The Population-Based Long-Term Impact of Anticoagulant and Antiplatelet Therapies in Low-Risk Patients With Atrial Fibrillation

Anjani Golive, MD[a], Heidi T. May, PhD[a], Tami L. Bair, RN[a], Victoria Jacobs, PhD[a], Brian G. Crandall, MD[a], Michael J. Cutler, DO, PhD[a], John D. Day, MD[a], Charles Mallender, MD[a], Jeffrey S. Osborn, MD[a], Scott M. Stevens, MD[a], J. Peter Weiss, MD[a], Scott C. Woller, MD[a], and T. Jared Bunch, MD[a,b,*]

Among patients with atrial fibrillation (AF), the risk of stroke risk is a significant concern. $CHADS_2$ and CHA_2DS_2-VASc ≤2 scoring have been used to stratify patients into categories of risk. Without randomized, prospective data, the need and type of long-term antithrombotic medications for thromboembolism prevention in lower risk AF patients remains controversial. We sought to define the long-term impact of anticoagulant and antiplatelet therapy use in AF patients at low risk of stroke. A total of 56,764 patients diagnosed with AF and a $CHADS_2$ score of 0 or 1, or CHA_2DS_2-VASc score of 0, 1, or 2 were studied. Antithrombotic therapy was defined as aspirin, clopidogrel (antiplatelet therapy), or warfarin monotherapy (anticoagulation) initiated within 6 months of AF diagnosis. End points included all-cause mortality, cerebrovascular accident, transient ischemic attack (TIA), and major bleed. The average age of the population was 67.0 ± 14.1 years and 56.6% were male. In total, 9,682 received aspirin, 1,802 received clopidogrel, 1,164 received warfarin, and 46,042 did not receive any antithrombotic therapy. Event rates differed between patients with a $CHADS_2$ score of 0 and 1; 18.5% and 37.8% had died, 1.7% and 3.4% had a stroke, 2.2% and 3.2% had a TIA, and 14% and 12.5% had a major bleed, respectively ($p < 0.0001$ for all). The rates of stroke, TIA, and major bleeding increased as antithrombotic therapy intensity increased from no therapy, to aspirin, to clopidogrel, and to warfarin (all $p < 0.0001$). Similar outcomes were observed in low-risk CHA_2DS_2-VASc scores (0 to 2). In low-risk AF patients with a $CHADS_2$ score of 0 to 1 or CHA_2DS_2-VASc score of 0 to 2, the use of aspirin, clopidogrel, and warfarin was not associated with lower stroke rates at 5 years compared with no therapy. However, the use of antithrombotic agents was associated with a significant risk of bleed. **(Am J Cardiol 2017;120:75−82)**

Using anticoagulants in low-risk atrial fibrillation (AF) patients exposes them to the risk of bleeding, and as low-risk patients tend to be younger, they would be exposed to the risk of this therapy for many additional years or even decades. The recommendations for anticoagulation therapies in lower risk AF patients are based on multiple observational studies which have reported variable rates of ischemic stroke.[1−5] As a consequence, more data from low-risk AF populations is needed to fully understand the risks and benefits of current antithrombotic approaches. To this end, our study defines the risks of cerebrovascular accident (CVA) and major complications from various antithrombotic therapies (including no therapy) when select "lower risk" groups ($CHADS_2$ ≤1 or CHA_2DS_2-VASc ≤2) receive monotherapy using aspirin, clopidogrel, warfarin, a combination of antiplatelet and anticoagulant therapies, or no antithrombotic therapy.

Methods

Low risk AF patients within the Intermountain Healthcare system with at least 3 years of follow-up were studied (1990 to 2003). Intermountain Healthcare is a large, electronically integrated healthcare organization that provides the majority of healthcare for the state of Utah and southeastern Idaho. The Intermountain Healthcare Institutional Review Board approved this study.

Low risk was defined as having a $CHADS_2$ score ≤1 or CHA_2DS_2-VASc score ≤2 at the time of enrollment. A total of 56,764 patients had a $CHADS_2$ score of 0 (n = 23,718) or 1 (n = 33,046), while a total of 41,537 patients had a CHA_2DS_2-VASc score of 0 (n = 7,428), 1 (n = 13,936), or 2 (n = 20,173). Patients were categorized based on the antithrombotic therapy received (including no therapy), for stroke prophylaxis, started within 6 months of AF diagnosis. The categories included no therapy, aspirin only, clopidogrel ± aspirin, warfarin only, and warfarin with antiplatelet therapy. We defined an escalating order of therapy

[a]Intermountain Medical Center Heart Institute, Intermountain Medical Center, Murray, Utah; and [b]Department of Internal Medicine, Stanford University, Palo Alto, California. Manuscript received January 22, 2017; revised manuscript received and accepted March 20, 2017.

See page 81 for disclosure information.

*Corresponding author: Tel: (801) 507-3513; fax: (801) 507-3584.
E-mail address: thomas.bunch@imail.org (T.J. Bunch).

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Table 1
Baseline characteristics of atrial fibrillation patients with a $CHADS_2$ score of 0 or 1

Variable	Overall (n=56,764)	$CHADS_2$=0 (n=23,718)	$CHADS_2$=1 (n=33,046)	p-value
Age (years)	67.0±14.1	59.4±13.0	72.5±12.2	<0.0001
Male	56.6%	60.8%	53.6%	<0.0001
Hypertension	22.2%	0.1%	38.1%	<0.0001
Hyperlipidemia	19.5%	11.6%	25.2%	<0.0001
Diabetes Mellitus	2.8%	0%	4.8%	<0.0001
Smoking	14.0%	10.7%	16.4%	<0.0001
Renal failure	3.6%	1.9%	4.7%	<0.0001
Heart failure	4.4%	0%	7.6%	<0.0001
Coronary Artery Disease	16.4%	9.2%	21.6%	<0.0001
Prior Myocardial Infarction	4.1%	2.4%	5.4%	<0.0001
Peripheral Vascular Disease	1.5%	0.7%	2.0%	<0.0001
Prior Pulmonary Embolism	2.0%	1.5%	2.4%	<0.0001
Sleep apnea	6.4%	3.8%	8.2%	<0.0001
Prior Genitourinary bleed	0.5%	0.3%	0.7%	<0.0001
Prior bleed	9.4%	6.3%	11.6%	<0.0001
Prior malignancy	6.8%	4.5%	8.4%	<0.0001
Prior Gastrointestinal bleed	1.8%	1.3%	2.1%	<0.0001
Body Mass Index	29.1±7.1 (kg/m^2)	28.8±6.9 (kg/m^2)	29.2±7.3 (kg/m^2)	<0.0001
Ejection fraction	57.2±12.7 (%)	58.0±11.6 (%)	56.7±13.2 (%)	<0.0001

as follows: no therapy → aspirin → clopidogrel ± aspirin → warfarin → warfarin + antiplatelet agent.

Clinical outcomes were evaluated at 3 and 5 years and included ischemic CVA, transient ischemic attack (TIA), gastrointestinal (GI) bleed, genitourinary (GU) bleed, and all-cause death. All outcomes, except death, were determined by International Classification of Diseases (ICD)-9 and 10 codes and were defined as follows: CVA: ICD-9 codes 436*, 433._1, and 434.1, and ICD-10: I63.x, I64.x; TIA: ICD-9 code 435* and ICD-10: G45.0x, G45.1x, G45.8, G45.9x, I167.848; GI bleed: ICD-9 code 578.x and ICD-10 code K92.x; and GU bleed: ICD-9 codes 599.70, 599.71, and 602.1, and ICD-10 codes N42.1, R31.9, R31.0, and T83.83XA. Deaths were determined by hospital records, state of Utah Health Department records (death certificates), and the Social Security Death Master Index. Patients not listed as deceased in any registry were considered to be alive.

The chi-square statistic, Fisher's exact test, Student's *t* test, and analysis of variance were used to evaluate baseline and clinical characteristics among the patient groups. Initial evaluation of end points used the chi-square statistic, the Fisher's exact test, the Kaplan-Meier survival estimates, and the log-rank test. To confirm associations determined by univariable analysis, multivariable Cox hazard regression (SPSS version 22.0, Chicago, IL) was performed to determine hazard ratios. Final models entered significant ($p < 0.05$) and confounding (10% change in hazard ratio) baseline covariables. Two-tailed p-values of ≤ 0.05 were designated to be nominally significant.

Results

Table 1 lists comparative demographic data of 56,764 patients with AF stratified by a $CHADS_2$ score of 0 versus 1 at arrhythmia diagnosis. With increasing CHADS2 score baseline risk factors for stroke increased. Similarly risk factors for bleed, including previous GI and GU bleeding, malignancy, age, and renal failure, were also higher in the $CHADS_2$ group with a score of 1.

The antiplatelet and antithrombotic therapies within this population are shown in Table 2. In a similar manner the population is compared by CHA2DS2-VASc score ≤ 2 (Table 3) and treatment allocation by score strata shown in Table 4.

The patients in the $CHADS_2$ group were followed on average after AF diagnosis for 7.5 ± 5.9 years ($CHADS_2$ 0: 9.3 ± 6.1 years, $CHADS_2$ 1: 6.2 ± 5.3 years). Among this population, 50,932 had 5 years of follow-up. The event rates at 3 and 5 years for CVA, TIA, GI bleeding, and GU bleeding are listed in Table 5. All end points, including death, were increased as the $CHADS_2$ score increased. Next, within this population, we analyzed event rates by treatment approach (Figure 1, Supplementary Table 1). Across all end points, risks were higher in those patients treated than in patients with no therapy. Warfarin monotherapy had lower event rates of CVA and GI bleeding compared with antiplatelet therapy. Dual therapy was associated with the highest risks in general.

The patients in the CHA_2DS_2-VASc group were followed on average after AF diagnosis for 8.1 ± 5.8 years (CHA_2DS_2-VASc 0: 10.2 ± 6.3 years, CHA_2DS_2-Vasc 1: 8.8 ± 5.8 years, CHA_2DS_2-VASc 2: 6.8 ± 5.3 years). Of this population, 37,109 had 5 years of follow-up. The event rates at 3 and 5 years for CVA, TIA, GI, and GU bleeding are listed in Table 6. Event rates increased as CHA_2DS_2-VASc scores increased. Regarding treatment, across all end points, risks were higher in those patients treated than in patients with no therapy (Figure 2, Supplementary Table 2). Warfarin monotherapy had lower event rates of CVA and bleeding compared with antiplatelet therapy. Dual therapy was associated with the highest risks compared with other therapies. Across all end points, risks were higher in those patients treated than in patients with no therapy. Warfarin monotherapy and aspirin had lower event rates of CVA and