Original article

Incidence of ischemic stroke or transient ischemic attack in patients with multiple risk factors with or without atrial fibrillation: a retrospective cohort study

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Abstract

Background:
The risk of stroke in atrial fibrillation (AF) increases with number of risk factors (RFs). However, the combined effect from multiple RFs on the incidence of ischemic stroke and transient ischemic attack (TIA) among US patients without AF has not been fully examined.

Methods and results:
Truven MarketScan Medicare Supplemental database was used to establish cohorts of patients ≥65 years old with and without AF. Index date was first occurrence of AF diagnosis (AF patients) or first medical encounter (non-AF patients) during the inception period from 2010 through 2011. Incidences of ischemic stroke/TIA in relation to number of baseline RFs (congestive heart failure, hypertension, advanced age, diabetes, and prior stroke/TIA, myocardial infarction) were determined during the follow-up period from the index date through March 2013. A total of 158,199 patients were included in the AF cohort and 1,181,273 patients in the non-AF cohort. Approximately 51% of AF patients had ≥3 RFs versus 18% in non-AF patients. Ischemic stroke/TIA were observed in 24,680 and 104,154 patients in the AF and non-AF cohorts, yielding incidence rate (SD) of 7.3 (0.05) and 3.2 (0.01) per 100 person-years, respectively. In the AF cohort, incidence rate of ischemic stroke/TIA was 2.3, 4.9, 9.4, and 16.9 per 100-person years for 0, 1–2, 3–4, and 5–6 RFs, respectively, compared with the corresponding rate of 1.3, 2.8, 6.4, and 12.3 per 100 person-years for the non-AF cohort. This positive association between the number of risk factors and incidence rates within each cohort was consistently observed in sensitivity analyses.

Conclusion:
In a large cohort of elderly patients without AF, the risk of ischemic stroke/TIA increased substantially in the presence of multiple RFs, highlighting potentially unmet medical needs. This observation implies that future studies may be warranted to investigate the effect of prophylactic anticoagulation in high risk non-AF patients.

Introduction

The incidence of stroke in the USA is approximately 800,000 people each year according to the Heart Disease and Stroke Statistics 2013 update of the American Heart Association. Atrial fibrillation (AF) is a leading cause of total and fatal ischemic strokes, and estimated to be responsible for 15% of all strokes. Atrial fibrillation is the most common cardiac arrhythmia with an estimated lifetime risk of 22% to 26%. Although AF alone has conferred approximately a five-fold increase in risk of stroke, studies have also shown...
that other comorbid conditions such as congestive heart failure, hypertension, advanced age (≥75 years), diabetes mellitus, and prior stroke or transient ischemic attack (TIA) are associated with additional risks of developing stroke in patients with AF. However, there is limited information on the assessment of these risk factors (RFs) in patients without AF.

In a study presented at the European Society of Cardiology (ESC) 2013 Congress, Dr. Benn Christiansen analyzed more than four million persons in the healthcare registries across Denmark. They reported that for patients without AF, the incidence of ischemic stroke was 4.88 and 7.27 per 100 person-years in patients with 3–4 and ≥5 RFs, respectively, which was not substantially lower than the 6.96 and 8.00 per 100 person-years for AF patients with similar RFs. In their study, the RFs included myocardial infarction (MI), peripheral artery disease, arterial embolism, excessive alcohol consumption, heart failure, carotid stenosis, retinal occlusion, chronic systemic inflammation, chronic kidney disease, venous thromboembolism, epilepsy, migraine, diabetes mellitus, hypertension, and age ≥75 years.

Although CHA2DS2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, previous stroke/TIA [transient ischemic attack] [double score]) and CHADS2-VASc (congestive heart failure, hypertension, age ≥75 years [double score], diabetes mellitus, previous stroke/TIA [double score], vascular disease, age 65–74 years, sex class [female]) tools have been used to determine the incidence of stroke or TIA in patients without AF, the effect of individual risk factors as well as the combined effect of multiple risk factors on events of ischemic stroke/TIA among patients without AF has not been fully examined in the US elderly population.

The objective of the present study was to further investigate this understudied area and quantify the potential unmet medical need of prevention of stroke/TIA in patients without AF, but with multiple RFs in the US elderly population. To put the study results into perspective, we also analyzed AF patients with multiple RFs in a similar fashion.

**Methods**

**Study design, data sources, and patient selection**

This was a retrospective cohort study that used the Truven MarketScan Medicare Supplemental and Coordination of Benefits (MDCR) database that contains electronic claims for Medicare-eligible active employees and retirees with employer-sponsored supplemental plans with medical and pharmacy coverage. The Medicare data contains over eight million lives enrolled from 2000 to 2013. The mean age of patients in the database was 72.3 years old, with 45% men and average enrollment of 3.3 years. The claims database captures diagnoses, procedures and prescription drug dispensing.

The MDCR database from the inception period of 2010–2011 was used to establish AF and non-AF study cohorts. The presence of AF was ascertained using ICD-9-CM code, and the accuracy of the coding (e.g., positive predictive value, specificity) was generally demonstrated in validation studies. Patients who were ≥65 years of age and had enrolled into the insurance coverage during the inception period and at least 1 year prior to the index date were considered eligible for the study. The index date was considered as the service date associated with first AF event during the inception period for the AF cohort, and for the non-AF cohort it was the service date associated with the first medical encounter. The study period was chosen to include patients under current clinical practice and with a potentially reasonable duration of follow-up (up to March 2013) from the index date throughout their period of continuous enrollment.

Patients who received new oral anticoagulants (NOACs, e.g., rivaroxaban, dabigatran) at any time during the study period were excluded as the study was not intended to investigate this new class of medications, which at the time had just received market authorization. Patients with a prior AF code were excluded from the non-AF cohort (N = 66,238). Patients were followed after the index date (or were censored at the time of the event) to identify the study endpoints of interest. Since AF patients with high risk scores should have received prophylactic anticoagulant therapy according to treatment guidelines, we further evaluated the study endpoints among AF patients in relation to prior exposure to warfarin therapy.

The analyses using the Truven MarketScan databases were reviewed by the New England Institutional Review Board (IRB) and determined to be exempt from board IRB approval. We obtain these de-identified patient-level records through a license agreement with the data holder.

**Main outcome measure**

Assessing the incidence rate of ischemic stroke/TIA in patients without AF was the primary aim of the study, in which the outcome was identified by using the ICD-9-CM codes present in any diagnosis field in the database. Given that the diagnostic distinction among stroke subtypes often requires an intensive clinical workup and TIA may be considered a soft endpoint, we also assessed the endpoint of overall stroke to corroborate the primary results. The overall stroke endpoint represents a broad category that includes ischemic and hemorrhagic stroke subtype as well as acute, ill-defined cerebral vascular disease and
several other cerebral vascular disorders that may be associated with or lead to cerebral infarction.

Comorbidities and medications assessment

Comorbid conditions such as hyperlipidemia, peripheral vascular disease, hyperthyroidism, chronic obstructive pulmonary disease, liver disease, renal disease, and cancer were identified using all medical claims from the previous 5 years through index date; whereas the pre-index period and post-index period medications were assessed using pharmacy dispensing claims 1 year prior to the index date or 1 year after the index date, respectively. For patients with AF, the post-index period warfarin and anti-platelet therapy were assessed using the records available during the entire follow-up period. In addition, the frequency of AF diagnosis recorded (e.g., potentially incident cases) during the follow-up period was investigated for non-AF patients. All the ICD-9-CM codes for cohort selection, outcomes identification, comorbidities and drug classification codes are available as a supplementary file.

Data analysis

Patient demographics, comorbidities, pre-index and post-index medications were summarized descriptively. Patients with RFs of hypertension, congestive heart failure, advanced age (≥75 years), diabetes, ischemic stroke or TIA, and MI were classified by the number of risk factors into categories of 0, 1–2, 3–4, and 5–6. Unlike in the CHADS2 metric, prior stroke/TIA was only counted as one risk factor in this analysis for reason of simplicity and MI was added because ischemic stroke is a common complication after the event. Patients in the AF cohort were stratified by warfarin use before and after the index date to further evaluate the study outcomes. The incidence of ischemic stroke/TIA per 100 person-years was calculated as: (events/total person-years) × 100 along with 95% confidence intervals (CIs), which were calculated using a normal approximation method. The Kaplan–Meier (K-M) method was used to plot the distribution of the incidence of ischemic stroke/TIA and overall stroke as time to event. All the analyses were carried out using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Sensitivity analysis

When conducting a data base study, there is a practical challenge to make an absolute distinction between an incident and a prevalent case because an existing condition (e.g., stroke) prior to the index date could be recorded in medical records during a subsequent visit. Therefore, a prevalent case could be potentially misclassified as an incident event. Hence, two sensitivity analyses were performed: 1) by excluding patients with a diagnosis of stroke 60 days prior to the index date, and 2) by using primary diagnosis codes only to identify ischemic stroke/TIA.

Results

Cohort selection

A total of 2,103,461 patients were identified from the database for the observation period from 2010 through 2011, of whom 1,994,703 patients met the eligibility criteria of ≥65 years of age. Excluding patients who did not have at least 1 year insurance coverage, who received NOACs, and patients with a prior diagnosis of AF (in the non-AF cohort), a total of 158,199 patients were included in the AF cohort with mean duration of follow up of 859 (SD: 271.4) days, and 1,181,273 patients were included in the non-AF cohort with mean duration of follow up of 1052 (SD: 179.7) days (Figure 1).
Patients in the AF cohort were older (74.6% ≥75 years; mean [SD] age: 79.9 [7.1] years) than patients in the non-AF cohort (49.7% ≥75 years; 75.6 [6.8] years). In this study, the proportion of males, rates of all risk factors, and comorbid conditions of interest examined were higher in the AF cohort than in the non-AF cohort (Table 1). Hypertension, hyperlipidemia, and cancer were the most common comorbidities observed in both cohorts. Approximately 51% of patients in the AF cohort had ≥3
risk factors compared with 18% patients in the non-AF cohort.

The most commonly used medications for pre-index and post-index periods in both the AF and non-AF cohorts were β-blockers, diuretics, statins, calcium channel antagonists, and angiotensin converting enzyme inhibitors. Generally, the proportions of patients using these medications were higher in the AF cohort than in the non-AF cohort. In both cohorts, there was an increase in the proportion of patients using these medications as post-index medications compared to their use as pre-index medications (Table 1), which may be in part due to an event observed during the index date.

In the AF cohort for patients receiving prior warfarin therapy, a greater number of risk factors were associated with a greater chance of discontinuation of warfarin therapy after the index date (e.g., discontinuation rate of 27.7%, 28.1%, 30.1%, and 34.4% for 0, 1–2, 3–4, and 5–6 RFs, respectively). However, for patients not receiving prior warfarin therapy, a greater number of risk factors seemed to be associated with a greater chance of receiving new warfarin therapy (e.g., an initiation rate of 4.6%, 7.6%, 8.3%, and 6.1% for the corresponding RF categories) (Table 2).

### Incidence of ischemic stroke or TIA

During the study period, events of ischemic stroke or TIA were observed in a total of 24,680 patients in the AF cohort and 104,154 patients in the non-AF cohort (Figure 2), yielding incidence rates (SDs) of 7.3 (0.05) and 3.2 (0.01) per 100 person-years, respectively.

For both AF and non-AF cohorts, the incidence rates of ischemic stroke or TIA increased substantially as the number of risk factors increased (Figure 2). In the AF cohort, the incidence rate of ischemic stroke/TIA was 2.3, 4.9, 9.4, and 16.9 per 100-person years for 0, 1–2, 3–4, and 5–6 RFs, respectively, compared with the corresponding incidence rate of 1.3, 2.8, 6.4, and 12.3 per 100 person-years for patients in the non-AF cohort. The difference in the incidence of ischemic stroke/TIA in non-AF population versus AF population became progressively narrower as the number of RFs increased from 0–2 RFs (~45%) to 3–6 RFs (~30%) (Figure 2). Also, the incidence rates of ischemic stroke/TIA for patients in the non-AF cohort with ≥3 risk factors were notably higher than patients in the AF cohort with <3 risk factors. However, this observation is simply descriptive and not meant for any direct comparison, because of heterogeneity across the cohorts. The Kaplan–Meier estimates showed similar results as the incidence rates (Figure 3).

In the AF cohort, incidence rates were similar for low risk categories regardless of warfarin use, although rates were numerically greater for non-warfarin users than for warfarin users across all risk groups (Figure 4, for ischemic stroke/TIA; Table 3, for overall stroke).

### Sensitivity analysis

The pattern of the results obtained from the sensitivity analysis was consistent with the primary analysis. After removing patients with a diagnosis of stroke within 60 days prior to the index date, the incidence of ischemic stroke/TIA for each cohort remained high. Interestingly for descriptive purposes, the rates were notably higher for patients in the non-AF cohort with ≥3 risk factors than for patients in the AF cohort with <3 risk factors (Table 4). One could also argue that using only the primary diagnosis code to identify the study endpoint represents the most conservative approach. Even with such conservative estimates, the incidence rates were high, i.e., 2.3 [3–4 RFs] and 4.6 [5–6 RFs] per 100 person-years for patients without AF and 3.5 [3–4 RFs] and 6.0 [5–6 RFs] patients with AF (Table 4).

### Discussion

In this study, we used a large healthcare database to examine the relationship between multiple risk factors and ischemic stroke/TIA in an elderly population with...
supplemental Medicare insurance. The results from this study suggest that risk of ischemic stroke/TIA among non-AF patients increases substantially in the presence of multiple risk factors, potentially highlighting this important public health issue. We hope these findings will help to draw the attention of both patients and healthcare providers and to promote an open and meaningful dialog about the management of potential thrombotic risk.

Several studies reported that in patients with AF the risk of stroke rises in a linear fashion in relation to CHADS2 and CHA2DS2-VASc scores and studies have also been performed to identify additional risk factor8,13,14. Also, a Danish study demonstrated that the risk of ischemic stroke for patients without AF but with multiple risk factors was substantially higher than that for patients with AF but with few risk factors9. Although our results based on the US elderly population appear confirmative, the definitions for the study endpoint and risk factors may slightly differ across the two studies. The underlying physiological mechanism for such an elevated risk is not clearly understood, but it has been speculated that many strokes may be due to undetected AF.

Hypothesizing that silent AF might be the cause of cryptogenic ischemic stroke or TIA, Gladstone et al.15 conducted a randomized study of 572 patients with such events investigating two different monitoring methods (in a 1:1 ratio) for detecting AF consisting of patients undergoing ambulatory ECG monitoring with a 30 day event-triggered loop recorder (intervention group), or one additional round of 24 hour Holter monitoring (control group). The study showed that about 16.1% (45/280) of patients in the intervention group were detected to have AF that lasted more than 30 seconds or longer within 90 days of being admitted into the study compared with 3.2% in the control group. In addition, Samol et al.16 conducted an ECG screening study of a limited number of patients (N = 132) without known AF who presented to clinics for diabetes, hypertension, and dyslipidemia, and reported that the prevalence of silent AF was higher in patients with multiple risk factors for stroke and AF.

![Graph showing incidences of ischemic stroke or TIA in the AF and non-AF patients by risk factors.](image-url)

**Figure 2.** Incidences of ischemic stroke or TIA in the AF and non-AF patients by risk factors. AF, atrial fibrillation; MDCR, Truven MarketScan Medicare Supplemental and Coordination of Benefits; PYs, patient-years; RFs, risk factors; TIA, transient ischemic attack.
Although these data indicate that while some ischemic stroke or TIA might be the consequence of undiagnosed AF, and intensive monitoring to improve the detection and treatment of AF may provide assurance to reduce the burden of recurrent strokes\textsuperscript{15}, the majority of events are not explained by the presence of AF. Interestingly, in our study, only a small proportion of patients initially without AF developed AF during the follow-up period, which would not explain the relatively high rate of ischemic events among non-AF patients with multiple risk factors. It is worth noting that if asymptomatic AF is commonly undetected, then underreporting will be reflected in our database as well. Unfortunately, this issue cannot be further assessed in our study.

Figure 3. Kaplan–Meier plot for ischemic stroke/TIA (a) and stroke (b) among patients in the AF and non-AF cohorts. AF/Afib, atrial fibrillation; TIA, transient ischemic attack.
Figure 4. Kaplan–Meier plot for ischemic stroke/TIA (a) and stroke (b) for patients in the AF cohort by warfarin use. AF/Afib, atrial fibrillation; TIA, transient ischemic attack.

Table 3. Incidence rate (per 100 person-years) of overall stroke among AF patients by warfarin use and risk factors.

| Risk Factor (RFs) | Total persons at risk | Persons at 1yr | Persons at 2yr | Persons at 3yr |
|------------------|-----------------------|---------------|---------------|---------------|
| 0                | 1422                  | 1307          | 1064          | 492           |
| 1–2              | 25216                 | 23643         | 18533         | 8679          |
| 3–4              | 25083                 | 22175         | 16343         | 7146          |
| 5–6              | 2505                  | 2000          | 1294          | 498           |

| Risk Factor (RFs) | Total persons at risk | Persons at 1yr | Persons at 2yr | Persons at 3yr |
|------------------|-----------------------|---------------|---------------|---------------|
| 0                | 3303                  | 3093          | 2215          | 716           |
| 1–2              | 47754                 | 42942         | 28615         | 8626          |
| 3–4              | 46968                 | 38461         | 23222         | 6421          |
| 5–6              | 5948                  | 4189          | 2163          | 521           |

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AF, atrial fibrillation; CI, confidence interval.
Other researchers also investigated the factors that affect the risk of ischemic stroke, although those studies may be constrained by either community studies or non-US population or studies of a patient population with a particular condition. Moreover, there has been a lack of information on the combined effect of multiple risk factors. Therefore, the results of this study can have important clinical implications in the US healthcare setting. Even in the absence of AF, patients with multiple RFs had a high risk of ischemic stroke/TIA, which is often associated with devastating clinical consequences. The risk of events compounds with the number of risk factors present, and in patients with 3–6 RFs the risk of ischemic stroke/TIA can be 70% of that in AF patients. Because a large proportion of patients are present with those risk factors (e.g., more than 15% of the study population), a large number of events would occur annually as demonstrated by the current study and corroborating research. Thus, the results of the present study suggest a large unmet medical need and calls for further investigation into whether thromboprophylactic therapy is warranted in a high risk population. The benefit–risk balance, primarily of stroke risk reduction relative to increased bleeding risk, would have to be prospectively evaluated in this patient population.

In the primary analysis, we used all the diagnosis codes (primary and secondary) to identify the ischemic stroke/TIA. As the database used does not allow for differentiation between incident and prevalent cases, this approach could potentially inflate the estimates of incidence rates. While we could not conduct chart review to confirm the cases, we did conduct two sensitivity analyses to assess the situation. From the perspective of a retrospective analysis (i.e., data were not prospectively collected for the main purpose of the current study), it is difficult to make an assertion regarding which method is preferable. For example, one could argue that using only primary diagnosis to identify the study endpoint is probably a very conservative approach; whereas the incidence rates would be underestimated by excluding patients with a prior history of stroke, since the history of such a disease is a significant predictor of the study endpoint. While the incidence estimates, as expected, varied by using different approaches, the overall finding of the study was quite consistent, i.e., that the risk of ischemic stroke/TIA among patients without AF, but having multiple RFs, was remarkable and noticeably higher than among patients with AF with fewer RFs. It was also reassuring that our results were generally consistent with other studies.

Our study has limitations. The data reflect privately insured populations with supplemental Medicare coverage and capture health care claims that were gathered in order to obtain reimbursement. Therefore, the data have limitations that are similar to those in other claims databases (e.g., coding practice and accuracy of the data reported, etc.). However, previous studies suggest that claims databases can be used reliably to identify and examine issues related to certain types of events, such as myocardial infarction, stroke, or other clinically important endpoints. Drug dispensing was recorded but adherence to the treatment could not be monitored actively. In addition, intensity of international normalization ratio (INR) control and monitoring for patients receiving warfarin could not be assessed. While we observed that a large proportion of AF patients who previously received warfarin therapy remained on the drug, we also found that a large proportion of AF patients did not receive or initiate warfarin therapy after the index date, for which we speculate that the commercial database might have not captured all drug dispensing records if patients were fully covered by Medicare for drug expenses. In addition, patients who received warfarin therapy had a lower event rate in ischemic stroke/TIA (as well as overall stroke rate) than patients receiving no warfarin therapy, which was particularly pronounced for patients with multiple RFs. However, the magnitude of the benefit was not as remarkable as observed with clinical trials or other observational studies. While these are interesting observations, we caution that the comparison of treatment benefit needs careful consideration of patient selection and adjustment for confounding factors, which is beyond the scope of this study.

**Conclusion**

The risk of ischemic stroke/TIA among elderly non-AF patients increases substantially in the presence of multiple
RFs, highlighting potentially unmet medical needs. The results of this study suggest that future studies may be warranted to investigate whether these high risk non-AF patients could benefit from thromboprophylactic therapy.

Transparency

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Declaration of financial/other relationships
Z.Y., P.R., C.N. and R.M. have disclosed that they are employees of Janssen Research and Development LLC, USA. T.S. and D.Y. have disclosed that they are employees of Janssen Scientific Affairs LLC, USA.

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