Comparing Major Bleeding Risk in Outpatients With Atrial Fibrillation or Flutter by Oral Anticoagulant Type (from the National Cardiovascular Disease Registry's Practice Innovation and Clinical Excellence Registry)

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Direct oral anticoagulants (DOACs) have a favorable bleeding risk profile in patients with atrial fibrillation (AF). However, the safety of individual DOACs relative to warfarin for specific bleeding outcomes is less certain. We identified 423,450 patients with AF between 2013 to 2015 in the NCDR PINNACLE national ambulatory registry matched to the Centers for Medicare and Medicaid Services database. Outcomes included time to first major bleed, intracranial hemorrhage (ICH), major gastrointestinal bleed (GIB), or other major bleed. We estimated the association of OAC with bleeding using Cox proportional hazard models. The median duration of follow-up was 1.4 years. OACs were used in 64% of AF patients (66% warfarin, 15% rivaroxaban, 12% dabigatran, and 7% apixaban). A major bleeding event occurred in 6.9% of patients. Compared with warfarin users, fewer patients experienced ICH with the use of rivaroxaban (HR 0.73; 95% CI 0.64 to 0.84), dabigatran (HR 0.56; 95% CI 0.48 to 0.65), and apixaban (HR 0.70; 95% CI 0.55 to 0.90). The risk of major GIB was higher in rivaroxaban users (HR 1.20; 95% CI 1.12 to 1.27), and lower in dabigatran (HR 0.88; 95% CI 0.82 to 0.95) and apixaban (HR 0.84; 95% CI 0.74 to 0.95) users. For any DOAC versus warfarin, age (≥75 or <75 years) interacted with major bleeding (HR 0.93 vs 0.78; p <0.001), GIB (HR 1.10 vs 0.82; p <0.001), and other major bleeding (HR 0.93 vs 0.80; p <0.001). In conclusion, our results suggest that the safety of DOACs is superior to warfarin in AF patients, except with rivaroxaban and GIB. Age ≥75 years attenuated the relative safety benefits of DOACs. **(Am J Cardiol 2020;125:1500−1507)**

Direct oral anticoagulants (DOACs) have emerged as cost-effective[1,2] and efficacious[3−5] alternatives to warfarin for cardioembolic prophylaxis in patients with atrial fibrillation or flutter (AF). Practice patterns across the United States reflect a growing adoption of DOACs in place of warfarin.[6] In clinical practice, the benefits of anticoagulation are counterbalanced against the potential harms of bleeding and DOACs are recommended over warfarin in current AF guidelines.[7] Clinical trial evidence has demonstrated differences in major bleeding rates with DOACs relative to warfarin, with lower intracranial hemorrhage (ICH) rates in each DOAC[8] but higher gastrointestinal bleeding (GIB) rates with dabigatran and rivaroxaban.[9] The purpose of this study was to examine the bleeding risk of each oral anticoagulant (OAC) in a large and diverse United States real-world cohort.

Methods

We examined the bleeding rates across OAC type in a national cohort of patients enrolled in American College of Cardiology's National Cardiovascular Disease Registry's Practice Innovation and Clinical Excellence (PINNACLE) registry. The PINNACLE registry is an office-based US outpatient quality improvement registry of patients with cardiovascular disease from academic and private practices that has been enrolling patients since 2008. Details of the registry have been published previously.[10] In 2018, patients enrolled in the PINNACLE database were linked to the Centers for Medicare & Medicaid Services (CMS) database. Data were analyzed from 2013 through 2014, as DOAC capture in PINNACLE began in January 2013.

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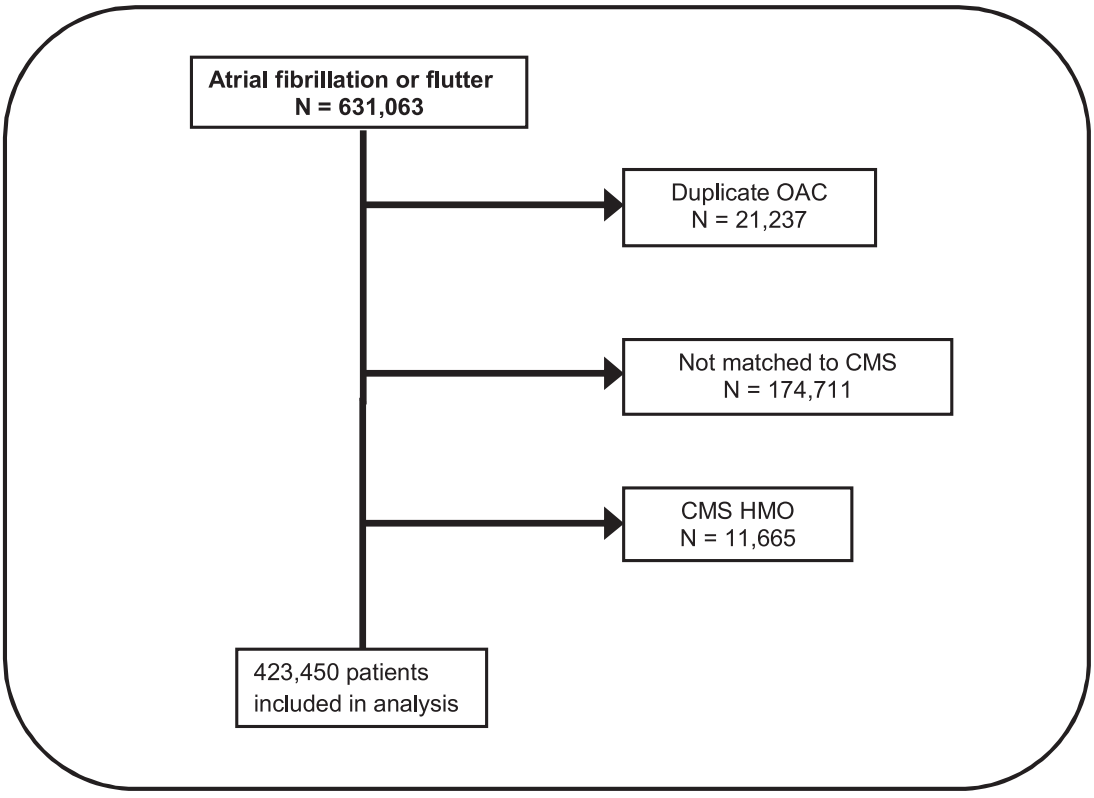

Figure 1. Flow diagram of patients from the PINNACLE registry included for analysis. CMS = centers for medicare and medicaid service; HMO = health maintenance organization; OAC = oral anticoagulant (warfarin, rivaroxaban, dabigatran, or apixaban).

Patient data were collected using data abstraction of the electronic medical record to capture the pertinent clinical information for PINNACLE. These data included demographics, co-morbid conditions, cardiac events, substance use, history and physical exam, laboratory and echocardiography, and medications. Patients were included in the analysis cohort if they had a diagnosis of AF. Patients were excluded if there were duplicate DOACs recorded or if the patient was not linked to the CMS database (Figure 1). CHA_2DS_2-VASc scores were calculated based on medical history (presence of congestive heart failure, hypertension, age 65 to 74 years, age >75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, sex category). Modified HAS-BLED scores were also calculated based on medical history (presence of hypertension or systolic blood pressure >160 mm Hg within the previous 2 years; a history of chronic kidney disease or serum creatinine >2.3 mg/dL; a history of chronic liver disease; a history of stroke; a history of intracranial hemorrhage or major nonintracranial hemorrhage; age >65 years; antiplatelet use including aspirin, clopidogrel, ticlopidine, prasugrel, aspirin/dipyridamole, ticagrelor, or NSAIDs; and >7 alcoholic drinks per week).

Bleeding outcomes were defined using ICD-9 codes (Online Figure 1) using the linked CMS database. We categorized bleeding as "Intracranial Bleeding", "Gastrointestinal Bleeding", "Other Major Bleeding", and "Any Major Bleeding". "Intracranial Bleeding" was subdivided into "Subarachnoid Hemorrhage", "Subdural Hemorrhage", and "Intracerebral Hemorrhage". Baseline characteristics were compared across OAC type by using student *t* tests for continuous variables and chi-square tests for categorical variables. Event rates were calculated for each outcome across OAC type. Cox proportional hazard models were used to calculate hazard ratios of each OAC for each outcome. Patients were censored if a bleeding outcome occurred, if they stopped or switched OAC, or to the last outcomes reported by the linked CMS database (October, 2015). We also performed a sensitivity analyses, performing the same hazard models removing patients who switched OACs during the study period.

Age, sex, the modified HAS-BLED score, and concomitant P-Glycoprotein (P-GP) and CYP3A4 inhibitor medication use (Online Figure 2) were used for multivariate adjustment. The HAS-BLED score has compared favorably to other stratification tools in predicting bleeding risk[11,12] and the modified HAS-BLED score has been studied previously.[13] We tested for interaction of bleeding outcomes comparing each DOAC with warfarin for the following subgroups: modified HAS-BLED ≥4, age ≥75, sex, antiplatelet use, and concomitant P-GP and CYP3A4 inhibitor use. We used a p value of 0.05 as significant for interaction testing. All analyses were performed using SAS version (SAS Institute, Inc., Cary, North Carolina).

Results

After exclusions, 423,450 AF patients were included for analyses. Of these, 177,318 patients (42%) were taking warfarin and 91,702 (22%) were taking a DOAC (Table 1). The median follow-up duration was 1.4 ± 0.6 years. Patients

Table 1
Baseline characteristics of 423,450 participants with atrial fibrillation or flutter, by oral anticoagulant type

Variable	None (n = 154,430)	Warfarin (n = 177,318)	Rivaroxaban (n = 40,994)	Dabigatran (n = 32,737)	Apixaban (n = 17,971)
Age (years)	77.1±8.5	77.3±7.5	75.6±7.3	75.5±7.3	76.5±7.4
Women	70,599 (47%)	75,946 (44%)	18,207 (46%)	13,335 (42%)	8,429 (48%)
Body mass index* (kg/m^2)	27.6 (24.2-31.8)	28.6 (25.0-33.4)	28.9 (25.3-33.4)	29.2 (25.6-33.7)	28.5 (25.0-33.1)
Heart failure	42,323 (28%)	62,787 (36%)	9,633 (24%)	8,848 (28%)	4,644 (27%)
Hypertension	119,349 (82%)	139,262 (84%)	31,446 (83%)	25,549 (84%)	13,713 (83%)
Diabetes mellitus	32,868 (23%)	43,069 (27%)	8,400 (23%)	6,990 (24%)	3,736 (24%)
Stroke/transient ischemic attack	7,432 (7%)	11,094 (9%)	2,267 (7%)	2,029 (9%)	1,127 (8%)
Peripheral arterial disease	11,901 (8%)	13,089 (8%)	2,583 (7%)	1,968 (6%)	1,199 (7%)
Coronary artery disease	78,692 (56%)	87,848 (54%)	15,988 (45%)	13,784 (48%)	7,249 (46%)
Myocardial infarction	24,265 (17%)	25,313 (16%)	4,433 (12%)	4,017 (13%)	2,033 (13%)
Chronic liver disease	384 (0.2%)	393 (0.2%)	73 (0.2%)	66 (0.2%)	31 (0.2%)
Dyslipidemia	96,257 (69%)	111,563 (70%)	24,112 (66%)	19,942 (70%)	10,484 (67%)
CHA_2DS_2-VASc	4.3±1.5	4.5±1.4	4.1±1.4	4.2±1.4	4.2±1.4
Modified HAS-BLED†	2.8±0.8	2.5±0.8	2.4±0.9	2.4±0.9	2.5±0.9
Left ventricular ejection fraction, %	56.4±12.4	53.9±13.2	56.0±12.4	55.8±12.3	56.3±12.3
Medication use					
Amiodarone	15,555 (10%)	21,347 (12%)	5,272 (13%)	3,926 (12%)	2,024 (11%)
Aggrenox	874 (0.6%)	366 (0.2%)	85 (0.2%)	58 (0.2%)	56 (0.3%)
Aspirin	117,374 (76%)	79,169 (45%)	18,923 (46%)	14,042 (43%)	8,925 (50%)
Clopidogrel	25,027 (16%)	11,932 (7%)	2,791 (7%)	1,833 (6%)	1,397 (8%)
Corticosteroids	11,167 (7%)	13,925 (8%)	2,816 (7%)	2,131 (7%)	1,176 (7%)
CYP3A4 inhibitor (any)	62,139 (40%)	78,896 (45%)	13,977 (34%)	14,119 (43%)	3,655 (20%)
Metformin	15,670 (10%)	22,575 (13%)	5,299 (13%)	4,279 (13%)	2,263 (13%)
NSAID	215 (0.1%)	121 (0.1%)	40 (0.1%)	42 (0.1%)	15 (0.1%)
P-Glycoprotein Inhibitor (any)	62,337 (40%)	79,847 (45%)	14,095 (34%)	14,206 (43%)	3,681 (21%)
Prasugrel	981 (0.6%)	376 (0.2%)	133 (0.3%)	97 (0.3%)	95 (0.5%)
Proton pump inhibitor	51,016 (33%)	54,253 (31%)	12,827 (31%)	10,194 (31%)	5,638 (31%)
Selective Serotonin Reuptake Inhibitor	20,285 (13%)	22,367 (13%)	4,806 (12%)	3,891 (12%)	2,090 (12%)
Statin therapy‡	39,531 (26%)	50,469 (29%)	9,687 (24%)	9,529 (29%)	3,802 (21%)
Ticagrelor	386 (0.2%)	200 (0.1%)	77 (0.2%)	30 (0.1%)	57 (0.3%)

* Body mass index expressed as median value with interquartile range.
† Modified HAS-BLED: One point is assigned to patients with a history of hypertension or systolic blood pressure > 160 mm Hg within the previous 2 years; a history of chronic kidney disease or serum creatinine > 2.3 mg/dL; a history of chronic liver disease; a history of stroke; a history of intracranial hemorrhage or major nonintracranial hemorrhage; age > 65 years; antiplatelet use (aspirin, clopidogrel, ticlopidine, prasugrel, aggrenox, ticagrelor, or NSAID); and > 7 alcoholic drinks per week.
‡ Includes atorvastatin, rosuvastatin, and simvastatin.

without OAC were more likely to have coronary artery disease (56% vs 51%), prior myocardial infarction (17% vs 15%), higher modified HAS-BLED score (2.8 vs 2.5), concurrent aspirin (75% vs. 45%), and concurrent $P2Y_{12}$ platelet inhibitors (clopidogrel, prasugrel, or ticagrelor) (17% vs. 7%).

There were 29,459 major bleeding events (6.9% of patients) that occurred during follow-up, with 3,303 ICH (0.8%), 11,455 major GIB (2.7%), and 22,401 other major bleeds (5.3%). The number of bleeding outcomes across each OAC type with adjusted hazard rates relative to warfarin are shown in Table 2. The adjusted rate of any major bleeding was highest in warfarin users (6.7% per year) and lowest in dabigatran users (4.8% per year). The adjusted rate of ICH and GIB was also highest in warfarin users (0.8% and 2.9% per year, respectively) and lowest in dabigatran users (0.4% and 2.0% per year, respectively).

Kaplan-Meier curves comparing major bleeding, ICH, and GIB by each OAC type are shown in Figure 2. Compared with warfarin users, the risk of any major bleed was lower in patients taking dabigatran (HR 0.79; 95% CI 0.75 to 0.82) and apixaban (HR 0.86; 95% CI 0.80 − 0.93), but not in patients taking rivaroxaban (HR 0.99; 95% CI 0.95 to 1.04). Compared with warfarin users, the risk of ICH was lower in patients taking rivaroxaban (HR 0.73; 95% CI 0.64 to 0.84), dabigatran (HR 0.56; 95% CI 0.48 to 0.65), and apixaban (HR 0.86; 95% CI 0.80 to 0.93). Compared to warfarin users, the risk of GI bleeding was lower in dabigatran (HR 0.88; 95% CI 0.82 to 0.95) and apixaban (HR 0.84; 95% CI 0.74 to 0.95) users and higher in rivaroxaban (HR 1.20; 95% CI 1.12 to 1.27). We performed a sensitivity analysis, repeating hazard models in 388,339 patients who were maintained on the same OAC during the study period and no significant differences were found.

We performed interaction analysis for each bleeding outcome (Figure 3, Supplemental Tables 1 to 4). Age ≥75 was a significant interaction term for many outcomes. Relative to warfarin, rivaroxaban was associated with more major bleeding in age ≥75 years (HR 1.06; 95% CI 1.01 to 1.12) but less major bleeding in age <75 years (HR 0.87; 95% CI 0.81 to 0.93). Relative to warfarin, dabigatran was associated with a higher risk of major bleeding in age ≥75 years

Table 2
Adjusted* bleeding outcomes in patients with atrial fibrillation or flutter according to oral anticoagulant type

Outcome	No OAC (n = 154,430)	Warfarin (n = 177,318)	Rivaroxaban (n = 40,994)		Dabigatran (n = 32,737)		Apixaban (n = 17,971)	
	Event rate *%/yr*	Event rate *%/yr*	Event rate *%/yr*	HR *(95% CI)*	Event rate *%/yr*	HR *(95% CI)*	Event rate *%/yr*	HR *(95% CI)*
Major bleed	4.94	6.67	6.33	0.99 (0.95 - 1.04)	4.78	0.79 (0.75 - 0.82)	5.72	0.86 (0.80 - 0.93)
Intracranial Hemorrhage	0.56	0.77	0.55	0.73 (0.64 - 0.84)	0.37	0.56 (0.48 - 0.65)	0.55	0.70 (0.55 - 0.90)
Subarachnoid Hemorrhage	0.12	0.15	0.11	0.73 (0.52 - 1.01)	0.06	0.55 (0.38 - 0.80)	0.10	0.80 (0.47 - 1.37)
Subdural Hemorrhage	0.27	0.34	0.23	0.72 (0.58 - 0.90)	0.16	0.50 (0.39 - 0.64)	0.20	0.70 (0.48 - 1.02)
Intracerebral Bleed	0.22	0.33	0.24	0.76 (0.61 - 0.94)	0.17	0.60 (0.48 - 0.76)	0.26	0.73 (0.50 - 1.05)
Major Gastrointestinal Bleed	1.84	2.51	2.88	1.20 (1.12 - 1.27)	2.00	0.88 (0.82 - 0.95)	2.02	0.84 (0.74 - 0.95)
Other Major Bleed	3.67	5.12	4.76	0.97 (0.93 - 1.03)	3.67	0.79 (0.74 - 0.83)	4.49	0.88 (0.81 - 0.96)

OAC = oral anticoagulants.

* Adjusted for age (per 10 years); modified HAS-BLED score, and P-GP or CYP3A4 inhibitor use. The modified HAS-BLED score includes a history of hypertension or systolic blood pressure > 160 mm Hg within the previous 2 years; a history of chronic kidney disease or serum creatinine > 2.3 mg/dL; a history of chronic liver disease; a history of stroke; a history of intracranial hemorrhage or major nonintracranial hemorrhage; age > 65 years; antiplatelet use (aspirin, clopidogrel, ticlopidine, prasugrel, aggrenox, ticagrelor, or NSAID); and > 7 alcoholic drinks per week.

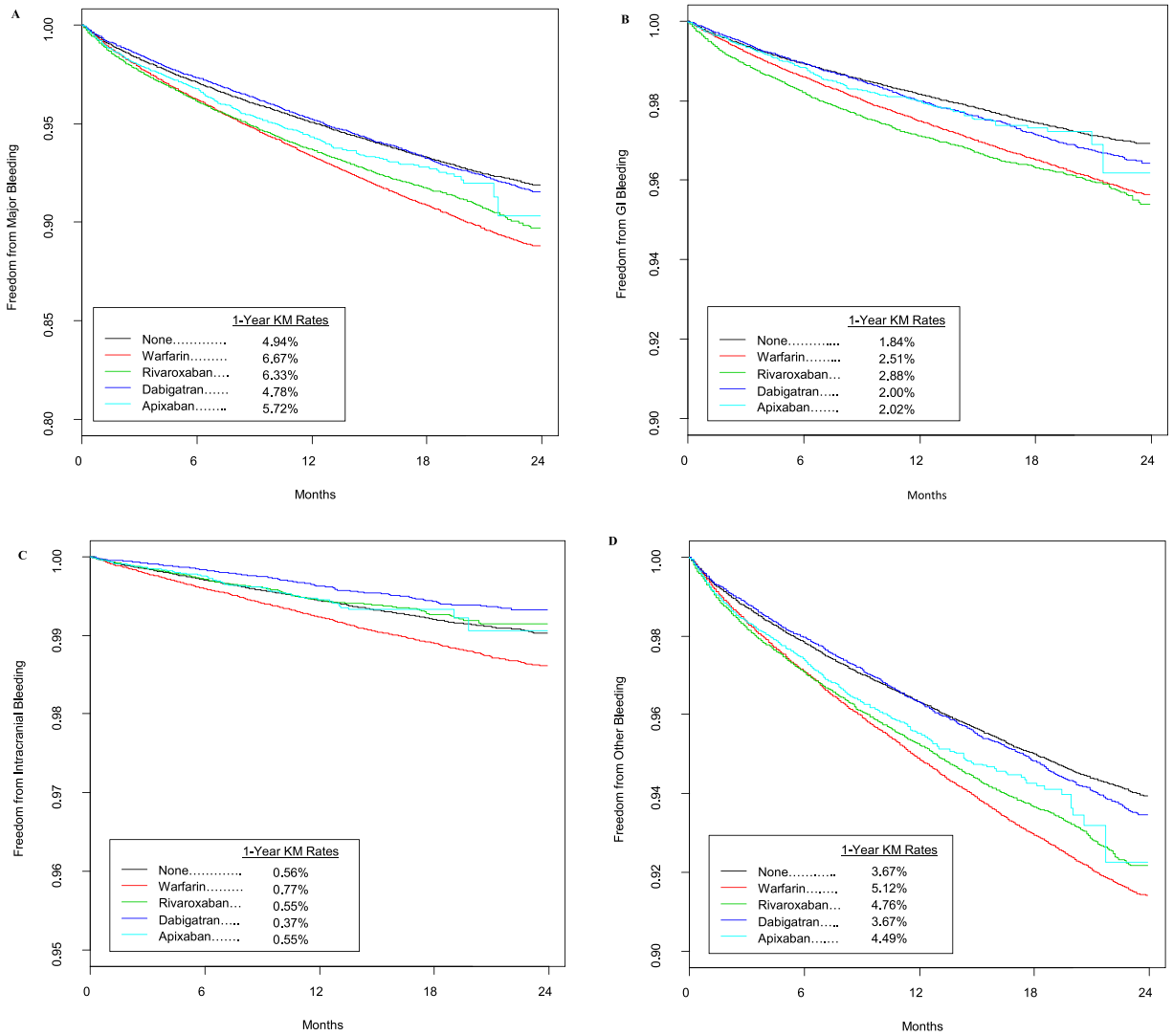

Figure 2. Kaplan-Meier curves for bleeding outcomes by oral anticoagulant type. Panel A shows the event rate for major bleeding. Panel B shows the event rate for gastrointestinal bleeding. Panel C shows the event rate for intracranial bleeding. Panel D shows the event rate for other major bleeding.
The 1-year Kaplan-Meier rates are unadjusted. ICD-9 codes were used to define all bleeding outcomes (see Supplemental Figure 1 for specific ICD-9 outcomes). Log rank <0.001 for panels A-D.

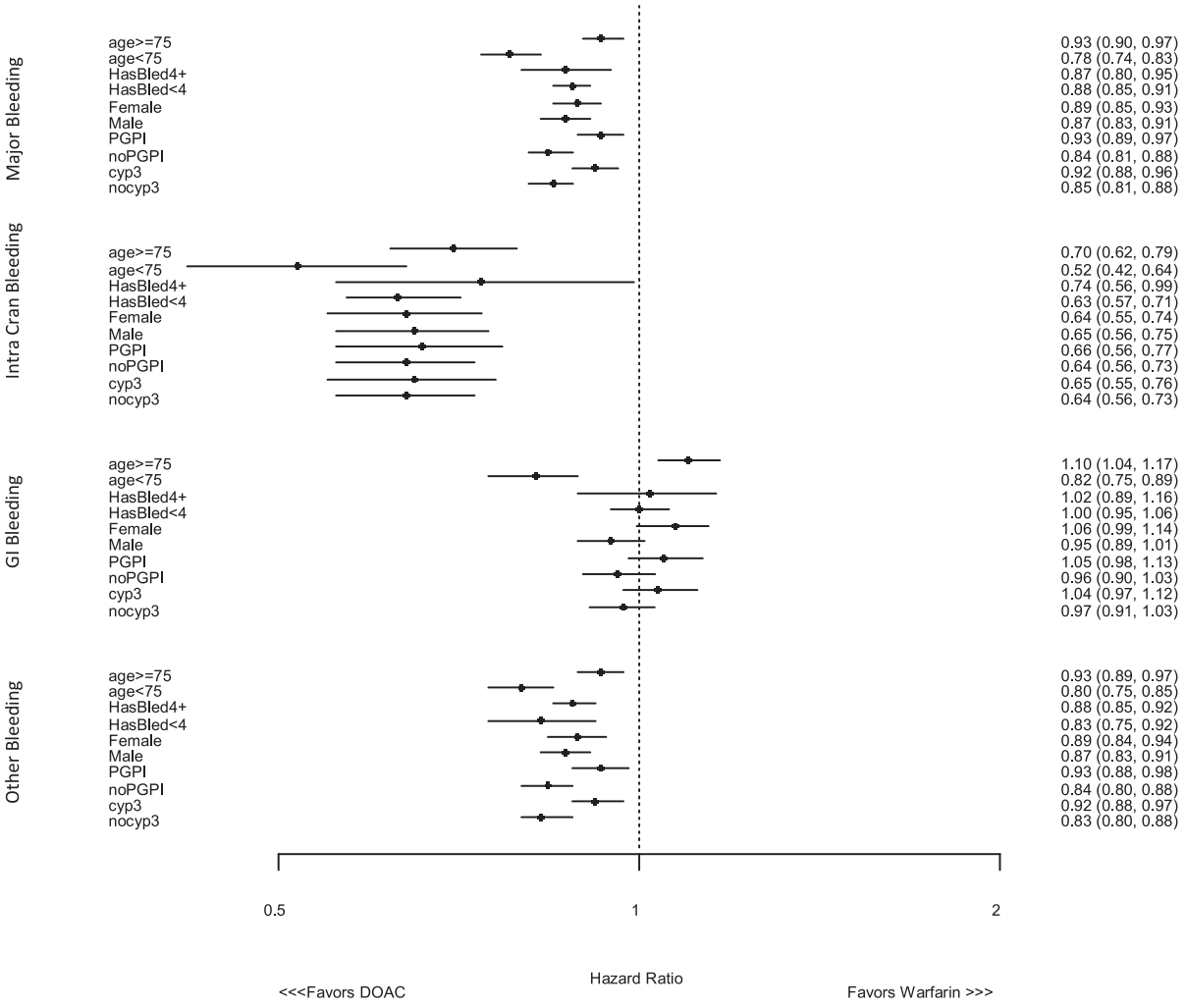

Figure 3. Relative risks of bleeding outcomes among selected subgroups by oral anticoagulant types (interaction plot). Prespecified subgroups are shown. The modified HAS-BLED was defined as follows: One point is assigned to patients with a history of hypertension or systolic blood pressure > 160 mm Hg within the previous 2 years; a history of chronic kidney disease or serum creatinine > 2.3 mg/dL; a history of chronic liver disease; a history of stroke; a history of intracranial hemorrhage or major nonintracranial hemorrhage; age > 65 years; antiplatelet use (aspirin, clopidogrel, ticlopidine, prasugrel, aggrenox, ticagrelor, or NSAID); and > 7 alcoholic drinks per week.

(HR 0.83; 95% CI 0.78 to 0.87) compared with age <75 (HR 0.70; 95% CI 0.65 to 0.76).

A similar interaction was seen in GIB with rivaroxaban (age ≥75: HR 1.32; 95% CI 1.22 to 1.42 vs age <75: HR 0.95; 95% CI 0.84 to 1.06), dabigatran (age ≥75: HR 0.95; 95% CI 0.87 to 1.03 vs age <75: HR 0.74; 95% CI 0.66 to 0.84), and apixaban (age ≥75: HR 0.93; 95% CI 0.80 to 1.07 vs age <75: HR 0.63; 95% CI 0.50 to 0.80). For the outcome of ICH, age also interacted with rivaroxaban (age ≥75: HR 0.81; 95% CI 0.69 to 0.96 vs age <75: HR 0.53; 95% CI 0.40 to 0.70) and dabigatran (age ≥75: HR 0.59; 95% CI 0.49 to 0.71 vs age <75: HR 0.46; 95% CI 0.34 to 0.62). Age did not interact with apixaban and the outcomes of major bleeding or ICH. For age ≥75 years, CHADS-VASC score, modified HAS-BLED score, history of coronary artery disease, or antiplatelet use was not significantly different across OACs. Antiplatelet use did not interact with any bleeding outcome.

A difference in major bleeding with rivaroxaban relative to warfarin was also observed in patients taking GP inhibitors (HR 1.05; 0.99 to 1.12) compared to nonusers (HR 0.94; 95% CI 0.89 to 0.99), and also with CYP3A4 inhibitors (HR 1.04; 95% CI 0.98 to 1.11) compared to nonusers (HR 0.95; 95% CI 0.90 to 1.00). Similarly, there was less major bleeding with dabigatran compared to warfarin in the subset of patients not taking GP (HR 0.74; 95% CI 0.69 to 0.79) or CYP3A4 inhibitors (HR 0.74; 95% CI 0.70 to 0.79) compared with patients taking those medications (HR 0.83; 95% CI 0.78 to 0.89; HR 0.83; 95% CI 0.77 to 0.88, respectively). GP nor CYP3A4 inhibitor use interacted with any DOAC for the outcome of ICH or GIB. There was also an interaction with gender in dabigatran users with GIB, as the risk in men was less than for women (HR 0.82; 95% CI 0.74 to 0.90 versus HR 0.95; 95% CI 0.86 to 1.05). Sex and HAS-BLED ≥4 did not interact with any other combination of DOAC and bleeding outcome.

Discussion

Our analysis, which included over 420,000 outpatients with AF from the PINNACLE registry, supports the overall bleeding safety of DOACs. This was true of ICH, the bleeding outcome associated with high mortality,[14] where each DOAC had a lower event rate compared with warfarin, consistent with randomized trial evidence.[3–5,15–17] Importantly, the rate of ICH among non-DOAC users was similar to DOAC users, reinforcing the safety of these medications. Our findings also suggest differences in the safety of individual DOACs relative to warfarin of other bleeding outcomes that merit further investigation (Figure 4).

We found a higher rate of major GIB in rivaroxaban compared with warfarin users (2.9 %/yr compared to 2.5), whereas dabigatran and apixaban rates were lower (2.0 %/yr). We also found that the safety of DOACs was modified by age. The relative GIB safety advantage of apixaban and dabigatran over warfarin was attenuated in patients ≥75 years. Similarly, rivaroxaban users ≥75 years experienced a higher major GIB rate compared with warfarin (HR 1.32; 95% CI 1.22 to 1.42), whereas younger patients did not (HR 0.95; 95% CI 0.84 to 1.06).

The risk associated with GIB among individual DOACs versus warfarin is less clear.[18–20] Randomized trials showed similar rates of GIB among apixaban[4] and low-dose (110mg bid) dabigatran users[3] compared with warfarin. However, high-dose (150mg bid) dabigatran and rivaroxaban[5] were associated with higher rates of GIB. Few fatal GIB occurred in these studies.[21] It is unclear why the PINNACLE data deviated from the randomized trial with respect to GIB, though it is noteworthy that this study did not differentiate by dabigatran dosage strength.

The mechanisms of higher observed GIB with rivaroxaban and dabigatran are uncertain. One possibility for dabigatran is the lower bioavailability (7.2%) and gut activation, which prolongs GI exposure time.[21] Rivaroxaban may have differential dosing and pharmacokinetics. Our findings highlight another possible factor: rivaroxaban users age ≥75 years had higher GIB rates over warfarin (HR 1.32; 95% CI 1.22 to 1.42), whereas GIB rates in age <75 years was not different (HR 0.95; 95% CI 0.84 to 1.06). In contrast, older (age ≥75 years) apixaban and dabigatran users had similar GIB rates compared with warfarin (HR 0.93 and 0.95, respectively). Although speculative, this raises the possibility that older patients are particularly susceptible to GIB with rivaroxaban compared to warfarin or other DOACs.

Regarding dabigatran, our findings stand in contrast to randomized trial evidence that both dabigatran 110 mg and 150 mg are at higher risk GIB compared with warfarin in the elderly (age ≥75 years),[8] though patient-level data for rivaroxaban, apixaban, and edoxaban was not available for this outcome in this age group. Certainly, GIB risk increases with age,[22] but more evidence is needed to better understand whether there are DOAC class-specific or individual drug-specific differences associated with higher GIB rates compared to warfarin.

Finally, we also studied the interaction between each DOAC versus warfarin for all bleeding outcomes in the subgroups of patients taking P-GP or CYP3A4 inhibitors. We found an interaction with rivaroxaban and dabigatran for the outcome of major bleeding, with higher major bleeding rates in the P-GP and CYP3A4 inhibitor groups. A post-hoc analysis of the RE-LY study showed that NSAID use was associated with higher major bleeding rates.[23] In the Taiwan National Health Insurance database, concomitant amiodarone, fluconazole, rifampin, and phenytoin were associated with higher bleeding rates in DOAC users.

This study has limitations to consider. First, data potentially relevant to bleeding rates were unavailable including DOAC dosage, warfarin international normalized ratio levels, medication adherence rates, cancer status, and blood urea nitrogen levels. Adherence rates may be higher in DOACs relative to warfarin, which more likely alters stroke risk than hemorrhage risk in patients with CHA_2DS_2-VASc ≥2.[24] More providers are prescribing dabigatran and

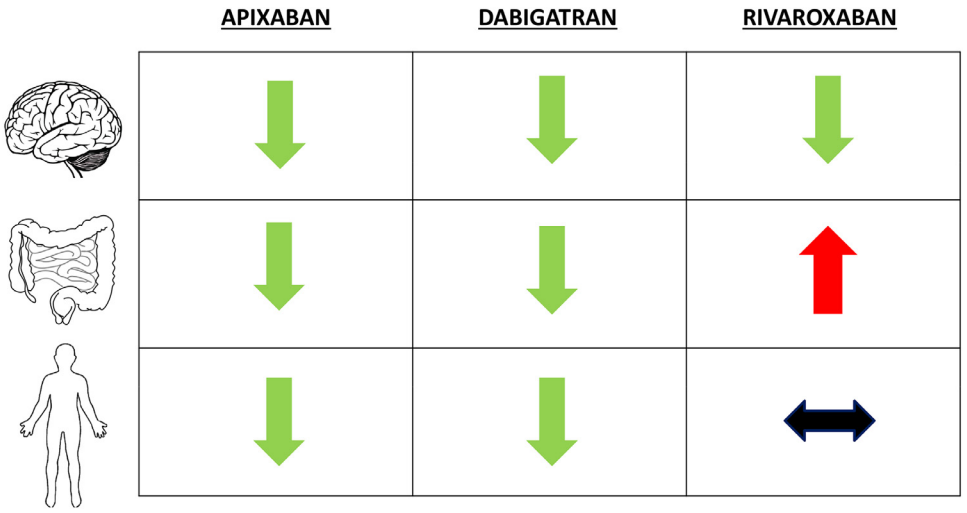

Figure 4. Summary of specific bleeding outcomes by individual DOACs relative to warfarin in PINNACLE. Top Row = intracerebral hemorrhage; Middle Row = gastrointestinal bleeding; Bottom Row = major bleeding; Green arrow = lower bleeding risk compared to warfarin; Black arrow = similar bleeding risk compared to warfarin; Red arrow = higher risk compared to warfarin.

rivaroxaban in dialysis patients, despite a lack of data that support their use in that population.[25] Second, this was an observational study and, therefore, unmeasured confounders may have been unevenly distributed across OAC type. Selection bias may have existed, as the provider rationale for treatment is uncertain. Third, we did not study OAC efficacy of CVA prevention, the other critical piece to prescription decision-making. However, the purpose of this study was to focus on specific bleeding outcomes, as the randomized control evidence shows DOAC efficacy as noninferior.

In conclusion, we observed lower ICH rates in each DOAC compared with warfarin; lower major bleeding, GIB, and other bleeding rates in apixaban and dabigatran compared with warfarin; and higher GIB rates in rivaroxaban compared with warfarin. Age interacted with the relationship between DOAC versus warfarin and all bleeding outcomes, as patients <75 years had further bleeding reduction with DOAC compared to patients ≥75 years.

Author Contributions

Jonathan M. Wong: Conceptualization, methodology, visualization, writing − original draft, review, & editing. **Thomas M. Maddox:** Writing − review & editing, supervision. **Kevin Kennedy**: Formal analysis, visualization. **Richard E. Shaw:** Methodology, supervision.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.02.028.

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