HHS Public Access

Author manuscript

JAMA. Author manuscript; available in PMC 2019 December 04.

Published in final edited form as:

JAMA. 2018 December 04; 320(21): 2221–2230. doi:10.1001/jama.2018.17242.

Association of Oral Anticoagulants and Proton-Pump-Inhibitor Co-Therapy with Hospitalization for Upper Gastrointestinal Bleeding

Wayne A. Ray, Ph.D., **Cecilia P. Chung, M.D., MPH**, **Katherine T. Murray, M.D.**, **Walter E. Smalley, MD, MPH**, **James R. Daugherty, M.S.**, **William D. Dupont, Ph.D.**, and **C. Michael Stein, MB, ChB**

Vanderbilt University School of Medicine: Department of Health Policy (WAR, JRD, WES); Departments of Medicine and Pharmacology, Divisions of Cardiology (KTM), Rheumatology (CPC, CMS), Clinical Pharmacology (CPC, CMS, KTM), Gastroenterology (WES), and Biostatistics (WDD) and the Veterans' Administration Tennessee Valley Health Care System (CPC, WES) Nashville, TN.

Abstract

Importance: Anticoagulant choice and proton pump inhibitor (PPI) co-therapy could affect risk of upper gastrointestinal bleeding, a frequent and potentially serious complication of oral anticoagulant treatment.

Objective: Compare upper gastrointestinal bleeding hospitalization incidence for individual anticoagulants without and with PPI co-therapy and determine variation according to underlying gastrointestinal bleeding risk.

Design, Setting, and Participants: Retrospective cohort study in Medicare patients between 1 January 2011 and 30 September 2015.

Exposures: Apixaban, dabigatran, rivaroxaban or warfarin treatment; PPI co-therapy; and gastrointestinal bleeding risk score encompassing patient characteristics, medication use, and comorbidity.

Main Outcomes and Measures: Upper gastrointestinal bleeding hospitalizations: adjusted incidence and risk difference (RD) per 10,000 person-years of anticoagulant treatment, incidence-rate-ratios (IRR).

Results: There were 1,643,123 patients with 1,713,183 new episodes of oral anticoagulant treatment (mean age 76.4 [std, 2.4] years, 56.1% female, 74.9% atrial fibrillation). During 754,389 treatment person-years without PPI co-therapy, the adjusted incidence of upper gastrointestinal

Corresponding author contact Information. Address: Wayne A. Ray Ph.D., Department of Health Policy, Village at Vanderbilt, Suite 2600, 1501 21st Ave South, Nashville, TN 37212. wayne.ray@vanderbilt.edu, Phone: 615-322-2017.

IRB. The Vanderbilt Institutional Review Board approved the study.

Authorship. Funding agencies had no role in study conduct or reporting. The listed authors were entirely responsible for study design, data analysis, manuscript preparation, and publication decisions. The first manuscript draft was written by the primary author, who vouches for the data and the analysis.

Conflict of interest. There are no conflicts of interest for any author to declare.

bleeding hospitalizations (N=7,119) was 115 (95% confidence interval, 112–118) per 10,000 person-years. The incidence for rivaroxaban (1,278 hospitalizations/114,168 person-years) was 144 (136–152) per 10,000 person-years, significantly greater than that for apixaban (279/43,970, IRR=1.97 [1.73–2.25], RD=71 [59 to 83]), dabigatran (629/79,739, IRR=1.19 [1.08–1.32], RD=23 [11 to 36]) and warfarin (4,933/516,512, IRR=1.27 [1.19–1.35], RD=30 [20 to 41]). The incidence for apixaban was significantly lower than that for dabigatran (IRR=0.61 [0.52–0.70], RD=−48 [−61 to −34]) and warfarin (IRR=0.64 [0.57–0.73], RD=−40 [−50 to −31]). When anticoagulant treatment with PPI co-therapy (264,447 person-years) was compared to that without PPI co-therapy, risk of upper gastrointestinal bleeding hospitalizations (N=2,245) was lower for each anticoagulant: apixaban—IRR=0.66 (0.52–0.85), RD=−24 (−38 to −11); dabigatran--IRR=0.49 (0.41–0.59), RD=−61 (−75 to −47); rivaroxaban:--IR=0.75 (0.68–0.84), RD=−36 (−49 to −22); warfarin—IRR=0.65 (0.62–0.69), RD=−39 (−44 to −34). Absolute differences between anticoagulants and treatment without/with PPI co-therapy were greater for patients with higher gastrointestinal bleeding risk scores. For patients in the upper quartile, the incidence for rivaroxaban without PPI was 327 (302–355) per 10,000 versus 120 (93–153) per 10,000 for apixaban with PPI (RD=208 [169 to 247]).

Conclusions and Relevance: Among Medicare patients initiating oral anticoagulant treatment, incidence of upper gastrointestinal bleeding hospitalization was highest for rivaroxaban and lowest for apixaban and for each anticoagulant, was lower among patients prescribed PPI co-therapy. These findings may inform assessment of risks and benefits when choosing anticoagulant agents.

Keywords

oral anticoagulants; warfarin; dabigatran; rivaroxaban; apixaban; proton-pump inhibitor; gastrointestinal bleeding

The risk of major upper gastrointestinal bleeding, a frequent and potentially serious complication of oral anticoagulant treatment,[1,2] could be affected by both anticoagulant choice[3] and proton-pump inhibitor (PPI) co-therapy.[4] In the pivotal efficacy trials, the non-vitamin K oral anticoagulants (NOACs) were non-inferior or better than warfarin for prevention of stroke, but had increased risk of major gastrointestinal bleeding.[1] Although the individual NOACs have not been compared in large clinical trials, recent observational data suggest that the incidence of serious anticoagulant-related gastrointestinal bleeding is greater for rivaroxaban than for dabigatran[5] and less for apixaban than for the other oral anticoagulants.[6–8] However, the clinical importance of anticoagulant choice for patients with elevated gastrointestinal bleeding risk is uncertain.

PPIs, which reduce gastric acid production, promote ulcer healing, and prevent ulcer recurrence,[9] could affect the relative upper gastrointestinal safety of oral anticoagulants, particularly in high-risk patients. PPI co-therapy is associated with reduced incidence of upper gastrointestinal bleeding during treatment with warfarin[4] and dabigatran;[10] the absolute reduction in risk increases with the prevalence of several known risk factors for gastrointestinal bleeding.[4] However, whether PPI co-therapy is associated with lower incidence of anticoagulant-related serious upper gastrointestinal bleeding for other NOACs

or alters the relative upper gastrointestinal safety of the individual oral anticoagulants is unknown.

This retrospective cohort study of Medicare beneficiaries initiating oral anticoagulant treatment sought to better define the association of both individual drug choice and PPI co-therapy with upper gastrointestinal safety. The primary objectives were: 1) compare the incidence of serious upper gastrointestinal bleeding for the individual anticoagulants both without and with PPI co-therapy; and 2) determine how the risk associated with individual anticoagulants and PPI co-therapy varied according to the patient's gastrointestinal bleeding risk.

Methods

Sources of Data

The study cohort was identified from computerized files for U.S. Medicare beneficiaries,[5] which record periods of enrollment and medical care encounters for pharmacy, hospital, outpatient, and nursing home services. These files provided an efficient means to identify the cohort and obtain study data.[11] The study population was restricted to beneficiaries with at least 1 year of enrollment in Medicare parts A, B, and D, and no enrollment in part C (managed care, with potentially less complete recording of medical care encounters). The data were accessed through the Virtual Research Data Center (VRDC), a cloud-based repository of de-identified Medicare files. The study was approved by the Vanderbilt University Medical Center Institutional Review Board, with waiver of informed consent.

Medication use was identified from pharmacy files that recorded filled prescriptions, with the dispensing date, drug, quantity, dose, and days of supply. Because of Medicare reimbursement restrictions, pharmacy files do not include information on low-dose aspirin, over-the-counter non-selective nonsteroidal anti-inflammatory drugs (NSAIDs), as well as most other over-the-counter medications. Although some PPIs are available over-the-counter, they are recommended at low doses and for 14 day-courses up to three times a year (http://www.fda.gov/Drugs/DrugSafety/ucm245011.htm).

Cohort

The cohort included persons 30 years of age or older with a qualifying prescription for apixaban, dabigatran, rivaroxaban, or warfarin (multiple drugs not allowed) filled from 1 January 2011 through 30 September 2015. Edoxaban was not considered because relatively few patients started treatment with this drug during the study period. Cohort members could not have had any oral anticoagulant prescription in the preceding year (eTable 1).[12] They had to have complete demographic information, full pharmacy benefits and, to assure regular contact with medical care, at least one outpatient visit and one filled prescription in the prior year. Exclusion criteria were end-stage renal disease, serious gastrointestinal illness predisposing to bleeding (e.g., esophageal varices or gastrointestinal cancer), or a bleeding-related hospitalization in the past year (eTable 1).

Patients entered the cohort on the day they filled their first study anticoagulant prescription. Followup ended on the first of: 30 September 2015, 365 days after no filling of the study

drug prescription, filling of a prescription for a different oral anticoagulant, loss of enrollment, failure to meet the cohort eligibility criteria, a bleeding-related hospitalization, or death. Patients could reenter the cohort if they subsequently met the eligibility criteria.

Medication Exposure

Because the association of study medications with the risk of bleeding is thought to be acute, each day of study followup was classified according to probable study medication use, as identified from filled prescriptions (eAppendix §2). The exposure period was based upon the dispensed days of supply.

Oral anticoagulant treatment during followup was the period during which patients were likely to have increased risk of anticoagulant-related bleeding. This period began on the date the prescription was filled, and, given potential residual anticoagulant effects, ended either 1 (apixaban, dabigatran, rivaroxaban) or 3 days (warfarin) after the end of the days of supply (eAppendix §2). All cohort followup and study analyses were restricted to periods of oral anticoagulant treatment.

There were three possible categories of PPI exposure during oral anticoagulant treatment (eAppendix §2). *PPI co-therapy*, person-days on which the patient was likely to be taking the PPI and thus for which a gastroprotective effect was most plausible, included the interval between the filling of a PPI prescription through the end of days of supply. *Former co-therapy* consisted of person-days for patients who had filled a PPI prescription in the past year, but whose days of supply had ended and thus should not benefit from co-therapy. Analysis of this person-time permitted assessment of confounding by unmeasured factors associated with receiving a PPI prescription. *No co-therapy* consisted of person-days with no filled PPI prescription in the past year.

Other medications for which current use is associated with increased risk of gastrointestinal bleeding were NSAIDs, antiplatelet drugs (ticlopidine, clopidogrel, prasugrel, ticagrelor, dipyridamole, cilostazol) and other anticoagulants (heparin, enoxaparin). For NSAIDs and anticoagulants, concurrent use included the interval between the prescription fill through the end of the days of supply; for antiplatelet drugs that irreversibly inhibit platelet aggregation, this interval was extended 7 days (eAppendix §2).

Endpoints

The primary study endpoint was hospitalization for upper gastrointestinal bleeding potentially preventable by PPI co-therapy (eAppendix §3). This included bleeding related to esophagitis, peptic ulcer disease, and gastritis, but excluded bleeding unlikely to be affected by PPIs (e.g., Mallory Weiss tear). Hospitalizations for other gastrointestinal bleeding (predominantly lower gastrointestinal with some gastrointestinal hemorrhages for which site not indicated, eAppendix §3) were analyzed as a negative outcome control.[13]

Bleeding-related hospitalizations were identified from hospital admissions with a previously validated algorithm (eAppendix §3).[14] The positive predictive value was 99% for all bleeding-related hospitalizations, 98% for all gastrointestinal bleeding, and 80% for upper gastrointestinal bleeding (eTable 2). The lower positive predictive value for upper

gastrointestinal bleeding resulted from occasional use of diagnosis codes that did not specify the site of the gastrointestinal bleeding.

Analysis

Covariates.—Because upper gastrointestinal bleeding risk could influence both anticoagulant choice and PPI co-therapy, the analysis controlled for 85 covariates plausibly associated with the risk of bleeding hospitalizations (eTable 3). These included demographic information, anticoagulant indication, time since treatment initiation, upper gastrointestinal disease or signs of bleeding, other gastrointestinal disease or symptoms, medications that affect bleeding risk, cardiovascular disease for which low-dose aspirin prophylaxis is recommended (surrogate for low-dose aspirin), other cardiovascular conditions or risk factors, indicators of frailty, alcohol abuse, liver disease, and recent medical care utilization. Because changes in covariates after cohort entry (e.g. start NSAID) were likely to be related to PPI co-therapy, these were updated for each followup day.

Statistical analysis.—Time-dependent Poisson regression models with all study covariates were fit to estimate the adjusted incidence of gastrointestinal bleeding hospitalizations according to both individual anticoagulants and PPI co-therapy (eAppendix §4). Because a single patient could have person-time with and without PPI co-therapy as well as multiple episodes of anticoagulant treatment that were considered to be independent in the primary analysis, sensitivity analyses were performed with patient as a random effect and with no cohort reentry (eAppendix §4). Models were fit for the entire cohort with an exposure variable with levels for individual anticoagulant-PPI co-therapy combinations or, for analyses of all anticoagulants, PPI co-therapy. Incidence rate-ratios (IRRs) for study comparisons were estimated from single-degree-of-freedom contrasts. The adjusted incidence of upper gastrointestinal bleeding hospitalizations for anticoagulant-PPI co-therapy categories was estimated from the regression model and from these, the absolute difference in incidence, or *risk difference* (RD) was estimated by subtraction (eAppendix §4). Comparisons were considered statistically significant if the 95% CIs excluded 1 (IRRs) or 0 (RDs); there was no adjustment for multiple comparisons. All statistical analyses were performed with SAS 9.4.

Gastrointestinal bleeding risk score.—Several analyses were stratified according to an internally derived integrated measure of gastrointestinal bleeding risk (eAppendix §5) that included all study covariates. It was calculated as a disease risk score,[15–17] the expected incidence of hospitalization for upper gastrointestinal bleeding given the study covariates (assuming warfarin treatment and no PPI co-therapy). Disease risk scores are a standard technique for risk stratification within a specific population because the covariate definitions and their weights are internally derived.[18,19] Consequently, they incorporate information from all measured patient factors and are specifically calibrated for the study endpoint. The score was expressed as a risk quantile from 0 to 19; thus, 0 indicates the lowest-risk 5% and 19 the highest-risk 5% of the cohort. The analysis of all anticoagulants classified the cohort according to risk score deciles; that for individual drugs according to risk score quartiles.

Sensitivity analyses.—These assessed how key patient/treatment characteristics influenced study findings, including analysis of patients with non-valvular atrial fibrillation and restriction of NOACs to usual doses for atrial fibrillation. Other analyses tested sensitivity to statistical assumptions (eAppendix §4), including considering death as a competing risk, and fixing covariates that were plausible causal pathway confounders at baseline. Covariate balancing was considered as an alternative to multivariable regression by propensity-score matching exposure groups according to baseline covariates. In this analysis, neither PPI co-therapy nor covariates were time-dependent and followup included only the first year of anticoagulant treatment, which prevented causal pathway confounding and reduced variation in both treatment duration and censoring (eAppendix §4). The potential magnitude of confounding by unmeasured factors associated with PPI co-therapy was assessed by considering both the association of former co-therapy with upper gastrointestinal bleeding hospitalizations (negative exposure variant) and that of current co-therapy for hospitalizations for gastrointestinal bleeding at other sites (negative outcome).[13]

Results

Cohort

There were 1,643,123 patients with 1,713,183 new episodes of oral anticoagulant treatment; the mean age was 76.4 (std, 2.4) years, 56.1% were female, and the indication was atrial fibrillation for 74.9%. Cohort followup included 754,389 person-years of anticoagulant treatment without PPI co-therapy (apixaban:43,970, dabigatran:79,739, rivaroxaban: 114,168, and warfarin:516,512) and 264,447 person-years with PPI co-therapy (apixaban: 14,989, dabigatran:26,572, rivaroxaban:38,958, warfarin:183,929).

For each individual oral anticoagulant, patients with PPI co-therapy had increased prevalence of risk factors for gastrointestinal bleeding (Table 1, eTable 4). These patients were more likely to have recent initiation of anticoagulant treatment, upper gastrointestinal disease history or signs of bleeding, and current use of medications that increase the risk of bleeding. Thus, patients with PPI co-therapy had an increase of one decile in the summary gastrointestinal bleeding risk score. Regardless of PPI co-therapy, patients with apixaban treatment had the highest gastrointestinal bleeding risk scores and those with dabigatran treatment had the lowest scores.

Individual Anticoagulant and PPI co-therapy

During anticoagulant treatment without PPI co-therapy, the adjusted incidence of upper gastrointestinal bleeding hospitalizations (N=7,119) was 115 (112–118) per 10,000 person-years. The incidence (Figure 1, Table 2) for rivaroxaban (144 [136–152] per 10,000) was significantly greater than that for apixaban (IRR=1.97 [1.73–2.25], RD=71 [59 to 83]), dabigatran (IRR=1.19 [1.08–1.32], RD=23 [11 to 36]) and warfarin (IRR=1.27 [1.19–1.35], RD=30 [20 to 41]). The incidence for apixaban was significantly less than that for dabigatran (IRR=0.61 [0.52–0.70], RD=−48 [−61 to −34]) and warfarin (IRR=0.64 [0.57–0.73], RD=−40 [−50 to −31]).

During anticoagulant treatment with PPI co-therapy, the adjusted incidence of upper gastrointestinal bleeding hospitalizations (N=2,245) was lower than that for treatment without PPI co-therapy (IRR=0.66 [0.62–0.69], RD=−39 [−44 to −35]). With PPI co-therapy, the incidence of upper gastrointestinal bleeding hospitalizations was significantly lower for each individual anticoagulant (Figure 1, Table 2). The lower incidence was most pronounced for dabigatran (IRR=0.49 [0.41–0.59], RD=−61 [−75 to −47]) and least pronounced for rivaroxaban (IRR=0.75 [0.68–0.84], RD=−36 [−49 to −22]). For patients with PPI co-therapy, the incidence of upper gastrointestinal hospitalizations for rivaroxaban was significantly greater than that for the other anticoagulants. However, apixaban and dabigatran no longer differed significantly.

Gastrointestinal Bleeding Risk

The risk of upper gastrointestinal bleeding hospitalizations was greater for higher deciles of the gastrointestinal bleeding risk score (Figure 2). For patients with no PPI co-therapy, the respective decile-specific incidences for the lowest and highest deciles were 15 (13–18) and 397 (381–414) per 10,000 person-years. There was a significant protective association with PPI co-therapy for all patients except those in the lowest risk decile. The absolute incidence difference increased with increasing risk, from an RD of 0 (−6 to 6) hospitalizations per 10,000 person-years for the lowest decile to −118 (−142 to −93) per 10,000 for the highest decile. When patients in decile 10 and decile 1 were compared (eTable 5), the former more often had: advanced age, Medicaid enrollment, nursing home residence, recent start of anticoagulant therapy, upper gastrointestinal disease history or signs of bleeding, current use of medications that increase bleeding risk, eligibility for aspirin prophylaxis, other cardiovascular disease, frailty, and a hospitalization or gastrointestinal emergency department visit in the past year.

The absolute difference between rivaroxaban and apixaban in the adjusted incidence of upper gastrointestinal bleeding hospitalizations was greater with higher gastrointestinal bleeding risk scores, regardless of PPI co-therapy (Figure 3). Patients in the upper risk quartile without PPI co-therapy treated with rivaroxaban or apixaban had 327 (302–355) and 162 (137–190) hospitalizations per 10,000 person-years, respectively (RD=166 [130 to 202]). For those with PPI co-therapy, the adjusted incidences per 10,000 person-years for rivaroxaban and apixaban were 258 (230–289) and 120 (93–153) respectively (RD=138 [97 to 179]). When rivaroxaban without PPI was compared to apixaban with PPI, the difference was 208 hospitalizations (169 to 247) per 10,000 person-years.

For patients in the upper quartile of the gastrointestinal bleeding risk score, the association between PPI co-therapy and reduced incidence of upper gastrointestinal bleeding hospitalizations was greatest for dabigatran (Figure 3). The adjusted incidence per 10,000 person-years was 299 (265–337) without co-therapy compared with 138 (112–171) with co-therapy (RD=−161 [−207 to −115]).

Sensitivity Analyses

Analyses that assessed the sensitivity of study results to changes in either the study population or the statistical methods (eTable6) focused on two key comparisons: apixaban vs

rivaroxaban in patients with no PPI co-therapy and PPI co-therapy vs no co-therapy for all study anticoagulants. For the first comparison, the IRR and RD from the primary analysis were 0.51 (0.44–0.58) and −71 (−83 to −59); the sensitivity analyses had IRRs between 0.45 (0.39–0.53) and 0.55 (0.47–0.65) and RDs between −93 (−109 to −77) and −63 (−74 to −53). For the second comparison, the IRR and RD from the primary analysis were 0.66 (0.62–0.69) and −39 (−44 to −35); the sensitivity analyses had IRRs between 0.64 (0.60–0.69) and 0.71 (0.66–0.75) and RDs between −48 (−59 to −38) and −33 (−37 to −29).

Discussion

In this large population-based study of new episodes of oral anticoagulant treatment, the incidence of hospitalizations for upper gastrointestinal bleeding was highest for rivaroxaban and lowest for apixaban, which is consistent with previous studies.[5–8,20] Because rivaroxaban is given as a single daily dose intended to maintain 24 hour therapeutic levels, the relative peak plasma concentrations are greater than those for other oral anticoagulants.[21] Given the steep rise of bleeding risk with increased NOAC concentration,[22] this may explain the elevated risk for upper gastrointestinal bleeding hospitalizations.

PPI co-therapy was associated with decreased incidence of upper gastrointestinal bleeding hospitalizations for all study anticoagulants. However, the reduction was most pronounced for dabigatran, which is consistent with the large decrease observed by Chan *et al.*[10] and may be explained by dabigatran-related upper gastrointestinal lesions, potentially the result of direct mucosal injury by the drug's tartaric acid core.[23,24] PPI co-therapy could prevent or heal these lesions, thus reducing the risk of bleeding during dabigatran treatment. Alternatively, some data indicate that PPIs decrease dabigatran bioavailability,[25,26] with the potential for reduced anticoagulation and decreased bleeding risk. The in-progress COMPASS trial[27] will provide further data on the benefits and risks of PPI co-therapy during anticoagulant treatment.

The association of both anticoagulant choice and PPI co-therapy with the risk of upper gastrointestinal bleeding hospitalizations varied markedly according to patient's underlying gastrointestinal risk. Indeed, the magnitude of absolute differences in incidence for the cohort was driven by the upper quartile of risk. For these patients, the difference in the annual incidence of upper gastrointestinal bleeding hospitalizations between the treatment strategies with the worst (rivaroxaban without PPI) and the best (apixaban with PPI) gastrointestinal safety was 2.1 hospitalizations per 100 person-years. These findings indicate the potential benefits of a gastrointestinal bleeding risk assessment prior to initiating anticoagulant treatment.

Limitations

This study had several limitations. First, there was potential misclassification of anticoagulant treatment, PPI co-therapy, and NSAID use, both because these were determined from filled prescriptions and Medicare restricted reimbursement for many over-the-counter drugs. Nevertheless, the resulting misclassification should bias to the null because it is likely to either be non-differential, or, as is probable for NSAIDs, which cause gastrointestinal bleeding and are positively correlated with PPI co-therapy,[4] lead to

underestimation of PPI effects. Second, there could be confounding by unmeasured factors, such as aspirin exposure (diagnosed cardiovascular disease for which aspirin prophylaxis is recommended was a surrogate) or *Helicobacter pylori* infection. However, the positive correlation between recorded risk factors for gastrointestinal bleeding and both apixaban and PPI co-therapy suggests bias due to unmeasured confounders should be conservative. The absence of protective associations of former PPI co-therapy with upper gastrointestinal bleeding and PPI co-therapy with bleeding at other gastrointestinal sites also suggests confounding does not explain study findings. Third, gastrointestinal bleeding risk was measured with a disease risk score,[15–17] an internal measure suitable for risk stratification within the study cohort[18,19] that has not been studied in other populations. Fourth, there are limits to study generalizability. The cohort excluded patients with prior gastrointestinal bleeding hospitalizations or who switched to a different anticoagulant and consisted of Medicare enrollees, a population with both increased prevalence of anticoagulant treatment and greater risk of major upper gastrointestinal bleeding relative to younger populations.

Conclusion

Among Medicare patients initiating oral anticoagulant treatment, incidence of upper gastrointestinal bleeding hospitalization was highest for rivaroxaban and lowest for apixaban and for each anticoagulant, was lower among patients prescribed PPI co-therapy. These findings may inform assessment of risks and benefits when choosing anticoagulant agents.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors have no conflicts of interest to declare. The study was supported by grants from the NHLBI (# HL114518), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (K23AR064768) and the Rheumatology Research Foundation Career Development K Supplement. Access to study data was provided by the Virtual Research Data Center of the U.S. Center for Medicare/Medicaid Services.

The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Dr. Ray, the principal investigator, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Support. Supported in part by a grant from the National Heart, Lung, and Blood Institute (HL114518). Dr. Chung was funded by grants from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (K23AR064768) and the Rheumatology Research Foundation Career Development K Supplement.

Reference List

1. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014;383(9921):955–962. [PubMed: 24315724]
2. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361(12):1139–1151. [PubMed: 19717844]

3. Mazurek M, Lip GYH. Gastrointestinal Bleeding and Direct Oral Anticoagulants Amongst Patients With Atrial Fibrillation in the “Real World”. Gastroenterology. 2017;152(5):932–934. [PubMed: 28259717]
4. 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(6):1105–1112.e1110. [PubMed: 27639805]
5. Graham DJ, Reichman ME, Wernecke M, et al. Stroke, Bleeding, and Mortality Risks in Elderly Medicare Beneficiaries Treated With Dabigatran or Rivaroxaban for Nonvalvular Atrial Fibrillation. JAMA internal medicine. 2016;176(11):1662–1671. [PubMed: 27695821]
6. Abraham NS, Noseworthy PA, Yao X, Sangaralingham LR, Shah ND. Gastrointestinal Safety of Direct Oral Anticoagulants: A Large Population-Based Study. Gastroenterology. 2017;152(5):1014–1022.e1011. [PubMed: 28043907]
7. Li XS, Deitelzweig S, Keshishian A, et al. Effectiveness and safety of apixaban versus warfarin in non-valvular atrial fibrillation patients in “real-world” clinical practice. A propensity-matched analysis of 76,940 patients. Thrombosis and haemostasis. 2017;117(6):1072–1082. [PubMed: 28300870]
8. Proietti M, Romanazzi I, Romiti GF, Farcomeni A, Lip GYH. Real-World Use of Apixaban for Stroke Prevention in Atrial Fibrillation: A Systematic Review and Meta-Analysis. Stroke. 2018;49(1):98–106. [PubMed: 29167388]
9. Brunner G, Creutfeldt W. Omeprazole in the long-term treatment of patients with acid-related disease resistant to ranitidine. Scand J Gastroenterol. 1989;24(Suppl 166):101–105.
10. Chan EW, Lau WC, Leung WK, et al. Prevention of Dabigatran-Related Gastrointestinal Bleeding With Gastroprotective Agents: A Population-Based Study. Gastroenterology. 2015;149(3):586–595.e583. [PubMed: 25960019]
11. Ray WA. Population-based studies of adverse drug effects. N Engl J Med. 2003;349:1592–1594. [PubMed: 14573730]
12. Ray WA. Evaluating medication effects outside of clinical trials: New-user designs. Am J Epidemiol. 2003;158:915–920. [PubMed: 14585769]
13. Uddin MJ, Groenwold RH, Ali MS, et al. Methods to control for unmeasured confounding in pharmacoepidemiology: an overview. International journal of clinical pharmacy. 2016;38(3):714–723. [PubMed: 27091131]
14. Cunningham A, Stein CM, Chung CP, Daugherty JR, Smalley WE, Ray WA. An automated database case definition for serious bleeding related to oral anticoagulant use. Pharmacol Drug Safety. 2011;20:560–566.
15. Arbogast PG, Kaltenbach L, Ding H, Ray WA. Adjustment of multiple cardiovascular risk factors with a summary risk score. Epidemiol. 2008;19:30–37.
16. Arbogast PG, Ray WA. Use of disease risk scores in pharmacoepidemiologic studies. Statistical Meth Med Res. 2009;18:67–80.
17. Arbogast PG, Ray WA. Performance of disease risk scores, propensity scores, and traditional multivariable outcome regression in the presence of multiple confounders. Am J Epi. 2011;174(5):613–620.
18. Glynn RJ, Gagne JJ, Schneeweiss S. Role of disease risk scores in comparative effectiveness research with emerging therapies. Pharmacoepidemiol Drug Saf. 2012;21 Suppl 2:138–147. [PubMed: 22552989]
19. Tadrous M, Gagne JJ, Sturmer T, Cadarette SM. Disease risk score as a confounder summary method: systematic review and recommendations. Pharmacoepidemiol Drug Saf. 2013;22(2):122–129. [PubMed: 23172692]
20. Vinogradova Y, Coupland C, Hill T, Hippisley-Cox J. Risks and benefits of direct oral anticoagulants versus warfarin in a real world setting: cohort study in primary care. Bmj. 2018;362:k2505. [PubMed: 29973392]
21. Gong IY, Kim RB. Importance of pharmacokinetic profile and variability as determinants of dose and response to dabigatran, rivaroxaban, and apixaban. Can J Cardiol. 2013;29(7 Suppl):S24–33. [PubMed: 23790595]

22. Reilly PA, Lehr T, Haertter S, et al. The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: the RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy). J Am Coll Cardiol. 2014;63(4):321–328. [PubMed: 24076487]
23. Singh S, Savage L, Klein M, Thomas C. Severe necrotic oesophageal and gastric ulceration associated with dabigatran. BMJ case reports. 2013;2013.
24. Zhang N, Liu XS, Li G, Liu T. Dabigatran-induced esophagitis: A frequently overlooked adverse effect. Int J Cardiol. 2016;212:358–359. [PubMed: 27057956]
25. Bolek T, Samos M, Stanciakova L, et al. The Impact of Proton Pump Inhibition on Dabigatran Levels in Patients With Atrial Fibrillation. American journal of therapeutics. 2017.
26. Liesenfeld KH, Lehr T, Dansirikul C, et al. Population pharmacokinetic analysis of the oral thrombin inhibitor dabigatran etexilate in patients with non-valvular atrial fibrillation from the RE-LY trial. Journal of thrombosis and haemostasis : JTH. 2011;9(11):2168–2175. [PubMed: 21972820]
27. Bosch J, Eikelboom JW, Connolly SJ, et al. Rationale, Design and Baseline Characteristics of Participants in the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) Trial. Can J Cardiol. 2017;33(8):1027–1035. [PubMed: 28754388]

Key Points

Question: Are anticoagulant drug treatment and PPI co-therapy associated with the risk of upper gastrointestinal bleeding for Medicare patients?

Findings: During 754,389 person-years of anticoagulation treatment with apixaban, dabigatran, rivaroxaban, and warfarin, the risk of hospitalization for upper gastrointestinal bleeding was highest for rivaroxaban, although the use of PPI co-therapy (264,447 person-years) was associated with a significantly lower overall risk of gastrointestinal bleeding for all anticoagulants (incidence rate ratio, 0.66).

Meaning: Drug choice and PPI co-therapy may be important during oral anticoagulant treatment, particularly for patients with elevated gastrointestinal bleeding risk.

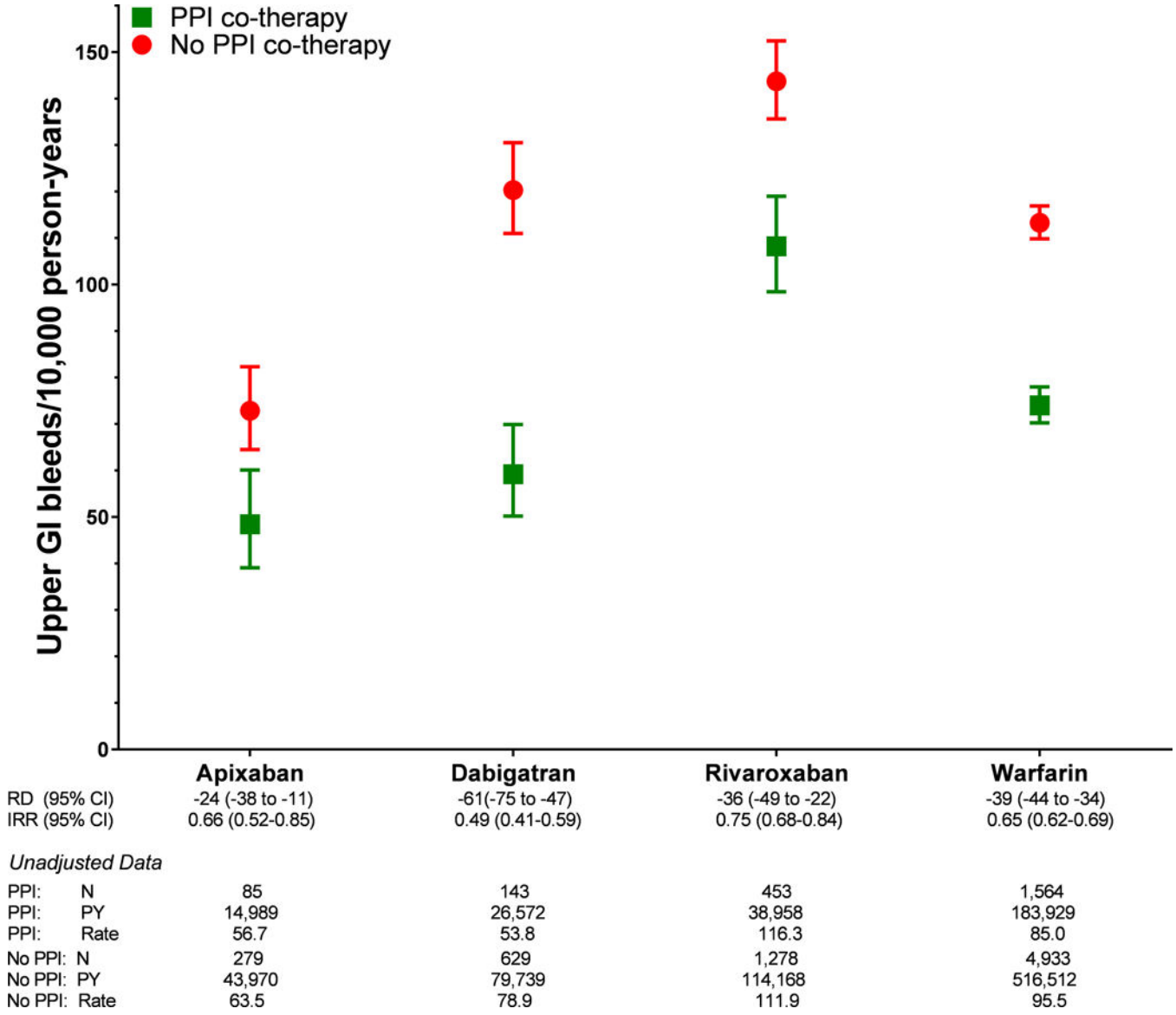
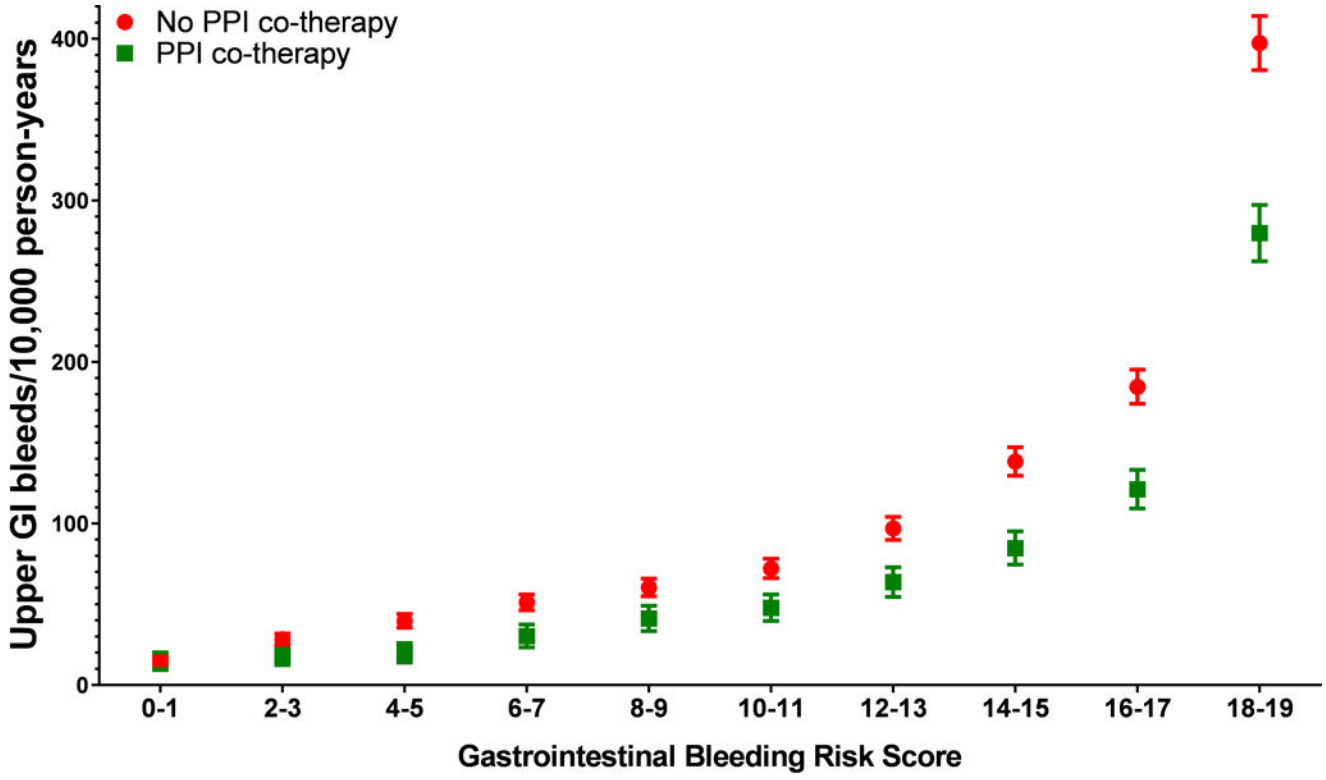


Figure 1.

Adjusted incidence of hospitalizations for upper gastrointestinal bleeding according to individual oral anticoagulants and proton-pump inhibitor (PPI) co-therapy. Adjusted for all of the variables in eTable 3. Intervals represent 95% confidence intervals. GI = gastrointestinal, PY = person-years, N = number of bleeding hospitalizations, Rate = unadjusted incidence per 10,000 person-years, IRR = incidence rate-ratio, RD = risk difference per 10,000 person-years.



RD (95% CI)	0 (-6 to 6)	-10 (-17 to -3)	-20 (-27 to -12)	-21 (-29 to -12)	-19 (-29 to -10)	-24 (-35 to -14)	-33 (-45 to -22)	-54 (-67 to -40)	- 63 (-79 to -47)	-118 (-142 to -93)
IRR (95% CI)	0.98 (0.79-1.20)	0.65 (0.55-0.78)	0.50 (0.43-0.59)	0.59 (0.52-0.67)	0.68 (0.61-0.76)	0.66 (0.60-0.71)	0.66 (0.60-0.71)	0.61 (0.57-0.66)	0.66 (0.62-0.70)	0.70 (0.68-0.73)
Unadjusted Data										
PPI: N	28	36	43	72	106	131	185	261	396	987
PPI: PY	18,924	19,460	21,537	23,709	25,679	27,384	29,036	30,774	32,664	35,281
PPI: Rate	14.8	18.5	20.0	30.4	41.3	47.8	63.7	84.8	121.2	279.8
No PPI: N	135	249	337	417	473	543	699	945	1,171	2,150
No PPI: PY	88,973	87,833	84,766	81,476	78,224	75,248	72,086	68,256	63,417	54,112
No PPI: Rate	17.7	31.9	44.0	56.1	65.9	78.2	104.2	147.3	184.7	397.3

Figure 2.

Unadjusted incidence of hospitalizations for upper gastrointestinal bleeding with and without proton-pump inhibitor (PPI) co-therapy, according to decile of the gastrointestinal bleeding risk score. The gastrointestinal bleeding risk score is the expected incidence of upper gastrointestinal bleeding hospitalization given the study covariates, expressed as a quantile between 0 and 19. A score of 0 represents patients with expected incidence less than the 5th percentile for the cohort, a score of 10 the 50-th to 54th percentile, and a score of 19 at or above the 95th percentile. The decile-specific incidence is not adjusted for covariates because residual confounding is limited within each decile. Intervals represent 95% confidence intervals. GI = gastrointestinal, IRR = incidence rate-ratio, RD = risk difference.

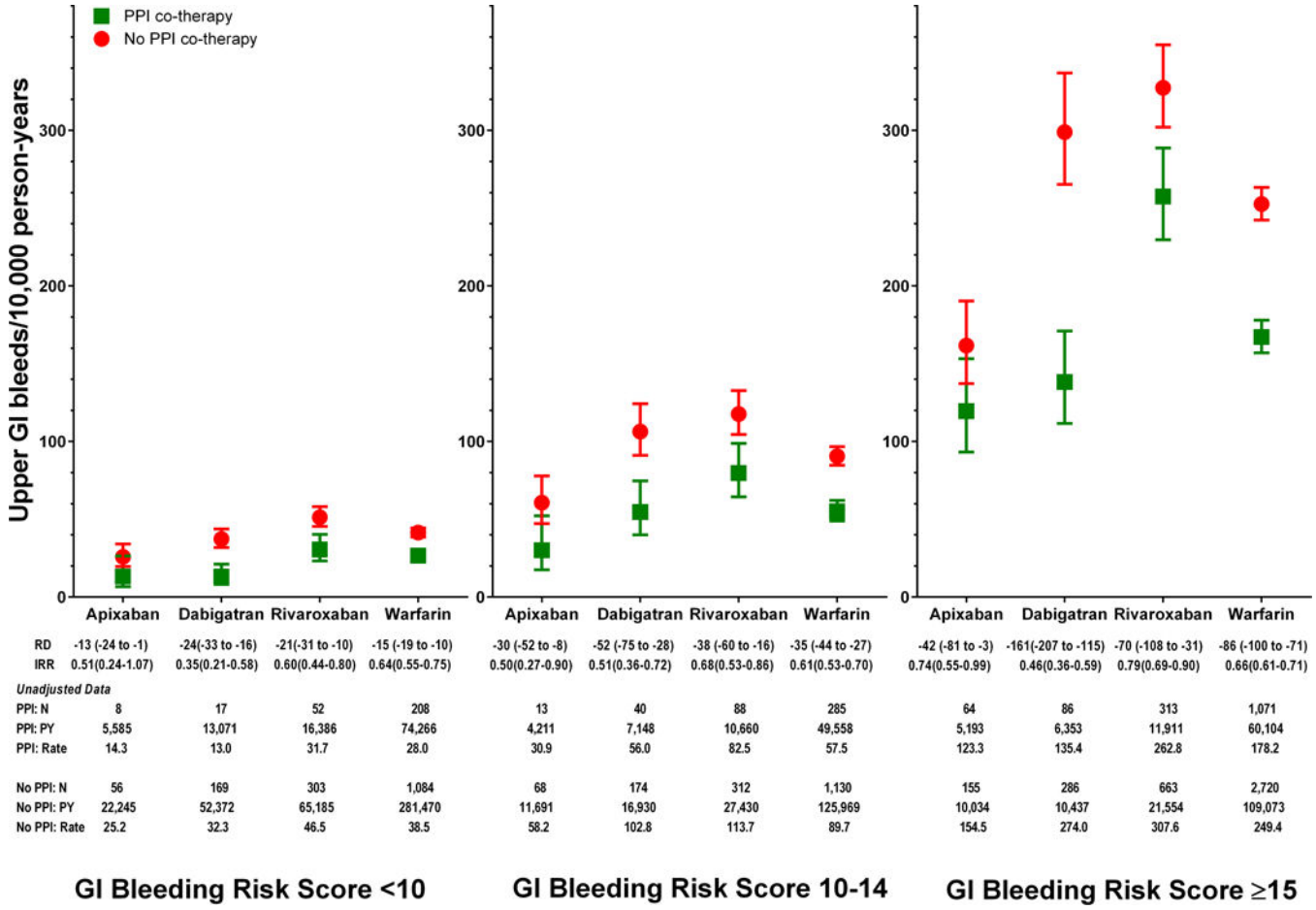


Figure 3.

Adjusted incidence of hospitalizations for upper gastrointestinal bleeding according to quartiles of gastrointestinal bleeding risk score, individual oral anticoagulant and proton-pump inhibitor (PPI) co-therapy. Quartiles 1 and 2 were combined because the absolute differences in incidence between these quartiles were much lower than those for the other quartiles. The gastrointestinal bleeding risk score is the expected incidence of upper gastrointestinal bleeding hospitalization given the study covariates, expressed as a quantile between 0 and 19. A score of 0 represents patients with expected incidence less than the 5th percentile for the cohort, a score of 10 the 50-th to 54th percentile, and a score of 19 at or above the 95th percentile. Incidence within each group is adjusted for all variables in eTable 3 to reduce residual confounding within the quartiles of the gastrointestinal bleeding risk score. Intervals represent 95% confidence intervals. GI = gastrointestinal, IRR = incidence rate-ratio, RD = risk difference.

Table 1.

Study covariates during followup according to proton-pump inhibitor (PPI) co-therapy and oral anticoagulant[a].

	No PPI Co-therapy				PPI Co-therapy			
	Apixaban	**Dabigatran**	**Rivaroxaban**	**Warfarin**	**Apixaban**	**Dabigatran**	**Rivaroxaban**	**Warfarin**
Patients, N	84,135	74,719	231,434	668,519	23,326	18,658	52,774	144,914
New episodes anticoagulant treatment, N	89,452	77,514	242,201	694,192	24,952	19,471	55,759	151,167
Person-years followup	43,970	79,739	114,168	516,512	14,989	26,572	38,958	183,929
Summary gastrointestinal bleeding risk score, mean (std)[b]	9.4 (1.5)	7.4 (1.6)	8.5 (1.5)	8.9 (1.5)	11.2 (1.2)	9.6 (1.4)	10.5 (1.2)	10.8 (1.3)
	% (person-years)				% (person-years)			
Patient and anticoagulant treatment characteristics								
Age, years: <65	2.9 (1,266)	3.3 (2,644)	5.7 (6,550)	8.5 (43,834)	5.2 (776)	6.0 (1,598)	9.8 (3,816)	12.8 (23,549)
65–74	32.1 (14,100)	33.4 (26,624)	35.4 (40,371)	29.9 (154,485)	31.2 (4,674)	31.7 (8,415)	33.5 (13,051)	28.9 (53,138)
75–84	42.0 (18,482)	44.3 (35,343)	40.7 (46,443)	40.0 (206,839)	40.9 (6,131)	42.7 (11,343)	38.5 (14,988)	37.1 (68,210)
≥85	23.0 (10,122)	19.0 (15,128)	18.2 (20,804)	21.6 (111,354)	22.7 (3,408)	19.6 (5,217)	18.2 (7,103)	21.2 (39,031)
Year of cohort entry: 2011	0.0 (0)	47.1 (37,585)	0.3 (347)	33.7 (173,923)	0.0 (0)	44.7 (11,888)	0.2 (91)	33.2 (61,136)
2012	0.0 (0)	29.5 (23,543)	18.3 (20,856)	29.2 (150,919)	0.0 (0)	31.0 (8,238)	16.7 (6,504)	29.3 (53,808)
2013	19.1 (8,419)	14.4 (11,484)	36.5 (41,697)	20.6 (106,493)	19.0 (2,846)	14.9 (3,958)	37.5 (14,609)	21.0 (38,661)
2014	53.1 (23,342)	7.3 (5,828)	34.5 (39,372)	12.8 (65,975)	52.8 (7,916)	7.7 (2,039)	35.3 (13,756)	12.9 (23,747)
2015	27.8 (12,209)	1.6 (1,299)	10.4 (11,896)	3.7 (19,202)	28.2 (4,226)	1.7 (449)	10.3 (3,996)	3.6 (6,578)
Sex: Female	52.7 (23,165)	49.6 (39,583)	52.4 (59,878)	53.9 (278,454)	59.3 (8,881)	58.1 (15,436)	60.1 (23,421)	62.3 (114,505)
Male	47.3 (20,805)	50.4 (40,156)	47.6 (54,290)	46.1 (238,058)	40.7 (6,108)	41.9 (11,136)	39.9 (15,537)	37.7 (69,424)
Medicaid enrollment	13.9 (6,099)	15.7 (12,544)	17.6 (20,124)	22.5 (116,092)	27.4 (4,103)	32.6 (8,650)	34.6 (13,495)	37.8 (69,584)
Race: White	92.6 (40,715)	92.9 (74,067)	91.3 (104,235)	89.9 (464,306)	91.3 (13,684)	90.2 (23,967)	88.7 (34,555)	88.1 (162,002)
Black	3.8 (1,659)	3.1 (2,474)	4.7 (5,363)	6.9 (35,515)	4.3 (638)	4.0 (1,058)	5.6 (2,179)	7.9 (14,492)
Other or unknown	3.6 (1,596)	4.0 (3,198)	4.0 (4,569)	3.2 (16,692)	4.5 (667)	5.8 (1,546)	5.7 (2,224)	4.0 (7,434)
Nursing home residence past year[c]	4.7 (2,061)	3.0 (2,388)	5.3 (6,065)	7.5 (38,948)	7.5 (1,127)	5.5 (1,461)	8.6 (3,337)	11.9 (21,873)
Indication: Atrial fibrillation	91.8 (40,376)	95.9 (76,438)	78.6 (89,772)	71.2 (367,933)	91.0 (13,633)	95.5 (25,381)	75.2 (29,297)	68.6 (126,252)
First 90 days of anticoagulant treatment[d]	35.4 (15,561)	17.4 (13,887)	29.3 (33,463)	22.1 (114,031)	34.8 (5,217)	16.1 (4,284)	27.7 (10,785)	20.5 (37,645)
Comorbidity[c]								
Upper gastrointestinal disease history or signs of bleeding	21.3 (9,367)	19.1 (15,224)	23.6 (26,986)	27.4 (141,403)	41.8 (6,266)	39.5 (10,504)	44.6 (17,370)	46.9 (86,234)

	No PPI Co-therapy				PPI Co-therapy			
	Apixaban	**Dabigatran**	**Rivaroxaban**	**Warfarin**	**Apixaban**	**Dabigatran**	**Rivaroxaban**	**Warfarin**
Other gastrointestinal symptoms or disease[e]	30.5 (16,796)	28.5 (26,827)	33.1 (44,683)	38.0 (218,047)	41.5 (10,512)	37.8 (16,853)	44.5 (27,627)	48.9 (129,768)
Non-gastrointestinal bleeding/abnormal coagulation profile[f]	10.6 (4,680)	10.6 (8,452)	13.2 (15,027)	17.9 (92,511)	12.5 (1,871)	11.8 (3,145)	15.3 (5,971)	22.1 (40,571)
Current medications that increase risk of bleeding[g]	10.4 (4,590)	8.7 (6,949)	10.0 (11,400)	10.0 (51,580)	15.1 (2,258)	13.8 (3,663)	14.8 (5,764)	13.6 (24,967)
Other medications that may increase risk of bleeding[h]	12.7 (5,575)	12.1 (9,677)	13.9 (15,900)	16.0 (82,815)	21.8 (3,261)	21.8 (5,804)	24.6 (9,587)	26.9 (49,500)
Meets criteria for low-dose aspirin prophylaxis[i]	46.6 (20,504)	52.6 (41,920)	43.9 (50,151)	45.8 (236,518)	51.2 (7,681)	58.6 (15,572)	49.0 (19,076)	51.6 (94,859)
Other cardiovascular disease[j]	72.0 (31,642)	70.1 (55,880)	69.9 (79,846)	76.4 (394,430)	80.3 (12,036)	80.0 (21,265)	79.5 (30,978)	83.8 (154,115)
Frailty or other conditions that indicate vulnerable patients[k]	28.8 (12,661)	25.7 (20,523)	31.0 (35,438)	35.9 (185,511)	40.1 (6,007)	38.5 (10,231)	43.4 (16,919)	48.7 (89,622)
Any hospitalization or gastrointestinal ED visit[l]	43.1 (18,953)	31.7 (25,299)	43.3 (49,404)	46.0 (237,819)	52.1 (7,816)	41.8 (11,113)	52.9 (20,597)	56.8 (104,394)

[a] The covariates are determined for every person-day of followup. Thus, for categorical variables, the proportion of followup person-days in the specific category is shown. The covariate distributions for the 143,152 person-years of former PPI co-therapy are not shown. Abbreviations: ED, emergency department.

[b] The gastrointestinal bleeding risk score is the expected incidence of upper gastrointestinal bleeding hospitalization given the study covariates, expressed as a quantile between 0 and 19. A score of 0 represents patients with expected incidence less than the 5th percentile for the cohort, a score of 10 the 50-th to 54th percentile, and a score of 19 at or above the 95th percentile.

[c] All comorbidities defined for the 365 days preceding the day of followup being classified, except for current medication use, which is defined as probable use on the followup day being classified. Each line presents a composite of several more specific comorbidities. The constituent covariates for each line and their distributions are presented in eTable 4.

[d] No more than 90 days of anticoagulant treatment since treatment initiation.

[e] Epigastric or abdominal pain, gastroesophageal reflux or dyspepsia, use of histamine$_2$ receptor antagonist, lower gastrointestinal disease, lower gastrointestinal symptoms.

[f] ICD9-CM diagnosis of 790.92

[g] NSAIDs, P2Y$_{12}$ inhibitors, dipyridamole, cilostazole, voraxapar.

[h] COXIBs, other anticoagulants, systemic corticosteroid, SSRI, antibiotic.

[i] Myocardial infarction, revascularization, thrombotic stroke, transient ischemic attacks.

[j] Examples include hemorrhagic stroke, heart failure peripheral vascular disease, diabetes.

[k] Fall or mobility impairment, fecal or urinary incontinence, malnutrition, home oxygen, alcohol-related conditions, liver disease.

[l] A hospitalization for any reason or an ED visit with a gastrointestinal diagnosis.

Table 2.

Comparative incidence of hospitalization for upper gastrointestinal bleeding for individual oral anticoagulants according to PPI co-therapy[a].

		No PPI Co-therapy		PPI Co-therapy	
		IRR (95% CI)	***RD (95% CI)***	***IRR (95% CI)***	***RD (95% CI)***
Apixaban vs	Dabigatran	0.61 (0.52–0.70)	−47.5 (−60.6 to −34.3)	0.82 (0.62–1.07)	−10.8 (−25.1 to 3.5)
	Rivaroxaban	0.51 (0.44–0.58)	−70.9 (−82.7 to −59.1)	0.45 (0.35–0.56)	−59.8 (−74.4 to −45.2)
	Warfarin	0.64 (0.57–0.73)	−40.5 (−50.0 to −31.0)	0.65 (0.52–0.82)	−25.6 (−36.7 to −14.4)
Dabigatran vs	Rivaroxaban	0.84 (0.76–0.92)	−23.4 (−36.2 to −10.6)	0.55 (0.45–0.66)	−49.0 (−63.2 to −34.9)
	Warfarin	1.06 (0.98–1.16)	7.0 (−3.3 to 17.3)	0.80 (0.67–0.95)	−14.8 (−25.3 to −4.3)
Rivaroxaban vs	Warfarin	1.27 (1.19–1.35)	30.4 (20.3 to 40.6)	1.46 (1.31–1.63)	34.2 (23.3 to 45.2)

The number of hospitalizations, person-years of followup, and unadjusted incidence per 10,000 person-years for no PPI co-therapy are:

Apixaban−−279/43,970=63.5; dabigatran−−629/79,739=78.9; rivaroxaban−−1,278/114,168=111.9; warfarin−−4,933/516,512=95.5.

The comparable data for PPI co-therapy are:

Apixaban−−85/14,989=56.7; dabigatran−−143/26,572=53.8; rivaroxaban−−453/38,958=116.3; warfarin−−1,564/183,929=85.0.

CI = confidence interval, PPI = proton-pump inhibitor. Incidence rate ratios (IRRs) < 1 and risk differences (RDs, per 10,000 person-years) < 0 imply that the upper gastrointestinal bleeding hospitalization incidence was lower for the first drug than for the second.

The IRRs and RDs are adjusted for calendar time, patient demographics, anticoagulant indication, time since anticoagulant start, prior history of gastrointestinal disease, bleeding or signs of bleeding, medications associated with increased risk of bleeding, cardiovascular disease, conditions, such as a prior fall, that indicate a vulnerable patient, and prior hospitalizations or gastrointestinal emergency department visits. eTable 3 presents the complete list of the 85 covariates included in the adjustment.