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MINI-FOCUS ISSUE: BLEEDING, THROMBOSIS, AND ATRIAL FIBRILLATION

ORIGINAL RESEARCH

Ibrutinib Is Associated With Increased Cardiovascular Events and Major Bleeding in Older CLL Patients

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ABSTRACT

BACKGROUND Early ibrutinib trials showed an association between ibrutinib use and risk of bleeding and atrial fibrillation (AF) in younger chronic lymphocytic leukemia (CLL) patients. Little is known about these adverse events in older CLL patients and whether increased AF rates are associated with increased stroke risk.

OBJECTIVES To compare the incidence of stroke, AF, myocardial infarction, and bleeding in CLL patients treated with ibrutinib with those who were treated without ibrutinib in a linked SEER-Medicare database.

METHODS The incidence rate of each adverse event for treated and untreated patients was calculated. Among those treated, inverse probability weighted Cox proportional hazards regression models were used to calculate HRs and 95% CIs for the association between ibrutinib treatment and each adverse event.

RESULTS Among 4,958 CLL patients, 50% were treated without ibrutinib and 6% received ibrutinib. The median age at first treatment was 77 (IQR: 73-83) years. Compared with those treated without ibrutinib, those treated with ibrutinib had a 1.91-fold increased risk of stroke (95% CI: 1.06-3.45), 3.65-fold increased risk of AF (95% CI: 2.42-5.49), a 4.92-fold increased risk of bleeding (95% CI: 3.46-7.01) and a 7.49-fold increased risk of major bleeding (95% CI: 4.32-12.99).

CONCLUSIONS In patients a decade older than those in the initial clinical trials, treatment with ibrutinib was associated with an increased risk of stroke, AF, and bleeding. The risk of major bleeding is higher than previously reported and underscores the importance of surveillance registries to identify new safety signals.
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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

BTK = Bruton's tyrosine kinase

CLL = chronic lymphocytic leukemia

DOAC = direct oral anticoagulant

IPW = inverse probability weighted

LMWH = low molecular weight heparin

MI = myocardial infarction

SEER = Surveillance, Epidemiology, and End Results

sHR = subdistribution hazard ratio

VKA = vitamin K antagonist

Ibrutinib, a first-in-class Bruton's tyrosine kinase (BTK) inhibitor, approved for treatment of chronic lymphocytic leukemia (CLL), is associated with a specific toxicity profile.[1] In an initial study including 111 patients with relapsed mantle cell lymphoma, 4 patients developed subdural hematomas, all of whom were also taking aspirin or warfarin.[2] Consequently, patients on warfarin were excluded from ibrutinib clinical trials.[3] In the pivotal phase II trial of relapsed CLL patients, 16% had a bleeding event.[4] Any grade bleeding was observed in 44% of patients, compared with 12% when treated with ofatumumab.[5] Two recently pooled analyses of clinical trial data comparing ibrutinib to other treatments showed an increased prevalence of bleeding events in ibrutinib-treated patients (35% vs 15%). However, when limited to major hemorrhage, events were infrequent and occurred at similar frequencies between groups.[6,7] In a randomized trial of acalabrutinib vs ibrutinib in previously treated CLL, bleeding events were more frequent with ibrutinib (51.3% vs 38%). However, major bleeding events were comparable[8] (5.3% vs 4.5%).

In addition to bleeding, patients treated with ibrutinib have increased incidence of atrial fibrillation (AF), reported to range between 5% and 20%.[9] Patients with AF have a stroke risk of 0.2% to 12.2%; this risk is further increased in cancer patients.[10,11] Anticoagulation in patients with AF has decreased stroke risk by 60%.[11] Patients who develop AF on ibrutinib present a clinical challenge, as they have an indication for anticoagulation therapy, but concomitant anticoagulation and ibrutinib significantly increases the risk of bleeding. There are several proposed mechanisms for the effect of ibrutinib on bleeding, including defects in platelet adhesion on von Willebrand factor, platelet aggregation, selective inhibition of platelet signaling downstream of collagen receptor glycoprotein VI, and treatment-induced thrombocytopenia.[12-15] Conversely, these effects on platelet aggregation may also provide protection from stoke via the same mechanisms, as seen with other antiplatelet therapies.[16,17]

In a pooled safety analysis of 4 randomized clinical trials of ibrutinib the median age at treatment was 67 years.[6] The median age of CLL diagnosis in the United States is 72 years, and the average time to first treatment is 4 to 5 years from the time of diagnosis.[18] Older age is associated with increased rate of serious adverse events in CLL patients.[19] Therefore, we sought to examine the incidence rate of stroke, AF, myocardial infarction (MI), and bleeding in CLL patients treated with ibrutinib, and to assess whether these incidence rates were markedly higher than those patients not treated with ibrutinib.

METHODS

This study was approved by Case Western Reserve University's Institutional Review Board (protocol # 2019-1029).

STUDY POPULATION. Using the Surveillance, Epidemiology, and End Results Program (SEER) data linked with Medicare claims, we identified patients diagnosed with CLL between 2007 and 2015 based on SEER primary site code of C420, C421, or C424, with a histology code of 9823 (n = 17,114). We required full coverage in Medicare Parts A, B, and D from the start of enrollment, having been enrolled in Medicare a minimum of 1 year before diagnosis of CLL, and receive their care exclusively through the traditional fee-for-service system during their entire follow-up time to ensure complete claims history. We included data from 2008 to 2014 to compare events in patients treated with ibrutinib to those not treated with ibrutinib. We excluded any patients under 66 years old at diagnosis date to allow for a 1-year look-back period during which we identified comorbid conditions. Our final analytic cohort was 4,958 individuals (**Figure 1**).

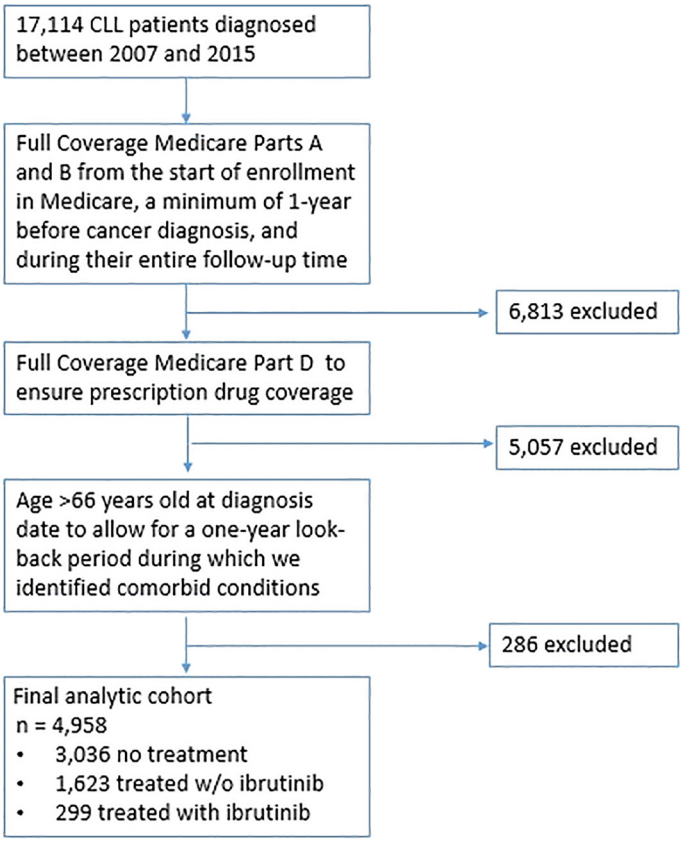
VARIABLES OF INTEREST. We categorized our primary exposure of interest, ibrutinib, as: 1) individuals who were never treated; 2) those who were treated but never received ibrutinib; and 3) those who were treated and received ibrutinib. For our primary analysis, we considered use of ibrutinib at any time as "treated with ibrutinib." We identified whether CLL patients were treated with any number of chemotherapy agents, using both generic names as well as Healthcare Common Procedure Coding System codes (Supplemental Table 1).

OUTCOMES OF INTEREST. Our outcomes of interest were stroke, AF, all bleeding events, bleeding limited to major bleeding, and MI. We identified an individual's first recorded date of these outcomes using ICD-9-CM and ICD-10-CM codes. If an individual patient had an event identified before diagnosis, we considered these complications to be prevalent. Those with a prevalent complication were excluded from their respective analysis. Although our study population was limited to those diagnosed in 2008 to 2016, to ensure we could capture treatment patterns,

we used data as far back as 2000 (the first year for which data were available in our database) to identify any prevalent event. Major bleeding was defined as bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, intra-articular, or pericardial, and acute posthemorrhagic anemia.[20] The codes for bleeding were identified using previously published literature and verified by the study team (Supplemental Table 2).[21,22]

COVARIATES. Demographic variables of interest included sex, race, age (at diagnosis), and county of residence (during diagnosis year). In SEER data, only the month and year of diagnosis and death are available. For that reason, we assumed both to be the 15th of the month. The Elixhauser comorbidities, which have been previously shown to be associated with negative health outcomes,[23] as well as hyperlipidemia, acute posthemorrhagic anemia, and intracranial hemorrhage (Supplemental Table 2), were identified in the year before cancer diagnosis, excluding the month before diagnosis to exclude potential cancer-related complications. For the Elixhauser comorbidities, we required at least 1 inpatient claim, or 2 outpatient claims at least 30 days apart. We identified advanced stage disease based on the presence of either anemia or thrombocytopenia. Finally, we identified anticoagulant and antiplatelet agent use among our patient cohort (Supplemental Tables 3 and 4). Anticoagulant agents were identified and operationalized based on the class of the agent. Because an individual may have been on different classes of anticoagulants, each class was treated as its own binary variable.

FIGURE 1 Cohort Selection



The flow diagram shows the identification of the final analytic cohort. CLL = chronic lymphocytic leukemia.

STATISTICAL ANALYSES. We calculated the total person-time each patient spent between time of CLL diagnosis, first non-ibrutinib treatment (if any), ibrutinib treatment, and complication. Follow-up time ended at the event, end of the study period (December 31, 2016), or death, whichever came first. From this, we calculated the crude incidence rate, per 1,000 person-years for each of our outcomes in each of our 3 groups.

Because our main goal of this study was to examine whether those patients on ibrutinib have a higher rate of complications vs other treatments, we focused our primary analysis on only those who were treated with either non-ibrutinib agents or ibrutinib, with time zero set at treatment initiation.

We recognize there are reasons a person may or may not receive ibrutinib, including availability (calendar time) as well as other clinical characteristics. To address this potential selection bias, our main analysis used inverse probability weighting (IPW) when examining the association between ibrutinib and our outcomes, after adjusting for confounding variables. Among patients who were treated (n = 1,922), a propensity score for ibrutinib (vs receipt of other therapy) was created using logistic regression. This was done by modeling the probability of receipt of ibrutinib based on sex, age (at first treatment or ibrutinib), class of anticoagulant drug use, antiplatelet use, statin use, and the Elixhauser comorbidities in the preceding 12 months of either first treatment or ibrutinib. For those who had received ibrutinib their weight was the inverse of the propensity score (1/P [ibrutinib]), whereas those who had not received ibrutinib were weighted as the inverse of 1 minus the propensity score or (1/[1-P (ibrutinib)]). Supplemental Figure 1 shows the mean differences in covariate balance between treatment groups before and after weighting.

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Given that most (73.9%) of individuals receiving ibrutinib had been on another agent before initiating ibrutinib, we treated ibrutinib as a time-varying covariate. Individuals who were treated with a different agent before receiving ibrutinib contribute time and the potential for a complication in the treated non-ibrutinib group, and when they first receive ibrutinib, then contribute time and the potential for a complication to the ibrutinib group. Each complication was analyzed independently. In addition to calculating the incidence rate, we used Cox proportional hazards models to evaluate the impact of ibrutinib on our outcomes, presenting findings from both the unadjusted and IPW-adjusted models. The resulting HRs and 95% CIs are equivalent to an adjusted incidence rate ratio.

We conducted sensitivity analyses limited to only those patients diagnosed in 2014 or later, as ibrutinib was not fully approved and widely available until that time. Sensitivity analyses were also conducted using a Fine-Gray competing risks approach to examine the competing risk of death in relation to complications. For these competing risks models, untreated patients and untreated time were also incorporated, with time zero set to time of CLL diagnosis and comorbidities captured at diagnosis, instead of at treatment initiation. Non-ibrutinib treatment and ibrutinib were both treated as time-varying covariates.

Descriptive data are presented as the median with 25th and 75th percentiles [IQR], and count (percentage) for categorical variables per relevant subgroup; HR are reported with 95% CIs. Data analysis was conducted in SAS version 9.4 (SAS Institute) and R (R Foundation for Statistical Computing) with statistical significance set at alpha of 0.05.

RESULTS

PATIENT CHARACTERISTICS. We identified 4,958 individuals diagnosed with CLL who met inclusion criteria. Of those, 3,036 (61.2%) were never treated, 1,623 (32.7%) were treated but not with ibrutinib, and 299 (6.0%) were treated with ibrutinib (**Table 1**). Seventy-eight patients (26.1%) received ibrutinib as their first-line therapy.

Median age in our study population was 78 years (IQR: 72-84 years). We observed notable variations by sex across the treatment groups. Although men and women were almost equally represented in the total study population (50.5% men and 49.5% women), women were slightly over-represented in the group receiving no treatment (51.6%), and considerably under-represented among those receiving ibrutinib (45.8%). Overall, 71.2% of all patients had at least 1 comorbidity, including 72.5% of patients never treated, 69.6% patients treated without ibrutinib, and 66.6% of those treated with ibrutinib. Although statin use was slightly higher in ibrutinib-treated patients compared with non-ibrutinib-treated patients (62.5% vs 59.6%), rates of hyperlipidemia were lower (38.1% vs 40.0%) (**Table 2**).

Prevalence of bleeding, AF, and stroke were lower at the time of diagnosis in patients who ultimately were treated with ibrutinib when compared with untreated or non-ibrutinib-treated patients (**Table 3**).

STROKE. We identified 3,754 patients eligible for incident stroke after CLL diagnosis. Untreated patients had a crude incidence rate of 45.6 strokes per 1,000 person-years. The incidence rate per 1,000 person-years was 50.7 for non-ibrutinib-treated patients and 72.9 for ibrutinib-treated patients (**Table 4**). Findings from the IPW-adjusted model, which only treated ibrutinib as a time-varying covariate, showed that those treated with ibrutinib had a 1.9-fold increased risk of first stroke (HR: 1.91; 95% CI: 1.06-3.45), compared with those patients treated with other therapies (**Table 5**). Our sensitivity analysis, limited to patients diagnosed in or after 2014, confirmed an increased rate of stroke in an unadjusted Cox proportional hazard model (HR: 3.46; 95% CI: 1.40-8.55). However, our IPW model had a wide confidence interval (HR: 2.13, 95% CI: 0.54-8.39) (Supplemental Table 6), and the adjusted difference was not statistically significant.

In a competing risks sensitivity analysis with untreated time, non-ibrutinib, and ibrutinib treatment considered as time-varying covariates, there was a 2.42-fold increased risk of stroke (95% CI: 1.36-4.31) in ibrutinib-treated patients when compared with untreated patients, including those who died without experiencing a stroke. The subdistribution HR (sHR) for non-ibrutinib-treated patients vs untreated patients crossed 1.0 (sHR: 1.21; 95% CI: 0.99-1.48) (Supplemental Table 5), indicating lack of statistical significance. As expected, among untreated patients, the prevalence of AF was higher among those patients who had a stroke compared with those who did not (51.9% vs 33.7%). Additionally, the crude incidence of stroke was higher in patients with AF compared with patients without AF (19.3% vs 10.1%) (Supplemental Table 7).

Although the numbers were small, among those patients who had an incident stroke, a higher percentage of ibrutinib-treated patients had prevalent AF (64.7%), compared with non-ibrutinib-treated patients (40.5%) and those who were untreated (51.9%) (Supplemental Table 7).

TABLE 1 Summary of Cohort of Patients With CLL From the Linked SEER-Medicare Database

		CLL		
	All CLL Patients (N = 4,958)	No Treatment (n = 3,036; 61.2%)	Treated, Not With Ibrutinib (n = 1,623; 32.7%)	Treated With Ibrutinib (n = 299; 6.0%)
Age at CLL diagnosis, y				
65 to <75	1,808 (36.5)	946 (31.2)	714 (44.0)	148 (49.5)
75 to <85	1,917 (38.7)	1,134 (37.4)	665 (41.0)	118 (39.5)
85+	1,233 (24.9)	956 (31.5)	244 (15.0)	33 (11.0)
Age at first treatment, y				
65 to <75			575 (35.4)	123 (41.1)
75 to <85			726 (44.7)	125 (41.8)
85+			322 (19.8)	51 (17.1)
Race				
White	4,504 (90.8)	2,744 (90.4)	1,490 (91.8)	270 (90.3)
Black	200 (4.0)	126 (4.2)	60 (3.7)	14 (4.7)
Other/unknown	254 (5.1)	166 (5.5)	73 (4.5)	15 (5.0)
Sex				
Male	2,503 (50.5)	1,469 (48.4)	872 (53.7)	162 (54.2)
Female	2,455 (49.5)	1,567 (51.6)	751 (46.3)	137 (45.8)
Advanced stage	2,344 (47.3)	1,428 (47.0)	786 (48.4)	130 (43.5)
Time from diagnosis to first treatment, mo	10.3 (2.0-26.7)		9.1 (1.9-26.1)	13.8 (4.1-29.3)
	17.6 ± 19.8		17.2 ± 19.9	19.6 ± 19.2
0	233 ± 12.1		209 ± 12.9	24 ± 8.0
1-6	549 ± 28.6		482 ± 29.7	67 ± 22.4
6-12	246 ± 12.8		285 ± 17.6	75 ± 25.1
12-24	360 ± 18.7		357 ± 22.0	79 ± 26.4
24-60	436 ± 22.7		206 ± 12.7	40 ± 13.4
60+	98 ± 5.1		84 ± 5.2	14 ± 4.7
Follow-up time, mo				
From diagnosis	34.1 (16.8-58.4)	28.4 (13.2-51.3)	40.1 (23.3-65.5)	53.3 (29.5-75.6)
From 1st treatment	25.6 (12.0-46.1)		22.5 (10.6-40.5)	29.0 (12.5-54.9)
From ibrutinib	10.4 (5.5-18.3)			10.4 (5.5-18.3)
Anticoagulant agent[a]				
Ever	1,964 (39.6)	984 (32.4)	835 (51.5)	145 (48.5)
VKA	919 (18.5)	517 (17.0)	344 (21.2)	58 (19.4)
Low molecular weight heparin	1,215 (24.5)	504 (16.6)	605 (37.3)	106 (35.5)
Direct thrombin inhibitors	142 (2.9)	70 (2.31)	59 (3.6)	13 (4.4)
DOAC	357 (7.2)	175 (5.8)	147 (9.1)	35 (11.7)
12-mo pretreatment or pre-ibrutinib			377 (23.2)	56 (18.7)
Antiplatelet agent	861 (17.4)	518 (17.1)	288 (17.7)	55 (18.4)
Statin	2,867 (57.8)	1712 (56.4)	968 (59.6)	187 (62.5)

Values are median (IQR), n (%), or mean ± SD. [a]For the class of anticoagulant, we identified what an individual was ever on, and thus the sum of these will be greater than the number of patients.

CLL = chronic lymphocytic leukemia; DOAC = direct oral anticoagulant; SEER = Surveillance, Epidemiology, and End Results program; VKA = vitamin K antagonist.

ATRIAL FIBRILLATION. We identified 3,637 patients eligible for incident AF analysis. The crude incidence rate per 1,000 person-years was 58.0 for untreated patients (**Table 4**). The incidence rate for non-ibrutinib-treated patients and ibrutinib-treated patients was 66.2 and 221.8 per 1,000-person years, respectively.

Those treated with ibrutinib had an increased risk of AF (HR: 3.65; 95% CI: 2.42-5.49), compared with those patients treated with other therapies (**Table 5**), in the IPW-adjusted model (**Central Illustration**). In a competing risks sensitivity analysis with untreated time, non-ibrutinib, and ibrutinib treatment considered as time-varying covariates, there was a 4.91-fold increased risk of AF (95% CI: 3.46-6.97) in ibrutinib-treated patients when compared with untreated patients. Non-ibrutinib-treated patients had a sHR of 1.21 (95% CI: 1.02-1.45) compared with untreated patients, including those who died without experiencing a stroke (Supplemental Table 5). The increased risk of AF persisted despite increased risk of death in the treated cohort.

TABLE 2 Prevalence of Elixhauser Comorbidities, Hyperlipidemia, and Bleeding of Patients With CLL From the Linked SEER-Medicare Database

	Prevalence, CLL		
	No Treatment (n = 3,036)	Treated (n = 1,623)	Treated With Ibrutinib (n = 299)
Congestive heart failure	314 (10.3)	110 (6.8)	<11
Valvular disease	200 (6.6)	118 (7.3)	13 (4.3)
Pulmonary circulation disease	43 (1.4)	23 (1.4)	<11
Peripheral vascular disease	390 (12.8)	143 (8.8)	21 (7)
Hypertension	1,666 (54.9)	851 (52.4)	135 (45.2)
Paralysis	41 (1.4)	<11	<11
Other neurological disorders	256 (8.4)	56 (3.5)	<11
Chronic pulmonary disease	414 (13.6)	180 (11.1)	29 (9.7)
Diabetes w/o complications	668 (22)	346 (21.3)	54 (18.1)
Diabetes w/ complications	208 (6.9)	99 (6.1)	19 (6.4)
Hypothyroidism	379 (12.5)	176 (10.8)	28 (9.4)
Renal failure	256 (8.4)	115 (7.1)	<11
Liver disease	25 (0.8)	14 (0.9)	<11
Peptic ulcer disease	<11	<11	<11
HIV/AIDS	<11	<11	<11
Lymphoma	39 (1.3)	28 (1.7)	<11
Metastatic cancer	<11	<11	<11
Solid tumor w/o metastasis	67 (2.2)	<11	<11
Rheumatoid arthritis	74 (2.4)	57 (3.5)	<11
Coagulopathy	118 (3.9)	73 (4.5)	14 (4.7)
Obesity	104 (3.4)	47 (2.9)	<11
Weight loss	104 (3.4)	24 (1.5)	<11
Fluid and electrolyte disorders	267 (8.8)	96 (5.9)	<11
Chronic blood loss anemia	22 (0.7)	16 (1.0)	<11
Deficiency anemias	508 (16.7)	272 (16.8)	29 (9.7)
Alcohol abuse	18 (0.6)	<11	<11
Drug abuse	<11	<11	<11
Psychoses	135 (4.4)	49 (3.0)	<11
Depression	156 (5.1)	65 (4.0)	<11
Hyperlipidemia	1,160 (38.2)	649 (40.0)	114 (38.1)
Acute post hemorrhagic anemia	53 (1.8)	21 (1.3)	<11
Intracranial hemorrhage	<11	<11	<11

Values are n (%).
Abbreviations as in Table 1.

BLEEDING RISK. We identified 3,197 patients eligible for incident bleeding analysis. The crude incidence rate per 1,000 person-years was 117.2 for untreated patients (Table 4). The incidence rate for non-ibrutinib-treated patients and ibrutinib-treated patients was 122.9 and 401.3 per 1,000-person years, respectively.

Among those patients who received any treatment, those treated with ibrutinib had a 4.9-fold increased risk of bleeding (HR: 4.92; 95% CI: 3.46-7.01), compared with those who were treated with other therapies in the IPW-adjusted model (Table 5).

TABLE 3 Prevalence of Outcomes of Interest At CLL Diagnosis

	Prevalent At Diagnosis		
	No Treatment	Treated, Non-Ibrutinib	Ibrutinib
n	3,036	1,623	299
Stroke	823 (27.1)	332 (20.5)	54 (18.1)
Atrial fibrillation	863 (28.4)	398 (24.5)	60 (20.1)
Bleeding	1130 (37.2)	545 (33.6)	78 (26.1)

Values are n (%).
CLL = chronic lymphocytic leukemia.

MAJOR BLEEDING RISK. We identified 4,957 patients eligible for incident major bleeding analysis. The crude incidence rate per 1,000 person-years was 13.2 for untreated patients (Table 4). The incidence rate for non-ibrutinib-treated patients and ibrutinib-treated patients was 17.9 and 86.3 per 1,000-person years, respectively.

Among patients receiving treatment, those treated with ibrutinib had a 7.5-fold increased risk of major bleeding compared with patients receiving other therapies (HR: 7.49; 95% CI: 4.32-12.99) in the IPW-adjusted model (Central Illustration, Table 5).

Both findings were confirmed in our sensitivity analysis, limiting to just cases diagnosed in 2014 or after (Supplemental Table 5). In a competing risk sensitivity analysis with untreated time, non-ibrutinib, and ibrutinib treatment considered as time-varying covariates, there was a 3.47-fold increased risk of bleeding (95% CI: 2.48-4.85) and a 4.18-fold increase in major bleeding (95% CI: 2.53-6.91) in ibrutinib-treated patients when compared with untreated patients, including those who died without experiencing a stroke. Non-ibrutinib-treated patients had a sHR of 0.99 (95% CI: 0.86-1.14) and a sHR of 1.10 (95% CI: 0.83-1.44) for bleeding and major bleeding, respectively, when compared with untreated patients (Supplemental Table 6).

Vitamin K antagonists (VKAs) were associated with the highest rates of bleeding in all patient groups. Low molecular weight heparin was associated with the lowest rate of bleeding in the non-ibrutinib-treated group (65.5%), whereas direct oral anticoagulants (DOACs) were associated with lower bleeding rates in ibrutinib-treated and untreated patients (68.6% and 61.4%, respectively). A total of 68.6% of patients on ibrutinib treated with a DOAC had a bleed, compared with 79% treated with a VKA. Although direct thrombin inhibitors were uncommonly prescribed (2.9% of all patients), they were associated with higher rates of bleeding than DOACs (Supplemental Table 8).

MYOCARDIAL INFARCTION. We identified 4,552 patients eligible for incident MI analysis. The crude incidence rate per 1,000 person-years was 27.5 for untreated patients (Table 4). The incidence rate for

non-ibrutinib-treated patients and ibrutinib-treated patients was 33.3 and 57.2 per 1,000-person years, respectively.

Among patients receiving treatment, those treated with ibrutinib had a 1.86-fold increased risk of MI compared with patients receiving other therapies (HR: 1.86; 95% CI: 1.03-3.36) in the IPW-adjusted model, albeit with a wide confidence interval approaching the null. In our sensitivity analysis, limited to cases diagnosed after 2014, although there was an increased incidence rate for those treated with ibrutinib (91.3 vs 40.8 per 1,000 person-years) the HR in the Cox proportional hazard model did not suggest a statistically meaningful difference (Supplemental Tables 6 and 9). In a competing risks sensitivity analysis with untreated time, non-ibrutinib, and ibrutinib treatment considered time-varying covariates, there was a 2.83-fold increased risk of MI (95% CI: 1.61-4.98) in ibrutinib-treated patients when compared with untreated patients, including those who died without experiencing a stroke. Non-ibrutinib-treated patients had a sHR of 1.25 (95% CI: 1.01-1.56) compared with untreated patients (Supplemental Table 5).

ANTICOAGULATION. A history of anticoagulation prescription was found in 32.4% (n = 984) of patients who had not received CLL treatment, 51.5% of patients treated with agents other than ibrutinib (n = 835), and 48.5% of patients treated with ibrutinib (n = 145). Among treated patients, anticoagulation in the 12 months preceding treatment was found in 23.2% of non-ibrutinib-treated patients and 18.7% of patients treated with ibrutinib (**Table 1**). Of the 835 non-ibrutinib-treated patients on an anticoagulant 83.35% received a prescription after starting CLL treatment. Of the 145 ibrutinib-treated patients who received anticoagulation, 60.69% were prescribed anticoagulation after receipt of ibrutinib. Anticoagulation was prescribed after CLL treatment start in 42.9% of non-ibrutinib-treated patients and in 40.8% of ibrutinib-treated patients. However, 29.4% of ibrutinib-treated patients were prescribed anticoagulation after ibrutinib start. The most commonly prescribed anticoagulant was low molecular weight heparin (LMWH). LMWH was more commonly prescribed in both treatment groups compared with nontreated patients. A VKA was prescribed in 19.4% of ibrutinib-treated patients compared with 21.2% of non-ibrutinib-treated patients. DOACs were prescribed in 11.74% of ibrutinib-treated patients compared with 9.1% of non-ibrutinib-treated patients (**Table 1**).

Among ibrutinib-treated patients with an incidence bleeding event, 30.2% had been prescribed anticoagulation in the preceding year, compared with 15.8% in patients without bleeding. Thirty-two ibrutinib-treated patients were prescribed anticoagulation, 50% (n = 16) had a bleeding episode.

TABLE 4 Crude Incidence Rates Between Untreated, Non-Ibrutinib-, and Ibrutinib-Treated Patients, With Treatments as Time-Varying

	Untreated	Non-Ibrutinib	Ibrutinib
Stroke, eligible, n = 3,754			
Total person-years	8,443.3	3,153.9	233.1
Incidence rate, per 1,000 person-years	45.6	50.7	72.9
Atrial fibrillation, eligible, n = 3,637			
Total person-years	8,085.7	3,038.5	189.4
Incidence rate, per 1,000 person-years	58.0	66.2	221.8
Bleeding, eligible, n = 3,197			
Total person-years	6,477.0	2,285.6	132.1
Incidence rate, per 1,000 person-years	117.2	122.9	401.3
Major bleeding, eligible, n = 4,957			
Total person-years	11,295.9	4,368.1	301.4
Incidence rate, per 1,000 person-years	13.2	17.9	86.3
Myocardial infarction, eligible, n = 4,552			
Total person-years	10,268.4	3,997.5	279.8
Incidence rate, per 1,000 person-years	27.5	33.3	57.2

MORTALITY. Ibrutinib-treated patients had an increased risk of all-cause mortality (HR: 3.17; 95% CI: 2.35-4.29), whereas non-ibrutinib-treated patients had a HR of 1.73 (95% CI: 1.56-1.92) compared with untreated patients (Supplemental Figure 2). Ibrutinib-treated patients had a 12.28-fold (95% CI: 8.44-17.87) greater subdistribution hazard of death from CLL (ie, CLL listed as the cause of death) compared with untreated patients, whereas non-ibrutinib patients had a 3.15-fold (95% CI: 2.67-3.75) greater subdistribution hazard to have CLL listed as the cause of death. All other causes of death were similar between ibrutinib and untreated patients (HR: 1.40, 95% CI: 0.92-2.14) and slightly increased in non-ibrutinib-treated patients (HR: 1.33; 95% CI: 1.19-1.50) (Supplemental Table 10).

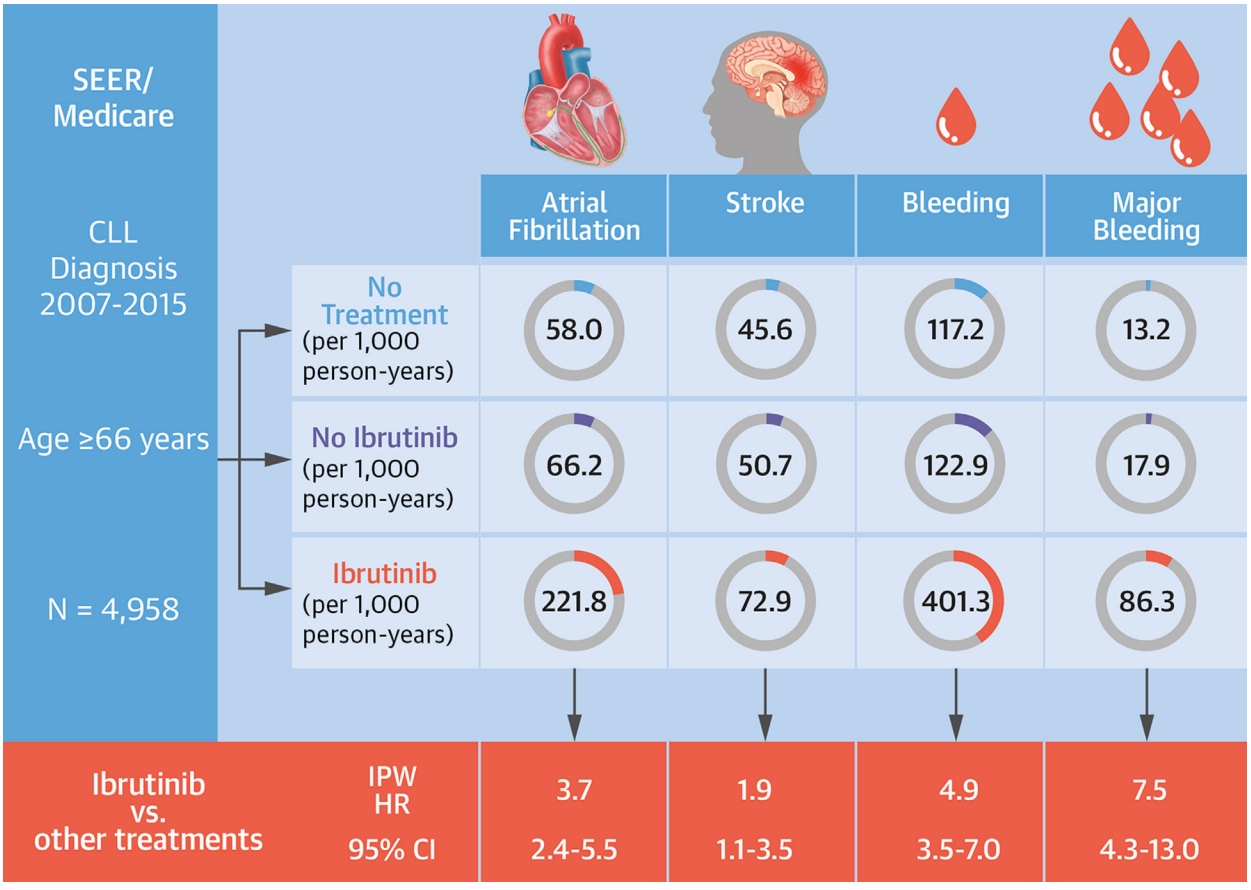
TABLE 5 Cox Proportional Hazard Model to Assess the Effect of Ibrutinib on the Complications of Interest

	HR (95% CI)	
	Unadjusted	IPW
Stroke	1.64 (0.98-2.75)	1.91 (1.06-3.45)
Atrial fibrillation	3.56 (2.56-4.95)	3.65 (2.42-5.49)
Bleeding	3.36 (2.47-4.57)	4.92 (3.46-7.01)
Major bleeding	4.60 (2.89-7.30)	7.49 (4.32-12.99)
Myocardial infarction	1.85 (1.10-3.11)	1.86 (1.03-3.36)

Values are HR (95% CI). Ibrutinib was compared with non-ibrutinib therapies, which were used as reference values.

IPW = inverse probability weighting.

CENTRAL ILLUSTRATION **Treatment Cohorts and Outcomes of Interest**



Diamond A, et al. J Am Coll Cardiol CardioOnc. 2023;5(2):233-243.

The figure shows the incidence according to 1,000 person-years (with the color denoting person-years if 1,000/1,000 person-years is represented by full circle), and HRs of each of the main outcomes of interest according to treatment group. CLL = chronic lymphocytic leukemia; IPW = inverse probability weighted; SEER = Surveillance, Epidemiology, and End Results program.

DISCUSSION

In this analysis of a linked SEER-Medicare dataset of CLL patients, ibrutinib use was associated with an increased risk of AF, bleeding, and major bleeding, and associated with stroke and MI, albeit at borderline statistical meaningfulness.

Recently, there has been increasing interest and concern regarding the cardiac toxicity of ibrutinib. The mechanism of this increased toxicity is not fully understood but may be linked to BTK expression in cardiac myocytes and downstream TEC inhibition that may affect the PI3K-Akt signaling pathway.[8] As additional BTK inhibitors with similar efficacy have become available, understanding the safety profile of each agent will be of increasing importance when deciding on the most appropriate therapy for individual patients. In recent studies, ibrutinib treated patients had higher rates of hypertension, new-onset AF, and total cardiac events, compared with acalabrutinib-treated patients.[8]

A study of ibrutinib-treated CLL patients showed increased 3-year incidence of AF related health care contact, hospital diagnosed bleeding, and heart failure, but no significant difference in stroke or MI.[24] Our data did identify an increased risk of stroke and MI, despite a wide confidence interval, when looking at an older patient population.

A single-center retrospective review of new onset AF in 217 ibrutinib-treated patients identified a 3-fold increased risk of AF and increased adjusted all-cause mortality in patients with prior coronary artery

disease, congestive heart failure, pulmonary hypertension, moderate valvular heart disease, and cardiac device implantation.[25] It would be prudent to evaluate all CLL patients for prior cardiac disease before initiating ibrutinib.

Understanding the side effect profile and toxicities of ibrutinib will continue to be important, as several recent trials have reaffirmed its place as the frontline treatment choice for many patients diagnosed with CLL.[26] Moreover, earlier prescription of CLL therapy is under investigation and awaiting final overall survival analysis.[27] An increasing number of patients can be expected to be prescribed ibrutinib or similar agents for longer periods of time.

Our data confirmed the potential for increased risk of AF for those patients on ibrutinib, similarly reported in clinical trial and smaller clinical studies with this agent. Despite any potential antiplatelet effect of ibrutinib, our competing risk sensitivity analysis showed an increased risk of stroke in ibrutinib-treated patients compared with untreated patients. The increased stroke risk should be further explored with larger numbers as ibrutinib use has become more prevalent. Although we were limited by a small number of patients who had both stroke and AF, there was an association between ibrutinib and AF potentially contributing to stroke—an important area for future studies. Our data suggest that the increased stroke risk is associated with increased rates of AF and highlights indication for anticoagulation in this population.

The risk of ibrutinib-associated bleeding events was also confirmed, with a significant increased risk of major bleeding. A recent clinical trial comparing ibrutinib, ibrutinib-rituximab to bendamustine-rituximab[26] for initial CLL treatment observed grade ≥3 bleeding in 3% of ibrutinib-treated patients, whereas no severe bleeding events occurred in the chemo-immunotherapy arm. Pooled analyses of clinical trials[6] had shown a 20% increase in all bleeding complications with ibrutinib over other treatments, although the difference did not reach statistical meaningfulness when the analysis was limited to major bleeding events. Compared with reported rates of major hemorrhage in clinical trials of (a 2-fold increase),[28] our analysis found ibrutinib was associated with a 4.9 -fold increase in bleeding events and a 7.5-fold increase in major bleeding. Potential differences between our findings and those reported from clinical trials may be due to the real-world observational nature of our study, reflecting potential increased toxicities in an older non-trial population. However, it may be due to the limited median follow-up of 16 months in the pooled clinical trial data or due to the different definition of major bleeding in the prospective data as compared with significant bleeding as determined by ICD codes. CLL is a chronic condition, and patients are treated with ibrutinib for an average duration of 57 months.[29] Long-term safety data may reveal risks otherwise not identified.

Advanced age could have accounted for increased bleeding risk because our study population was approximately a decade older than the patient population enrolled in the initial 3 ibrutinib trials. These findings suggest that the increased risk of bleeding may reflect the ibrutinib toxicity in an aged patient population outside of the context of a clinical trial. In the randomized phase 3 trial, which showed better safety of acalabrutinib compared with ibrutinib, the median age was 66 years.[8] Suggesting that continued observation for these outcomes in an older population will remain important. Moreover, anticoagulant prescription among ibrutinib-treated patients in our cohort was more frequent than on trials, where anticoagulant use was discouraged or outright excluded. In our dataset, patients with bleeding events were twice as likely to be prescribed an anticoagulant in the prior year. This observation highlights the high risk of bleeding with combined anticoagulation and ibrutinib therapy.

Currently there are no guidelines for ibrutinib-associated AF management; however, treatment algorithms have been proposed.[30] Decisions regarding anticoagulation must be carefully balanced, and although CHA_2DS_2-VASc and HAS-BLED may help identify patients at highest risk or stroke and bleeding, respectively, they have not been validated in this clinical setting.[3] Stroke risk has been shown to be significantly higher in cancer patients with AF compared with noncancer patients, and interestingly, $CHADS_2$ score has been shown to better identify stroke risk than CHA_2DS_2-VASc.[10,11] Although Ganatra et al advise the use of warfarin with close INR monitoring or LMWH, Warfarin use was excluded from the clinical trials, and therefore limited data are available regarding its safety in this setting. The European Medicine Society advises against VKA use with ibrutinib.[31] Direct thrombin inhibitors have significant drug-drug interactions with ibrutinib and should be avoided.[1] Indeed, a very small percentage of patients in our analysis received this class of medication. In patients requiring anticoagulation, there is generally no consensus on management, some experts recommend a DOAC and others recommend discontinuing ibrutinib.[1,31] LMWH has been recommended off label if there are no other appropriate CLL

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treatments available.[1] Given the increased risk in major bleeding seen in older patients in our study and the recently approved CLL treatments with a lower risk of bleeding, discontinuation of ibrutinib in older patients with AF may be prudent.

Our study identified a significantly increased risk of CLL-related death in ibrutinib-treated patients compared with untreated patients. Patients with CLL are initially observed until increased disease burden warrants therapy; therefore, patients who require CLL-directed therapy are expected to have more advanced disease and are more likely to die from progressive disease. Considering our study evaluated ibrutinib use in the early days of ibrutinib availability, it is possible patients with more advanced disease were prescribed this agent.

STUDY LIMITATIONS. First, we were not able to capture the use of all antiplatelet agents because these are frequently available over the counter. Second, due to ibrutinib being an oral treatment, we were limited to Medicare Part D patients, which limited sample size and our ability to analyze stroke outcomes in greater detail. This may have contributed to wide confidence intervals in stroke and MI. There may have been selection bias in the patients treated with ibrutinib, reflected by a significant increase in CLL-related deaths and a slight increase in antiplatelet and statin use. Third, although we assessed comorbidities, we were unable to ascertain patients' overall health and fitness. To address selection bias, we used the IPW approach; even so, we were able to control only for factors that were available in our database. As our competing risks sensitivity analysis considered untreated time, non-ibrutinib, and ibrutinib treatment as time-varying covariates, we were only able to consider comorbidities at time of diagnosis and not at treatment start. However, our IPW model did consider comorbidities at time of treatment initiation. Fourth, follow-up of ibrutinib-treated patients was shorter than the follow-up of the other cohorts due to the recent approval of ibrutinib during the study period. Although our competing risk sensitivity analysis showed an increased risk of the complications of interest in ibrutinib-treated patients compared with untreated patients, ibrutinib-treated patients had shorter follow-up and increased risk of CLL related death; survivor bias and lead time bias may still be present. Fifth, we were not able to assess pretreatment lab values or Binet and Rai staging, which may have guided treatment decisions. Finally, we did not account for duration of or adherence to treatment—an important consideration for future work examining treatment patterns and outcomes.

CONCLUSIONS

Our analysis included data of CLL treatment patterns and therapy-related toxicities from the initial years after ibrutinib regulatory approval. In alignment with clinical trial results, these data show that ibrutinib patients have a significant increased risk of AF and bleeding compared to patients treated with other therapies. We found a significant increase in major bleeding and a borderline increased risk of stroke, which has not been previously reported. CLL patients who develop AF remain a clinical challenge, and studies are needed to identify the best strategy for continued CLL control without risk of additional complications.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In older patients treated with ibrutinib for CLL, rates of cardiac toxicities, including AF and bleeding, may be higher than previously reported.

TRANSLATIONAL OUTLOOK: Future studies should determine risk factors for developing AF and bleeding on Bruton's tyrosine kinase inhibitors to help identify patients at highest risk.

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KEY WORDS atrial fibrillation, bleeding, CLL, ibrutinib, major bleeding, stroke

APPENDIX For supplemental figures and tables, please see the online version of this paper.