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Factors Driving Anticoagulant Selection in Patients with Atrial Fibrillation in the United States

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Abstract

With the introduction of novel oral anticoagulants (NOACs), the factors driving anticoagulant selection in atrial fibrillation (AF) in real-world practice are unclear. The goal was to examine whether and to what extent utilization has been driven by predictions of stroke risk (treatment benefit), bleeding risk (treatment harm), or prescription benefits' coverage. We extracted a cohort of non-valvular AF patients initiating anticoagulation from Oct 2010-Dec 2012 from a large US database of commercial and Medicare supplement claims. Multivariable regression examined associations between ischemic stroke (CHA₂DS₂-VASc) and bleeding (ATRIA) risk scores and benefits' generosity (proportion of costs covered by patients relative to total) with warfarin and NOAC selection and also between dabigatran and rivaroxaban. C-statistics and partial chi-square statistics were used to assess the variation explained. Of 70,498 patients initiating anticoagulation, 29.9% and 7.9% used dabigatran and rivaroxaban, respectively. Compared with warfarin, patients were less likely to receive a NOAC with high ischemic stroke risk (CHA₂DS₂-VASc 2) (Adjusted Relative Risk [aRR]: 0.75, 95% CI: 0.72-0.77) and high bleeding risk (ATRIA 5)

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DISCLOSURES

Dr. Rhoney, Dr. Fang, Dr. Gehi, and Dr. Lauffenburger have nothing relevant to declare. Dr. Brookhart has received research support from Amgen for unrelated projects and has served as a scientific advisor for Amgen, Merck, and GSK (honoraria paid to institution). He received consulting fees from RxAnte and WHIC. Dr. Farley has received consulting support for unrelated projects from Daiichi-Sankyo.

(aRR: 0.66, 95% CI: 0.64-0.69) but more likely with good benefits' generosity (20% of costs borne by patient) (aRR: 2.03, 95% CI: 1.92-2.16). Prescription generosity explained almost twice the model variation as either risk score. Compared with dabigatran, patients were more likely to fill rivaroxaban with high bleeding risk (aRR: 1.16, 95% CI: 1.09-1.24). In conclusion, patients with higher bleeding and ischemic stroke risk were more likely to initiate warfarin, but generous benefits more strongly predicted NOAC usage and drove more selection.

Keywords

Atrial fibrillation; anticoagulants; warfarin; dabigatran; rivaroxaban

INTRODUCTION

For decades, warfarin had been the primary oral anticoagulant for patients with atrial fibrillation (AF).¹ Recent availability of novel oral anticoagulants (NOACs) provided additional options.^{2,3,4} It is unclear the extent to which risk of ischemic stroke, bleeding risk, or prescription benefits' generosity may affect anticoagulant selection in clinical practice, particularly with these newer anticoagulant options available. Therefore, the goal of this study is to investigate whether and to what extent anticoagulant selection in AF patients has been driven by clinical predictions of treatment benefit and harm and prescription benefits' generosity in a large national real-world US database. We sought to 1) assess the associations of predictions of ischemic stroke risk, bleeding risk, and benefits' generosity with warfarin selection versus NOACs, 2) assess these factors' associations with selection between dabigatran and rivaroxaban, and 3) explore the extent of the variation in anticoagulant selection driven by these factors.

METHODS

This is a retrospective cohort study using the Truven Health MarketScan® Commercial Claims and Encounters and Medicare supplement databases for the years 2009-2012. These data files include patient-specific medical inpatient and outpatient claims, physician office visits, outpatient pharmaceutical data and enrollment data with an encrypted unique patient identifier from over 100 nationwide insurers for approximately 40 million individuals annually. These databases were linked using the encrypted patient identifier to ensure that each patient was only included once. Prescription medication use was identified through National Drug Codes (NDCs) in the prescription files, including anticoagulants.

A cohort of AF patients was selected based on the following inclusion criteria: 1) filling 1 prescription for warfarin or a NOAC (dabigatran or rivaroxaban) after 10/19/2010 (dabigatran FDA approval date), hereafter referred to as the "index fill"; 2) 18 years of age; 3) receiving at least 1 inpatient or 2 outpatient International Classification of Diseases, 9th edition (ICD-9) codes for AF (ICD-9: 427.31) occurring on separate days within 12 months prior to the index fill date (1 outpatient claim could occur after the index date); and 4) were continuously enrolled for 12 months prior to the index fill. The first fill of any of these anticoagulants after 10/19/2010 was designated as the index fill. The 2 ICD-9 codes

were required on separate days to eliminate the possibility of the code used as a rule-out condition.

Patients were excluded from the study if they had an anticoagulant prescription fill in the 12 months prior to the index fill to examine new anticoagulation users. Because dabigatran and rivaroxaban are only indicated in non-valvular AF, patients with ICD-9 codes corresponding to valvular and transient AF in the 12-month baseline were excluded to ensure appropriate comparisons (Appendix Table 1). These exclusions are similar to those used in trials for FDA approval and in previous studies, including patients with valve replacements, coagulation deficiencies, liver disease, atrial flutter, or hyperthyroidism.⁵⁻⁷

Ischemic stroke and bleeding risk were measured in the 12 months prior to anticoagulation initiation using ICD-9 codes in the inpatient and outpatient claims files based on previously-used algorithms (Appendix Table 1).^{8,9} Ischemic stroke risk was calculated through the CHA₂DS₂-VASc score, which incorporates congestive heart failure (+1), hypertension (+1), age 65-74 years (+1), age ≥ 75 years (+2), diabetes (+1), prior ischemic stroke (+2), female gender (+1), coronary artery disease (+1), and peripheral vascular disease (+1). Following guideline conventions, the CHA₂DS₂-VASc score was categorized into three levels: 0 (low risk), 1 (intermediate risk), and ≥ 2 (high risk). Bleeding risk was measured through the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) score, which includes anemia (+3), severe renal disease (+3), age ≥ 75 years (+2), previous hemorrhage (+1), and hypertension (+1). The ATRIA score was categorized as follows: ≤ 3 (low risk), 4 (intermediate risk), and ≥ 5 (high risk), conforming to previously validated standards. Of the bleeding clinical prediction risk scores, the ATRIA score is considered to be more reliably measured in secondary medical claims.^{10,9,11}

Because overall copayment burden may influence a patient's predisposition towards a certain therapy, the patients' cost-sharing proportion for all prescriptions in the 12 months prior to the index fill divided by total drug payments was calculated as a benefits' generosity measure.¹² This proportion was categorized into three levels paid by patients: > 0.80 ("No/Poor coverage"), 0.20-0.80 ("Fair coverage"), and ≤ 0.20 ("Good coverage"). In other words, at the "No/poor coverage" level, more than 80% of the actual prescription costs over the previous 12 months were covered by patients out of the total paid.

Patient demographic characteristics thought to be associated with anticoagulation and not already included in the risk scores were identified in the 12-month baseline, including region of residence (north central, northeast, south, west) and type of health plan (comprehensive, health maintenance organization, point-of-service, preferred provider organization, consumer-driven health plan). In addition to those in the risk scores, other comorbidities were identified in the baseline period using ICD-9 codes in the outpatient or inpatient claims based on previous literature, including venous thromboembolism (VTE), peptic ulcer disease, hyperlipidemia, dementia and sleep apnea. Concomitant medications with known associations with anticoagulation were also measured, including antiplatelets, gastroprotective agents, antiarrhythmics, rate control therapies (e.g., digoxin, beta-blockers, calcium channel blockers), and statins.

In the analytic plan, sociodemographic and clinical characteristics among patients receiving anticoagulation were described, examining their association with the selection of warfarin and newer anticoagulants. Multivariable modified Poisson regression models were used to examine the associations between the CHA₂DS₂-VASc score, ATRIA score and benefits' generosity and anticoagulant selection. Multivariable modified Poisson regression models generate the estimated relative risk (RRs) with robust standard errors.¹³ Two multivariable models were constructed. We first modeled the selection of NOACs compared with warfarin. Next, we predicted the selection of rivaroxaban with dabigatran as the referent group, restricting analysis to when both agents were FDA-approved for AF (after 11/4/2011). These models were adjusted for all measured patient baseline characteristics not already included in the clinical prediction risk scores to avoid collinearity. We conducted a number of sensitivity analyses adjusting for calendar quarter, stratifying before and after Nov 2011 in the analyses, including patients diagnosed with AF within 60 days after the index fill date, and including gender as a covariate alongside the risk scores. To assess the extent of selection driven by the risk scores and benefits' generosity measures, c-statistics were applied to examine how the prediction of the anticoagulant selection may be changed by removing the variable of interest (e.g., risk scores and benefits' generosity) from the full model. In addition, partial chi-square tests were used to compare the strength of these variables of interest in predicting anticoagulant selection and the proportion of model variance explained relative to the full model chi-square.¹⁴ Statistical significance was determined using 2-sided tests with alpha=0.05. All analyses were conducted using SAS 9.3 (Cary, NC). The UNC Institutional Review Board approved this study.

RESULTS

In total, 70,498 AF patients met study criteria (Figure 1). Of these, 43,865 (62%) used warfarin, 21,070 (30%) used dabigatran and 5,563 (8%) used rivaroxaban. Measured baseline characteristics of the AF patients beyond the risk scores are provided in Table 1. The mean age of the cohort was 70 years (standard deviation [SD] 12), and 42,334 (60%) were male. Patients using warfarin for the first time were also more likely to have experienced relevant comorbidities, particularly ischemic stroke, congestive heart failure, and VTE. Compared with warfarin, new users of dabigatran and rivaroxaban had lower mean ischemic stroke and bleeding risk scores but had better benefits' generosity in the previous 12 months (Table 2). Patients who were newly-initiating anticoagulation with rivaroxaban had greater bleeding risk than dabigatran but slightly lower ischemic stroke risk and similar benefits' generosity. Patients receiving warfarin were more likely to have lower benefits' generosity compared with NOAC users.

The multivariable regression models indicate that clinical predictions of risk are associated with selecting a particular anticoagulant in treatment-naïve AF patients. Table 3 shows the relative risk predictions of anticoagulant treatment selection adjusted for all model covariates for the 3 primary variables of interest (bleeding risk, ischemic stroke risk, and benefits' generosity). The relative risks and 95% CIs for the full model including all covariates are shown in Appendix Table 2. Ischemic stroke and bleeding risk predictions were associated with anticoagulant selection even after adjusting for all other measured baseline characteristics not already included in the risk scores. In particular, high ischemic

stroke risk was associated with selecting warfarin as opposed to a NOAC. Patients at high ischemic stroke risk (CHA₂DS₂-VASc = 2) were 25% less likely to receive a NOAC compared with warfarin. Clinical predictions of bleeding risk were also associated with warfarin selection. Patients at high bleeding risk (ATRIA = 5) were 34% less likely to receive a NOAC compared with warfarin. Moreover, patients with good benefits' generosity in the previous 12 months were more than 2 times as likely to fill a NOAC compared with warfarin. Among patients initiating NOACs, the likelihood of filling rivaroxaban compared with dabigatran was also examined (Table 3). After adjusting for measured covariates, patients with high ischemic stroke risk were no less likely to initiate rivaroxaban compared with dabigatran. By contrast, patients with high bleeding risk were 16% more likely to initiate rivaroxaban compared with dabigatran. Lastly, having good prescription benefits in the previous 12 months was also not associated with selection of either NOAC. In the sensitivity analyses, the results were not substantively changed. A description of the sensitivity analyses and corresponding results is provided in Appendix Table 3.

For the analysis comparing NOACs to warfarin, the extent of variation in anticoagulant selection was not largely driven by the risk scores (Table 4). However, the benefits' generosity was relatively more predictive of anticoagulant selection than either risk score (e.g., change in c-statistic: -0.013 for benefits' generosity vs. -0.009 for ATRIA or -0.008 for CHA₂DS₂-VASc). Benefits' generosity also had the highest partial chi-square (explaining 14% of the total model variation); however, no variable accounted for a large proportion of the total chi-square of the full model. For the analysis comparing rivaroxaban to dabigatran, none of the variables of interest added considerable prediction to anticoagulant selection, although prediction of bleeding was the strongest factor (change in c-statistic: -0.004 for ATRIA vs. -0.001 for CHA₂DS₂-VASc or benefits' generosity). In addition, the c-statistic for the full rivaroxaban vs. dabigatran model was also relatively low (0.557). The ATRIA score had the relative highest partial chi-square in selecting between rivaroxaban and dabigatran (explaining 14% of the total model variation).

DISCUSSION

In this large study of AF patients initiating anticoagulation, we found strong associations between ischemic stroke risk, bleeding risk, and prescription benefits' generosity and anticoagulant selection. Patients with high ischemic stroke risk and bleeding risk were much less likely to initiate a NOAC versus warfarin. However, the extent of anticoagulant selection driven independently by ischemic stroke risk (predictions of treatment benefit) and bleeding risk (prediction of treatment harm) was marginal, as neither score explained much variation in the multivariable adjusted regression model. By contrast, benefits' generosity was strongly associated with anticoagulant selection, even after adjusting for all other measured covariates and appeared to drive anticoagulant selection more strongly than ischemic stroke or bleeding risk predictions. Among NOAC initiators, we also found that patients initiating rivaroxaban had higher bleeding risk scores than patients initiating dabigatran, but patients using dabigatran had higher ischemic stroke risk scores. The generosity of the prescription benefit slightly differed between the NOACs, and none of the variables of interest drove much variation in selection between NOACs.

These results concur in part with previous research suggesting that some selection (or channeling) away from dabigatran has occurred, particularly in patients with high ischemic stroke and bleeding risk.^{15,16} While these studies were generally small in sample size or limited to younger patients, they too found that patients newly-initiating dabigatran had lower bleeding risk and fewer comorbidities. However, in contrast to a recent study published by Steinberg et al., we found that bleeding risk was more strongly associated with initial anticoagulant selection than ischemic stroke risk.¹⁷ Their study found an overall lack of familiarity with bleeding risk guidelines by physicians for patients enrolled in a registry; however, the study did not examine rivaroxaban or the contribution of patients' prescription benefits. By contrast, the results in our study suggest that physicians may already selectively prescribe NOACs for patients at lower risk of bleeding. However, to our knowledge, no study has yet examined the concurrent influence of treatment benefit, risks, and cost-sharing on the decision of treatment selection, nor yet conducted a similar examination of characteristics in such a large, nationwide database.^{15,16}

The large randomized-controlled trials used for initial approval of the NOACs broadly found similar efficacy in preventing ischemic stroke and systemic embolism between NOACs and warfarin but significantly better safety, particularly in reducing intracranial bleeding and hemorrhagic stroke.^{4,6,7} Our results suggest that clinicians may be differentially choosing warfarin in real-world clinical practice for patients with both high stroke risk and bleeding risk, indicating possible concerns about the lack of a reversal agent for the NOACs. Future research needs to continue to address this concern.

More importantly, while both ischemic stroke risk and bleeding risk were associated with overall anticoagulant selection, neither factor largely drove selection, but instead, selection was relatively driven more by benefits' generosity. This observation has important implications for the process and outcomes of treatment decision-making in clinical practice. Though clinical guidelines recommend that clinicians weigh the balance of benefit with the risk of harm of available treatment options,^{2,18} our study showed that benefits' generosity was a much more important factor driving anticoagulant selection in practice, even though previous studies have found that provider-patient discussions on prescription costs are often limited.^{19,20} Moreover, high treatment costs and low insurance coverage may also affect patient adherence. Previous research in other contexts has shown that high patient cost-sharing burden can lead to lower medication adherence and high rates of medication discontinuation^{21,22}, which in this setting could leave AF patients at high risk of stroke. Further research may be necessary to confirm these observations.

In addition, overall stroke risk, bleeding risk, prescription benefit and other patient characteristics in our analyses drove little variation in anticoagulant selection between NOACs and warfarin (the c-statistics ranged from 0.66 to 0.68). The large unexplained variation in treatment selection among anticoagulant initiators may indicate that possible clinical equipoise exists between the selection of NOACs and warfarin. The treatment selection may be in large part influenced by clinicians through preferences or other factors unrelated to patient clinical or prognostic characteristics. Recent guidelines from the American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) suggested that clinical equipoise may exist between all the anticoagulants

for patients at high risk of stroke.² This possible clinical equipoise may be exploited to assess the comparative effectiveness of different anticoagulants, particularly among the NOAC initiators.

Our study has several strengths and limitations. First, prescription refill records from commercial claims databases may not fully reflect medication use. However, prescription refill records have been shown to have good validity, correlation, and similar sensitivity/specificity as other measurements, including self-report, pill counts, and electronic records.^{23,24} Some warfarin fills may also not be captured due to market influences and cash payments, such as low-cost generic programs in pharmacies.^{25,26} The ATRIA score has been used less frequently but has been shown to be better validated in claims data.^{9,11} While we could not measure provider preferences directly or cluster by provider, our study sought to disentangle how patient characteristics influenced selection. As for strengths, our study used a large database of nationally-representative commercially-insured patients, including some Medicare beneficiaries. To our knowledge, most previous research examining the NOACs has been conducted in Europe or smaller databases. In addition, this study studied both dabigatran and rivaroxaban a full 2 years after NOAC availability. Lastly, while the clinical prediction risk scores have been thought to be only moderately associated with the true risk of outcomes in AF, the CHA₂DS₂-VASc has been thought to have better real-world concordance than the CHADS₂ and could be considered a strength of our study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Cohort Flow Diagram for identification of the cohort

The flow diagram for the selection of the patients with atrial fibrillation (AF) newly-initiating therapy is shown. Of the 412,448 patients who filled 1 anticoagulant prescription, 70,498 patients met the study criteria.

Table 1

Baseline characteristics of patients with atrial fibrillation newly-initiating anticoagulation, 2010-2012

Baseline Characteristic	Warfarin	Dabigatran	Rivaroxaban
Sample size	43865 (62.2%)	21,070 (29.9%)	5563 (7.9%)
Age (years)			
< 55	3886 (8.9%)	2963 (14.1%)	796 (14.3%)
55-64	10146 (23.1%)	6443 (30.6%)	1762 (31.7%)
65-74	9792 (22.3%)	4838 (23.0%)	1233 (22.6%)
75	20041 (45.7%)	6826 (32.4%)	1772 (31.9%)
Male Gender	25562 (58.3%)	13363 (63.4%)	3409 (61.3%)
Region			
Northeast	7589 (17.3%)	3513 (16.7%)	808 (14.5%)
North Central	15408 (35.1%)	6107 (29.0%)	1609 (28.9%)
South	12181 (27.8%)	7,864 (37.3%)	2288 (41.1%)
West	7732 (17.6%)	3259 (15.5%)	782 (14.1%)
Insurance plan			
Comprehensive	15701 (35.8%)	6812 (32.3%)	1716 (30.9%)
Health maintenance organization	6368 (14.5%)	1723 (8.2%)	404 (7.3%)
Point-of-service	1973 (4.5%)	1226 (5.8%)	264 (4.8%)
Preferred provider organization	16689 (38.5%)	9766 (46.4%)	2715 (48.8%)
Consumer driven health plan	707 (1.6%)	464 (2.2%)	113 (2.0%)
Ischemic Stroke	4710 (10.7%)	1495 (7.1%)	338 (6.1%)
Heart Failure	12414 (28.3%)	3851 (18.3%)	966 (17.4%)
Venous thromboembolism	5385 (12.3%)	538 (2.6%)	136 (2.4%)
Hyperlipidemia	21710 (49.5%)	10456 (49.6%)	2966 (53.3%)
Hypertension	32043 (73.1%)	14578 (69.2%)	4028 (72.4%)
Myocardial infarction	2001 (4.6%)	500 (2.4%)	141 (2.5%)
Coronary artery disease	15000 (34.2%)	5942 (28.2%)	1576 (28.3%)
Peripheral vascular disease	3892 (8.9%)	1150 (5.5%)	316 (5.7%)
Renal impairment	5517 (12.6%)	1210 (5.7%)	362 (6.5%)
Diabetes	13957 (31.8%)	5610 (26.6%)	1432 (25.7%)
Major bleeding	5975 (13.6%)	1983 (9.4%)	581 (10.4%)
Anemia	8736 (19.9%)	2241 (10.6%)	730 (13.1%)
Peptic Ulcer disease	320 (0.7%)	93 (0.4%)	31 (0.6%)
Sleep Apnea	4546 (10.4%)	2526 (12.0%)	738 (13.3%)
Cognitive deficiency	438 (1.0%)	126 (0.6%)	34 (0.6%)
Hospitalizations (1)	25231 (57.5%)	9431 (44.8%)	2597 (46.7%)
Catheter ablation	391 (0.9%)	459 (2.2%)	102 (1.8%)
Antiplatelet therapy	5726 (13.1%)	2684 (12.7%)	736 (13.2%)
Gastroprotective agent	5558 (12.7%)	2267 (10.8%)	683 (12.3%)
Antiarrhythmic	9991 (22.8%)	5344 (25.4%)	1482 (26.6%)
Digoxin	7435 (17.0%)	2973 (14.1%)	748 (13.5%)

Baseline Characteristic	Warfarin	Dabigatran	Rivaroxaban
Sample size	43865 (62.2%)	21,070 (29.9%)	5563 (7.9%)
Beta-blocker	29513 (67.3%)	14132 (67.1%)	3728 (67.1%)
Calcium channel blocker	18501 (42.2%)	8602 (40.8%)	2304 (41.4%)
Angiotensin-converting-enzyme inhibitor/angiotensin receptor blocker	25001 (57.0%)	11891 (56.4%)	3149 (56.6%)
Statin	23964 (53.6%)	11205 (53.2%)	2907 (52.3%)
Hormone	1626 (3.7%)	959 (4.6%)	258 (4.6%)

Table 2

Clinical prediction risk scores, prescription benefits and anticoagulant selection among patients with atrial fibrillation newly-initiating anticoagulation, 2010-2012

	Warfarin (N=43,865)	Dabigatran (N=21,070)	Rivaroxaban (N=5,563)
Risk Score			
CHA2DS2-VASC (Ischemic stroke risk)			
0	2182 (5.0%)	1881 (8.9%)	489 (8.8%)
1	5121 (11.7%)	3981 (18.9%)	1068 (19.2%)
2	36562 (83.4%)	15208 (72.2%)	4006 (72.0%)
Mean (SD)	3.34 (1.81)	2.69 (1.72)	2.69 (1.73)
ATRIA (Bleeding risk)			
<4	30667 (69.9%)	17602 (83.5%)	4482 (80.6%)
4	4158 (9.5%)	1501 (7.1%)	454 (8.2%)
5	9040 (20.6%)	1967 (9.3%)	627 (11.3%)
Mean (SD)	2.87 (2.39)	1.98 (1.89)	2.11 (2.01)
Prescription benefits			
Benefits' generosity			
None/poor	1,625 (3.7%)	61 (0.3%)	23 (0.4%)
Fair	21,410 (48.8%)	9769 (46.4%)	2500 (44.9%)
Good	19,595 (44.7%)	10,611 (50.4%)	2,896 (52.1%)
Mean (SD)	0.27 (0.21)	0.21 (0.14)	0.21 (0.14)

Table 3

Association between clinical risk scores, costs, and anticoagulant selection among patients newly-initiating anticoagulation

Predictive factor	Novel oral anticoagulant vs. Warfarin (referent) [§]		Rivaroxaban vs. Dabigatran (referent) ^{§†}	
	Adjusted relative Risk	95% CI	Adjusted relative risk	95% CI
CHA ₂ DS ₂ -VASC (ref: 0)				
1	0.95	0.91-0.98**	1.00	0.92-1.09
2	0.75	0.72-0.77**	0.98	0.90-1.06
ATRIA (ref: 0-3)				
4	0.86	0.83-0.90**	1.08	1.00-1.17*
5	0.66	0.64-0.69**	1.16	1.09-1.24**
Benefits' generosity (ref: none/poor)				
Fair (0.20-<0.80)	1.79	1.69-1.90**	1.11	0.98-1.27
Good (<0.20)	2.03	1.92-2.16**	1.12	0.98-1.27

[§] Adjusted for all other measured baseline covariates, except for those already included in risk scores

[†] Analysis restricted to when both were approved for atrial fibrillation (analyses conducted in 9,997 dabigatran initiators and 5,541 rivaroxaban initiators)

* p<0.05

** p<0.001

Table 4

Treatment selection driven by clinical prediction risk scores and prescription benefits' generosity among patients with atrial fibrillation newly-initiating anticoagulation

Model	C-statistic	Change in c-statistic (95% CI)	Chi-square for full model [§]	Partial chi-square
Warfarin v. novel oral anticoagulants				
Full Model with all covariates [§]	0.679	-	5635.021	-
Subtracting variables of interest:				
- CHA ₂ DS ₂ -VASC	0.671	-0.008 (-0.009, -0.007) **	-	507.496 **
- ATRIA	0.670	-0.009 (-0.011, -0.008) **	-	584.062 **
- Benefits' generosity measure	0.666	-0.013 (-0.014, -0.011) **	-	778.018 **
Rivaroxaban v. dabigatran[†]				
Full Model with all covariates [§]	0.557	-	139.126	-
Subtracting variables of interest:				
- CHA ₂ DS ₂ -VASC	0.556	-0.001 (-0.001, 0.001)	-	0.631
- ATRIA	0.553	-0.004 (-0.008, -0.001) *	-	19.684 **
- Benefits' generosity measure	0.556	-0.001 (-0.001, 0.002)	-	2.889

[§] Includes all baseline characteristics and variables of interest

* p<0.05

** p<0.001

[†] Analysis restricted to when both were approved for atrial fibrillation