Supplementary Online Content

Ray WA, Chung CP, Murray KT, et al. Association of oral anticoagulants and proton pump inhibitor cotherapy with hospitalization for upper gastrointestinal tract bleeding. *JAMA*. doi:10.1001/jama.2018.17242

This supplementary material has been provided by the authors to give readers additional information about their work.

The eAppendix provides additional details on the methods and results for the study of oral anticoagulants and proton-pump inhibitors (PPIs) and should be read in conjunction with the primary manuscript (MS).

eAppendix. Additional methods and results

eTable 1. Qualifying episodes of oral anticoagulant use.

eFigure 1. Medication use patterns for 7 hypothetical oral anticoagulant (OAC) patients.

eTable 2. Performance of modified algorithm for upper gastrointestinal (GI) bleeds.

eTable 3. Study covariates and IRRs for gastrointestinal bleeding risk score.

eTable 4. All study covariates according to PPI co-therapy and oral anticoagulant.

eTable 5. Summary covariates for highest versus lowest decile of gastrointestinal bleeding risk score. See footnotes for MS Table 1.

eTable 6. Sensitivity analyses.

eTable 7. Gastrointestinal bleeding hospitalizations for all study oral anticoagulants according to PPI co-therapy.

eReferences.

§1. Cohort

eTable 1 shows the cohort inclusion-exclusion criteria and the numbers retained after application of each criterion.

eTable 1. Qualifying episodes of oral anticoagulant use.

Criterion	Episodes / Persons
1. Filled prescription for an oral anticoagulant during study period with at least one edited day of supply. No other oral anticoagulant prescription in the past year.	4,701,613 / 4,486,605
2. Enrolled in a category that provides full pharmacy benefits, which excludes enrollees in Medicare managed care programs.	2,927,407 / 2,804,780
3. Date of birth and sex known.	2,927,406 / 2,804,779
4. Enrolled for the past 12 months.	1,955,787 / 1,868,290
5. Age 30 years or older.	1,951,287 / 1,864,087
6. At least one outpatient visit and one filled prescription in the past year, excluding lab claims, to assure that patients have had regular contact with medical care.	1,923,004 / 1,837,670
7. No end-stage renal disease (ESRD), defined as a patient with either an ESRD diagnosis or a procedure indicating dialysis outside of the hospital.	1,842,654 / 1,761,835
8. No serious upper GI illness predisposing to frequent GI bleeding /altering the pathology of peptic ulcer disease in the past year. This excludes persons who may have frequent care for bleeding from other causes, such as esophageal varices or gastrointestinal cancer.	1,768,865 / 1,692,366
9. No hospitalization in past year meeting the definition for a study endpoint. This improved the positive predictive value of the endpoint definition; for patients with a recent bleed it was difficult to distinguish a new bleeding episode from continuing treatment for a prior episode.	1,743,192 / 1,668,670
10. If in the hospital (single day stays not considered as hospitalization) on the date of the anticoagulant prescription, this must be either the day of or the day prior to discharge. The patient must be alive on the following day.	1,719,792 / 1,646,924
11. Prescription not for edoxaban or multiple study anticoagulants.	1,713,183 / 1,643,123

Patients entered the cohort on the date of the study oral anticoagulant prescription fill. Patients left the cohort on the first of the following dates:

1. End of oral anticoagulant use: after one year with no filled prescription;
2. Switch to a different oral anticoagulant;
3. The last day of the study, 9/30/2015;
4. Last day of enrollment, including either loss of enrollment or transition to a category without full pharmacy benefits. Transfer to Medicare Part C was considered loss of enrollment.
5. Day prior to failure to meet inclusion/exclusion criteria;
6. Day of a study endpoint;
7. Date of death.

Patients who left the cohort could reenter if they subsequently met the study criteria, including one year with no filled oral anticoagulant prescription. This included patients with an endpoint if they subsequently had at least one year with no endpoint. Because a single person could have multiple endpoints, which could violate statistical independence assumptions, we performed sensitivity analyses that did not allow patients to re-enter the cohort and that used repeated measures to control for within-patient effects.

§2. Study Medication Use during Followup

The study analysis required identifying periods of exposure to oral anticoagulants, PPIs, and antiplatelet drugs/NSAIDs. Because these medications are thought to alter the risk of bleeding only while the patients are taking the drugs, we tracked study medication exposure during followup on a day-by-day basis.

Cohort drug exposure was determined from records of filled prescriptions. Periods of drug exposure were defined according to the date the prescription was filled and the dispensed days of supply. Although the dispensed days of supply was never missing, it was inconsistent with the quantity dispensed for <1% of prescriptions (e.g., 90 tablets, 1 day of supply). In this circumstance, we edited the days of supply; however, the prescription was excluded from dose analyses. The maximum days of supply per prescription was 90 days. Because medication regimens often change during a hospital stay, we ended the prescription days of supply when the patient was admitted to the hospital. Study medication use would resume if and when the patient refilled the medication after hospital discharge.

Some of the study drugs can affect the risk of bleeding for a few days following cessation of use. Thus, to avoid treatment or covariate misclassification, the definitions of the exposure periods varied slightly according to drug, as described below.

Oral anticoagulant treatment. The risk of anticoagulant-related bleeding should only be present while patients are taking the drug. Thus, all study analyses were restricted to periods of anticoagulant treatment during followup, defined as the interval from the date the prescription was filled through 1 (apixaban, dabigatran, rivaroxaban) to 3 (warfarin) days after the end of the days of supply, representing approximately two half-lives.

In some analyses, we considered anticoagulant dose (except for warfarin). Person-time (<1%) with inconsistencies between days of supply and quantity dispensed was considered to have missing dose and thus excluded.

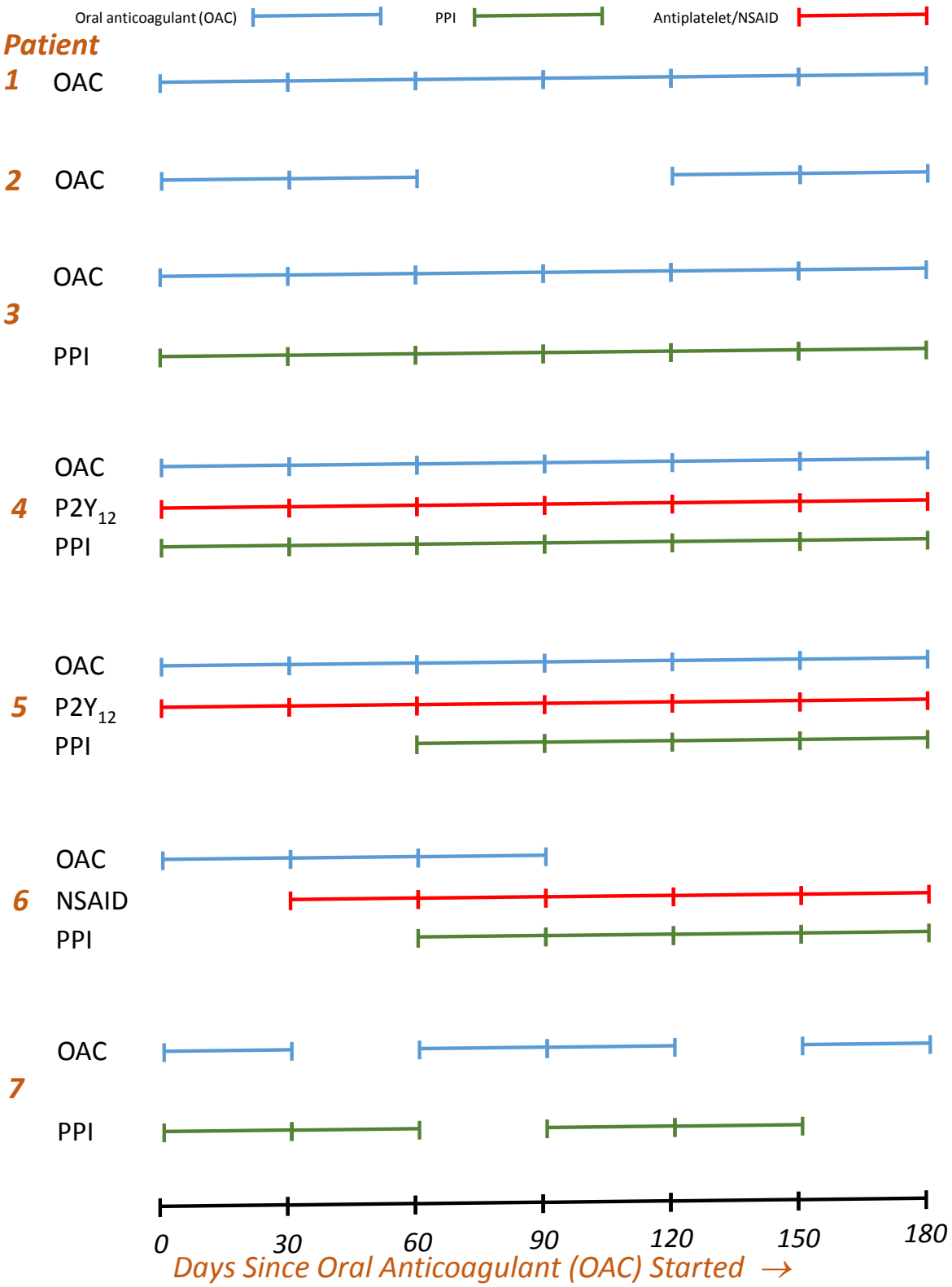
PPI co-therapy. All oral anticoagulant treatment was classified into three categories according to concomitant use of PPIs (dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole). :

- *PPI co-therapy* was the period during which gastroprotective effects were most plausible, defined as the interval from the filling of the prescription through the end of the dispensed days of supply.
- *No co-therapy* indicated person-time for which no PPI prescription had been filled in the past 365 days.
- *Former PPI co-therapy* indicated person-time for persons who had received a PPI prescription but should not have gastroprotection. This category permits assessment of confounding by unmeasured factors associated with being prescribed a PPI. It was defined as a) the period between the end of current co-therapy and the beginning of no co-therapy; or b) the first day for a new course of therapy (none past 365 days), given the implausibility of a gastroprotective effect on that day and the possibility that the PPI was started to treat a gastrointestinal bleed. Non-current use also includes person-time during which PPI exposure may be misclassified because patients were taking the drug on an as-needed schedule.

Concurrent antiplatelet drug/NSAID use. The study antiplatelet drugs were $P2Y_{12}$ inhibitors and other antiplatelet drugs (dipyridamole, cilostazol, vorapaxar). NSAIDs comprised the non-selective, nonsteroidal anti-inflammatory drugs other than aspirin. Concurrent antiplatelet drug/NSAID use during followup was dichotomized as either present or absent. For antiplatelet drugs (except for ticagrelor), concurrent use was present for the interval from the filling of the prescription through 7 days following the end of the days of supply, given that these medications irreversibly inhibit platelets. The period of concurrent use for non-aspirin NSAIDs was the interval from the filling of the prescription through the end of the days of supply.

Medication use examples. eFigure 1 provides examples of the medication use definitions. For convenience, the examples only depict the first 180 days of cohort followup. There are seven hypothetical patients with anticoagulant treatment, each illustrating a common pattern of anticoagulant use.

1. Patient starts anticoagulant therapy and has no other study medications. The entire followup period is included in the analysis as anticoagulant treatment.
2. Patient receives two 60 day courses of warfarin separated by 60 days. The interval between the anticoagulant courses is not considered anticoagulant treatment and is excluded from the analysis. Thus, patient 2 would contribute 63+60 = 123 person-days of anticoagulant treatment to study analyses, noting that warfarin treatment extends 3 days beyond the days of supply to account for residual effects. The remaining 57 days of person-time for that patient would not be considered.
3. Patient is started on anticoagulant and a PPI. The entire 180 days of followup will be classified as anticoagulant treatment with PPI co-therapy.
4. A patient begins anticoagulant, a PPI, and a $P2Y_{12}$ inhibitor. The entire 180 days of followup will be classified as anticoagulant treatment with concurrent antiplatelet drug/NSAID use and PPI co-therapy.
5. A patient begins anticoagulant and a $P2Y_{12}$ inhibitor, but there is no PPI prescription within the past year. The entire 180 days of followup will be classified as anticoagulant treatment with concurrent antiplatelet drug/NSAID use. A PPI is started at day 61. Days 1 through 60 will be classified as no PPI co-therapy and days 62 through 180 as PPI co-therapy. Day 61 is classified as former PPI co-therapy.
6. Patient receives 90 days of anticoagulant therapy with no history of PPI use in the past year. Shortly after therapy begins, an NSAID is started. Subsequent to the NSAID, a PPI prescription is filled. The first 30 days of followup is classified as anticoagulant treatment with neither PPI co-therapy nor concurrent antiplatelet drug/NSAID use. The next 30 days is anticoagulant treatment with concurrent antiplatelet drug/NSAID use, but with no PPI co-therapy. The remaining person-time is anticoagulant treatment with both concurrent antiplatelet drug/NSAID use and PPI co-therapy.
7. Patient has intermittent anticoagulant and PPI therapy. The gaps in anticoagulant therapy are not included in the study analysis. The periods where anticoagulant and PPI use overlap are anticoagulant treatment with PPI co-therapy, the other periods of anticoagulant therapy are anticoagulant treatment with former PPI co-therapy.



eFigure 1. Medication use patterns for 7 hypothetical oral anticoagulant (OAC) patients. 1) Long-term OAC use, no other study medications 2) Two 60 day OAC courses separated by 60 days; 3) OAC with PPI; 4) OAC + PPI + $P2Y_{12}$; 5) OAC + $P2Y_{12}$, PPI starts after OAC; 6) 90 day OAC course, NSAID after OAC start and subsequently PPI; 7) Intermittent OAC and PPI therapy.

§3. Serious Bleeding Endpoints.

Serious bleeding endpoints were hospitalizations with diagnoses and procedures indicating that the hospitalization was primarily related to a major bleed. These hospitalizations were classified according to the probable site of the bleeding:

1. Gastroduodenal;
2. Esophageal, other than gastroesophageal reflux disease;
3. Upper gastrointestinal, unspecified as to esophageal or gastroduodenal;
4. Upper gastrointestinal, angiodysplasia;
5. Lower gastrointestinal;
6. Unspecified gastrointestinal, possibly esophageal, upper, or lower;
7. Multiple gastrointestinal;
8. Genitourinary;
9. Cerebral;
10. Other specified site;
11. Unspecified site;
12. Multiple sites.

The upper GI sites were classified as those that should (1 and 3) or should not (2 and 4) be affected by PPI co-therapy. The primary study endpoint, upper gastrointestinal bleeding, was the composite of sites 1 and 3. The other GI site endpoint was the composite of sites 2, 4, 5, 6, 7.

We identified bleeding-related hospitalizations and assigned a bleeding site using a previously validated algorithm[1] with minor modifications. The primary modification was of the method for distinguishing upper and lower GI bleeding when the hospital discharge diagnosis was 578.1 or 578.9, which can indicate either an upper or lower site. Previously, we relied upon procedure codes: for example, if there was a procedure code for upper GI endoscopy, but no diagnosis compatible with upper GI bleeding, we would assign an upper site. We modified this definition because an endoscopy coupled with discharge diagnoses not indicating upper GI bleeding may reflect a negative diagnostic evaluation. The revised algorithm is available from the authors on request.

We assessed the performance of the modified algorithm for the primary study endpoint of upper gastrointestinal bleeding (UGIB). This utilized the 239 completed chart adjudications for bleeding hospitalizations from our previous validation study.[1] The performance of algorithms for identifying any gastrointestinal bleeding did not change: Positive predictive value (PPV) = 102/103 = 99.0%; sensitivity = 102/103 = 99.0%. UGIB performance was based on 103 cases of gastrointestinal bleeding identified by both algorithms and with completed chart adjudication (eTable 2)

For the published algorithm, the PPV was 77.3% and the sensitivity 87.1%. For the revised algorithm, the PPV was 80.5% and the sensitivity was 84.6%.

We also assigned a date of the bleeding onset. For 92% of the cases of the primary endpoint, this was the date of the hospital admission. When there was evidence that the bleeding began earlier (e.g., hospitalization for bleeding peptic ulcer with preceding day ED visit with hematemesis diagnosis) the date was reset: 6% to the day prior to hospital admission, 1% 2-7 days prior, and 1% 8-30 days prior.

eTable 2. Performance of modified algorithm for upper gastrointestinal (GI) bleeds.

Published algorithm			
	Upper GI Bleed	No Upper GI Bleed	All
Computer UGIB	34	10	44
No Computer UGIB	5	54	59
All	39	64	103
Revised Algorithm			
	Upper GI Bleed	No Upper GI Bleed	All
Computer UGIB	33	8	41
No Computer UGIB	6	56	62
All	39	64	103

§4. Statistical Analysis

Anticoagulant treatment. For each patient in the cohort, the analysis was restricted to person-days with oral anticoagulant treatment (eAppendix §2). Treatment days were considered as consecutive with between 1 and 1734 anticoagulant days for each patient. This constitutes a time-on-treatment time scale, which has the advantages that: 1) when patients with a given duration of followup are compared, the analysis automatically controls for anticoagulant treatment duration, and 2) the estimators often have lower variance than those that result from a time-on-study time scale.[2]

PPI co-therapy. In the primary analysis and several of the sensitivity analyses, PPI co-therapy was characterized for every day of anticoagulant treatment as no, former, or current co-therapy (eAppendix §2). PPI co-therapy could be initiated at any time prior to baseline or during followup.

Time-dependent covariates. Many of the factors that influence the likelihood of hospitalization for upper gastrointestinal bleeding are plausibly time-dependent. Of particular importance are medications such as NSAIDs and antiplatelet drugs that may both increase the risk of bleeding and lead to PPI use. To control for this type of confounding, the study covariates (eTable 3) could change on each person-day of followup.

Analytic approaches. Given the two independent exposure variables, one of which could vary with time, as well as covariates that could change on each day of followup, we considered several analytic options:

Marginal structural models—These provide a theoretically elegant analysis for time-varying exposures and confounders, particularly when the confounders are on the causal pathway between the exposure and the outcome.[3,4] Marginal structural models work by calculating a set of inverse probability of treatment/censoring weights for each study time point, which in our study are the 1734 potential followup days. Informally, the weights are inversely proportional to time-dependent probability of the observed treatment (exposure) and censoring history, conditional on both covariate and treatment history. Because the weights are the reciprocals of the cumulative product of terms always less than one (often considerably so) they will become quite large, even if stabilized variants[3-5] are estimated. In the best of circumstances, the variance of estimates is increased, making marginal structural model analyses less efficient than alternatives.[6] Furthermore, the weights are highly sensitive to both misspecification of the model linking covariates to treatment and departures from the necessary positivity assumption (in the anticoagulant study, the treatment variables for subsequent days are highly correlated), leading to bias.[7,8] There are published examples of large studies where the weight for a single subject determined study findings.[9] In practice, researchers nearly always deal with the problem of unstable weights by truncating them at the 95th, 97.5th, or 99th percentile. However, there is no theory to guide such truncation and choice of the truncation boundary can materially influence findings. For these reasons, marginal structural models will work best if there are a small to moderate number of more widely spaced time points; many of the published examples have covariate update time points 90 to 180 days apart.[10] In contrast, we updated covariates every day because it was important to capture brief, but potentially hazardous exposures, such as an NSAID prescription that could lead to an episode of bleeding.

Propensity scores—Propensity-score based analyses[11-13] have become nearly a *de facto* method for pharmacoepidemiology studies. They have two primary advantages: 1) they provide an elegant solution to the degrees of freedom problem (large number of covariates relative to number of endpoints); and 2) they separating modeling of the exposure from that of the outcome, enabling analyses that balance covariates across treatment groups and thus rely on fewer assumptions than standard multivariable regression approaches.[11-13] However, propensity scores work best for binary exposures; the extensions to more complex exposures (the primary anticoagulant exposure variable has 8 levels) are cumbersome.[14,15] The extension to time-dependent propensity scores also is complex and violations of the positivity assumption may occur if, as is the case for the anticoagulant study, covariates change on a day-by-day basis.[6]

New user design with multivariable regression and time-dependent covariates—Given the limitations of the above methods, the large number of time points, and that the number of endpoints in our study was adequate for the study covariates, we implemented a standard multivariable regression analysis with time-dependent covariates. The new user design reduces the problems inherent in this approach for time-varying data because it assures that the baseline covariates--measured before oral anticoagulant use begins--are free of the effects of potential causal pathway confounders. Furthermore, the most troublesome causal pathway scenario is

Exposure → Confounder → Outcome, for example:
Statin → Decreased LDL → Lower AMI risk.

However, for some of the strongest potential confounders in our study, such as antiplatelet drugs, this scenario is unlikely, as initiation of PPI co-therapy should not, for example, influence subsequent use of an NSAID or $P2Y_{12}$ inhibitor. Nevertheless, we recognize that some time-dependent covariates, particularly those related to upper gastrointestinal disease, are potentially on the causal pathway between anticoagulants and major upper gastrointestinal bleeding. Thus, a pre-specified sensitivity analysis fixed these at the time of anticoagulant initiation. An additional sensitivity analysis for key pairwise comparisons fixed PPI co-therapy and all covariates at anticoagulant initiation and balanced the groups by propensity-score matching.

Poisson regression. In the context of a variable followup cohort study with individual subjects each of whom either experiences the endpoint or is censored by the end of followup, a computationally efficient, analytic framework is the piecewise exponential model,[16]

$$\log\{\lambda_{it}\} = \beta_0 + \beta_1 * a_{it} + \boldsymbol{\beta}_2 * \mathbf{z}_{\text{it}} \quad (1)$$

where i represents cohort subjects, t a discrete time period, a_{it} is the treatment (exposure) variable, $\boldsymbol{z}_{it}$ the covariate vector for subject i, period t, and λ_{it} is the expected event rate for subject i in period t. This assumes the event rate for $z_{it} = 0$ is constant; however, varying incidence over time is accommodated by including covariates for time since start of followup[a]. Estimation of parameters for model (1) is known to be equivalent to estimation of those for a Poisson count variable model in an independent pseudo-population of $\sum t_i$ subjects, where each subject corresponds to a single time period.[16-18] In this model

$$\log\{E[y_{it}]\} = \log(s_{it}) + \beta_0 + \beta_1 * a_{it} + \boldsymbol{\beta_2} * \boldsymbol{z}_{it} \quad (2)$$

where y_{it} is the outcome variable and s_{it} the length of the time interval. This formulation has the computational advantage that if we summarize the data across subjects and time intervals for which treatment and covariates are constant, the model is

$$\log\{E[n_t]\} = \log(m_t) + \beta_0 + \beta_1 * a_t + \boldsymbol{\beta}_2 * \mathbf{z}_t$$

[a] More generally, the first term is β_{0t}, which relaxes the constant hazard assumption. However, non-constant hazard can be accommodated with indicator covariates for time periods during which the intercept changes, hence the term "piecewise". In the anticoagulant study, the time intervals in days are 1-30, 31-90, 91-365, 366-730, and >730.

where n_t is the number of outcomes and m_t the total person-time for interval t. In practice this approach often substantially decreases computation times[b]. It has the additional advantage that the cumulative incidence can be directly modeled and we can estimate marginal means and their differences.

IRR estimation. For most of the primary analyses, effects of joint anticoagulant treatment—PPI co-therapy were estimated via a categorical treatment variable with 4 (individual anticoagulant) x 3 (PPI co-therapy: current, former, none) = 12 levels. The primary analyses focused on the 8 comparisons corresponding to individual anticoagulants and current or no PPI co-therapy, as depicted by the diagram below.

Apixaban		*Dabigatran*		*Rivaroxaban*		*Warfarin*	
PPI+	*PPI-*	*PPI+*	*PPI-*	*PPI+*	*PPI-*	*PPI+*	*PPI-*
1	2	3	4	5	6	7	8

The regression analysis estimates the log of the incidence rate-ratio (IRR) for the first 7 of these cells, with the 8th (warfarin, no PPI) the reference category. The log of the IRR for all other comparisons (and the 95% CI) can be estimated with a single degree of freedom contrast. For example, that for apixaban:PPI vs apixaban:no PPI is estimated as 1 – 2. That for rivaroxaban:no PPI vs apixaban:no PPI is estimated as 6 – 2. The IRR (and the 95% CI) are calculated via exponentiation. Because this procedure estimates a separate parameter for every anticoagulant-PPI co-therapy combination, there is no assumption regarding interaction between individual anticoagulant and PPI co-therapy.

In some analyses, PPI co-therapy was studied for all anticoagulants, in which case the treatment variable had 3 levels and indicator variables for individual anticoagulants were included as potential confounders in the model.

Risk difference. We calculate the adjusted annual incidence of serious upper gastrointestinal bleeding with marginal means calculated by prediction at the means for the entire population[19] using the SAS LSMEANS statement. For example, if group 1 is patients with PPI co-therapy) and group 0 no PPI co-therapy then the adjusted incidence for the groups is derived as follows.

$\gamma_1 = \mathbf{z_1}'\boldsymbol{\beta}$ where $\mathbf{z_1}$ is the vector of covariate values with the indicator variables set to denote PPI co-therapy and all other covariate values set to their means for the entire population.

$\gamma_0 = \mathbf{z_0}'\boldsymbol{\beta}$ where $\mathbf{z_0}$ is analogous to $\mathbf{z_1}$ but with the indicator variables set to denote no PPI co-therapy.

The $\boldsymbol{\beta}$ are the regression coefficients from the Poisson regression, with the offset and intercept term combined. Then,

$I_1 = \exp(\gamma_1)$ and $I_0 = \exp(\gamma_0)$ are the adjusted incidences.

The *risk difference* (RD) is defined as

$$RD = I_1 - I_0.$$

The variance of the RD is

$$\text{var}(I_1) + \text{var}(I_0) - 2\text{cov}(I_1, I_0).$$

Using the delta method, we can derive for j = 0, 1

[b] The anticoagulant study had more than 400 million followup person-days. Each person-day would have to be included in time-dependent risk sets for proportional hazards analyses, which thus were not computationally feasible for the VRDC. The modelling for Poisson regression included approximately 20 million intervals, a 20-fold reduction. We did cross-check the Poisson approach with proportional hazards in a sample that included all person-days with endpoints and a random 1 in 20 sample of other person-days; results were essentially identical.

$var(I_j) = var(\exp(\gamma_j)) = I_j^2 var(\gamma_j)$, noting $d/d\gamma(\exp(\gamma)) = \exp(\gamma)$

and

$cov(I_1, I_0) = cov(\exp(\gamma_1), \exp(\gamma_0)) = I_1 I_0 cov(\gamma_1, \gamma_0)$.

Statistical sensitivity analyses. We performed several statistical sensitivity analyses:

Competing risks—In the primary analysis, subjects who died were censored. A sensitivity analysis considered death as a competing risk. Deaths during followup occurred if: 1) the date of death was a day of anticoagulant treatment; or 2) there was hospital admission on the last treatment day and death within 30 days, in which case the date of hospital admission was considered the date of death. We adapted the subdistribution method of Fine and Grey for competing risks[20] for Poisson regression.

Causal pathway confounding— In the primary analysis, all covariates could change during anticoagulant treatment, since PPI co-therapy could be initiated for gastrointestinal conditions that developed after cohort entry. However, some covariates could be on the causal pathway between study exposures and upper gastrointestinal bleeding hospitalization. In the sensitivity analysis all covariates were fixed as of the time of anticoagulant initiation, with the exception of treatment duration, PPI co-therapy, and concurrent use of drugs associated with gastrointestinal bleeding. To minimize misclassification related to covariate changes during treatment, the analysis was restricted to the first year of followup. This would be expected to increase the absolute incidence, because the first year of anticoagulant therapy is a period of elevated risk; however, it should have little effect on ratio and difference measures of effect.

*Non-independence: cohort restriction—A*lthough a single patient could have person-time both with and without PPI co-therapy and could reenter the cohort, because the time periods are non-overlapping, independence assumptions held unless a patient had multiple endpoints. Because the second exposure of a patient to anticoagulants was separated by at least one year with no recorded anticoagulant therapy, the primary analysis considered each episode as independent, even if a patient had multiple endpoints. If this assumption was incorrect, variance estimates would be too small and CIs too narrow. One sensitivity analysis addressed this potential source of bias by not permitting cohort reentry.

Non-independence: repeated measures—An alternative sensitivity analysis used repeated measures and considered patient as a random effect.

Propensity score matching—The primary analysis relied on multivariable regression to control for confounding. An alternative approach, particularly for binary exposures, is to balance the confounder distribution across exposure groups using the propensity score. Inverse probability of treatment weighting is an elegant theoretical method for such balancing; however, for studies with large numbers of time points it is subject to the effects of weight instability (see above). We thus used matching: an alternative propensity score approach for balancing the covariate distributions. Because this analysis works best for pairwise comparisons, we chose two of the comparisons which we considered potentially the most subject to unmeasured confounding: 1) the PPI co-therapy vs no co-therapy comparison for all anticoagulants (higher risk patients are channeled to PPIs) and 2) the comparison between apixaban and rivaroxaban for patients without PPI co-therapy (largest difference between NOACs).

We calculated the propensity score at baseline and did not allow any covariates, including PPI status, to vary with time. To reduce the potential for confounding by duration, informative censoring and covariate misclassification, followup was restricted to the year after anticoagulant initiation. We matched on propensity score by dividing it's distribution into 100 centiles (calculated for 1--the PPI co-therapy and 2--the apixaban groups). Within the strata defined by centiles patients were randomly matched. If there were insufficient patients in either group, subjects were randomly dropped. This approach had the advantage of excluding patients who according to the measured covariates were highly unlikely to receive the assigned treatment, who thus could have greater likelihood of unmeasured confounders. After matching, we examined the distribution of the covariates and calculated the standardized difference, which was always <10%. Given the successful matching, IRRs and RDs were calculated without adjustment for covariates.

§5. Gastrointestinal bleeding risk score.

Motivation and definition. The consequences of both anticoagulant and PPI co-therapy choice are likely to vary according to the patient's underlying risk of major gastrointestinal bleeding. Because this is a function of many factors, it is useful to express the risk as a scalar. Widely used scores such as HAS-BLED[21] do not target upper gastrointestinal bleeding nor do they encompass the effects of several study covariates that plausibly affect the risk of gastrointestinal bleeding. Thus, we calculated a *disease risk score* to summarize the risk of gastrointestinal bleeding as a function of all of the study covariates. The disease risk score, often described as the prognostic analogue of the propensity score,[22] is the risk of the study endpoint as a function of the covariates, given the reference category for the exposure.[23-25] Although the disease risk score often is used as a scalar covariate summary in the analysis, it also is a standard method for internal risk stratification.[26,27] In this context, its advantages are that it includes all of the study covariates and does not rely on approximate weights (e.g., the commonly used "points" approach[21]). It thus *"provides an important axis for evaluation of possibly varying effects and for characterization of subgroup specific absolute treatment effects"*.[26] Because it is designed for internal risk stratification, the covariates and their weights are specific to the individual study and the exact score may not be applicable to other populations.

Calculation. The disease risk score was calculated from a Poisson regression for the entire study cohort that modeled the expected incidence of hospitalization for upper gastrointestinal bleeding as a function of all study covariates. Given the parameter estimates for this model, we calculate the linear predictor $\mathbf{z}'\beta$ ($\mathbf{z}$ is the covariate vector and β the parameter estimates from the regression), which is the predicted value with the indicator variables set to warfarin treatment and no PPI co-therapy. The score estimates the logarithm of the expected incidence under the assumption of warfarin treatment without PPI co-therapy (treatment condition with the largest numbers of patients). Although it is possible to directly estimate the score in the subgroup of patients with no PPI co-therapy and warfarin use, experience indicates that in the absence of modification of the covariate effects by study exposures (which inspection suggested was true), the estimate is better if the entire cohort is used.[25] eTable 3 shows how each of the study covariates influenced the risk score.

Expression/Analysis. We classified cohort followup into the 20 quantiles (0-19) according to the linear predictor, a monotonic function of the expected incidence of upper gastrointestinal bleeding hospitalizations. Thus, a score of 0 indicates the lowest-risk 5% and 19 the highest-risk 5% of the cohort. For the risk-stratified analyses, the cohort was stratified according to risk score deciles (all anticoagulants) or quartiles (individual anticoagulants).

eTable 3. Study covariates and IRRs for gastrointestinal bleeding risk score.

	IRR	CL_Low	CL_High	p
Age, years	1.02	1.02	1.03	0.0000
Female sex	1.06	1.02	1.10	0.0063
Age < 65 years	1.15	1.06	1.26	0.0015
Medicaid enrollment	1.19	1.14	1.25	0.0000
Race white	0.87	0.82	0.92	0.0000
Nursing home residence past year	0.90	0.85	0.95	0.0004
Year of cohort entry: 2011	1.10	1.01	1.19	0.0230
2012	1.03	0.95	1.11	0.5050
2013	1.01	0.94	1.10	0.7237
2014	1.03	0.96	1.12	0.3979
2015	1.00	1.00	1.00	.
Indication: Atrial fibrillation	1.49	1.35	1.63	0.0000
Deep-vein thrombosis	1.57	1.43	1.73	0.0000
Other cardiovascular	1.63	1.44	1.84	0.0000
Other or unknown	1.00	1.00	1.00	.
Days since anticoagulant start: 1-30	3.14	2.90	3.40	0.0000
31-90	1.69	1.56	1.84	0.0000
91-365	1.35	1.25	1.45	0.0000
366-730	1.17	1.08	1.26	0.0001
>730	1.00	1.00	1.00	.
Peptic ulcer disease past 90 days	1.32	1.18	1.48	0.0000
Peptic ulcer disease past 91-365 days	1.28	1.17	1.40	0.0000
Gastritis past 90 days	1.31	1.16	1.47	0.0000
Gastritis past 91-365 days	1.06	0.96	1.17	0.2745
Other upper gastrointestinal disease past 90 days	1.18	1.07	1.31	0.0013
Other upper gastrointestinal disease 91-365 days	1.07	0.97	1.17	0.1644
Blood stool/GI bleeding past 90 days	0.98	0.86	1.11	0.7292
Blood stool/GI bleeding past 91-365 days	1.36	1.24	1.50	0.0000
Anemia or iron prescription past 90 days	1.69	1.61	1.78	0.0000
Anemia or iron prescription past 91-365 days	1.33	1.26	1.40	0.0000
Transfusion past 90 days	1.35	1.25	1.46	0.0000
Transfusion past 91-365 days	1.18	1.08	1.27	0.0001
Epigastric/abdominal pain past 90 days	1.19	1.12	1.27	0.0000
Epigastric/abdominal pain past 91-365 days	0.98	0.93	1.04	0.5767
GERD/dyspepsia past 90 days	1.01	0.96	1.07	0.6360
GERD/dyspepsia past 91-365 days	0.90	0.86	0.96	0.0003
H2RA past 90 days	0.90	0.83	0.96	0.0022
H2RA past 91-365 days	0.89	0.80	0.99	0.0296

	IRR	CL_Low	CL_High	p
Lower GI disease past 90 days	0.98	0.92	1.04	0.5567
Lower GI symptoms past 91-365 days	0.93	0.88	0.99	0.0217
Lower GI symptoms past 90 days	1.16	1.06	1.26	0.0007
Lower GI symptoms past 91-365 days	0.97	0.90	1.04	0.3815
Non-GI anticoagulant-related bleeding past 90 days	1.00	0.92	1.08	0.9889
Non-GI anticoagulant-related bleeding past 91-365 days	1.00	0.93	1.06	0.9290
Abnormal coagulation profile past 90 days	1.13	1.04	1.24	0.0053
Abnormal coagulation profile past 91-365 days	1.07	0.97	1.18	0.1558
NSAID, current use	2.32	2.15	2.49	0.0000
NSAID, recent use	1.49	1.36	1.63	0.0000
P2Y12 inhibitors, current use	1.93	1.82	2.05	0.0000
P2Y12 inhibitors, recent use	1.30	1.15	1.47	0.0000
Other antiplatelet drug, current use	1.54	1.32	1.80	0.0000
Coxib, current use	1.09	0.93	1.28	0.2810
Other anticoagulant, current use	1.99	1.73	2.27	0.0000
Corticosteroid (systemic), current use	1.25	1.16	1.35	0.0000
SSRI, current use	1.02	0.97	1.08	0.3771
Antibiotic, current use	1.24	1.17	1.32	0.0000
Aspirin-eligible	1.08	1.03	1.14	0.0030
Angina	0.91	0.86	0.97	0.0048
Coronary artery revascularization	1.06	1.01	1.12	0.0299
Acute myocardial infarction	1.16	1.09	1.24	0.0000
Stroke, thrombotic	1.10	1.05	1.16	0.0001
Transient ischemic attacks	0.89	0.82	0.96	0.0027
Other cerebrovascular disease	1.04	0.98	1.10	0.2283
Stroke, hemorrhagic	0.89	0.74	1.08	0.2482
Heart failure	1.15	1.10	1.21	0.0000
Diabetes	1.06	1.00	1.11	0.0407
Peripheral vascular disease	1.15	1.10	1.21	0.0000
Renal failure	1.24	1.18	1.29	0.0000
Smoking	1.31	1.25	1.37	0.0000
Hypovolemia	1.18	1.12	1.24	0.0000
Digoxin	0.93	0.88	0.98	0.0073
Loop diuretic	1.33	1.28	1.39	0.0000
Insulin	1.08	1.02	1.15	0.0109
Oral hypoglycemic	0.98	0.93	1.04	0.5085
Fall or mobility impairment (wheelchair/other device)	0.95	0.91	0.99	0.0270
Other frailty	1.02	0.97	1.07	0.4577
Home oxygen	1.10	1.05	1.16	0.0001
Alcohol abuse and related illnesses	1.44	1.31	1.58	0.0000
Liver disease	1.14	1.06	1.23	0.0002
GI hospitalization past 90 days	1.03	0.87	1.22	0.7076
GI hospitalization past 91-365 days	0.99	0.86	1.13	0.8260
Other hospitalization past 90 days	1.22	1.15	1.29	0.0000
Other hospitalization past 91-365 days	1.01	0.96	1.07	0.6682
ED visit, GI, past 90 days	1.16	1.00	1.35	0.0495
ED visit, GI, past 91-365 days	1.12	1.00	1.25	0.0470

§6. Additional Study Results

eTable 4 shows the distribution of all study covariates according to PPI co-therapy and individual oral anticoagulant.

eTable 4. All study covariates according to PPI co-therapy and oral anticoagulant. See footnotes for MS Table 1.

		No PPI Co-therapy				PPI Co-therapy		
	Apixaban	Dabigatran	Rivaroxaban	Warfarin	Apixaban	Dabigatran	Rivaroxaban	Warfarin
Person-years followup	43,970	79,739	114,168	516,512	14,989	26,572	38,958	183,929
Demographics								
Age, mean, years	78.0	77.4	76.4	76.6	77.6	77.0	75.6	75.6
Female sex	52.7%	49.6%	52.4%	53.9%	59.3%	58.1%	60.1%	62.3%
Age < 65 years	3.0%	3.7%	6.1%	9.1%	5.5%	6.8%	10.4%	13.8%
Medicaid enrollment	13.9%	15.7%	17.6%	22.5%	27.4%	32.6%	34.6%	37.8%
Race white	92.6%	92.9%	91.3%	89.9%	91.3%	90.2%	88.7%	88.1%
Nursing home residence past year	4.7%	3.0%	5.3%	7.5%	7.5%	5.5%	8.6%	11.9%
Year of cohort entry, mean	2014.1	2011.9	2013.4	2012.2	2014.1	2011.9	2013.4	2012.2
Indication								
Atrial fibrillation	91.8%	95.9%	78.6%	71.2%	91.0%	95.5%	75.2%	68.6%
Deep-vein thrombosis	2.8%	0.5%	12.4%	18.9%	3.5%	0.7%	15.7%	22.2%
Other cardiovascular	3.4%	2.1%	3.3%	4.2%	3.5%	2.2%	4.0%	4.3%
Other or unknown	2.0%	1.6%	5.6%	5.7%	2.0%	1.5%	5.1%	4.8%
Time since anticoagulant treatment initiated, days								
1-30	15.3%	7.6%	14.0%	9.8%	14.1%	6.5%	11.8%	8.0%
31-90	20.1%	9.8%	15.3%	12.3%	20.7%	9.6%	15.9%	12.4%
91-365	47.8%	31.1%	40.4%	32.8%	49.3%	32.0%	42.8%	35.1%
366-730	16.4%	26.6%	23.4%	25.1%	15.5%	27.2%	23.3%	25.3%
>730	0.9%	25.7%	7.6%	20.8%	0.9%	25.6%	7.0%	19.9%
Upper gastrointestinal disease history or signs of bleeding								
Peptic ulcer disease past 90 days	0.7%	0.7%	0.8%	0.7%	3.7%	3.7%	4.1%	3.5%
Peptic ulcer disease past 91-365 days	1.7%	1.7%	1.9%	1.9%	9.2%	9.1%	9.6%	9.1%
Gastritis past 90 days	0.5%	0.4%	0.6%	0.5%	2.4%	2.6%	2.8%	2.3%
Gastritis past 91-365 days	1.2%	1.2%	1.4%	1.4%	5.8%	6.1%	6.6%	6.0%
Other upper gastrointestinal disease past 90 days	0.7%	0.6%	0.8%	0.8%	3.8%	3.6%	3.9%	3.5%
Other upper gastrointestinal disease 91-365 days	1.5%	1.4%	1.6%	1.7%	7.8%	7.6%	7.9%	7.6%
Blood stool/GI bleeding past 90 days	0.6%	0.6%	0.7%	0.7%	1.4%	1.2%	1.6%	1.5%
Blood stool/GI bleeding past 91-365 days	1.2%	1.5%	1.4%	1.5%	3.0%	2.9%	3.1%	3.5%
Anemia or iron prescription past 90 days	7.2%	5.7%	8.7%	9.9%	12.5%	10.5%	14.2%	15.2%
Anemia or iron prescription past 91-365 days	10.2%	9.3%	10.6%	12.8%	16.3%	15.6%	17.4%	19.8%
Transfusion past 90 days	0.7%	0.5%	1.3%	2.1%	1.4%	0.9%	2.0%	3.0%
Transfusion past 91-365 days	1.4%	1.2%	1.9%	3.5%	2.8%	2.4%	3.8%	6.4%

	No PPI Co-therapy				PPI Co-therapy			
	Apixaban	Dabigatran	Rivaroxaban	Warfarin	Apixaban	Dabigatran	Rivaroxaban	Warfarin
Other gastrointestinal symptoms or diseases								
Epigastric/abdominal pain past 90 days	4.1%	3.2%	4.3%	4.8%	8.6%	7.3%	9.4%	9.4%
Epigastric/abdominal pain past 91-365 days	8.6%	7.5%	9.2%	10.3%	16.9%	15.1%	17.8%	18.8%
GERD/dyspepsia past 90 days	7.7%	5.3%	7.9%	8.6%	24.3%	19.1%	24.6%	24.1%
GERD/dyspepsia past 91-365 days	12.0%	10.2%	11.9%	13.2%	32.2%	29.4%	32.0%	32.1%
H2RA past 90 days	4.7%	4.8%	4.9%	6.6%	4.4%	4.2%	4.6%	4.2%
H2RA past 91-365 days	1.9%	1.6%	1.8%	2.1%	3.2%	3.2%	3.5%	3.6%
Lower GI disease past 90 days	5.0%	4.0%	5.5%	5.6%	8.2%	6.7%	8.9%	8.8%
Lower GI symptoms past 91-365 days	9.6%	8.9%	10.3%	10.9%	16.2%	14.5%	17.0%	18.1%
Lower GI symptoms past 90 days	2.0%	1.5%	1.9%	2.1%	3.3%	2.7%	3.4%	3.7%
Lower GI symptoms past 91-365 days	4.1%	3.4%	4.1%	4.6%	7.1%	6.1%	7.3%	8.2%
Non-gastrointestinal bleeding or abnormal coagulation profile								
Non-GI anticoagulant-related bleeding past 90 days	3.5%	3.4%	4.6%	4.1%	4.0%	3.6%	5.1%	4.6%
Non-GI anticoagulant-related bleeding past 91-365 days	6.6%	6.7%	7.8%	8.1%	7.7%	7.5%	9.3%	9.5%
Abnormal coagulation profile past 90 days	0.2%	0.2%	0.3%	2.9%	0.3%	0.2%	0.4%	3.8%
Abnormal coagulation profile past 91-365 days	0.5%	0.5%	0.6%	4.2%	0.7%	0.7%	0.9%	6.3%
Medications that increase the risk of bleeding, current use								
NSAID, current use	2.6%	2.6%	2.9%	2.4%	4.6%	5.2%	5.3%	4.1%
NSAID, recent use	2.0%	1.9%	2.5%	2.1%	2.8%	3.0%	3.4%	2.8%
P2Y12 inhibitors, current use	4.5%	3.2%	3.4%	4.4%	5.9%	4.5%	4.9%	5.5%
P2Y12 inhibitors, recent use	1.3%	0.8%	1.0%	0.9%	1.8%	1.1%	1.3%	1.1%
Other antiplatelet drug, current use	0.4%	0.5%	0.4%	0.6%	0.7%	0.6%	0.6%	0.8%
Other medications that may increase the risk of bleeding								
Coxib, current use	0.9%	1.0%	1.2%	1.0%	1.8%	2.4%	2.7%	1.7%
Other anticoagulant, current use	0.0%	0.0%	0.1%	0.5%	0.0%	0.0%	0.1%	0.6%
Corticosteroid (systemic), current use	2.7%	2.2%	2.8%	3.3%	4.8%	4.2%	5.4%	6.2%
SSRI, current use	9.5%	9.4%	10.5%	12.0%	16.6%	16.7%	18.4%	20.6%
Antibiotic, current use	5.0%	4.8%	5.5%	5.9%	7.6%	7.3%	8.5%	9.0%
Meets criteria for low-dose aspirin prophylaxis								
Angina	7.0%	5.4%	5.8%	5.8%	10.0%	8.5%	9.3%	8.6%
Coronary artery revascularization	24.1%	18.1%	19.0%	15.4%	26.7%	20.7%	20.7%	18.2%
Acute myocardial infarction	4.1%	2.2%	3.0%	3.8%	5.7%	3.3%	4.3%	5.4%
Stroke, thrombotic	22.1%	18.3%	18.7%	21.3%	25.9%	22.2%	23.4%	25.6%
Transient ischemic attacks	6.5%	4.9%	5.0%	5.0%	7.3%	5.8%	6.0%	5.9%

	No PPI Co-therapy				PPI Co-therapy			
	Apixaban	Dabigatran	Rivaroxaban	Warfarin	Apixaban	Dabigatran	Rivaroxaban	Warfarin
Other cardiovascular disease								
Other cerebrovascular disease	7.8%	6.3%	6.9%	8.8%	10.0%	8.7%	9.7%	11.9%
Stroke, hemorrhagic	0.7%	0.4%	0.5%	0.7%	0.8%	0.5%	0.7%	0.9%
Heart failure	31.7%	26.4%	26.5%	31.4%	39.3%	35.9%	34.7%	39.7%
Diabetes	31.2%	32.1%	31.3%	35.4%	38.6%	40.4%	39.0%	41.3%
Peripheral vascular disease	11.9%	10.6%	11.2%	13.4%	14.5%	13.5%	13.8%	15.7%
Renal failure	15.2%	10.4%	11.7%	16.3%	20.3%	15.0%	16.6%	22.0%
Smoking	19.1%	11.8%	17.9%	17.6%	22.6%	16.3%	22.5%	22.4%
Hypovolemia	6.3%	4.2%	6.0%	7.1%	9.7%	7.3%	9.9%	11.5%
Digoxin	12.2%	16.8%	12.0%	14.0%	12.8%	18.8%	12.6%	13.5%
Loop diuretic	32.9%	32.1%	29.5%	38.7%	42.9%	44.2%	40.0%	48.8%
Insulin	7.1%	6.8%	6.9%	9.8%	10.2%	10.5%	10.6%	13.9%
Oral hypoglycemic	19.5%	20.3%	19.3%	21.3%	23.5%	25.6%	23.8%	23.9%
Frailty or other condition that indicates vulnerable patients								
Fall or mobility impairment (wheelchair/other device)	11.4%	9.5%	13.4%	15.9%	15.9%	14.4%	18.5%	21.9%
Other frailty	9.6%	7.9%	10.5%	13.2%	14.8%	13.3%	16.8%	20.2%
Home oxygen	10.1%	10.1%	9.9%	12.0%	15.4%	16.3%	15.6%	17.9%
Alcohol abuse and related illnesses	1.6%	1.3%	1.8%	1.8%	2.1%	1.9%	2.2%	2.5%
Liver disease	2.9%	2.4%	3.4%	3.6%	5.0%	4.2%	5.7%	6.0%
Hospitalization or gastrointestinal ED visit								
GI hospitalization past 90 days	0.5%	0.3%	0.5%	0.6%	0.9%	0.7%	1.0%	1.1%
GI hospitalization past 91-365 days	1.2%	1.0%	1.3%	1.6%	2.7%	2.2%	2.9%	3.6%
Other hospitalization past 90 days	16.9%	10.3%	17.6%	18.2%	18.2%	12.1%	18.1%	19.5%
Other hospitalization past 91-365 days	24.7%	20.0%	24.0%	26.1%	31.2%	27.2%	31.9%	34.6%
ED visit, GI, past 90 days	0.9%	0.6%	0.9%	1.0%	1.6%	1.2%	1.8%	1.8%
ED visit, GI, past 91-365 days	2.1%	1.7%	2.3%	2.6%	4.5%	3.6%	4.8%	5.4%

eTable 5 shows the distribution of summary study covariates for the lowest and highest deciles of the gastrointestinal bleeding risk score.

eTable 5. Summary covariates for highest versus lowest decile of gastrointestinal bleeding risk score. See footnotes for MS Table 1.

	Decile 1	Decile 10
Person-years followup	116,199	116,199
Age, years	69.9	77.6
Female sex	41.1%	60.9%
Age < 65 years	15.8%	10.2%
Medicaid enrollment	12.3%	43.9%
Race white	95.7%	81.3%
Nursing home residence past year	1.2%	21.8%
Year of cohort entry	2012.2	2012.7
Indication: Atrial fibrillation	72.1%	67.1%
First 90 days of anticoagulant therapy	2.0%	66.5%
Upper gastrointestinal disease or signs of bleeding	4.1%	77.2%
Other gastrointestinal symptoms or disease	34.7%	77.5%
Non-gastrointestinal bleeding or abnormal coagulation profile	11.1%	26.4%
Current medications that increase risk of bleeding	0.3%	39.3%
Other medications that may increase risk of bleeding	11.2%	28.6%
Meets criteria for low-dose aspirin prophylaxis	31.0%	62.9%
Other cardiovascular disease	41.2%	96.6%
Frailty or other conditions that indicate vulnerable patients	16.4%	65.9%
Hospitalization or gastrointestinal ED visit	12.8%	91.4%

eTable 6 shows the results of several sensitivity analyses:

a. *Non-valvular atrial fibrillation indication.* Restricts patients to those with a diagnosis of non-valvular atrial fibrillation and excludes patients who at the time of anticoagulant initiation had encounters in the past year indicating mitral stenosis, mechanical heart valves, transplant, or antiphospholipid syndrome.
b. *Usual doses.* Restricts cohort to the usual daily doses for apixaban (10mg), dabigatran (300mg), and rivaroxaban (20mg). No restrictions for warfarin.
c-g. *Statistical sensitivity analyses.* See §4.

Sensitivity analysis findings were essentially similar to those of the primary analysis. For analyses restricted to the first year of followup—(d) and (g)—the absolute magnitude of the incidence difference was expected to be increased given greater risk of bleeding early in anticoagulant treatment.

eTable 6. Sensitivity analyses.

	No PPI, Apixaban vs Rivaroxaban[a]		Entire Cohort, PPI vs no PPI[b]	
	IRR (95% CI)	*RD (95% CI)*	*IRR (95% CI)*	*RD (95% CI)*
Primary analysis	0.51 (0.44-0.58)	-70.9 (-82.7 to -59.1)	0.66 (0.62-0.69)	-39.5 (-44.0 to -35.0)
Sensitivity analyses				
a. Non-valvular atrial fibrillation	0.51 (0.44-0.59)	-65.8 (-78.6 to -53.0)	0.64 (0.60-0.69)	-39.4 (-43.0 to -35.8)
b. Usual anticoagulant dose	0.55 (0.47-0.65)	-64.0 (-78.1 to -49.8)	0.66 (0.63-0.70)	-39.1 (-43.8 to -34.5)
c. Death a competing risk	0.51 (0.45-0.58)	-63.4 (-74.0 to -52.9)	0.68 (0.65-0.72)	-33.2 (-37.4 to -29.0)
d. Confounders fixed at baseline[c]	0.49 (0.43-0.57)	-92.9 (-108.8 to -77.0)	0.71 (0.66-0.75)	-43.8 (-48.4 to -39.2)
e. No cohort reentry	0.51 (0.45-0.58)	-70.0 (-82.0 to -58.0)	0.66 (0.62-0.69)	-39.8 (-42.7 to -36.8)
f. Repeated measures	0.51 (0.44-0.58)	-67.7 (-78.9 to -56.5)	0.66 (0.62-0.69)	-37.7 (-42.0 to -33.4)
g. Propensity-score matched[c]	0.45 (0.39-0.53)	-83.9 (-100.8 to -67.0)	0.68 (0.63-0.74)	-48.5 (-58.7 to -38.3)

[a]Comparisons adjusted for the variables in eTable 3.
[b]Comparisons adjusted for the variables in eTable 3 and individual oral anticoagulants.
[c]Followup restricted to the first year of anticoagulant treatment.

eTable7 shows the risk of all gastrointestinal bleeding hospitalizations for all study oral anticoagulants according to PPI co-therapy. The adjusted IRR is adjusted for the variables in eTable 3 as well as individual oral anticoagulants.

eTable 7. Gastrointestinal bleeding hospitalizations for all study oral anticoagulants according to PPI co-therapy.

	No Co-therapy	Former Co-therapy	PPI Co-therapy
Person-years	754,389	143,152	264,447
Upper Gastrointestinal			
Bleeding hospitalizations	7,119	2,248	2,245
Rate/10,000	94.4	157.0	84.9
Adjusted IRR (95% CI)		1.00 (0.95-1.05)	0.66 (0.62-0.69)
Other Gastrointestinal			
Bleeding hospitalizations	14,639	4,953	7,447
Rate/10,000	194.1	346.0	281.6
Adjusted IRR (95% CI)		1.10 (1.06-1.14)	1.10(1.06-1.13)

Reference List

1. 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.
2. Westreich D, Cole SR, Tien PC, et al. Time scale and adjusted survival curves for marginal structural cox models. *Am J Epi.* 2010;171:691-700.
3. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology.* 2000;11:550-560.
4. Daniel RM, Cousens SN, De Stavola BL, Kenward MG, Sterne JAC. Methods for dealing with time-dependent confounding. *Stat Med.* 2013;32(9):1584-1618.
5. Cole SR, Hernan MA. Constructing inverse probability weights for marginal structural models. *Am J Epi.* 2008;168(6):656-664.
6. Ray WA, Liu Q, Shepherd BE. Performance of time-dependent propensity scores: a pharmacoepidemiology case study. *Pharmacoepidemiol Drug Saf.* 2015;24:98-106.
7. Westreich D, Cole SR. Invited Commentary: Positivity in Practice. *Am J Epi.* 2010;171:674-677.
8. Platt RW, Delaney JA, Suissa S. The positivity assumption and marginal structural models: the example of warfarin use and risk of bleeding. *Eur J Epidemiol.* 2012;27(2):77-83.
9. Seeger JD, Bykov K, Bartels DB, Huybrechts K, Schneeweiss S. Propensity Score Weighting Compared to Matching in a Study of Dabigatran and Warfarin. *Drug Saf.* 2017;40(2):169-181.
10. Ali MS, Groenwold RH, Belitser SV, et al. Methodological comparison of marginal structural model, time-varying Cox regression, and propensity score methods: the example of antidepressant use and the risk of hip fracture. *Pharmacoepidemiol Drug Saf.* 2016;25 Suppl 1:114-121.
11. Shadish WR, Steiner PM. A primer on propensity score analysis. *Newborn & Infant Nursing Reviews.* 2010;10(1):19-26.
12. Austin PC. An introduction to propensity score methods for reducing the effects of confounding on observational studies. *Multivariate Behav Res.* 2011;46:399-424.
13. Haukoos JS, Lewis RJ. The Propensity Score. *Jama.* 2015;314(15):1637-1638.
14. Imbens GW. The role of the propensity score in estimating dose-response functions. *Biometrika.* 2000;87(3):706-710.
15. Rassen JA, Shelat AA, Franklin JM, Glynn RJ, Solomon DH, Schneeweiss S. Matching by propensity score in cohort studies with three treatment groups. *Epidemiology.* 2013;24(3):401-409.
16. Friedman M. Piecewise exponential models for survival data with covariates. *Annals of Statistics.* 1982;10(1):101-113.
17. Holford TR. The analysis of rates and survivorship using log-linear models. *Biometrics.* 1980;36:299-305.
18. Laird N, Olivier D. Covariance analysis of censored survival data using log-linear analysis techniques. *J Am Stat Assoc.* 1981;76:231-240.
19. Muller CJ, MacLehose RF. Estimating predicted probabilities from logistic regression: different methods correspond to different target populations. *Int J Epidemiol.* 2014;43(3):962-970.
20. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *Journal of the American Statistical Association.* 1999;94(446):496-509.
21. Dzeshka MS, Lane DA, Lip GY. Stroke and bleeding risk in atrial fibrillation: navigating the alphabet soup of risk-score acronyms (CHADS2 , CHA2 DS2 -VASc, R2 CHADS2 , HAS-BLED, ATRIA, and more). *Clinical cardiology.* 2014;37(10):634-644.
22. Hansen BB. The prognostic analogue of the propensity score. *Biometrika.* 2008;95(2):481-488.
23. Arbogast PG, Kaltenbach L, Ding H, Ray WA. Adjustment of multiple cardiovascular risk factors with a summary risk score. *Epidemiol.* 2008;19:30-37.
24. Arbogast PG, Ray WA. Use of disease risk scores in pharmacoepidemiologic studies. *Statistical Meth Med Res.* 2009;18:67-80.
25. 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.
26. 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.

27. 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.