Original Contribution

Higher Incidence of Ischemic Stroke in Patients Taking Novel Oral Anticoagulants

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Background and Purpose—The increased use of novel oral anticoagulants (NOACs) to control atrial fibrillation is largely driven by the assumption that they are equally effective as warfarin at preventing ischemic stroke while putting patients at lower risk of hemorrhages. To test this hypothesis, a retrospective study of the relative incidence of strokes among patients taking NOACs versus those taking warfarin is performed.

Methods—Relative stroke incidence in the 2 groups of patients was compared using odds ratios and Fisher exact tests for significance using a data set of 71 365 on NOACs and 59 546 patients on warfarin. In addition, the 7033 patients with a record of both warfarin and NOAC use were analyzed as a separate cohort.

Results—There is a significantly higher (odds ratio=1.29, $P<0.001$) frequency of ischemic strokes among patients prescribed NOACs compared with those on warfarin. The relative frequency of ischemic strokes was also higher for every individual NOAC compared with warfarin (these higher frequencies are statistically significant for dabigatran and apixaban, though not for edoxaban and rivaroxaban). There is a lower incidence of intracranial hemorrhages and nontraumatic hemorrhages in general among patients taking NOACs, consistent with the published literature. Comparisons of the demographic and clinical profiles of the patients taking NOACs to those on warfarin do not show significantly higher background stroke risk in NOAC patients; in fact, patients on NOACs tend to be at lower background risk overall for ischemic strokes.

Conclusions—Because NOAC use is associated with higher ischemic stroke risk together with a lower risk of hemorrhages than warfarin use, it can be concluded that patients on warfarin are more strongly anticoagulated. The observed effect could be a secondary consequence of dosage control or alternatively a result of different anticoagulant effects among the different medications. **(*Stroke*. 2018;49:00-00. DOI: 10.1161/STROKEAHA.118.022636.)**

Key Words: anticoagulants ■ atrial fibrillation ■ risk ■ stroke ■ warfarin

Atrial fibrillation (AFib) is an important risk factor for acute ischemic stroke because AFib is associated with the formation of thrombi, which can ultimately lead to embolisms.[1] Consequently, one of the primary reasons AFib patients is prescribed anticoagulants as long-term medication is to reduce the risk of suffering an acute ischemic stroke. For decades, the standard of care for AFib was to prescribe the vitamin K antagonist warfarin (also known as Coumadin and numerous other trade names) as a prophylactic. Warfarin primary disadvantages as a medication to treat the consequences of AFib is the difficulty of dosage control because of its long (>40 hours) half-life,[2,3] and the long time interval required to acclimate patients to a given dose as a result of delayed effect onset.[4]

Partly because of these substantial drawbacks, new non-vitamin K antagonist anticoagulants have been developed which are increasingly being used as an alternative to warfarin. Among these novel oral anticoagulants (NOACs) are the thrombin inhibitor dabigatran (Pradaxa) and the Xa factor inhibitors, such as rivaroxaban (Xarelto), apixaban (Eliquis), and edoxaban (Savaysa/Lixiana). In the more recent literature, these anticoagulants are often referred to as direct-acting oral anticoagulants because of their comparatively rapid onset of action. This rapid onset of anticoagulant effect, as well as the comparatively short half-lives (14–17 hours for dabigatran, typically <10 hours for the Xa inhibitors), provide an advantage of simpler dosage control than warfarin.[5] In addition, NOACs are associated with a lower incidence of side effects such as intracranial hemorrhages.[6,7]

Nevertheless, there are disadvantages associated with NOACs. Among these are their relatively high price, as well as the general absence of simple and reliable tests to assess their efficacy. For example, the standard prothrombin time (PT) test used for warfarin is not a reliable indicator of dabigatran efficacy and is of marginal value for assessing the efficacy of the Xa inhibitors.[8] Furthermore, until recently the absence of Food and Drug Administration approved medications to reverse the actions of NOACs other than dabigatran[9]

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was another drawback to their use (as of 2018, the Food and Drug Administration approved Andexxa as a reversal agent for rivaroxaban and apixaban[10]).

In spite of these concerns, the use of NOACs to treat AFib and thromboses has increased significantly because of their initial introduction several years ago. One recent survey[11] documents NOAC global use increasing from <3% of prescribed anticoagulants in 2013 to >15% in 2015. In recent years, NOAC use had surpassed that of warfarin in the United States. Because of their ubiquitous use, it is of vital interest to accurately evaluate the side effects and relative efficacies of these medications in comparison to warfarin. A number of clinical trials and meta-analyses of prospective studies have compared stroke incidence in AFib patients on warfarin to those on NOACs and have generally found either no significant differences.[12,13]

However, because of highly controlled patient selection, dosing and compliance, analyses of clinical trial data may provide imprecise predictors of real-world patient outcomes. The goal of this study is to perform a retrospective analysis of the relative frequencies of acute ischemic stroke in AFib patients taking warfarin as a home medication in comparison to those patients who are taking NOACS (these will be referred to as warfarin patients and NOAC patients, respectively, throughout the article). These analyses will provide insight into the question of whether NOACs are indeed as effective at stroke prevention in the AFib patient population. The relative frequencies of intracranial hemorrhages in particular and nontraumatic bleeds in general between NOAC and warfarin patients will also be considered for comparison.

Methods

This retrospective study uses enterprise-wide data from all patients with registered encounters (hospitalizations) throughout the Hospital Corporation of America Healthcare network of US hospitals during the 2015 to 2016 calendar years. As the patient data were collected retrospectively and deidentified, the study was exempt from Institutional Review Board approval. All data were obtained from the Hospital Corporation of America Healthcare's Teradata Enterprise Data Warehouse—a centralized SQL server that functioning as a repository of electronic health record data that is periodically updated enterprise-wide via data dumps from the Electronic Health Record databases of individual hospitals and other Hospital Corporation of America facilities.[14] Enterprise Data Warehouse Teradata was queried using SQL scripts embedded in R code, and all statistical analyses of the data were performed using R version 3.3.2. The data used in this study can be obtained from Hospital Corporation of America by contacting the corresponding author to submit a request for data release, all scripts used for data analysis can also be obtained from the corresponding author.

The flowchart in Figure 1 summarizes the workflow in the analysis. The first query retrieves patient records for all individuals taking an anticoagulant as home medication, based on information self-reported by the patients or their families at the time they were hospitalized (indicating that the anticoagulants were taken before the stroke occurrence in the case of stroke patients). The queries were run using generic and trade names for warfarin and the NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban). Patients who have records of being on both warfarin and a NOAC (or whose records indicated more than a single NOAC) were considered as a separate category. It is possible that many of these multiple anticoagulant cases represent instances where patients were prescribed one type of anticoagulant and subsequently placed on a different one. The available data does not indicate which of these patients were initially on warfarin and then placed on NOACs versus vice-versa. Therefore, this data class will be treated as a single category, potentially indicative of patients who failed to respond well to at least 1 anticoagulant before being prescribed another.

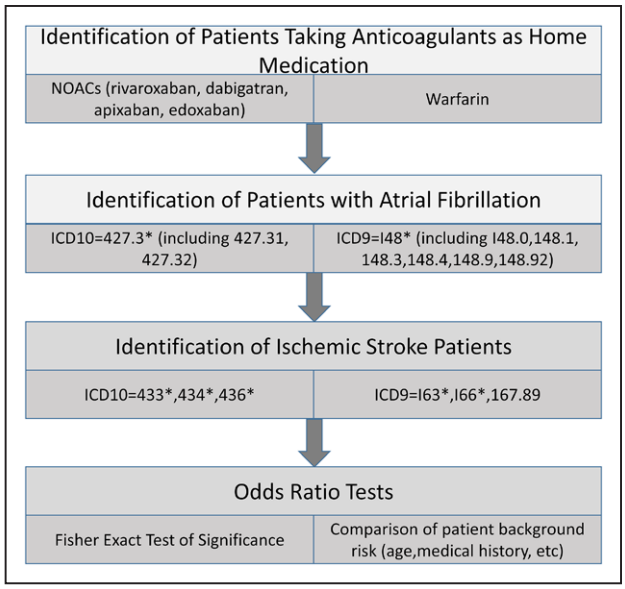

Figure 1. Flowchart for the study. Including the *International Classification of Diseases Ninth Revision* (*ICD-9*) and *Tenth Revision* (*ICD-10*) codes for atrial fibrillation. The * refers to a wildcard search term for the diagnostic code suffixes. NOACs indicates novel oral anticoagulants.

The set of patients taking anticoagulants as home medication was filtered further so that only individuals with a diagnosis of AFib would be considered for the analysis. These patients were classified according to whether they experienced an acute ischemic stroke during the time that they were on anticoagulants. Additionally, patients who experienced intracranial hemorrhages (including subarachnoid hemorrhages and intracerebral hemorrhages) were identified, as well as all patients who suffered from any nontrauma-induced hemorrhage. All records were obtained by searching *International Classification of Diseases Ninth Revision* (*ICD-9*) and *Tenth Revision* (*ICD-10*) diagnostic codes. These codes are summarized for AFib and ischemic stroke in Figure 1 while Table I in the online-only Data Supplement provides a summary of all of the diagnostic query codes, including those for intracranial hemorrhage.

The relative incidence of acute ischemic strokes (and all other conditions of interest) between the NOAC and warfarin cohorts was compared using odds ratios (ORs) and assessed for statistical significance using Fisher exact tests. Comparisons between NOACs and warfarin were made both by pooling all patients on NOACs into a single cohort, followed by analyses that compared the relative performance of warfarin to each NOAC individually.

To determine whether observed differences in stroke incidence are specifically related to anticoagulant choice, as opposed to differences in underlying stroke risk factors, demographics, and comorbid health conditions were compared between the 2 patient groups using a risk score analogous to the CHADS2 scores[15,16] commonly used to predict stroke risk. There was insufficient information to calculate CHADS2 directly because a previous history of ischemic stroke or transient ischemic attack was not reliably available from the data sources. However, the following key risk factors for ischemic stroke could be assessed: age ≥75, female sex, diagnosis of diabetes mellitus, diagnosis of hypertension, and history of congestive heart failure. As in the CHADS2 calculation, an individual is assigned a score of 1 if the factor is present and 0 otherwise, with the cumulative score for the patient is determined by the sum over all individual risk factors. The fraction of patients with coagulopathy and cerebrovascular disease (including small vessel disease and cranial atherosclerosis) is also considered to estimate the relative incidence of stroke events that may be unrelated to AFib or its treatment.

In addition, National Institutes of Health Stroke Scale (NIHSS) scores at admission between the 2 groups of AFib patients were compared to determine whether stroke severity differed between patients taking NOACs versus warfarin. The same was done for PTs in the 2 sets of patients, excluding patients on dabigatran in the NOAC set. All comparisons of outcome and risk scores between NOAC and warfarin patients were assessed using *t* tests.

Results

Within the group of 126 777 patients taking NOACs and 118 527 patients taking warfarin, there are 67 262 and 59 066 unique records of NOAC and warfarin patients with AFib, respectively (as well as 7033 patients recorded as having used both warfarin and a NOAC).

Ischemic Stroke Incidence

The fraction of ischemic stroke occurrence among the surveyed group of AFib patients taking NOACs is over higher than among those taking warfarin as a home medication, with an incidence OR of 1.29 (Table 1; Figure 2 for summaries). This difference is statistically significant ($P<0.001$) and indicative of greater ischemic stroke risk associated with the use of NOACs.

Acute ischemic stroke incidence in individual NOACs in comparison to warfarin is qualitatively similar, with 2 exceptions. Specifically, the incidence of ischemic strokes in patients taking edoxaban and rivaroxaban is higher than in those taking warfarin, but unlike apixaban and dabigatran, these differences are not statistically significant, as can be seen in Table 2. Note the comparatively small number of patients on edoxaban, which accounts for the Fisher exact test $P>0.05$ in spite of the high OR.

The relative incidence of ischemic stroke risk factors among the 2 groups of patients is summarized in Table 3. For all risk factors of ischemic stroke considered, there is actually a higher prevalence among the warfarin patients. The mean sum of risk factors (ie, the presence of each variable =+1, with a maximum value=5) in NOAC patients is 2.66 versus 2.85 for the warfarin patients, suggesting that NOAC patients are overall at a slightly lower background risk for ischemic stroke than the patients on warfarin, which is contrary to the observed pattern of stroke incidence.

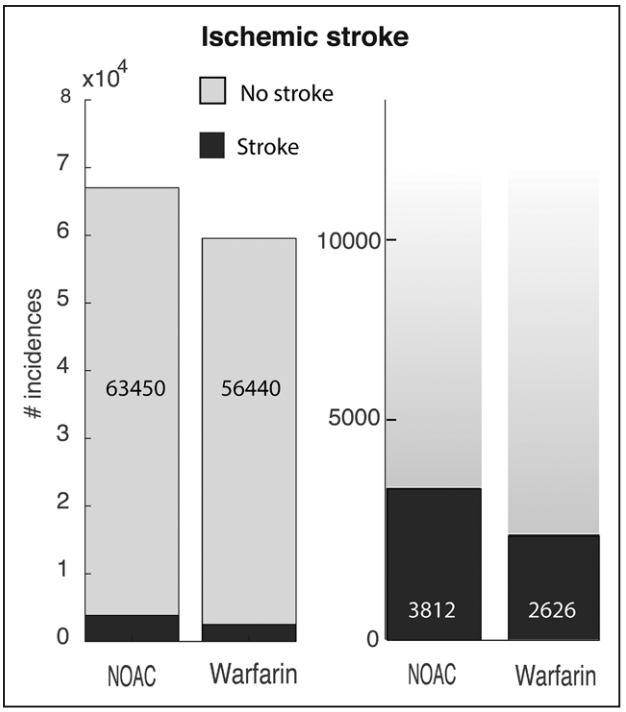

Figure 2. Ischemic stroke incidence. The relative incidence of ischemic strokes among atrial fibrillation (AFib) patients taking novel oral anticoagulants (NOACs) is significantly greater than in those taking warfarin as home medication. Note that the number of incidences in the left-hand bars are nonstroke cases rather than the total.

Cerebrovascular diseases, considered separately from the other risk factors, are rare among this group of AFib patients: 0.2% of the NOAC patients and 0.3% of warfarin patients have cerebrovascular disease. A comparison of stroke severity based on NIHSS scores does indicate marginally greater stroke severity among patients who take warfarin, this difference is small (mean NIHSS for NOAC patients is 4.78 versus 5.23 for warfarin patients), but nevertheless statistically significant ($t=-2.55$, $P=0.011$).

The mean PT for the AFib patients on warfarin is much higher, 19.66 minutes, compared with 13.02 minutes for the NOAC patients ($t=-42.24$, $P<0.001$).

Table 1. Summary of Stroke and Hemorrhage Incidence for Patients on NOACs, Warfarin, and Both

Acute Ischemic Stroke	No. of Patients	Odds Ratio and *P* Value (Fisher Exact Test)
NOAC vs warfarin	3812, 2626	1.291, $P<<0.001$
Both vs NOAC	713, 3812	1.878, $P<<0.001$
Both vs warfarin	713, 2626	2.425, $P<<0.001$
Intracranial hemorrhage		
NOAC vs warfarin	320, 397	0.7064, $P<<0.001$
Both vs NOAC	41, 320	1.227, $P=0.208$
Both vs warfarin	41, 397	0.867, $P>0.437$
General nontraumatic hemorrhage		
NOAC vs warfarin	6479, 7892	0.691, $P<<0.001$
Both vs NOAC	1266, 6479	2.059, $P<<0.001$
Both vs warfarin	1266, 7892	1.423, $P<<0.001$

NOAC indicates novel oral anticoagulant.

Table 2. Relative Incidence of Acute Ischemic Strokes in Patients Taking Individual NOACs Versus Patients on Warfarin

NOAC	No. of Patients on NOAC (No. of Patients With Stroke)	OR Stroke Incidence Compared With Warfarin (Fisher Exact Test *P* Value)
Edoxaban	443 (25)	1.399 (0.117)
Apixaban	40 535 (2446)	1.447 (<0.001)
Rivaroxaban	28 793 (1305)	1.069 (0.055)
Dabigatran	8202 (444)	1.289 (<0.001)

As in Figure 1, the total number of AFib patients taking warfarin is 59 546, of whom 2531 had strokes. AFib indicates atrial fibrillation; NOAC, novel oral anticoagulant; and OR, odds ratio.

Table 3. Risk Factors for Ischemic Stroke

	NOAC	Warfarin	Both
Hypertension, n (*P*)	52 993 (0.788)	44 671 (0.756)	5630 (0.801)
Diabetes mellitus, n (*P*)	24 804 (0.368)	24 386 (0.413)	3611 (0.513)
≥75 y of age, n (*P*)	38 048 (0.525)	34 271 (0.580)	3442 (0.492)
History of congestive heart failure, n (*P*)	33 821 (0.503)	38 150 (0.646)	7000 (0.995)
Sex (number and proportion female)	32 118 (0.478)	27 127 (0.459)	3538 (0.503)
Mean sum of risk factors (maximum=5 per patient)	2.662	2.854	3.304

Mean sum of risk factor comparison t=−23.54, P<<0.001. The values in each column are the raw counts and (relative frequency), respectively. Note that the total numbers in each category may differ slightly from one another, reflecting different numbers of unique patient records with available data. NOAC indicates novel oral anticoagulant.

Hemorrhage Incidence

In contrast to the greater relative frequency of acute ischemic strokes, the frequency of intracranial hemorrhages is consistently much lower in patients taking NOACs (OR=0.706, P<<0.001) than among the warfarin patients, as summarized in Figure 3. It is noted that warfarin patients also have a somewhat higher incidence of coagulopathies that potentially put them at risk for intracranial hemorrhage: 5.1% of the warfarin patients have coagulopathy versus 1.3% of NOAC patients (and 2.2% among patients who have a history of both NOAC and warfarin use).

These results are consistent with, and indeed a special instance of, the fact that all nontrauma-induced hemorrhages (spontaneous bleed occurrences at any site/organ of the body, including intracranial) are significantly less frequent among patients taking NOACs, that is OR=0.691 (Table 1; Figure I in the online-only Data Supplement).

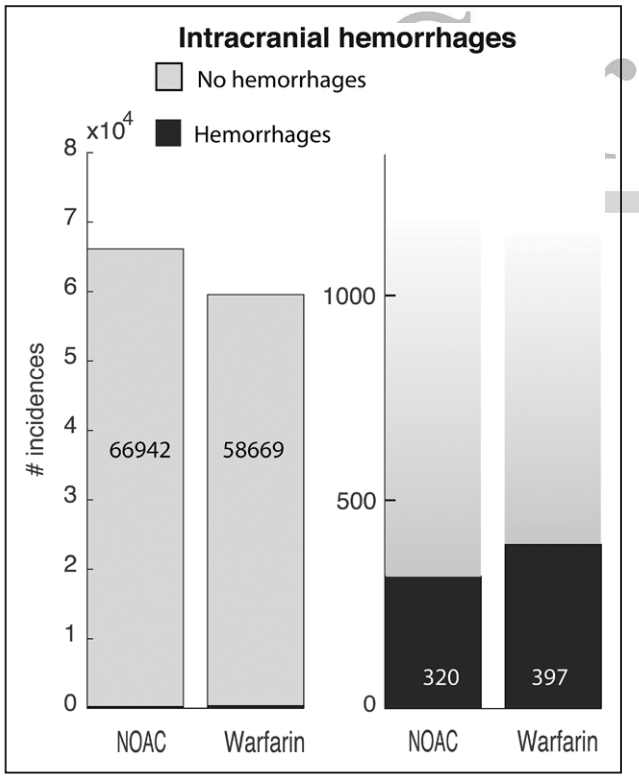

Figure 3. Intracranial hemorrhage incidence. The relative incidence of intracranial hemorrhages is nearly 2-fold higher in atrial fibrillation (AFib) patients on warfarin than in those on novel oral anticoagulants (NOACs). The numbers in the left-hand bars are the number of nonhemorrhage cases rather than the total.

Multianticoagulant Patients

Patients with a history of using both warfarin and a NOAC (nonsimultaneously) differ significantly from those on only a single anticoagulant with respect to both stroke incidence and risk factors, as can be seen in Tables 1 and 3, respectively. Multianticoagulant patients a higher incidence of acute stroke than either warfarin-only patients (OR=2.42, P<<0.001) or NOAC-only patients (OR=1.88, P<<0.001). They also have a significantly higher incidence of nontraumatic hemorrhages generally (although their incidence of intracranial hemorrhages specifically is not significantly different from the single-anticoagulant patients).

Multianticoagulant patients also seem to have a higher frequency of the most risk factors for stroke and hemorrhaging—with a sum of risk factors at 3.30 out of 5. Most notably, 99.5% of these multianticoagulant patients have a history of congestive heart failure, compared with 64.6% and 50.3%, respectively, for warfarin and NOAC-only patients. In contrast, they do not differ significantly from warfarin or NOAC patients with respect to experienced stroke severity (mean NIHSS=5.37 for both versus 5.33 and 4.83 for warfarin and NOAC respectively, with t test P>0.05 for both comparisons).

Summary and Discussion

One of the principal arguments made in both the published literature and in clinical practice favoring the treatment of AFib using NOACs rather than warfarin is the well-documented lower risk of hemorrhaging, particularly intracranial hemorrhages.[6] The results presented in this article suggest that this reduced risk of nontraumatic bleeding potentially comes at the cost of a higher risk of ischemic strokes in NOAC patients. This finding should be a matter of particular concern in view of the fact that ischemic strokes are more common than intracranial hemorrhages by an order of magnitude. Furthermore, the lower relative occurrence of background stroke risk factors in the sample set of NOAC patients in comparison to those on warfarin strongly suggest that the observed higher frequency of ischemic stroke in NOAC patients is not simply an artifact of confounding variables. In fact, in spite of insufficient data to calculate CHADS2 or CHA2DS2-VASc scores, the available information suggests that if anything, warfarin patients

would be expected to experience higher stroke incidence because of greater age and comorbidities, when in fact they have a lower incidence of stroke than is observed in the patients taking NOACs.

As a qualification to the general trend of higher stroke incidence among NOAC patients overall, it is noted that when NOACs are considered individually rather than collectively, higher ischemic stroke risk is especially strong for apixaban and dabigatran, whereas the results are more ambiguous for edoxaban (high OR but not statistically significant because of small sample size), as well as for rivaroxaban, which has an OR for ischemic stroke relative to warfarin that is only marginally >1. Additionally, although the risk of ischemic stroke does seem to be higher in patients who take NOACs, it does not seem to be the case that stroke severity is greater. The differences in NIHSS at admission between patients taking NOACs versus those who take warfarin are small (<1), with slightly lower values in the patients on NOACs. The latter effect may be because of the slightly higher age and prevalence of other stroke factors in the warfarin cohort.

A third class of patients, those with a record of both warfarin and NOAC use, seem to constitute a special case, being characterized by both higher stroke risk (particularly congestive heart failure) and a significantly higher incidence of stroke than patients on a single anticoagulant. These findings support the hypothesis that many if not most of these patients represent cases of anticoagulant failures, that is these individuals may have been initially on warfarin (or a NOAC) and subsequently switched to another medication because of poor response. The distinct clinical characteristics of the multiple anticoagulant patients support treating them as a separate cohort with respect to stroke risk regardless of potential within-group heterogeneities.

The increased risk of acute ischemic strokes, considered together with the decreased risk of nontraumatic hemorrhages (particularly hemorrhagic strokes) in NOAC patients with AFib compared with warfarin patients suggests that NOAC patients may be less strongly or less consistently anticoagulated, an interpretation consistent with lower ischemic stroke risk and elevated intracranial hemorrhage risk in patients who are strongly anticoagulated. This interpretation is also given partial qualitative support by the observed higher PTs for patients on warfarin in comparison to NOACs other than dabigatran (the latter was excluded from PT comparison because this measure of anticoagulation is not meaningful for thrombin inhibitors; however, PT does correlate with Xa-inhibitor dosage and can be a useful heuristic proxy for anticoagulation for these NOACs, albeit without the precision of PT assays for warfarin.[8,17]

These considerations raise of question of why patients on NOACs may be less strongly and consistently anticoagulated. One possible explanation lies in the relationship between drug properties and dosage/prescription compliance. Specifically, warfarin has a long effect onset time compared with NOACs, which may lead to compensatory overdosing and consequently higher anticoagulation. In addition, warfarin is characterized by a long half-life (>40 hours), which means that its effects will persist for some time even if patients are not fully compliant with their prescription regimens. In contrast, the much shorter half-lives (<10 hours for apixaban and rivaroxaban and <20 for dabigatran) imply that failures to take prescription doses on a regular basis—that is daily or twice a day—results in the loss of anticoagulation.[18] Unfortunately, there are no data available on patient compliance in the records used for this study to evaluate this explanation of the results in comparison to alternative causes, such as intrinsic differences in the medication among dosage-compliant patients.

Although the higher incidence of intracranial hemorrhages in warfarin patients observed in this study is consistent with much of the published literature, it is remarked that the results on higher incidence of ischemic strokes in NOAC patients seem to contradict a number of recent studies. For example, Hicks et al[12] describe a significant reduction in ischemic stroke risk associated with NOAC use collectively, while Coleman et al[13] found a significant reduction in stroke incidence associated with rivaroxaban relative to warfarin and no significant difference in acute ischemic stroke incidence between the other NOACs and warfarin. It should be emphasized that most of the publications on ischemic stroke incidence in relation to anticoagulant use are either prospective clinical trials or meta-analyses of multiple prospective studies. In clinical trials, both patient demographic profiles and clinical history are carefully controlled for, and patient compliance with prescribed medication tends to be good. Consequently, this retrospective analysis, on account of the much larger sample size and the wide distribution of patients, may be a more representative set of outcomes for accurate comparison.

The discrepancies between the results outlined above and previous studies suggest a need for closer consideration of background covariate risk factors across cohorts in future studies, especially in the clinical trial cohorts. Clinically, these findings also indicate that monitoring levels of anticoagulation among patients who take NOACs may be an important unfilled need in stroke prevention and that the phasing out of warfarin use among AFib patients may in some instances be contra-indicated.

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Disclosures

None.

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