Effectiveness and Safety of Direct Oral Anticoagulants and Warfarin, Stratified by Stroke Risk in Patients With Atrial Fibrillation

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The objective of the study was to examine how the comparative effectiveness and safety of direct oral anticoagulants (DOACs) and warfarin differ across subgroups of patients with atrial fibrillation defined by stroke risk (CHA2DS2-VASc score ≤3, 4 to 5, ≥6). Using Medicare claims data, we identified patients newly diagnosed with atrial fibrillation in 2013 to 2014 who initiated warfarin (n=12,354), apixaban (n=2,358), dabigatran (n=1,415), or rivaroxaban (n=5,139), and categorized them according to their CHA2DS2-VASc score (≤3, 4 to 5, ≥6). Primary outcomes included the combined risk of ischemic stroke, other thromboembolic event and death, and the risk of bleeding. We constructed Cox proportional hazard models that included terms for treatment, CHA2DS2-VASc subgroup, and the interaction between them, and controlled for demographics and a comprehensive list of clinical characteristics. We found that DOACs were generally more effective than warfarin, but this effect was most pronounced in the lowest risk subgroup. Specifically, the hazard ratio for the primary effectiveness outcome with apixaban compared with warfarin was 0.46 (95% confidence interval [CI] 0.32 to 0.65) for CHA2DS2-VASc ≤3, 0.71 (95% CI 0.61 to 0.86) for 4 to 5, and 0.86 (95% CI 0.74 to 1.01) for ≥6 (p value for interaction = 0.005). The comparative safety profile of DOACs versus warfarin did not change with CHA2DS2-VASc score. In conclusion, DOACs are more effective than warfarin, but this effect is more pronounced in patients with lower risk of stroke. Further research is needed to validate these findings in other patient cohorts and uncover their underlying mechanisms. **(Am J Cardiol 2018;122:69–75)**

Since 2010, there have been 4 direct oral anticoagulants (DOACs) that have gained Food and Drug Administration approval for stroke prevention in atrial fibrillation (AF), including the thrombin inhibitor dabigatran, and the factor Xa inhibitors rivaroxaban and apixaban. Several post hoc analyses of the clinical trials that supported the approval of these agents explored whether the comparative efficacy and safety of DOACs and warfarin are consistent across subgroups of patients with AF, finding important interactions between clinical characteristics and treatment effects.[1–6] However, no analyses have evaluated how the comparative effectiveness and safety of DOACs and warfarin differ across levels of stroke risk defined by CHA2DS2-VASc score.[7] Examining comparative effectiveness and safety outcomes across CHA2DS2-VASc subgroups with real-world data is particularly important because high-risk patients were underrepresented in clinical trials.[8] In this study, we used 2013 to 2014 Medicare claims data to evaluate whether the effectiveness and safety of apixaban, dabigatran, and rivaroxaban, relative to warfarin, differed across 3 subgroups of patients with AF defined by CHA2DS2-VASc score (≤3, 4 to 5, ≥6).

Methods

We obtained 2012 to 2014 claims data from a 5% random sample of Medicare Part D beneficiaries from the Centers for Medicare and Medicaid Services (CMS). The data used in this study will not be made publically available because claims data were obtained under a data user agreement that does not allow data sharing before CMS approval. We used the CMS Chronic Condition Data Warehouse indicator of AF to identify patients whose first AF diagnosis happened between January 1, 2013 and December 31, 2014 (Figure 1).[9] After excluding those who were not continuously enrolled in Medicare Part D, we collected the prescriptions filled for warfarin and any approved doses of the DOACs apixaban, dabigatran, and rivaroxaban between the first AF diagnosis and December 31, 2014. Our sample included 12,354 warfarin initiators, 2,358 apixaban initiators, 1,415 dabigatran initiators, and 5,139 rivaroxaban initiators. Study participants were categorized in 3 CHA2DS2-VASc subgroups (≤3, 4 to 5, ≥6),[7] and followed from the date of the first prescription filled for an oral anticoagulant agent after the first AF diagnosis (index date) until discontinuation of treatment (defined as having a gap of therapy of at least 60 days),[10–13] switch of oral anticoagulation therapy, death, or end of the study (December 31, 2014). CHA2DS2-VASc score was defined on index date, and our

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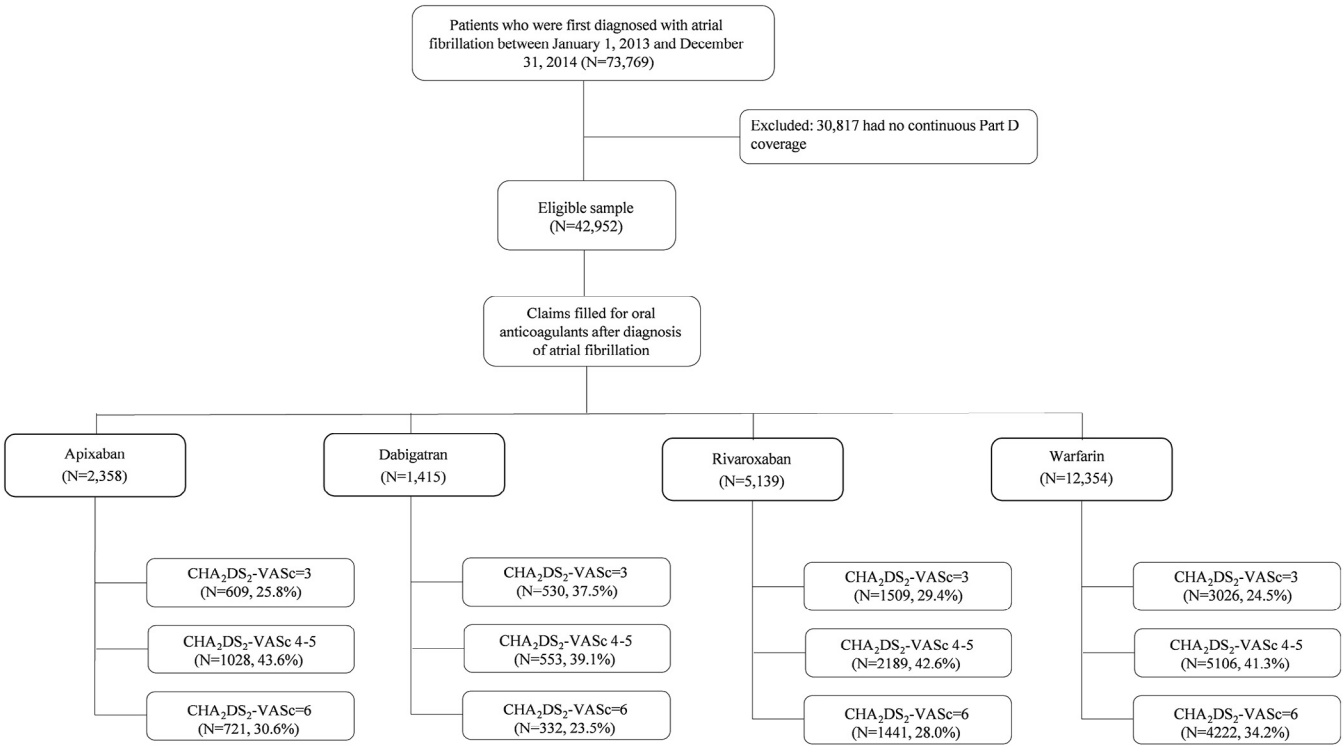

Figure 1. Study sample selection. Notes: We used Medicare claims data from a 5% random sample and identified patients whose first diagnosis of atrial fibrillation was in 2013 to 2014. After excluding those with no continuous Part D enrollment, we categorized the sample according to the first oral anticoagulant agent used after atrial fibrillation diagnosis, and stratified each treatment group by CHA2DS2-VASc score.

study did not capture potential changes in CHA2DS2-VASc score across the study period. For example, if a patient CHA2DS2-VASc score on index date was 3 but after turning 75 years old it was 4, the patient would still remain on the CHA2DS2-VASc ≤3 subgroup. This study was deemed exempt by the Institutional Review Board at the University of Pittsburgh.

The primary effectiveness outcome was the composite of ischemic stroke, other thromboembolic (TE) event, and death, and the primary safety outcome was any bleeding. Secondary effectiveness outcomes included ischemic stroke, other TE event, and death, and the secondary safety outcome was gastrointestinal (GI) bleeding. In defining outcomes, we followed previously published definitions (Supplementary Table S1).[10–14]

Baseline characteristics included demographics and clinical characteristics, and were measured on index date. Demographic characteristics included age, gender, race, and eligibility for Medicaid. Clinical characteristics included CHA2DS2-VASc score,[7] HAS-BLED score,[15] chronic kidney disease, hypertension, a history of stroke or transient ischemic attack, diabetes, heart failure, number of other CMS priority conditions,[9] liver disease, vascular disease, alcohol or drug use, a recent history of bleeding, recent use of antiplatelet agents, and recent use of nonsteroidal anti-inflammatory drugs. Because Medicare claims do not contain international normalized ratio levels, the HAS-BLED score was calculated as the sum of all factors included in this risk score except labile international normalized ratio.[15] We used CMS Chronic Condition Data Warehouse definitions to define covariates that were CMS priority conditions.[9] The definitions for the remaining covariates can be found in Supplemental Methods.

We compared baseline patient characteristics across 4 drug groups within CHA2DS2-VASc subgroups using analysis of variance for continuous variables and chi-square for categorical variables. We constructed Kaplan-Meier curves to estimate unadjusted cumulative incidence rates of primary and secondary outcomes at 1-year of follow-up. To estimate whether the treatment effect of DOACs compared with warfarin differed across CHA2DS2-VASc subgroups, we constructed Cox proportional hazard models that included terms for treatment group, CHA2DS2-VASc score subgroup, and their interaction, and controlled for all covariates mentioned earlier. Time 0 was index date, and the time at risk was censored at switch of treatment, discontinuation, death, or end of the study, except for time-to-event analyses constructed for the outcome of death or for the composite of stroke, other TE event, and death, where death was not a censoring event but the outcome of interest. Because we compared outcomes of each DOAC and warfarin in 3 patient subgroups, we applied Bonferroni correction to mitigate the increased chance of type I error, and set significance level at 0.016 (0.05/3). All analyses were conducted with statistical software SAS 9.4 (SAS Institute Inc., Cary, North Carolina).

Results

Consistently across CHA2DS2-VASc subgroups, patients initiating apixaban were older, and patients initiating

warfarin were more likely to be also eligible for Medicaid, black, and have chronic kidney disease (Table 1). The use of nonsteroidal anti-inflammatory drugs and of other antiplatelet agents was more common in patients initiating DOACs compared with warfarin initiators.

For all CHA2DS2-VASc subgroups, the cumulative incidence rate for the composite risk of stroke, other TE event, and death was higher for warfarin than apixaban, dabigatran, and rivaroxaban (Supplementary Table S2). Consistently across CHA2DS2-VASc subgroups, the cumulative incidence rate of stroke and of death did not differ across treatment groups.

Except for the comparison between apixaban and warfarin for the CHA2DS2-VASc ≥6 subgroup, DOACs were more effective in preventing stroke, other TE event, and death than warfarin across all CHA2DS2-VASc subgroups (Figure 2 and Table 2). Nevertheless, the superiority of DOACs was most pronounced in the lowest risk group. For example, the hazard ratio (HR) for the primary effectiveness outcome for apixaban versus warfarin was 0.46 (95% confidence interval [CI] 0.32 to 0.65) for CHA2DS2-VASc ≤3, 0.71 (95% CI 0.58 to 0.86) for 4 to 5, and 0.86 (95% CI 0.74 to 1.01) for ≥6 (p value for the interaction between treatment effect and CHA2DS2-VASc subgroup = 0.005). Although the HR for the comparison between dabigatran and warfarin was also lower in the lower risk subgroup, the interaction between treatment effect and CHA2DS2-VASc subgroup was not significant (p value = 0.184).

The comparative risk of stroke with apixaban or rivaroxaban compared with warfarin was consistent across CHA2DS2-VASc subgroups (Table 2 and Supplementary Figure S1). However, the HR for stroke for dabigatran versus warfarin differed across CHA2DS2-VASc subgroups (p value for interaction = 0.031). The comparative risk of other TE event showed a pattern similar to that of the primary effectiveness outcome: the superior effectiveness of DOACs was more pronounced in the lower risk subgroups, with the interaction between treatment effect and CHA2DS2-VASc subgroup being significant for rivaroxaban (p value = 0.012), and marginally significant for apixaban (p value = 0.051). Finally, for CHA2DS2-VASc ≤3 or 4 to 5, the risk of death was lower on apixaban than warfarin, but this effect was not observed for those with CHA2DS2-VASc ≥6 (p value for the interaction = 0.004).

There were no differences in the unadjusted risk of bleeding between treatment groups among patients with CHA2DS2-VASc ≤3 or 4 to 5. The cumulative incidence rate of bleeding was, however, higher for patients with CHA2DS2-VASc ≥6 who initiated warfarin or rivaroxaban than for those who initiated apixaban.

The comparative safety of DOACs and warfarin was consistent across CHA2DS2-VASc subgroups (Table 2). We observed no differences in the risk of bleeding between apixaban or dabigatran and warfarin. However, for patients with CHA2DS2-VASc score 4 to 5, the risk of any bleeding event and GI bleeding was higher for rivaroxaban than warfarin.

Discussion

To our knowledge, our study is the first to evaluate the comparative effectiveness and safety of DOACs relative to warfarin by subgroups of patients with AF defined by CHA2DS2-VASc score. Our analysis yielded 3 main findings. First, we found that the superior effectiveness of DOACs in the prevention of stroke, other TE event, and death is more pronounced in patients at lower risk of stroke. Second, in the case of apixaban and rivaroxaban, a similar effect was observed for the prevention of TE events other than stroke. However, the superiority of dabigatran was more pronounced in the lower risk subgroup for the outcome of stroke prevention, but not for the prevention of other TE events. Third, the comparative safety profile of DOACs relative to warfarin was similar across CHA2DS2-VASc subgroups.

Although previous researchers have conducted subgroup analyses of the results from the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibitor Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) and the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trials,[4–6,16] none have stratified their results by levels of stroke risk. Subgroup analyses by CHADS2 score have, however, been reported for the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial,[17] but showed no differences in the comparative efficacy and safety of dabigatran and warfarin across 3 CHADS2 subgroups (0 to 1, 2, and ≥3).[17] A meta-analysis of the RE-LY, ROCKET-AF, and ARISTOTLE trials found that the comparative efficacy of DOACs and warfarin did not change with CHADS2 score; however, this meta-analysis only examined 2 subgroups (CHADS2 0 to 1 and ≥2).[2] In addition to the categorization of patients into only 2 low-to-moderate risk subgroups, the different results of our study may be explained by 2 other reasons: First, clinical trials results for the comparative efficacy and safety of DOACs relative to warfarin have not necessarily translated into similar findings in the real-world practice. Second and more importantly, high-risk patients were underrepresented in clinical trials,[8] particularly in the RE-LY and ARISTOTLE trials, and the ROCKET-AF trial did not include patients with CHADS2 score 0 to 1.[18] For this reason, post hoc analyses or meta-analyses of clinical trials would likely be underpowered to detect heterogeneity of treatment effects between low-risk and high-risk subgroups.

Our study has limitations. First, it is possible that our study was underpowered to detect differences in the risk of secondary outcomes with low incidence such as stroke across treatment groups within CHA2DS2-VASc subgroups; however, this should not be concerning because previous analyses of the overall sample showed similar results for this outcome.[11] Second, although we adjusted our analyses for a comprehensive list of patient characteristics, our study based on observational data may still be subject to residual confounding due to unobserved effects. For example, because dabigatran is associated with an increased risk of GI distress, it is more likely that patients on the dabigatran treatment group used proton pump inhibitors concomitantly than patients on other groups, which could have led to an underestimation of the HR of GI bleeding for dabigatran compared with warfarin. Third, we did not use propensity score methods because we would not have been able to explore interactions between treatment effect and CHA2DS2-VASc score if we had balanced each subgroup separately. Fourth, because our sample was

Table 1
Baseline patient characteristics, by treatment group and CHA2DS2-VASc subgroup

Variable	CHA2DS2-VASc ≤ 3				
	Apixaban (n = 609)	Dabigatran (n = 530)	Rivaroxaban (n = 1509)	Warfarin (n = 3026)	P-Value
Follow-up (days), mean (SD)	192 (142)	290 (185)	259 (178)	289 (192)	<0.001
Low-dose DOAC	53 (8.7%)	34 (6.4%)	219 (14.5%)	–	<0.001
Age (years), mean (SD)	71.25 (7.42)	69.25 (6.99)	70.39 (7.46)	68.55 (10.25)	<0.001
Men	454 (74.6%)	366 (69.1%)	1050 (69.6%)	2158 (71.3%)	0.097
White	542 (89.0%)	469 (88.5%)	1348 (89.3%)	2503 (82.7%)	<0.001
Black	24 (3.9%)	22 (4.2%)	55 (3.6%)	265 (8.8%)	<0.001
Hispanic	14 (2.3%)	15 (2.8%)	42 (2.8%)	135 (4.5%)	0.005
Other	29 (4.8%)	24 (4.5%)	64 (4.2%)	123 (4.1%)	0.862
Medicaid eligibility	71 (11.7%)	95 (17.9%)	236 (15.6%)	834 (27.6%)	<0.001
CHA2DS2-VASc score, mean (SD)	2.57 (0.63)	2.51 (0.68)	2.50 (0.67)	2.46 (0.73)	0.002
CHA2DS2-VASc score 0–1	44 (7.2%)	50 (9.4%)	127 (8.4%)	352 (11.6%)	<0.001
HAS-BLED score*, mean (SD)	3.13 (0.74)	2.93 (0.74)	3.01 (0.80)	2.86 (0.84)	<0.001
CKD	104 (17.1%)	61 (11.5%)	238 (15.8%)	699 (23.10%)	<0.001
Hypertension	489 (80.3%)	394 (74.3%)	1146 (75.9%)	2076 (68.6%)	<0.001
Previous stroke or TIA	2 (0.3%)	2 (0.4%)	11 (0.7%)	35 (1.2%)	0.082
Diabetes mellitus	117 (19.2%)	106 (20.0%)	223 (14.8%)	662 (21.9%)	<0.001
CHF	85 (14.0%)	96 (17.9%)	211 (14.0%)	680 (22.5%)	<0.001
No. of other CMS priority comorbidities, mean (SD)	4.02 (2.16)	3.20 (2.15)	3.77 (2.19)	3.49 (2.37)	<0.001
Liver disease	9 (1.5%)	7 (1.3%)	18 (1.2%)	46 (1.5%)	0.843
Vascular disease	27 (4.4%)	24 (4.5%)	97 (6.4%)	209 (6.9%)	0.039
Alcohol or drug use	12 (1.97%)	10 (1.89%)	23 (1.5%)	47 (1.6%)	0.831
History of bleeding	69 (11.3%)	54 (10.2%)	177 (11.7%)	380 (12.6%)	0.407
Use of antiplatelet agents	42 (6.9%)	29 (5.5%)	92 (6.1%)	182 (6.0%)	0.782
Use of NSAIDs	84 (13.8%)	55 (10.4%)	189 (12.5%)	277 (9.2%)	<0.001
Variable	CHA2DS2-VASc 4–5				
	Apixaban (n = 1028)	Dabigatran (n = 553)	Rivaroxaban (n = 2189)	Warfarin (n = 5106)	P-Value
Follow-up (days), mean (SD)	186 (139)	307 (200)	253 (183)	273 (186)	<0.001
Low-dose DOAC	264 (25.7%)	119 (21.5%)	723 (33.0%)	–	<0.001
Age (years), mean (SD)	77.61 (8.32)	76.81 (7.94)	77.37 (7.83)	76.55 (9.46)	<0.001
Men	387 (37.7%)	213 (38.5%)	858 (39.2%)	2099 (41.1%)	0.109
White	908 (88.3%)	484 (87.5%)	1935 (88.4%)	4353 (85.3%)	<0.001
Black	52 (5.1%)	23 (4.2%)	113 (5.2%)	406 (8.0%)	<0.001
Hispanic	36 (3.5%)	20 (3.6%)	88 (4.0%)	207 (4.1%)	0.831
Other	32 (3.1%)	26 (4.7%)	53 (2.4%)	170 (2.7%)	0.032
Medicaid eligibility	201 (19.6%)	130 (23.5%)	403 (18.4%)	1399 (27.4%)	<0.001
CHA2DS2-VASc score, mean (SD)	4.45 (0.50)	4.47 (0.50)	4.48 (0.50)	4.51 (0.50)	0.003
HAS-BLED score*, mean (SD)	3.53 (0.70)	3.50 (0.72)	3.58 (0.72)	3.60 (0.75)	0.001
CKD	317 (30.8%)	142 (25.7%)	680 (31.1%)	2125 (41.6%)	<0.001
Hypertension	1001 (97.4%)	535 (96.8%)	2139 (97.7%)	4918 (96.3%)	0.012
Previous stroke or TIA	78 (7.6%)	51 (9.2%)	186 (8.5%)	493 (9.7%)	0.126
Diabetes mellitus	443 (43.1%)	261 (47.2%)	958 (43.8%)	2341 (45.9%)	0.146
CHF	463 (45.0%)	246 (44.5%)	1014 (46.3%)	2812 (55.1%)	<0.001
No. of other CMS priority comorbidities, mean (SD)	5.61 (2.27)	5.27 (2.38)	5.77 (2.30)	5.67 (2.39)	<0.001
Liver disease	14 (1.4%)	3 (0.5%)	28 (1.3%)	59 (1.2%)	0.486
Vascular disease	219 (21.3%)	123 (22.2%)	507 (23.2%)	1286 (25.2%)	0.021
Alcohol or drug use	13 (1.3%)	4 (0.7%)	30 (1.4%)	76 (1.5%)	0.516
History of bleeding	149 (14.5%)	82 (14.8%)	324 (14.8%)	900 (17.6%)	0.004
Use of antiplatelet agents	98 (9.5%)	52 (9.4%)	218 (10.0%)	463 (9.1%)	0.688
Use of NSAIDs	105 (10.2%)	68 (12.3%)	280 (12.8%)	490 (9.6%)	<0.001

(*continued*)

Table 1
(*continued*)

Variable	CHA2DS2-VASc ≥ 6				
	Apixaban (n = 721)	Dabigatran (n = 332)	Rivaroxaban (n = 1441)	Warfarin (n = 4222)	P-Value
Follow-up (days), mean (SD)	176 (138)	279 (192)	253 (180)	262 (183)	<0.001
Low-dose DOAC	308 (42.7%)	120 (36.1%)	695 (48.2%)		<0.001
Age (years), mean (SD)	82.2 (6.6)	80.6 (7.2)	81.1 (7.2)	80.8 (7.9)	<0.001
Men	161 (22.3%)	86 (25.9%)	337 (23.4%)	1069 (25.3%)	0.196
White	624 (86.6%)	262 (78.9%)	1170 (81.2%)	3441 (81.5%)	0.004
Black	36 (5.0%)	29 (8.7%)	110 (7.6%)	446 (10.6%)	<0.001
Hispanic	32 (4.4%)	22 (6.6%)	103 (7.2%)	216 (5.1%)	0.012
Other	29 (4.0%)	19 (5.7%)	58 (4.0%)	119 (2.8%)	0.006
Medicaid eligibility	191 (26.5%)	118 (35.5%)	443 (30.7%)	1513 (35.8%)	<0.001
CHA2DS2-VASc score, mean (SD)	6.79 (0.91)	6.70 (0.88)	6.82 (0.91)	6.83 (0.93)	0.050
HAS-BLED score*, mean (SD)	4.45 (0.88)	4.36 (0.83)	4.41 (0.88)	4.44 (0.85)	0.266
CKD	382 (53.0%)	157 (47.3%)	644 (44.7%)	2422 (57.4%)	<0.001
Hypertension	716 (99.3%)	329 (99.1%)	1431 (99.3%)	4196 (99.4%)	0.927
Previous stroke or TIA	414 (57.4%)	194 (58.4%)	907 (62.9%)	2554 (60.5%)	0.071
Diabetes mellitus	495 (68.7%)	230 (69.3%)	995 (69.1%)	2982 (70.7%)	0.539
CHF	535 (74.2%)	252 (75.9%)	1065 (73.9%)	3353 (79.4%)	<0.001
No. of other CMS priority comorbidities, mean (SD)	5 (0.7)	1 (0.3)	19 (1.3)	43 (1.0)	0.289
Liver disease	406 (56.3%)	178 (53.6%)	800 (55.5%)	2511 (59.5%)	0.012
Vascular disease	2 (0.3%)	2 (0.6%)	17 (1.2%)	44 (1.0%)	0.174
Alcohol or drug use	7.14 (2.23%)	6.84 (2.33%)	7.30 (2.30%)	7.22 (2.36%)	0.012
History of bleeding	140 (19.4%)	51 (15.4%)	268 (18.6%)	934 (22.1%)	0.001
Use of antiplatelet agents	177 (24.6%)	71 (21.4%)	330 (22.9%)	789 (18.7%)	<0.001
Use of NSAIDs	84 (11.7%)	44 (13.3%)	183 (12.7%)	426 (10.1%)	0.020

Abbreviations: DOAC = Direct Oral Anticoagulant; CMS = Centers for Medicare and Medicaid Services; CKD = Chronic Kidney Disease; TIA = Transient Ischemic Attack; AMI = Acute Myocardial Infarction; CHF = Congestive Heart Failure; NSAIDs = Non-Steroidal Anti-inflammatory Drug.

* Because claims data do not contain INR levels, we calculated the HAS-BLED score as the sum of all factors included in the calculation of this score except labile INR.[15]

mostly representative of high-risk patients, we were underpowered to detect differences in the comparative effectiveness and safety profiles of DOACs relative to warfarin in patients with CHA2DS2-VASc score 0 to 1. As more recent data become available, it will be important to repeat similar analyses and evaluate the comparative effectiveness and safety profiles of DOACs and warfarin in this low-risk population. Fifth, because the objective of our study was to evaluate how the comparative effectiveness and safety of DOACs relative to warfarin differed across CHA2DS2-VASc subgroups, we grouped low-dose and high-dose DOAC initiators together, which could have biased our results. Nevertheless, this should not be especially concerning because previous studies have shown that results of observational studies for DOACs are robust to the grouping of high- and low-dose users.[19]

Nevertheless, our study has important clinical implications. We found that the superiority of the factor Xa inhibitors apixaban and rivaroxaban in the prevention of the combined risk of stroke, other TE event, and death was most pronounced in lower risk patients. When we evaluated separately each of these outcomes, we observed that this effect was mostly attributable to the higher superiority of apixaban and rivaroxaban in preventing other TE events. Although for the primary outcome of combined risk of stroke, other TE event, and death, the interaction between the comparative effectiveness of dabigatran and warfarin and CHA2DS2-VASc subgroup was not significant, HRs were once again lower for patients with lower risk of stroke. For the case of dabigatran, however, the superiority in lower risk patients was attributable to stroke prevention rather than to prevention of other TE events. These differences in the comparative effectiveness of DOACs and warfarin across CHA2DS2-VASc subgroups may be related to the mechanism of action of these agents. The superiority of DOACs may not be as strong in high-risk patients because dabigatran only inhibits thrombin, and apixaban and rivaroxaban only inhibit factor Xa, whereas warfarin inhibits the synthesis of coagulation factors VII, IX, X, and thrombin. Then, in patients with high CHA2DS2-VASc score, who maintain a prothrombotic state, warfarin may be as effective as DOACs because of its ability to suppress the intrinsic, extrinsic, and common coagulation pathways.[20] Similarly, the differences observed in the findings for dabigatran compared with apixaban and rivaroxaban may be due to dabigatran being a direct thrombin inhibitor, whereas rivaroxaban and apixaban inhibit factor Xa.

Our findings add to the body of literature demonstrating that the comparative outcomes of DOACs versus warfarin differ substantially across patient subgroups[1–6] and reinforce the importance of tailoring anticoagulation therapy to patient characteristics. Our findings suggest that DOACs may be particularly preferred over warfarin in patients with low-to-moderate risk of stroke. Although for the highest risk patients DOACs were still superior to warfarin, it is unclear whether this smaller clinical difference justifies the 15-fold higher acquisition costs of DOACs.[21] Further research should validate

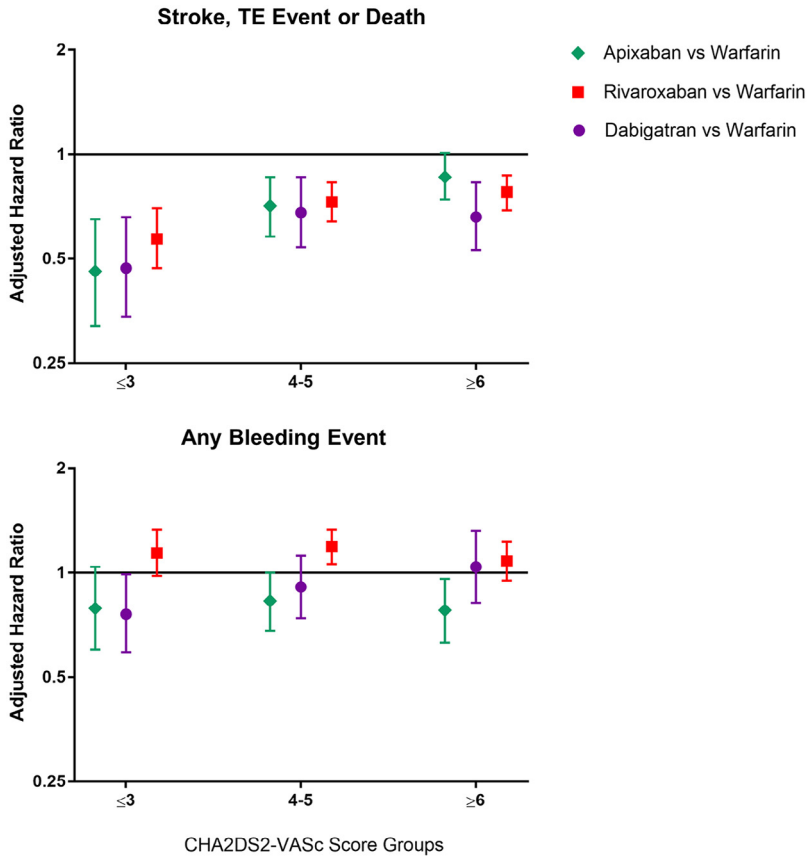

Figure 2. Adjusted hazard ratios of primary effectiveness outcomes, by treatment group and CHA2DS2-VASc subgroup. Hazard ratios were estimated using Cox proportional hazard models that included terms for treatment, CHA2DS2-VASc score subgroups, and the interaction between them; and controlled for demographics and clinical characteristics listed in the covariates section. Estimates for the adjusted hazard ratios are also reported in Table 2. TE event = thromboembolic event.

Table 2
Adjusted hazard ratios of effectiveness and safety outcomes, by treatment group and CHA2DS2-VASc subgroup

	Adjusted Hazard Ratio (95% CI)					
Apixaban vs Warfarin	Stroke, TE Event or Death	Stroke	Other TE Event	Death	Any bleeding event	GI Bleeding
CHA2DS2-VASc ≤ 3	**0.46 (0.32–0.65)**	0.79 (0.51–1.20)	**0.26 (0.14–0.52)**	**0.17 (0.04–0.67)**	0.79 (0.60–1.04)	0.62 (0.35–1.10)
CHA2DS2-VASc 4–5	**0.71 (0.58–0.86)**	**1.03 (0.81–1.31)**	**0.33 (0.22–0.51)**	**0.52 (0.31–0.88)**	0.83 (0.68–1.00)	0.76 (0.54–1.07)
CHA2DS2-VASc ≥ 6	0.86 (0.74–1.01)	1.01 (0.84–1.22)	**0.57 (0.41–0.79)**	1.14 (0.78–1.67)	0.78 (0.63–0.96)	0.75 (0.52–1.07)
P-Value for Interaction*	0.005	0.523	0.051	0.004	0.910	0.817
Dabigatran vs Warfarin						
CHA2DS2-VASc ≤ 3	**0.47 (0.34–0.66)**	**0.56 (0.35–0.88)**	**0.45 (0.27–0.75)**	0.48 (0.21–1.10)	0.76 (0.59–0.99)	0.63 (0.37–1.07)
CHA2DS2-VASc 4–5	**0.68 (0.54–0.86)**	1.07 (0.83–1.39)	**0.43 (0.28–0.68)**	**0.28 (0.12–0.68)**	0.91 (0.74–1.12)	0.95 (0.67–1.34)
CHA2DS2-VASc ≥ 6	**0.66 (0.53–0.83)**	0.77 (0.59–0.99)	**0.53 (0.34–0.84)**	0.72 (0.39–1.33)	1.04 (0.82–1.32)	1.19 (0.83–1.71)
P-Value for Interaction*	0.184	0.031	0.792	0.222	0.238	0.147
Rivaroxaban vs Warfarin						
CHA2DS2-VASc ≤ 3	**0.57 (0.47–0.70)**	0.81 (0.62–1.05)	**0.40 (0.28–0.56)**	**0.54 (0.33–0.89)**	1.14 (0.98–1.33)	**1.39 (1.07–1.82)**
CHA2DS2-VASc 4–5	**0.73 (0.64–0.83)**	0.88 (0.74–1.04)	**0.50 (0.39–0.63)**	0.87 (0.66–1.17)	**1.19 (1.06–1.33)**	**1.37 (1.14–1.64)**
CHA2DS2-VASc ≥ 6	**0.78 (0.69–0.87)**	**0.80 (0.70–0.92)**	**0.69 (0.56–0.84)**	0.86 (0.64–1.17)	1.08 (0.95–1.23)	1.27 (1.04–1.54)
P-Value for Interaction*	0.036	0.696	0.012	0.224	0.561	0.809

Abbreviations: TE Event = Thromboembolic Event; GI = Gastrointestinal.

* Denotes p-value for the interaction between treatment group, and the categorical variable for CHA2DS2-VASc subgroup.

Bold denotes statistically significant differences at the alpha level of 0.016, after the application of Bonferroni correction.

Hazard ratios were estimated using Cox proportional hazard models that included terms for treatment, CHA2DS2-VASc score subgroups, and the interaction between them; and controlled for demographics and clinical characteristics listed in the covariates section.

our observations in cohorts of patients of lower age and using data sources other than claims data, and explore whether for high-risk patients DOACs are still a cost-effective alternative to warfarin.

In conclusion, in this observational study, DOACs were more effective than warfarin in preventing stroke, other TE event, and death, but the relative superiority of DOACs was most pronounced in low-risk patients. Further research is needed to validate these findings in other patient cohorts and uncover their underlying mechanisms.

Disclosures

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Supplementary Data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.amjcard.2018.03.012.

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