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Novel Oral Anticoagulant Use Among Patients with Atrial Fibrillation Hospitalized with Ischemic Stroke or Transient Ischemic Attack

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Abstract

Background—Novel oral anticoagulants (NOACs) have been shown to be at least as good as warfarin for preventing stroke or transient ischemic attack (TIA) in patients with atrial fibrillation (AF), yet diffusion of these therapies and patterns of use among AF patients with ischemic stroke and TIA have not been well characterized.

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Methods and Results—Using data from Get With The Guidelines®–Stroke, we identified a cohort of 61,655 AF patients with ischemic stroke or TIA hospitalized between 10/2010–09/2012 and discharged on warfarin or NOAC (either dabigatran or rivaroxaban). Multivariable logistic regression was used to identify factors associated with NOAC versus warfarin therapy. In our study population, warfarin was prescribed to 88.9%, dabigatran to 9.6%, and rivaroxaban to 1.5%. NOAC use increased from 0.04% to a 16–17% plateau during the study period, though anticoagulation rates among eligible patients did not change appreciably (93.7% vs. 94.1% from first quarter 2011 to second quarter 2012), suggesting a trend of switching from warfarin to NOACs rather than increased rates of anticoagulation among eligible patients. Several bleeding risk factors and CHA_2DS_2-VASc scores were lower among those discharged on NOAC versus warfarin therapy (47.9% vs. 40.9% with CHA_2DS_2-VASc 5, p<0.001 for difference in CHA_2DS_2-VASc).

Conclusions—NOACs have had modest but growing uptake over time among AF patients hospitalized with stroke or TIA and are prescribed to patients with lower stroke risk compared to warfarin.

Keywords

Atrial fibrillation (AF) affects more than 2.5 million people in the United States, and the attributable risk for thromboembolic events ranges from 1.5% to 23.5% depending on a person's age.[1] Anticoagulation with warfarin reduces this risk by approximately 66%. For decades, warfarin was the only oral anticoagulant available for thromboembolic prophylaxis.[2] Nevertheless, warfarin therapy is cumbersome for patients and medical providers due to numerous food and drug interactions, a narrow therapeutic index, and a need for frequent monitoring.

Recently, novel oral anticoagulants (NOACs) have become available for the prevention of thromboembolic events; specifically, the direct thrombin inhibitor dabigatran and the factor Xa inhibitors rivaroxaban and apixaban. Clinical trials show that these agents are at least non-inferior to warfarin with regard to thromboembolic prophylaxis for AF and potentially safer regarding the risk of intracranial hemorrhage.[3–5] At the same time, these NOACs carry practical advantages including a decreased need for routine monitoring, a more predictable anticoagulant effect, and cost-effectiveness in high stroke risk populations.[6,7] Yet provider inexperience and a lack of clear antidote for patients with bleeding complications on NOACs may have initially tempered enthusiasm for these drugs, even though clinical trials have demonstrated similar risks of major bleeding and significant reductions in intracranial hemorrhage compared with warfarin therapy.[3–5] Little is known about the real-world uptake of these new anticoagulants, particularly in patients with ischemic stroke and transient ischemic attack (TIA).

To address this knowledge gap, we used data from Get With The Guidelines®-Stroke (GWTG-Stroke), a national quality improvement initiative and registry with >1800 participating hospitals, to characterize the prevalence, patterns, and predictors of NOAC

versus warfarin therapy at discharge among AF patients hospitalized with ischemic stroke or TIA.

Methods

GWTG-Stroke

GWTG-Stroke is a national quality improvement initiative aimed at improving stroke care. Details of the GWTG-Stroke program design have been previously published.[8] Hospitals that participate must receive approval through their local institutional review boards or a waiver of individual consent under the common rule. Trained personnel regularly review hospital records to identify patients admitted to participating centers with stroke or TIA. Medical history and demographic data from patient records are abstracted, and de-identified data are entered into a central database using a web-based patient management tool. Quintiles (Cambridge, MA) is the data collection coordination center for the American Heart Association/American Stroke Association Get With the Guidelines® programs. The Duke Clinical Research Institute (Durham, NC) serves as the data analysis center and has an agreement to analyze the aggregate, de-identified data for research purposes. The data are monitored and audited for quality and integrity.[9]

Study Population

Using GWTG-Stroke, we analyzed patients with AF who were hospitalized for ischemic stroke or TIA and discharged on warfarin or NOAC between October 19, 2010 and September 27, 2012. This time period spanned the two-year time interval after the Food and Drug Administration's (FDA's) approval of dabigatran (the first NOAC on the market for AF stroke prophylaxis), as well as the initial 15 months after the FDA's approval of rivaroxaban. As a result, for the purposes of this study, NOAC refers to dabigatran and rivaroxaban only, since apixaban had not yet been approved for general use during the study period. We excluded sites with >25% missing information in the medical history panel, patients with hemorrhagic stroke or other documented contraindications to anticoagulant therapy, and patients who had no documented discharge destination or transferred out of the initial hospital. Of the 128,740 patients hospitalized with ischemic stroke/TIA and AF during the study period, 22,236 were excluded due to transferring out from the original facility or not having a documented discharge destination, 30,857 were excluded due to a documented contraindication to anticoagulant therapy, 4,771 were excluded due to lack of being discharged on any anticoagulant, 7,214 were excluded for anticoagulant choice other than NOAC or warfarin, and 2,007 were excluded due to conflicting or missing information. The final study population was comprised of 61,655 patients.

Statistical Analysis

Contingency tables were generated to identify important covariables, including demographics, clinical data, medical history, and hospital characteristics. Descriptive data are reported as percentages or as medians with interquartile ranges (IQRs). Pearson chi-square and Wilcoxon tests were used to assess univariate differences among patients discharged on NOACs versus warfarin. Hospital and patient factors associated with discharge NOAC therapy were identified using a multivariable logistic regression model and

reported as odds ratios (ORs) with 95% confidence intervals (CIs). The following variables were included in the initial model: age, sex, race, insurance status, stroke diagnosis (TIA vs. ischemic stroke), creatinine, systolic blood pressure, pre-admission anticoagulant use, heart failure, hypertension, diabetes, prior stroke/TIA, use of pre-admission anticoagulants, prosthetic heart valve, coronary disease/prior myocardial infarction, carotid stenosis, peripheral vascular disease, smoker, dyslipidemia, ambulatory status at discharge, aspirin or clopidogrel at discharge, discharge to home, hospital size, type, and region, and annual intravenous tissue plasminogen activator and stroke volumes. Patients missing information regarding creatinine, systolic blood pressure, ambulatory status, use of pre-admission anticoagulants, and site characteristics were excluded from the regression model for the main analysis (n=14,856 total exclusions). For patients included in logistic regression analysis, missing rates for remaining variables were less than 5%, with the exception of insurance status with a rate of 11.4%. Missing insurance status was imputed based on age as follows: if age ≥65 then insurance imputed to "Medicare," if age <65 and insurance present then insurance imputed to "other." If insurance was not documented then insurance status was imputed to "self-pay/no insurance." Missing values for medical history were imputed to "no," and missing race was imputed to "Caucasian." Backward selection was used to eliminate highly insignificant factors (p-value >0.1), and generalized estimating equations were used to account for within-hospital clustering. Generalized estimating equation (GEE) methods posit a working correlation structure. For this study, we used exchangeable or compound symmetric working correlation and empirical standard errors (i.e., sandwich variance). Additionally, we performed a sensitivity analysis including patients with missing data for anticoagulant prior to admission, serum creatinine, systolic blood pressure, and ambulatory status using multiple imputation to handle missing data (total n=61,408 after excluding patients from sites with high missing rates). For categorical variables with k categories, we used a Wald test with k-1 degrees of freedom and report p-value for overall relationship across levels. Temporal changes of discharge anticoagulant use were assessed by calendar quarter using Cochran-Mantel-Haenszel statistics. In order to assess anticoagulation rates among eligible patients, patients discharged on no anticoagulant (n=4,771) or a non-NOAC/non-warfarin agent (n=7,214) (including low molecular weight heparin, unfractionated heparin, fondaparinux, intravenous direct thrombin inhibitors, or "other" anticoagulants) were also included in the temporal analysis. Additional descriptive data were generated, including $CHADS_2$ (1 point each for C=congestive heart failure, H=hypertension, A=age ≥75, D=diabetes mellitus, 2 points for S_2=prior stroke/TIA) and CHA_2DS_2-VASc (as with $CHADS_2$ with exception of A_2=2 points for Age ≥75, V=1 point for vascular disease, A=1 point for age 65–74, Sc=1 point for female sex) distribution among patients discharged on NOAC versus warfarin, and site-based utilization of NOAC and warfarin at hospital discharge. For descriptive data, missing rates for all variables were ≤3% with the exception of missing rates of >10% for admission medications, insurance status, and admission ambulatory status, as well as missing rates of >20% for admission laboratory and physical exam values, National Institute of Health (NIH) stroke scale, and ambulatory status at discharge. All statistical analyses were performed using SAS version 9.1 software (SAS Institute, Cary, NC).

Results

Overall Utilization

We identified a study population of 61,655 patients from 1,542 hospitals with AF/atrial flutter who were admitted with ischemic stroke or TIA and discharged on warfarin or NOAC during our study period; 79.1% of the population suffered ischemic stroke, and the remainder (20.9%) experienced TIA. Atrial fibrillation or atrial flutter was newly diagnosed in 33% of the study population, and this proportion did not differ among those discharged on NOAC or warfarin. Among those discharged on NOAC or warfarin, dabigatran was prescribed to 9.6% (n=5,925), rivaroxaban to 1.5% (n=904), and warfarin to 88.9% (n=54,820).

Patient Characteristics (Tables 1 and 2)

For patients discharged on NOAC versus warfarin, 51.8% versus 53.3% (p=0.016) were female and the median age was 77 (IQR 69–84) versus 79 (IQR 70–85, p<0.001). The majority of patients discharged on NOAC or warfarin were white (82.7% vs. 80.8%, respectively, p=0.001), and slightly higher proportions of patients discharged on NOAC versus warfarin had private/health maintenance organization (HMO) insurance (41.7% vs. 37.6%) than Medicare (39.0% vs. 42.3%), Medicaid (5.4% vs. 6.3%), or self-pay (1.4% vs. 2.2%; p<0.001 for insurance status). Considerably fewer patients were receiving anticoagulation at hospital admission among those discharged on NOAC versus warfarin (33.1% vs. 46.6%, p<0.001). Among patients with non-missing information regarding anticoagulant use at admission and NOAC or warfarin use at discharge, use of NOAC versus warfarin was 8.1% versus 91.9% (n=2263 vs. 25562) for those on anticoagulation prior to hospitalization, and 13.9% versus 86.1% (n=3684 vs. 22908) for those not on anticoagulation prior to hospitalization.

In univariate analyses, rates of diabetes (26.7% vs. 30.0%, p<0.001), prior stroke/TIA (33.6% vs. 34.9%, p=0.041), and heart failure (12.8% vs. 17.3%, p<0.001)—all well-established risk factors for AF thromboembolism—were significantly lower among those discharged on NOAC versus warfarin. Moreover, patients discharged on NOAC had lower $CHADS_2$ and $CHA_2DS_2\text{-}VASc$ scores than those discharged on warfarin therapy (p<0.001, Figure 1), with 38.0% versus 31.3% of patients having $CHADS_2$ score 3 and 47.9% versus 40.9% with $CHA_2DS_2\text{-}VASc$ 5.

Patients discharged on NOAC versus warfarin had less severe ischemic stroke (median NIH stroke scale=3 [IQR 1–8] vs. 5 [IQR 2–11], p<0.001), shorter length of stay (3 [IQR 2–5] vs. 4 [IQR 2–6] days, p<0.001), and higher proportions of patients who could ambulate at admission (32.5% vs. 26.1%, p<0.001) and discharge (47.5% vs. 39.2%, p<0.001). More patients discharged on NOAC were discharged to home (65.0%) than a healthcare facility, compared with 52.4% of patients prescribed warfarin being discharged to home (p<0.001).

Predictors of NOAC Therapy

Table 3 shows the results of a multivariable logistic regression model for prescription of NOAC versus warfarin therapy at hospital discharge. Anticoagulation prior to admission

was associated with lower odds for NOAC versus warfarin therapy at discharge (OR 0.52, 95% CI 0.48–0.56, p<0.001). Consistent with the prevalent use of dabigatran among NOACs during the study period and safety recommendations, worsening creatinine and prosthetic heart valves were strongly associated with less NOAC therapy. Impaired ambulation, increasing age, discharge antiplatelet therapy, and Medicare or Medicaid insurance status were also associated with reduced NOAC use. Medical history of coronary disease had no association with NOAC therapy despite controversy regarding increased myocardial infarction risk with dabigatran therapy. A sensitivity analysis using multiple imputation for missing variables did not show appreciably different results, but did additionally identify female sex, heart failure, and ischemic stroke (vs. other type of stroke) to be associated with reduced NOAC use (Supplementary Table 1), which is consistent with the observation that higher stroke risk is associated with lower NOAC use. While hospitals in the south had higher odds of NOAC prescription, there was no association with hospital type (academic vs. not), bed number, or urban/rural location on NOAC therapy; however, considerable site-level variation in discharge NOAC utilization was observed. Out of 1,347 sites with >5 NOAC prescriptions during the study period, the median rate of discharge NOAC versus warfarin therapy was 9.6% (IQR 4.0–16.7), with a range from 0 to 62.5% (Figure 2).

Temporal Variability

We did observe increased NOAC use over time (p for non-zero correlation <0.001, Figure 3). Dabigatran was FDA approved for AF stroke prophylaxis in the fourth quarter of 2010, yet NOAC use was nearly absent until the third quarter of 2011 when it increased to 6.4% among patients eligible for anticoagulation. This was the same quarter in which rivaroxaban was approved by the FDA for AF stroke prophylaxis and the quarter following the updated American College of Cardiology/American Heart Association/Heart Rhythm Society update on the management of patients with AF using dabigatran.[10] There was subsequent rapid uptake with overall NOAC use leveling off in the 16–17% range for the remainder of the study period. Warfarin use and non-NOAC/non-warfarin anticoagulant use declined from the first quarter of 2011 to the second quarter of 2012 (78.8% to 72.4% for warfarin and 14.6% to 4.7% for non-NOAC/non-warfarin agents). Over these same quarters, the proportion of eligible patients who were not anticoagulated at hospital discharge did not change appreciably (from 6.3% to 5.9%).

Discussion

In this study, we examined the diffusion of NOACs in a high stroke risk population using the largest available registry of ischemic stroke and TIA patients. While other studies have also demonstrated a modest uptake in NOAC use, this is the largest study to evaluate the use of NOACs in a high-risk population with confirmed stroke or TIA.[11–14] We also observed considerable variations in NOAC use among hospitals and important differences in risk for recurrent stroke/TIA and several bleeding risk factors among patients receiving discharge NOAC versus warfarin therapy. Moreover, we found that unique non-traditional factors, such as ambulatory status and discharge destination, are significant predictors of NOAC use.

Adoption of new therapies may take well over a decade—even when clinical practice guidelines with robust evidence are available.[15,16] For example, in the first several years following publication of pivotal trials demonstrating warfarin's efficacy in stroke prevention, such as Atrial Fibrillation, Aspirin, Anticoagulation Study, 1989 (AFASAK) and Stroke Prevention in Atrial Fibrillation Study, 1991 (SPAF), there were only modest increases in warfarin utilization among AF patients from 13% in 1989 to near 25% in 1991. While utilization of anticoagulation for stroke prevention in AF has slowly increased over time, the current anticoagulation rate near 60% suggests there remain opportunities for improvement.[12] Despite potential practical advantages of NOACs over warfarin, such as reduced need for monitoring and lower intracranial hemorrhage rates, our study shows similarly modest early adoption rates for NOAC therapy. Our observed rate of uptake at 16–17% falls in the upper range of estimates among studies describing early utilization patterns. A report from the Danish National Register showed 5.2% uptake by fourth quarter 2011, while reports from the United States have shown higher early adoption rates—12% in the Outcomes Registry for Better Informed Treatment of AF (ORBIT-AF) Registry by August 2011 to as high as 16.9% in a report from the National Disease and Therapeutic Index survey by December 2011.[13,14]

In part, the modest adoption rate of NOACs in the acute ischemic stroke and TIA population may be due to differences in the patient population encountered in acute ischemic stroke and TIA care compared with the pivotal AF trials evaluating NOACs. Compared with the patients studied in those clinical trials, our study population was older (~77–79 vs. ~71–73), with a higher proportion of women (~48.6–62.5% vs. ~33.1–46.6%), and with higher mean $CHADS_2$ scores (3.87 vs. 2.10 in the Randomized Evaluation of Long-Term Anticoagulation [RE-LY] and 3.48 in Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in AF [ROCKET-AF]), consistent with our high-risk confirmed ischemic stroke/TIA population.[3–5,17] Therefore, it is not surprising that the use of NOACs is different given the differences in treating inpatients hospitalized with stroke or TIA compared with the trial populations, which treated predominantly ambulatory patients with AF.

Previous reports from ORBIT-AF, the National Disease and Therapeutic Index, and the Danish National Patient Register also focused on outpatients or a mix of outpatients/inpatients with AF. In contrast, our patient population was exclusively inpatient and had higher $CHADS_2$ and CHA_2DS_2-VASc stroke risk scores.[13,14] Nevertheless, our data agree with these prior studies by suggesting cautious uptake of NOAC therapy by physicians, mirroring the risk-treatment mismatch previously observed for warfarin therapy in AF, with higher age, bleeding risk, and stroke risk being associated with less warfarin use.[18–20] NOACs confer equal or better protection from stroke than warfarin with a lower intracerebral hemorrhage risk and no increase in major bleeding rates,[3–5] and our current analysis showed patients discharged on NOACs had lower $CHADS_2$ stroke risk scores. Moreover, NOAC use had less association with bleeding risk factors such as older age, concurrent antiplatelet therapy, and impaired ambulation.[21–23] While bleeding risk is an important clinical consideration, reports of real-world dabigatran use compared with warfarin in United States- and Denmark-based registries showed no increases in bleeding. In fact, these reports found lower intracerebral hemorrhage rates.[24,25] Although information on

real-world rivaroxaban use is limited, these reports suggest that bleeding events described in case studies and series may overstate the actual bleeding risk compared with clinical trials and population-based registries, highlighting the need for further investigation into the real-world efficacy and bleeding risk for NOAC-treated patients.

Similar to ORBIT-AF, we also identified racial and financial differences in anticoagulant choice. We found that white patients had a higher odds of NOAC prescription than other races, echoing racial disparities previously described for AF anticoagulation.[14,19,26] Closely related to this, it would appear that financial access to NOACs was a major determinant of their use, since lack of health insurance, Medicaid, and Medicare were associated with a lower odds of NOAC therapy compared with warfarin. High out-of-pocket costs are a deterrent to new prescription drug adherence, and even with health insurance, affordability may have been a concern due to substantial co-pays or cumbersome pre-approvals.[27] Given the favorable risk-benefit profile of NOACs compared with warfarin, further work is needed to close the gap conferred by financial and social barriers.

One question of interest is whether patients who are being treated with NOACs are newly initiated or switched from warfarin to NOAC therapy. GWTG-Stroke does not collect information on the specific admission anticoagulant, but it is reasonable to assume that patients on anticoagulation prior to hospitalization were likely on warfarin therapy during this study period. Using this assumption, as many as 38% of patients could have been warfarin to NOAC switchers, whereas 62% were possibly new starts. While discharge NOAC use increased during this study period, the use of warfarin (and especially non-NOAC/non-warfarin agents such as low molecular weight heparins) decreased markedly. Nonetheless, the total percentage of eligible patients discharged to home without an anticoagulant did not change appreciably (from 6.6% to 5.9%). Therefore, rather than "growing the pie" of patients anticoagulated for AF, NOACs may be preferentially prescribed in place of non-NOAC/non-warfarin anticoagulants, and to a lesser degree, in place of warfarin. Lastly, 1.4% of patients discharged on NOACs had prosthetic heart valves and 30.9% had coronary artery disease despite the possibility of adverse events while on dabigatran, which was the predominant NOAC during this study period.[3,28,29] Further education regarding the risks and benefits of NOAC therapy may be needed to increase familiarity with these drugs and prevent risk-treatment mismatches or adverse events.

Our study had several limitations. First, GWTG-Stroke is a voluntary quality improvement program and may not represent prescribing patterns at non-participating hospitals. For example, GWTG hospitals compared with American Hospital Association Hospitals were more likely to be teaching hospitals (45.2 vs. 23.7%, p<0.001), less likely to be rural (12.5 vs. 35.1%, p<0.001), and were larger (median bed size 255 vs. 88, p<0.001). Second, prescription patterns among those being discharged after ischemic stroke or TIA could differ from those of ambulatory patients with AF treated in the outpatient setting. Moreover, prior exposure to anticoagulants may have been an important confounder in the decision to either discharge on anticoagulation or on the choice of anticoagulant. Third, we only evaluated those patients discharged on oral anticoagulant therapy, and available data did not allow us to assess patterns of prescribing for new starts at hospital follow-up. Fourth, we were unable to assess adherence to discharge anticoagulant therapy after hospital discharge. Fifth, it must

be noted that rivaroxaban was only available for the latter 15 months of the study period, and with current availability of apixaban and the ongoing dissemination of information regarding NOACs, current usage patterns may differ. Sixth, we were unable to perform a formal bleeding risk assessment because we lacked data for key components of well-validated bleeding risk models such as prior bleeding episodes, and we did not include a formal assessment of stroke severity in logistic regression modeling since the NIH stroke scale had a high missing rate (29%).[21,23,30] Finally, residual measured and unmeasured confounders may still exist, particularly since we were unable to determine all clinical and social circumstances that could have influenced treatment selection from the registry such as patient choice, prescribing physician specialty, or payer mix and decisions.

In conclusion, among AF patients hospitalized with ischemic stroke or TIA, use of NOACs have been modestly integrated into clinical practice, though they tend to be used in patients with lower stroke risk and better functional status. Use of NOACs varied widely by hospital and overall anticoagulation rates at hospital discharge among eligible stroke and TIA patients did not increase appreciably. Future investigations should consider linking to claims data to further explore adherence rates, longitudinal outcomes, and safety of NOACs in clinical practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Distribution of CHADS2 Score by Choice of Anticoagulation
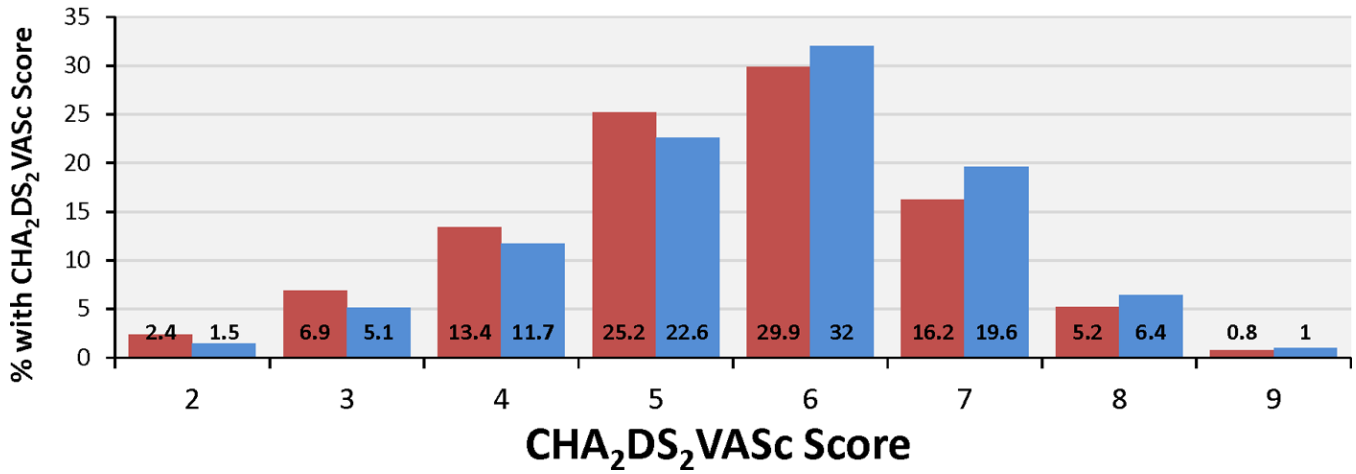
Figure 1. Distribution of CHADS$_2$ and CHA$_2$DS$_2$-VASc Scores by Choice of Anticoagulation

CHADS$_2$ and CHA$_2$DS$_2$-VASc scores were lower among patients discharged on NOAC vs. warfarin therapy among AF patients hospitalized with ischemic stroke or TIA and discharged on either warfarin or NOAC (p<0.001 for difference in CHADS$_2$ and CHA$_2$DS$_2$-VASc vs. warfarin).

AF indicates atrial fibrillation; NOAC, novel oral anticoagulant; CHADS$_2$: C=congestive heart failure, H=hypertension, A=age 75, D=diabetes mellitus, S=prior stroke or TIA; CHA$_2$DS$_2$-VASc: CHADS$_2$ plus V=vascular disease, A=age 65–74, S=female sex; TIA, transient ischemic attack
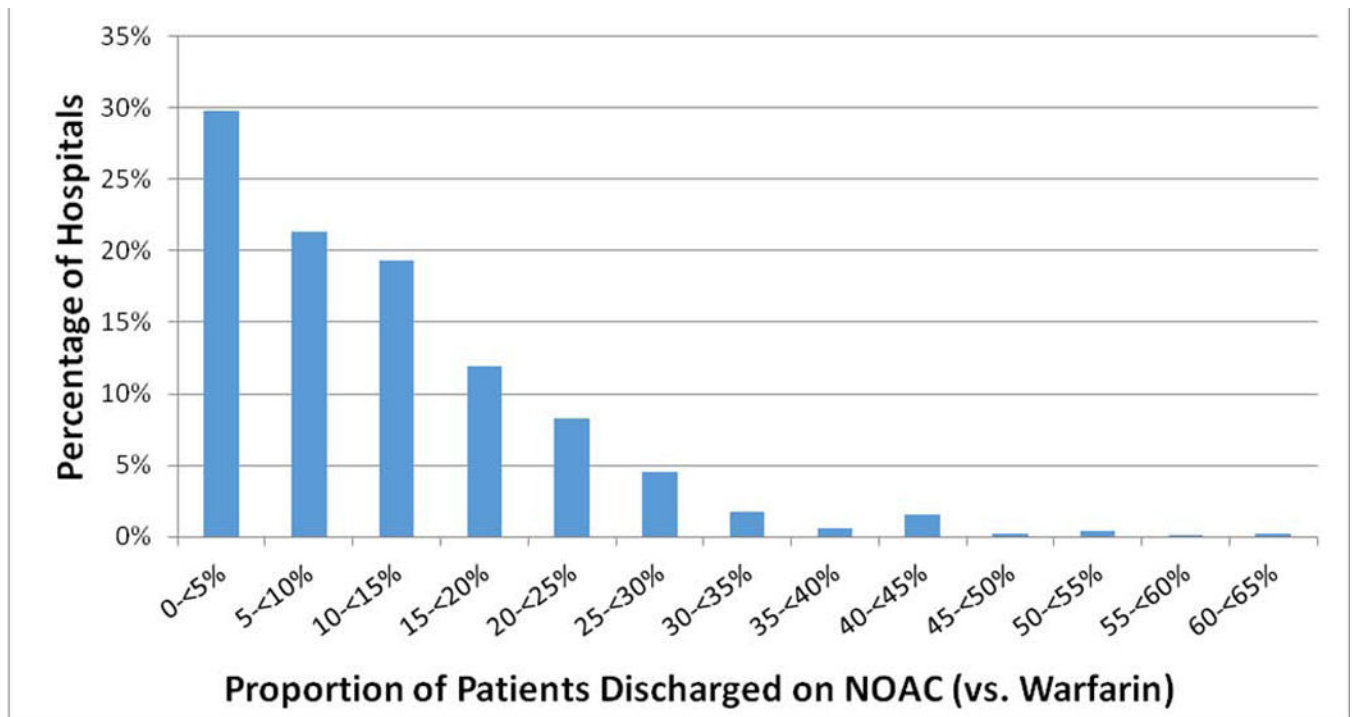
Figure 2. Hospital-level NOAC Use at Discharge

There was considerable site-level variation in NOAC use at hospital discharge among patients hospitalized with ischemic stroke/TIA and AF. Among 1347 sites with >5 NOAC prescriptions during the study period, the median rate of discharge NOAC versus warfarin therapy was 9.6% (IQR 4.0–16.7), with a range from 0 to 62.5%.

AF indicates atrial fibrillation; IQR, interquartile range; NOAC, novel oral anticoagulant; TIA, transient ischemic attack
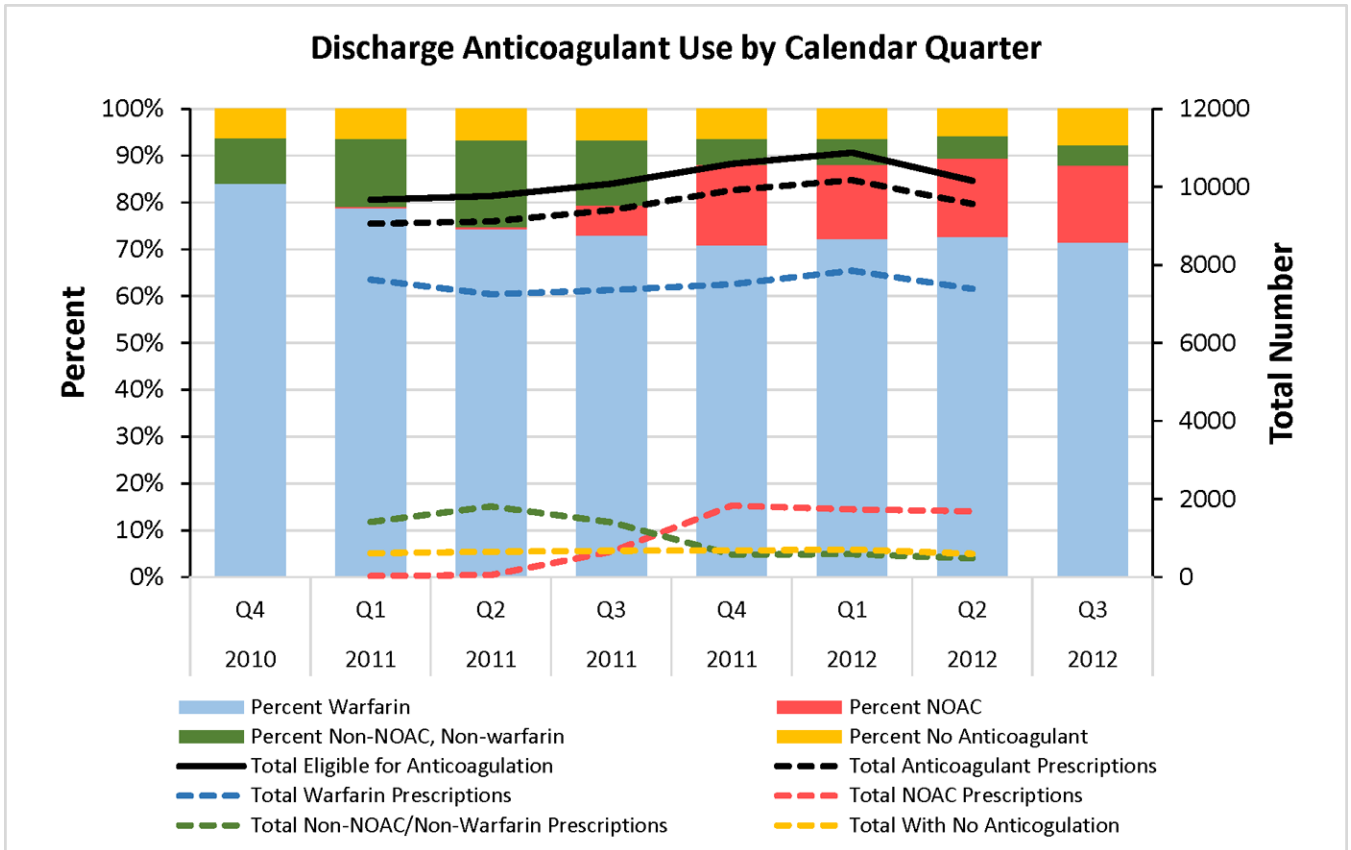
Figure 3. Discharge Anticoagulant Use by Calendar Quarter
NOAC use increased over time from 0.3 to 16.6% from first quarter of 2011 to second quarter of 2012 (p for non-zero correlation <0.001). Warfarin use and non-NOAC/non-warfarin anticoagulant use declined during the same time period (78.8% to 72.4% for warfarin and 14.6% to 4.7% for non-NOAC/non-warfarin agents). The proportion of eligible patients who were not anticoagulated at hospital discharge did not change appreciably (from 6.3% to 5.9%), suggesting that NOAC use did not increase the proportion of patients anticoagulated at hospital discharge, but were used in place of other anticoagulation strategies. Note: The total number lines were not extended to Q4 2010 and Q3 2012 because these quarters were truncated by our pre-specified study period, thereby limiting the number of patients included for those quarters.
NOAC indicates novel oral anticoagulant; Q, quarter

Table 1

Patient Characteristics by Discharge NOAC and Warfarin Use

Variable	Total Population (n=61655)	Discharged on NOAC (n=6835)	Discharged on Warfarin (n=54820)	p-value
Female sex	53.1	51.8	53.3	0.016
Age	79 (70–85)	77 (69–84)	79 (70–85)	<0.001
75	64.4	59.2	65.1	<0.001
Race/ethnicity				0.001
White	81.0	82.7	80.8	
Black	8.7	7.3	8.9	
Hispanic	4.8	4.8	4.8	
Asian	2.0	1.9	2.0	
Medical history				
Heart failure	16.8	12.8	17.3	<0.001
Hypertension	79.9	79.3	79.9	0.211
Diabetes mellitus	29.6	26.7	30.0	<0.001
Prior stroke/TIA	34.7	33.6	34.9	0.041
Prior atrial fibrillation/flutter	77.0	77.1	77.0	0.911
Coronary artery disease	34.3	30.9	34.8	<0.001
Peripheral vascular disease	5.7	4.9	5.9	0.001
Carotid stenosis	4.2	4.0	4.2	0.400
Dyslipidemia	48.5	48.6	48.5	0.957
Prosthetic heart valve	3.9	1.4	4.2	<0.001
Smoker	8.2	8.0	8.2	0.528
Admission medications				
Antiplatelet therapy	40.4	45.4	39.8	<0.001
Anticoagulation	45.1	33.1	46.6	<0.001
Admission exam/labs:				
Systolic BP (mmHg)	150(133–170)	151(134–172)	150(133–169)	<0.001
Diastolic BP (mmHg)	80 (69–92)	80 (70–92)	80 (69–92)	<0.001
Heart rate	78 (68–92)	77 (67–91)	78 (68–92)	0.001
Body mass index	27.0 (23.6–31.2)	27.0 (23.8–31.2)	27.0 (23.6–31.2)	0.460
Hemoglobin A1c	6.9 (6.2–7.9)	6.9 (6.2–7.9)	6.9 (6.2–7.9)	0.799
Creatinine (mg/dL)	1.0 (0.8–1.3)	1.0 (0.8–1.2)	1.0 (0.8–1.3)	<0.001
GFR 30 mg/dL/1.73m^2	73.1	75.2	72.9	<0.001
Total cholesterol	151(126–179)	152(128–181)	150(126–179)	0.002
Median NIH stroke scale	5 (2–11)	3 (1–8)	5 (2–11)	<0.001
NIH stroke scale 11	18.3	14.0	18.8	<0.001
Insurance status				<0.001
Medicare	42.0	39.0	42.3	
Medicaid	6.2	5.4	6.3	
Insured/HMO	38.0	41.7	37.6	

Variable	Total Population (n=61655)	Discharged on NOAC (n=6835)	Discharged on Warfarin (n=54820)	p-value
Self-pay	2.1	1.4	2.2	

Values represent percentages or medians (interquartile range).

BP indicates blood pressure; GFR, glomerular filtration rate; HMO, health maintenance organization; NIH, National Institute of Health (higher scores on NIH stroke scale indicate greater stroke severity); NOAC, novel oral anticoagulant

Table 2

Discharge Patient and Hospital Characteristics by Discharge NOAC and Warfarin Use

Variable	Total Population (n=61655)	Discharged on NOAC (n=6835)	Discharged on Warfarin (n=54820)	p-value
Discharge medications				
Aspirin	49.6	41.8	50.6	<0.001
Clopidogrel	6.2	5.0	6.4	<0.001
Aspirin and clopidogrel	2.7	2.6	2.8	0.57
Length of stay (excluding transfers)	4 (2–6)	3 (2–5)	4 (2–6)	<0.001
Length of stay 5 days	40.6	27.1	42.3	<0.001
Ambulatory status at discharge				<0.001
Unable to ambulate	10.7	6.2	11.2	
Ambulate with assistance	25.6	22.2	26.0	
Ambulate independently (with or without device)	40.1	47.5	39.2	
Discharge destination				
Other health care facility	46.2	35.0	47.6	<0.001
Home	53.8	65.0	52.4	<0.001
Hospital factors				
Hospital size (mean no. beds)	348 (243–503)	349 (240–527)	348 (243–503)	0.261
Annual stroke/TIA discharges				0.157
>300	41.4	40.9	41.4	
101–300	51.5	51.4	51.5	
100	7.1	7.7	7.1	
Region				<0.001
West	19.6	17.6	19.8	
South	30.7	37.3	29.8	
Midwest	19.7	18.4	19.9	
Northeast	30.1	26.7	30.5	
Location				0.009
Rural	5.0	4.3	5.1	
Urban	94.2	95.1	94.1	
Hospital type				0.004
Academic	49.0	46.9	49.3	
Non-academic	40.1	41.2	40.0	

Values represent percentages or medians (interquartile range).

TIA indicates transient ischemic attack; All other abbreviations can be found in Table 1.

Table 3

Factors Associated with NOAC Use (vs. Warfarin Use): Multivariable GEE Analysis

Variable	Odds Ratio	Lower Limit of 95% CI	Upper Limit of 95% CI	p-value
Age (per 10 year increase)	0.94	0.91	0.97	<0.001
Sex (female vs. male)	0.94	0.88	1.01	0.100
Race (white vs. other)	1.20	1.09	1.32	<0.001
Insurance status (vs. other)				<0.001
Medicaid	0.84	0.72	0.97	
Medicare	0.91	0.84	0.99	
No insurance	0.45	0.35	0.57	
Medical history				
Previous stroke/TIA	1.13	1.05	1.21	0.001
Carotid stenosis	1.20	1.03	1.40	0.020
Heart failure	0.93	0.84	1.02	0.120
Prosthetic heart valve	0.40	0.31	0.53	<0.001
Smoking	0.82	0.73	0.93	0.002
Anticoagulant therapy prior to admission	0.52	0.48	0.56	<0.001
Serum creatinine (per 1mg/dL unit increase)	0.75	0.69	0.81	<0.001
Systolic BP (per 10 mmHg unit increase)	1.02	1.00	1.03	0.010
Discharge medications				
Aspirin	0.72	0.66	0.77	<0.001
Clopidogrel	0.70	0.60	0.82	<0.001
Discharge to home (vs. other)	1.43	1.31	1.56	<0.001
Ambulatory status (vs. ambulate independently)				<0.001
Unable to ambulate	0.58	0.51	0.67	
Ambulate with assistance	0.87	0.80	0.95	
Region (vs. Northeast)				0.001
Midwest	1.05	0.89	1.25	
South	1.29	1.11	1.49	
West	0.91	0.75	1.11	
Number of beds (per 100 increase)	1.00	1.00	1.00	0.127
Rural vs. urban	0.75	0.55	1.04	0.080

CI indicates confidence interval; GEE, generalized estimating equations; All other abbreviations can be found in Tables 1 and 2; n=42,094