JAMA | Original Investigation

Association of Rivaroxaban vs Apixaban With Major Ischemic or Hemorrhagic Events in Patients With Atrial Fibrillation

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IMPORTANCE The comparative effectiveness of rivaroxaban and apixaban, the most frequently prescribed oral anticoagulants for ischemic stroke prevention in patients with atrial fibrillation, is uncertain.

OBJECTIVE To compare major ischemic and hemorrhagic outcomes in patients with atrial fibrillation treated with rivaroxaban or apixaban.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort study using computerized enrollment and claims files for US Medicare beneficiaries 65 years or older. Between January 1, 2013, and November 30, 2018, a total of 581 451 patients with atrial fibrillation began rivaroxaban or apixaban treatment and were followed up for 4 years, through November 30, 2018.

EXPOSURES Rivaroxaban (n = 227 572) and apixaban (n = 353 879), either standard or reduced dose.

MAIN OUTCOMES AND MEASURES The primary outcome was a composite of major ischemic (stroke/systemic embolism) and hemorrhagic (intracerebral hemorrhage/other intracranial bleeding/fatal extracranial bleeding) events. Secondary outcomes were nonfatal extracranial bleeding and total mortality (fatal ischemic/hemorrhagic event or other death during follow-up). Rates, hazard ratios (HRs), and rate differences (RDs) were adjusted for baseline differences in comorbidity with inverse probability of treatment weighting.

RESULTS Study patients (mean age, 77.0 years; 291 966 [50.2%] women; 134 393 [23.1%] receiving reduced dose) had 474 605 person-years of follow-up (median [IQR] of 174 [62-397] days). The adjusted primary outcome rate for rivaroxaban was 16.1 per 1000 person-years vs 13.4 per 1000 person-years for apixaban (RD, 2.7 [95% CI, 1.9-3.5]; HR, 1.18 [95% CI, 1.12-1.24]). The rivaroxaban group had increased risk for both major ischemic events (8.6 vs 7.6 per 1000 person-years; RD, 1.1 [95% CI, 0.5-1.7]; HR, 1.12 [95% CI, 1.04-1.20]) and hemorrhagic events (7.5 vs 5.9 per 1000 person-years; RD, 1.6 [95% CI, 1.1-2.1]; HR, 1.26 [95% CI, 1.16-1.36]), including fatal extracranial bleeding (1.4 vs 1.0 per 1000 person-years; RD, 0.4 [95% CI, 0.2-0.7]; HR, 1.41 [95% CI, 1.18-1.70]). Patients receiving rivaroxaban had increased risk of nonfatal extracranial bleeding (39.7 vs 18.5 per 1000 person-years; RD, 21.1 [95% CI, 20.0-22.3]; HR, 2.07 [95% CI, 1.99-2.15]), fatal ischemic/hemorrhagic events (4.5 vs 3.3 per 1000 person-years; RD, 1.2 [95% CI, 0.8-1.6]; HR, 1.34 [95% CI, 1.21-1.48]), and total mortality (44.2 vs 41.0 per 1000 person-years; RD, 3.1 [95% CI, 1.8-4.5]; HR, 1.06 [95% CI, 1.02-1.09]). The risk of the primary outcome was increased for rivaroxaban in both those receiving the reduced dose (27.4 vs 21.0 per 1000 person-years; RD, 6.4 [95% CI, 4.1-8.7]; HR, 1.28 [95% CI, 1.16-1.40]) and the standard dose (13.2 vs 11.4 per 1000 person-years; RD, 1.8 [95% CI, 1.0-2.6]; HR, 1.13 [95% CI, 1.06-1.21]) groups.

CONCLUSIONS AND RELEVANCE Among Medicare beneficiaries 65 years or older with atrial fibrillation, treatment with rivaroxaban compared with apixaban was associated with a significantly increased risk of major ischemic or hemorrhagic events.

Editorial page 2372

Supplemental content

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An estimated 3 million to 6 million persons in the US have atrial fibrillation, and these numbers are projected to reach 6 million to 16 million by 2050.[1] Atrial fibrillation increases the risk of stroke 5-fold and is thought to cause 15% of all strokes[2]; thus, anticoagulation to prevent ischemic strokes is a critical component of management for this chronic disease.[3] Direct oral anticoagulants—with more predictable pharmacokinetics, greater ease of use, and equally good or better clinical outcomes than vitamin K antagonists—are the preferred anticoagulants for patients with atrial fibrillation.[3] Of the 4 drugs in this class licensed in the US for use in atrial fibrillation, rivaroxaban and apixaban now account for nearly all direct oral anticoagulant prescriptions and are prescribed more frequently than warfarin.[4]

The beneficial and adverse effects of direct oral anticoagulants are closely related to plasma concentrations; plasma concentrations that are too low fail to prevent ischemic strokes or systemic embolisms and those that are too high increase the risk of severe bleeding.[5-7] Although apixaban and rivaroxaban are both reversible inhibitors of activated factor X (Xa) and have comparable elimination half-lives,[5] apixaban is taken twice daily, whereas there is only a single daily dose for rivaroxaban. Thus, there is substantially greater peak-trough variation in rivaroxaban concentrations,[5,8] which raises the concern that this medication may have poorer efficacy and safety. Because differences in the clinical outcomes of rivaroxaban and apixaban would have major health implications for the millions of patients with prolonged use for stroke prevention, the objective of this retrospective cohort study was to compare major ischemic and hemorrhagic outcomes in Medicare beneficiaries with atrial fibrillation who initiated anticoagulation treatment with rivaroxaban or apixaban.

Key Points

Question Is there a difference in risk of major ischemic or hemorrhagic events in patients with atrial fibrillation treated with rivaroxaban vs apixaban?

Findings In this retrospective cohort study that included 581 451 patients 65 years or older enrolled in Medicare with atrial fibrillation, the adjusted incidence of major ischemic or hemorrhagic events was 16.1 per 1000 person-years for rivaroxaban vs 13.4 per 1000 person-years for apixaban, a difference that was statistically significant.

Meaning Among older adults with atrial fibrillation, treatment with rivaroxaban compared with apixaban was associated with a significantly increased risk of major ischemic or hemorrhagic events.

Methods

Cohort and Follow-up

Medicare Data

The computerized files of the US Medicare program, which provides health care insurance for US citizens 65 years or older and younger persons with disabilities,[9] provided the study data. Files included the Medicare Master Beneficiary Summary File, which includes enrollment status and identifies deaths for beneficiaries,[9] as well as claims files for medical care services (pharmacy, hospital, outpatient, and nursing home). The data resided in the Centers for Medicare & Medicaid Services Chronic Condition Warehouse and were accessed through the Virtual Research Data Center, a cloud-based repository of deidentified Medicare files.[10] In accordance with the Centers for Medicare & Medicaid Services policy, no table cells with fewer than 11 patients were reported. The study was approved by the Vanderbilt University Medical Center Institutional Review Board, with waiver of informed consent.

Cohort

The cohort (eTable 1 in the Supplement) consisted of Medicare beneficiaries 65 years or older with fee-for-service (Parts A and B) and prescription drug (Part D) coverage. Medicare Advantage (Part C) enrollees were excluded because the encounter data were considered less reliable during the study years.[9] Participants had to have complete demographic information and fill a prescription for apixaban or rivaroxaban with either the standard (5 mg twice daily for apixaban and 20 mg once daily for rivaroxaban) or reduced (2.5 mg twice daily for apixaban and 15 mg once daily for rivaroxaban) dose for atrial fibrillation between January 1, 2013 (first year of apixaban use Medicare), and November 30, 2018 (most recent data). The reduced dose is indicated for patients with factors likely to increase plasma concentrations.[2,11]

During the preceding year, study patients had to have continuous enrollment in Medicare and, to ensure regular contact with medical care, at least 1 outpatient visit and 1 filled prescription (other than the study anticoagulant). They could not have terminal illness, long-term care residence (except <30 days following inpatient stay), mitral valve stenosis, or severe chronic kidney disease (stage 4, 5, or end-stage). The primary analysis included patients with heart valve replacement, because direct oral anticoagulants are an option for those with bioprosthetic heart valves. For those with mechanical heart valves, direct oral anticoagulants are contraindicated and thus those patients would be excluded from the cohort.[3] There could be no evidence of outpatient oral anticoagulant use during the past year (eTable 1 in the Supplement), thus restricting the cohort to new users of oral anticoagulants.[12]

Participants had to have a diagnosis of atrial fibrillation/flutter in the past 90 days. They could not have had conditions that can cause reversible atrial fibrillation (eg, thyrotoxicosis[13]) or an alternative oral anticoagulant indication in the past 30 days (eTable 1 in the Supplement). Cohort members could not have had a stroke or bleeding-related hospitalization in the past 30 days, because subsequent readmissions might be confused with new events.

Follow-up

Cohort members were followed up for up to 4 years, beginning the day after filling the initial oral anticoagulant prescription. Follow-up ended (eAppendix §1 in the Supplement) with a gap of more than 30 days in anticoagulant days of supply (indicating discontinuation); the filling of a prescription for a different

anticoagulant; change in anticoagulant dose; development of stage 4, 5, or end-stage chronic kidney disease; the last study day (November 30, 2018, or 4 years after anticoagulant initiation); loss of full fee-for-service Medicare enrollment; occurrence of any study outcome; or death. Patients who left the cohort could not reenter. The proportion of patients who discontinued or changed the study anticoagulant by the median time of follow-up was estimated with the cumulative incidence function, considering other causes of loss to follow-up as censoring.

Outcomes

Definitions

The primary study outcome was the following major ischemic or hemorrhagic events: ischemic stroke, systemic embolism, hemorrhagic stroke, other intracranial bleeding, and fatal extracranial bleeding (death within 30 days[14,15] of bleeding onset). Secondary outcomes were nonfatal extracranial bleeding and total mortality, which included fatal ischemic or hemorrhagic events (death within 30 days of event onset) and other deaths during follow-up.

Identification

Strokes and bleeding events were identified from hospital principal discharge diagnosis codes (eAppendix §2 in the Supplement). The codes for strokes (eAppendix §2.1 and eTable 2 in the Supplement) have positive predictive values greater than 95% and sensitivity of 87% for strokes seen in the hospital.[16,17] Intracranial and extracranial bleeding were identified by a previously validated algorithm (eAppendix §2.2, eFigure, eTables 3 and 4 in the Supplement) with positive predictive values of 89% for probable bleeds and 99% for probable/possible bleeds[18,19] and a sensitivity of 93% for bleeds with hospitalization.[20] The codes for intracranial bleeding also included those for traumatic intracranial hemorrhages (except those indicating open wounds) to capture fall-related events. The outcome occurrence date was generally that of hospital admission, but was set to the prior day when appropriate (eg, emergency department visit on prior day with stroke diagnosis; see eAppendix §2 in the Supplement).

Statistical Analyses

Study comparisons controlled for 208 covariates potentially associated with both outcomes and anticoagulant choice. The covariates (eTable 5 in the Supplement), defined from enrollment history and claims in the year preceding cohort entry, were chosen based on previous studies of anticoagulants,[9,15,18,19,21,22] standard measures of comorbidity,[23] and indicators of frailty.[24] They included demographic characteristics, cardiovascular conditions (including components of the claims-based CHA_2DS_2-VASc [congestive heart failure, hypertension, age ≥75 years (doubled), diabetes, stroke/transient ischemic attack/thromboembolism (doubled), vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)] score[25-28]), risk factors for bleeding, respiratory illness, neurologic conditions, measures of frailty, cancer, and medical care utilization. Race (self-reported to the US Social Security Administration via fixed categories) was included as a marker of social, environmental, and genetic factors that potentially influence anticoagulant outcomes.[29]

The analysis controlled for covariates with stabilized inverse probability of treatment weights calculated from the propensity score.[30] The propensity score, the probability of rivaroxaban use given baseline covariates,[30] was estimated with logistic regression that was stratified by anticoagulant dose because factors influencing anticoagulant choice could differ with dose. The propensity score distributions in the rivaroxaban and apixaban groups had good overlap (eTable 6 in the Supplement).

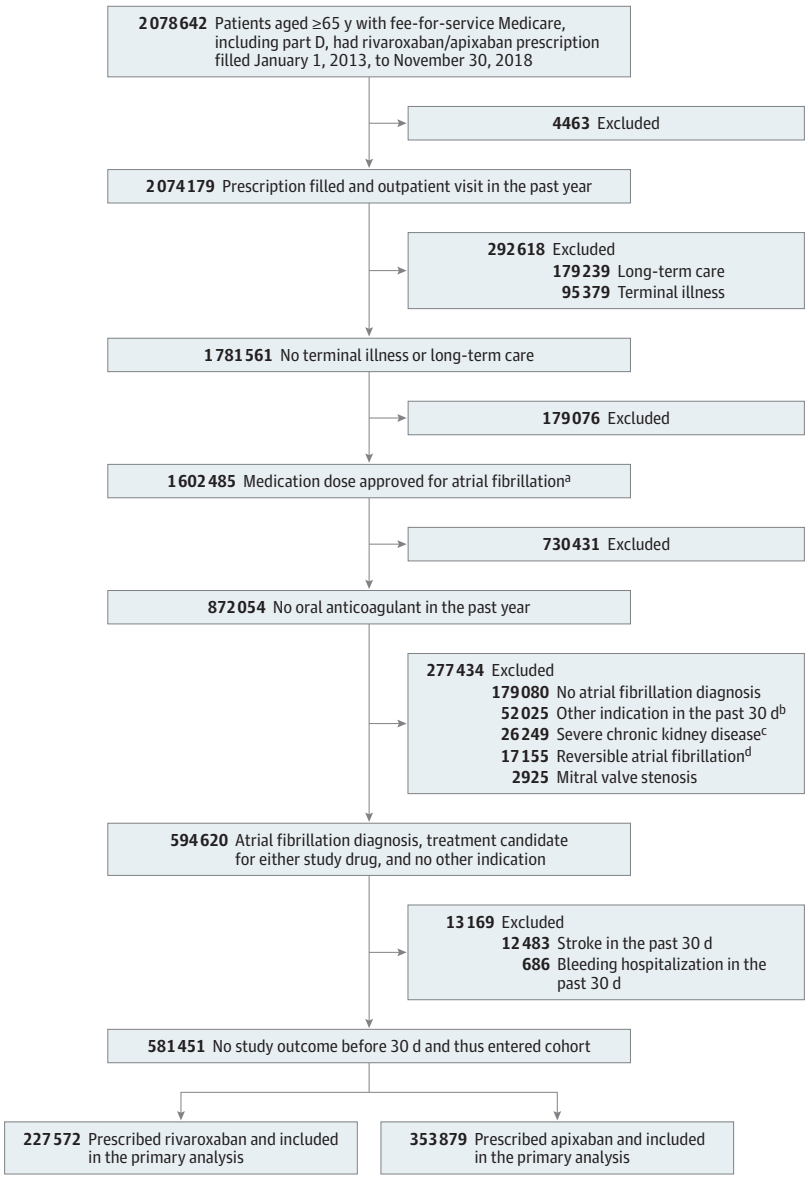
With a properly constituted propensity score, inverse probability of treatment weighting controls for confounding by eliminating imbalances in measured covariates between the study groups. The magnitude of covariate imbalances was assessed with the standardized difference; differences of less than 0.10 are considered to indicate acceptable balance.[30]

The adjusted relative risk of the outcomes was estimated with hazard ratios (HRs) calculated from an inverse probability of treatment-weighted proportional hazards regression. The regression was stratified by dose, permitting the hazard function to differ according to dose.[31] Weighting-induced dependencies were corrected with modified sandwich variance estimation.[31] The rate difference (RD), or difference in the absolute adjusted incidence between rivaroxaban and apixaban, was estimated assuming the Poisson distribution, with variances calculated via generalized estimating equations to compensate for weighting-induced dependencies. In a prespecified analysis, HRs and RDs were calculated for patients according to dose.

Sensitivity analyses assessed the effects of alternative study definitions or statistical analyses. Cohort eligibility criteria were modified to exclude patients with heart valve replacement (limited data supporting direct oral anticoagulant use[3]), unspecified or stage 3 chronic kidney disease (rivaroxaban elimination more dependent on kidney function[32]), or extreme propensity scores (trimming first percentile contrary to prediction, which can reduce unmeasured confounding[33]). Follow-up was limited to the year following cohort entry (up to 4 years in the primary analysis), which reduced the effects of changes in baseline covariates and censoring for discontinuation or switching of medication. The maximum allowed gap in anticoagulant days of supply was decreased from 30 days to 7 days, which would reduce exposure misclassification. The stroke definition was broadened to identify strokes with both the principal and secondary hospital discharge diagnoses (eAppendix §2 in the Supplement), which would increase the sensitivity to 93%.[17] Other alternative analyses included propensity score–matched treatment groups and estimation of HRs from a proportional hazards regression with all of the study covariates in place of the propensity score weighting. The potential influence of unmeasured confounding on findings was assessed by calculating the E-value, the minimum strength of the association of an unmeasured confounder with both the primary outcome and the initiation of rivaroxaban treatment required to explain the observed study HR.[34]

All statistical analyses were performed with SAS, version 9.4 (SAS Institute). Statistical significance was defined as a 95%

Figure 1. Selection and Inclusion of Participants in a Study of the Association of Rivaroxaban vs Apixaban With Major Ischemic or Hemorrhagic Events in Atrial Fibrillation



[a] Apixaban (2.5 mg or 5 mg twice/d) or rivaroxaban (15 mg or 20 mg once/d).

[b] Deep vein thrombosis/pulmonary embolism, hip/knee replacement, femur/tibia/patella fracture, thrombectomy, or chronic hypercoagulable state.

[c] Stage 4 or 5 or end-stage chronic kidney disease.

[d] Diagnosis of hyperthyroidism or open coronary artery bypass graft/open cardiac valve surgery.

CI that excluded 0 (RD) or 1 (HR). Because CIs were not adjusted for multiple comparisons, analyses of secondary end points should be interpreted as exploratory.

Results

Cohort

The cohort included 581 451 patients with atrial fibrillation initiating oral anticoagulant treatment, with 227 572 patients in the rivaroxaban group and 353 879 in the apixaban group (**Figure 1**). Participants had a mean age of 77.0 years, 291 966 (50.2%) were women, and 134 393 (23.1%) received the reduced anticoagulant dose. Prior to inverse probability of treatment weighting, patients in the rivaroxaban group (**Table 1**; eTable 5 in the Supplement) were younger (76.3 vs 77.4 years), were less likely to be women (48.3% vs 51.4%), and had a lower mean CHA_2DS_2-VASc score (4.2 vs 4.4) than patients in the apixaban group. Patients in the rivaroxaban group also had lower prevalence of several risk factors for study outcomes, including history of stroke or intracranial bleeding (8.5% vs 9.8%), myocardial infarction (5.6% vs 6.8%), heart failure (27.9% vs 31.2%), acute kidney failure (7.6% vs 10.5%), stage 3 or unspecified chronic kidney disease (13.8% vs 17.9%), history of bleeding (14.4% vs 15.6%), anemia (24.6% vs 27.1%), unintentional fall (9.5% vs 11.5%), and hospitalization in the 30 days before anticoagulant initiation (26.7% vs 29.0%). After weighting (Table 1; eTable 5 in the Supplement), differences in covariate prevalence were minimal, with all standardized differences no more than 0.01.

Table 1. Participant Demographics, Medical History, and Medications at Baseline in a Study of the Association of Rivaroxaban vs Apixaban With Major Ischemic or Hemorrhagic Events in Atrial Fibrillation[a,b]

Characteristic	Unweighted			Weighted		
	Rivaroxaban, %	Apixaban, %	Standardized difference	Rivaroxaban, %	Apixaban, %	Standardized difference
No. of participants	227 572	353 879		227 572	353 879	
Anticoagulant dose reduced	23.0	23.2	0.0039	23.2	23.1	0.0012
Demographics						
Age, mean (SD), y	76.3 (6.8)	77.4 (7.2)	0.1586	77.0 (7.1)	77.0 (7.0)	0.0023
Year anticoagulant started, mean	2015.5	2016.3	0.5409	2016.0	2016.0	0.0018
Women	48.3	51.4	0.0627	50.0	50.0	0.0007
Men	51.7	48.6	0.0627	50.0	50.0	0.0007
Race and ethnicity[c]						
Asian	1.6	1.3	0.0205	1.5	1.4	0.0014
Black	3.6	3.7	0.0017	3.6	3.7	0.0008
Hispanic	1.2	1.0	0.0182	1.1	1.0	0.0087
North American Native	0.3	0.2	0.0162	0.3	0.2	0.0092
White	92.0	92.6	0.0224	92.4	92.4	0.0020
Other	1.2	1.1	0.0100	1.1	1.2	0.0081
Region of residence						
West	16.1	14.1	0.0567	15.0	15.0	0.0002
Southwest	10.6	10.6	0.0007	10.6	10.6	0.0006
Midwest	22.2	21.3	0.0226	21.5	21.5	0.0010
Southeast	33.1	36.7	0.0747	35.4	35.3	0.0020
Northeast	17.9	17.3	0.0153	17.5	17.6	0.0018
Dual Medicare-Medicaid enrollment	13.9	12.8	0.0332	13.1	13.2	0.0032
Cardiologist-prescribed anticoagulant	49.1	49.0	0.0030	49.8	49.6	0.0037
Medical history (past year unless otherwise noted)						
CHA_2DS_2-VASc score, mean[d]	4.2	4.4	0.1276	4.3	4.3	0.0038
Hypertension	89.7	90.7	0.0309	90.3	90.3	0.0008
Diabetes	35.0	34.8	0.0031	34.8	34.9	0.0009
Heart failure	27.9	31.2	0.0723	29.8	29.8	0.0005
Anemia	24.6	27.1	0.0572	26.1	26.1	0.0018
Chronic obstructive pulmonary disease	21.9	22.9	0.0249	22.3	22.3	0.0003
Cancer other than nonmelanoma skin cancer	17.8	18.4	0.0174	18.1	18.2	0.0008
Bleeding at gastrointestinal or other sites	14.4	15.6	0.0314	15.1	15.1	0.0006
Kidney disease, stage 3 or unspecified chronic	13.8	17.9	0.1113	16.3	16.3	0.0002
Percutaneous coronary intervention	11.4	12.9	0.0447	12.3	12.3	0.0004
Dysphagia/malnutrition	11.1	12.9	0.0559	12.2	12.2	0.0004
Coronary artery bypass graft	9.8	10.9	0.0339	10.4	10.4	0.0001
Fall	9.5	11.5	0.0637	10.7	10.7	0.0003
Cardioversion	8.9	9.4	0.0147	9.2	9.2	0.0012
Ischemic stroke, systemic embolism, intracranial bleeding	8.5	9.8	0.0466	9.3	9.2	0.0019
Acute kidney failure	7.6	10.5	0.0999	9.3	9.3	0.0006
Alzheimer disease and other dementia	6.9	8.2	0.0496	7.7	7.7	0.0005
Transient ischemic attack	6.2	6.8	0.0263	6.6	6.5	0.0009
Myocardial infarction	5.6	6.8	0.0498	6.3	6.3	0.0005
Inpatient discharge past 30 d	26.7	29.0	0.0512	27.2	27.3	0.0032

(continued)

Table 1. Participant Demographics, Medical History, and Medications at Baseline in a Study of the Association of Rivaroxaban vs Apixaban With Major Ischemic or Hemorrhagic Events in Atrial Fibrillation[a,b] (continued)

Characteristic	Unweighted			Weighted		
	Rivaroxaban, %	Apixaban, %	Standardized difference	Rivaroxaban, %	Apixaban, %	Standardized difference
Medication history (past year)						
Angiotensin-converting enzyme inhibitor/receptor blocker	61.5	61.7	0.0053	61.6	61.7	0.0018
Proton pump inhibitors	30.2	31.5	0.0281	31.0	31.0	0.0003
Loop diuretics	26.1	28.9	0.0634	27.7	27.8	0.0005
Oral corticosteroids	24.2	25.7	0.0334	25.0	25.0	0.0006
Diltiazem or verapamil	21.5	21.1	0.0091	21.2	21.2	0.0003
Nonselective nonsteroidal anti-inflammatory drugs	17.3	16.3	0.0261	16.7	16.7	0.0002
Platelet ADP P2Y12 receptor inhibitors and other antiplatelet drugs	15.1	16.6	0.0404	16.0	16.0	0.0004
Amiodarone	10.9	11.8	0.0275	11.4	11.4	0.0005
Home oxygen	9.8	10.6	0.0266	10.2	10.2	0.0000
Insulin	6.1	6.6	0.0188	6.4	6.4	0.0015
Dronedarone	2.7	2.6	0.0099	2.7	2.6	0.0006
No. of medications, mean	11.8	12.1	0.0577	12.0	12.0	0.0043

[a] Some important covariates selected by the authors as examples of the study covariates; see eTable 5 in the Supplement for the complete set of covariates.

[b] The standardized difference (absolute value of the difference between variable means divided by the SD of the difference) is a measure of balance of covariates between treatment groups, with values <0.1 considered to indicate good balance.

[c] Self-reported race and ethnicity excludes 2369 patients in the rivaroxaban group and 3703 in the apixaban group for whom information was unknown. The categories are as defined in the Medicare data, including the "other" category. The low proportion of Black participants may be related to the substantially lower incidence of atrial fibrillation in this population.[29]

[d] The CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years [doubled], diabetes, stroke/transient ischemic attack/thromboembolism [doubled], vascular disease [prior myocardial infarction, peripheral artery disease, or aortic plaque]) score for stroke risk stratification[25] gives 1 point for age 65-74 y, female sex, heart failure, hypertension, diabetes, vascular disease (myocardial infarction, peripheral artery disease, aortic plaque) and 2 points for age ≥75 y, stroke/transient ischemic attack/thromboembolism. The claims-based version of the score[26-28] in the table was calculated from Medicare encounters.

Follow-up

Between January 1, 2013, and November 30, 2018, participants had 474 605 person-years of follow-up, with median (IQR) follow-up of 174 (62-397) days (171 [59-407] d for rivaroxaban and 176 [64-392] d for apixaban). By day 174 of follow-up, patients treated with rivaroxaban were more likely to discontinue the study drug or switch to a different oral anticoagulant than patients treated with apixaban (discontinue: 33.4% [95% CI, 33.1%-33.6%] vs 30.4% [95% CI, 30.3%-30.6%]; switch: 7.0% [95% CI, 6.9%-7.1%] vs 4.5% [95% CI, 4.5%-4.6%]; eTable 7 in the Supplement).

Primary Outcome

There were 6946 (14.6 per 1000 person-years) major ischemic or hemorrhagic events during follow-up: 3807 (8.0/1000 person-years) ischemic events and 3139 (6.6/1000 person-years) hemorrhagic events. The risk of the primary outcome (**Figure 2**; **Table 2**) was greater for rivaroxaban, with adjusted rates of 16.1 vs 13.4 per 1000 person-years (RD, 2.7 [95% CI, 1.9-3.5] per 1000 person-years; HR, 1.18 [95% CI, 1.12-1.24]). The rivaroxaban group had increased risk for both major ischemic events (adjusted rate, 8.6 vs 7.6 per 1000 person-years; RD, 1.1 [95% CI, 0.5-1.7]; HR, 1.12 [95% CI, 1.04-1.20]) and major hemorrhagic events (adjusted rate, 7.5 vs 5.9 per 1000 person-years; RD, 1.6 [95% CI, 1.1-2.1]; HR, 1.26 [95% CI, 1.16-1.36]). Patients treated with rivaroxaban had increased risk for ischemic stroke (adjusted rate, 8.3 vs 7.2 per 1000 person-years; RD, 1.1 [95% CI, 0.5-1.6]; HR, 1.12 [95% CI, 1.05-1.21]), hemorrhagic stroke (adjusted rate, 2.5 vs 1.7 per 1000 person-years; RD, 0.8 [95% CI, 0.5-1.1]; HR, 1.48 [95% CI, 1.30-1.70]), and fatal extracranial bleeding (adjusted rate, 1.4 vs 1.0 per 1000 person-years; RD, 0.4 [95% CI, 0.2-0.7]; HR, 1.41 [95% CI, 1.18-1.70]).

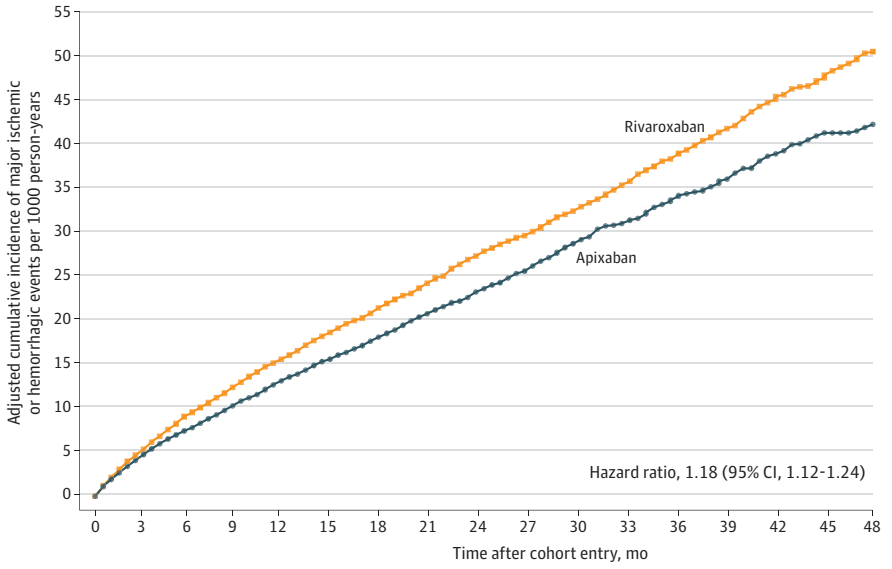
Secondary Outcomes

Patients receiving rivaroxaban had increased risk of the secondary outcomes (Table 2). The risk for nonfatal extracranial bleeding in the rivaroxaban group was increased relative to that in the apixaban group (39.7 vs 18.5 per 1000 person-years; RD, 21.1 [95% CI, 20.0-22.3]; HR, 2.07 [95% CI, 1.99-2.15]), including the risk for bleeding at gastrointestinal sites (35.2 vs 16.3 per 1000 person-years; RD, 19.0 [95% CI, 17.9-20.1]; HR, 2.09 [95% CI, 2.01-2.18]), the most common location for extracranial bleeding. Although the unadjusted rate for total mortality for rivaroxaban was less than for apixaban (39.2 vs 45.3 per 1000 person-years), the rivaroxaban group had increased total mortality after adjustment (44.2 vs 41.0 per 1000 person-years; RD, 3.1 [95% CI, 1.8-4.5]; HR, 1.06 [95% CI, 1.02-1.09]), including increased risk for fatal ischemic or hemorrhagic events (4.5 vs 3.3 per 1000 person-years; RD, 1.2 [95% CI, 0.8-1.6]; HR, 1.34 [95% CI, 1.21-1.48]).

Dose

There were 134 393 patients beginning treatment with reduced doses (23% of patients in each group). Patients receiving

Figure 2. Primary Outcome in a Study of the Association of Rivaroxaban vs Apixaban With Major Ischemic or Hemorrhagic Events in Atrial Fibrillation



No. of participants at risk

Apixaban	353879	174291	96974	59800	37560	34769	13576	7657	3731
Rivaroxaban	227572	110654	64836	40716	26621	18224	12392	8452	5507

Adjusted cumulative incidence of major ischemic (ischemic stroke or systemic embolism) or hemorrhagic (hemorrhagic stroke, other intracranial bleeding, fatal extracranial bleeding) events. The median (IQR) follow-up time was 5.8 (2.1-13.2) months. Adjusted with inverse probability of treatment weighting; the variables used in the adjustment are shown in eTable 5 in the Supplement.

Table 2. Outcomes in a Study of the Association of Rivaroxaban vs Apixaban With Major Ischemic or Hemorrhagic Events in Atrial Fibrillation[a]

Outcome	Rivaroxaban (191 153 person-years)		Apixaban (283 452 person-years)		Adjusted Rate per 1000 person-years			
	Patients with event, No.	Rate/1000 person-years	Patients with event, No.	Rate/1000 person-years	Rivaroxaban	Apixaban	Rate difference (95% CI)	Hazard ratio (95% CI)
Primary outcome and its components								
Major ischemic or hemorrhagic event	2838	14.8	4108	14.5	16.1	13.4	2.7 (1.9 to 3.5)	1.18 (1.12 to 1.24)
Ischemic event	1514	7.9	2293	8.1	8.6	7.6	1.1 (0.5 to 1.7)	1.12 (1.04 to 1.20)
Ischemic stroke	1447	7.6	2196	7.7	8.3	7.2	1.1 (0.5 to 1.6)	1.12 (1.05 to 1.21)
Systemic embolism	67	0.4	97	0.3	0.4	0.3	0.0 (−0.1 to 0.1)	1.05 (0.75 to 1.46)
Hemorrhagic event	1324	6.9	1815	6.4	7.5	5.9	1.6 (1.1 to 2.1)	1.26 (1.16 to 1.36)
Hemorrhagic stroke	459	2.4	515	1.8	2.5	1.7	0.8 (0.5 to 1.1)	1.48 (1.30 to 1.70)
Other intracranial hemorrhage	624	3.3	994	3.5	3.5	3.2	0.3 (−0.1 to 0.7)	1.09 (0.98 to 1.22)
Fatal extracranial bleeding	241	1.3	306	1.1	1.4	1.0	0.4 (0.2 to 0.7)	1.41 (1.18 to 1.70)
Secondary outcomes								
Nonfatal extracranial bleeding	6919	36.2	5672	20.0	39.7	18.5	21.1 (20.0 to 22.3)	2.07 (1.99 to 2.15)
Gastrointestinal	6132	32.1	4974	17.5	35.2	16.3	19.0 (17.9 to 20.1)	2.09 (2.01 to 2.18)
Other or unspecified	787	4.1	698	2.5	4.4	2.3	2.2 (1.8 to 2.5)	1.89 (1.69 to 2.11)
Total mortality	7497	39.2	12 839	45.3	44.2	41.0	3.1 (1.8 to 4.5)	1.06 (1.02 to 1.09)
Fatal ischemic or hemorrhagic event	767	4.0	1039	3.7	4.5	3.3	1.2 (0.8 to 1.6)	1.34 (1.21 to 1.48)
Other death during follow-up	6730	35.2	11 800	41.6	39.7	37.7	1.9 (0.6 to 3.2)	1.03 (0.995 to 1.07)

[a] Adjusted rates, rate differences, and hazard ratios are adjusted with inverse probability of treatment weighting. The variables used in the adjustment are shown in eTable 5 in the Supplement.

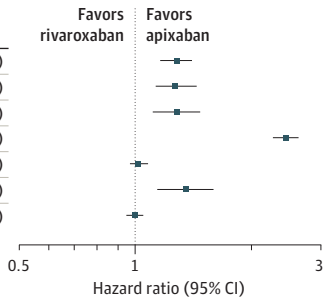
reduced doses, compared with patients receiving standard doses (eTable 8 in the Supplement), were older (82.8 vs 75.2 years), were more likely to be women (62.8% vs 46.4%), and had greater prevalence of other risk factors for stroke (mean CHA_2DS_2-VASc score, 5.0 vs 4.1) and bleeding.

For patients treated with reduced doses, the rivaroxaban group had increased risk for the primary outcome (adjusted rate, 27.4 vs 21.0 per 1000 person-years; RD, 6.4 [95% CI, 4.1-8.7]; HR, 1.28 [95% CI, 1.16-1.40]) and its ischemic and hemorrhagic components (**Figure 3**; eTable 9 in the Supplement).

Figure 3. Outcomes by Medication Dose in a Study of the Association of Rivaroxaban vs Apixaban With Major Ischemic or Hemorrhagic Events in Atrial Fibrillation

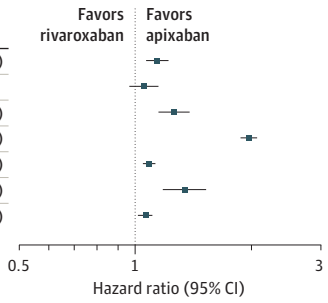
A Reduced dose

Outcome	Rate per 1000 person-years		Rate difference (95% CI)	Hazard ratio (95% CI)
	Rivaroxaban	Apixaban		
Major ischemic/hemorrhagic event	27.4	21.0	6.4 (4.1 to 8.7)	1.28 (1.16 to 1.40)
Ischemic	15.5	11.9	3.6 (1.9 to 5.3)	1.27 (1.13 to 1.44)
Hemorrhagic	11.9	9.1	2.8 (1.3 to 4.3)	1.28 (1.11 to 30.0)
Nonfatal extracranial bleeding	57.5	22.5	35.0 (31.9 to 38.1)	2.44 (2.26 to 34.0)
Total mortality	87.0	82.7	4.2 (-0.1 to 8.6)	1.02 (0.97 to 1.08)
Fatal ischemic/hemorrhagic event	8.5	6.2	2.3 (1.1 to 3.6)	1.35 (1.14 to 1.59)
Other death during follow-up	78.4	76.5	1.9 (-2.3 to 6.0)	1.00 (0.95 to 1.05)



B Standard dose

Outcome	Rate per 1000 person-years		Rate difference (95% CI)	Hazard ratio (95% I)
	Rivaroxaban	Apixaban		
Major ischemic/hemorrhagic event	13.2	11.4	1.8 (1.0 to 2.6)	1.13 (1.06 to 1.21)
Ischemic	6.8	6.4	0.5 (-0.1 to 1.0)	1.05 (.96 to 1.14)
Hemorrhagic	6.3	5.0	1.3 (0.8 to 1.8)	1.25 (1.14 to 1.37)
Nonfatal extracranial bleeding	35.0	17.5	17.5 (16.3 to 18.7)	1.94 (1.85 to 2.03)
Total mortality	32.9	29.7	3.1 (1.9 to 4.4)	1.08 (1.04 to 1.12)
Fatal ischemic/hemorrhagic event	3.4	2.5	0.9 (0.5 to 1.3)	1.33 (1.17 to 1.51)
Other death during follow-up	29.4	27.2	2.2 (1.0 to 3.4)	1.06 (1.01 to 1.10)



Adjusted incidence of study outcomes according to anticoagulant dose. Rates, rate differences, and hazard ratios were adjusted with inverse probability of treatment weighting; the variables used in the adjustment are shown in eTable 5 in the Supplement. See eTable 9 in the Supplement for numbers of events.

Patients receiving reduced-dose rivaroxaban had greater risk for nonfatal extracranial bleeding, whereas total mortality did not differ significantly from those receiving apixaban.

For patients treated with the standard dose (Figure 3; eTable 9 in the Supplement), those receiving rivaroxaban had increased risk for the primary outcome (adjusted rate, 13.2 vs 11.4 per 1000 person-years; RD, 1.8 [95% CI, 1.0-2.6]; HR, 1.13 [95% CI, 1.06-1.21]) and major hemorrhagic events; however, the risk for major ischemic events was not significantly increased. Patients receiving standard-dose rivaroxaban had increased risk for both nonfatal extracranial bleeding and total mortality.

Sensitivity Analyses

The adjusted estimates of incidence, HRs, and RDs changed little with the exclusion of patients with cardiac valve replacement, stage 3 or unspecified chronic kidney disease, or extreme propensity scores (eTable 10 in the Supplement). The estimates did not change materially with restriction of follow-up to 1 year after initiation of the anticoagulant, reduction of the allowable gap in drug supply from 30 days to 7 days, use of a stroke definition with more complete ascertainment, propensity-score matched treatment groups, or estimation of HRs without use of propensity scores. The respective E-values (HRs) for the point estimate and lower confidence bound for major ischemic or hemorrhagic events were 1.64 and 1.48.

Discussion

In this retrospective cohort study of Medicare beneficiaries 65 years or older with atrial fibrillation, initiation of anticoagulation treatment with rivaroxaban compared with apixaban was associated with a significantly increased risk of major ischemic or hemorrhagic events. Although previous retrospective cohort studies have examined the comparative effectiveness of rivaroxaban and apixaban in atrial fibrillation,[15,21,22] the present study makes 3 distinct contributions to the evidence needed to guide clinical practice. First, the cohort, with 581 451 new users of rivaroxaban or apixaban, is larger than those of previous studies and consisted entirely of patients 65 years or older, who have both the highest incidence of atrial fibrillation and greatest risk of major ischemic or hemorrhagic events.[35,36] The greater sample size permitted more precise quantification of the occurrence of infrequent, but clinically important events, such as fatal extracranial bleeding.

Second, in contrast to other studies,[15,21] the cohort included patients treated with reduced doses (23% of participants), whose baseline comorbidity indicated greater susceptibility to differences in anticoagulant efficacy and safety. Although the incidence of major ischemic or hemorrhagic events was increased for patients receiving rivaroxaban in either dose, both the relative and absolute increase in

risk were most pronounced for those with reduced doses, which underscores the importance of anticoagulant choice in this population.

Third, the primary study outcome was an integrated measure of the benefits and harms of anticoagulation for patients with atrial fibrillation. Previous studies reported both an efficacy outcome—ischemic stroke or systemic embolism—and a separate safety outcome that consisted of major bleeding, predominantly gastrointestinal events. However, the relative clinical importance of nonfatal gastrointestinal or other extracranial bleeding vs strokes or other intracranial bleeding has been controversial.[37] In contrast, the hemorrhagic component of the primary outcome for the present study included only the most severe extracranial bleeding, that which was fatal, thus permitting a single measure of the clinical impact of anticoagulant choice.

Limitations

This study has several limitations. First, residual confounding by unmeasured factors, including geographic variation in the preferences of patients and physicians, is possible. The effects of such variables could have been reduced by the propensity score analysis, which controlled for 208 covariates derived from medical care encounters that reflected patient health across multiple domains. One investigation that linked such encounter data for direct oral anticoagulants with electronic health records reported that after propensity score adjustment, minimal differences remained between glomerular filtration rate, weight, low-dose aspirin use, and other factors.[38] In the study cohort, covariate differences between the 2 groups prior to propensity score adjustment were small (most standardized differences were less than 0.1), which suggests limited channeling of patients to a specific anticoagulant. The differences that were present, as summarized by the CHA_2DS_2-VASc score, indicated that the rivaroxaban group had lower risk of study outcomes, which is consistent with an unadjusted total mortality rate that was less than that for apixaban. Thus, residual confounding may have caused underestimation of the additional risk associated with rivaroxaban use.

Second, there was potential misclassification of exposure and outcomes. There was no information about adherence, which could bias findings if differential. However, when the cohort was restricted to patients with no more than 7 days between refills—a marker for adherence—findings were unchanged. Study outcomes were identified from the principal inpatient discharge diagnoses. Although these had positive predictive values of greater than 90%, there was the potential for underascertainment of strokes. However, findings did not change materially with use of a more sensitive stroke definition based on all discharge diagnoses. Study outcomes did not include ischemic or hemorrhagic events without hospitalization, unless they resulted in death.

Third, as in other anticoagulant cohort studies[9,15] and long-term trials of medications for prevention of cardiovascular disease,[39] a substantial proportion of patients discontinued treatment. However, a sensitivity analysis that reduced censoring effects by limiting follow-up to 1 year had results entirely consistent with those of the primary analysis.

Fourth, although it has been hypothesized that greater fluctuation in rivaroxaban plasma concentrations[5,8,40] would lead to poorer clinical outcomes, the study data do not permit investigation of mechanisms. Other differences, such as the greater dependence of rivaroxaban bioavailability on food,[41] could also be important.

Fifth, the composition of the population studied limits the generalizability of findings. The study was restricted to Medicare beneficiaries in the US 65 years or older. Although more than 90% of persons in this age group have Medicare coverage,[42] the study cohort was limited to those beneficiaries with both fee-for-service coverage and enrollment in the Part D program for prescription medications.

Conclusions

Among Medicare beneficiaries aged 65 or older with atrial fibrillation, treatment with rivaroxaban compared with apixaban was associated with a significantly increased risk of major ischemic or hemorrhagic events.

ARTICLE INFORMATION

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Author Contributions: Dr Ray had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Ray, Chung, Stein, Smalley, Zimmerman, Hung, Murray.
Acquisition, analysis, or interpretation of data: Ray, Chung, Stein, Zimmerman, Dupont, Daugherty, Dickson, Murray.
Drafting of the manuscript: Ray, Dickson, Murray.
Critical revision of the manuscript for important intellectual content: Ray, Chung, Stein, Smalley, Zimmerman, Dupont, Hung, Daugherty, Murray.
Statistical analysis: Ray, Zimmerman, Dupont.
Obtained funding: Ray.
Administrative, technical, or material support: Ray, Chung, Zimmerman, Hung, Daugherty, Dickson, Murray.
Supervision: Ray.

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Supplemental Online Content

Ray WA, Chung CP, Stein CM, et al. Association of Rivaroxaban vs Apixaban With Major Ischemic or Hemorrhagic Events in Patients With Atrial Fibrillation. *JAMA.* Published online December 21, 2021. doi:10.1001/jama.2021.21222

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

1. Cohort and Followup

Cohort. eTable 1 shows the cohort eligibility criteria and the numbers of patients qualifying for the cohort at each step.

eTable 1. Cohort eligibility criteria.

	Criterion	Patients
1.	**Study drug prescription.** Outpatient prescription for apixaban or rivaroxaban between 1/1/2013 and 11/30/2018. On t_0, the day following the prescription fill, the beneficiary had to be alive, a resident of the United States, 65 years of age or older, have known sex, and have enrollment in the month of t_0 and for the past 12 months in Medicare fee for service (parts A, B, and D with no enrollment in Medicare part C). *Note a.*	2,078,642
2.	**Medical care.** At least one outpatient visit and one filled prescription in [t_0-365, t_0-2], excluding lab claims, to assure regular contact with medical care. The interval does not include t_0-1, the anticoagulant fill date, to ensure history prior to anticoagulant initiation.	2,074,179
3.	**Terminal illness.** Not in hospice for the period [t_0-365,t_0-1] or diagnosis indicating terminal illness. *Note b.*	1,978,800
4.	**Long-term care.** Not in a nursing home in [t_0-365, t_0-1], except stays <30 days following hospital discharge. No hospital discharge in [t_0-365,t_0-1] for a stay >30 days, which could indicate long-term care. *Note c.*	1,781,561
5.	**Atrial fibrillation dose.** Approved dose for atrial fibrillation. Apixaban 2.5 or 5mg, twice/day, rivaroxaban 15 or 20mg once/day.	1,602,485
6.	**New user.** For [t_0-365, t_0], no other filled prescription for any oral anticoagulant. *Note d.*	872,054
7.	**Atrial fibrillation.** Diagnosis atrial fibrillation/flutter in [t_0-90, t_0-1]. *Note e.*	692,974
8.	**Mitral valve stenosis.** No diagnosis mitral valve stenosis in [t_0-365, t_0-1].	690,049
9.	**Reversible AF.** No evidence in [t_0-30, t_0-1] of frequent causes of reversible or transient atrial fibrillation: diagnosis of hyperthyroidism or open coronary artery bypass graft/open cardiac valve surgery.	672,894
10.	**Other indication.** No evidence [t_0-30, t_0-1] other oral anticoagulant indication: DVT/PE, hip or knee replacement, femur/tibia/patella fracture, thrombectomy, chronic hypercoagulable state.	620,869
11.	**Severe CKD.** No Medicare ESRD enrollment basis or diagnosis in [t_0-365, t_0-1] of severe chronic kidney disease (CKD): stage 4/5/ESRD.	594,620
12.	**Stroke/SE.** No stroke/systemic embolism in [t_0-30, t_0-1], as defined in §2. A single clot can spawn multiple emboli and thus lead to readmissions.	582,137
13.	**Major bleed.** No anticoagulant-related bleeding hospitalization in [t_0-30, t_0-1], as defined in §2, which avoids confusion of new bleeds with continuing treatment for a prior outcome.	581,451

Notes for eTable 1

a. Study period. The starting date was the first year apixaban was available in Medicare. The latest Medicare data available were for calendar 2018. The last day of the study was 30 days before the end of the year to assure capture of deaths within 30 days of a study outcome as well as hospitalizations identified from the 2018 MedPar file, which is based on date of discharge.

b. Terminal illness. Hospice: identified by a claim in the hospice file, an HCPCS procedure indicating hospice care (G0182, T2042, T2043, T2044, T2045, T2046), or place of service=34, hospice. Diagnoses indicating terminal illness are do not resuscitate (ICD-9, V49.86; ICD-10, Z66), encounter for palliative care (ICD-9, V66.7; ICD-10, Z51.5), or persistent vegetative state (ICD-9, 780.03; ICD-10, R40.3).

c. Nursing home. Nursing home stays are inferred from 2 or more outpatient encounters in [t_0-365, t_0-1] separated by at least 28 days indicating nursing home place of service (CPT4 procedure codes 93304-93318 or place of service codes 31 or 32[a]) or a single external cause of injury diagnosis code (ICD-9, E849.7; ICD-10, Y92.12*) indicating institution residence.

d. New user. Excludes persons who fill prescriptions for multiple anticoagulants on t_0-1 or who start a second oral anticoagulant on t_0. Excludes patients with prior warfarin or betrixaban (very limited use for thromboprophylaxis in hospitalized patients). Because warfarin is inexpensive, its use occasionally is not recorded in the part D files. Thus, we excluded patients with evidence of undocumented use of warfarin in [t_0 - 365, t_0-31]; defined as:

[a] Agreement is very good between these fields but occasionally the place of service is missing.

i. Two or more codes, separated by at least 7 days, indicating anticoagulant use:
ICD-9: V85.61, long-term anticoagulant use
ICD-10: Z79.01, long-term (current) anticoagulant use
CPT: 85610, prothrombin time.

ii. For the period [t_0-365, t_0-31], a prescription or injection for subcutaneous anticoagulant (dalteparin, enoxaparin, fondaparinux) within 30 days of a code indicating anticoagulant use, likely to indicate bridging warfarin for patients with procedures.

e. Atrial fibrillation.

ICD-9	Rubric	ICD-10	Rubric
427.31	Atrial fibrillation	I48.0	Paroxysmal atrial fibrillation
427.32	Atrial flutter	I48.1	Persistent atrial fibrillation
		I48.2	Chronic atrial fibrillation. Note code expanded to I48.20, I48.21 in FY20
		I48.3	Typical atrial flutter, Type I atrial flutter
		I48.4	Atypical atrial flutter, Type II atrial flutter
		I48.91	Unspecified atrial fibrillation
		I48.92	Unspecified atrial flutter

Followup. Cohort followup began on t_0. It ended on t_1, the first of the following dates:

1. **Discontinue anticoagulant.** End of use of a study oral anticoagulant: day 30 following the last day of supply with t_1 the last day of supply + 30. Data from our prior study[1] suggested this definition both limited misclassification and early loss to followup. A sensitivity analysis tests the effect of shortening the allowable gap in days of supply.
2. **Switch anticoagulant.** Day prior to filling of a prescription for a different oral anticoagulant, including non-study anticoagulants.
3. **Change anticoagulant dose.** Day prior to filling of prescription with either a decrease or increase in dose. Also censors with filling of prescription for which the days of supply and quantity dispensed are inconsistent with treatment of atrial fibrillation.
4. **Development of CKD.** Day prior to filling of an anticoagulant prescription such that there is a diagnosis of severe chronic kidney disease (CKD): stage 4/5/ESRD in the year preceding the fill date.
5. **Last study day.** Four years after start of followup (day 1460) or 11/30/2018.
6. **Lose enrollment.** Last day[b] of full Medicare enrollment (parts A, B, D; no part C).
7. **Outcome/death.** Any study outcome or other death.

Patients who leave the cohort cannot reenter.

Given the total mortality outcome, we do not censor for long-term care or terminal illness. First, such factors could be a consequence of the anticoagulant, such as a stroke leading to hospice[c] or long-term care entry. Second, if the patient stops the anticoagulant, censoring will occur automatically in 30 days following the last day of supply[d].

[b] Because Medicare enrollment is on a monthly basis, this is the day prior to the beginning of the first month after t_0 without Medicare enrollment. For example, if there was no enrollment in July, t_1 would be 30 June.
[c] Most hospice stays in Medicare are for few (often 1) days following hospital discharge. Thus, censoring these would exclude many deaths directly related to anticoagulant use.
[d] This will automatically censor for long hospital stay as the anticoagulant prescription should not be refilled in the hospital.

2. Study Outcomes

2.1 Stroke/Systemic Embolism

A stroke or systemic embolism was defined as a hospital encounter with a principal discharge diagnosis in eTable 2. The stroke type was classified according to the principal hospital discharge diagnosis. The date of stroke occurrence generally was the date of admission for the qualifying hospitalization, but was set to the prior day if there was an encounter with a matching diagnosis (eTable 2, any position) on that day, or, for stroke, a procedure for CT or MRI imaging of the head. For strokes, the types did not have to agree, and a diagnosis of transient ischemic attack was considered matching.

eTable 2. Diagnosis codes for strokes and systemic embolism.

a. Ischemic strokes. Does not include codes for iatrogenic strokes.

ICD9-CM	Rubric	ICD10-CM	Rubric
362.30	Retinal vascular occlusion, unspecified	G46.3	Brain stem stroke syndrome
362.31	Central retinal artery occlusion	G46.4	Cerebellar stroke syndrome
362.32	Retinal vascular occlusion, arterial branch	G46.5	Pure motor lacunar syndrome
362.33	Retinal vascular occlusion, partial arterial occlusion	G46.6	Pure sensory lacunar syndrome
433.*1	Occlusion and stenosis of precerebral artery with cerebral infarction	G46.7	Other lacunar syndromes
434.*1	Occlusion and stenosis of cerebral artery with cerebral infarction	H34.1*	Central retinal artery occlusion
436	Acute, but ill-defined, cerebrovascular disease	H34.21*	Partial retinal artery occlusion
		H34.23*	Retinal artery branch occlusion
		H34.9	Unspecified retinal vascular occlusion
		I63.****	Cerebral infarction, includes occlusion and stenosis of cerebral and precerebral arteries, resulting in vascular infarction

b. Hemorrhagic stroke

ICD9-CM	Rubric	ICD10-CM	Rubric
430	Subarachnoid hemorrhage	I60.**	Nontraumatic subarachnoid hemorrhage
431	Intracerebral hemorrhage	I61.*	Nontraumatic intracerebral hemorrhage

c. Systemic embolism

ICD9-CM	Rubric	ICD10-CM	Rubric
444.**	Arterial embolism and thrombosis	I74.**	Arterial embolism and thrombosis

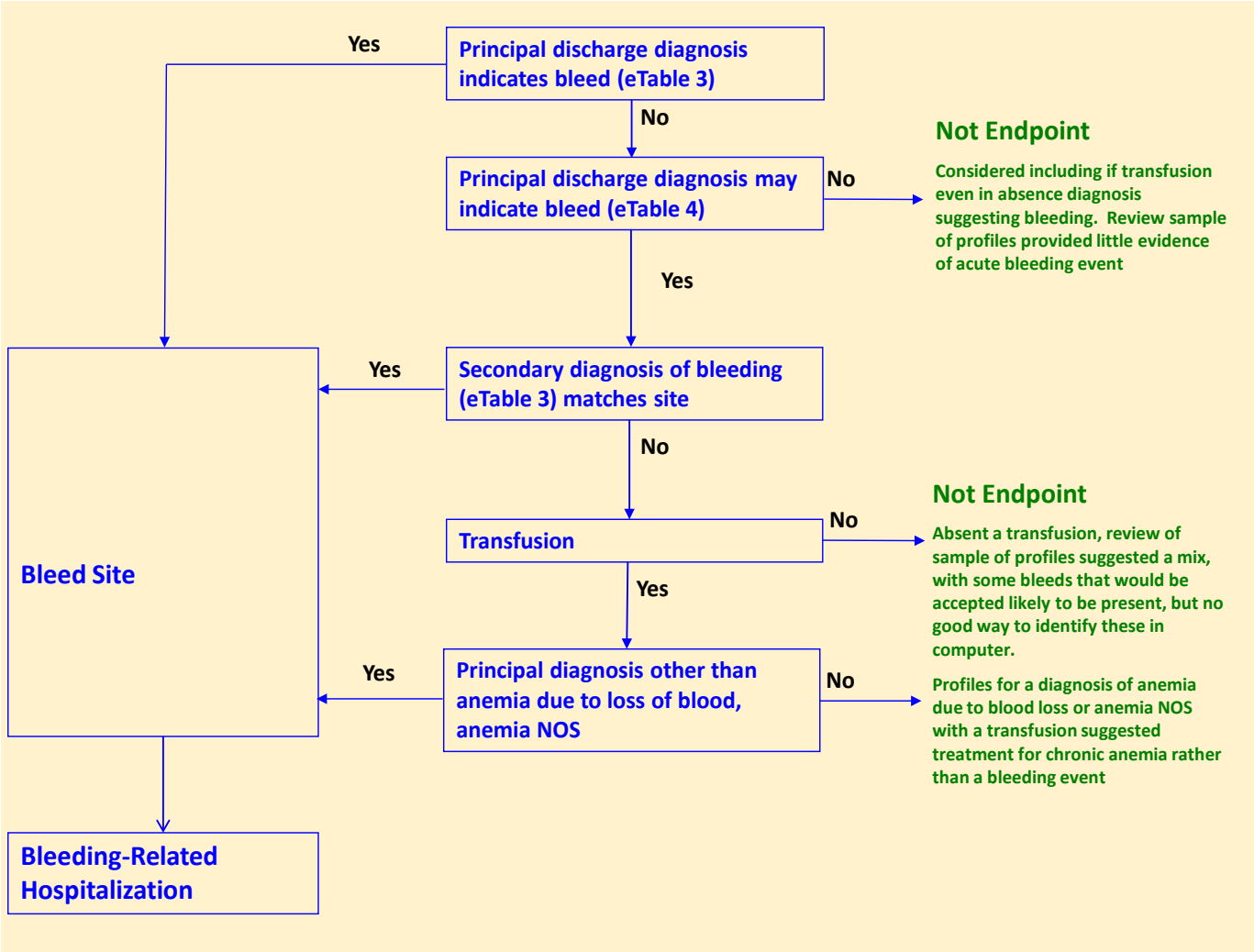
In a sensitivity analysis, all diagnoses were considered to identify strokes, which would improve completeness of ascertainment.[2] In addition to any diagnosis code for stroke, there had to be a procedure for CT or MRI imaging of the head on the day of or preceding hospital admission. Review of profiles suggested that in other cases the stroke occurred in hospital, often the result of a procedure. If the secondary diagnoses included both ischemic and hemorrhagic strokes, priority was given according to diagnosis order (first priority second diagnosis, etc).

2.2 Bleeding.

Bleeding-related hospitalizations were identified from a previously published algorithm (eFigure).[1,3,4] Hospitalizations with 2 types of principal diagnoses were considered: those indicating a definite bleed (eTable 3), and those indicating a potential bleed (eTable 4). For the latter, we required confirmation by a secondary diagnosis indicating a definite bleed (eTable 3) for a site (intracranial, gastrointestinal, genitourinary, other) concordant with that of the principal diagnosis[e] or, so long as the principal diagnosis was not anemia due to blood loss/anemia NOS, a code indicating a transfusion.

[e] An unspecified' site was concordant with all other sites.

eFigure. Algorithm for identifying bleeding-related hospitalizations



The algorithm was validated by review of medical records which found that 89% of hospitalizations identified were clinically confirmed bleeds and 10% were possible bleeds.[3] The sites (intracranial, gastrointestinal, genitourinary, other) matched for 99% of clinically confirmed cases. Minor changes to the diagnosis codes were made during the conduct of prior anticoagulant studies in the Medicare population.[1,4] For the present study, we updated the algorithm to include ICD-10-CM diagnosis, using the CMS General Equivalence Mappings (GEMS) when these indicated direct equivalence, or by investigator review for those for which the mapping indicated approximate equivalence or non-one-to-one mappings.

The site of the bleeding was determined from the principal diagnosis of the hospitalization so long as the site was specified. If the principal diagnosis did not specify a bleeding site (e.g., the ICD-10 code R58, hemorrhage, not elsewhere classified), the site was identified from the secondary diagnoses, giving priority to those indicating definite bleeding.

The date of the bleeding occurrence was generally the hospital admission date but was set back to the prior day if there was an encounter with a diagnosis for bleeding at the same site. For intracranial bleeds, we also set the date back when there were encounters with a procedure for CT or MRI imaging of the head.

eTable 3. Diagnosis codes indicating bleeding, according to site.

Intracranial		Gastrointestinal						Genitourinary	Other	Unspecified
No trauma	Trauma	Gastroduodenal	Esophageal	Upper, Unspecified	Upper, Other	Lower	Un-specified		Other	
ICD-9-CM										
432.0 432.1 432.9	852.0* 852.2* 852.4* 853.0*	531.0* 531.2* 531.4* 531.6* 532.0* 532.2* 532.4* 532.6* 533.0* 533.2* 533.4* 533.6* 534.0* 534.2* 534.4* 534.6* 535.01 535.11 535.21 535.31 535.41 535.51 535.61	456.0 456.20 530.21 530.7 530.82	578.0	537.83 537.84	562.02 562.03 562.12 562.13 569.3 569.85	578.1 578.9	599.70 599.71 623.8 626.6 627.1	363.61 363.62 376.32 377.42 379.23 423.0 568.81 719.1* 729.7* 729.92 784.7 784.8 786.30 786.39	286.7 459.0
ICD-10-CM										
I62.1 I62.00 I62.01 I62.02 I62.03 I62.9	S06.6X*A S06.5X*A S06.4X*A S06.34*A S06.35*A S06.36*A	K25.0 K25.2 K25.4 K25.6 K26.0 K26.2 K26.4 K26.6 K27.0 K27.2 K27.4 K27.6 K28.0 K28.2 K28.4 K28.6 K29.01 K29.31 K29.41 K29.51 K29.61 K29.21 K29.71 K29.91 K29.81	I85.01 I85.11 K22.11 K22.6	K92.0	K31.811 K31.82	K57.01 K57.11 K57.13 K57.21 K57.31 K57.33 K57.41 K57.51 K57.53 K57.81 K57.91 K57.93 K62.5 K55.21 K50.011 K50.111 K50.811 K50.911 K51.011 K51.211 K51.311 K51.411 K51.511 K51.811 K51.911	K92.1 K92.2	R31.0 R31.9 N89.8 N93.8 N95.0 N93.0 N93.8 N93.9	H31.30* H31.31* H05.23* H47.02* H43.1* I31.2 K66.1 M25.0** M79.A** M79.81 R04.0 R04.1 R04.2 R04.89 R04.9	D68.32 R58

eTable 4. Diagnosis codes that may indicating bleeding.

Intracranial		Gastrointestinal						Genitourinary	Other	Unspecified
No trauma	Trauma	Gastroduodenal	Esophageal	Upper, Unspecified	Upper, Other	Lower	Un-specified			
ICD-9-CM										
		456.1 456.21 530.10 530.12 530.20 531.1* 531.3* 531.5* 531.7* 531.9* 532.1* 532.3* 532.5* 532.7* 532.9* 533.1* 533.3* 533.5* 533.7* 533.9* 534.1* 534.3* 534.5* 534.7* 534.9* 535.00 535.10 535.20 535.30 535.40 535.50 535.60 537.82				455.* 562.00 562.01 562.10 562.11 569.84		599.72 623.8		280.0 285.1 285.9 287.9 790.92
ICD-10-CM										
		I85.00 I85.10 K20.9 K22.10 K25.1 K25.3 K25.5 K25.7 K25.9 K26.1 K26.3 K26.5 K26.7 K26.9 K27.1 K27.3 K27.5 K27.7 K27.9 K28.1 K28.3 K28.5 K28.7 K28.9 K29.00 K29.20 K29.30 K29.40 K29.50 K29.60 K29.70 K29.80 K29.90 K31.819				K64.* K57.00 K57.10 K57.12 K57.20 K57.30 K57.32 K57.40 K57.50 K57.52 K57.80 K57.90 K57.92 K55.20				D50.0 D62 D64.9 D69.9 R79.1

3. Analysis

3.1 Covariates

Some covariates based on diagnoses or procedures were initially defined with ICD-9-CM codes. These were converted to ICD-10-CM with the CMS General Equivalence Mappings (GEMs); the resulting codes were inspected, the prevalence of covariates for periods with exclusive use of each system was compared, and potential inconsistencies were resolved by the investigators.

eTable 5 shows the distributions of all study covariates, before and after IPT weighting.

eTable 5. Distribution of covariates according to study anticoagulant, with the standardized difference (SD).

	Rivaroxaban	Apixaban	SD	Rivaroxaban	Apixaban	SD
N	227,572	353,879	.	227,572	353,879	.
Age, years	76.3	77.4	0.1586	77.0	77.0	0.0023
Female	48.3%	51.4%	0.0627	50.0%	50.0%	0.0007
Asian[a]	1.6%	1.3%	0.0204	1.4%	1.4%	0.0015
Black	3.6%	3.6%	0.0017	3.6%	3.6%	0.0006
Hispanic	1.2%	1.0%	0.0182	1.1%	1.0%	0.0088
North American Native	0.3%	0.2%	0.0161	0.3%	0.2%	0.0092
Other	1.2%	1.1%	0.0099	1.1%	1.2%	0.0079
White	91.1%	91.7%	0.0208	91.4%	91.4%	0.0016
Unknown	1.0%	1.1%	0.0005	1.0%	1.1%	0.0104
Medicaid enrollee	13.9%	12.8%	0.0332	13.1%	13.2%	0.0032
West	16.1%	14.1%	0.0567	15.0%	15.0%	0.0002
Southwest	10.6%	10.6%	0.0007	10.7%	10.6%	0.0006
Midwest	22.2%	21.3%	0.0226	21.5%	21.5%	0.0010
Southeast	33.1%	36.7%	0.0747	35.4%	35.3%	0.0020
Northeast	17.9%	17.3%	0.0153	17.5%	17.6%	0.0018
Calendar year 2013	14.7%	2.4%	0.4513	7.2%	7.3%	0.0030
Calendar year 2014	19.4%	9.7%	0.2771	13.5%	13.5%	0.0005
Calendar year 2015	16.5%	16.8%	0.0096	16.7%	16.7%	0.0002
Calendar year 2016	15.5%	21.9%	0.1653	19.4%	19.4%	0.0001
Calendar year 2017	18.9%	21.6%	0.0681	20.6%	20.5%	0.0017
Calendar year 2018	15.1%	27.6%	0.3083	22.7%	22.7%	0.0001
Cardiologist	49.1%	49.0%	0.0030	49.8%	49.6%	0.0037
Internal medicine	18.7%	18.8%	0.0014	18.3%	18.4%	0.0021
Family practice/general medicine	8.6%	7.4%	0.0426	7.8%	7.8%	0.0001
Nurse practitioner/physician assistant	10.7%	12.6%	0.0602	11.8%	11.8%	0.0017
Other	12.9%	12.2%	0.0206	12.4%	12.4%	0.0016
Mitral valve insufficiency	27.8%	30.5%	0.0601	29.4%	29.4%	0.0000
Aortic valve stenosis or insufficiency	19.5%	23.2%	0.0891	21.8%	21.7%	0.0007
Disorders tricuspid, pulmonary, or unspecified valve	17.6%	20.2%	0.0678	19.1%	19.2%	0.0006
Cardiac valve replacement or repair	2.4%	3.0%	0.0417	2.8%	2.8%	0.0008
Hypertension	89.8%	90.7%	0.0309	90.3%	90.3%	0.0008
Myocardial infarction	5.6%	6.8%	0.0498	6.3%	6.3%	0.0005
Old myocardial infarction	8.8%	10.0%	0.0396	9.5%	9.5%	0.0000
Angina	10.4%	11.1%	0.0232	10.8%	10.8%	0.0004
Coronary artery bypass graft	9.8%	10.9%	0.0339	10.5%	10.4%	0.0001
Percutaneous intervention	11.4%	12.9%	0.0447	12.3%	12.3%	0.0004
Pulmonary heart disease	8.6%	10.0%	0.0494	9.4%	9.4%	0.0005
Cardiomyopathy, endocarditis, myocarditis	11.3%	12.4%	0.0337	12.0%	12.0%	0.0005
Pacemaker	14.0%	16.0%	0.0547	15.5%	15.4%	0.0036
Implantable cardiac defibrillator	3.9%	4.4%	0.0258	4.3%	4.2%	0.0009

Cardioablation	1.9%	1.8%	0.0050	1.8%	1.8%	0.0001
Cardioversion	9.0%	9.4%	0.0147	9.2%	9.2%	0.0012
New cardiac procedure past 90 days	18.8%	20.8%	0.0487	19.9%	20.0%	0.0005
Heart failure	27.9%	31.2%	0.0723	29.8%	29.8%	0.0005
Heart failure hospitalization past 90 days	11.0%	13.5%	0.0764	12.2%	12.3%	0.0028
Ill-defined or unspecified descriptions or complications of heart disease	22.4%	24.3%	0.0442	23.5%	23.5%	0.0003
Hemorrhagic stroke or other intracranial bleeding	0.6%	0.9%	0.0285	0.8%	0.8%	0.0001
Ischemic or unspecified stroke	7.5%	8.7%	0.0461	8.2%	8.2%	0.0001
Systemic embolism	0.8%	0.8%	0.0050	0.8%	0.8%	0.0009
Other occlusion/stenosis of precerebral/cerebral arteries	13.7%	15.2%	0.0416	14.6%	14.6%	0.0016
Transient ischemic attack (TIA)	6.2%	6.8%	0.0263	6.6%	6.6%	0.0009
History TIA/cerebral infarction without residual defects	7.7%	9.5%	0.0641	8.7%	8.7%	0.0001
Stroke/systemic embolism/TIA new past 90 days	5.9%	6.8%	0.0349	6.4%	6.4%	0.0001
Other cerebrovascular disease	6.0%	7.2%	0.0482	6.7%	6.7%	0.0003
Cerebrovascular disease, late effects	3.1%	3.6%	0.0307	3.4%	3.4%	0.0006
CT or MRI imaging of head	19.3%	22.0%	0.0668	20.8%	20.8%	0.0003
Aortic plaque	5.0%	5.9%	0.0431	5.5%	5.6%	0.0004
Peripheral artery disease	18.2%	19.3%	0.0294	18.8%	18.8%	0.0000
Aortic aneurysm or dissection	5.6%	6.0%	0.0194	5.8%	5.8%	0.0006
Deep vein thrombosis/pulmonary embolism	3.7%	3.7%	0.0036	3.7%	3.7%	0.0004
Congenital anomalies, cardiovascular	2.0%	1.8%	0.0116	1.9%	1.9%	0.0003
Diabetes	35.0%	34.8%	0.0031	34.8%	34.9%	0.0009
Hypotension	8.6%	10.0%	0.0504	9.4%	9.4%	0.0004
Hyperlipidemia	81.3%	82.2%	0.0220	81.9%	81.8%	0.0010
Obesity, not morbid or unspecified	20.4%	21.7%	0.0317	21.2%	21.2%	0.0005
Obesity, morbid	10.4%	11.2%	0.0238	10.9%	10.9%	0.0001
Smoking or other tobacco use	29.0%	32.4%	0.0741	30.9%	30.9%	0.0001
Cardiac symptoms, cardiac murmer or other abnormal heart sounds	4.7%	4.9%	0.0100	4.8%	4.8%	0.0009
Acute renal failure	7.6%	10.5%	0.0999	9.3%	9.3%	0.0006
Chronic kidney disease, Stage 1-2	3.2%	3.9%	0.0376	3.6%	3.6%	0.0016
Chronic kidney disease, Stage 3 or unspecified	13.9%	17.9%	0.1113	16.3%	16.3%	0.0002
Renal failure, unspecified	1.3%	1.5%	0.0171	1.4%	1.4%	0.0005
Other kidney disorders	15.9%	18.2%	0.0598	17.3%	17.3%	0.0008
Gastrointestinal bleeding	4.9%	5.4%	0.0242	5.2%	5.2%	0.0007
Genitourinary	6.9%	7.4%	0.0212	7.2%	7.2%	0.0003
Other specified site	3.9%	4.1%	0.0106	4.0%	4.0%	0.0001
Hemorrhagic conditions or coagulation defects	7.9%	9.5%	0.0558	8.9%	8.9%	0.0019
Iron-deficiency anemias	7.2%	8.2%	0.0388	7.8%	7.8%	0.0005
Anemia, other	7.7%	9.0%	0.0465	8.5%	8.5%	0.0009
Anemia, unspecified	18.1%	20.1%	0.0499	19.3%	19.2%	0.0009
Hemolytic and aplastic anemias	1.1%	1.2%	0.0133	1.2%	1.2%	0.0006
Bleeding, transfusion	1.6%	1.9%	0.0259	1.8%	1.8%	0.0002
Peptic ulcer disease without bleeding	1.8%	2.0%	0.0173	1.9%	1.9%	0.0004
Esophagitis or esophageal ulceration/gastritis/ duodenitis/angiodysplasia without bleeding	9.2%	9.4%	0.0063	9.3%	9.3%	0.0007
Diverticulitis/divirticulosis/angiodysplasia without bleeding	12.4%	12.8%	0.0136	12.6%	12.6%	0.0002
Hemorrhoids	6.1%	6.1%	0.0004	6.1%	6.1%	0.0008
Gastroparesis, intestinal obstruction	2.1%	2.5%	0.0241	2.3%	2.3%	0.0001
G.I. symptoms, abdominal pain	19.2%	20.1%	0.0239	19.7%	19.7%	0.0003
Colonoscopy	10.1%	9.7%	0.0135	9.8%	9.8%	0.0006
Pneumonia	11.1%	12.6%	0.0483	11.9%	11.9%	0.0003
Influenza	1.8%	2.2%	0.0283	2.1%	2.1%	0.0008
Chronic obstructive pulmonary disease	21.9%	22.9%	0.0249	22.3%	22.3%	0.0003
Asthma	11.9%	12.1%	0.0065	12.0%	12.0%	0.0010

Pleurisy	9.8%	12.0%	0.0706	11.0%	11.0%	0.0005
Interstitial pulmonary disease	3.1%	3.6%	0.0276	3.4%	3.4%	0.0005
Other respiratory diseases	7.7%	8.1%	0.0166	7.9%	7.9%	0.0003
Other chronic bronchitis	1.8%	2.1%	0.0182	2.0%	2.0%	0.0006
Continuous positive airway pressure	7.9%	8.2%	0.0121	8.1%	8.1%	0.0006
Asphyxia or hypoxemia	7.4%	8.3%	0.0344	7.9%	7.9%	0.0002
Home oxygen	9.8%	10.6%	0.0266	10.2%	10.2%	0.0000
Respiratory failure/respirator/tracheostomy	6.1%	8.0%	0.0725	7.2%	7.2%	0.0008
Hemiplegia/hemiparesis, quadriplegia, paraplegia, other paralytic syndromes	2.0%	2.7%	0.0440	2.4%	2.4%	0.0004
Heriditary, traumatic, and other major neurologic disorders	5.3%	6.4%	0.0453	5.9%	5.9%	0.0007
Alzheimers and other dementias	6.9%	8.2%	0.0496	7.7%	7.7%	0.0005
Other cognitive impairment	4.3%	4.9%	0.0294	4.7%	4.7%	0.0001
Altered mental status or disorientation	4.9%	6.3%	0.0615	5.7%	5.7%	0.0005
Disturbance of speech	2.8%	3.6%	0.0470	3.3%	3.3%	0.0002
Parkinsons and other movement disorders	5.4%	6.0%	0.0268	5.8%	5.7%	0.0004
Seizure disorders and convulsions	2.1%	2.3%	0.0148	2.2%	2.2%	0.0007
Fracture of femur, pelvis, or vertebral column	2.0%	2.3%	0.0245	2.2%	2.2%	0.0003
Major head trauma	3.7%	4.3%	0.0299	4.1%	4.1%	0.0011
Hip or knee replacement	5.6%	5.9%	0.0162	5.8%	5.8%	0.0000
Osteoporosis	12.4%	13.6%	0.0345	13.1%	13.1%	0.0005
Unintentional fall (not vigorous activity)	9.5%	11.5%	0.0637	10.7%	10.7%	0.0003
Abnormalities of gait, mobility, coordinatoin	11.5%	14.4%	0.0877	13.3%	13.3%	0.0005
Limited mobility, cane or walker	3.6%	4.1%	0.0273	3.9%	3.9%	0.0008
Wheelchair or other ADL limitations	3.1%	3.5%	0.0194	3.3%	3.3%	0.0004
Urinary/fecal incontinence or catheter	7.2%	8.0%	0.0324	7.7%	7.7%	0.0004
Malnutrition/abnormal weight loss/feeding problems	8.0%	9.4%	0.0506	8.8%	8.8%	0.0009
Dysphagia	5.1%	5.9%	0.0339	5.6%	5.5%	0.0007
Chronic skin ulcer	4.2%	4.5%	0.0166	4.4%	4.4%	0.0006
Muscle atrophy	6.9%	8.2%	0.0477	7.7%	7.7%	0.0011
Debility, not specified	1.6%	1.3%	0.0230	1.4%	1.4%	0.0001
Mood disorder	14.6%	15.6%	0.0262	15.2%	15.2%	0.0006
Substance use disorder or dependence, including alcohol	3.9%	3.9%	0.0006	3.9%	3.9%	0.0004
Cancer, lymphatic and hematopoietic tissue	2.6%	2.9%	0.0186	2.8%	2.8%	0.0006
Cancer, breast	3.4%	3.5%	0.0057	3.5%	3.5%	0.0001
Cancer, gastrointestinal	2.0%	2.2%	0.0089	2.1%	2.1%	0.0001
Cancer, lung	1.8%	2.0%	0.0141	1.9%	1.9%	0.0010
Cancer, metastasis	1.7%	2.0%	0.0189	1.9%	1.9%	0.0005
Cancer, other	5.6%	6.0%	0.0153	5.8%	5.8%	0.0002
Cancer, prostate	5.6%	5.5%	0.0037	5.5%	5.5%	0.0003
Swelling, mass, or lump: head, neck, chest, abdomen	4.0%	4.0%	0.0012	4.0%	3.9%	0.0001
Cancer chemotherapy/radiotherapy	7.6%	9.4%	0.0653	8.6%	8.6%	0.0001
Cancer, neoplasm uncertain or unspecified behavior	4.8%	5.2%	0.0183	5.0%	5.0%	0.0005
Enlarged lymph nodes	2.5%	2.8%	0.0180	2.7%	2.7%	0.0002
Elevated white blood cell count	4.9%	6.0%	0.0467	5.5%	5.5%	0.0003
Urinary tract infections	19.1%	20.6%	0.0374	20.0%	20.0%	0.0003
Hypovolemia	7.3%	8.5%	0.0475	8.0%	8.0%	0.0005
Fluid overload	1.4%	1.8%	0.0318	1.6%	1.6%	0.0016
Angiotensin converting enzyme inhibitors	36.3%	35.7%	0.0135	35.9%	35.9%	0.0008
Angiotensin receptor blocker	28.2%	29.0%	0.0177	28.7%	28.7%	0.0002
Nitrates and other antianginals	11.0%	12.1%	0.0345	11.6%	11.6%	0.0001
Anti-arrhythmics, amiodarone	10.9%	11.8%	0.0275	11.4%	11.4%	0.0005
Antiarrhythmics, dronedarone	2.7%	2.6%	0.0099	2.7%	2.6%	0.0006
Antiarrhythmics, flecainide	4.1%	4.0%	0.0023	4.1%	4.1%	0.0013
Antiarrhythmics, propafenone	2.3%	2.0%	0.0198	2.1%	2.1%	0.0013

Antiarrhythmics, sotalol	5.5%	5.2%	0.0134	5.4%	5.3%	0.0006
Antihypertensives, Other	7.7%	8.3%	0.0241	8.1%	8.1%	0.0010
P2Y12 inhibitors and other antiplatelet drugs	15.1%	16.6%	0.0404	16.0%	16.0%	0.0004
Beta-blockers, metoprolol	48.1%	50.4%	0.0466	49.4%	49.4%	0.0001
Beta-blockers, other	27.5%	28.0%	0.0109	27.9%	27.9%	0.0004
Diltiazem or verapamil	21.5%	21.1%	0.0091	21.2%	21.2%	0.0003
Calcium channel blockers, other	27.3%	28.8%	0.0332	28.1%	28.1%	0.0004
Digoxin and other inotropic agents	8.5%	7.2%	0.0484	7.7%	7.7%	0.0005
Diuretics, Loop	26.1%	28.9%	0.0634	27.7%	27.8%	0.0005
Diuretics, Thiazide	24.1%	24.0%	0.0022	24.0%	24.0%	0.0006
Diuretics, Potassium Sparing (and with hydrochlorothiazide)	8.8%	9.3%	0.0164	9.1%	9.1%	0.0015
Potassium	16.2%	17.2%	0.0256	16.8%	16.8%	0.0006
Stop antihypertensive medication	25.5%	27.0%	0.0329	26.5%	26.4%	0.0009
Hypoglycemics, Insulin	6.1%	6.6%	0.0188	6.4%	6.4%	0.0015
Hypoglycemics, Metformin	16.2%	15.8%	0.0089	16.0%	16.0%	0.0002
Hypoglycemics, Sulfonylureas	8.4%	8.3%	0.0048	8.4%	8.3%	0.0001
Hypoglycemics, DPP4 Inhibitors	4.1%	4.1%	0.0031	4.1%	4.1%	0.0008
Thiazolidinediones and other hypoglycemics	3.4%	3.6%	0.0123	3.5%	3.5%	0.0000
Lipid-lowering Drugs, Statins	61.3%	63.0%	0.0338	62.3%	62.4%	0.0009
Lipid-lowering Drugs, Fibrates	4.3%	4.1%	0.0079	4.2%	4.2%	0.0003
Lipid-lowering Drugs, Ezetimibe	3.6%	3.4%	0.0097	3.5%	3.5%	0.0005
NSAIDs, non-selective	17.3%	16.3%	0.0261	16.7%	16.7%	0.0002
Coxibs	3.0%	2.8%	0.0131	2.9%	2.9%	0.0007
DMARDs, including methotrexate	3.1%	3.2%	0.0088	3.1%	3.2%	0.0001
Systemic oral corticosteroids	24.2%	25.7%	0.0334	25.0%	25.0%	0.0006
Immunosuppressants	2.1%	2.2%	0.0033	2.2%	2.2%	0.0009
P2Y12 and other antiplatelet drugs, current use	10.4%	11.2%	0.0248	10.9%	10.9%	0.0003
Non-selective NSAIDs, current use	5.0%	4.6%	0.0204	4.7%	4.7%	0.0000
Systemic corticosteroids, current use	4.9%	5.1%	0.0125	4.9%	4.9%	0.0007
PPIs, current use	20.8%	21.8%	0.0238	21.4%	21.4%	0.0000
Proton-pump inhibitors	30.2%	31.5%	0.0281	31.0%	31.0%	0.0003
H2RA	6.5%	7.2%	0.0281	7.0%	7.0%	0.0002
Sucralfate/misoprostol	2.0%	2.1%	0.0121	2.1%	2.1%	0.0005
Antiemetics used in cancer chemotherapy	4.6%	5.5%	0.0412	5.2%	5.2%	0.0005
Beta-agonists	16.5%	17.2%	0.0202	16.8%	16.8%	0.0018
Bronchodilators, other	8.3%	8.5%	0.0080	8.3%	8.3%	0.0001
Asthma treatment	5.4%	5.8%	0.0205	5.7%	5.6%	0.0009
Inhaled corticosteroids	20.7%	20.9%	0.0038	20.8%	20.8%	0.0010
Alzheimer's medications	3.6%	3.9%	0.0175	3.8%	3.8%	0.0006
Parkinson's medications	3.2%	3.4%	0.0158	3.3%	3.3%	0.0004
Anticonvulsants, infrequent use outside of seizure disorders	1.6%	1.8%	0.0117	1.7%	1.7%	0.0007
Bisphosphonates and other medications for osteoporosis	5.8%	5.8%	0.0007	5.7%	5.8%	0.0006
Opioid analgesics	35.5%	35.4%	0.0022	35.4%	35.4%	0.0005
Anticonvulsants, Primary Use Pain	11.8%	13.0%	0.0371	12.5%	12.5%	0.0009
Antipsychotics/mood stabilizers	3.1%	3.1%	0.0042	3.1%	3.1%	0.0010
SSRIs/SNRIs	18.1%	18.8%	0.0187	18.5%	18.5%	0.0002
Trazodone	3.5%	4.0%	0.0254	3.8%	3.8%	0.0004
Other antidepressants	5.9%	6.2%	0.0163	6.1%	6.1%	0.0000
Benzodiazepines	16.8%	17.5%	0.0177	17.3%	17.3%	0.0001
Zolpidem or other z-drug	6.6%	5.9%	0.0292	6.2%	6.2%	0.0005
Antibiotics, Ciprofloxacin	13.3%	13.3%	0.0012	13.2%	13.2%	0.0001
Other 3A4/PGP inhibitors (noncardiovascuar)	6.5%	6.6%	0.0042	6.6%	6.5%	0.0018
Antiviral agents	5.7%	6.3%	0.0239	6.1%	6.1%	0.0002
Antibiotics, Penicillins	23.2%	23.8%	0.0149	23.5%	23.5%	0.0000
Antibiotics, Cephalosporins first, second generation	15.4%	16.4%	0.0270	16.0%	16.0%	0.0004

Antibiotics, Cephalosporins third generation	3.7%	4.2%	0.0304	4.0%	4.0%	0.0001
Antibiotics, Azithromycin	18.2%	18.3%	0.0035	18.2%	18.2%	0.0000
Antibiotics, Tetracyclines	9.6%	10.6%	0.0339	10.2%	10.2%	0.0000
Antibiotics, Sulfonomides	9.0%	9.3%	0.0112	9.2%	9.2%	0.0002
Antibiotics, UTI	4.4%	5.2%	0.0392	4.9%	4.9%	0.0004
Antibiotics, Other Fluoroquinolones	11.9%	11.9%	0.0018	11.8%	11.8%	0.0008
Home health visit day anticoagulant prescription	4.9%	6.0%	0.0492	5.5%	5.5%	0.0003
Inpatient discharge days 91-365 before t0	7.5%	7.8%	0.0129	7.8%	7.8%	0.0022
Inpatient discharge days 31-90 before t0	6.0%	7.7%	0.0657	7.2%	7.1%	0.0026
Inpatient discharge days 1-30 before t0	13.0%	14.4%	0.0428	13.6%	13.6%	0.0014
Inpatient discharge day of anticoagulant prescription	13.7%	14.5%	0.0237	13.6%	13.7%	0.0028

[a]The proportions differ slightly from those in Table 1 because participants with unknown race were included in the study and thus are in the denominator for eTable 5. In the logistic regression for calculating the propensity score, the races other than White or Black were grouped into a single category because the proportions were all less than 2%. As the SDs for weighted proportions show, good balance was achieved.

3.2 Propensity Score

eTable 6 shows the distribution of the propensity score.

eTable 6. Propensity score distribution according to study anticoagulant.

	Rivaroxaban	Apixaban
Min	0.051550	0.051489
P1	0.165040	0.131390
P5	0.222516	0.177150
P10	0.256330	0.205760
P25	0.320909	0.258431
P50	0.411301	0.325922
P75	0.579575	0.404852
P90	0.784915	0.517865
P95	0.824711	0.600508
P99	0.876745	0.804306
Max	0.961530	0.051489

4. Additional Results

eTable 7 shows the unadjusted and adjusted probabilities of discontinuation or switching by the median day of followup, according to study drug.

eTable 7. Discontinuation/switching probabilities[a] by the median (174) day of followup.

	Rivaroxaban	Apixaban
	% (95% CI)	
Unweighted		
Discontinue study anticoagulant	33.4 (33.1-33.6)	30.4 (30.3-30.6)
Switch to different oral anticoagulant	7.0 (6.9-7.1)	4.5 (4.5-4.6)
Weighted		
Discontinue study anticoagulant	33.4 (33.2-33.7)	30.7 (30.5-30.8)
Switch to different oral anticoagulant	6.9 (6.8-7.1)	4.7 (4.7-4.8)

[a]Calculated as the estimated cumulative incidence function on the median followup day with proportional hazards regression with a separate stratum for rivaroxaban and apixaban. All causes of loss to followup other that discontinuation or switching were treated as censoring. The adjusted probability was calculated with inverse probability of treatment weighting with robust variance estimation.

eTable 8. Cohort characteristics according to dose. See MS Table 1 for footnotes

a. Reduced dose

	Unweighted			Weighted		
	Rivaroxaban	Apixaban	SD	Rivaroxaban	Apixaban	SD
N	52,374	82,019		52,374	82,019	
Demographics						
Age, years, mean (std)	81.0 (6.9)	83.9 (6.3)	0.4370	82.9 (6.9)	82.8 (6.6)	0.0119
Year anticoagulant started, mean	2,015.4	2,016.2	0.5683	2,015.9	2,015.9	0.0001
Female	59.5%	64.8%	0.1095	62.4%	62.4%	0.0012
Male	40.5%	35.2%	0.1095	37.6%	37.6%	0.0012
Race[c]						
Asian	2.7%	2.5%	0.0130	2.6%	2.6%	0.0002
Black	4.4%	4.1%	0.0160	4.2%	4.2%	0.0007
Hispanic	1.7%	1.6%	0.0015	1.7%	1.6%	0.0067
North American Native	0.3%	0.2%	0.0151	0.3%	0.3%	0.0083
Other	1.4%	1.3%	0.0033	1.2%	1.4%	0.0169
White	89.5%	90.2%	0.0220	89.9%	89.9%	0.0026
Region of residence						
West	16.5%	15.0%	0.0409	15.7%	15.8%	0.0003
Southwest	10.9%	11.4%	0.0144	11.3%	11.2%	0.0021
Midwest	21.6%	19.5%	0.0539	20.1%	20.1%	0.0003
Southeast	32.3%	35.7%	0.0730	34.3%	34.3%	0.0004
Northeast	18.6%	18.4%	0.0060	18.6%	18.6%	0.0016
Dual Medicare-Medicaid enrollment	18.3%	16.5%	0.0473	17.1%	17.2%	0.0041
Cardiologist prescribed anticoagulant	46.8%	45.6%	0.0266	46.6%	46.6%	0.0000
Medical history, past year unless otherwise specified						
CHA_2DS_2-VASc score[d], mean	4.9	5.1	0.1239	5.0	5.0	0.0109
Hypertension	93.7%	93.2%	0.0219	93.3%	93.4%	0.0016
Diabetes	38.5%	33.8%	0.0968	35.6%	35.7%	0.0021
Heart failure	40.0%	41.2%	0.0247	40.7%	40.7%	0.0009
Anemia	34.4%	36.9%	0.0539	36.0%	35.9%	0.0030
Chronic obstructive pulmonary disease	26.7%	26.6%	0.0016	26.3%	26.4%	0.0012
Cancer other than non-melanoma skin cancer	18.6%	19.0%	0.0082	18.8%	18.8%	0.0005
Bleeding at gastrointestinal or other sites	17.0%	18.0%	0.0275	17.7%	17.7%	0.0009
Chronic kidney disease, Stage 3 or unspecified	30.3%	30.5%	0.0048	30.4%	30.4%	0.0007
Percutaneous coronary intervention	14.4%	14.1%	0.0100	14.1%	14.1%	0.0024
Dysphagia/malnutrition	14.5%	18.8%	0.1172	17.0%	17.2%	0.0031
Coronary artery bypass graft	12.7%	12.2%	0.0161	12.4%	12.4%	0.0000
Fall	13.1%	16.6%	0.0998	15.2%	15.3%	0.0007
Cardioversion	7.7%	6.3%	0.0573	6.8%	6.8%	0.0023
Ischemic stroke, systemic embolism, intracranial bleeding	10.9%	12.2%	0.0397	11.7%	11.6%	0.0004
Acute kidney failure	14.8%	16.1%	0.0365	15.4%	15.4%	0.0008
Alzheimers and other dementias	11.6%	14.7%	0.0903	13.5%	13.5%	0.0014
Transient ischemic attack	7.6%	8.7%	0.0396	8.2%	8.2%	0.0012
Myocardial infarction	7.8%	8.4%	0.0226	8.1%	8.0%	0.0014
Inpatient discharge past 30 days	33.7%	33.4%	0.0067	32.5%	32.5%	0.0013

Medications, past year unless otherwise specified						
Angiotensin converting enzyme inhibitor/receptor blocker	64.2%	60.8%	0.0706	62.0%	62.0%	0.0004
Proton-pump inhibitors	33.4%	33.2%	0.0048	33.1%	33.2%	0.0025
Loop diuretics	37.3%	37.8%	0.0097	37.7%	37.7%	0.0005
Oral corticosteroids	24.4%	24.6%	0.0061	24.3%	24.5%	0.0024
Diltiazem or verapamil	21.2%	20.6%	0.0156	20.6%	20.6%	0.0013
NSAIDs, non-selective	15.0%	13.0%	0.0564	13.7%	13.7%	0.0002
P2Y12 inhibitors and other antiplatelet drugs	20.0%	19.6%	0.0107	19.7%	19.9%	0.0030
Amiodarone	14.7%	14.6%	0.0040	14.5%	14.5%	0.0001
Home oxygen	11.2%	10.9%	0.0086	10.9%	10.9%	0.0005
Insulin	7.9%	6.2%	0.0644	6.8%	6.8%	0.0006
Dronedarone	2.8%	2.2%	0.0383	2.5%	2.5%	0.0020
Number of medications, mean	12.8	12.5	0.0472	12.6	12.6	0.0042

b. Standard dose.

	Unweighted			Weighted		
	Rivaroxaban	Apixaban	SD	Rivaroxaban	Apixaban	SD
N	175,198	271,860	.	175,198	271,860	
Demographics						
Age, years, mean (std)	74.9 (6.1)	75.5 (6.2)	0.0909	75.2 (6.2)	75.2 (6.1)	0.0014
Year anticoagulant started, mean	2,015.5	2,016.4	0.5335	2,016.0	2,016.0	0.0024
Female	44.9%	47.4%	0.0491	46.2%	46.3%	0.0007
Male	55.1%	52.6%	0.0491	53.8%	53.7%	0.0007
Race[c]						
Asian	1.3%	1.0%	0.0249	1.1%	1.1%	0.0019
Black	3.4%	3.5%	0.0076	3.5%	3.5%	0.0008
Hispanic	1.1%	0.8%	0.0254	1.0%	0.9%	0.0096
North American Native	0.3%	0.2%	0.0165	0.3%	0.2%	0.0095
Other	1.2%	1.1%	0.0123	1.1%	1.1%	0.0052
White	92.8%	93.4%	0.0230	93.1%	93.2%	0.0036
Region of residence						
West	16.0%	13.8%	0.0616	14.7%	14.7%	0.0002
Southwest	10.5%	10.4%	0.0054	10.5%	10.5%	0.0001
Midwest	22.4%	21.9%	0.0134	21.9%	21.9%	0.0012
Southeast	33.4%	37.0%	0.0753	35.7%	35.5%	0.0025
Northeast	17.7%	17.0%	0.0183	17.2%	17.3%	0.0019
Dual Medicare-Medicaid enrollment	12.6%	11.6%	0.0289	11.9%	12.0%	0.0029
Cardiologist prescribed anticoagulant	49.9%	50.0%	0.0043	50.7%	50.5%	0.0049
Medical history, past year unless otherwise specified						
CHA_2DS_2-VASc score[d], mean	3.9	4.1	0.1330	4.1	4.1	0.0024
Hypertension	88.6%	89.9%	0.0435	89.4%	89.4%	0.0008
Diabetes	33.9%	35.1%	0.0253	34.6%	34.6%	0.0006
Heart failure	24.3%	28.2%	0.0886	26.5%	26.5%	0.0005
Anemia	21.7%	24.2%	0.0584	23.2%	23.1%	0.0011
Chronic obstructive pulmonary disease	20.4%	21.8%	0.0332	21.1%	21.1%	0.0007
Cancer other than non-melanoma skin cancer	17.5%	18.3%	0.0202	17.9%	17.9%	0.0009
Bleeding at gastrointestinal or other sites	13.7%	14.8%	0.0325	14.3%	14.4%	0.0011
Chronic kidney disease, Stage 3 or unspecified	8.9%	14.1%	0.1627	12.1%	12.1%	0.0001
Percutaneous coronary intervention	10.6%	12.5%	0.0625	11.7%	11.7%	0.0002
Dysphagia/malnutrition	10.1%	11.1%	0.0337	10.7%	10.7%	0.0015
Coronary artery bypass graft	8.9%	10.4%	0.0506	9.9%	9.9%	0.0000
Fall	8.5%	9.9%	0.0506	9.3%	9.3%	0.0005
Cardioversion	9.3%	10.3%	0.0335	9.9%	10.0%	0.0009
Ischemic stroke, systemic embolism, intracranial bleeding	7.7%	9.1%	0.0489	8.6%	8.5%	0.0027
Acute kidney failure	5.5%	8.8%	0.1288	7.4%	7.5%	0.0007
Alzheimers and other dementias	5.5%	6.3%	0.0329	6.0%	6.0%	0.0001
Transient ischemic attack	5.8%	6.3%	0.0216	6.1%	6.0%	0.0016
Myocardial infarction	5.0%	6.4%	0.0594	5.8%	5.8%	0.0001
Inpatient discharge past 30 days	24.5%	27.6%	0.0698	25.5%	25.7%	0.0040

Medications past year						
Angiotensin converting enzyme inhibitor/receptor blocker	60.7%	62.0%	0.0280	61.5%	61.5%	0.0025
Proton-pump inhibitors	29.2%	30.9%	0.0381	30.3%	30.3%	0.0011
Loop diuretics	22.7%	26.2%	0.0816	24.7%	24.8%	0.0006
Oral corticosteroids	24.2%	26.0%	0.0415	25.3%	25.2%	0.0015
Diltiazem or verapamil	21.6%	21.3%	0.0072	21.3%	21.3%	0.0000
NSAIDs, non-selective	18.0%	17.35	0.0176	17.6%	17.6%	0.0003
P2Y12 inhibitors and other antiplatelet drugs	13.6%	15.6%	0.0577	14.8%	14.8%	0.0004
Amiodarone	9.8%	11.0%	0.0382	10.5%	10.5%	0.0009
Home oxygen	9.3%	10.5%	0.0375	10.0%	10.0%	0.0002
Insulin	5.6%	6.7%	0.0454	6.2%	6.3%	0.0018
Dronedarone	2.7%	2.7%	0.0016	2.7%	2.7%	0.0002
Number of medications, mean	11.5	12.0	0.0898	11.8	11.8	0.0045

eTable 9. Outcomes according to dose.

a. Reduced dose	Rivaroxaban (PY=39,199)		Apixaban (PY=61,558)		Adjusted			
					Rivaroxaban	Apixaban	*Rate Difference (95% CI)*	*Hazard Ratio (95% CI)*
	Patients w event, N	*Rate/ 1000 PY*	*Patients w event, N*	*Rate/ 1000 PY*	*Rate/ 1000 PY*	*Rate/ 1000 PY*		
Primary outcome and its components								
Major ischemic or hemorrhagic event	949	24.2	1,402	22.8	27.4	21.0	6.4 (4.1 to 8.7)	1.28 (1.16-1.40)
Ischemic	544	13.9	776	12.6	15.5	11.9	3.6 (1.9 to 5.3)	1.27 (1.13-1.44)
Ischemic stroke	519	13.2	750	12.2	14.8	11.5	3.3 (1.6 to 5.0)	1.26 (1.11-1.43)
Systemic embolism	25	0.6	26	0.4	0.7	0.4	0.3 (0.0 to 0.6)	1.67 (0.94-2.97)
Hemorrhagic	405	10.3	626	10.2	11.9	9.1	2.8 (1.3 to 4.3)	1.28 (1.11-1.47)
Hemorrhagic stroke	107	2.7	145	2.4	3.0	2.2	0.8 (0.1 to 1.5)	1.35 (1.03-1.78)
Other intracranial hemorrhage	204	5.2	344	5.6	6.1	4.9	1.3 (0.2 to 2.4)	1.24 (1.03-1.50)
Fatal extracranial bleeding	94	2.4	137	2.2	2.8	2.1	0.7 (0.0 to 1.4)	1.29 (0.97-1.73)
Secondary outcomes								
Nonfatal extracranial bleeding	2,046	52.2	1,474	23.9	57.5	22.5	35.0 (31.9 to 38.1)	2.44 (2.26-2.63)
Gastrointestinal	1,843	47.0	1,287	20.9	52.0	19.6	32.3 (29.4 to 35.3)	2.52 (2.33-2.73)
Other or unspecified	203	5.2	187	3.0	5.5	2.9	2.7 (1.7 to 3.7)	1.85 (1.48-2.32)
Total mortality	2,929	74.7	5,632	91.5	87.0	82.7	4.2 (-0.1 to 8.6)	1.02 (0.97-1.08)
Fatal ischemic or hemorrhagic event	280	7.1	426	6.9	8.5	6.2	2.3 (1.1 to 3.6)	1.35 (1.14-1.59)
Other death during followup	2,649	67.6	5,206	84.6	78.4	76.5	1.9 (-2.3 to 6.0)	1.00 (0.995-1.05)

b. Standard dose	Rivaroxaban (PY=151,954)		Apixaban (PY=221,894)		Adjusted			
					Rivaroxaban	Apixaban	*Rate Difference (95% CI)*	*Hazard Ratio (95% CI)*
	Patients w event, N	*Rate/ 1000 PY*	*Patients w event, N*	*Rate/ 1000 PY*	*Rate/1000 PY*	*Rate/1000 PY*		
Primary outcome and its components								
Major ischemic or hemorrhagic event	1,889	12.4	2,706	12.2	13.2	11.4	1.8 (1.0 to 2.6)	1.13 (1.06-1.21)
Ischemic	970	6.4	1,517	6.8	6.8	6.4	0.5 (-0.1 to 1.0)	1.05 (0.96-1.14)
Ischemic stroke	928	6.1	1,446	6.5	6.6	6.1	0.5 (-0.1 to 1.1)	1.06 (0.97-1.15)
Systemic embolism	42	0.3	71	0.3	0.3	0.3	0.0 (-0.2 to 0.1)	0.84 (0.56-1.26)
Hemorrhagic	919	6.0	1,189	5.4	6.3	5.0	1.3 (0.8 to 1.8)	1.25 (1.14-1.37)
Hemorrhagic stroke	352	2.3	370	1.7	2.4	1.5	0.8 (0.5 to 1.2)	1.53 (1.31-1.79)
Other intracranial hemorrhage	420	2.8	650	2.9	2.9	2.8	0.1 (-0.3 to 0.4)	1.02 (0.90-1.17)
Fatal extracranial bleeding	147	1.0	169	0.8	1.1	0.7	0.4 (0.2 to 0.6)	1.51 (1.19-1.91)
Secondary outcomes								
Nonfatal extracranial bleeding	4,873	32.1	4,198	18.9	35.0	17.5	17.5 (16.3 to 18.7)	1.94 (1.85-2.03)
Gastrointestinal	4,289	28.2	3,687	16.6	30.8	15.3	15.5 (14.3 to 16.6)	1.94 (1.85-2.04)
Other or unspecified	584	3.8	511	2.3	4.1	2.1	2.0 (1.6 to 2.4)	1.90 (1.67-2.16)
Total mortality	4,568	30.1	7,207	32.5	32.9	29.7	3.1 (1.9 to 4.4)	1.08 (1.04-1.12)
Fatal ischemic or hemorrhagic event	487	3.2	613	2.8	3.4	2.5	0.9 (0.5 to 1.3)	1.33 (1.17-1.51)
Other death during followup	4,081	26.9	6,594	29.7	29.4	27.2	2.2 (1.0 to 3.4)	1.06 (0.995-1.10)

eTable 10. Sensitivity analyses.

	Rivaroxaban			Apixaban			Adjusted			
	Person-years	*Patients w event, N*	*Rate/ 1000 PY*	*Person-years*	*Patients w event, N*	*Rate/ 1000 PY*	**Rivaroxaban** *Rate/ 1000 PY*	**Apixaban** *Rate/ 1000 PY*	*Rate Difference (95% CI)*	*Hazard Ratio (95% CI)*
Primary analysis										
Major ischemic or hemorrhagic event	191,153	2,838	14.8	283,452	4,108	14.5	16.1	13.4	2.7 (1.9 to 3.5)	1.18 (1.12-1.24)
Ischemic		1,514	7.9		2,293	8.1	8.6	7.6	1.1 (0.5 to 1.7)	1.12 (1.04-1.20)
Hemorrhagic		1,324	6.9		1,815	6.4	7.5	5.9	1.6 (1.1 to 2.1)	1.26 (1.16-1.36)
No cardiac valve replacement[a]										
Major ischemic or hemorrhagic event	187,619	2,759	14.7	276,515	3,951	14.3	15.9	13.3	2.7 (1.9 to 3.5)	1.18 (1.12-1.25)
Ischemic		1,469	7.8		2,201	8.0	8.5	7.4	1.1 (0.5 to 1.7)	1.12 (1.04-1.20)
Hemorrhagic		1,290	6.9		1,750	6.3	7.4	5.8	1.6 (1.1 to 2.1)	1.26 (1.16-1.36)
No CKD stage 3/unspecified[a]										
Major ischemic or hemorrhagic event	170,143	2,378	14.0	240,973	3,220	13.4	15.0	12.5	2.5 (1.7 to 3.3)	1.19 (1.12-1.26)
Ischemic		1,264	7.4		1,802	7.5	8.1	7.0	1.1 (0.5 to 1.7)	1.13 (1.04-1.22)
Hemorrhagic		1,114	6.5		1,418	5.9	7.0	5.5	1.5 (0.9 to 2.0)	1.26 (1.16-1.37)
Propensity-score trimmed[b]										
Major ischemic or hemorrhagic event	170,420	2,547	14.9	273,324	3,891	14.2	16.0	13.5	2.5 (1.7 to 3.3)	1.17 (1.11-1.23)
Ischemic		1,350	7.9		2,169	7.9	8.5	7.5	1.0 (0.4 to 1.6)	1.11 (1.03-1.19)
Hemorrhagic		1,197	7.0		1,722	6.3	7.5	5.9	1.5 (1.0 to 2.1)	1.25 (1.16-1.35)
First year of followup										
Major ischemic or hemorrhagic event	123,206	2,062	16.7	191,902	3,133	16.3	18.1	15.1	3.0 (2.0 to 4.0)	1.19 (1.12-1.26)
Ischemic		1,138	9.2		1,785	9.3	10.0	8.6	1.4 (0.6 to 2.1)	1.14 (1.05-1.24)
Hemorrhagic		924	7.5		1,348	7.0	8.1	6.5	1.6 (1.0 to 2.3)	1.25 (1.14-1.36)
Maximum 7 days off drug										
Major ischemic or hemorrhagic event	100,140	1,559	15.6	151,279	2,299	15.2	16.8	14.1	2.7 (1.6 to 3.8)	1.18 (1.10-1.26)
Ischemic		839	8.4		1,319	8.7	9.1	8.1	1.0 (0.2 to 1.8)	1.10 (1.01-1.21)
Hemorrhagic		720	7.2		980	6.5	7.7	6.0	1.7 (1.0 to 2.4)	1.28 (1.15-1.42)
Alternate definition of stroke[c]										
Major ischemic or hemorrhagic event	190,847	3,107	16.3	282,978	4,464	15.8	17.7	14.7	3.1 (2.2 to 3.9)	1.19 (1.13-1.25)
Ischemic		1,755	9.2		2,616	9.2	10.0	8.6	1.4 (0.8 to 2.0)	1.14 (1.07-1.22)
Hemorrhagic		1,352	7.1		1,848	6.5	7.7	6.0	1.6 (1.1 to 2.2)	1.26 (1.17-1.36)
Propensity-score matched[d]										
Major ischemic or hemorrhagic event	150,514	2,266	15.1	169,022	2,154	12.7	15.1	12.7	2.3 (1.5 to 3.1)	1.16 (1.10-1.23)
Ischemic		1,200	8.0		1,200	7.1	8.0	7.1	0.9 (0.3 to 1.5)	1.10 (1.01-1.19)
Hemorrhagic		1,066	7.1		954	5.6	7.1	5.6	1.4 (0.9 to 2.0)	1.25 (1.14-1.36)
All variables in model[e]										
Major ischemic or hemorrhagic event	191,153	2,838	14.8	283,452	4,108	14.5	17.1	14.5	2.6 (1.7 to 3.5)	1.18 (1.12-1.24)
Ischemic		1,514	7.9		2,293	8.1	9.0	8.1	0.9 (0.3 to 1.6)	1.11 (1.04-1.20)
Hemorrhagic		1,324	6.9		1,815	6.4	8.0	6.4	1.6 (1.1 to 2.3)	1.26 (1.16-1.36)

[a]Propensity score and IPT weights were recalculated for these subgroups of the cohort. CKD is chronic kidney disease.

[b]Analysis restricted to those for whom the propensity score was greater than or equal to the 1st percentile in the rivaroxaban group and less than or equal to the 99th percentile in the apixaban group.

[c]Identifies strokes from the principal diagnosis and all secondary diagnoses.

[d]Greedy algorithm with a caliper of .01.

[e]A proportional hazards regression with all covariates and an indicator variable for rivaroxaban in the model. Stratified according to dose. For each of the three outcomes analyzed, there were more than 10 events per variable in the model.

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