REGULAR ARTICLE

blood advances

Cumulative incidence, risk factors, and management of atrial fibrillation in patients receiving ibrutinib

Tracy E. Wiczer,[1] Lauren B. Levine,[1] Jessica Brumbaugh,[1] Jessica Coggins,[1] Qiuhong Zhao,[2] Amy S. Ruppert,[2] Kerry Rogers,[2] Anli McCoy,[1] Luay Mousa,[2] Avirup Guha,[3] Nyla A. Heerema,[4] Kami Maddocks,[2] Beth Christian,[2] Leslie A. Andritsos,[2] Samantha Jaglowski,[2] Steven Devine,[2] Robert Baiocchi,[2] Jennifer Woyach,[2] Jeffrey Jones,[2] Michael Grever,[2] Kristie A. Blum,[2] John C. Byrd,[2] and Farrukh T. Awan[2]

[1]Department of Pharmacy and [2]Division of Hematology, The James Cancer Hospital and Solove Research Institute at The Ohio State University, Columbus, OH; [3]Division of Cardiology, The Ohio State University Wexner Medical Center, Columbus, OH; and [4]Department of Pathology, The Ohio State University, Columbus, OH

Key Points

- Ibrutinib increases the incidence of AF in patients with hematologic malignancies treated on or off a clinical trial.
- Patients with a history of AF and those with a high FHS-AF risk score are at highest risk for developing AF while on ibrutinib.

Atrial fibrillation (AF) has been reported in up to 16% of patients taking ibrutinib. Data regarding the management of AF in this patient population are limited, and stroke prevention poses a challenge because of increased risk of bleeding with ibrutinib treatment. Our study sought to describe the incidence of AF in adult patients treated with ibrutinib for a hematologic malignancy, assess management strategies, evaluate stroke and bleeding outcomes, and identify risk factors for occurrence. Of 582 patients treated with ibrutinib, 76 developed AF. With a median follow-up of 32 months, the estimated cumulative incidence at 6 months, 1 year, and 2 years was 5.9% (95% confidence interval [CI]: 4.2-8.0), 7.5% (95% CI: 5.5-9.9), and 10.3% (95% CI: 8.0-13.0), respectively. Median time to onset of AF was 7.6 months. History of AF and Framingham Heart Study (FHS) AF risk score were found to be significant risk factors for development of AF. Most patients were treated with rate control–only strategies (61.8%), and concomitant aspirin or anticoagulant therapy with ibrutinib was used in 52.6% and 28.9% of patients, respectively. One patient on aspirin developed symptoms consistent with stroke. Nine major bleeds were noted in 7 patients, and 34 clinically relevant nonmajor bleeds were noted in 24 patients. Twenty-one bleeds (4 major bleeds) occurred in 18 patients on aspirin, and 10 bleeds (all clinically relevant nonmajor bleeds) occurred in 6 patients with anticoagulant therapy. These results provide risk factor assessment, impact of management strategies, and outcomes of patients with AF on ibrutinib and serve as basis for formal guidelines.

Introduction

Ibrutinib is an irreversible inhibitor of Bruton tyrosine kinase (BTK) and is currently approved for the treatment of chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), and Waldenström macroglobulinemia (WM).[1-3] Ibrutinib's primary target is BTK; however, it also targets several other kinases, including ITK, BMK, TEC, RLK, EGFR, Erb2, Erb4, BLK, and JAK3, at clinically achievable concentrations.[4] The unintended impact of ibrutinib on these kinases results in a myriad of potentially beneficial or adverse events including atrial fibrillation (AF), which is putatively related either to reduced activity of the BTK-regulated PI3K/Akt pathway in cardiac myocytes, to reduced activity of other relevant tyrosine kinase pathways, or to as-yet unidentified mechanisms.[5-10]

AF has been identified as a particularly concerning adverse effect impacting 2% to 16% of patients with CLL, MCL, and WM treated with ibrutinib.[1-3,5,11-22] A recent meta-analysis has demonstrated a pooled

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incidence rate of 3.3 per 100 person-years (95% confidence interval [CI] 2.5-4.1) among ibrutinib recipients. This rate is substantially higher than clinical trial participants receiving nonibrutinib therapy (0.84 per 100 person-years with 95% CI 0.32-1.6) and the general population of men and women aged 65 to 74 years (1.8 and 1.0 per 100 person-years, respectively).[20,23] Available literature also suggests that most patients develop AF within the first 4 months of ibrutinib treatment.[16-21]

The fundamental principles of managing patients with AF are rate or rhythm control and stroke prevention.[24] Stroke prevention in patients with AF who are taking ibrutinib is complicated by the inherent bleeding risk associated with ibrutinib treatment, and there are no clear guidelines on use of anticoagulants or antiplatelet agents in this population.[25] Comprehensive studies evaluating risk factors for the development of AF during ibrutinib treatment are limited by the small number of cases, but have suggested preexisting diabetes, hypertension, and prior history of AF as potentially significant risk factors.[16-21] However, the risk of AF in the setting of ibrutinib treatment is poorly understood.

In this report, we describe patients who developed AF in a large cohort of patients taking ibrutinib for hematologic malignancies treated at a single institution. The primary objective of this study was to describe the cumulative incidence of AF in patients treated with ibrutinib. The secondary objectives were to describe the management of AF, including rhythm control and stroke prevention, to evaluate outcomes of AF patients, including bleeding complications and stroke, and to identify risk factors for the development of AF.

Methods

Study design

A retrospective, single-center study was performed to describe the cumulative incidence and management of AF in patients managed and treated with ibrutinib between December 2009 and March 2016 at The James Comprehensive Cancer Hospital of The Ohio State University after obtaining approval from the Institutional Review Board. This study was conducted in accordance with the Declaration of Helsinki. Patients were identified using electronic medical record ibrutinib prescription data. Patients were included if they were ≥18 years old and treated with ibrutinib for a hematologic malignancy including but not limited to CLL, MCL, WM, and other non-Hodgkin lymphomas. Patients were excluded if they had incomplete electronic medical records for the variables of interest, were enrolled in an ibrutinib/placebo blinded clinical trial, or were incarcerated or pregnant.

Clinical data were retrospectively collected from the electronic medical records for the duration of ibrutinib therapy. Baseline and serial demographic and clinical data were collected. In addition, the risk of development of AF was calculated for all patients according to the Framingham Heart Study (FHS) AF score. Scores ≤10%, between 10% and 20%, and >20% were classified as low, intermediate, and high risk, respectively. The FHS-AF risk score is extensively validated and provides an opportunity to use risk factors for AF, including age, sex, body mass index, systolic blood pressure, treatment of hypertension, PR interval, presence of significant murmur, and heart failure to estimate the patient's specific 10-year risk for AF.[23]

To identify the primary outcome of AF, patients were designated to the AF group if they had electrocardiogram-confirmed AF. Incident AF was defined as new AF in patients with no history of AF, whereas recurrent AF was defined as an AF event in those patients with a history of AF at ibrutinib start. AF episodes were graded according to the Common Terminology Criteria for Adverse Events v4.03.[26] Data pertaining to AF arrhythmia management as well as stroke prevention strategies were recorded. CHADS2 score was assigned to all patients at the time of AF onset, which estimates patient stroke risk based on the presence or absence of validated risk factors.[27] A Naranjo Probability Score was calculated for each AF event to determine the likelihood that ibrutinib contributed to the event.[28]

Bleeding events were categorized as major bleeds or clinically relevant nonmajor bleeds (CRNMB) according to the International Society on Thrombosis and Haemostasis (ISTH) criteria.[29,30] Major bleeding was defined as fatal bleeding, symptomatic bleeding in a critical organ (eg, intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, intramuscular, gastrointestinal), or bleeding that resulted in a hemoglobin drop of at least 2 g/dL or required at least 2 units of blood.[29] CRNMB was defined as bleeding that did not meet the ISTH criteria for major bleed but met at least 1 of the following criteria: required medical intervention, hospitalization, or face-to-face evaluation.[30] New stroke was defined as documentation of magnetic resonance imaging consistent with either ischemic or hemorrhagic stroke. New transient ischemic attack (TIA) was defined as documentation of symptoms consistent with TIA. Bleeding and stroke outcomes were collected after an established diagnosis of AF only (including those with a history of AF at baseline).

Statistical analysis

Descriptive statistics were used to summarize patient characteristics. Fisher's exact test was used to compare the use of management strategies between groups as appropriate. Survival analysis techniques were used to estimate the cumulative incidence of AF and to evaluate the risk factors for AF. Development of AF during ibrutinib treatment was considered an event, and time to event was defined as the time from the date of starting ibrutinib treatment until the onset date of AF. Discontinuation of ibrutinib and death prior to an AF event, whichever occurred first, were treated as competing events at the time of discontinuation or death. Patients on ibrutinib with no occurrence of AF were censored at the last assessment date. The cumulative incidence of AF was estimated, and Gray's test was used to compare differences in the cumulative incidence rates between groups of interest. The person-year incidence rate for AF event was calculated using the number of AF events occurring during ibrutinib treatment divided by the total person years of ibrutinib use until first AF onset.

The Fine and Gray regression model accounting for competing risks was used to examine the association between patient characteristics and risk of developing AF. Risk factors that were not known at baseline but developed during ibrutinib use were treated as time-dependent covariates in the regression model. Covariates with significance level of $P < .20$ from univariable analyses were further evaluated in a multivariable analysis using a stepwise selection procedure, retaining those with $P < .05$ in the final model. Analyses were performed using Stata 14, S-Plus, Graphpad Prism, and the statistical tests were 2-sided with statistical significance defined as $P < .05$.

Results

Study population

Five hundred eighty-two patients treated with ibrutinib for hematologic malignancies were included (Figure 1). Table 1 summarizes

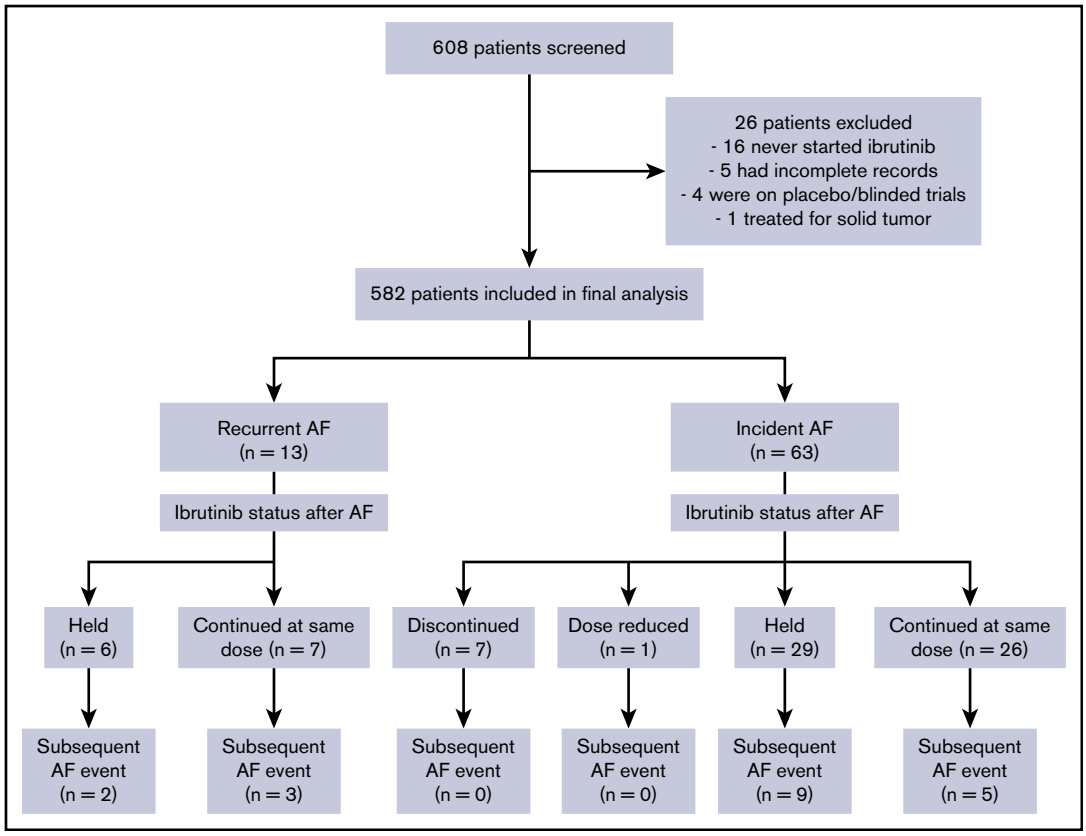

Figure 1. Study population.

the baseline characteristics of all patients and CLL patients separately at the start of therapy with ibrutinib. Patients had a median age of 65 years and were predominantly men (69.8%), white (92.8%), with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 (92.5%). Concomitant anticancer therapy with ibrutinib was used in 175 (30.1%) patients with monoclonal antibodies being the most common concomitant therapy (24.9%). Comorbidities that increase the risk of AF were prevalent in this population, and 34 (5.8%) patients had a prior history of AF. Baseline characteristics for these patients are detailed in supplemental Table 1. One hundred ten (18.9%) patients were treated with commercial ibrutinib, and 472 (81.1%) were treated with ibrutinib on a clinical trial. Supplemental Table 2 details the baseline characteristics based on the source of ibrutinib.

Cumulative incidence and risk factors of AF

With a median follow-up of 32 months (range 0.7-73), 63 patients developed incident AF and 13 patients developed recurrent AF while on ibrutinib for a total of 76 (13%) events. Supplemental Table 3 lists characteristics of patients based on whether they experienced an AF event during the study. The estimated cumulative incidence of AF at 6 months, 1 year, and 2 years was 5.9% (95% CI: 4.2-8.0), 7.5% (95% CI: 5.5-9.9), and 10.3% (95% CI: 8.0-13.0), respectively (Figure 2A). Among those with an AF event, median time of onset was 7.6 months (range 0.2-63.4). Cumulative incidence curves according to incident or recurrent AF are shown in Figure 2B. Among those with an AF event, median time of onset was 10.9 months (range 0.2-63.4) for incident AF and 2.2 months (range 0.2-35.2) for recurrent AF.

Univariable analyses (Figure 3A) identified age ≥75 years, male sex, FHS-AF risk score, and history of diabetes, coronary artery disease, coronary artery bypass grafting, congestive heart failure, cardiac murmur, baseline blood pressure, and prior history of AF as significant risk factors for AF in the entire patient cohort. Multivariable analysis (Figure 3B) identified FHS-AF score (score of 10% to 20% vs <10%: hazard ratio [HR] 2.14, 95% CI 1.03-4.44, $P = .042$; score >20% vs <10%: HR 4.58, 95% CI 2.34-8.96, $P < .001$) and history of AF (HR 3.63, 95% CI 1.67-7.92, $P = .001$) as risk factors for the development of AF during ibrutinib treatment.

Although no significant difference was observed in the risk of AF in the CLL patient cohort as compared with the non-CLL patients ($P = .32$), a subgroup analysis was conducted for CLL patients only (n = 433). Univariable analyses identified age, male sex, FHS-AF risk score, and history of diabetes, coronary artery bypass grafting, baseline blood pressure, and prior history of AF as significant factors for AF (supplemental Figure 1). Multivariable analysis in this subgroup (Figure 3B) also identified FHS-AF score (score >20% vs <10%: HR 3.34, 95% CI 1.54-7.26, $P = .002$) and history of AF (HR 4.03, 95% CI 1.34-12.16, $P = .013$) as well as presence of trisomy 12 (HR 2.46, 95% CI 1.21-4.99, $P = .013$) as risk factors for the development of AF during ibrutinib treatment.

Information was available for a total of 1032 person-years of ibrutinib exposure, during which 76 patients developed AF, which corresponds to an estimated incidence of 7.4 events per 100 person-years for all patients. In the subgroup of CLL patients, 61 AF

Table 1. Baseline population demographics

	All patients (n = 582)	CLL patients (n = 433)
Age, median (range), y	65 (23 to >89)	65 (26 to >89)
Sex, male, n (%)	406 (69.8)	301 (69.5)
Race, n (%)		
White	540 (92.8)	398 (91.9)
Black	31 (5.3)	27 (6.2)
Others*	11 (1.8)	8 (1.9)
ECOG performance status, n (%)		
0-1	530 (92.5)	402 (94.6)
2	39 (6.8)	23 (5.4)
3-4	4 (0.6)	0 (0)
Primary malignancy, n (%)		
CLL	433 (74.4)	433 (100)
MCL	57 (9.8)	–
WM	12 (2.1)	–
Others†	80 (13.7)	–
CLL, Rai stage (n = 433), n (%)		
0 (low risk)	–	3 (0.7)
1-2 (intermediate risk)	–	118 (27.2)
3-4 (high risk)	–	307 (70.9)
Unknown	–	5 (1.2)
CLL, risk stratification (n = 433), n (%)		
Del11q22	–	138 (32.7)
Trisomy 12	–	88 (21)
Del13q14	–	219 (51.9)
Del17p13	–	160 (37.9)
IGHV mutated, >2%	–	78 (21.4)
Cancer stage (MCL, WM, other) (n = 149), n (%)		
1-2	8 (5.4)	–
3-4	114 (76.5)	–
Not applicable, unknown	27 (18.1)	–
Treatment history, n (%)		
Prior therapies, median (range)	3 (0-18)	3 (0-18)
Untreated	37 (6.4)	26 (6.0)
Prior anthracycline	134 (23)	29 (11.3)
Prior autologous HSCT	38 (6.5)	4 (0.9)
Prior allogeneic HSCT	21 (3.6)	10 (2.3)
Concomitant therapies with ibrutinib, n (%)		
Any anticancer therapy	175 (30.1)	102 (23.6)
Anthracyclines	9 (1.5)	8 (1.9)
MoAb therapy	143 (24.6)	91 (21.0)
Baseline AF risk factors		
Hypertension, n (%)	262 (45)	187 (43.2)
Diabetes mellitus, n (%)	76 (13.1)	50 (11.6)
Myocardial infarction, n (%)	36 (6.2)	28 (6.5)
Coronary artery disease, n (%)	66 (11.3)	49 (11.3)
Congestive heart failure, n (%)	14 (2.4)	11 (2.5)
Obstructive sleep apnea, n (%)	46 (7.9)	36 (8.3)
Valvular heart disease, n (%)	22 (3.8)	20 (4.6)
Hyperthyroidism, n (%)	5 (0.9)	5 (1.2)
Coronary artery bypass graft, n (%)	12 (2.1)	9 (2.1)
TIA or stroke, n (%)	22 (3.8)	13 (3.0)
History of AF	34 (5.8)	23 (5.3)
Cardiac murmur, n (%)	67 (11.5)	52 (12.0)
Smoking, n (%)	262 (45)	195 (45.1)
Baseline systolic BP, median (range), mm Hg	129 (86-186)	128 (90-174)
Baseline PR interval,‡ median (range), ms	156 (80-302)	156 (80-302)
Predicted AF risk		
FHS-AF risk,§ median (range), %	6.8 (0.02 to >30)	6.8 (0.1 to >30)
Low risk (<10%), n (%)	257 (63.3)	177 (63.0)
Intermediate risk (10%-20%), n (%)	94 (23.2)	68 (24.2)
High risk (>20%), n (%)	55 (13.6)	36 (12.8)
Missing data, n (%)	176 (30.2)	152 (35.1)

–, Not applicable; BP, blood pressure; ECOG, Eastern Cooperative Oncology Group; HSCT, hematopoietic stem cell transplant; MoAb, monoclonal antibody.

*Hispanic, Asian, mixed.

†Diffuse large B-cell lymphoma, graft-versus-host disease, marginal zone lymphoma, hairy cell leukemia, follicular lymphoma; BP, normal considered <120 mm Hg.

‡Normal range = 120-200 ms.

§FHS 10-y risk of first AF, calculated according to Schnabel et al[24] using the following variables: age, sex, body mass index, systolic blood pressure, treatment of hypertension, PR interval, significant murmur, prevalent heart failure.

events occurred during 887 person-years of ibrutinib exposure, corresponding to an estimated incidence of 6.9 events per 100 person-years. Despite a nonsignificant difference in cumulative incidence between patients treated on a clinical trial and patients treated on commercial ibrutinib, the person-year incidence rates were 6.6 and 13.8 per 100 person-years, respectively (rate ratio = 2.1, 95% CI 1.2-3.7). However, the median follow-up for those on a clinical trial was 25.2 months and substantially longer than the median follow-up of 10.8 months for those receiving commercial ibrutinib. In addition, the AF incidence is higher early in the study and diminishes over time, which violates the assumption of constant risk. Together, this compromises the comparison of person-year incident rates between the 2 groups. Among patients with an AF event while on ibrutinib (15 on commercial, 61 on clinical trials), there were 9 subsequent AF in 5 patients treated with commercial ibrutinib vs 19 subsequent AF in 14 patients treated on clinical trials with ibrutinib. Supplemental Figures 2-4 detail the univariable and multivariable analyses of risk factors within these subgroups using regression models for cumulative incidence.

With regard to strong cytochrome P450 3A4 inhibitors, 25 patients were on a concomitant inhibitor during ibrutinib therapy at some point. Five patients who developed AF were exposed to an inhibitor while on ibrutinib therapy; however, only 1 patient was on the inhibitor at the time of AF onset. Three patients who developed AF were exposed to the inhibitor after AF onset, none of which experienced a recurrent AF event during inhibitor exposure.

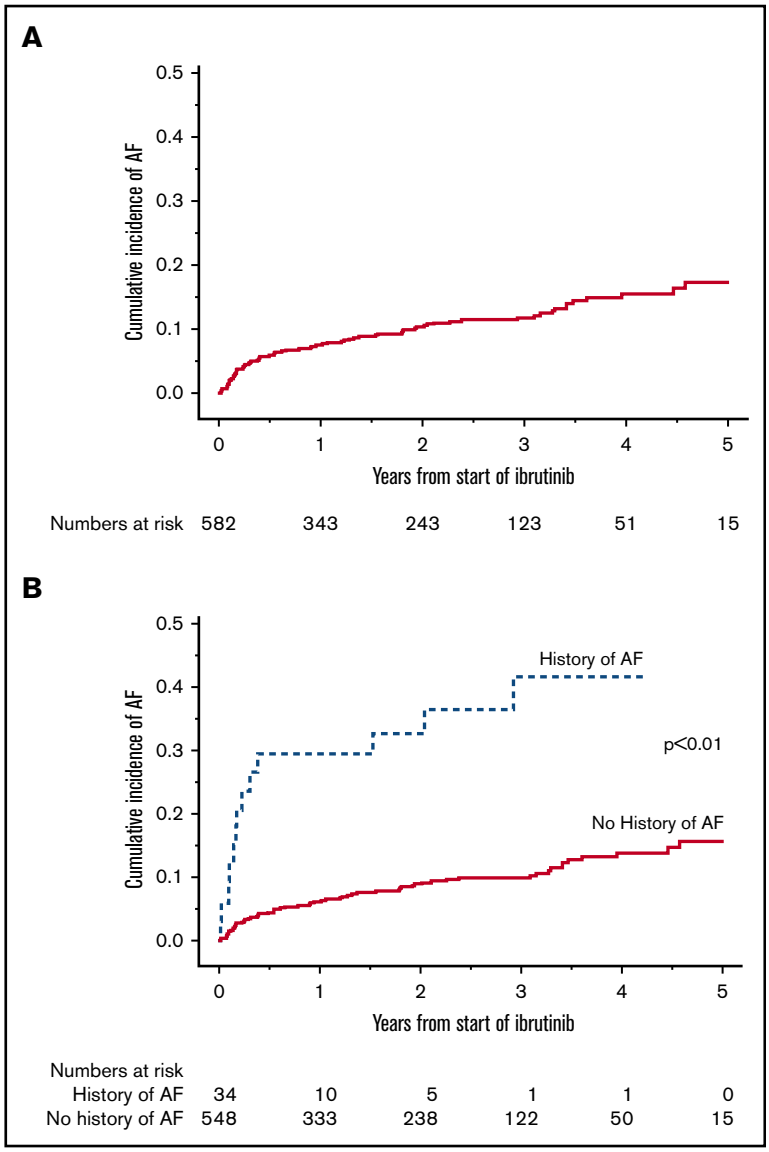

Figure 2. AF incidence. (A) Cumulative incidence of AF in patients receiving ibrutinib. (B) Cumulative incidence of AF based on history of AF.

Management of AF

Management of AF events is described in Table 2. Most AF events were grade 2 (65 events [85.5%]), and 69 (90.8%) patients required treatment of their AF event. A majority of patients were treated with medical rate control alone (61.8%) as compared with medical rhythm control alone (5.3%) or a combination of both strategies (15.8%).

Stroke prevention strategies are listed in Table 2 and by CHADS2 score in supplemental Table 4. Twenty-two (28.9%) patients were prescribed an anticoagulant and 40 (52.6%) patients were prescribed aspirin. Two (2.6%) patients were prescribed an anticoagulant and aspirin concomitantly. Twenty-six (34.2%) patients had a CHADS2 score of 2 or higher and only 5 (19.2%) were prescribed anticoagulant therapy.

Thirty-three (43.4%) patients continued ibrutinib at full dose; 35 (46.1%) had ibrutinib held; 1 (1.3%) patient was dose reduced (from 560 mg to 420 mg); and 7 (9.2%) discontinued ibrutinib for the initial AF event. No subsequent AF events were observed in patients who discontinued or had the ibrutinib dose reduced. Eleven patients (31.4%) had 17 subsequent AF events when ibrutinib was restarted at full dose after a temporary hold, and 8 patients (24.2%) had 11 subsequent AF events when ibrutinib was continued at the same dose. Two patients discontinued ibrutinib because of a subsequent AF event. The Naranjo probability score indicated a definite association with ibrutinib in 7 (9.2%) patients, probable in 36 (47.4%), and possible in 33 (43.4%).

Outcomes after AF event

Stroke and bleeding outcomes are outlined in Table 3. One (1.3%) patient with a CHADS2 score of 1 on aspirin 325 mg developed symptoms consistent with stroke 16 months after the onset of AF; however, this event could not be confirmed on magnetic resonance imaging.

In the 76 patients with AF at any point during the study period, 8 major bleeding events (5 grade 2, 3 grade 3) occurred in 7 patients.

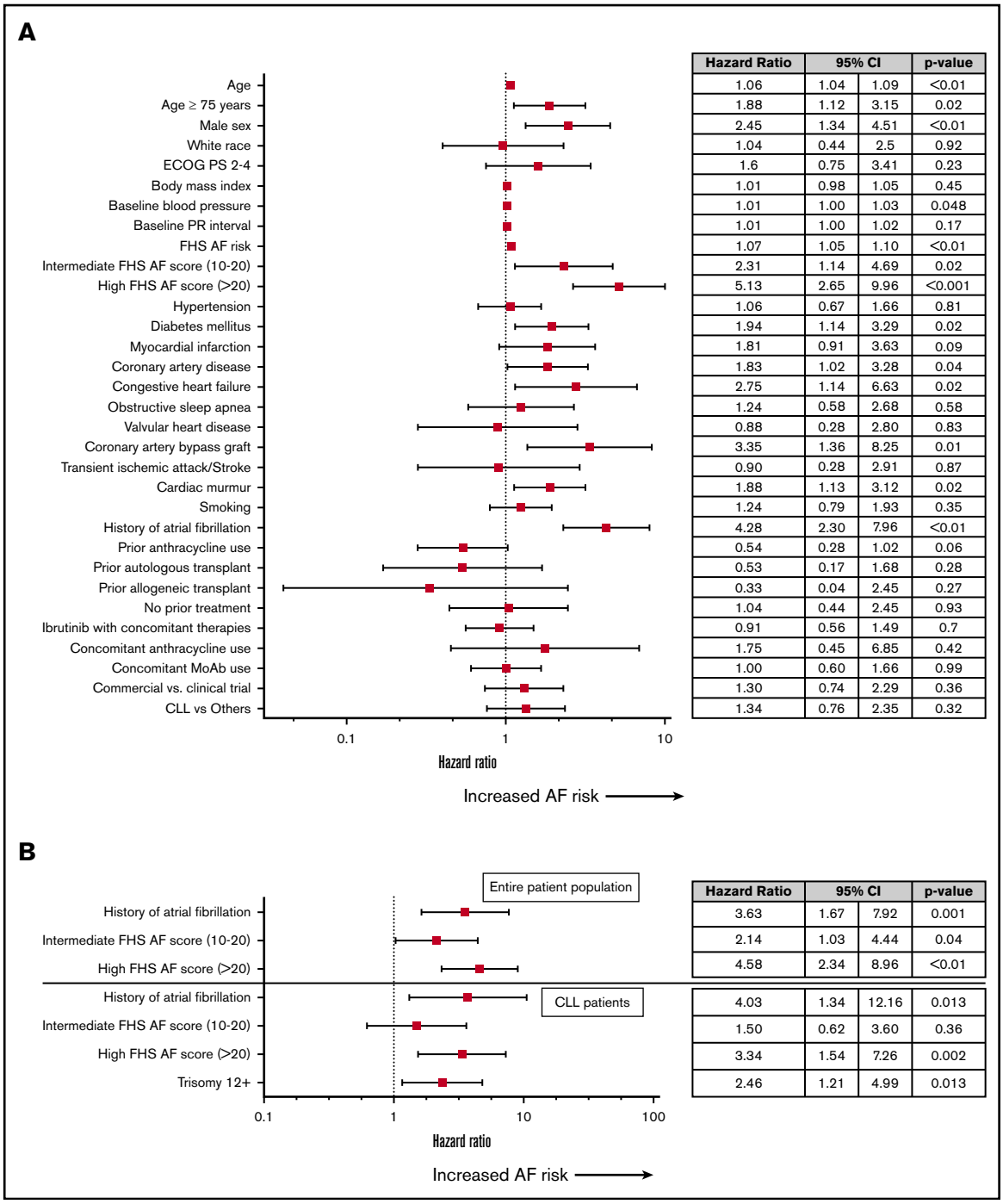

Figure 3. AF risk factor analysis. (A) Univariable analysis for AF risk factors for entire population. (B) Multivariable analysis for AF risk factors for entire population. PS, performance status.

Four major bleeds occurred with concomitant aspirin use and none with concomitant anticoagulant use. Ibrutinib was continued during 1 major bleed, temporarily held during 6 major bleeds, and discontinued after 1 major bleed. There were 26 CRNMB events (9 grade 1, 14 grade 2, 3 grade 3) in 19 patients. Twelve (46%) of these events occurred with concomitant aspirin use and 7 (27%) with concomitant anticoagulant use. Ibrutinib was continued during 16 CRNMB events, held during 9 events, and discontinued as a result of 1 event.

Discussion

Our study details an extensive single-center experience with AF during treatment with ibrutinib. Our data support that the risk of AF is highest in the first several months of ibrutinib therapy, with an estimated cumulative incidence of 5.9% at 6 months and increasing to 10.3% by 2 years. Our study may underestimate the true AF incidence because patients were diagnosed when they presented

Table 2. Management of AF events

	All AF (n = 76)	Incident AF (n = 63)	Recurrent AF (n = 13)	P
AF Common Terminology Criteria for Adverse Events v4.03 grade, n (%)				
1	6 (7.9)	4 (6.3)	2 (15.4)	.43
2	65 (85.5)	54 (85.7)	11 (84.6)	
3	5 (6.6)	5 (7.9)	0	
4-5	0	0	0	
AF management, n (%)				
None	7 (9.2)	5 (7.9)	2 (15.4)	.34
Yes	69 (90.8)	58 (92.1)	11 (84.6)	
Rate control	60 (78.9)	50 (79.4)	10 (76.9)	.99
Class II agents*	43 (56.6)	35 (55.6)	8 (61.5)	.77
Class IV agents†	33 (43.4)	28 (44.4)	5 (38.5)	.77
Class V agents‡	5 (6.6)	5 (7.9)	0	.58
Rhythm control	16 (21.1)	14 (22.2)	2 (15.4)	.72
Class I agents§	8 (10.5)	7 (11.1)	1 (7.7)	.99
Class III agents‖	11 (14.5)	10 (15.9)	1(7.7)	.68
Cardiac ablation	3 (3.9)	3 (4.8)	0	.99
Cardioversion	11 (14.5)	10 (15.9)	1 (7.7)	.68
Pacemaker¶	3 (3.9)	3 (4.8)	0	.99
AF management, n (%)				
Medical rate control alone	47 (61.8)	39 (61.9)	8 (61.5)	.91
Medical rhythm control alone	4 (5.3)	4 (6.3)	0	
Medical rate and rhythm control combined	12 (15.8)	10 (15.9)	2 (15.4)	
Others#	13 (17.1)	10 (15.9)	3 (23.1)	
Anticoagulation, n (%)				
No	54 (71.1)	42 (66.7)	12 (92.3)	.09
Yes	22 (28.9)	21 (33.3)	1 (7.7)	
Specific anticoagulant use, n (%)				
Enoxaparin	5 (22.7)	5 (23.8)	0	.58
Rivaroxaban	6 (27.3)	6 (28.6)	0	.58
Apixaban	3 (13.6)	2 (9.5)	1 (7.7)	.44
Dabigatran	2 (9.1)	2 (9.5)	0	.99
Warfarin	4 (18.2)	4 (19)	0	.99
Heparin	3 (13.6)	3 (14.3)	0	.99
Antiplatelet therapy, n (%)				
No	36 (47.4)	33 (52.4)	3 (23.1)	.07
Yes	40 (52.6)	30 (47.6)	10 (76.9)	
Aspirin 81 mg	11 (27.5)	8 (26.7)	3 (30)	.99
Aspirin 162 mg	1 (2.5)	1 (3.3)	0	
Aspirin 325 mg	28 (70)	21 (70)	7 (70)	
Ibrutinib status after AF event, n (%)				
No change	33 (43.4)	26 (41.3)	7 (53.8)	.63
Temporary hold	35 (46.1)	29 (46)	6 (46.2)	
Dose reduction	1 (1.3)	1 (1.6)	0	
Discontinued	7 (9.2)	7 (11.1)	0	

*Labetalol, metoprolol, carvedilol, atenolol.
†Diltiazem.
‡Digoxin.
§Propafenone, flecainide.
‖Amiodarone, dronedarone, sotalol.
¶None of the patients with pacemaker got ablation.
#Ablation, cardioversion, pacemaker, no treatment.

with clinically significant AF and asymptomatic episodes may not have been captured because systematic monitoring for AF was not mandated.

The person-year incidence rate in our study is 7.4 per 100 person-years, which is in contrast to earlier reported incidence rates of 2 to 4 per 100 person-years and exceeds expected baseline rates for older community-dwelling adults.[20,23] However, person-year incidence rates can be influenced by the length of exposure, particularly when the risk of an event is not constant over time. The meta-analysis from the 20 studies had a median follow-up up to 26 months, which is shorter than the follow-up in our study.

There is a lack of consensus on the optimal stroke prophylaxis in patients taking ibrutinib. In the general population, CHADS2 score can be used to gauge risk of embolic stroke, and evidence-based guidelines exist regarding the use of stroke prophylaxis. No consistent stroke prevention strategy has yet been reported for ibrutinib-treated patients. Existing evidence comes from an international retrospective study of 56 CLL patients who developed AF during treatment with ibrutinib and reported 1 ischemic stroke in a patient who was not on pharmacologic stroke prophylaxis and 8 grade 3 to 4 bleeding events (14%). Among the grade 3 to 4 bleeding events, 3 patients were on warfarin, 1 on aspirin, 1 on both aspirin and clopidogrel, and 3 not on any anticoagulant or antiplatelet agents.[19]

Given both our and the CLL community's early clinical observation of the increased risk for bleeding-related complications in patients undergoing treatment with ibrutinib, especially those on concomitant anticoagulation, our institutional practice has generally been conservative with regards to the use of anticoagulation or antiplatelet therapy.[1,11,13,14,19,31] Our conservative stroke prevention strategy is reflected in the proportion of patients with AF who did not receive anticoagulation despite having a high CHADS2 score. Fortunately, only 1 stroke event was observed despite the modest rate of anticoagulation use, where only 19% of patients with a CHADS2 score >1 were treated with anticoagulation. This strategy may have contributed to the low number of major or CRNMB events. We found 15 of 40 (38%) patients with concomitant aspirin treatment experienced 16 bleeding events, compared with 5 of 22 (23%) patients with concomitant anticoagulant treatment who experienced 7 bleeding events ($P = .27$).

Our study validates a history of prior AF as a significant risk factor for the development of AF.[17,20,21] However, this observation is limited by the small number of patients at risk beyond the first year of treatment on ibrutinib. We further describe the utility of the

Table 3. Stroke and bleeding outcomes after AF onset

	All AF (n = 76)	Incident AF (n = 63)	Recurrent AF (n = 13)
Stroke/TIA, n (%)	1 (1.3)	0	1 (7.7)
Major bleeding events,* n	8	7	1
Major bleed type, no. of events			
Intracranial	2	2	0
Intraocular	2	2	0
Gastrointestinal	1	0	1
Surgical	2	2	0
Other	1	1	0
Concomitant antiplatelet, n	4	3	1
Concomitant anticoagulant, n	0	0	0
Ibrutinib status after bleed, n			
No change	1	1	0
Temporary hold	6	6	0
Discontinued	1	0	1
CRNMB†			
CRNMB events, n	26	23	3
CRNMB type, no. of events			
Genitourinary	9	8	1
Pulmonary	3	2	1
Gastrointestinal	4	3	1
Dermatologic	4	4	0
Epistaxis	3	3	0
Oral	0	0	0
Surgical	1	1	0
Ecchymosis	0	0	0
Other	2	2	0
Concomitant antiplatelet, n	12	9	3
Concomitant anticoagulant, n	7	7	0
Ibrutinib status after bleed, n			
No change	16	14	2
Temporary hold	9	8	1
Discontinued	1	1	0

*Major bleed is defined as fatal bleeding, symptomatic bleeding in a critical organ (eg, intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, intramuscular), or bleeding that resulted in a hemoglobin drop of at least 2 g/dL or required at least 2 units of blood; major bleeding is reported on an event level (patients could have multiple bleeding events).

†CRNMB is defined as bleeding that did not meet the ISTH criteria for major bleed but met at least 1 of the following criteria: (1) required medical intervention, (2) hospitalization, or (3) face-to-face evaluation; CRNMB is reported on an event level (patients could have multiple bleeding events).

previously validated FHS-AF risk score as an effective clinically useful tool for the assessment of AF risk in patients taking ibrutinib.[23] Increased FHS-AF risk score was confirmed as a significant risk factor on multivariable analysis. This tool can be used in the clinic for risk assessment and can potentially be useful for prospective studies in this population. Because hypertension is a known risk factor for the development of AF and its incidence increases with time on ibrutinib, we identified 262 patients with hypertension at baseline and 37 who developed it while on treatment. We analyzed the association between hypertension and AF, treating hypertension as a time-dependent covariate in the regression model; however, this association was not found to be significant with crude HR = 1.06 (0.67-1.66), $P = .81$. Trisomy 12 was also found to be a risk factor for the development of AF among CLL patients during ibrutinib treatment, although the physiological and clinical significance of this finding is unknown. Because of the small number of patients on concomitant strong cytochrome P450 3A4 inhibitor therapy, conclusions cannot be drawn regarding the association between cytochrome P450 3A4 inhibition and the development of AF.

Our data also suggest that risk for subsequent AF events may be reduced by ibrutinib discontinuation. No subsequent AF events were observed in 7 patients in whom this strategy was employed, whereas among the 68 patients who were rechallenged or continued ibrutinib at the same dose, 19 experienced clinically significant subsequent AF. Our data supporting ibrutinib dose reductions to reduce the risk of subsequent AF events are limited, because only 1 patient had this strategy employed. However, data from other centers suggest that this strategy may be effective and should be further investigated, because it is clear that outcomes are poor after ibrutinib discontinuation, especially among patients with CLL.[15-17,21,32]

Our study is inherently limited by its retrospective design but reflects detailed outcomes of a large cohort of patients treated with ibrutinib, including a substantial number of patients treated outside of clinical trials, and is also reflective of a real-world experience. Until a prospective study of AF during ibrutinib treatment is undertaken, large retrospective studies such as this are the best way to gain valuable insights into the management of AF as a complication of ibrutinib therapy.

In conclusion, our study, although confirming previous findings of an increased incidence of AF during ibrutinib treatment, suggests that the incidence may be higher than previously reported. We identified factors that increase risk, especially prior history of AF, that need to be considered when prescribing ibrutinib. We also provide rationale for the utility of the FHS risk assessment as a clinically utilizable tool for determining the risk of AF. Based on our experiences and existing data, we recommend identification and optimal management of known risks factors, especially hypertension, prior to starting ibrutinib. Closer monitoring, especially during the first 6 months of therapy, is required for patients with a previous history of AF for a recurrent event while on ibrutinib, in conjunction with cardiology consultation for management. Rate control strategies appear to be frequently used and well tolerated, whereas rhythm control strategies have demonstrated limited success.[17] Early detection and aggressive medical management can potentially result in prolonging the time on ibrutinib, and dose reductions can be employed to enable continuation of therapy. Drug discontinuation should only be considered based on physician and patient preference and disease factors because outcomes after discontinuation are poor. Given the well-recognized bleeding risk associated with ibrutinib, we recommend caution with the concomitant use of antiplatelet agents and anticoagulants, with novel anticoagulants possibly providing a safer alternative to warfarin. Together, these results improve our understanding of the risk factors, evaluation, and management of patients with AF on ibrutinib treatment and provide the basis for the development of formal consensus guidelines.

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Authorship

Contribution: T.E.W., L.B.L., J.B., J.C., L.M., and F.T.A. collected and analyzed the data, and wrote and edited the manuscript; Q.Z. and A.S.R. analyzed the data, and wrote and edited the manuscript; A.M., K.R., A.G., N.A.H., K.M., B.C., L.A.A., S.J., S.D., R.B., J.W., J.J., M.G., K.A.B., J.C.B., and F.T.A. provided insight to the study design and patient care, reviewed the data, and wrote and edited the manuscript.

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Correspondence: Farrukh T. Awan, Division of Hematology, The Ohio State University Comprehensive Cancer Center, 320 W 10th Ave, Columbus, OH 43210; e-mail: farrukh.awan@osumc.edu.

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