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# Association of Oral Anticoagulants and Proton Pump Inhibitor Cotherapy With Hospitalization for Upper Gastrointestinal Tract Bleeding

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**IMPORTANCE** Anticoagulant choice and proton pump inhibitor (PPI) cotherapy could affect the risk of upper gastrointestinal tract bleeding, a frequent and potentially serious complication of oral anticoagulant treatment.

**OBJECTIVES** To compare the incidence of hospitalization for upper gastrointestinal tract bleeding in patients using individual anticoagulants with and without PPI cotherapy, and to determine variation according to underlying gastrointestinal bleeding risk.

**DESIGN, SETTING, AND PARTICIPANTS** Retrospective cohort study in Medicare beneficiaries between January 1, 2011, and September 30, 2015.

**EXPOSURES** Apixaban, dabigatran, rivaroxaban, or warfarin with or without PPI cotherapy.

**MAIN OUTCOMES AND MEASURES** Hospitalizations for upper gastrointestinal tract bleeding: adjusted incidence and risk difference (RD) per 10 000 person-years of anticoagulant treatment, incidence rate ratios (IRRs).

**RESULTS** There were 1 643 123 patients with 1 713 183 new episodes of oral anticoagulant treatment included in the cohort (mean [SD] age, 76.4 [2.4] years, 651 427 person-years of follow-up [56.1%] were for women, and the indication was atrial fibrillation for 870 330 person-years [74.9%]). During 754 389 treatment person-years without PPI cotherapy, the adjusted incidence of hospitalization for upper gastrointestinal tract bleeding (n = 7119) was 115 per 10 000 person-years (95% CI, 112-118). The incidence for rivaroxaban (n = 1278) was 144 per 10 000 person-years (95% CI, 136-152), which was significantly greater than the incidence of hospitalizations for apixaban (n = 279; 73 per 10 000 person-years; IRR, 1.97 [95% CI, 1.73-2.25]; RD, 70.9 [95% CI, 59.1-82.7]), dabigatran (n = 629; 120 per 10 000 person-years; IRR, 1.19 [95% CI, 1.08-1.32]; RD, 23.4 [95% CI, 10.6-36.2]), and warfarin (n = 4933; 113 per 10 000 person-years; IRR, 1.27 [95% CI, 1.19-1.35]; RD, 30.4 [95% CI, 20.3-40.6]). The incidence for apixaban was significantly lower than that for dabigatran (IRR, 0.61 [95% CI, 0.52-0.70]; RD, −47.5 [95% CI,−60.6 to −34.3]) and warfarin (IRR, 0.64 [95% CI, 0.57-0.73]; RD, −40.5 [95% CI, −50.0 to −31.0]). When anticoagulant treatment with PPI cotherapy (264 447 person-years; 76 per 10 000 person-years) was compared with treatment without PPI cotherapy, risk of upper gastrointestinal tract bleeding hospitalizations (n = 2245) was lower overall (IRR, 0.66 [95% CI, 0.62-0.69]) and for apixaban (IRR, 0.66 [95% CI, 0.52-0.85]; RD, −24 [95% CI, −38 to −11]), dabigatran (IRR, 0.49 [95% CI, 0.41-0.59]; RD, −61.1 [95% CI, −74.8 to −47.4]), rivaroxaban (IRR, 0.75 [95% CI, 0.68-0.84]; RD, −35.5 [95% CI, −48.6 to −22.4]), and warfarin (IRR, 0.65 [95% CI, 0.62-0.69]; RD, −39.3 [95% CI, −44.5 to −34.2]).

**CONCLUSIONS AND RELEVANCE** Among patients initiating oral anticoagulant treatment, incidence of hospitalization for upper gastrointestinal tract bleeding was the highest in patients prescribed rivaroxaban, and the lowest for patients prescribed apixaban. For each anticoagulant, the incidence of hospitalization for upper gastrointestinal tract bleeding was lower among patients who were receiving PPI cotherapy. These findings may inform assessment of risks and benefits when choosing anticoagulant agents.

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Supplemental content

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The risk of major upper gastrointestinal tract bleeding, a frequent and potentially serious complication of oral anticoagulant treatment,[1,2] could be affected by the specific anticoagulant prescribed[3] and proton pump inhibitor (PPI) cotherapy.[4] In pivotal efficacy trials, non-vitamin K oral anticoagulants (NOACs) were at least as effective as warfarin for prevention of stroke, but some were associated with an increased risk of major gastrointestinal bleeding.[1] Although individual NOACs have not been compared in large clinical trials, observational data suggest that the incidence of serious anticoagulant-related gastrointestinal bleeding is higher in patients prescribed rivaroxaban than dabigatran[5] and lower in patients prescribed apixaban than other oral anticoagulants.[6-8] However, the clinical importance of anticoagulant choice for patients with elevated gastrointestinal bleeding risk is unknown.

PPIs, which reduce gastric acid production, promote ulcer healing, and prevent ulcer recurrence,[9] could affect the relative safety of oral anticoagulants, particularly in high-risk patients. PPI cotherapy is associated with reduced incidence of upper gastrointestinal tract bleeding in patients prescribed 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 cotherapy is associated with a lower incidence of anticoagulant-related serious upper gastrointestinal tract bleeding for other NOACs or alters the relative upper gastrointestinal tract safety associated with individual oral anticoagulants is unknown.

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

### Key Points

**Question** Are anticoagulant drug choice and proton pump inhibitor (PPI) cotherapy associated with the risk of upper gastrointestinal tract bleeding in Medicare beneficiaries?

**Findings** During 754 389 person-years of anticoagulation treatment with apixaban, dabigatran, rivaroxaban, and warfarin, the risk of hospitalization for upper gastrointestinal tract bleeding was highest for rivaroxaban. The use of PPI cotherapy (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 cotherapy may be important during oral anticoagulant treatment, particularly for patients with elevated risk of gastrointestinal bleeding.

## Methods

### Sources of Data

The study cohort was identified from computerized US Medicare beneficiary files,[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; potentially less complete records of medical care encounters). The data were accessed through the Virtual Research Data Center, a cloud-based repository of deidentified 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 and included 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 nonselective 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 3 times a year (http://www.fda.gov/Drugs/DrugSafety/ucm245011.htm). Information on race was obtained from Medicare enrollment files and served as a proxy for socioeconomic and genetic factors.

### Cohort

The cohort included patients at least 30 years of age initiating oral anticoagulation treatment with apixaban, dabigatran, rivaroxaban, or warfarin (patients with prescriptions for multiple drugs were not included) filled from January 1, 2011, through September 30, 2015. Edoxaban was not considered because relatively few patients started treatment with this drug during the study period. Patients had to have complete demographic information available in their Medicare files, full pharmacy benefits, and, to ensure regular contact with medical care clinicians, at least 1 outpatient visit and 1 filled prescription in the past year. Patients could not be included in the cohort if they were prescribed any oral anticoagulant in the past year (eTable 1 in Supplement 1).[12] Exclusion criteria were end-stage renal disease, serious gastrointestinal illness predisposing to bleeding (eg, esophageal varices, gastrointestinal cancer), and bleeding-related hospitalization in the past year (eTable 1 in Supplement 1).

An episode of anticoagulation treatment began on the day a patient filled their first qualifying anticoagulant prescription. Follow-up ended on whichever of the following came first: September 30, 2015; 365 days of not filling the study prescription; filling a prescription for a different oral anticoagulant; loss of Medicare 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 before September 30, 2015.

## Medication Exposure

Because the association of medications included in this study with the risk of bleeding is thought to be acute, each day of study follow-up was classified according to probable study medication use, identified from filled prescriptions (eAppendix §2 in Supplement 1). The exposure period was based on the dispensed days of supply.

Oral anticoagulant treatment during follow-up 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 day (for patients prescribed apixaban, dabigatran, or rivaroxaban) or 3 days (for patients prescribed warfarin) after the end of the days of supply (eAppendix §2 in Supplement 1). All cohort follow-up and study analyses were restricted to periods of oral anticoagulant treatment.

There were 3 possible categories of PPI exposure during oral anticoagulant treatment (eAppendix §2 in Supplement 1). PPI cotherapy, or person-days on which the patient was likely to be taking the PPI and thus for which a gastroprotective effect was most plausible, was defined as the interval between the date a PPI prescription was filled through the end of days of supply. Former cotherapy consisted of person-days for patients who filled a PPI prescription in the past year, but whose days of supply ended and, thus, should not benefit from cotherapy. Analysis of this person-time permitted assessment of confounding by unmeasured factors associated with receiving a PPI prescription. No cotherapy was defined as person-days with no filled PPI prescription in the past year.

Other medications associated with increased risk of gastrointestinal bleeding were NSAIDs, antiplatelet drugs (eg, ticlopidine, clopidogrel, prasugrel, ticagrelor, dipyridamole, cilostazol), and other anticoagulants (eg, heparin, enoxaparin). For NSAIDs and anticoagulants, concurrent use included the interval between the date the prescription was filled through the end of the days of supply; for antiplatelet drugs that irreversibly inhibit platelet aggregation, this interval was extended 7 days (eAppendix §2 in Supplement 1).

## End Points

The primary study end point was hospitalization for upper gastrointestinal tract bleeding that was potentially preventable by PPI cotherapy (eAppendix §3 in Supplement 1). This end point included bleeding related to esophagitis, peptic ulcer disease, and gastritis, and excluded bleeding unlikely to be affected by PPIs (eg, bleeding caused by a Mallory Weiss tear). Hospitalization for other gastrointestinal bleeding (eAppendix §3 in Supplement 1) was analyzed as a negative outcome control.[13]

Bleeding-related hospitalizations were identified from the hospital admission date with a previously validated algorithm (eAppendix §3 in Supplement 1).[14] The positive predictive value was 99% for all bleeding-related hospitalizations, 98% for all hospitalization for gastrointestinal bleeding, and 80% for hospitalization for upper gastrointestinal tract bleeding (eTable 2 in Supplement 1). The lower positive predictive value for upper gastrointestinal tract bleeding resulted from occasional use of diagnosis codes that did not specify the site of the gastrointestinal bleeding.

## Analysis

### Covariates

Because the risk of upper gastrointestinal tract bleeding could influence both anticoagulant choice and PPI cotherapy, the analysis controlled for 85 covariates plausibly associated with the risk of hospitalization for gastrointestinal bleeding (eTable 3 in Supplement 1; Supplement 2 shows codes for the study covariates). These covariates included demographic information, anticoagulant indication, time since treatment initiation, history of upper gastrointestinal tract disease or signs of bleeding, other gastrointestinal disease or symptoms, medications that affect bleeding risk, cardiovascular disease for which low-dose aspirin prophylaxis (surrogate for low-dose aspirin) is recommended, other cardiovascular conditions or risk factors, medical care encounters indicating frailty or alcohol abuse, liver disease, and recent hospitalizations or emergency department visits. Because changes in covariates (eg, initiation of NSAID use) after cohort entry were likely to be related to PPI cotherapy, these were updated for each follow-up day.

### Statistical Analysis

Time-dependent Poisson regression models with all study covariates were fit to estimate the adjusted incidence of hospitalization for gastrointestinal bleeding according to both individual anticoagulants and PPI cotherapy (eAppendix §4 in Supplement 1). Because a patient could have person-time with and without PPI cotherapy as well as multiple episodes of anticoagulant treatment that were considered to be independent in the primary analysis, sensitivity analyses were performed with the patient as a random effect and with no cohort reentry (eAppendix §4 in Supplement 1). Models were fit for the entire cohort with an exposure variable with levels for individual anticoagulant-PPI cotherapy combinations or, for analyses of all anticoagulants, PPI cotherapy. Incidence rate ratios (IRRs) for study comparisons were estimated from single degree-of-freedom contrasts. The adjusted incidence of hospitalization for upper gastrointestinal tract bleeding associated with anticoagulant-PPI cotherapy categories was estimated from the regression model, and, from these estimates, the risk difference (RD) was calculated by subtraction (eAppendix §4 in Supplement 1). 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 version 9.4 (SAS Institute).

### Gastrointestinal Bleeding Risk Score

Several analyses were stratified according to an internally derived integrated measure of gastrointestinal bleeding risk (eAppendix §5 in Supplement 1) that included all study covariates. This measure was calculated as a disease risk score,[15-17] which was defined as the expected incidence of hospitalization for upper gastrointestinal tract bleeding given the study covariates (assuming warfarin treatment and

no PPI cotherapy). 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, the scores incorporate information from all measured patient factors and are specifically calibrated for the study end point. Scores were expressed as a risk quantile from 0 to 19, in which 0 indicates patients with an expected incidence less than the fifth percentile for the cohort, 10 indicates patients with an expected incidence in the 50th to 54th percentile, and 19 indicates patients with an expected incidence at or above the 95th percentile. The cohort was classified according to risk score deciles in the analysis of all anticoagulants and according to quartiles in the analysis for individual anticoagulants. In the former analysis, the decile-specific incidence was not adjusted for covariates because residual confounding is limited within each decile.

### Sensitivity Analyses

Sensitivity analyses assessed how key patient and treatment characteristics influenced study findings, including analysis of patients with nonvalvular atrial fibrillation and restriction of NOACs to usual doses for atrial fibrillation. Other analyses were performed to test sensitivity to statistical assumptions (eAppendix §4 in Supplement 1), including considering death as a competing risk and fixing the values of 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 cotherapy nor covariates were time-dependent, and follow-up included only the first year of anticoagulant treatment, which prevented causal pathway confounding and reduced variation in both treatment duration and censoring (eAppendix §4 in Supplement 1). The potential magnitude of confounding by unmeasured factors associated with PPI cotherapy was assessed by considering the association of both former cotherapy with hospitalizations for upper gastrointestinal tract bleeding (negative exposure variant) and current cotherapy 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 included in the cohort and 1 161 989 person-years of follow-up; the mean (SD) age of the patients during follow-up was 76.4 (2.4) years, 651 427 person-years of follow-up (56.1%) were for women, and the indication was atrial fibrillation for 870 330 person-years (74.9%). Cohort follow-up included 754 389 person-years of anticoagulant treatment without PPI cotherapy (apixaban, 43 970; dabigatran, 79 739; rivaroxaban, 114 168; and warfarin, 516 512) and 264 447 person-years with PPI cotherapy (apixaban, 14 989; dabigatran, 26 572; rivaroxaban, 38 958; and warfarin, 183 929).

For each individual oral anticoagulant, patients with PPI cotherapy had a higher prevalence of risk factors for gastrointestinal bleeding (**Table 1**; eTable 4 in Supplement 1). These patients were more likely to have recent initiation of anticoagulant treatment, a history of upper gastrointestinal tract disease or signs of bleeding, and use of medications that increase the risk of bleeding. Thus, patients with PPI cotherapy had an increase of 1 decile in the gastrointestinal bleeding risk score. Regardless of PPI cotherapy, patients receiving apixaban treatment had the highest gastrointestinal bleeding risk scores, and patients receiving dabigatran treatment had the lowest scores.

### Individual Anticoagulant and PPI Cotherapy

In patients receiving anticoagulant treatment without PPI cotherapy, the adjusted incidence of hospitalization for upper gastrointestinal tract bleeding (n = 7119) was 115 per 10 000 person-years (95% CI, 112-118). The incidence for rivaroxaban (144 per 10 000 person-years [95% CI, 136-152]) was significantly greater than the incidence for apixaban (73 per 10 000 person-years; IRR, 1.97 [95% CI, 1.73-2.25]; RD, 70.9 [95% CI, 59.1-82.7]), dabigatran (120 per 10 000 person-years; IRR, 1.19 [95% CI, 1.08-1.32]; RD, 23.4 [95% CI, 10.6-36.2]), and warfarin (113 per 10 000 person-years; IRR, 1.27 [95% CI, 1.19-1.35]; RD, 30.4 [95% CI, 20.3-40.6]) (**Figure 1** and **Table 2**). The incidence of hospitalization for upper gastrointestinal tract bleeding in patients prescribed apixaban was significantly lower than the incidence for patients prescribed dabigatran (IRR, 0.61 [95% CI, 0.52-0.70]; RD, −47.5 [95% CI, −60.6 to −34.3]) and warfarin (IRR, 0.64 [95% CI, 0.57-0.73]; RD, −40.5 [95% CI, −50.0 to −31.0]).

For patients receiving anticoagulant treatment with PPI cotherapy, the adjusted incidence of hospitalization for upper gastrointestinal tract bleeding (n = 2245; 76 per 10 000 person-years) was lower than the incidence in patients receiving treatment without PPI cotherapy (IRR, 0.66 [95% CI, 0.62-0.69]; RD, −39.5 [95% CI, −44.4 to −35.0]). With PPI cotherapy, the incidence of hospitalization for upper gastrointestinal tract bleeding was significantly lower for each individual anticoagulant (Figure 1 and Table 2). The lower incidence was most pronounced with dabigatran (IRR, 0.49 [95% CI, 0.41-0.59]; RD, −61.1 [95% CI, −74.8 to −47.4]) and least pronounced with rivaroxaban (IRR, 0.75 [95% CI, 0.68-0.84]; RD, −35.5 [95% CI, −48.6 to −22.4]). For patients receiving PPI cotherapy, the incidence of hospitalization for upper gastrointestinal tract bleeding during treatment with rivaroxaban was significantly greater than during treatment with the other anticoagulants. However, the incidence during treatment with apixaban and dabigatran did not differ significantly.

### Gastrointestinal Bleeding Risk

The risk of hospitalization for upper gastrointestinal tract bleeding was greater for higher deciles of the gastrointestinal bleeding risk score (**Figure 2**). For patients with no PPI cotherapy, the respective decile-specific incidences for the lowest and highest deciles were 15 (95% CI, 13-18) and 397 (95% CI, 381-414) per 10 000 person-years. There was

Table 1. Study Covariates During Follow-up According to Proton Pump Inhibitor (PPI) Cotherapy and Oral Anticoagulant[a]

| | No PPI Cotherapy | | | | PPI Cotherapy | | | |
|---|---|---|---|---|---|---|---|---|
| Patient Characteristic | Apixaban | Dabigatran | Rivaroxaban | Warfarin | Apixaban | Dabigatran | Rivaroxaban | Warfarin |
| Patients, No. | 84 135 | 74 719 | 231 434 | 668 519 | 23 326 | 18 658 | 52 774 | 144 914 |
| New episodes of anticoagulant treatment, No. | 89 452 | 77 514 | 242 201 | 694 192 | 24 952 | 19 471 | 55 759 | 151 167 |
| Person-years of follow-up | 43 970 | 79 739 | 114 168 | 516 512 | 14 989 | 26 572 | 38 958 | 183 929 |
| Overall GI bleeding risk score, mean (SD)[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) |
| Covariate, person-years (%) | | | | | | | | |
| Age, y | | | | | | | | |
| <65 | 1266 (2.9) | 2644 (3.3) | 6550 (5.7) | 43 834 (8.5) | 776 (5.2) | 1598 (6.0) | 3816 (9.8) | 23 549 (12.8) |
| 65-74 | 14 100 (32.1) | 26 624 (33.4) | 40 371 (35.4) | 154 485 (29.9) | 4674 (31.2) | 8415 (31.7) | 13 051 (33.5) | 53 138 (28.9) |
| 75-84 | 18 482 (42.0) | 35 343 (44.3) | 46 443 (40.7) | 206 839 (40.0) | 6131 (40.9) | 11 343 (42.7) | 14 988 (38.5) | 68 210 (37.1) |
| ≥85 | 10 122 (23.0) | 15 128 (19.0) | 20 804 (18.2) | 111 354 (21.6) | 3408 (22.7) | 5217 (19.6) | 7103 (18.2) | 39 031 (21.2) |
| Year of cohort entry | | | | | | | | |
| 2011 | 0 | 37 585 (47.1) | 347 (0.3) | 173 923 (33.7) | 0 | 11 888 (44.7) | 91 (0.2) | 61 136 (33.2) |
| 2012 | 0 | 23 543 (29.5) | 20 856 (18.3) | 150 919 (29.2) | 0 | 8238 (31.0) | 6504 (16.7) | 53 808 (29.3) |
| 2013 | 8419 (19.1) | 11 484 (14.4) | 41 697 (36.5) | 106 493 (20.6) | 2846 (19.0) | 3958 (14.9) | 14 609 (37.5) | 38 661 (21.0) |
| 2014 | 23 342 (53.1) | 5828 (7.3) | 39 372 (34.5) | 65 975 (12.8) | 7916 (52.8) | 2039 (7.7) | 13 756 (35.3) | 23 747 (12.9) |
| 2015 | 12 209 (27.8) | 1299 (1.6) | 11 896 (10.4) | 19 202 (3.7) | 4226 (28.2) | 449 (1.7) | 3996 (10.3) | 6578 (3.6) |
| Sex | | | | | | | | |
| Male | 20 805 (47.3) | 40 156 (50.4) | 54 290 (47.6) | 238 058 (46.1) | 6108 (40.7) | 11 136 (41.9) | 15 537 (39.9) | 69 424 (37.7) |
| Female | 23 165 (52.7) | 39 583 (49.6) | 59 878 (52.4) | 278 454 (53.9) | 8881 (59.3) | 15 436 (58.1) | 23 421 (60.1) | 114 505 (62.3) |
| Medicaid enrollment | 6099 (13.9) | 12 544 (15.7) | 20 124 (17.6) | 116 092 (22.5) | 4103 (27.4) | 8650 (32.6) | 13 495 (34.6) | 69 584 (37.8) |
| Race | | | | | | | | |
| White | 40 715 (92.6) | 74 067 (92.9) | 104 235 (91.3) | 464 306 (89.9) | 13 684 (91.3) | 23 967 (90.2) | 34 555 (88.7) | 162 002 (88.1) |
| Black | 1659 (3.8) | 2474 (3.1) | 5363 (4.7) | 35 515 (6.9) | 638 (4.3) | 1058 (4.0) | 2179 (5.6) | 14 492 (7.9) |
| Other or unknown | 1596 (3.6) | 3198 (4.0) | 4569 (4.0) | 16 692 (3.2) | 667 (4.5) | 1546 (5.8 | 2224 (5.7) | 7434 (4.0) |
| Nursing home residence past year[c] | 2061 (4.7) | 2388 (3.0) | 6065 (5.3) | 38 948 (7.5) | 1127 (7.5) | 1461 (5.5) | 3337 (8.6) | 21 873 (11.9) |
| Atrial fibrillation | 40 376 (91.8) | 76 438 (95.9) | 89 772 (78.6) | 367 933 (71.2) | 13 633 (91.0) | 25 381 (95.5) | 29 297 (75.2) | 126 252 (68.6) |
| ≤90 d of anticoagulant treatment | 15 561 (35.4) | 13 887 (17.4) | 33 463 (29.3) | 114 031 (22.1) | 5217 (34.8) | 4284 (16.1) | 10 785 (27.7) | 37 645 (20.5) |
| Comorbidity[c] | | | | | | | | |
| Signs of bleeding or history of upper GI disease | 9367 (21.3) | 15 224 (19.1) | 26 986 (23.6) | 141 403 (27.4) | 6266 (41.8) | 10 504 (39.5) | 17 370 (44.6) | 86 234 (46.9) |
| Other GI symptoms or disease[d] | 16 796 (30.5) | 26 827 (28.5) | 44 683 (33.1) | 218 047 (38.0) | 10 512 (41.5) | 16 853 (37.8) | 27 627 (44.5) | 129 768 (48.9) |
| Non-GI bleeding/abnormal coagulation profile[e] | 4680 (10.6) | 8452 (10.6) | 15 027 (13.2) | 92 511 (17.9) | 1871 (12.5) | 3145 (11.8) | 5971 (15.3) | 40 571 (22.1) |
| Medications that increase risk of bleeding[f] | 4590 (10.4) | 6949 (8.7) | 11 400 (10.0) | 51 580 (10.0) | 2258 (15.1) | 3663 (13.8) | 5764 (14.8) | 24 967 (13.6) |
| Medications that may increase risk of bleeding[g] | 5575 (12.7) | 9677 (12.1) | 15 900 (13.9) | 82 815 (16.0) | 3261 (21.8) | 5804 (21.8) | 9587 (24.6) | 49 500 (26.9) |
| Meets criteria for low-dose aspirin prophylaxis[h] | 20 504 (46.6) | 41 920 (52.6) | 50 151 (43.9) | 236 518 (45.8) | 7681 (51.2) | 15 572 (58.6) | 19 076 (49.0) | 94 859 (51.6) |
| Other cardiovascular disease[i] | 31 642 (72.0) | 55 880 (70.1) | 79 846 (69.9) | 394 430 (76.4) | 12 036 (80.3) | 21 265 (80.0) | 30 978 (79.5) | 154 115 (83.8) |
| Frailty[j] | 12 661 (28.8) | 20 523 (25.7) | 35 438 (31.0) | 185 511 (35.9) | 6007 (40.1) | 10 231 (38.5) | 16 919 (43.4) | 89 622 (48.7) |
| Any hospitalization or GI-related ED visit[k] | 18 953 (43.1) | 25 299 (31.7) | 49 404 (43.3) | 237 819 (46.0) | 7816 (52.1) | 11 113 (41.8) | 20 597 (52.9) | 104 394 (56.8) |

Abbreviations: ED, emergency department; GI, gastrointestinal.

[a] The covariates are determined for every person-day of follow-up. Thus, for categorical variables, the proportion of follow-up person-days in the specific category is shown. The covariate distributions for the 143 152 person-years of former PPI cotherapy are not shown.

[b] The GI bleeding risk score is the expected incidence of upper hospitalization for GI bleeding given the study covariates, expressed as a quantile between 0 and 19. A score of 0 represents patients with lowest expected and a score of 19 represents patients with the highest.

[c] All comorbidities defined 365 days before the day of follow-up being classified, except for current medication use, which is defined as probable use on the follow-up 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 in Supplement 1.

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

[e] *ICD-9-CM* diagnosis of 790.92.

[f] Nonsteroidal anti-inflammatory drugs, P2Y$_{12}$ inhibitors, dipyridamole, cilostazole, voraxapar.

[g] Cyclooxygenase-2 inhibitors, other anticoagulants, systemic corticosteroids, selective serotonin reuptake inhibitors, antibiotics.

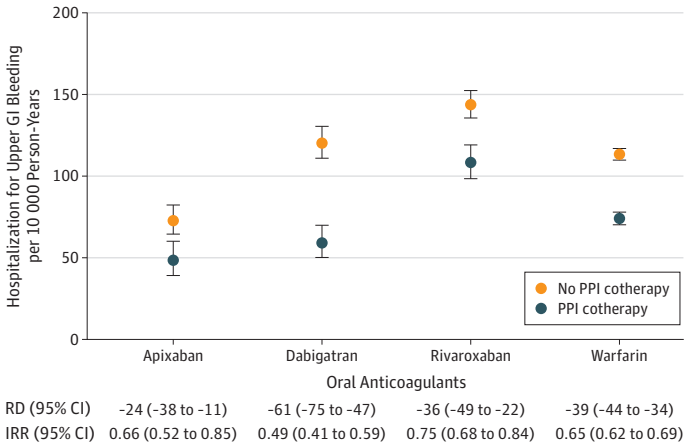
[h] Myocardial infarction, revascularization, thrombotic stroke, transient ischemic attacks.

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

[j] Indications of frailty or other conditions that indicate vulnerable patients included falls or mobility impairment, fecal or urinary incontinence, malnutrition, home oxygen, alcohol-related conditions, and liver disease.

[k] Defined as hospitalization for any reason or an ED visit that resulted in a GI-related diagnosis.

Figure 1. Adjusted Incidence of Hospitalization for Upper Gastrointestinal (GI) Tract Bleeding by Individual Oral Anticoagulants[a]




| | Apixaban | Dabigatran | Rivaroxaban | Warfarin |
|---|---|---|---|---|
| RD (95% CI) | -24 (-38 to -11) | -61 (-75 to -47) | -36 (-49 to -22) | -39 (-44 to -34) |
| IRR (95% CI) | 0.66 (0.52 to 0.85) | 0.49 (0.41 to 0.59) | 0.75 (0.68 to 0.84) | 0.65 (0.62 to 0.69) |

IRR indicates incidence rate ratio; PPI, proton pump inhibitor; RD, rate difference per 10 000 person-years. Error bars indicate 95% CIs.

[a] Adjusted for all covariates listed in eTable 3 in Supplement 1.

Table 2. Comparative Incidence of Hospitalization for Upper Gastrointestinal Tract Bleeding for Individual Oral Anticoagulants According to PPI Cotherapy[a]

| | No PPI Cotherapy | | | PPI Cotherapy | | |
|---|---|---|---|---|---|---|
| | Hospitalizations | Person-years | Adjusted incidence/ 10 000 person-years (95% CI) | Hospitalizations | Person-years | Adjusted incidence/ 10 000 person-years (95% CI) |
| Apixaban | 279 | 43 970 | 72.9 (64.5 to 82.3) | 85 | 14 989 | 48.5 (39.1 to 60.1) |
| Dabigatran | 629 | 79 739 | 120.4 (111.0 to 130.5) | 143 | 26 572 | 59.2 (50.2 to 69.9) |
| Rivaroxaban | 1278 | 114 168 | 143.8 (135.6 to 152.4) | 453 | 38 958 | 108.3 (98.5 to 119.0) |
| Warfarin | 4933 | 516 512 | 113.3 (109.9 to 116.9) | 1564 | 183 929 | 74.0 (70.2 to 78.0) |
| | RD (95% CI) | IRR (95% CI) | | RD (95% CI) | IRR (95% CI) | |
| Apixaban vs | | | | | | |
| Dabigatran | −47.5 (−60.6 to −34.3) | 0.61 (0.52 to 0.70) | | −10.8 (−25.1 to 3.5) | 0.82 (0.62 to 1.07) | |
| Rivaroxaban | −70.9 (−82.7 to −59.1) | 0.51 (0.44 to 0.58) | | −59.8 (−74.4 to −45.2) | 0.45 (0.35 to 0.56) | |
| Warfarin | −40.5 (−50.0 to −31.0) | 0.64 (0.57 to 0.73) | | −25.6 (−36.7 to −14.4) | 0.65 (0.52 to 0.82) | |
| Dabigatran vs | | | | | | |
| Rivaroxaban | −23.4 (−36.2 to −10.6) | 0.84 (0.76 to 0.92) | | −49.0 (−63.2 to −34.9) | 0.55 (0.45 to 0.66) | |
| Warfarin | 7.0 (−3.3 to 17.3) | 1.06 (0.98 to 1.16) | | −14.8 (−25.3 to −4.3) | 0.80 (0.67 to 0.95) | |
| Rivaroxaban vs | | | | | | |
| Warfarin | 30.4 (20.3 to 40.6) | 1.27 (1.19 to 1.35) | | 34.2 (23.3 to 45.2) | 1.46 (1.31 to 1.63) | |

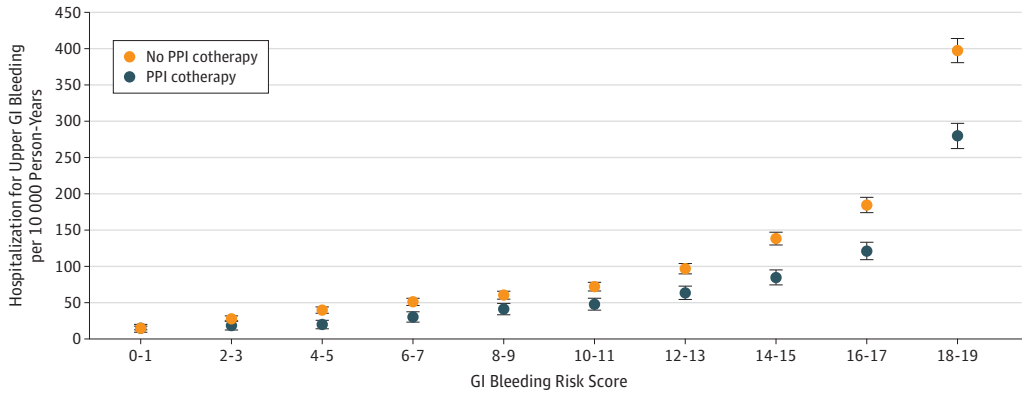
Abbreviations: IRR, incidence rate ratio; PPI, proton-pump inhibitor; RD, risk difference per 10 000 person-years.

[a] The IRRs and RDs are adjusted for 85 covariates included in eTable 3 in Supplement 1. IRR < 1 and RD < 0 indicate that the incidence of hospitalization for upper gastrointestinal tract bleeding was lower for the first drug than for the second.

a significant protective association between PPI cotherapy and the risk of hospitalization for upper intestinal tract bleeding for all patients except those in the lowest risk decile. The difference in absolute incidence increased with increasing risk, from an RD of −0.4 hospitalizations per 10 000 person-years (95% CI, −6.4 to 5.7) for the lowest decile to −117.5 per 10 000 person-year (95% CI, −141.8 to −93.3) for the highest decile. When patients in decile 10 and decile 1 were compared (eTable 5 in Supplement 1), the former more often were of advanced age, were enrolled in Medicaid, resided in a nursing home, recently started anticoagulant therapy, had a history of upper gastrointestinal tract disease or signs of bleeding, used medications that increase bleeding risk, were eligible for aspirin prophylaxis, had other cardiovascular disease, met criteria for frailty, and were hospitalized or had a gastrointestinal-related emergency department visit in the past year.

The absolute difference between rivaroxaban and apixaban in the adjusted incidence of hospitalization for upper gastrointestinal tract bleeding was greater in patients with higher gastrointestinal bleeding risk scores, regardless of PPI cotherapy (**Figure 3**). Patients in the upper risk quartile without PPI cotherapy who were prescribed rivaroxaban or apixaban had 327 (95% CI, 302-355) and 162 (95% CI, 137-190) hospitalizations per 10 000 person-years, respectively (RD, 165.7 [95% CI, 129.7-201.7]). For patients receiving PPI

Figure 2. Unadjusted Incidence of Hospitalization for Upper Gastrointestinal (GI) Tract Bleeding With and Without Proton-Pump Inhibitor (PPI) Cotherapy by Gastrointestinal Bleeding Risk Score




| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 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 to 1.20) | 0.65 (0.55 to 0.78) | 0.50 (0.43 to 0.59) | 0.59 (0.52 to 0.67) | 0.68 (0.61 to 0.76) | 0.66 (0.60 to 0.71) | 0.66 (0.60 to 0.71) | 0.61 (0.57 to 0.66) | 0.66 (0.62 to 0.70) | 0.70 (0.68 to 0.73) |
| PPI | | | | | | | | | | |
| Hospitalizations | 28 | 36 | 43 | 72 | 106 | 131 | 185 | 261 | 396 | 987 |
| Person-years | 18924 | 19460 | 21537 | 23709 | 25679 | 27384 | 29036 | 30774 | 32644 | 35281 |
| No PPI cotherapy | | | | | | | | | | |
| Hospitalizations | 135 | 249 | 337 | 417 | 473 | 543 | 699 | 945 | 1171 | 2150 |
| Person-years | 88973 | 87833 | 84766 | 81476 | 78224 | 75248 | 72086 | 68256 | 63417 | 54112 |

The gastrointestinal bleeding risk score is the expected incidence of hospitalization for upper gastrointestinal tract bleeding given the study covariates, expressed as a quantile from 0 to 19, with 0 indicating the lowest incidence and 19 indicating the highest. The decile-specific incidence is not adjusted for covariates because residual confounding is limited within each decile. IRR indicates incidence rate ratio; RD, risk difference. Error bars indicate 95% CIs.

cotherapy, the adjusted incidences per 10 000 person-years for rivaroxaban and apixaban were 258 (95% CI, 230-289) and 120 (95% CI, 93-153), respectively (RD, 138.0 [95% CI, 96.7-179.3]). When rivaroxaban treatment without PPI cotherapy was compared with apixaban treatment with PPI cotherapy, the difference was 208 hospitalizations per 10 000 person-years (95% CI, 169-247).

For patients in the upper quartile of the gastrointestinal bleeding risk score, the association between PPI cotherapy and reduced incidence of hospitalization for upper gastrointestinal tract bleeding was greatest for dabigatran (Figure 3). The adjusted incidence per 10 000 person-years was 299 (95% CI, 265-337) without cotherapy compared with 139 (95% CI, 112-171) with cotherapy (RD, −160.7 [−206.6 to −114.8]).

### Sensitivity Analyses

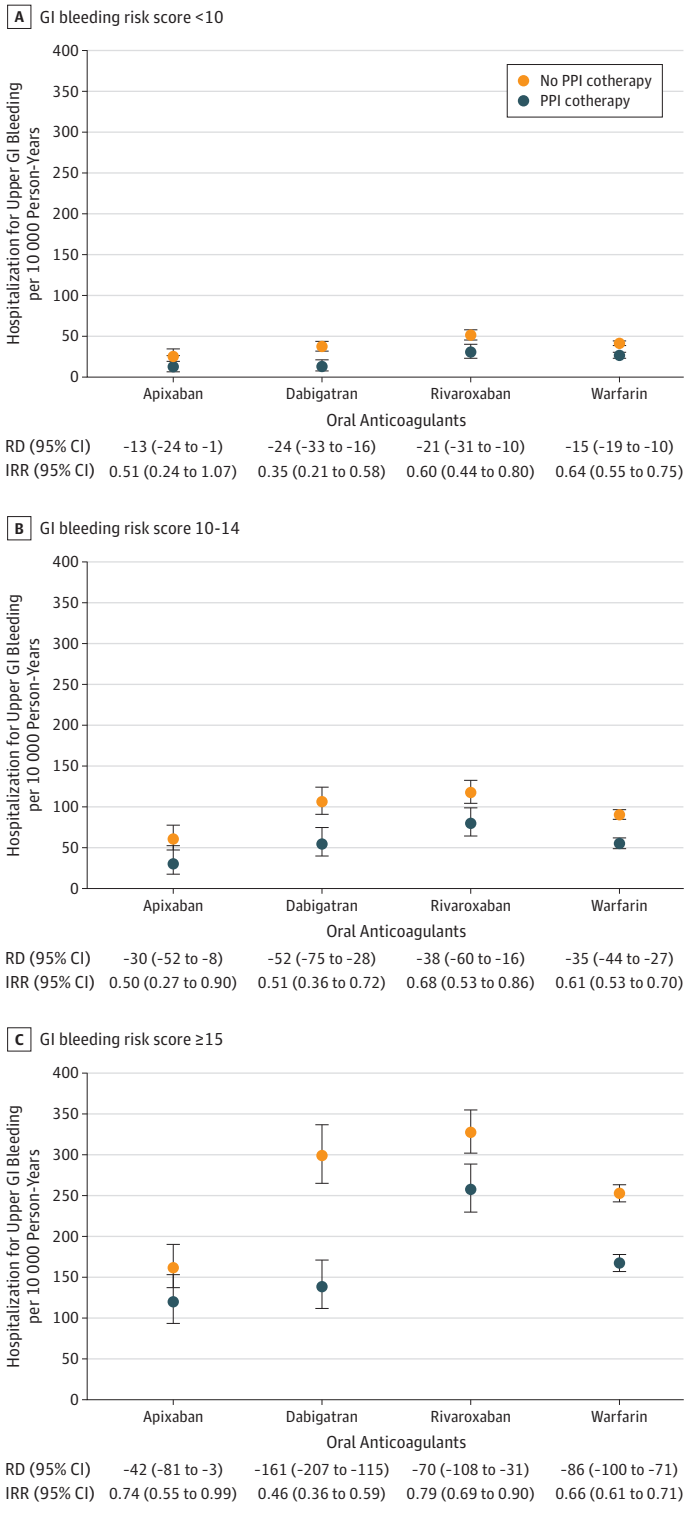
Analyses that assessed the sensitivity of study results to changes in either the study population or the statistical methods (eTable 6 in Supplement 1) focused on 2 key comparisons: apixaban vs rivaroxaban in patients not receiving PPI cotherapy and PPI cotherapy vs no cotherapy for all anticoagulants. For the first comparison, the IRR and RD from the primary analysis were 0.51 (95% CI, 0.44-0.58) and −71 (95% CI, −83 to −59), respectively; the sensitivity analyses had IRRs between 0.45 (95% CI, 0.39-0.53) and 0.55 (95% CI, 0.47-0.65) and RDs between −93 (95% CI, −109 to −77) and −63 (95% CI, −74 to −53). For the second comparison, the IRR and RD from the primary analysis were 0.66 (95% CI, 0.62-0.69) and −39 (95% CI, −44 to −35), respectively; the sensitivity analyses had IRRs between 0.64 (95% CI, 0.60-0.69) and 0.71 (95% CI, 0.66-0.75) and RDs between −48 (95% CI, −59 to −38) and −33 (95% CI, −37 to −29).

## Discussion

In this large population-based study of new episodes of oral anticoagulant treatment, the incidence of hospitalizations for upper gastrointestinal tract bleeding was the highest for patients prescribed rivaroxaban and the lowest for patients prescribed 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 higher than those for other oral anticoagulants.[21] The steep rise of the risk of bleeding associated with increased NOAC concentration[22] may explain the elevated risk of hospitalization for upper gastrointestinal tract bleeding.

PPI cotherapy was associated with a lower incidence of hospitalization for upper gastrointestinal tract bleeding for all anticoagulants included in the study. However, the difference was most pronounced for dabigatran, which is consistent with the large reduction in the risk of gastrointestinal bleeding observed by Chan et al when analyzing the effects of dabigatran with vs without cotherapy with gastroprotective agents[10] and may be explained by dabigatran-related upper gastrointestinal tract lesions that are potentially the result of

Figure 3. Adjusted Incidence of Hospitalizations for Upper Gastrointestinal (GI) Tract Bleeding According to Quartiles of Gastrointestinal Bleeding Risk Score, Individual Oral Anticoagulant, and Proton Pump Inhibitor (PPI) Cotherapy




Quartiles 1 and 2 (A) were combined because the absolute differences in incidence between these quartiles were much lower than those for quartiles 3 (B) and 4 (C). The GI bleeding risk score is the expected incidence of hospitalization for upper GI bleeding given the study covariates, expressed as a quantile between 0 and 19. A score of 0 represents the lowest incidence and 19 represents the highest. Incidence within each group is adjusted for all covariates in eTable 3 in Supplement 1 to reduce residual confounding within the quartiles of the gastrointestinal bleeding risk score. IRR indicates incidence rate ratio; RD, risk difference. Error bars indicate 95% CIs.

direct mucosal injury by the drug's tartaric acid core.[23,24] PPI cotherapy 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 ongoing COMPASS

trial[27] will provide further data on the benefits and risks of PPI cotherapy during anticoagulant treatment.

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

### Limitations

This study had several limitations. First, there was potential misclassification of anticoagulant treatment, PPI cotherapy, and NSAID use among patients because these variables were determined from filled prescriptions, and Medicare restricts reimbursement for many over-the-counter drugs. Nevertheless, the resulting misclassification should bias to the null because it is likely to either be nondifferential, or, as is probable for NSAIDs, which cause gastrointestinal bleeding and are positively correlated with PPI cotherapy,[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 covariate) or *Helicobacter pylori* infection. However, the positive correlation between recorded risk factors for gastrointestinal bleeding and apixaban and PPI cotherapy suggests that bias due to unmeasured confounders should be conservative. The absence of protective associations of former PPI cotherapy with upper gastrointestinal tract bleeding and PPI cotherapy with bleeding at other gastrointestinal sites also suggests that confounding does not explain the 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 who were previously hospitalized for gastrointestinal bleeding or who switched to a different anticoagulant during the study period, and consisted of Medicare enrollees, a population with a greater prevalence of anticoagulant treatment and risk of major upper gastrointestinal tract bleeding compared with younger populations.

## Conclusions

Among patients initiating oral anticoagulant treatment, incidence of hospitalization for upper gastrointestinal tract bleeding was the highest for rivaroxaban and lowest for apixaban. For each anticoagulant, the incidence was lower among patients receiving PPI cotherapy. These findings may inform assessment of risks and benefits when choosing anticoagulant agents.


### ARTICLE INFORMATION

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### REFERENCES


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. doi:10.1016/S0140-6736(13)62343-0

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. doi:10.1056/NEJMoa0905561

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. doi:10.1053/j.gastro.2017.02.027

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. doi:10.1053/j.gastro.2016.08.054

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 Intern Med*. 2016;176(11):1662-1671. doi:10.1001/jamainternmed.2016.5954

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. doi:10.1053/j.gastro.2016.12.018

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. *Thromb Haemost*. 2017;117(6):1072-1082. doi:10.1160/TH17-01-0068

**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. doi:10.1161/STROKEAHA.117.018395

**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. doi:10.3109/00365528909091254

**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):586-95.e3. doi:10.1053/j.gastro.2015.05.002

**11**. Ray WA. Population-based studies of adverse drug effects. *N Engl J Med*. 2003;349(17):1592-1594. doi:10.1056/NEJMp038145

**12**. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol*. 2003;158(9):915-920. doi:10.1093/aje/kwg231

**13**. Uddin MJ, Groenwold RH, Ali MS, et al. Methods to control for unmeasured confounding in pharmacoepidemiology: an overview. *Int J Clin Pharm*. 2016;38(3):714-723.

**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. *Pharmacoepidemiol Drug Saf*. 2011;20(6):560-566. doi:10.1002/pds.2109

**15**. Arbogast PG, Kaltenbach L, Ding H, Ray WA. Adjustment for multiple cardiovascular risk factors using a summary risk score. *Epidemiology*. 2008;19(1):30-37. doi:10.1097/EDE.0b013e31815be000

**16**. Arbogast PG, Ray WA. Use of disease risk scores in pharmacoepidemiologic studies. *Stat Methods Med Res*. 2009;18(1):67-80. doi:10.1177/0962280208092347

**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 Epidemiol*. 2011;174(5):613-620. doi:10.1093/aje/kwr143

**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. doi:10.1002/pds.3231

**19**. Tadrous M, Gagne JJ, Stürmer T, Cadarette SM. Disease risk score as a confounder summary method: systematic review and recommendations. *Pharmacoepidemiol Drug Saf*. 2013;22(2):122-129. doi:10.1002/pds.3377

**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. doi:10.1136/bmj.k2505

**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(suppl 7):S24-S33. doi:10.1016/j.cjca.2013.04.002

**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. doi:10.1016/j.jacc.2013.07.104

**23**. Singh S, Savage L, Klein M, Thomas C. Severe necrotic oesophageal and gastric ulceration associated with dabigatran [published online April 2, 2013]. *BMJ Case Rep*. doi:10.1136/bcr-2013-009139

**24**. Zhang N, Liu XS, Li G, Liu T. Dabigatran-induced esophagitis: A frequently overlooked adverse effect. *Int J Cardiol*. 2016;212:358-359. doi:10.1016/j.ijcard.2016.03.178

**25**. Bolek T, Samoš M, Stančiaková L, et al. The impact of proton pump inhibition on dabigatran levels in patients with atrial fibrillation [published online April 25, 2017]. *Am J Ther*. doi:10.1097/MJT.0000000000000599

**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. *J Thromb Haemost*. 2011;9(11):2168-2175. doi:10.1111/j.1538-7836.2011.04498.x

**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. doi:10.1016/j.cjca.2017.06.001