Recurrent Stroke Risk in Pilots with Atrial Fibrillation

Jessica Tedford; Valerie Skaggs; Ann Norris; Farhad Sahiar; Charles Mathers

INTRODUCTION: Atrial fibrillation (AF) is one of the most common cardiac arrhythmias in the general population and is considered disqualifying aeromedically. This study is a unique examination of significant outcomes in aviators with previous history of both AF and stroke.

METHODS: Pilots examined by the FAA between 2002 and 2012 who had had AF at some point during his or her medical history were reviewed, and those with an initial stroke or transient ischemic attack (TIA) during that time period were included in this study. All records were individually reviewed to determine stroke and AF history, medical certification history, and recurrent events. Variables collected included medical and behavior history, stroke type, gender, BMI, medication use, and any cardiovascular or neurological outcomes of interest. Major recurrent events included stroke, TIA, cerebrovascular accident, death, or other major events. These factors were used to calculate CHA_2DS_2-VASc scores.

RESULTS: Of the 141 pilots selected for the study, 17.7% experienced a recurrent event. At 6 mo, the recurrent event rate was 5.0%; at 1 yr, 5.8%; at 3 yr 6.9%; and at 5 yr the recurrent event rate was 17.3%. No statistical difference between CHA_2DS_2-VASc scores was found as it pertained to number of recurrent events.

DISCUSSION: We found no significant factors predicting risk of recurrent event and lower recurrence rates in pilots than the general population. This suggests CHA_2DS_2-VASc scores are not appropriate risk stratification tools in an aviation population and more research is necessary to determine risk of recurrent events in aviators with atrial fibrillation.

KEYWORDS: neurology, cardiology, atrial fibrillation, stroke, anticoagulation, cardiovascular risk, recurrent stroke, fitness to fly, aeromedical qualification.

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Atrial fibrillation (AF) is the most common type of serious arrhythmia in the general population, and its incidence increases with age. Data from the AnTicoagulation and Risk Factors in Atrial Fibrillation study gave a range of prevalence from 0.1% among adults less than 55 yr of age to 9% in those patients over the age of 80 with an overall prevalence for atrial fibrillation at 1%.[9,10,15] Moreover, the proportion of a given population developing atrial fibrillation has been shown to be as high as 7.5% in a longitudinal study of Air Force recruits over the course of 44 yr, with an overall incidence of 1.94 cases per thousand person-years.[11] Studies have demonstrated the risk of developing atrial fibrillation is higher in men than women and in those between the ages of 44–95.[12–14] Furthermore, the morbidity and mortality associated with AF has been shown to be a significant socioeconomic burden.[2,5,7] A recent publication[6] reported a 21.5% 5-yr recurrence rate of incident ischemic stroke, which is significantly higher than previous population studies of patients with AF. Moreover, this study documented the significantly worse outcomes found with atrial fibrillation related stroke (AF-stroke) vs. those patients experiencing stroke without atrial fibrillation.

Epidemiological studies of AF are limited within the aviation arena, with most studies restricted to case review studies, which have considered lone AF and individualized fitness to fly assessments based on perceived risk of future medical events.[1,8,16] Some medical assessors have argued for a zero tolerance policy toward AF in airmen due to the risk of hypotension or thromboembolic event.[17,18] Because of this conservative approach toward AF, the current body of knowledge concerning atrial fibrillation in an aeromedical population has not

From the Office of Aerospace Medicine, Federal Aviation Administration, Oklahoma City, OK, USA.

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Address correspondence to: Jessica Tedford, LT, MC, USN, Flight Surgeon, CVW 5, Unit 200136, Box Box 80, FPO AP, 96601, USA; jltedford@gmail.com.

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addressed aviators with AF who have also experienced stroke or transient ischemic attack (TIA).

The most commonly used risk-stratification tool for defining the likelihood of thromboembolic event in a person with atrial fibrillation was developed from the Atrial Fibrillation Investigators and Stroke Prevention and Atrial Fibrillation in 1994 to assess a patients' needs for anticoagulation based on their risk of a stroke or associated medical event due to underlying AF.[4] The $CHADS_2$[5] risk stratification tool assigned value to each risk factor found by the 1994 investigators to best predict the risk of any stroke, recurrent or primary, in a patient with atrial fibrillation: congestive heart failure, hypertension, age >75 yr, diabetes mellitus, and prior stroke or TIA. The tool was later renamed CHA_2DS_2-VASc and modified to include age >65, vascular disease, and female sex.[12] Although pilots are traditionally considered a healthier and more robust group than the general population, as pilots continue to age, the incidence and prevalence of AF-stroke and AF-TIA and their inherent risk is expected to rise, similar to the general population. This increase may affect a pilot's capability to maintain medical certification and flying privileges. Thus, investigation of the aviation population is needed to obtain data and analyze the prevalence of AF-stroke or AF-TIA in the population of airmen certified by the Federal Aviation Administration (FAA). These data will more clearly outline the risk associated with medically certifying a population using the $CHADS_2$ and CHA_2DS_2-VASc scores as predictors of the likelihood of a pilot sustaining a recurrent and possibly incapacitating event during flight due to AF-stroke or AF-TIA.

Per the FAA's *Guide for Aviation Medical Examiners*, atrial fibrillation within the past 5 yr is considered a disqualifying condition that requires special issuance authorization (i.e., waiver) from the FAA in order for a pilot to receive medical certification.[3] To gain a waiver, a pilot is required to send in a report from a cardiovascular evaluation per an FAA prescribed specification sheet, summarizing his or her medical condition between the last FAA examination and the onset of atrial fibrillation. They are also required to send in results of laboratory tests, including thyroid function studies, a 24-h Holter monitor, exercise stress test, and M-mode transthoracic echocardiogram. If the patient is taking warfarin, he or she must give monthly International Normalized Ratio results for the preceding 6 mo and 80% of those values must be within goal range. According to the same FAA guidelines, any neurological event of TIA or completed stroke (either ischemic or hemorrhagic) is disqualifying.

To obtain a waiver for this neurological condition, the airman is required to report and release all medical documentation from any medical workup that was performed to find any correctable underlying cause for the TIA or stroke. Information needed from the workup includes a current neurological evaluation with detailed reports of his or her motor, sensory, language, and cognitive function, imaging of the head and neck with either magnetic resonance angiogram or computed topography angiogram, current fasting blood sugar and lipid panel laboratory studies, carotid artery ultrasound studies, cardiovascular evaluation with an exercise stress test, 24-h Holter monitor, and echocardiogram. Neurocognitive testing is required for all strokes and may be required for TIA as clinically indicated. The FAA neurology panel will review the case following a 2-yr wait period or sooner if a cause for the event can be found, and the panel may recommend a special issuance at that time or may request further workup. This study was performed to combine the body of evidence surrounding AF and stroke and investigate the uses of current risk stratification tools for the FAA aviation population.

METHODS

Subjects

Mirroring the criteria defined in the Hayden paper,[6] patients with atrial fibrillation and incident stroke or TIA were ascertained from the FAA airman population over a 10-yr period from January 1, 2002, to December 31, 2012, using one medical pathology code for AF and two separate pathology codes for stroke and TIA. Inclusion criteria consisted of: 1) index event of first stroke of any subtype or TIA during the 10-yr ascertainment period; and 2) previously diagnosed or newly detected AF within the ascertainment period. Patients were excluded if there was a record of stroke or TIA that occurred prior to the ascertainment period, stroke or TIA was associated with a traumatic event, AF was not thoroughly documented, or if there was no follow-up aeromedical examination after the index event. Additionally, the $CHADS_2$ and CHA_2DS_2-VASc scores of airmen with unknown or uncertain risk factor values were recorded as unexposed to that particular risk factor in the final statistical analyses. The FAA Institutional Review Board applied exempt criteria to this project due to the nature of the research making use of solely archival data, where all information recorded could not be identified directly in the analysis.

Equipment

We ascertained our patient population from the Data Information Workflow System (DIWS) used by the FAA to document and maintain records of pilot medical information. To understand the airman population for whom we were interested in inferring risk, we obtained 1,085,631 airmen as our source population using unique applicant identification numbers within DIWS regardless of the number of exams attached to each applicant identification number, guaranteeing that airmen would not be counted more than one time.

Procedure

Each case was followed until the last medical examination in the system. They were individually reviewed by a fourth year medical student and an FAS-neurology consultant at the FAA using the definition of AF consistent with the American Heart Association guidelines[10] and the World Health Organization definition of stroke: rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting >24 h with no apparent cause other than that of vascular origin. TIA was defined using the same criteria with the exception of time: rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting <24 h. Stroke subtype (ischemic, intracerebral hemorrhage, subarachnoid hemorrhage, or mixed pathology) was confirmed by brain imaging reports made available to the FAA and stored in the airman's medical record. $CHADS_2$ and CHA_2DS_2-VASc scores were calculated for each patient using historical data found in DIWS at the baseline study period. Recurrent event was defined as myocardial infarction, stroke, TIA, cerebrovascular accident, death, or other major event following the initial stroke.

Death data were obtained by matching airmen records from DIWS with records obtained from the Center for Disease Control's National Death Index. These data also provided the underlying cause of death noted on the death certificate. If a death was linked to one of the airmen in the study during the 2002–2016 study period and the underlying cause of death was due to one of the primary endpoints, then it was included as a death.

Statistical Analysis

Statistical analyses were performed using Statistical Analysis Software v.9.4 (SAS; SAS Institute, Cary, NC, USA). Statistical analyses included parametric and nonparametric analyses of continuous variables such as Student *t*-test or Wilcoxon rank-sum test where appropriate. Comparisons of categorical variables were performed using the Fisher's exact tests due to the small sample size of the variable categories in pilots who had a recurrent outcome. Survival analysis was performed measuring time to recurrent event, using lifetables and Kaplan-Meier survival curves, with censoring of patients who did not return for medical certification or were lost to follow-up. The log-rank test was used for comparison of maintenance of a valid aeromedical certificate in the FAA system and recurrence rates across groups identified using CHA_2DS_2-VASc scoring. We assumed an alpha of 0.05 as the level of significance for all tests.

RESULTS

Using the search criteria outlined in the methods, 16,059 airmen were identified in DIWS as having atrial fibrillation. Of these, 317 airmen were listed as having both atrial fibrillation and stroke or TIA pathology codes. After further review, 153 patients met both American Heart Association and World Health Organization definitions for new stroke or TIA and AF, and only 141 airmen met the study criterion of follow-up aeromedical examination after the index event. Pathological subtypes of the index event were 47.5% TIA (67/141), 45.4% ischemic (64/141), 2.8% hemorrhagic (4/141), 2.1% other (3/141), and 2.1% unknown (3/141). AF was identified pre-stroke in 49.6% (70/141), 25.5% at the time of stroke (36/141), and 24.8% were discovered to have AF after the initial stroke event. Clinical characteristics of the study population by recurrent outcome status are outlined in **Table I**.

A 5-yr survival analysis was performed for the 141 participants in the study and is displayed in **Fig. 1**. At 3 yr, 61% of airmen with history of AF-stroke or AF-TIA continued to apply for certification in the FAA medical system, but within 5 yr only 40.4% remained. No statistical significance was found between the different risk stratification groups when stratified by CHA_2DS_2-VASc scores as shown in **Fig. 2**. However, airmen with a score ≥6 often failed to apply for or continue to maintain a valid medical certification, with only 25% (3/12) maintaining a valid medical certificate in the system after 4 yr. In contrast, more than half of the people with a score of less than 6 maintained a valid medical after 4 yr.

Table I. Clinical Characteristics of Patients with Atrial Fibrillation Related Stroke and TIA ($N = 141$).

CHARACTERISTIC	RECURRENT EVENT *N* (%)	NO RECURRENT EVENT *N* (%)	*P*-VALUE
Age			
<65	12 (48.0)	63 (54.3)	0.2377
65–74	11 (44.0)	33 (28.5)	
≥75	2 (8.0)	20 (17.2)	
BMI (Overweight/Obese)	21 (84.0)	88 (75.9)	0.3783
AF before Stroke	11 (44.0)	59 (50.9)	0.5337
Diabetes mellitus	2 (8.0)	9 (7.8)	1.000
Hypertension	15 (60.0)	73 (62.9)	0.7837
Hyperlipidemia	12 (48.0)	53 (45.7)	0.8335
Ever Smoker*	9 (40.9)	32 (36.0)	0.6664
Vascular Disease	8 (32.0)	35 (30.2)	0.8517
Congestive Heart Failure	0 (0.0)	2 (1.7)	1.0000
Alcohol*	18 (75.0)	58 (66.7)	0.4366
Prior DVT or Hypercoagulability	2 (8.0)	5 (4.3)	0.6075
Sleep Apnea	1 (4.0)	15 (12.9)	0.3048
$CHADS_2$ Score			
2–3	22 (88.0)	93 (80.2)	0.5695
4–5	3 (12.0)	23 (19.8)	
CHA_2DS_2-VASc			
2–3	13 (52.0)	56 (48.3)	0.6704
4–5	9 (36.0)	51 (44.0)	
6+	3 (12.0)	9 (7.8)	

$CHADS_2$ scored by congestive heart failure, hypertension, diabetes mellitus, age >75, and prior stroke or TIA. CHA_2DS_2-VASc scored by congestive heart failure, hypertension, age <65, 65–74 yr of age, and ≥75 yr of age, diabetes mellitus, prior stroke, transient ischemic attack, or thromboembolism, vascular disease, and female sex.
* Indicates 21.3% of the data values are missing.

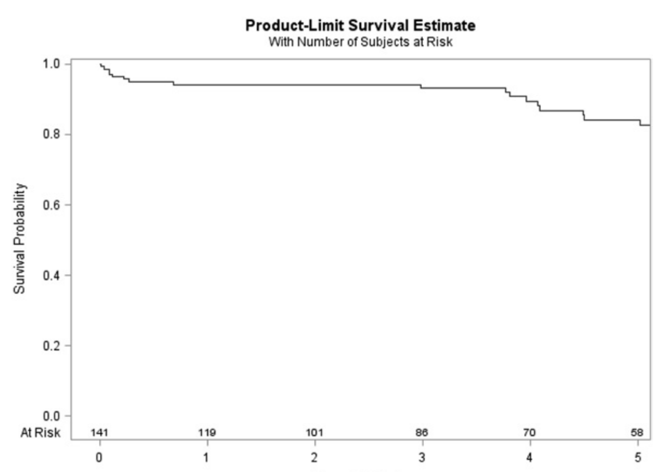

Fig. 1. Kaplan-Meier curve of 5-yr survival analysis of all pilots continuing to apply for aeromedical certification in the system after AF-stroke or AF-TIA.

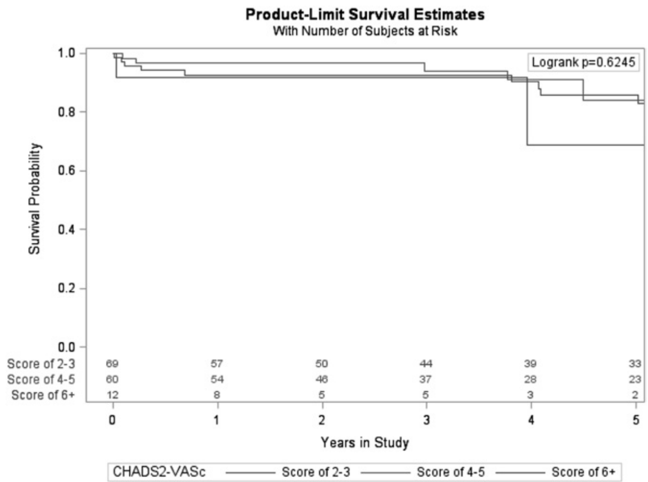

Fig. 2. Kaplan-Meier curve of 5-yr survival analysis of pilots maintaining in the system after atrial fibrillation related stroke or TIA stratified by CHA_2DS_2-VASc score. CHA_2DS_2-VASc identifies risk factors of congestive heart failure: hypertension, age <65, 65–74 yr of age, and ≥75 yr of age, diabetes mellitus, prior stroke, transient ischemic attack or thromboembolism, vascular disease, and female sex.

Of the 141 airmen, only 17.7% (25/141) experienced a recurrent event. When comparing those who had a recurrent event with those who did not, none of the variables of the CHA_2DS_2-VASc scores demonstrated statistical significance (Table I): congestive heart failure ($P = 1.00$), diabetes mellitus ($P = 1.000$), hypertension ($P = 0.7837$), and vascular disease ($P = 0.8571$). Age categories of less than 65, 65–74, and 75+ were also not significantly different ($P = 0.2377$). Moreover, differences in CHA_2DS_2-VASc and $CHADS_2$ scores were not statistically associated with stroke recurrence ($P = 0.6704$ and $P = 0.5695$, respectively). Additional variables of airman historical data were compared and yielded no significant association between risk factor and likelihood of recurrent event: sleep apnea ($P = 0.3048$), hyperlipidemia ($P = 0.8335$), BMI > 25 ($P = 0.3783$), and history of deep vein thrombosis (DVT) or hypercoagulability ($P = 0.6075$). Use of different medications was not shown to correlate to a lower likelihood of recurrent events: statin ($P = 0.9619$), antihypertensive medication ($P = 0.5328$), and antiplatelet medication ($P = 0.5663$). Anticoagulant medication therapy approached statistical significance ($P = 0.0506$). **Table II** outlines the pharmacological characteristics of our study population. Further investigation of social habits like smoking prior to the index event and alcohol use prior to the index event did not show any relationship with the likelihood of recurrent event either ($P = 0.6664$ and $P = 0.4366$, respectively).

Table II. Pharmacological Characteristics of Patients with Atrial Fibrillation Related Stroke and TIA ($N = 141$).

MEDICATION	RECURRENT EVENT *N* (%)	NO RECURRENT EVENT *N* (%)	*P*-VALUE
Statin	15 (60.0)	69 (59.5)	0.9619
Antihypertensive	18 (72.0)	76 (65.5)	0.5328
Anti-Platelet	12 (48.0)	63 (54.3)	0.5663
Anticoagulant	21 (84.0)	74 (63.8)	0.0506*

Medication therapy in patients with recurrent event showed a trend toward significance with patients more likely to have a recurrent event and be on anticoagulation therapy.
* Value greater than 0.05 and not considered statistically significant for the purposes of this study as per the methods section.

DISCUSSION

In our retrospective, closed cohort study, we found that use of anticoagulation therapy was the most significant factor concerning risk of recurrent event ($P = 0.0506$). This apparent association may be because those with enough risk factors to qualify for anticoagulation would be expected to be at a higher risk of recurrence. Therefore, the anticoagulation variable may be a surrogate for other residual confounders that were not recorded and analyzed. Moreover, our primary aim of the study was to determine the usefulness of $CHADS_2$ and CHA_2DS_2-VASc scores as predictors for recurrent outcomes in this population of airmen, and we failed to observe a significant difference between the risk-stratification groups designated in the Stroke Prevention and Atrial Fibrillation by Atrial Fibrillation Investigators. Although many factors could be contributing to the otherwise nonsignificant associations of our study, our data suggests that $CHADS_2$ or CHA_2DS_2-VASc scoring are not appropriate tools for stratifying risk in an aviation population and further studies are needed to verify these results and generate new tools for this special population. On the other hand, the lack of significance with these variables may indicate that the medical certification system is not designed to gather the level of detail from demographic and medically related patient history required to adequately assess risk of these specific outcomes. Furthermore, self-selection bias may exist, where the pilots missing from our study may have failed to obtain a medical certificate in the first place if they knew they were too sick to fly. Therefore, our results may be a product of the "healthy worker effect," where the pilots in the system exhibit lower overall outcomes because the relatively stringent surveillance excludes the sicker pilots from flying. Thus, our results may not be generalizable to the other populations of nonpilots.

Further analysis is required to find the statistical significance of the difference between our study population and many of the studies reviewed for this research. For example, the overall mean age of our study participants (64.0) was 10 yr younger than the population of the North Dublin population (76.5) described in the Hayden paper.[6] Additionally, we noted that of the original 16,059 aviators screened, less than 1% were found to have a neurological outcome, whereas other studies have demonstrated higher rates. Our use of survival analysis is designed to follow an airman's capability of continuing to apply for a valid medical certificate in the FAA system, regardless of issuance, compared with survival analysis to demonstrate actual survival and mortality. Overall, our cohort is much healthier than the North Dublin population, who suffered significant morbidity and mortality in the study conducted by Hayden et al. The 5-yr recurrence rate in the North Dublin Population Stroke Study was 21.5%, whereas our cohort had a 5-yr recurrence rate of only 17.3%. This rate was also below the range of previously published population-based studies of between 18% and 32%.[14,15,19]

Limitations of our study include lack of power in statistical calculations, inherent information bias, and violation of the noninformative censoring assumption. Certain variables we analyzed to estimate association with recurrence of stroke were trending toward significance; however, we were unable to establish any statistically significant association at an alpha of 0.05. Because of the stringent aeromedical requirements and expectations in the FAA, it is likely that we only accounted for a narrow range of health status. Moreover, our limited number of study subjects lowered the statistical power of our study and eliminated the option to perform multivariate analyses.

Reporting bias, such as exposure or outcome misclassification, was very likely due to the nature of aeromedical certification. However, as previously stated, we anticipate these misclassifications to be nondifferential and likely underestimate the results. Pilots with a desire to maintain medical certification for personal or financial reasons have possible conflicts of interest with an aviation medical examiner and may withhold information or get numerous medical opinions and decide to send in the most favorable report. Ascertainment of patients with AF and AF-stroke using the DIWS pathology codes could have increased the possibility of exposure misclassification due to the lack of specificity of the pathology codes for stroke and TIA, which also include 13 additional disease states. However, misclassification was controlled for by meticulous case review and verification according to the previously stated definitions for AF and stroke. To maintain consistency in our study approach, any patients with inadequate documentation were excluded from our cohort.

Given the likelihood of participants dropping out of the study may have been based on reasons related to our recurrent outcome, the noninformative censoring assumption is violated. In other words, airmen in our study who were lost to follow-up may have suffered a recurrent event that was never recorded in our medical records because they became too sick to continue to obtain a medical certificate. Aeromedical certification is a rigorous and thorough examination for airmen with or without prior disease states, and many pilots recognize when they cannot pass the medical certification, as the practice of "self-grounding" is a time-honored tradition among aviation personnel and required in accordance with 14 CFR Part 61.53. Based on what is known about the incidence, prevalence, morbidity, and mortality of AF-stroke, it is possible that airmen's outcomes were completely missed within the FAA medical records because they never returned for aeromedical certification. This "self-grounding" effect may have been reflected in both the 7.84% (12/153) of the original study population who were excluded because the airmen in this group did not return for aeromedical examination after their initial stroke and the portion of airmen lost to follow-up. Without data to assess their disease state following an index event, we cannot assume information about these airmen who never returned for aeromedical examination. However, the study conducted by Hayden and others assessed a similarly aged population and demonstrated significant disability in individuals with comparable medical events.[6] Therefore, data concerning recurrent events from censored pilots in our study may have been inadvertently excluded, leading to nondifferential outcome misclassification and likely biasing our risk of recurrence toward the null since the outcomes occurred after the information was recorded for all exposures on the medical certificates.

While our study possesses certain limitations, it is one of the first of its kind to perform detailed analyses of the relationships between CHA_2DS_2-VASc risk factors, medications, historical data, social habits, recurrent events, and airman certificate maintenance within the U.S. FAA-certificated pilot population. Our cohort study opens the door to further investigation of the benefits of CHA_2DS_2-VASc risk stratification of pilots with AF and perhaps with further expansion of this project to those who have suffered AF-stroke. In the future, collaboration between all aeromedical certification organizations worldwide may yield a more generalizable cohort and inform decisions about aeromedical fitness to fly.

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Authors and affiliations: Jessica Tedford, M.D., Naval Flight Surgeon, FPO, AP, USA; Valerie Skaggs, Ph.D., and Ann Norris, Ph.D., Aviation Safety, AAM-003, and Farhad Sahiar, M.D., M.S., and Charles H. Mathers, M.D., M.P.H., FAsMA, Branch AAM320, Aerospace Medical Certification Division, Civil Aerospace Medical Institute, Federal Aviation Administration, Oklahoma City, OK, USA.

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