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Gastrointestinal Safety of Direct Oral Anticoagulants: A Large Population-Based Study

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BACKGROUND & AIMS: Direct oral anticoagulant (DOAC) agents increase the risk of gastrointestinal (GI) bleeding. We investigated which DOAC had the most favorable GI safety profile and compared differences among these drugs in age-related risk of GI bleeding. **METHODS:** We conducted a retrospective, propensity-matched study using administrative claims data from the OptumLabs Data Warehouse of privately insured individuals and Medicare Advantage enrollees. We created 3 propensity-matched cohorts of patients with non-valvular atrial fibrillation with incident exposure to dabigatran, rivaroxaban, or apixaban from October 1, 2010 through February 28, 2015. We compared data on rivaroxaban vs dabigatran for 31,574 patients, data on apixaban vs dabigatran for 13,084 patients, and data on apixaban vs rivaroxaban for 13,130 patients. Cox proportional hazards models, stratified by age, were used to estimate rates of total GI bleeding. **RESULTS:** Baseline characteristics were well balanced among sub-cohorts. GI bleeding occurred more frequently in patients given rivaroxaban than dabigatran (hazard ratio [HR], 1.20; 95% confidence interval [CI], 1.00−1.45). Apixaban was associated with a lower risk of GI bleeding than dabigatran (HR, 0.39; 95% CI, 0.27−0.58; $P < .001$) or rivaroxaban (HR, 0.33; 95% CI, 0.22−0.49; $P < .001$). Rates of events for all DOACs increased among patients 75 years or older. Apixaban had a lower risk of association with GI bleeding in the very elderly than dabigatran (HR, 0.45; 95% CI, 0.29−0.71) or rivaroxaban (HR, 0.39; 95% CI, 0.25−0.61). Median times to GI bleeding were <90 days for apixaban and rivaroxaban and <120 days for dabigatran. **CONCLUSIONS:** In a population-based study of patients receiving DOAC agents, we found apixaban had the most favorable GI safety profile and rivaroxaban the least favorable profile. GI bleeding events among patient aged 75 years or older taking DOACs increased with age; the risk was greatest among persons 75 years. Apixaban had the most favorable GI safety profile among all age groups.

Keywords: Gastrointestinal Hemorrhage; Comparative Safety; Anticoagulant; Atrial Fibrillation.

Direct oral anticoagulant (DOAC) agents, also known as non−vitamin K antagonist oral anticoagulants,[1] including dabigatran, rivaroxaban, apixaban, and edoxaban, are at least equivalent to warfarin for the prevention of stroke and systemic embolism in patients with non−valvular atrial fibrillation (AF). With their convenient, fixed-dose and no requirement for monitoring, DOACs have gained broad acceptance and are increasingly the preferred anticoagulant for patients with AF. Recent data suggest that DOACs account for approximately 62% of new anticoagulant prescriptions.[2] The safety of DOACs compared to warfarin in the context of gastrointestinal (GI) bleeding has been studied extensively. Randomized controlled trials, systematic reviews, and observational studies have demonstrated a 25%–30% increased risk of GI bleeding with DOACs when compared to warfarin.[3–5] However, relatively little is known about the comparative risk of GI bleeding across the Food and Drug Administration (FDA)-approved DOACs.

The absence of head-to-head comparative safety of DOACs prevents comparison of GI adverse events among existing choices. This information is critical when discussing treatment choices with patients, especially those that might be at higher risk for GI bleeding, regarding the risk−benefit of their anticoagulation options. Indirect comparisons using clinical trial data are of limited utility as the pivotal trials that were used for FDA approval of each of the DOACs are different with regard to study design, populations, comparator group, and outcomes. Furthermore, the idealized settings of a clinical trial may not adequately reflect the real-world safety profile of DOACs as they are prescribed in routine clinical practice. The necessity for such head-to-head comparison studies was recently highlighted as a key gap to clarify which anticoagulant would be the best choice for AF patients.[6]

Examination of comparative effectiveness and safety of DOAC is achievable using large-scale observational studies and has been assessed previously (in comparison to warfarin) by our group and others.[7–11] We have

Abbreviations used in this paper: **AF, atrial fibrillation; ARR, absolute risk reduction; CI, confidence interval; DOAC, direct oral anticoagulant; GI, gastrointestinal; HR, hazard ratio; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; IQR, interquartile range; NNH, number needed to harm.**

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previously examined the cardiac effectiveness of DOACs to each other, as published elsewhere.[12] Our aim was to expand the literature by comparing DOACs in a head-to-head fashion to assess the GI safety profile specifically. In addition, we examined the risk of DOACs among the very elderly (those patients 75 years and older), which is the most common, high-risk group for pharmacologically induced GI bleeding.

Methods

Data Source

The data for this analysis came from OptumLabs Data Warehouse, which includes a geographically diverse adult population covered through both commercial insurance and Medicare Advantage in the United States.[3] Inpatient, outpatient, and pharmacy claims data are available on >120 million enrollees. Medical claims include International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes, ICD-9 procedure codes, Current Procedural Terminology, Version 4 procedure codes, Healthcare Common Procedure Coding System procedure codes, site of service codes, and provider specialty codes.

Patient Identification

Adult non-valvular AF patients, 18 years of age or older, were identified by their index prescription of dabigatran, rivaroxaban, or apixaban between October 1, 2010 and February 28, 2015. The date of the first filled prescription was considered the index date and used to assign patients to a subcohort of exposure. During the period of observation, edoxaban had a very limited market share, and was excluded due to small sample size.

We excluded patients with any prior dispensed prescription for a DOAC during the 12 months before index date and those who lacked evidence of 12 months continuous enrollment in the medical and pharmacy plan, which was defined as the baseline period. To be included, patients were required to have at least 1 inpatient or outpatient AF diagnostic code (ICD-9-CM code 427.31) at baseline. Patients with valvular heart disease, chronic hemodialysis, or peritoneal dialysis and kidney transplant were excluded.

Exposures and Primary Outcome

The exposures of interest were dabigatran, rivaroxaban, and apixaban. Exposure was considered continuous as defined from index date (t0) to occurrence of outcome, disenrollment from the health care plan, switch to another anticoagulant, or treatment termination as defined by the absence of a new prescription by the end of the 30-day period from the last identified index medication fill. The last date of follow-up was February 28, 2015.

The primary outcome of interest was GI bleed, as defined previously by Lewis et al.[13] Each event was identified using inpatient hospital claims for relevant primary and secondary discharge diagnoses. Time to event and the follow-up time to GI bleed was assessed in days and expressed as a median with interquartile range (IQR). We also calculated the number needed to harm (NNH) on the annualized rate of GI bleeding. We have previously examined the effectiveness of DOACs in the prevention of ischemic or hemorrhagic stroke or systemic embolism.[12]

Variables of Interest

Baseline characteristics (age, sex, and race), geographic region, comorbidities, CHA_2DS_2-VASc score, HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly) score and pharmacologic risk factors for GI bleeding were assessed as potential confounding variables. Age was stratified into 3 categories (18–64 years, 65–74 years, and 75 years and older). Pharmacologic factors assessed included concomitant prescription of antiplatelet agents, nonsteroidal anti-inflammatory drugs, and anti-ulcer agents. We identified whether patients had prior experience with warfarin before index DOAC prescription. Comorbid conditions were identified by ICD-9-CM codes in the primary or secondary position on any claim during the baseline period and included congestive heart failure, hypertension, diabetes, history of prior GI bleed or cardioembolic phenomenon (stroke, transient ischemic attack, systemic embolism), vascular disease, and renal disease. Overall comorbidity burden was assessed using the Charlson−Deyo comorbidity index.[14]

Statistical Analysis

To examine the effect of dabigatran, rivaroxaban, and apixaban on the risk of GI bleeding, we created 3 matched cohorts (rivaroxaban vs dabigatran, dabigatran vs apixaban, rivaroxaban vs apixaban) using 1:1 propensity score matching without replacement and with a caliper of 0.01. Matching variables included baseline sociodemographic variables, comorbidities, and prior warfarin use. The standardized difference was used to assess for imbalance between baseline characteristics after matching. A standardized difference of <10% was considered acceptable.[15] Cox Proportional Hazards models were used to compare the GI bleeding risk of the comparator DOACs in each of the 3 propensity score matched cohorts, with robust sandwich estimates to account for clustering within cohorts.[16] The proportional hazard assumption was tested by examination of Schoenfeld residuals[17] and was valid for all outcomes. The hazard ratio (HR) and 95% confidence intervals (CIs) for each outcome of interest was calculated. The analytic data set was created and manipulated using SAS, version 9.3 (SAS Institute Inc, Cary, North Carolina) and STATA, version 13.1 (Stata Corp, College Station, Texas).

Sensitivity Analyses

Sensitivity analyses were conducted to examine for bias associated with secular trends in DOAC availability (dabigatran was the first to market and apixaban was the last to market). We performed Cox regression limiting our cohort to those who had an index date between January 1, 2013 and February 28, 2015, the time period corresponding to availability of all DOACs of interest. Finally, we censored patients at 6 months to minimize potential impact of variable follow-up associated with each drug.

Results

Baseline Characteristics

There were 372,380 continuously enrolled patients who filled prescriptions for DOACs in the period of observation (October 1, 2010 to February 28, 2015) of which 182,896 had AF at baseline. After exclusion of patients with valvular heart disease, dialysis, kidney transplant, or end-stage renal disease (n = 180,328) we were left with a source population of 43,303 patients (6576 apixaban, 17,426 dabigatran, and 19,301 rivaroxaban), from which to create the propensity score matched sub-cohorts for comparison (Figure 1). After matching, 6542 patients were included in the apixaban vs dabigatran cohort; 6565 patients in the apixaban vs rivaroxaban cohort; and, 15,787 patients in the rivaroxaban vs dabigatran cohort.

Tables 1, 2, and 3 highlight the baseline characteristics of each cohort before and after matching. After propensity score matching, standardized differences of all baseline characteristics were <10%, demonstrating similarity of comparators with regard to important sociodemographic, comorbidity, and pharmacologic risk factors. Among all subcohorts, the mean (SD) age ranged from 69.2 (11.6) years to 72.2 (11.1) years, mean CHA_2DS_2-VASc score was between 3.2 and 4.0, and mean HAS-BLED score was between 2.2 and 2.4. Between 29% and 39% of patients had been previously been treated with warfarin before index DOAC prescription. The use of proton pump inhibitor (PPI) was similar for all cohorts (approximately 20%) and the standardized differences between matched groups ranged from 1% to 5%, well below the 10% threshold for meaningful difference.

Risk of Gastrointestinal Bleeding With Rivaroxaban vs Dabigatran

In the propensity score matched cohort of rivaroxaban and dabigatran users (n = 15,787), the median time of follow-up among patients with an index prescription for rivaroxaban was 113 (IQR, 30−271) days and 120 (IQR, 30−340) days for dabigatran. There were 222 GI bleed events in rivaroxaban patients, occurring with a median time to event of 75 (IQR, 27−164) days. Among patients prescribed dabigatran, 215 GI bleed events occurred with a median time to event of 119 (IQR, 28−259) days.

Table 4 shows the overall incidence rate per 100 person-years and the age-stratified analysis of GI bleed risk. The overall incidence of rivaroxaban GI bleed events was 2.74/100 patient-years and 2.02/100 patient-years with dabigatran. A 20% increase in GI bleeding events was observed with rivaroxaban when compared to dabigatran (HR, 1.20; 95% CI, 1.00−1.45). Patients aged 18–64 years on rivaroxaban had a 2-fold increase in GI bleeding events when compared to patients of a similar age prescribed dabigatran. However, the increased risk of a GI bleed for

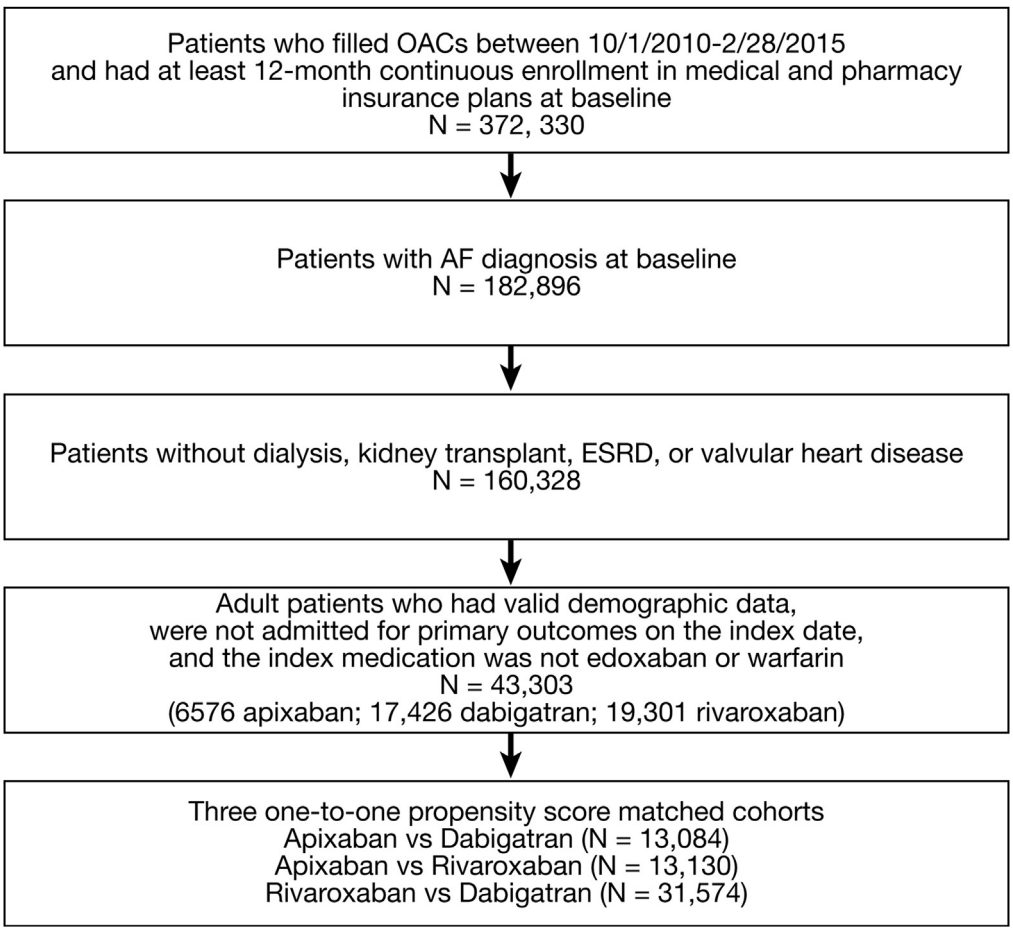

Figure 1. Study flow diagram.

Table 1. Baseline Characteristics of Rivaroxaban and Dabigatran Users

Characteristic	Before propensity score match			After propensity score match		
	Rivaroxaban (n = 19,301)	Dabigatran (n = 17,426)	Standardized difference (%)	Rivaroxaban (n = 15,787)	Dabigatran (n = 15,787)	Standardized difference (%)
Age group, *y*						
Mean (SD)	70.6 (11.4)	68.8 (11.4)	15.7	69.2 (11.6)	69.7 (11.2)	−4.2
18−64, %	28.5	35.3	−14.7	33.6	31.9	3.6
65−74, %	31.4	30.3	2.3	31.2	31.0	0.3
≥75, %	40.2	34.4	11.9	35.2	37.0	−3.9
Male, %	57.1	60.5	−6.8	59.7	58.9	1.7
Race, %						
Asian	2.5	2.6	−0.5	2.6	2.6	0.0
Black	9.1	8.9	1.0	9.1	9.1	0.0
Hispanic	5.0	4.5	2.5	4.7	4.7	0.1
Unknown	4.7	4.6	0.1	4.6	4.6	0.1
White	78.6	79.4	−1.9	78.9	78.9	−0.1
CHA_2DS_2-VASc						
Mean (SD)	3.8 (1.9)	3.6 (1.9)	11.1	3.6 (1.9)	3.7 (1.9)	−2.0
0−1, %	12.4	15.0	−7.6	14.5	14.0	1.3
2−3, %	31.8	34.0	−4.8	33.5	32.8	1.3
≥4, %	55.8	51.0	9.8	52.1	53.2	−2.2
HAS-BLED						
Mean (SD)	2.4 (1.2)	2.2 (1.2)	14.3	2.2 (1.2)	2.3 (1.2)	−2.3
≥3, %	42.9	37.3	11.5	38.3	39.5	−2.5
Charlson−Deyo Index						
Mean (SD)	2.6 (2.6)	2.3 (2.3)	12.5	2.4 (2.5)	2.4 (2.3)	1.8
0−1, %	41.7	45.8	−8.3	44.9	44.5	0.9
2−3, %	30.0	30.1	−0.2	30.1	30.1	0.1
≥4, %	28.3	24.1	9.6	25.0	25.4	−1.1
Heart failure, %	28.9	26.9	4.4	27.2	27.5	−0.7
Hypertension, %	84.7	84.4	0.7	84.3	84.4	−0.1
Diabetes, %	34.4	34.1	0.8	34.4	34.1	0.6
Previous stroke/TIA/SE, %	14.5	13.9	1.8	14.2	14.0	0.4
Vascular disease, %	47.7	46.3	2.6	46.8	46.6	0.6
Renal disease, %	16.6	12.7	11.0	13.3	13.7	−1.1
History of bleeding, %	32.8	29.8	6.5	30.2	30.8	−1.3
Antiplatelet or NSAID, %	12.1	10.7	4.3	10.8	11.1	−1.0
Anti-ulcer agents, %	21.3	18.6	6.8	19.5	21.4	−4.7
Warfarin experienced, %	33.2	42.9	−20.1	39.3	37.7	3.3

NOTE. Variables in the CHA_2DS_2-VASc score: CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥ 75, diabetes mellitus, stroke, TIA or PE, vascular disease, age 65-74 and sex.
HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly; NSAID, nonsteroidal anti−inflammatory drug; SE, systemic embolism; TIA, transient ischemic attack.

patients on rivaroxaban between the ages of 65 and 74 years was only 44% greater compared to dabigatran. The risk of GI bleed for patients older than the age of 75 years was similar, regardless of exposure group.

Risk of Gastrointestinal Bleeding With Apixaban vs Dabigatran

In the propensity score matched cohort of apixaban and dabigatran users (n = 13,084), median time of follow-up with an index prescription for apixaban was 89 (IQR, 30−194) days and 120 (IQR, 30−338) days in dabigatran users. There were 33 bleeding events with apixaban with a median time to event of 51 (IQR, 30−126) days. Among dabigatran users, 121 GI bleeding events occurred, with a median time to event of 104 (IQR, 33−252) days.

Table 5 shows the incidence rates and associated HRs for this comparison. The incidence of GI bleeds was 1.38/100 patient-years with apixaban vs 2.73/100 patient-years with dabigatran. A 61% reduction in events was observed with apixaban when compared to dabigatran (HR, 0.39; 95% CI, 0.27−0.58). With both agents, the incidence rate of GI bleed increased with advancing age. Age-stratified analysis demonstrated fewer events with apixaban when compared to dabigatran across all age groups, including age 75 years and older (HR, 0.45; 95% CI, 0.29−0.71).

Risk of Gastrointestinal Bleeding With Apixaban vs Rivaroxaban

In this propensity score matched sub-cohort (n = 6565 patients), the median follow-up time for apixaban was 89

Table 2. Baseline Characteristics of Apixaban and Dabigatran Users

Characteristic	Before propensity score match			After propensity score match		
	Apixaban (n = 6576)	Dabigatran (n = 17,426)	Standardized difference (%)	Apixaban (n = 6542)	Dabigatran (n = 6542)	Standardized difference (%)
Age group, *y*						
Mean (SD)	72.3 (11.1)	68.8 (11.4)	30.7	72.2 (11.1)	72.1 (10.5)	1.0
18−64, %	24.0	35.3	−25.0	24.1	24.5	−1.0
65−74, %	30.3	30.3	0.0	30.4	30.0	0.9
≥75, %	45.8	34.4	23.3	45.5	45.4	0.1
Male, %	54.0	60.5	−13.2	54.1	53.9	0.4
Race, %						
Asian	2.5	2.6	−0.8	2.5	2.8	−2.0
Black	9.1	8.9	0.7	9.0	8.5	1.8
Hispanic	5.1	4.5	2.8	5.1	5.2	−0.5
Unknown	4.8	4.6	0.6	4.8	4.5	1.6
White	78.6	79.4	−2.0	78.6	79.0	−1.0
CHA_2DS_2−VASc						
Mean (SD)	4.0 (1.9)	3.6 (1.9)	23.5	4.0 (1.9)	4.0 (1.9)	1.2
0−1, %	9.1	15.0	−18.1	9.2	9.4	−0.9
2−3, %	29.9	34.0	−9.0	30.0	30.7	−1.4
≥4, %	61.0	51.0	20.3	60.9	59.9	1.9
HAS-BLED						
Mean (SD)	2.4 (1.2)	2.2 (1.2)	21.3	2.4 (1.2)	2.4 (1.2)	2.2
≥3, %	45.0	37.3	15.7	44.7	43.9	1.6
Charlson−Deyo Index						
Mean (SD)	2.7 (2.5)	2.3 (2.3)	15.5	2.7 (2.5)	2.6 (2.5)	2.3
0−1, %	39.0	45.8	−13.8	39.2	40.4	−2.4
2−3, %	31.8	30.1	3.6	31.8	30.6	2.6
≥4, %	29.2	24.1	11.6	29.0	29.0	−0.1
Heart failure, %	31.5	26.9	10.1	31.3	31.0	0.7
Hypertension, %	86.5	84.4	6.0	86.5	85.8	1.9
Diabetes, %	35.5	34.1	3.0	35.4	35.2	0.4
Previous stroke/TIA/SE, %	15.5	13.9	4.4	15.4	15.7	−0.8
Vascular disease, %	50.1	46.3	7.5	50.0	48.8	2.4
Renal disease, %	19.2	12.7	17.9	18.8	18.3	1.3
History of bleeding, %	31.5	29.8	3.7	31.4	30.2	2.6
Antiplatelet or NSAID, %	12.3	10.7	5.1	12.2	11.9	1.0
Anti-ulcer agents, %	22.1	18.6	8.7	22.5	20.9	3.9
Warfarin experienced, %	29.4	42.9	−28.4	29.6	29.0	1.3

NOTE. Variables in the CHA_2DS_2-VASc score: CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥ 75, diabetes mellitus, stroke, TIA or PE, vascular disease, age 65-74 and sex.
HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly; NSAID, nonsteroidal anti−inflammatory drug; SE, systemic embolism; TIA, transient ischemic attack.

(IQR, 30−194) days and 106 (IQR, 30−260) days for rivaroxaban. There were 116 bleeding events in the rivaroxaban group occurring with a median time to event of 67 (IQR, 25−187) days. In the apixaban group, there were 32 events with a median time to event of 60.5 (IQR, 28.5−132) days.

As shown in Table 6, the overall incidence rate of GI bleed events with apixaban was 1.34/100 patient-years, and with rivaroxaban it was 3.54/100 patient-years. The incidence rate of GI bleeding events increased with advancing age in both DOAC exposure groups. Overall, apixaban was 66% safer (HR, 0.33; 95% CI, 0.22−0.49) than rivaroxaban. Across elderly age categories (65–74 years and 75 years and older) apixaban had fewer GI bleeds than rivaroxaban. Apixaban was 82% safer among patients 65–74 years (HR, 0.18; 95% CI, 0.07−0.47) and 61% safer among patients 75 years and older (HR, 0.39; 95% CI, 0.25−0.61), when compared to rivaroxaban.

Calculation of the absolute risk reduction (ARR) and the NNH based on the annualized rate of GI bleeding (Supplementary Table 1) demonstrated the more favorable GI safety profile of apixaban when compared to rivaroxaban (ARR = −2.20; 95% CI, −3.00 to −1.40; NNH = 45) or dabigatran (ARR = −1.35; 95% CI, −2.03 to −0.67; NNH = 74). The most pronounced ARR in GI bleeding was seen when apixaban was compared to rivaroxaban, highlighting the least favorable GI safety profile of rivaroxaban.

Sensitivity Analysis

Sensitivity analysis revealed similar results to those from the main analyses. There were no observed differences

Table 3. Baseline Characteristics of Apixaban and Rivaroxaban Users

Characteristic	Before propensity score match			After propensity score match		
	Apixaban (n = 6576)	Rivaroxaban (n = 19,301)	Standardized difference (%)	Apixaban (n = 6565)	Rivaroxaban (n = 6565)	Standardized difference (%)
Age group, *y*						
Mean (SD)	72.3 (11.1)	70.6 (11.4)	14.8	72.3 (11.1)	72.1 (11.2)	1.2
18−64, %	24.0	28.5	−10.3	24.0	24.8	−1.8
65−74, %	30.3	31.4	−2.4	30.3	29.7	1.3
≥75, %	45.8	40.2	11.3	45.7	45.5	0.3
Male, %	54.0	57.1	−6.3	54.0	54.4	−0.8
Race, %						
Asian	2.5	2.5	−0.3	2.5	2.3	0.9
Black	9.1	9.1	−0.3	9.1	8.8	0.8
Hispanic	5.1	5.0	0.3	5.1	5.0	0.3
Unknown	4.8	4.7	0.5	4.8	4.5	1.2
White	78.6	78.6	−0.1	78.6	79.3	−1.7
CHA_2DS_2−VASc						
Mean (SD)	4.0 (1.9)	3.8 (1.9)	12.3	4.0 (1.9)	4.0 (1.9)	1.3
0−1, %	9.1	12.4	−10.5	9.1	9.7	−2.1
2−3, %	29.9	31.8	−4.1	29.9	30.1	−0.3
≥4, %	61.0	55.8	10.4	61.0	60.2	1.5
HAS-BLED						
Mean (SD)	2.4 (1.2)	2.4 (1.2)	6.8	2.4 (1.2)	2.4 (1.2)	1.8
≥3, %	45.0	42.9	4.2	44.9	43.7	2.5
Charlson−Deyo Index						
Mean (SD)	2.7 (2.5)	2.6 (2.6)	2.6	2.7 (2.5)	2.7 (2.6)	−0.1
0−1, %	39.0	41.7	−5.4	39.1	40.1	−2.1
2−3, %	31.8	30.0	3.8	31.7	31.0	1.6
≥4, %	29.2	28.3	2.0	29.2	28.9	0.6
Heart failure, %	31.5	28.9	5.7	31.4	31.7	−0.7
Hypertension, %	86.5	84.7	5.2	86.5	86.3	0.5
Diabetes, %	35.5	34.4	2.2	35.5	35.0	0.9
Previous stroke/TIA/SE, %	15.5	14.5	2.7	15.4	15.6	−0.4
Vascular disease, %	50.1	47.7	4.9	50.0	48.8	2.3
Renal disease, %	19.2	16.6	6.9	19.1	19.0	0.4
History of bleeding, %	31.5	32.8	−2.8	31.5	31.0	1.1
Antiplatelet or NSAID, %	12.3	12.1	0.7	12.3	11.7	1.6
Anti-ulcer agents, %	22.1	21.3	−1.9	22.5	22.2	0.7
Warfarin experienced, %	29.4	33.2	−8.2	29.5	29.3	0.5

NOTE. Variables in the CHA_2DS_2-VASc score: CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥ 75, diabetes mellitus, stroke, TIA or PE, vascular disease, age 65-74 and sex.
HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly; NSAID, nonsteroidal anti−inflammatory drug; SE, systemic embolism; TIA, transient ischemic attack.

in outcomes when the study population was limited to patients with index dates for DOAC initiation between January 1, 2013 and February 28, 2015. This confirmed there were no unmeasured secular prescription trends biasing our study results (data not shown).

Discussion

This study directly compared the comparative risk of GI bleeding for each of the 3 DOACs (dabigatran, rivaroxaban, and apixaban) frequently used for the treatment of nonvalvular AF patients. Our use of a large administrative claims database of commercially insured US adult patients and enrollees in Medicare Advantage permitted the direct comparison between multiple DOACs using 1:1 propensity score matched sub-cohorts and Cox regression. We showed that there were significant differences in the risk of GI bleeding across the 3 DOACs. Apixaban had the most favorable GI bleeding profile and rivaroxaban had the least favorable GI safety profile. The clarification of age-related increase in GI bleeding among all DOACs is particularly important. Prior observational studies of dabigatran and rivaroxaban compared to warfarin[3,18,19] have demonstrated a trend toward age-related risk of DOAC bleeding. These studies suggested that in the very elderly (75 years and older), warfarin may be a safer choice. Two subsequent meta-analyses of observational and clinical trial data[20,21] comparing dabigatran or rivaroxaban to warfarin support elderly age as a DOAC-related GI bleeding risk. However, these studies are all indirect comparisons of DOAC risk, as they compare DOAC to

Table 4. Stratified Analysis in Propensity Score Matched Rivaroxaban vs Dabigatran Users

	Rivaroxaban (n = 15,787)		Dabigatran (n = 15,787)		Rivaroxaban vs dabigatran (n = 31,574)	
Variable	Events, n	IR	Events, n	IR	HR (95% CI)	*P* for interaction
Overall	222	2.74	215	2.02	1.20 (1.00–1.45)	
Age						
18–64 y	26	1.05	14	0.46	2.03* (1.06–3.90)	.10
65–74 y	66	2.54	54	1.56	1.44* (1.00–2.06)	
≥75 y	130	4.29	147	3.54	1.06 (0.84–1.34)	

NOTE. *P* value in the table is for interaction; *$P < .05$.
IR, incidence rate per 100 person-years.

warfarin. Our study extends the literature by direct comparison of DOACs confirming DOAC-related GI bleeding increases with advancing age. With our direct comparison of DOACs we are able to further clarify the magnitude of age-related GI bleeding risk differs by specific DOAC agent. Of all agents examined, apixaban appears to be the safest for patients older than 75 years. Nonetheless, the risk of GI bleeds with apixaban, or any of the examined DOACs, is not inconsequential in this age group and is significantly higher in magnitude compared to the risk in younger patients.

Strengths and Weaknesses

Our study is unique and distinguished by its ability to directly compare multiple DOACs, including more than 6000 patients prescribed apixaban with regard to an important and common safety outcome. We are aware of no such other head-to-head comparison in either clinical trials or observational studies. Furthermore, we assess multiple DOAC risk and benefit over a wide range of ages in a broadly representative cohort of adult Americans. The latter would be impossible using a Medicare or Veterans Affairs cohort. The observational nature of our data also limits ability to draw causal inference regarding GI bleeding risk and is susceptible to variation in coding and billing. Nonetheless, these methods have been used extensively and validated previously. The propensity score matched sub-cohorts were statistically similar, but we cannot completely exclude the potential for unmeasured residual confounding. Reliance on pharmacy claims data prevents confirmation of adherence to medication instructions and assurance that the medication was taken by the patient. The decision to study an incident cohort of DOAC users limits generalizability to a prevalent cohort. However, we did account for prior exposure to warfarin in all incident users of DOACs. In the United States, a 110-mg dose of dabigatran is not approved, as it is in Europe. We are unable to assess the GI bleeding rates of patients who were prescribed a dose other than 150 mg dabigatran twice a day. In addition, there was differential follow-up time across the 3 agents due to differences in FDA approval dates. However, sensitivity analyses comparing these agents after the approval of apixaban did not change the interpretation of the results. Finally, we were not able to capture the potential modulating effect of over-the-counter aspirin, nonsteroidal anti-inflammatory drugs or PPI use. However, our data do demonstrate no significant difference in rates of prescribed nonsteroidal anti-inflammatory drugs, aspirin, and PPI, and we do not believe that there would be a differential rate of over-the-counter use of these agents among the propensity score matched sub-cohorts that would substantially impact our estimates of bleeding risk.

Interpretation of Findings

Previously published indirect comparisons of dabigatran to rivaroxaban have suggested equivalent bleeding risk between rivaroxaban and dabigatran 150 mg,[22,23] while other studies suggest increased major bleeding with rivaroxaban when compared with dabigatran.[7,8] We too demonstrate a 20% increase in GI bleeding events with rivaroxaban when compared to dabigatran overall. However, this difference in risk is among

Table 5. Stratified Analysis in Propensity Score Matched Apixaban vs Dabigatran Users

	Apixaban (n = 6542)		Dabigatran (n = 6542)		Apixaban vs dabigatran (n = 13,084)	
Variable	Events, n	IR	Events, n	IR	HR (95% CI)	*P* for interaction
Overall	33	1.38	121	2.73	0.39*** (0.27–0.58)	
Age						
18–64 y	2	0.34	7	0.73	0.38 (0.08–1.84)	.54
65–74 y	5	0.69	29	2.12	0.25** (0.10–0.65)	
≥75 y	26	2.43	85	4.06	0.45*** (0.29–0.71)	

NOTE. *P* value in the table is for interaction; **$P < .01$; ***$P < .001$ indicates significance for the HR.
IR, incidence rate per 100 person-years.

Table 6. Stratified Analysis in Propensity Score–Matched Apixaban vs Rivaroxaban Users

	Apixaban (n = 6565)		Rivaroxaban (n = 6565)		Apixaban vs rivaroxaban (n = 13,130)	
Variable	Events, n	IR	Events, n	IR	HR (95% CI)	*P* for interaction
Overall	32	1.34	116	3.54	0.33*** (0.22–0.49)	
Age						
18–64 y	2	0.34	6	0.81	0.38 (0.08–1.89)	.36
65–74 y	5	0.69	32	3.24	0.18*** (0.07–0.47)	
≥75 y	25	2.32	78	5.05	0.39*** (0.25–0.61)	

NOTE. *P* value in the table is for interaction; ***$P < .001$ indicates significance for the HR.
IR, incidence rate per 100 person-years.

those under the age of 75 years. There is no difference in risk of bleeding across these agents among those older than the age of 75 years. The heterogeneity of a real-world population would not be possible to achieve in clinical trials or prior observational studies[7,8,10,11] which included few young patients.

Apixaban has the lowest risk of GI bleeding compared to both dabigatran and rivaroxaban across all age groups. These results are consistent with those seen in network meta-analyses, which suggest that apixaban has lower risk of major bleeding compared to dabigatran and rivaroxaban.[24,25] However, none of these studies assessed the comparative risk of GI bleeding. These initial results assessing the real-world safety would suggest that apixaban may be the safest anticoagulant from the GI bleeding perspective, especially among the elderly.

Implications for Health Care Professionals and Patients

GI bleeding is a significant source of morbidity among patients initiating anticoagulation and is one of the key issues to consider when assessing the risk–benefit tradeoffs. This is especially important among the elderly, as GI bleeding often has a poor prognosis and can significantly affect quality of life. As DOACs become more commonly prescribed among patients with AF, assessing the risk of GI bleeding becomes more critical. To date, there has been very limited information to guide clinicians when comparing the DOACs in the context of risk. In this study we find that apixaban may be the preferred agent when GI bleeding is an important consideration in guiding treatment decisions. The magnitude of ARR associated with apixaban vs rivaroxaban or dabigatran is reflected in the NNH. Very few patients would need to be treated with rivaroxaban (45 patients) or dabigatran (74 patients), as opposed to apixaban, to incur 1 additional GI bleeding event. This is true across all age groups, but is especially important among those older than the age of 75 years, where the risk of GI bleeding is generally much greater. Time to event analyses revealed that among all DOACs, the first GI bleeding event occurred within the first 120 days of exposure. Median time to first GI bleed event was shortest (<90 days) with apixaban and rivaroxaban, and slightly longer with dabigatran (<120 days). Confirmation of our results by other investigators will help guide clinical decision-making when individualizing treatment preferences based on patient indication, age, and preference for anticoagulation.

Our study is one of the first to evaluate the comparative GI safety across DOACs and provides evidence to facilitate risk–benefit consideration by patients and providers. These data highlight GI safety concerns of DOAC use among older individuals, given the risk of bleeding across all DOACs. However, among DOACs, apixaban appears to have the fewest GI adverse events, even among the oldest segment of exposed patients (75 years and older).

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2016.12.018.

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Drafting of the manuscript: Drs Abraham, Shah, and Ms Sangaralingham. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: Dr Yao and Ms Sangaralingham. Study supervision: Drs Abraham and Shah.

Conflicts of interest
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Supplementary Table 1. Absolute Risk Reduction and Number Needed to Harm

No. of GI bleed events per 100 patient-years				No. of GI bleed events per 100 patient-years				No. of GI bleed events per 100 patient-years			
Rivaroxaban	Dabigatran	ARR (95% CI)	NNH	Apixaban	Dabigatran	ARR (95% CI)	NNH	Apixaban	Rivaroxaban	ARR (95% CI)	NNH
2.74	2.02	0.72*** (0.27 to 1.17)	139	1.38	2.73	−1.35*** (−2.0 to −0.67)	74	1.34	3.54	−2.20*** (−3.00 to −1.40)	45

***$P < .001$.