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Paroxysmal atrial fibrillation and the hazards of under-treatment

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ABSTRACT

Background and Purpose: Oral anticoagulants are highly efficacious for the prevention of stroke in atrial fibrillation, and are the preferred treatment by current guidelines. The purpose of our study was to assess the utilization of antithrombotic drugs in atrial fibrillation patients at the time of ischemic stroke and the factors associated with their use.

Methods: We enrolled 759 consecutive patients admitted with ischemic stroke at Boston Medical Center, Geisinger Health System, and the University of Alabama. To be eligible, patients had to have electrocardiographically-confirmed atrial fibrillation at the time of admission or within 6 months of the index stroke. All stroke events and electrocardiograms were validated by study physicians. Patients with newly diagnosed atrial fibrillation were not eligible.

Results: The mean age was 78 years, 43% were male, 19% black, and the mean $CHADS_2$ score is 3.0. Atrial fibrillation was paroxysmal in 31%. At presentation, 181 (24%) patients were taking warfarin only, 96 (13%) both warfarin and aspirin, 294 (39%) aspirin alone, and 189 (25%) no antithrombotic therapy. The mean international normalized ratio was 1.6. Among patients with paroxysmal atrial fibrillation, one in five was taking warfarin. Although increasing stroke risk was associated with a greater likelihood of warfarin use, only 39% of highest risk $CHADS_2$ 3–6 were taking warfarin at the time of stroke.

Conclusions: Among high-risk individuals with atrial fibrillation, only 37% were taking warfarin at the time of stroke. Paroxysmal atrial fibrillation was associated with the highest risk of not receiving warfarin.

1. Introduction

Stroke is a highly prevalent disease in the United States affecting more than 6.8 million Americans with an incidence of 795,000 persons/year. It is projected that by 2030 four million more people will suffer a stroke [1,2], and the overall medical cost associated with stroke will rise to 184.3 billion dollars. This cost represents a 157% relative increase from 2013 [3]. Atrial fibrillation (AF) is an independent risk factor for stroke, increasing the risk by 5-fold. Data from the Framingham study and the Austrian stroke registry have demonstrated that strokes associated with AF have up to two times higher mortality, higher recurrence rate, and are associated with worse neurological and functional outcomes compared to non-AF strokes [4,5].

Oral anticoagulation (OAC) reduces the rate of ischemic stroke as well as the severity of and mortality from stroke [6]. The increased utilization of OAC in patients with AF between 1992 and 2002 resulted in a reduction in ischemic stroke rates from 46.7 to 19.5 per 1000 patient-years [7]. Use of OAC at the time of the stroke reduces the severity of ischemic stroke [8], the short term stroke-associated mortality [9], and results in more favorable long-term outcomes [10]. Aspirin is substantially less efficacious compared to OAC (20% vs. 60% risk reduction accordingly) [11], and currently is recommended only for the lowest risk patients [12–14].

Despite the strong evidence supporting the use of OAC for stroke prevention in patients with AF, it remains significantly underused [15–17]. Analysis of Medicare data reveals that cost related to strokes in AF patients who are not on OAC rises to 4.8 billion USD [18]. Given the significant impact of OAC underuse, we sought to identify factors associated with OAC use at the time of ischemic stroke among individuals with previously diagnosed AF.

2. Methods

2.1. Study population

Patients admitted with ischemic stroke were identified over a 5-year period (2006–2010) from three health systems: Boston Medical Center (BMC), Geisinger Health System

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in Pennsylvania (GHS), and the University of Alabama at Birmingham (UAB). BMC is a teaching hospital and a major safety net hospital for the city of Boston. GHS is a highly integrated health care system that serves a predominantly rural population in Pennsylvania. UAB is part of the southeastern "stroke belt" and cares for a widely diverse patient population. To be eligible, patients had to have electrocardiogram (ECG)-confirmed AF at the time of admission or within 6 months prior to the stroke, if paroxysmal. Patients with newly diagnosed AF at the time of stroke were not eligible for this study. Patients with mechanical heart valves were excluded as were patients whose stroke was secondary to a vascular procedure, infection, tumor, or vasculitis. Race was defined by self-report. Socioeconomic status was determined using zip codes. All stroke events and AF ECGs were confirmed by study physicians. Antithrombotic therapy, stroke risk factors, and the international normalized ratio (INR) were determined from stroke admission records. Antithrombotic therapy includes antiplatelet therapy with aspirin and OAC with warfarin. In this cohort, non-vitamin K oral anticoagulants were not utilized. The study was approved by the institutional review committees of the participating institutions and subjects gave informed consent.

2.2. Identification of stroke cases

Stroke events were identified using ICD-9 codes for ischemic stroke (433–434, 436). To ensure the most comprehensive search, we included ICD-9 codes identified in any position—primary or secondary. Among these ICD-9 identified stroke events, those cases associated with AF (ICD-9 code 427.31) were subject to detailed medical record review. A valid ischemic stroke was defined as a neurologic deficit of sudden onset that persisted for >24 h, corresponded to a vascular territory, and was not explained by other etiologies, such as intracerebral hemorrhage, tumor, infection, or vasculitis [19,20]. Stroke cases were adjudicated by site investigators based on review of the medical record. All stroke events underwent final review by site neurologists.

2.3. Statistical analysis

Analyses were performed using SAS software (version 9.3; SAS Institute, Cary, NC). Continuous variables are summarized as means ± standard deviations and categorical variables as counts (percentages). Bivariate analyses were performed with contingency tables, and p-values were derived with the Chi-square statistic. Multiple logistic regression analysis was performed to evaluate for independent factors associated with antithrombotic use at the time of admission. The variables included in univariate and multivariate analysis were pre-specified and based on clinically relevant factors. All p-values correspond to two-sided tests and the alpha criterion was set to 0.05.

3. Results

3.1. Patient characteristics

Across the three sites, 759 patients were identified (BMC: 176, GHS: 297, and UAB: 286; Table 1). The mean age of the study participants was 78 years and the mean $CHADS_2$ score is 3.0 ± 1.4. Forty-three percent (328) of participants were male, 19% (143) black, and 4% (27) had a race different than white or black. Approximately one-third of patients had paroxysmal AF (PAF) and one-half were older than 80 years of age. At presentation, 24% (181) of patients were on OAC only, 13% (96) on both OAC and aspirin, 39% (293) on aspirin only, and 25% (189) were receiving neither OAC nor aspirin. The mean INR of the patients taking OAC was 1.6. 188 patients (33.6%) had INR within the therapeutic range (2.0 to 3.0) and 371 patients (66.4%) had sub-therapeutic INR. Twenty one (2.7%) patients had a prior intracranial hemorrhage and none of them was receiving OAC.

Although increasing stroke risk was associated with a greater likelihood of OAC use, only 39% of patients at highest risk $CHADS_2$ scores of 3–6 were taking OAC at the time of stroke (Fig. 1). Patients who were 80 years of age and older were less likely to be taking OAC compared to those younger than 80 years of age (45.1% vs. 54.9%, $p = 0.034$, Fig. 2). Among patients with PAF, approximately one in five was taking OAC compared to those patients with persistent or permanent AF (21% vs. 43.6%, $p < 0.001$, Fig. 2). We found no difference in $CHADS_2$ scores between the groups: PAF, mean $CHADS_2$ 2.97 versus permanent AF, mean $CHADS_2$ 3.08. There was no difference in OAC use by sex ($p = 0.18$), income ($p = 0.68$), or race ($p = 0.18$).

3.2. Independent factors associated with OAC use

Patients with permanent AF had a 3-fold higher likelihood of taking OAC at baseline compared to those individuals with PAF (OR: 3.25, 95%

Table 1
Baseline characteristics according to antithrombotic medication at time of ischemic stroke.

Variable		Overall	Aspirin only	Anticoagulant only	Aspirin + Anticoagulant	No aspirin or anticoagulant
		n = 759	n = 293	n = 181	n = 96	n = 189
Age, years	Mean (SD)	77.8 (11.0)	78.8 (11.2)	77.4 (9.8)	78.2 (9.4)	76.6 (12.4)
Age, %, (n)	≥80	50.2% (381)	54.9% (161)	45.3% (82)	44.8% (43)	50.3% (95)
	<80	49.8% (378)	45.1% (132)	54.7% (99)	55.2% (53)	49.7% (94)
Sex, %, (n)	Female	56.8% (431)	53.6% (157)	59.7% (108)	54.2% (52)	60.3% (114)
	Male	43.2% (328)	46.4% (136)	40.3% (73)	45.8% (44)	39.7% (75)
Race, %, (n)	White	77.6% (589)	77.5% (227)	78.5% (142)	86.5% (83)	72.5% (137)
	Black	18.8% (143)	19.1%(56)	18.2% (33)	10.4% (10)	23.3% (44)
	Other	3.6% (27)	3.4% (10)	3.3% (6)	3.1% (3)	4.2% (8)
Median income, $	Mean (SD)	47,706 (17,190)	47,597 (17,423)	48,939 (17,845)	46,517 (13,413)	47,300 (17,932)
AF type, %, (n)	Paroxysmal	31.4% (238)	37.5% (110)	17.7% (32)	18.8% (18)	41.3% (78)
	Permanent	68.6% (521)	62.5% (183)	82.3% (149)	81.3% (78)	58.7% (111)
Hypertension, %, (n)		91.2% (692)	92.2% (270)	90.6% (164)	91.7% (88)	89.9% (170)
Diabetes mellitus, %, (n)		38.6% (293)	40.6% (119)	39.8% (72)	40.6% (39)	33.3% (63)
Congestive heart failure; %, (n)		39.1% (297)	43.0% (126)	37.0% (67)	47.9% (46)	30.7% (58)
Coronary artery disease (prior MI, CABG, PCI); %, (n)		42.3% (321)	44.0% (129)	41.4% (75)	60.4% (58)	31.2% (59)
Peripheral vascular disease, %, (n)		10.8% (82)	11.6% (34)	7.2% (13)	14.6% (14)	11.1% (21)
Chronic kidney disease, %, (n)		18.8% (143)	20.8% (61)	12.7% (23)	17.7% (17)	22.2% (42)
Active malignancy (chemo, XRT, palliative care), %, (n)		10.7% (81)	13.3% (39)	8.8% (16)	9.4% (9)	9.0% (17)
Dementia, %, (n)		17.1% (130)	17.4% (51)	14.9% (27)	19.8% (19)	17.5% (33)
Hepatitis, %, (n)		0.7% (5)	0.7% (2)	0.0% (0)	0.0% (0)	1.6% (3)
Cirrhosis, %, (n)		1.1% (8)	1.0% (3)	0.6% (1)	1.0% (1)	1.6% (3)
COPD, %, (n)		16.2% (123)	15.7% (46)	20.4% (37)	16.7% (16)	12.7% (24)
Asthma, %, (n)		7.6% (58)	5.8% (17)	10.5% (19)	7.3% (7)	7.9% (15)
Sleep apnea, %, (n)		7.1% (54)	7.2% (21)	7.2% (13)	9.4% (9)	5.8% (11)
Prior CVA, %, (n)		27.3% (207)	24.9% (73)	32.6% (59)	34.4% (33)	22.2% (42)
Prior ICH, %, (n)		2.8% (21)	2.7% (8)	0.0% (0)	0.0% (0)	6.9% (13)
Prior TIA, %, (n)		14.6% (111)	11.3% (33)	16.6% (30)	18.8% (18)	15.9% (30)
Prior DVT or PE, %, (n)		10.3% (78)	7.8% (23)	12.7% (23)	17.7% (17)	7.9% (15)
Admitted from SNF, %, (n)		12.0% (91)	12.3% (36)	6.6% (12)	9.4% (9)	18.0% (34)

AF: atrial fibrillation, CABG: coronary artery bypass grafting, COPD: chronic obstructive pulmonary disease, CVA: cerebrovascular accident, DVT: deep vein thrombosis, ICH: intracranial hemorrhage, MI: myocardial infarction, PCI: percutaneous coronary intervention, PE: pulmonary embolism, SD: standard deviation, SNF: skilled nursing facility, TIA: transient ischemic attack, XRT: radiation therapy.