Atrial Fibrillation Diagnosis Timing, Ambulatory ECG Monitoring Utilization, and Risk of Recurrent Stroke

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Background—The risk of recurrence after an initial ischemic stroke or transient ischemic attack (TIA) may be impacted by undiagnosed atrial fibrillation (AF). We therefore assessed the impact of AF diagnosis and timing on stroke/TIA recurrence rates in a large real-world sample of patients.

Methods and Results—Using commercial claims data (Truven Health Analytics MarketScan), we performed a retrospective cohort study of patients with an index stroke or TIA event recorded in years 2008 through 2011. Patients were characterized by baseline oral anticoagulation, $CHADS_2$ and CHA_2DS_2-VASc scores, AF diagnosis and timing with respect to the index stroke, and presence or absence of post-index ambulatory cardiac monitoring. The primary outcome was the recurrence of an ischemic stroke or TIA. Of 179 160 patients (age 67±16.2 years; 53.7% female), the Kaplan-Meier estimate for stroke/TIA recurrence within 1 year was 10.6%. Not having oral anticoagulation prescribed at baseline and having AF first diagnosed >7 days post-stroke (late AF) was highly associated with recurrent stroke/TIA (hazard ratio, 2.0; 95% confidence interval, 1.9–2.1). Among patients with at least 1 year of follow-up, only 2.6% and 9.7% had ambulatory ECG monitoring in the 7 days and 12 months post-stroke, respectively.

Conclusions—AF diagnosed after stroke is an important hallmark of recurrent stroke risk. Increasing the low utilization of cardiac monitoring after stroke could identify undiagnosed AF earlier, leading to appropriate oral anticoagulation treatment and a reduction in stroke/TIA recurrence.

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Key Words: arrhythmias, cardiac ■ atrial fibrillation ■ electrocardiography, ambulatory ■ recurrence ■ retrospective studies ■ stroke

The prevention of ischemic stroke, including stroke recurrence, is an important public health concern. Nearly 1 in 4 strokes in the United States are recurrent strokes (185 000 of 795 000), and 87% of all strokes are ischemic.[1] Stroke causes approximately 1 in 20 deaths in the United States, accounting for 128 932 deaths in 2011, despite a 35.1% reduction in stroke-related mortality rates in the preceding 10 years.[1] In addition, stroke is a leading cause of serious disability, the prevalence of which increases with age. At 6 months post-stroke, moderate to severe neurological deficits have been observed in 43% of elderly stroke survivors.[2]

Atrial fibrillation (AF) is a known risk factor for stroke, with embolism of thrombi in the left atrial appendage accounting for approximately 10% of all ischemic strokes.[3] AF is also the most common cardiac arrhythmia, and its prevalence increases substantially with age; thus, early detection combined with appropriate oral anticoagulation (OAC) therapy is an important strategy for reducing stroke recurrences.[4,5] Unfortunately, it is not uncommon for a stroke to be the impetus for the first AF diagnosis. The detection rate for AF after stroke is highly dependent on the type and duration of cardiac monitoring used, ranging from 2.8% to 13.7% at the initial hospitalization and increasing with further ambulatory monitoring after discharge.[6–8] On the basis of the evidence that more prolonged monitoring detects higher rates of paroxysmal AF, current guidelines include a new recommendation for rhythm monitoring of approximately 30 days duration within 6 months of a cryptogenic stroke event.[9]

Observational research on large study populations could facilitate an understanding of the complicated interactions between the existence and the detection of risk factors, treatment patterns, and stroke recurrence, especially because the cause of ischemic stroke is unknown in 20% to 40% of cases.[10] We therefore sought to determine the association between the timing of AF diagnosis after the index stroke/TIA and the outcome of recurrent stroke/TIA, and secondarily to characterize the real-world usage of post-stroke ambulatory cardiac monitoring. We hypothesized that timely detection of AF after stroke is associated with anticoagulation and is also associated with reduced risk of recurrent stroke.

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WHAT IS KNOWN

- The cause of ischemic stroke is not identified in up to 40% of cases.
- This may be due to variability in the type and duration of monitoring for atrial fibrillation (AF) after stroke, especially when AF is paroxysmal and harder to detect.

WHAT THE STUDY ADDS

- In a retrospective commercial claims cohort of 180 000 US patients with stroke, not having oral anticoagulation prescribed at time of stroke and having AF first diagnosed >7 days post-stroke resulted in doubling the risk of stroke.
- Only 2.6% and 9.7% of stroke patients had ambulatory ECG monitoring in the 7 days and 12 months post-stroke; new AF was diagnosed more post-stroke when ambulatory ECG monitoring was performed.
- Ambulatory cardiac monitoring is used infrequently after stroke, but could lead to detection and treatment of undiagnosed AF to reduce stroke recurrence.

Methods

Data Source

The data source utilized for this retrospective cohort study was administrative claims data from the Truven Health Analytics MarketScan Commercial Claims and Encounters and Medicare Supplemental Databases, which contain data on over 180 million patients since 1995. These databases contain fully integrated patient-level healthcare utilization data from a US population of employees, spouses, and dependents who are covered by employer-sponsored private health insurance. They also include retirees with Medicare supplemental coverage that is paid for by employers.[11]

Patient Selection

The study population included patients with an index ischemic stroke or TIA between January 2008 and December 2011, identified by *International Classification of Diseases*, Ninth Revision, Clinical Modification (ICD-9-CM) codes of 435.x, 436, 433.x1, or 434.x1.[12–14] Patients with evidence of a stroke before the index stroke diagnosis, including ICD-9-CM codes 438.x for late effects of stroke or V12.54 for history of stroke, were excluded. Continuous health plan enrollment was required for a minimum of 1 year before a patient's first recorded stroke to allow sufficient data to categorize the patient with respect to risk factors and also to increase the likelihood that this index stroke was the patient's first stroke event. Because of the difficulty in distinguishing healthcare utilization for follow-up of an index stroke from utilization due to a second stroke, only strokes with inpatient or emergency department (ED) utilization were included.

Survival Population

Patients who met the inclusion and exclusion criteria for this study were defined as the survival population as a result of their use in all statistical survival modeling. This population had no required period of minimum enrollment after their index stroke, thus their duration of follow-up varied. Survival modeling methodology properly takes into account the varying drop-off in population size because of loss of follow-up, allowing the use of the largest sample size and all available follow-up information, and thus avoiding a potential source of survival bias.

12-Month Analysis Population

A subset of the survival population, meeting an additional requirement of at least 1 year of follow-up enrollment, was defined as the 12-month analysis population. This population was utilized for all summary statistics to allow a uniform and interpretable follow-up period for calculation of unadjusted yearly rates.

Primary Exposure Variables

Three types of risk factors for stroke recurrence were analyzed in this study: (1) the category of AF/OAC risk, a combination of AF diagnosis and timing with OAC utilization status at baseline (with OAC or no OAC); (2) index stroke characteristics, utilized as proxies for severity level; and (3) $CHADS_2$ and CHA_2DS_2-VASc risk scores, as summaries of risk due to comorbid conditions. To create the primary risk classifications, each patient was assigned to 1 of 3 categories, as follows: (i) no AF diagnosis seen within ±12 months of the index stroke (no AF), (ii) AF first diagnosed within 12 months before or within 7 days after the index stroke (early AF), or (iii) AF first diagnosed >7 days after the index stroke (late AF). This AF timing category was then combined with baseline OAC status, as determined by a record of OAC utilization in the 12 months before the index stroke, to create an AF/OAC risk classification variable with 6 categories.

Covariates

Index stroke/TIA severity was categorized into 3 levels: occlusion of cerebral or precerebral arteries with infarction (stroke), acute but ill-defined cerebrovascular disease, and TIA. Patients with multiple diagnoses on the index day were categorized according to the highest recorded level. Additional markers of stroke severity were separate indicators for inpatient hospitalization and ED utilization on the day of the index stroke diagnosis, at least one of which was required for inclusion.

$CHADS_2$ and CHA_2DS_2-VASc risk scores were calculated for each patient based on their sex and age at the time of their index stroke/TIA and on recorded diagnoses of the component comorbid conditions within the year immediately prior. The $CHADS_2$ score included 1 point each for evidence of congestive heart failure, hypertension, age ≥75 years, and diabetes mellitus, with 2 points for the index stroke. Similarly, the CHA_2DS_2-VASc score included 1 point each for evidence of congestive heart failure, hypertension, age 65 to 74 years, diabetes mellitus, and vascular disease, with 2 points for age ≥75 years and 2 points for the index stroke. As defined, all patients had minimum $CHADS_2$ and CHA_2DS_2-VASc risk scores of 2 due to their index stroke.[15,16] Finally, 2 additional classification variables were created by crossing AF/OAC risk with $CHADS_2$ and CHA_2DS_2-VASc risk scores.

Outcomes

The primary outcome of interest, stroke recurrence within 1 year, was defined by ICD-9-CM diagnosis codes combined with an inpatient hospitalization or ED visit, to conform to the definition used for index strokes. Strokes occurring within 7 days after the index stroke diagnosis or during the initial inpatient hospitalization were excluded to ensure that all second strokes, as captured, were new events. Overall stroke recurrence rates, as well as stroke recurrence by $CHADS_2$ and CHA_2DS_2-VASc risk scores, were summarized for the 12-month analysis population.

The overall incidence of new AF, first detected after the index stroke, was also of interest. Baseline prevalence of AF in the stroke population was defined by an ICD-9-CM diagnosis code 427.31 or antiarrhythmic drug utilization in the year before the index stroke. Thus, patients with new AF were defined as the population of patients with evidence of AF in the year after the index stroke, but with no evidence in the year prior. Both baseline and new AF were summarized for the 12-month analysis population as a whole, as well as by $CHADS_2$ and CHA_2DS_2-VASc risk scores.

We also secondarily examined the incidence and type of ambulatory cardiac monitoring utilization in the year after index stroke.[6] This monitoring incidence was ascertained via records of Current

Procedural Terminology diagnosis codes for one or more of the following: mobile cardiac outpatient telemetry, external loop recorder, Holter monitor, implantable loop recorder, or extended ECG recordings. (Current Procedural Terminology copyright 2014 American Medical Association. All rights reserved. Current Procedural Terminology is a registered trademark of the American Medical Association.) Monitoring rates were summarized for the overall 12-month analysis population, as well as for the subsets of the population with and without a recurrent stroke within 12 months after their index stroke.

Statistical Models

Survival analysis methods were used to model the time from the index ischemic stroke/TIA event to a recurrence in the survival population. These methods correctly incorporate censoring information for those patients with incomplete follow-up. Kaplan-Meier models were used to derive product limit estimates for ischemic stroke recurrence rates at each level of the AF/OAC/$CHADS_2$ and AF/OAC/CHA_2DS_2-VASc risk classification variables. Thus, Kaplan-Meier estimates are univariate estimates based on a single predictor variable that includes category, for each mutually exclusive and collectively exhaustive combination of AF, OAC, and risk score levels.

We used multivariable Cox regression to estimate the hazard ratios for stroke recurrence within 1 year at each level of CHA_2DS_2-VASc score, AF/OAC risk category, index stroke severity, and inpatient or ED utilization on the day of the index stroke diagnosis. Each hazard ratio represents the recurrence risk associated with the particular level of the predictor variable compared with the reference level of that same predictor, after adjusting for all remaining predictors in the model. In other words, the hazard ratio can be interpreted as the relative risk of a stroke recurrence within 1 year for a patient with the particular risk factor level compared with a patient with the reference value of the same risk factor, given that both patients have the same levels of every remaining risk factor in the model. Patient characteristics that comprise the CHA_2DS_2-VASc score were not also included separately in the multivariable model to avoid collinearity.

All data used to perform this analysis were deidentified, accessed in compliance with the Health Insurance Portability and Accountability Act, and therefore exempt from Institutional Review Board review under 45 CFR 46.101(b)(4). A request to review this claim of exemption was submitted to the New England Institutional Review Board and exemption was obtained (New England Institutional Review Board No. 13-398). All analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC).

Results

There were 179 160 patients (age 67±16.2 years; 53.7% female) who met the criteria for inclusion in the study cohort (survival population), with a subset of 79 062 (age 67±15.7 years; 53.8% female) having a minimum of 1 year of follow-up after their index stroke (12-month analysis population; Figure).

Patient characteristics were similar across the 2 primary populations, but with a slightly lower proportion of strokes versus TIA in the 12-month analysis population than in the survival population. The lowest $CHADS_2$ and CHA_2DS_2-VASc scores in these populations were values of 2 due to index stroke. Two-thirds of the populations had a $CHADS_2$ risk score of 3 or 4, and three-quarters had a CHA_2DS_2-VASc risk score between 3 and 6 (Table 1).

The overall baseline prevalence of diagnosed AF was 13.7%, with higher rates seen as risk scores increased. The overall baseline utilization of OAC medications was 9.2%, also increasing with risk. New AF was detected in the year after the index stroke in 6.6% of the 12-month analysis population, varying from 3.0% to 10.5% in subsets with increasing risk scores. The overall rate

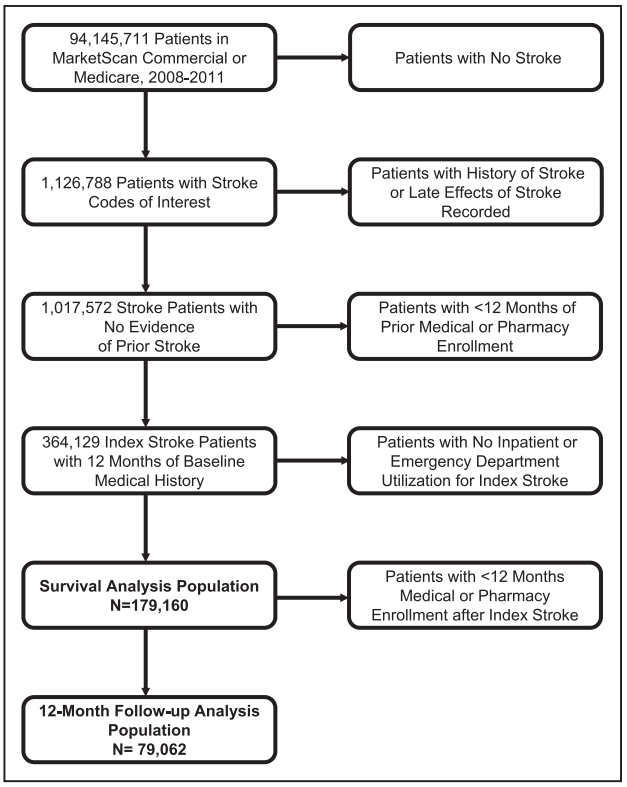

Figure. Flow chart of patient selection.

of recurrent stroke within the year after index stroke was 9.7%, increasing from 5.5% to 16.4% by risk category (Table 2).

The prevalence of ambulatory cardiac monitoring within the year after the index stroke was 9.7%, compared with 4.4% in the year prior. Thus, the increase in monitoring prevalence attributable to stroke was only 5.3%. Patients with a stroke recurrence had a slightly higher monitoring rate (13.3%) than patients without recurrent stroke (9.3%) in the year after the index stroke, reflecting the totality of the monitoring after the index stroke and any follow-up monitoring after the recurrence that also occurred within a year of the index stroke. Only 2.6% of patients had post-stroke monitoring initiated within a week after the index stroke (Table 3). As expected, new AF was diagnosed in more patients with ambulatory cardiac monitoring than in patients without this additional monitoring (17.0% versus 5.5%; $P<0.0001$).

Kaplan-Meier models showed higher estimates of 1-year stroke recurrence for patients with AF than for patients without AF, particularly when the AF was not detected until later. Patients with no AF or early AF had only small differences in recurrence estimate profiles, but patients with late AF had substantially higher recurrence rates if they were not already on OAC at baseline. Regardless of the category of AF detection and OAC utilization, stroke recurrence rates increased steadily with both $CHADS_2$ and CHA_2DS_2-VASc risk scores. Models of AF/OAC/$CHADS_2$ and AF/OAC/CHA_2DS_2-VASc categories both showed high levels of significance for the categorizations, with log-rank P values <0.0001. The Kaplan-Meier product limit estimate for 1-year stroke recurrence in the overall population was 10.6% (Table 4).

Table 1. Patient Characteristics

Patient Characteristics	Survival Population (N=179 160)		12-mo Population (N=79 062)	
	n	%	n	%
Age at index stroke, year				
0–17	804	0.4	363	0.5
18–29	2181	1.2	814	1.0
30–39	6081	3.4	2507	3.2
40–49	16 334	9.1	7104	9.0
50–59	33 390	18.6	14 860	18.8
60–69	36 397	20.3	15 941	20.2
70–79	35 002	19.5	16 980	21.5
80+	48 971	27.3	20 493	25.9
Mean (SD)	67	(16.2)	67	(15.7)
Sex				
Male	82 919	46.3	36 535	46.2
Female	96 241	53.7	42 527	53.8
Baseline OAC within 1 year				
Prescription filled	17 937	10.0	7237	9.2
No fill recorded	161 223	90.0	71 825	90.8
Healthcare utilization on index stroke date				
Inpatient	111 374	62.2	48 445	61.3
Emergency department	148 865	83.1	66 271	83.8
Inpatient and emergency	179 160	100.0	79 062	100.0
Index stroke type				
TIA	64 099	35.8	30 716	38.9
CVA	21 926	12.2	9498	12.0
Stroke	93 135	52.0	38 848	49.1
$CHADS_2$ score				
2	33 971	19.0	15 405	19.5
3	58 738	32.8	26 753	33.8
4	57 154	31.9	25 518	32.3
5	24 273	13.5	9671	12.2
6	5024	2.8	1715	2.2
CHA_2DS_2-VASc score				
2	10 732	6.0	4715	6.0
3	30 865	17.2	13 747	17.4
4	35 078	19.6	15 822	20.0
5	35 202	19.6	15 898	20.1
6	34 286	19.1	15 518	19.6
7	21 857	12.2	9235	11.7
8	9245	5.2	3482	4.4
9	1895	1.1	645	0.8

CVA indicates cerebrovascular disease; OAC, oral anticoagulation; and TIA, transient ischemic attack.

The Cox regression model showed that CHA_2DS_2-VASc score, the combination of AF detection and OAC utilization, stroke type and healthcare utilization at index stroke were all highly significant independent predictors of recurrent stroke. Hazard ratios for stroke recurrence within 1 year ranged from 1.2 to 3.0, with increasing CHA_2DS_2-VASc score.

Among the categories of AF diagnosis and baseline OAC utilization, patients with late AF and no record of baseline OAC usage had the highest hazard ratio for stroke recurrence within 1 year relative to patients with neither AF diagnosis nor OAC utilization (hazard ratio 2.0; 95% CI 1.9–2.1). Acute, ill-defined cerebrovascular disease conferred a hazard ratio for stroke recurrence within 1 year of 1.2 relative to TIA, whereas occlusion and infarction of cerebral or precerebral arteries (stroke) resulted in a hazard ratio for stroke recurrence within 1 year of 1.5. Inpatient hospitalization and ED utilization resulted in equal increases in risk of stroke recurrence, with hazard ratios of 1.4 each (Table 5).

Discussion

In this study, our principal finding was that belatedly diagnosed AF is associated with increased risk of recurrent stroke. Indeed, patients with late AF and no record of baseline OAC usage have the highest hazard ratio relative to patients with neither AF diagnosis nor OAC utilization. We also found that only a small percentage of the ischemic stroke population receives any ambulatory monitoring within the year after their index stroke.

The impact of AF on stroke recurrence rates cannot be overstated. Kamel et al[17] followed a prospective cohort of 5575 hospitalized stroke patients and reported an 18.9% one-year Kaplan-Meier estimate of recurrent stroke rate for patients with new AF diagnosed in the year after discharge versus 4.5% for all other patients, including those with AF diagnosed before or at the index stroke hospitalization. Ischemic stroke was also associated with a substantially increased risk of incident AF, particularly among individuals with higher $CHADS_2$ or CHA_2DS_2-VASc scores.

Many additional patients with AF may remain undetected at 1 year after the index stroke because of low rates of ambulatory cardiac monitoring in asymptomatic patients and the lack of sensitivity of traditional monitoring techniques to detect paroxysmal AF. AF detection rates rise with the frequency and duration of intermittent monitoring, yet remain substantially inferior to continuous monitoring, as shown by sampling from continuous readings to simulate various monitoring strategies in patients with implanted cardiac devices.[18,19] In the current study, only 6.6% of the total 12-month analysis population had new AF in the year after stroke, which is the equivalent of a 7.6% rate in the subset of patients without baseline AF. This newly detected AF resulted from only a 9.7% rate of any ambulatory cardiac monitoring in the year after the index stroke, which reflects the real-world mix of types and durations of cardiac monitoring.

Studies that report detection of new AF in cryptogenic stroke after longer duration cardiac monitoring report higher rates than those seen in this study, as well as higher rates than seen in control cohorts with standard of care or shorter duration monitoring.[9,20,21] In particular, the CRYSTAL AF (Cryptogenic Stroke and Underlying Atrial Fibrillation)

Table 2. Summary of Risks and Outcomes: 12-Month Analysis Population (N=79 062)

	Risk Group	Baseline AF 12-mo Pre-Index		Baseline OAC 12-mo Pre-Index		New AF 12-mo Pre-Index		Recurrent Stroke 12-mo Pre-Index	
Risk Category	N	n	% of N	n	% of N	n	% of N	n	% of N
$CHADS_2$ score									
2	15 405	612	4.0	535	3.5	565	3.7	947	6.1
3	26 753	2450	9.2	1771	6.6	1532	5.7	2389	8.9
4	25 518	4229	16.6	2685	10.5	1966	7.7	2763	10.8
5	9671	2787	28.8	1763	18.2	988	10.2	1294	13.4
6	1715	748	43.6	483	28.2	171	10.0	273	15.9
CHA_2DS_2-VASc score									
2	4715	167	3.5	123	2.6	143	3.0	261	5.5
3	13 747	497	3.6	454	3.3	484	3.5	900	6.5
4	15 822	1147	7.2	886	5.6	774	4.9	1373	8.7
5	15 898	2038	12.8	1452	9.1	1134	7.1	1612	10.1
6	15 518	3004	19.4	1847	11.9	1338	8.6	1742	11.2
7	9235	2433	26.3	1496	16.2	922	10.0	1161	12.6
8	3482	1262	36.2	798	22.9	365	10.5	511	14.7
9	645	278	43.1	181	28.1	62	9.6	106	16.4
Total population	79 062	10 826	13.7	7237	9.2	5222	6.6	7666	9.7

AF indicates atrial fibrillation; and OAC, oral anticoagulation.

trial discovered acutely undetected AF within 12 months after cryptogenic stroke in 12.4% of patients monitored via implantable loop recorder versus only 2.0% of controls with conventional follow-up.[20] Favilla et al[10] found a 14% rate of AF in a cohort of consecutive patients monitored by 28-day mobile cardiac outpatient telemetry after cryptogenic stroke or TIA. Similarly, Flint et al[8] reported an 11% rate of new AF after cryptogenic stroke with 30-day ECG loop recording. Interestingly, 55% of this new AF was not detected until after day 10 of the recording, with 31% first detected within days 11 to 20 and 24% first detected within days 21 to 30. Indeed, it is possible that a significantly higher rate of new AF would have been detected in the current study population if a higher rate and longer duration of cardiac monitoring had been utilized. Further study is required to determine whether more rigorous post-stroke arrhythmia monitoring can lead to increased AF detection and OAC utilization, thus resulting in a reduction of stroke recurrence.

The overall 1-year rate of recurrent stroke in this study was estimated to be 10.6% based on Kaplan-Meier methods that utilized the entire survival population, and the observed rate was 9.7% within the subgroup of patients with a full year of follow-up. The observed rate may be lower because of the requirement of 1-year follow-up, which necessarily precludes mortality due to stroke recurrence. The true recurrence rate, including fatal recurrences, may even be higher than 10.6% because survival methodology cannot fully compensate for a strong correlation between follow-up time and likelihood of recurrence. Specifically, strokes that were immediately fatal would not be captured because of the requirement for a patient to survive long enough to incur inpatient or ED utilization at the time of the event. This conservative bias toward low estimated rates may be exacerbated in the higher risk patient subgroups, where stroke recurrence rates are highest.

Finally, detection of AF is alone unlikely to improve outcomes unless it is linked to care structure and care processes

Table 3. Cardiac Monitoring Prevalence in Ischemic Stroke Patients: 12-Month Analysis Population (N=79 062)

	Overall Population		Patients Without Recurrent Stroke		Patients With Recurrent Stroke	
	N=79 062		N=71 396		N=7666	
Timing Relative to Index Stroke	Count	Percentage	Count	Percentage	Count	Percentage
Within 12 mo before	3461	4.4	3064	4.3	397	5.2
Day 0 to day 7	2064	2.6	1841	2.6	223	2.9
Day 8 to 12 mo after	6031	7.6	5169	7.2	862	11.2
Day 0 to 12 mo after	7667	9.7	6648	9.3	1019	13.3

Table 4. Kaplan–Meier Product Limit Estimates of Stroke Recurrence Rates Within 1 Year: Survival Population (N=179 160)

Risk Score	No AF No OAC		No AF With OAC		Early AF No OAC		Early AF With OAC		Late AF No OAC		Late AF With OAC	
	n	%	n	%	n	%	n	%	n	%	n	%
$CHADS_2$ score												
2	30 875	6.0	807	11.2	1161	9.6	401	9.1	670	17.4	57	6.3
3	48 771	8.3	1697	11.1	4073	12.6	2181	13.3	1819	21.8	197	17.2
4	41 667	10.9	1747	10.4	6671	13.5	4290	14.7	2495	23.7	284	16.0
5	13 575	13.3	843	12.2	4476	16.8	3804	14.5	1361	23.8	214	21.5
6	2067	16.8	155	14.6	1267	21.1	1216	16.8	275	26.9	44	14.6
CHA_2DS_2-VASc score												
2	9884	5.4	201	6.6	357	7.7	86	8.2	191	18.9	13	7.7
3	28 176	6.5	691	11.4	1008	10.7	359	8.4	582	18.1	49	15.0
4	30 104	8.2	1005	11.3	1958	11.4	992	13.5	917	22.2	102	15.9
5	27 162	10.0	1181	11.2	3245	13.6	2033	12.6	1419	22.8	162	14.0
6	23 476	11.2	1096	10.4	4711	13.8	3152	13.9	1664	22.8	187	19.9
7	12 966	12.7	694	12.0	3821	15.5	2975	15.2	1225	23.9	176	17.5
8	4413	13.9	323	13.6	2064	18.1	1839	17.4	512	25.5	94	21.1
9	774	17.0	58	10.8	484	25.5	456	17.8	110	27.0	13	0.0

AF indicates atrial fibrillation; and OAC, oral anticoagulation.
The Kaplan–Meier product limit estimate for 1-year stroke recurrence in the overall population is 10.6%.
Early AF is within 1 year pre-index stroke up to 7 days post-index stroke. Late AF is day 8 to 1 year post-index stroke.
OAC is defined as prescription utilization within the year before the index stroke.

that improve utilization of evidence-based treatment. Many studies have consistently shown suboptimal rates of anticoagulation use in AF patients across multiple healthcare systems, including use of aspirin monotherapy in patients with $CHADS_2$ and CHA_2DS_2-VaSC scores ≥2.[22,23] The American Heart Association Get With The Guidelines-Stroke hospital-based quality improvement program has been shown to improve OAC prescription for secondary stroke prevention.[24]

Limitations

This study had several limitations related to the dependence on information available in claims data to define both outcomes and risks. Risk factors were limited to diagnosis and procedure data available via administrative medical coding. Lifestyle factors, such as smoking history and exercise habits, were unavailable. Additional risks, like obesity, have relevant diagnosis codes but are severely underreported.[25] There may also be other confounding variables, including frailty and other comorbidities outside the CHA_2DS_2-VASc score.

Foremost among the data limitations are those related to the definition of stroke events and the lack of information on death occurring outside an inpatient hospitalization. Because of the definition of stroke used in this study, both the mildest strokes, not associated with inpatient or ED treatment, and the most serious strokes, resulting in death before an inpatient or ED visit, are excluded. Mortality data from 2011 have shown that ≈57% of all stroke death occurs outside the hospital setting, thus suggesting that the stroke recurrence rates seen in this study are substantially lower than actual rates. In addition, early recurrences, within 1 week of the index stroke or during hospitalization for the index event, were not captured. Johnston et al[26] found that 5.3% of TIA patients evaluated in the ED experienced a stroke within 2 days, whereas Petty et al[27] found 2.9% of patients with ischemic stroke had recurrences within 7 days. Because early recurrences account for a large proportion of total 1-year recurrences, the inability to distinguish second events within an index hospitalization could be another factor in the underestimation of recurrence rates based on claims data.

Utilization of OAC as a risk factor in this study was limited to baseline usage, so it is unknown how the existence and timing of any new post-index OAC utilization may have impacted stroke recurrence. The relationships between the timing of patients' first OAC treatment, any new AF diagnoses, use or nonuse of cardiac monitoring, and any stroke recurrences are likely quite complex and would require further study to elucidate. Patient adherence to OAC therapy and maintenance of international normalized ratio within the therapeutic target range (for those taking warfarin) are additional unknown factors that may influence stroke recurrence risk. We did not consider differences in outcomes between patients treated with warfarin or NOACs because the data source for this analysis included claims from 2008 to 2011. For an analysis to differentiate NOACs, especially one that would not be confounded by trends in uptake of NOACs, more contemporary data would be needed.

Similarly, the timing and duration of the ambulatory cardiac monitoring that was seen in this study could not be ascertained nor could the results of the monitoring. In particular, it is unclear whether the higher rate of monitoring seen in patients with stroke recurrence versus patients without recurrence (13.3% versus 9.3%) was simply a matter of patients with more risk factors receiving more diagnostic testing or whether the increase in monitoring occurred as a consequence

Table 5. Cox Regression Model Results for Stroke Recurrence Survival: Survival Population (N=179 160)

Predictor Category	Hazard Ratio (95% Confidence Limits)	χ^2 *P* Value
CHA_2DS_2-VASc=3 (vs 2)	1.2 (1.1, 1.3)	<0.0001
CHA_2DS_2-VASc=4 (vs 2)	1.5 (1.4, 1.7)	<0.0001
CHA_2DS_2-VASc=5 (vs 2)	1.8 (1.7, 2.0)	<0.0001
CHA_2DS_2-VASc=6 (vs 2)	2.0 (1.9, 2.2)	<0.0001
CHA_2DS_2-VASc=7 (vs 2)	2.4 (2.2, 2.6)	<0.0001
CHA_2DS_2-VASc=8 (vs 2)	2.6 (2.3, 2.8)	<0.0001
CHA_2DS_2-VASc=9 (vs 2)	3.0 (2.6, 3.5)	<0.0001
No AF, with OAC (vs no AF or OAC)	1.1 (1.0, 1.2)	0.0042
Early AF, no OAC (vs no AF or OAC)	1.3 (1.2, 1.3)	<0.0001
Early AF, with OAC (vs no AF or OAC)	1.3 (1.2, 1.3)	<0.0001
Late AF, no OAC (vs no AF or OAC)	2.0 (1.9, 2.1)	<0.0001
Late AF, with OAC (vs no AF or OAC)	1.6 (1.3, 1.8)	<0.0001
CVA (vs TIA)	1.2 (1.1, 1.2)	<0.0001
Stroke (vs TIA)	1.5 (1.4, 1.5)	<0.0001
Inpatient hospitalization on index stroke date	1.4 (1.3, 1.4)	<0.0001
ED utilization on index stroke date	1.4 (1.3, 1.4)	<0.0001

AF indicates atrial fibrillation; CVA, cerebrovascular disease; ED, emergency department; OAC, oral anticoagulation; and TIA, transient ischemic attack.

Each hazard ratio represents the component risk for the particular predictor after adjusting for all of the other predictors in the model.

of the stroke recurrence. In addition, the choice of a 7-day post-stroke cutoff for defining early versus late AF diagnosis may be confounded by other factors that affect length of stay, resulting in misclassification. Finally, our study population of all ischemic stroke patients would naturally include patients with known nonembolic causes for whom long-term monitoring would not be typical.

Despite the limitations of this study, it is a reasonable assumption that the resulting biases are not likely to be differential across risk cohorts, thus allowing valid interpretation of the incremental effects of various risks. The AF/OAC combination categories add valuable information to the current literature as they provide a level of detail not previously available. The identical hazard ratios seen for patients with early AF, with and without previous OAC utilization, after adjusting for risk scores, seem to suggest that these patients have been properly managed relative to their risk level. In contrast, the higher hazard ratios associated with late AF suggest that early and more aggressive diagnostic measures may be appropriate, particularly because late AF in the absence of previous OAC imparts the highest hazard of any AF/OAC combination.

Conclusions

In patients with ischemic stroke or TIA, a new diagnosis of AF occurring >7 days post-stroke is associated with increased risk of recurrent stroke. On the basis of the low utilization of ambulatory cardiac monitoring seen in this ischemic stroke population, increased utilization would likely lead to additional and more timely AF diagnosis. Earlier AF detection, in turn, could increase the number of patients receiving appropriate OAC treatment, potentially reducing their risk of recurrent stroke.

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