were between 50 and 80 years old, and most were male.

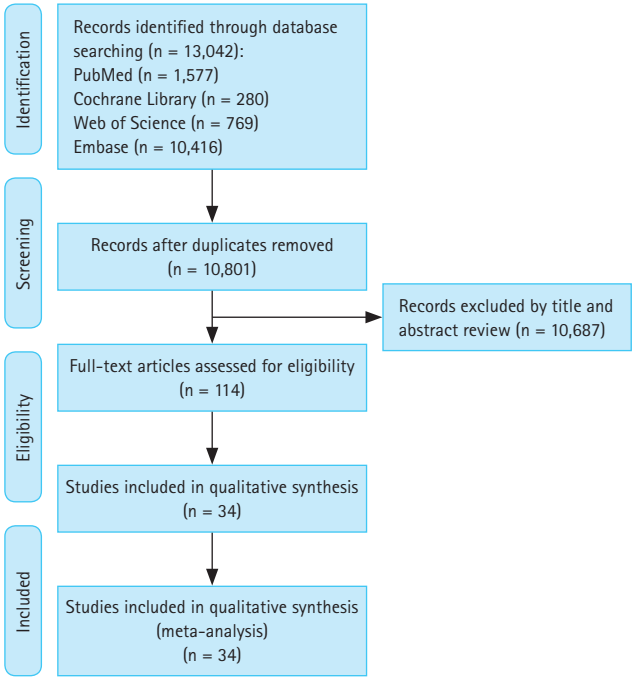


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis flowchart.

Risk of bias assessment

The risk of bias was serious across all identified studies, each presenting risk of bias in at least 1 domain or item (Supplementary Table 2). Among the 34 included studies, 26 were retrospective, which may have introduced classification bias [19-21,23-25,27-29,31,34,36-49,51,52]. We detected evidence of publication bias through visual assessment of asymmetry of the funnel plot for each pooled predictor in those that included at least 10 studies (Supplementary Table 2). Certainty in evidence was downgraded for imprecision, given that the CI suggests that there may be no association. 2 of the 33 risk factors studies did not clearly describe appropriate outcome measurement [37,38]. Supplementary Table 3 and 4 provide detailed judgments for each risk of bias domain criteria.

Analysis of risk factors of anticoagulant-associated gastrointestinal bleeding

Investigated were 48 candidate risk factors for GIB from 34 studies. Supplementary Table 2 provides the evidence profile for anticoagulant-associated GIB risk factors. Supplementary Figure (S1-S48) provides the forest plots of the meta-analysis of each of the risk factors.

Demographic factors

We found moderate-certainty evidence that there is probably an association between risk of GIB and older age (OR, 1.95; 95% CI, 1.36–2.79) [19,23,24,28,33,36,45,47], age growth (age per year increase; OR, 1.03; 95% CI, 1.01–1.06; age increase per five years; OR, 1.11; 95% CI, 1.06–1.17) [40,50,51], and obesity (weight > 120 kg; OR, 1.44; 95% CI, 1.01–2.05) [25]. We found low-certainty evidence that there may be little to no association between risk of GIB and sex (male vs. female; OR, 0.95; 95% CI, 0.72–1.26) [20,26,28,36,39,40,47].

Functional factors

There was moderate-certainty evidence for a probable association between the risk of GIB and any international normalized ratio (INR) (OR, 2.43; 95% CI, 1.30–4.53) [24,41]. We found very-low-certainty evidence that there may be little to no association between the risk of GIB and Has-Bled-Score (≥ 3; OR, 1.20; 95% CI, 0.06–22.63) [19,41].

Medical illness and patient history factors

We identified moderate-certainty evidence for an association between the risk of GIB and kidney disease (OR, 1.69; 95% CI, 1.24–2.31) [19,36,45,46,52], cirrhosis (OR, 6.24; 95% CI, 2.63–14.83) [24,52], liver failure (OR, 7.01; 95% CI, 4.78–10.27) [26], and heart failure (HF) (OR, 1.30; 95% CI, 1.14–1.49) [28,36,46]. Subgroup analysis showed that congestive HF (OR, 1.29; 95% CI, 1.06–1.57) [28,36] and chronic HF (OR, 1.31; 95% CI, 1.09–1.58) [46] were statistically significant. We found moderate-certainty evidence that there is probably an association between the risk of GIB and history of bleeding (OR, 3.26; 95% CI, 1.86–5.73) [28], myocardial infarction (OR, 2.23; 95% CI, 1.12–4.43) [28], renal failure (OR, 3.18; 95% CI, 1.44–6.99) [34,47], coronary artery disease (OR, 1.36; 95% CI, 1.10–1.69) [36], *Helicobacter pylori* infection (OR, 4.75; 95% CI, 1.93–11.68) [36], anemia (OR, 1.48; 95% CI, 1.10–1.98) [36,50], history of sleep apnea (OR, 1.60; 95% CI, 1.22–2.10) [50], psychiatric illness, defined as schizophrenia, affective psychosis, paranoia, or other nonorganic psychosis (OR, 1.20; 95% CI, 1.03–1.39) [46], venous thromboembolism including deep vein thrombosis (OR, 1.21; 95% CI, 1.02–1.44) [36,46].

Furthermore, we identified low-certainty evidence that there may be little to no association between the risk of GIB and peripheral vascular disease including peripheral artery disease (OR, 2.33; 95% CI, 0.66–8.20) [28,36], mechanical valve implantation (OR, 1.97; 95% CI, 0.43–9.07) [45], liver disease (OR, 1.31; 95% CI, 0.99–1.74) [46], diabetes (OR, 1.08; 95% CI, 0.96–1.21) [36,46], and chronic obstructive pulmonary disease (OR, 2.01; 95% CI, 0.69–5.83) [50,52].

We found very-low-certainty evidence that there may be an association between the risk of GIB and history of peptic ulcer/GIB (OR, 5.26; 95% CI, 2.76–10.05) [19,23,24,28,30,39,41,45,47,48,50-52].

Laboratory and physical examination factors

There was moderate certainty evidence of a probable association between the risk of GIB and creatinine level (per 1 mg/dL increase; OR, 1.38; 95% CI, 1.09–1.74) [40] and diastolic BP (decrease to < 80 mmHg; OR, 1.10; 95% CI, 1.05–1.16) [50]. We identified low-certainty evidence that there may be an association between the risk of GIB and creatinine clearance (< 60 mL/min; OR, 1.06; 95% CI, 1.01–1.12) [50].

Medication factors

We found moderate-certainty evidence that there is probably an association between the risk of GIB and concomitant use of aspirin (OR, 2.07; 95% CI, 1.17–3.66)

https://doi.org/10.3904/kjim.2023.098

[22,23,26,27,47] and concomitant with non-steroidal anti-inflammatory drugs (NSAIDs) (OR, 2.37; 95% CI, 1.61–3.50) [26,39,43,47]. Subgroup analysis showed that combination of paracetamol (OR, 1.47; 95% CI, 1.35–1.60) [26] and combination of COX-2 inhibitor (OR, 1.97; 95% CI, 1.59–2.40) [26] were statistically significant. We found moderate-certainty evidence that there is probably an association between the risk of GIB and antiplatelet therapy (OR, 1.45; 95% CI, 1.11–1.90) [19,27,36,39,42,47,48,50,51], concomitant use of dronedarone (OR, 1.29; 95% CI, 1.04–1.62) [29], concomitant use of CYP3A4 or P-glycoprotein inhibitors (OR, 1.47; 95% CI, 1.15–1.88) [31], combination of digoxin (OR, 1.50; 95% CI, 1.19–1.88) [36], combination of gemfibrozil (OR, 2.29; 95% CI, 1.61–3.25) [38], combination of verapamil or diltiazem (OR, 2.33; 95% CI, 1.82–2.98) [44], and long-term acetylsalicylic acid (ASA) use at screening (OR, 1.47; 95% CI, 1.26–1.72) [50].

However, low-quality evidence showed that there may be little to no association between the risk of GIB and combination of clopidogrel (OR, 2.37; 95% CI, 1–5.65) [19], combination of corticosteroid (OR, 2.14; 95% CI, 0.98–4.72) [19,41], combination of thienopyridines (OR, 2.37; 95% CI, 0.75–7.44) [47].

We identified low-certainty evidence that there may be an association between the risk of GIB and concomitant use of oral glucocorticoid (OR, 1.83; 95% CI, 1.30–2.59) [32].

Other factors

There was moderate-certainty evidence of a probable association between risk of GIB and social risk factors, defined as lack of housing, inadequate housing, inadequate material resources, persons living alone, no other household member able to render care, or non-compliance with medical treatment (OR, 1.29; 95% CI, 1.12–1.48) [46]. We also identified moderate-certainty evidence that there is probably an association between risk of GIB and alcohol use (OR, 3.46; 95% CI, 2.30–5.19) [26,36] and smoking (OR, 1.26; 95% CI, 1.18–1.35) [26,50], anticoagulant treatment time (≤ 100 d; OR, 4.94; 95% CI, 2.66–9.17) [47-49], and substance abuse, defined as alcohol dependence, drug dependence, or non-dependent abuse, excluding tobacco use disorder (OR, 1.41; 95% CI, 1.07–1.87) [46].

We identified low-certainty evidence that there may be an association between the risk of GIB and dabigatran 150 mg twice daily (OR, 1.53; 95% CI, 1.39–1.69) [21,35].

DISCUSSION

We evaluated 48 risk factors for anticoagulant-associated GIB. We also identified several statistically significant predictors, such as social risk factors, alcohol consumption, smoking, co-administration of aspirin, co-administration of NSAIDs, renal disease, cirrhosis, liver failure, INR, older age, age growth, obesity (weight > 120 kg) et al., which supported by moderate certainty of the evidence.

Therefore, in addition to anticoagulation therapy, which can affect GIB, other risk factors should also be noted. We can intervene in undesirable behaviors such as drinking and smoking through behavior-based education, minimize the combination of drugs such as aspirin, NSAIDs, antiplatelet drugs, verapamil or diltiazem, and anticoagulants, and actively treat kidney disease, cirrhosis, liver failure, and HF to reduce the occurrence of GIB.

Our study identified candidate risk factors for GIB, such as age, smoking, alcohol consumption, the combination of aspirin, the combination of NSAID, antiplatelet therapy, diabetes, cirrhosis, peripheral vascular disease, renal disease, etc. These risk factors have been considered in the analysis of some developed and widely used RAMs in daily practice, such as New Score, RIETE Score, Cuschieriet al. Score, and de Groot et al. Score [52-55]. However, some factors that we identified as having a probable association with GIB, based on our meta-analysis results, were not included or considered in the development of most of the RAMs, such as history of sleep apnea, co-administration of CYP3A4 or P-glycoprotein antagonists, co-administration of digoxin, co-administration of gemfibrozil, co-administration of verapamil or diltiazem, INR, HF, myocardial infarction, long-term ASA use at screening. This deserves our special concern. In addition, we found that antiplatelet theapy was associated with GIB risk. This observation was opposite to Nawarawong et al.'s study [42]. Antiplatelet theapy showed no association with GIB risk in their study. We believe that such reverse causation, given the study design, may be plausible. However, given the small sample size, the finding warrants further investigations in primary studies.

We found that dabigatran dose 150 mg is associated with GIB, which is an interesting point. Of note, in a previous meta-analysis by our research team, a higher risk of GIB with dabigatran than with warfarin had been demonstrated [56]. This result should draw clinicians' attention to the possible benefit of monitoring patients' risk of GIB after administra-

tion of dabigatran 150 mg.

In our meta-analyses, proton pump inhibitor (PPI) use decreased the risk of GIB by half (HR, 0.5), which closely reflects the findings of Ray et al. [57], who reported that PPI use was associated with a substantial reduction in the risk of warfarin-related upper GIB (HR, 0.76). Although PPI therapy was not included in either the HAS-BLED score, ATRIA score or ORBIT score, PPI use is an important means of preventing GIB in the long term.

We also did subgroup analyses to explore the sources of heterogeneity in history of peptic ulcer/GIB (I^2 = 97%). Subgroup analysis by population, design type, sample size, and study quality showed that retrospective cohort studies were the main cause of heterogeneity, with little heterogeneity in the RCT group.

The greatest advantage of our study is the comprehensiveness of the study results, which may have some clinical significance in preventing the occurrence of anticoagulant-associated GIB.

The study also has some limitations. Since most of the studies included in this review were retrospective, classification and recall bias may lead to potential limitations. In addition, potential limitations of the included studies related to the inconsistency and variability across eligibility criteria in the original studies and variability in study design, study type, sample size, and definitions of the risk factors. For example, in our study, 22 studies included only atrial fibrillation indications, while others 11 studies included venous thromboembolism, pulmonary embolism, deep vein embolism, and stroke in addition to atrial fibrillation. In anticoagulation, different populations will influence the choice of drug as well as the dose and duration of drug therapy and significantly affect the outcome of GIB in each study. Study effect OR value is closely related to outcomes, and we found significant differences in OR value for the same variables across studies. Of note, the process of meta-analysis may cause variables that were originally risk factors to become nonsignificant, or even to become protective factors.

Research may be needed to reevaluate existing RAMs, as the developers of the models may not have been able to use the variables we identified, given the limitations in the existing databases. However, full development or improvement of a RAM that supports clinical practice requires further investigation of all the prognostic factors we identified in our study. Therefore, more rigorous and large-scale studies are needed to confirm our findings, and further analysis is necessary to provide a more reliable basis for clinical work.

KEY MESSAGE

1. In this systematic review, we identified all reported risk factors for anticoagulation-associated GIB (e.g., alcohol consumption, smoking, co-administration of aspirin).
2. Some risk factors not included in current GIB risk prediction models (e.g., anemia, history of sleep apnea, co-administration of digoxin).
3. Our findings will help inform experts in developing population-based guidelines and accurate, user-friendly RAMs to guide individual patient management better.

REFERENCES

1. Hirsh J, Guyatt G, Albers GW, Harrington R, Schünemann HJ. Antithrombotic and thrombolytic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133(6 Suppl):110S-112S.
2. Abraham NS, Noseworthy PA, Yao X, Sangaralingham LR, Shah ND. Gastrointestinal safety of direct oral anticoagulants: a large population-based study. Gastroenterology 2017;152:1014-1022.e1.
3. Jingke W, Zhiyi L, Guiqing L, et al. [Current status and progress of oral combination antithrombotic drug therapy]. Int J Cardiovasc Dis 2017;44:132-135. Chinese.
4. Choudari CP, Palmer KR. Acute gastrointestinal haemorrhage in patients treated with anticoagulant drugs. Gut 1995;36:483-484.
5. Rothberg MB, Celestin C, Fiore LD, Lawler E, Cook JR. Warfarin plus aspirin after myocardial infarction or the acute coronary syndrome: meta-analysis with estimates of risk and benefit. Ann Intern Med 2005;143:241-250.
6. Sørensen R, Hansen ML, Abildstrom SZ, et al. Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data. Lancet 2009;374:1967-1974.
7. van Leerdam ME, Vreeburg EM, Rauws EA, et al. Acute upper GI bleeding: did anything change? Time trend analysis of incidence and outcome of acute upper GI bleeding between

https://doi.org/10.3904/kjim.2023.098

1993/1994 and 2000. Am J Gastroenterol 2003;98:1494-1499.
8. Hearnshaw SA, Logan RF, Lowe D, Travis SP, Murphy MF, Palmer KR. Acute upper gastrointestinal bleeding in the UK: patient characteristics, diagnoses and outcomes in the 2007 UK audit. Gut 2011;60:1327-1335.
9. Rosenstock SJ, Møller MH, Larsson H, et al. Improving quality of care in peptic ulcer bleeding: nationwide cohort study of 13,498 consecutive patients in the Danish Clinical Register of Emergency Surgery. Am J Gastroenterol 2013;108:1449-1457.
10. Darzi AJ, Karam SG, Charide R, et al. Prognostic factors for VTE and bleeding in hospitalized medical patients: a systematic review and meta-analysis. Blood 2020;135:1788-1810.
11. Riley RD, Moons KGM, Snell KIE, et al. A guide to systematic review and meta-analysis of prognostic factor studies. BMJ 2019;364:k4597.
12. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700.
13. Tang SW, Zhang Y, Tao BL, Yang ZR, Sun F, Zhan SY. [Risk of bias assessment: (7) assessing bias in studies of prognostic factors]. Zhonghua Liu Xing Bing Xue Za Zhi 2018;39:1003-1008. Chinese.
14. Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. Ann Intern Med 2013;158:280-286.
15. Reeves BC, Deeks JJ, Higgins JPT, Wells GA. Including non-randomized studies. In: Higgins JPT, Thomas J, Chandler J, et al., eds. Cochrane Handbook for Systematic Reviews of Interventions. Cochrane, 2008:391.
16. Iorio A, Spencer FA, Falavigna M, et al. Use of GRADE for assessment of evidence about prognosis: rating confidence in estimates of event rates in broad categories of patients. BMJ 2015;350:h870.
17. Grant RL. Converting an odds ratio to a range of plausible relative risks for better communication of research findings. BMJ 2014;348:f7450.
18. Wang Z. Converting odds ratio to relative risk in cohort studies with partial data information. J Stat Softw 2013;55:1-11.
19. Agudo-Fernández S, Castaño Milla C, González Blanco A, Olmos Jerez JA, Calvo Morillas I, Sancho Del Val L. RHEDAR study: determination of the risk of gastrointestinal hemorrhage in treatment with dabigatran, acenocoumarol and rivaroxaban. J Gastroenterol Hepatol 2021;36:2794-2802.
20. Fanning L, Wong ICK, Li X, et al. Gastrointestinal bleeding risk with rivaroxaban vs aspirin in atrial fibrillation: a multinational study. Pharmacoepidemiol Drug Saf 2020;29:1550-1561.
21. Graham DJ, Reichman ME, Wernecke M, et al. Cardiovascular, bleeding, and mortality risks in elderly Medicare patients treated with dabigatran or warfarin for nonvalvular atrial fibrillation. Circulation 2015;131:157-164.
22. Aisenberg J, Chatterjee-Murphy P, Friedman Flack K, et al. Gastrointestinal bleeding with edoxaban versus warfarin: results from the ENGAGE AF-TIMI 48 trial (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction). Circ Cardiovasc Qual Outcomes 2018;11:e003998.
23. Chan EW, Lau WC, Leung WK, et al. Prevention of dabigatran-related gastrointestinal bleeding with gastroprotective agents: a population-based study. Gastroenterology 2015;149:586-595.e3.
24. Chen WC, Chen YH, Hsu PI, et al. Gastrointestinal hemorrhage in warfarin anticoagulated patients: incidence, risk factor, management, and outcome. Biomed Res Int 2014;2014:463767.
25. Coates J, Bitton E, Hendje A, et al. Clinical outcomes of dabigatran use in patients with non-valvular atrial fibrillation and weight >120 kg. Thromb Res 2021;208:176-180.
26. Delaney JA, Opatrny L, Brophy JM, Suissa S. Drug drug interactions between antithrombotic medications and the risk of gastrointestinal bleeding. CMAJ 2007;177:347-351.
27. Douros A, Renoux C, Yin H, Filion KB, Suissa S, Azoulay L. Concomitant use of direct oral anticoagulants with antiplatelet agents and the risk of major bleeding in patients with nonvalvular atrial fibrillation. Am J Med 2019;132:191-199.e12.
28. Ferroni E, Denas G, Gennaro N, Fedeli U, Pengo V. Gender related differences in gastrointestinal bleeding with oral anticoagulation in atrial fibrillation. J Cardiovasc Pharmacol Ther 2022;27:10742484211054609.
29. Gandhi SK, Reiffel JA, Boiron R, Wieloch M. Risk of major bleeding in patients with atrial fibrillation taking dronedarone in combination with a direct acting oral anticoagulant (from a U.S. Claims Database). Am J Cardiol 2021;159:79-86.
30. Garcia DA, Fisher DA, Mulder H, et al. Gastrointestinal bleeding in patients with atrial fibrillation treated with Apixaban or warfarin: insights from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial. Am Heart J 2020;221:1-8.
31. Holm J, Mannheimer B, Malmström RE, Eliasson E, Lindh JD. Bleeding and thromboembolism due to drug-drug interac-

tions with non-vitamin K antagonist oral anticoagulants-a Swedish, register-based cohort study in atrial fibrillation outpatients. Eur J Clin Pharmacol 2021;77:409-419.
32. Holt A, Blanche P, Zareini B, et al. Gastrointestinal bleeding risk following concomitant treatment with oral glucocorticoids in patients on non-vitamin K oral anticoagulants. Heart 2022;108:626-632.
33. Kato ET, Giugliano RP, Ruff CT, et al. Efficacy and safety of edoxaban in elderly patients with atrial fibrillation in the ENGAGE AF-TIMI 48 trial. J Am Heart Assoc 2016;5:e003432.
34. Kalil RS, Kaboli PJ, Liu X, Vaughan-Sarrazin M. Association between renal function and bleeding risk for dabigatran after switching from warfarin. Am J Nephrol 2016;44:11-18.
35. Kolb JM, Flack KF, Chatterjee-Murphy P, et al. Locations and mucosal lesions responsible for major gastrointestinal bleeding in patients on warfarin or dabigatran. Dig Dis Sci 2018;63:1878-1889.
36. Lauffenburger JC, Rhoney DH, Farley JF, Gehi AK, Fang G. Predictors of gastrointestinal bleeding among patients with atrial fibrillation after initiating dabigatran therapy. Pharmacotherapy 2015;35:560-568.
37. Lee SR, Choi EK, Jung JH, et al. Body mass index and clinical outcomes in asian patients with atrial fibrillation receiving oral anticoagulation. Stroke 2021;52:521-530.
38. Leonard CE, Brensinger CM, Bilker WB, et al. Gastrointestinal bleeding and intracranial hemorrhage in concomitant users of warfarin and antihyperlipidemics. Int J Cardiol 2017;228:761-770.
39. Maruyama K, Yamamoto T, Aoyagi H, et al. Difference between the upper and the lower gastrointestinal bleeding in patients taking nonvitamin K oral anticoagulants. Biomed Res Int 2018;2018:7123607.
40. Murata N, Okumura Y, Nagashima K, et al.; SAKURA AF Registry Investigators. Gastrointestinal bleeding from oral anticoagulant therapy among Japanese patients with atrial fibrillation identified from the SAKURA atrial fibrillation registry. Circ J 2020;84:1475-1482.
41. Nantsupawat T, Soontrapa S, Nantsupawat N, et al. Risk factors and prevention of dabigatran-related gastrointestinal bleeding in patients with atrial fibrillation. J Arrhythm 2017;34:30-35.
42. Nawarawong N, Pongprasobchai S, Tanwandee T. Acute gastrointestinal bleeding in anticoagulated patients: prevalence and predictors of significant endoscopic lesions and change of the management. J Med Assoc Thai 2018;101:135.
43. Olsen AS, McGettigan P, Gerds TA, et al. Risk of gastrointestinal bleeding associated with oral anticoagulation and non-steroidal anti-inflammatory drugs in patients with atrial fibrillation: a nationwide study. Eur Heart J Cardiovasc Pharmacother 2020;6:292-300.
44. Pham P, Schmidt S, Lesko L, Lip GYH, Brown JD. Association of oral anticoagulants and verapamil or diltiazem with adverse bleeding events in patients with nonvalvular atrial fibrillation and normal kidney function. JAMA Netw Open 2020;3:e203593.
45. Pourafkari L, Ghaffari S, Zamani N, et al. Upper gastrointestinal bleeding in the setting of excessive warfarin anticoagulation: risk factors, and clinical outcome. Cor et Vasa 2017;59:e128-e133.
46. Schauer DP, Moomaw CJ, Wess M, Webb T, Eckman MH. Psychosocial risk factors for adverse outcomes in patients with nonvalvular atrial fibrillation receiving warfarin. J Gen Intern Med 2005;20:1114-1119.
47. Sherid M, Sifuentes H, Sulaiman S, et al. Gastrointestinal bleeding with dabigatran, a comparative study with warfarin: a multicenter experience. Korean J Gastroenterol 2015;65:205-214.
48. Sherid M, Sifuentes H, Sulaiman S, et al. Risk of gastrointestinal bleeding with dabigatran: a head-to-head comparative study with rivaroxaban. Digestion 2014;90:137-146.
49. Sherid M, Sulaiman S, Samo S, et al. Risk of gastrointestinal bleeding with rivaroxaban: a comparative study with warfarin. Gastroenterol Res Pract 2016;2016:9589036.
50. Sherwood MW, Nessel CC, Hellkamp AS, et al. Gastrointestinal bleeding in patients with atrial fibrillation treated with rivaroxaban or warfarin: ROCKET AF trial. J Am Coll Cardiol 2015;66:2271-2281.
51. Youn SH, Lim H, Ju Y, et al. Effect of gastroprotective agents on upper gastrointestinal bleeding in patients receiving direct oral anticoagulants. Scand J Gastroenterol 2018;53:1490-1495.
52. Shimomura A, Nagata N, Shimbo T, et al. New predictive model for acute gastrointestinal bleeding in patients taking oral anticoagulants: a cohort study. J Gastroenterol Hepatol 2018;33:164-171.
53. López-Jiménez L, Montero M, González-Fajardo JA, et al.; RIETE Investigators. Venous thromboembolism in very elderly patients: findings from a prospective registry (RIETE). Haematologica 2006;91:1046-1051.
54. Cuschieri JR, Drawz P, Falck-Ytter Y, Wong RC. Risk factors for acute gastrointestinal bleeding following myocardial infarction in veteran patients who are prescribed clopidogrel. J Dig Dis 2014;15:195-201.

https://doi.org/10.3904/kjim.2023.098

55. de Groot NL, Hagenaars MP, Smeets HM, Steyerberg EW, Siersema PD, van Oijen MG. Primary non-variceal upper gastrointestinal bleeding in NSAID and low-dose aspirin users: development and validation of risk scores for either medication in two large Dutch cohorts. J Gastroenterol 2014;49:245-253.
56. Xu W, Lv M, Wu S, et al. Severe bleeding risk of direct oral anticoagulants versus vitamin K antagonists for stroke prevention and treatment in patients with atrial fibrillation: a systematic review and network meta-analysis. Cardiovasc Drugs Ther 2023;37:363-377.
57. Ray WA, Chung CP, Murray KT, et al. Association of proton pump inhibitors with reduced risk of warfarin-related serious upper gastrointestinal bleeding. Gastroenterology 2016;151:1105-1112.e10.

Received : March 1, 2023
Revised : April 26, 2023
Accepted : August 11, 2023

Correspondence to
Jinhua Zhang, Ph.D.
Department of Pharmacy, Fujian Maternity and Child Health Hospital College of Clinical Medicine for Obstetrics & Gynecology and Pediatrics, Fujian Medical University, #18 Daoshan Road, Fuzhou, 350001, China
Tel: +86-591-83357896-8301, Fax: +86-591-83357896
E-mail: pollyzhang2006@126.com
https://orcid.org/0000-0002-5629-0348

CRedit authorship contributions
Fuxin Ma: data curation, writing - original draft, writing - review & editing), Shuyi Wu: formal analysis, project administration; Shiqi Li: data curation, project administration; Zhiwei Zeng: conceptualization, project administration; Jinhua Zhang: methodology, writing - review & editing

Conflicts of interest
The authors disclose no conflicts.

Funding
None

https://doi.org/10.3904/kjim.2023.098

Supplementary Table 1. Baseline table

Reference	Age (yr), Mean ± SD (range)	Sex, male, n (%)	Drug	Population	Sample size	Time	Study design	Number of GIB	Risk factor
Agudo-Fernández et al., 2021 [19]	72.6 ± 14.6	639 (52.7)	Dabigatran Rivaroxaba Acenocoumaro	AF	1,213	January 1, 2012 to May 31, 2016	Retrospective cohort study	GIB 68	History of gastrointestinal bleeding (OR = 2.422, 95% CI: 1.101–5.327, p = 0.028); Concomitant therapy with clopidogrel (OR = 2.373, 95% CI: 0.996–5.652, p = 0.051); HasBled-Score (OR = 0.291, 95% CI: 0.170–0.496, p = 0.000) Age (OR = 0.825, 95% CI: 0.455–1.497, p = 0.527); Anticoagulant therapy (OR = 0.886, 95% CI: 0.591–1.330, p = 0.561); Chronic kidney disease (OR = 1.505, 95% CI: 0.815–2.780, p = 0.191); Other antiplatelet (OR = 4.497, 95% CI: 0.954–5.635, p = 0.242); Corticosteroids (OR = 1.757, 95% CI: 0.719–4.295, p = 0.216); Chads2-Score (OR = 0.765, 95% CI: 0.337–1.739, p = 0.523)
Fanning et al., 2020 [20]	Median age CDARS: 78 THIN: 74	CDARS 14,492 (50) THIN 6,172 (53)	Aspirin Rivaroxaban	Af[a)]	CDARS: 29,213 THIN: 11,549	CDARS: 2010–2018 THIN: 2011–2017	Retrospective cohort study	GIB CDARS: 23,743 THIN: 10,111	Rivaroxaban 20 mg/day vs. aspirin (HR = 1.57, 95% CI: 1.08–2.29); PPIs/H2RAs (HR = 1.96, 95% CI: 1.14–3.37); Women (HR = 1.91, 95% CI = 1.08–3.40, p = 0.53)
Graham et al., 2014 [21]	-	65,191 (48.5)	Dabigatran Warfarin	AF[a)]	134,414	October 19, 2010–December 31, 2012	Retrospective cohort study	2,715	Dabigatran 150 mg bid (HR = 1.51, 95% CI: 1.32–1.73)
Aisenberg et al., 2018 [22]	MGIB 75.0 (68.0–79.0) No MGIB 72.0 (64.0–78.0)	MGIB 382 (66.0) No MGIB 12 638 (61.8)	Edoxaban Warfarin	AF[a)]	21,105	-	RCT	MGIB 579	Concomitant aspirin intake (AHR = 1.31, 95% CI: 1.08–1.58, p = 0.006)

Supplementary Table 1. Continued

Reference	Age (yr), Mean ± SD (range)	Sex, male, n (%)	Drug	Population	Sample size	Time	Study design	Number of GIB	Risk factor
Chan et al., 2015 [23]	72.0 ± 10.9	2,412 (47.8)	Dabigatran	AF, Prophylaxis of VTE	5,041	January 1, 2010 to December 31, 2013	Retrospective cohort study	GIB 124	Age ≥ 75 yr (IRR = 2.47, 95% CI: 1.66–3.68, $p < 0.05$); History of peptic ulcer/GIB (IRR = 2.31, 95% CI, 1.54–3.46, $p < 0.05$); Concomitant use of aspirin (IRR = 1.52, 95% CI, 1.03–2.24, $p < 0.05$); Gastroprotective agents (IRR = 0.52, 95% CI: 0.35–0.77, $p < 0.05$); Histamine type-2–receptor antagonists (IRR = 0.61, 95% CI: 0.40–0.94, $p < 0.05$); Proton pump inhibitors (IRR = 0.53, 95% CI: 0.31–0.91, $p < 0.05$); Histamine type-2–receptor antagonists Proton pump inhibitors both (IRR = 0.15, 95% CI: 0.06–0.39, $p < 0.05$)
Chen et al., 2014 [24]	65.2 ± 16.6	234 (58)	Warfarin	DVT, AF, PE Valvular replacement other	401	July 1993 to May 2012	Retrospective cohort study	GIB 36	Age > 65 yr (RR = 2.5, 95% CI: 1.2–5.5, $p = 0.02$); Mean INR > 2.1 (RR = 2.1, 95% CI: 1.0–4.2, $p = 0.04$); History of GIB (RR = 5.1, 95% CI: 1.9–13.5, $p = 0.001$); Cirrhosis (RR = 6.9, 95% CI: 2.0–24.5, $p = 0.003$)
Coates et al., 2021 [25]	63.9	70.2%	Dabigatran	AF[a)]	4,299	September 1, 2016–June 30, 2019	Retrospective cohort study	GIB 73	Weight > 120 kg (AHR = 1.44, 95% CI: 1.01–2.05)
Delaney et al., 2007 [26]	Cases 69.3 ± 17.6 Control 69.1 ± 17.7	Cases 2,171 (53.9) Control 17,237 (42.9)	Warfarin	PE, DVT Stroke AF Congestive heart-failure	Cases 4,028 Control 40,171	January 1, 2000 to December 31, 2005	Case-control	GIB 4,028	Male (ARR = 1.50, 95% CI: 1.40–1.62); Heavy alcohol use (ARR = 4.00, 95% CI: 3.45–4.63); Smoking (ARR = 1.23, 95% CI: 1.15–1.34); Acetaminophen (paracetamol) use (ARR = 1.47, 95% CI: 1.35–1.60); Liver failure (ARR = 7.00, 95% CI: 4.78–10.27); Warfarin + ASA (ARR = 6.48, 95% CI: 4.25–9.87); Warfarin + NSAID (ARR = 4.79, 95% CI: 2.79–8.21); Warfarin + COX-2 inhibitor (ARR = 4.62, 95% CI: 1.48–14.43)

https://doi.org/10.3904/kjim.2023.098

https://doi.org/10.3904/kjim.2023.098

Supplementary Table 1. Continued

Reference	Age (yr), Mean ± SD (range)	Sex, male, n (%)	Drug	Population	Sample size	Time	Study design	Number of GIB	Risk factor
Douros et al., 2019 [27]	DOAC 75.5 ± 9.1 VKA 78.0 ± 9.0	DOAC 2,819 (53.2) VKA 4,709 (51.7)	DOACs VKA	AF[a)]	14,407	January 2011 to March 2014	Retrospective cohort study	GIB 253	Current concomitant DOAC-antiplatelet use (AHR = 1.08, 95% CI: 0.81–1.45); Current concomitant rivaroxaban-antiplatelet use (AHR = 1.18, 95% CI: 0.75–1.87); Current concomitant DOAC-ASA use (AHR = 1.15, 95% CI: 0.82–1.62); Current concomitant use of a DOAC with multiple antiplatelets (AHR = 1.13, 95% CI: 0.63–2.04); Current concomitant dabigatran-antiplatelet use (AHR = 1.10, 95% CI: 0.79–1.54)
Ferroni et al., 2022 [28]	Male: DOAC 77.8 VKA 77.1 Female: DOAC 80.3 VKA 79.4	28,963 (48)	DOACs VKA	AF[a)]	59,880	July 1, 2013 to September 30, 2017	Retrospective cohort study	-	Female (AHR = 1.48, 95% CI: 1.02–2.16, p = 0.04); > 85 (AHR = 2.28, 95% CI: 1.36–3.85, p = 0.01); 74–84 (AHR = 1.47, 95% CI: 0.90–2.42, p = 0.121); History of GI disease (AHR = 1.89, 95% CI: 0.87–4.09, p = 0.10); Congestive heart failure (AHR = 1.46, 95% CI: 0.90–2.35, p = 0.11); History of bleeding (AHR = 3.27, 95% CI: 1.86–5.73, p < 0.01); Myocardial infarction (AHR = 2.23, 95% CI: 1.12–4.43, p = 0.03); Peripheral artery disease (AHR = 4.63, 95% CI: 2.24–9.56, p < 0.01)
Gandhi et al., 2021 [29]	-	95,583 (60.3)	Apixaban Dabigatran Rivaroxaban	AF[a)]	158,476	January 2007–September 2017	Retrospective cohort study	GIB 4,290	Dabigatran + dronedarone (AHR = 1.40, 95% CI: 1.01–1.93, p = 0.04); Rivaroxaban + dronedarone (AHR = 1.39, 95% CI: 0.98–1.95, p = 0.06); Apixaban + dronedarone (AHR = 0.75, 95% CI: 0.39–1.44, p = 0.38)
Garcia et al., 2019 [30]	Prior GI Bleed 73.5 (67.0–78.0) No Prior GI Bleed 70.0 (62.0-76.0)	Female Prior GI Bleed 205 (26.1) No Prior GI Bleed 6,211 (35.7)	Apixaban Warfarin	AF[a)]	18,197	-	RCT ARISTOTLE Trial	MGIB 218 Lower GI bleeding 97 Upper GI bleeding 118	Major GI bleeding: prior lower GI bleed (HR = 1.72, 95% CI: 0.86–3.42); prior upper GI bleed (HR = 3.13, 95% CI: 1.97–4.96) Upper GI bleeding: prior upper GI bleed (HR = 3.42, 95% CI: 2.02–5.81) Lower GI bleeding: prior lower GI bleed (HR = 5.47, 95% CI: 2.53–11.80)

Supplementary Table 1. Continued

Reference	Age (yr), Mean ± SD (range)	Sex, male, n (%)	Drug	Population	Sample size	Time	Study design	Number of GIB	Risk factor
Holm et al., 2020 [31]	72.1 ± 12.9	129,857 (53)	DOACs	AF[a)]	244,597	2008–2017	Retrospective cohort study	GIB 156,280	Rivaroxaban: co-treatment pharmacodynamic effect (HR = 1.68, 95% CI: 1.37–2.05); CYP3A4 and/or P-gp-inhibitors (HR = 1.54, 95% CI: 1.02–2.32); Apixaban:co-treatment pharmacodynamic effect (HR = 1.51, 95% CI: 1.28–1.78); CYP3A4 and/or P-gp-inhibitors (HR = 1.44, 95% CI: 1.06–1.95)
Holt et al., 2021 [32]	Median (IQR) 75 (68–82)	55,169 (56.1)	DOACs	AF[a)]	98,376	2012–2018	Retrospective case-control	GIB 4,946	Oral glucocorticoid < 20 mg daily dose (HR = 1.54, 95% CI: 1.29–1.84); Oral glucocorticoid ≥ 20 mg (HR = 2.19, 95% CI: 1.81–2.65)
Kato et al., 2016 [33]	< 65 yr: 59 (55.0–62.0) 65–74 yr: 70 (67.0–72.0) ≥ 75 yr: 79 (76.0–82.0)	< 65 yr: 3,987 (73) 65–74 yr: 4,381 (61) ≥ 75 yr: 4,697 (55)	Edoxaban Warfarin	AF[a)]	21,105	-	RCT ENGAGE AF–TIMI 48 Trial	MGIB 579	≥ 75 yr (HR = 1.32, 95% CI: 1.01–1.72)
Kalil et al., 2016 [34]	Dabigatran 73.74 ± 6.86 Warfarin 73.85 ± 6.75	-	Dabigatran Warfarin	AF[a)]	69,467/25,74	June 1, 2010 to December 31	Retrospective cohort study	GIB 35	GFR 50–80 mL/min/1.73 m^2 (HR = 2.94, 95% CI: 1.24–7.02, $p = 0.015$)
Kolb et al., 2018 [35]	-	-	Dabigatran Warfarin	AF[a)]	18,113	2005–2009	RCT (RE-LY) Trial	GIB 1,158	MGIB: D150 vs. W (RR = 1.57, 95% CI: 1.28–1.92, $p < 0.01$); Life-threatening or fatal GI bleeding: D150 vs. W (RR = 1.62, 95% CI: 1.20–2.18, $p < 0.01$); Upper GI: D150 vs. W (RR = 1.13, 95% CI: 0.81–1.58, $p = 0.49$); Lower GI: D150 vs. W (RR = 2.23, 95% CI: 1.47–3.38, $p < 0.01$)

https://doi.org/10.3904/kjim.2023.098

https://doi.org/10.3904/kjim.2023.098

Supplementary Table 1. Continued

Reference	Age (yr), Mean ± SD (range)	Sex, male, n (%)	Drug	Population	Sample size	Time	Study design	Number of GIB	Risk factor
Lauffenburger et al., 2015 [36]	67.5 ± 12.4	No GIB Bleeding 13,104 (63.7) GI Bleeding 238 (53.4)	Dabigatran	AF[a)]	21,033	October 19, 2010 to December 31, 2012	Retrospective cohort study	GIB 446	65–74 (AHR = 2.72, 95% CI: 1.59–4.65, $p < 0.001$); ≥ 75 (AHR = 4.52, 95% CI: 2.68–7.64, $p < 0.001$); Congestive heart failure (AHR = 1.25, 95% CI: 1.01–1.56, $p < 0.05$); Coronary artery disease (AHR = 1.37, 95% CI: 1.10–1.69, $p < 0.05$); Renal impairment (AHR = 1.67, 95% CI: 1.24–2.25, $p < 0.001$); Bleeding (AHR = 1.32, 95% CI: 1.01–1.72, $p < 0.05$); Alcohol abuse (AHR = 2.57, 95% CI: 1.52–4.35, $p < 0.001$); *Helicobacter pylori* infection (AHR = 4.75, 95% CI: 1.93–11.68, $p < 0.05$); Antiplatelet agent (AHR = 1.49, 95% CI: 1.19–1.88, $p < 0.001$); Male sex (AHR = 0.78, 95% CI: 0.64–0.95, $p < 0.05$); Digoxin use (AHR = 1.49, 95% CI: 1.19–1.88, $p < 0.05$)
Lee et al., 2021 [37]	71.3 ± 10.0	25,868 (59.9)	DOACs	AF[a)]	43,173	January 2015 to December 2017	Retrospective cohort study	Hospitalization of GIB 314	BMI ≥ 30 kg/m^2 (AHR = 0.810, 95% CI: 0.494–1.328, $p = 0.018$); BMI per 5 kg/m^2 increase (AHR = 0.785, 95% CI: 0.658–0.937, $p = 0.007$)
Leonard et al., 2016 [38]	Mean age 71	87,576 (37)	Warfarin	AF, VTE Valvular heart disease	236,691	1999–2011	Cohort	GIB 2,035	Warfarin + gemfibrozil (AHR = 2.29, 95% CI: 1.61–3.25)
Maruyama et al., 2018 [39]	72.2 ± 10.0	448 (68.1)	DOACs	AF[a)]	658	April 2011–November 2015	Cohort	GIB 27: Upper GI 9 Lower GI 18 MGIB 12	Upper gastrointestinal bleeding: PPI (AHR = 0, 95% CI: 0–2E + 134, $p < 0.001$); Past digestive ulcer (AHR = 29.114, 95% CI: 7.265–116.678, $p < 0.001$); Lower gastrointestinal bleeding: NSAIDs (AHR = 12.6, 95% CI: 3.2–49.1, $p < 0.001$); Dual antiplatelet (AHR = 8.6, 95% CI: 2.7–27.1, $p < 0.001$); Past GIB (AHR = 15.1, 95% CI: 3.2–72.0, $p = 0.001$); Female (AHR = 3.2, 95% CI: 0.1–0.8, $p = 0.019$)

Supplementary Table 1. Continued

Reference	Age (yr), Mean ± SD (range)	Sex, male, n (%)	Drug	Population	Sample size	Time	Study design	Number of GIB	Risk factor
Murata et al., 2020 [40]	Warfarin 72.2 ± 9.3 DOAC 71.8 ± 9.5	2,390 (74)	Warfarin, DOACs	AF[a)]	3,237	2013–2015	Prospective cohort	GIB 68	Creatinine (per mg/dL increase) (AHR = 1.379, 95% CI: 1.091–1.743, $p = 0.007$); Age (per year increase) (AHR = 1.027, 95% CI: 0.996–1.059, $p = 0.86$); Hemoglobin (per g/dL) (AHR = 0.814, 95% CI: 0.705–0.941, $p = 0.005$)
Nantsupawat et al., 2017 [41]	Mean age 72.2	128 (51.8)	Dabigatran	AF[a)]	247	2010–2013	Retrospective cohort study	GIB 10	History of GIB (OR = 25.14, 95% CI: 2.85–221.47, p < 0.01); HAS-BLED ≥ 3 (OR = 5.85, 95% CI:1.31–26.15, $p = 0.021$); Corticosteroid use (OR = 4.30, 95% CI: 0.81–22.79, $p = 0.087$)
Nawarawong et al., 2018 [42]	71.6 ± 10.8	47 (50)	Warfarin, UFH, LMWH, NOAC	AF, vascular thrombosis, Stroke, Valvular heart diseases	94	October 2010 to February 2013	Retrospective cohort study	Acute GIB 94	Hematochezia (OR = 4.90, 95% CI: 1.22–19.50, $p = 0.024$); INR < 4 (OR = 4.07, 95% CI: 1.17–14.27, $p = 0.028$); Concomitant antiplatelets (OR = 0.32, 95% CI: 0.12–0.88, $p = 0.027$)
Olsen et al., 2019 [43]	Moderate age 70 (IQR 64–78)	22,651 (55)	VKA DOACs	AF[a)]	41,183	January 1, 2012–December 31, 2015	Retrospective cohort study	GIB 1,642	NSAIDs + NOAC vs. NOAC (HR = 2.01, 95% CI: 1.40–2.61); NSAIDs + VKA vs. VKA (HR = 1.95, 95% CI: 1.21–2.69); NSAIDs + apixaban vs. apixaban (HR = 2.98, 95% CI: 1.82-4.87); NSAIDs + rivaroxaban vs. rivaroxaban (HR = 1.94, 95% CI: 1.06–3.55); NSAIDs + dabigatran vs. dabigatran (HR = 1.52, 95% CI: 0.92–2.50)
Pham et al., 2020 [44]	-	-	DOACs	AF[a)]	48,442	October19, 2010 to June 30, 2015	Retrospective cohort study	GIB 687	Overall GI bleeding:dabigatran with verapamil or diltiazem vs amlodipine (AHR = 2.16, 95% CI: 1.30–3.60, $p < 0.05$); dabigatran + verapamil or diltiazem vs. metoprolol (AHR = 2.32, 95% CI: 1.42–3.79, $p < 0.05$); GI minor bleeding: dabigatran with verapamil or diltiazem vs. amlodipine (AHR = 2.16, 95% CI: 1.29–3.63, $p < 0.05$); dabigatran + verapamil or diltiazem vs. metoprolol (AHR = 2.33, 95% CI: 1.42–3.82, $p < 0.0$); Major/moderate GI bleeding: dabigatran + verapamil or diltiazem vs. metoprolol (AHR = 5.49, 95% CI: 1.67–18.03, $p < 0.05$)

https://doi.org/10.3904/kjim.2023.098

https://doi.org/10.3904/kjim.2023.098

Supplementary Table 1. Continued

Reference	Age (yr), Mean ± SD (range)	Sex, male, n (%)	Drug	Population	Sample size	Time	Study design	Number of GIB	Risk factor
Pourakari et al., 2016 [45]	No GI bleeding 63.8 ± 16.8 GI bleeding 68.6 ± 13.1	121 (43.5)	Warfarin	AF, DVT, Mechanical heart, Valve implantation	278	2003–2015	Retrospective cohort study	UGIB 41	History of peptic ulcer (HR = 111.19, 95% CI: 26.56–465.56, $p < 0.001$); Older age (HR = 1.032, 95% CI: 0.985–1.081, $p = 0.183$); Mechanical valve implant (HR = 1.971, 95% CI: 0.428–9.070, $p = 0.384$); Chronic kidney disease (HR = 0.542, 95% CI: 0.143–2.047, $p = 0.366$)
Schauer et al., 2005 [46]	73 ± 13.8	2,974 (31.8)	Warfarin	AF[a)]	9,345	January 1, 1997 to May 31, 2002	Retrospective cohort study	GIB 864	Substance abuse (AHR = 1.41, 95% CI: 1.07–1.87); Psychiatric illness (AHR = 1.19, 95% CI: 1.03–1.39); Social risk factors (AHR = 1.28, 95% CI: 1.12–1.48); Chronic heart failure (AHR = 1.31, 95% CI: 1.09–1.58); Liver disease (AHR = 1.31, 95% CI: 0.99–1.74); Renal disease (AHR = 1.61, 95% CI: 1.39–1.87); Deep vein thrombosis (AHR = 1.22, 95% CI: 1.02–1.47); Diabetes mellitus (AHR = 1.03, 95% CI: 0.90–1.18); Refill time 432 d (AHR = 0.79, 95% CI: 0.69–0.91)
Sherid et al., 2015 [47]	Dabigatran 72.72 Warfarin 71.83	Dabigatran 104 (50.0) Warfarin 96 (45.9)	Dabigatran Warfarin	AF, DVT, PE Portal venous thrombosis	417	2010–2012	Retrospective cohort study	GIB 31	Dabigatran group: duration < 100 days (AOR = 8.176, 95% CI: 1.993–38.547, $p = 0.0007$); Age > 65 yr (AOR = 2.989, 95% CI: 1.785–24.782, $p = 0.0453$); Previous GI bleeding (AOR = 6.284, 95% CI: 0.612–28.591, $p = 0.036$); Sex (female) (AOR = 2.732, 95% CI: 0.514–14.509, $p = 0.238$); Race (Caucasian) (AOR = 0.612, 95% CI: 1.33–2.816, $p = 0.528$); GFR ≤ 30 mL/min/1.73 m^2 (AOR = 4.534, 95% CI: 0.682–30.138, $p = 0.118$); Concomitant with aspirin (AOR = 1.739, 95% CI: 1.64–4.781, $p = 0.657$); Concomitant with thienopyridines (AOR = 1.051, 95% CI: 0.752–7.438, $p = 0.279$); Concomitant with dual antiplatelet (AOR = 0.856, 95% CI: 0.675–9.409, $p = 0.492$); Concomitant with NSAIDs (AOR = 1.297, 95% CI: 1.824–5.721, $p = 0.573$)

Supplementary Table 1. Continued

Reference	Age (yr), Mean ± SD (range)	Sex, male, n (%)	Drug	Population	Sample size	Time	Study design	Number of GIB	Risk factor
Sherid et al., 2014 [48]	Rivaroxaban 68.25 ± 14.97 Dabigatran 72.71 ± 12.37	Rivaroxaban 70 (47.62) Dabigatran 114 (50.22)	Rivaroxaban Dabigatran	AF VTE treatment VTE prophylaxi	374	2010–2013	Retrospective cohort study	GIB 19	Rivaroxaban group: ≤ 40 days vs. > 40 days (OR = 2.8, p = 0.023); DAPT with rivaroxaban (OR = 7.4, p = 0.0378); Prior GI bleeding (OR = 15.5, p = 0.0002); Dabigatran group:dabigatran for ≤ 40 days when compared to ≥ 40 days (OR = 8.3, p < 0.0001)
Sherid et al., 2016 [49]	Rivaroxaban 68.25 ± 14.97 Warfarin 71.35 ± 13.09	Rivaroxaban 70 (47.62) Warfarin 70 (45.75)	Rivaroxaban Warfarin	AF VTE treatment VTE prophylaxi	300	2011–2013	Retrospective cohort study	GIB 22	Rivaroxaban group: ≤ 40 days vs. > 40 days (OR = 2.8, p = 0.023); DAPT with rivaroxaban (OR = 7.4, p = 0.0378); Prior GI bleeding (OR = 15.5, p = 0.0002)
Sherwood et al., 2015 [50]	73 (65–78)	8,591 (60)	Rivaroxaban Warfarin	AF[a)]	14,236	2010-2011	RCT (Rocket AF Trial)	GIB 684	Anemia at baseline (HR = 1.70, 95% CI: 1.41–2.04, p < 0.0001); Previous GI bleeding (HR = 2.11, 95% CI: 1.62–2.76, p < 0.0001); Long-term ASA use at screening HR = 1.47, 95% CI: 1.26–1.72, p < 0.0001); Age (for each 5-yr increase) (HR = 1.11, 95% CI: 1.06–1.17, p < 0.0001); Diastolic BP (for each 5 mmHg decrease to < 80 mmHg) (HR = 1.10, 95% CI: 1.05–1.16, p = 0.0002); Smoking history (current or former) (HR = 1.37, 95% CI: 1.16–1.62), p = 0.0002); History of sleep apnea (HR = 1.60, 95% CI: 1.22–2.10, p = 0.0007); PPI at baseline (HR = 1.36, 95% CI: 1.12–1.65, p = 0.0018); Creatinine clearance (for each 5-U decrease to < 60 mL/min) (HR = 1.06, 95% CI: 1.01–1.12, p = 0.015); COPD (HR = 1.30, 95% CI: 1.05–1.61, p = 0.016); Male (HR = 1.21, 95% CI: 1.01–1.44, p = 0.037); Baseline antiplatelet (other than ASA) (HR = 1.50, 95% CI: 1.02–2.21, p = 0.039)

https://doi.org/10.3904/kjim.2023.098

https://doi.org/10.3904/kjim.2023.098

Supplementary Table 1. Continued

Reference	Age (yr), Mean ± SD (range)	Sex, male, n (%)	Drug	Population	Sample size	Time	Study design	Number of GIB	Risk factor
Shimomura et al., 2018 [52]	69.4 ± 9.9	329 (64.8)	Warfarin DOACs	AF, Valve replacement or valvuloplasty history	508	2001–2015	Retrospective cohort study	GIB 42	PPI therapy (AHR = 0.52, 95% CI: 0.27–1.0, p = 0.053); Chronic kidney disease (AHR = 6.7, 95% CI: 2.3–19.6, p < 0.001); COPD (AHR = 4.0, 95% CI: 1.4–11.2, p = 0.011); History of peptic ulcer disease (AHR = 1.8, 95% CI: 0.95–3.6, p = 0.071); Liver cirrhosis (AHR = 5.6, 95% CI: 1.7–18.6, p = 0.005)
Youn et al., 2018 [51]	Mean Non-GPA 70.4 (18–99) GPA 73.3 (22–96)	Male Non-GPA 837 (48.8) GPA 164 (45.6)	DOACs	AF, VTE, DVT, PE, ACS Prophylaxis of DVT/PTE	2,076	2008–2016	Retrospective cohort study	UGIB 30	Age, 1-year increase (HR = 1.041, 95% CI: 1.000–1.083, p = 0.048); Antiplatelet agent use (HR = 3.121, 95% CI: 1.265–7.702, p = 0.014); History of peptic ulcer/UGIB (HR = 5.931, 95% CI: 2.504–14.049, p < 0.001)

ACS, acute coronary syndrome; ARR, adjust risk ratio; DVT, deep vein thrombosis; IRR, incidence risk ratio; PE, pulmonary embolism; RR, risk raito.
[a)]The populations of 23 studies were only stroke patients.

Supplementary Table 2. Evidence profile for bleeding-related prognostic factors

No. of studies	Certainty assessment domains						Overall certainty in the evidence about this prognostic factor	Relative effect, OR (95% CI)
	Study design	Risk of bias	Indirect	Inconsistent	Imprecise	Publication bias		
History of peptic ulcer/GIB (yes vs. no) [19,23,24,28,30,39,41,45,47,48,50-52]								
13	Observational	Serious	Not serious	Serious	Not serious	Serious	⊕⊙⊙⊙ VERY LOW	5.26 (2.76–10.05)
Concomitant therapy with clopidogrel (yes vs. no) [19]								
1	Observational	Serious	Not serious	Not serious	Serious	Undetected	⊕⊕⊙⊙ LOW	2.37 (1–5.65)
HasBled-Score (≥ 3 vs. < 3) [19,41]								
2	Observational	Serious	Not serious	Serious	Serious	Undetected	⊕⊙⊙⊙ VERY LOW	1.20 (0.06–22.63)
Older age (yes vs. no) [19,23,24,28,33,36,45,47]								
8	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕⊙ MODERATE	1.95 (1.36–2.79)
Age: for each 1-year increase (yes vs. no) [40,51]								
2	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕⊙ MODERATE	1.03 (1.01–1.06)
Age: for each 5-year increase (yes vs. no) [50]								
1	Observational	Serious	Not serious	Not serious	Serious	Undetected	⊕⊕⊙⊙ LOW	1.11 (1.06–1.17)
Kidney disease (yes vs. no) [19,36,45,46,52]								
5	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕⊙ MODERATE	1.69 (1.24–2.31)
Combination of corticosteroid (yes vs. no) [19,41]								
2	Observational	Serious	Not serious	Not serious	Serious	Undetected	⊕⊕⊙⊙ LOW	2.14 (0.98–4.72)
Dabigatran dose (dabigatran 150 mg twice daily vs. warfarin) [21,35]								
2	Observational	Serious	Not serious	Serious	Not serious	Undetected	⊕⊕⊙⊙ LOW	1.53 (1.39–1.69)
Concomitant use of aspirin (yes vs. no) [22,23,26,27,47]								
5	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕⊙ MODERATE	2.07 (1.17–3.66)
INR (> 2.1 vs. ≤ 2.1; ≥ 4 vs. < 4) [24,41]								
2	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕⊙ MODERATE	INR > 2.1: 2.05 (1.00–4.20) INR < 4: 4.09 (1.17–14.27)
Cirrhosis (yes vs. no) [24,52]								
2	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕⊙ MODERATE	6.24 (2.63–14.83)
Obesity (weight > 120 vs. ≤ 120 kg) [25]								
1	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕⊙ MODERATE	1.44 (1.01–2.05)
Alcohol use (yes vs. no) [26,36]								
2	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕⊙ MODERATE	3.46 (2.30–5.19)

https://doi.org/10.3904/kjim.2023.098

Supplementary Table 2. Continued

No. of studies	Certainty assessment domains						Overall certainty in the evidence about this prognostic factor	Relative effect, OR (95% CI)
	Study design	Risk of bias	Indirect	Inconsistent	Imprecise	Publication bias		
Smoking (yes vs. no) [26,50]								
2	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕⊙ MODERATE	1.26 (1.18–1.35)
Liver failure (yes vs. no) [26]								
1	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕⊙ MODERATE	7.01 (4.78–10.27)
Concomitant with NSAIDs: including paracetamol, COX-2 inhibitor (yes vs. no) [26,39,43,47]								
4	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕⊙ MODERATE	NSAIDs use: 2.37 (1.61–3.50) Paracetamol use: 1.47 (1.35–1.60) COX-2 inhibitor use: 1.97 (1.59–2.40)
Antiplatelet agent use (yes vs. no) [19,27,36,39,42,47,48,50,51]								
9	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕⊙ MODERATE	1.45 (1.11–1.90)
HF (congestive HF vs. no congestive HF; chronic HF vs. no chronic HF) [28,36,46]								
3	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕⊙ MODERATE	Any HF: 1.30 (1.14–1.49) Chronic HF: 1.31 (1.09–1.58) Congestive HF: 1.29 (1.06–1.57)
History of bleeding (yes vs. no) [28]								
1	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕⊙ MODERATE	History of bleeding: 3.26 (1.86–5.73)
Sex (male vs. female) [20,26,28,36,39,40,47]								
2	Observational	Serious	Not serious	Serious	Not serious	Undetected	⊕⊕⊙⊙ LOW	0.95 (0.72–1.26)
Myocardial infarction (yes vs. no) [28]								
1	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕⊙ MODERATE	2.23 (1.12–4.43)
Peripheral vascular disease: including peripheral artery disease (yes vs. no) [28,36]								
2	Observational	Serious	Not serious	Not serious	Serious	Undetected	⊕⊕⊙⊙ LOW	2.33 (0.66–8.20)
Concomitant use of dronedarone (yes vs. no) [29]								
1	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕⊙ MODERATE	1.29 (1.04–1.62)
Combination of CYP3A4 and/or P-gp-inhibitors (yes vs. no) [31]								
1	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕⊙ MODERATE	1.47 (1.15–1.88)
Oral glucocorticoid use (yes vs. no) [32]								
1	Observational	Serious	Not serious	Serious	Not serious	Undetected	⊕⊕⊙⊙ LOW	1.83 (1.30–2.59)

Supplementary Table 2. Continued

No. of studies	Certainty assessment domains						Overall certainty in the evidence about this prognostic factor	Relative effect, OR (95% CI)
	Study design	Risk of bias	Indirect	Inconsistent	Imprecise	Publication bias		
Renal failure (yes vs. no) [34,47]								
2	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕⊙ MODERATE	Total: 3.18 (1.44–6.99) GFR 50–80 mL/min /1.73 m^2: 2.95 (1.24–7.02) GFR ≤ 30 mL/min/1.73 m^2: 4.53 (0.68–30.14)
Coronary artery disease (yes vs. no) [36]								
1	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕⊙ MODERATE	1.36 (1.10–1.69)
Helicobacter pylori infection (yes vs. no) [36]								
1	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕⊙ MODERATE	4.75 (1.93–11.68)
Combination of digoxin (yes vs. no) [36]								
1	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕⊙ MODERATE	1.50 (1.19–1.88)
Combination of gemfibrozil (yes vs. no) [38]								
1	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕⊙ MODERATE	2.29 (1.61–3.25)
Creatinine level (per 1 mg/dL increase) (yes vs. no) [40]								
1	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕⊙ MODERATE	1.38 (1.09–1.74)
Creatinine clearance < 60 mL/min (yes vs. no) [50]								
1	Observational	Serious	Not serious	Not serious	Serious	Undetected	⊕⊕⊙⊙ LOW	1.06 (1.01–1.12)
Combination of verapamil or diltiazem (yes vs. no) [44]								
1	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕⊙ MODERATE	2.33 (1.82–2.98)
Mechanical valve implant (yes vs. no) [45]								
1	Observational	Serious	Not serious	Not serious	Serious	Undetected	⊕⊕⊙⊙ LOW	1.97 (0.43–9.07)
Substance abuse: defined as alcohol dependence, drug dependence, or non-dependent abuse, excluding tobacco use disorder (presence vs. absence) [46]								
1	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕⊙ MODERATE	1.41 (1.07–1.87)
Psychiatric illness: defined as schizophrenia, affective psychosis, paranoia, or other nonorganic psychosis (presence vs. absence) [46]								
1	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕⊙ MODERATE	1.20 (1.03–1.39)
Social risk factors: defined as lack of housing, inadequate housing, inadequate material resources, persons living alone, no other household member able to render care, or non-compliance with medical treatment [46]								
1	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕⊙ MODERATE	1.29 (1.12–1.48)

https://doi.org/10.3904/kjim.2023.098

Supplementary Table 2. Continued

No. of studies	Certainty assessment domains						Overall certainty in the evidence about this prognostic factor	Relative effect, OR (95% CI)
	Study design	Risk of bias	Indirect	Inconsistent	Imprecise	Publication bias		
Liver disease (yes vs. no) [46]								
1	Observational	Serious	Not serious	Not serious	Serious	Undetected	⊕⊕⊙⊙ LOW	1.31 (0.99–1.74)
Venous thromboembolism: including deep vein thrombosis (yes vs. no) [36,46]								
2	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕⊙ MODERATE	1.21 (1.02–1.44)
Diabetes (yes vs. no) [36,46]								
2	Observational	Serious	Not serious	Not serious	Serious	Undetected	⊕⊕⊙⊙ LOW	1.08 (0.96–1.21)
Anticoagulant treatment time (≤ 100 vs. > 100 d) [47-49]								
3	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕⊙ MODERATE	4.94 (2.66–9.17)
Combination of thienopyridines use (yes vs no) [47]								
1	Observational	Serious	Not serious	Not serious	Serious	Undetected	⊕⊕⊙⊙ LOW	2.37 (0.75–7.44)
Long-term ASA use at screening (yes vs. no) [50]								
1	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕⊙ MODERATE	1.47 (1.26–1.72)
Anemia (yes vs. no) [36,50]								
2	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕⊙ MODERATE	1.48 (1.10–1.98)
Diastolic BP (for each 5 mmHg decrease to < 80 mmHg) (presence vs. absence) [50]								
1	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕⊙ MODERATE	1.10 (1.05–1.16)
History of sleep apnea (presence vs. absence) [50]								
1	Observational	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕⊙ MODERATE	1.60 (1.22–2.10)
COPD (yes vs. no) [50,52]								
2	Observational	Serious	Not serious	Not serious	Serious	Undetected	⊕⊕⊙⊙ LOW	2.01 (0.69–5.83)

GRADE Working Group grades of evidence:

1. High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
2. Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
3. Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
4. Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations:

1. Risk of bias: The retrospective enrollment of patients may have introduced classification bias, certainty in evidence was downgraded for risk of bias.
2. Certainty in evidence was downgraded for high heterogeneity.
3. Imprecise: Certainty in evidence was downgraded for imprecision, given that the 95% CI suggests that there may be no association.

Supplementary Table 3. Risk of bias assessments using PROBUST for risk assessment model studies

Reference	Year	Participants	Predictors	Outcome	Analysis	Total
Shimomura et al. [52]	2017	High	Low	Low	Low	High

PROBUST, Prediction Study Risk of Bias Assessment Tool.

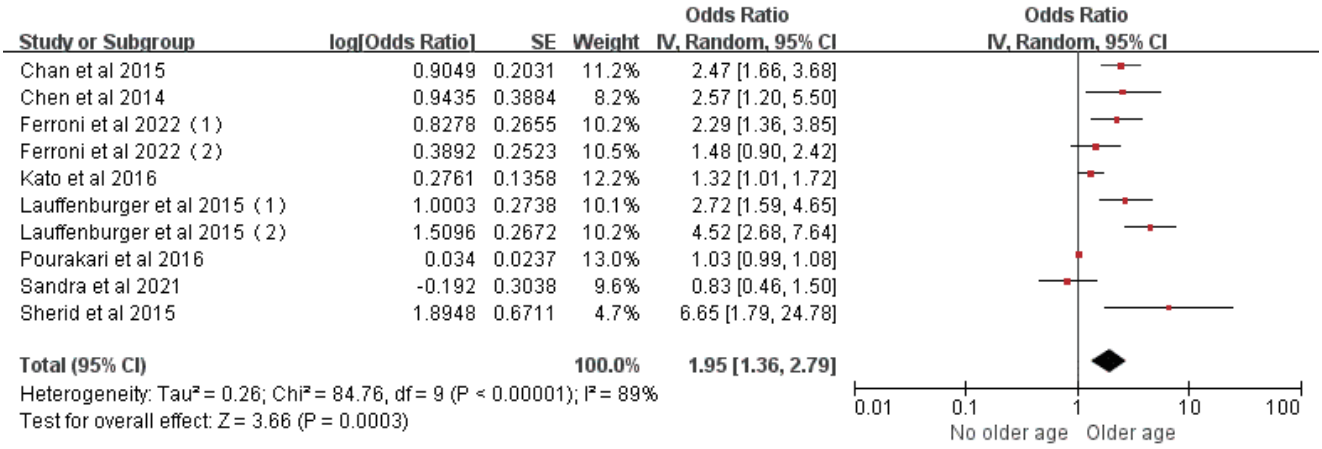
Supplementary Table 4. Risk of bias assessments using QUIPS for prognostic factor studies

Reference	Year	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting
Agudo-Fernández et al. [19]	2021	Low	Low	Low	Low	Low	Low
Fanning et al. [20]	2020	Low	Low	Low	Low	Low	Low
Graham et al. [21]	2014	Low	Low	Moderate	Low	Low	Low
Aisenberg et al. [22]	2018	Low	Low	Moderate	Low	Low	Low
Chan et al. [23]	2015	Low	Low	Low	Low	Moderate	Low
Chen et al. [24]	2014	Low	Low	Low	Low	Low	Low
Coates et al. [25]	2021	Low	Low	Low	Low	Moderate	Low
Delaney et al. [26]	2007	Low	Low	Low	Low	Low	Low
Douros et al. [27]	2019	Low	Low	Low	Low	Low	Low
Ferroni et al. [28]	2022	Low	Low	Moderate	Low	Low	Low
Gandhi et al. [29]	2021	Low	Low	Low	Low	Low	Low
Garcia et al. [30]	2019	Low	Low	Low	Low	Low	Low
Holm et al. [31]	2020	Low	Low	Low	Low	Low	Low
Holt et al. [32]	2021	Low	Low	Low	Low	Low	Low
Kato et al. [33]	2016	Low	Low	Low	Low	Low	Low
Kalil et al. [34]	2016	Low	Low	Low	Low	Low	Low
Kolb et al. [35]	2018	Low	Low	Low	Low	Low	Low
Lauffenburger et al. [36]	2015	Low	Low	Low	Low	Low	Low
Lee et al. [37]	2021	Low	Low	Low	Moderate	Low	Low
Leonard et al. [38]	2016	Low	Low	Moderate	Moderate	Moderate	Low
Maruyama et al. [39]	2018	Low	Low	Moderate	Low	Moderate	Low
Murata et al. [40]	2020	Low	Low	Low	Low	Moderate	Low
Nantsupawat et al. [41]	2017	Low	Low	Moderate	Low	Moderate	Low
Nawarawong et al. [42]	2018	Low	Low	Moderate	Low	Moderate	Low
Olsen et al. [43]	2019	Low	Low	Low	Low	Low	Low
Pham et al. [44]	2020	Low	Low	Low	Low	Low	Low
Pourakari et al. [45]	2016	Low	Low	Low	Low	Low	Low
Schauer et al. [46]	2005	Low	Low	Low	Low	Low	Low
Sherid et al. [47]	2015	Low	Low	Low	Low	Low	Low
Sherid et al. [48]	2014	Low	Low	Low	Low	Low	Low
Sherid et al. [49]	2016	Low	Low	Low	Low	Low	Low
Sherwood et al. [50]	2015	Low	Low	Moderate	Low	Low	Low
Youn et al. [51]	2018	Low	Low	Low	Low	Low	Low

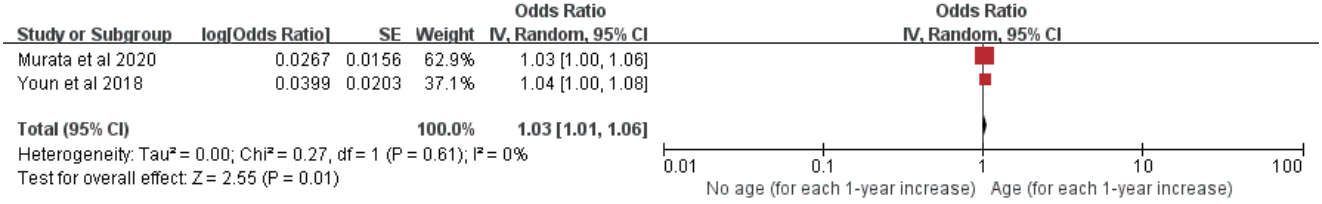
QUIPS, Quality in Prognosis Studies.

https://doi.org/10.3904/kjim.2023.098

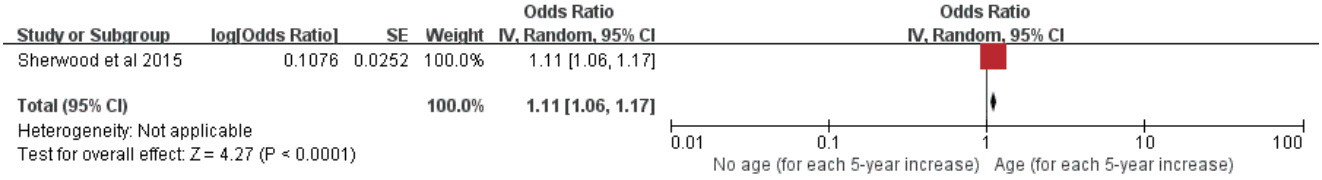
Supplementary Figure. Forest plots showing the association between risk factors and GIB (from S1-S49).



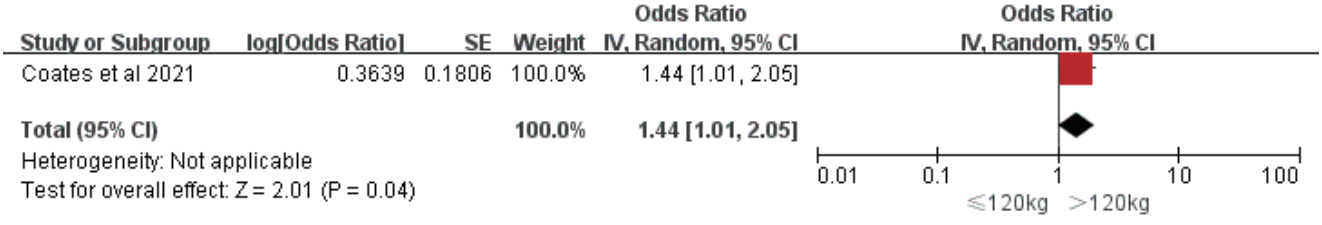
S1. Forest plot showing the association between older age and GIB.



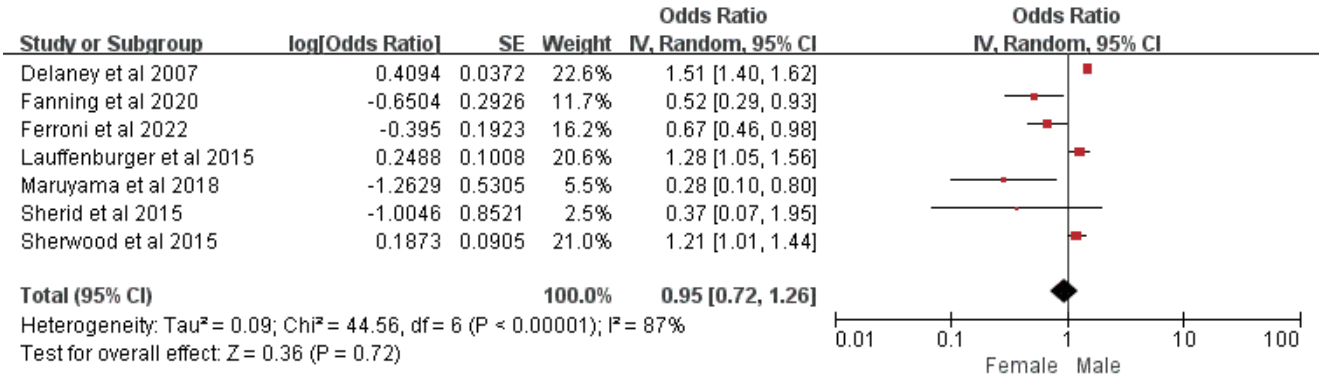
S2. Forest plot showing the association between age: for each 1-year increase and GIB.



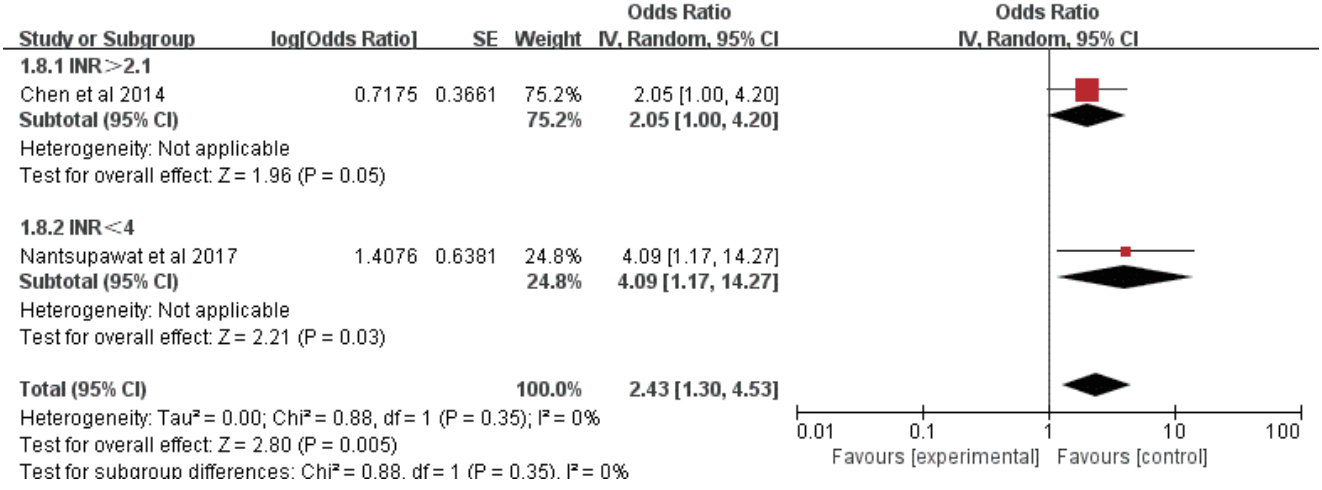
S3. Forest plot showing the association between age for each 5-year increase and GIB.



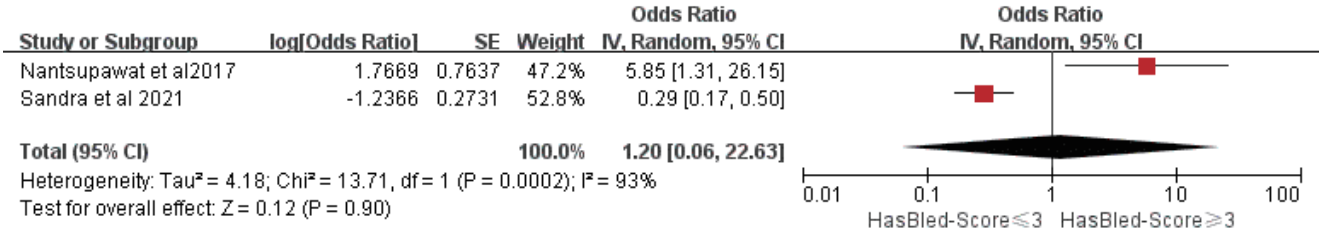
S4. Forest plot showing the association between obesity and GIB.



S5. Forest plot showing the association between sex and GIB.

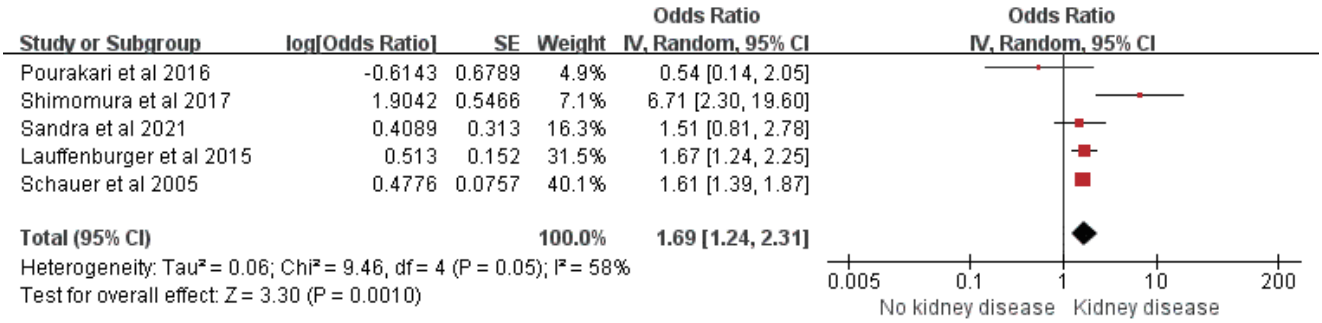


S6. Forest plot showing the association between INR and GIB.

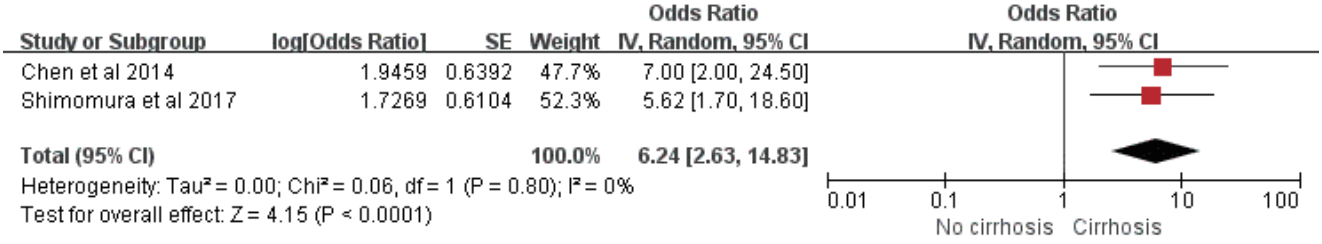


S7. Forest plot showing the association between HasBled-Score > 3 and GIB.

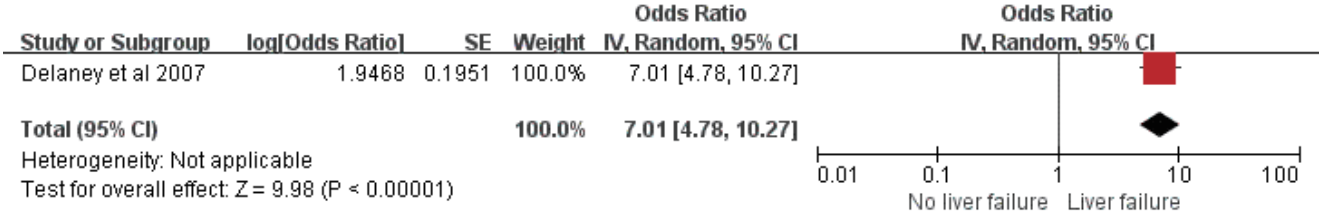
https://doi.org/10.3904/kjim.2023.098



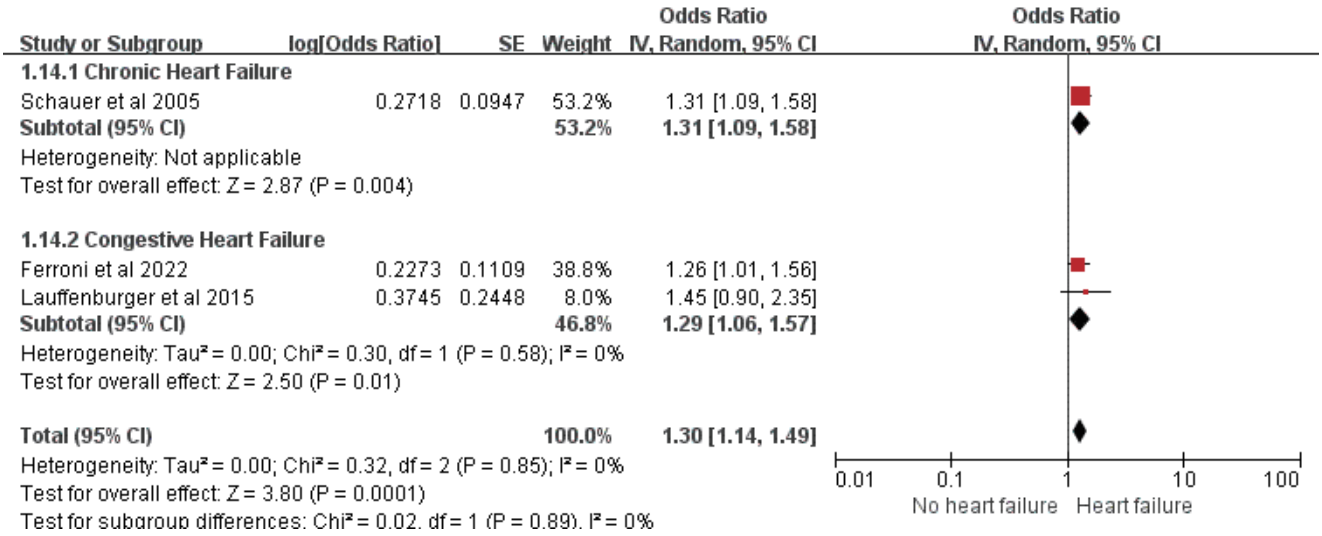
S8. Forest plot showing the association between kidney disease and GIB.



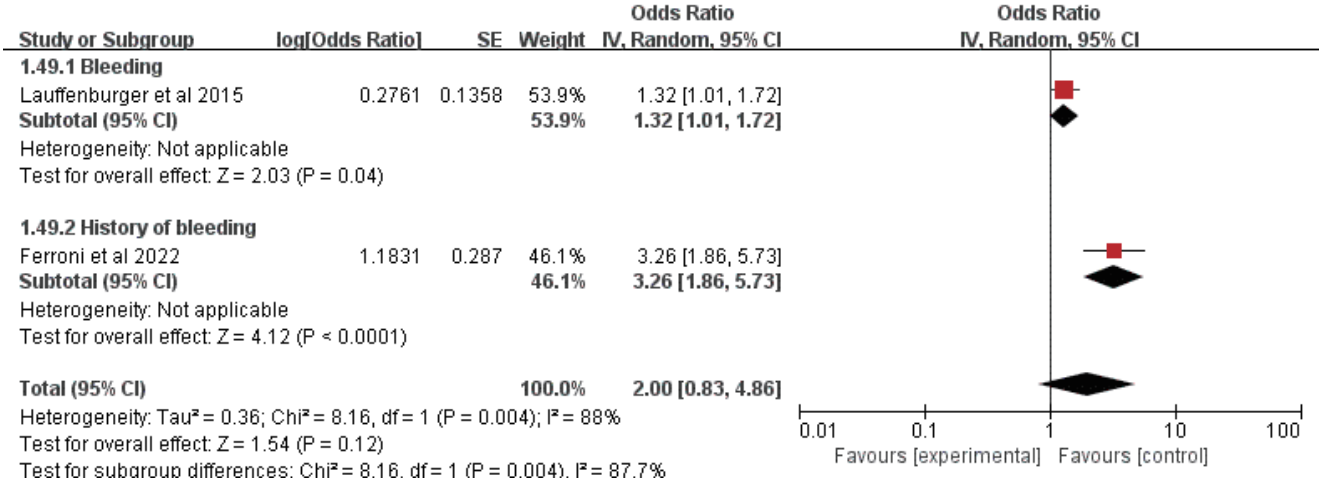
S9. Forest plot showing the association between cirrhosis and GIB.



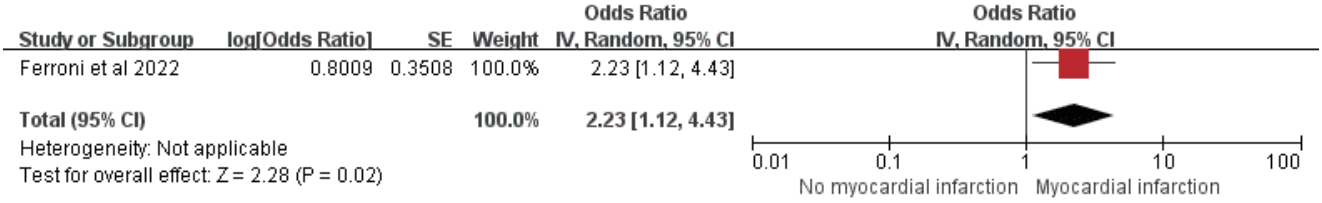
S10. Forest plot showing the association between liver failure and GIB.



S11. Forest plot showing the association between heart failure (HF) and GIB.

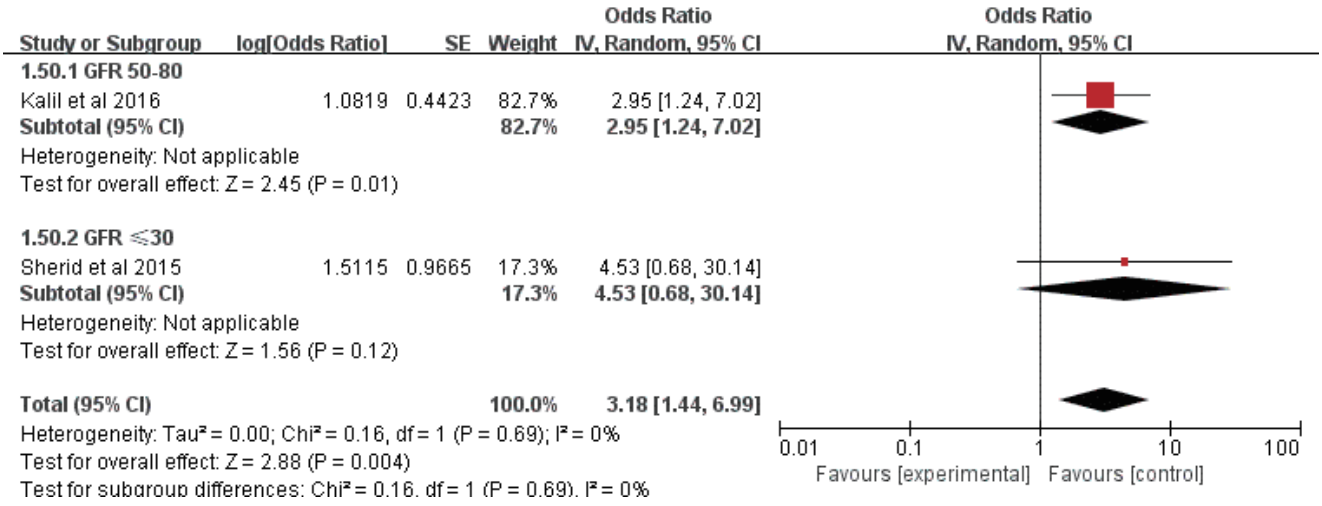


S12. Forest plot showing the association between bleeding and GIB.

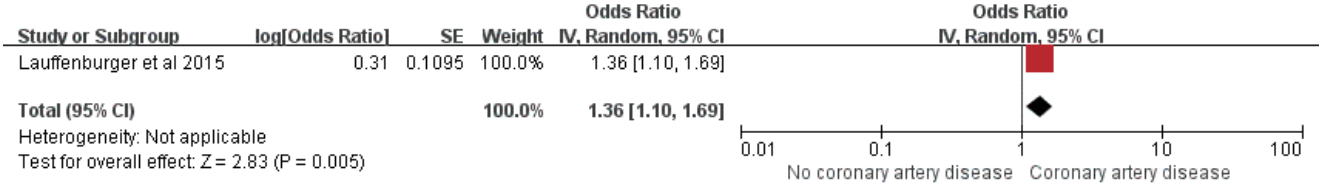


S13. Forest plot showing the association between myocardial infarction and GIB.

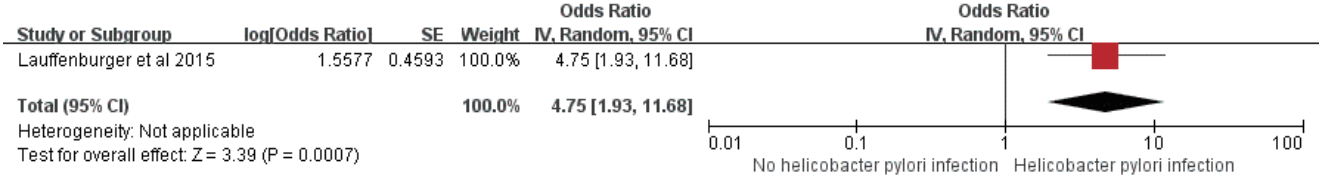
https://doi.org/10.3904/kjim.2023.098



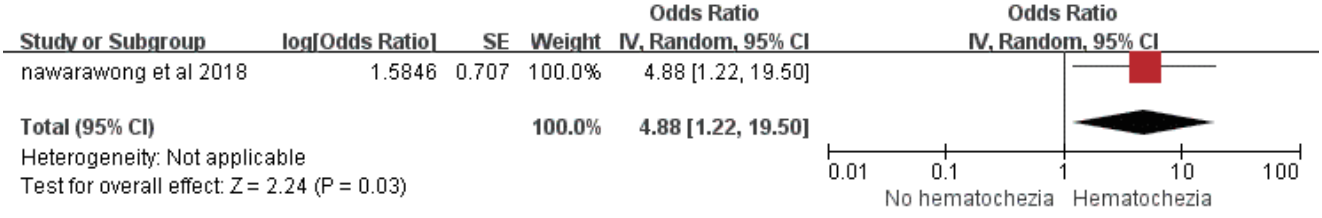
S14. Forest plot showing the association between renal failure and GIB.



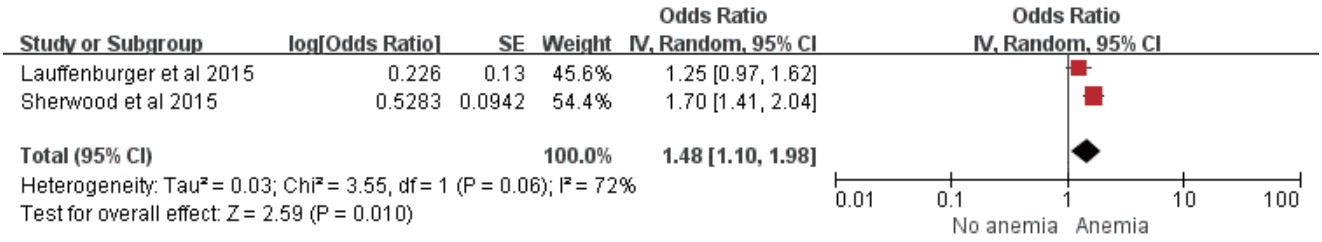
S15. Forest plot showing the association between coronary artery disease and GIB.



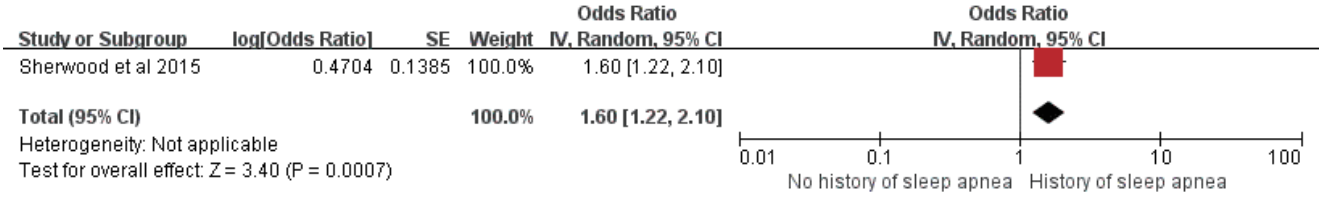
S16. Forest plot showing the association between helicobacter pylori infections and GIB.



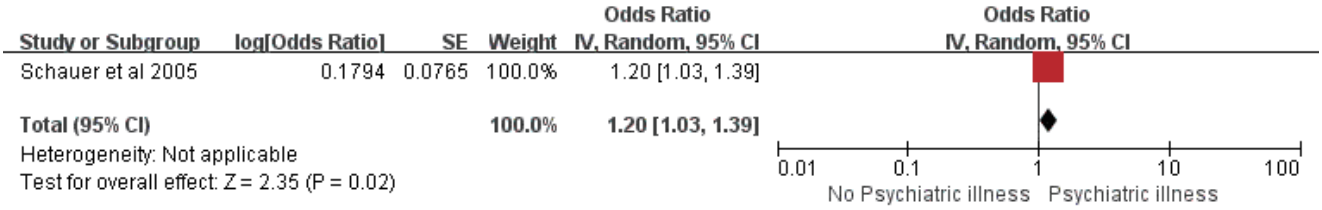
S17. Forest plot showing the association between hematochezia and GIB.



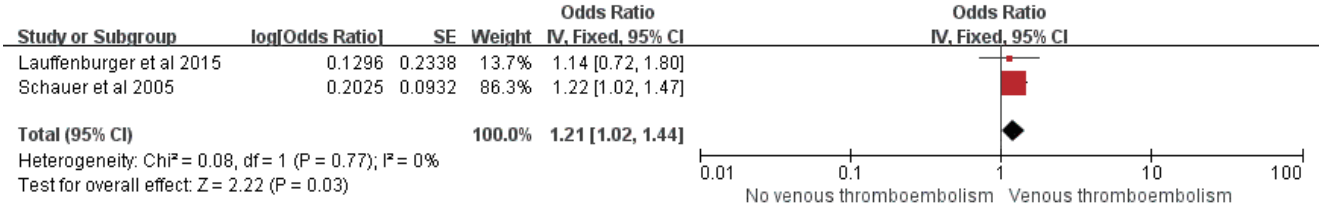
S18. Forest plot showing the association between anemia and GIB.



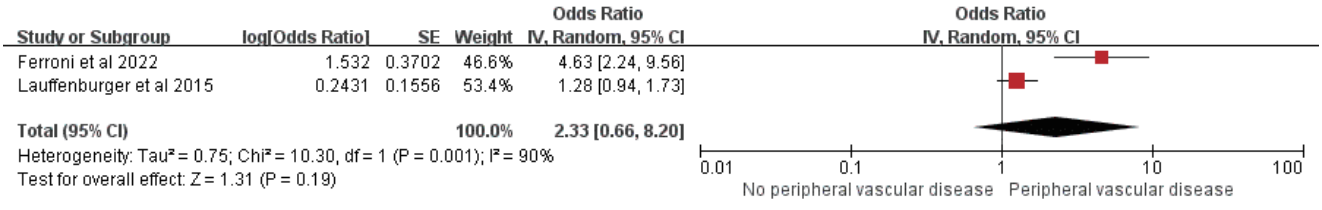
S19. Forest plot showing the association between history of sleep apnea and GIB.



S20. Forest plot showing the association between psychiatric illness and GIB.

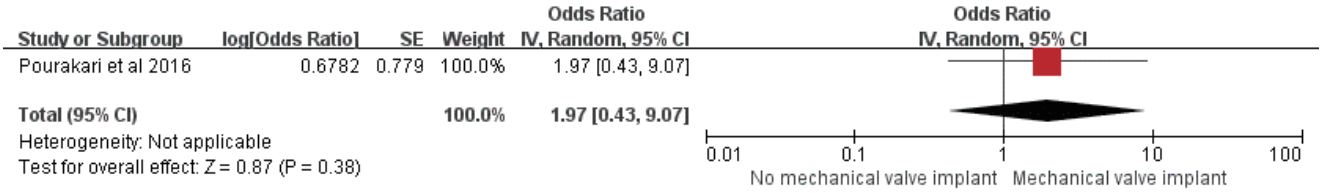


S21. Forest plot showing the association between venous thromboembolism and GIB.

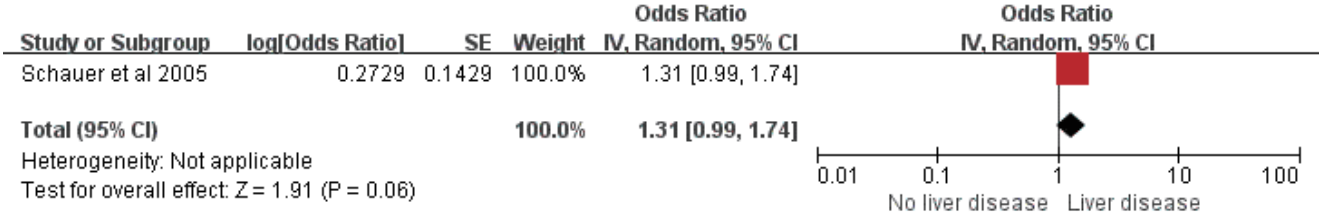


S22. Forest plot showing the association between peripheral vascular disease andGIB.

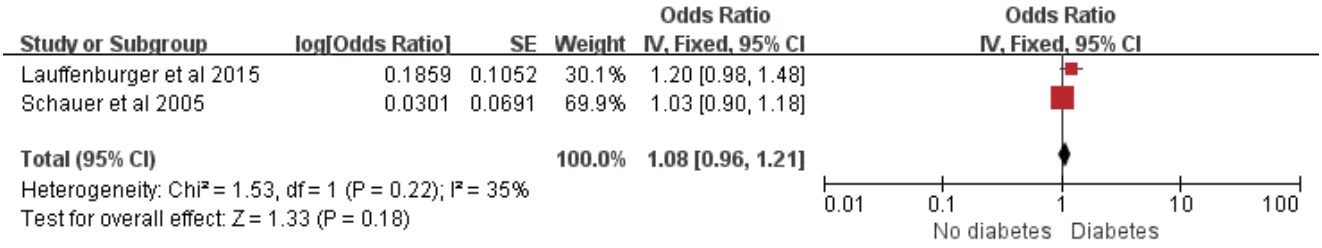
https://doi.org/10.3904/kjim.2023.098



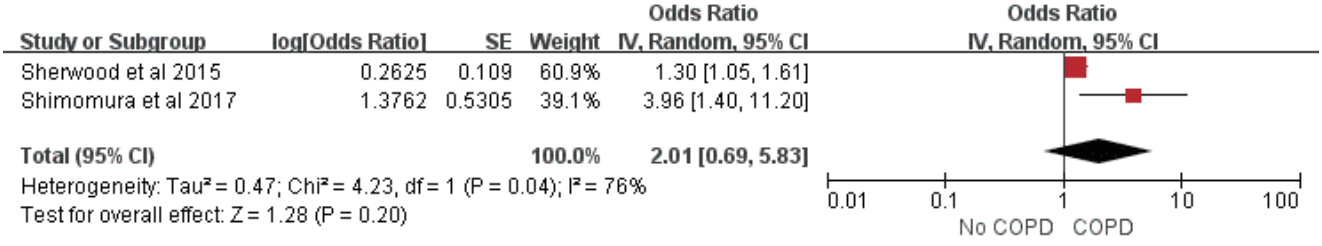
S23. Forest plot showing the association between mechanical valve implant and GIB.



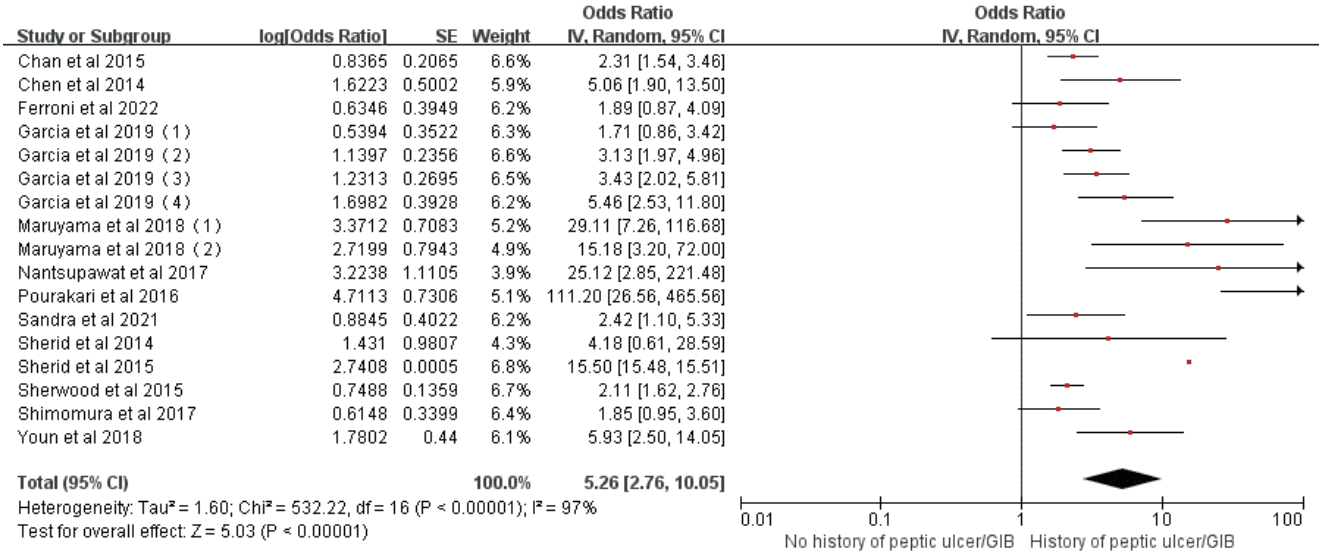
S24. Forest plot showing the association between liver disease and GIB.



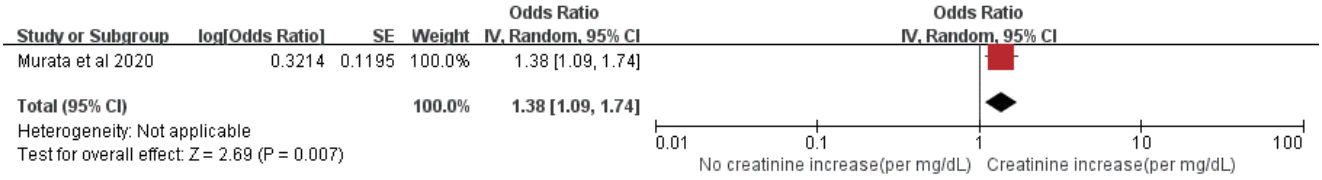
S25. Forest plot showing the association between diabetes and GIB.



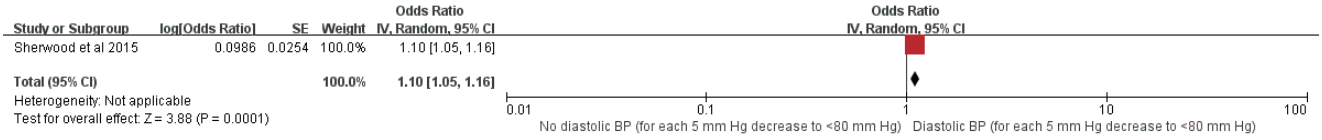
S26. Forest plot showing the association between COPD and GIB.



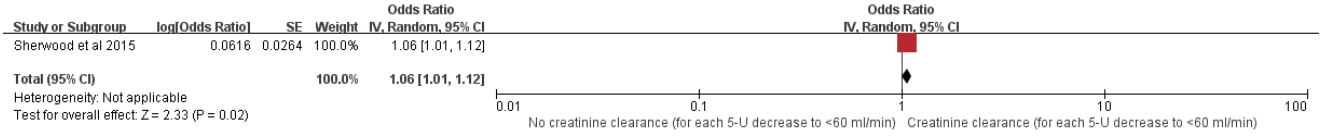
S27. Forest plot showing the association between history of peptic ulcer/GIB and GIB.



S28. Forest plot showing the association between creatinine level (per 1 mg/dL increase) and GIB.

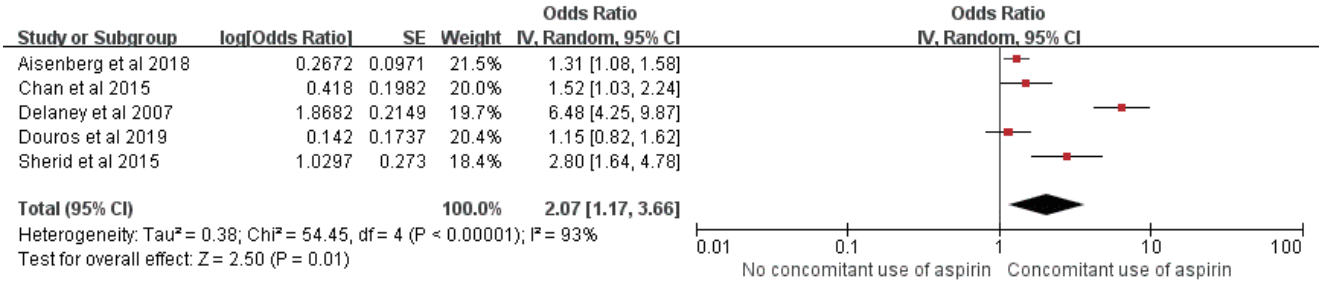


S29. Forest plot showing the association between diastolic BP and GIB.

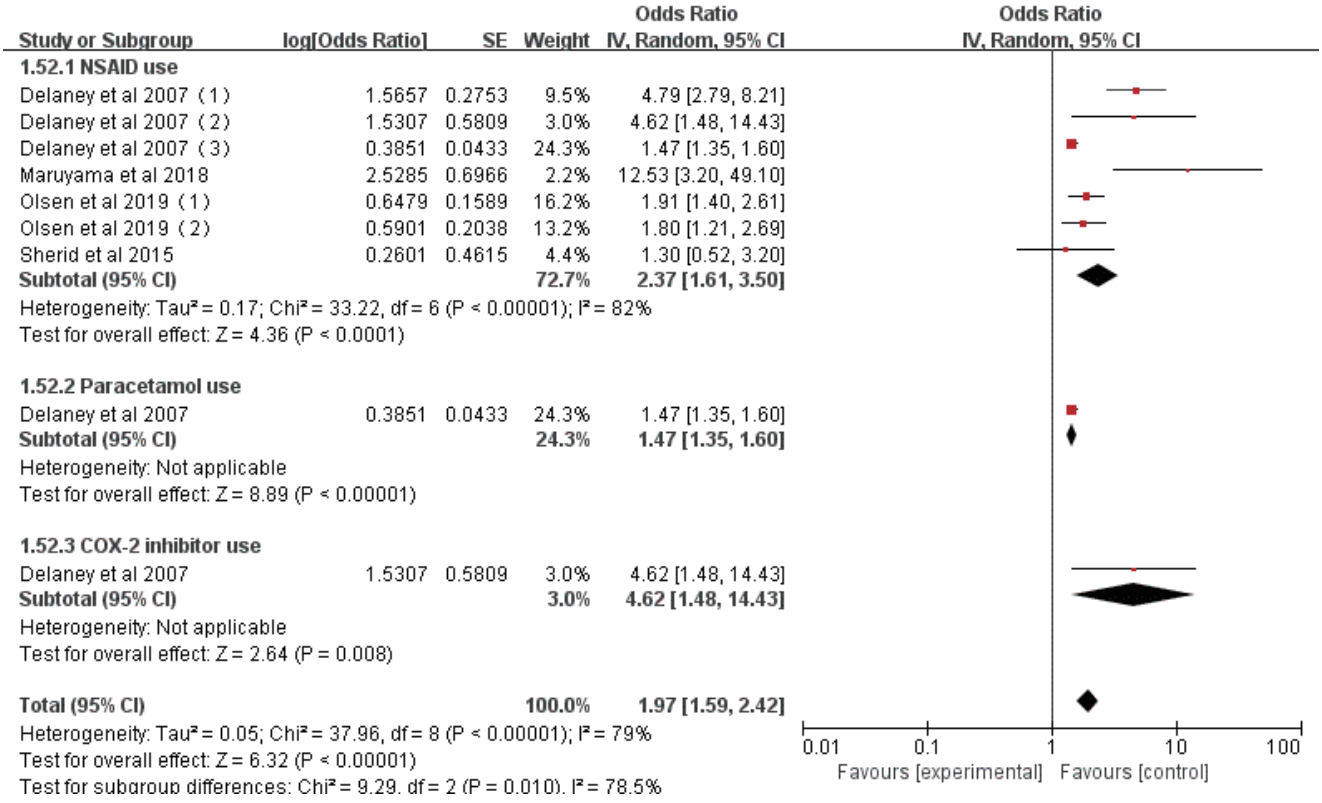


S30. Forest plot showing the association between creatinine clearance < 60 ml/min and GIB.

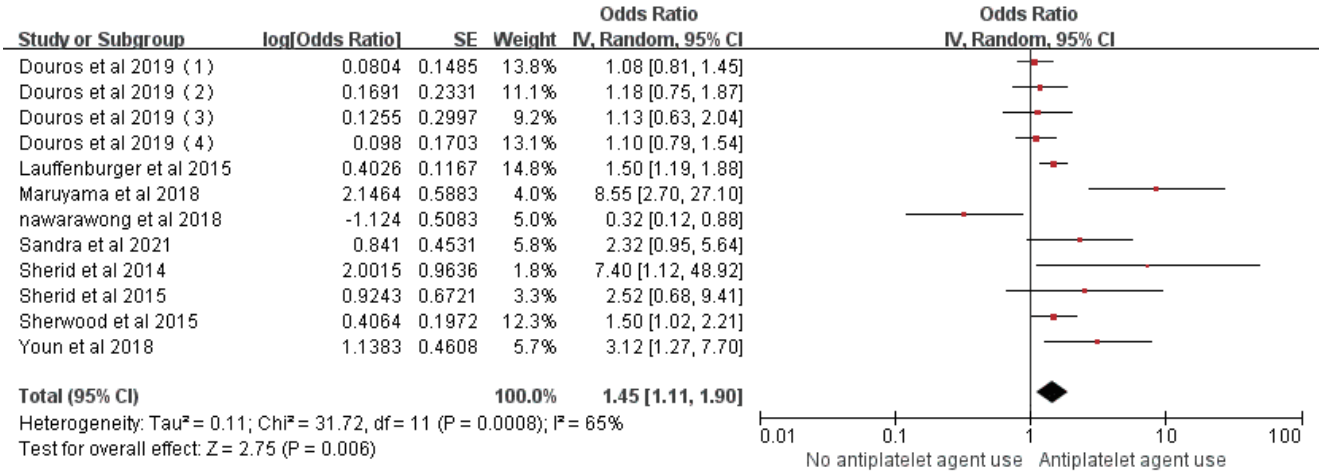
https://doi.org/10.3904/kjim.2023.098



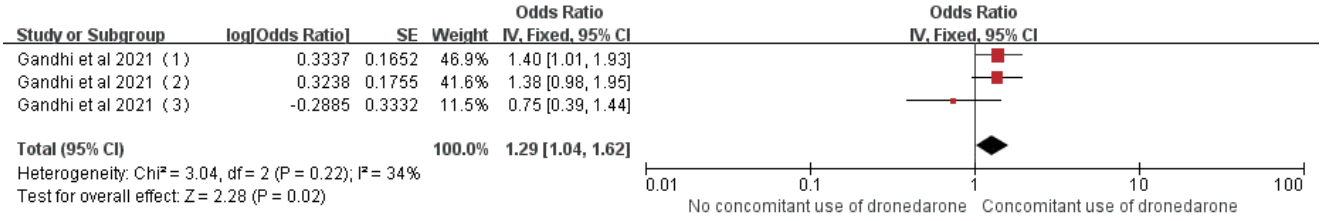
S31. Forest plot showing the association between concomitant use of aspirin and GIB.



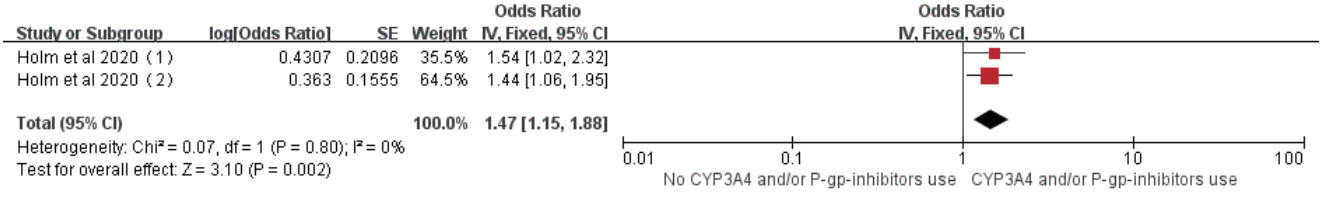
S32. Forest plot showing the association between concomitant with NSAID and GIB.



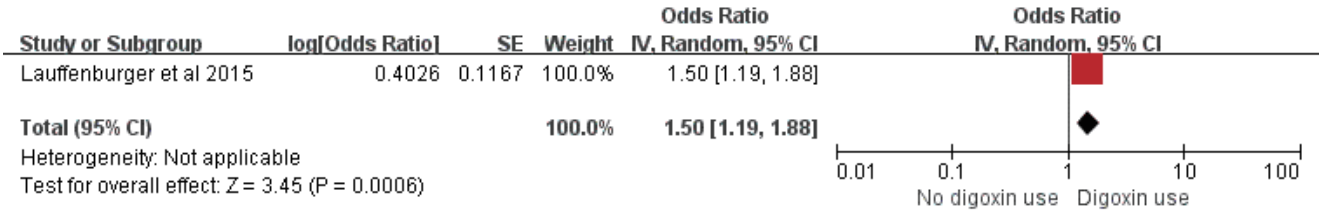
S33. Forest plot showing the association between antiplatelet theapy and GIB.



S34. Forest plot showing the association between concomitant use of dronedarone and GIB.

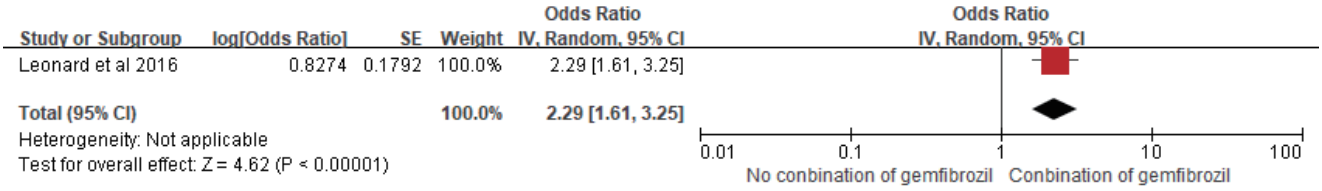


S35. Forest plot showing the association between conbination of CYP3A4 and/or P-gp-inhibitors and GIB.

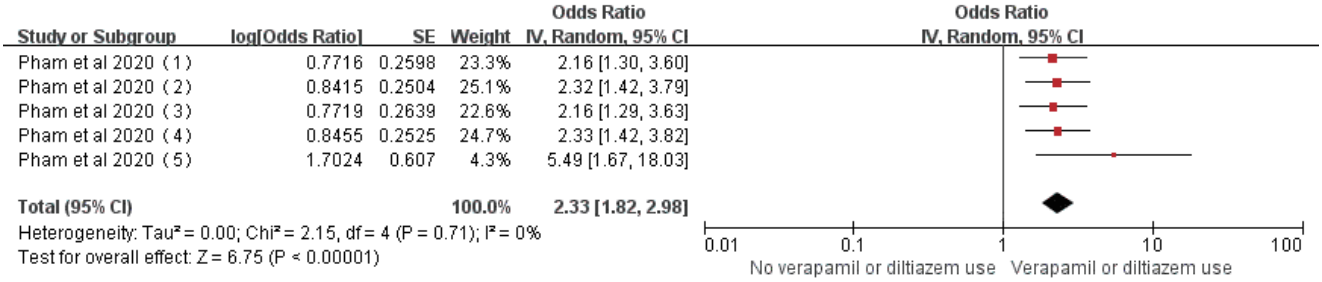


S36. Forest plot showing the association between conbination of digoxin and GIB.

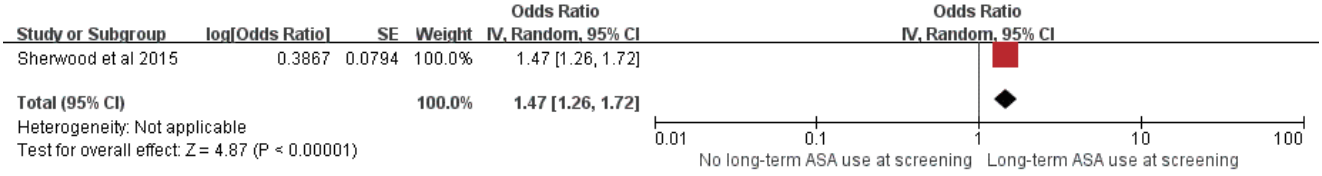
https://doi.org/10.3904/kjim.2023.098



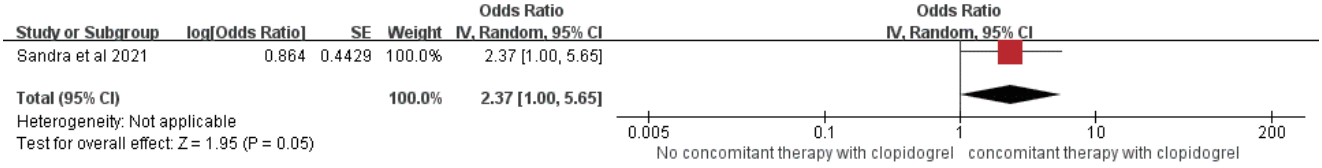
S37. Forest plot showing the association between conbination of gemfibrozil and GIB.



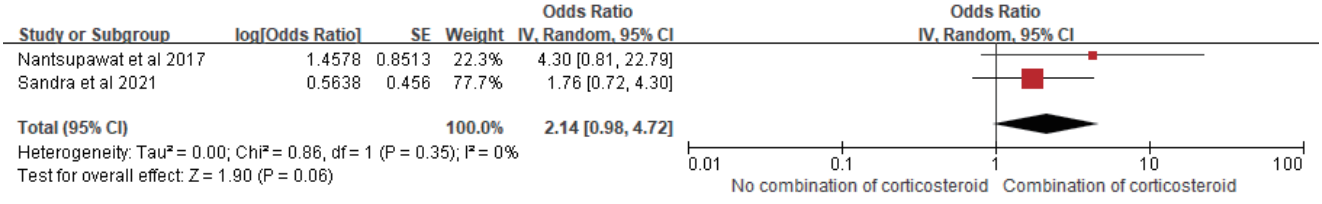
S38. Forest plot showing the association between conbination of verapamil or diltiazem and GIB.



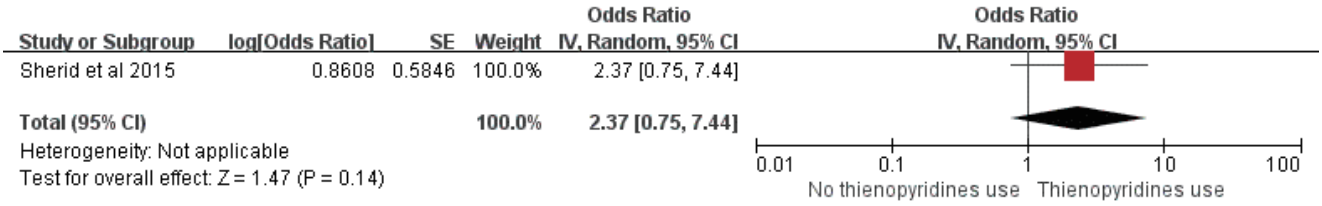
S39. Forest plot showing the association between long-term ASA use at screening and GIB.



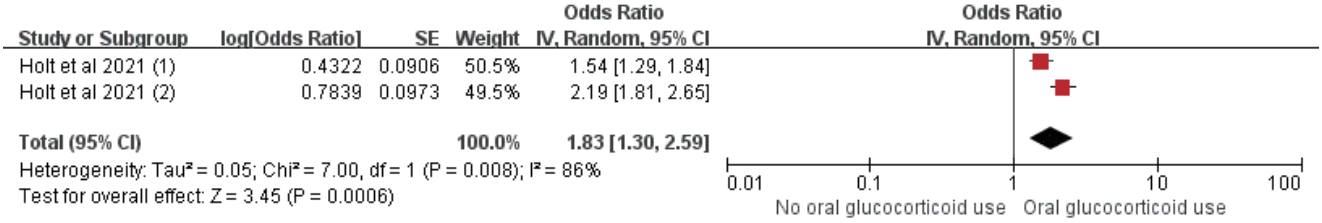
S40. Forest plot showing the association between concomitant therapy with clopidogrel and GIB.



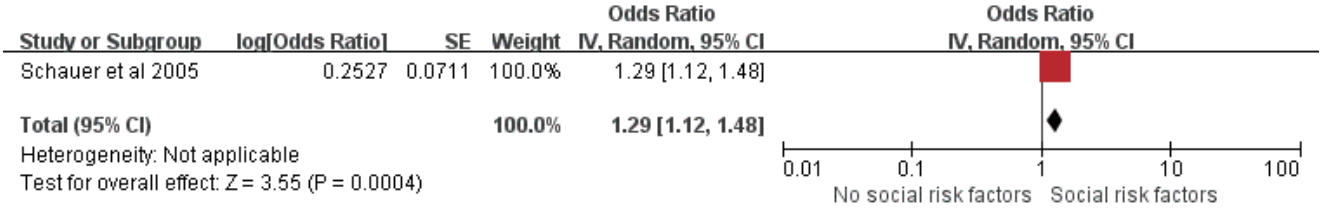
S41. Forest plot showing the association between combination of corticosteroid and GIB.



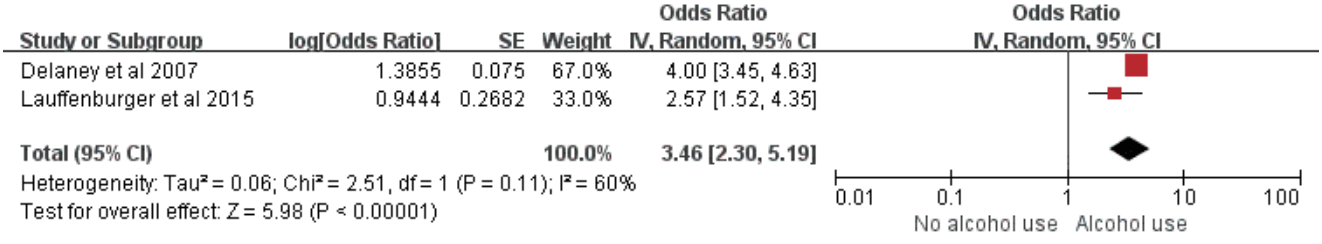
S42. Forest plot showing the association between conbination of thienopyridines and GIB.



S43. Forest plot showing the association between conbination of oral glucocorticoid and GIB.

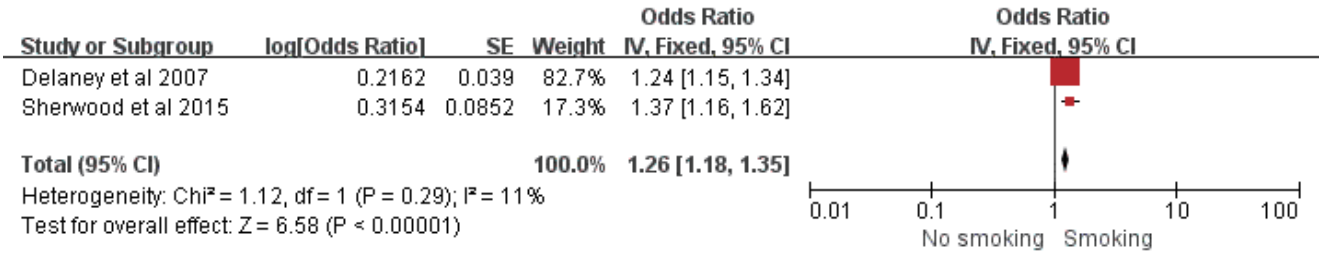


S44. Forest plot showing the association between social risk factors and GIB.

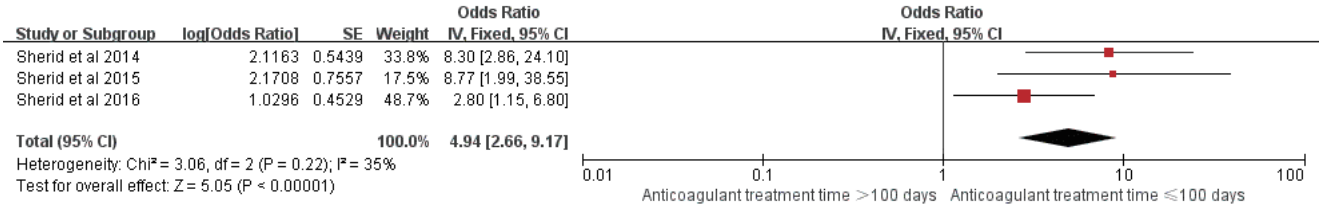


S45. Forest plot showing the association between alcohol use and GIB.

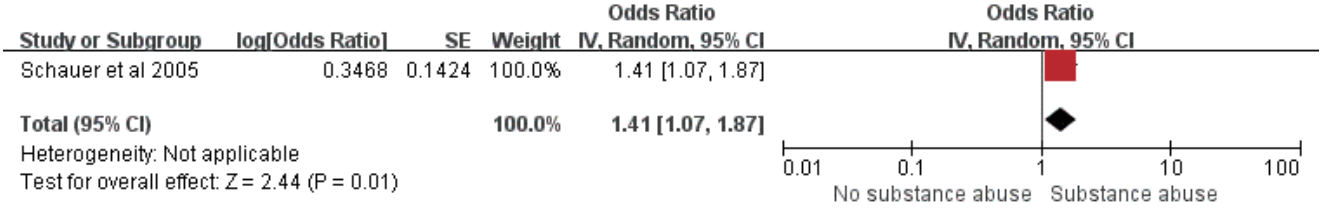
https://doi.org/10.3904/kjim.2023.098



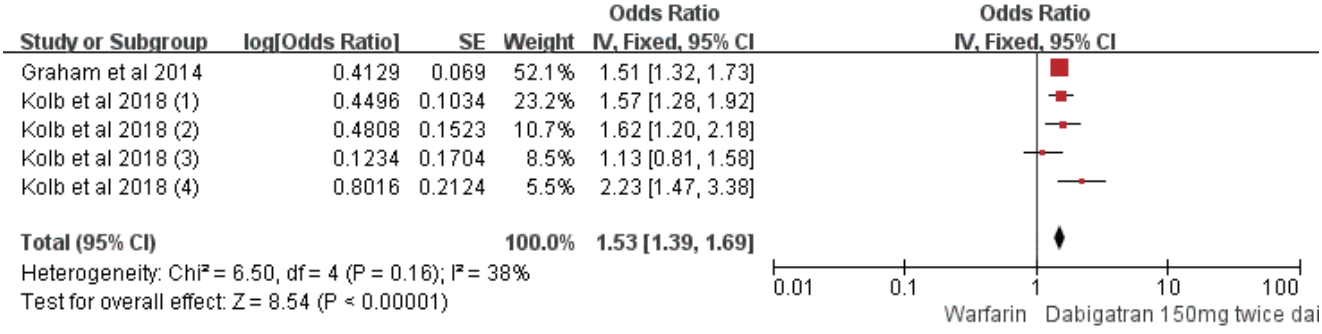
S46. Forest plot showing the association between smoking and GIB.



S47. Forest plot showing the association between anticoagulant treatment time ≤ 100days and GIB.



S48. Forest plot showing the association between substance abuse and GIB.



S49. Forest plot showing the association between dabigatran 150mg and GIB.

Supplementary Material 1. Search strategy.

PubMed: 1577
#1:anticoagulants [Mesh]
#2: "anticoagulant*"[Title/Abstract] OR "anticoagulant agent*"[Title/Abstract] OR "anticoagulation agent*"[Title/Abstract] OR "indirect thrombin inhibitor*"[Title/Abstract] OR "anticoagulant drug*"[Title/Abstract] OR "Anticoagulant therapy"[Title/Abstract]
#3:heparin[Mesh] OR Fondaparinux[Mesh] OR Heparin, Low-Molecular-Weight[Mesh]
#4:heparin[Title/Abstract] OR enoxaparin*[Title/Abstract] OR dalteparin*[Title/Abstract] OR tinzaparin*[Title/Abstract] OR nadroparin*[Title/Abstract] OR Fondaparinux[Title/Abstract] OR "heparin low molecular weight"[Title/Abstract] OR "heparin low molecular weight"[Title/Abstract] OR "Low Molecular Weight Heparin"[Title/Abstract] OR LMWH[Title/Abstract] OR "Unfractionated heparin"[Title/Abstract] OR UFH[Title/Abstract]
#5:Warfarin[MeSH Terms]
#6:Warfarin[Title/Abstract] OR "vitamin k antagonist*"[Title/Abstract] OR vka*[Title/Abstract]
#7:Dabigatran[MeSH] OR Rivaroxaban[MeSH] OR Factor Xa Inhibitors[MeSH]
#8:dabigatran[Title/Abstract] OR Pradaxa[Title/Abstract] OR rivaroxaban[Title/Abstract] OR Xarelto[Title/Abstract] OR apixaban[Title/Abstract] OR Eliquis[Title/Abstract] OR edoxaban[Title/Abstract] OR Savaysa[Title/Abstract] OR betrixaban[Title/Abstract] OR "factor xa inhibitor*"[Title/Abstract] OR "factor 10a inhibitor*"[Title/Abstract] OR "factor iia inhibitor*"[Title/Abstract] OR "direct thrombin inhibitor*"[Title/Abstract] OR "non vitamin k antagonists oral anticoagulant*"[Title/Abstract] OR "non vitamin k antagonist*"[Title/Abstract] OR noac*[Title/Abstract] OR "direct oral anticoagulant*"[Title/Abstract] OR doac*[Title/Abstract] OR "novel oral anticoagulant*"[Title/Abstract] OR "new oral anticoagulant*"[Title/Abstract] OR "new orally active anticoagulant*"[Title/Abstract] OR bivalirudin[Title/Abstract] OR Argatroban[Title/Abstract]
#9:gastrointestinal hemorrhage[MeSH Terms]
#10: "gastrointestinal hemorrhage"[Title/Abstract] OR "gastrointestinal bleeding"[Title/Abstract] OR GIB[Title/Abstract] OR "gi bleeding"[Title/Abstract] OR "gi hemorrhage"[Title/Abstract] OR "upper gastrointestinal hemorrhage"[Title/Abstract] OR "lower gastrointestinal hemorrhage"[Title/Abstract]
#11:risk factors[MeSH Terms] OR Causality[MeSH Terms] OR probability[MeSH Terms] OR Prognosis[MeSH Terms] OR risk assessment[MeSH Terms]
#12:"risk factor*"[Title/Abstract] OR Causality[Title/Abstract] OR cause*[Title/Abstract] OR probability[Title/Abstract] OR Prognosis[Title/Abstract] OR "risk assessment"[Title/Abstract] OR "Prediction model"[Title/Abstract] OR "Predicting"[Title/Abstract] OR "Predicting risk"[Title/Abstract] OR "Risk prediction"[Title/Abstract] OR "Risk Score"[Title/Abstract] OR "Risk Factor Score"[Title/Abstract] OR "Relative Risk"[Title/Abstract]
#13:#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#14:#9 OR #10
#15:#11 OR #12
#16:#13 AND #14 AND #15
Cochrane: 280
#1 MeSH descriptor: [anticoagulants] explode all trees
#2 (Anticoagulant* OR "anticoagulant agent*" OR "Anticoagulation Agent*" OR "indirect thrombin inhibitor*" OR "Anticoagulant Drug*" OR "Anticoagulant therapy"):ti,ab,kw
#3 MeSH descriptor: [heparin] explode all trees
#4 MeSH descriptor: [Fondaparinux] explode all trees
#5 MeSH descriptor: [Heparin, Low-Molecular-Weight] explode all trees
#6 (Heparin OR Enoxaparin* OR dalteparin* OR tinzaparin* OR nadroparin* OR Fondaparinux OR "Heparin, Low-Molecular-Weight" OR "Low Molecular Weight Heparin" OR LMWH OR "Unfractionated heparin" OR UFH):ti,ab,kw
#7:MeSH descriptor: [warfarin] explode all trees
#8:(Warfarin OR "vitamin K antagonist*" OR VKA*):ti,ab,kw
#9:MeSH descriptor: [Dabigatran] explode all trees
#10:MeSH descriptor: [Rivaroxaban] explode all trees
#11:MeSH descriptor: [Factor Xa Inhibitors] explode all trees
#12:("dabigatran" OR "Pradaxa" OR "rivaroxaban" OR "Xarelto" OR "apixaban" OR "Eliquis" OR (Rivaroxaban OR Xarelto OR dabigatran OR Pradaxa OR apixaban OR Eliquis OR edoxaban OR Savaysa OR betrixaban OR "factor Xa inhibitor*" OR "factor 10a inhibitor*" OR "factor IIa inhibitor*" OR "direct thrombin inhibitor*" OR "non-vitamin K antagonists oral anticoagulant*" OR "non-vitamin K antagonist*" OR NOAC* OR "direct oral anticoagulant*" OR DOAC* OR "novel oral anticoagulant*" OR "new oral anticoagulant*" OR new orally active anticoagulant* OR bivalirudin OR Argatroban):ti,ab,kw

https://doi.org/10.3904/kjim.2023.098

#13:MeSH descriptor: [gastrointestinal hemorrhage] explode all trees
#14:("gastrointestinal hemorrhage" OR "gastrointestinal bleeding" OR GIB OR "GI bleeding" OR "GI hemorrhage" OR "upper gastrointestinal hemorrhage" OR "lower gastrointestinal hemorrhage"):ti,ab,kw
#15:MeSH descriptor: [risk factors] explode all trees
#16：MeSH descriptor:[Causality] explode all trees
#17:MeSH descriptor:[probability] explode all trees
#18:MeSH descriptor:[Prognosis] explode all trees
#19:MeSH descriptor:[risk assessment] explode all trees
#20:("risk factor*" OR Causality OR cause* OR probability OR Prognosis OR "risk assessment" OR "Prediction model" OR Predicting OR "Predicting risk" OR "Risk prediction" OR "Risk Score" OR "Risk Factor Score" OR "Relative Risk"):ti,ab,kw
#21:#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
#22:#13 OR #14
#23:#15 OR #16 OR #17 OR #18 OR #19 OR #20
#24:#21 AND #22 AND #23
Web of science: 769
#1:TS=Anticoagulant* OR "anticoagulant agent*" OR "Anticoagulation Agent*" OR "indirect thrombin inhibitor*" OR "Anticoagulant Drug*" OR "Anticoagulant therapy"
#2:TS=Heparin OR Enoxaparin* OR dalteparin* OR tinzaparin* OR nadroparin* OR Fondaparinux OR "Heparin, Low-Molecular-Weight" OR "Low Molecular Weight Heparin" OR LMWH OR "Unfractionated heparin" OR UFH
#3:TS=Warfarin OR "vitamin K antagonist*" OR VKA*
#4:TS= Rivaroxaban OR Xarelto OR dabigatran OR Pradaxa OR apixaban OR Eliquis OR edoxaban OR Savaysa OR betrixaban OR "factor Xa inhibitor*" OR "factor 10a inhibitor*" OR "factor IIa inhibitor*" OR "direct thrombin inhibitor*" OR "non-vitamin K antagonists oral anticoagulant*" OR "non-vitamin K antagonist*" OR NOAC* OR "direct oral anticoagulant*" OR DOAC* OR "novel oral anticoagulant*" OR "new oral anticoagulant*" OR new orally active anticoagulant* OR bivalirudin OR Argatroban
#5:TS="gastrointestinal hemorrhage" OR "gastrointestinal bleeding" OR GIB OR "GI bleeding" OR "GI hemorrhage" OR "upper gastrointestinal hemorrhage" OR "lower gastrointestinal hemorrhage"
#6:TS="risk factor*" OR Causality OR cause* OR probability OR Prognosis OR "risk assessment" OR "Prediction model" OR Predicting OR "Predicting risk" OR "Risk prediction" OR "Risk Score" OR "Risk Factor Score" OR "Relative Risk"
#7:#1 OR #2 OR #3 OR #4
#8:#7 AND #5 AND #6
Embase: 10146
#1 'anticoagulant agent '/exp
#2 anticoagulant*:ti,ab,kw OR 'anticoagulant agent*':ti,ab,kw OR 'anticoagulation agent*':ti,ab,kw OR 'indirect thrombin inhibitor*':ti, ab, kw OR 'anticoagulant drug*':ti,ab,kw OR 'anticoagulant therapy':ti,ab,kw
#3 'heparin'/exp OR 'fondaparinux'/exp OR 'low molecular weight heparin'/exp
#4heparin:ti,ab,kw OR fondaparinux:ti,ab,kw OR 'heparin, low-molecular-weight':ti,ab,kw OR 'low molecular weight heparin':ti,ab,kw OR lmwh:ti,ab,kw OR 'unfractionated heparin':ti,ab,kw OR ufh:ti,ab,kw OR enoxaparin*:ti,ab,kw OR dalteparin*:ti,ab,kw OR tinzaparin*:ti,ab,kw OR nadroparin*:ti,ab,kw
#5'warfarin'/exp
#6warfarin:ti,ab,kw OR 'vitamin k antagonist*':ti,ab,kw OR vka*:ti,ab,kw
#7 'dabigatran'/exp OR 'rivaroxaban'/exp OR 'apixaban'/exp OR 'edoxaban'/exp OR 'blood clotting factor 10a inhibitor'/exp OR 'betrixaban'/exp OR 'bivalirudin'/exp OR 'argatroban'/exp
#8rivaroxaban:ti,ab,kw OR xarelto:ti,ab,kw OR dabigatran:ti,ab,kw OR pradaxa:ti,ab,kw OR apixaban:ti,ab,kw OR eliquis:ti,ab,kw OR edoxaban:ti,ab,kw OR savaysa:ti,ab,kw OR betrixaban:ti,ab,kw OR 'factor xa inhibitor*':ti,ab,kw OR 'factor 10a inhibitor*':ti,ab,kw OR 'factor iia inhibitor*':ti,ab,kw OR 'direct thrombin inhibitor*':ti,ab,kw OR 'non-vitamin k antagonists oral anticoagulant*':ti,ab,kw OR 'non-vitamin k antagonist*':ti,ab,kw OR noac*:ti,ab,kw OR 'direct oral anticoagulant*':ti,ab,kw OR doac*:ti,ab,kw OR 'novel oral anticoagulant*':ti,ab,kw OR 'new oral anticoagulant*':ti,ab,kw OR 'new orally active anticoagulant*':ti,ab,kw OR bivalirudin:ti,ab,kw OR argatroban:ti,ab,kw
#9'gastrointestinal hemorrhage'/exp
#10'gastrointestinal hemorrhage':ti,ab,kw OR 'gastrointestinal bleeding':ti,ab,kw OR gib:ti,ab,kw OR 'gi bleeding':ti,ab,kw OR 'gi hemorrhage':ti,ab,kw OR 'upper gastrointestinal hemorrhage':ti,ab,kw OR 'lower gastrointestinal hemorrhage':ti,ab,kw
#11'risk factor'/exp OR 'causality'/exp OR 'probability'/exp OR 'prognosis'/exp OR 'risk assessment'/exp
#12'risk factor*':ti,ab,kw OR causality:ti,ab,kw OR cause*:ti,ab,kw OR probability:ti,ab,kw OR prognosis:ti,ab,kw OR 'risk assess-

ment':ti,ab,kw OR 'prediction model':ti,ab,kw OR predicting:ti,ab,kw OR 'predicting risk':ti,ab,kw OR 'risk prediction':ti,ab,kw OR 'risk score':ti,ab,kw OR 'risk factor score':ti,ab,kw OR 'relative risk':ti,ab,kw
#13:#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#14:#9 OR #10
#15:#11 OR #12
#16:#13 AND #14 AND #15

https://doi.org/10.3904/kjim.2023.098